Title Page

The Utility of Right Ventricular Speckle Tracking Echocardiography Strain Analysis in the Intensive Care Unit and Perioperative Period

Dr James Patrick Gerrard McErlane

MBBS MA MSc MRCP

Submitted in the fulfilment of the requirements for the Degree of Doctor of Medicine

School of Medicine, Veterinary and Life Sciences
University of Glasgow

December 2024

Dedication

To Hannah, Atticus, and Lucian.

This thesis was only possible because of you.
I doubt it will make for good bedtime reading, but it is for you all nonetheless.

To my parents.

Thank you for your eternal love, encouragement, and support through all my life's adventures.

Abstract

Right ventricular (RV) function is highly important, but underappreciated, in the intensive care unit (ICU) and the perioperative period. Right ventricular dysfunction (RVD) has been shown to be common in ICU and it is associated with poor outcomes in patients with sepsis and acute respiratory distress syndrome (ARDS). The prevalence and impact of RVD in patients in the perioperative period is less well understood. Global assessment of RV function is challenging, with conventional RV echocardiography parameters often only assessing localised function, and perform poorly compared with gold standard methods such as cardiovascular magnetic resonance imaging. RV speckle tracking echocardiography (STE) is a novel parameter thought to overcome some of these limitations. This thesis aims to assess the utility of RV-STE in ICU and the perioperative period.

The fundamentals of RV anatomy and function are firstly described in Chapter 1. This includes a discussion about invasive and non-invasive methods for assessing RV function. The conventional echocardiography parameters are described, with which RV-STE is compared.

The principles underlying RV-STE are described in Chapter 2. Consensus guidelines recommend the use of peak RV free wall longitudinal strain (RVFWLS), and this is the primary measure of RV-STE assessed in this work. Reference ranges and the effects of different strain software are described.

A framework for utility is defined in Chapter 3, forming the basis for assessment of RVFWLS utility. Utility is assessed by three domains: feasibility, reproducibility, and validity. Feasibility is defined as the percentage of echocardiography studies of adequate image quality for RVFWLS analysis. Validity is explored via three subtypes; concurrent (comparing RVFWLS to a gold standard), predictive, and construct validity (hypothesis testing where expected relationships between variables and RV function are analysed using RVFWLS as a surrogate for RV function).

To establish the current body of work investigating the utility of RVFWLS, a literature review is presented (Chapter 4). This review is divided into two parts, examining ICU and the perioperative period separately. Meta-analysis identified that RVFWLS feasibility in ICU is improved by prospective study design whereas increasing proportions of patients receiving mechanical ventilation reduces feasibility. In the perioperative group, preoperative echocardiography scans had better feasibility than postoperative. Reproducibility of RV-STE was high in both ICU and perioperative groups. In ICU patients, predictive validity was demonstrated with regards the association between RVFWLS and short-term mortality in patients with sepsis and coronavirus disease 2019 (COVID-19). Concurrent and construct validity was less well investigated in these groups.

The COVID-RV study (Chapter 5) investigated the utility of RVFWLS in patients with COVID-19 requiring invasive mechanical ventilation. Patients underwent echocardiography post-intubation. High RVFWLS feasibility was identified, with excellent reproducibility. Abnormal RVFWLS was found in 28.7% of patients, and was independently associated with 30-day and one-year mortality. Abnormal RVFWLS was also associated with raised cardiac biomarkers and raised ventilatory driving pressures, implicating myocardial injury and injurious mechanical ventilation in the manifestation of RVD. These findings support the predictive and construct validity of RVFWLS in this setting.

The RV exercise study was undertaken (Chapter 6) to assess RVFWLS as a measure of dynamic RV function when undertaking exercise stress echocardiography (termed right ventricular contractile reserve: RVCR) in a perioperative group undergoing lung resection. Postoperative exertional symptoms are common in this group and this study aimed to investigate if impaired RVCR contributes to these symptoms. Results showed that exercise stress echocardiography was tolerable to patients, and RVFWLS feasibility and reproducibility were again high. There was no improvement in RVFWLS when patients underwent exercise pre- or postoperatively, however RVFWLS-rate was shown to increase pre-operatively when exercising and this relationship was lost postoperatively. This suggests that RVFWLS-rate may be the better measure for identifying RVCR, and that RVCR is impaired in patients following lung resection.

This thesis provides a comprehensive assessment supporting the utility of RV-STE in ICU and the perioperative period. The utility of RV-STE in the perioperative setting will be further investigated by the "IMPRoVE study", set up by the author and his supervisors. This study aims, for the first time, to investigate the prevalence of perioperative RVD across a range of surgical specialties, and elucidate the mechanisms and impact of perioperative RVD on patient outcomes using RVFWLS as the primary measure of RV function.

Table of Contents

List of tables

List of figures

List of publications and presentations

Publications and presentations obtained / written by the author directly pertaining to the work carried out in the preparation of this thesis.

Peer reviewed publications (grouped by relevance to thesis chapter):

Chapter 4

McErlane J, Shelley B, McCall P. Feasibility of 2-dimensional speckle tracking echocardiography strain analysis of the right ventricle with trans-thoracic echocardiography in intensive care: a literature review and meta-analysis. Echo Res Pract. 2023 Jul 20;10(1):11.

Chapter 5

McErlane J, McCall P, Willder J, Berry C, Shelley B; COVID-RV investigators. Right ventricular free wall longitudinal strain is independently associated with mortality in mechanically ventilated patients with COVID-19. Ann Intensive Care. 2022 Nov 12;12(1):104.

McErlane J, McCall P, Willder J, Berry C, Shelley B. Cardiac biomarkers and right ventricular dysfunction are associated independently with 1-year mortality in patients with COVID-19 receiving mechanical ventilation: a prospective cohort study. CHEST Critical Care. 2023;1,100015.

Chapter 6

McErlane J, Glass A, Soosay A, McCall P, Shelley B. Feasibility of Strain Assessment of Right Ventricular Contractile Reserve in Patients Undergoing Lung Resection. J Cardiothorac Vasc Anesth. 2024 Jan;38(1):344-346.

Shelley B, Glass A, Keast T, **McErlane J**, Hughes C, Lafferty B, Marczin N, McCall P. Perioperative cardiovascular pathophysiology in patients undergoing lung resection surgery: a narrative review. Br J Anaesth. 2023 Jan;130(1):e66-e79

Chapter 7

Keast T, **McErlane J**, Kearns R, McKinlay S, Raju I, Watson M, Robertson, KE Berry, C, Greenlaw N, Ackland G, McCall P, Shelley B. Study protocol for IMPRoVE: a multicentre prospective observational cohort study of the incidence, impact and mechanisms of perioperative right ventricular dysfunction in non-cardiac surgery. BMJ Open. 2023 Sep 6;13(9):e074687.

Abstract Publications:

McErlane J, McCall P, Shelley B. Right ventricular free wall longitudinal strain is independently associated with 1-yr mortality in patients with COVID-19 requiring mechanical ventilation. Br J Anaesth. 2024 May;132(5):1010-1011.

McErlane J, Glass A, Soosay A, McCall P, Shelley B. Feasibility of right ventricular free wall longitudinal strain assessment of contractile reserve in patients undergoing lung resection. Br J Anaesth. 2023 Feb;(2):e206-207.

Oral Presentations:

Right ventricular free wall longitudinal strain is independently associated with one year mortality in ventilated patients with COVID-19. Scottish Right Heart Symposium 2023, Golden Jubilee National Hospital.

Feasibility of Right Ventricular Free Wall Longitudinal Strain Assessment of Contractile Reserve in Patients Undergoing Lung Resection. European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTAIC) Annual Congress 2023 - Budapest.

Feasibility of Right Ventricular Free Wall Longitudinal Strain Assessment of Contractile Reserve in Patients Undergoing Lung Resection. Anaesthesia Research 2022 - York.

Right ventricular free wall longitudinal strain as a predictor of mortality in medically ventilated COVID-19 patients. University of Glasgow School of Medicine, Dentistry, and Nursing Postgraduate Research Day 2022.

Poster presentations:

Right Ventricular Dysfunction and Abnormal N-terminal pro-B-type Natriuretic Peptide are Independently Associated with One Year Survival in Ventilated Patients with COVID-19. Scottish Intensive Care Society Meeting 2023 – St Andrew's, Scotland.

Prizes

Year One Award. University of Glasgow School of Medicine, Dentistry, and Nursing Postgraduate Research Day 2022. Right ventricular free wall longitudinal strain as a predictor of mortality in medically ventilated COVID-19 patients.

1st Prize. Dhruva Prakash Memorial Prize abstract competition. Scottish Right Heart Symposium 2023, Golden Jubilee National Hospital. Right ventricular free wall longitudinal strain is independently associated with one year mortality in ventilated patients with COVID-19.

Acknowledgement

My supervisor Professor Ben Shelley, Honorary Professor and Consultant in Cardiothoracic Anaesthesia and Intensive Care, thank you for all your wisdom, enthusiasm, and patience, and for helping me embark on my research journey.

My supervisor Dr Philip McCall, Consultant in Cardiothoracic Anaesthesia and Intensive Care, thank you for your constant support and encouragement, for assisting with my speckle tracking strain training, dual reporting of scans, and for broadening my wider understanding of echocardiography.

Dr Adam Glass for producing the ANCOVA analysis figures in Chapter 6, for recommending the research job to me, and for his friendship and support.

Dr Alvin Soosay for his involvement with running the RV exercise study, and for his initial echocardiography analysis.

Dr Tom Keast for his help setting up the IMPRoVE study, and for his ongoing friendship and (at times much needed) support.

Dr Jennifer Willder for her involvement with setting up the COVID-RV study.

The medical physics team at the Golden Jubilee National Hospital for their help setting up Tomtec strain software, and for allowing me to use their office for 6 months to perform strain analysis.

ICU clinicians at the COVID-RV study sites, for performing echocardiography scans and supporting research during a very physically and emotionally stressful period.

Echocardiographers at the Golden Jubilee National Hospital for their support of the RV exercise study and for performing exercise stress echocardiography.

The research nurses at the COVID-RV study sites and Golden Jubilee National Hospital, for their invaluable help in recruiting patients and running the COVID-RV and RV exercise studies.

Mr Alan Kirk, Consultant Cardiothoracic Surgeon at the Golden Jubilee National Hospital, for permitting his patients to participate in the RV exercise study.

Medical Research Scotland and the National Institute of Academic Anaesthesia for providing funding for the studies within this thesis.

Professor Tara Quasim and the Academic Unit of Anaesthesia, Critical Care and Perioperative Medicine group for their support and inspiration throughout these research years.

And finally, to all the patients and relatives who were involved with the COVID-RV study and RV exercise study. Their selflessness and willingness to support research while afflicted by COVID-19/lung cancer is remarkable.

Author's declaration

I declare that, except where reference is made to the contribution of others, this thesis is a result of my own work, written entirely by myself and has not been submitted for any other degree at the University of Glasgow or any other institution.

Dr James McErlane

Word count: 47,309

Abbreviations

A2C	apical two chamber
A3C	apical three chamber
A4C	apical four chamber
ACP	acute cor pulmonale
ACS	acute coronary syndrome
AKI	acute kidney injury
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APACHE	acute physiology and chronic health evaluation
ARDS	acute respiratory distress syndrome
ASE	American society of echocardiography
AUROCC	area under the receiver operated characteristic curve
BE	base excess
BMI	body mass index
BNP	B-type natriuretic peptide
BPM	beats per minute
BSE	British society of echocardiography
CAD	coronary artery disease
CAP	community acquired pneumonia
CCCC	coronavirus clinical characterisation consortium
CI	confidence interval
CMR	cardiac magnetic resonance
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
CoV	co-efficient of variation
COVID-19	corona virus disease 2019
COVID-RV	Right Ventricular Dysfunction in Ventilated Patients with COVID-19
CPA	cardiac performance analysis
CPAP	continuous positive airway pressure
CPB	cardiopulmonary bypass
CPET	cardiopulmonary exercise testing
CrCl	creatinine clearance
CRP	C-reactive protein
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CVP	central venous pressure
DAH_{30}	Days alive and at home at 30 days postoperatively
DICOM	digital imaging and communications in medicine
DVT	deep vein thrombosis
EACVI	European association of cardiovascular imaging
ECG	electrocardiography
ECMO	extracorporeal membrane oxygenation
ED	end-diastole

EQ-5D-5L	EuroQol-5 Dimension-5 Level Health Related Quality of Life Questionnaire
EQ VAS	EuroQol visual analogue scale
EuroSCORE	European system for cardiac operative risk evaluation
FAC	fractional area change
FEV1	forced expiratory volume in 1 second
FICE	focused intensive care echocardiography
FiO_2	fraction of inspired oxygen
FVC	forced vital capacity
GI	gastrointestinal
GJNH	Golden Jubilee National Hospital
HCM	hypertrophic cardiomyopathy
HF	heart failure
HR	hazard ratio
hsTn	high sensitivity troponin
IBM SPSS	International Business Machines Statistical Package for the Social Sciences
ICC	intraclass correlation co-efficient
ICU	intensive care unit
IMPRoVE	incidence, impact, and mechanisms of perioperative right ventricular dysfunction
IMV	invasive mechanical ventilation
IPF	idiopathic pulmonary fibrosis
IVCT	isovolumic contraction time
IVF	intravenous fluid
IVRT	isovolumic relaxation time
LOA	limits of agreement
LV	left ventricular
LVD	left ventricular dysfunction
LVEDD	left ventricular end diastolic diameter
LVEI	left ventricular eccentricity index
LVGLS	left ventricular global longitudinal strain
MAP	mean arterial pressure
MD	mean difference
MI	myocardial infarction
mPAP	mean pulmonary artery pressure
MRC	Medical Research Council
NHS	national health service
NIV	non-invasive ventilation
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
NYHA	New York Heart Association
OLV	one lung ventilation
OR	odds ratio

PA	pulmonary artery
PAAT	pulmonary artery acceleration time
$PaCO_2$	partial pressure of arterial carbon dioxide
PAH	pulmonary arterial hypertension
PaO_2	partial pressure of arterial oxygen
PAP	peak airway pressure
PASP	pulmonary artery systolic pressure
PBW	predicted body weight
PCWP	pulmonary capillary wedge pressure
PE	pulmonary embolism
PEEP	peak expiratory pressure
P/F ratio	ratio of arterial oxygen partial pressure to the fraction of inspired oxygen
PGD3	primary graft dysfunction grade three
PH	pulmonary hypertension
PHEIC	public health emergency of international concern
PMI	postoperative myocardial injury
PSAX	parasternal short axis
PVR	pulmonary vascular resistance
RASS	Richmond agitation-sedation score
RIMP	right ventricular index of myocardial performance
ROI	region of interest
RR	respiratory rate
RRT	renal replacement therapy
RV	right ventricle/ventricular
RVCR	right ventricular contractile reserve
RVD	right ventricular dysfunction
RVEDD	right ventricular end diastolic diameter
RVEDP	right ventricular end diastolic pressure
RVEDV	right ventricular end diastolic volume
RVEF	right ventricular ejection fraction
RVF	right ventricular failure
RVFAC	right ventricular fractional area change
RVFWLS	right ventricular free wall longitudinal strain
RVGLS	right ventricular global longitudinal strain
RVOT	right ventricular outflow tract
RVSP	right ventricular systolic pressure
RV-STE	right ventricular speckle tracking echocardiography
S’	S’ wave velocity at the tricuspid annulus
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SOFA	sequential organ failure assessment
sPAP	systolic pulmonary artery pressure
STE	speckle tracking echocardiography
StEP COMPAC	standardised endpoints and core outcome measures for perioperative and anaesthetic care
SV	stroke volume
TAPSE	tricuspid annular plane systolic excursion

TDI	tissue doppler imaging
TLCO	transfer factor of the lung for carbon-monoxide
TOE	transoesophageal echocardiography
TR	tricuspid regurgitation
TTE	transthoracic echocardiography
TV	tricuspid valve
V-V ECMO	veno-venous extracorporeal membrane oxygenation
VO_2max	maximal rate of oxygen consumption
WHODAS	World Health Organisation disability assessment schedule

Chapter 1 Introduction

1.1 General introduction

Patients who are admitted to the intensive care unit (ICU), or who undergo non-cardiac surgery, can experience poor functional outcomes and a substantial risk of mortality. Poor outcomes in these groups have been closely associated with impairment of cardiac function, this suggests that reliable and accurate measures of cardiac function may allow tailored therapies and improve patients' outcomes[1,2].

The left ventricle (LV) has received thorough research, both in the settings of the intensive care unit (ICU) and the perioperative period, however the right ventricle (RV) has been relatively overlooked[3]. The fundamental function of the RV requires it to eject the blood that it receives from the systemic venous system to the lungs through the pulmonary artery (PA) under varying loading conditions, thereby maintaining cardiac output and a low systemic venous pressure[4]. Right ventricular dysfunction (RVD) is an impairment of RV function such that the RV is unable perform this role (RVD is further defined in section 1.2.10). Importantly, RVD may manifest in a covert manner that can cause clinically important organ dysfunction. RV failure (RVF) is a syndrome of clinical signs and symptoms resulting from impaired cardiac output and systemic venous congestion associated with RVD[5]. RVF can present insidiously and is often difficult to diagnose with the acute signs being non-specific, including acute liver injury, acute kidney injury (AKI), bowel dysfunction, and a raised central venous pressure (CVP) with reduced central venous oxygen saturation[5].

RVD is common in ICU and associated with both poor short- and long-term outcomes[2,6]. The incidence of RVD in the perioperative period is less well defined, but it is suspected to be more frequent than currently appreciated, and a significant contributor to perioperative morbidity[7]. Chapter 1 will first explore the importance of RV function in ICU and the perioperative period, followed by a description of RV anatomy and physiology, setting the scene for the investigations of RV function (assessed by echocardiography) in ICU and the perioperative period.

1.1.1 The importance of right ventricular function in the intensive care unit

Impairment of RV function in ICU is a common occurrence, with a recent prospective echocardiography study demonstrating that 14.0-33.0% of all ICU patients have evidence of impaired RV function (prevalence varying depending on the echocardiography measure used to diagnose RVD)[8]. Right ventricular dysfunction can present both acutely, or as an exacerbation of chronic RVD. Disease processes themselves, as well as ICU interventions, can precipitate RVD.

Many acute illnesses requiring ICU admission are associated with RVD. Right ventricular dysfunction is frequently associated with septic shock, with a prevalence of 28.3-35.3%, and has been shown to be associated with in-hospital mortality independent of LV dysfunction[9,10]. Acute pulmonary embolism (PE) can cause an acute rise in pulmonary artery pressures increasing RV afterload. A high prevalence of RVD of 40.0-70.0% has been demonstrated in patients with PE[11]. Patients with pulmonary parenchymal disease have also been shown to have a substantial prevalence of RVD. RVD is present in 21.0-50.0% of patients with acute respiratory distress syndrome (ARDS)[12,13] and 6.3-76.2% of patients with coronavirus disease 2019 (COVID-19) pneumonitis[14,15], and is strongly associated with mortality in both groups[12,16].

Pulmonary hypertension (PH) can result in pre-existing RVD. Bauchmuller et al have shown that patients with underlying PH admitted to ICU for medical causes have high rates of mortality, with an overall hospital mortality rate of 40.7%, rising to 88.9% in those requiring invasive mechanical ventilation (IMV)[17]. Mortality was associated with clinical signs of venous congestion that can arise due to RVD, such as raised CVP, raised urea and creatinine, and raised bilirubin. Huynh et al found that in 99 patients with PH, RVD was the cause for ICU admission in 52.0%[18], highlighting the important clinical consequences of RVD in this group.

RVD is not only a complication of the acute illness that ICU patients can present with, but it is also a complication that can arise from ICU interventions, with the use of both mechanical ventilation and inappropriate intravenous fluid (IVF)

administration being implicated. Invasive mechanical ventilation has been shown to cause RV impairment. Schulman et al and Mitaka et al demonstrated that incremental positive end expiratory pressure (PEEP) recruitment manoeuvres induced an increase in RV end diastolic volume[19], and a reduction in RV ejection fraction respectively[20]. Non-invasive mechanical ventilation has also been shown to cause an acute impairment in RV function in patients with obstructive sleep apnoea; echocardiography during continuous positive airway pressure (CPAP) in these patients demonstrated a significant increase in pulmonary artery pressure accompanied by a significant reduction in RV global longitudinal strain (RVGLS, an echocardiographic measure of RV function described in Chapter 2) compared to baseline[21].

Inappropriate IVF administration with resulting fluid overload can cause RV dilatation and functional tricuspid regurgitation (TR) regurgitation[22]. Price et al conducted a systematic review to investigate optimal management strategies of RV failure in ICU, with the recommendation that "volume loading of the RV may worsen its performance: all fluid challenges should be closely monitored"[23]. Specific to ICU populations, patients with septic shock and echocardiography evidence of RVD are frequently unresponsive to a fluid challenge[24]. It been demonstrated that in patients with septic shock, a positive 12h fluid balance and raised CVP (>12mmHg) was associated with increased mortality compared to patients with a positive fluid balance and normal CVP[25]. Together these data suggest that inappropriate IVF may contribute to RVD and could be harmful to patients in ICU.

RVD in ICU is a common and potentially lethal complication of not only the disease processes that ICU patients experience, but also ICU therapies. This highlights the need for early diagnosis and treatment strategies to optimise RV function in these groups.

1.1.2 The importance of right ventricular function in the perioperative period

Perioperative myocardial injury[A] (PMI) is a frequent finding after surgery[26]. A recent multicentre study in 21,842 patients who underwent major non-cardiac surgery demonstrated 19.7% of patients had a raised troponin, and that raised troponin without ischaemic symptoms was associated with 30-day mortality (hazard ratio 3.2, 95%CI 2.4-4.3)[27]. Despite myocardial injury after major non-cardiac surgery being common, it is unclear how and where this injury is occurring. An often-cited hypothesis, although lacking evidence, is that PMI arises from an imbalance in myocardial oxygen supply and demand, due to increased oxygen requirement combined with impaired haemodynamics during the perioperative period[28]. This may arise due to several causes such as surgical insult, anaesthesia, and postoperative inflammatory state. Left ventricular or global cardiac dysfunction has frequently been implicated as the source of PMI however the evidence for this is lacking[29]. A potentially overlooked aspect of the PMI model is the RV, where the incidence of preoperative and postoperative RVD has not been rigorously investigated, nor its association with patient outcomes. Although not well studied, a small body of research has suggested that perioperative RVD is not uncommon, and that it is clinically important. Chou et al investigated the association between preoperative RVD (identified by transthoracic echocardiography using qualitative visual assessment of RV function by two expert reporters) and postoperative morbidity in 108 patients who underwent non-emergency vascular surgery[30]. They found that preoperative RVD was present in 10% of patients, with multivariable analysis showing that preoperative RVD, but not LV dysfunction (LVD), was independently associated with major adverse cardiovascular events. Right ventricular dysfunction, but not LVD, was also associated with a 50% longer length of hospital stay. Chou et al repeated their investigation in 122 patients undergoing non-emergency open abdominal surgery and found preoperative RVD in 5.7% of patients, this was independently associated with in-hospital mortality[31]. In a mixed surgical cohort requiring urgent echocardiography for haemodynamic instability, Markin et al

[A] Post operative myocardial injury is typically diagnosed by a dynamic rise in troponin level above the 99th centile upper reference limit in absence of overt cardiac ischaemia. Specifically, there is absence of symptoms, electrocardiography, imaging, or coronary angiography suggestive of ischaemia[26].

investigated RVD in the postoperative period where it was found to be present with similar frequency to LVD (24.1% vs 22.2% respectively)[32].

The impact of newly acquired RVD during the perioperative period on patient outcomes in the non-cardiac surgery setting has not been well investigated. Of the few studies available, new postoperative RVD has been associated with atrial arrythmias and prolonged ICU stay in patients undergoing thoracic surgery[33,34], and new intraoperative RVD was associated with requirement for intraoperative inotropic support in an orthopaedic surgery cohort[35]. The impact of postoperative RVD upon outcomes across other major surgery specialities currently remains unknown.

There are several mechanisms which may result in RVD during the perioperative period. Inappropriate IVF administration may result in excessive preload, and cardiac contractility may be impaired by myocardial ischaemia and inflammation. Increased afterload would seem a logical consequence in many circumstances during the perioperative period. One lung ventilation (with or without pulmonary artery clamping), bi-lung mechanical ventilation (particularly in those with underlying pulmonary disease or underlying RVD), lung resection, and PE all represent mechanisms that may increase pulmonary vascular resistance and RV afterload[36-39].

Work by the author's supervisors has investigated the effects of lung resection surgery on RV and LV function. A cohort of 27 patients underwent contemporaneous cardiac magnetic resonance (CMR) imaging and transthoracic echocardiography (TTE) pre and post lung resection. Sustained postoperative RV impairment was demonstrated at day-2 and 2-months postoperatively, whereas LV function remained unchanged. Additionally, there was a significant association between worse post operative day-2 CMR RV ejection fraction (RVEF) and both higher levels of brain natriuretic peptide (BNP) and longer ICU length of stay[34]. Again, this implicates RVD as an important factor in the manifestation of myocardial injury and patient outcomes. Further research by the group has identified a possible role for inflammation as a driver for PMI and RVD; Murphy et al conducted a study in 15 patients who underwent lobectomy with perioperative T1 CMR imaging[40]. RVD (but not LVD) was identified on post operative day-2, as previously seen. T1 CMR imaging (a measure of water

content within tissues) identified a significant increase in native T1 time and extracellular volume compared to preoperative images. This oedema in the RV myocardium is suggestive of inflammation, implicating inflammation as a driver of PMI.

Right ventricular dysfunction in the perioperative period is an important, and often underappreciated, complication that impacts patients' outcomes. Accurate diagnosis of RVD, and a deeper understanding of the mechanisms underlying RVD, are key to identifying patients at risk of developing RVD and devising preventative strategies. Accurate and reliable methods for assessing RV function are therefore vital.

A description of RV anatomy and physiology will now be presented, followed by an overview of the methods used for assessing RV function, including invasive and non-invasive methods. The conventional echocardiography measures of RV function will then be considered, and compared with novel RV speckle tracking echocardiography (RV-STE) strain analysis which is the focus of this thesis.

1.2 The right ventricle

1.2.1 Right ventricular anatomy

The RV resides in the mediastinum, anterior to the left ventricle. It receives systemic venous blood from the right atrium and propels it through the RV outflow tract into the pulmonary artery. The RV is divided into three functional regions, the sinus, apex, and infundibulum (Figure 1-1). The sinus is the RV inflow, the apex consists of trabeculated myocardium, and the infundibulum is composed of smooth myocardium and is the RV outflow[41].

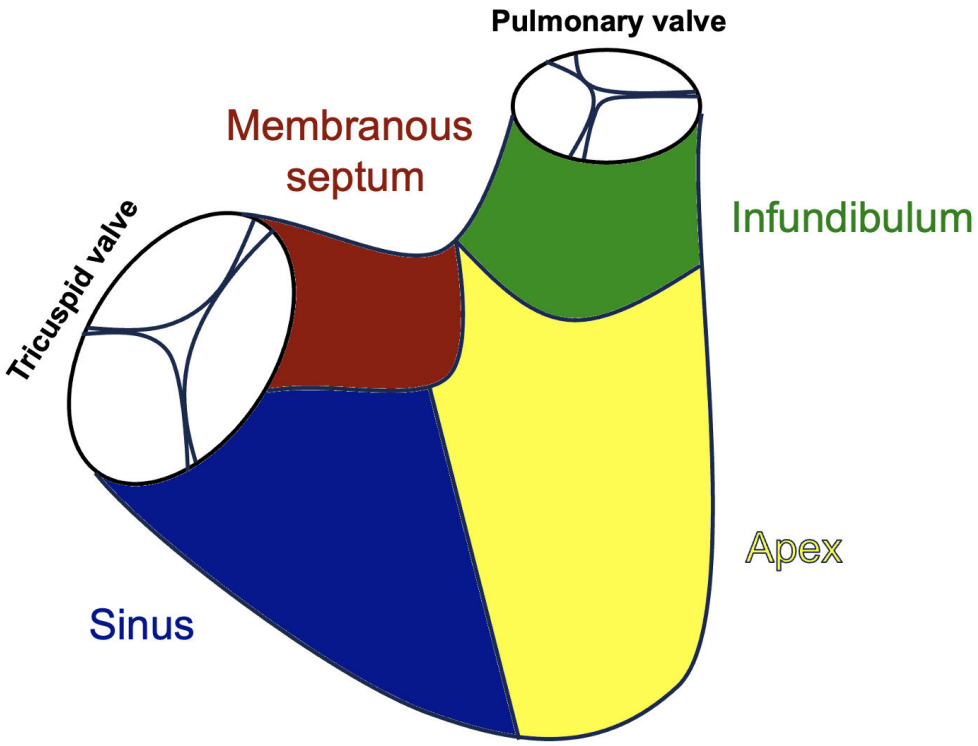


Figure 1-1 Anatomy of the right ventricle
The RV is anatomically and functionally divided into the sinus (blue), apex (yellow) and infundibulum (green). Redrawn and adapted from Haddad et al[42]

The RV has a thin free wall that wraps around the left ventricle, giving a complex geometric shape which is triangular in the long axis, and crescent shaped in the short axis. The RV free wall comprises of two layers of muscle fibres, the deep muscle fibres run in a longitudinal direction from base to apex and the superficial fibres run in a circumferential orientation, continuing into the subendocardial fibres of the left ventricle[43]. The interventricular septum is a shared structure by the right and left chambers. Under normal physiology it is

concave with respect to the left ventricle, giving rise to the crescent shape of the RV in short axis, and circular shape of the LV. The heart is wrapped in the poorly distensible fibrous pericardium, this means that changes in volume or pressure in one ventricle will affect the anatomy and physiology of the other ventricle[22,43]. This characteristic, combined with the shared interventricular septum, gives rise to ventricular interdependence. Ventricular interdependence describes the property of the heart where a change in the volume or pressure within one ventricle can alter the function of the other ventricle via the shared septum. Signs of ventricular dependence can be subtle, such as the normal physiological variation in systemic blood pressure that occurs during normal tidal breathing where inspiration increases RV preload with an associated small reduction in LV output, or more readily apparent such as when an acute PE causes RV volume/pressure overload with bowing of the interventricular septum into the LV impairing its output[44].

1.2.2 Right ventricular perfusion

The blood supply to the RV is dependent on the dominance of the coronary arterial system. In 80% of the population, there is a right dominant system where the RV is supplied by the right coronary artery[45]. Unlike the left ventricle, under normal physiology the RV generates a low tension within its free wall during systole, allowing it to be perfused both in diastole and systole. Exceptions to this occur when there is high RV wall tension (either from acute pressure overload or chronic pressure overload and RV hypertrophy) resulting in reduced perfusion of the RV myocardium during systole[41].

1.2.3 Right ventricular physiology

The right and left ventricles can be thought of as two pumps connected in series, which therefore must have the same cardiac output. The RV has a much thinner free wall, and a muscle mass of only 1/6th of the left ventricle, however it is still able to match its cardiac output[41]. This is due to low pulmonary vascular resistance (1/10th of the systemic vascular resistance[43]) and high distensibility of the pulmonary vasculature, allowing the RV to function by generating much lower pressure gradients than the left ventricle.

To generate its cardiac output, the RV contracts in a peristaltic manner, with the wave of contraction beginning at the sinus, followed by the apex, and then through the infundibulum. There is therefore a lag of 20-50ms between sinus contraction and infundibulum contraction[46]. Approximately 80% of RV systolic ejection is generated by contraction of the deep longitudinal myocardial fibres, with the radial contraction of the superficial fibres producing a "bellows-like" effect that provides a lesser contribution[47].

Three important factors that affect RV function will now be described, RV preload, contractility, and afterload.

1.2.4 Right ventricular preload

Right ventricular preload is defined as the "load present before contraction", and is influenced by many factors including venous return, ventricular compliance, and heart rate.[41] The concept of preload relates to the Frank-Starling mechanism (heterometric autoregulation), where the force of myocardial contraction is dictated by the arrangement of actin and myosin within the sarcomere. Under physiological conditions, as preload to the RV is increased, myocardial muscle fibres become stretched, and at end diastole the increased sarcomere length will result in a more optimal alignment of actin and myosin for crosslinking and sarcomere contraction[48]. Surrogate indices of RV preload include RV end diastolic volume (RVEDV) and RV end diastolic pressure (RVEDP).

The thin free wall of the RV, and greater ratio of surface area to blood volume mean that it is more compliant than the left ventricle. Increases in right ventricular volume are therefore better tolerated than the left ventricle[46].

1.2.5 Right ventricular contractility

Right ventricular contractility describes the intrinsic force generated by cardiac myocytes independent of preload and afterload. Contractility can be modulated by autonomic stimulation, primarily through adrenergic signalling pathways[46]. Direct cardiac sympathetic innervation and increases in catecholamine release by the adrenal gland will result in adrenaline (and to a lesser extent

noradrenaline) binding beta-adrenergic receptors on the surface of cardiac myocytes. Binding of beta-adrenergic receptors activates a G-protein coupled receptor pathway resulting in calcium release and the sensitisation of sarcomeres culminating in increased force of contraction[49].

Increases in heart rate will also enhance contractility through the Bowditch effect, where shorter diastole time results in less time for removal of intracellular calcium into the sarcoplasmic reticulum. The higher resting concentration of intracellular calcium increases the myocyte force of contraction during systole[50].

Contractility can be intuitively understood by analysing pressure-volume loops, described in section 1.2.7.

1.2.6 Right ventricular afterload

Right ventricular afterload is defined as "the load the RV has to overcome during ejection"[41]. RV afterload is frequently described using pulmonary vascular resistance, calculated from the equation[44]:

$$PVR = \frac{mPAP - PCWP}{CO}$$

PVR = Pulmonary vascular resistance (expressed as dynes.seconds.cm^{-5}), mPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, CO = cardiac output.

Pulmonary vascular resistance (PVR) represents static RV afterload, and may underestimate total afterload since it does not consider the contribution of pulsatile afterload. Pulsatile RV afterload includes the forces of pulse wave reflection, inertia, capacitance, and resistance[34]. The RV can compensate for modest increases in RV afterload via the Anrep effect (homeometric autoregulation). This occurs via autocrine and paracrine pathways activated by myocardial stretch and release of angiotensin-II and endothelin, resulting in an increased intracellular calcium concentration increasing the force of contraction[48]. This mechanism allows effective RV ejection to be maintained in the presence of increased RV afterload. It must be noted that the RV is relatively intolerant of increases in afterload compared to the left ventricle due

to its lower muscle mass. The Anrep effect cannot compensate for large increases in RV afterload, and RV decompensation ensues with a reduction in RV systolic function (Figure 1-2).

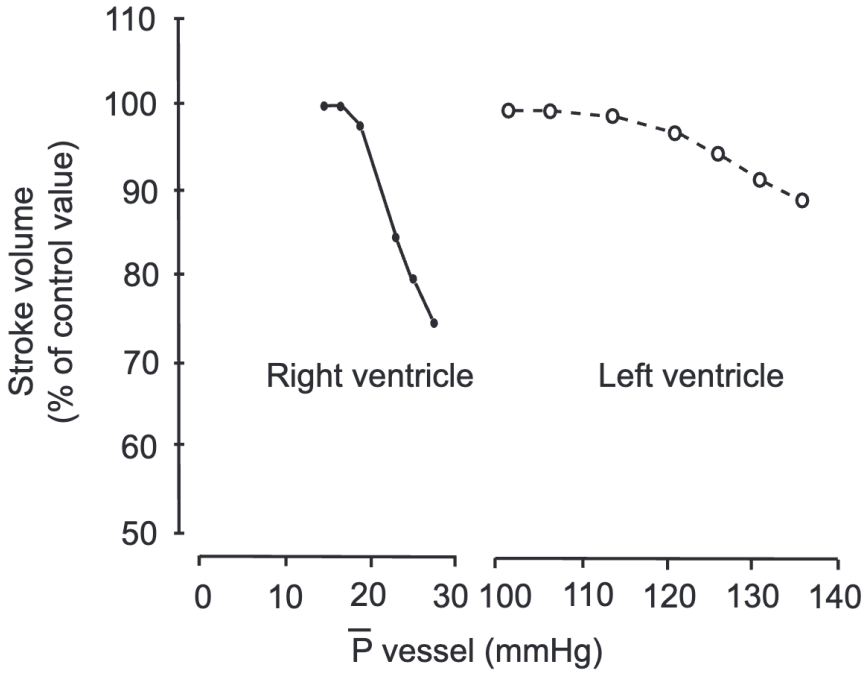


Figure 1-2 The response of the right ventricle to changes in afterload.
As pulmonary arterial pressure increases (particularly when greater than 20mmHg), right ventricular stroke volume rapidly declines. Conversely the left ventricle is more tolerant to increases in afterload; as systemic arterial pressure increases by a similar degree, left ventricular stroke volume is relatively maintained. Reproduced from Haddad et al[41,51]. P = pulmonary/systemic arterial pressure.

1.2.7 Pressure volume loops

Pressure volume loops, traditionally acquired using right heart catheterisation, give an insight into the RV response to different loading condition and changes in contractility. A conductance catheter assesses the volume and pressure within the RV during the cardiac cycle, allowing a pressure volume loop to be generated (Figure 1-3A)[46]. Measurements should be taken at end expiration to minimise the changes in intrathoracic pressure associated with spontaneous ventilation. RV loading conditions can be altered using manoeuvres such as Valsalva and external abdominal compression, allowing multiple loops to be plotted on a single graph (Figure 1-3B)[52]. The end systolic pressure volume relationship (ESPRV, also called end systolic elastance, E_{es}) can then be calculated as the gradient of the line passing through the end systolic pressure volume points of multiple loops under different loading conditions, this represents load independent RV contractility. Steeper gradients of the ESPRV are

associated with better contractility, such as could occur with initiation of inotropic therapy. It is noteworthy that identifying the end systolic pressure-volume point for RV PV loops is challenging since there is a less defined isovolumic relaxation period (compared to the LV), resulting in a trapezoid shaped curve.

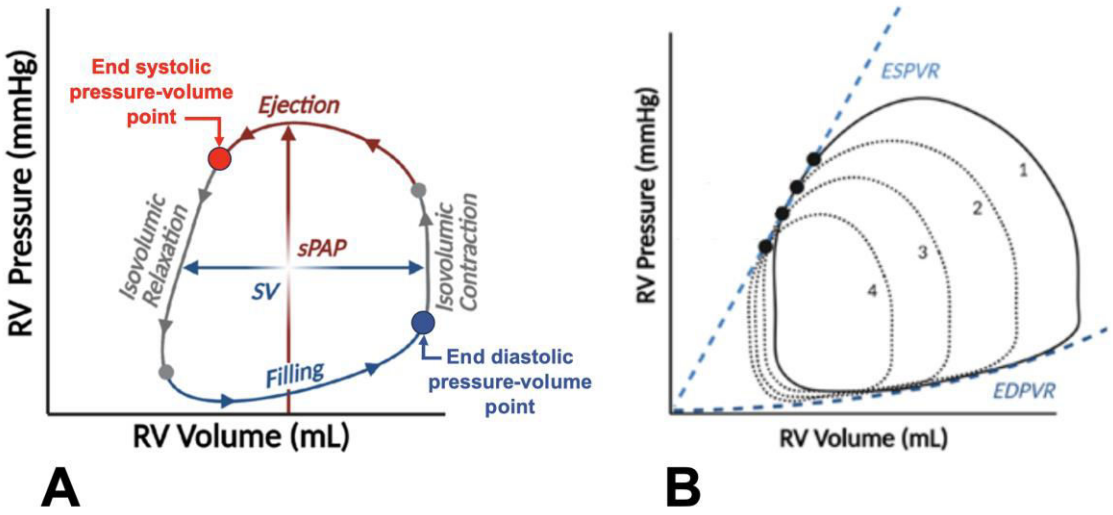


Figure 1-3 The right ventricular pressure-volume loop
A. A single RV pressure-volume loop. End systolic pressure-volume and end diastolic pressure-volume points are highlighted in red and blue respectively. B. RV pressure loops constructed from multiple beats. The end systolic pressure-volume relationship (ESPVR) can be calculated as the gradient of a line passing through the end systolic pressure-volume points. Similarly, the end diastolic pressure-volume relationship (EDPVR) can be calculated as the gradient of a line passing through the end diastolic pressure-volume points. RV = right ventricular, sPAP = systolic pulmonary artery pressure, SV = stroke volume. Image adapted from Brener et al[52].

1.2.8 Interplay between contractility and loading conditions

Thus far the effects of altering afterload, preload, and contractility have been considered in isolation. However, there is a physiological interplay between the three.

A simplified model is useful to describe this interplay. If we consider an isolated myocyte contracting against a load (Figure 1-4), on initial stimulation of the myocyte a tension will be generated however this tension will be insufficient to overcome the load (analogous to isovolumic contraction, a-b on Figure 1-4). Once the tension is sufficient, the load will be overcome, and the myocyte will begin to shorten (b-c). The peak velocity of myocyte shortening is the peak gradient of the length vs time curve, occurring just after myocyte shortening commences.

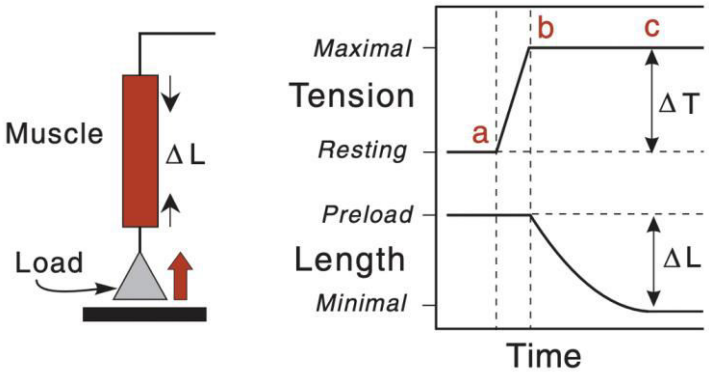


Figure 1-4 Simplified model of myocyte contraction
A single cardiac myocyte contracting against a load. As the myocyte contracts, initially there is isometric contraction where the myocyte generates a tension but this is insufficient to overcome the load (a-b), once myocyte tension overcomes the load, myocyte shortening commences (b-c). The peak velocity during myocyte shortening is the steepest gradient on the length vs time curve, occurring at the initial point of myocyte shortening. Image adapted from Cardiovascular Physiology Concepts by Klabunde[50]

If the load (afterload) is increased, a greater tension is required for myocyte shortening, and the peak velocity during shortening will be reduced (Figure 1-5A+B). This inverse relationship between afterload and velocity of myocyte shortening is the basis of the force-velocity relationship, demonstrated graphical in Figure 1-5B[50]. In Figure 1-5B it can be seen that as afterload increase (a>b>c), the force required for contraction increases with a reduction in the peak velocity achieved. Once afterload exceeds the maximal force the myocyte can generate, the maximal isometric force has been achieved (Figure 1-5B intercept on X axis). A theoretical maximum velocity of myocyte shortening (Figure 1-5B,

the Y intercept "V_{max}") can be extrapolated, representing the intrinsic ability of the myocyte to generate force independent of load (which can be thought of as the contractility state of the myocyte). Note that the peak velocities achieved during shortening, plotted at points a, b, and c in Figure 1-5B, are different from the theoretical maximal velocity of myocyte shortening, V_{max}, when afterload is zero.

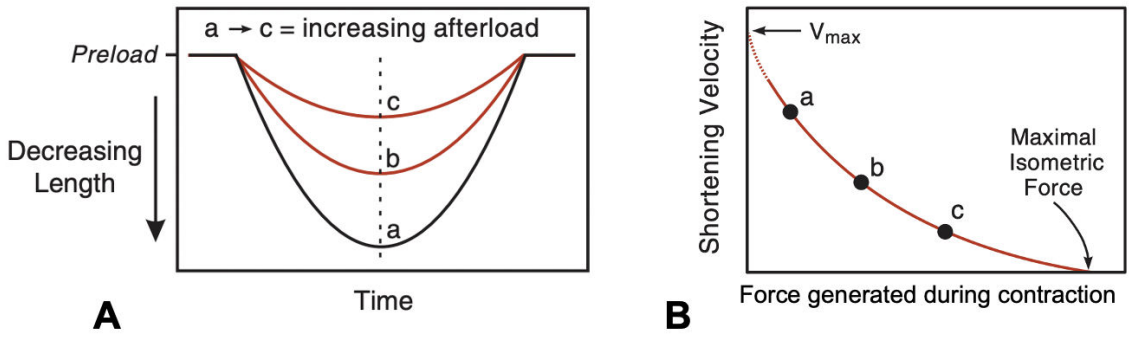


Figure 1-5 Effect of afterload on force-velocity relationship
A+B. As afterload is increased (a>b>c) under steady preload and contractility conditions, the force generated during myocyte contraction also increases with a reduction in the peak velocity of myocyte shortening that is achieved during contraction with an overall reduction in the length of myocyte shortening that is achieved. **B.** The maximal isometric force that can be achieved is shown as the x-axis intercept. A theoretical maximal velocity of myocyte shortening "V_{max}" can be extrapolated from the force-velocity curve at the y intercept. Points a, b, and c represent the maximal velocity and maximal force generated during contraction at points a, b, and c in Figure 1-5A. Images from Cardiovascular Physiology Concepts by Klabunde[50]

Changing preload and contractility can alter the force-velocity relationship. Increasing preload shifts the force-velocity curve to the right (Figure 1-6A) and increases the velocity of myocyte shortening at a given workload, however theoretical maximal velocity of shortening is unchanged. Increasing levels of inotropy causes an upward shift in the force-velocity curve (Figure 1-6B). The velocity of contraction at a given workload increases, and importantly the theoretical maximal velocity of myocyte shortening also increases, demonstrating that contractility has also increased[50].

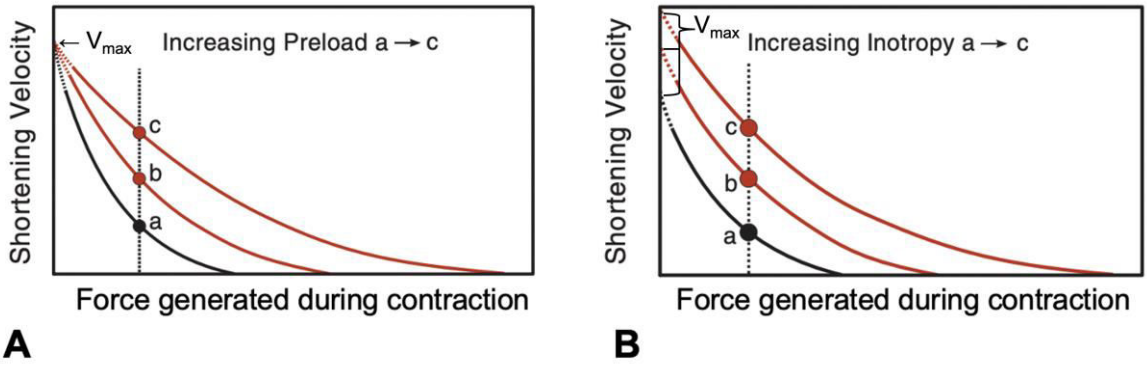


Figure 1-6 Effect of preload and contractility on force-velocity relationship
A. When preload is increased under fixed afterload and contractility conditions, the force-velocity curve shifts to the right, where the force generated during contraction to overcome afterload remains constant (since afterload has not changed), but the peak velocity of myocyte shortening during contraction increases (points a>b>c). As preload increases, the maximal force that can be generated during contraction (x axis intercept) increases, whereas the theoretical maximal velocity of myocyte shortening (V_{max}, y axis intercept) stays the same demonstrating contractility has not changed. **B.** When inotropy increases under fixed preload and afterload conditions, the force-velocity curve shifts upward, the peak velocity of myocyte shortening increases while the force generated during contraction stays the same. As inotropy increases (increasing from a>b>c), the maximal velocity of myocyte shortening (V_{max}, y axis intercepts) also increases, demonstrating that the intrinsic ability of the myocyte to generate force independent of load has increased (i.e. increased contractility). Images adapted from Cardiovascular Physiology Concepts by Klabunde[50]

In summary, the velocity of myocyte shortening is altered by afterload, preload, and contractility. An isolated increase in RV afterload would cause a reduction in the velocity of myocyte shortening under these conditions, however the RV can adapt by increasing preload and/or contractility to restore the velocity of myocyte shortening. The interaction between RV afterload and RV contractile function is termed right ventricle-pulmonary artery coupling, and this is described further in the next section.

1.2.9 Right ventricle-pulmonary artery coupling

Fundamental to RV function is the ability of the RV to couple its contractility to the load it encounters in the pulmonary arterial system (RV "afterload"). Right ventricle-pulmonary artery (RV-PA) coupling explains the situation where RV afterload increases (e.g. acutely from PE, or chronically from pulmonary hypertension), where the RV can adapt acutely via homeometric mechanisms (Anrep effect) or more slowly via hypertrophy to increase its contractility to match the increase in PVR, maintaining normal RV-PA coupling[53]. Pressure volume loops allow quantitative assessment of RV-PA coupling. RV contractility is defined as the ESPVR (more commonly termed end systolic elastance E_{es} in this context). The RV afterload is defined as pulmonary arterial elastance (E_a), which is a lumped sum of PA pressure and intrinsic vascular properties encountered by the RV (Figure 1-7)[53]. The ratio of E_{es}:E_a determines RV-PA coupling from RV pressure volume loops. The optimal ratio for E_{es}:E_a for maximal RV mechanical efficiency has been shown to lie between 1.5-2[54].

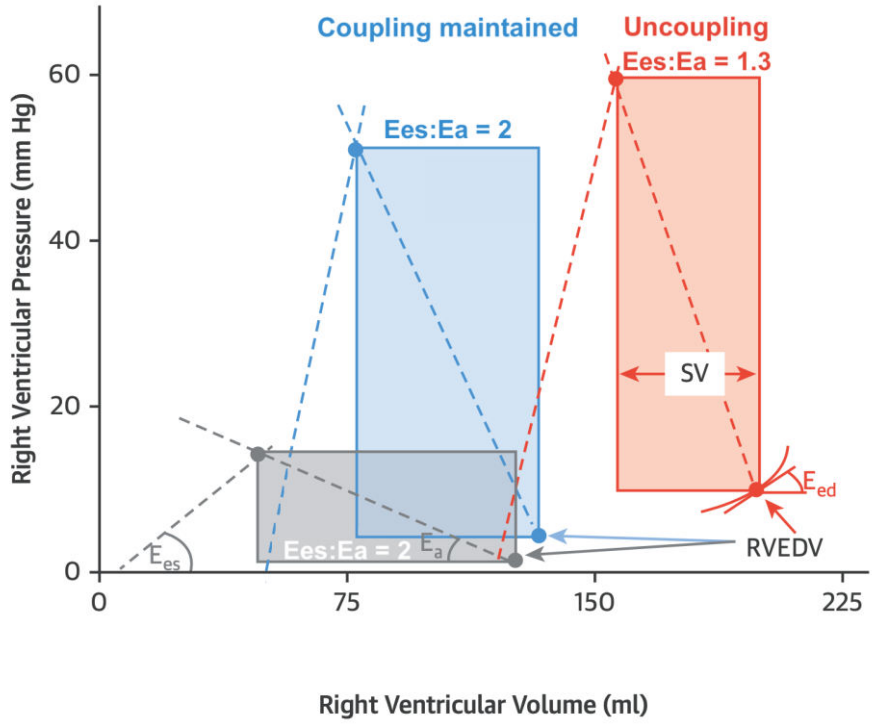


Figure 1-7 Assessment of RV-PA coupling using pressure-volume loops
Schematic RV pressure volume loops demonstrate RV contractility (end systolic elastance, E_{es}) which is derived from the end systolic pressure volume relationship. End systolic arterial elastance (E_a) represents RV afterload, it is calculated from the gradient of the line connecting the end systolic pressure volume point with the end diastolic volume. The ratio of E_{es}:E_a represents RV-PA coupling. The grey RV pressure volume loop shows normal physiological RV-PA coupling, with shallow gradients of E_a and E_{es} (representing low RV afterload and appropriately coupled low RV contractility), and a physiological coupling ratio of 2. The blue RV pressure volume loop shows raised RV afterload (demonstrated by a steeper E_a gradient), and appropriately increased RV contractility (steeper E_{es} gradient), with a maintained RV-PA coupling ratio of 2. The red RV pressure volume loop shows the situation where RV afterload has increased to the point where the RV can no longer compensate and increase contractility to match the increased RV afterload, and uncoupling has occurred, with an uncoupled E_{es}:E_s ratio of 1.3. The RV has also become dilated (with increased RVEDV), with a reduction in SV. RV = right ventricular, PA = pulmonary artery. RVEDV = right ventricular end diastolic volume, SV = stroke volume. Image reproduced from Noordegraaf et al[55].

1.2.10 Right ventricular dysfunction

As described in the introduction, a simplistic description of RV function is its ability to eject the blood that it receives from the systemic venous system to the lungs under varying loading conditions, while maintaining low systemic venous pressure. However, it is apparent from the above discussions that a number of interacting properties contribute to RV function, and it is therefore not surprising that RV dysfunction is not a well-defined entity. RV function includes contractility and PA-RV coupling, both contributing to the RV's ability to adapt to changes in preload and afterload. Many authors have found it easier to define RV failure, whereby it is "a complex clinical syndrome characterized by insufficient delivery of blood from the RV in the setting of elevated systemic

venous pressure at rest or exercise”[54]. RV dysfunction can therefore be seen to represent a state of “pre-RV failure”, where changes in RV preload and afterload can be compensated by changes in contractility and RV-PA coupling thus maintaining cardiac output. Depending on the method used to assess RV function, RVD will be diagnosed differently. Methods which measure PV loops (such as right heart catheters) are ideal for assessing RV-PA coupling and contractility. More simple measures (such as ejection fraction) give an index of systolic function, and a cut-off for diagnosis of RVD, that may not fully represent RV function (such as the load dependence of RV ejection fraction being one of its limitations). In summary, RV function incorporates a number of interacting properties of the RV, and dysfunction of any of these properties may contribute to RVD. A comprehensive diagnosis of RVD requires assessment of contractility and RV-PA coupling, however many current methods rely on simplistic measurements of RV systolic function. Methods for assessing RV function will now be described below.

1.3 Assessment of right ventricular function

Methods for assessing RV function fall into two main categories, invasive methods (using right heart catheters) and non-invasive methods. The non-invasive methods include cardiovascular magnetic resonance (CMR) imaging and echocardiography. Generally, each method has its intrinsic benefits with specific limitations. Right heart catheters give excellent data on pulmonary pressures, but less data on RV anatomy. CMR provides detailed RV geometry data, however it requires patients to lie supine for a prolonged period and is not suitable for all patient populations. Echocardiography is the most accessible method, frequently done at the patient's bedside, providing data on RV anatomy and flows. While the least invasive, transthoracic echocardiography is reliant on finding acoustic windows between the patient's rib spaces (in addition to other factors that can limit image quality). Right heart catheters (conductance catheter and pulmonary artery catheter), CMR imaging, and echocardiography assessment of RV function will now be described in greater detail below.

1.3.1 Conductance catheter

Conductance catheters are invasive catheters that continually measure RV volume and pressure, allowing generation of pressure volume loops (described above). Conductance catheters incorporate a series of twelve electrodes with a current passed between them, and a pressure sensor (Figure 1-8)[52]. An alternating current is passed between the most proximal and distal electrodes, generating a voltage within the RV cavity. Blood within the RV conducts electrical charge well, with the RV myocardium being a poor conductor. Conductance is therefore highest when the RV cavity is filled with blood (at end diastole) and drops when the RV empties. The twelve electrodes measure the changes in voltage, with the drop in voltage between successive pairs of electrodes being inversely proportional to the cross-sectional area of the ventricle. The series of cross-sectional areas are multiplied by the distance between the electrodes giving an estimated RV volume[52]. The use of conductance catheters give real-time continuous analysis of RV function that is ideal for dynamic studies. The data acquired can be used generate the pressure volume loops (section 1.2.7) allowing assessment of RV contractility and RV-PA coupling. Conductance catheters have become the invasive gold standard

assessment of RV function.[56] Conductance catheters are however limited by their invasiveness, requirement for specialised equipment and expertise in their placement and interpretation. They are therefore not suitable for routine assessment of RV function in many clinical settings[41].

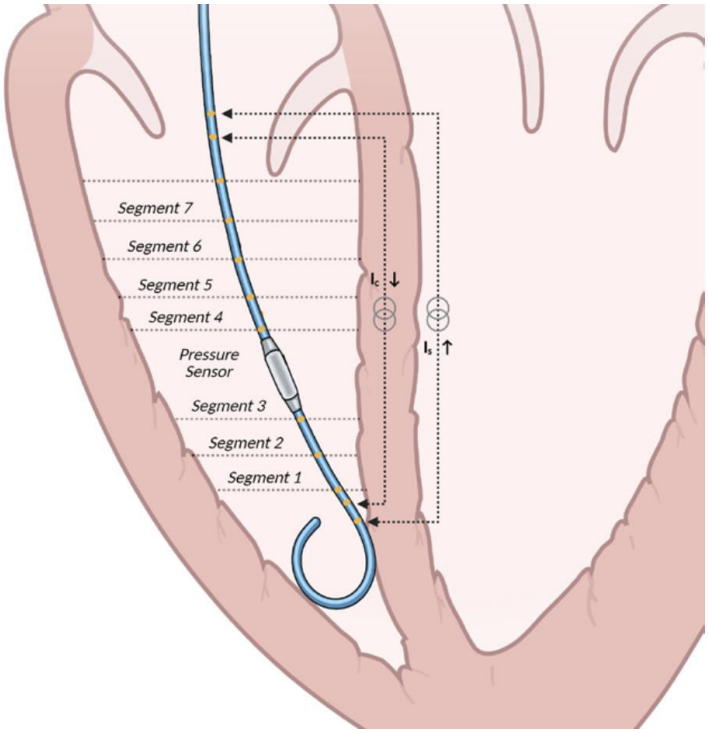


Figure 1-8 Right ventricular conductance catheter
RV conductance catheter correctly sited in the RV cavity, the pig-tailed tip of the catheter is at the apex of the RV. Twelve electrodes are present along the length of the catheter, with a pressure sensor present between the 7th and 8th electrodes. RV = right ventricular. Image reproduced from Brener et al[52].

1.3.2 Pulmonary artery catheter

The PA catheter was adopted for widespread bedside use after the Swann-Ganz flotation catheter was introduced in 1971[57]. The PA catheter allows invasive measurement of haemodynamics, where it can directly measure right atrial (RA) pressure, RV pressure, PA pressure, and pulmonary capillary wedge pressure (PCWP). Cardiac output can be measured using the thermodilution technique. Pulmonary and systemic vascular resistances can then be calculated from cardiac output and pressure data. Pulmonary artery catheters offer detailed assessment of RV and PA pressures, however they are an invasive procedure with rare but serious risks associated with their insertion[58]. Arrhythmia, haemothorax, pneumothorax, accidental arterial insertion, and PA perforation have been reported. The use of PA catheters in ICU and during the perioperative period for

non-cardiac surgery has therefore declined due to the lack of evidence of benefit and potential for harm[59].

Fast response volumetric PA catheters include a rapid response thermistor that can be used to calculate RVEF. Using measured RVEF and cardiac output, RV end diastolic and RV end systolic volumes can be derived[60]. The accuracy of volumetric catheters has been subject to scrutiny, with poor agreement with reference methods being reported[56].

1.3.3 Cardiovascular resonance imaging

CMR imaging is a non-invasive and non-ionising radiation technique for assessing RV function. CMR images are of excellent quality, and not limited by acoustic windows or geometric assumptions, meaning detailed and accurate data on RV volumes and ejection fraction can be calculated[61]. CMR derived RV ejection fraction is the gold standard non-invasive assessment of RV systolic function[61], it is the reference measure used by the European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) to which TTE RV parameters are compared[62].

Although CMR is the gold standard non-invasive method of RV function assessment, it is not without its limitations. The use of strong magnetic fields precludes its use in patients with ferromagnetic material in their body. Additionally, it is costly and time consuming, taking 45-60 minutes to perform. CMR requires IV cannulation and injection of a gadolinium-based contrast agent, and therefore may not be suitable for patients with renal dysfunction or contrast allergy [63].

1.3.4 Echocardiography measures of RV systolic function

Transthoracic echocardiography assessment of RV function is a non-invasive method that is convenient for both the patient and operator. The use of ultrasound waves means that it is safe for the patient, and provides real time images for interpretation by the echocardiographer. It is an ideal method for assessing RV function in patients who are clinically unstable since it can be done at the patient's bedside without transfer. It is highly reliant on finding adequate

acoustic windows and obtaining high quality images for RV assessment. The echocardiographic measures of RV systolic function most commonly reported are tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (RVFAC), S' wave velocity at the tricuspid annulus (S'), and the right ventricular index of myocardial performance (RIMP)[64]. These measures are analysed by TTE from the RV focussed apical four chamber (A4C) view[65]. A description of each measure will be given, followed by a discussion of the TTE measures of RV afterload. A comparison between the RV systolic function measures will then be presented. Right ventricular speckle tracking echocardiography (RV-STE) strain, a novel measure of RV function that will be investigated in this thesis, will also be compared to the conventional RV TTE parameters.

1.3.4.1 Tricuspid annular plane systolic excursion

TAPSE is acquired by passing an M-mode line through the lateral aspect of the tricuspid annulus in the A4C view (Figure 1-9). The peak distance that the annulus travels towards the apex during systole is reported, with larger values being associated with better RV function[64]. Normal TAPSE is ≥17mm.[65] Advantages of TAPSE include that it is easy to measure, highly reproducible, and it has been validated across many populations. TAPSE is substantially limited in that it reports a value of regional RV function that is used as a representation of the whole ventricle, showing poor correlation with CMR RVEF in patients with regional RV function abnormalities[66]. It is also angle and load dependent[61].

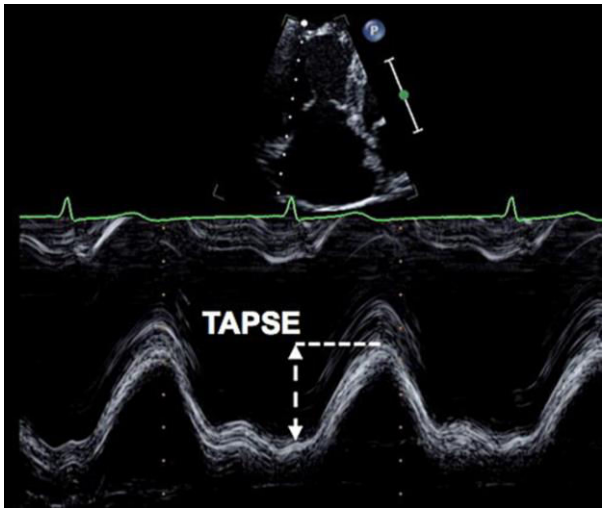


Figure 1-9 Tricuspid annular plane systolic excursion
To measure TAPSE, an M mode line is passed through the lateral aspect of the tricuspid annulus. The peak displacement of the tricuspid annulus is then measured from the M mode waveform (shown by the white double ended arrow). TAPSE = tricuspid annular plane systolic excursion. Image reproduced from Zaidi et al[65].

1.3.4.2 Right ventricular fractional area change

Right ventricular fractional area change is the percentage of the area that the RV reduces by during systole, measured from the A4C view (Figure 1-10). The myocardial border during end diastole and end systole is traced, and the reduction in area calculated. Greater RVFAC values are associated with better function. Normal RVFAC in males is ≥30%, and ≥35% in females[65].

Advantages of RVFAC include that it incorporates both longitudinal and radial contraction of the RV free wall, being analogous to a 2D representation of RVEF. RVFAC however requires high quality echocardiography study images, is load dependent, not as reproducible as other parameters, and does not measure function of the RV outflow tract (RVOT)[61,62].

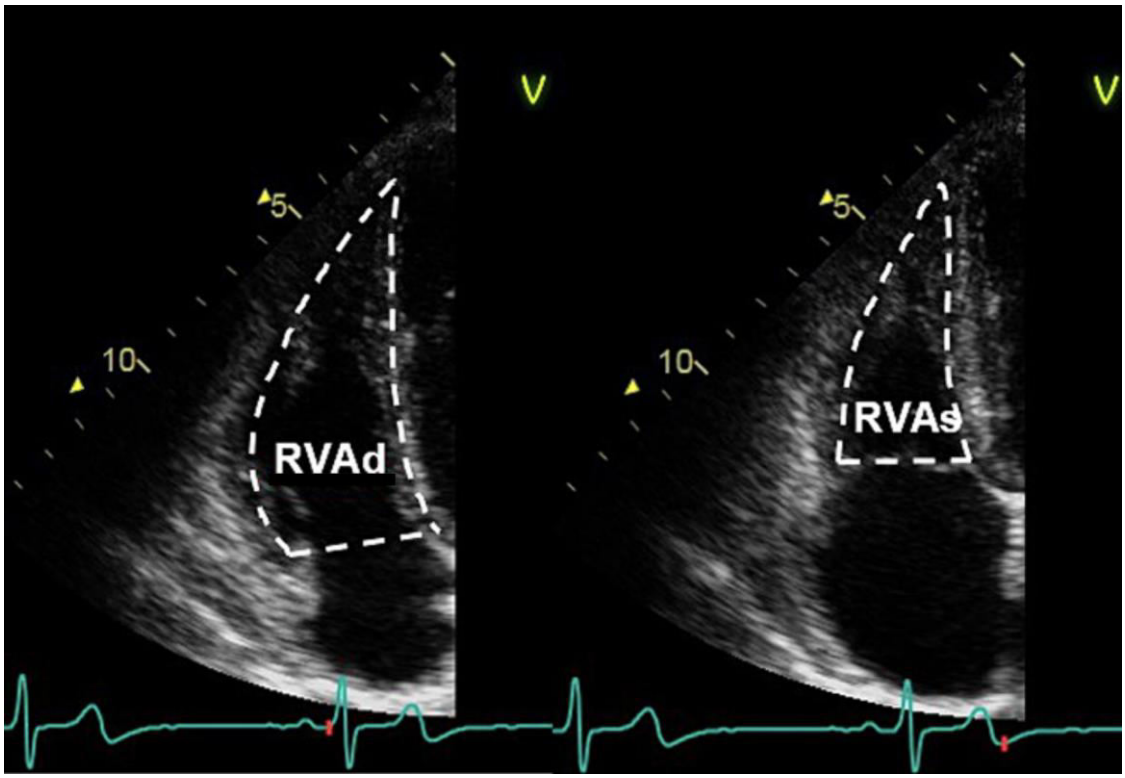


Figure 1-10 Right ventricular fractional area change
To measure RVFAC, firstly the RV area at end-diastole (RVAd) and at end-systole (RVAs) from the apical four chamber view are measured. RVFAC is the percentage that the RV area reduces by during contraction, given by the equation (RVAd-RVAs)/RVAd x 100. RVFAC = Right ventricular fractional area change. Image reproduced from Zaidi et al[65].

1.3.4.3 S' wave velocity at the tricuspid annulus

S' is a measurement of the peak tissue doppler velocity at the tricuspid annulus (or through the middle of the basal RV free wall)[64]. S' is measured using pulse wave tissue doppler from the A4C view (Figure 1-11), with a normal value ≥9cm/s. It is technically easy to perform and reproducible, S' can also be analysed offline using colour coded tissue doppler images[65].

S' uses doppler ultrasound, it is therefore angle dependent, and correct alignment with the longitudinal axis of the free wall is important to not underestimate S'. An additional limitation of S' (and to all methods that use tissue doppler imaging) is that it is prone to the phenomenon of "tethering", where a diseased or scarred portion of myocardium is passively pulled through the ultrasound beam by the surrounding normal myocardium, S' may report a falsely normal value for that portion of pathological myocardium[67]. Similar to TAPSE, a limitation of S' is that it measures regional RV function of the basal free wall which is used to represent global RV function. Like TAPSE and RVFAC, S' is a load dependent measure of RV function[61].

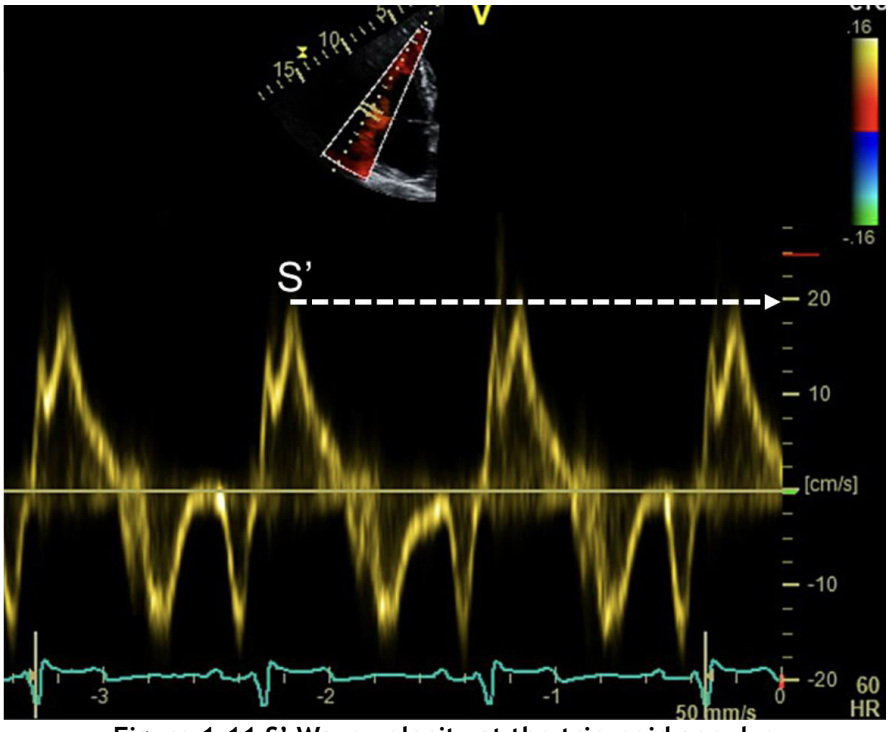


Figure 1-11 S' Wave velocity at the tricuspid annulus
S' is measured by passing a tissue doppler pulse wave through the lateral tricuspid annulus in the apical four chamber view. The peak velocity of the S wave is then measured from the tissue doppler waveform, shown as "S'" on the figure. The dashed white line shows that S' is approximately 20cm/s in this image (a normal value). Image adapted from Zaidi et al[65].

1.3.4.4 Right ventricular index of myocardial performance

The RIMP is a measure of both systolic and diastolic RV function. It is the ratio of the time the RV spends in both isovolumic contraction and isovolumic relaxation compared to ejection time. A small ratio of isovolumic time to ejection time indicates better RV function[64].

RIMP can be calculated using pulse wave tissue doppler. Tissue doppler RIMP is calculated from the same tissue doppler waveform as used for S' (Figure 1-12). Normal tissue doppler RIMP is <0.54[65]. Advantages of RIMP are similar to S', it does not make assumptions about the geometric shape of the RV, and it does not require TR for its measurement. Disadvantages include that it has been shown to be load dependent. This is particularly apparent when right atrial pressures are raised, causing reduction in the isovolumic relaxation time and pseudo-normalisation of RIMP[61].

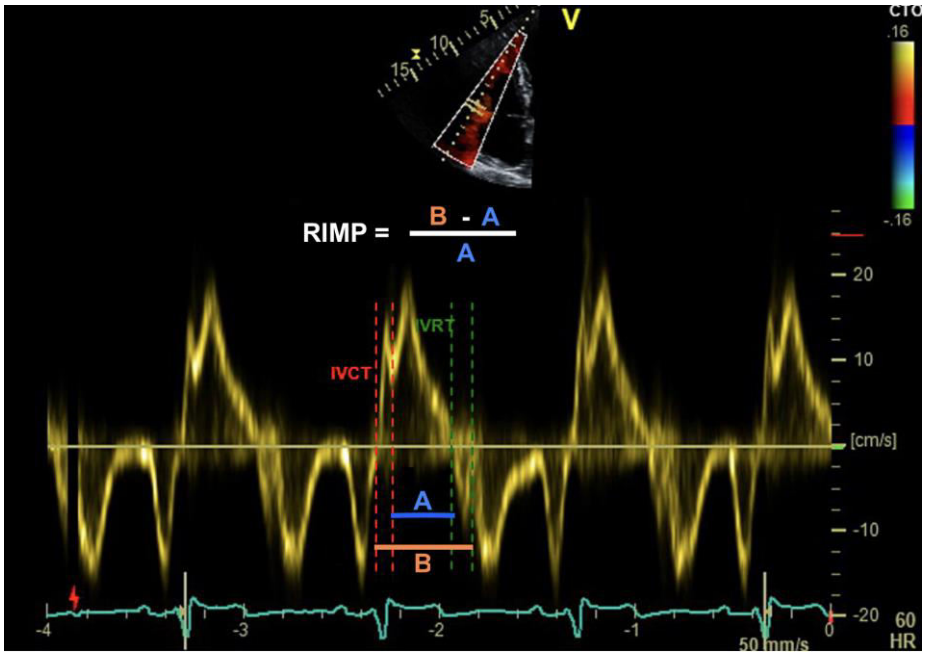


Figure 1-12 Right ventricular index of myocardial performance
Tissue doppler RIMP is measured by passing a tissue doppler pulse wave through the lateral tricuspid annulus in the apical four chamber view. RIMP is a measure of the proportion of time the RV spends in isovolumic contraction (IVCT) and isovolumic relaxation (IVRT), compared to the time it spends ejecting blood (shown as the blue line A). The orange line B represents the total time the RV spends isovolumic and ejecting. RIMP is therefore calculated by B-A/B. RIMP = right ventricular index of myocardial performance. Image adapted from Zaidi et al[65].

1.3.5 Echocardiography measures of RV afterload

1.3.5.1 Left ventricular eccentricity index

The LV eccentricity Index (LVEI) is a ratio of the internal diameter of the LV cavity viewed on the parasternal short axis (PSAX) view comparing the anterior-inferior axis with the septal-lateral axis (Figure 1-13). Under normal physiology the LV cavity is circular shaped, and the ratio will be 1:1. If the RV becomes volume or pressure overloaded, the interventricular septum bows into the LV cavity, with a reduction in the septal-lateral internal diameter, and therefore an increased anterior-inferior : septal-lateral internal diameter ratio[68]. A LVEI ratio >1.1 is considered abnormal. Isolated LVEI >1.1 at end-diastole represents RV volume overload, if this occurs at end-systole it represents RV pressure overload and can be indicative of increased RV afterload.

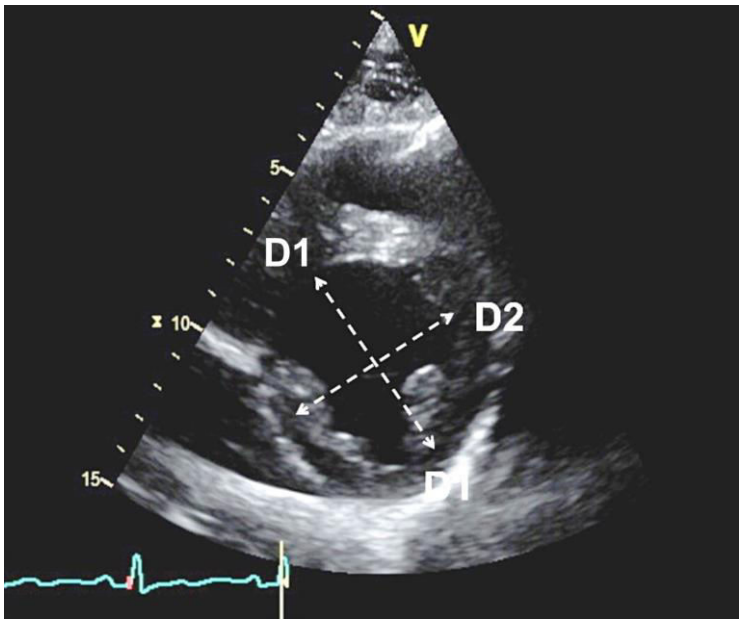


Figure 1-13 Left ventricular eccentricity index

The LVEI is calculated as the ratio of the anterior-inferior internal diameter (D2) compared to the septal-lateral diameter (D1). LVEI is measured from the parasternal short axis view at the midpapillary level. In this figure, LVEI has been calculated at end diastole, with the cursor on the upstroke of the QRS complex on the ECG. LVEI = left ventricular eccentricity index, ECG = electrocardiography. Image reproduced from Zaidi et al[65].

1.3.5.2 Pulmonary artery systolic pressure

The peak pressure gradient across the tricuspid valve (TV) can be estimated using the TR jet (if present). Continuous wave doppler ultrasound is passed through the TV (Figure 1-14), the TR peak pressure gradient is then estimated from the peak velocity of the TR jet using the simplified Bernoulli equation[64]:

$$TR\ peak\ pressure\ gradient\ =\ 4\ x\ (peak\ velocity\ across\ TV)^2$$

Right ventricular systolic pressure (RVSP) is equal to TR peak pressure gradient plus right atrial pressure. Central venous pressure is often used as a surrogate for right atrial pressure, which can be directly measured from a central venous catheter or estimated using ultrasound assessment of inferior vena cava size. Under normal conditions without RVOT narrowing or obstruction, RVSP is equal to the PA systolic pressure (PASP). If the doppler waveform is weak, it may be enhanced with IV injection of agitated saline. Echocardiography derived PASP >35mmHg are suggestive of raised pulmonary pressures[64]. PASP is an easy to obtain and non-invasive surrogate of RV afterload. Limitations of PASP measurement include the reliance of presence of a TR jet, it is also an unreliable measure with severe TR[68].

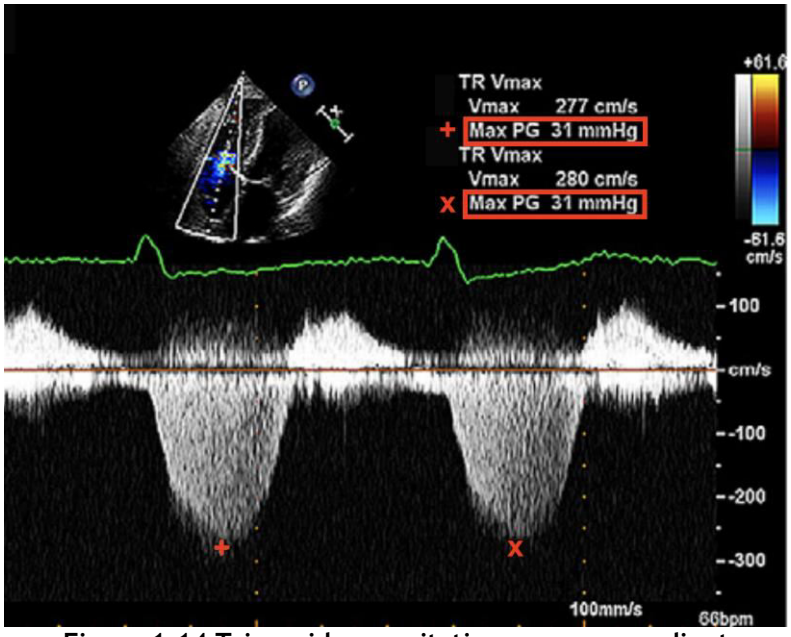


Figure 1-14 Tricuspid regurgitation pressure gradient
Continuous wave doppler is passed through the tricuspid valve on the apical four chamber view. The peak of the tricuspid regurgitation waveform is then identified (representing peak velocity of the tricuspid regurgitant jet, shown as the red + and x on the figure), and this is converted into a peak pressure gradient using the modified Bernoulli equation. Image adapted from Rudski et al[64].

1.3.5.3 Pulmonary artery acceleration time

Pulmonary artery acceleration time (PAAT) is measured from the RV inflow-outflow view, which is acquired from the PSAX view with the ultrasound beam tilted upwards towards the patients left shoulder. PAAT is measured using pulse wave doppler at the RVOT, just before the pulmonary cusps on the RV side (Figure 1-15). As pulmonary pressures increase the PAAT shortens, with a PAAT <105ms being suggestive of raised pulmonary artery pressures[68].

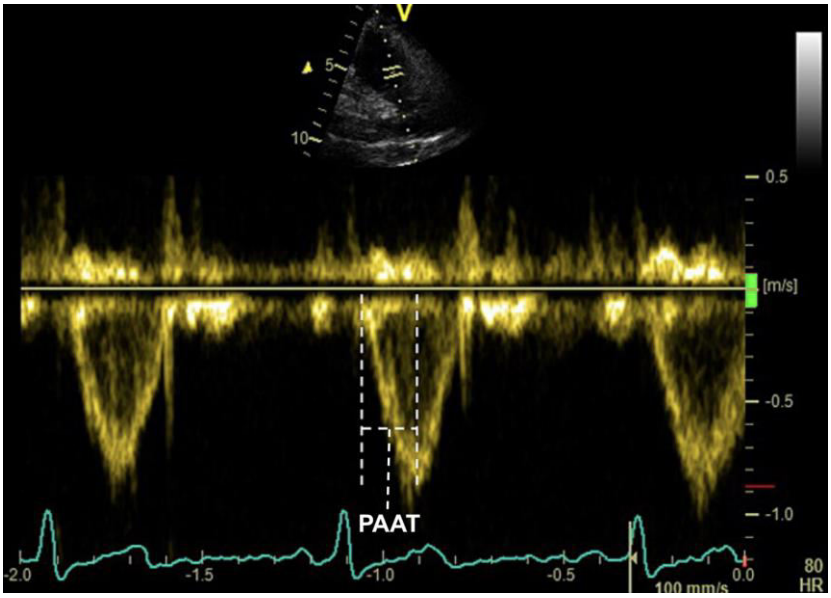


Figure 1-15 Pulmonary artery acceleration time
PAAT time is measured using pulse wave doppler at the RVOT. A crisp pulse wave doppler envelope should be seen, demonstrating the laminar flow at the RVOT. The time from onset of blood flow through the RVOT to the peak velocity is then measured (shown by the white dashed lines in the figure), this represents the PAAT. PAAT = pulmonary artery acceleration time, RVOT = right ventricular outflow tract. Image adapted from Zaidi et al[65].

1.3.5.4 Pulmonary systolic notching

The same RVOT pulse wave doppler waveform used for calculating the PAAT can be visually inspected for presence of pulmonary systolic notching, a measure of raised PA pressure (Figure 1-16). After systole, the pressure and flow waveform in the PA is reflected at the vessel bifurcation back towards the RV. When there is increased PA stiffness (as is present in pulmonary hypertension), the velocity of the reflected wave is increased[69]. This allows it to arrive at the RVOT at the end of systole before the pulmonary valve has closed, resulting in a "notched" profile on the pulse wave doppler waveform. Pulmonary notching is thought to primarily represent pre-capillary pulmonary hypertension from increased PVR and poor vascular compliance.[68]

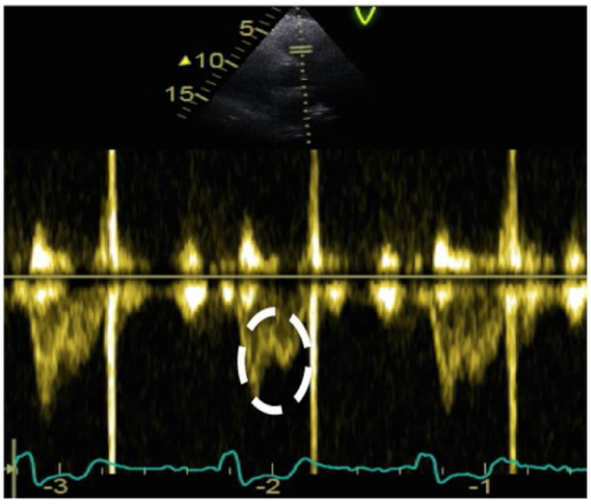


Figure 1-16 Pulmonary systolic notching
Echocardiography image of pulse wave doppler at the right ventricular outflow tract. Presence of systolic pulmonary notching, shown in white dashed circle. Figure reproduced from Augustine et al[68].

1.3.6 Comparison between echocardiography measures of systolic function

Studies have compared how the conventional RV TTE parameters perform with regards their ability to identify RVD. The majority of studies have examined association between RV echocardiography parameters and gold standard CMR RVEF, as shown in Table 1-1. TAPSE modestly correlates with CMR RVEF (r= 0.27-0.65, Table 1-1), as does S' (r= 0.20-0.52). RVFAC has been shown to have good correlation with CMR RVEF in some studies, but with poor correlation in others (r= 0.14-0.77). RIMP appears to correlate poorly with CMR RVEF (r= -0.12, -0.36). The RV-STE measure right ventricular free wall longitudinal strain (RVFWLS, described in detail in Chapter 2) has been shown to consistently correlate with CMR RVEF (r= -0.48 to -0.86).

The discriminative ability of RV TTE parameters to identify CMR RVEF diagnosed RVD has been assessed using area under the receiver operated characteristic curves (AUROCC, see Table 1-2 for levels of discrimination boundaries). Again, RVFWLS appears to perform superiorly compared to the conventional RV echocardiography parameters. The AUROCC for TAPSE to identify RVD (as diagnosed by CMR RVEF) has been shown to be 0.65-0.77, RVFAC 0.58-0.78, S' 0.72-0.78, and RIMP 0.32-0.68 (Table 1-2). None of these parameters have shown excellent discriminative ability (AUROCC >0.8) to diagnose RVD in any study. In

comparison, RVFWLS has been shown to have an AUROCC of 0.70-0.92 (Table 1-2), strikingly better than the conventional RV echocardiography parameters.

Using AUROCC curves to measure discriminative ability of a diagnostic tool is a well-recognised method, however it does not fully represent the characteristics of the diagnostic tool in different circumstances. A good example of this was demonstrated by Focardi et al, they noticed that in certain patients there was a discordance between TAPSE values and CMR RVEF (where TAPSE values were high, but CMR RVEF values were abnormally low). Using RVFWLS to interrogate this disparity identified that in patients with high TAPSE but low CMR RVEF, the RVFWLS values of basal segments were high (more negative, i.e. better function), but the RVFWLS mid and apical segment values were low (less negative, indicating RV impairment). This example highlights the superiority of RVFWLS as a global measure of RV free wall function, whereas TAPSE is limited by its assessment of regional function at the tricuspid annulus. Pavlicek et al performed a sensitivity study, where they repeated AUROCC analysis assessing the discriminative ability of RV echocardiography parameters to identify severe RVD (CMR RVEF <30%) compared their ability to identify moderate RVD (CMR RVEF <50%). They found that RVFWLS performed well in its ability to diagnose both severe and moderate RVD (AUROCC 0.88 $p<0.01$ vs 0.70 $p<0.01$). An interesting finding was that the discriminative ability of RIMP to identify severe RVD was much superior to its ability to identify moderate RVD (AUROCC 0.95 $p<0.01$ vs 0.68 $p<0.01$), suggesting that the RV echocardiography parameters may perform differently in their ability to diagnose subtle versus severe RVD.

Table 1-1 Association between RV echocardiography parameters and CMR RVEF

Study	Study population	n	TAPSE		RVFAC		S'		RIMP		RVFWLS[A]	
			r	p	r	p	r	p	r	p	r	p
Leong et al 2012[70]	Heart failure patients (n = 66) Healthy volunteers (n = 17)	83	0.65	<0.01	0.71	<0.01	0.51	<0.01	0.28	0.03	0.77	<0.01
Lu et al 2015[71]	Mixed population with cardiac disease	60	0.27	0.05	0.33	0.02	0.20	NS	-0.36	NS	0.54	<0.01
Focardi et al 2015[72]	Mixed population with cardiac disease	63	0.45	0.01	0.77	<0.01	0.52	0.01	-	-	-0.86	<0.01
McCall et al 2019[69]	Lung resection cohort	27	0.34	<0.01	0.14	0.37	0.29	0.02	-0.12	0.36	-0.48	<0.01

r = pooled Pearson's correlation coefficient for all, NS = not significant (given if p reported as "not significant" but numerical value not reported)
A = the correlation co-efficient will vary from a positive or negative value depending on if the study reported RVFWLS as a positive or negative value.
A dash (-) is given where data has not been reported. RV = right ventricular, CMR = cardiac magnetic resonance, RVEF = right ventricular ejection fraction, TAPSE = tricuspid annular plane systolic excursion, RVFAC = right ventricular fractional area change, S' = S' wave velocity at the tricuspid annulus, RIMP = right ventricular index of myocardial performance, RVFWLS = right ventricular free wall longitudinal strain

Table 1-2 Discriminative ability of echocardiography parameters to diagnose RVD compared with CMR RVEF

Study	Study population	n	TAPSE		RVFAC		S'		RIMP		RVFWLS	
			AUC	p	AUC	p	AUC	p	AUC	p	AUC	p
Pavlicek et al 2011[73]	Mixed population with cardiac disease *RVD defined as CMR RVEF <50%*	223	0.72	<0.01	0.73	<0.01	0.78	<0.01	0.68	<0.01	0.70	<0.01
Leong et al 2012[70]	Heart failure patients (n= 66) Healthy volunteers (n= 17) *RVD defined as CMR RVEF ≤45%*	83	0.77	-	0.69	-	0.76	-	0.32	-	0.80	-
Lu et al 2015[71]	Mixed population with cardiac disease *RVD defined as CMR RVEF ≤48%*	60	0.68	NS	0.58	NS	0.72	NS	0.57	NS	-	-
Focardi et al 2015[72]	Mixed population with cardiac disease *RVD defined as CMR RVEF ≤45%*	63	0.66	-	0.78	-	-	-	-	-	0.92	-
McCall et al 2019[74]	Lung resection cohort *RVD defined as CMR RVEF ≤45%*	27	0.65	0.04	-	-	-	-	-	-	0.76	<0.01

An AUC value of 0.5 shows no discriminative ability to diagnose RVD, >0.5-0.7 = poor discrimination, >0.7-0.8 = acceptable discrimination, >0.8-0.9 = excellent discrimination, >0.9 = outstanding discrimination[75]. A dash (-) is given where data has not been reported.

AUC = area under the receiver operated characteristic curve, NS = not significant (given if p reported as "not significant" but numerical value not reported), RVD = right ventricular dysfunction, CMR RVEF = cardiac magnetic resonance right ventricular ejection fraction, TAPSE = tricuspid annular plane systolic excursion, RVFAC = right ventricular fractional area change, S' = S' wave velocity at the tricuspid annulus, RIMP = right ventricular index of myocardial performance, RVFWLS = right ventricular free wall longitudinal strain

In summary, the conventional TTE measures of RV systolic function (TAPSE, RVFAC, S', and RIMP) have limitations specific to each method. Association between these variables and CMR RVEF is inconsistent, and their discriminative ability to identify RVD (when diagnosed by gold standard CMR RVEF) is limited. In the studies discussed, RV-STE strain (specifically RVFWLS) was more strongly associated with CMR RVEF, and had better discriminative ability to identify RVD, compared to the conventional TTE measures. RV-STE strain analysis may represent a superior method of RV function assessment compared to conventional RV echocardiography parameters, with the above evidence supporting this in populations with cardiac disease[70-73]. The utility of RV-STE in ICU and the perioperative period however has not been established. Given its potential superiority as a measure of RV function, investigating the utility of RV-STE in these settings is a clinically important question that this thesis addresses. An overview of the background and principles of RV-STE will now be presented in Chapter 2. Chapter 3 will examine how the utility of a test can be assessed. A review of the literature describing the utility of RV-STE in ICU and the perioperative period will be conducted in Chapter 4, followed by experiments examining the utility of RV-STE in ICU (Chapter 5) and the perioperative period (Chapter 6).

Chapter 2 The fundamentals of strain

As discussed in Chapter 1, RV speckle tracking echocardiography (STE) strain, is a novel measure thought to overcome some of the limitations of conventional RV echocardiography parameters, and it is the focus of this thesis. Chapter 2 describes the fundamental principles of strain, gives an account of how software analyses strain, discusses references ranges, and how changes in loading conditions/contractility affect strain values. After the fundamentals of strain have been addressed in Chapter 2, the following chapters in the thesis expand upon this and investigate the utility of RV-STE strain in ICU and the perioperative period.

2.1 Background

The concept of strain describes the change in myocardial shape that occurs during the cardiac cycle. The term "strain" is synonymous with "deformation". Strain echocardiography was developed to overcome some of the limitations of conventional echocardiography parameters. When considering a ventricle there are three directions in which strain can occur (Figure 2-1)[76]:

- Longitudinal - Direction of movement basal to apical.

- Radial - Direction of movement towards the centre of the ventricle on the short axis plane, and therefore represents myocardial thickening and thinning.

- Circumferential - Direction of movement is circular on the short axis plane. This is applicable to the LV where there is twisting of the myocardial fibres across each other, it does not occur in the RV.

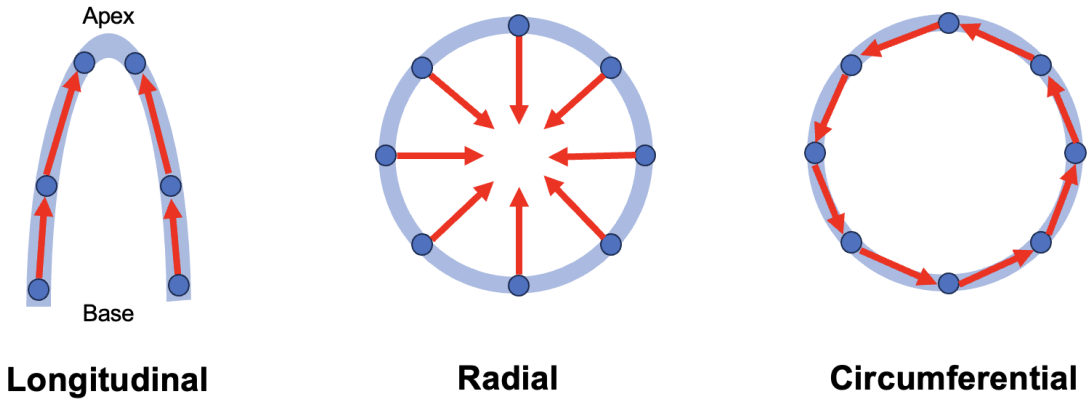


Figure 2-1 Types of strain.
A graphical depiction of longitudinal, radial, and circumferential strain. Redrawn from Blessberger et al 2010[77].

Right ventricular systolic longitudinal strain globally assesses systolic RV function, and therefore may be superior to methods that assess localised RV function (such as TAPSE and S' which assess RV longitudinal function at the base) as a surrogate of global RV function. As highlighted by the American Thoracic Society, global assessment may allow strain to detect subtle RV dysfunction conventional parameters cannot[54].

Strain is described as a percentage, which represents the degree to which a length of myocardium has shortened or lengthened in relation to its original length during the cardiac cycle (Figure 2-2). Negative strain values represent myocardial shortening with more negative values representing greater shortening and thus better myocardial function, and positive strain values represent myocardial lengthening. Strain may be derived in two ways by using; tissue doppler imaging (TDI) and STE, these will now be described.

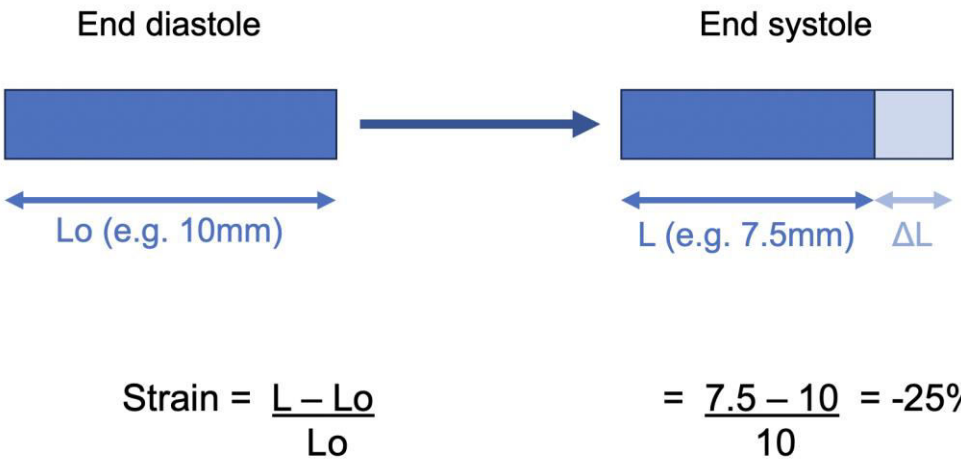


Figure 2-2 Basic description of strain calculation
Strain describes the change in length that occurs over time. In this example a section of myocardium that was 10mm at end diastole has contracted to 7.5mm at end systole, representing a 25% reduction in length, and a strain value of -25%. Redrawn from Orde at el[76]

2.2 Strain analysis: tissue doppler imaging vs speckle tracking echocardiography

The first method for strain analysis used TDI and was developed in 2000[78]. Since then, STE has superseded TDI as the preferred method of echocardiography strain analysis. The initial validation of STE analysis was first described in 2004, demonstrating no difference in strain values reported by STE compared to TDI[79,80]. A basic description of both methods is described below.

TDI compares the relative velocities of different pixels (representing different locations within the RV free wall myocardium), calculating a strain rate along the transducer line. TDI strain-rate is calculated from the following formula[81]:

$$Strain\ rate = \frac{v1 - v2}{d}$$

Where *v1* and *v2* represent the TDI calculated velocities of two myocardial pixels analysed along the transducer beams, and *d* represents the distance between them. Strain is then calculated as the first integral of strain-rate with respect to time. It is unsurprising that a key limitation of TDI strain is that it is heavily angle dependent since it is measuring a tissue doppler derived velocity from myocardium along the axis of the transducer line. If the transducer axis is misaligned, TDI strain will therefore report falsely low strain values.

Speckle tracking echocardiography relies on tracking the speckled appearance of myocardium throughout the cardiac cycle. When ultrasound beams pass through myocardium, the reflection of ultrasound waves through the myocardial matrix gives a particular area of myocardium a signature speckled appearance (called a "kernel"). Different pieces of myocardium can therefore be tracked throughout the cardiac cycle, and the change in their spatial location in relation to one another calculated by speckle tracking software, resulting in an overall strain value. Speckle tracking strain is calculated using the Lagrangian method[81]:

$$Strain = \frac{L - Lo}{Lo}$$

Where *Lo* is the original distance between two speckles, and *L* is the new distance between speckles. This proportion is then described as a percentage (Figure 2-2).

To summarise, the main differences; TDI uses tissue velocities, and its primary derived value is therefore strain-rate, STE uses change in myocardial speckle locations, and its primary derived value is therefore strain. The relationship between TDI, STE and strain and strain-rate is shown in Figure 2-3. STE can be analysed on any echocardiography study images with adequate views, whereas TDI strain requires tissue doppler images. STE is less angle dependent and has superior reproducibility, and its use therefore has superseded TDI in strain analysis[82].

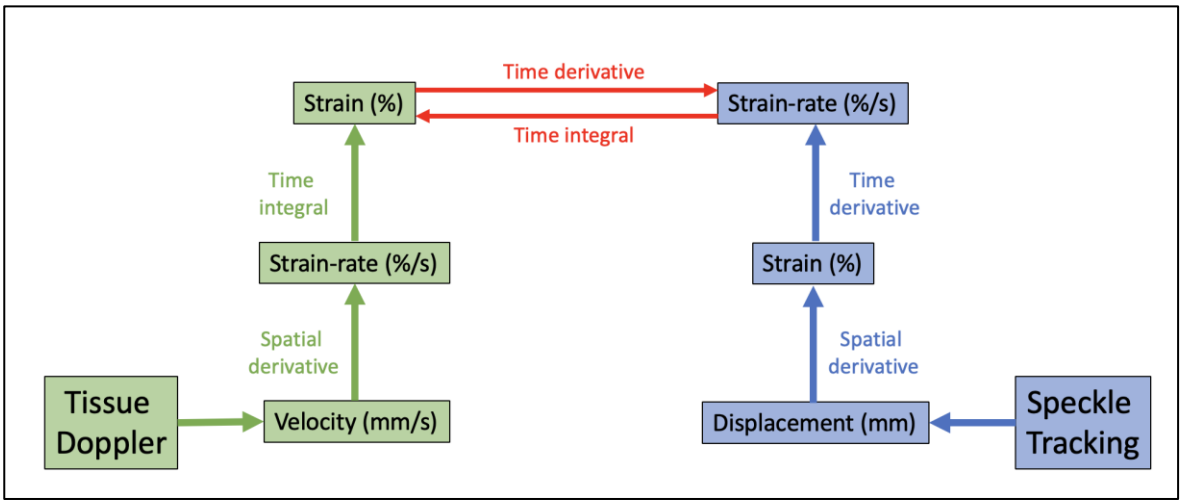


Figure 2-3 Comparison of strain analysis by TDI and STE.
The relationship between displacement, velocity, strain, and strain rate is shown, and how these interrelate when tissue doppler and speckle tracking methods are used to analyse strain. Redrawn and adapted from Houghton 2014[83].

2.3 Principles of speckle tracking echocardiography

2.3.1 General principles of speckle tracking echocardiography

When performing echocardiography, ultrasound waves interact with the myocardial matrix undergoing internal reflection and scatter within the tissue before returning to the probe. These internal reflections within the myocardial matrix give the myocardium a speckled appearance. A cluster of speckles is called a kernel, and it represents an echocardiographic signature for that specific area of myocardium[77]. STE strain software identifies many kernels along the length of the myocardium, and tracks their movement throughout the cardiac cycle (Figure 2-4). Typically, the RV free wall contains 30-50 kernels in the longitudinal orientation[83]. STE software can compare the displacement between kernels, and generate a strain value for each segment of the RV. A frame rate of 50-100Hz is required to allow adequate temporal resolution for the software to track speckles[76].

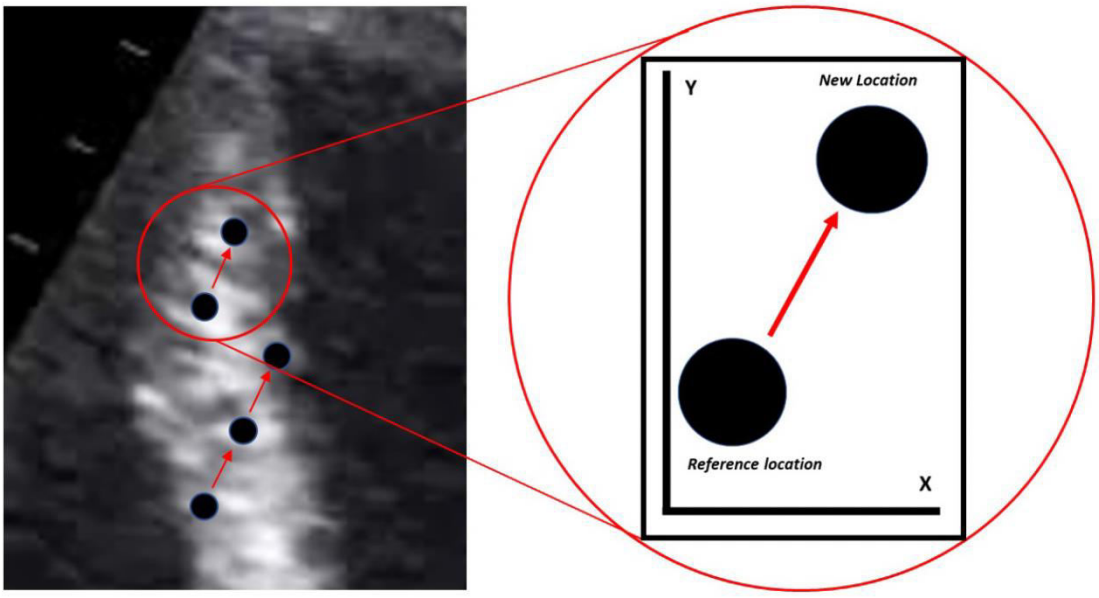


Figure 2-4 Principles of speckle tracking
Multiple kernels are tracked throughout the cardiac cycle, the change in location between kernels is compared by the speckle tracking software using a vector scale to generate a strain value. Reproduced from Johnson et al[84].

2.3.2 Right ventricular strain, segmental strain, and strain rate

The RV can be divided into six longitudinal segments (Figure 2-5). RV strain conventionally is calculated from either the three free wall segments, termed RV free wall longitudinal strain (RVFWLS), or all six segments within the free wall and interventricular septum, termed RV global longitudinal strain (RVGLS). Less frequently, individual segmental strain from each RV segment can be reported. Although the interventricular septum contributes to RV function, it is mainly a component of the left ventricle. Due to its independence from LV function and the associated contribution of the interventricular septum, RVFWLS has become the preferred method over RVGLS for RV-STE assessment of RV function. EACVI and ASE consensus guidelines have recommended RVFWLS as the primary reported measure of RV-STE strain, stating "two-dimensional STE-derived strain, particularly of the RV free wall, appears to be reproducible and feasible for clinical use"[62,85]. RVFWLS is calculated by STE strain software performing speckle tracking of the RV free wall apical, middle, and basal segments throughout the cardiac cycle. These three segmental strain curves are then combined to give an overall RVFWLS curve (Figure 2-6). From this combined RVFWLS curve the peak RVFWLS is then reported, this is a negative percentage describing the degree by which the length of myocardium has shortened, with more negative values indicating better RV function (Figure 2-6).

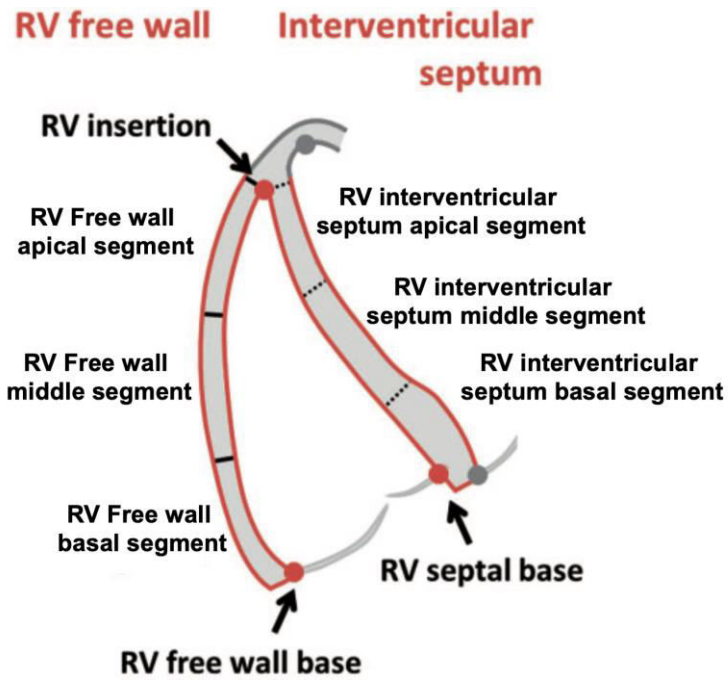


Figure 2-5 Right ventricle longitudinal segments
View of the six right ventricle segments as seen from an apical four chamber view. RV = right ventricular. Adapted from Badano et al[85].

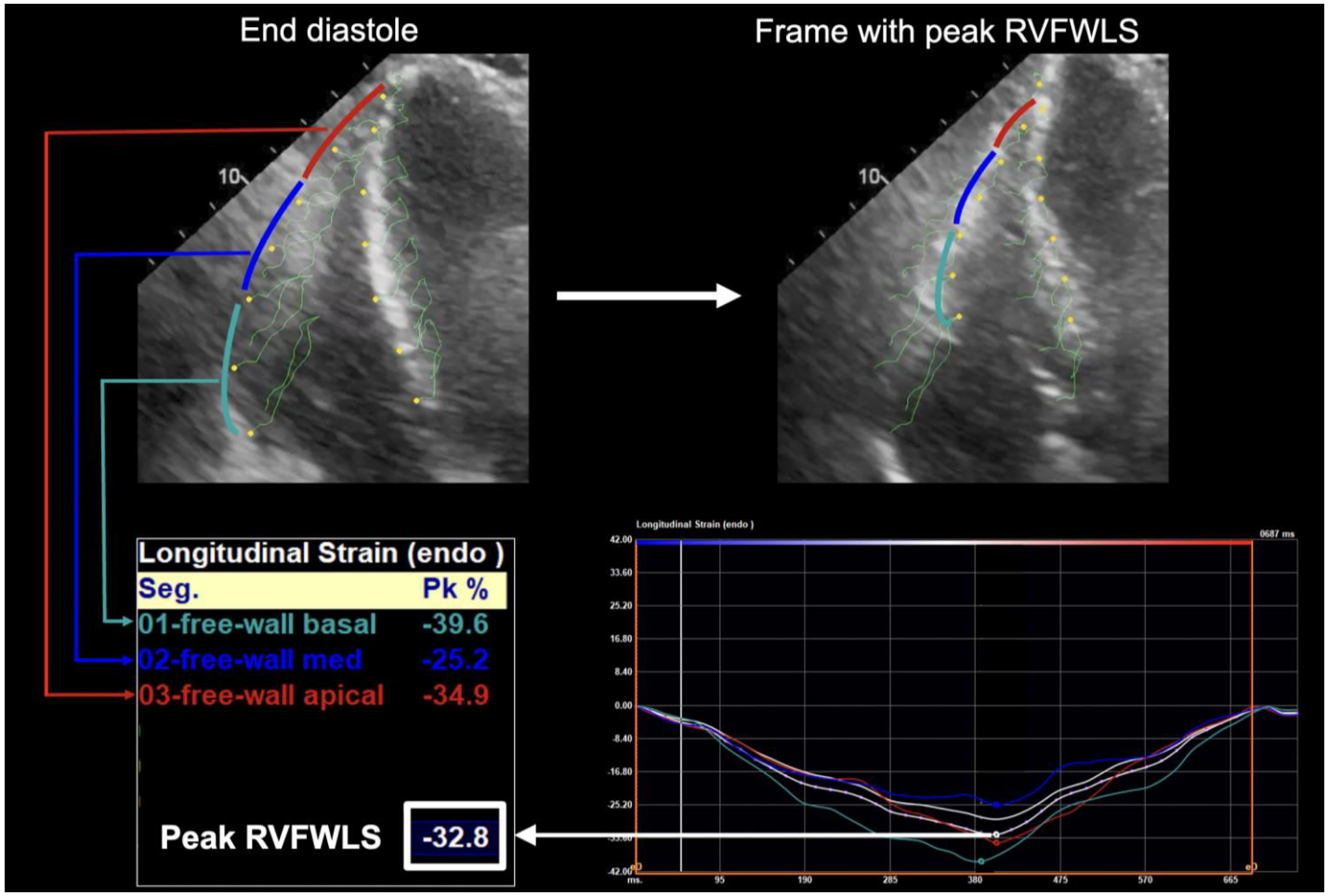


Figure 2-6 RVFWLS segmental and overall strain curves
Example of Tomtec 2D CPA STE strain software. The strain software allows visualisation of speckle tracking, shown by the yellow dots in the two top echocardiography images. The change in strain over time is represented by strain curves (shown in the bottom right), which shows segmental strain for the three RV free wall segments against time. These three segmental strain curves (red, blue, and turquoise) are combined to give an overall strain curve (white curve with pink dots) from which peak RVFWLS can be calculated (-32.8%). RVFWLS = right ventricular free wall longitudinal strain, STE = speckle tracking echocardiography, CPA = cardiac performance analysis. Image drawn by the author using Tomtec 2D CPA software.

Segmental RV strain has not been as rigorously investigated as RVFWLS or RVGLS. The six individual longitudinal RV segments may not be directly comparable, and the normal values for segmental strain remain uncertain. Studies have shown conflicting segmental strain values; one demonstrating that STE strain becomes incrementally more negative (i.e. better RV function) from the basal to apical segments in the free wall and interventricular septum[86], whereas another had contrasting results with the basal segment of the free wall having more negative strain values than the middle or apical segments[87]. Other studies have shown that the RV free wall middle segment has more negative strain than either the basal and apical segments[88]. Given this inconsistency, no segmental strain analysis will be reported in this thesis.

RV strain rate is the first differential of strain with respect to time (Figure 2-7). Strain rate has (somewhat contentiously) been reported as being a more load independent measure of RV function than RV strain[76], and may be better suited to detect changes in RV contractility occurring during exercise (described in section 2.10.5). RV strain rate has however been studied considerably less than RV strain. Wang et al performed a meta-analysis to investigate normal RV-STE and RV-STE-rate values in 2021; they identified 32 studies reporting RVFWLS, whereas only 6 studies reported RVFWLS-rate[89]. Given the sparsity of studies, it is unsurprising that current consensus guidelines do not suggest a cut-off value for normal RV strain rate. A further limitation of RV strain rate is the reliance on a high frame rate (especially at high heart rates) for accurate values. RV strain rate will therefore not be a focus in this thesis, apart from in Chapter 6 where its utility is specifically explored in the exercise stress echocardiography setting.

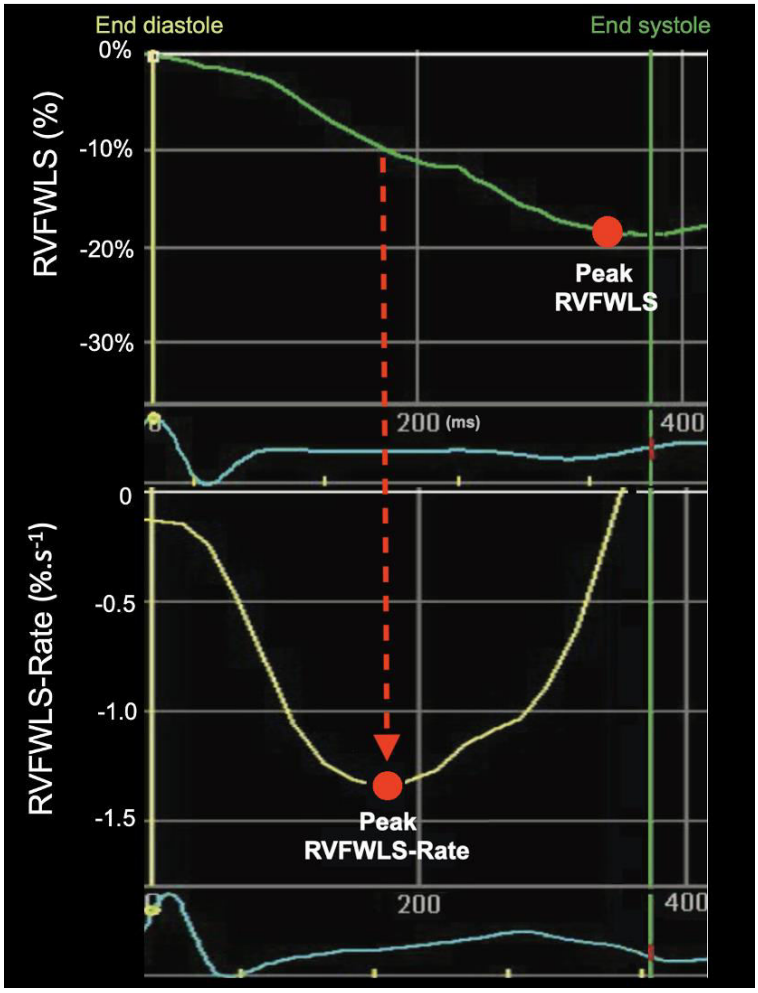


Figure 2-7 Relationship between RVFWLS and RVFWLS-rate
RVFWLS (top) and RVFWLS-rate curves (bottom) are shown. RVFWLS-rate is the first differential of RVFWLS with respect to time. The steepest gradient of the RVFWLS curve corresponds to the peak RVFWLS-rate. Peak RVFWLS and peak RVFWLS-rate may therefore occur at different times. RVFWLS = right ventricular free wall longitudinal strain. Adapted from Orde et al[76].

2.3.3 Left ventricular strain

Left ventricular global longitudinal strain (LVGLS) requires a more complex image set for analysis than for RVFWLS/RVGLS. LVGLS is briefly described because it will be referenced during this thesis. LVGLS requires three views, the A4C, apical two chamber (A2C), and apical three chamber (A3C)[84]. These three views are then analysed simultaneously by STE strain software, resulting in 17 LV segments from which peak LVGLS is calculated.

2.3.4 End systolic and peak systolic strain

RV systolic strain can be reported as either end systolic strain, or peak systolic strain (Figure 2-8). It is recommended that RV end-systole should be identified at the point of closure of the pulmonary valves using doppler ultrasound[85]. Peak systolic strain can occur at any time during the systolic period, including end

systole. EACVI and ASE consensus guidelines state that “peak systolic values of RV myocardial deformation parameters should be reported routinely, with other parameters specified explicitly” due to the more rigorous validation and prognostic value across different patient populations of peak systolic compared to end systolic strain[85,90,91]. As described in section 2.3.2, these groups also favour the use of RVFWLS over RVGLS[62]. This thesis will therefore focus on peak systolic RVFWLS as the primary measure of RV-STE, however peak systolic RVGLS will also be assessed.

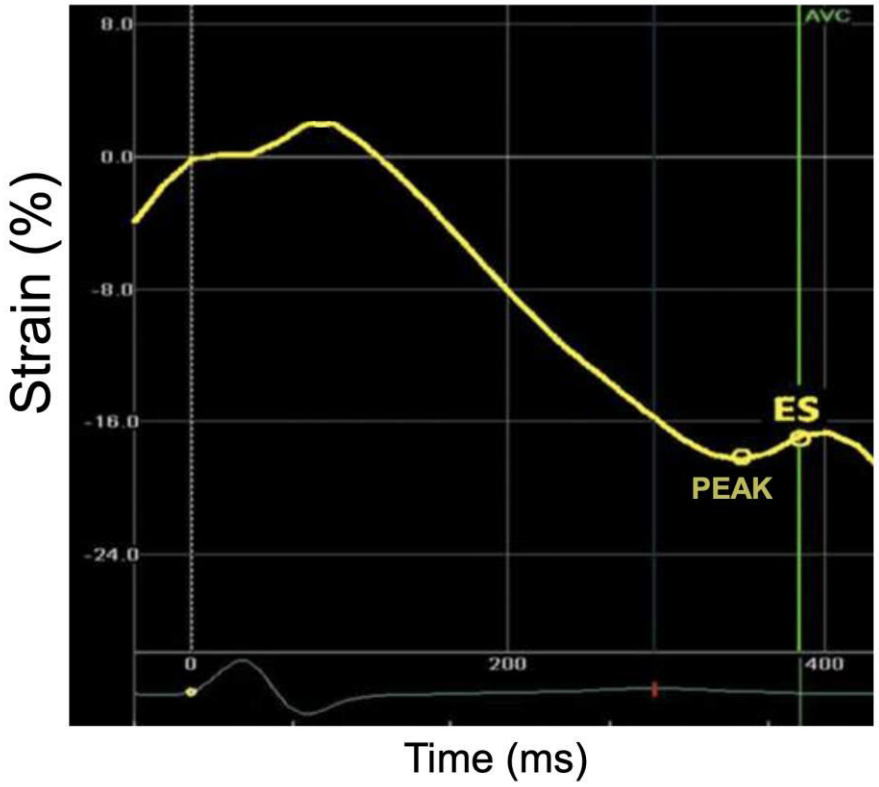


Figure 2-8 Peak systolic and end systolic strain
Strain curve demonstrating the difference between end systolic strain (ES) and peak systolic strain (PEAK). Adapted from Voigt et al[92].

2.4 Software

There are currently several vendors providing speckle tracking strain software. Each software uses an individual proprietary algorithm to calculate a strain value from the images[93], and as such values may differ between vendors. Additionally, strain software may be vendor specific where the software is specific to the ultrasound machine manufacturer (such as EchoPAC strain software which is specific to GE ultrasound images[94]), or strain software may be "vendor neutral" where the software can analyse images from different ultrasound vendor images (such as Tomtec image arena which can analyse Digital Imaging and Communications in Medicine [DICOM] images from any ultrasound machine manufacturer[94]). Speckle tracking strain software can be manual, where the reporter adjusts the tracking of the region of interest (ROI) throughout the cardiac cycle to ensure adequate tracking; semi-automated, where the strain software suggests tracking of the region of interest that can be manually optimised; or fully automated where the software calculates a strain value without adjustment of speckle tracking by the reporter. The effects of vendor will now be discussed, followed by a review of manual vs semi-automated vs fully automated speckle tracking.

2.4.1 Speckle tracking strain software vendors

Most of the work investigating the effect of software vendors has focused on assessment of LV strain. A large study conducted by the EACVI/ASE/Industry Task Force assessed the effect of vendor on LVGLS values[93]. This study examined 9 different strain software vendors. Sixty-two patients presenting for routine echocardiography underwent sequential echocardiography studies, undertaken by the same ultrasonographer using a range of ultrasound machines from different vendors. LVGLS was then analysed by a single reporter. Mean LVGLS values ranged from 17.9% to 21.4%, demonstrating small but significant variability between reported strain values by the different software ($p<0.001$, Figure 2-9).

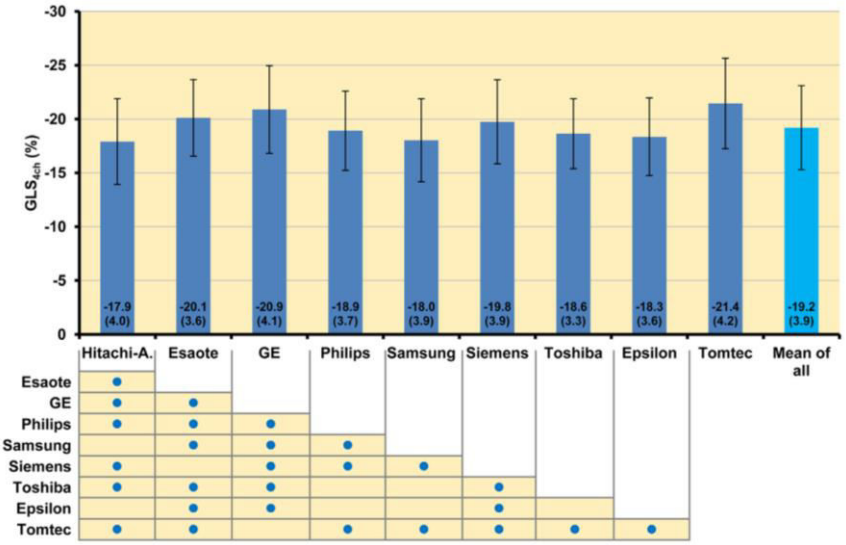


Figure 2-9 The effect of speckle tracking software vendor on reported LVGLS values
Mean (standard deviation) LVGLS reported by different strain software. The table below compares the reported LVGLS values between strain software, with a blue dot indicating a significant difference between the two software. LVGLS = left ventricular global longitudinal strain. Reproduced from Farsalinos et al[93]

Less work has been done to investigate the effect of strain software vendor on RV-STE strain values. A small study was conducted by Il'Giovine et al who investigated the effect that ultrasound machine vendor (GE vs Philips) and strain software (where GE and Philips were vendor specific software, and Tomtec was vendor neutral) had upon reported RVGLS[95]. They demonstrated no significant differences in the reported RVGLS when vendor specific software was used (i.e. GE ultrasound machine and strain software vs Philips ultrasound machine and strain software). There were no significant differences in RVGLS reported by vendor neutral Tomtec and vendor specific GE/Philips strain software when vendor neutral and vendor specific software were used to report the same echocardiography study images, although the variability of the results was widespread but without any systematic differences. This small study suggests that it may be appropriate to compare RVGLS values analysed from different ultrasound machines and using different strain software (specifically between GE/Philips ultrasound machines and between GE/Philips/Tomtec strain software). Larger studies are required to establish the effect of different strain software on RV-STE values.

2.4.2 Manual, semi-automated, and fully automated speckle tracking strain software

Speckle tracking strain software is reliant on accurate tracking of the RV free wall during the cardiac cycle. The ROI is identified as either a line tracing the RV endocardial border ignoring trabeculations (as used by Tomtec 2D cardiac performance analysis [CPA][96], Figure 2-10A), or a box overlying the RV myocardium (such as Philips and GE strain software[97], Figure 2-11). Manual, semi-automated, and fully automated strain software are available to identify the ROI and perform speckle tracking. These terms (particularly semi-automated software) are not well defined, and the strain software vendors interpret them slightly differently. In general, manual strain software requires the reporter to identify the region of interest manually at both end diastole and end systole, and visually inspect the speckle tracking during the cardiac cycle to ensure it is tracking correctly. Semi-automated strain software can refer to software which suggests a ROI that requires manual adjustment before speckle tracking is performed (such as Tomtec 2D CPA[96], Figure 2-10), or it can refer to a software which automatically identifies the ROI and performs speckle tracking, reporting a strain value, the reporter can then adjust the ROI to ensure speckle tracking is occurring accurately (this is how Philips performs semi-automated strain analysis[97]). Fully automated strain software requires no input from the reporter, with the software identifying the ROI and performing speckle tracking analysis autonomously, the reporter does not adjust the ROI. It is therefore apparent that the first version of semi-automated software described is closer to manual strain software, and the second version of semi-automated strain software is closer to fully automated strain software (only differing in that after strain has been autonomously analysed and calculated, the reporter can then go back and adjust the ROI).

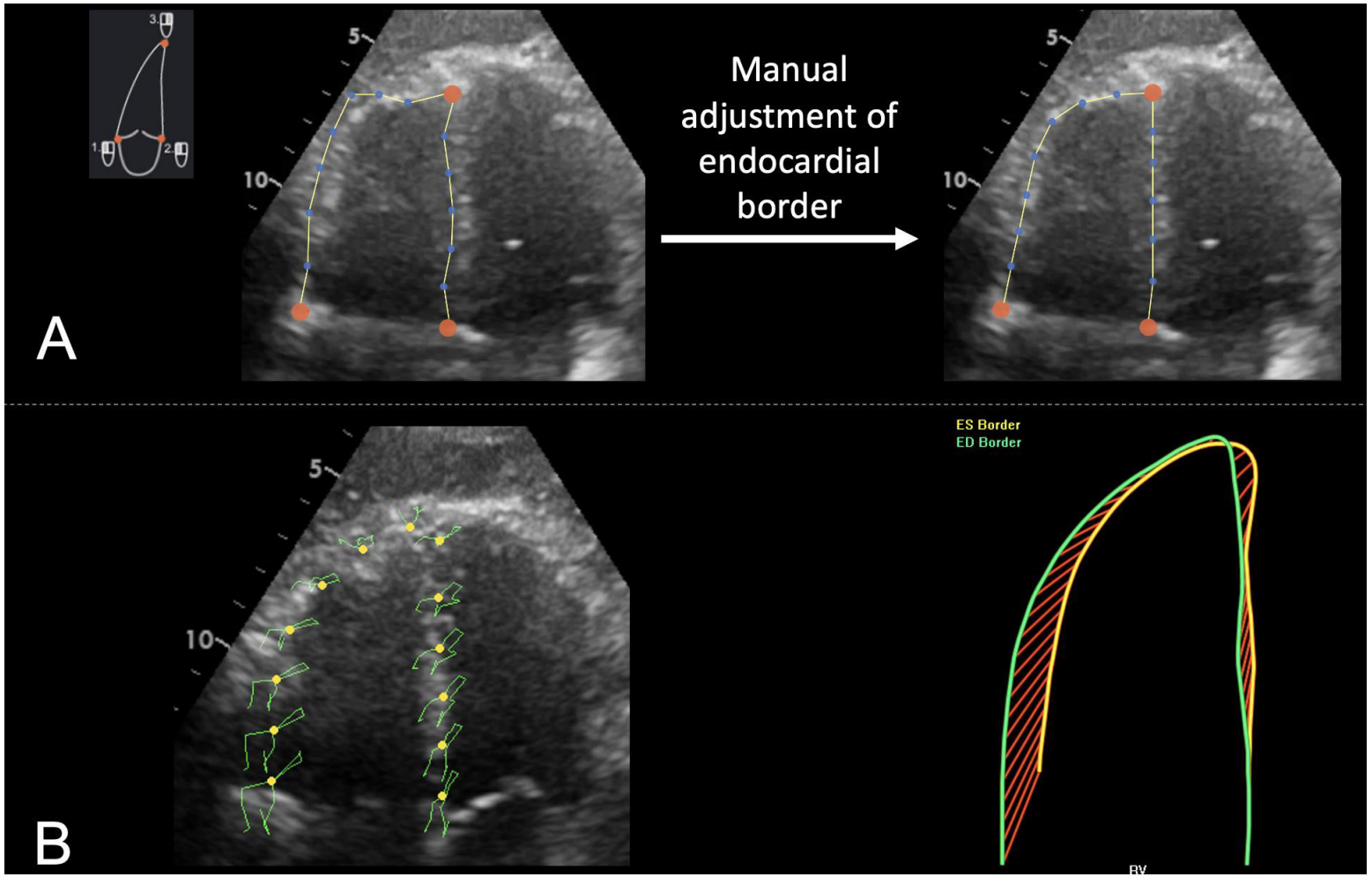


Figure 2-10 Tomtec speckle tracking strain analysis
A. Tomtec 2D CPA uses the endocardial border as the region of interest for strain analysis. Semi-automated strain software suggests a ROI which can be manually adjusted by the reporter. In the figure the suggested ROI by requires manual adjustment so that it correctly traces the RV endocardium. **B.** After the ROI has been identified, speckle tracking strain analysis occurs, requiring confirmation of adequate speckle tracking via visual inspection by the reporter. CPA = cardiac performance analysis, RV = right ventricular, ROI = region of interest, ES = end systolic, ED = end diastolic. Figure produced by the author using Tomtec 2D CPA.

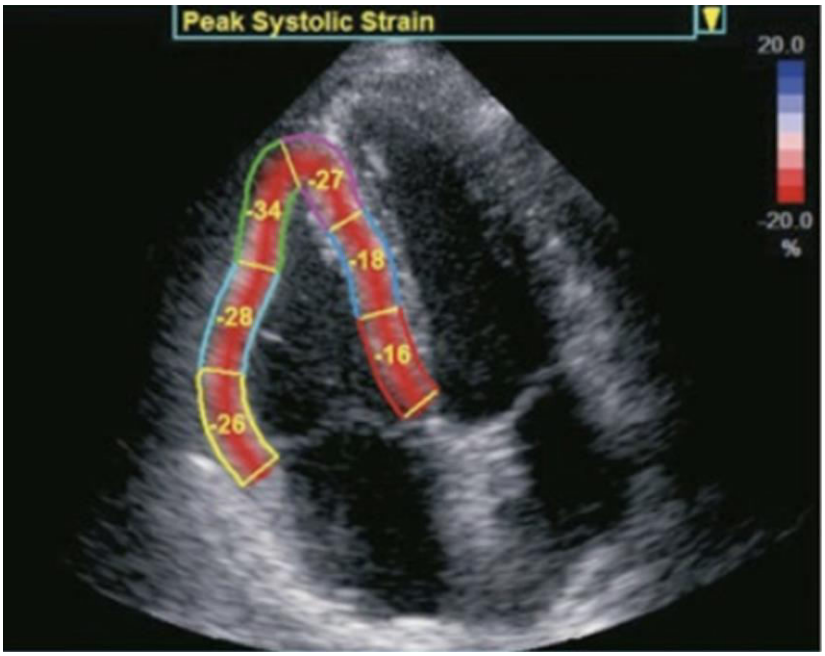


Figure 2-11 Identification of the region of interest by GE EchoPAC strain software
GE EchoPAC strain software identifies the right ventricular myocardium and places a box across its full length and thickness as the region of interest for speckle tracking strain analysis. Image reproduced from Sirico et al[98].

Manual strain analysis has been used as the gold standard against which semi-automated and automated strain are compared. Two studies have investigated the effects of manual, semi-automated, and fully automated strain analysis on reported RV-STE strain values. Peng et al compared manual strain software with semi-automated software in healthy volunteers [97], and Li et al compared manual strain software against semi-automated and fully automated software in a mixed cohort of volunteers and patients undergoing clinically indicated TTE [99]. Both studies used Philips strain software. Peng et al identified that manual strain software reported significantly more negative RVFWLS strain values than the semi-automated software. Li et al similarly found that manual strain reported significantly more negative RVFWLS than semi-automated and fully automated strain software. Li et al identified strong association between manual and semi-automated/fully automated strain values ($r=0.708$ and $r=0.850$ respectively, $p< 0.001$ for both). Both studies identified that manual strain software analysis takes significantly longer than semi-automated or fully automated strain analysis, highlighting that semi-automated and fully automated strain software may be more efficient in the clinical setting if the results can be convincingly validated against manual strain software results.

2.4.3 Choice of speckle tracking software

Semi-automated speckle tracking strain analysis has been shown to be an efficient method of strain analysis that strongly correlates with gold standard manual strain software[99]. Of the semi-automated speckle tracking software software, Tomtec 2D CPA is closest to gold standard manual strain software analysis, with the only automated component of the process being a suggested endocardial border ROI after the apex and lateral/septal recesses of the tricuspid annulus have been identified by the reporter (Figure 2-10A). Tomtec 2D CPA is a vendor neutral software, offering the distinct advantage that it can analyse any DICOM echocardiography images regardless of the vendor of ultrasound machine. Normal and abnormal cut-off values for Tomtec software have also been rigorously studied (described below in section 2.9). Given the numerous advantages described, semi-automated Tomtec 2D CPA speckle tracking software will be the strain software used for the scientific investigations in Chapters 5 and 6.

2.5 Learning curve

There has been only one study investigating the learning curve associated with conducting RV-STE analysis using speckle tracking software. Chamberlain et al assessed the number of echocardiography studies a novice reporter needed to perform RVFWLS analysis upon before achieving expert competency and consistency (demonstrated by an intraclass correlation coefficient of >0.9 comparing novice reporter to expert reporter, Figure 2-12)[100]. RVFWLS analysis of 100 echocardiography studies was required before novice reporters achieved expert level. It is noteworthy that the same group performed a similar study of the LV-STE reporting learning curve, demonstrating novice reporters required only 50 echocardiography studies to achieve expert level competency[101]. This highlights the need for a prolonged period of training before a reporter is competent to report RV-STE.

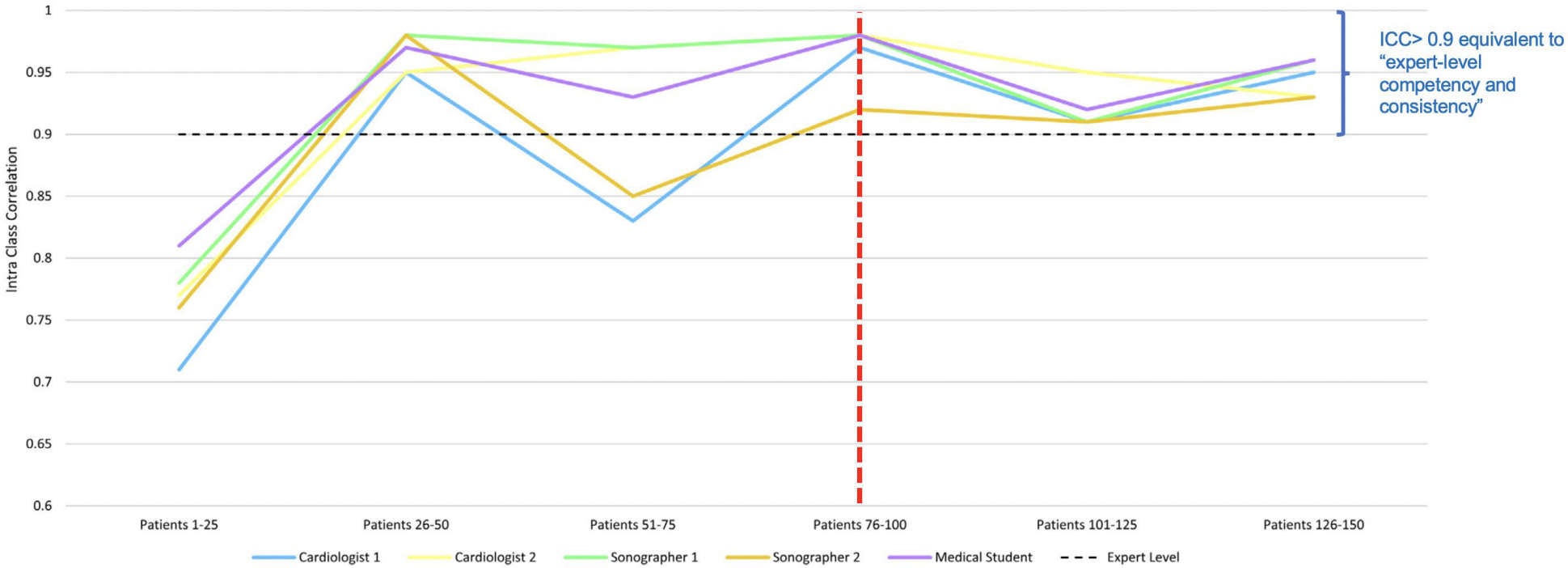


Figure 2-12 RVFWLS learning curve
RVFWLS learning curve for five novice reporters, demonstrating that reporting of RVFWLS for 100 echocardiography studies was required before expert level was achieved (demonstrated by dashed red line). The reproducibility of novice RVFWLS reporting was compared to an expert using interobserver intraclass correlation coefficient (ICC), with ICC >0.9 representing excellent agreement, and that the novice had attained an expert level of reporting. RVFWLS = right ventricular free wall longitudinal strain. Adapted from Chamberlain et al[100].

2.6 Echocardiography study image quality

The basis of STE analysis requires echocardiography study images that visualise the entirety of the RV free wall and septum, with clearly defined speckles within the myocardium[92]. It would therefore seem intuitive that accurate and reproducible STE strain analysis would require high quality echocardiography study images, however few studies have investigated the effect that image quality has upon STE strain analysis (with none specifically investigating the effect of image quality upon RV-STE strain). Consensus guidance from the EACVI and ASE warn that "images of varying quality and different spatial and temporal resolution produce a potential variability in the results of deformation imaging"[92], and although this may seem like a logical statement, it has not been conclusively demonstrated for RV-STE strain analysis.

Two studies investigating the effect of echocardiography study image quality upon LV-STE strain analysis have been performed, with conflicting results. Nagata et al performed a LV-STE study in 308 adult patients undergoing routine TTE[102]. Echocardiography was performed on patients using "old- and new-generation ultrasound imaging systems" (Vivid 7 and Vivid E95). The newer system produced images of a significantly higher quality, and these higher quality images were associated with better LVGLS inter-observer reproducibility (assessed by Bland-Altman plots and ICCs, see Chapter 3 for further details on methods for assessing reproducibility). Conversely, Wilke et al performed LVGLS STE analysis in 127 children undergoing clinically indicated exercise stress echocardiography. They described the quality of echocardiography study images as "optimal (95–100% accurate myocardial wall visualization), suboptimal (70–95% visualization) and limited (<70% visualization)". Wilke et al found no difference in the intra- and inter-observer reproducibility of echocardiography study images of different quality (assessed by Bland-Altman plot mean difference and limits of agreement)[103]. Although these two study groups are very different both in age and patient physiology (i.e. one at rest and one during incremental exercise), the fact that they have identified disparate results suggests further research is required to establish the effect of image quality upon LV-STE strain analysis. Given the lack of evidence, there is a need for studies to investigate the effect of echocardiography study image quality upon RV-STE strain analysis.

2.7 3D Strain

Three-dimensional (3D) STE strain analysis is an advanced technique that at present is mainly used in the research setting. 3D STE uses a specialised 3D matrix array transducer to acquire real-time 3D images of the heart, which then undergoing speckle tracking analysis by dedicated software (Figure 2-13). 3D STE has some theoretical advantages over 2D STE. Limitations of 2D-STE strain analysis include the influence that foreshortened images have upon results, and loss of speckles due to out of 2D plane motion, 3D STE is not affected by foreshortening or out of plane motion[104]. Additionally, 3D RV-STE is able to assess the RV outflow tract, an area of the RV that is missed during 2D RV-STE longitudinal strain analysis (since the RVOT is not present on the A4C view used for 2D longitudinal RV-STE)[104]. Although these theoretical advantages are desirable for RV-STE strain analysis, validation of 3D RV-STE is still in its infancy. Li et al conducted a study in 81 patients requiring echocardiography and CMR, and compared 3D RVFWLS and 2D RVFWLS with CMR derived RVFWLS[105]. They demonstrated that 3D RVFWLS correlated better with CMR derived RVFWLS than 2D RVFWLS ($r=0.85$ $p<0.001$ vs $r=0.62$ $p<0.001$ respectively). 3D RVFWLS had better agreement with CMR derived RVFWLS than 2D RVFWLS, with a smaller mean difference and narrower limits of agreement. Another study demonstrated that 3D RVGLS was better able to predict a diagnosis of obstructive sleep apnoea than the conventional 2D RV echocardiography parameters (TAPSE, S', and RVFAC)[106]. Although 3D RV-STE may have advantages over 2D RV-STE and the conventional RV echocardiography parameters, 3D RV-STE requires further investigation to establish its relationship with 2D RV-STE values, to define normal ranges, and to understand the effect that different 3D STE strain software has upon 3D RV-STE values. As such, 3D RV-STE remains primarily a research tool with limited clinical utility at present.

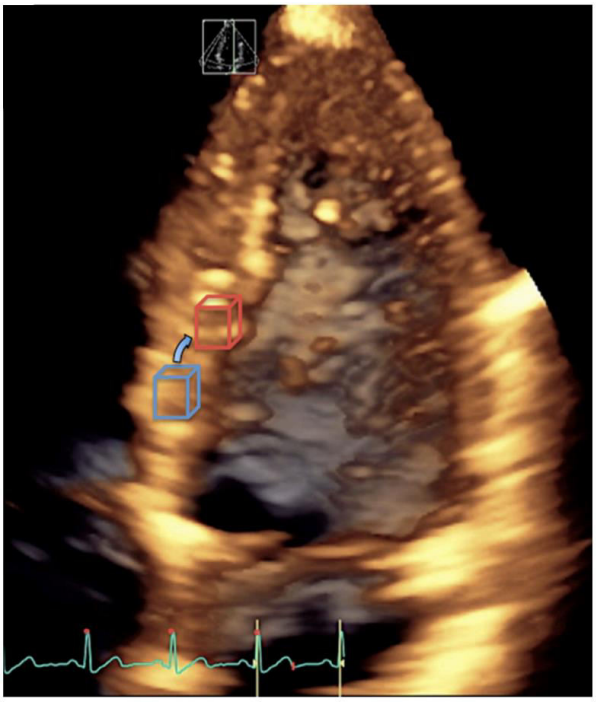


Figure 2-13 Principles of 3D speckle tracking echocardiography strain analysis
3D strain software recognises natural acoustic markers of 3D volumes of myocardium, described as "blocks" (analogous to 2D STE "kernels"). "Block matching" is then performed, where the block is tracked in the 3D space throughout the cardiac cycle (shown as the translocation of the blue and red cubes). STE = speckle tracking echocardiography. Images reproduced from Muaru et al[104].

2.8 Transthoracic vs transoesophageal speckle tracking echocardiography

The use of transoesophageal echocardiography (TOE) STE analysis is gaining popularity for intraoperative assessment of cardiac function, particularly in the cardiac surgery setting[107]. Transthoracic and transoesophageal echocardiography obtain images of the heart from different orientations and therefore may not yield equivalent strain values. Two studies have reported comparative assessment of RV-STE strain analysis using TTE and TOE images. Tousignant et al firstly compared STE derived RVGLS values obtained from TTE and TOE images after anaesthetic induction in 21 patients undergoing coronary artery bypass grafting[108]. The RVGLS values were similar, with a mean TTE RVGLS of -20.0% (3.2) and a TOE RVGLS of -20.3% (9.7) (no p value given). It is noteworthy that TOE images appeared to result in a higher RVGLS feasibility than TTE images, where all six RV segments could be tracked in 73% of patients when TOE was used compared to only 38% when TTE was used. Kurt et al repeated a similar study, performing TTE and TOE in 34 healthy patients undergoing investigation for patent foramen ovale[109]. Patients did not receive general anaesthesia or sedation. Mean TTE and TOE RVGLS values again were comparable, with a mean TTE RVGLS of -22.2% (2.9) and a TOE RVGLS of -23.0% (3.0) (p=0.21). This study also included a Bland-Altman plot comparing TTE RVGLS with TOE RVGLS, demonstrating no systematic bias, with a mean difference of 0.8% (LOA 7.7, -6.1%). Both studies used GE EchoPAC strain software for analysis. These two studies, in two different patient populations and settings, suggest that TTE and TOE RV-STE may be comparable, however further studies are required to establish if they can be used interchangeably. TOE RV-STE values may have different normal value cut-offs, and the effects of different strain software on TOE RV-STE strain analysis has yet to be explored. Given that TOE is rarely used in ICU and the perioperative setting (outside of cardiac surgical populations), TTE RV-STE will be the focus for the remainder of the thesis.

2.9 Reference ranges of resting strain

As described above, RV-STE values can vary depending on the strain software used. Other patient characteristics (such as age and gender) may also affect RV-STE values. These factors mean it has been difficult to establish clear normal ranges for RV-STE. The most studied parameter is RVFWLS; the three largest studies investigating the normal ranges for RVFWLS are a meta-analysis by Wang et al[89] (32 studies using many different strain software) and two subsequent large studies focussing on Tomtec (Addetia et al[110]) and GE EchoPAC strain software (Espersen et al[111]) (Table 2-1). It is difficult to directly compare these studies since they use data from quite different patient populations. Tomtec strain software may report more negative strain values (then GE EchoPAC), with an abnormal RVFWLS cut-off of -20.0% (of note this is the cut-off suggested by the ASE prior to this study[62]). GE EchoPAC strain software reported less negative RVFWLS values than Tomtec in its European population, with an abnormal RVFWLS cut-off of -16.5%. Both Addetia et al and Espersen et al demonstrated that RVFWLS was significantly less negative in male subjects, and that RVFWLS became less negative with advancing age, suggesting that both Tomtec and GE EchoPAC strain software detect gender and age-related changes in RVFWLS. For the reasons described in section 2.4.3, Tomtec strain software will be used in the scientific experiments conducted in Chapters 5 and 6, and an abnormal cut-off for RVFWLS of -20.0% will therefore be used.

Now that the normal range for resting RV-STE has been described, the effects that loading conditions, heart rate, contractility, and exercise have upon RV-STE will be described. These principles will form the basis of the scientific experiment within Chapter 6, where the effects of lung resection upon RV-STE during exercise stress echocardiography are explored.

Table 2-1 Normal ranges of RVFWLS

Study	Number of subjects	Strain Software	Mean RVFWLS (SD)	Lower limit of normal (lower 95%CI bound)
Wang et al 2021[89]	3673 across 32 studies Mixed populations of healthy adults and patients across Europe, North America, South America, Asia, and Australasia.	EchoPAC (GE), QLab (Philips), Tomtec, Velocity Vector Imaging, Aplio Artida, Epsilon	-26.9% (95CI% -28.0%, -25.9%)	-18.0%
Addetia et al 2021[110]	1913 Healthy adults across Europe, North America, South America, Africa, Asia, and Australasia	Tomtec	-28.3% (SD 4.3%)	-20.0%
Espersen et al 2023[111]	1297 Healthy adults from Copenhagen	EchoPAC (GE)	-26.7% (SD 5.2%)	-16.5%

RVFWLS = right ventricular free wall longitudinal strain, SD = standard deviation, CI = confidence interval.

2.10 Effects of loading conditions, heart rate, contractility, and exercise upon RV-STE

2.10.1 Preload and RV-STE

As described above (section 1.2.4), under physiological conditions, increasing RV preload will increase the force of myocyte contraction via the Frank-Starling mechanism. It would therefore seem logical that RV-STE might improve with RV preload. It has been shown that an increase in RV preload via a 500ml 0.9% saline intravenous fluid bolus induces a small increase in RVGLS (i.e. becomes more negative) in young healthy adults (-22.6% [20.7-25.4] pre-fluid challenge vs -23.5% [22.0, 26.1] post-fluid challenge, p=0.05)[112]. Conversely in patients with repair of atrial septal defects reducing RV preload (via closure of the left to right shunt), RVGLS was shown to become significantly less negative (i.e. more impaired), RVGLS-rate did not change[113]. Schlangen et al performed a similar study in patients with hypoplastic left heart syndrome with modified Fontan circulation (redirection of systemic venous blood into the pulmonary arteries, with a fenestrated intra-atrial tunnel modification). These patients underwent right heart catheterisation, with inflation of a balloon in the intra-atrial tunnel, acutely decreasing RV preload. This demonstrated a reduction in RVGLS, again with no effect on RVGLS-rate[114]. Animal studies have also suggested that RVGLS-rate is not a sensitive measure of change in preload, but that it can identify changes in contractility[115]. An overview of the studies investigating the effects of loading conditions, heart rate, and contractility on RV-STE is shown in Table 2-2.

Table 2-2 Overview of how altering preload, afterload, heart rate, and contractility affect RV strain and RV strain-rate

Parameter modified		Study	Method for altering parameter	Effect on strain	
				RV strain	RV strain-rate
Preload	↑	Beyls et al 2021[112]	500ml bolus of intravenous 0.9% NaCl	↑	↔
	↓	Jategaonkar et al 2009[113]	Closure of atrial septal defect	↓	↔
		Schlangen et al 2014[114]	Balloon occlusion of intra-atrial tunnel	↓	↔
Afterload	↑	Ewalts et al 2021[116]	Inhalation of deoxygenated air (FiO_2 0.12)	↔	↔
		Pezzuto et al 2018[117]	Inhalation of deoxygenated air (FiO_2 0.12)	↔	NA
		Goebel et al 2013[118]	Inhalation of deoxygenated air (FiO_2 0.10)	↑	↑
		Yang et al 2020[119]	High altitude	↓	NA
		Yuan et al 2021[120]	High altitude	↓	NA
	↓	Wright et al 2017[121]	Commencement of pulmonary vasodilator therapy in patients with PH	↑	NA
		Sunbul et al 2015[122]	Pulmonary endarterectomy in patients with CTEPH	↑	NA
Heart rate	↑	Yuchi et al 2022[123]	Canine model, heart rate increased by right atrial pacing	↔	↑
		Terlizzi et al 2022[124]	Increasing heart in patients with implanted pacemakers	↑	NA
Contractility	↑	Yang et al 2010[125]	Dobutamine infusion	↔	↑
			Dynamic exercise	↑	↑
		Schlangen et al 2014[114]	Dobutamine infusion	↔	↑

↑ = significant improvement in strain/strain-rate, ↓ = significant impairment in strain/strain-rate, ↔ = no significant change in strain/strain-rate, NA = data not available or not investigated in paper. RV = right ventricular, NaCl = sodium chloride, FiO_2 = fraction of inspired oxygen, PH = pulmonary hypertension, CTEPH = chronic thromboembolic pulmonary hypertension. All studies conducted in humans unless stated.

2.10.2 Afterload and RV-STE

The RV does not tolerate acute increases in RV afterload (section 1.2.6), it might therefore seem logical that RV-STE would become impaired with increasing RV afterload. Patients with pulmonary hypertension (PH) secondary to chronic thromboembolic pulmonary hypertension (CTEPH), and therefore raised RV afterload, have been shown to have impaired RVGLS[122]. In healthy subjects, acutely increasing pulmonary pressures via hypoxia induced pulmonary vasoconstriction has been induced in two ways experimentally; via inhalation of deoxygenated air (FiO_2 typically 0.1-0.15), and through exposure to acute altitude. Studies using acute inhalation of deoxygenated air have demonstrated an acute rise in pulmonary pressures, with either no change in RVFWLS or RVGLS[116,117], or a small but significant increase (i.e. more negative) in RVFWLS[118] (Table 2-2).The improvement in RV-STE associated with hypoxic breathing in healthy volunteers may be due to the hypoxic vasoconstriction induced increase in RV afterload and associated Anrep effect increasing contractility (which would be an anticipated response in the healthy RV)[48]. Acute altitude in healthy subjects has also been shown to be associated with increased pulmonary pressures, however this has been found to be associated with impaired RVGLS[119,120]. It is important to note that altitude has cardiovascular effects beyond increasing RV afterload, such as a decrease in plasma volume with reduced RV preload. A reduction in preload may contribute to the observed acute impairment of RVGLS at high altitude in addition to increased RV afterload[126].

Fewer studies have investigated the effect of a reduction in RV afterload on RV-STE. A study in patients with PH demonstrated that after commencing pulmonary vasodilator therapy, pulmonary pressures fell, RVFWLS significantly improved, and this was associated with enhanced RV-PA coupling[121]. Patients with CTEPH who have undergone pulmonary endarterectomy have similarly been shown to experience an improvement in RVGLS postoperatively following the reduction in RV afterload[122].

Overall, the above evidence suggests that RV-STE is a dependent on preload and afterload. Load dependence is not unique to RV-STE, as discussed in section

1.3.4, and the conventional RV echocardiography parameters (TAPSE, RVFAC, S', and RIMP) have all been shown to be load dependent[61,65,67,113].

2.10.3 Heart rate and RV-STE

The effect that heart rate (HR) has upon RV-STE has received little investigation. The few recent studies that have examined this have used pacemaker devices to alter heart rate (rather than using pharmacological agents which often have an inotropic effect in addition to chronotropy). A recent study in canines using incremental increases in heart rate via right atrial pacing demonstrated no significant change in RVFWLS or RVGLS, although RVGLS-rate increased significantly at higher heart rates[123]. Similarly, a small study in sheep demonstrated a trend towards increased RVGLS-rate when ovine heart was paced at higher frequencies[115]. In humans only one study has been performed to examine the effects of heart rate on RV-STE, investigating patients with chronic heart failure who had pacing devices in situ. In this study a small but significant improvement was observed in RVFWLS and RVGLS as heart rate was incrementally increased from 60 to 90 beats per minute, RVFWLS-rate and RVGLS-rate were not examined[124]. A reason for the improved RVFWLS/RVGLS observed with increased HR could be explained by the Bowditch effect (section 1.2.5)[127]. A subset of patients experienced a deterioration in RVFWLS and RVGLS at higher heart rates. Of note these patients had significantly more impaired LVGLS with higher pulmonary pressures at baseline, compared to patients that experienced no-change or an improvement in RVFWLS/RVGLS at higher heart rates. This suggests that LV failure and associated increase in RV afterload may have contributed to the deterioration in RVFWLS/RVGLS in these patients.

2.10.4 Contractility and RV-STE

Studies investigating the effects of contractility upon RV-STE have used inotropic infusions or dynamic exercise to increase contractility. An early stress echocardiography study by Yang et al investigated the effect of dobutamine infusion compared to dynamic exercise on RV-STE (Table 2-2)[125]. This study showed a similar increase in RVEF in both dobutamine and exercise groups, with a significant increase in heart rate in both groups (with dobutamine provoking a slightly higher increase in HR compared to exercise). Dobutamine did not cause any significant change in RVFWLS, however exercise caused a significant increase (i.e. became more negative) in RVFWLS (mid and basal segments, apical segment not reported). In both dobutamine and exercise groups, a significant increase in RVFWLS-rate was observed. This data could suggest that RVFWLS-rate is identifying the increase in contractility and/or HR associated with dobutamine infusion and exercise, whereas increasing RVFWLS possibly reflects changes in venous return and RV preload associated with dynamic exercise (described further below).

Schlangen et al performed a more recent study in patients with hypoplastic left heart syndrome investigating the effects of dobutamine infusion (and preload, as described above in section 2.10.1) on RV-STE[114]. They demonstrated that dobutamine caused no significant change in RVGLS, but significantly increased RVGLS-rate. An acute reduction in preload was associated with impaired RVGLS, but no effect on RVGLS-rate. Additionally, RVGLS did not correlate with RV end-systolic elastance (E_{es}, a load independent measure of RV contractility, see section 1.2.7), whereas RVGLS-rate significantly correlated with E_{es}. Schlangen et al's findings support those of Yang et al, suggesting that RVGLS is sensitive to changes in preload, whereas RVGLS-rate may be an important load independent index of contractility. Animal studies have shown similar results, with dobutamine inducing a significant increase in RVGLS-rate from baseline, and esmolol decreasing RVGLS-rate from baseline[115].

In summary, based off the small body of research described, it would appear that changes in preload and afterload are identified by RV strain, with a lesser effect on RV strain-rate (Table 2-2). Changes in heart rate appear to influence both RV strain and RV strain-rate. Alterations in contractility appear to only

affect RV strain-rate. The possible load independence of RV strain-rate (compared to RV strain) may represent a unique and useful characteristic for exercise studies. Dynamic exercise may result in alterations of preload, afterload, heart rate, and contractility. The measurement and definitions of exercise intensity are described below, followed by a discussion about studies that have investigated the effect of dynamic exercise upon RV-STE. This will lay the foundation for the scientific investigation in Chapter 6, where the effects of lung resection upon RV-STE during exercise stress echocardiography are explored.

2.10.5 Exercise and RV-STE

2.10.5.1 The cardiovascular system response to dynamic exercise

As the body undergoes dynamic exercise (exercise that involves movement of the limbs with rhythmic contraction and relaxation of the muscles), a number of physiological changes occur in the cardiovascular system. The oxygen requirement of skeletal muscle increases as it metabolises adenosine triphosphate, resulting in kinetic and thermal energy. The oxygen delivery by the cardiovascular system must increase to meet this requirement[128]. Cardiac output by the RV increases 4-6 fold during strenuous exercise (with a concomitant increase in minute ventilation), increasing the delivery of oxygenated blood to the systemic circulation[44]. As dynamic exercise is commenced there is an increase in heart rate and contractility, resulting in an increase in cardiac output. The ability of the RV to increase its output when exercising is termed “RV contractile reserve”[129]. Due to the increase in blood flow through the pulmonary vascular bed, there is an acute rise in pulmonary pressures (RV afterload), which is blunted by pulmonary vasodilation[130]. These mechanisms, and the use of RV-STE to measure these effects are described below.

2.10.5.2 Effects of dynamic exercise on RV preload, afterload, heart rate and contractility

Dynamic exercise increases venous return to the RV. During dynamic exercise two pump systems are activated; the skeletal muscle pump which increases

venous return by the compression of veins during skeletal muscle contraction, and the respiratory pump which facilitates venous drainage from the abdomen to the thorax during inspiration via increased negative intrathoracic pressure combined with increased intrabdominal pressure from diaphragm flattening[131]. Additionally there is venoconstriction of splanchnic and hepatic capacitance vessels (mediated via the sympathetic nervous system) further enhancing venous return[132].

Although RV venous return increases during dynamic exercise, preload may not increase during exercise due to the increase in stroke volume (resulting in a reduced RV end systolic volume and therefore less residual blood that can be added to during diastolic filling), and increase in heart rate (resulting in a reduced length of diastole for RV filling). Exercise studies with healthy subjects have shown a slight decrease in RV preload (measured using RVEDV as a surrogate) during dynamic exercise[129,133]. Importantly some studies have shown an increase in RVEDV (possibly as a result of uncoupled RV contractile reserve in susceptible populations) upon exercising in patients post lobectomy[134], patients with mixed PH[135], and patients with CTEPH[129].

After commencing dynamic exercise, the increased blood flow in the face of unchanged pulmonary vascular resistance results in an acute rise in pulmonary pressures (which is mitigated via pulmonary vasodilation, termed the pulmonary vascular reserve[129]). The increase in pulmonary artery pressure represents an increase in RV afterload[117,136,137].

Exercise also induces an increase in heart rate. This is predominantly mediated by increased activity of the sympathetic nervous system, and inhibition of the parasympathetic nervous system[44]. During exercise, increased activity of the sympathetic nervous system induces increased contractility of the heart directly via noradrenaline release at sympathetic nerve terminals, and indirectly via release of adrenaline from the adrenal gland[44].

The overall effect of dynamic exercise upon RV strain and RV strain-rate will depend on the relative contributions to the changes in loading conditions, heart rate, and contractility. At low to moderate intensity exercise, increased cardiac output is thought to be due to a combination of the increases in preload, heart

rate, and contractility. However at moderate to high intensity exercise, typically 50-60% maximal oxygen consumption, stroke volume plateaus, and further increases in cardiac output are due to increases in heart rate[128]. Measurement and definitions of exercise intensity are described below, followed by a discussion about studies that have investigated the effect of dynamic exercise on RV-STE.

2.10.5.3 Exercise intensity

As a patient commences exercise, several physiological changes occur in the cardiovascular system which can be used as surrogates for intensity of exercise. Cardiopulmonary exercise testing (CPET) invasively measures markers of aerobic (and anaerobic) respiration, such as the rate of maximal oxygen consumption (VO_2max) as a measure of exercise intensity. Whilst CPET gives a detailed and comprehensive assessment of the cardiovascular changes during exercise, it is not feasible in all patients due to its many absolute and relative contraindications[138]. A commonly used measure of exercise intensity is heart rate, or more specifically the percentage of age predicted maximal heart rate (ppHRmax). A linear relationship between ppHRmax and VO_2max has been demonstrated[139], it is therefore a practical parameter that can be used in patients to estimate intensity of exercise. Since 1990 the America College of Sports Medicine have (recurrently) recommended ppHRmax as a measure of exercise intensity to guide training in patients and athletes (Table 2-3)[140]. ppHRmax has been used in many previous studies to investigate the relationship between exercise intensity and RV-STE[141-143].

Table 2-3 Measures of exercise exertion

Exercise intensity	ppHRmax (%)	%VO_2max	Perceived exertion
Very light	<57	<37	Very light
Light	57-63	37-45	Very light-fairly light
Moderate	64-76	46-63	Fairly light to somewhat hard
Vigorous	77-95	64-90	Somewhat hard to very hard
Near maximal to maximal	≥96	≥91	Very hard

America College of Sports Medicine recommended measures of exercise exertion. ppHRmax = percentage predicted maximal heart rate, %VO_2max = percentage of rate of maximal oxygen consumption. Table redrawn using data from Garber et al[140].

2.10.5.4 Exercise studies and RV-STE

Studies that have investigated the effects of dynamic exercise upon RV-STE can be divided into those that have used healthy subjects and those in patients with disease states. The most common form of dynamic exercise used has been cycling ergometry[117,141,144-147], with fewer studies using treadmill exercise[137,148,149]. Most studies have performed TTE during exercise, with a smaller number performing echocardiography immediately after cessation of exercise[137,149].

2.10.5.5 Exercise studies in healthy subjects and RV-STE

Early dynamic exercise investigations in healthy subjects produced mixed findings. Initial studies with small numbers of participants identified that RVFWLS and RVGLS became less negative (i.e. more impaired) during exercise[141,148]. Recent larger studies have demonstrated a small but significant improvement in RVFWLS when exercising (Figure 2-14A)[117,136,137,142-144]. It is remarkable that two studies, Chia et al (the largest RV-STE exercise study in healthy subjects, with 121 participants) and Stewart et al, found identical changes in RVFWLS during exercise (-27.3% at rest, -28.4% during exercise for both studies) despite using different exercise protocols (recumbent cycling ergometry and treadmill exercise respectively), suggesting that a small improvement in RV strain is a robust finding[137,144]. Fewer studies have investigated RV strain-rate, but they have all shown an increase in RV strain-rate during dynamic exercise[136,144].

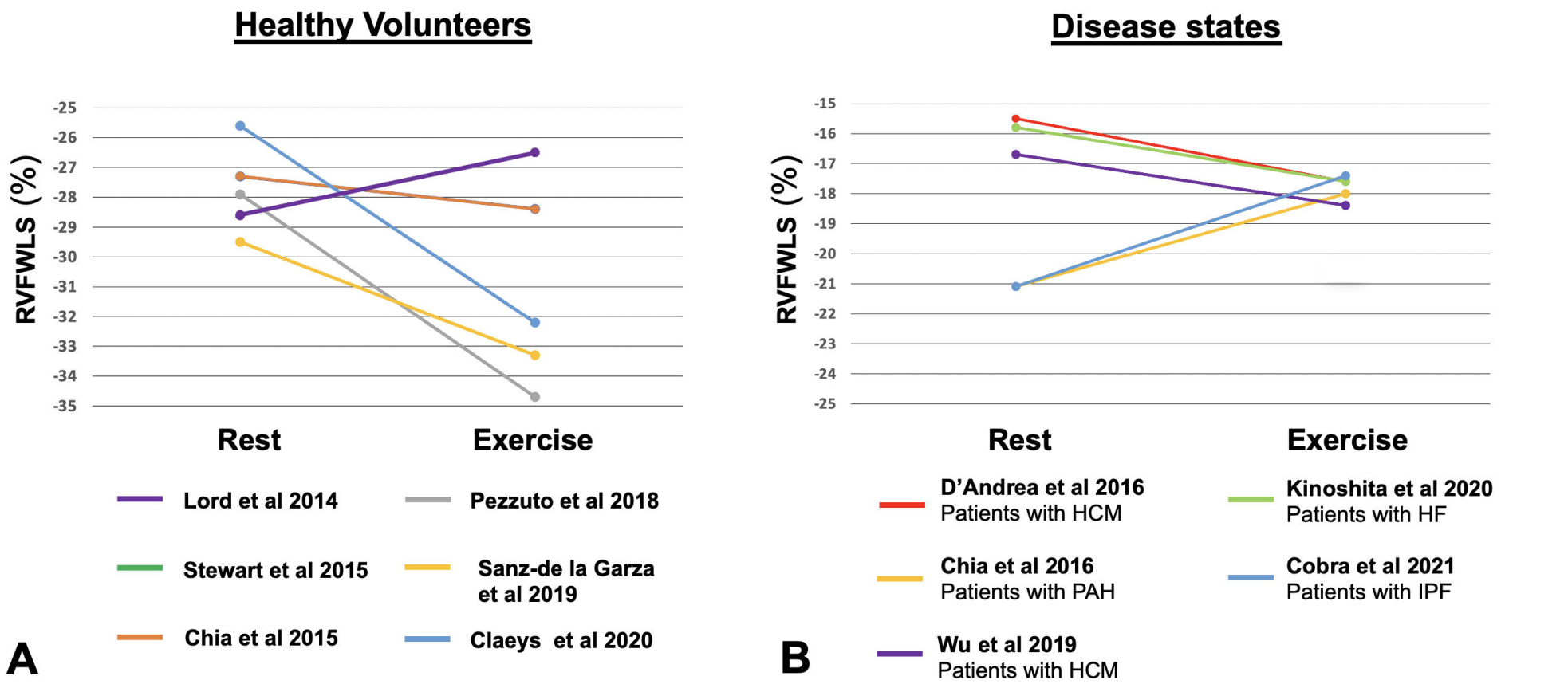


Figure 2-14 Overview of the change in RVFWLS during exercise
A. Mean RVFWLS at rest and during exercise for respective studies are presented. Healthy volunteers undergoing dynamic exercise have been shown to have a small but consistent improvement (i.e. becomes more negative) in RVFWLS. Note that Chia et al and Stewart et al reported identical RVFWLS values at rest and during exercise, their lines therefore overlap. **B.** Mean RVFWLS at rest and during exercise for respective studies are presented. Patients experiencing cardiovascular disease states demonstrate a blunted response to exercise, with RVFWLS either improving slightly, or deteriorating (i.e. becoming less negative) during exercise. **Note that the range of RVFWLS values on the y axis are different for the healthy volunteer and disease state graphs.** RVFWLS = right ventricular free wall longitudinal strain, HCM = hypertrophic cardiomyopathy, HF = heart failure, IPF = idiopathic pulmonary fibrosis, PAH = pulmonary arterial hypertension. Studies included in this figure: Lord et al[141], Stewart et al[144], Chia et al 2015[137], Sanz-de la Garza et al[143], Claeys et al[136], Pezzuto et al[117], D'Andrea et al[150], Kinoshita et al[146], Wu et al[145], Cobra et al[147], Chia et al 2016[149].

2.10.5.6 Exercise studies in the context of disease states and RV-STE

Exercise studies in disease states examining RV-STE have investigated patients with pulmonary arterial hypertension (PAH) and patients with cardiac disease. In 2016, Chia et al compared the effects of dynamic exercise on RV-STE between patients with systemic sclerosis (who had normal PA pressure), patients with PAH (of mixed aetiology), and healthy controls[149]. They found that RVFWLS became more negative during exercise in both healthy controls and patients with systemic sclerosis, however in patients with PAH RVFWLS deteriorated, becoming less negative during exercise (Figure 2-14B). There was no difference when comparing the change in RVFWLS during exercise between patients with systemic sclerosis and healthy controls, however there was a difference between the change in RVFWLS-rate during exercise, with healthy controls experiencing a significant increase in RVFWLS-rate compared to patients with systemic sclerosis. The authors suggest that RVFWLS-rate can detect subtle dysfunction in RV contractile reserve in patients with systemic sclerosis, which RVFWLS cannot. The observation that RVFWLS deteriorates after commencing dynamic exercise in patients with PH (secondary to idiopathic pulmonary fibrosis) was replicated in a more recent study by Cobra et al 2021, they did not describe RVFWLS-rate[147].

Two studies have examined the effects of dynamic exercise on RVFWLS in patients with hypertrophic cardiomyopathy (HCM). D'Andrea et al[150] and Wu et al[145] both found that patients with HCM have impaired RVFWLS at baseline, and when exercising there was a small improvement in RVFWLS (but less improvement than that seen in healthy controls) (Figure 2-14B). Wu et al also reported RVFWLS-rate, and found that RVFWLS-rate increased in healthy subjects, and that the increase in RVFWLS-rate was impaired in patients with HCM (representing impairment of RV contractile reserve). A more recent study by Kinoshita et al investigated patients admitted to hospital with heart failure (either decompensated chronic heart failure or acute heart failure)[146]. All patients with heart failure had impaired RVFWLS at baseline. They divided patients into those with preserved VO_2max (≥14ml/kg/min) and low VO_2max (<14ml/kg/min). Patients with preserved VO_2max demonstrated a significant improvement in RVFWLS when performing light dynamic exercise compared to

patients with low VO_2max (who experienced no change in RVFWLS when exercising compared to baseline). Of note patients with low VO_2max had significantly higher pulmonary pressures compared to patients with preserved VO_2max. This data would support the findings described by Chia et al and Wu et al in patients with PAH and HCM[147,149]; RVFWLS appears particularly susceptible to impairment/deterioration during dynamic exercise in patients with heart failure.

In summary, in healthy subjects RV strain and RV strain-rate appear to improve (i.e. become more negative) during dynamic exercise, although it must be noted that the improvement in RV strain during exercise appears to be small. Upon exercise, patients with pulmonary vascular and cardiac disease may not demonstrate physiological enhancement in RV function (as detected using RV strain and particularly RV strain-rate) possibly indicating impaired RV contractile reserve.

2.11 The role of RV-STE analysis outside of ICU and the perioperative period

The role of RV-STE analysis outside of ICU and the perioperative period has received much attention over the past 20 years. RV-STE analysis has been thoroughly studied within the clinical specialities of cardiology and pulmonary vascular disease. RV-STE has been shown to significantly correlate with gold standard CMR RVEF in patient populations with chronic heart failure[151] and pulmonary hypertension[152]. RV-STE has also been shown to be an independent predictor of mortality in patients with ischaemic heart disease[153], chronic heart failure[154], and pulmonary hypertension[155]. The role of RV-STE analysis in ICU and the perioperative period has received comparatively little investigation, representing an area for further research.

2.12 Conclusion

Strain analysis using RV-STE is becoming a well-established measure of RV systolic function, having superseded tissue doppler imaging strain analysis. RV-STE of the free wall (RVFWLS) is likely the method most representative of RV function, and peak systolic strain is recommended as the optimal time in the cardiac cycle for strain reporting. Strain values are subject to variations depending on the strain software used. Current data suggests that for Tomtec software (the software that will be used in the scientific investigations in Chapters 5 and 6), a cut-off for RVFWLS of > -20% (i.e. less negative than -20%) represents abnormal RV function. When investigating changes in RV function during states of increased inotropy (such as during exercise or dobutamine infusion), it appears that measurement of RV strain-rate is particularly important, with RV strain-rate possibly identifying changes in RV contractility independent of loading conditions. The important effects that echocardiography study image quality may have upon RV-STE strain feasibility and reproducibility has not been studied, this thesis will also aim to address this knowledge gap.

As described above, RV-STE analysis in patient populations in ICU and the perioperative period has received little attention. It is therefore the aim of this thesis to investigate the role and utility of RV-STE within ICU and the perioperative period. Chapter 3 will first outline the definition and components

that contribute to clinical utility of a diagnostic measure, laying a framework for the assessment of utility. A literature review will be performed in Chapter 4 to outline the current knowledge basis with regards the utility of RV-STE in ICU and the perioperative period. Chapters 5 and 6 will then investigate the utility of RV-STE in ICU and perioperative patient populations respectively.

Chapter 3 The utility of a diagnostic measure

3.1 Introduction

To assess the utility of RVFWLS in ICU and the perioperative period, we must first consider what is meant by the term "utility". To assess utility, different characteristics of a diagnostic measure need to be investigated. The Consensus based Standards for the selection of health Measurement INstruments (COSMIN) initiative states that "the evidence of the quality of the outcome measurement instrument" (i.e. the utility of a diagnostic measurement) can be examined by assessing the measurement instrument's "reliability [/reproducibility], validity…, as well as aspects of feasibility"[156]. Rubenfeld et al similarly state that "the quality of diagnostic criteria is judged by three measures: feasibility, validity, reliability [/reproducibility]"[157]. Assessing the feasibility, reproducibility, and validity of a diagnostic measurement or test allows us to gauge its overall utility in a particular setting. Feasibility pertains to how easy it is to perform the test and obtain a result, reproducibility describes how reliable the acquired result is when retested, and validity represents how well the test measures what it purports to measure. These three aspects of utility will be described in greater detail, and will give a framework to assess the utility of RV-STE in ICU and the perioperative period throughout the thesis.

3.2 Feasibility

The feasibility of an echocardiography measurement can be defined as the proportion of echocardiography studies that have adequate image quality to allow interpretation of the measurement of interest compared to the total number of echocardiography studies performed[158,159]. The resulting feasibility is often quoted as a percentage. The feasibility of RV-STE analysis for a research study therefore would be:

$$\frac{\text{Number of echocardiography studies of adequate image quality for RV-STE analysis}}{\text{Total number of echocardiography studies}}$$

There remains some contention as to what represents the minimum quality of an echocardiography study for reliable RV-STE analysis. Gold-standard echocardiography images for RV-STE require that all RV segments (three free-wall segments for RVFWLS, and all six RV segments for RVGLS) are visualised and tracked by the speckle-tracking software throughout the cardiac cycle. For RVFWLS, EACVI/ASE consensus guidelines and BSE guidelines advocate only using echocardiography images that demonstrate adequate speckle-tracking of all three RV free-wall segments[65,85]. However, as will be demonstrated in Chapter 4 (section 4.1.3.1) not all research studies will adhere to this gold-standard, and research studies may accept RV-STE analysis of an echocardiography study with images that have missing RV segments, which will improve the feasibility of RV-STE they report compared to if they had only accepted images that had all RV segments with adequate speckle tracking. For RV-STE to have high feasibility is desirable, with fewer patients' echocardiography studies needing to be excluded from a research study, however including poorer quality echocardiography images with inadequately tracked RV segments may affect the RV-STE values reported and the reproducibility of RV-STE analysis. In Chapter 4, a literature review will be conducted to investigate the variation in quality of echocardiography images that research studies have deemed acceptable for RV-STE analysis, and to investigate factors that affect RV-STE feasibility in ICU and the perioperative period. The effect that image quality has upon RV-STE values and reproducibility will be investigated in all the clinical studies within Chapters 4, 5 and 6.

3.3 Reproducibility

The reproducibility of an echocardiography measurement refers to the "variation of the same measurement made on a subject under changing conditions"[160]. A change in time or the observer reporting the measurement can represent a change in condition for that reported measurement. When the measurement of a variable from the same study is re-reported by the same reporter at a different time, reproducibility (also called repeatability in this setting[161]) is a measurement of the intra-observer variation in the reported results. When the measurement of a variable from the same study is re-reported by a different reporter, reproducibility is a measure of the inter-observer variation. There are different methods for assessing reproducibility, however before these are described a number of terms need to be considered; accuracy, precision, agreement, and correlation.

3.3.1 Reproducibility terms

Accuracy refers to how close re-reported values are overall to the originally reported set of values[162] (Figure 3-1). Accuracy also introduces us to the concept of systematic bias, for example where the one reporter might be consistently reporting higher values than the other. This can be visually represented, as seen in Bland-Altman plots (Figure 3-2B).

Precision refers to the variability or spread of re-reported values around the originally reported set[162]. Reproducibility with high precision will have a narrow spread of re-reported values. Note that precision and accuracy refer to different aspects of reproducibility. Both accuracy and precision of reproducibility are desirable, however inaccuracy can be present but with precision, and imprecision can be present but with accuracy (Figure 3-1).

Agreement is defined as "how close two measurements are from one another when on the same scale"[160], incorporating both accuracy and precision.

Correlation describes the extent which two variables are linearly associated (i.e. they vary at a constant rate). This is not the same as agreement between values, since correlated values may be different but share the same linear

relationship[163]. Correlation in isolation is an inappropriate measure for assessing reproducibility and will not be considered further in this context.

Three commonly used methods for assessing reproducibility will now be considered, which examine different aspects of reproducibility. These are the co-efficient of variation, intraclass correlation co-efficient (ICC), and Bland-Altman plots.

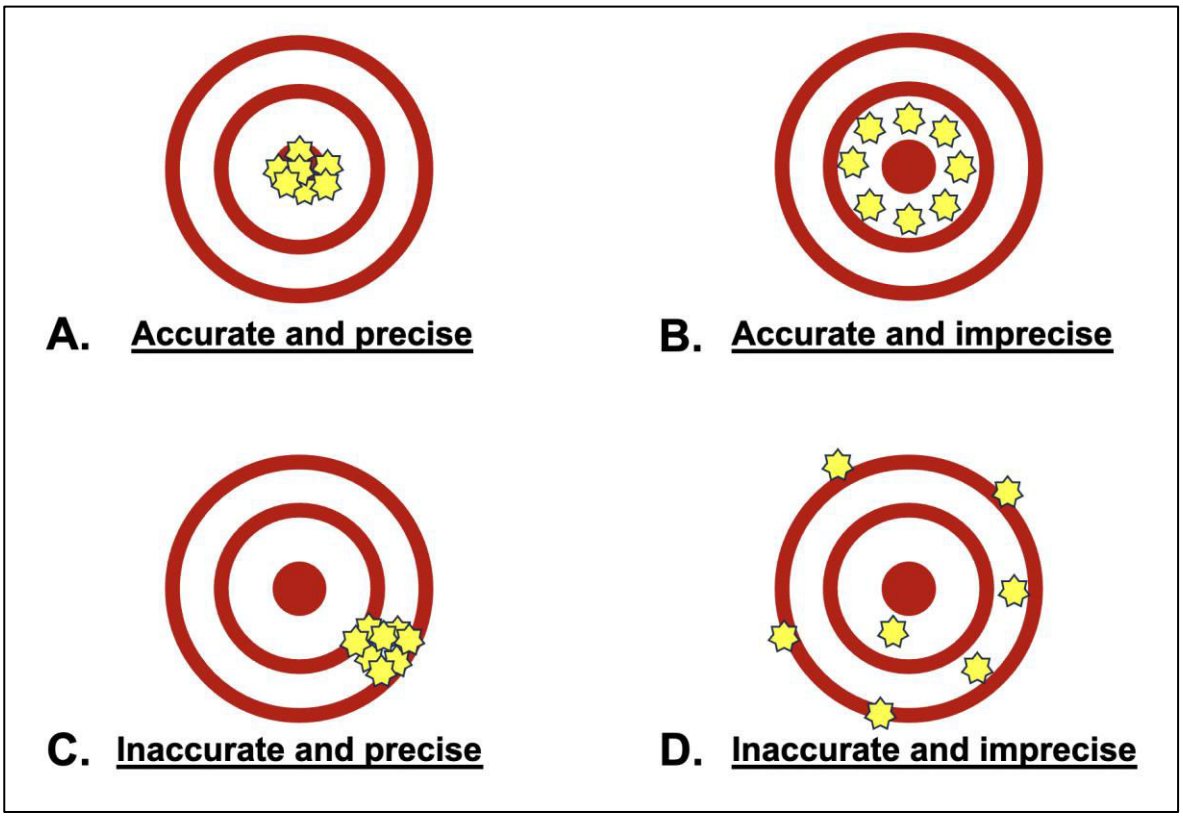


Figure 3-1 Accuracy and precision
Diagrammatic representation of accuracy and precision using a bull's eye analogy. If we consider inter-observer reproducibility, the overall value reported by the first reporter would represent the Bull's eye, and the "shots" around the Bull's eye would be the second reporter's values. **A.** This demonstrates accurate and precise re-reported values, which are closely bunched around the value reported by the first reporter. **B.** This demonstrates re-reported values that are accurate (in that an "average" shot would lie in the Bull's eye), but imprecise compared to the originally reported value. **C.** This demonstrates inaccurate re-reported value, which all lie far away from the Bull's eye, but with good precision since all re-reported values are tightly bunched. **D.** This demonstrates both inaccurate and imprecise re-reported values. Image redrawn from Cecconi et al[162].

3.3.2 Methods of assessing reproducibility

3.3.2.1 Co-efficient of variation

The co-efficient of variation (CoV) is a measure of precision, it describes variability, accounting for the size of the data set by comparing the standard deviation with the mean[164]:

$$Co\,efficient\ of\ variation\ (\%) = \frac{Standard\ deviation}{Mean} x\ 100$$

When the CoV is used to assess reproducibility, it is a measure of the variability of the difference between repeated measures (Table 3-1). It is important to highlight that while precision of repeated measures is desirable, it does not necessarily equate to agreement. It is therefore important that the CoV is not used in isolation, and should be used with another form of agreement analysis (e.g. Bland-Altman or ICC).

Table 3-1 Interpretation of measures of reproducibility

Co-efficient of variation (%)	Intraclass correlation co-efficient	Interpretation
>15	<0.5	Poor
10-15	0.5-0.75	Acceptable/Moderate
<10	0.75-0.9	Good
	>0.9	Excellent

Adapted from Holm et al[165] and Koo et al[166].

3.3.2.2 Intraclass correlation co-efficient

The ICC is a measure that describes both the agreement and correlation of repeated measurements. There are many forms of ICC, which can be divided into those that measure agreement and those that measure consistency. As described by Koo et al, the definition of agreement "concerns if different raters assign the same score to the same subject", whereas the definition of consistency "concerns if raters scores to the same group of subjects are correlated in an additive manner"[166]. A simple mathematical model to describe the difference between consistency and agreement would be the relationship between a first reporter's values (x), and a second reporter's values (y). Consistency describes how one reporter equates their values with the other with a systematic bias (i.e. $y = x + c$), whereas agreement describes how closely y is

directly equal to *x*. When re-reporting echocardiography measurements using a sample from the original set of subjects and comparing the results between a single observer or between two observers, it is appropriate to use ICCs measuring absolute agreement rather than consistency. ICCs are reported as a value between 0-1, with higher values indicating better agreement (Table 3-1).

3.3.2.3 Bland-Altman plot

The Bland-Altman plot is a graphical depiction of intra-observer/inter-observer agreement. It is a scatter plot where the mean of the two reported values is plotted against the X axis, and the difference between the two values is plotted against the Y axis (Figure 3-2A). This allows visualisation of three properties of data reproducibility. The mean difference line represents the mean difference in reported values between a first reported value and a second reported value (which may be by the same person or a different person), summarising the overall bias between the observer(s). The mean difference gives an indication of the accuracy of re-reported measurements[162]. Figure 3-2B demonstrates a Bland-Altman plot where a first reporter consistently reports more positive RVFWLS than a second reporter. The limits of agreement (LOA) show the 95% confidence interval of the scatter in data around the mean difference. LOAs give an indication of the precision of re-reported values[162]. Finally, the data points themselves can be visually inspected for outliers, bias, and differences in reproducibility as the measured values get larger or smaller (e.g. do both observers have good agreement with regards an echocardiography measurement when RV function is impaired, but poorer agreement when RV function is normal, as shown in Figure 3-2D). The importance of visualizing the Bland Altman plot is apparent when we consider that Figure 3-2A (with little bias), and Figure 3-2C (with proportional bias), and Figure 3-2D (with good agreement when RV function is impaired but poorer agreement when RV function is better) all have the same mean difference and LOAs, the scatter of the data must be observed to appreciate when proportional bias is present and differences in agreement as RVFWLS varies.

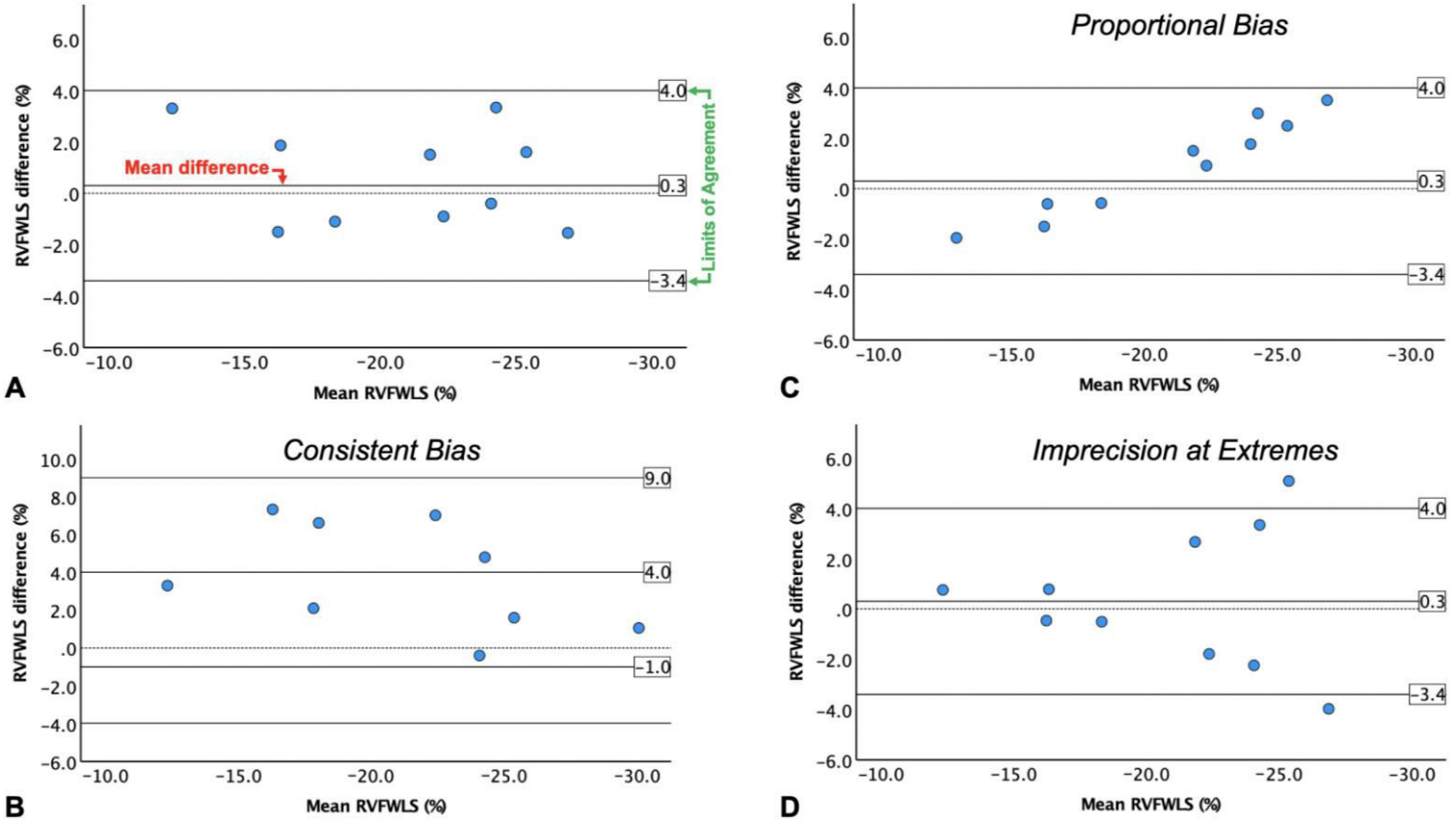


Figure 3-2 Bland Altman plots

A. Example of a Bland Altman plot, comparing agreement between two reporters of RVFWLS. The two reporters report a RVFWLS value for a patient. The mean of these two values is plotted against the X-axis. The difference between the two reporters (Reporter 1 – Reporter 2) is plotted against the Y axis. The mean difference (shown in red), and limits of agreement (mean difference ±1.96SD, shown in green) are then plotted. **B.** An example of a consistent bias where Reporter 1 is consistently reporting more positive RVFWLS than Reporter 2, demonstrated by a mean difference of +4%. **C.** An example of proportional bias where Reporter 1 initially reports more negative RVFWLS values, but as RVFWLS values get more negative, reporter 1 reports less negative RVFWLS values compared to Reporter 2[167]. **D.** An example where precision varies across RVFWLS values. In this example both reporters have good agreement at less negative RVFWLS values (representing poorer RV function), but have poor agreement at more negative RVFWLS values (when RV function is better). RVFWLS = right ventricular free wall longitudinal strain, RV = right ventricular. All data in this figure is factitious. Figure drawn by the author using IBM SPSS.

3.4 Validity

An important concept when assessing the utility of a new diagnostic test is to consider its validity. Validity has been defined in many ways, in 2003 Rubenfeld et al gave the definition [157]:

> *"Validity is defined as the ability of a test or definition to capture what the investigator truly seeks to measure"*

Seven years later this definition was further refined. As part of the COSMIN initiative, a study was undertaken to identify the key measurement properties that are relevant for assessing a new medical diagnostic test, and to establish a consensus on the terminology and definitions used when describing these measurement properties. Forty-three experts from across the world (with backgrounds in statistics, epidemiology, psychology, and clinical medicine) participated in this study using a Delphi method. The agreed upon definition of validity was:

> *"The degree to which an instrument measures the construct(s) it purports to measure"*[168]

This definition introduces an important concept, that of the "construct" (described in further detail below). The COSMIN study further described and defined many concepts that relate to validity, including its subtypes, and this study has been used as the basis for the description of validity testing described in this thesis. The importance of the validity of a test has been recognised by the disciplines of the social sciences, particularly psychology, and even branches of philosophy. The need to establish validity for a diagnostic test is gaining appreciation in the field of medicine. Several validity subtypes have been recognised, again the definitions and meanings of these have been subject to debate over the years, with the COSMIN initiative providing consensus. The three broad subtypes of validity are: content validity (which includes face validity), criterion validity (including concurrent and predictive validity), and construct validity (see Table 3-2 for an overview).

Table 3-2 Validity subtypes

Validity Subtype	Subdivision	Definition
Content Validity		The degree to which the content of an instrument is an adequate reflection of the construct to be measured.
	Face Validity	The degree to which (the items of) an instrument indeed looks as though they are an adequate reflection of the construct to be measured.
Criterion Validity		The degree to which the scores of an instrument are an adequate reflection of a ‘‘gold standard’’.
	Concurrent Validity*	The degree to which an instrument score agrees with the “gold standard” when measured at the same time.
	Predictive Validity*	The degree to which an instrument is able to predict the score for the “gold standard” measurement in the future.
Construct Validity		The degree to which the scores of an instrument are consistent with hypotheses (for instance with regards to internal relationships, relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the instrument validly measures the construct to be measured.
	Structural Validity	The degree to which the scores of an instrument are an adequate reflection of the dimensionality of the construct to be measured.
	Hypothesis testing	Idem [i.e the same as] construct validity.
	Cross cultural Validity	The degree to which the performance of the items on a translated or culturally adapted instrument are an adequate reflection of the performance of the items of the original version of the instrument.

* concurrent and predictive validity were not included in the original table and have been added. Table redrawn from Mokkink et al[156].

A key premise that underpins the assessment of validity is the conceptualisation of a construct model, and this needs to be established before attempting to assess for the various subtypes of validity. The first term that needs to be defined is “construct”, a construct is essentially what we wish to measure with our diagnostic test. A more elaborate definition is:

> “A well-defined and precisely demarcated subject of measurement.”[168]

Constructs can vary in their degree of complexity. If we wish to measure blood pressure, the construct could simply be the systolic/diastolic blood pressure, and this would represent a one-dimensional construct. However, if we wish to measure cardiovascular health, this could encompass blood pressure, heart rate, cardiac function, exercise capacity, and many other variables. Cardiovascular health would therefore be a more complex multidimensional construct, and a diagnostic test would need to address these multiple dimensions. Once we have decided upon the construct we wish to measure, we can start to build a conceptual model for our construct. This model includes “items” that are related to the construct of interest. Two broad conceptual models exist, formative and reflective models.

The formative model involves the relationship between formative items that act upon and alter the construct, using the blood pressure (or more specifically hypertension) as our construct again, such formative items could include cigarette smoking, salt intake, endocrine pathology, and genetic predisposition resulting in raised blood pressure. The reflective model is one where reflective items are variables that are altered as a result of changes in the construct, these items could be hypertensive retinopathy, hypertensive nephropathy, and hypertensive cardiac hypertrophy that occur as a results of increases in blood pressure.

A conceptual model that fully explains the dimensionality of the construct we are interested in, that incorporates formative and reflective items, and an

understanding of the relationship between these items and the construct is key for testing validity. An example of a conceptual model for an instrument that measures RV function is shown in Figure 3-3, using a definition of RV function as described in section 1.2.10 as the construct. Now that a conceptual model has been described, we can assess the validity of the diagnostic measurement of interest. The subtypes of validity; content, concurrent, and construct validity are described below.

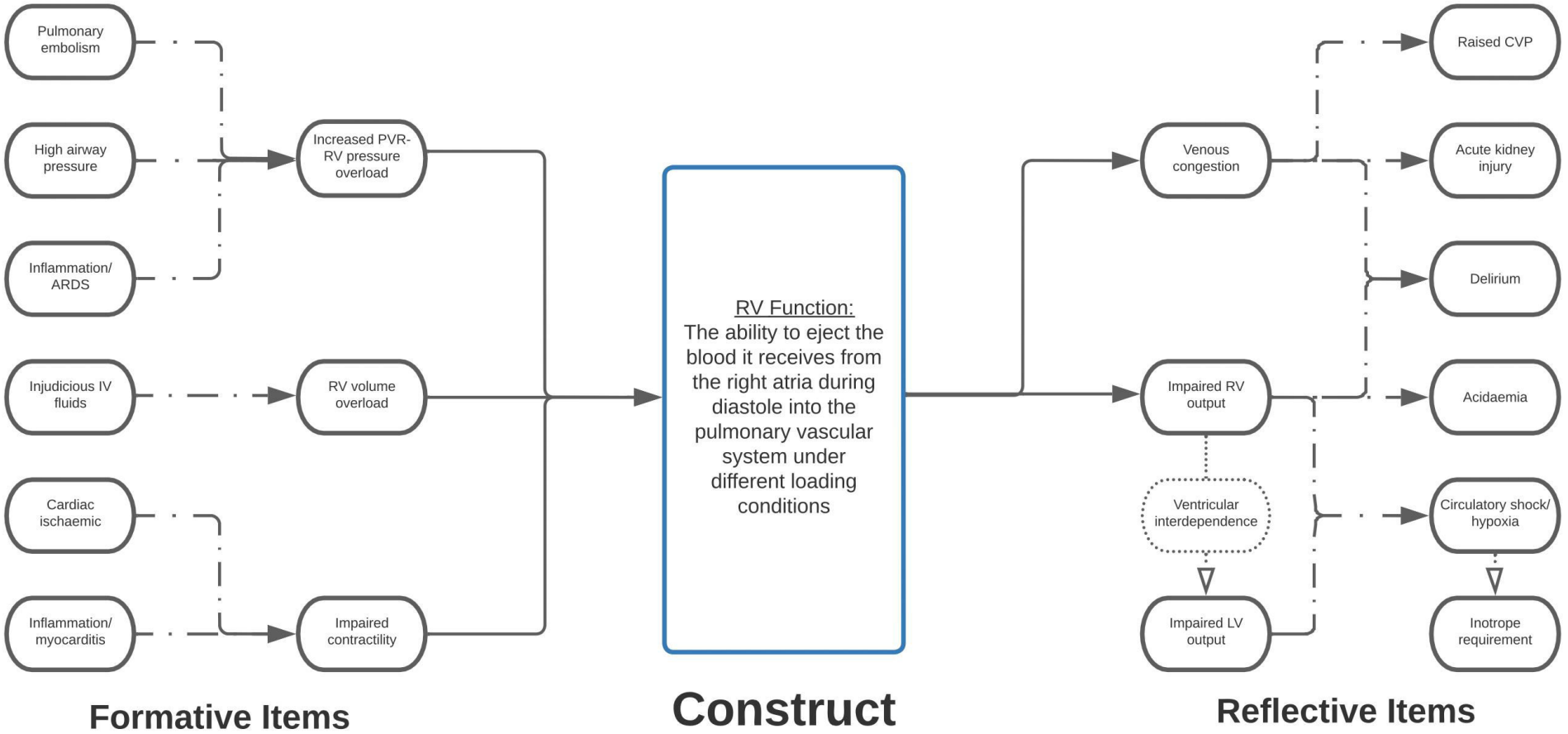


Figure 3-3 Conceptual model for assessing the construct validity of an instrument measuring right ventricular function in an ICU and perioperative context
Construct validity is assessed by examining the relationship between the construct (i.e. what the new tool purports to measure, in this case RV function) and formative and reflective items. Formative items are items that will impact upon the construct (e.g. pulmonary embolism impairing RV function), whereas reflective items will be impacted by changes in the construct (e.g. acute kidney injury occurring due to RV dysfunction). ARDS = acute respiratory distress syndrome, IV = intravenous, PVR = pulmonary vascular resistance, CVP = central venous pressure, RV = right ventricular. Image drawn by author.

3.4.1 Content validity

The COSMIN initiative gave content validity the definition of:

> *"the degree to which the content of a measurement instrument is an adequate reflection of the construct to be measured"*[168]

Content validity seeks to evaluate if a new diagnostic instrument can specifically measure all aspects of the construct to be measured. For a one-dimensional construct a simple diagnostic test may be adequate (e.g. a sphygmomanometer to measure blood pressure), whereas a more complex diagnostic test will be needed for multidimensional constructs. The diagnostic test needs to be both comprehensive and relevant to the construct it measures.

The first step in establishing content validity is to assess for face validity. Face validity concerns:

> *"the degree to which a measurement instrument, indeed, looks as though it is an adequate reflection of the construct to be measured"*[168]

Face validity of a new diagnostic test is a global and subjective assessment by the investigator(s) to decide if they believe that the new diagnostic test measures what it purports to measure. Lack of face validity is a robust screening test, and if it is felt a diagnostic test lacks face validity, it is often appropriate to not use the new test.

If it is believed that face validity exists for the new diagnostic test, we can then proceed with assessing content validity. Content validity begins with a complete description of the construct to be measured, including all its dimensions. We then consider the new diagnostic test, and assess the distinct aspects of its measurement (using a new questionnaire as an example, each question would be examined to see exactly what information it gathers). Then we match the distinct measurements of the new diagnostic test to the various dimensions of the construct that it is supposed to measure. For example, it would be desirable that a test measuring RV systolic function reflects global function, loading conditions, contractility, and RV-PA coupling. The two key principles of content

validity are that the new diagnostic test should be comprehensive in measuring every dimension of the construct, and that the new diagnostic test does not report information that is irrelevant or redundant to the construct of interest (i.e. the test should measure all dimensions of the construct required and nothing extra).

3.4.2 Criterion validity

Criterion validity is defined as

> *"the degree to which the scores of a measurement instrument are an adequate reflection of a gold standard"*[168]

It is reliant on a gold standard measure (the criterion) of the construct of interest existing. It is useful to define *a priori* an acceptable level of agreement between the gold standard and new measurement test which would allow us to deem the new measurement test as valid. Statistical methods to assess agreement include area under the receiver operated characteristic curves (AUROCC), ICCs, and Bland-Altman plots (as described above). Criterion validity is subdivided into concurrent validity and predictive validity depending on the temporal relationship between measurements from the new diagnostic test and the gold standard measurements, these are described below.

3.4.2.1 Concurrent validity

Concurrent validity describes the comparison between the new diagnostic measurement and the gold standard at the same time. For the new diagnostic test to have concurrent validity, it should be able to distinguish patients with the diagnosis of interest from those that do not (as diagnosed by the gold standard test). As described in section 1.3.6, many of the RV-STE validation studies to date have compared the discriminative ability of RVFWLS to identify patients with RVD diagnosed by gold standard non-invasive CMR. These studies have therefore been investigating the criterion validity of RVFWLS.

3.4.2.2 Predictive validity

Predictive validity described the ability of the new diagnostic test to predict the score for the gold standard measurement in the future. It also describes the ability of the new diagnostic test to predict an outcome of interest in the future compared to the predictive ability of the gold standard. An example of predictive validity given by one of the defining textbooks in the area, Measurements in Medicine, describes the validation of the European System for Cardiac Operative Risk Evaluation (EuroSCORE) as a predictor of in hospital mortality for patients undergoing open heart surgery [169 170]. These authors used AUROCC analysis (with an excellent discrimination score of 0.91, (95%CI 0.86–0.97) to demonstrate that the EuroSCORE was a strong predictor of mortality, and concluded that predictive validity had been demonstrated. Similarly, abnormal RVFWLS has been shown to be associated with mortality in patients with myocardial infarction, heart failure, and PH[90,91,171]. This demonstration of the predictive validity of RVFWLS supported the ASE/EACVI's decision to recommend the use of RVFWLS in consensus guidelines [62].

3.4.3 Construct validity

Construct validity relates to "the degree to which the scores of a measurement instrument are consistent with hypotheses, e.g. with regard to internal relationships, relationships with scores of other instruments or differences between relevant groups"[168]. Three types of construct validity exist: structural, hypothesis testing, and cross-cultural validity.

3.4.3.1 Structural validity

Structural Validity is defined as "the degree to which the scores of a measurement instrument are an adequate reflection of the dimensionality of the construct to be measured" [168]. There are obvious overlaps with content validity in that the new diagnostic test needs to comprehensively address each of the construct's dimensions. Structural validity takes this a step further, and analyses if all dimensions of the construct are being measured by the new diagnostic test using confirmatory factor analysis. This is commonly done for questionnaire

based diagnostic tests, where the diagnosis of interest (the construct) is broken down into its various dimensions (which are called factors), and each question is then assessed to see if it matches a factor. Structural validity is useful for psychological diagnostic tests, but less so for measuring physical parameters, it will therefore not be discussed further in this thesis.

3.4.3.2 Hypothesis testing

Hypothesis testing is the most important component of construct validity. It relies on a clear and comprehensive conceptual model that adequately describes the relationships between formative items (items that act upon the construct), reflective items (items that the construct acts upon) and the construct. Hypotheses are then generated about the expected relationships, and to see if these relationships are maintained in different situations. For example, does an increase in PVR that impairs RV function result in impaired RV-STE measurements (an example of the relationship of a formative item with the construct), or is impaired RV-STE associated with items that are affected by RV dysfunction, such as AKI (an example of a reflective item relationship with the construct)? This sort of hypothesis testing makes up a large proportion of the research that has been undertaken to date to investigate the validity RV-STE strain analysis. It is important to highlight that hypothesis testing is entirely dependent on the assumed relationship between the construct and item being true. If an incorrect relationship is assumed, the assessment of construct validity for the new measurement tool will also be invalid.

A clinical example of hypothesis testing with construct validity was demonstrated by Ely et al[172]. These investigators wished to assess the construct validity of the Richmond Agitation-Sedation Score (RASS), a scoring system used in ICU to judge the depth of sedation of patients and guide titration of sedative and analgesia medication. Ely et al used consciousness level as their construct. They examined the relationship between RASS scores and dose of sedation given in the 8h prior to RASS assessment (where sedation dose represents a formative item that would be expected to result in lower levels of consciousness). They demonstrated a correlation between sedation dose and RASS scores, and therefore concluded that construct validity was present (with regards this formative item relationship). The authors also examined the relationship

between RASS scores and successful extubation, representing the relationship between consciousness level and a reflective item. They demonstrated that lower RASS scores were associated with unsuccessful extubation, again concluding that construct validity was present (with regards a reflective item relationship in this instance). The fact that this study examined the relationship between both formative and reflective items with the construct strengthens the conclusion that construct validity was demonstrated, and future studies examining construct validity should replicate this.

3.4.3.3 Cross-cultural validity

Cross-cultural validation concerns "the degree to which the performance of the items on a translated or culturally adapted patient reported outcome instrument are an adequate reflection of the performance of items in the original version of the instrument" [168]. This form of validation is typically done if a questionnaire has been translated, or if it is to be used in a new unvalidated population. Cross-cultural validation in its strict definition does not have much application to RV-STE validation, however if we expand the meaning of cross-culture to include cross-population validation, it may have much importance. It would be essential to examine if RV-STE has validity in different disease populations, since the presence of validity in one population does not necessarily mean it will be present in the other. This is a key principle embedded in the research question of this thesis, by assessing RV-STE utility in two different patient populations, i.e. in ICU and perioperative period.

3.4.4 Responsiveness

The final aspect of validity, and one which some would argue does not strictly fall under the category of validity, is responsiveness. Responsiveness concerns the validity of a measurement test to measure a change in score over time. This would be pertinent for the observation of the efficacy of a treatment. The COSMIN panel view responsiveness as an intrinsic property of validity, and that their definition for validity *("The degree to which an … instrument measures the construct(s) it purports to measure"*), inherently includes measurement of a change in the construct over time. The COSMIN panel suggest that

responsiveness should be assessed in parallel when assessing validity at a single time point, and that the same subtypes of validity be used.

3.5 Conclusion

The utility of a diagnostic measurement requires a thorough analysis of its feasibility, reproducibility, and validity. Feasibility and reproducibility may not be independent from each other, and there may be a trade-off between them[173]. For RV-STE to be highly feasible, it may be necessary for a research study to accept lower quality echocardiography study images, however these lower quality images may result in reduced reproducibility. The converse may also be true, where high reproducibility will require high quality echocardiography study images to be used, therefore excluding lower quality studies (reducing the feasibility of RV-STE). Validity has many forms, a diagnostic test may have validity in certain contexts and circumstances, but not others. All aspects of validity should be assessed to fully appreciate the utility of a diagnostic test in different contexts. It may become apparent that a test has validity in certain areas or clinical contexts where it lacks validity in others.

Feasibility, reproducibility, and validity will be used as the framework for examining the utility of RV-STE in this thesis; this will be done as part of the literature review in Chapter 4, and for the scientific experiments conducted in Chapters 5 and 6. The effect of image quality upon reproducibility will also be examined across Chapters 4, 5 and 6.

Chapter 4 The utility of right ventricular speckle tracking echocardiography in the intensive care unit and the perioperative period: a review of the literature

To explore the current body of work exploring RV-STE in ICU and the perioperative period, a literature review was performed. This literature review was composed of two separate searches, divided into ICU studies and perioperative studies. The relevant literature was then used to examine RV-STE utility in this setting using the feasibility, reproducibility, and validity framework described in Chapter 3.

4.1 The utility of right ventricular speckle tracking echocardiography in the intensive care unit: a review of the literature

4.1.1 Search strategy methods

The search strategy was created by the author, and was reviewed and approved by Mr. Paul Cannon (University of Glasgow College Librarian) on 07/10/2021. The literature search was performed on the National Health Service (NHS) Greater Glasgow and Clyde library network on 07/10/2021. The search strategy was conducted using Ovid Medline (R) Database, 1946 to Present. It is presented below with the numbers in right hand column representing number of hits:

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to October 07, 2021>

1	Critical Care/	56105
2	critical care.mp.	78291
3	intensive care.mp.	193284
4	icu.mp.	65421
5	intensive therapy.mp.	5083
6	itu.mp.	986
7	sepsis.mp.	133514
8	septic shock.mp.	24205
9	acute respiratory distress syndrome.mp.	17728
10	ards.mp.	15352
11	covid 19.mp.	151959
12	covid.mp.	152645
13	pulmonary embolism.mp.	55792
14	mechanical ventilation.mp.	47677
15	Positive-Pressure Respiration/	17723
16	Ventricular Function, Right/	7119
17	Ventricular Dysfunction, Right/	6443
18	(right adj3 ventric*).mp.	70333
19	(echo* adj5 speckle).mp.	3945
20	(track* adj5 speckle).mp.	5785
21	(strain adj7 echo*).mp.	3452
22	deformation.mp. 50238	
23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	613683
24	16 or 17 or 18	70333
25	19 or 20 or 21 or 22	56231
26	23 and 24 and 25	168

Studies were included if they investigated 2D RV-STE using transthoracic echocardiography. Studies investigating 3D RV-STE, or using trans-oesophageal echocardiography, were excluded. Abstracts were reviewed for the 168 articles identified, with 24 being identified as relevant to the literature review area of interest. One study of relevance was identified from reviewing the reference lists, resulting in a total of 25 studies included in the literature review. An overview of these studies is shown in Appendix Table 1. A discussion of the feasibility, reproducibility, and validity of RV-STE in ICU studies is described below.

4.1.2 Feasibility of RV-STE in ICU: Methods

Twenty-five studies investigating RV-STE strain analysis in ICU patients were identified by the literature search. Seven studies did not report RV-STE feasibility since they did not describe the number of echocardiography studies they excluded due to poor image quality. Four studies reported a combined feasibility of RV- and LV-STE feasibility and, unless the feasibility was 100%, were therefore excluded (since echocardiography studies that were excluded due to inadequate views for LV-STE may have had adequate views for RV-STE). Four studies used data from an almost identical set of patients, three were therefore excluded (Sun et al[174], Xie et al[175], and Zhang et al[176]), and one was included (Li et al[16], which specifically investigated RV-STE). Eleven studies in total were therefore included for the review of RV-STE feasibility, these are shown in Table 4-1. Feasibility for this literature review was defined as the percentage of echocardiography studies that were deemed by the authors of the study to have images of adequate quality for RV-STE strain analysis.

Table 4-1 ICU Studies that describe RV-STE feasibility in ICU identified by literature search

Study	ICU Group	Patients that underwent echocard-iography (N)	Number of echo studies with adequate images for strain analysis (n)	Study design	Strain analysis performed	IMV (% of N)	Approach to inadequately tracking RV segments during strain analysis	Feasibility (n/N as %)	Comment
Bonizzoli et al 2018[177]	ARDS	30	28	Prospective	RVFWLS	100%	Inadequately tracked segments excluded from strain analysis, remaining segments analysed	93.3%	
Lemarie et al 2020[178]	ARDS	48	48	Prospective	RVGLS	100%	Inadequately tracked segments excluded from strain analysis	100%	Two observers for all analyses Effort made to echo patients in left lateral position and obtain RV focused A4C view.
Li et al 2020[16]	COVID-19	144	120	-	RVFWLS	-	Echo study excluded if all three segments not adequately tracked	83.3%	
Kim et al 2020[179]	COVID-19	34	34	Mixed prospective/ retrospective	RVFWLS, RVGLS and LVGLS	20%	Not defined	100%	
Baycan et al 2020[180]	COVID-19	100	100	Prospective	RVFWLS and LVGLS	-	Inadequately tracked segments excluded from strain analysis	100%	

Bursi et al 2020[181]	COVID-19	49	37-38	Retrospective	RVFWLS and RVGLS	22.4%	Inadequately tracked segments excluded from strain analysis	RVFWLS 77.5% RVGLS 75.5%	"High percentage" of patients were in a sitting position due to NIV, making scanning difficult.
Bleakley et al 2021[15]	COVID-19	90	51	Retrospective	RVFWLS	100%	Echo study excluded if > one segment not adequately tracked	56.7%	RV focused A4C views obtained 42.2% of patients receiving V-V ECMO
Stockenhuber et al 2021[182]	COVID-19	35	30	Prospective	RVFWLS	36.7%	Echo study excluded if all three segments not adequately tracked	85.7%	
Jain et al 2021[183]	COVID-19	52	36	-	RVGLS	50%	Not defined	69.2%	RV focused views obtained. Prone patients included, "fewer than five"
Khemasuwan et al 2015[184]	PE	235	203	Retrospective	RVGLS	-	Not defined	86.4%	Qualitative assessment of image quality: 46.8% images "optimal" 37.9% images "suboptimal" 1.7% images "poor" 13.6% images unusable
Dahhan et al 2016[185]	PE	95	69	Retrospective	RVGLS and RVFWLS	-	Inadequately tracked segments excluded from strain analysis	72.6%	

- = not described in main text or supplementary material.
RV-STE = right ventricular speckle tracking echocardiography, ICU = intensive care unit, IMV = invasive mechanical ventilation, ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, PE = pulmonary embolism, RV = right ventricular, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, echo = echocardiography, A4C = apical four chamber, NIV = non-invasive ventilation, V-V ECMO = venovenous extracorporeal membrane oxygenation.

4.1.3 Feasibility of RV-STE In ICU studies: Results

There was considerable variability in the feasibility of RV-STE in ICU studies. Feasibility ranged from 56.7% (Bursi et al) to 100% (Lemarie et al, Baycan et al, Kim et al)[178-181]. The image quality of echocardiography studies was largely described dichotomously, as either adequate or inadequate. Only Khemasuwan et al included a qualitative assessment of image quality, describing images as either "optimal", "suboptimal", "poor", or "inadequate" for analysis[184]. The effect of study image quality upon STE strain analysis of the RV in ICU cohorts has not been described, and the validity of suboptimal image analysis has not been established.

4.1.3.1 Feasibility of RV-STE with inadequately tracking segments

The RV is often difficult to visualise with echocardiography[186]. When faced with echocardiography studies of suboptimal image quality, researchers must decide how they will interpret them. Should they discard the echocardiography study from the research study entirely, or do they exclude inadequately tracked segments from strain analysis and analyse the remaining adequately tracked segments? This is an important decision, however there was much variability in how it was described across these investigations. Two studies (Li et al and Stockenhuber) explicitly stated that all three RV free wall segments were required for RVFWLS analysis, if any segments were missing the echocardiography study was excluded from the research study[16,182]. This strict protocol for echocardiography study inclusion would intuitively reduce feasibility, however both studies report high feasibility, with Li et al reporting 83.3% and Stockenhuber et al reporting 85.7%. As discussed below, the prospective design of these two studies may have enhanced their feasibility. Seven studies excluded inadequately tracking segments from the strain analysis, analysing the remaining segments to calculate RFWLS/RVGLS values. Only Bleakley et al specifically stated how many inadequately tracking segments resulted in them deeming an echocardiography study to have images inadequate for RVFWLS analysis (more than one segment)[15]. It is unclear how many inadequately tracking segments the remaining studies accepted before deciding an echocardiography study was of excessively poor quality for RV-STE strain analysis.

Consensus guidance has been published by the European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) on how to obtain optimal images for valid RV-STE analysis (specifically for RVFWLS), they state "reliable measurements of RV strain require that all three segments of the RV free wall are adequately tracked"[85]. It is apparent that a significant proportion of studies do not adhere to this standard; this may reflect pragmatism in clinical practice where echocardiography studies with suboptimal image quality are felt to be good enough to answer a clinical question. It is concerning that there is such variability with the management of echocardiography studies with suboptimal image quality since speckle tracking is entirely dependent on adequate image quality across the entire region of interest.

4.1.3.1.1 Feasibility of RV-STE: A meta-analysis

To investigate variables that might influence RV-STE feasibility, a meta-analysis of the relevant 11 studies identified by the search was performed.

4.1.3.1.2 Meta-analysis methods

Meta-analysis was performed using Comprehensive Meta-Analysis Version 4 (Biostat, Inc). A random effects model was used for analyses given that the true effect size will likely differ between studies (rather than assuming the same true effect size between studies when using a fixed effect model). A point estimate of RV-STE feasibility was generated with a 95% confidence interval.

The random effects model for the meta-analysis and meta-regression assigns weight to studies by calculating the inverse sum of both the within-study error variance and the between-study variance[187]. This is described by the following equation:

$$W_i = \frac{1}{V_i + T^2}$$

Where W_i is the weighting of study i, V_i is the within study error variance of study i (this is unique to each study), and T^2 is the between study variance (this is common to all studies).

4.1.3.1.3 Effect measure

Feasibility data was extracted as the number of echocardiography studies of adequate quality for RV-STE to be analysed (the number of "events", shown as "n" in Table 4-1) and the number of echocardiography studies performed (shown as "N" in Table 4-1). Where studies reported both RVFWLS and RVGLS, the RVFWLS was used due to its more rigorous validation (the exception to this is the RVFWLS vs RVGLS subgroup meta-analyses described below)[85].

4.1.3.1.4 Basic meta-analysis statistics

Statistics used within the meta-analysis included:

Z value: The z value, with its accompanying p-value, is a measure of the number of standard deviations a point estimate is away from the value zero. For this meta-analysis, it tests the null hypothesis that the RV-STE feasibility is not significantly different than zero.

Q Statistic: The Q-statistic, and the accompanying p-value, tests the null hypothesis that there is zero heterogeneity in true effects between studies, and all studies therefore have the same true effect size.

Tau²: Tau² describes the variance in true effects that is observed between studies.

I²: The I^2 statistic describes, as a percentage, the proportion of variance in observed effect size that is attributable to true effect variation, with the rest of the variation being attributed to sampling error.

4.1.3.1.5 Publication bias

Publication bias was assessed by creating funnel plots of the studies included in the meta-analysis. In a funnel plot, studies are plotted with the logit event rate (i.e. the logit of proportional RV-STE feasibility) on the x axis, compared to the standard error along the y-axis. As such, studies with larger sample sizes (and therefore smaller standard error) tend to appear at the top of the plot, with smaller studies being at the bottom. Visual inspection of funnel plots allows identification of asymmetry, and to assess if there is a bias in the meta-analysis for larger or smaller studies to report higher or lower feasibility. The impact of bias can then be assessed using the Duval and Tweedie's 'trim and fill' method[188]. With this method imbalanced studies are identified and are removed (or "trimmed") from the funnel plot so that it is symmetrical. An adjusted point estimate for RV-STE feasibility is calculated from the remaining studies. The trimmed studies are then added back, and theoretical counter-balancing studies are imputed and added to the plot, a truer estimate of variability around the adjusted point estimate is then calculated.

4.1.3.1.6 Meta-regression

Logistic meta-regression was used to assess the effect of continuous variables (i.e. IMV) upon RV-STE feasibility. Again, a random effects model was used. First a univariate meta-regression was conducted, followed by a multivariable meta-regression. Borenstein et al state "in primary studies some have recommended a ratio of at least ten subjects for each covariate, which would correspond to ten studies for each covariate in meta-regression. In fact, though, there are no hard and fast rules in either case."[189]. There were 7 studies available for multivariable analysis in the present study. Given that there is not an established rule, it was decided to allow one covariate to be added to the meta-regression model per 7 studies, whilst interpreting all results with the caveat that the sample size of studies was small.

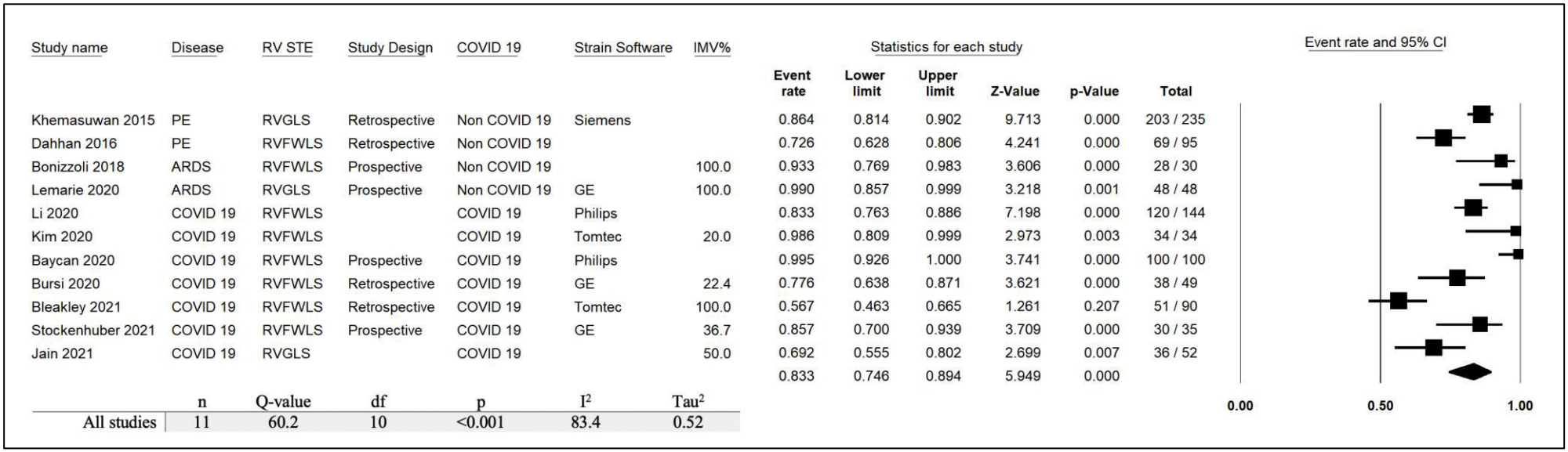


Figure 4-1 Overall meta-analysis to assess the feasibility of RV-STE in ICU studies

The forest plot shows the individual point estimate and 95% confidence interval of each study as a box and line respectively, with the size of the box being representative of the weight attributed to that study. The overall point estimate is shown as a diamond, with the ends of the diamond representing the 95% confidence interval. RV-STE = right ventricular speckle tracking echocardiography, COVID-19 = coronavirus disease 2019, IMV = invasive mechanical ventilation, PE = pulmonary embolism, ARDS = acute respiratory distress syndrome, RVGLS = right ventricular global longitudinal strain, RVFWLS = right ventricular free wall longitudinal strain, CI = confidence interval.

4.1.3.2 Feasibility of RV-STE: Meta-analysis results

A meta-analysis of the eleven studies gave a point estimate for RV-STE feasibility of 83.3% (95%CI 74.6-89.4, Figure 4-1). There was a high level of dispersion, with an estimated variance of true effects (Tau^2) of 0.52, and an accompanying high level of heterogeneity across the studies, with an I^2 of 83.4 demonstrating that 83.4% of the variability between the observed feasibilities across the studies is due to true effect variation.

Assessment for publication/small study bias was performed using a funnel plot (Figure 4-2). On inspection, it was apparent there was asymmetry, with three points at the bottom right of the plot (indicating small studies that have reported high RV-STE feasibility), with no counter balancing studies observed in the bottom left of the plot. From this we can infer that small studies reporting high feasibility might be more likely to have been published than small studies reporting low feasibility. When the Duval and Tweedie "trim and fill" procedure was used (Figure 4-3, Table 4-2), a reduced point estimate of RV-STE feasibility of 76.9% (95%CI 65.9-85.2) was identified, possibly representing a more accurate point estimate when accounting for the bias associated with the lack of smaller studies reporting reduced RV-STE feasibility.

To further characterise variables contributing to the heterogeneity of the observed true effect point estimate, subgroup meta-analysis and meta-regression was performed. Subgroup meta-analysis aimed to investigate if the following variables affected RV-STE feasibility: type of RV-STE analysed (RVFWLS vs RVGLS), study design (prospective vs retrospective), strain software used, COVID-19 studies, and proportion of IMV.

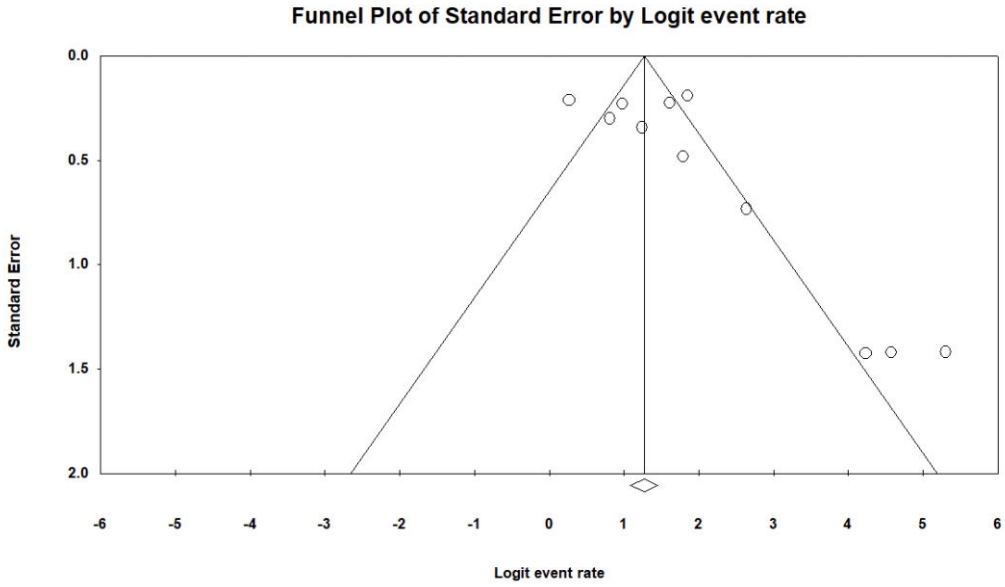


Figure 4-2 Funnel plot of ICU studies included in the RV-STE feasibility meta-analysis
The combined point estimate of all studies is shown as a white diamond. Asymmetry is observed, with three small studies in the bottom right reporting high RV-STE feasibility. ICU = intensive care unit, RV-STE = right ventricular speckle tracking echocardiography

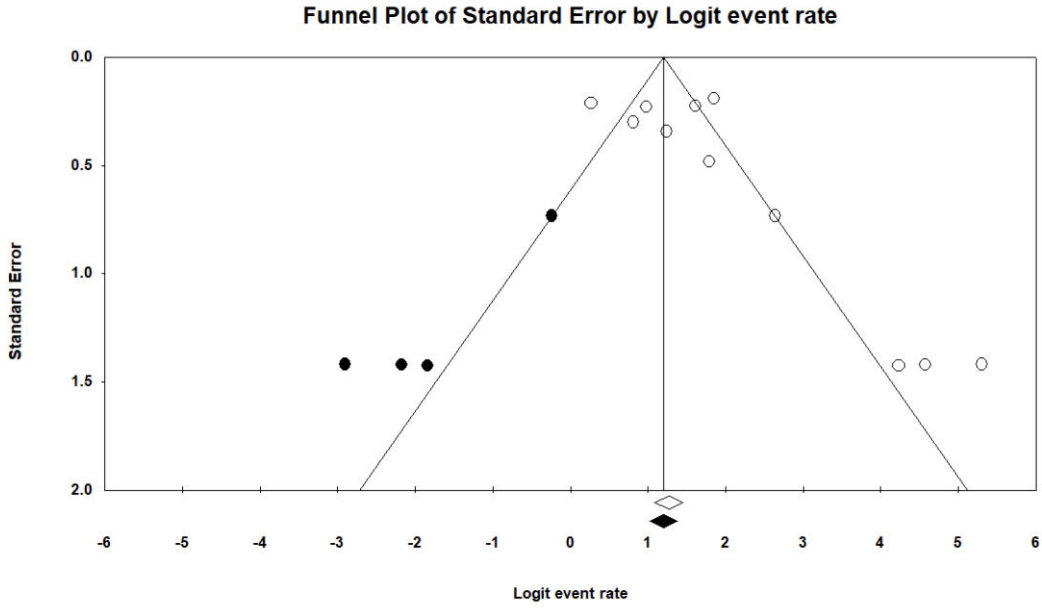


Figure 4-3 Funnel plot of ICU studies included in the RV-STE feasibility meta-analysis using "trim and fill" method
The four studies on the bottom right of the plot are first removed to make the plot symmetrical and an adjusted point estimate calculated. These studies are added back with imputed counter balancing studies (solid black circles) added, variance around the adjusted point estimate is then calculated. The original combined point estimate is shown as a white diamond, with the adjusted point estimate shown as a solid black diamond. ICU = intensive care unit, RV-STE = right ventricular speckle tracking echocardiography

Table 4-2 "Trim and Fill" adjustment of ICU studies included in the RV-STE feasibility meta-analysis

Outcome		Studies trimmed	Point estimate (%)	95%CI	Q value
RV-STE feasibility	Observed Adjusted	4	83.3 76.9	74.6-89.4 65.9-85.2	60.2 83.1

RV-STE = right ventricular free wall longitudinal strain, CI = confidence interval.

Subgroup category	Subgroup (n=)	Feasibility (%) (95% CI)	Q-value	p value	I^2 (%)	Tau^2
RVSTE	RVFWLS (8)	83.2 (72.1-90.4)	41.0		82.9	0.58
	RVGLS (6)	81.3 (70.1-89.0)	22.4		77.6	0.36
	Total between		**0.1**	**0.788**		
Study Design	Prospective (4)	95.7 (83.8-99.0)	8.2		63.5	1.30
	Retrospective (4)	74.7 (58.5-86.1)	31.2		90.4	0.51
	Total between		**5.9**	**0.015**		
COVID 19 Study	COVID 19 (7)	81.4 (68.3-89.8)	37.1		83.8	0.62
	Non-COVID 19 (4)	86.9 (73.8-94.0)	15.4		80.5	0.48
	Total between		**0.6**	**0.460**		
Strain Software	GE (3)	86.7 (68.3-95.2)	5.6		64.3	0.56
	Philips (2)	96 (40.3-99.9)	6.6		84.9	5.79
	Siemens (1)	86.4 (81.4-90.2)	0.0		0.0	0.0
	Tomtec (2)	88.1 (13.5-99.7)	7.6		86.8	6.83
	Total between		**0.54**	**0.912**		
OVERALL (n=11)		**83.3 (74.6-89.4)**	**60.2**		**83.4**	**0.52**

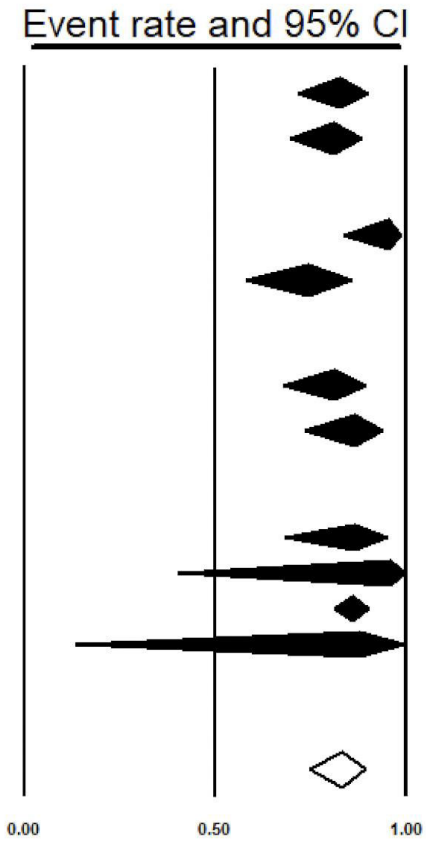


Figure 4-4 Subgroup meta-analyses to investigate variables affecting RV-STE feasibility in ICU studies

Subgroup meta-analyses to investigate the effect that RV-STE type (RVFWLS vs RVGLS), study design (retrospective vs prospective), COVID-19 study status (COVID-19 study or not), and strain software has upon RV-STE feasibility. RV-STE = right ventricular speckle tracking echocardiography, COVID-19 = coronavirus disease 2019, RVGLS = right ventricular global longitudinal strain, RVFWLS = right ventricular free wall longitudinal strain, CI = confidence interval.

4.1.3.3 The effect of RVFWLS versus RVGLS on feasibility

The type of RV-STE (RVFWLS or RVGLS) assessed may alter reported feasibility. RVGLS examines all six segments of the RV (three free-wall and three septal), whereas RVFWLS only assesses the three free wall segments. It might be expected that RVGLS would have poorer feasibility due to the higher number of visualised segments required for analysis.

Of the 11 studies identified, five reported only RVFWLS feasibility, three reported only RVGLS, and three reported both RVFWLS and RVGLS. Where both RVFWLS and RVGLS were reported, both feasibilities were included in the RVFWLS vs RVGLS subgroup meta-analysis, resulting in 8 "studies" reporting RVFWLS and 6 reporting RVGLS (Figure 4-4). The subgroup meta-analysis identified no difference in the feasibility between RVFWLS and RVGLS, with similar point estimates for feasibility (83.2% (95%CI 72.1-90.4) and 81.3% (95%CI 70.1-89.0) respectively, p=0.788).

4.1.3.4 The effect of study design on RV-STE feasibility

Study design may affect the feasibility of RV-STE strain analysis, with prospective studies possibly having higher feasibility. To investigate this, subgroup meta-analysis was performed (Figure 4-4). Of the 11 studies described above, only 8 explicitly stated that they were prospective or retrospective.

Interestingly, study design subgroup meta-analysis demonstrated a significant difference between the feasibility of studies, with a prospective design having a higher point estimate for RV-STE feasibility compared to retrospective (95.7% [95%CI 83.8-99.0] vs 74.7% [95%CI 58.5-86.1] p=0.015, Figure 4-4). Both types of study design demonstrated considerable heterogeneity, but with prospective studies having less heterogeneity than retrospective (I^2 63.5 vs 90.4).

It is worth considering why prospective studies may have better feasibility. Prospective studies might be designed to specifically investigate RV-STE strain analysis. Echocardiography study image acquisition may therefore center on obtaining a high-quality RV focused image, leading to higher feasibility. A good example of how prospective design improves feasibility is seen with Lemarie et

al[178], the echocardiographers made a specific effort to position patients in a left lateral position optimising the position of the heart for ultrasound windows, and endeavouring to obtain an RV focused view during all echocardiography studies. Prospective study could be viewed as the gold standard for improving the feasibility of RV-STE strain analysis in ICU groups. It is important to note that although desirable, prospective study design is not without its own limitations. Selection bias could result in studies reporting higher RV-STE feasibility than retrospective studies due to the selective inclusion of patients with high quality echocardiography images in prospective studies. Selection bias must therefore be avoided in future prospective studies investigating the feasibility of RV-STE.

4.1.3.5 The effect of strain software on RV-STE feasibility

As described in section 2.4, different strain software use different technology for speckle tracking, and may therefore differ in their abilities to adequately track the RV endo/myocardium during the cardiac cycle. It is therefore possible that RV-STE feasibility would differ between strain software vendors.

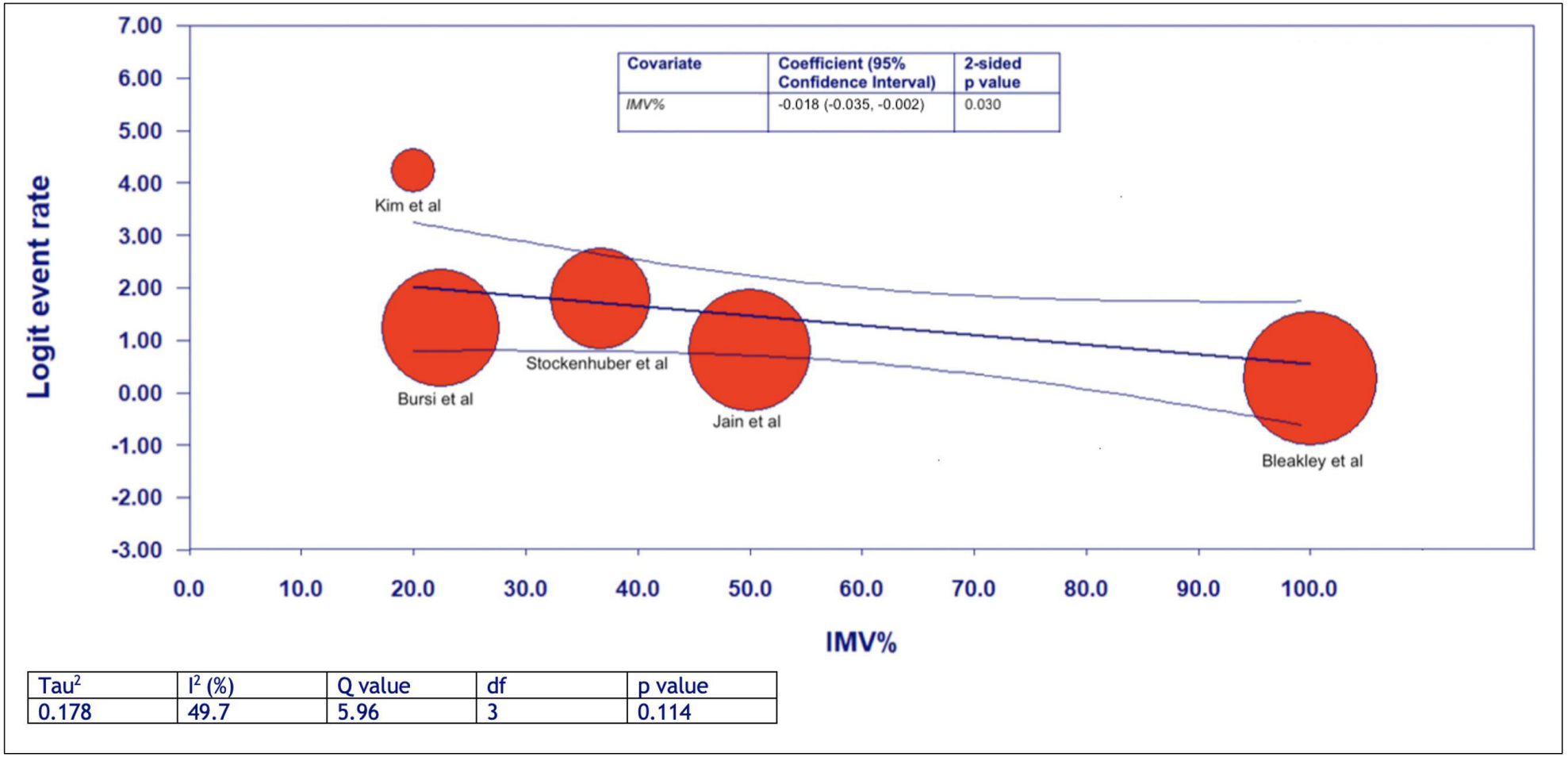
Eight studies reported the strain software used (three GE, two Philips, one Siemens, and two Tomtec). The strain software subgroup meta-analysis identified no difference in RV-STE feasibility across strain software (p=0.912), however it must be noted there were small numbers of studies for each software manufacturer so it may be unsurprising that a difference was not identified.

4.1.3.6 Feasibility of RV-STE in different ICU groups

Feasibility varied across ICU disease groups. Two ICU groups that may pose a particular challenge in obtaining echocardiography studies with good image quality are patients with COVID-19 and patients undergoing IMV. Patients with COVID-19 frequently require non-invasive ventilation, are difficult to optimally position for echocardiography, and there is the additional time and psychological pressure to perform a focused echocardiography study to limit infection risk to the ultrasonographer. Bursi et al commented on the difficulty encountered when scanning patients in the upright position whilst receiving non-invasive ventilation, and that scanning was hampered by “cumbersome personal protective equipment with limited scan time”[181]. The author of this thesis

completed Focused Intensive Care Echocardiography (FICE) accreditation during the first COVID-19 wave, and would reiterate how difficult it can be to obtain high quality echocardiography study images in this patient group. Tiny acoustic windows were often encountered with patients sitting bolt upright while receiving non-invasive ventilation, made more difficult to navigate through a fogging visor. Positive pressure IMV can make echocardiography image acquisition problematic, with hyperinflation and caudal displacement of the pericardial sac resulting in poor acoustic windows. The feasibility of RV-STE in patients with COVID-19 and patients receiving invasive mechanical ventilation were investigated using subgroup meta-analysis and meta-regression.

On univariate analysis, the COVID-19 subgroup meta-analysis did not show any association between COVID-19 study status and RV-STE feasibility (p=0.460, Figure 4-4). There was large heterogeneity within both the COVID-19 group and the non-COVID-19 group (I^2 83.8% vs 80.5%). Five COVID-19 studies reported the incidence of IMV. A univariate meta-regression was performed on these studies to see if IMV affected the feasibility of RV-STE in COVID-19 studies (Figure 4-5). In this meta-regression, IMV proportion was significantly associated with RV-STE feasibility, where higher proportions of IMV were associated with poorer feasibility, demonstrated by the negative gradient of the regression line (co-efficient -0.018 (95%CI -0.035, -0.002), p=0.030). As an extension to this univariate meta-regression in COVID-19 studies, non-COVID-19 studies were added to investigate if COVID-19 studies (as a covariate) were associated with poorer feasibility.



Tau^2	I^2 (%)	Q value	df	p value
0.178	49.7	5.96	3	0.114

Figure 4-5 Univariate meta-regression of RV-STE feasibility in COVID-19 studies with proportion of IMV as a continuous variable
Only COVID-19 studies included. Proportion of patients receiving IMV is included as a continuous variable. RV-STE feasibility is described as logit event rate. The bubble plot demonstrates the weight of each study in the meta-regression, with larger bubbles having greater weight. RV-STE = right ventricular speckle tracking echocardiography, IMV = invasive mechanical ventilation.

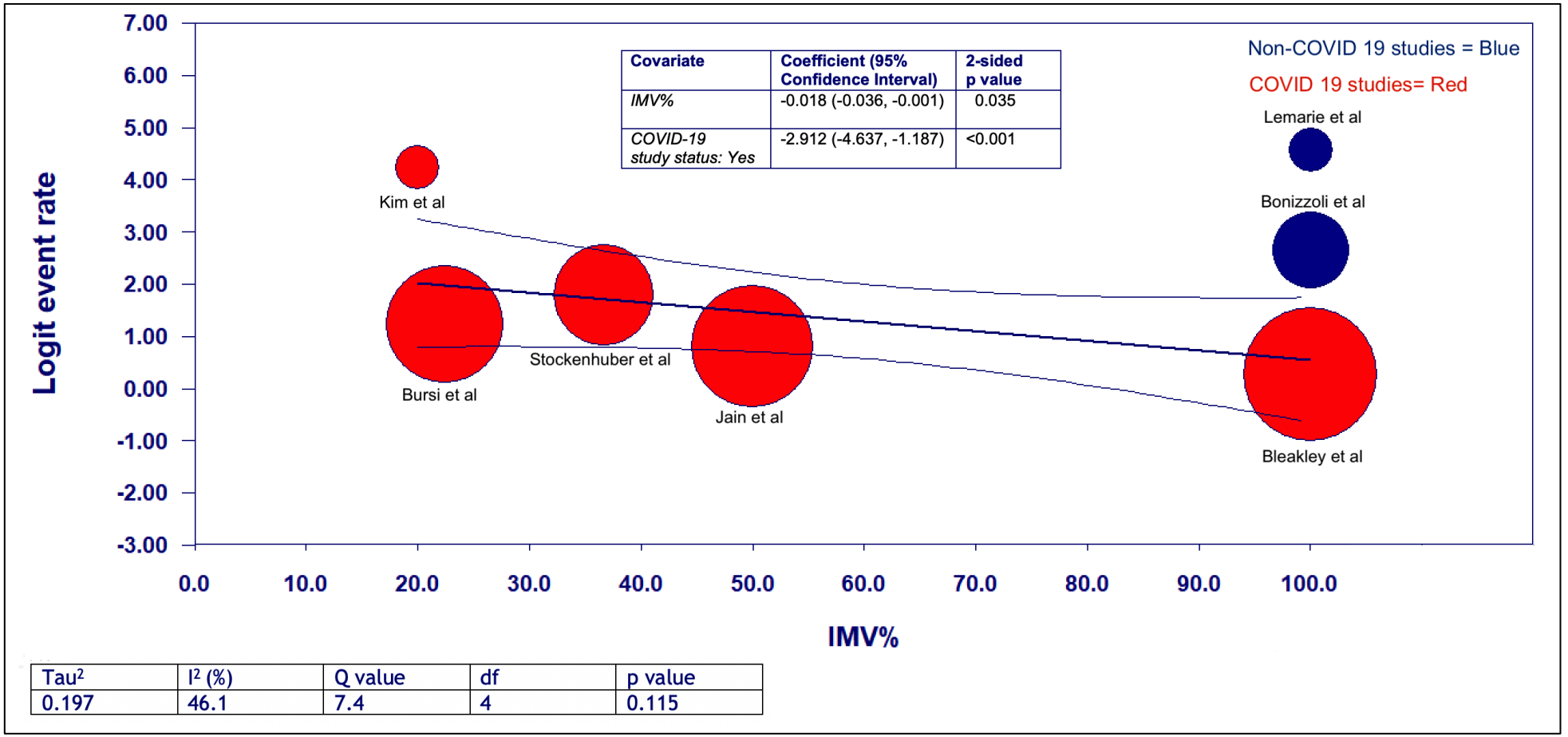


Figure 4-6 Multivariable meta-regression of RV-STE feasibility with proportion of IMV as continuous variable and COVID-19 study status as a covariate
Proportion of patients receiving IMV is included as a continuous variable. COVID-19 study status is included as a covariate. RV-STE feasibility described as the logit event rate. The bubble plot demonstrates the weight of each study in the meta-regression, with larger bubbles having greater weight. RV-STE = right ventricular speckle tracking echocardiography, IMV = invasive mechanical ventilation, COVID-19 = coronavirus disease 2019.

This multivariable meta-regression model demonstrated that both the proportion of IMV (p=0.035) and COVID-19 status (p<0.001) were significantly associated with RV-STE feasibility (Figure 4-6). The goodness of fit test reported a p-value of 0.115 (Figure 4-6), resulting in us accepting the null hypothesis that unexplained variance is zero (i.e. this model could explain all variance observed). The I^2 value of 46.1% demonstrated a low level of heterogeneity with a low proportion of the variability in observed effects being attributable to true effects variability. R^2 analysis further characterised this (Figure 4-7). R^2 for this model was 73%, meaning that 73% (i.e. the majority) of the variability in true effects across the seven studies is described by this multivariable meta-regression model.

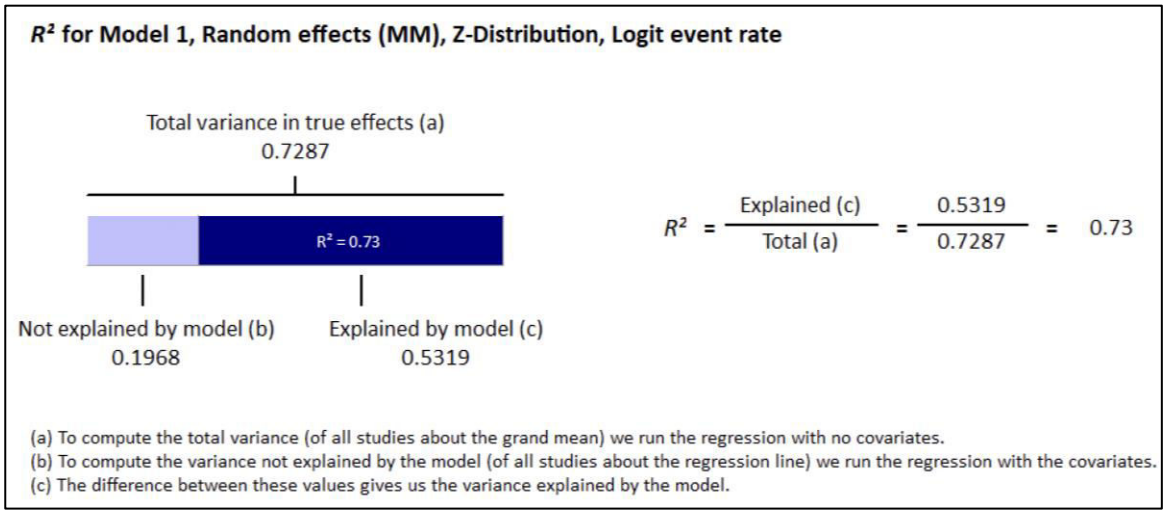


Figure 4-7 R-squared analysis of multivariable meta-regression investigating the feasibility of RV-STE

R-squared (R^2) describes the proportion of variability in true effects between studies that is described by the model. In this instance R^2 is 0.73, meaning that 73% of the variability in the seven ICU RV-STE feasibility studies is described by a model including proportion of IMV and COVID-19 study status. ICU = intensive care unit, RV-STE = right ventricular speckle tracking echocardiography, IMV = invasive mechanical ventilation, COVID-19 = coronavirus disease 2019.

Through subgroup meta-analysis and meta-regression, an association has been demonstrated between COVID-19 status, incidence of IMV, and the feasibility of RV-STE. Given the small number of studies, caution must be taken in extrapolating these results and applying them to other ICU populations receiving IMV and those with COVID-19.

4.1.3.7 Conclusion on feasibility of RV-STE in ICU studies

Meta-analysis of ICU studies demonstrated a point estimate of RV-STE feasibility of 83.3% (95%CI 74.6-89.4), suggesting that the feasibility of RV-STE is high in this population. This is comparable to the feasibility of the conventional RV echocardiography parameters in ICU populations (RVFAC 19.2-83.3%, TAPSE 75.0-94.0%, S' 84.6-93.3%)[15,181,183,190].

Literature review and meta-analysis suggests optimal feasibility of RV-STE strain analysis in ICU groups will be attained by a prospective design, with an emphasis on optimal patient positioning and RV focused views. Meta-analysis and meta-regression identified retrospective design, COVID-19 studies, and increasing proportion of IMV as being associated with poorer feasibility. Overall, the description of feasibility was generally not well reported. A dichotomous classification of echocardiography study image quality as 'adequate' and 'inadequate' for RV-STE strain analysis does not convey the spectrum of image quality that lies between these two points. To optimise this, it would be prudent for future studies to include a quantitative and qualitative description of image quality. To fully appreciate the utility of RV-STE strain analysis as a clinical tool, it will be necessary to investigate how the inclusion of echocardiography studies of suboptimal, but potentially adequate, image quality affects reproducibility and the strain values that they report compared to optimal images. These investigations will be performed in Chapters 5 and 6.

4.1.4 Reproducibility of RV-STE in ICU studies

Of 25 studies investigating RV-STE strain analysis in ICU, 11 reported reproducibility analysis. Intra-observer and inter-observer reproducibility was analysed using three main methods:

- Coefficient of variation (2/11 studies)
- Intraclass Correlation Coefficient (6/11 studies)
- Bland-Altman plot (5/11 studies)

Three of these studies used *both* Bland-Altman plots and ICCs to assess reproducibility. Results from these different methods are described in this order below.

4.1.4.1 Coefficient of variation assessment of RV-STE reproducibility in ICU

Dalla et al used the coefficient of variation (CoV) for assessing RVFWLS intra and inter-observer reproducibility in two studies[191,192]. This statistical method describes the precision of RVFWLS reporting, and is a measure of the variability of the difference between repeated measures. The CoV for intra- and inter-observer variation was low (≤ 10%) in both Dalla et al 2015 and 2019, which suggests the precision of repeated RVFWLS measurements is excellent. It is important to note that while precision of repeated measures is desirable, it does not necessarily equate to agreement. It is therefore important that CoVs are not used in isolation, and should be used with another form of agreement analysis (e.g. ICC or Bland-Altman)[162].

4.1.4.2 Intraclass correlation coefficient assessment of RV-STE reproducibility in ICU

The intraclass correlation coefficient is a measure that describes both agreement and correlation of repeated measures. There are many forms of ICC, which can be divided into those that measure agreement and those that measure consistency. As described in section 3.3, the appropriate measurement for the re-reporting or dual reporting of RV-STE is absolute agreement. The specific ICC

test used should be explicitly described to ensure we know the correct ICC test was used. Lemarie et al was the only study to state that they used ICC with absolute agreement[178].

Intra-observer ICC for RVFWLS and/or RVGLS was excellent (>0.9) in the three studies where it was used (Li et al, Kim et al, Baycan et al, Table 4-3) [16,179,180]. Inter-observer ICC for RVFWLS and/or RVGLS was described in six studies, ranging from 0.82 (Garcia-Montilla et al) to 0.96 (Kim et al)[179,193].

Two papers, both investigating RV-STE in ARDS populations, compared inter-observer ICC for RVFWLS and RVGLS with conventional RV echocardiography parameters, shown in Table 4-4. Garcia-Montilla et al showed that the inter-observer ICC for RVFWLS was higher than TAPSE, S', and RVFAC[193]. Lemarie et al showed an inter-observer ICC for RVGLS of 0.87, considerably better than RVFAC, with an ICC of 0.57[178]. From these studies it appears that the reproducibility of RV-STE strain analysis is consistently high, whereas there is considerable variability with other RV echocardiography parameters. This suggests that RVFWLS and RVGLS are the more reproducible RV echocardiography parameters.

Table 4-3 ICC analysis of ICU studies reporting RV-STE

Study	(n)	Group	Design	Strain measured	Intraclass Correlation Coefficient		Reproducibility analysis method
					Intra-observer	Inter-observer	
Garcia-Montilla et al 2017[193]	51	ARDS	Retrospective	RVFWLS	-	0.82	15 scans selected at random for inter-observer agreement analysis
Lemarie et al 2020[178]	48	ARDS	Prospective	RVGLS	-	0.87 (0.72-0.93) (p<0.001)	Two-way mixed-effects model with absolute agreement
Li et al 2020[16]	120	COVID-19	Not described	RVFWLS	0.95	0.91	20 scans selected at random intra- and inter-observer agreement analysis two weeks after initial analysis
Kim et al 2020[179]	40	COVID-19	Mixed	RVFWLS	0.94 (p<0.001)	0.96 (p<0.001)	All scans re-reported for intra- and inter-observer agreement analysis
				RVGLS	0.96 (p<0.001)	0.94 (p<0.001)	
Baycan et al 2020[180]	100	COVID-19	Prospective	RVFWLS	0.92 (0.88-0.94)	0.89 (0.82-0.94)	20 scans selected at random for intra- and inter-observer agreement analysis
Park et al 2021[194]	48	COVID-19	Retrospective	RVFWLS	-	0.84	-
				RVGLS	-	0.86	-

ICC given with 95% CI and p value, when described. A dash (-) is given when the data was not presented in the study. ICU = intensive care unit, RV-STE = right ventricular speckle tracking echocardiography, ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain.

Table 4-4 Comparison of the ICCs of RV-STE and conventional RV echocardiography parameters

Echocardiography parameter	Inter-observer ICC	
	Garcia-Montilla et al 2017	Lemarie et al 2020
RVFWLS	0.82	-
RVGLS	-	0.87 (0.72-0.93, p<0.001)
TAPSE	0.71	0.88 (0.78-0.93, p<0.001)
S'	0.65	0.94 (0.89-0.97, p<0.001)
RVFAC	0.63	0.57 (0.35-0.73, p=0.001)

ICC given with 95% CI and p value, when described. A dash (-) is given when the data was not presented in the study. ICC = intraclass correlation coefficient, RV-STE = right ventricular speckle tracking echocardiography, RV = right ventricular, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RVFAC = right ventricular fractional area change

4.1.4.3 Bland Altman plot assessment of RV-STE reproducibility in ICU

As described in section 3.3.2.3, Bland-Altman plots are used to investigate intra- and inter-observer agreement. They can also be used for easy detection of outliers and systematic bias. Intra-observer agreement showed a small mean difference, varying from -0.1% (+/- 0.7, 2 standard deviations [SD]) in Bursi et al to -1.4% (+/- 0.9, 1SD) in Orde et al[181,195]. Inter-observer agreement also showed a small mean difference, varying between -0.3% (+/- 1.7, 2SDs) in Bursi et al, and -2% (+/- 1.2, 1SD) in Orde et al. Descriptions of measures of variance around the mean difference differed, with studies using a mixture of one standard deviation, two standard deviations, and limits of agreement (+/- 1.96SDs, which includes 95% of the data points). Regardless of which measure was used, variance was small.

Importantly, only one study included a diagram of the Bland-Altman plot (Kim et al[179]). As discussed in Chapter 3, a strength of the Bland-Altman plot is that it allows the reader to visually assess the spread of data, and if there is systematic bias in agreement across reported STE strain values. On inspection of Kim et al's Bland-Altman plots for RVFWLS/RVGLS intra- and inter-observer reproducibility,

data points appeared to have equally random scatter, suggesting that there was no systematic bias in RVFWLS and RVGLS reporting.

Table 4-5 Bland-Altman analysis of ICU studies reporting RV-STE

Study	(n)	Group	Design	Strain measured	Bland-Altman analysis of agreement		Reproducibility analysis method
					Intra-observer	Inter-observer	
Orde et al 2014[195]	74	Sepsis	Prospective	RVFWLS	-1.4% (+/- 0.9) (MD +/- 1SD)	-2% (+/- 1.2) (MD +/- 1SD)	10% of scans selected at random for inter-observer agreement analysis
Garcia-Montilla et al 2017[193]	51	ARDS	Retrospective	RVFWLS	-	0.7% (+/- 8.0) (MD +/- LOA)	15 scans selected at random for inter-observer agreement analysis
Li et al 2020[16]	120	COVID-19	Not described	RVFWLS	0.33% (-2.19, 1.54) (MD +/- LOA)	0.7% (-3.08, 4.49) (MD +/- LOA)	20 scans selected at random for intra and inter-observer agreement analysis two weeks after initial analysis
Bursi et al 2020[181]	49	COVID-19	Retrospective	RVFWLS	-0.5% (+/- 1.5) (MD +/- 2 SD)	0.8% (+/- 2.2) (MD +/- 2 SD)	10 scans selected at random for intra- and inter-observer agreement analysis
				RVGLS	-0.1% (+/- 0.7) (MD +/- 2 SD)	-0.3% (+/- 1.7) (MD +/- 2 SD)	
Kim et al 2020[179]	40	COVID-19	Mixed	RVFWLS/ RVGLS	Band-Altman plots supplied in supplementary material, but without any numerical data.		All scans re-reported for intra and inter-observer agreement analysis

Limits of agreement = lower and upper value of mean difference +/- 1.96 SD. A dash (-) is given when the data was not presented in the study. ICU = intensive care unit, RV-STE = right ventricular speckle tracking echocardiography, ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, MD = mean difference, SD = standard deviation, LOA = limits of agreement.

4.1.4.4 The role of automated strain software and reproducibility

From a technical perspective, where it was described, all studies used semi-automated or fully automated 2D RV-STE analysis. The software will identify a region of interest for the RV endocardium that assists in improving reproducibility. Although semi-automated and fully automated software may help improve reproducibility by consistently identifying the same region of interest, this does not mean that the strain values will be accurate. The suggested region of interest may be incorrect and require manually adjusted (otherwise strain values, while reproducible, could be erroneously high or low).

4.1.4.5 Echocardiography study image quality and reproducibility

The reviewed literature suggests that RV-STE strain analysis is highly reproducible. There is a caveat to this, none of the reproducibility analyses assessed reproducibility against the image quality of echocardiography studies. It is logical to hypothesise that echocardiography studies with poorer image quality are more likely to have less reproducible strain values. As image quality deteriorates, the assessment by the observer of where the RV endocardium border lies becomes more subjective. The effect of echocardiography study image quality upon reproducibility of strain values is an important area for future research.

4.1.5 Validity of RV-STE in ICU studies

Four disease groups were identified from the literature search of ICU studies investigating RV-STE; sepsis, ARDS, COVID-19, and PE. The validity of RV-STE in each of these groups is described in this order below.

4.1.5.1 Validity of RV-STE in ICU patients with sepsis

Four studies were identified from the literature search that investigated RV-STE strain analysis in patients with sepsis. Predictive validity and construct validity were investigated in these studies. They are described below and are summarised in Table 4-6.

4.1.5.1.1 Predictive validity of RV-STE in patients with sepsis

Evidence to support the predictive validity of RV-STE has been found by two studies. Orde et al prospectively assessed the ability of RV-STE strain to predict 6-month mortality in 60 patients admitted to ICU with sepsis[195]. They found that RVFWLS was –16.0% (5.7) in non-survivors, significantly worse than -19.3% (4.9) in survivors ($p<0.05$, Table 4-6). De Braga Lima Carvalho Canesso et al performed a similar study in patients with sepsis, and found RVGLS was significantly reduced in non-survivors at -16.3% (6.1) compared to -21.3%, (4.9) in survivors ($p=0.042$)[196]. It is striking how similar the RV-STE strain values are in non-survivors and survivors in both studies, this consistent finding represents a convincing association between impaired RV-STE and mortality, and supports the predictive validity of RV-STE strain analysis in patients with sepsis. Although the association identified is supportive of predictive validity, it is important to recognise that predictive statistics have not been performed (which would provide stronger evidence). Both studies did not identify any significant difference between RVFAC values in non-survivors and survivors, suggesting that this conventional RV echocardiography parameter does not have the same predictive validity in this group.

4.1.5.1.2 Construct validity of RV-STE in patients with sepsis

Dalla et al investigated the construct validity of STE strain analysis in patients with sepsis[191]. Their hypothesis was that patients with sepsis would demonstrate a septic cardiomyopathy, and that RVFWLS would be able to detect this, representing the relationship between a formative item (sepsis induced cardiomyopathy) and impaired RV function. Patients with sepsis, and septic cardiomyopathy, would therefore be expected to have impaired RVFWLS, compared to trauma patients and healthy controls. The group found that RVFWLS was significantly impaired in patients with sepsis compared to trauma patients and healthy controls (Table 4-6). Patients with sepsis were however older with more physiologically derangement (higher Simplified Acute Physiology Score II scores) and higher rates of IMV compared to the trauma group. It is noteworthy that when De Braga Lima Carvalho Canesso et al[196] adjusted for sequential organ failure assessment (SOFA) score (as a measure of physiological derangement, Table 4-6), they still found impaired RVGLS to be independently associated with mortality in patient with sepsis. It is therefore possible that the same is true for the Dalla et al study, and that RVFWLS might still be associated with mortality if physiological derangement was adjusted for. However, even if we were to conclude that RVFWLS is impaired in sepsis compared to trauma patients, Dalla et al did not demonstrate that impaired RV-STE is identifying a septic cardiomyopathy since it did not demonstrate that patients with sepsis had septic cardiomyopathy using conventional echocardiography, electrocardiography (ECG), or biomarker measures[197]. Whilst construct validity was suggested, it was not convincingly demonstrated.

A few years later, the same group performed an interesting small study in 11 patients with sepsis which demonstrated that RV-STE strain improves with higher mean arterial blood pressure (MAP). Dalla et al 2019 used a randomised crossover design to titrate noradrenaline to a high MAP (90mmHg) and low MAP (60mmHg) target, from a usual target of 75mmHg[192]. MAPs were held at the high or low level for 10 minutes, with contemporaneous echocardiography. A PA catheter was used to measure cardiac output and PVR during the experiment. Compared to the baseline MAP of 75mmHg, RVFWLS became significantly impaired at a MAP of 60mmHg, and significantly improved at a MAP of 90mmHg

(Table 4-6). TAPSE and S' values were normal at all MAP targets. Physiologically, there is sound logic that noradrenaline could improve RVFWLS, possible mechanisms for this include a combination of increased coronary perfusion from higher systemic pressures, venoconstriction with improved preload, and noradrenaline induced inotropy from beta adrenoreceptor agonism. The relationship between higher MAPs from noradrenaline administration and RV function could therefore represent a formative item relationship, with the expected incremental improvement in RVFWLS being observed with increasing noradrenaline dose and higher MAP. These findings represent construct validity with respect to this formative item relationship.

Overall, the studies described have convincingly shown that RV-STE strain is reduced in patients with sepsis, and this is associated with mortality suggesting predictive validity. Construct validity was demonstrated with regards the observation of the expected relationship between higher MAPs (from noradrenaline administration) and improved RVFWLS. Vasopressor therapy was shown to improve RV-STE strain, and this may represent an aspect of the efficacy of vasopressor treatment.

Table 4-6 ICU studies investigating RV-STE validity in patients with sepsis

Type of validity	Study	(n)	Study overview	Result				
Predictive validity	Orde et al 2014[195]	60	Prospective study RVFWLS analysis in patients with sepsis. Association with 6-month mortality.	RVFWLS (%)		Survivors (n=31) -19.3 (4.9)	Non survivors (n=29) -16.0 (5.7)	p-value <0.05
				RVFWLS as predictor of mortality using multivariable logistic regression adjusting for IMV:				
				Severe impairment (>-13%) vs non-severe impairment (<-13%)		OR 11.9	95%CI 1.9-232	p-value 0.03
	de Braga Lima Carvalho Canesso et al 2019[196]	26	Prospective study RVGLS in patients with sepsis. Association with in-hospital mortality	Hospital mortality RVGLS (%)		Survivors (n=19) -21.3 (4.9)	Non-survivors (n=7) -16.3 (6.1)	p-value 0.042
				RVGLS as predictor of mortality using multivariable logistic regression adjusting for SOFA score:				
				RVGLS/%		OR 0.76 (95%CI 0.59-0.98)		p-value 0.033
Construct validity	Dalla et al 2015[191]	88	Retrospective study RVFWLS in patients with sepsis and trauma.		Healthy controls (n=16)	Sepsis (n=48)	Trauma (n=24)	p-value Sepsis vs trauma
				RVFWLS (%)	-28.8 (2.8)	-19.5 (5.4)	-24.7 (5)	<0.001
				Subgroup of LVEF>50% RVFWLS (%)		-20.8 (5.5)	-25.0 (5)	p-value 0.008
	Dalla et al 2019[192]	11	Prospective study RVFWLS in patients with septic shock	MAP (mmHg)	60	75	90	Repeated measures ANOVA p=0.003
				RVFWLS (%)	-19 (4)	-21 (5)	-25 (5)	

p-values are for unpaired T-test, unless otherwise stated. Strain values are given as mean (standard deviation). ICU = intensive care unit, RV-STE = right ventricular speckle tracking echocardiography, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, OR = odds ratio, SOFA = sequential organ failure assessment, LVEF = left ventricular ejection fraction, MAP = mean arterial pressure, ANOVA = analysis of variance.

4.1.5.2 Validity of RV-STE in ICU patients with ARDS

Patients with ARDS experience pathophysiological processes that can impair RV function. Atelectasis, hypoxic pulmonary vasoconstriction, combined with positive pressure ventilation adversely affect RV afterload and RV function. It would seem logical therefore that RV-STE will be impaired in this cohort, with inherent face validity. Four studies have investigated RV-STE strain in patients with ARDS, exploring predictive and construct validity (Table 4-7). RV-STE strain analysis in ARDS patients has not been compared to a gold standard, concurrent criterion validity has therefore yet to be investigated.

4.1.5.2.1 Predictive validity of RV-STE in patients with ARDS

Two groups have investigated the predictive validity of RV-STE strain analysis in ARDS patients, with conflicting results. In 2018, Bonizzoli et al were the first group to investigate RV-STE as a predictor of mortality in moderate to severe ARDS (as defined by the Modified Berlin criteria)[177]. RVFWLS was significantly associated with mortality (Table 4-7). Of note TAPSE was also significantly associated with mortality, however values were within the normal range for both non-survivors and survivors making it less useful for prognostication. AUROCC of RVFWLS as a predictor of survival was 0.69, with a cut-off of -13% (sensitivity 0.73, specificity 0.77) having the highest level of discrimination. It is noteworthy that -13% is the same RVFWLS cut-off Orde et al (Table 4-6) found for predicting survival in septic shock, suggesting this may be a useful cut-off across different system pathologies.

A French group, Lemarie et al, repeated a similar study to Bonizzoli et al, with 48 patients with moderate to severe ARDS[178]. Unusually, they analysed STE of the RV free wall, septum, and inferior wall (using a RV focused apical 2 chamber approach). STE analysis of the inferior RV wall has not been described in any other ICU group and has therefore not been validated. By day 90, 29.2% patients had died, similar to 33.3% in the Bonizzoli study. They found no association between RV free, septal, or inferior wall STE strain and mortality (Table 4-7). The mean RVFWLS was -18.7% (7.5) in day 28 non-survivors, compared to -20.3% (6.1) in survivors (p=0.49). These RVFWLS values are considerably better than

the those found by Bonizzoli et al. Patients in both studies were of similar ages, and appeared to have similar severity of ARDS with comparable PaO_2:FiO_2 ratios and levels of PEEP (there were no descriptions of other airway pressure parameters in the Bonizzoli study). Pneumonia was the main cause of ARDS in both studies. There was higher vasopressor use in the Lemarie study (66.6%) compared with the Bonizzoli study (36.7%), but with similar systolic blood pressures. As described by Dalla et al 2015[191] (Table 4-6), vasopressor support has been shown to improve RVFWLS, so this may have contributed to the better strain seen by Lemarie et al. Of note, TAPSE again was significantly associated with mortality, and was borderline abnormal in day 28 non-survivors. Given these conflicting findings, the predictive validity of RVFWLS in the ARDS population remains to be established.

Table 4-7 ICU studies investigating RV-STE validity in patients with ARDS

Type of validity	Study	(n)	Study overview	Result			
Predictive validity	Bonizzoli et al 2018[177]	30	Prospective study RVFWLS in patients with ARDS Mortality outcome- ICU survival		Survivors (n=20)	Non-survivors (n=10)	p-value
				RVFWLS (%) TAPSE (mm)	-16.3 (0.1) 21.5 (4)	-10.4 (0.05) 18.3 (3)	0.001 0.034
				RVFWLS AUROCC for predicting mortality in ICU: 0.69 (95%CI 0.55–0.84) p= 0.014. Optimal cut-off -13%			
	Lemarie et al 2020[178]	48	Prospective study RVFWLS and RVGLS (including RV inferior wall) in patients with ARDS Mortality outcome- D28 survival		Survivors (n=34)	Non-survivors (n=14)	p-value
				RVFWLS (%) TAPSE (mm)	-20.3 (6.1) 19.6 (4.7)	-18.7 (7.5) 15.8 (5)	0.49 0.02
Construct validity	Mercado et al 2018[198]	24	Prospective study Effect of a period of high PEEP on RVFWLS in patients with ARDS		Baseline PEEP (11 +/-4cmH_2O)	PEEP 40cmH_2O	p-value
				RVFWLS (%) TAPSE (mm)	-19 (5) 19.3 (6)	-14 (6) 15.1 (6)	<0.05 <0.005
	Franchi et al 2013[199]	20	Prospective study **(NON-ARDS)** Effect of different levels of PEEP on RVGLS in non-hypoxic patients requiring intubation for airway protection	PEEP (cmH_2O)	5	10	15	p-value (5 vs 15)
				RVGLS (%)	-20.2 (2.1)	-19.9 (2.9)	-16.3 (1.2)	<0.05
	Garcia-Montilla et al 2017[193]	51	Retrospective study RVFWLS as a measure of fluid balance status in patients with ARDS.	RVFWLS correlated with CVP: Pearson's r=0.74 p<0.001 U-shaped relationship observed between RVFWLS and creatinine.			

p-values are for paired/unpaired T-test, unless otherwise stated. Continuous variables are presented as mean (standard deviation). ICU = intensive care unit, RV-STE = right ventricular speckle tracking echocardiography, ARDS = acute respiratory distress syndrome, RVFWLS = right ventricular free wall longitudinal strain, TAPSE = tricuspid annular plane systolic excursion, AUROCC = area under the receiver operated characteristic curve, PEEP = positive end expiratory pressure, RVGLS = right ventricular global longitudinal strain, CVP = central venous pressure.

4.1.5.2.2 Construct validity of RV-STE in ICU patients with ARDS

Positive pressure ventilation with high airway pressures can be associated with alveolar distension and impaired blood flow through capillary beds resulting in increased PVR, as has been well described by the West zone model[200]. The associated increase in RV afterload can impair RV function, representing the relationship between a formative item and RV function. If RV-STE is impaired in patients receiving positive pressure ventilation with higher airway pressures, it will have demonstrated construct validity with regards to this formative item relationship. Mercado et al investigated RVFWLS in patients with ARDS undergoing a recruitment manoeuvre with high PEEP[198]. In a single centre prospective study, 20 patients with moderate to severe ARDS underwent a stepwise recruitment manoeuvre, whereby PEEP was first set at 25cmH_2O from baseline, and increased by 5cmH_2O every 2 minutes until a maximal level of 40cmH_2O. Contemporaneous echocardiography was performed at baseline PEEP (11 +/- 4cmH_2O) and at a PEEP of 40cmH_2O. As expected, PaO_2 significantly improved during the recruitment manoeuvre. Baseline RVFWLS was -19% (5), similar to that found by Lemarie et al[178]. There was a significant deterioration in RVFWLS to -14% (6) at a PEEP of 40cmH_2O ($p<0.05$, Table 4-7). This was also associated with a significant decrease in TAPSE, but no change in S'. These parameters all normalised once the recruitment manoeuvre ceased. This study suggests that RVFWLS detected the expected impairment in RV function associated with very high airway pressures during recruitment manoeuvre in patients with ARDS receiving IMV, which conventional RV echocardiography parameters, such as S', did not identify. A limitation of the study is that a single RVFWLS value was obtained at an extreme level of PEEP. From this study it is not clear what happens RVFWLS at modest levels of PEEP. This question was addressed by investigating the effect of mechanical ventilation in non-ARDS patients by Franchi et al[199]. This group measured RVGLS at three levels of PEEP (5, 10, and 15cmH_2O) in 20 patients requiring intubation for non-hypoxic indications. They found that as PEEP increased, RVGLS became more impaired, with RVGLS of -20.2% (2.1) at PEEP of 5cmH_2O deteriorating to -16.3% (1.2) at 15cmH_2O ($p<0.05$, Table 4-7). This study is important because the incremental levels of PEEP used in the study are commonly encountered in ICU and may have

clinically relevant implications. Between the two studies described, there is strong evidence for RV-STE strain analysis demonstrating construct validity in ARDS patients (and those who are receiving IMV for non-hypoxic indications).

Garcia-Montilla et al also investigated the construct validity of RV-STE in patients with ARDS[193]. Their study focused on investigating for association between RV strain and venous congestion (a reflective item with regards RV function) in patients with ARDS. They firstly identified a significant correlation between CVP and RVFWLS, with higher CVPs being associated with more impaired RVFWLS. A U-shaped response was observed between creatinine levels and RVFWLS, with the nadir of creatinine level corresponding to a RVFWLS value of -24%, with rising creatinine levels at higher and lower RVFWLS values. The authors concluded that the U-shaped response represented hypovolaemia with impending pre-renal AKI at more negative RVFWLS, and AKI secondary to RV failure and associated venous congestion at less negative RVFWLS. A key step the study did not address was establishing a U-shaped relationship between CVP and creatinine which would have strengthened their hypothesised relationships between RVFWLS, CVP, and AKI. As such the construct validity of RVFWLS with respect to the reflective item relationship between venous congestion (as measured by CVP) and RV function was demonstrated, however the expected relationship between renal function and RV function was not convincingly established by RVFWLS.

Overall, the studies discussed provide strong evidence for the construct validity of RV-STE analysis in patients with ARDS; specifically with regards to the ability of RV-STE to identify the expected impairment of RV function associated with higher airway pressures (a formative item relationship), and the anticipated increases in CVP associated with impaired RV function (a reflective item relationship). There are conflicting results with regards predictive validity, representing an area where further research is required.

4.1.5.3 Validity of RV-STE in ICU patients with COVID-19

A total of 13 studies were identified from the literature search investigating RV-STE in patients with COVID-19. Four of these studies were from the same research group: Li et al, Sun et al, Xie et al, and Zhang et al[16,174-176]. These studies used an overlapping data set, and the majority of patients were therefore the same in each study. These studies have only been included where they have investigated a different aspect of validity so to not duplicate results and artificially skew any observed effect. No studies compared RV-STE strain analysis to gold standard CMR RVEF, concurrent criterion validity has therefore not been investigated. Several studies have provided data to assess predictive and construct validity. These are described below.

4.1.5.3.1 Predictive validity of RV-STE in patients with COVID-19

The predictive validity of RV-STE strain analysis in patients with COVID-19 has focused on identifying a difference between RV-STE strain values in patients with COVID-19 who survived compared to those that died. Some studies have taken this further, and used a mixture of cox regression, logistic regression, and log rank analysis to predict the risk of mortality associated with impaired RV-STE strain. Several studies have used AUROCC analysis to identify optimal RV-STE strain cut-off values for predicting mortality. These three forms of predictive analyses will be described in this order.

Four studies analysed the difference in RV-STE strain values between patients with COVID-19 that survived and those that died (Table 4-8). Li et al, Stockenhuber et al, and Bursi et al found significantly worse RVFWLS values in patients who died compared to survivors[16,181,182].

Table 4-8 Comparison of RV-STE values between survivors and non-survivors in ICU COVID-19 studies

Study	(n)	Mortality measure	Mortality (%)	RV-STE analysis	All	Survivors	Non-survivors	p-value (T test)
Li et al 2020[16]	120	Median 51 day follow up	15.0%	RVFWLS (%)	-23.5 (4.7)	-24.4 (4.4)	-18.5 (3.1)	<0.001
Stockenhuber et al 2021[182]	34	30-day mortality	44.1%	RVFWLS (%)	-20.4 (1.6)	-24.3 (1.9)	-15.6 (1.7)	0.002
Bursi et al 2020[181]	49	In-hospital mortality	32.7%	RVFWLS (%) RVGLS (%)	-18.0 (6.0) -15.0 (5.0)	-19.0 (5.0) -17.0 (5.0)	-14.0 (6.0) -12.0 (4.0)	0.015 0.008
Park et al 2021[194]	48	In-hospital mortality	27.1%	RVFWLS (%) RVGLS (%)	-16.5 (no SD) Not described	-16.3 (1.1) -14.5 (5.6)	-16.5 (7.9) -14.8 (5.9)	0.94 0.88

Continuous variables are presented as mean (standard deviation). RV-STE = right ventricular speckle tracking echocardiography, ICU = intensive care unit, COVID-19 = coronavirus disease 2019, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain. SD = standard deviation.

Park et al reported no significant difference in RVFWLS or RVGLS values between patients who died and those who survived (Table 4-8)[194]. They reported a more impaired mean RVFWLS of -16.5% (no SD) for all patients with COVID-19 compared to the other three studies. It is not immediately apparent why Park et al found a more impaired overall mean RVFWLS compared to other studies, or why they did not find an association between impaired RV-STE and mortality when other studies did. Comparing patient demographics across the four studies showed that patients were of similar ages, with a comparable incidence of cardiovascular risk factors. Park et al did not report an incidence of IMV, however this was likely to be considerable with patients receiving a mean of 12.6 ventilator days. Gibson et al investigated RVFWLS in patients with COVID-19 who all received IMV, reporting a RVFWLS of -17% (6), similar to Park et al[201]. In addition to the probable high rates of IMV, Park et al used a triage system to decide which patients received echocardiography due to the scarcity of resources during the COVID-19 surge. Echocardiography was preferentially performed on patients who had cardiovascular instability felt to be out of keeping with their COVID-19 illness, and the authors acknowledge this may have biased that data was collected on sicker patients, resulting in a more impaired RVFWLS compared to other studies. This may also have resulted in biasing clinicians, in that they selected patients that were more likely to die to undergo echocardiography, and could explain the lack of association between RVFWLS and mortality.

Three studies used different predictive analyses to assess the ability of RV-STE strain analysis to predict subsequent mortality (Table 4-9). Li et al performed a multivariate cox regression for RVFWLS and found a statistically significant hazard ratio of 1.33 (95%CI 1.15-1.53) where RVFWLS was independently associated with a higher likelihood of mortality when controlling for gender and the presence of ARDS[16]. Stockenhuber et al found a statistically significant hazard ratio supporting a RVFWLS less negative than -20% as a predictor of mortality[182]. Bursi et al performed logistic regression to investigate both RVFWLS and RVGLS as predictors of mortality, they similar found association between more impaired RVFWLS/RVGLS and mortality[181]. Of the three studies, Li et al would appear to have found the most convincing association, with the largest sample size, and small hazard ratio confidence interval. This finding is further

supported by their use of AUROCC analysis described below. Since all three studies used different statistical approaches to prediction analysis it is difficult to directly compare them, however the general finding appears that impaired RVFWLS is predictive of mortality.

Table 4-9 Predictive analysis of RV-STE and mortality in ICU COVID-19 studies

Study	(n)	Mortality (%)	Predictive analysis for mortality	Result
Li et al 2020[16]	120	15.0% (Median 51 day follow up)	Multivariable cox regression: RVFWLS/%	Hazard ratio (95% CI) 1.33 (1.15-1.53) p<0.001
Stocken-huber et al 2021[182]	34	44.1% (30-day mortality)	Log rank analysis: RVFWLS ≤-20% vs >-20%	Hazard ratio (95% CI) 3.19 (1.29-12.91) p=0.02
Bursi et al 2020[181]	49	32.7% (In-hospital mortality)	Univariate logistic regression: RVFWLS/% RVGLS/%	Odds ratio (95% CI) 1.18 (1.03-1.36) p=0.02 1.22 (1.03-1.45) p=0.02

RV-STE = right ventricular speckle tracking echocardiography, ICU = intensive care unit, COVID-19 = coronavirus disease 2019, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, CI = confidence interval.

Li et al and Bursi et al performed AUROCC analysis for prediction of mortality using RV-STE strain (Table 4-10)[16,181]. Li et al found a high AUROCC for RVFWLS of 0.87 (p <0.001). The optimal RVFWLS cut-off was identified as -23%, with a high sensitivity of 94.4% and modest specificity of 64.7%. Although the high sensitivity associated with a cut-off of RVFWLS of -23% is desirable, a RVFWLS cut-off value of -23% is of questionable clinical use. As described in Chapter 2 (section 2.9), the ASE and EACVI have defined an abnormal cut-off RVFWLS strain of >-20%[62]. A RVFWLS cut-off of -23% would therefore be seen as a normal RV strain value, and it may be difficult to justify using this normal RV strain value to guide treatment decisions in COVID-19 patients who are felt unlikely to survive. Bursi et al did not find a statistically significant AUROCC for RVFWLS, but found that RVGLS had a statistically significant AUROCC of 0.79, with an optimal RVGLS cut-off of -18%.

Table 4-10 AUROCC analysis of RV-STE predicting mortality in ICU COVID-19 studies

Study	(n)	Mortality (%)	AUROCC for predicting mortality (SD)	Optimal cut-off value
Li et al 2020[16]	120	15.0% (Median 51 day follow up)	RVFWLS 0.87 (no SD) p<0.001	-23% (sensitivity 94.4%, specificity 64.7%).
Bursi et al 2020[181]	49	32.7% (In-hospital mortality)	RVFWLS 0.77 (0.08) p=0.08 RVGLS 0.79 (0.04) p=0.04	-13.5% (sensitivity 62%, specificity 83%). -18% (sensitivity 69%, specificity 64%)

AUROCC = area under the receiver operated characteristic curve, RV-STE = right ventricular speckle tracking echocardiography, ICU = intensive care unit, COVID-19 = coronavirus disease 2019, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain. SD = standard deviation.

4.1.5.3.2 Construct validity of RV-STE in ICU patients with COVID-19

Much research has been performed in patients with COVID-19 that provides evidence to investigate the construct validity of RV-STE in this group, with hypothesis testing forming the basis of construct validity assessment. As described in Chapter 3, when we conduct hypothesis testing for construct validity, we must have a clearly formed conceptual model of the construct that we are interested in that includes the relationship between formative items and the construct, and between reflective items and the construct. The relationship between mixed items (items that include aspects of both formative and reflective items) can also be assessed. This part of the review will be split into three sections, discussing the construct validity of RV-STE in COVID-19 patients using formative items (i.e. variables that are thought to alter RV function in some way), reflective items (i.e. variables that are thought to be altered as result of a change in RV function), and mixed items. The key to establishing construct validity lies in the demonstration of the expected relationship between the formative/reflective item and RV function (represented by RV-STE). Figure 4-8 gives an overview of this.

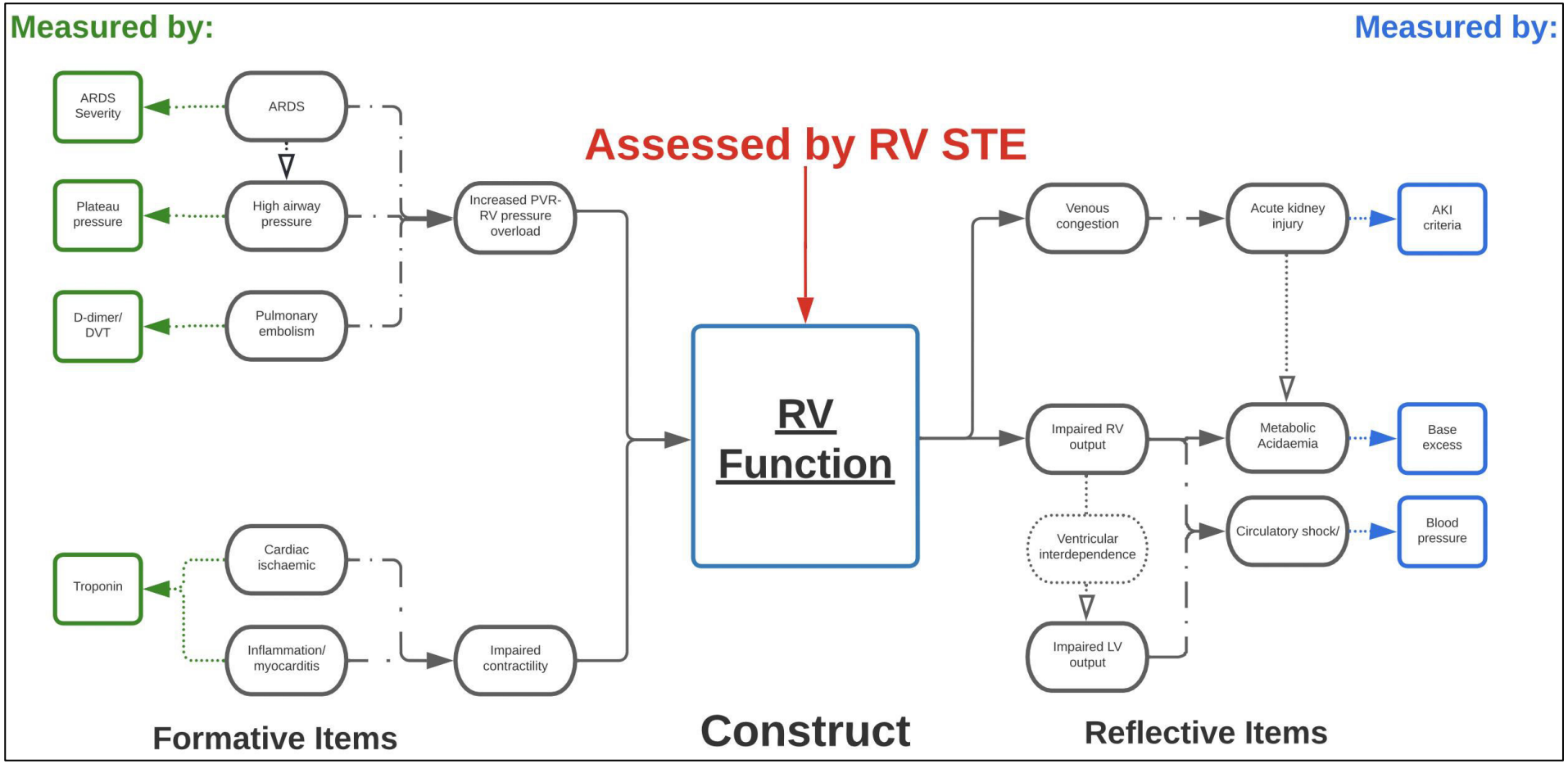


Figure 4-8 Conceptual model for construct validity of RV-STE in ICU patients with COVID-19
The conceptual model shows the construct (RV function) in the centre of the model. Formative items (which are expected to impact upon RV function) are shown on the left, measurements of formative items are shown in green. Reflective items (which are expected to be impacted by changes in RV function) are shown on the right, the measurements of reflective items are shown in blue. RV-STE = right ventricular speckle tracking echocardiography, ICU = intensive care unit, COVID-19 = coronavirus disease 2019, RV = right ventricular ARDS = acute respiratory distress syndrome, DVT = deep vein thrombosis, PVR = pulmonary vascular resistance, AKI = acute kidney injury.

4.1.5.3.3 Construct validity of RV-STE in ICU patients with COVID-19: Formative items

As COVID-19 severity increases, an ARDS phenotype ensues. A number of studies have investigated the relationship between ARDS severity and RV-STE in patients with COVID-19. ARDS represents a formative item that can impair RV function by many mechanisms, including an increase in PVR and RV afterload secondary to atelectasis, hypoxic pulmonary vasoconstriction, and requirement for positive pressure ventilation[5,202]. Li et al investigated the frequency of ARDS in patients with COVID-19 when RV-STE was stratified into tertiles based on RVFWLS values (Table 4-11)[16]. They showed that ARDS was significantly more frequent in patients with more impaired RVFWLS, however they did not find a difference in PaO_2:FiO_2 ratios (a component of the Modified Berlin criteria for defining ARDS severity[203]) between RVFWLS tertiles. Gibson et al also did not find any significant difference between groups with normal and impaired RVFWLS and PaO_2:FiO_2 ratios, nor FiO_2 requirements (Table 4-11)[201]. Contrary to expected findings, Gibson et al found that patients with impaired RV-STE values were associated with significantly greater lung compliance and lower plateau pressures compared to patients with normal RV-STE, they did not hypothesise a mechanism that might explain this counterintuitive finding. Bursi et al did not find any association between RVFWLS and PaO_2:FiO_2 ratios, nor did they find association between RVFWLS and SpO_2 (Table 4-11)[181]. In summary a consistent relationship between ARDS severity and COVID-19 has not been convincingly demonstrated as would be expected based on the conceptual model, therefore construct validity has not been established in this regard. Figure 4-9 provides shows an overview of the conceptual model assessing construct validity annotated with the evidence provided by the relevant literature (for the currently described formative items, and reflective items described below).

COVID-19 is primarily a disease of the pulmonary system, however it also a multisystem disease. A prothrombotic state has been recognised with COVID-19, with increased incidence of thrombosis[204,205]. Additionally myocardial injury has been identified as a common disease manifestation[206]. Both presence of pulmonary embolism and myocardial injury are likely to impair RV function, and

are therefore formative items in the conceptual model. If a relationship between pulmonary embolism and myocardial injury and RV-STE can be demonstrated, this will support construct validity. This is described below.

Three studies have investigated the relationship between a prothrombotic state in patients with COVID-19 and RV-STE, with conflicting results. Baycan et al found a significant positive correlation between impaired RVFWLS values and higher D-dimer values, suggestion thrombosis is associated with RV dysfunction (Table 4-11)[180]. Li et al found significantly higher rates of deep vein thrombosis (DVT) in patients with more impaired RVFWLS values when divided into tertiles, however they did not find an association between impaired RVFWLS and D-dimer levels (although this did approach significance; p=0.053, Table 4-11)[16]. Finally, Stockenhuber et al found no difference in D-dimer values between impaired and normal RVFWLS groups[182]. It is important to note that none of the studies described if patients were receiving pharmacological prophylaxis for venous thromboembolism or full anticoagulation treatment. This possibly introduced heterogeneity diluting any true association between RVFWLS and D-dimer. A final consideration is that D-dimer has previously been shown to have poor specificity for diagnosing pulmonary embolism[207], which could result in a lack of association between D-dimer impaired RVFWLS. D-dimer may therefore not represent a perfect measure of venous thromboembolism for use in the formative item relationship with RV function, as used in the conceptual model for construct validity (Figure 4-8).

Four studies have investigated the relationship between myocardial injury and RV-STE, with inconsistent outcomes. Xie et al conducted one of the largest studies with 132 patients, they found significantly more impaired mean RVFWLS of -21.1% (3.8) in patients with cardiac injury compared to a mean RVFWLS value of -23.5% (5.2) in patients without cardiac injury (p=0.009, Table 4-11)[175]. Baycan et al similarly found a significant correlation between more impaired RVFWLS values and rising troponin values[180]. Two studies have however found conflicting results. Stockenhuber et al showed higher troponin values in patients with impaired RVFWLS compared to normal RVFWLS, but this did not reach significance (this study was not powered for this secondary outcome)[182]. Gibson et al conducted a small study in 32 invasively mechanically ventilated

patients[201]. They found no significant difference between troponin values in groups with normal and impaired RVFWLS, and found a significant negative correlation between RVFWLS and troponin values, whereby better (more negative) RVFWLS values were correlated with higher troponin measurements (Table 4-11). The authors did not suggest a mechanism to explain this result. It is questionable if there is biological plausibility to support why more impaired RV strain values would be associated with lower troponin values. A possible explanation would be that the assumed relationship between RVD and troponin release is incorrect, and that the increased troponin level is from a pathology separate to RVD. Overall, the results from these studies have been inconsistent in establishing a relationship between myocardial injury and RV-STE.

Table 4-11 ICU COVID-19 studies assessing construct validity of RV- STE using formative item relationships

Type of validity	Study	(n)	Result				
Construct validity **Formative items:** ARDS severity	Li et al 2020[16]	120		RVFWLS upper tertile (-25.5 to -35.7%)	RVFWLS middle tertile (-20.6 to -25.4%)	RVFWLS lower tertile (-10.3 to -20.5%)	p-value (one way ANOVA/ Kruskal Wallis)
			ARDS (%)	25	25	52.5	0.011
			PaO_2:FiO_2 (mmHg)	254 [221.9-287.9]	167.5 [152.7-269.6]	178.8 [140-210.8]	0.282
			D-dimer (mg/l)	0.76 [0.35-2.64]	2.10 [0.49-6.72]	1.84 [0.83-6.13]	0.053
			DVT (%)	30	30	62.5	0.003
Pulmonary embolism Myocardial injury	Gibson et a 2021[201]	32		Normal RVFWLS (≤-20%) (n=11)	Impaired RVFWLS (>-20%) (n=21)	p-value (T-test/ Wilcoxon)	Spearman correlation coefficient
			FiO_2 (%)	50 [40-70]	50 [40-60]	0.457	
			PaO_2:FiO_2 (mmHg)	180 [171-201]	178 [137-258]	0.785	
			Plateau pressure (cmH_2O)	24 (3.0)	21 (4.4)	0.043	
			Lung compliance (ml/cmH_2O)	27.5 [24.4-33.2]	33.3 [32.3-45.7]	0.004	
			D-dimer (ng/ml)	2203 [1351-4184]	2032 [110-3016]	0.457	r= -0.402
			Troponin (ng/l)	31 [16-54]	19 [11-35]	0.656	(p=0.034)
	Bursi et al 2020[181]	49	Correlation between RVFWLS and clinical parameters associated with severity of COVID-19 disease				
					Pearson correlation coefficient with RVFWLS		
					r	p-value	
			PaO_2:FiO_2		0.007	0.967	
			SpO_2		-0.202	0.223	
			CT severity lung score		-0.05	0.781	

	Baycan et al 2020[180]	100		Spearman correlation coefficient with RVFWLS		
				r	p-value	
			D-dimer Troponin	0.620 0.608	<0.001 <0.001	
	Stockenhu-ber et al 2021[182]	35		Normal RVFWLS (≤-20%)	Impaired RVFWLS (>-20%)	p-value (T-test)
			D-dimer (Units not given) Troponin (Units not given)	9212 (2721) 479 (208)	12540 (4480) 1144 (602)	0.51 0.26
			Normal RVFWLS n= 17, impaired RVFWLS n= 13			
	Xie et al 2021[175]	132		All	Cardiac injury (n=40)	No cardiac injury (n=92)	p-value (T-test)
			RVFWLS (%)	-22.8 (4.9)	-21.1 (3.8)	-23.5 (5.2)	0.009
			Significant difference in TAPSE between no-cardiac injury and cardiac injury group (but with normal values in each group), no difference in S' or RVFAC between groups Cardiac injury defined as HsTn >99th centile			

ICU = intensive care unit, COVID-19 = coronavirus disease 2019, RV-STE = right ventricular speckle tracking echocardiography, RVFWLS = right ventricular free wall longitudinal strain, FiO_2 = fraction of inspired oxygen, PaO_2 = partial pressure of oxygen, SpO_2 = peripheral oxygen saturation, ARDS = acute respiratory distress syndrome, DVT = deep vein thrombosis, CT = computed tomography, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RVFAC = right ventricular fractional area change, HsTn = high sensitivity troponin, ANOVA = analysis of variance.

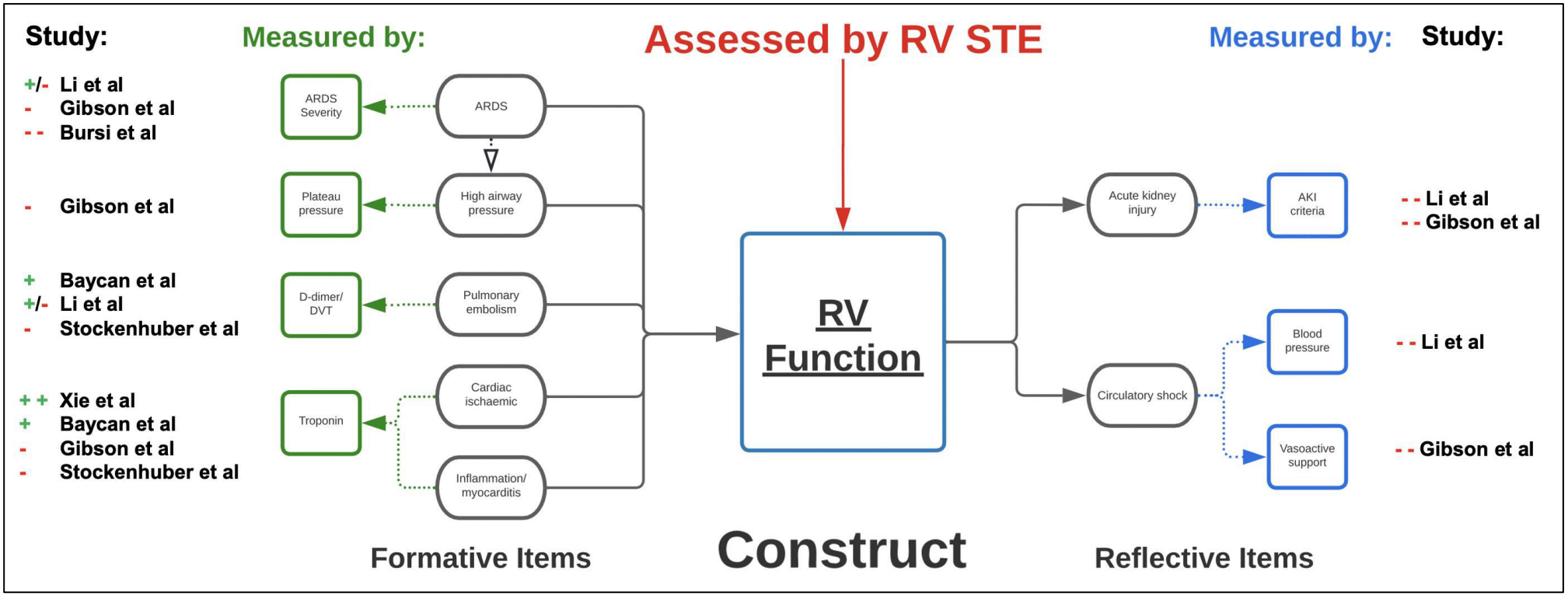


Figure 4-9 Literature assessing construct validity of RV-STE in ICU patients with COVID-19

The conceptual model for the construct validity of RV-STE in ICU patients with COVID-19 includes the relevant research studies identified by the literature search. A positive and minus coding system has been used to provide an overview if the study provides evidence that supports or opposes the hypothesised relationship between formative/reflective items and the construct (RV function as assessed by RV-STE).

++ = strongly suggests relationship present, + = suggests expected relationship is present,

+/- = mixed evidence for presence of relationship,

- = evidence against relationship, - - = strong evidence against relationship.

ARDS = acute respiratory distress syndrome, DVT = deep vein thrombosis, RV-STE = right ventricular speckle tracking echocardiography, RV = right ventricular.

4.1.5.3.4 Construct validity of RV-STE in ICU patients with COVID-19: Reflective items

A substantial amount of data exists to investigate the relationship between formative items and RV-STE in patients with COVID-19, but less is available for reflective items. Reflective items are clinical parameters that are altered due to a change in RV function. Acute kidney injury due to venous congestion, and requirement for cardiovascular support are two variables that are likely to be influenced by RV dysfunction; two studies have sought association between RVFWLS and these variables (Table 4-12). Li et al and Gibson et al found no association between impaired RVFWLS and AKI (p=0.259 and p=0.41 respectively)[16,201]. Li et al found no association between RVFWLS and systolic blood pressure (p=0.812), similarly Gibson et al also found no association between impaired RVFWLS and vasoactive inotropic scores (p=0.73).

The currently available data does not support the construct validity of RV-STE when assessed by reflective items, however this interpretation is substantially limited by the sparsity of studies.

Table 4-12 ICU COVID-19 studies assessing construct validity of RV- STE using reflective item relationships

Type of validity	Study	(n)	Result				
Construct validity **Reflective items:**	Li et al 2020[16]	120	 AKI (%) SBP (mmHg)	RVFWLS upper tertile 7.5 131 (22)	RVFWLS middle tertile 12.5 129 (29)	RVFWLS lower tertile 20 132 (19)	p-value (one way ANOVA/ Kruskal Wallis) 0.259 0.812
AKI Hypotension/ cardiovascular support	Gibson et al 2021[201]	32	 AKI (%) Vasoactive inotropic score		Normal RVFWLS (≤-20%) (n=11) 64 6.2 [1.39-13.8]	Impaired RVFWLS (>-20%) (n=21) 48 4.7 [0-10.5]	p-value (T-test/Wilcoxon rank sum) 0.41 0.73

COVID-19 = coronavirus disease 2019, RV-STE = right ventricular speckle tracking echocardiography, AKI = acute kidney injury, RVFWLS = right ventricular free wall longitudinal strain, SBP = systolic blood pressure, ANOVA = analysis of variance.

4.1.5.3.5 Construct validity of RV-STE in ICU patients with COVID-19: Mixed items

Studies investigating RV-STE in patients with COVID-19 have frequently assessed for association between RV-STE and COVID-19 severity scores. Two scoring systems were encountered during the literature search. The first was a COVID-19 specific severity stratification system, this was issued by the National Health Commission and State Administration of Traditional Chinese Medicine in March 2020[208]. As shown in Table 4-13, using this scoring system, severe/critical COVID-19 is defined by both the severity of the respiratory disease (with criteria similar to that for a diagnosis of ARDS, including the need for mechanical ventilation), but also including signs of end organ dysfunction. As described above, the severity of COVID-19 ARDS and effects of mechanical ventilation fall under formative items in the conceptual model (Figure 4-8), whereas end organ failure could present because of RV dysfunction, and therefore be classified as a reflective item. This COVID-19 severity score can be regarded as encompassing both formative and reflective items, and is therefore a mixed item.

The second COVID-19 scoring system encountered was a general classification of COVID-19 pneumonia severity as described by the American Thoracic Society and Infectious Diseases Society of America criteria for community acquired pneumonia[209]. Similarly, this score includes a mixture of severity of respiratory disease as well as signs of end organ dysfunction, and is therefore a composite of formative and reflective items in the conceptual model (Figure 4-8). Recognising the limitation that we cannot distinguish associations between specific item-construct relationships, we can proceed to evaluate the construct validity of RV-STE using COVID-19 severity scores. This will be described using the two severity scores in the order that they were introduced above.

Sun et al conducted a large study with 160 patients using the National Health Commission and State Administration of Traditional Chinese Medicine COVID-19 severity stratification system[174]. They showed that a significantly reduced mean RVFWLS of -18.8% (3.6) in patients with critical COVID-19 disease compared to a mean RVFWLS of -23.9% (4.4) in non-critical COVID-19 disease ($p<0.001$, Table 4-

13). Of note, TAPSE, S', and RVFAC values did not significantly differ between COVID-19 disease severity groups. Baycan et al performed a similar study in 100 COVID-19 patients[180]. They compared RV-STE strain between patients with severe/critical COVID-19 and non-severe/non-critical COVID-19, with the inclusion of a healthy control group for baseline data. Interestingly, they found comparable results to Sun et al, with a mean RVFWLS strain of -17.2% (2.3) in patients with severe/critical COVID-19, significantly worse than non-severe/non-critical COVID-19 patients who had a RVFWLS of -20.5% (3.2) ($p<0.05$, Table 4-13). Again, no difference was found in TAPSE, S', and RVFAC values between the COVID-19 disease severity groups. These two large studies provide strong evidence for an association between RVFWLS and COVID-19 disease severity, when the National Health Commission and State Administration of Traditional Chinese Medicine disease severity system is used. The conventional echocardiography parameters TAPSE, S', and RVFAC did not show the same association with COVID-19 disease severity.

Kim et al used a different approach and investigated for a relationship between RV-STE strain analysis and COVID-19 severity using the American Thoracic Society and Infectious Diseases Society of America criteria for community acquired pneumonia[179,209]. This classification was published in October 2019, pre-dating the COVID-19 pandemic, and was therefore not designed specifically for COVID-19. They found no difference between median RVFWLS or RVGLS values in severe and non-severe COVID-19 pneumonia groups, although p values approached significance ($p=0.07$ and $p=0.06$ respectively). This was a small study consisting of 40 patients, with no power analysis and as such is at risk of type-2 error. The authors acknowledged the limitations of small sample size, and describe the drop in COVID-19 cases from February-March 2020 in South Korea as the underlying reason. A further reason why this study may not have found an association between RV-STE strain values and COVID-19 severity groups is that Kim et al used a classification system designed for general community acquired pneumonia, whereas Sun et al and Baycan et al used a classification system designed specifically for COVID-19. Given that Kim et al performed their study prior to the release of the COVID-19 severity stratification recommended by the National Health Commission and State Administration of Traditional Chinese

Medicine, it would seem acceptable that they used a general community acquired pneumonia severity score at this early stage in the pandemic.

Beyond COVID-19 scoring systems, general measures of organ dysfunction and their relationship with RV-STE have been reported. SOFA scores provide a global score for dysfunction of the respiratory, cardiovascular, renal, hepatobiliary, central nervous (CNS), and haematological organ systems[210]. SOFA score therefore consists of both formative items (measures of ARDS severity: requirement for IMV, FiO_2, and PaO_2) and reflective items (such as renal and hepatobiliary dysfunction secondary to venous congestion from RVD) and is therefore a mixed item. Gibson et al and Bursi et al investigated SOFA scores, finding no association between SOFA scores and impaired RVFWLS (p=0.63 and p=0.686 respectively)[181,201]. Given that the SOFA score incorporates organ systems that may not be influenced by RVD (such as the haematological system), this may have weakened any signal and true association between RV-STE and organ systems that may induce or be affected by RVD that are included in the SOFA score.

In conclusion, RV-STE has construct validity when used to assess for an association between RVD and worse COVID-19 disease severity defined by the National Health Commission and State Administration of Traditional Chinese Medicine classification system. RV-STE strain analysis did not show an association with COVID-19 disease severity when non-specific disease classification systems were used (such as that for community acquired pneumonia), nor when general organ dysfunction scoring systems (i.e. SOFA) were used. The formative items of prothrombotic state (as assessed by higher D-dimer levels and confirmed DVT) and myocardial injury (as assessed by troponin) inconsistently associated with impaired RV-STE, suggesting possible presence of construct validity for these formative item relationships which requires further research to firmly establish. ARDS severity did not demonstrate a convincing relationship with RV-STE as was expected from the conceptual model. Similarly, no substantial evidence was found to support relationships between reflective items (AKI, hypotension/requirement for cardiovascular support) and RV-STE. Given the sparsity of data available to investigate the construct validity of RV-STE in patients with COVID-19 using reflective items, this is an obvious area that would

benefit from further research. Reflective items that could be used include signs of venous congestion, signs of renal and liver impairment, vasopressor and inotropy requirement, and acid-base balance disorder.

Table 4-13 ICU COVID-19 studies assessing construct validity of RV- STE using mixed item relationships

Type of validity	Study	(n)	Result				
Construct validity **Mixed items** COVID-19 severity SOFA score	Sun et al 2021[174]	160	RVFWLS (%)	All patients -22.3 (4.8)	Critical (n=50) -18.8 (3.6)	Non-critical (n=110) -23.9 (4.4)	p-value (T-test) p<0.001
			No significant difference in TAPSE, S', and RVFAC between critical and non-critical groups Critical= respiratory failure requiring mechanical ventilation, shock, or organ dysfunction requiring ICU				
	Baycan et al 2020[180]	100		Healthy control (n=45)	Severe/Critical (n=44)	Non-severe/ Non-critical (n=56)	p-value (T-test) (severe/critical vs non-severe/non-critical)
			RVFWLS (%)	-27.3 (3.1)	-17.2 (2.3)	-20.5 (3.2)	p<0.05
			No significant different in TAPSE, S', RVFAC between severe and non-severe groups Severe/Critical COVID-19 = RR ≥30 at rest, SpO_2 <93%, PaO_2:FiO_2 <300mmHg, septic shock, multiorgan failure requiring ICU, or mechanical ventilation.				
	Kim et al 2020[179]	40		Severe (n=13)		Non-severe (n=27)	p-value (Mann-Whitney U Test)
			RVFWLS (%)	-22.7 [-27.2, -18.6]		-28.8 [-30.4, -24.1]	p=0.07
			RVGLS (%)	-19.3 [-23.9, -18.4]		-24.3 [-26, -22.6]	p=0.06
			Severe COVID-19 pneumonia defined by American Thoracic Society and Infectious Diseases Society of America criteria for CAP[209], one of two major criteria (septic shock with need for vasopressors or respiratory failure requiring mechanical ventilation), or three out of nine minor criteria.				
	Gibson et al 2021[201]	32	SOFA score	Normal RVFWLS (≤-20%) 8.1 (2.2)		Impaired RVFWLS (>-20%) 8.5 (2.5)	p-value (T-test/Wilcoxon) p=0.63
	Bursi et al 2020[181]	49	SOFA score	Pearson correlation coefficient (r) with RVFWLS -0.69 p=0.686			

COVID-19 = coronavirus disease 2019, RV-STE = right ventricular speckle tracking echocardiography, SOFA = sequential organ failure assessment, RVFWLS = right ventricular free wall longitudinal strain TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RVFAC = right ventricular fractional area change, RR = respiratory rate, PaO_2 = partial pressure of oxygen, FiO_2 = fraction of inspired oxygen, ICU = intensive care unit, CAP = community acquired pneumonia.

4.1.5.4 Validity of RV-STE in ICU patients with pulmonary embolism

Three studies were identified by the literature search investigating the validity of RV-STE in ICU patients with PE. All three studies described RV STE strain analysis as a predictor of mortality for patients with acute pulmonary embolism in ICU, with conflicting results (Table 4-14). The studies did not investigate any other forms of validity.

Two studies provided strong evidence to support the predictive validity of RV-STE strain analysis in patients with PE. Kanar et al performed a large prospective study in 146 patients to investigate for association between RVGLS and 30-day mortality[211]. They found a significantly more impaired mean RVGLS of -16.8% (4.4) in non-survivors compared to -19.6% (3.4) in survivors (p=0.02, Table 4-14). Dahhan et al also found RVGLS to be a significantly associated with 30-day mortality, with a median RVGLS in non-survivors of -15.7% [-19.2, -12.1%] compared to -18.6% [-21.8, -15.6%] in survivors (p=0.05, Table 4-14)[185]. The RVGLS values in survivors and non-survivors are similar in both studies. Additionally, both studies performed logistic regression, yielding similar odds ratios for RVGLS as a predictor of mortality. These consistent findings suggest predictive validity based on these two studies.

A large retrospective study performed by Khemasuwan et al found conflicting results, they found no association between RVGLS or RVFWLS and mortality, even after they conducted a sensitivity analysis and performed strain analysis only on echocardiography studies they deemed “optimal” (Table 4-14)[184]. They did not however provide any data on RV strain values in their paper, so it is difficult to establish where the differences lie between this study and the other two. The incidence of mortality was similar between all three studies. TAPSE values in non-survivors and survivors were almost identical in Kanar et al and Khemasuwan et al, additionally systolic pulmonary artery pressures were similar in non-survivors and survivors in these two studies suggesting that afterload was similar in both groups. Baseline demographics were not presented by Khemasuwan et al, so it is not possible to compare underlying co-morbidities of the groups.

An area where the studies may have differed was the time that echocardiography was performed after PE diagnosis. Khemasuwan included patients if echocardiography was performed <72h after PE diagnosis, Dahhan included patients only if they had an echocardiography 24-48h after diagnosis, and Kanar et al included patients who had an echocardiography at "the onset of acute episode" which given the prospective design was likely to be soon after PE diagnosis. If Khemasuwan et al performed echocardiography at a later time period than the other two studies this could have introduced survivorship bias where patients with impaired RVGLS had already died before echocardiography took place, and this may explain why RVGLS was not significantly different between groups. A further area where the studies may have differed is in exclusion criteria. Kanar et al excluded patients with a history of left ventricular systolic dysfunction, valvular disease, cardiomyopathy, and coronary artery disease, whereas Khemasuwan et al included these patients. If the patient groups in Khemasuwan et al had impaired RVGLS prior to PE due to cardiac disease, this may explain why no difference in RVGLS was found between them. The vendor of strain analysis software differed between all three studies, this may have introduced some variation in the results found.

In summary, the consistent findings by the large prospective study by Kanar et al and the smaller retrospective trial by Dahhan et al, and limitations discussed with the contradictory Khemasuwa study, suggests that the predictive validity of RV-STE strain analysis in ICU patients with acute PE has been established.

Table 4-14 ICU studies investigating RV-STE validity in patients with pulmonary embolism

Type of validity	Study	(n)	Study overview	Result			
Predictive validity	Kanar et al 2019[211]	142	Prospective study RVGLS and association with 30-day mortality in patients with PE		Non-survivors (n=28)	Survivors (n=114)	p-value (T-test)
				RVGLS (%)	-16.8 (4.4)	-19.6 (3.4)	0.02
				TAPSE (mm)	15.0 (2.3)	18.3 (3.4)	0.001
				sPAP (mmHg)	56 (27)	43 (20)	0.06
				Incidence of 30-day mortality 19.7%. No significant difference in RIMP or S' values between non-survivors and survivors Univariate logistic regression analysis of strain association with survival: RVGLS/%: OR 0.81 (0.67, 0.97) (p=0.02)			
	Dahhan et al 2016[185]	69	Retrospective study RVGLS and RVFWLS and association with 30-day mortality in patients with PE		Non-survivors (n=14)	Survivors (n=55)	p-value (Kruskal-Wallis)
				RVGLS (%)	-15.7 [-19.2, -12.1]	-18.6 [-21.8, -15.6]	0.05
				RVFWLS (%)	-15 [-18.7, -10.3]	-19.2 [-23.2, -14.3]	0.04
				TAPSE (mm)	19 [16-22]	21 [1.2-2.4]	0.82
				Incidence of 30-day mortality 20.3%. Univariate logistic regression analysis of strain association with survival: RVGLS/%: OR 0.88 (0.78, 0.99) (p=0.03) RVFWLS/%: OR 0.9 (0.82, 1.00) (p=0.05)			
	Khemasuwan et al 2015[184]	211	Retrospective study RVGLS and RVFWLS and association with in-hospital mortality in patients with PE		Non-survivors (n=38)	Survivors (n=173)	p-value (T-test)
				TAPSE (mm)	15 (4)	17 (5)	0.02
				sPAP (mmHg)	52 (23)	42 (17)	0.01
				Incidence of in-hospital mortality 18.0%. No association with RVGLS or RVFWLS and mortality outcomes. Data not supplied in main text or supplementary materials.			

ICU = intensive care unit, RV-STE = right ventricular speckle tracking echocardiography, PE = pulmonary embolism, RVGLS = right ventricular global longitudinal strain, RVFWLS = right ventricular free wall longitudinal strain, TAPSE = tricuspid annular plane systolic excursion, sPAP = systolic pulmonary artery pressure, RIMP = right ventricular index of myocardial performance, S' = S' wave velocity at the tricuspid annulus, OR = odds ratio.

4.2 The utility of right ventricular speckle tracking echocardiography in the perioperative period: a review of the literature

4.2.1 Search strategy methods

The search strategy was created by the author, and was reviewed and approved by Mr. Paul Cannon (University of Glasgow College Librarian) on 07/10/2021. The literature search was performed on the NHS Greater Glasgow and Clyde library network on 07/10/2021. The search strategy was conducted using Ovid Medline (R) Database, 1946 to Present. It is presented below with the numbers in right hand column representing number of hits:

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to October 07, 2021>

1	Perioperative Medicine/ or Perioperative Care/ or Perioperative Period/ or Perioperative Nursing/	25700
2	periop*.mp.	117568
3	peri-op*.mp.	7973
4	preop*.mp.	360759
5	pre-op*.mp.	37663
6	postop*.mp.	897127
7	post-op*.mp.	83360
8	Ventricular Function, Right/	7119
9	Ventricular Dysfunction, Right/	6443
10	right ventric*.mp.	63907
11	(echo* adj5 speckle).mp.	3945
12	(track* adj5 speckle).mp.	5785
13	deformation.mp.	50238
14	1 or 2 or 3 or 4 or 5 or 6 or 7	1186297
15	8 or 9 or 10	65898
16	11 or 12 or 13	54732
17	14 and 15 and 16	125

Studies were included if they investigated 2D RV-STE using transthoracic echocardiography. Studies investigating 3D RV-STE, or that used trans-oesophageal echocardiography, were excluded. Abstracts were reviewed for the 125 articles identified by the search, with 7 studies being identified as relevant to the literature review area of interest. No further studies of relevance were identified from reviewing the reference lists. An overview of these studies is shown in Appendix Table 2. A discussion of the feasibility, reproducibility, and validity of RV-STE in perioperative studies is described below.

4.2.2 Feasibility of RV-STE in perioperative studies: Methods

Of the seven relevant studies identified from the literature search, five reported RV-STE feasibility (shown in Table 4-15). Two studies did not report an RV-STE feasibility since they did not describe the number of echocardiography studies they excluded due to poor image quality, and these research studies were therefore excluded from the feasibility review. Five studies in total were therefore included for literature review of RV-STE feasibility, a meta-analysis was performed on these studies using the methods described above in section 4.1.3.1.2.

Table 4-15 Perioperative studies that describe RV-STE feasibility identified by literature search

Study	Perioperative group	Number of echo studies performed (N)	Number of echo studies with adequate images for strain analysis (n)	Study design (retrospective /prospective)	Strain analysis performed	Approach to inadequately tracking RV segments during strain analysis	Feasibility (n/N as %)	Comment
Sunbul et al 2015[122]	Pulmonary endarterectomy	90	80 (40 pre op + 40 post op)	Prospective	RVFWLS	Not described	88.9%	
McCall et al 2019[74]	Lung resection	69	66	Prospective	RVFWLS and RVGLS	Inadequately tracked segments excluded	95.7%	
Perez-Teran et al 2015[212]	Lung transplant	120	120	Retrospective	RVFWLS	Not described	100%	Pre-op echocardiography (within 1y of surgery)
Perez-Teran et al 2016[213]	Lung transplant	72	70	Prospective	RVFWLS	Not described	97.2%	Pre-op echocardiography (immediately before surgery)
Kumaresan et al 2020[214]	Elective caesarian section (pre-op)	98	79	Prospective	RVFWLS	Not described	80.6%	Echocardiography immediately before surgery and 1-2h post op
	Elective caesarian section (postop)	98	68				69.4%	

RV-STE = right ventricular speckle tracking echocardiography, echo = echocardiography, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, pre-op = preoperative, post op = postoperative.

4.2.3 Feasibility of RV-STE in perioperative studies: Meta-analysis

Of the five studies included from the literature review, the overall meta-analysis identified a high RV-STE feasibility point estimate of 93.5% (95%CI 82.2-97.8, Figure 4-10). The five studies included in the meta-analysis were assessed for publication bias using a funnel plot. On visual inspection it was apparent there was asymmetry, with an absence of data points in the bottom left quadrant of the plot, indicating a lack of small studies reporting low RV-STE feasibility (Figure 4-11). This is similar to the study publication bias identified during the RV-STE meta-analysis of ICU studies described in section 4.1.3.2. When Duval and Tweedie's trim and fill method was used to account for this bias (Figure 4-12, Table 4-16), a reduced point estimate of RV-STE feasibility of 80.0% (95%CI 57.6-92.1) was calculated, possibly representing a "truer" point estimate.

It appeared that perioperative studies might have higher RV-STE feasibility than the ICU studies described in section 4.1.3.2. On subgroup meta-analysis, there was a trend towards perioperative studies having higher RV-STE feasibility than ICU studies (93.5% [95%CI 82.2-97.8] vs 83.3% [95%CI 74.6-89.4], p=0.097, Figure 4-13), possibly suggesting it is easier to acquire echocardiography studies of adequate image quality for RV-STE from patients in the perioperative period than patients in ICU. Of note, no patients in the perioperative studies were receiving IMV at the time of echocardiography. It was identified during the meta-regression of ICU studies that IMV was associated with poorer RV-STE feasibility, therefore the proportion of patients receiving IMV in the ICU group of studies may have contributed to the lower RV-STE feasibility when compared to perioperative studies.

Two studies performed only preoperative echocardiography studies, reporting a high feasibility of 98.4% (95%CI 91.7-99.7). Three studies used both preoperative and postoperative echocardiography, reporting this is a lumped feasibility, meta-analysis of these reported a lower RV-STE feasibility of 87.8% (95%CI 71.5-95.4), with subgroup meta-analysis demonstrating a significant difference in feasibility between studies using only preoperative echocardiography studies compared to studies that used both pre-and postoperative echocardiography (p=0.037, Figure 4-14). Kumaresan et al specifically reported preoperative and postoperative

RVFWLS, with a substantially lower feasibility postoperatively than preoperatively (69.4% vs 80.6%)[214]. In this study, patients had postoperative echocardiography performed within 1-2h after caesarian section. It is unsurprising that it may have been difficult to acquire high quality images in patients who will be uncomfortable, possibly with residual neuraxial block, factors that might make optimal patient positioning and acquiring high-quality images more difficult.

Given that only one study had a retrospective design, it is difficult to meaningfully compare the RV-STE feasibility across prospective and retrospective perioperative studies. However, when meta-analysis was performed including both perioperative studies and ICU studies, prospective studies were again found to have significantly higher RV-STE feasibility than retrospective studies (prospective feasibility 93.0% [95%CI 85.3-96.9] vs retrospective feasibility 79.6% [95%CI 63.6-89.7], p=0.037, Figure 4-15), in keeping with the findings of the meta-analysis of ICU studies alone in section 4.1.3.4. Further research is needed to investigate if perioperative studies have better RV-STE feasibility when a prospective design is used.

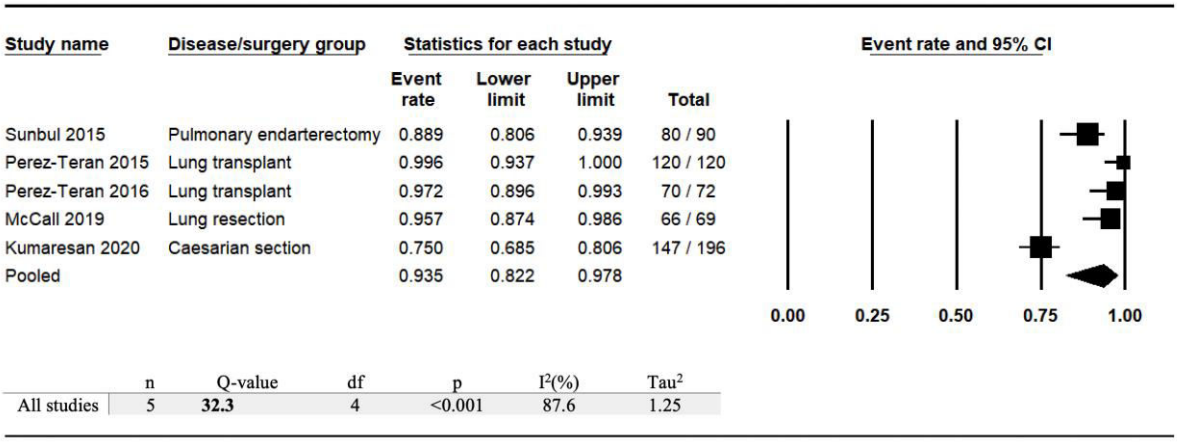


Figure 4-10 Overall meta-analysis to assess the feasibility of RV-STE in perioperative studies
The forest plot shows the individual point estimate and 95% confidence interval of each study as a box and line respectively, with the size of the box being representative of the weight attributed to that study. The overall point estimate is shown as a diamond, with the ends of the diamond representing the 95% confidence interval. RV-STE = right ventricular speckle tracking echocardiography

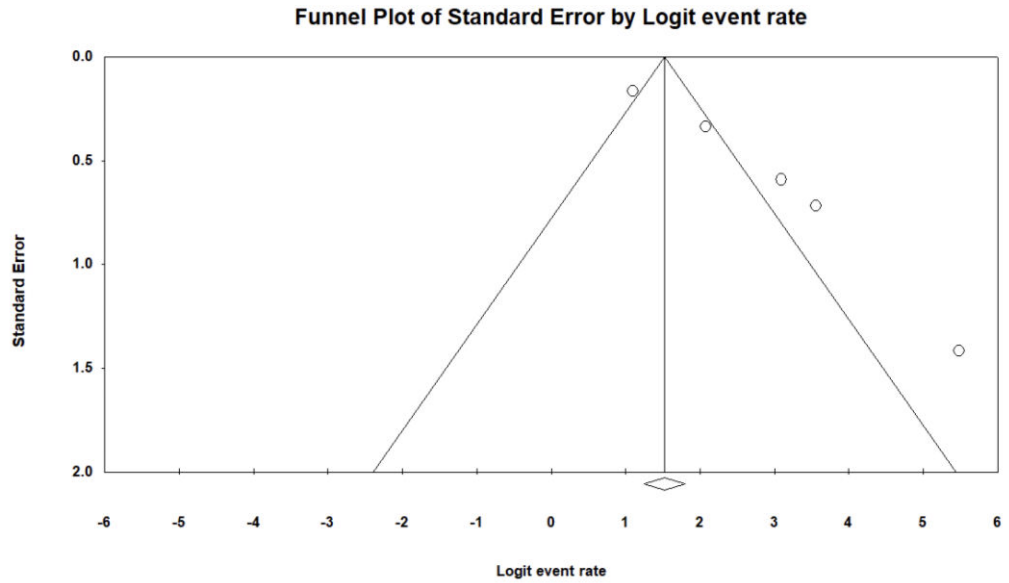


Figure 4-11 Funnel plot of perioperative studies included in RV-STE feasibility meta-analysis
Funnel plot of perioperative studies included in RV-STE meta-analysis to examine for publication bias. The combined point estimate of all studies is shown as a white diamond. Asymmetry is observed, with three small studies on the right outside the funnel reporting high RV-STE feasibility. RV-STE = right ventricular speckle tracking echocardiography.

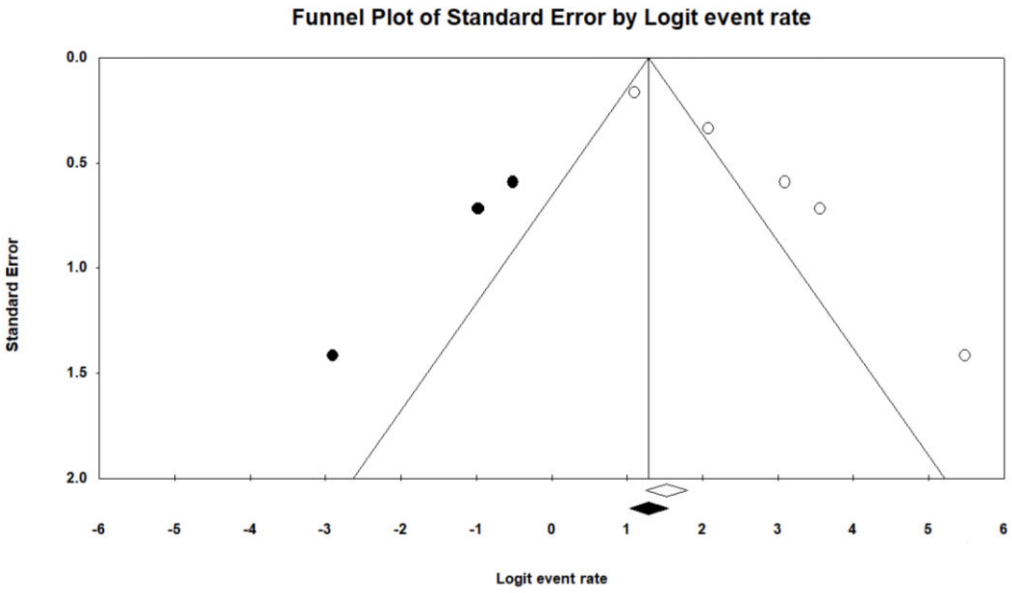


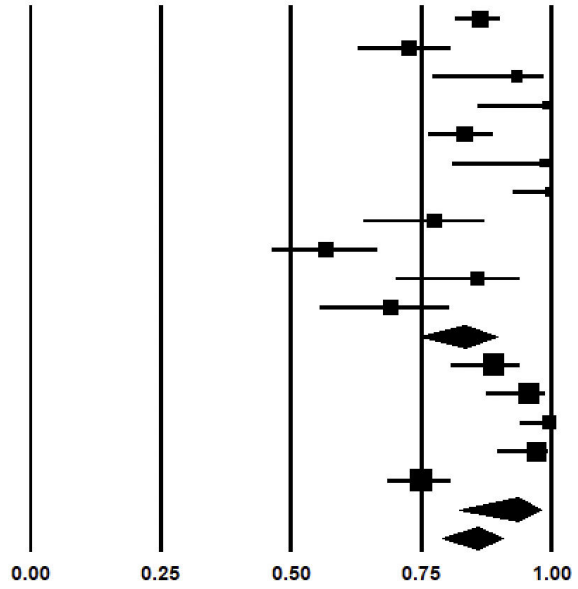
Figure 4-12 Funnel plot of perioperative studies included in RV-STE feasibility meta-analysis using "trim and fill" method
The three studies (represented by open circles) on the right-hand side of the plot are first removed to make the plot symmetrical and an adjusted point estimate calculated. These studies are added back with imputed counter balancing studies (solid black circles) added, variance around the adjusted point estimate is then calculated. The original combined point estimate is shown as a white diamond, with the adjusted point estimate shown as a solid black diamond. RV-STE = right ventricular speckle tracking echocardiography.

Table 4-16 "Trim and fill" adjustment of perioperative studies included in the RV-STE feasibility meta-analysis

Outcome		Studies trimmed	Point estimate (%)	95%CI	Q value
RV-STE feasibility	Observed		93.5	82.2-97.8	32.3
	Adjusted	3	80.0	57.6-92.1	63.0

RV-STE = right ventricular speckle tracking echocardiography, CI = confidence interval.

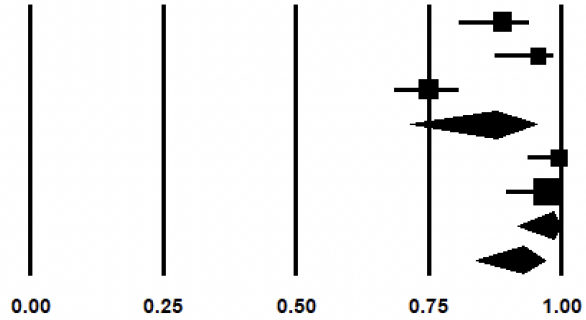
Group by Study type	Study name	Disease/surgery group	Event rate	Lower limit	Upper limit	Total
ICU	Khemasuwan 2015	PE	0.864	0.814	0.902	203 / 235
ICU	Dahhan 2016	PE	0.726	0.628	0.806	69 / 95
ICU	Bonizzoli 2018	ARDS	0.933	0.769	0.983	28 / 30
ICU	Lemarie 2020	ARDS	0.990	0.857	0.999	48 / 48
ICU	Li 2020	COVID-19	0.833	0.763	0.886	120 / 144
ICU	Kim 2020	COVID-19	0.986	0.809	0.999	34 / 34
ICU	Baycan 2020	COVID-19	0.995	0.926	1.000	100 / 100
ICU	Bursi 2020	COVID-19	0.776	0.638	0.871	38 / 49
ICU	Bleakley 2021	COVID-19	0.567	0.463	0.665	51 / 90
ICU	Stockenhuber 2021	COVID-19	0.857	0.700	0.939	30 / 35
ICU	Jain 2021	COVID-19	0.692	0.555	0.802	36 / 52
ICU	Pooled		0.833	0.746	0.894	
Perioperative	Sunbul 2015	Pulmonary endarterectomy	0.889	0.806	0.939	80 / 90
Perioperative	McCall 2019	Lung resection	0.957	0.874	0.986	66 / 69
Perioperative	Perez-Teran 2015	Lung transplant	0.996	0.937	1.000	120 / 120
Perioperative	Perez-Teran 2016	Lung transplant	0.972	0.896	0.993	70 / 72
Perioperative	Kumaresan 2020	Caesarian section	0.750	0.685	0.806	147 / 196
Perioperative	Pooled		0.935	0.822	0.978	
Overall	Pooled		0.857	0.788	0.907	



	n	Q-value	df	p	I^2 (%)	Tau^2
ICU Studies	11	60.2	10	<0.01	83.4	0.519
Perioperative Studies	5	32.3	4	<0.01	87.6	1.248
Total between		**2.2**	**1**	**0.097**		

Figure 4-13 Subgroup meta-analysis of RV-STE feasibility comparing perioperative and ICU studies
Sub-group meta-analysis to compare the effect that study status (perioperative studies vs ICU studies) has upon RV-STE feasibility. RV-STE = right ventricular speckle tracking echocardiography, ICU = intensive care unit, PE = pulmonary embolism, ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, CI = confidence interval.

Group by Time of echo	Study name	Disease/surgery group	Statistics for each study			
			Event rate	Lower limit	Upper limit	Total
Pre and postop	Sunbul 2015	Pulmonary endarterectomy	0.889	0.806	0.939	80 / 90
Pre and postop	McCall 2019	Lung resection	0.957	0.874	0.986	66 / 69
Pre and postop	Kumaresan 2020	Caesarian section	0.750	0.685	0.806	147 / 196
Pre and postop	Pooled		0.878	0.715	0.954	
Preop only	Perez-Teran 2015	Lung transplant	0.996	0.937	1.000	120 / 120
Preop only	Perez-Teran 2016	Lung transplant	0.972	0.896	0.993	70 / 72
Preop only	Pooled		0.984	0.917	0.997	
Overall	Pooled		0.928	0.840	0.969	

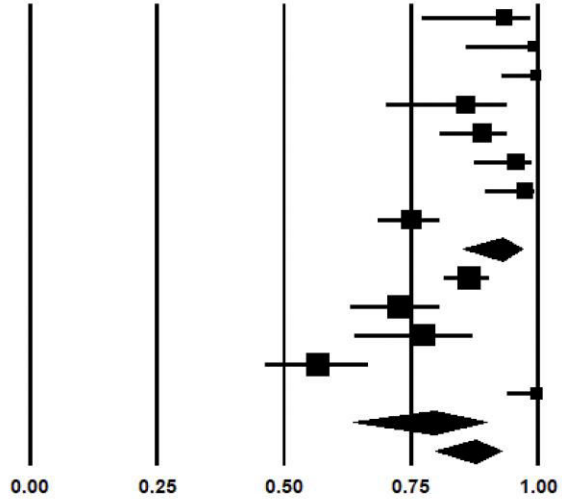


	n	Q-value	df	p	I^2 (%)	Tau^2
Pre and postop	3	15.6	2	<0.01	87.2	0.723
Preop only	2	1.48	1	0.22	32.2	0.600
Total between		**15.2**	**1**	**0.037**		

Figure 4-14 Subgroup meta-analysis of RV-STE feasibility comparing studies reporting pre- and postoperative feasibility with studies only reporting preoperative feasibility

RV-STE = right ventricular speckle tracking echocardiography, echo = echocardiography, preop = preoperative, postop = postoperative, CI = confidence interval.

Group by Study Design	Study name	Disease/surgery group	Statistics for each study			
			Event rate	Lower limit	Upper limit	Total
Prospective	Bonizzoli 2018	ARDS	0.933	0.769	0.983	28 / 30
Prospective	Lemarie 2020	ARDS	0.990	0.857	0.999	48 / 48
Prospective	Baycan 2020	COVID-19	0.995	0.926	1.000	100 / 100
Prospective	Stockenhuber 2021	COVID-19	0.857	0.700	0.939	30 / 35
Prospective	Sunbul 2015	Pulmonary endarterectomy	0.889	0.806	0.939	80 / 90
Prospective	McCall 2019	Lung resection	0.957	0.874	0.986	66 / 69
Prospective	Perez-Teran 2016	Lung transplant	0.972	0.896	0.993	70 / 72
Prospective	Kumaresan 2020	Caesarian section	0.750	0.685	0.806	147 / 196
Prospective	Pooled		0.930	0.853	0.969	
Retrospective	Khemasuwan 2015	PE	0.864	0.814	0.902	203 / 235
Retrospective	Dahhan 2016	PE	0.726	0.628	0.806	69 / 95
Retrospective	Bursi 2020	COVID-19	0.776	0.638	0.871	38 / 49
Retrospective	Bleakley 2021	COVID-19	0.567	0.463	0.665	51 / 90
Retrospective	Perez-Teran 2015	Lung transplant	0.996	0.937	1.000	120 / 120
Retrospective	Pooled		0.796	0.636	0.897	
Overall	Pooled		0.875	0.798		



	n	Q-value	df	p	I^2 (%)	Tau^2
Prospective	8	38.5	7	<0.01	81.8	0.978
Retrospective	5	40.6	4	<0.01	90.2	0.654
Total between		**6.9**	**1**	**0.037**		

Figure 4-15 Subgroup meta-analysis of RV-STE feasibility comparing study design in ICU and perioperative studies
Sub-group meta-analysis to compare the effect that ICU and perioperative study status (prospective studies vs retrospective studies) has upon RV-STE feasibility. RV-STE = right ventricular speckle tracking echocardiography, ICU = intensive care unit, ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, PE = pulmonary embolism, CI = confidence interval.

4.2.4 Reproducibility of RV-STE in the perioperative period

Of the seven perioperative studies, only one reported reproducibility (McCall et al[74], Table 4-17). This study reported inter-observer ICC values. Similar to the findings of RV-STE reproducibility studies in ICU studies, both RVFWLS and RVGLS had excellent inter-observer reproducibility. RVFAC was shown to have poor reproducibility. It is noteworthy that the model used for ICCs was reported (absolute agreement), which was reported infrequently in ICU studies.

Table 4-17 Reproducibility of RV-STE in the perioperative period

Study	(n)	Surgical group	Reproducibility		Comment
McCall et al 2019[74]	66	Lung resection	Inter-observer ICC		25% of scans analysed by a second expert reporter. Absolute agreement model for ICC used.
			RVFWLS RVGLS TAPSE S' RVFAC	0.91 0.91 0.94 0.91 0.12	

RV-STE = right ventricular speckle tracking echocardiography, ICC = intraclass correlation coefficient, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RVFAC = right ventricular fractional area change.

4.2.5 Validity of RV-STE in the perioperative period

RV-STE strain analysis has been used in several patient groups and settings during the perioperative period. The literature search identified six studies that have investigated concurrent criterion, predictive, and construct validity (Table 4-18). These patient groups include lung resection, lung transplant, septoplasty, and pulmonary endarterectomy.

4.2.5.1 Concurrent criterion validity of RV-STE in the perioperative period

McCall et al performed the only study investigating concurrent criterion validity of RV-STE strain analysis in the perioperative period, comparing RVFWLS and RVGLS against gold-standard CMR RVEF in patients undergoing lung resection[74]. RV-STE strain was performed pre-operatively, at day-2, and 2 months postoperatively with contemporaneous CMR. No correlation was identified between either RVFWLS or RVGLS and CMR RVEF (although RVFWLS trended towards significance ($r=0.31$, $p=0.05$, Table 4-18). A correlation was identified between the change in RVFWLS and change in CMR RVEF ($r= -0.32$ $p=0.02$) between pre- and postoperative timepoints. No correlation was found between TAPSE, S', RIMP or RVFAC and CMR RVEF in any of the analyses. RVFWLS showed the greatest ability to discriminate between patients with impaired RV function (defined as CMR RVEF <45%) with an AUROCC of 0.76 ($p<0.01$) and a clinically relevant optimal cut-off of -20.0 %. This study suggests that conventional RV echocardiography parameters correlate poorly with CMR RVEF, however RVFWLS trends towards a correlation with CMR RVEF and has the greatest ability to discriminate between patients with impaired RV function. Overall, RVFWLS does not achieve concurrent criterion validity in this lung resection cohort, however it appears to perform substantially better than conventional RV echocardiography parameters.

Table 4-18 Perioperative studies investigating RV-STE validity

Type of validity	Study	(n)	Patient group/study overview	Result
Concurrent criterion validity	McCall et al 2019[74]	66	**Lung resection** RVFWLS and RVGLS pre op, day-2 and 2-months post op. Contemporaneous CMR.	Correlation between CMR derived RVEF and RV-STE strain analysed using Pearson's co-efficient.
				Pooled analysis: r / p-value; Within-subject analysis (ANCOVA): r / p-value RVFWLS: -0.48 / <0.01; 0.31 / 0.05 RVGLS: -0.41 / <0.01; 0.12 / 0.45
				Correlation between change in CMR derived ΔRVEF and ΔRV-STE strain analysed using Pearson's co-efficient.
				r / p-value ΔRVFWLS: -0.32 / 0.02 ΔRVGLS: -0.12 / 0.38
				AUROCC for ability of echocardiography parameters to detect CMR RVEF <45%
				AUROCC / p-value RVFWLS: 0.76 / <0.01 — Optimal cut-off -20.0% RVGLS: 0.74 / <0.01 — Optimal cut-off -17.7% TAPSE: 0.65 / 0.04
				S' and RIMP did not show any significant ability to identify RV dysfunction (CMR RVEF <45%)
Predictive validity	Perez-Teran et al 2015[212]	120	**Lung transplant** Association between RVFWLS and primary graft dysfunction grade three. PA catheter while under GA.	RVFWLS / Healthy controls (n=20) / All patients (n=120) / p-value / PGD3 (n=56) / No PGD3 (n=64) / p-value (T-test) All segments (%): -25 (5) / -18 (6) / <0.001 / -19 (7) / -18 (5) / 0.56 Basal (%): -31 (9) / -22 (8) / <0.001 / -24 (9) / -20 (6) / 0.039 Middle (%): -27 (6) / -19 (6) / <0.001 / -19 (6) / -19 (6) / 0.81 Apical (%): -18 (6) / -13 (6) / 0.002 / -12 (8) / -14 (6) / 0.37 sPAP (mmHg): 48 (20) / 41 (41) / 0.048
				No difference in TAPSE, S', or RVFAC values between PGD3 and no PGD3
	Perez-Teran et al 2016[213]	70	**Lung transplant** Prospective validation of the findings of Perez-Teran et al 2015 study[212]	RVFWLS / PGD3 (n=31) / No PGD3 (n=39) / p-value (T-test) All segments (%): -21.6 (6.1) / -19.1 (5.4) / 0.15 Basal (%): -25.7 (7.3) / -19.5 (6.6) / <0.01 Middle (%): -23.0 (7.3) / -19.9 (6.6) / 0.14 Apical (%): -16.9 (6.5) / -16.9 (5.6) / >0.99 sPAP (mmHg): 46 (19) / 41 (22) / 0.30

Construct validity	Simsek and Simsek 2018[215]	58	**Septoplasty** RVGLS in 58 patients pre op and 3-months post op		Pre-op	3m post-op	p-value (T-test)
				RVGLS (%)	-21.1 (2.1)	-22.5 (1.9)	0.013
				sPAP (mmHg)	32.5 (5.2)	24.2 (4.6)	0.001
				SpO_2 (%)	93.5 (0.8)	95.6 (0.8)	0.001
				No significant change in S' between pre op and post op groups			
	Sunbul et al 2015[122]	80	**Pulmonary endarterectomy for CTEPH** RVFWLS in 40 patients pre op and 3-months post op		Pre-op	3m post-op	p-value (T-test)
				RVFWLS (%)	-14.6 (4)	-16.9 (3.8)	<0.001
				RVEDD (mm)	41.2 (3.7)	37.7 (4)	<0.001
				sPAP (mmHg)	84.8 (25.3)	37.2 (15.9)	<0.001
				6MWT(m)	216.6 (131.4)	410.5 (61.5)	<0.001
				No significant difference between S', TAPSE, and RIMP values pre and post op. Values within normal range in both groups. Correlation between pre op 6MWT and pre op RVFWLS: r=0.36 p=0.023 No correlation between post op 6MWT and post op RVFWLS. No analysis of correlation between change in RVFWLS against change in 6MWT.		
	Marston et al 2015[216]	60	**Pulmonary endarterectomy for CTEPH** Echocardiography and right heart catheter pre op and day-1 post op.		Pre-op	Post op	p-value (T-test)
				Basal RVFWLS (%)	-24.3 (8)	-18.9 (6)	0.005
				mPAP (mmHg)	44 (15)	29 (9)	<0.001
				PVR (dyne/s/cm^5)	950 (550)	31 (160)	<0.001
				No other RV segment strain analysis. No other RV echocardiography parameters reported.			

RV-STE = right ventricular speckle tracking echocardiography, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, pre op = preoperative, post op = postoperative, CTEPH = chronic thromboembolic pulmonary hypertension, CMR = cardiac magnetic resonance, RVEF = right ventricular ejection fraction, AUROCC = area under the receiver operated characteristic curve, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, right ventricular index of myocardial performance, PGD3 = primary graft dysfunction grade three, sPAP = systolic pulmonary artery pressure, IPF = idiopathic pulmonary fibrosis, CI = confidence interval, RVFAC = right ventricular fractional area change, SpO_2 = peripheral oxygen saturation, RVEDD = right ventricular end diastolic diameter, 6MWT = six minute walk test, ANCOVA = analysis of covariance, mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular resistance.

4.2.5.2 Predictive validity of RV-STE in the perioperative period

One group has provided strong evidence to support the predictive validity of RV-STE strain analysis in patients undergoing lung transplant. Perez-Teran et al investigated the association of RVFWLS with primary graft dysfunction grade three (PGD3) in patients post lung transplant[212]. PGD3 was defined as the presence of pulmonary oedema on radiological imaging combined with a PaO_2:FiO_2 ratio <200mmHg. In 2015 they performed a retrospective study identifying preoperative basal segment RVFWLS as a predictor of PGD3, with patients who developed PGD3 having better (I.e. more negative) preoperative basal RVFWLS than those that did not develop PGD3 (Table 4-18). Additionally, patients who developed PGD3 had significantly higher preoperative systolic PA pressures (sPAP). The authors confirmed their findings using a prospective study in 70 patients in 2016, again finding that patients who develop PGD3 had significantly better RVFWLS specifically in the basal segment preoperatively compared to those that did not develop PGD3[213]. The authors proposed a pathophysiological mechanism whereby patients that have underlying lung pathology causing raised arterial pulmonary pressures (such as pulmonary fibrosis or COPD, which made up the majority of patients in PGD3 group) develop an RV that is conditioned to pump against increased afterload. After lung transplantation, patients with a 'well-trained' RV are at an increased risk of shear stress and ischaemia-reperfusion lung injury due to the hyperdynamic RV pumping against the reduced pulmonary vasculature resistance in the transplanted lungs, and these patients develop PGD3. This mechanism seems plausible and is well supported by their retrospective and prospective findings. It is very interesting to observe better (more negative) RVFWLS values as a risk factor for poor postoperative outcome, and this is the only example of this identified by the literature search. Given the retrospective and subsequent prospective validation of outcomes in these two studies, basal segment RVFWLS appears to have strong predictive validity in this specific patient group.

4.2.5.3 Construct validity RV-STE in the perioperative period

Three studies have investigated the construct validity of RV-STE strain analysis in patients undergoing septoplasty and pulmonary endarterectomy for CTEPH.

Simsek and Simsek 2018 performed septoplasty in patients with nasal septal deviation[215]. They demonstrated that preoperatively these patients had borderline hypoxia and sPAP at the higher range of normal, with a baseline RVGLS of -21.1% (2.1). Three months postoperatively patients had a significantly improved mean RVGLS of -22.5% (1.9) ($p=0.013$, Table 4-18), with significantly higher SpO_2 levels and lower sPAP. There is a sound physiological basis for these observed results. Patients post septoplasty may experience improved alveolar ventilation with enhanced alveolar oxygenation (as observed with increasing SpO_2) and reduced hypercapnoea. This might reduce pulmonary vascular tone (as seen by decreased sPAP), and therefore decrease RV afterload with improved RVGLS. The relationship between RV afterload and RV function represents a formative item for the construct validity of RV-STE. Given that the reduction in pulmonary pressures and expected improvement in RVGLS has been observed, this study supports the construct validity of RV-STE with respect to this formative item relationship. Of note, there was no difference in mean S' values between the groups, suggesting RV-STE strain analysis is better suited to identify the subtle changes in improved oxygenation and reduced pulmonary vascular tone.

Sunbul et al performed a study with similar results in patients undergoing pulmonary endarterectomy for CTEPH[122]. They demonstrated that at baseline, patients with CTEPH had high sPAPs and impaired RVFWLS with a mean of -14.6% (4). Three months post pulmonary endarterectomy, patients had a significantly improved RVFWLS of -16.9% (3.8) ($p<0.001$, Table 4-18), with significantly reduced sPAP and improved 6-minute walk test results. Again, these findings would support the construct validity of RV-STE, with reduced pulmonary artery thrombus burden reducing RV afterload (a formative item with regards RV function) resulting in improved RVFWLS. Interestingly, the conventional RV echocardiography parameters of S', TAPSE and RIMP values were not significantly different pre and postoperatively.

Marston et al also investigated RVFWLS in patients with CTEPH undergoing pulmonary endarterectomy at a different postoperative time point, with strikingly conflicting results[216]. Unusually, they only analysed RV-STE strain of the basal free wall segment, with the authors choosing this segment because of its distance away, and therefore assumed isolation, from the left ventricle. Basal RVFWLS was performed preoperatively and postoperatively on average at day 9 (much earlier than 3 months postoperatively as analysed by Sunbul et al). The authors found that basal RVFWLS was -24.3% (8) preoperatively and became significantly impaired post operatively with a value of -18.9% (6) (p=0.005, Table 4-18). Similar to Sunbul et al, Marston et al found that PA pressures improved significantly post operatively, with reduced pulmonary vascular resistance. Although these results initially appear contradictory, it may be possible to reconcile the findings that RVFWLS was initially impaired post endarterectomy by Marston et al but was also found to improve compared to baseline at 3 months postoperatively by Sunbul et al. A study by Giusca et al demonstrated that TAPSE is significantly impaired 1-week post-pulmonary endarterectomy, and that TDI derived RV strain is initially unchanged, however both parameters slowly improved over 3-months postoperatively[217]. Patients undergoing pulmonary endarterectomy are placed on cardiopulmonary bypass (CPB) to allow the surgeon to open the pulmonary arteries and excise thrombus. Khani et al have shown that RV-STE strain is significantly reduced after undergoing CPB for coronary artery bypass grafting[218]. It is possible that CPB and postoperative myocardial stunning leads to impaired RV function and impaired RVFWLS immediately postoperatively in patients undergoing endarterectomy, and that RV function improves above baseline in the later postoperative period. The relationship between pulmonary endarterectomy with CPB and early postoperative RV dysfunction could represent a formative item relationship, with RVFWLS becoming more impaired postoperatively as expected. Marston et al may therefore have also demonstrated construct validity with respect to this formative item relationship with RV function.

In summary, RV-STE strain analysis has been less extensively investigated in the perioperative period compared to ICU groups. Construct validity has been demonstrated in patients undergoing septoplasty, and patients undergoing pulmonary endarterectomy. Concurrent criterion validity has not been

conclusively demonstrated, although RVFWLS appears to compare with CMR RVEF more favourably than conventional RV echocardiography parameters. Predictive validity has been examined in lung transplant patients, with more negative basal segment RVFWLS being a predictor of PGD3. Given the sparse number of studies investigating RV-STE strain analysis in the perioperative period, it is clear that this is an area in its infancy requiring further research.

4.3 Conclusion

From the literature reviews of ICU and perioperative studies some conclusions can be drawn from the current evidence that support RV-STE utility. Feasibility varied, but was high overall, with point estimates from ICU studies and perioperative studies of of 83.3% (95%CI 74.6-89.4) and 93.5% (95%CI 82.2-97.8) respectively. Meta-analysis revealed that prospective studies are associated with improved RV-STE feasibility, and COVID-19 studies and higher proportions of IMV are associated with poorer feasibility. All studies apart from one used a dichotomous description of feasibility: studies were either adequate or inadequate for RV-STE analysis. Future studies should investigate qualitative and quantitative descriptions of feasibility, and the effect that image quality has on RV-STE values and RV-STE reproducibility.

RV-STE was shown to have high intra- and inter-observer reproducibility in both ICU and perioperative studies, comparing favourably with conventional RV echocardiography parameters. Most studies used either ICCs or Bland-Altman mean difference (with LOA / SD) to investigate this, very few used both (and only one study published the actual Bland-Altman plot). Future studies should use a combination of these agreement measures. Additionally, no studies investigated the effect that image quality had upon reproducibility, representing a future avenue for research.

When examining the validity of RV-STE, only one study investigated concurrent criterion validity, comparing RV-STE to gold standard CMR[34]. This is obviously a challenging area (especially in ICU patients), where a hospital transfer to and from the MRI scanner for research purposes may be unsafe for unstable ICU/ postoperative patients. Efforts still need to be made to further investigate the concurrent criterion validity of RV-STE.

Many RV-STE studies investigated the predictive validity of RV-STE, ICU studies demonstrated the predictive validity of RV-STE with regards mortality in patients with sepsis, COVID-19, and PE[16,182,185,195,196,211], whereas perioperative studies demonstrated predictive validity of RV-STE with regards postoperative graft dysfunction in patients undergoing lung transplantation[212,213]. The predictive validity of RV-STE for long term outcomes, specifically in COVID-19 patients, is one area that requires further research.

Construct validity was investigated in different groups. Formative item relationships with RV function were most consistently demonstrated by RV-STE. This was shown in ICU groups including patients with sepsis and patients with ARDS. It was also demonstrated by perioperative studies in patients undergoing septoplasty and pulmonary endarterectomy[122,215]. Reflective item relationships were less frequently reported. The only instance where a RV-STE identified the expected relationship between RV function and a reflective item was in patients with sepsis, where impaired RV-STE correlated with CVP[193]. COVID-19 studies did not demonstrate construct validity with regards reflective item relationships, and further examination is needed to establish the construct validity of RV-STE with regards reflective item relationships in this group.

Mixed items (those that reflect an aspect of both formative and reflective item relationships) were infrequently investigated (only in COVID-19 studies), and these did not perform well in demonstrating construct validity. Mixed items tended to be represented by general scoring systems (e.g. SOFA score), and are therefore somewhat non-specific in their representation of formative and reflective items. It therefore is not unexpected that an association was not demonstrated between these mixed items and RV function.

The feasibility, reproducibility, and validity of RV-STE will be investigated in Chapters 5 and 6. Chapter 5 will use RV-STE to assess RV function in ICU patients with COVID-19 requiring IMV. Chapter 6 will use RV-STE to assess dynamic RV function during exercise in a perioperative lung resection cohort. The current gaps in knowledge with regards feasibility, reproducibility, and validity described above will be specifically addressed to further our understanding of the utility of RV-STE.

Chapter 5 The utility of RV-STE in patients with COVID-19 requiring invasive mechanical ventilation

5.1 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2, also known as coronavirus disease 2019 [COVID-19]), caused a world-wide pandemic, with the World Health Organisation declaring it a public health emergency of international concern (PHEIC) from January 2020 - May 2023[219]. COVID-19, in its most severe form, results in ARDS, with many patients requiring admission to ICU and invasive mechanical ventilation (IMV). During the first COVID-19 wave, it was widely reported, but not well substantiated, that COVID-19 ARDS was associated with RVD. The Right Ventricular Dysfunction in Ventilated Patients with COVID-19 (COVID-RV) study was conceived by (the author's supervisors) Dr Philip McCall and Prof Ben Shelley to identify the prevalence of RVD in patients with COVID-19 requiring IMV in ICU, and examine for association between RVD and 30-day mortality. The COVID-RV study was a prospective, ICU clinician delivered, multicentre, echocardiography study. The primary analysis of COVID-RV used an echocardiography definition of RVD diagnosed by severe RV dilatation and interventricular septal flattening (i.e. severe acute cor pulmonale). The study identified a prevalence of RVD of 6% and an association between RVD and 30-day mortality (p=0.05). RV-STE strain analysis of the COVID-RV echocardiography studies was a planned secondary analysis[220]. Since completion of the COVID-RV study, RVD has been recognised as a common finding in patients with COVID-19 suffering from severe acute respiratory failure, both in those requiring, and not requiring IMV[16,201,221-226]. Previous studies examining RV-STE in patients with COVID-19 have shown impaired RV-STE to be independently associated with mortality, where other conventional RV echocardiography parameters have not[16,181]. STE studies investigating RVD in patients with COVID-19 have however been limited by small sample size, retrospective design, varying requirements for IMV, and the use of clinically necessitated echocardiography studies (e.g. for cardiovascular instability) rather than research dedicated scans[183,194]. RV-STE analysis of the COVID-RV study affords the opportunity to examine the utility of

RV-STE in an ICU cohort receiving IMV. As described in Chapter 2 (section 2.3.2), RVFWLS will be used as the primary measure of RV-STE, as recommended by consensus guidelines[85]. The utility of RV-STE in this setting will be examined by assessing feasibility, reproducibility, and validity. The author had no input in the design or running of the COVID-RV study. The author was permitted to perform a secondary analysis of the COVID-RV echocardiography studies to assess RV-STE by Prof Ben Shelley (chief investigator) and Dr Philip McCall (co-investigator). The author performed all the echocardiography reporting and statistical analysis described below.

5.2 Methods and statistics

5.2.1 Study design and setting

The COVID-RV study was a prospective observational cohort multicentre study across 10 ICUs in NHS Scotland. Ethics approval was obtained from Scotland A Research Ethics Committee (who approved the study for patients under the Adults with Incapacity [Scotland] Act, 2000 - 20/SS/0059). Informed consent was obtained from a legal representative for all patients.

5.2.2 Participants

Inclusions criteria included: patients with a confirmed diagnosis of COVID-19 who were more than 16 years old requiring IMV for acute respiratory failure. A single echocardiography study was performed at the time point between 48 hours after intubation and before day 14 of ICU admission.

Exclusion criteria included: pregnancy, extracorporeal membrane oxygenation (for respiratory or cardiovascular failure), prior participation in COVID-RV, ongoing participation in a research study that may have undermined the scientific basis of the study, and end of life care (where the patient was not expected to survive longer than 24 hours). COVID-RV was registered at ClinicalTrials.gov (NCT04764032), with a pre-published protocol written by Dr Jennifer Willder, Dr Philip McCall, and Prof Ben Shelley[220].

5.2.3 Clinical and laboratory data

Study data was collected and stored on REDCap (an electronic data managing tool), hosted by the University of Glasgow. The REDCap database was created by Dr Jennifer Willder.

All data were prospectively collected. This included baseline demographics, chronic comorbidities, acute comorbidities since hospital admission, severity of COVID-19 illness, and follow-up data. Clinical data relating to potential causative mechanisms for RV dysfunction were also collected. On the day of echocardiography, a blood sample was taken for high sensitivity troponin (hsTn) (T or I, subject to the assay used at each site) and N-terminal pro B-type Natriuretic Peptide (NT-proBNP).

5.2.4 Echocardiography

A single study TTE was performed between 48 hours after intubation and before day 14 of ICU admission. A focused intensive care echocardiography (FICE) study was requested as the minimum image data set, to reflect day-to-day clinical practice in ICU. The FICE study included an RV focussed apical four-chamber (A4C) view for RV-STE analysis. Echocardiographers performing the scan were asked to determine the following diagnoses based off the images they obtained: severe RV dilatation (diagnosed if the RV:LV area was >1 at end diastole on a A4C view), the presence of interventricular flattening diagnosed at either end diastole or end systole on a midpapillary parasternal short axis (PSAX) view, and subjective RV and LV dysfunction diagnosed if there was a reduction in myocardial thickening and motion as seen on parasternal long axis, PSAX, and A4C views.

Images that would allow analysis of conventional echocardiography parameters were obtained if the echocardiographer had the experience to do so (such as M-mode for TAPSE, and tissue doppler imaging for S' and RIMP). These images then underwent offline analysis by the author in accordance with current British Society of Echocardiography (BSE) guidelines (the steps used for assessing these measurements are described in Chapter 1 section 1.3.4) [65]. TAPSE was performed on an A4C view using M-mode, with an abnormal cut-off of <17mm[65].

S' and RIMP were performed using tissue doppler imaging across the lateral tricuspid annulus on the A4C view. An abnormal cut-off of <9cm/s for S', and >0.54 for tissue doppler RIMP was used[65]. The RV:LV ratio of basal diameter was calculated from the A4C at end diastole. LV eccentricity index (LVEI) was calculated from PSAX view at the midpapillary level. End diastole was identified at the peak of the R wave on ECG, and end systole when the LV cavity was at its smallest. The LVEI index was calculated as the ratio of the LV cavity anterior-inferior diameter to the septal-lateral diameter.

Offline RV-STE strain and conventional RV echocardiography parameter analysis was performed by the author, who was blinded to all patient data and outcomes. RV-STE strain analysis was performed using Tomtec Imaging Systems 2D Cardiac Performance Analysis (CPA). Details of the training process undertaken by the author prior to COVID-RV RV-STE analysis are found in Appendix 3. Four beats were recorded with ECG monitoring, to capture a minimum of one full cardiac cycle. A frame rate of 60-80 frames/s was used to ensure adequate temporal resolution for speckle tracking. RV-STE analysis was conducted in accordance with ASE and EACVI guidelines (section 2.3.2)[85]. The endocardial border was manually traced at end diastole and end systole. Speckle tracking was then performed, with manual adjustments made to the endocardial contours as required to ensure adequate tracking throughout the cardiac cycle. If the patient was in sinus rhythm, single beat RV-STE values were reported, if in atrial fibrillation the average RV-STE value of three beats was used. Peak longitudinal strain values were generated for RVFWLS and RVGLS. Strain values were reported as negative values; no segmental analysis was performed. RVFAC was automatically reported as part of the 2D CPA strain analysis, an abnormal cut-off of <30% in males and <35% in females was used[65]. Echocardiography studies that did not include an A4C view were excluded. Studies where all RV free wall segments were not seen to be adequately tracking were also excluded. A well validated abnormal cut-off for RVFWLS of >-20% was used (see section 2.9), in accordance with ASE guidelines[62,110]. Given this clearly defined RVFWLS cut-off has been established, it was decided to primarily dichotomise patients into groups with abnormal RVFWLS and normal RVFWLS rather than use RVFWLS as a continuous variable. An abnormal cut-off for RVGLS is less well defined. A large multinational study investigated normal RV-STE values (reported by Tomtec

software) in >1900 patients[110]. The abnormal cut-off for RVGLS was identified as >-18.2%, this cut-off was used for the COVID-RV study.

Echocardiographer specialty (intensive care clinician or cardiac physiologist / departmental echocardiographer), and echocardiography accreditation (none, FICE, FICE mentor, BSE Critical Care accreditation, BSE full accreditation, or other) were also recorded.

5.2.5 RV-STE feasibility and image quality

In Chapter 4 (section 4.1.3) it was demonstrated that a diagnosis of COVID-19 and requirement for IMV were factors associated with reduced RV-STE feasibility, whilst a prospective study design conferred better feasibility. Patients eligible for the COVID-RV study were required to have both a diagnosis of COVID-19 and to be receiving IMV, and were therefore likely to be a very challenging population to acquire echocardiography studies of high image quality. To maximise RV-STE feasibility, a prospective plan was therefore made to obtain an RV focussed A4C view (as recommended by consensus guidelines[85]). An aspect of RV-STE feasibility that has received little attention, is how the experience of echocardiographer affects the image quality of echocardiography study acquired for RV-STE analysis. A feasibility sub-study was included to investigate the feasibility of RV-STE from echocardiography studies acquired by echocardiographers with a range of experience.

The definition of RV-STE feasibility, specifically RVFWLS feasibility, was the percentage of echocardiography studies of adequate quality for RVFWLS analysis to be performed. For an echocardiography study to be "adequate", appropriate speckle tracking of all three free-wall segments was visually confirmed.

When assessing echocardiography study image quality for RV-STE, previous studies have been limited by describing image quality in a binary fashion (i.e. an echocardiography study is either adequate or inadequate). Given that image quality is a spectrum, it was described semi-quantitively. Work by Nagata et al semi-quantitively described image quality for LV-STE[102], whereby the endocardial delineation for each segment of the LV was rated. This was replicated in the current work for the right ventricle, where the endocardial

delineation scores for a segment were: 0 = not visible, 1 = fairly visible, and 2 = clearly visible during the entire cardiac cycle. Each segment therefore received a score between 0-2, with a maximal score of 12 for all six RV segments. Echocardiography study image quality was assessed using semi-quantitative scoring to see whether it affected the reproducibility of RV-STE, and to assess whether image quality affected the RV-STE values reported (i.e. were poorer quality images associated with impaired RV-STE). Echocardiography studies were also reported with a qualitative global rating of "good", "adequate", "poor", or "unusable" (as recommended by BSE guidelines[227]), with the aim of assessing how qualitative image quality affected reproducibility and RV-STE values.

5.2.6 RV-STE reproducibility

As described in Chapter 3 and 4, the most frequent methods used to assess RV-STE reproducibility are ICCs and Bland-Altman plots. To assess RV-STE reproducibility, ICCs with two-way mixed effects and absolute agreement were described. Bland-Altman plots with mean difference and LOAs (mean difference +/- 1.96 SD) were also reported. Importantly the Bland-Altman plots themselves are presented (which were frequently omitted in studies identified in Chapter 4 (section 4.1.4.3), allowing assessment for systematic bias. A total of 20 anonymised echocardiography studies were re-reported by the author two weeks after initial report to assess intra-observer agreement, and 20 were reported by a second reporter (Dr Philip McCall) to assess inter-observer agreement. Re-reported echocardiography studies were blinded with regards the initial reported RV-STE result.

As a reproducibility sub-study, the image quality of echocardiography studies was analysed, comparing the reproducibility of echocardiography studies with high-quality images to lower quality images.

5.2.7 Statistical considerations

Continuous data are presented as mean (standard deviation) or median [interquartile range] if the distribution was normal or not respectively. Ordinal and categorical data are presented as n (%). Between group differences were analysed using Student's unpaired T test, one-way analysis of variance (ANOVA),

Mann-Whitney test and Kruskal-Wallis Test for continuous variables, categorical variables were analysed using Chi Squared-test or Fisher's Exact test as appropriate. To assess for association between variables, Pearson's and Spearman's correlation co-efficients were calculated as appropriate.

Univariate survival analysis was performed using Kaplan–Meier plots and log-rank analysis. Multivariable cox regression sought to assess for an independent association between abnormal RVFWLS and 30-day mortality with an a-priori analysis plan to adjust for patient demographics (age, gender, ethnicity), phase of disease (time from intubation to echocardiography) and baseline severity of illness (Acute Physiology And Chronic Health Evaluation II score within 24 h of ICU admission)[220]. Variables in the cox regression were assessed for an interaction between time variable and covariate to establish that the proportional hazard's function assumption was met.

All statistical analyses were performed on International Business Machines Statistical Package for the Social Sciences (IBM SPSS) version 28.0.0.0. A two-sided p value < 0.05 was considered statistically significant.

5.3 Results

Results are presented in the following order: study recruitment, feasibility, generic results, assessment of echocardiography image quality, reproducibility, and validity of RV-STE.

5.3.1 Study recruitment and patient demographics

One-hundred-and-twenty-one patients were recruited across 10 ICUs to COVID-RV between 2/9/2020 and 22/3/2021 (Figure 5-1). Three patients were excluded after recruitment - two due to technical factors preventing echocardiography and one was extubated prior to echocardiography. Due to technical issues in storage and transfer, echocardiography studies for offline analysis for 14 patients were unable to be obtained, resulting in 104 studies for RV-STE analysis. Of the 104 echocardiography studies, 94 were of adequate quality for RV-STE analysis.

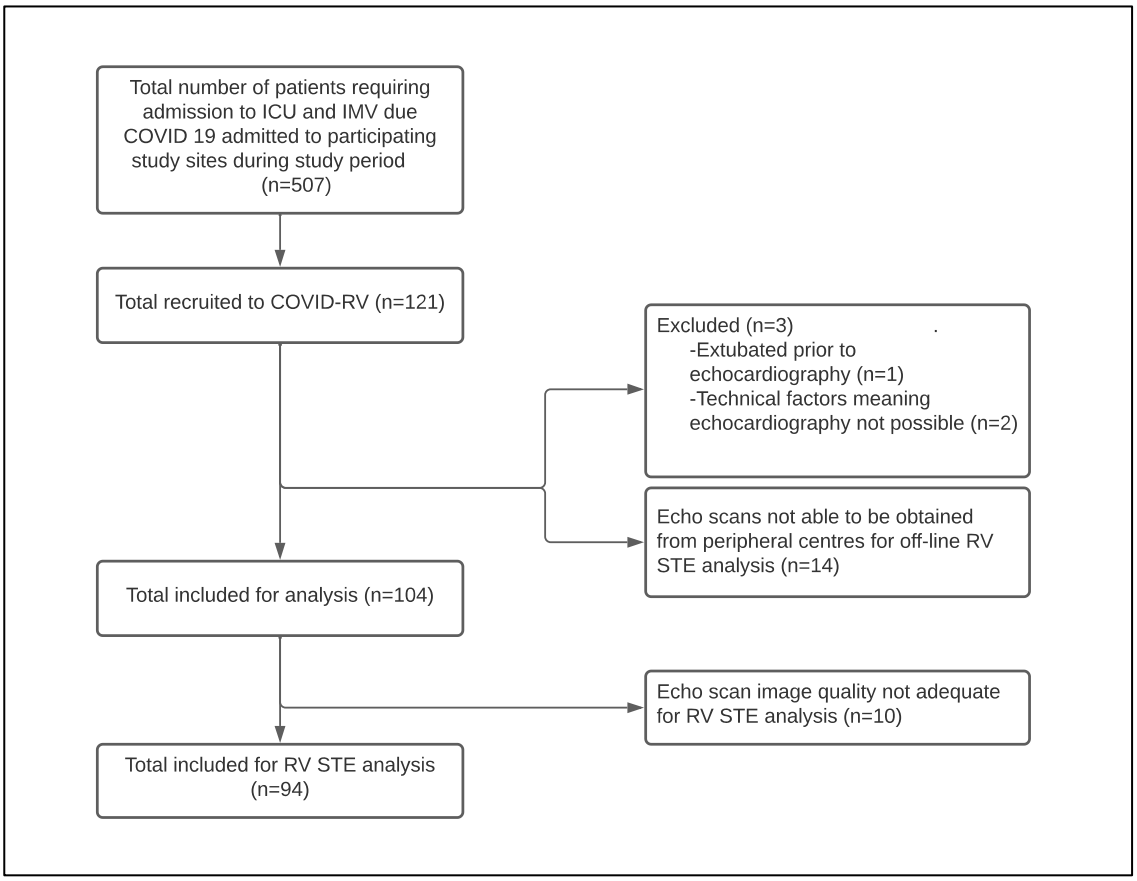


Figure 5-1 Flowchart of enrolment to COVID-RV study
Flowchart of enrolment to COVID-RV. A total of 104 patients had echocardiography studies available for feasibility analysis. Ten echocardiography studies were excluded due to poor images quality, the remaining 94 underwent RV-STE analysis. ICU = intensive care unit, IMV = invasive mechanical ventilation, COVID-19 = coronavirus disease 2019, RV-STE = right ventricular speckle tracking echocardiography, echo = echocardiography

5.3.2 Feasibility

Ninety-four out of 104 echocardiography studies had images of sufficient quality for RVFWLS analysis, giving an overall RVFWLS feasibility of 90.4%. ICU clinicians performed 76.9% (80/104) of studies. There was no difference in feasibility between echocardiography studies acquired by echocardiographers of different levels of accreditation (p = 0.672, Table 5-1).

Table 5-1 Feasibility of RVFWLS and echocardiographer accreditation

Group	Number of echo studies of sufficient quality for RVFWLS/ Total number of echo studies performed (%)	p-value
All	94/104 (90.4%)	
Echo speciality		
Critical care	72/80 (90%)	>0.999*
Cardiac physiologist/departmental echocardiographer	22/24 (91.7%)	
Echo accreditation		
None	13/14 (92.9%)	0.672ω
FICE	1/1 (100%)	
FICE mentor	33/35 (94.3%)	
BSE full accreditation	43/50 (86.0%)	
BSE Critical Care accreditation	4/4 (100%)	

Between-group differences were assessed using Pearson Chi-Square test (*) and Fisher's Exact test (ω). Echo = echocardiography, RVFWLS = right ventricular free wall longitudinal strain, FICE = focused intensive care echocardiography, BSE = British Society of Echocardiography.

5.3.3 Generic results

Of the 94 patients included in RV-STE analysis, the median age was 59 years [53, 67.3], and 57 (60.6%) patients were male (Table 5-2). Patients admitted to ICU with COVID-19 had a substantial burden of cardiovascular co-morbidities, with a median BMI of 31.6 [29.5, 36.2], 43.6% of patients had a smoking history, 31.9% had hypertension and 33.0% had diabetes mellitus. The demographics of the 10 patients who had echocardiography studies with images of inadequate quality for RV-STE were broadly similar to the 94 patients in whom RV-STE was feasible (Table 5-2).

Table 5-2 Patient demographics

Patient Demographics		Patients in whom RV-STE was feasible		Patients in whom RV-STE was not feasible	
		n	Descriptive Statistics	n	Descriptive Statistics
Age, years		94	59 [53, 67.3]	10	55.5 (14.6)
Male		94	57 (60.6%)	10	8 (80%)
BMI, kg/m^2		92	31.6 [29.5, 36.2]	9	34.5 (9.3)
Ethnicity	White Non-white	82	82 (87.2%) 12 (12.8%)	10	9 (90%) 1 (10%)
Clinical frailty score		93	2 [2, 3]	10	3 [1.8, 3.0]
APACHE II score		89	16 [13, 19]	10	16.9 (8.2)
CCCC		87	10.3 (2.8)	10	9.7 (3.0)
Comorbidities					
Smoking	Non-smoker Ex-smoker > 1 year Current or within 1 year	94	53 (56.4%) 34 (36.2%) 7 (7.4%)	10	7 (70%) 2 (20%) 1 (10%)
Alcohol history	None Minimal Moderate Excess	92	33 (35.9%) 45 (48.9%) 6 (6.5%) 8 (8.7%)	10	3 (30%) 5 (50%) 1 (10%) 1 (10%)
Hypertension		94	30 (31.9%)	10	4 (40%)
Coronary artery disease		94	8 (8.5%)	10	1 (10%)
Diabetes mellitus		94	31 (33%)	10	3 (30%)
Asthma		94	12 (12.8%)	10	2 (20%)
COPD		94	7 (7.4%)	10	1 (10%)

RVFWLS = right ventricular free wall longitudinal strain, BMI = body mass index, APACHE= acute physiology and chronic health evaluation, CCCC = Coronavirus Clinical Characterisation Consortium, COPD = chronic obstructive pulmonary disease

5.3.3.1 Generic RV-STE results

Ninety-four patients had RVFWLS reported, with a mean value of -23.0% (5.2). Twenty-seven patients (28.7%) had abnormal RVFWLS (>-20%, Figure 5-2). It is noteworthy that the distribution of RVFWLS appears bimodal. Patients with abnormal RVFWLS had a median of 21 days [16, 27.5] from symptom onset to echocardiography, significantly longer than patients with normal RVFWLS (18 days [13, 21], p=0.011). There was no difference in time from intubation to echocardiography, with a median of 5 days [3, 9] in abnormal RVFWLS and 5 days [4, 8] in normal RVFWLS groups (p=0.794).

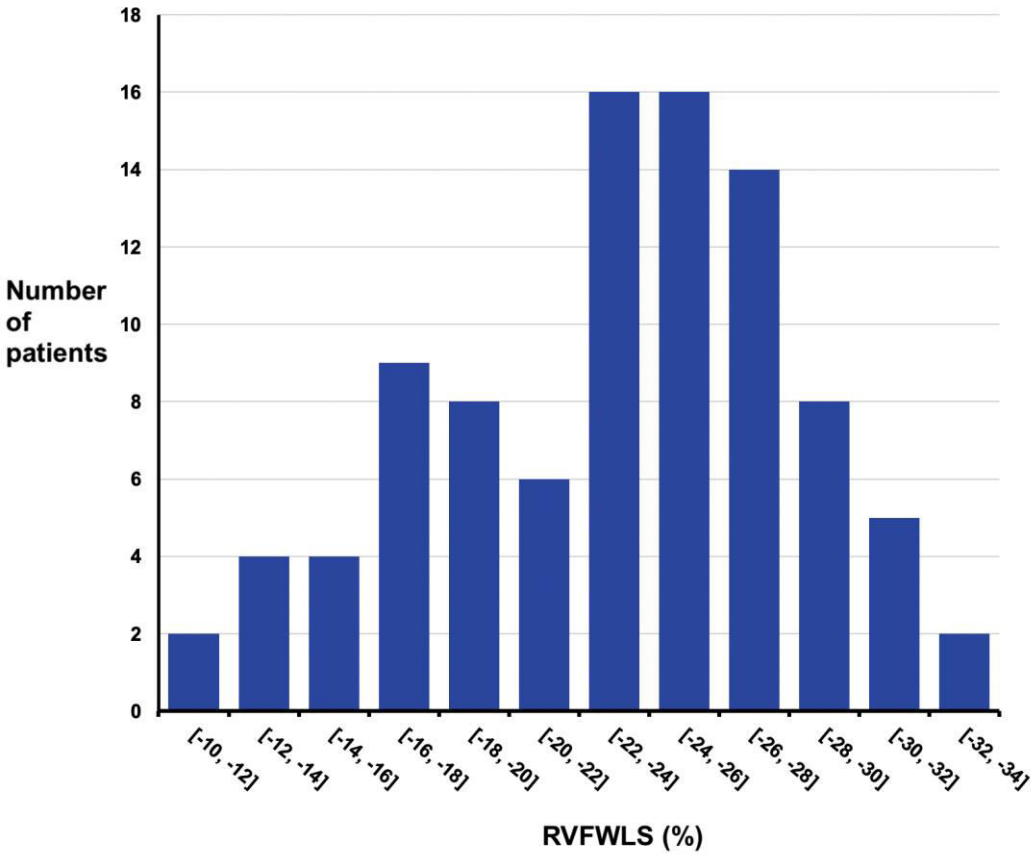


Figure 5-2 Histogram displaying the distribution of RVFWLS
Number of patients in each 2% grouping of RVFWLS are shown by the histogram bars. RVFWLS = right ventricular free wall longitudinal strain.

5.3.4 Echocardiography study image quality

5.3.4.1 Echocardiography accreditation

Of the 104 patients who underwent echocardiography, there was no difference in qualitative global assessment scores between accreditation groups (p=0.381, Figure 5-3, Table 5-3). It is noteworthy that echocardiographers with no accreditation appeared proficient in performing echocardiography, with images of “good” quality being the most frequently acquired.

Of the 94 patients in whom RV-STE was feasible, the median endocardial delineation score was 7 [5,9]. There was no significant difference in endocardial delineation scores across echocardiography accreditation groups (p=0.070, Table 5-4), although some groups such as FICE and BSE Critical Care accreditation had small numbers. Although BSE Critical Care accredited echocardiographers were a small group (n=4), on inspection of the data it is interesting to note they appeared to acquire echocardiography studies of higher image quality than FICE mentors and BSE Full accreditation groups, with median endocardial delineation scores of 9 [8, 11.5] vs 7 [5, 8.5] and 7 [5, 9] respectively (no statistical analysis performed due to small numbers). This perhaps reflects that BSE Critical Care accredited echocardiographers have the most experience in performing echocardiography for ICU patients. Similar to the above finding with qualitative global assessment scores, echocardiographers with no accreditation also appeared to acquire echocardiography studies of high image quality when assessed semi-quantitatively (median endocardial delineation score of 9 [7.5, 10.5], Table 5-4), this may reflect that there is a body of ICU clinicians who have significant echocardiography experience, without having attained formal accreditation.

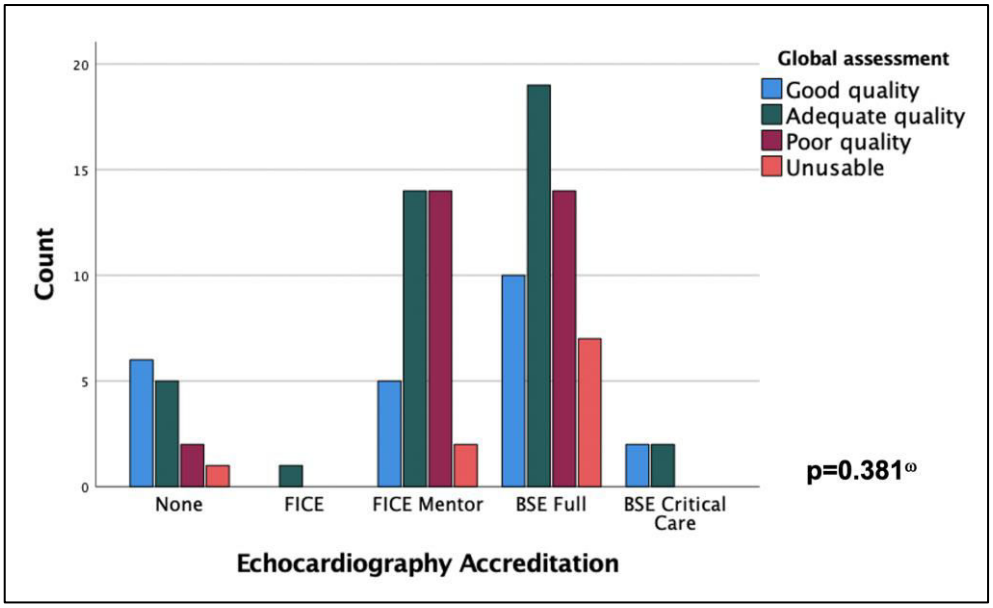


Figure 5-3 Qualitative global assessment of echocardiography study image quality and echocardiography accreditation
Histograms comparing echocardiography image quality between echocardiography accreditation groups. FICE = Focused Intensive Care Echocardiography, BSE = British Society of Echocardiography. Fisher's Exact test (ω). Total N = 104

Table 5-3 Qualitative global assessment of echocardiography study image quality and echocardiography accreditation

Echo accreditation	Qualitative global Assessment of Image Quality				p-value
	Good	Adequate	Poor	Unusable	
None (n=14)	6 (42.9%)	5 (35.7%)	2 (14.3%)	1 (7.1%)	0.381ω
FICE (n=1)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	
FICE mentor (n=35)	5 (14.3%)	14 (40.0%)	14 (40.0%)	2 (5.7%)	
BSE full accreditation (n=50)	10 (20.0%)	19 (38.0%)	14 (28.0%)	7 (14.0%)	
BSE Critical Care accreditation (n=4)	2 (50.0%)	2 (50.0%)	0 (0%)	0 (0%)	

Data are presented as n (%). Fisher's Exact test (ω). Echo = echocardiography, RVFWLS = right ventricular free wall longitudinal strain, FICE = focused intensive care echocardiography, BSE = British Society of Echocardiography.
Total N = 104

Table 5-4 Endocardial delineation score by echocardiographer accreditation

Echo accreditation	Endocardial delineation score (0-12)	p-value
None (n=13)	9 [7.5, 10.5]	0.070†
FICE (n=1)	-	
FICE mentor (n=33)	7 [5, 8.5]	
BSE full accreditation (n=43)	7 [5, 9]	
BSE Critical Care accreditation (n=4)	9 [8, 11.5]	

Data are presented median [interquartile range]. Between-group differences were assessed using Kruskal-Wallis Test (†). Echo = echocardiography, RVFWLS = right ventricular free wall longitudinal strain, FICE = focused intensive care echocardiography, BSE = British Society of Echocardiography. Total N = 94

5.3.4.2 Echocardiography study image quality and reported RVFWLS

There was no association between endocardial delineation scores and RVFWLS (Spearman's r=0.058, p=0.579). There was no difference in RVFWLS when comparing echocardiography studies with higher (≥8) and lower (<8) endocardial delineation scores (p=0.852, Table 5-5). The cut-off value of ≥8 was used because it resulted in groups sizes that were approximately equal. These data suggest that echocardiography study image quality, as measured by the endocardial delineation score, did not influence the RVFWLS reported. When examining qualitative global assessment of the 94 echocardiography studies for which RVFWLS could be analysed, 23 (24.5%) echocardiography studies were assessed as "good quality", 41 (43.6%) as "adequate quality", 30 (31.9%) as "poor quality". Similar to endocardial delineation scores, there was no significant difference in RVFWLS across the different qualitative global assessment scores (p=0.463). This suggests that image quality, assessed qualitatively, also does not influence the RVFWLS reported.

Table 5-5 Endocardial delineation score and RVFWLS

	All (n=94)	Endocardial delineation score <8 (n=49)	Endocardial delineation score ≥8 (n=45)	p value (T-test)
RVFWLS (%)	-23.0 (5.2)	-22.9 (4.7)	-23.1 (5.7)	0.852

RVFWLS = right ventricular free wall longitudinal strain.

5.3.5 Reproducibility

RVFWLS showed excellent intra-observer reproducibility, with an ICC of 0.91 (p<0.001, Table 5-6). Bland–Altman analysis demonstrated a small mean difference of −1.24% (LOA 5.39, −6.87, Figure 5-4) with no obvious systematic bias. RVFWLS also had very good inter-observer reproducibility: ICC 0.88 (p<0.001) with a small mean difference of 0.52% (7.41, −8.45, Figure 5-5). RVGLS had an intra-observer ICC of 0.85 (p<0.001), with a small mean difference of -1.59% (3.75, -6.93). RVGLS inter-observer reproducibility was similarly good, with an ICC of 0.84 (p<0.001), and mean difference of -1.38% (4.99, -7.75). When comparing RV-STE to the conventional RV echocardiography parameters, a direct comparison cannot be made using Bland-Altman analysis because of the different units involved in each measurement. There was good to excellent intra and inter-observer reproducibility for RVFAC, TAPSE, S', and RIMP when assessed

by ICCs (Table 5-7, ICC ≥ 0.84 for all, p values non-significant for some likely due to small number of measures dual reported). Overall, these data suggest that offline RV-STE analysis is highly reproducible, and at least comparable to offline reporting of the conventional RV echocardiography parameters.

Echocardiography study image quality appeared to influence the reproducibility of RV-STE. The effect of endocardial delineation scores on reproducibility was assessed by dividing patients into groups with a score >8 and ≤8 since it resulted in two groups of equal size. The ICCs for intra- and inter-observer reproducibility were higher for RVFWLS and RVGLS when images had endocardial delineation scores >8 compared with ≤8 (RVFWLS intra-observer ICC 0.93 vs 0.83, RVFWLS inter-observer ICC 0.92 vs 0.76, RVGLS intra-observer ICC 0.89 vs 0.74, RVGLS inter-observer ICC 0.93 vs 0.60 respectively, Table 5-6). Similarly, images that were globally assessed as being “good” or “adequate” appeared to have better intra- and inter-observer reproducibility assessed by ICCs than images that were of “poor” quality for both RVFWLS and RVGLS (Table 5-6), noting that the imbalance in the groups sizes may have influenced the observed results (“good” or “adequate” n = 12, “poor” n = 8). In summary, as might be anticipated, it appears that echocardiography studies with higher quality images, either assessed semi-quantitively or by a qualitative global assessment, appear to result in better RVFWLS and RVGLS reproducibility.

Table 5-6 Agreement analysis of RV-STE and image quality

	Bland Altman MD (%)	Bland Altman SD (%)	Bland Altman LOA (%)	Intraclass correlation coefficient
RVFWLS				
Intra-observer- All (n=20)	**-1.24**	**2.87**	**5.39, -6.87**	**0.91 (p<0.001)**
Average endocardial delineation score >8 (n=10)	-1.75	2.72	3.58, -7.08	0.93 (p<0.001)
Average endocardial delineation score ≤8 (n=10)	-0.73	3.07	5.29, -6.75	0.83 (p=0.009)
Scans qualitatively assessed image quality “good” or “adequate” (n=12)	-1.99	2.66	3.22, -7.20	0.92 (p<0.001)
Scans qualitatively assessed image quality as "poor" (n=8)	-0.11	2.97	5.71, -5.93	0.87 (p=0.01)
Inter-observer- All (n=20)	**-0.52**	**4.04**	**7.40, -8.45**	**0.88 (p<0.001)**
Average endocardial delineation score >8 (n=10)	1.77	4.28	10.16, -6.62	0.92 (p<0.001)
Average endocardial delineation score ≤8 (n=10)	-2.81	2.14	4.29, -9.91	0.76 (p=0.001)
Scans qualitatively assessed image quality “good” or “adequate” (n=12)	0.71	3.97	8.49, -7.07	0.92 (p<0.001)
Scans qualitatively assessed image quality as "poor" (n=8)	-2.36	3.62	4.74, -9.46	0.72 (p=0.037)
RVGLS				
Intra-observer- All (n=20)	**-1.59**	**2.72**	**3.75, -6.93**	**0.85 (p<0.001)**
Average endocardial delineation score >8 (n=10)	-2.11	1.97	1.75, -5.97	0.89 (p<0.001)
Average endocardial delineation score ≤8 (n=10)	-1.07	3.34	5.48, -7.62	0.74 (p=0.028)
Scans qualitatively assessed image quality “good” or “adequate” (n=12)	-2.68	2.28	1.79, -7.15	0.84 (p<0.001)
Scans qualitatively assessed image quality as "poor" (n=8)	0.04	2.64	5.21, -5.13	0.87 (p=0.01)
Inter-observer- All (n=20)	**-1.38**	**3.25**	**4.99, -7.75**	**0.84 (p<0.001)**
Average endocardial delineation score >8 (n=10)	0.60	2.98	6.44, -5.24	0.93 (p<0.001)
Average endocardial delineation score ≤8 (n=10)	-3.35	2.19	0.94, -7.64	0.6 (p=0.007)
Scans qualitatively assessed image quality “good” or “adequate” (n=12)	-0.29	2.85	5.30, -5.88	0.93 (p<0.001)
Scans qualitatively assessed image quality as "poor" (n=8)	-3.00	3.30	3.47, -9.47	0.56 (p=0.074)

MD = mean difference, SD = standard deviation, LOA = limits of agreement, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain

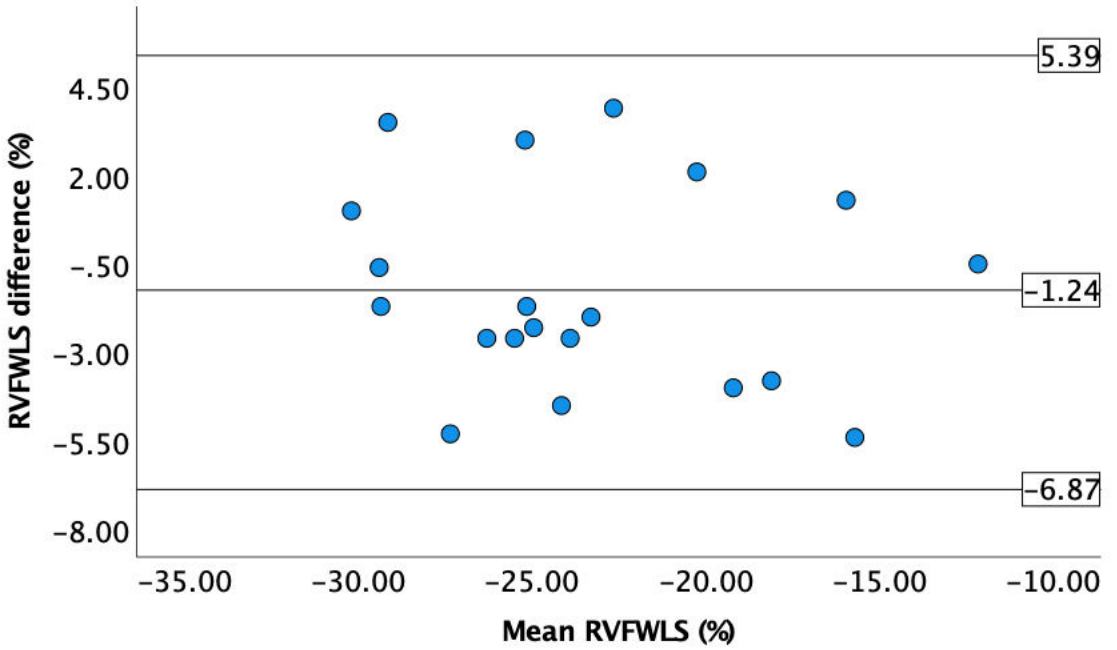


Figure 5-4 Bland-Altman plot for RVFWLS intra-observer agreement
Solid horizontal middle line represents mean difference and outer solid lines represent 95% limits of agreement. RVFWLS = right ventricular free wall longitudinal strain.

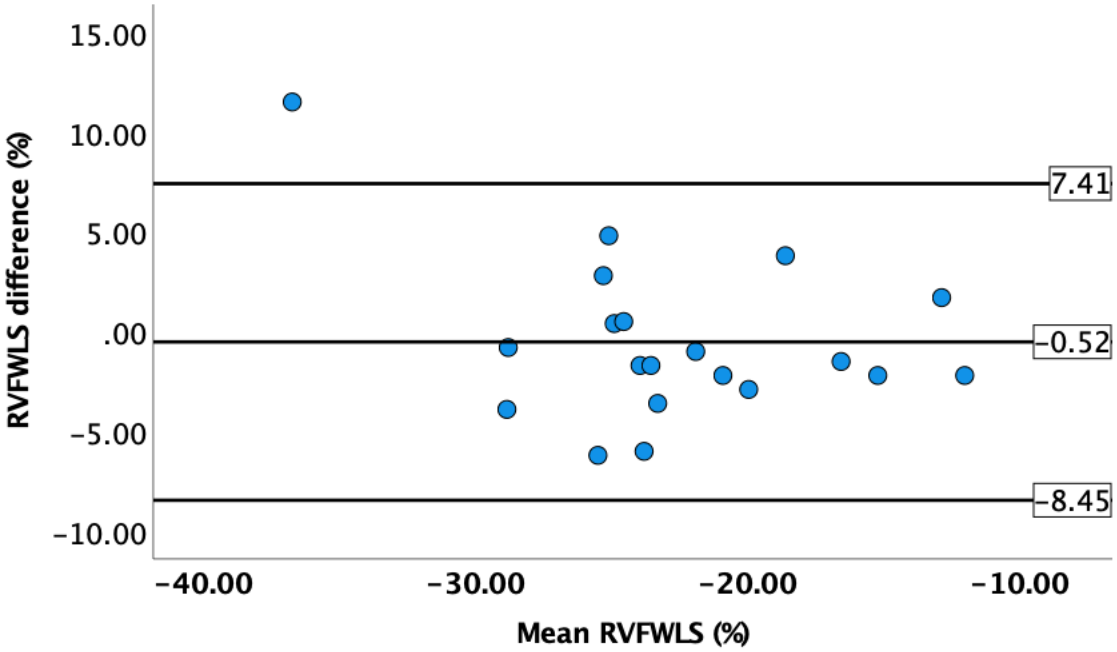


Figure 5-5 Bland-Altman plot for RVFWLS inter-observer agreement
Solid horizontal middle line represents mean difference and outer solid lines represent 95% limits of agreement. RVFWLS = right ventricular free wall longitudinal strain.

Table 5-7 Agreement analysis of conventional RV echocardiography parameters

	Bland Altman MD (%)	Bland Altman SD (%)	Bland Altman LOA (%)	Intraclass correlation coefficient
RVFAC (%)				
Intra-observer (n=20)	3.23	5.19	13.41, -6.96	0.87 (p<0.001)
Inter-observer (n=20)	2.21	5.72	13.42, -9.00	0.84 (p<0.001)
TAPSE (mm)				
Intra-observer (n=4)	-0.35	1.80	3.17, -3.87	0.92 (p=0.480)
Inter-observer (n=3)	-0.20	1.15	2.06, -2.45	0.97 (p=0.036)
S' (cm/s)				
Intra-observer (n=8)	-0.25	0.46	0.66, -1.16	0.99 (p<0.001)
Inter-observer (n=6)	1.00	1.10	3.06, -0.86	0.86 (p=0.005)
RIMP				
Intra-observer (n=8)	-0.001	0.035	0.067, -0.070	0.99 (p<0.001)
Inter-observer (n=8)	0.036	0.089	1.790, -1.720	0.89 (p=0.005)
LVEI diastolic				
Intra-observer (n= 16)	0.021	0.080	0.178, -0.135	0.97 (p<0.001)
Inter-observer (n=8)	-0.020	0.092	0.160, -0.200	0.77 (p=0.043)
LVEI systolic				
Intra-observer (n=16)	-0.019	0.107	0.190, -0.228	0.94 (p<0.001)
Inter-observer (n=8)	0.028	0.135	0.293, -0.238	-0.08 (p 0.536)
RV basal diameter end diastole (mm)				
Intra-observer (n=15)	-0.44	2.23	3.93, -4.81	0.96 (p<0.001)
Inter-observer (n=13)	-0.17	2.78	5.28, -5.62	0.92 (p<0.001)
LV basal diameter end diastole (mm)				
Intra-observer (n=15)	-0.19	3.08	5.85, -6.22	0.95 (p<0.001)
Inter-observer (n=13)	2.64	3.26	9.03, -3.75	0.87 (p<0.001)

MD = mean difference, SD = standard deviation, LOA = limits of agreement, RVFAC = right ventricular fractional area change, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RIMP = right ventricular index of myocardial performance, LVEI = left ventricle eccentricity index, RV = right ventricular, LV = left ventricular

5.3.6 Validity

5.3.6.1 Concurrent criterion validity

Although gold standard CMR was not used in COVID-RV, a comparison can be made between RV-STE and standard conventional echocardiography measures of systolic RV function. If an association is observed between RV-STE and the conventional RV echocardiography measures, it suggests that RVFWLS has concurrent criterion validity (although we cannot say this for sure since we are not comparing RVFWLS to a gold standard measure). It must be noted that given there are intrinsic limitations in all the conventional echocardiography parameters abilities to measure RV function (compared to gold standard CMR), and the possible superiority of RVFWLS in this regard, a perfect association between RVFWLS and the conventional echocardiography measures is not expected. RVFWLS showed significant association with RVFAC, TAPSE, S', and RIMP (Table 5-8). The strongest association was seen with RVFAC (r=-736, p<0.001), however it must be noted that Tomtec 2D CPA software automatically calculated RVFAC during RV-STE analysis, so it may not be surprising this was observed.

Table 5-8 Correlation between conventional RV echocardiography parameters and RVFWLS

	Correlation coefficient	p-value
RVFAC (n=94)	-0.736¥	<0.001
TAPSE (n=45)	-0.358¥	0.016
S' (n=42)	-0.555ç	<0.001
RIMP (n=38)	0.654¥	<0.001

Pearson's correlation coefficient (ç), Spearman's correlation coefficient (¥)
RV = right ventricular, RVFWLS = right ventricular free wall longitudinal strain, RVFAC = right ventricular fractional area change, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RIMP = right ventricular index of myocardial performance

Twenty-seven patients had abnormal RVFWLS (>-20%). Patients with abnormal RVFWLS more frequently had abnormal RVFAC, TAPSE, S', and RIMP compared to patients with normal RVFWLS (Table 5-9), suggesting that abnormal RVFWLS detects impaired RV function that is also identified by the conventional echocardiography measures of RV systolic function. Of note, there was no significant difference in RV:LV basal diameter, and the prevalence of severe RV dilatation between abnormal RVFWLS and normal RVFWLS groups, suggesting that RVFWLS may not be a good surrogate measure of RV dilatation. This finding may represent a desirable property of RVFWLS, implying that RVFWLS is independent of the change in loading conditions associated with RV dilatation.

Table 5-9 Comparison of echocardiography parameters between normal and abnormal RVFWLS groups

Echocardiography parameter		All (n=94)	Normal RVFWLS (≤-20%) (n=67)	Abnormal RVFWLS (>-20%) (n=27)	p-value
Time from symptom onset to echocardiography (days)	n (n missing)	93 (1) 18 [13.5, 22]	67 (0) 18 [13, 21]	26 (1) 21 [16, 27.5]	0.011§
Time from intubation to echocardiography (days)		5 [4, 8]	5 [4, 8]	5 [3, 9]	0.794 §
RVGLS %		-20.3 (4.4)	-22.5 (3.1)	-15.3 (2.3)	<0.001η
RVFAC %		34.1 [26.2, 38.5]	36.0 (6.9)	25.6 (6.1)	<0.001η
TAPSE mm	n (n missing)	45 (49) 23.7 [20.3, 25.5]	32 (35) 24.1 (2.9)	13 (14) 19.1 (4.6)	0.002η
S' cm/s	n (n missing)	42 (52) 15.2 (3.4)	28 (39) 16.5 (2.7)	14 (13) 12.6 (3.3)	<0.001η
RIMP	n (n missing)	38 (56) 0.42 [0.30, 0.54]	25 (42) 0.38 [0.3, 0.43]	13 (14) 0.62 [0.53, 0.87]	<0.001§
LVEI Diastole	n (n missing)	51 (43) 1.04 [0.95, 1.54]	35 (32) 1.07 (0.23)	16 (11) 1.12 (0.27)	0.449η
LVEI Systole	n (n missing)	52 (42) 1.04 [0.94, 1.18]	36 (31) 1.06 (0.19)	16 (11) 1.09 (0.26)	0.653η
RV:LV Basal Diameter ED	n (n missing)	56 (38) 0.84 (0.13)	39 (28) 0.82 (0.12)	17 (10) 0.87 (0.13)	0.167η
Severe RV dilatation† (RV:LV >1:1)	n (n missing)	90 (4) 23 (25.6%)	66 (1) 15 (22.7%)	24 (3) 8 (33.3%)	0.308*
Septal flattening†	n (n missing)	90 (4) 9 (10%)	66 (1) 4 (6.1%)	24 (3) 5 (20.8%)	0.053ω
Subjective RV dysfunction†	n (n missing)	93 (1) 16 (17.2%)	67 (0) 7 (10.4%)	26 (1) 9 (34.6%)	0.012ω
Subjective LV dysfunction†	n (n missing)	92 (2) 11 (12%)	66 (1) 8 (12.1%)	26 (1) 3 (11.5%)	>0.999ω

Data are presented as mean (SD), median [IQR] or n (%). Data are complete unless indicated by n (n missing).
Between-group differences were assessed using Student's T-test (η), Mann-Whitney U test (§), Fisher's Exact test (ω), and Pearson Chi-Square test (*).
† = these diagnoses were made by the echocardiographer at the bedside, the author did not report them.
RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, RVFAC = right ventricular fractional area change, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RIMP = right ventricular index of myocardial performance, LVEI = left ventricular eccentricity index, RV = right ventricular, LV = left ventricular, ED = end diastole.

5.3.6.2 Predictive validity

The predictive validity of RVFWLS was investigated in the following ways; the association between abnormal RVFWLS and 30-day and one-year mortality, subsequent requirement for renal replacement therapy (RRT), prone IMV, and referral for extra corporeal membrane oxygenation (ECMO). These predictive associations were also assessed using the conventional RV echocardiography parameters.

5.3.6.2.1 RVFWLS and predicting survival

At 30 days from ICU admission, 39 (41.5%) patients had died (Table 5-10, Figure 5-6). Sixteen (59.3%) patients with abnormal RVFWLS had died, compared to 23 (34.3%) with normal RVFWLS (p=0.026). Similarly, a strong association was found between abnormal RVGLS and 30-day mortality (p=0.011). Abnormal RVFAC, abnormal TAPSE, abnormal S', and abnormal RIMP were not associated with 30-day mortality. This suggests that RVFWLS has predictive validity with regards 30-day mortality in this cohort, whereas the conventional RV echocardiography parameters do not. The association between abnormal RVFWLS and 30-day mortality remained in multivariable analysis, adjusting for age, gender, ethnicity, phase of disease and baseline severity of illness (hazard ratio 2.22 [1.14, 4.39], p=0.020, Table 5-11). This finding demonstrates that abnormal RVFWLS was independently associated with 30-day mortality, and that patients with abnormal RVFWLS had over twice the probability of dying during the 30-day study period compared to controls.

Table 5-10 Thirty-day mortality rate between normal and abnormal echocardiography parameter groups

Echocardiography parameter	All	Normal echocardiography parameter	Abnormal echocardiography parameter	p-value
RVFWLS (n=94)	39 (41.5%)	23 (34.3%)	16 (59.3%)	0.026*
RVGLS (n=94)	39 (41.5%)	20 (32.3%)	19 (59.4%)	0.011*
RVFAC (n=94)	39 (41.5%)	24 (41.4%)	15 (41.7%)	0.978*
TAPSE (n=45)	19 (42.2%)	15 (38.5%)	4 (66.7%)	0.377ω
S' (n=42)	17 (40.5%)	16 (40.0%)	1 (50.0%)	>0.999ω
RIMP (n=38)	15 (39.5%)	9 (31.0%)	6 (66.7%)	0.115ω

Fisher's Exact test (ω), and Pearson Chi-Square test (*).
RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, RVFAC = right ventricular fractional area change, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RIMP = right ventricular index of myocardial performance

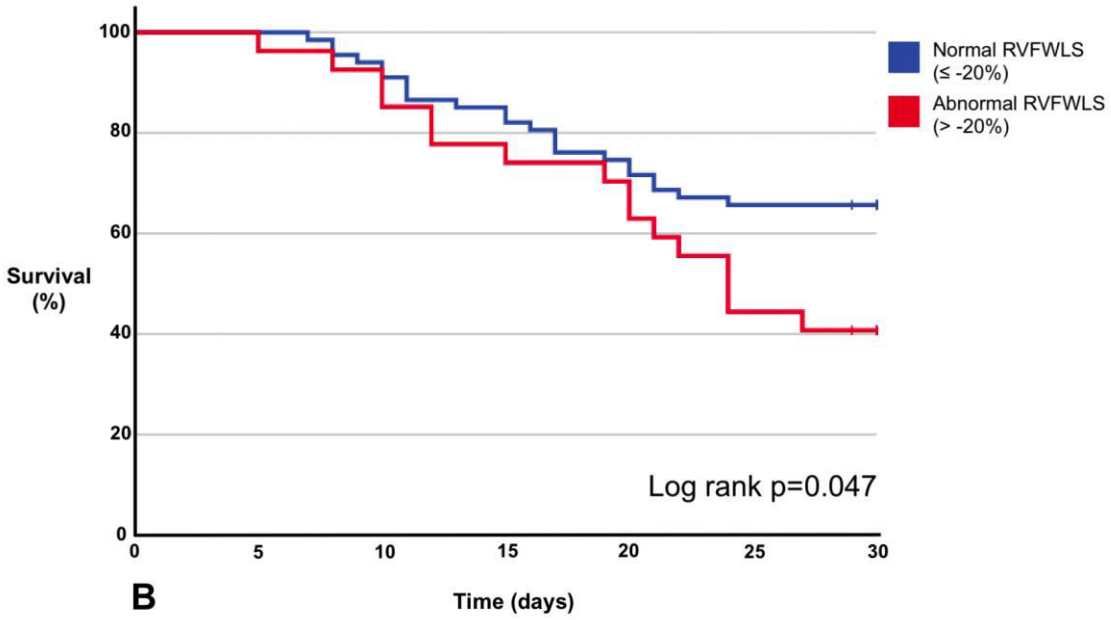


Figure 5-6 Thirty-day survival and RVFWLS
Kaplan-Meier with log rank analysis comparing thirty-day survival between groups with normal and abnormal RVFWLS. RVFWLS = right ventricular free wall longitudinal strain. N = 94.

Table 5-11 Multivariable cox regression for 30-day mortality adjusting for remaining variables in table

	HR (95% CI)	p-value
Abnormal RVFWLS (>-20%)	2.22 (1.14, 4.39)	0.020
Age in years (per 1-year increase)	1.06 (1.01, 1.10)	0.009
Female Gender	0.86 (0.44, 1.71)	0.674
Non-white ethnicity	1.00 (0.28, 3.60)	0.994
APACHE II score on admission to ICU (per 1-score increase)	1.06 (1.00, 1.11)	0.040
Time from intubation to echo (per 1-day increase)	0.91 (0.81, 1.03)	0.123

RVFWLS = right ventricular free wall longitudinal strain, APACHE = acute physiology and chronic health evaluation, echo = echocardiography, HR = hazard ratio. N = 89

When looking at long term mortality outcomes, abnormal RVFWLS was not associated with one-year mortality on univariate analysis (Figure 5-7), however a strong association between abnormal RVFWLS and one-year mortality was again observed on multivariable analysis (Hazard Ratio 2.14 [1.18, 3.89], p=0.012, Table 5-12). The strong independent associations between abnormal RVFWLS and both short- and long-term mortality suggests that RVFWLS has predictive validity in this patient group.

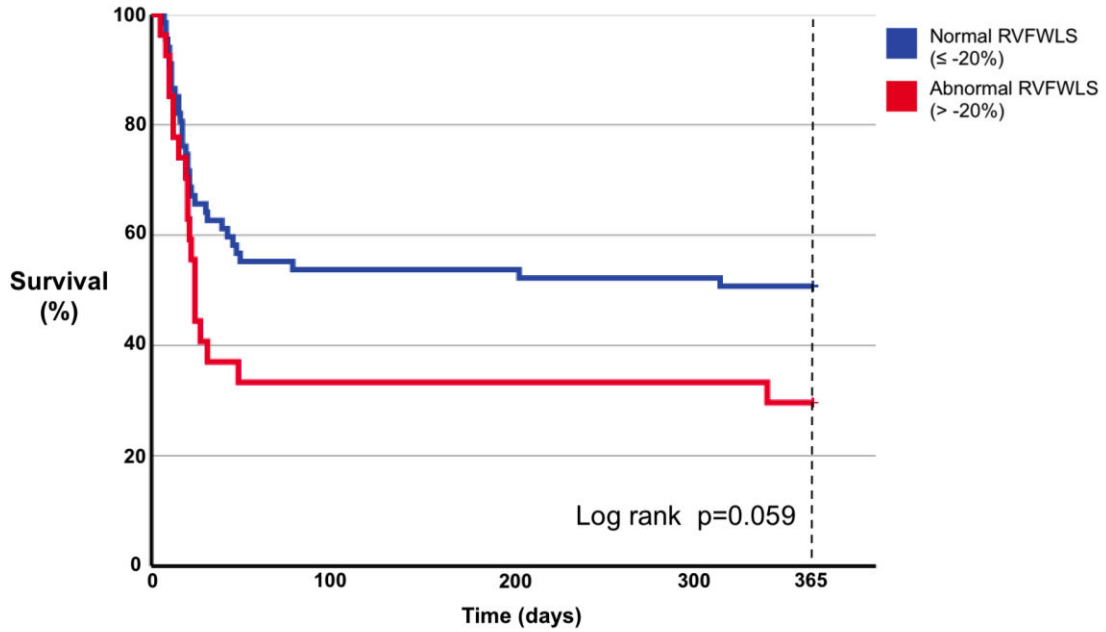


Figure 5-7 One year survival and RVFWLS
Kaplan-Meier with log rank analysis comparing one year survival between groups with normal and abnormal RVFWLS. RVFWLS = right ventricular free wall longitudinal strain N = 94

Table 5-12 Multivariable cox regression for one-year mortality adjusting for remaining variables in table

	HR (95% CI)	p-value
Abnormal RVFWLS (>-20%)	2.14 (1.18, 3.89)	0.012
Age in years (per 1-year increase)	1.06 (1.02, 1.10)	0.002
Female Gender	0.93 (0.52, 1.67)	0.816
Non-white ethnicity	0.97 (0.36, 2.64)	0.959
APACHE II score on admission to ICU (per 1-score increase)	1.06 (1.01, 1.11)	0.018
Time from intubation to echo (per 1-day increase)	0.97 (0.89, 1.07)	0.568

RVFWLS = right ventricular free wall longitudinal strain, APACHE = acute physiology and chronic health evaluation, HR = hazard ratio. N = 89

5.3.6.2.2 The predictive validity of RVFWLS and other patient outcomes

Beyond mortality, other patient outcomes investigated included new requirement for RRT, requirement for prone IMV, and need for ECMO referral. Neither abnormal RVFWLS, abnormal RVGLS, nor abnormality of the conventional RV echocardiography parameters were associated with the need for RRT, prone IMV, or ECMO referral (Tables 5-13, 5-14, 5-15). The exception to this is abnormal RVFAC, which was associated with patients not requiring prone IMV, p=0.020. This data may indicate that patient factors beyond RVD may impact upon the need for RRT, prone IMV, and ECMO referral. Given that these outcomes were explorative, and the study was not powered to detect the effect of RVD upon these outcomes, it is also possible that a true association has been missed. The finding that abnormal RVFAC was associated with patients not requiring prone IMV is puzzling since it would be anticipated that patients with

worse ARDS would require proning, and worse ARDS is likely to be associated with more impaired RV function (and therefore abnormal RVFAC). It is possible that this finding may represent a type 1 error given the multiple comparisons conducted.

Table 5-13 Requirement for RRT at 30 days from ICU admission

	All	Normal echo parameter	Abnormal echo parameter	p-value
RVFWLS (n=94)	22 (23.4%)	15 (22.4%)	7 (25.9%)	0.760*
RVGLS (n=94)	22 (23.4%)	12 (19.4%)	10 (31.3%)	0.395*
RVFAC (n=94)	22 (23.4%)	12 (20.7%)	10 (27.8%)	0.707ω
TAPSE (n=45)	14 (31.1%)	12 (30.8%)	2 (33.3%)	>0.999ω
S' (n=42)	11 (26.2%)	11 (27.5%)	0 (0.0%)	>0.999ω
RIMP (n=38)	10 (26.3%)	9 (31.0%)	1 (11.1%)	0.316ω

Fisher's Exact test (ω), and Pearson Chi-Square test (*).
RRT = renal replacement therapy, ICU – intensive care unit, Echo = echocardiography, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, RVFAC = right ventricular fractional area change, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RIMP = right ventricular index of myocardial performance.

Table 5-14 Requirement for prone IMV at 30 days from ICU admission

	All	Normal echo parameter	Abnormal echo parameter	p-value
RVFWLS (n=94)	42 (44.7%)	32 (47.8%)	10 (37%)	0.578*
RVGLS (n=94)	42 (44.7%)	29 (46.8%)	13 (40.6%)	0.652*
RVFAC (n=94)	42 (44.7%)	32 (55.2%)	10 (27.8%)	0.020*
TAPSE (n=45)	23 (51.1%)	22 (56.4%)	1 (16.7%)	0.159ω
S' (n=42)	20 (47.6%)	20 (50.0%)	0 (0.0%)	0.384ω
RIMP (n=38)	19 (50.0%)	14 (48.3%)	5 (55.6%)	>0.999

Fisher's Exact test (ω), and Pearson Chi-Square test (*).
IMV = invasive mechanical ventilation, ICU = intensive care unit, Echo = echocardiography. RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, RVFAC = right ventricular fractional area change, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RIMP = right ventricular index of myocardial performance.

Table 5-15 Referred for ECMO at 30 days from ICU admission

	All	Normal echo parameter	Abnormal echo parameter	p-value
RVFWLS (n=94)	12 (12.8%)	9 (13.4%)	3 (11.1%)	0.343ω
RVGLS (n=94)	12 (12.8%)	9 (14.5%)	3 (9.4%)	0.394ω
RVFAC (n=94)	12 (12.8%)	7 (12.1%)	5 (13.9%)	0.533ω
TAPSE (n=45)	5 (11.1%)	5 (12.8%)	0 (0.0%)	>0.999ω
S' (n=42)	4 (9.5%)	4 (10.0%)	0 (0.0%)	>0.999ω
RIMP (n=38)	4 (10.5%)	3 (10.3%)	1 (11.1%)	>0.999ω

Fisher's Exact test (ω), and Pearson Chi-Square test (*).
ECMO = extra corporeal membrane oxygenation, ICU = intensive care unit, echo = echocardiography, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, RVFAC = right ventricular fractional area change, TAPSE = tricuspid annular plane systolic excursion, S' = S' wave velocity at the tricuspid annulus, RIMP = right ventricular index of myocardial performance

5.3.6.3 Construct validity

The construct validity of RV-STE as a measure of RV function was assessed by the COVID-RV study. Data for formative items, reflective items, and mixed items were collected at various time points during patients' admission in ICU. These are described in the order above.

5.3.6.3.1 Formative items

As described in Chapter 3 (section 3.4.3), construct validity hypothesis testing assessed by formative items relates to observing the expected relationship between RV-STE (as a measure of RV function) and variables that will have an impact upon RV function. The various formative items examined by COVID-RV are shown in green in Figure 5-8.

As described in section 4.1.5.2, more severe ARDS can result in increased PVR and increased RV afterload, negatively impacting RV function. In the present study however, measures of ARDS severity such as FiO_2, PaO_2, $PaCO_2$, Murray lung injury scores, and PaO_2/FiO_2 ratio were not associated with abnormal RVFWLS ($p \geq 0.251$ for all, Table 5-16), however there was a trend between worse dynamic compliance and abnormal RVFWLS (p=0.071). These findings are in keeping with those reported by previous studies, with Li et al, Gibson et al, and Bursi et al all finding no association between RVFWLS and PaO_2/FiO_2 ratios[16,181,201]. Ventilator strategies using higher airway pressures may also increase PVR and RV afterload, and although there was no association between plateau pressure, PEEP, or peak airway pressure (PAP), and abnormal RVFWLS (p=0.397, p=0.110, and p=0.185), there was an association between higher driving pressure and abnormal RVFWLS (p=0.040).

PE represents another formative item that may detrimentally impact upon RV function. A trend was demonstrated between confirmed or suspected PE and abnormal RVFWLS (Table 5-16, p=0.097), however no association was found between D-dimer and abnormal RFWLS (p=0.230).

Pre-existing lung disease (with a resulting increase in PVR) also represents a formative that could impact upon RV function. There was no association

between previous smoking history, or COPD diagnosis, and abnormal RVFWLS (Table 5-16, p=0.837 and 0.815).

COVID-19 pathological mechanisms that impair cardiac contractility represent formative items that would impair RV function. There was a strong association between raised cardiac biomarkers and abnormal RVFWLS (troponin I p=0.032, troponin T p<0.001, NT-proBNP p=0.004, Table 5-16). Raised troponin and NT-proBNP may represent myocardial injury (due to e.g. ischaemia or inflammatory injury) and haemodynamic cardiac stress respectively, which can negatively impact RV function. It would appear that RV-STE has construct validity in its ability to identify the changes in RV function that may have resulted due to myocardial injury and haemodynamic cardiac stress. These findings are in keeping with previous studies discussed in section 4.1.5.3.3 which found association between RVFWLS and troponin levels [175,180]. Neutrophil count and C-reactive protein (CRP) were used as laboratory measures of cardiac inflammation. A trend was found between neutrophil count and abnormal RVFWLS (p=0.058), however no association was found between CRP and abnormal RVFWLS (p=0.877). Pre-existing cardiac disease could also impair RV function, however no association was found between coronary artery disease and abnormal RVFWLS (Table 5-16, p=0.235).

Treatment with intravenous corticosteroids, a formative item that may be associated with RV protection and therefore better RV function (possibly via mitigation of inflammatory cardiac injury or dampening the severity of ARDS, shown in blue on Figure 5-8), was not associated with abnormal RVFWLS (p=0.567).

Overall, abnormal RVFWLS was strongly associated with cardiac biomarkers and demonstrated association with driving pressure. These findings suggest RVFWLS has construct validity with respect to these formative items.

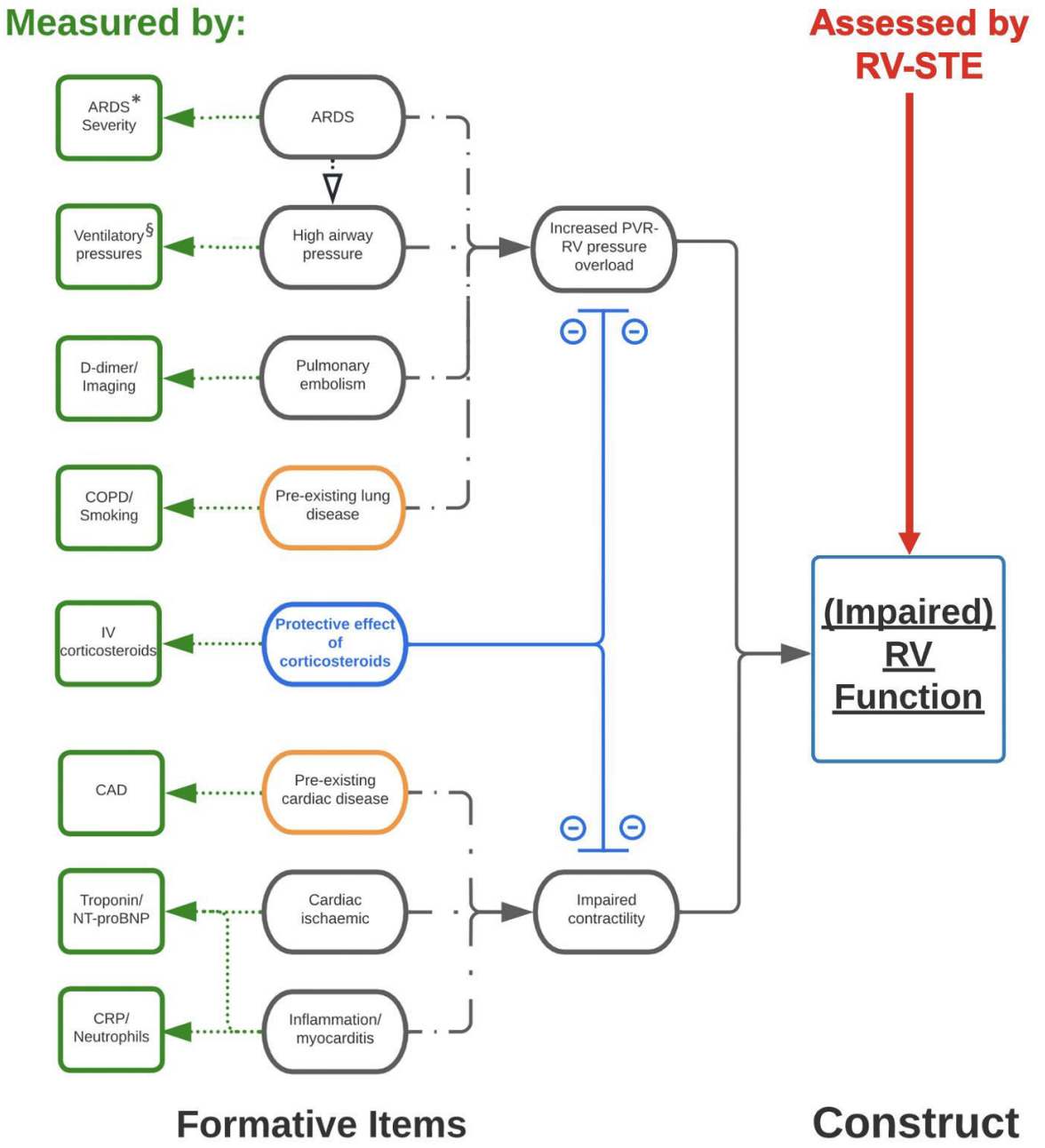


Figure 5-8 Relationship between formative items and RV function

*Specific parameters measured include FiO_2, P/F ratio, PaO_2, $PaCO_2$, Murray lung injury scores, dynamic compliance. §Specific parameters measured include plateau pressure, PEEP, PAP, driving pressure, tidal volumes.

ARDS = acute respiratory distress syndrome, COPD = chronic obstructive pulmonary disease, IV = intravenous, CAD = coronary artery disease, CRP = C reactive protein, PVR = pulmonary vascular resistance, RV = right ventricular, STE = speckle tracking echocardiography, FiO_2 = fraction of inspired oxygen, P/F ratio = ratio of arterial oxygen pressure to the fraction of inspired oxygen, PaO_2 = partial pressure of oxygen, $PaCO_2$ = partial pressure of carbon dioxide, PEEP = positive end expiratory pressure, PAP = peak airway pressure.

Table 5-16 Formative items investigated in COVID-RV

		All (n=94)	Normal RVFWLS (≤-20%) (n=67)	Abnormal RVFWLS (>-20%) (n=27)	p-value
ARDS severity on day of echocardiography					
FiO_2		0.55 [0.45, 0.7]	0.5 [0.45, 0.65]	0.55 [0.45, 0.8]	0.373§
P/F ratio	n (n missing)	93 (1) 17.5 [12.9, 21.9]	67 (0) 17.5 [13.3, 21.8]	26 (1) 17.8 [12.3, 22,5]	0.918§
PaO_2, kPa	n (n missing)	93 (1) 9.2 [8.5, 10.1]	67 (0) 9.1 [8.5, 10]	26 (1) 9.6 [8.6, 10.6]	0.251§
$PaCO_2$, kPa	n (n missing)	89 (5) 7 [6.1, 8.0]	65 (2) 7 [6.2, 8]	24 (3) 6.5 [5.9, 8.6]	0.781§
Murray lung injury score	n (n missing)	82 (12) 2.8 [2.3, 3]	58 (9) 2.8 [2.2, 3]	24 (3) 2.8 [2.35, 3.2]	0.479§
Dynamic compliance, ml/cmH_2O	n (n missing)	48 (46) 28.1 [19.1, 39.7]	34 (33) 31.2 [21.6, 40.1]	14 (13) 21.2 [16.5, 35.1]	0.071§
Ventilation parameters on day of echocardiography					
Plateau pressure, cmH_2O	n (n missing)	48 (46) 25 (5.3)	34 (33) 24.6 (5.6)	14 (13) 26.1 (4.7)	0.397η
PAP, cmH_2O	n (n missing)	91 (3) 26 [19, 30]	65 (2) 25 [19, 29]	26 (1) 27 [20, 31]	0.185§
Tidal volume, ml/kg (PBW)	n (n missing)	89 (5) 6.6 [5.9, 7.3]	64 (3) 6.5 [5.9, 7.2]	25 (2) 7.0 [5.9, 7.5]	0.335§
PEEP, cmH_2O	n (n missing)	93 (1) 10 [8, 12]	66 (1) 10 [8, 12]	27 (0) 10 [6, 10]	0.110§
Driving pressure, cmH_2O	n (n missing)	48 (46) 13 [11 17.75]	34 (33) 12 [10, 16.25]	14 (13) 16.5 [12, 20]	0.040§
Presence of pulmonary embolism					
Confirmed or suspected PE	Radiologically confirmed Clinically suspected No Unknown	4 (4.3%) 4 (4.3%) 84 (89.4%) 2 (2.1%)	1 (1.5%) 4 (6.0%) 61 (91.0%) 1 (1.5%)	3 (11.1%) 0 (0.0%) 23 (85.2%) 1 (3.7%)	0.097*
D-Dimer, mg/L FEU	n (n missing)	66 (28) 1432.5 [652-2811]	46 (21) 1224 [534-3079]	20 (7) 1918.5 [952-2682]	0.230§

Presence of pre-existing lung disease					
Smoking history	Non-smoker Ex-smoker > 1 year Current or within 1 year	53 (56.4%) 34 (36.2%) 7 (7.4%)	39 (58.2%) 23 (34.3%) 5 (7.5%)	14 (51.9%) 11 (40.7%) 2 (7.4%)	0.837*
COPD diagnosis		7 (7.4%)	5 (7.5%)	2 (7.4%)	0.815*
Presence of cardiac ischaemia/injury					
ACS diagnosis from hospital admission		5 (5.3%)	3 (4.5%)	2 (7.4%)	0.623ω
hsTn I, ng/L	n (n missing)	57 (37) 13 [5, 39.5]	43 (24) 9 [4, 23]	14 (13) 39.5 [9, 146]	0.032§
hsTn T, ng/L	n (n missing)	35 (59) 18 [10, 29]	22 (45) 12.5 [9.3, 19.8]	13 (14) 27 [21.5, 47]	<0.001§
NT-proBNP, ng/L	n (n missing)	84 (10) 461 [109, 1798]	58 (9) 377 [165, 947]	26 (1) 1697 [302, 23271]	0.004§
Presence of cardiac inflammation on day of echocardiography					
Neutrophils, $x10^9$/L		10.4 [8.5, 14.2]	10.2 [8.4, 13.1]	12.3 [8.6, 19.4]	0.058§
CRP, mg/L		52.5 [9, 158]	54 [9, 169]	51 [12, 119]	0.877§
Pre-existing cardiac disease					
Coronary artery disease		8 (8.5%)	5 (7.5%)	3 (11.1%)	0.235*
Treatment before intubation					
Intravenous corticosteroids		62 (66%)	43 (64.2%)	19 (70.4%)	0.567*

Data are presented as mean (SD), median [interquartile range- IQR] or n (%). Data are complete unless indicated by n (n missing).
Between-group differences were assessed using Student's T-test (η), Mann-Whitney U test (§), Fisher's Exact test (ω), and Pearson Chi-Square test (*).
RVFWLS = right ventricular free wall longitudinal strain, ARDS = acute respiratory distress syndrome, FiO_2 = Fraction of Inspired Oxygen, P/F ratio = ratio of arterial oxygen pressure to the fraction of inspired oxygen, PaO_2 = partial pressure of oxygen, $PaCO_2$ = partial pressure of carbon dioxide, PAP = Peak Airway Pressure PBW = Predicted Body Weight, PEEP = Positive End Expiratory Pressure, PE = pulmonary embolism, COPD = Chronic Obstructive Pulmonary Disease, ACS = acute coronary syndrome, hsTn = High Sensitivity Troponin, NT-proBNP = N-terminal pro B-type Natriuretic Peptide, CRP = C reactive protein

5.3.6.3.2 Reflective items

Reflective items relate to variables that will be impacted upon by changes in RV function, where construct validity is identified by assessing the association between these items and RV-STE (where RV-STE is a surrogate of the RV function "construct"). The conceptual model for reflective items investigated by the COVID-RV study is shown in Figure 5-9.

Impaired RV function might be expected to result in venous congestion, venous congestion therefore represents a reflective item. CVP was used a surrogate measure of venous congestion, however there was no association found between CVP and abnormal RVFWLS (p=0.485, Table 5-17). Impaired RV function could also result in AKI (via venous congestion and back pressure to the kidneys). Measures of AKI were therefore used as reflective items. A trend between requirement for RRT on the day of echocardiography and abnormal RVFWLS was identified (p=0.056). Of the laboratory measurements of AKI on the day of echocardiography, neither creatinine nor creatinine clearance were associated with abnormal RVFWLS (p=0.176, p=0.383 respectively), similarly no association was observed between base excess (a variable that could be worsened by metabolic acidosis from AKI) and abnormal RVFWLS. It is possible that if more patients with abnormal RVFWLS were receiving RRT on the day of echocardiography, then creatinine and base excess in the abnormal RVFWLS group might have been artificially normalised and a true association missed. Overall, from the available evidence there does not appear to be a clear association between abnormal RVFWLS and AKI, suggesting that construct validity has not been identified in this regard. These findings are in keeping with the previous research discussed in section 4.1.5.3.4.

Impaired RV function (and the phenomenon of ventricular interdependence) can result in circulatory shock, circulatory shock is consequently a reflective item (Figure 5-9). Lower systemic blood pressure was expected to be associated with abnormal RVFWLS, however no association was observed (p=0.164). An association was observed between vasopressor use and abnormal RVFWLS, 34.3% of patients with normal RVFWLS were receiving vasopressors compared to 63.0% of patient with abnormal RVFWLS (p=0.011). This may suggest that hypotension

induced by abnormal RVFWLS resulted in the increased use of vasopressors in the group with abnormal RVFWLS. The use of vasopressors may also explain the lack of association between systemic blood pressure and abnormal RVFWLS. This contrasts with Gibson et al[201], who did not find an association between abnormal RVFWLS and administration of vasopressors/inotropes in patients with COVID-19, however their much smaller sample size (n=32) may have diminished the chance of finding a true association. Of note no patients in the COVID-RV study were receiving inotropes, which may have been an appropriate therapy for RVD. Heart rate was noted to be higher in the abnormal RVFWLS group (p=0.028), further reinforcing the link between cardiovascular instability and abnormal RVFWLS.

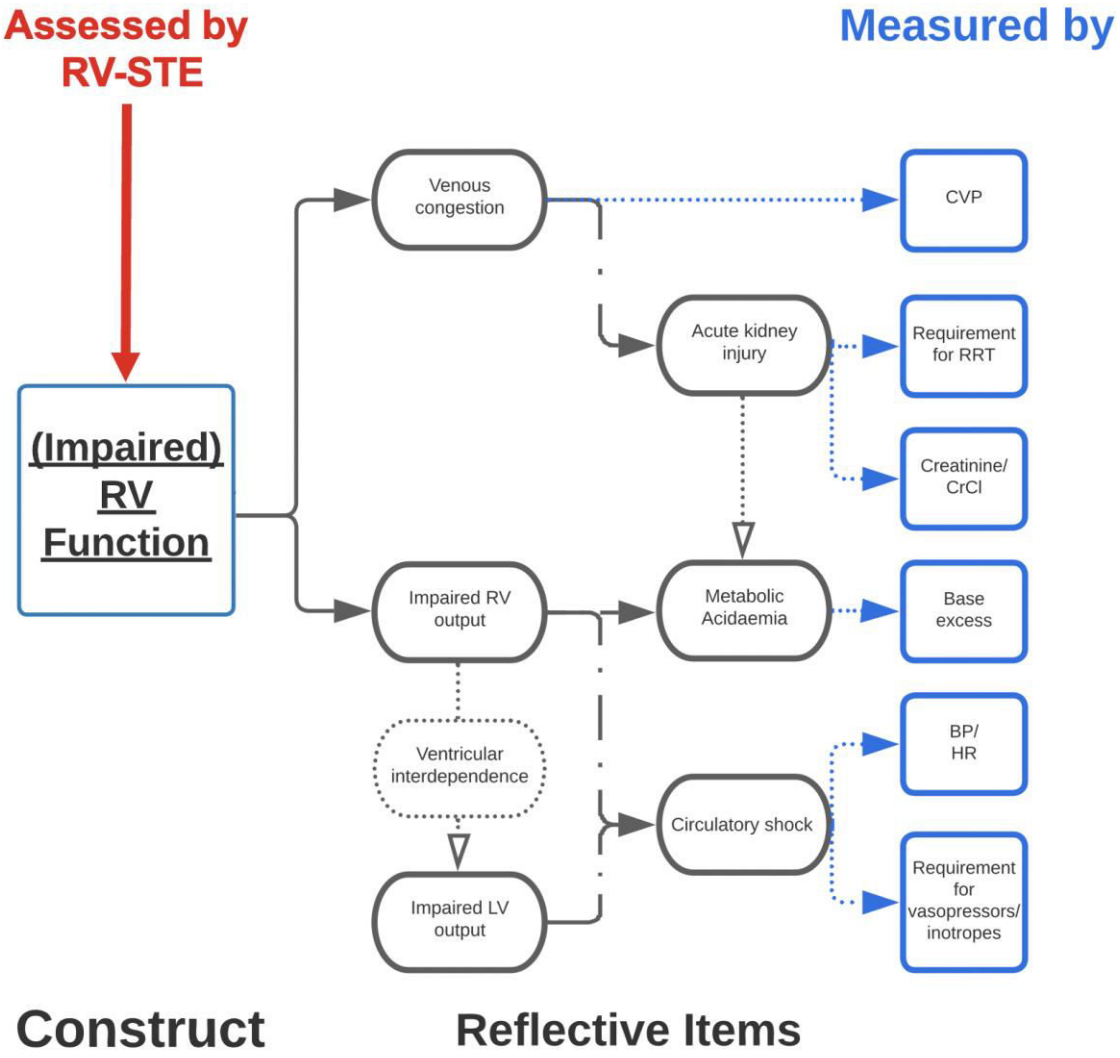


Figure 5-9 Relationship between reflective items and RV function
RV = right ventricular, STE = speckle tracking echocardiography, LV = left ventricular, CVP = central venous pressure, RRT = renal replacement therapy, CrCl = creatinine clearance, BP = blood pressure, HR = heart rate

Table 5-17 Reflective items investigated in COVID-RV

		All (n=94)	Normal RVFWLS (≤-20%) (n=67)	Abnormal RVFWLS (>-20%) (n=27)	p-value
Presence of venous congestion					
CVP, mmHg	n (n missing)	59 (35) 7 [3, 12]	45 (22) 7 [2.5, 12]	14 (13) 8.5 [4.5, 12.5]	0.485§
Presence of renal dysfunction					
Requirement for RRT		12 (12.8%)	6 (9.0%)	6 (22.2%)	0.056*
Creatinine, µmol/L		67.5 [52.8, 105]	65 [39.8, 97]	88 [57, 108]	0.176§
CrCl of patients not receiving RRT (ml/min)	n (n missing)	79 (15) 138.9 [84.1, 176.4]	60 (7) 140 [87.9, 174.4]	19 (8) 133 [74.9, 176.8]	0.383§
Presence of metabolic acidaemia					
BE, mmol	n (n missing)	90 (4) 6.1 (6.6)	66 (1) 6.4 (6.2)	24 (3) 5.1 (7.7)	0.404η
Presence of cardiovascular compromise					
HR, bpm	n (n missing)	92 (2) 79 [65, 96]	67 (0) 77 [63, 95]	25 (2) 84 [74, 99]	0.028§
Mean BP, mmHg	n (n missing)	89 (5) 77 [71, 87]	64 (3) 79 [72, 88]	25 (2) 76 [69, 86]	0.164§
Requirement for vasoactive support					
Vasopressors		40 (42.6%)	23 (34.3%)	17 (63%)	0.011*
Inotropes		0 (0%)	0 (0%)	0 (0%)	NA

All data collected on day of echocardiography. Data are presented as mean (SD), median [IQR] or n (%). Data are complete unless indicated by n (n missing).
Between-group differences were assessed using Student's T-test (η), Mann-Whitney U test (§), and Pearson Chi-Square test (*).
RVFWLS = right ventricular free wall longitudinal strain, CVP = central venous pressure, RRT = renal replacement therapy, CrCl = creatinine clearance, BE = base excess, HR = heart rate, BPM = beats per minute, BP = blood pressure, NA = not applicable

5.3.6.3.3 Mixed items

Mixed items studied during the COVID-RV study include SOFA scores (as discussed in section 4.1.5.3.5). No association was identified between higher SOFA scores and abnormal RVFWLS (p=0.130, Table 5-18). Similarly, APACHE II and Coronavirus Clinical Characterisation Consortium (CCCC) scores (where the CCCC incorporates both measures of ARDS severity and kidney function), did not demonstrate an association between abnormal RVFWLS and worse scores (p=0.103, p=0.189 respectively). The lack of association between RVFWLS and SOFA score is in keeping with the literature reviewed in section 4.1.5.3.5.

Direct measures of acid-base balance will be both affected by the respiratory component and the metabolic component (I.e. [H+] and unstandardised bicarbonate), and therefore they include both formative and reflective items, and are mixed items. Neither [H+] or unstandardised bicarbonate were associated with abnormal RVFWLS (p=0.700, and p=0.353, Table 5-18), suggesting that construct validity was not demonstrated by assessing for an association between acid-base balance and abnormal RVFWLS.

Table 5-18 Mixed items investigated in COVID-RV

		All (n=94)	Normal RVFWLS (≤-20%) (n=67)	Abnormal RVFWLS (>-20%) (n=27)	p-value
APACHE II score at ICU admission	n (n missing)	89 (5) 16 [13, 19]	63 (4) 16 [14, 19]	26 (1) 14.5 [11, 18.25]	0.103§
CCCC at ICU admission	n (n missing)	87 (7) 10.3 (2.8)	63 (4) 10.5 (2.6)	24 (3) 9.7 (3.1)	0.189η
SOFA score on day of echo	n (n missing)	93 (1) 8 [6, 10]	67 (0) 7 [6, 10]	26 (1) 9 [7, 10]	0.130§
[H+], nmol/L on day of echo	n (n missing)	88 (6) 39.7 [36, 46.9]	65 (2) 40 [37, 46.9]	23 (4) 39 [34, 48]	0.700§
Bicarbonate, mmol/L on day of echo	n (n missing)	90 (4) 31.7 [27, 41.9]	65 (2) 31.9 [28, 35.6]	25 (2) 30 [25, 36.5]	0.353§

Data are presented as mean (SD), median [IQR] or n (%). Data are complete unless indicated by n (n missing).
Between-group differences were assessed using Student's T-test (η), Mann-Whitney U test (§)
RVFWLS = right ventricular free wall longitudinal strain, APACHE = acute physiology and chronic health evaluation, CCCC = Coronavirus Clinical Characterisation Consortium, SOFA = sequential organ failure assessment, echo = echocardiography.

5.4 Discussion

The COVID-RV study is the largest prospective study in patients with COVID-19 requiring IMV investigating RV-STE; it identified the novel finding that abnormal RVFWLS was independently associated with 30-day and one-year mortality, demonstrating the predictive validity of RVFWLS. The conventional RV echocardiography parameters were inconsistent in their association with mortality, and this is in keeping with previous non-COVID-19 ARDS studies[177,178].

Despite this being a very challenging population to perform echocardiography upon, the feasibility of RVFWLS was high (90.4%), supporting the utility of RVFWLS in ICU. Echocardiography was performed predominantly by ICU clinicians in difficult circumstances; due to COVID-19 areas often receiving poor quality echocardiography equipment, the challenges in finding acoustic windows in patients undergoing IMV with high airway pressures, combined with the hindrance from wearing awkward personal-protection-equipment. The high feasibility of RVFWLS in a COVID-19 cohort despite these obstacles would suggest that RVFWLS may be very feasible in other ICU populations. There was no difference in RVFWLS feasibility between images acquired by expert and non-expert echocardiographers suggesting that acquiring images for RVFWLS may be feasible in routine ICU clinical practice.

The intra- and inter-observer reproducibility of RVFWLS was high, with ICCs suggesting very good to excellent reproducibility. Bland-Altman plots showed small mean differences, with narrow limits of agreement, and no systematic bias on visual inspection of the plots. Echocardiography study image quality assessment (by both semi-quantitative endocardial delineation score and qualitative global assessment) demonstrated that echocardiography images of higher quality appeared to improve intra-observer and inter-observer reproducibility. These findings suggest that endocardial delineation scores >8 (out of 12), and echocardiography studies with images qualitatively rated as “adequate” or “good” will provide better reproducibility, and images of this quality may be preferred for future RV-STE studies.

The prevalence of RVD when diagnosed by abnormal RVFWLS in COVID-RV was 28.7%. A large meta-analysis of COVID-19 studies (studies reporting a mixture of patients requiring and not requiring IMV) reported a similar prevalence of RVD of 20.4%[228].

The RVFWLS values in the COVID-RV study are comparable to those reported by two smaller COVID-19 studies investigating RVFWLS in patients requiring IMV. The mean RVFWLS in COVID-RV was -23.0% (5.2), similar to -24.1% (6.9) reported by Bleakley et al[15]. Of note both COVID-RV and Bleakley et al used TomTec strain software. Gibson et al reported a mean RVFWLS of -17.0% (6.0) with a prevalence of RVD (RVFWLS >-20%) of 65.6% in a comparable patient population[201]. Patients in this study did not appear to have more severe COVID-19 disease compared to COVID-RV, with similar PaO_2/FiO_2 ratios and SOFA scores. The conventional RV echocardiography parameters (TAPSE and S') were also similar in both studies. The more impaired RVFWLS and higher prevalence of RVD reported by Gibson et al may be partly explained by their inclusion of echocardiography studies from 15 (46.9%) patients with severe ARDS in the prone position (validation of RVFWLS in this position has not been performed). Additionally, Gibson et al used Epsilon software for RVFWLS analysis, compared to the TomTec software used in COVID-RV, Epsilon software has been shown to report significantly less negative (and therefore more impaired) RVFWLS values[93], possibly contributing to differences in RVFWLS values reported by both studies. As discussed in Chapter 2 (section 2.4), this again highlights one of the key challenges encountered with RV-STE; there may be differences in strain values calculated by the different unique proprietary algorithms.

When looking at the distribution of RVFWLS in COVID-RV (Figure 5-10A), it is apparent that there was a bimodal distribution, with a peak between -16% and -18%, and another peak between -22% and -26%. This bimodal distribution, with peaks at similar RVFWLS values, was previously demonstrated in patients with COVID-19 by Li et al (Figure 5-10B), although it was not commented on by the authors[16]. These authors also found that healthy controls did not demonstrate this bimodal distribution. The findings from COVID-RV and Li et al may suggest that there is a subgroup of patients who have a common predisposition to developing RVD when suffering from COVID-19 ARDS. Identification of ARDS

cardiovascular phenotypes is becoming an area of increasing interest, with the hope that patients at risk of developing a particular ARDS cardiovascular phenotype can be identified and have a tailored therapeutic strategy instigated[229,230].

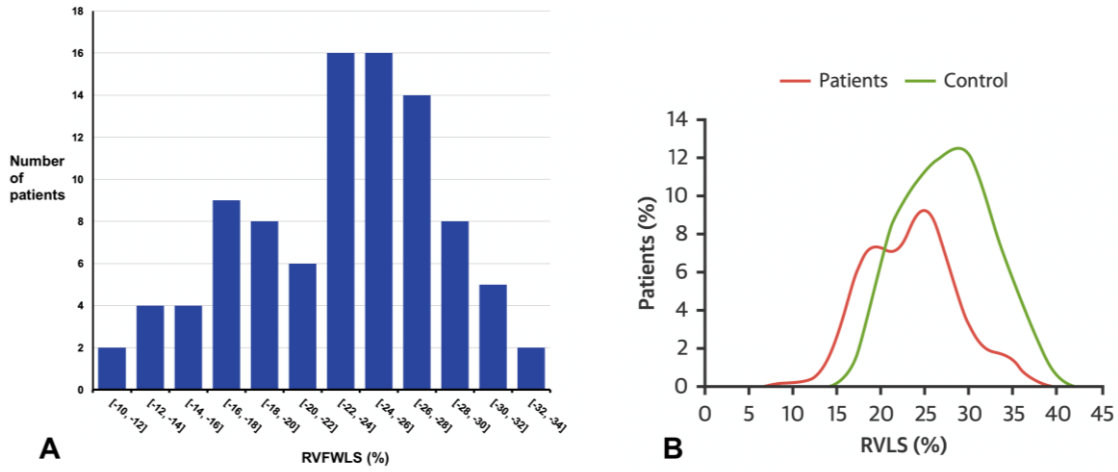


Figure 5-10 Bimodal distribution of RVFWLS
Histograms showing the bimodal distribution of RVFWLS in **A.** COVID-RV and **B.** Reproduced from Li et al[16].

A low prevalence of subjective LVD was found (12%). There was no difference in the prevalence of LVD between normal and abnormal RVFWLS groups suggesting that isolated RVD was identified (and it has not arisen in conjunction with, or secondary to, LVD). Previous COVID-19 studies have shown no difference in LV ejection fraction between abnormal and normal RVFWLS groups supporting this finding[16,182].

COVID-RV allowed in-depth assessment of the validity of RV-STE. Concurrent criterion validity was demonstrated with respect to the ability of RVFWLS to associate with the conventional RV echocardiography parameters. The COVID-RV study did not assess true concurrent criterion validity via association of RVFWLS with gold standard non-invasive measurement of RV function (CMR RVEF, as discussed in section 1.3.3), however given the impracticality of transferring patients with ARDS requiring IMV to an MRI scanner for research purposes, it is highly unlikely any study will investigate true concurrent criterion validity in this population.

Construct validity with respect to formative item relationships was demonstrated by RV-STE. The relationship between formative items and RV function also allows us to identify exploratory associations between abnormal

RVFWLS and putative mechanisms of RVD[175,180,201,231]. A strong association between RVD and myocardial injury was identified, with higher troponin and NT-proBNP levels found in patients with abnormal RVFWLS. This suggests RVFWLS has construct validity in its ability to identify RVD associated with myocardial injury. Significantly higher driving pressures in patients with abnormal RVFWLS were identified (p=0.040) with a trend towards lower lung compliances (p=0.071), suggesting that injurious positive pressure ventilation (a formative item) may be a mechanism contributing to RVD, supporting the construct validity of RVFWLS with regards this formative item relationship. An association between high driving pressures and RVD has previously been identified in a non-COVID-19 ARDS population, supporting the validity of this formative item relationship[224].

It is remarkable that an association between abnormal RVFWLS and prevalence of acute PE was not found, given that associations between RVD and PE have previously been reported[184,232]. A prevalence of PE of 16–31% was found in ICU patients during the early phase of the COVID-19 pandemic[204,205]. The COVID-RV study identified a lower prevalence of radiologically confirmed/clinically suspected PE of 8.5%. The lower prevalence of PE reported by COVID-RV may be partly due to the updated clinical guidance that came into place in the later phases of the pandemic; with the effects of immunotherapies and more frequent use of pharmacological PE prophylaxis (with higher recommended dosing regimens). In support of these possible effects, other studies conducted later in the pandemic similarly identified a lower prevalence of PE[233]. It is important to note that patients in COVID-RV were not systematically screened for acute PE, and it is therefore possible acute PE prevalence has been under-reported and true association between abnormal RVFWLS and acute PE missed.

Construct validity of RV-STE with respect to reflective items was not demonstrated in COVID-RV, in keeping with previous studies. It is possible that the reflective items measured in COVID-RV are too downstream from the RV in terms of their functional relationship, and there may have been other factors affecting the reflective items (e.g. thrombosis of renal vessels affecting renal function). It is also possible that the expected relationship between RV-STE and the reflective items is incorrect. An example of this was demonstrated by Chotalia et al, who found that measures of RV systolic function in patients with

COVID-19 were not associated with AKI, but RV dilatation was[234]. It is possible that RV dilatation is more closely associated with venous congestion and AKI than measures of RV systolic function (such as RV-STE).

5.4.1 Strengths

Strengths of the COVID-RV study include its prospective design and that echocardiography studies were acquired predominantly by ICU clinicians with a range of echocardiography experience (reflecting routine clinical practice). A recent editorial commenting on a COVID-19 echocardiography study highlighted the limitations of retrospective design, stating that "echocardiography exams were performed on clinical indication and not standardised which inferred some selection bias and some missing data"[235]. COVID-RV mandated standardised research study echocardiography scans performed prospectively (they were not performed due to a clinical indication), giving an accurate representation of RVFWLS in all COVID-19 patients requiring IMV. COVID-RV had a pre-published protocol and data analysis plan.

5.4.2 Limitations

Limitations of COVID-RV include that echocardiography was performed at a single timepoint, RVD may therefore have been under-reported. Multivariable analysis included time from intubation to echocardiography as a variable to adjust for echocardiography being performed a different times during patients' disease. A second limitation is that there was no information on pre-existing RVD or pulmonary hypertension, with few patients having previous echocardiography. This could represent a confounder. A third limitation is that LV-STE was not measured, which would have been an ideal comparator for RV-STE. As described in section 2.3.3, LV-STE requires a more advanced image set which was beyond the aims of this pragmatic ICU clinician delivered study. Measures of RV afterload were also not reported due to the focussed echocardiography image set. Similarly, there was substantial missing data for the conventional RV echocardiography parameters (TAPSE, S', and RIMP) and left ventricular eccentricity index, which represents a further limitation of the study. This again was because not all echocardiographers had the expertise to acquire the more advanced image set for reporting of these parameters. Finally, COVID-RV was

not powered to identify associations between abnormal RVFWLS and possible causative mechanisms, and these results are therefore purely explorative.

5.5 Conclusion

RVFWLS analysis in patients with COVID-19 receiving IMV was highly feasible and reproducible. RVFWLS demonstrated concurrent criterion validity by associating with conventional RV echocardiography parameters. Predictive validity was also established the finding of a strong association between abnormal RVFWLS and 30-day and one-year mortality. RVFWLS demonstrated construct validity with regards to formative item relationships, but was less consistent with reflective and mixed items. The principal novel finding from COVID-RV study is that abnormal RVFWLS is independently associated with 30-day and one-year mortality in patients with COVID-19 requiring IMV. A future area of study would be to investigate if early identification (and subsequent treatment) of RVD by RVFWLS analysis is of therapeutic benefit to patients with COVID-19 (or other ARDS populations) receiving IMV.

COVID-RV investigated the utility of RV-STE to assess resting RV function in an ICU population. In Chapter 6 the RV exercise study will now investigate the utility of RVFWLS in assessing dynamic RV function during exercise in a perioperative lung resection cohort, enabling the utility of RVFWLS to be assessed in a contrasting patient population experiencing the haemodynamic stress of exercise.

Chapter 6 The utility of RV-STE in assessing dynamic RV function in the perioperative period

6.1 Introduction

In Chapter 5, RV-STE demonstrated utility in patients with COVID-19 requiring IMV, where it was used to assess resting RV function. As described in Chapter 2 (section 2.10.5), an important aspect of RV function is the dynamic response when faced with increased workload, such as during exercise. The ability of RV function to enhance during exercise is termed RV contractile reserve (RVCR)[51]. The importance of RVCR is well described in patients with pulmonary hypertension, it has been shown to strongly correlate with 6 minute-walk-test and is independently associated with survival[236]. Importantly, patients with pulmonary hypertension with preserved resting RV function have been demonstrated to have impaired RVCR, highlighting the importance of exertional assessment[237,238]. Previous work by the author's supervisors and Dr Adam Glass has shown that lung resection results in impaired resting RV function[34,69].

Post-lung resection exertional dyspnoea and functional limitation is common, with a study identifying exertional dyspnoea in 63% of patients[239]. These exertional symptoms are not well explained by the reduction in lung function, with Pelletier et al demonstrating the R^2 for association between change in forced expiratory volume in 1 second (FEV1) and maximal work rate during exercise to be only 0.3[240]. Larsen et al similarly demonstrated that change in forced vital capacity (FVC) after lung resection was poorly associated with the change in maximal rate of oxygen consumption (VO_2max) during exercise, with an R^2 of 0.18[241]. Given the exertional nature of patients' symptoms, and that RV function has been shown to be impaired post-lung resection, it is logical to hypothesise RV function when exercising might also become impaired resulting in patients' exertional dyspnoea (i.e. impaired postoperative RVCR)[242].

A research group in the 1990's investigated RVCR in patients undergoing lung resection using volumetric PA catheters. Okada et al showed that resting RVEF 3-weeks post-lung resection was reduced compared to preoperatively. Importantly

they demonstrated that during exercise, RVEF was also significantly reduced postoperatively compared to preoperatively[134]. The group replicated their work, seeking association between impaired RVCR and postoperative outcomes. They identified that impaired preoperative RVCR was associated with an increase in cardiopulmonary complications and hospital length of stay[243]. Whilst plausible, the validity of these results have since been called into question. As described in section 1.3.2, the reliability of volumetric PA catheters as measures of RV volume and ejection fraction has been shown to be poor[56,244]. Additionally, the overall use of invasive PA catheters has generally fallen out of favour outside specialised cardiac centres[245,246]. However, the perioperative assessment of RVCR remains a promising avenue of research in patients undergoing lung resection.

A means to assess RVCR that is non-invasive, with a protocol that is acceptable to patients, is currently elusive. Recent European Society of Cardiology and European Respiratory Society consensus guidelines highlighted the potential utility of RV-STE as a measure of global RV function over conventional RV echocardiography parameters in the assessment of RV function during exercise[247]. The "RV exercise study" was thus designed to examine the utility of non-invasive RV-STE assessment of RVCR using submaximal exercise stress echocardiography in patients undergoing lung resection. Previous work examining LV contractile reserve using LVGLS and LVGLS-rate has shown that LV contractile reserve is demonstrated by a linear relationship between increasing exercise intensity and LVGLS/LVGLS-rate[248,249]. No study has yet described the relationship between exercise intensity and RV-STE/RV-STE-rate. The utility of RV-STE was assessed by examining its feasibility (both the patient tolerability of undergoing exercise stress echocardiography, and the technical feasibility of performing RV-STE analysis on the images acquired), the reproducibility of RV-STE, and by examining the validity of RV-STE in this setting.

6.1.1 Assessing the validity of RV-STE during exercise in patients undergoing lung resection

The validity of RV-STE was primarily investigated by construct validity. The aspect of construct validity underpinning this was hypothesis testing the formative item relationship between the effect of exercise upon RV function

(Figure 6-1). The expected relationship was one where increasing exercise intensity results in enhanced RV function. As described in section 2.10.5.5, RV-STE has been shown to minimally change during exercise, and it therefore was not expected that RV-STE would demonstrate this formative item relationship. RV-STE-rate however has been repeatedly shown to increase with exercise intensity (section 2.10.5.5), and it was therefore expected that preoperatively as exercise intensity increased, RV-STE-rate would also increase (i.e. become more negative). If this was demonstrated, construct validity would be present with regards this formative item relationship. Other conventional RV echocardiography parameters were investigated in a similar manner.

Postoperatively, it was hypothesised that RVCR would be impaired. Previous work by the author's supervisors research group has shown that after lung resection, RV afterload increases and CMR imaging correlates of inflammation within the RV myocardium are present (possible indicating direct myocardial damage impairing RV contractility)[34,40,69]. These mechanisms could impair RV function during exercise (Figure 6-1). Therefore, construct validity in the postoperative setting was to be investigated by examining the formative item relationship between exercise and RV function, with the expectation that this relationship would be impaired (i.e. demonstrating a loss of RVCR postoperatively). Construct validity with regards to the relationship between exercise and RV function would be demonstrated if there was presence of a relationship between increasing exercise intensity and enhancement of RV-STE-rate preoperatively, and impairment of this relationship post-lung resection.

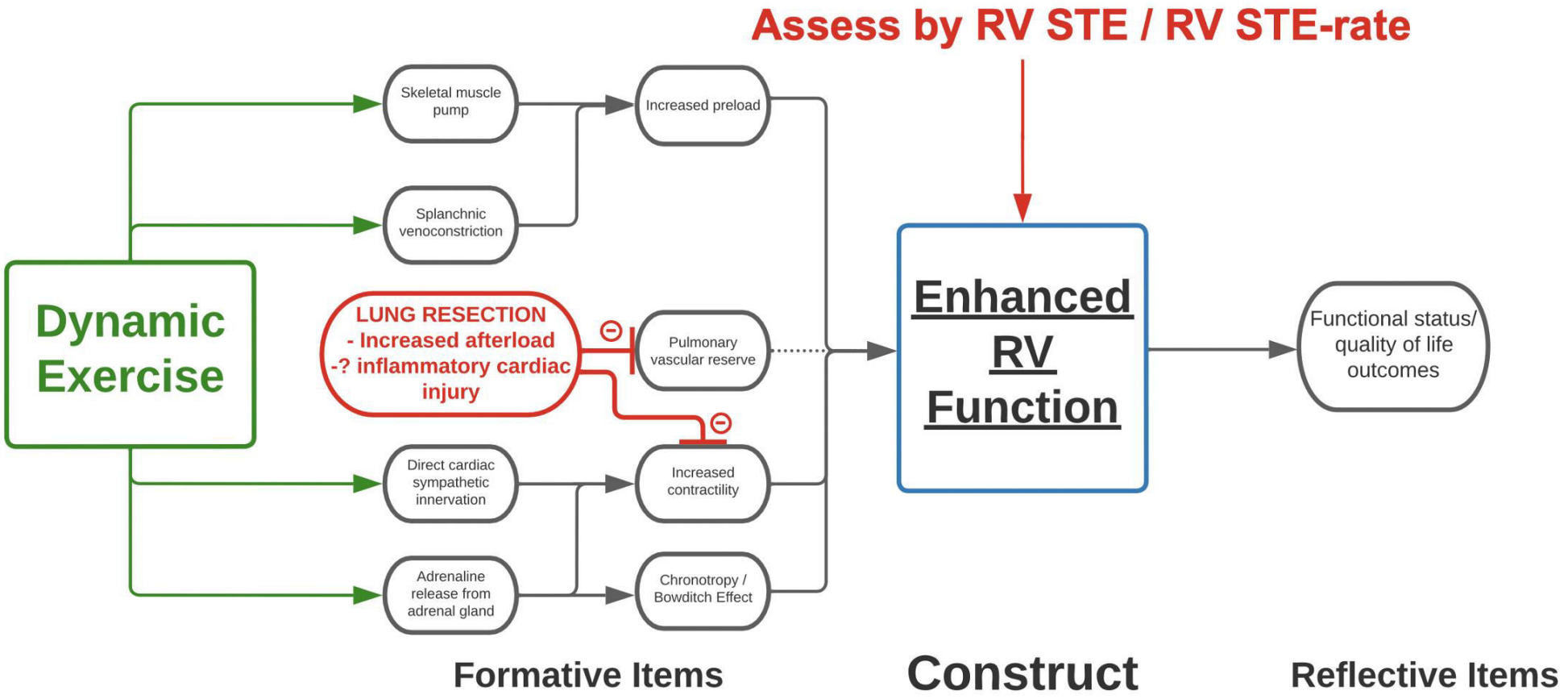


Figure 6-1 Conceptual model of relationship between dynamic exercise and RV function
Dynamic exercise is a formative item that will enhance RV function. Lung resection may impair RV function through the inhibitory mechanisms shown in red. Functional status and quality of life outcomes may be affected by postoperative RVD and therefore represent reflective items that are investigated by the RV exercise study. RV = right ventricular, RV-STE = right ventricular speckle tracking echocardiography.

6.2 Methods and statistics

6.2.1 Study setting and population

The RV exercise study was a prospective single centre observational feasibility study conducted at the Golden Jubilee National Hospital (GJNH). Ethical approval was obtained (Research Ethics Committee reference 17/EE/0134). Consenting patients who were >16 years of age and undergoing planned elective video-assisted thoracoscopic single lobe lobectomy were included. Exclusion criteria included: pregnancy, wedge, segmental or sub-lobar lung resection, pneumonectomy, isolated right middle lobectomy, and contraindication to exercise echocardiography (as per BSE guidelines)[250]. Pneumonectomy was excluded due to the potential postoperative disruption of normal mediastinal anatomy which would alter echocardiography acoustic windows. In addition to this, pneumonectomy is performed less frequently than lobectomy, and although it will likely cause greater physiological derangement, inclusion of pneumonectomy would potentially limit the application of study results. Conversely, isolated right middle lobectomy was excluded because it will likely cause less physiological derangement than resection of the other lobes, its inclusion may therefore have made it more difficult to detect a change in RV contractile reserve postoperatively. The author performed all STE strain reporting and statistical analysis described below, but had no part in the design or running of the RV exercise study.

6.2.2 Clinical and laboratory data

Baseline data were collected for demographics, comorbidities, and preoperative pulmonary function. Intraoperative data were collected for type of surgery, length of surgery, and duration of one-lung ventilation.

Troponin I and B-type natriuretic peptide (BNP) were collected preoperatively and on postoperative days two, three, and four. Blood samples were analysed using the Alere Triage® ProfilER SOB™ Panel system (Alere Ltd. Stockport, UK). Sample handling and quality control measures were undertaken as per the manufacturer's guidelines.

Functional status and quality of life outcomes were assessed preoperatively and two months postoperatively using patient questionnaires. These questionnaires were self-administered. Functional status was assessed using the Medical Research Council (MRC) breathlessness scale (an integer score ranging from 1-5, where increasing values represent worse breathlessness on exertion)[251], and the New York Heart Association (NYHA) class (an integer score ranging from 1-4 where increasing values represent increasing severity of breathlessness/angina symptoms on exertion)[252]. Quality of life was assessed using the EuroQol Visual Analogue Scale (EQ VAS)[253]. The EQ VAS is a global rating of health, measured on a vertical visual analogue scale (0-100), where the opposite ends of the scale are "The best health you can imagine" and "The worst health you can imagine". Higher scores are associated with better health.

Patients completed a self-administered questionnaire which assessed how tolerable exercise stress echocardiography was to them. After completion of exercise they were asked if they would undertake exercise stress echocardiography again ("yes" or "no" tick box). Clinical and laboratory data were collected by research nurses at the GJNH.

6.2.3 Exercise protocol

The exercise protocol was designed to assess submaximal exercise stress echocardiography. Patients were allowed to stop exercising at any point if they experienced discomfort. A semi-supine cycle ergometer was used for exercise with patients cycling at the incremental workloads 0W, 15W, 30W, 45W, and 60W (each for 3 minutes). Transthoracic echocardiography was performed at rest, and during the last minute of exercise at each workload by BSE accredited ultrasonographers. Peripheral oxygen saturation (SpO_2), heart rate, non-invasive blood pressure (BP), and 12-lead ECG monitoring were used throughout, with BP, heart rate, and SpO_2 being recorded 2 minutes after each exercise increment. Age adjusted maximum heart rate was calculated from the heart rate recorded at each workload using the formula:

$$Age\ adjusted\ maximum\ heart\ rate\ =\ 208 - (0.7\ x\ age)$$

Tanaka et al[254]

As a surrogate of exercise intentity, the heart rate achieved at each workload was converted to the percentage of the age adjusted predicted maximal heart rate (ppHRmax, see section 2.10.5.3).

Criteria for termination of exercise stress echocardiography was in keeping with the GJNH exercise protocol and BSE guidelines[250], this included:

- Decrease in BP >20mmHg below baseline systolic blood pressure (SBP)
- Blood pressure greater than 240 mmHg systolic and/or 120mmHg diastolic
- Intractable cardiovascular symptoms (angina/breathlessness)
- Supraventricular and complex ventricular arrhythmias
- >85% ppHRmax achieved
- Significant ST segment changes on ECG
- Patient request

As part of the feasibility study, tolerability of exercise stress echocardiography was assessed. A patient was deemed to have 'tolerated' exercise at a given workload if they did not meet any of the above termination criteria during the three minutes of exercise. Tolerability was therefore defined as the percentage of patients able to complete exercise at a given workload. The reason for termination of exercise was recorded.

6.2.4 Echocardiography

Transthoracic echocardiography was performed at rest, 15W, 30W, 45W, and 60W. The data set included a parasternal long and short axis views, RV focussed apical four chamber view (A4C), and RV inflow-outflow view. Tissue doppler images were collected from the A4C view to allow offline analysis of TAPSE and S'.

The echocardiography studies were anonymised for both patient identity and workload. Studies were then randomised before analysis. RV-STE (peak RVFWLS and peak RVGLS) was analysed offline by the author. RV-STE was assessed from the RV focussed A4C view using Tomtec 2D CPA, using the same methods as described in Chapter 5 (section 5.2.4). Peak RVFWLS-rate and peak RVGLS-rate was automatically reported in conjunction with RV-STE analysis by the Tomtec 2D CPA software. As described in section 2.3.2, RVFWLS-rate/RVGLS-rate is the first differential of strain with respect to time, with the unit of $\%.s^{-1}$. Peak RVFWLS-rate/RVGLS-rate therefore represents the maximal rate of free wall/global myocardial shortening that occurs during RV contraction, and this can occur at a different time from peak RVFWLS/RVGLS (see Figure 2-7). TAPSE, S', and LVEI were analysed as described in section 5.2.4. RV-STE and RV-STE-rate were reported as negative values, with more negative values indicating better RV function. Colour doppler was used to identify the presence of a tricuspid regurgitant (TR) jet, in the presence of a TR jet, continuous wave doppler was then used to measure the peak velocity of the TR jet (section 1.3.5.2). The peak TR velocity was converted to the TR peak pressure gradient using the simplified Bernoulli equation, with higher TR peak pressure gradients being associated with higher pulmonary artery pressures[68]. Pulmonary artery acceleration time (PAAT) was reported using the RV inflow-outflow image. PAAT was calculated using pulsed wave doppler, placing the cursor just below the pulmonary valve (on the ventricular side of the valve)[68]. The time from onset to peak velocity was then measured from the doppler envelope, representing PAAT (section 1.3.5.3), with shorter PAAT times being associated with higher pulmonary artery pressures[68].

6.2.5 Feasibility

The feasibility of performing RV-STE analysis (specifically RVFWLS, as assessed in Chapter 5) was termed “technical feasibility”. Technical feasibility was defined as the percentage of echocardiography studies that were of adequate image quality for RVFWLS analysis at a given workload. For an echocardiography study to be “adequate”, satisfactory speckle tracking of all three RV free-wall segments had to be seen. Echocardiography study image quality was assessed using semi-quantitative endocardial delineation scores, where each of the six RV segments was given an integer score from 0-2 describing how clearly the endocardial border was seen, giving a total score out of 12, with higher scores representing better image quality (as described in Chapter 5, section 5.2.5). A qualitative global assessment of image quality (good, adequate, poor, or unusable) was also reported.

Overall feasibility was the combination of tolerability of exercise stress echocardiography and technical feasibility at a given workload (i.e. if six out of seven patients tolerated exercise stress echocardiography at 15W, and four out of these six echocardiography studies were adequate for RVFWLS analysis, the overall feasibility at 15W would be 4/7 [57.1%]).

6.2.6 Reproducibility

Intra-observer reproducibility for echocardiography parameters was assessed using Bland-Altman plots with mean difference and limits of agreement (LOA; mean difference +/- 1.96 SD), and ICCs using two-way mixed effects with absolute agreement. A total of 20 echocardiography studies (10 preoperative and 10 postoperative) were re-reported by the author two weeks after initial reporting to assess intra-observer agreement. A reproducibility sub-study was performed to investigate the effect echocardiography study image quality had upon RVFWLS reproducibility. As described in section 5.3.5, the reproducibility of echocardiography studies with a semi-quantitative endocardial delineation score >8 (reflecting higher quality images) was compared to images with an endocardial delineation score of ≤8 (reflecting poorer quality images). The effect of subjective image quality upon reproducibility was assessed using qualitative global assessments of echocardiography study image quality, comparing “good” quality images to “adequate” and “poor” quality images.

6.2.7 Assessment of RV contractile reserve

6.2.7.1 Individual patient data

Individual patient data for RV function was plotted against exercise intensity (ppHRmax), data points were joined together to give a line graph. Both preoperative and postoperative data were included on the same graph to allow direct subjective comparison. Perioperative RVCR was assessed in individual patients by examining the relationship between the measure of RV function and exercise intensity (ppHRmax). This type of assessment has not been previously published, therefore a system for visually assessing RVCR was conceived by the author with guidance from his supervisors. ppHRmax was plotted against RV function, and the line graphs were visually inspected. RVCR was assessed in two parts. Firstly, graphs were assessed for an increase in RV function as ppHRmax increased, and this was defined as an increase in RV function from the lowest ppHRmax (i.e. resting) compared to highest ppHRmax achieved. Secondly, graphs were assessed for presence of uncoupling between ppHRmax and RV function. Uncoupling was present when there was a deterioration in RV function as ppHRmax increased. If a deterioration in RV function was seen to recover

during the next increment in exercise intensity, uncoupling was deemed not to be present (i.e. the “uncoupled” data point was judged to be erroneous or reflecting measurement error). More severe uncoupling was present if uncoupling occurred at lower exercise intensities. Therefore, for RVCR to be present, both an increase in RV function as ppHRmax increased needed to be observed, with the absence of uncoupling.

Given that a maximum of 7 complete data sets were to be available, a decision was made to ordinally rank patient RVCR from best to worst. The ordinal categories from best to worst included:

- Presence of RVCR preoperatively and postoperatively
- Presence of RVCR preoperatively that uncoupled postoperatively
- Uncoupling of RVCR preoperatively with preserved RVCR postoperatively
- Uncoupling of RVCR preoperatively and postoperatively

Patient graphs were assessed by two observers (the author and Prof Ben Shelley), with agreement between both observers being required before further data analysis.

6.2.7.2 Grouped patient data

RVCR was investigated by assessing for a linear relationship between exercise intensity (ppHRmax) and the measure of RV function. RVCR was deemed to be present when there was a statistically significant linear association between the intensity of exercise and the measure of RV function.

6.2.7.3 RVCR and clinical/laboratory data

Data for cardiac biomarkers, hospital length of stay, and functional status/quality of life were compared between patients who were divided into groups using RVCR ordinal ranking. This aimed to see if patients who had more severe impairment of RVCR experienced a greater increase in cardiac biomarkers, longer length of hospital stay, and worse functional status/quality

of life outcomes compared to patients with better RVCR. Given the small number of patients, there was no statistical analysis plan for this data.

6.2.8 Statistical considerations

Continuous data are presented as mean (standard deviation) or median [interquartile range] as appropriate to the distribution of data. Ordinal and categorical data are presented as n (%). Between group differences comparing preoperative and postoperative parameters were analysed using paired student's T test or Wilcoxon Signed Rank test for continuous variables.

RVCR was assessed using grouped patient data, assessing for correlation between ppHRmax (the measure of exercise intensity) and the measure of RV function. Pooled correlations were analysed using Pearson's and Spearman's correlation co-efficient. To account for within subject correlation associated with the repeated measures nature of the study, analysis of covariance (ANCOVA) was performed with the subject as a covariate.

There was no sample size was calculation for this feasibility study. All statistical analyses were performed on International Business Machines Statistical Package for the Social Sciences (IBM SPSS) version 28.0.0.0. IBM SPSS General Linear Model function was used to perform ANCOVA. A two-sided p value < 0.05 was considered statistically significant.

6.3 Results

6.3.1 Generic results

Seven patients were recruited to the RV exercise study between 15/11/2017 and 26/06/2018. The mean age was 67.4 (12.6) years, and five (71.4%) patients were female (Table 6-1). Six (85.7%) patients had a history of cigarette smoking, and all patients had a diagnosis of primary lung malignancy. All patients underwent lobectomy, of which six (85.7%) were right sided. The duration of surgery and one-lung ventilation was 156.1 (27.9) and 115.4 (27.9) minutes respectively. Median hospital length of stay was 6 [4, 16] days.

Table 6-1 Generic Results

Characteristic	**Result**
Age (y)	67.4 (12.6)
Female	5 (71.4%)
Cigarette smoking	
None	1 (14.3%)
Former	5 (71.4%)
Active	1 (14.3%)
Comorbidities*	
History of previous cancer	0 (0)
COPD	3 (42.9%)
Hypertension	3 (42.9%)
Ischaemic heart disease	0 (0%)
Diabetes mellitus	1 (14.3%)
Peripheral vascular disease	0 (0%)
Obesity	2 (28.6%)
Alcohol dependency	0 (0%)
Thoracoscore (%)§	2.40 (1.83)
Preoperative pulmonary function	
SpO_2 on air (%)	97 [95, 97]
FEV1 (L)	2.5 (0.5)
Actual FEV1:predicted FEV1 (%)	99.8 (23.9)
FEV1:FVC (%)	69.5 (11.0)
TLCO (mmol/kPa/min)	5.7 (1.2)
Actual TLCO:predicted TLCO (%)	67.5 (14.9)
Operative Variables	
Lobectomy	7 (100%)
Right sided procedure	6 (85.7%)
Duration of surgery (min)	156.1 (27.9)
Duration of OLV (min)	115.4 (27.9)
Intraoperative fluid (mL)	785.7 (224.9)
Outcomes	
Hospital length of stay (days)	6 [4, 16]

*Per Thoracic Surgery Scoring System definition of comorbidities[255]
§Predicted % risk of in-hospital death post thoracic surgery.
COPD = chronic obstructive pulmonary disease, SpO_2 = peripheral oxygen saturation, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, TLCO = transfer factor of the lung for carbon monoxide, OLV = one lung ventilation

6.3.2 Cycle-ergometer exercise and tolerability

All seven patients underwent exercise stress echocardiography preoperatively and 2-months postoperatively. All patients were able to exercise up to 45W preoperatively. Two patients were unable to exercise at 60W, one due to shortness of breath and the other due to knee pain. Two-month postoperative tolerability was poorer; at 15W, 30W, and 45W, six (85.7%) patients were able to exercise, one patient was unable to exercise at any work rate due to joint pains (Figure 6-2A). At 60W, tolerability was very poor, with only three patients (42.9%) able to exercise at this workload. Of the four unable to exercise at 60W postoperatively, two had severe joint pains, and two experienced intolerable shortness of breath. All patients reported they would be willing to perform exercise stress echocardiography again after exercising preoperatively, and after repeating the test at 2-months postoperatively six of the seven patients said they would be willing to repeat exercise stress echocardiography.

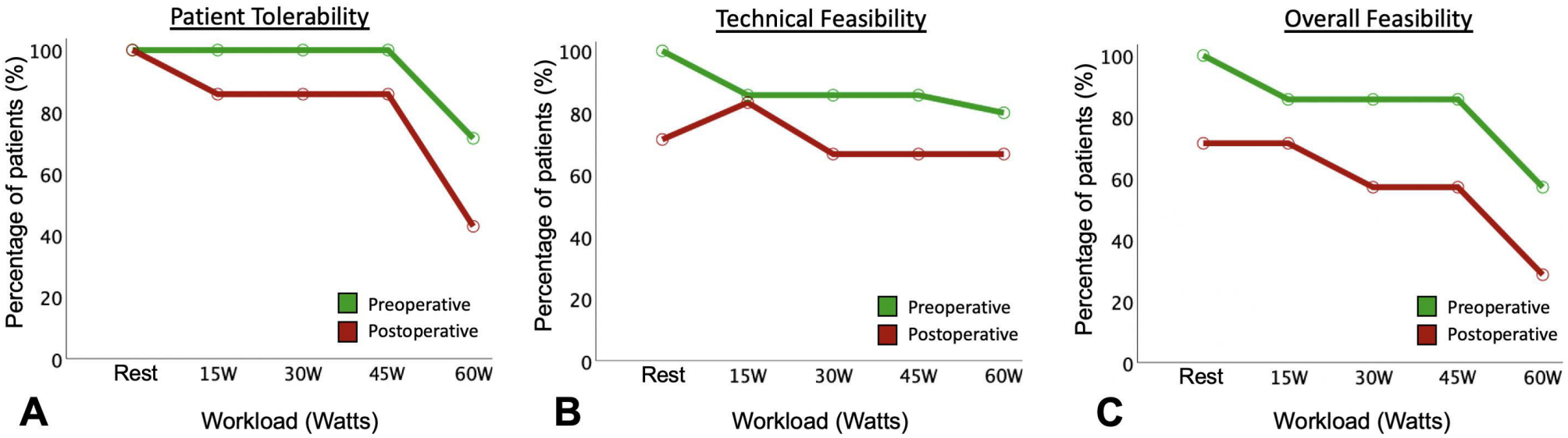


Figure 6-2 Tolerability, technical feasibility, and overall feasibility of exercise stress echocardiography
Line chart showing the tolerability (A), technical feasibility (B), and overall feasibility (C) of exercise stress echocardiography RV-STE analysis at rest, 15W, 30W, 45W, and 60W. RV-STE = right ventricular speckle tracking echocardiography.

6.3.3 Echocardiography, technical feasibility, and image quality

All patients underwent exercise stress echocardiography pre- and postoperatively. Echocardiography studies were viewed offline for reporting of RV-STE and other RV echocardiography parameters. When accessing the imaging archive, tissue doppler imaging had been lost from the echocardiography data set. It was therefore not possible to perform offline analysis of TAPSE, or S'. Measures of these variables had been performed during the conduct of the study by Dr Alvin Soosay. Dr Soosay's measurements have been included (with permission) in Table 6-5 to highlight that consideration was made to compare RV-STE to the conventional RV echocardiography parameters. No further analysis has been performed on the results of TAPSE and S' since their measurements were not performed by the author. The incorrect spectral doppler was used when acquiring RV inflow-outflow images for PAAT (continuous rather than pulse wave doppler), which may result in higher velocities and inaccurate acceleration times being reported[256]. PAATs were therefore not analysed. Peak TR velocity could only be acquired for one patient at all workloads. Given the potential inaccuracy of PAAT values and lack of peak TR velocity values, RV-PA coupling was not investigated.

The technical feasibility of RVFWLS was high preoperatively; 100% at rest, 85.6% at 15W, 30W, and 45W, falling to 80% at 60W (Figure 6-2B, Table 6-2). Postoperatively, technical feasibility was poorer; 71.4% at rest, and dropping to 66.7% at 30W, 45W, and 60W. The image quality of echocardiography studies was assessed semi-quantitatively using endocardial delineation scores and subjectively using qualitative global assessment. The endocardial delineation score at each workload was higher preoperatively than postoperatively (Table 6-2). Similarly, qualitative global assessment identified preoperative images to be of higher quality than postoperative, with >50% of images being rated good or adequate at all workloads preoperatively, whereas at all postoperative workloads ≥50% of images were rated as poor or inadequate (Figure 6-3). Previous work by the author's supervisors examining RV echocardiography in patients undergoing lung resection highlighted the difficulty in acquiring good quality images post-lung resection, with the apex of the heart being particularly difficult to visualise[74].

Table 6-2 Tolerability, technical feasibility, and overall feasibility of exercise stress echocardiography RV-STE analysis

	Rest	15W	30W	45W	60W
Tolerability of exercise stress eschocardiography					
Preoperative	7/7 (100%)	7/7 (100%)	7/7 (100%)	7/7 (100%)	5/7 (71.4%)
Postoperative	7/7 (100%)	6/7 (85.7%)	6/7 (85.7%)	6/7 (85.7%)	3/7 (42.9%)
Technical feasibility of RVFWLS					
Preoperative	7/7 (100%)	6/7 (85.7%)	6/7 (85.7%)	6/7 (85.7%)	4/5 (80%)
Postoperative	5/7 (71.4%)	5/6 (83.3%)	4/6 (66.7%)	4/6 (66.7%)	2/3 (66.7%)
Image quality: Endocardial delineation score (out of 12)					
Preoperative	8.86 (1.57)	8.29 (2.93)	7.71 (2.50)	8.14 (3.58)	7.2 (2.49)
Postoperative	6.43 (2.99)	7.5 (3.89)	7 (2.68)	7.33 (2.16)	6.67 (2.31)
Overall Feasibility					
Preoperative	7/7 (100%)	6/7 (85.7%)	6/7 (85.7%)	6/7 (85.7%)	4/7 (57.1%)
Postoperative	5/7 (71.4%)	5/7 (71.4%)	4/7 (57.1%)	4/7 (57.1%)	2/7 (28.6%)

Continuous variables presented as mean (standard deviation). RV-STE = right ventricular speckle tracking echocardiography, RVFWLS = right ventricular free wall longitudinal strain.

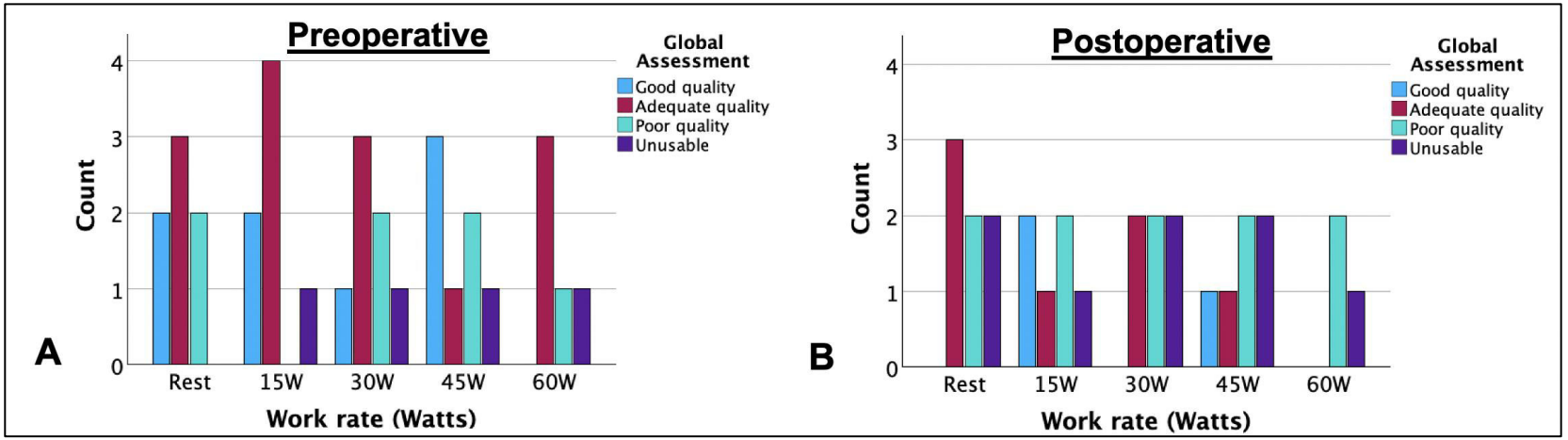


Figure 6-3 Qualitative global assessment of echocardiography image quality during exercise

Histograms comparing pre- and postoperative qualitative global assessment of echocardiography image quality during exercise

6.3.4 Overall feasibility

Overall feasibility was 100% at rest preoperatively, this remained high (85.7%) at 15W, 30W, and 45W (Figure 6-2C, Table 6-2). Overall feasibility at 60W preoperatively fell to 57.1%. Postoperative feasibility was poorer, it was 71.4% at rest, falling further to 57.1% at 30W and 45W, and was only 28.6% at 60W. It would appear that exercise stress echocardiography is better suited as a preoperative investigation, and that 45W may represent the optimal maximum workload in this population. Given the poor overall feasibility at 60W, this data was excluded from further analysis.

6.3.5 Reproducibility

Intra-observer reproducibility was assessed for RV-STE parameters reported by the author, comparing preoperative reproducibility to postoperative reproducibility for each parameter (Table 6-3). RVFWLS had ICCs >0.9 preoperatively and postoperatively, indicating excellent agreement. Bland-Altman plots showed a small mean difference with narrow LOAs and no obvious systematic bias (Figure 6-4, Figure 6-5, Table 6-3). RVGLS showed good agreement preoperatively and postoperatively (ICCs 0.84 for both). Reproducibility of RVFWLS-rate and RVGLS-rate was poorer than for RVFWLS and RVGLS. RVFWLS-rate demonstrated moderate to good agreement preoperatively (ICC 0.74), which was reduced postoperatively (ICC 0.64). RVGLS-rate had poor reproducibility both preoperatively and postoperatively (ICC 0.42 and 0.44 respectively).

The effect of image quality was examined using semi-quantitative endocardial delineation scores and qualitative global assessment of image quality. Image quality did not appear to affect RVFWLS reproducibility, there were no substantial differences in agreement between images with endocardial delineation scores of >8 compared to ≤8, nor were there any notable differences between images with globally assessed ratings of “good” compared to “adequate”, or “poor quality images (ICCs 0.91-0.94 for all). Echocardiography study image quality did however seem to affect the reproducibility of RVFWLS-rate. Echocardiography study images with endocardial delineation scores >8 had higher RVFWLS-rate agreement (ICC 0.79) compared to images with endocardial

delineation scores ≤8 (ICC 0.62). Interestingly, images that were of higher quality when globally assessed did not have better RVFWLS-rate agreement than those of lower quality (ICC 0.58 for “good” quality images, vs ICC 0.79 for “adequate” quality, vs ICC 0.65 for “poor” quality).

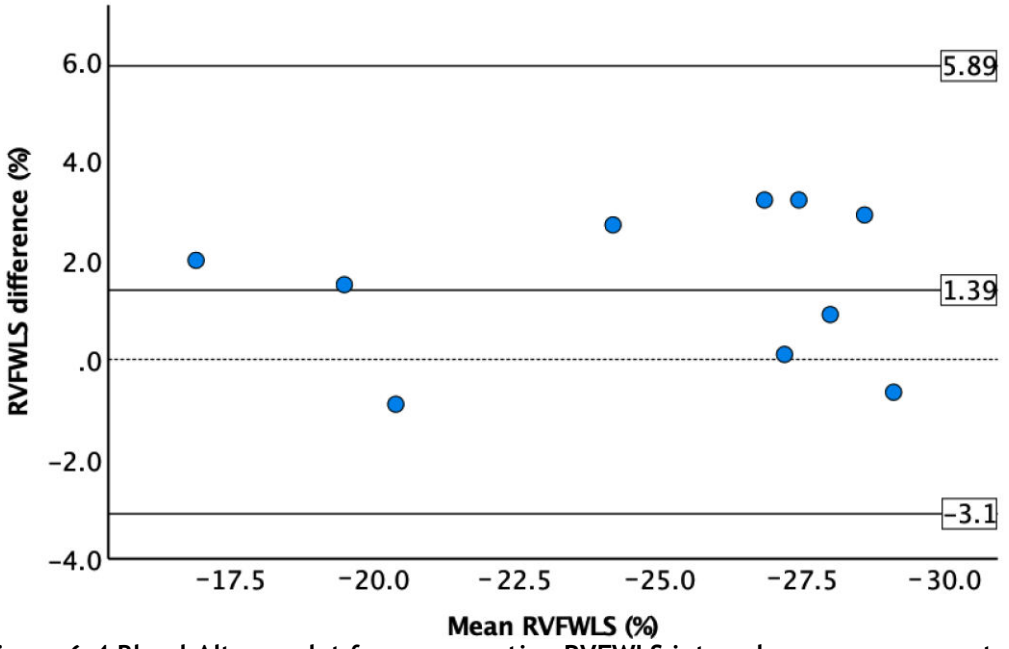


Figure 6-4 Bland-Altman plot for preoperative RVFWLS intra-observer agreement
Solid horizontal middle line represents mean difference and outer solid lines represent 95% limits of agreement. RVFWLS = right ventricular free wall longitudinal strain.

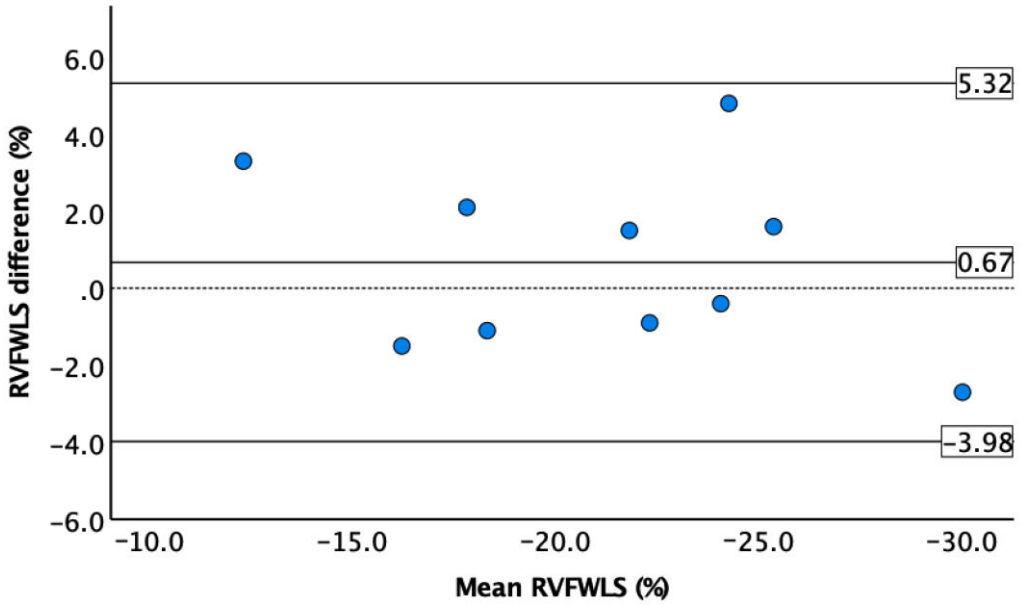


Figure 6-5 Bland-Altman plot for postoperative RVFWLS intra-observer agreement
Solid horizontal middle line represents mean difference and outer solid lines represent 95% limits of agreement. RVFWLS = right ventricular free wall longitudinal strain.

Table 6-3 Intraobserver reproducibility of RV-STE and conventional RV echocardiography parameters

	Bland Altman MD (%)	Bland Altman SD (%)	Bland Altman LOA (%)	ICC
RVFWLS				
Preoperative (n=10)	1.39	2.29	5.89, -3.10	0.92 (p<0.001)
Postoperative (n=10)	0.67	2.37	5.32, -3.98	0.95 (p<0.001)
Average endocardial delineation score >8 (n=11)	0.46	2.25	4.87, -3.95	0.94 (p<0.001)
Average endocardial delineation score ≤8 (n=9)	1.72	2.29	6.21, -2.77	0.94 (p<0.001)
Qualitatively assessed image "good" (n=5)	1.38	1.68	4.67, -1.91	0.93 (p=0.006)
Qualitatively assessed image "adequate" (n=10)	0.55	2.52	5.49, -4.4	0.94 (p<0.001)
Qualitatively assessed image "poor" (n=5)	1.64	2.59	6.72, -3.44	0.91 (p=0.015)
RVFWLS-Rate				
Preoperative (n=10)	0.13	0.38	0.87, -0.62	0.74 (p=0.029)
Postoperative (n=10)	-0.08	0.40	0.72, -0.87	0.64 (p=0.08)
Average endocardial delineation score >8 (n=11)	0.12	0.37	0.85, -0.61	0.79 (p=0.009)
Average endocardial delineation score ≤8 (n=9)	-0.09	0.42	0.73, -0.91	0.62 (p=0.104)
Qualitatively assessed image "good" (n=5)	0.18	0.52	1.20, -0.84	0.58 (p=0.225)
Qualitatively assessed image "adequate" (n=10)	0.07	0.24	0.54, -0.40	0.79 (p=0.014)
Qualitatively assessed image "poor" (n=5)	-0.22	0.49	0.74, -1.18	0.65 (p=0.170)
RVGLS				
Preoperative (n=10)	0.45	3.7	7.7, -6.80	0.84 (p=0.008)
Postoperative (n=10)	2.21	3.00	8.09, -3.67	0.84 (p=0.002)
RVGLS-Rate				
Preoperative (n=10)	0.15	0.37	0.87, -0.58	0.42 (p=0.202)
Postoperative (n=10)	-0.05	0.39	0.82, -0.72	0.44 (p=0.218)

RV-STE = right ventricular speckle tracking echocardiography, RV = right ventricular, MD = mean difference, SD = standard deviation, LOA = limits of agreement, ICC = intraclass correlation co-efficient, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain,

6.3.6 Response to exercise

6.3.6.1 Cardiovascular response to exercise

When undergoing exercise, the expected incremental rise in heart rate was observed as workload increased (Table 6-4). This occurred both preoperatively and postoperatively. The mean heart rate and ppHRmax achieved at each workload was similar pre- and postoperatively, indicating that patients would likely have experienced a similar level of exercise intensity. The response to exercise for physiological and echocardiography parameters was compared from rest to 45W (the peak workload that most patients were able to exercise to, Table 6-2). There was a significant increase in blood pressure from rest to 45W both preoperatively and postoperatively (p=0.008 and p=0.027, Table 6-5).

Table 6-4 Pre- and postoperative paired heart rates and ppHRmax at different workloads

	Heart rate (BPM)		ppHRmax (%)	
	Preoperative	Postoperative	Preoperative	Postoperative
Rest (n=7)	73.1 (14.2)	77.3 (12.8)	45.6 (9.2)	48.2 (8.8)
15W (n=6)	90.0 (13.9)	94.8 (4.8)	56.1 (8.5)	59.3 (5.5)
30W (n=6)	99.3 (11.4)	102.3 (11.8)	62.0 (7.7)	64.0 (9.1)
45W (n=4)	105.3 (12.9)	102.8 (6.9)	66.1 (6.6)	64.6 (4.3)
60W (n=3)	118.3 (7.8)	113.7 (6.5)	75.0 (7.3)	71.9 (5.8)

Mean (standard deviation). BPM= beats per minute, ppHRmax = percentage of predicted maximal heart rate.

6.3.7 Exercise and echocardiography

During exercise stress echocardiography, there was no significant difference in either RV end diastolic diameter (RVEDD) between rest and 45W preoperatively or postoperatively (Table 6-5), nor was there a change in LV end diastolic diameter (LVEDD). Preoperatively there was however a significant change in RVEDD:LVEDD ratio from rest compared to 45W (0.78 (0.09) at rest and 0.85 (0.10) at 45W, p=0.049). Postoperatively, the RVEDD:LVEDD ratio was almost identical at rest and at 45W (0.84 (0.11) vs 0.83 (0.16), p=0.828), possibly suggesting that postoperatively the RV had become relatively dilated at rest.

There was no significant difference in RVFWLS from rest to 45W preoperatively (-23.6% (6.6) at rest vs -24.3% (4.0) at 45W, p=0.937) or postoperatively (-20.0% (2.6) vs -19.4% (6.7), p=0.940). There was however a significant increase in RVFWLS-rate from rest to 45W preoperatively (-1.15%.s^{-1} (0.35) at rest vs -1.57%.s^{-1} (0.18) at 45W, p=0.019, Figure 6-6), and the increase in RFWLS-rate

when exercising was lost postoperatively (-0.88%.s^{-1} (0.13) at rest vs -0.83%.s^{-1} (0.40) at 45W, p=0.772).

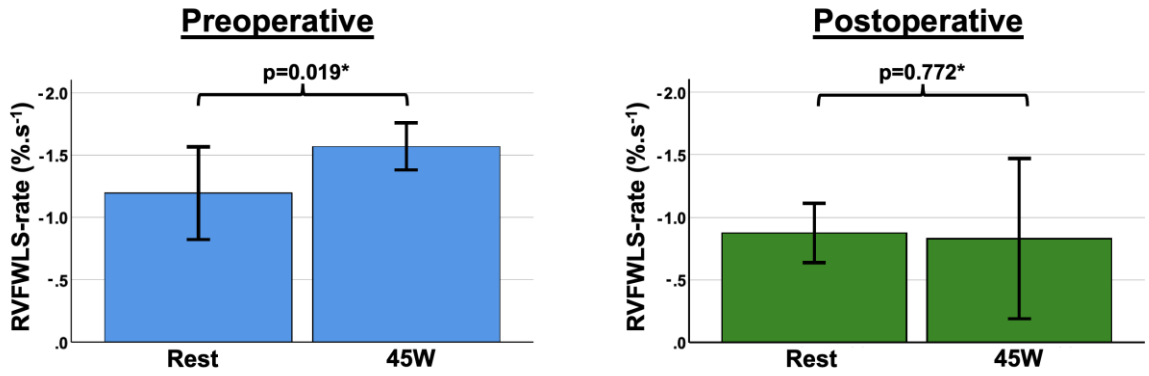


Figure 6-6 RVFWLS-rate response to exercise
Preoperatively RVFWLS-rate significantly increased (becomes more negative) when exercising at 45W compared to rest, indicating improvement in RV function. No significant change in RVFWLS-rate was observed when exercising compared to rest post-lung resection. RVFWLS = right ventricular free wall longitudinal strain. * paired T test

A significant increase from rest to 45W in TAPSE preoperatively was observed (p=0.028), with no increase seen postoperatively (p=0.239). No increase in S' was observed preoperatively from rest to 45W (p=0.549), however an increase was seen from rest to 45W postoperatively (p=0.004). As stated above, given that TAPSE and S' values were not reported by the author, these measures were not analysed further.

Table 6-5 Effect of exercise on physiology and echocardiography parameters pre- and postoperatively

		Preoperatively			Postoperatively		
		Rest	45W	p-value	Rest	45W	p-value
SpO_2 (%)		96.9 (1.9)	95.6 (2.1)	0.150*	96.9 (1.8)	93.0 (5.5)	0.231*
SBP (mmHg)		135.9 (16.0)	183.6 (19.0)	**0.008***	141.0 (18.6)	154.3 (6.7)	**0.027***
	n (n missing)	7 (0)	6 (1)		7 (0)	4 (3)	
RVEDD (mm)		35.1 (5.9)	40.4 (4.7)	0.240*	40.3 (6.5)	42.4 (8.9)	0.682*
	n (n missing)	6 (1)	6 (1)		5 (2)	4 (3)	
LVEDD (mm)		45.0 (7.1)	47.6 (4.2)	0.700*	47.9 (6.0)	50.7 (2.7)	0.555*
	n (n missing)	6 (1)	6 (1)		5 (2)	4 (3)	
RVEDD:LVEDD		0.78 (0.09)	0.85 (0.10)	**0.049***	0.84 (0.11)	0.83 (0.16)	0.828*
	n (n missing)	6 (1)	6 (1)		5 (2)	4 (3)	
Sys LVEI		1.16 (0.26)	1.31 (0.33)	0.654*	1.03 (0.12)	1.17 (0.17)	0.390*
	n (n missing)	6 (1)	4 (3)		5 (2)	4 (3)	
Dia LVEI		1.10 (0.21)	1.27 (0.25)	0.270*	0.94 (0.14)	1.10 (0.21)	0.292*
	n (n missing)	6 (1)	4 (3)		5 (2)	4 (3)	
RVFWLS (%)		-23.6 (6.6)	-24.3 (4.0)	0.937*	-20.0 (2.6)	-19.4 (6.7)	0.940*
	n (n missing)	7 (0)	7 (0)		5 (2)	4 (3)	
RVFWLS-Rate ($\%.s^{-1}$)		-1.15 (0.35)	-1.57 (0.18)	**0.019***	-0.88 (0.13)	-0.83 (0.40)	0.772*
	n (n missing)	7 (0)	7 (0)		5 (2)	4 (3)	
RVGLS (%)		-19.8 (6.8)	-21.2 (1.3)	0.762*	-18.4 (3.8)	-19.3 (4.9)	0.211*
	n (n missing)	7 (0)	7 (0)		5 (2)	4 (3)	
RVGLS-Rate ($\%.s^{-1}$)		-1.04 [0.75, 1.30]	-1.22 [1.18, 1.46]	0.173§	-0.84 (0.17)	-0.83 (0.28)	0.756*
	n (n missing)	7 (0)	7 (0)		5 (2)	4 (3)	
TAPSE (mm)[A]		18.0 [17.0, 21.0]	24.0 [23.0, 24.0]	**0.028§**	20.6 (3.4)	24.0 (5.7)	0.239*
	n (n missing)	7 (0)	7 (0)		5 (2)	4 (3)	
S' ($cm.s^{-1}$)[A]		11.5 (3.1)	13.0 (2.5)	0.549*	11.0 (0.4)	14.5 (1.0)	**0.004***
	n (n missing)	7 (0)	6 (1)		5 (2)	4 (3)	
TR peak pressure (mmHg)		14.4 (12.5)	34.7 (21.2)	0.155*	19.6 (10.9)	42.7 (8.3)	0.111*
	n (n missing)	4 (3)	4 (3)		5 (2)	3 (4)	

A = not reported by the author, * paired T-test, § Wilcoxon Signed Rank test. SpO_2 = peripheral oxygen saturation, SBP = systolic blood pressure, RVEDD = right ventricular end diastolic diameter, LVEDD = left ventricular end diastolic diameter, RV = right ventricular, LV = left ventricular, Sys = systolic, Dia = diastolic, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, TAPSE= tricuspid annular plane systolic excursion, S' = S' Wave velocity at the tricuspid annulus, TR = tricuspid regurgitation.

6.3.8 Assessment of RV contractile reserve

6.3.8.1 Individual assessment of RV contractile reserve

Four patients had complete data sets for rest to 45W pre- and postoperatively. Using RVFWLS, RVGLS, RVFWLS-rate and RVGLS-rate, patients fell into the following ordinal ranking groups:

RVFWLS

Presence of RVCR preoperatively and postoperatively: Patient 3 (Figure 6-7)

Presence of RVCR preoperatively that uncouples postoperatively: Not applicable

Uncoupling of RVCR preoperatively with preserved RVCR postoperatively: Not applicable

Uncoupling of RVCR preoperatively and postoperatively: Patient 4, patient 1 and patient 7. Patient 4 appears to have the least impaired RVCR during exercise, although uncoupling occurs during exercise, it does not substantially decrease beneath resting RVFWLS (which does occur with patient 1 and patient 7). Patient 1 demonstrates an initial increase in RFWLS as exercise intensity increases both pre- and postoperatively, but at 60W uncoupling occurs, notably the uncoupling is worse postoperatively compared to preoperatively. Patient 7 appears to have the most impaired RVCR, with no initial increment of RVFWLS observed as exercise intensity increases pre- or postoperatively.

The order of RVCR (analysed by RVFWLS) from best to worst is therefore patient 3, patient 4, patient 1, and patient 7.

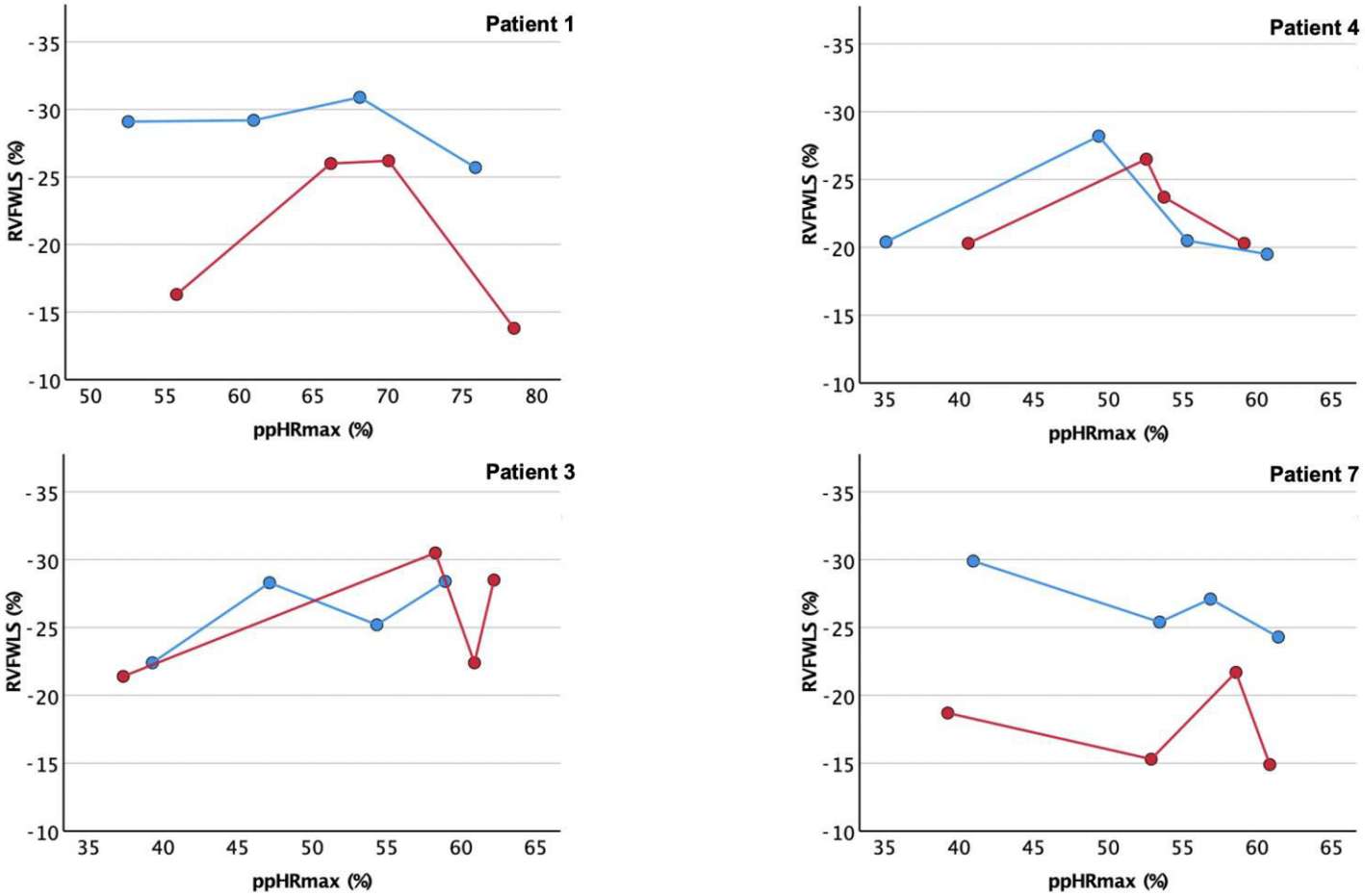


Figure 6-7 Individual patient data of RVFWLS response to exercise
Data presented of individual patients during exercise stress echocardiography preoperatively (blue) and postoperatively (red). RVCR assessed by examining the relationship between ppHRmax and RVFWLS. Data points are present for rest, 15W, 30W, and 45W. RVFWLS = right ventricular free wall longitudinal strain, RVCR = right ventricular contractile reserve, ppHRmax = percentage predicted maximal heart rate.

RVGLS

Presence of RVCR preoperatively and postoperatively: Not applicable

Presence of RVCR preoperatively that uncouples postoperatively:
Patient 4 (Figure 6-8)

Uncoupling of RVCR preoperatively with preserved RVCR postoperatively:
Patient 3

Uncoupling of RVCR preoperatively and postoperatively: Patient 1 and patient 7. Patient 7 appears to have the most impaired RVCR, with no initial increment of RVFWLS observed as exercise intensity increases (whereas this does occur postoperatively with patient 1)

The order of RVCR (analysed by RVGLS) from best to worst is therefore patient 4, patient 3, patient 1 and patient 7.

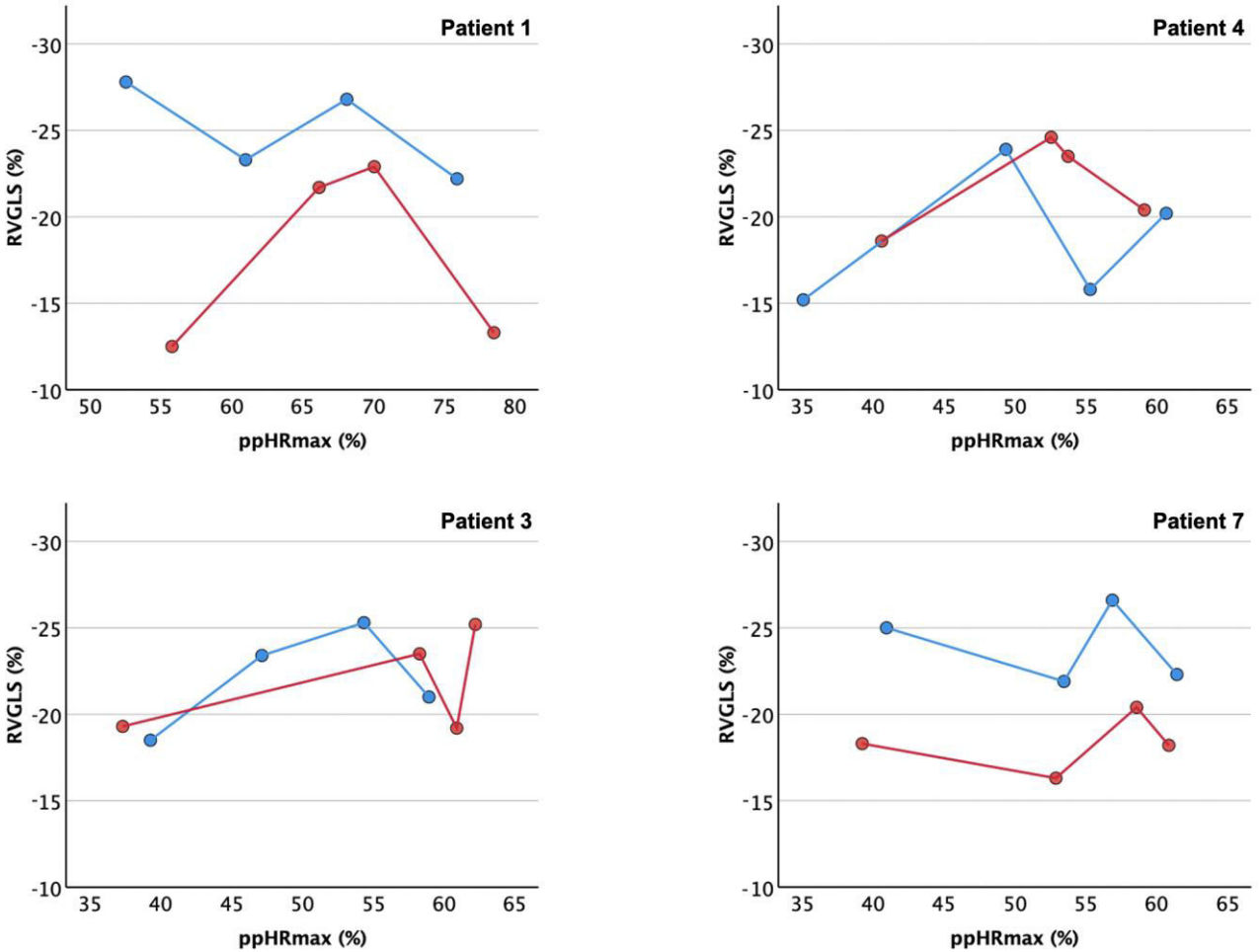


Figure 6-8 Individual patient data of RVGLS response to exercise
Data presented of individual patients during exercise stress echocardiography preoperatively (blue) and postoperatively (red). RVCR assessed by examining the relationship between ppHRmax and RVGLS. Data points are present for rest, 15W, 30W, and 45W. RVGLS = right ventricular global longitudinal strain, RVCR = right ventricular contractile reserve, ppHRmax = percentage predicted maximal heart rate.

RVFWLS-rate

Presence of RVCR preoperatively and postoperatively: Patient 4 (Figure 6-9)

Presence of RVCR preoperatively that uncouples postoperatively: Patient 3 and 7. Given that all postoperative data points lay beneath the preoperative data points for patient 7 (representing a substantial drop in overall RV function postoperatively), it was deemed that patient 7 had worse RVCR that patient 3.

Uncoupling of RVCR preoperatively with preserved RVCR postoperatively: Not applicable

Uncoupling of RVCR preoperatively and postoperatively: Patient 1, with greater uncoupling demonstrated postoperatively compared to preoperatively.

The order of RVCR (as analysed by RVWLS-rate) from best to worst is therefore patient 4, patient 3, patient 7, patient 1.

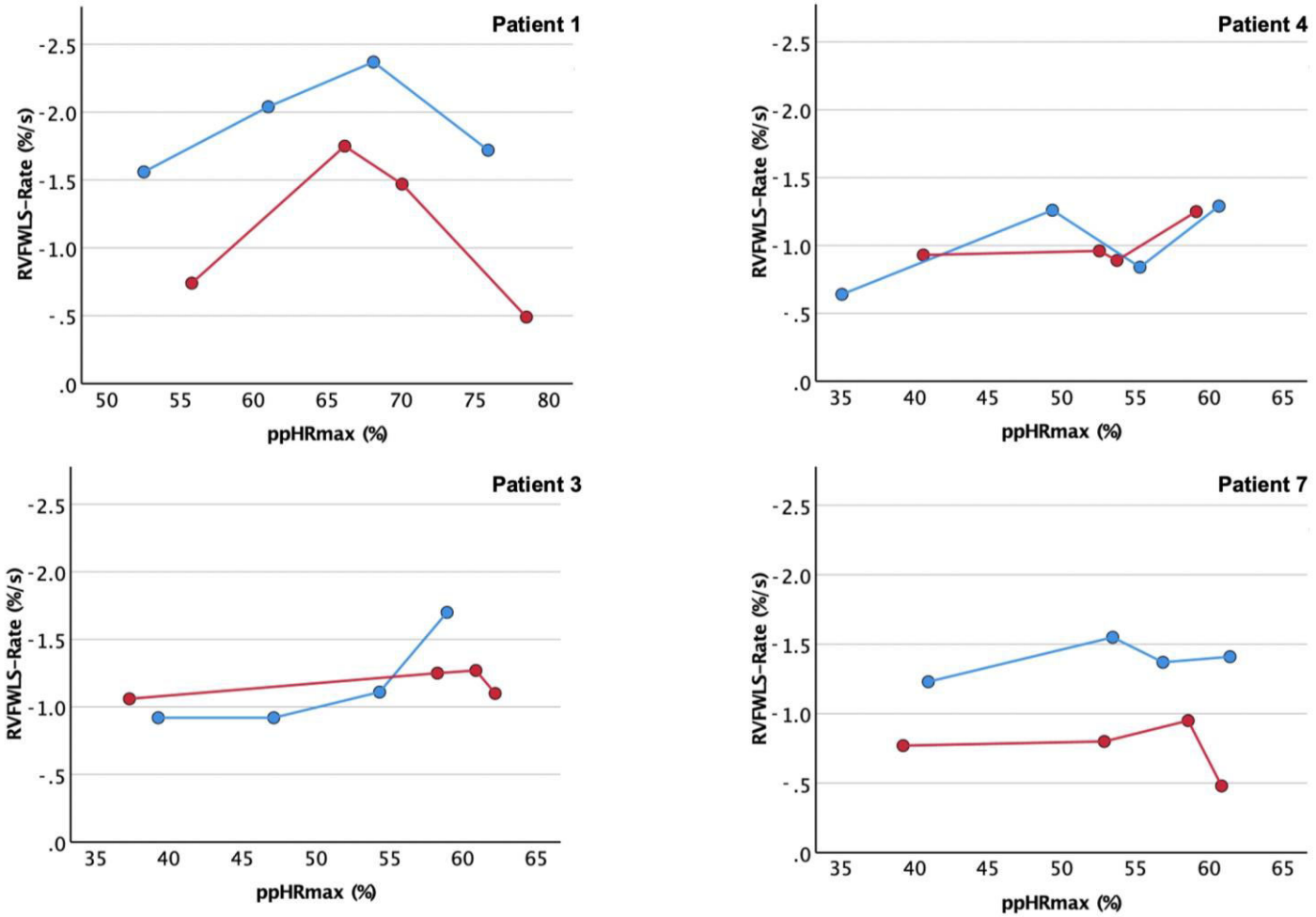


Figure 6-9 Individual patient data of RVFWLS-rate response to exercise

Data presented of individual patients during exercise stress echocardiography preoperatively (blue) and postoperatively (red). RVCR assessed by examining the relationship between ppHRmax and RVFWLS-rate. Data points are present for rest, 15W, 30W, and 45W. RVFWLS = right ventricular free wall longitudinal strain, RVCR = right ventricular contractile reserve, ppHRmax = percentage predicted maximal heart rate.

RVGLS-rate

Presence of RVCR preoperatively and postoperatively: Patient 4 (Figure 6-10)

Presence of RVCR preoperatively that uncouples postoperatively: Patient 3

Uncoupling of RVCR preoperatively with preserved RVCR postoperatively: Not applicable

Uncoupling of RVCR preoperatively and postoperatively: Patient 7 and patient 1. Patient 1 appears to have the most impaired RVCR, with steeper uncoupling occurring both preoperatively and postoperatively compared to patient 7.

The order of RVCR (analysed by RVGLS-rate) from best to worst is therefore patient 4, patient 3, patient 7, patient 1.

The differences in RVCR assessed by RVFWLS, RVGLS, RVWFLS-rate, and RVGLS-rate are striking. All measures appeared to agree that patient 3 and patients 4 have better RVCR, and patients 1 and patient 7 have more impaired RVCR. RVFWLS-rate and RVGLS-rate both resulted in the ordinal ranking of patient 4, patient 3, patient 7, and patient 1 (from better to worse RVCR).

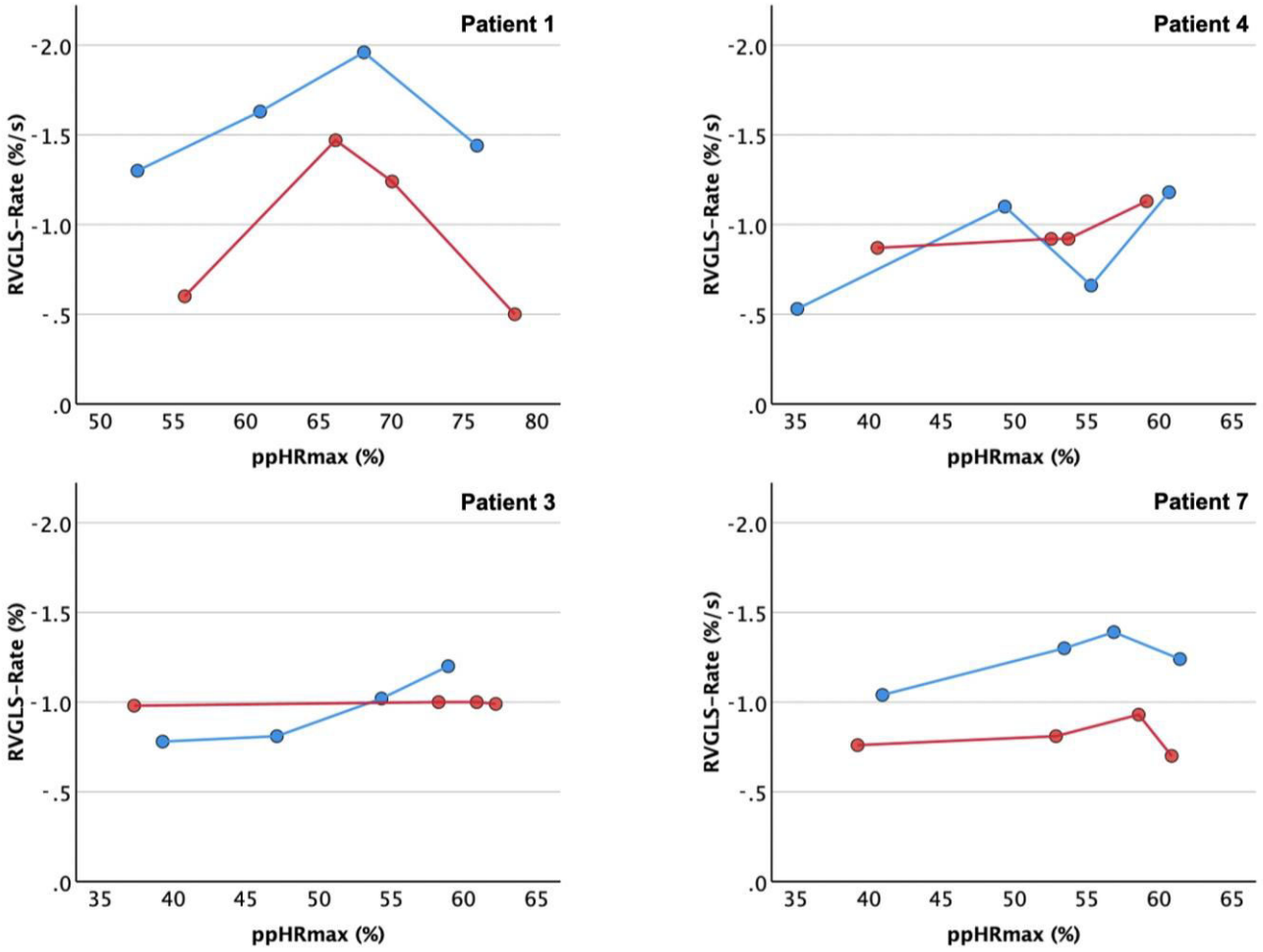


Figure 6-10 Individual patient data of RVGLS-Rate response to exercise
Data presented of individual patients during exercise stress echocardiography preoperatively (blue) and postoperatively (red). RVCR assessed by examining the relationship between ppHRmax and RVGLS-rate. Data points are present for rest, 15W, 30W, and 45W. RVGLS = right ventricular global longitudinal strain, RVCR = right ventricular contractile reserve, ppHRmax = percentage predicted maximal heart rate.

6.3.8.2 Grouped assessment of RV contractile reserve

Four patients had data points at all workloads from rest to 45W pre- and postoperatively, these were included in the grouped ANCOVA analysis. Patient 6 had two paired points of data (at rest and 15W), these were also included. ANCOVA analysis found no association between ppHRmax and RVFWLS pre- or postoperatively (r=-0.018, p= 0.950, and r=-0.163, p=0.578 respectively, Figure 6-11A+B and Table 6-6). Similarly, no association was found between ppHRmax and RVGLS pre- or postoperatively (r= -0.152, p=0.604 and r=-0.283, p=0.328 respectively). This suggests that RVFWLS and RVGLS were not able to demonstrate RVCR pre- or postoperatively. There was an association between ppHRmax and RVFWLS-rate preoperatively that was lost postoperatively (r=-0.579, p=0.030, and r=-0.048, p=0.870 respectively, Figure 6-11C+D and Table 6-6). Similarly, an association was found between ppHRmax and RVGLS-rate preoperatively that was not present postoperatively (r=-0.560, p=0.037 and r=-0.063, p=0.843 respectively).

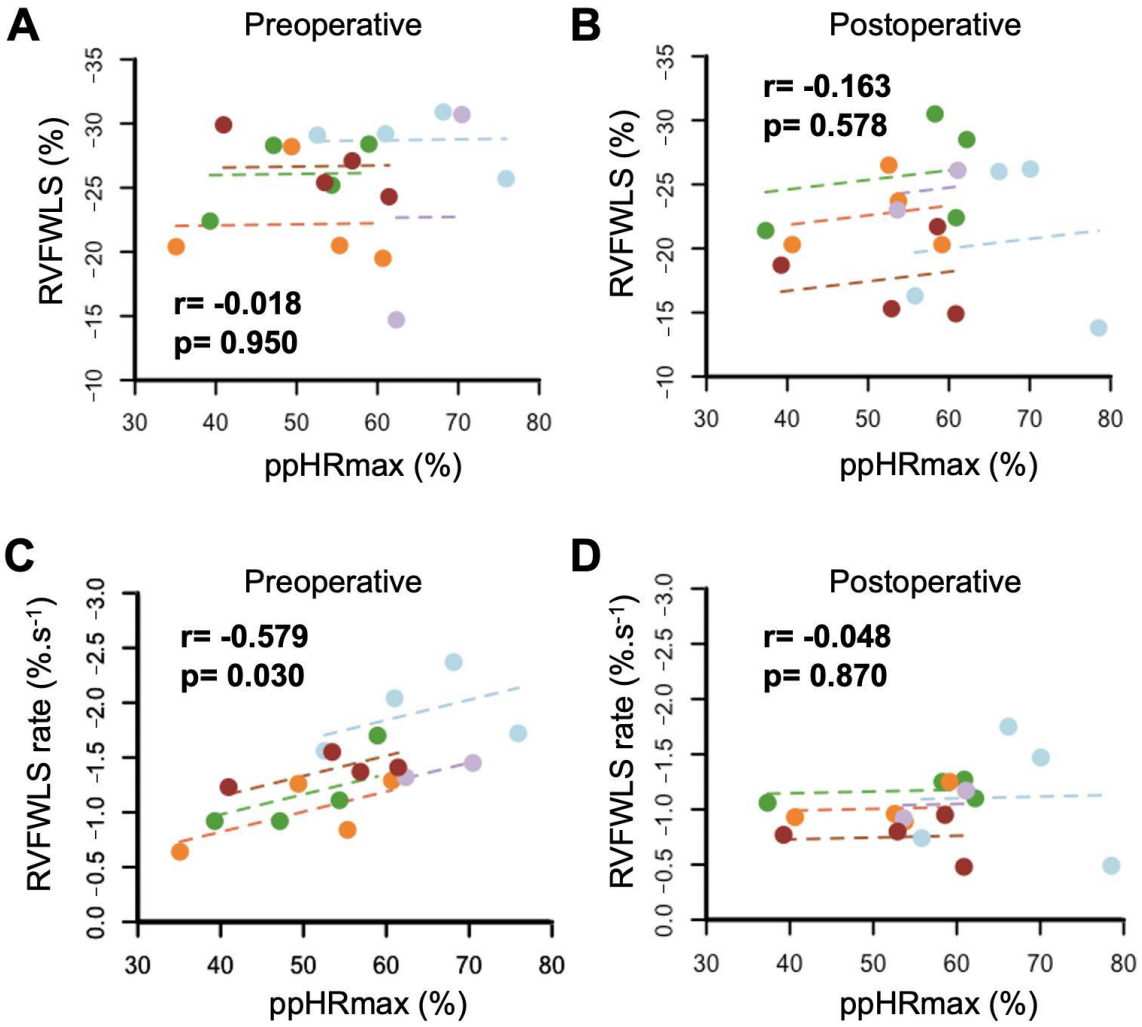


Figure 6-11 Grouped patient data of RVFWLS and RVFWLS-rate response to exercise
Pre- and postoperative scatter plots of ppHRmax rate versus RVFWLS (A and B) and RVFWLS-rate (C and D). Individual patient data points are shown in the same colour in all plots. All available paired data from patients has been included in each scatter plot. Correlation coefficients were calculated using the analysis of covariance (ANCOVA). RVFWLS = right ventricular free wall longitudinal strain, ppHRmax = percentage predicted maximal heart rate. Thank you to Dr Adam Glass for producing these ANCOVA scatter plots using R statistical software.

Table 6-6 Grouped patient data analysing relationship between RV-STE with ppHRmax

	RVFWLS		RVFWLS-Rate		RVGLS		RVGLS-Rate	
	Preop	**Postop**	**Preop**	**Postop**	**Preop**	**Postop**	**Preop**	**Postop**
Pooled analysis correlation co-efficient (r)	-0.136*	-0.059*	**-0.686***	-0.162*	-0.114*	0.15*	**-0.721***	-0.091*
p-value	0.591	0.817	**0.002**	0.520	0.651	0.953	**<0.001**	0.718
Within subject analysis (ANCOVA) (r)	-0.018	-0.163	**-0.579**	-0.048	-0.152	-0.283	**-0.560**	-0.063
p-value	0.950	0.578	**0.030**	0.870	0.604	0.328	**0.037**	0.843

*Pearson's correlation co-efficient. RV-STE = right ventricular speckle tracking echocardiography, ppHRmax = percentage predicted maximal heart rate, ANCOVA = analysis of covariance, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, preop = preoperative, postop = postoperative

6.3.9 RV contractile reserve and cardiac biomarkers and patient outcomes

To assess the effect that impaired RVCR had upon cardiac biomarker release and patient outcomes, the ordinal ranking system described in section 6.2.7.1 was used. On grouped analyses, RVFWLS-rate and RVGLS-rate were shown to demonstrate presence of RVCR preoperatively that was lost postoperatively. When ordinally ranking impairment of RVCR of individual patients, both RVFWLS-rate and RVGLS-rate identified the order of patient 4, patient 3, patient 7, and patient 1 (from better RVCR to worse RVCR). Cardiac biomarkers and patient outcomes were therefore compared between patients using this ordinal ranking.

There was no obvious relationship identified between worsening RVCR and increase in troponin or BNP (Table 6-7). Similarly, there did not appear to be any association between worsening RVCR and MRC breathlessness scale, NYHA grade, and EQ VAS scores. Hospital length of stay did appear to increase as RVCR worsened, with the patient with the “best” RVCR (patient 4) having a length of stay of 4 days, compared to 21 days for the patient with the “worst” RVCR (patient 1).

Table 6-7 Laboratory and clinical outcomes

Laboratory/Clinical variable	Better RV contractile reserve → Worse RV contractile reserve				Interpretation
	Patient 4	Patient 3	Patient 7	Patient 1	
Cardiac biomarkers					
Troponin preop (ng/ml)	<0.05	<0.05	<0.05	<0.05	No apparent change in troponin
Troponin postop[A] (ng/ml)	<0.05	<0.05	<0.05	<0.05	
Δ Troponin (ng/ml)	**NA**	**NA**	**NA**	**NA**	
BNP preop (ng/L)	9.7	83.2	11.4	42.7	No obvious increase in preoperative BNP, postoperative BNP, or Δ BNP as RVCR worsens.
BNP postop[A] (ng/L)	138	211	93.2	191	
Δ BNP (ng/L)	**128.3**	**127.8**	**81.8**	**148.3**	
Hospital Length of Stay	4	6	6	21	Hospital length of stay appears to have increased as RVCR has worsened.
Functional status / quality of life outcomes					
MRC breathlessness scale preop	1	3	1	4	No obvious consistent trend in preoperative, postoperative, or Δ for MRC scales, NYHA grades, or EQ VAS as RVCR worsens.
MRC breathlessness scale postop	2	2	2	3	
Δ MRC breathlessness scale	**1**	**-1**	**1**	**-1**	
NYHA grade preop	1	1	1	3	
NYHA grade postop	2	2	1	2	
Δ NYHA grade	**1**	**1**	**0**	**-1**	
EQ VAS preop	80	85	90	37	
EQ VAS postop	80	30	89	80	
Δ EQ VAS	**0**	**55**	**-1**	**-43**	

Subjective assessment of RV contractile reserve, assessed by both RVFWLS-rate and RVGLS-rate, identified the ordinal ranking of patient 4, patient 3, patient 7, and patient 1 (from better RVCR to worse RVCR). A = highest postoperative value. RV = right ventricular, preop = preoperatively, postop = postoperatively, Δ Troponin = change in troponin from preoperative to highest postoperative value, BNP = B-type natriuretic peptide, Δ BNP = change in B-type natriuretic peptide from preoperative to highest postoperative value, MRC = Medical Research Council, NYHA = New York Heart Association, EQ VAS = EuroQol visual analogue scale, RVCR = right ventricular contractile reserve, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain.

6.4 Discussion

This exercise stress echocardiography study investigated the relationship between exercise intensity and RV-STE in the assessment of RVCR in seven patients undergoing lung resection. Patients in the current study had similar demographics (age and sex) and co-morbidities to a usual West of Scotland lung resection cohort[34]. All patients underwent lobectomy, experiencing a prolonged period of OLV (mean 115.4 minutes [27.9]) representing a substantial acute stress on the right ventricle.

All patients underwent exercise stress echocardiography preoperatively and postoperatively. Exercise was tolerated in all patients up to 45W preoperatively, and six (85.7%) patients were able to exercise up to 45W postoperatively. Exercise at 60W was not as well tolerated, especially postoperatively. Importantly, all patients reported they would be willing to perform exercise stress echocardiography again preoperatively. These results suggest that semi-supine cycle ergometer exercise stress echocardiography (up to 45W) is an acceptable form of exercise testing to patients undergoing lung resection.

RVFWLS technical feasibility was high preoperatively (≥85.7% at rest, 15W, 30W, and 45W) and poorer postoperatively (<85% at all workloads), suggesting exercise stress echocardiography strain analysis may be better suited as a preoperative investigation. As previously reported, technical feasibility became poorer at higher workloads, likely due to increased body movement making echocardiography difficult, and the challenges in acquiring images relating to the increased depth/rate of respiration, and tachycardia[141]. Only one previous study has investigated the technical feasibility of RVFWLS during exercise stress echocardiography. Lord et al studied RVFWLS technical feasibility on 19 healthy volunteers undergoing exercise in the upright position on a cycle ergometer[141]. They studied technical feasibility at 50% ppHRmax, 70% ppHRmax, and 90% ppHRmax. The preoperative technical feasibility of the current study was higher than Lord et al's study at all comparable ppHRmax levels (Table 6-8), possibly due to the lower technical feasibility encountered with the upright cycling position used by Lord et al. This suggests that the preoperative exercise protocol, and use of semi-supine cycle ergometer, yields echocardiography images of a high quality for RV-STE analysis.

Table 6-8 Exercise intensity and RVFWLS technical feasibility

		RVFWLS technical feasibility (%)
Lord et al[141]:	Rest supine	89
Lord et al:	Rest upright	80
RV Exercise study preop:	Rest	100
Lord et al:	ppHRmax 50% (upright)	59
RV Exercise study preop 15W:	ppHRmax mean 45.6% (9.2)	86
Lord et al:	ppHRmax 70% (upright)	21
RV Exercise study preop 45W:	ppHRmax mean 66.1% (6.6)	86

Comparison between the RVFWLS technical feasibility described by Lord et al[141] and the RV exercise study. The closest to equivalent ppHRmax achieved during the RV exercise study preoperatively was compared to the designated ppHRmax level from Lord et al study. RVFWLS = right ventricular free wall longitudinal strain, RV = right ventricular, preop = preoperatively, ppHRmax = percentage predicted maximal heart rate

Exercise stress echocardiography represents a physiological test for examining the effects of physical cardiovascular stress on RV function. An alternative method is pharmacological cardiovascular stress in the form of dobutamine stress echocardiography. Dobutamine stress echocardiography has shown high RV-STE technical feasibility in previous studies. Yang et al report an RVGLS feasibility of 94.3% (33/35) in patients undergoing routine dobutamine stress echocardiography, and Schlangen et al reported a RVGLS feasibility of 98.1% (51/52) in a population of patients who had undergone correction of congenital heart defect surgery[114,125]. Although less physiological, dobutamine stress echocardiography may represent a more tolerable alternative to patients, especially in those with musculoskeletal issues (two patients complained of joint pains during postoperative exercise in the present study). Additionally, acquiring echocardiography images may be easier since there will be less exercise induced movement artefact. However, it must be noted that the inodilator effects of dobutamine could mitigate the increase in PVR observed after lung resection[34,69]. This reduction in RV afterload may treat the impairment in RV function previously demonstrated after lung resection, and dobutamine stress echocardiography may therefore not be a truly representative model of the RV response to exercise in the lung resection setting. Bearing this potential limitation in mind, dobutamine stress echocardiography RV-STE analysis may represent an interesting avenue of further research, especially in the postoperative setting where exercise stress echocardiography was both poorly tolerated and had low technical feasibility in the current patient cohort.

The intraobserver reproducibility of RVFWLS was high (preoperative ICC 0.92, postoperative ICC 0.95), but poorer for RVFWLS-rate (preoperative ICC 0.74,

postoperative ICC 0.64). An explanation for this may be that RVFWLS has better reproducibility since it is the primary value reported by STE software, whereas RVFWLS-rate is the secondary derived value. One other study has investigated the intraobserver reproducibility of RV-STE during exercise stress echocardiography. Lord et al reported mean differences (and LOAs) for RVFWLS and RVFWLS-rate during upright cycling exercise at a ppHRmax of 50% (they did not report ICCs)[141]. Lord et al found similar mean differences and LOAs for RVFWLS and RVFWLS-rate compared to the current study (both pre- and postoperatively, Table 6-9). This suggests that the RV-STE reproducibility of the current study is in keeping with the expected reproducibility for an exercise study.

Table 6-9 Intraobserver reproducibility of RVFWLS/RVFWLS-rate during exercise stress echocardiography

	Bland-Altman MD (LOA)	
	RVFWLS	**RVFWLS-rate**
Lord et al[141]	0.9% (-6.9, 8.8)	0.2%.s^{-1} (-0.7, 1.1)
RV exercise study:		
Preoperatively	1.4% (-3.1, -5.9)	0.1%.s^{-1} (-0.6, 0.9)
Postoperatively	0.7% (-4.0, 5.3)	-0.1%.s^{-1} (-0.9, 0.7)

RVFWLS = right ventricular free wall longitudinal strain, MD = mean difference, LOA = limit of agreement, RV = right ventricular

When assessing the effect echocardiography study image quality had upon reproducibility, use of higher quality images, as identified by both semi-quantitative endocardial delineation scores and qualitative global assessment, did not improve the reproducibility of RVFWLS. Higher quality echocardiography study images, identified by semi-quantitative endocardial delineation scores (endocardial delineation score >8), did however improve reproducibility of RVFWLS-rate, whereas the use of qualitative global assessment to identify higher quality images did not. This may suggest semi-quantitative scoring is superior to simple qualitative global assessments of image quality when used to identify optimal images for RVFWLS-rate analysis. Further research is required to confirm if this observation is true both in lung resection cohorts and other patient groups at risk of impaired RVCR.

This work is the first to investigate the use of an ordinal ranking system to describe a spectrum of the change in RVCR after lung resection from normal to increasing levels of impairment. Visual inspection of line graphs allowed easy

categorisation of a patient's RVCR. Depending on the measure of RV function (RVFWLS/RVFWLS-rate, RVGLS/RVGLS-rate) used, there was variability in patient ranking from better perioperative RVCR to worse RVCR. Given the small data set, no robust conclusions can be made from ordinally ranked RVCR patient data, however it was interesting that hospital length of stay increased across patients ranked with better to worse perioperative RVCR when RVCR was analysed using RVFWLS-rate and RVGLS-rate. Okada et al 1996 similarly demonstrated that patients with impaired preoperative RVCR (RVCR identified as a decrease in RVEF when exercising) had a longer length of stay after lung resection compared to patients with normal RVCR.[243] Further work is needed to confirm if impaired RVCR (both pre-existing impaired RVCR and newly acquired postoperative impaired RVCR) is associated with poorer patient outcomes.

Grouped analysis demonstrated that RVFWLS and RVGLS were both not associated with ppHRmax preoperatively (r=-0.018, p= 0.950, and r= -0.152, p=0.604 respectively) or postoperatively, (r=-0.163, p=0.578, and r=-0.283, p=0.328 respectively). As described in Chapter 2 (section 2.10.5.5), previous studies have shown RVFWLS/RVGLS does not markedly change with exercise in healthy volunteers[136,141,143,144]. Chia et al performed the largest study investigating this in 121 healthy volunteers, demonstrating RVFWLS increased by only 1.1% when exercising compared to rest[137]. This would suggest RVFWLS minimally increases with exercise. Given the present study sample had only seven patients, it is possible the sample was too small to detect this modest change in RVFWLS when exercising, and a type-2 error may have occurred.

Two studies have investigated the response of RVFWLS to exercise in patients with pulmonary hypertension. Chia et al and Cobra et al demonstrated RVFWLS values worsened (becoming less negative) when exercising, compared to rest in patients with pulmonary hypertension[147,149]. It is possible our patient population may also have impaired preoperative RVCR, which may have contributed to why the expected small increase in RVFWLS when exercising was not observed. Three out of seven patients in the present study had a history of COPD, predisposing to pulmonary hypertension. When examining preoperative peak TR pressures, the absolute values of peak TR pressure increased from 14.4mmHg (12.5) at rest to 34.7mmHg (21.2) at 45W (p=0.155, Table 5-5). A rise in TR peak pressure of

>20mmHg during exercise has been previously shown to be indicative of exercise induced pulmonary hypertension[257]. As described in Chapter 2 (section 2.10.5.1), when undergoing exercise, RV cardiac output and flow through the pulmonary arteries substantially increases. To blunt the rise in pulmonary pressures associated with increased flow, pulmonary vasodilation occurs ("pulmonary vascular reserve"). It appears that patients in the current study may have a degree of pre-existing pulmonary vascular reserve impairment, which would result in increased RV afterload during exercise, and predispose to impaired RVCR at baseline. It must be noted peak TR pressures during exercise tend to increase with age, and given that the mean age of patients was 67.4 (12.6) years it cannot be said with certainty patients had pulmonary hypertension when exercising[257]. It was hypothesised in the introduction that RVFWLS and RVGLS would not demonstrate an association with exercise intensity, and this expected lack of association was found.

Grouped analysis showed that RVFWLS-rate and RVGLS-rate were associated with exercise intensity preoperatively (r=-0.579, p=0.030 and r=-0.560, p=0.037 respectively, Table 6-6), and these associations were lost postoperatively (r=-0.048, p=0.870 and r=-0.063, p=0.843 respectively). This suggests that RVFWLS-rate and RVGLS-rate identified the presence of RVCR preoperatively, that was lost postoperatively. RVFWLS-rate has consistently been shown to increase (i.e. become more negative) with exercise in healthy subjects[136,144,149], and in patients with pulmonary hypertension[149]. The preoperative finding that RVFWLS-rate is associated with exercise intensity confirms the previously observed results. It was hypothesised in the introduction that preoperatively RVFWLS-rate and RVGLS-rate would demonstrate an association with exercise intensity. Construct validity with respect to the formative item relationship between exercise intensity and RV function (as measured by RVFWLS-rate and RVGLS-rate) was therefore demonstrated.

The finding that preoperatively, RVFWLS-rate/RVGLS-rate were associated with exercise intensity, and RVFWLS/RVGLS were not associated with exercise intensity is in keeping with previous studies. Similar to the present study, Chia et al demonstrated that RVFWLS-rate was associated with exercise workload in healthy volunteers (r=-0.4, p=0.001), they also did not find an association

between RVFWLS and exercise workload (r=-0.14, p non-significant). Previous studies examining the effects of dobutamine stress echocardiography and RV-STE have shown that RVGLS-rate increases with inotropy, with no change in RVGLS[114,125]. Schlangen et al performed dobutamine stress echocardiography with contemporaneous invasive measurement of pulmonary haemodynamics to assess RV end systolic elastance (E_{es}, a load independent measure of contractility, section 1.2.7)[114]. They demonstrated an association between RVGLS-rate and E_{es} (-0.47, p<0.001), with no association between RVGLS and E_{es} (0.07, p=0.5) suggesting RVGLS-rate may be a superior correlate of contractility in this setting. Similarly, results from the current study suggest that RVFWLS-rate/RVGLS-rate identify the enhancement in RV function during preoperative exercise (which RVFWLS/RVGLS do not), and may therefore be better measures of RV contractility. This suggests that RVFWLS-rate/RVGLS-rate are more suited than RVFWLS/RVGLS to assessing RVCR perioperatively. Although RVFWLS-rate demonstrated construct validity with its ability to detect enhancement in RV function during exercise preoperatively, RVFWLS-rate had poorer reproducibility compared with RVFWLS. There is a trade-off between the better construct validity of RVFWLS-rate compared to RVFWLS, at the expense of poorer reproducibility, and this must be taken into consideration when selecting the preferred measure for assessing RVCR.

It was hypothesised RVCR would become impaired after lung resection. As anticipated, the associations between RVFWLS-rate/RVGLS-rate and exercise intensity were lost postoperatively. This suggests construct validity was demonstrated with regards the formative item relationship between lung resection and its detrimental effect upon RVCR (assessed by RV-STE-rate as shown in the conceptual model in Figure 6-1). Given that the current study suggests RVCR is impaired after lung resection, further research is needed to investigate if patients who experience loss of RVCR (as assessed by RVFWLS-rate/RVGLS-rate) experience poorer postoperative outcomes.

Previously the author's supervisors, and Dr Adam Glass, have shown RV pulsatile afterload increases after lung resection and remains raised at 2 months[34,69]. RV-PA coupling was intended to be assessed during the RV exercise study (using TR peak pressure gradient and PAAT as surrogates of RV afterload), however this

was not possible since few patients had TR, and incorrect spectral doppler imaging was used for PAATs. A previous study in patients with CTEPH has shown an impairment in the ability of the pulmonary vasculature to vasodilate during exercise (termed pulmonary vascular reserve), and blunt the rise in pulmonary vascular resistance (a component of RV afterload)[129]. Further RV-STE exercise studies should aim to investigate the effect of lung resection upon pulmonary vascular reserve and RV afterload. If impaired pulmonary vascular reserve is identified in patients after lung resection, it may represent an exertional aspect of RV afterload that may impair RV function during exercise, contributing to patients' exertional and functional symptoms.

6.4.1 Strengths

Strengths of this study include its prospective design with an a priori plan to assess RVCR using RV-STE and RV-STE-rate. There was a focus on the feasibility of exercise stress echocardiography RV-STE analysis, with an emphasis on patient tolerability and with the aim to identify an exercise test that is practical to implement.

6.4.2 Limitations

Limitations of this study include its exploratory nature with a small sample size, and the study is therefore at risk of type-1 and type-2 error. Given that this was a feasibility study, the small sample size was deliberate, however this will have reduced the power of the study. Mean TR peak pressures appeared to increase markedly during exercise pre- and postoperatively when exercising compared to rest, however the difference was not statistically significant. A larger sample size may have revealed an association which would have allowed assessment for exercise induced pulmonary hypertension and analysis of RV-PA coupling. Another limitation is that the incorrect doppler imaging was used for PAAT, further limiting RV afterload data. A linear association between ppHRmax and RV-STE/RV-STE-rate was assumed based off previous observations of LV-STE/LV-STE-rate response to exercise in healthy volunteers, which may not represent the true relationship between RV-STE/RV-STE-rate and ppHRmax.

6.5 Conclusion

The RV exercise study has demonstrated that RV-STE-rate has utility in assessing RVCR in patients undergoing lung resection. Exercise stress echocardiography is tolerable to patients, especially preoperatively, with RVFWLS having high technical feasibility up to 45W. RVFWLS and RVGLS had high intra-observer reproducibility, RVFWLS-rate and RVGLS-rate had lower reproducibility, especially postoperatively. Image quality assessed by endocardial delineation scores appeared to identify high quality images which improved RVFWLS-rate reproducibility. RVFWLS and RVGLS were not associated with exercise intensity pre- or postoperatively, and therefore did not identify the presence of RVCR. RVFWLS-rate and RVGLS-rate demonstrated an association with exercise intensity that was lost postoperatively, suggesting RVCR was identified preoperatively which was lost postoperatively. These findings support the construct validity of using RV-STE-rate to assess RVCR. Further research is needed to investigate the concurrent criterion and predictive validity of RV-STE-rate in the assessment of RVCR. Further studies are also needed to assess the clinical significance of impaired RVCR diagnosed by RVFWLS-rate/RVGLS-rate in patients undergoing lung resection, and explore the potential for their use in preoperative assessment to identify a cohort of high-risk patients in whom perioperative RV protective interventions may be warranted. To further assess the utility of RVFWLS-rate/RVGLS-rate as a measure of RVCR, it would be prudent to examine these measures during exercise in other patient populations experiencing exertional dyspnoea who may be at risk of impaired RV function.

Chapter 7 Major findings, conclusions, and future directions

7.1 Major findings

This thesis investigated the utility of RV-STE in ICU and the perioperative period by literature review and meta-analysis (Chapter 4), in an ICU population with COVID-19 undergoing IMV (Chapter 5), and in a lung resection population undergoing exercise (Chapter 6). The major findings from these studies, and overarching conclusions are now described (Figure 7-1 and 7-2 provide an overview), followed by a plan for future investigations that will further investigate RV-STE utility.

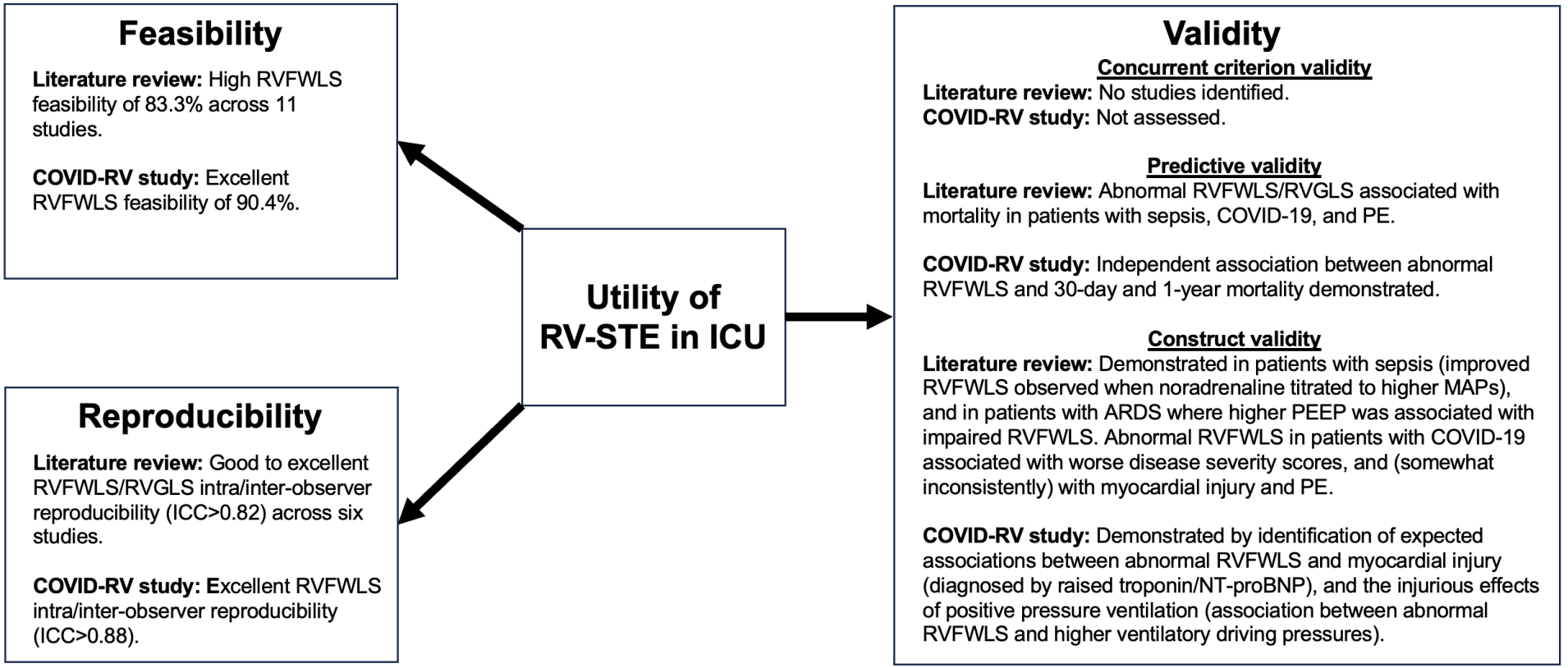


Figure 7-1 Major findings from investigations into the utility of RV-STE in ICU
The major findings from this thesis assessing the utility of RV-STE in ICU are described. Utility is divided into the domains of feasibility, reproducibility, and validity. The literature review findings have been summarised from Chapter 4, and the findings from the COVID-RV study have been summarised from Chapter 5. ICU = intensive care unit, RVFWLS = right ventricular free wall longitudinal strain, COVID-RV = Right Ventricular Dysfunction in Ventilated Patients with COVID-19, ICC = intra-class correlation coefficient, RV-STE = right ventricular speckle tracking echocardiography, RVGLS = right ventricular global longitudinal strain, COVID-19 = corona virus disease 2019, PE = pulmonary embolism, MAP = mean arterial pressure, PEEP = positive end expiratory pressure, NT-proBNP = N-terminal pro B-type Natriuretic Peptide

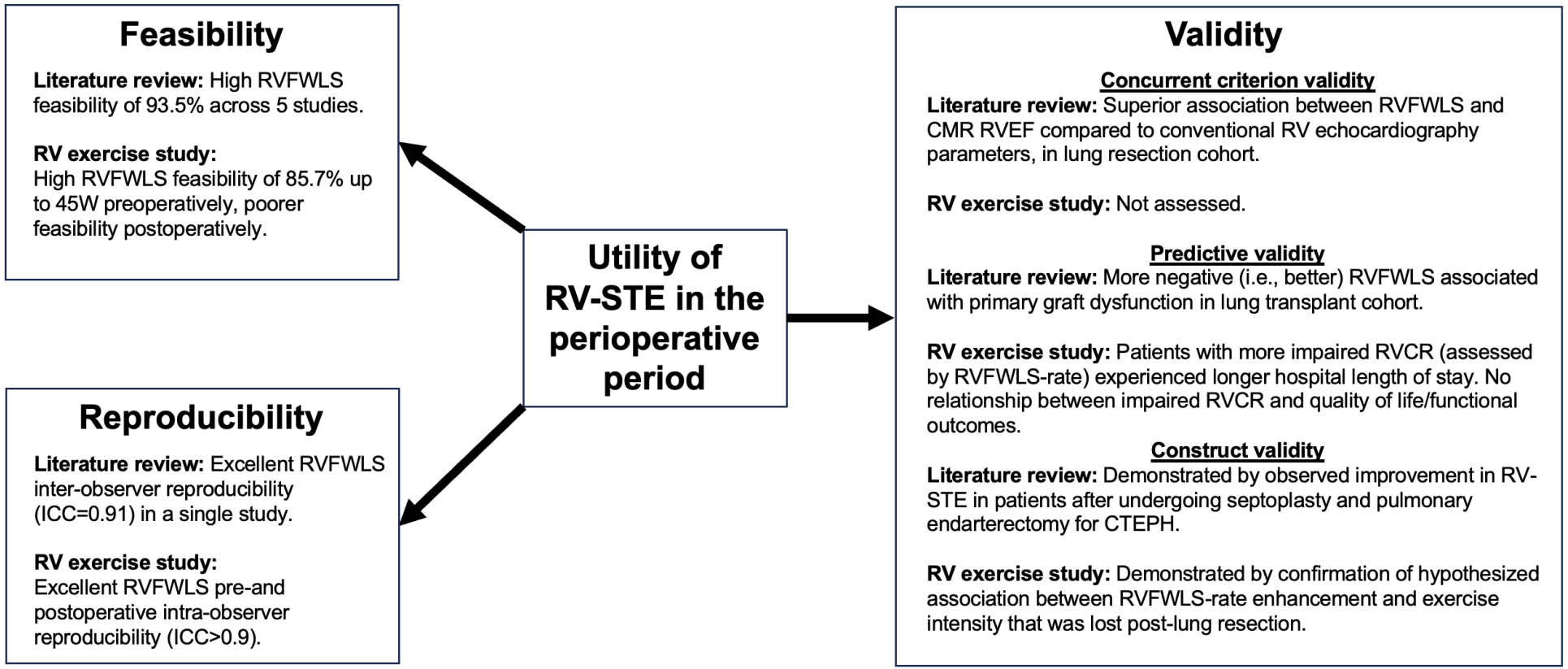


Figure 7-2 Major findings from investigations into the utility of RV-STE in the perioperative period
The major findings from this thesis assessing the utility of RV-STE in the perioperative period are described. Utility is divided into the domains of feasibility, reproducibility, and validity. The literature review findings have been summarised from Chapter 4, and the findings from the RV exercise study have been summarised from Chapter 6. RVFWLS = right ventricular free wall longitudinal strain, ICC = intraclass correlation coefficient, RV-STE = right ventricular speckle tracking echocardiography, CMR RVEF = cardiac magnetic resonance right ventricular ejection fraction, RV = right ventricular, RVCR = right ventricular contractile reserve, CTEPH = chronic thromboembolic pulmonary hypertension

7.1.1 Chapter 4

Literature review and meta-analyses demonstrated that the feasibility of RV-STE is high in both ICU studies (83.3% [95%CI 74.6-89.4]) and perioperative studies (93.5% [95%CI 82.2-97.8]). Within ICU studies, feasibility was found to be lower in COVID-19 cohorts and in patients requiring IMV. Prospective study design can improve RV-STE feasibility. There were inadequate numbers of perioperative studies to make firm conclusions about variables that affect RV-STE feasibility in the perioperative setting.

The intra- and inter-observer reproducibility of RV-STE in ICU studies was primarily described using ICCs and Bland-Altman plots. RV-STE was found to be highly reproducible, comparing favourably to conventional RV echocardiography parameters. RV-STE reproducibility was only reported in one perioperative study, future work is therefore required to explore this further.

Evidence supporting the validity of RV-STE analysis was investigated in ICU groups with sepsis, ARDS, COVID-19, and PE. No studies investigated concurrent criterion validity (comparing RV-STE to gold standard CMR RVEF). Predictive and construct validity were demonstrated in patients with sepsis and COVID-19. The predictive validity of RV-STE was also proven in patients with PE. There was conflicting evidence to support the predictive validity of RV-STE in patients with ARDS. RVFWLS however did demonstrate construct validity in patients with ARDS, where increased levels of PEEP were associated with impaired RVFWLS values.

Evidence supporting the validity of RV-STE analysis was investigated in perioperative groups requiring lung resection, lung transplantation, septoplasty, and pulmonary endarterectomy. Concurrent criterion validity of RV-STE was assessed in a single lung resection cohort, with RV-STE performing better than conventional RV echocardiography parameters. The ability of RV-STE to predict primary graft dysfunction after lung transplantation was demonstrated, and the construct validity of RV-STE was supported in groups undergoing septoplasty and pulmonary endarterectomy. Overall, few perioperative studies assessed RV-STE

validity (particularly concurrent criterion validity) and further research is required in this area.

The COVID-RV study (Chapter 5) and RV exercise study (Chapter 6) addressed knowledge gaps identified by the literature review. Particularly areas focussed on included the effects of echocardiographer experience upon RV-STE feasibility, the effects of echocardiography study image quality upon reproducibility, and a robust assessment of the construct validity of RV-STE as a measure of resting and dynamic RV function.

7.1.2 Chapter 5

Chapter 5 prospectively investigated RV-STE in an ICU cohort with COVID-19 requiring IMV as part of the COVID-RV study. This study showed high RVFWLS feasibility of 90.4%, and excellent intra-observer and inter-observer reproducibility. No difference was found in RVFWLS feasibility between images acquired by expert and non-expert echocardiographers.

Abnormal RVFWLS was found to be independently associated with 30-day and one-year mortality, establishing its predictive validity in this cohort. Conventional RV echocardiography parameters were not associated with mortality. Construct validity was demonstrated by identifying the association between abnormal RVFWLS and abnormal cardiac biomarkers (troponin and NT-proBNP), suggesting that RVFWLS may identify RVD occurring with myocardial injury. Abnormal RVFWLS was also associated with higher ventilator driving pressures, indicating RVFWLS may identify RVD arising due to the deleterious effects of IMV.

The COVID-RV study demonstrated that RVFWLS analysis is both highly feasible and reproducible, with predictive and construct validity in this ICU population.

7.1.3 Chapter 6

Chapter 6 investigated the use of RV-STE analysis during exercise stress echocardiography as a measure of RV contractile reserve (RVCR) in a lung resection cohort.

The RV exercise study demonstrated exercise stress echocardiography is tolerable to patients, particularly preoperatively. RVFWLS had high technical feasibility up to 45W preoperatively. RVFWLS was highly reproducible, however RVFWLS-rate had lower reproducibility, especially postoperatively. Analysis of echocardiography study image quality by semi-quantitative endocardial delineation scoring found that higher quality images improved RVFWLS-rate reproducibility.

As anticipated from previous research, RVFWLS was not associated with exercise intensity pre- or postoperatively. RVFWLS-rate strongly associated with exercise intensity preoperatively; an association that was lost postoperatively, suggesting the presence of RVCR preoperatively which was then lost postoperatively. These findings support the construct validity of using RVFWLS-rate to assess RVCR in this setting. Further research is needed to assess the clinical significance of impaired RVCR diagnosed by RVFWLS-rate in patients undergoing lung resection.

7.2 General conclusions

The main findings from this thesis are that RV-STE is highly feasible, reproducible, and demonstrates many aspects of validity in both ICU and the perioperative period.

The use of RV-STE in an ICU population demonstrated that RVFWLS has predictive validity in its independent association with 30-day mortality in patients with COVID-19 requiring IMV. Construct validity was also present in this setting with regards the association between abnormal RVFWLS and myocardial injury, and between abnormal RVFWLS and the injurious effects of IMV.

The use of RV-STE in a perioperative lung resection exercise study demonstrated that RVFWLS-rate can detect the presence of RVCR preoperatively, and that RVCR is lost postoperatively. This demonstrated construct validity with regards the ability of RVFWLS-rate to detect exercise induced improvements in RV function preoperatively, and that postoperatively RVFWLS-rate detected impairment in RVCR possibly due to the deleterious effects of lung resection on RV function.

Overall, this thesis has provided clear evidence supporting the utility of RV-STE in ICU and the perioperative setting. There are areas which require additional investigation, particularly in the perioperative period, to further establish the utility of RV-STE. Ongoing research, in which the author is a co-investigator, that will address these knowledge gaps is described below.

7.3 Future directions

7.3.1 Incidence, impact, and mechanisms of perioperative right ventricular dysfunction study

7.3.1.1 Study background

The incidence of RVD in ICU disease populations (e.g. sepsis and ARDS) has been well defined. However, as described in the literature review in Chapter 4, the incidence of RVD in perioperative groups has received considerably less attention. Additionally, the mechanisms underlying perioperative RVD remain elusive. The incidence, impact, and mechanisms of perioperative right ventricular dysfunction (IMPRoVE) study is a prospective multicentre clinical trial that has been designed to address these gaps in the literature. The IMPRoVE study will investigate the incidence of perioperative right ventricular dysfunction after major non-cardiac surgery (five surgical groups: thoracic, upper gastrointestinal, vascular, colorectal and orthopaedic), and the association between RVD and patient outcomes in these groups. Thirty-five patients will be recruited from each surgical group, resulting in a total of 175 patients. Transthoracic echocardiography will be performed preoperative and on day 2-4 postoperatively (Figure 7-3). As evidenced in this thesis, RVFWLS is a robust measure of subtle RVD. RVFWLS >-20% will therefore be the primary measure for diagnosing RVD in the IMPRoVE study, and vendor neutral Tomtec 2D CPA strain analysis software will again be used for this analysis. Echocardiography studies from the different sites will be transferred to the Golden Jubilee National Hospital for central reporting. A sub-study will be performed on 10 patients in each surgical group (50 patients in total), who will undergo contemporaneous CMR imaging preoperative and postoperatively in conjunction with echocardiography.

Funding for the IMPRoVE study was successfully acquired by the author's supervisor Prof Ben Shelley (British Oxygen Company Chair of Anaesthesia, awarded 12/02/2021). The author, together with supervisors Dr Philip McCall, Prof Ben Shelley, and Clinical Research Fellow Dr Tom Keast, have drafted and published a study protocol, gained ethical approval, gained research and development approval, and designed case report forms for the IMPRoVE study (see Appendix 4)[258]. The author constructed the REDCap database for the study.

The IMPRoVE study opened for recruitment in May 2023, and is expected to run for three years.

7.3.1.2 Further investigation of RV-STE feasibility in the perioperative period

The IMPRoVE study will provide thorough assessment of the utility of RV-STE in the perioperative period. The IMPRoVE study will allow, for the first time, assessment of the feasibility of RV-STE across five surgical specialities. Assessment of echocardiography study image quality for pre and postoperative TTE will be performed, allowing analysis of the impact of surgery upon the feasibility of RV-STE (e.g. lung resection may alter the anatomical location of the RV, potentially reducing feasibility, whereas primary lower limb arthroplasty may not be expected to have such an effect).

7.3.1.3 Further investigation of RV-STE reproducibility in the perioperative period

The IMPRoVE study will allow detailed assessment of the reproducibility of RV-STE across the five surgical groups (which, as highlighted in Chapter 4, was very poorly reported by the current research base). Intra- and inter-observer reproducibility will be assessed using ICCs and Bland-Altman plots, with a sub-study to investigate the effects that qualitative and semi-quantitative (i.e. endocardial delineation scores) image quality have upon reproducibility. No study has yet performed an in-depth assessment of RV-STE reproducibility across a range of perioperative groups.

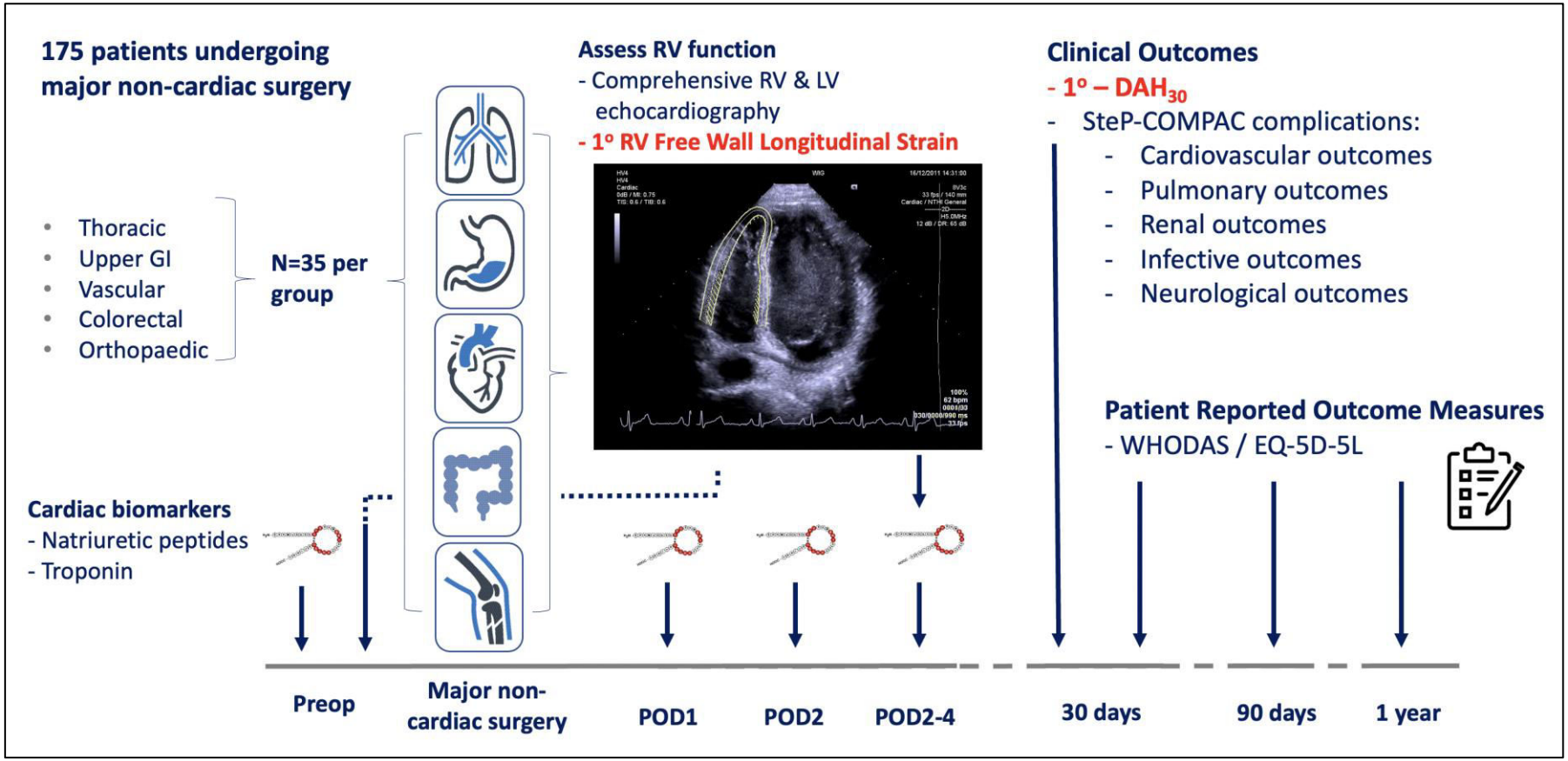


Figure 7-3 Overview of the IMPRoVE study

Overview of the main IMPRoVE study. One-hundred and seventy-five patients (35 from each surgical group) will undergo echocardiography and cardiac biomarker testing pre- and postoperatively. RVD will be diagnosed by RVFWLS >-20%.

IMPRoVE = incidence, impact, and mechanisms of perioperative right ventricular dysfunction, RVD = right ventricular dysfunction, GI = gastrointestinal, RV = right ventricular, LV = left ventricular, DAH_{30} = Days alive and at home at 30 days postoperatively, StEP-COMPAC = Standardised Endpoints and Core Outcome Measures for Perioperative and Anaesthetic Care, WHODAS = WHO Disability Assessment Schedule 2.0, EQ-5D-5L = EuroQol-5 Dimension Health Related Quality of Life Questionnaire, POD = postoperative day. Reproduced from Keast et al[258].

7.3.1.4 Further investigation of RV-STE validity in the perioperative period

The IMPRovE study will also allow thorough assessment of the validity of RV-STE in the perioperative period. As described in the literature review in Chapter 4, concurrent validity (comparing RV-STE to gold standard CMR) has been poorly reported, and requires rigorous assessment in the perioperative period. The IMPRoVE study will directly address this knowledge gap in five different surgical groups. Predictive validity in these groups will also be assessed, analysing for association between RVD (diagnosed by abnormal RVFWLS) and 30-day mortality. Construct validity will be investigated, examining for the expected relationships between formative items, reflective items, and RVD (diagnosed by abnormal RVFWLS >-20%). Hypothesised formative items that may affect RV function include a diagnosis of perioperative myocardial injury, duration of bi-lung positive pressure ventilation, duration of one-lung ventilation time, and duration of PA clamping. Reflective items that may be affected by RVD include renal, pulmonary, infective, and neurological outcomes, as well as patient functional and quality of life outcomes (as informed by the Standardised Endpoints and Core Outcome Measures for Perioperative and Anaesthetic Care initiative[259]). Beyond the dichotomous division of patients into groups with normal RV function (identified by RVFWLS ≤-20%) and RVD (identified by abnormal RFWLS >-20%), as a method to explore for associations between RVD and the items described above, the effect of the change in preoperative to postoperative RVFWLS will also be investigated. It is possible that patients will experience a deterioration in RVFWLS postoperatively, but have "normal" RVFWLS (i.e. ≤-20%) both preoperatively and postoperatively. It will be important to investigate if these subtle alterations in RV function (measured using the change in RVFWLS as a continuous variable) are associated with changes in the formative and reflective items described above, and if they are associated with patients' outcomes. Additionally, LV-STE will be assessed analogously to RV-STE, affording an unparalleled insight into the utility of LV-STE in the perioperative period.

The IMPRoVE study will greatly contribute to the assessment of RV-STE utility in the perioperative period, addressing many of the knowledge gaps highlighted during the investigations within this thesis. It is ultimately hoped that once the incidence and mechanisms of perioperative RVD have been elucidated, an interventional randomised control trial will be designed that uses a preventative

strategy (e.g. perioperative inhaled pulmonary vasodilators) in the treatment arm to assess if preventing RVD is of therapeutic benefit to patients at high risk of developing perioperative RVD.

7.4 Final conclusion

This thesis established the current understanding of RV-STE's utility within ICU and the perioperative period via rigorous literature review. Investigation into RV-STE's utility was expanded upon through the experiments within the COVID-RV study and RV exercise study. RV-STE was shown to be highly feasible, highly reproducible, and it demonstrated many aspects of validity. The evidence supporting the utility of RV-STE within this thesis has directly led to RV-STE being chosen as the primary measure of RV function for the IMPRoVE study, this will afford an unparalleled insight into the utility of RV-STE in the perioperative period.

Appendices

Appendix 1 - Overview of ICU studies investigating RV-STE utility identified by literature search

Appendix 2 - Overview of perioperative studies investigating RV-STE utility identified by literature search

Appendix 3 - Speckle tracking echocardiography training

Appendix 4 - IMPRoVE study protocol

Appendix 1 - Overview of ICU studies investigating RV-STE utility identified by literature search

Appendix Table 1 Overview of ICU studies investigating RV-STE utility identified by literature search

Study (Year)	(n)	Study Overview	Results	Comment
Sepsis				
Orde et al 2014[195]	74	Prospective single centre study investigating RVFWLS and survival in patients with severe sepsis/septic shock.	Abnormal RVFWLS (>-21%) found in 72% (43/60) patients. Severely impaired RVFWLS (>-13%) associated with 6m mortality.	Single reporter of RVFWLS
Dalla et al 2015[191]	72	Retrospective single centre study investigating RVFWLS in patients with septic shock/severe sepsis (n=48) compared to patients with major trauma (n=24).	RVFWLS significantly lower in patients with sepsis compared to trauma.	Sepsis group older and sicker than trauma patients (higher SAPS II score, lower MAP, higher proportion of patients receiving IMV, longer ICU stay)
Dalla et al 2019[192]	11	Prospective single centre study investigating RVFWLS in patients with septic shock. Noradrenaline dose altered to maintain MAP of 60, 75, and 90mmHg for 10 minute periods.	Improved RVFWLS at higher doses of noradrenaline.	All patients receiving IMV.
de Braga Lima Carvalho Canesso et al 2019[196]	26	Prospective single centre study investigating RVGLS in patients with sepsis. Comparison of RVGLS in survivors and non-survivors at ICU admission and 7 days post ICU admission.	RVGLS significantly improved from ICU admission to day 7 in sepsis survivors. No change observed in RVGLS from admission to day 7 in sepsis non-survivors.	65% of patients receiving IMV.
ARDS				

Garcia-Montilla et al 2017[193]	51	Retrospective single centre study investigating RVFWLS in patients with ARDS receiving IMV. Aiming to predict optimal RV filling pressure.	CVP of 13mmHg identified as the optimal filling pressure for RV function (RVFWLS of -21%). U shaped relationship between creatinine and RVFWLS	Single snapshot RVFWLS vs CVP. No control of CVP over time, only CVP at time of echocardiography.
Bonizzoli et al 2018[177]	30	Prospective single centre study investigating RVFWLS in patients with ARDS receiving IMV.	RVFWLS impaired in non-survivors compared to survivors	
Mercado et al 2018[198]	24	Prospective single centre study investigating effect of recruitment manoeuvres on RVFWLS in patients with ARDS receiving IMV.	RVFWLS significantly impaired during recruitment manoeuvre.	Intravascular volume optimised before recruitment manoeuvre.
Lemarie et al 2020[178]	48+6 controls	Prospective study in two centres investigating RVGLS in patients with ARDS receiving IMV, and compared to controls (ICU patients requiring IMV for airway protection).	RVGLS significantly more impaired in ARDS group compared to controls.	ARDS patients older than controls (mean age 61 vs 51).
Invasive Mechanical Ventilation				
Franchi et al 2013[199]	20	Prospective single centre study investigating RVGLS in patients requiring IMV for hypoxia. Investigated effect of incremental levels of PEEP on RVGLS.	Higher levels of PEEP associated with more impaired RVGLS.	ICU patients with mixed pathologies: intracerebral haemorrhage, encephalitis, polytrauma, cerebral ischaemia, and sepsis.
COVID-19				
Baycan et al Aug 2020[180]	100	Prospective single centre study investigating RVFWLS in population of patients with COVID-19. Compared patients with non-severe COVID-19 vs severe COVID-19.	RVFWLS significantly more impaired in patients with “severe” COVID-19 compared to “non-severe” COVID-19. Correlations between RVFWLS and troponin, D-dimer, sPAP, and SpO2.	Unclear what proportion of patients receiving IMV.
Krishnamoorthy et al	12	Single centre study investigating RVFWLS and RVGLS in patients with	RVFWLS and RVGLS significantly more impaired in patients who died or	Unclear if prospective or retrospective study.

Aug 2020[260]		COVID-19, predominantly not requiring IMV.	subsequently required IMV than patients who did not.	Echocardiography only performed when clinically indicated. Two patients receiving IMV during echocardiography despite subsequent requirement for IMV being an outcome.
Bursi et al Sep 2020[181]	49	Retrospective single centre study investigating RVFWLS and RVGLS in patients with COVID-19, predominantly not receiving IMV. Survival analysis for in hospital mortality.	No difference in RVFWLS between survivors and non-survivors. RVGLS impaired in non-survivors compared to survivors.	Echocardiography only performed when clinically indicated.
Kim et al Oct 2020[179]	40	Mixed prospective/retrospective multicentre study investigating RVFWLS and RVGLS in patients with COVID-19, predominantly not requiring IMV.	Trend towards RVFWLS and RVGLS being more impaired in patients with "severe" COVID-19 compared to "non-severe" COVID-19.	Plan had been for prospective study but due to rapid decline in COVID-19 cases a prospective/retrospective design was used.
Li et al Nov 2020[16]	120	Single centre study investigating RVFWLS in mixed population of patients with COVID-19 requiring and not requiring IMV. Patients grouped into tertiles depending on RVFWLS. Survival analysis with median follow up of 51 days.	RVFWLS significantly more impaired in bottom tertile compared to top tertile. AUROCC RVFWLS optimal cut off for predicting survival -23% (sensitivity 94.4, specificity 64.7 $p<0.001$).	Unclear if prospective or retrospective study. AUROCC identified a "normal" RVFWLS value as AUROCC cut off for predicting survival.
Jain et al Jan 2021[183]	36	Single centre study investigating RVGLS in mixed population of patients with COVID-19 requiring and not requiring IMV.	RVGLS -19.5% [-23.0, -15.2%].	Unclear if prospective or retrospective study. Supine and prone patients ("fewer than 5 in prone").

Xie et al Jan 2021[175]	132	Prospective single centre study investigating RVFWLS in mixed population of patients with COVID-19 requiring and not requiring IMV. Cardiac injury defined as high-sensitivity troponin >99th centile.	RVFWLS significantly impaired in patients with myocardial injury compared to those without myocardial injury.	**Similar patient cohort as Li et al Nov 2020[16].**
Stockenhuber et al Feb 2021[182]	35	Prospective single centre pilot study investigating RVFWLS in patients with COVID-19, predominantly not requiring IMV. Survival analysis for 30 day mortality.	RVFWLS significantly impaired in non-survivors compared to survivors.	Echocardiography only performed when clinically indicated.
Zhang et al Feb 2021[176]	128	Single centre study investigating RVFWLS in mixed population of patients with COVID-19 requiring and not requiring IMV.	RVFWLS significantly impaired in patients with "critical" COVID-19 compared to those with "severe" and "general" COVID-19.	**Similar patient cohort as Li et al Nov 2020[16].** Unclear if prospective or retrospective study.
Bleakley et al March 2021[15]	90	Retrospective single centre study investigating RVFWLS in patients with COVID-19 all receiving IMV.	Mean RVFWLS -24.1 (6.9)%.	42% of patients receiving VV ECMO.
Park et al June 2021[194]	45	Retrospective single centre study investigating RVFWLS and RVGLS in patients with COVID-19. Survival analysis for in hospital mortality.	No difference in RVFWLS or RVGLS between survivors and non-survivors.	Proportion of patients requiring IMV not described.
Sun et al June 2021[174]	160	Retrospective single centre study investigating RVFWLS in mixed population of patients with COVID-19 requiring and not requiring IMV.	RVFWLS significantly impaired in patients with "critical" COVID-19 compared to "non-critical" COVID-19.	**Similar patient cohort as Li et al Nov 2020[16].**

Gibson et Aug al 2021[201]	32	Prospective single centre study investigating RVFWLS in patients with COVID-19 requiring IMV.	Mean RVFWLS -17% (SD +/- 6%). Abnormal RVFWLS (>-20%) present in 66% (21/32).	15/32 patients prone at time of echocardiography. RVFWLS not validated in this position.
Pulmonary embolism				
Khemasuwan et al 2015[184]	235	Retrospective single centre study investigating RVFWLS and RVGLS in patients presenting with PE.	RVGLS and RVFWLS associated with requirement for IMV, but not associated with survival. Details on actual strain values not given.	No patients requiring IMV at time of TTE
Dahhan et al 2016[185]	69	Retrospective single centre study investigating RVFWLS and RVGLS in patients with PE. Survival analysis for 30-day mortality.	RVFWLS and RVGLS impaired in non-survivors compared to survivors.	No information on proportion of patients ventilated.
Kanar et al 2019[211]	146	Prospective single centre study investigating RVGLS in patients with PE. Survival analysis for in-hospital mortality.	RVGLS impaired in non-survivors compared to survivors.	17.6% of patients receiving IMV.

Appendix 2 - Overview of perioperative studies investigating RV-STE utility identified by literature search

Appendix Table 2 Overview of perioperative studies investigating RV-STE utility identified by literature search

Study (Year)	(n)	Study Overview	Results	Comment
Lung transplant				
Perez-Teran et al 2015[212]	120	Retrospective single centre study investigating RVFWLS, including segmental analysis, in patients undergoing lung transplantation. Sought association between preoperative RVFWLS and primary graft dysfunction grade 3 (PGD3).	Patients who developed PGD3 had significantly better basal segment RVFWLS than patients who did not develop PGD3.	Authors explanation of findings: pathological haemodynamic forces ('pulmonary hyperflow' and shear stress to endothelium) caused by a 'well trained' RV contracting against the reduced PVR of the implanted lungs resulting in PGD3.
Perez-Teran et al 2016[213]	72	Prospective single centre study investigating RVFWLS, in patients undergoing lung transplantation. Sought association between preoperative RVFWLS and PGD3.	Patients who developed PGD3 had significantly better basal segment RVFWLS than patients who did not develop PGD3.	Prospective study confirming Perez-Teran et al 2015 findings.
Lung Resection				
McCall et al 2019[74]	27	Prospective single centre study investigating RVFWLS and RVGLS in patients undergoing lung resection. Echocardiography preoperatively, day 2 and 2 months postoperatively. Compared echocardiography parameters to CMR RVEF.	Correlation between CMR RVEF and RVFWLS, RVGLS, TAPSE, S', and RIMP with pooled analysis. Only RVFWLS approached significance when with-in subject analysis (ANCOVA) used ($r= 0.31$, $p=0.05$) RVFWLS and RVGLS demonstrated better ability to predict CMR RVEF<45% using AUROCC than TAPSE, S', and RIMP.	Effort to ensure echocardiography and CMR happened as closely as possible (often during same transfer to MRI).

Pulmonary endarterectomy				
Sunbul et al 2015[122]	40	Prospective single centre study investigating RVFWLS pre- and 3-monts post-pulmonary endarterectomy for patients with chronic thromboembolic pulmonary hypertension (CTEPH).	RVFWLS impaired preoperatively. RVFWLS significantly improved after pulmonary endarterectomy compared to preoperatively.	
Marston et al 2015[216]	30	Single centre study investigating basal segment RVFWLS pre- and post-pulmonary endarterectomy (mean of 9 days) for patients with CTEPH.	RVFWLS significantly impaired postoperatively compared to preoperatively.	Unclear if prospective or retrospective study. Only assessed basal RVFWLS.
Caesarean section				
Kumaresan et al 2020[214]	98	Prospective single centre study investigating RVFWLS in patients pre and 2 hours post-caesarian section under regional anaesthesia.	No significant change in RVFWLS.	
Septoplasty				
Simsek and Simsek 2018[215]	58	Prospective single centre study investigating RVGLS in patients pre and 3-months post-septoplasty for upper airway obstruction.	RVGLS significantly improved after septoplasty compared to preoperatively.	Mild pulmonary hypertension seen in patients preoperatively.

Appendix 3 - Speckle tracking echocardiography training

The author underwent a number of training steps to become competent in analysis two-dimensional RV-STE of transthoracic echocardiography images. Firstly the author completed three interactive one-day modules run by the Tomtec Academy which included hands on tutorials for using Tomtec 2D-CPA. These modules were:

"Left Ventricular Strain- How, When, and Why?"- 21/07/2021

"Right Ventricular Strain- How, When, and Why?"- 16/09/2021

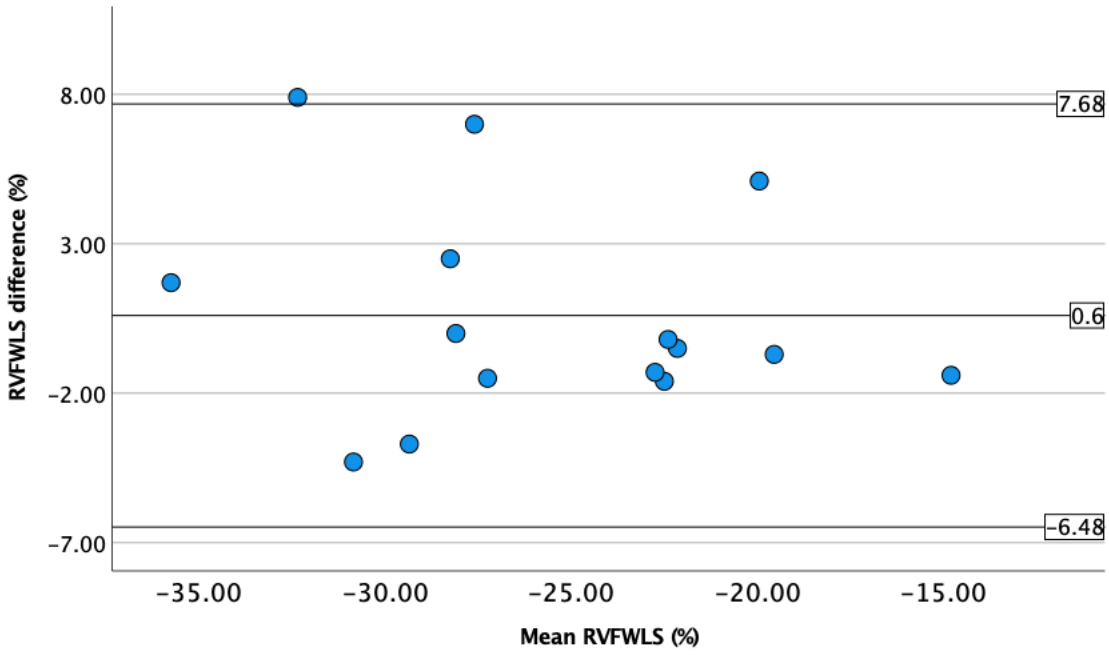
"Left Atrial Strain- How, When, and Why?"- 19/10/2021

After completing these modules, the author then performed RV-STE analysis on the echocardiography images acquired during the "RV study"[34], and assessed intra-observer and inter-observer reproducibility. These echocardiography studies were preoperative and postoperative scans from thoracic patients who underwent lung resection at the GJNH. Previous work has shown that RVFWLS analysis of minimum of 100 echocardiography studies are required before a reporter can be expected to achieve "expert-level competency"[100]. A total of 120 studies were therefore reported before analysing the COVID-RV study and RV exercise study datasets. The RV study echocardiography studies were anonymised and RV-STE analysed in a randomised order. At the end of RV-STE training, reproducibility of the reported RV-STE values was assessed using ICCs and Bland-Altman plots. Intra-observer agreement was assessed by the author re-reporting 15 random echocardiography studies two weeks after initial report. Inter-observer agreement was assessed by a second expert reporter (Dr Phil McCall) reporting RV-STE for 15 random echocardiography studies. Intra-observer and interobserver reproducibility were high for RV-STE analysis of the RV study training set (Appendix Table 3), with very good to excellent ICCs for RVFWLS reproducibility. No obvious systematic bias was detected on visual assessment of Bland-Altman plots (Appendix Figures 1-4).

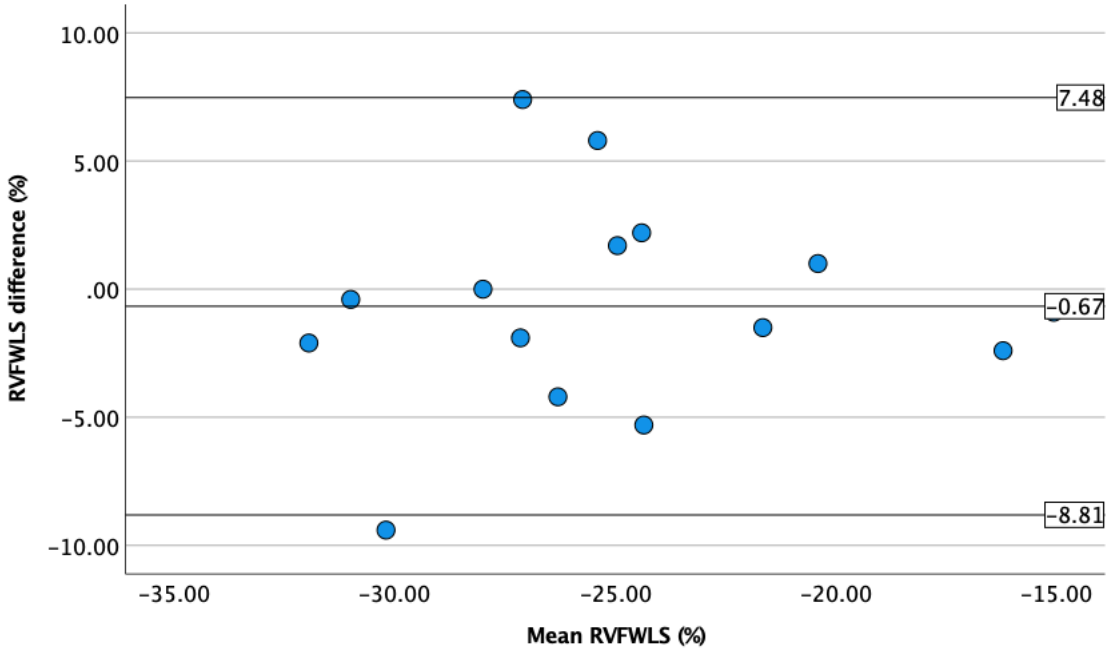
Appendix Table 3 Intra-observer and interobserver reproducibility from the RV study

		Mean Difference (%)	Standard deviation (%)	Limits of agreement (mean difference +/- 1.96 SD)	ICC (absolute agreement, two-way mixed)
RVFWLS	Intra-observer agreement	0.60	3.61	7.68, -6.48	0.90 (p<0.001)
	Inter-observer agreement	-0.67	4.15	7.48, -8.81	0.83 (p=0.001)
RVGLS	Intra-observer agreement	0.67	2.22	5.03, -3.69	0.95 (p<0.001)
	Inter-observer agreement	-0.42	4.67	8.74, -9.58	0.63 (p=0.043)

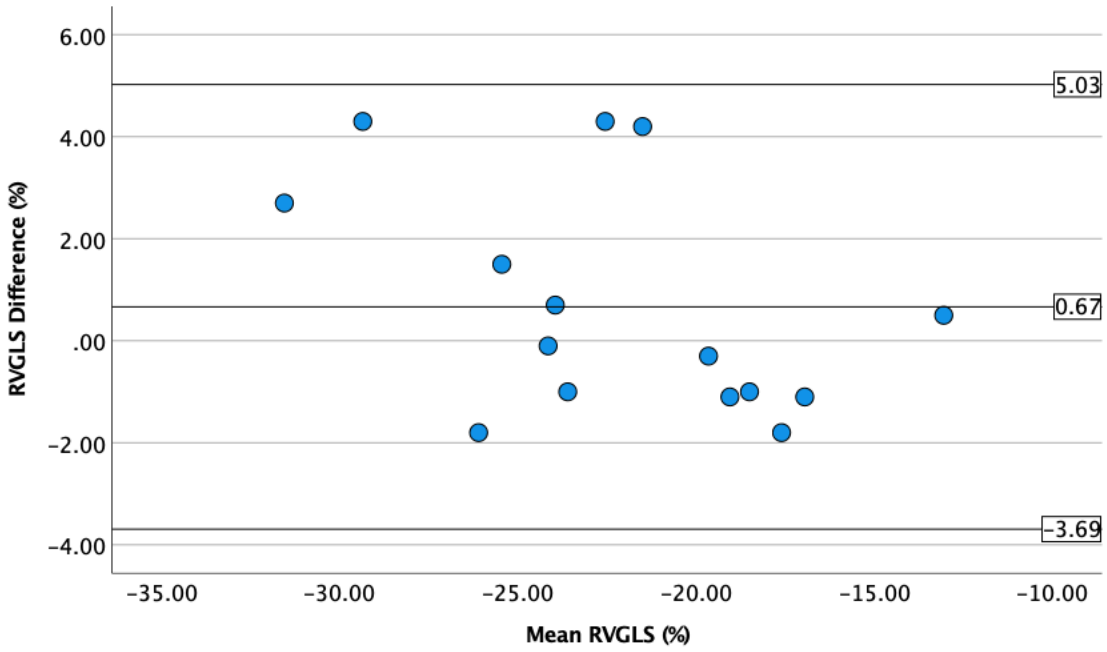
RV = right ventricular, RVFWLS = right ventricular free wall longitudinal strain, RVGLS = right ventricular global longitudinal strain, SD = standard deviation, ICC = intraclass correlation coefficient



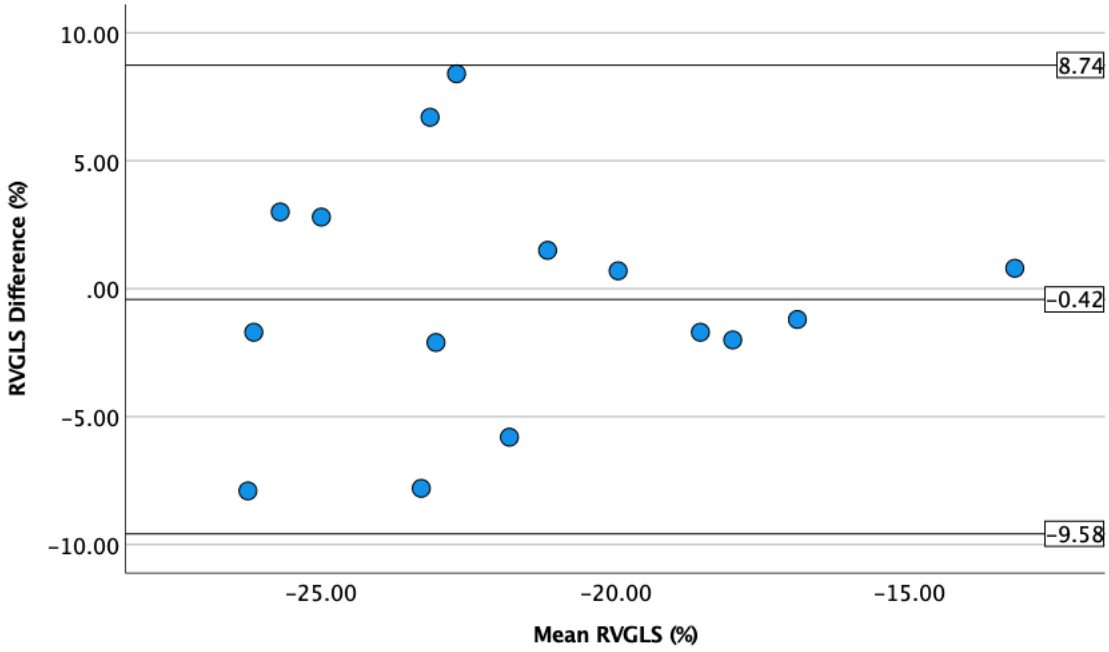
Appendix Figure 1 Bland-Altman RVFWLS intra-observer agreement



Appendix Figure 2 Bland-Altman RVFWLS inter-observer agreement



Appendix Figure 4 Bland-Altman RVGLS intra-observer agreement



Appendix Figure 4 Bland-Altman RVGLS inter-observer agreement

Appendix 4 - IMPRoVE study protocol

Copy of incidence, impact and mechanisms of perioperative right ventricular dysfunction (IMPRoVE) study protocol published in BMJ Open[258]. Reproduced under the CC BY-NC creative commons license.

Open access Protocol

BMJ Open

Study protocol for IMPRoVE: a multicentre prospective observational cohort study of the incidence, impact and mechanisms of perioperative right ventricular dysfunction in non-cardiac surgery

Thomas Keast,[1,2] James McErlane ,[1,2] Rachel Kearns,[1,3] Sonya McKinlay,[3] Indran Raju,[4] Malcolm Watson,[4] Keith E Robertson,[5] Colin Berry,[6] Nicola Greenlaw,[7] Gareth Ackland,[8] Philip McCall,[1,2] Benjamin Shelley [1,2]

To cite: Keast T, McErlane J, Kearns R, *et al*. Study protocol for IMPRoVE: a multicentre prospective observational cohort study of the incidence, impact and mechanisms of perioperative right ventricular dysfunction in non-cardiac surgery. *BMJ Open* 2023;**13**:e074687. doi:10.1136/bmjopen-2023-074687

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-074687).

TK and JM are joint first authors.

Received 13 April 2023
Accepted 21 August 2023

For numbered affiliations see end of article.

Correspondence to
Dr James McErlane;
james.mcerlane@glasgow.ac.uk

ABSTRACT

Introduction Perioperative myocardial injury evidenced by elevated cardiac biomarkers (both natriuretic peptides and troponin) is common after major non-cardiac surgery. However, it is unclear if the rise in cardiac biomarkers represents global or more localised cardiac injury. We have previously shown isolated right ventricular (RV) dysfunction in patients following lung resection surgery, with no change in left ventricular (LV) function. Given that perioperative RV dysfunction (RVD) can manifest insidiously, we hypothesise there may be a substantial burden of covert yet clinically important perioperative RVD in other major non-cardiac surgical groups. The Incidence, impact and Mechanisms of Perioperative Right VEntricular dysfunction (IMPRoVE) study has been designed to address this knowledge gap.

Methods and analysis A multicentre prospective observational cohort study across four centres in the West of Scotland and London. One hundred and seventy-five patients will be recruited from five surgical specialties: thoracic, upper gastrointestinal, vascular, colorectal and orthopaedic surgery (35 patients from each group). All patients will undergo preoperative and postoperative (day 2–4) echocardiography, with contemporaneous cardiac biomarker testing. Ten patients from each surgical specialty (50 patients in total) will undergo T1-cardiovascular magnetic resonance (CMR) imaging preoperatively and postoperatively. The coprimary outcomes are the incidence of perioperative RVD (diagnosed by RV speckle tracking echocardiography) and the effect that RVD has on days alive and at home at 30 days postoperatively. Secondary outcomes include LV dysfunction and clinical outcomes informed by Standardised Endpoints in Perioperative Medicine consensus definitions. T1 CMR will be used to investigate for imaging correlates of myocardial inflammation as a possible mechanism driving perioperative RVD.

Ethics and dissemination Approval was gained from Oxford C Research Ethics Committee (REC reference 22/SC/0442). Findings will be disseminated by various methods including social media, international presentations and publication in peer-reviewed journals.

Trial registration number NCT05827315.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to investigate the incidence of perioperative right ventricular dysfunction (RVD) after major non-cardiac surgery, and the association between RVD and patient outcomes in this group.
⇒ T1-cardiovascular MR substudy to investigate whether inflammation is a mechanism underlying perioperative RVD.
⇒ A large prospective multicentre study with appropriate statistical power analysis.
⇒ It is difficult to predict the incidence of perioperative RVD in surgical groups other than lung resection since there are such limited data.

INTRODUCTION

Perioperative myocardial injury (PMI) is common after major non-cardiac surgery, with a recent large international observational study demonstrating an elevated postoperative high-sensitivity troponin level in 19.7% of patients undergoing major non-cardiac surgery.[1] Perioperative PMI has also been shown to be associated with poor cardiovascular outcomes in patients undergoing non-cardiac surgery.[2] Similarly, natriuretic peptides increase following surgery, and this is associated with an increased risk of cardiovascular complications and mortality.[3] Our group has demonstrated that peak postoperative brain natriuretic peptide is associated with postoperative complications and length of hospital stay after thoracic surgery.[4] Although

an increase in cardiac biomarkers after major non-cardiac is well described, there has been little research to investigate the location of the myocardial injury (although it is frequently attributed to injury of the left ventricle with little evidence to substantiate this assertion). A study in a mixed surgical population requiring 'rescue' echocardiography demonstrated that postoperative right ventricular (RV) dysfunction (RVD) was as prevalent as left ventricular (LV) dysfunction (LVD), occurring in 24.1% of patients.[5] Postoperative RVD is difficult to diagnose, manifesting with subtle clinical signs; it is therefore unsurprising that its importance may have been overlooked.[6] In addition to postoperative RVD, it has been shown that there may be a considerable burden of preoperative RVD in patients undergoing non-cardiac surgery. A study in patients undergoing major vascular surgery found a prevalence of preoperative RVD of 10%, and this was associated with postoperative major cardiac complications.[7] The incidence and significance of perioperative RVD in other non-cardiac surgical populations has been poorly described. We have previously shown that patients undergoing lung resection experience significant impairment of RV function postoperatively with no change in LV function.[8] Further research is needed to investigate the incidence and impact of perioperative RVD on patient outcomes in other non-cardiac surgery groups. Additionally, the mechanisms underlying perioperative RVD require elucidation to allow effective preventative and treatment strategies to be devised. The Incidence, impact and Mechanisms of Perioperative Right VEntricular dysfunction (IMPRoVE) study has been conceived to address this gap in our understanding of perioperative RVD.

Potential mechanisms of perioperative RVD

The mechanisms of postoperative RVD likely reflect a complex interplay between pre-existing RVD, patient susceptibility, surgical risk and a multitude of potential perioperative insults.

As described above,[7] RVD may predate surgery. In the general population, RVD is more prevalent in the elderly, and in people with hypertension, diabetes mellitus, ischaemic heart disease and lung disease[9]; risk factors which are over-represented in the surgical population. As anticipated, in our previous thoracic surgery cohort we found a high prevalence of pre-existing RVD of 50%.[8]

The perioperative period exposes patients to many insults that may contribute to RVD. Excess preload may occur in the form of injudicious intravenous fluid administration, resulting in RV distension and tricuspid regurgitation.[6 10] Impaired contractility may occur due to myocardial ischaemia. RV afterload may increase by many mechanisms, including:

- Pulmonary thromboembolism: Occurring subclinically in up to 28% of patients undergoing elective intermediate to high-risk non-cardiac surgery.[11]
- Lung injury and inflammation: Due to pre-existing lung disease and the combined deleterious effects of ventilator induced lung injury, systemic inflammation and fluid overload.[6]
- Positive-pressure mechanical ventilation: Especially one-lung ventilation (OLV).[6]
- Lung resection: Recently, we have demonstrated the pulsatile component of RV afterload significantly increases after lung resection.[12]

Inflammation and PMI

Although it is widely hypothesised that PMI results predominantly from ischaemia secondary to myocardial oxygen supply/demand imbalance, this hypothesis remains unproven and is challenged by important observations; in excess of 90% of patients with PMI have no ischaemic symptoms to support a diagnosis of myocardial infarction,[1] and the extent and severity of coronary artery disease does not correlate closely with the occurrence of PMI.[13]

The inflammatory response is an important contributor to the myocardial injury seen after myocardial infarction and cardiac surgery, but the extent to which systemic inflammation is involved in the pathogenesis of PMI after non-cardiac surgery is not known. Ackland *et al* recently demonstrated that PMI was associated with an elevated neutrophil-to-lymphocyte ratio, suggesting systemic inflammation may predispose patients to PMI.[14] Using T1-weighted cardiovascular magnetic resonance (T1-CMR) imaging, our group has described the presence of imaging correlates of perioperative RV (but not LV) myocardial inflammation in patients following lung resection.[15]

In summary, with greater understanding of the incidence, impact and underlying mechanisms of perioperative RVD provided through this investigation, preventative interventions targeted at patients at greatest risk may offer a unique therapeutic opportunity to provide a personalised approach to perioperative management and improve patient outcomes across a wide range of surgical populations.

Hypotheses

- RVD after major non-cardiac surgery is a common covert contributor to perioperative morbidity.
- Inflammatory injury to the RV is a significant contributing factor to PMI.

METHODS AND ANALYSIS

Summary: A multicentre prospective observational cohort study in patients undergoing major non-cardiac surgery in five surgical specialties. Main study: 175 patients to undergo transthoracic echocardiography (TTE) preoperatively and postoperatively (figure 1). Substudy: 50 patients to undergo T1-CMR preoperatively and postoperatively.

Centres: Three hospitals in the West of Scotland (Golden Jubilee National Hospital (GJNH), Queen Elizabeth University Hospital and Glasgow Royal Infirmary) and one London hospital (Royal London Hospital).

Keast T, *et al*. *BMJ Open* 2023;**13**:e074687. doi:10.1136/bmjopen-2023-074687

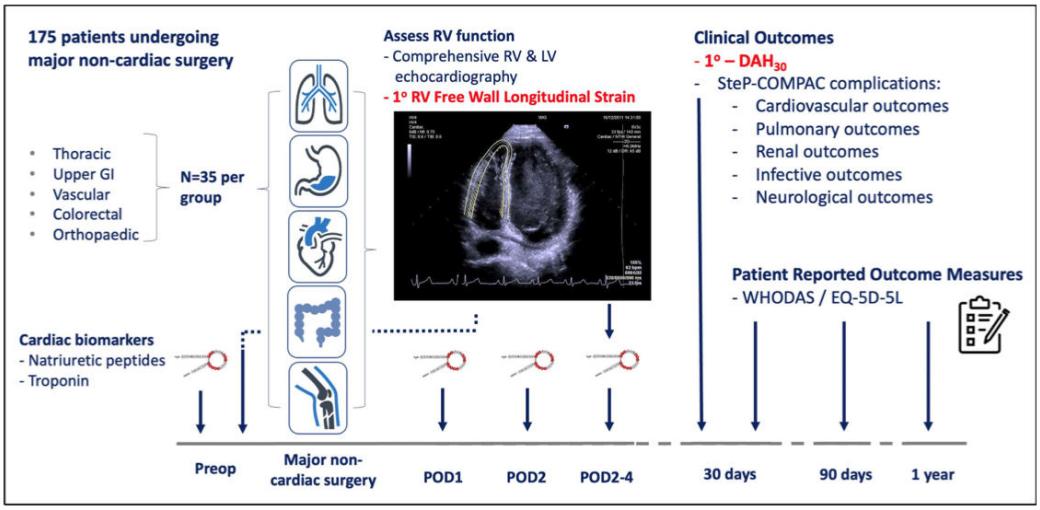


Figure 1 Overview of IMPRoVE Main Study. One hundred and seventy-five patients (35 from each surgical group) will undergo echocardiography and cardiac biomarker testing preoperatively and postoperatively. Coprimary outcomes are the incidence of RV dysfunction, diagnosed by RV free wall longitudinal strain, and DAH_{30} (shown in red). DAH_{30}, days alive and at home at 30 days postoperatively; EQ-5D-5L, EuroQol-5 Dimension-5 Level; GI, gastrointestinal; IMPRoVE, Incidence, impact and Mechanisms of Perioperative Right VEntricular dysfunction; LV, left ventricular; POD, postoperative day; RV, right ventricular; StEP-COMPAC, Standardised Endpoints and Core Outcome Measures for Perioperative and Anaesthetic Care; WHODAS, WHO Disability Assessment Schedule 2.0.

Study status: Grant funding was secured on 12th February 2021, with ethical approval on 12th January 2023 (REC reference 22/SC/0442). Recruitment commenced in May 2023 with an anticipated study duration of 36 months.

Selection of study subjects

Inclusion criteria

- Patient aged >18 years.
- Patient undergoing planned elective primary hip or knee joint replacement under spinal anaesthesia, major colorectal, major vascular surgery or major surgery requiring OLV with or without lung resection.
- Provision of informed consent.

Main study exclusion criteria

- Pregnancy.
- Ongoing participation in any investigational research which could undermine the scientific basis of the study.
- Major surgery within previous 3 months.
- Previous participation in the IMPRoVE study.
- Inadequate comprehension of English resulting in inability to comply with instructions while undergoing interventions required for main study and substudy.

Risk factors for RVD are likely to be over-represented in patients presenting for surgery and participants with pre-existing RVD could represent an important population that may face greater consequences of acute perioperative insults to the RV. For this reason, although not a specific inclusion or exclusion criteria, patients with pre-existing RVD, including when identified on preoperative echocardiography will be included in the study.

T1-CMR substudy exclusion criteria

- Contraindication to T1-CMR (see online supplemental material).
- Atrial fibrillation at baseline.
- Acute or chronic kidney disease.
- Allergy to intravenous contrast.

Study conduct

Recruitment

Patients will be identified from hospital waiting lists. Patients will be informed of the study, offered a patient information sheet and invited to participate at the earliest possible opportunity after they have been informed of their decision for surgery. Following appropriate time to consider participation, informed consent will be obtained by a member of the research team.

Consent

Written informed consent will be obtained, following a face-to-face discussion about the study by a member of the study team. Signing of consent form and preoperative blood sampling and imaging may take place at any time in the 30 days prior to surgery or on the day of surgery.

Table 1 Schedule of assessments for all patients enrolled into IMPRoVE study

Visit window	Preoperative	Day of surgery (day 0)	POD1	POD2	Day of echocardiography (POD 2–4)	Discharge	30 days	3 months	12 months
Informed consent	x								
Inclusion/exclusion criteria	x								
Baseline demographics and risk scoring	x								
BNP/HsTn	x		x	x	x				
NT-proBNP	x								
Immediate perioperative data		x							
Laboratory data	x		x	x	x				
Echocardiography	x				x				
T1-CMR*	x				x				
QoR-15	x				x				
Organ-specific complications (Clavien-Dindo ≥2)			x	x	x	x	x		
Unplanned ICU admission			x	x	x	x			
Length of hospital stay						x			
Length of ICU/HDU stay					x	x			
Mortality					x	x	x	x	x
DAH_{30}							x		
Hospital readmission							x		
EQ-5D-5L	x						x	x	x
WHODAS 2.0	x						x	x	x

*Ten patients from each of the five surgical groups (50 in total).
BNP, brain natriuretic peptide; DAH_{30}, days alive and at home at 30 days; EQ-5D-5L, EuroQol-5 Dimension-5 Level; HDU, high-dependency unit; HsTn, high sensitivity troponin; ICU, intensive care unit; IMPRoVE, Incidence, impact and Mechanisms of Perioperative Right VEntricular dysfunction; NT-proBNP, N-terminal prohormone of BNP; POD, Post operative day; QoR-15, quality of recovery-15 score; T1-CMR, T1 cardiovascular magnetic resonance; WHODAS 2.0, WHO Disability Assessment Schedule 2.0.

Medical management

Medical management will be according to the standard of care at each treating site and is not influenced by this study protocol.

Study interventions

Table 1 shows the general schedule of assessments/study interventions that patients will undergo.

Echocardiography conduct and analysis

TTE will be performed on all 175 patients by a British Society of Echocardiography (BSE) accredited echocardiographers preoperatively and between postoperative days 2 and 4. Echocardiography will acquire the minimum BSE image dataset.[16] In addition to this minimum image dataset, we will acquire an RV focused apical four chamber view for RV free-wall peak longitudinal strain (FWLS) analysis (optimising feasibility as per consensus guidelines).[17 18] All echocardiography study images will be sent centrally for offline analysis: anonymised images will be transferred via routine clinical imaging systems to the GJNH.

A full echocardiography data set will be used to assess for RVD (the primary outcome) and LVD. Offline RV and LV two-dimensional (2D) speckle tracking strain analysis will be performed using Tomtec 2D Cardiac Performance Analysis software. Twenty echocardiography scans will be randomly selected and re-reported by the same reporter a minimum of 2 weeks after initial reporting, and reported by a second reporter, to allow assessment of intraobserver and interobserver agreement. Reproducibility will be assessed by intraclass correlation coefficient using two-way mixed effects with absolute agreement and Bland-Altmann plots.

T1-CMR conduct

A subcohort of 50 patients (10 from each surgical group) will undergo a preoperative T1-CMR scan and a single postoperative scan (between postoperative days 2–4). Replicating our previous protocol,[8] CMR will be undertaken on a 1.5 or 3.0 Tesla scanner, by band 7 Health and Care Professions Council accredited radiographers. T1-weighted scans will be performed preintravenous and postintravenous gadolinium administration.

Postprocessing will be protocolised and dual reported by blinded observers.

Laboratory sampling

Where possible samples will be drawn contemporaneously with routine clinical blood tests. Cardiac biomarkers will be batch analysed at University of Glasgow Laboratories.

DAH_{30} conduct

Days alive and at home at 30 days postoperatively (DAH_{30}) will be assessed by telephone on postoperative day 30 (up to +5 days). A script will be used to ensure that DAH_{30} is reliably and consistently recorded.

Data collection will be performed by the local study team on case report forms (CRFs), which will be filed and securely stored at participating sites. The data will be anonymised at site and a unique numeric study number allocated. Completed CRFs will be entered onto a secure online database in a linked anonymised form. Electronic data will be stored in an encrypted and anonymised format for 15 years following the completion of the trial. At the end of this period, the dataset will be destroyed according to DoD 5220.22-M standards. All data will be held in accordance with the General Data Protection Regulation (2018).

Laboratory data

Laboratory data (full blood count, urea and electrolytes, liver function tests and C reactive protein) will be obtained from the local biochemistry and haematology laboratory reporting systems perioperatively, on the day of echocardiography and if clinically indicated, at follow-up.

Clinical data

Baseline demographic information will be collected including chronic comorbidities. We will specifically gather information on sleep apnoea status and previous COVID-19 infection since these may affect baseline RV function. Preoperative data will include previous pulmonary function tests, cardiopulmonary exercise testing, CT thorax imaging (for coronary artery calcium scoring), American College of Surgeons National Surgical Quality Improvement Programme risk scoring, and baseline questionnaires (Duke Activity Status Index, quality of recovery-15, EuroQol-5 Dimension-5 Level (EQ-5D-5L) and WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)). Immediate perioperative data will include the operation performed, duration of surgery and anaesthesia, duration of OLV (if applicable), and use of vasopressor/inotropic support.

Study outcomes

Coprimary outcomes

Incidence of postoperative RVD

RVD defined as:

- 2D-speckle tracking derived RV free wall longitudinal strain (RVFWLS) less negative than −20%.[17 19]
- (When RVFWLS is not available) two of tricuspid annular plane systolic excursion <16 mm, S' wave velocity at the tricuspid annulus <10 cm/s or tissue doppler RV index of myocardial performance >0.55.[20]

Clinical impact of postoperative RVD

Days alive and at home at 30 days postoperatively (DAH_{30}). DAH_{30} is a continuous number between 0 and 30 which reflects, out of the 30 days following surgery, the total number of those days that a patient spends alive and at home. If a patient dies within those 30 days, their value is set to 0.

Justification for coprimary outcomes

Incidence of postoperative RVD

There is currently no consensus on how best to measure RV function in the context of clinical trials.[21] However, recent work (by our group and others) has demonstrated the superiority and increased reproducibility of RVFWLS in identifying RVD compared with 'conventional indices'.[22–24] A recent American Thoracic Society Research Statement has advocated the use of RVFWLS due to its ability to assess RVD at an early stage and to detect differences when other traditional measurements fail to do so.[21]

Clinical impact of perioperative RV

Days alive and at home at 30 days postoperatively (DAH_{30}) is a novel, well-validated clinical endpoint describing all facets of the perioperative experience and has been recommended as a patient-centred outcome by the Standardising Endpoints in Perioperative (StEP) Medicine initiative. DAH_{30} is sensitive to prolonged stay due to complications, discharge to a rehabilitation or nursing care facility, readmission to hospital after discharge and mortality thus integrating efficacy, quality and safety.[25 26]

Exploratory outcomes

Exploratory outcomes that we will investigate are shown in table 2.

Statistical considerations

All statistical analyses will be performed in conjunction with the Robertson Centre for Biostatistics at the University of Glasgow.

Analysis of coprimary outcomes

Incidence of perioperative RVD

The identified incidence of postoperative RVD will be compared with the null hypothesis that the incidence equals zero using a one-sample binomial test; 95% CIs for the incidence will be defined using the Clopper-Pearson method. In addition, we will perform sensitivity analyses to identify the incidence of patients that develop new postoperative RVD, and identify the incidence of those that have pre-existing RVD maintained through to the postoperative period. Subgroup analyses will estimate the incidence rate of postoperative LVD and RVD within surgical subgroups and compare the incidence in patients with chronic obstructive pulmonary disease (COPD) versus no COPD, in operations involving mechanical

Table 2 Exploratory outcomes

Left ventricular dysfunction	Defined by two-dimensional echocardiography derived biplane ejection fraction
Cardiac biomarkers	NT-proBNP, BNP, hsTn
Clinical outcomes informed by StEP trials consensus definitions:	
Cardiovascular outcomes[27]	Myocardial infarction Myocardial injury Cardiac death Non-fatal cardiac arrest Coronary revascularisation Major adverse cardiac event
Pulmonary outcomes[28]	Pneumonia Atelectasis Acute respiratory distress syndrome Pulmonary aspiration
Renal outcomes[29]	Acute kidney injury Need for renal replacement therapy
Infection outcomes[30]	Fever Clinical suspicion of infection
Neurological outcomes[31]	Delirium Stroke
Major complications	Sequential Organ Failure Assessment Score
Clinical indicators	Need for unplanned HDU or ICU admission Requirement for new invasive or non-invasive ventilation Length of postoperative critical care and hospital stay Mortality at 30 days
Patient quality of recovery	QoR-15
Patient-centred outcomes	EQ-5D-5L WHODAS 2.0 (assessed at 30 days, 3 months and 12 months postoperatively)
T1-CMR	Preoperative and postoperative T1-CMR. T1 weighted CMR preintravenous and postintravenous gadolinium to calculate T1 signal and extracellular volume (imaging correlates of myocardial inflammation)

BNP, brain natriuretic peptide; EQ-5D-5L, EuroQol-5 Dimension-5 Level; HDU, high-dependency unit; HsTn, high sensitivity troponin; ICU, intensive care unit; NT-proBNP, N-terminal prohormone of BNP; QoR-15, quality of recovery-15; StEP, Standardised Endpoints in Perioperative; WHODAS 2.0, WHO Disability Assessment Schedule 2.0.

ventilation and no mechanical ventilation (orthopaedic surgery under spinal anaesthesia), OLV versus no OLV, in videoscopic versus open surgeries, and in patients with ischaemic heart disease (IHD) versus no IHD. Secondary analyses will explore the association between preoperative and postoperative cardiac biomarker levels and perioperative LVD and RVD.

With a one sample binomial test at a one-sided significance level of 5% with 80% power, 31 patients would be required to confidently identify an incidence of postoperative RVD of 5% as different from zero in any individual surgical subgroup. As such, recruiting 35 patients per group provides a 10% margin for lost to follow-up and withdrawals. This results in a total sample size of 175.

Clinical impact of perioperative RVD

Assuming the incidence of RVD is proven to be different from zero in any group (highly likely given our previous findings[8]), then additional analyses will be performed in pooled data across all surgical groups to assess the clinical impact of postoperative LVD or RVD. Sensitivity analyses will be performed to assess the clinical impact of RVD on patients that develop new postoperative RVD, compared with the clinical impact of pre-existing RVD, which is maintained through to the postoperative period.

DAH_{30} postoperatively will be compared between the groups with and without postoperative RVD using negative binomial regression analysis adjusting for age and other known predictors of DAH_{30}.[25 26] It will also be explored how adjustment for further variables (including cardiac biomarker profile) affects results. We will conduct the same DAH_{30} analysis on the sensitivity analysis groups described above.

Performing power analysis for this comparison is challenging given the large number of unknowns in terms of the incidence of RVD, and the potential effect size. As such, an indicative power analysis was performed exploring sample sizes from 50 to 200 patients, an incidence of RVD 15%–50% and for a difference in DAH_{30} of 2 or 3 days. The anticipated power is in excess of 0.8 in all simulations containing over 125 patients suggesting that in the 175-patient sample should have sufficient power in most conceivable scenarios (figure 2).

Exploratory outcomes

LVD will be analysed analogously to RVD as a secondary analysis.

Secondary outcomes from the postoperative period will be used to compare their incidence in patients with and without the primary outcome (RVD). We will assess for association between RVD and PMI (via cardiac biomarkers), cardiovascular complications, major complications, patient recovery, length of intensive care unit and hospital stay. Analysis of intraoperative data will be used with the aim to identify mechanisms by which RVD may have arisen. Where appropriate, multivariate analysis will be used.

We will use 30-day mortality as our primary survival end point and will assess for association with RVD via appropriate survival analyses.

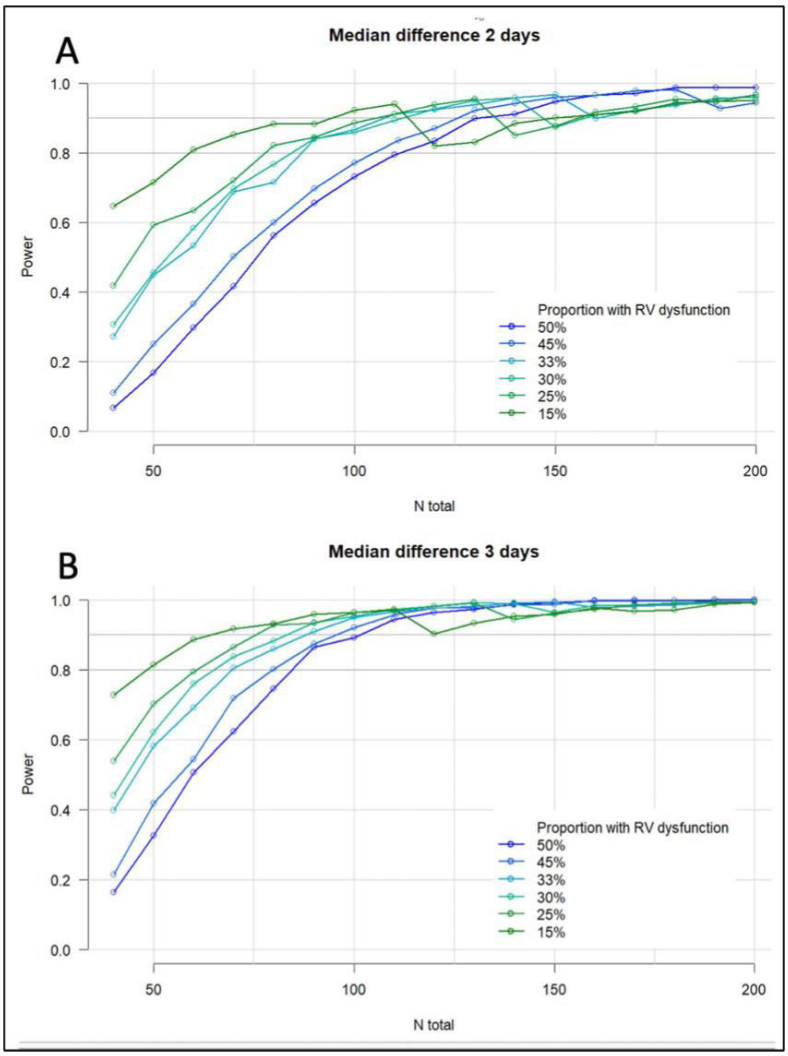


Figure 2 Simulated power analysis for impact of RVD on days alive and at home at 30 days. Assuming for 1% of the patients DAH_{30}=0, for the remainder DAH_{30} follows a negative binomial distribution with parameters chosen such that the median DAH_{30} is 24/25 in one group and 27 in the other group and the shape of the distribution is similar to that seen in the validation cohorts. The simulated DAH_{30} was then compared between groups using negative binomial regression (repeated) in 1000 samples. The figures show the resulting estimated power for incidences of postoperative RVD from 15% to 50%[#], and for a clinical effect size of 2 (A) or 3 (B) days difference in DAH_{30}*. [#]In our previous work the incidence of postoperative RVD was 50% in thoracic surgical patients but may be significantly less in, for example, an orthopaedic population. *In Chou *et al*'s study preoperative RV dysfunction prolonged hospital length of stay by over 50%, but this cohort was a very high-risk vascular surgical population.[7] DAH_{30}, days alive and at home at 30 days postoperatively; RVD, right ventricular dysfunction.

We will also assess the intermediate-term and long-term impact of RVD on patients by assessing association between RVD and health-related quality of life (via EQ-5D-5L) and functional status (via WHODAS 2.0) at 30-day, 3-month and 1-year postoperatively.

Preoperative and postoperative T1-CMR will explore for association between imaging correlates of myocardial inflammation (T1 and extracellular volume) and both RVD and PMI. This substudy will also aim to confirm our previous findings of elevated

postoperative T1/extracellular volume in patients after thoracic surgery,[15] and replicate this in other surgical groups.

Patient and public involvement

Our programme of work was presented to the Society of Cardiothoracic Surgeons 'RESOLVES' Patient and Public Involvement (PPI) group with very positive feedback. This PPI group was unanimously in favour of our research and its obvious benefits to patients.

Ethics and dissemination

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the Good Clinical Practice Guidelines. UK wide ethical approval was obtained from the South Central- Oxford C Research Ethics Committee (REC reference 22/SC/0442) and will comply with all applicable UK legislation. Local research and development approval was obtained from each participating site. All local site Standardised Operating Procedures (SOPs) will be followed.

All publications and presentations relating to this study will be authorised by the trial chief investigator (BS). Authorship will be determined according to the international committee of medical journal editors' recommendations. The results of the study will be first reported to study collaborators. Subsequently, we will communicate our results by reporting them to the funder and presentation at national meetings, with publication in appropriate peer-reviewed journals. Further details about the trial results and final report will be available on request to the scientific community in a timely manner.

Author affiliations
[1]Anaesthesia, Critical Care & Peri-operative Medicine Research Group, University of Glasgow, Glasgow, UK
[2]Department of Anaesthesia, Golden National Jubilee Hospital, Clydebank, UK
[3]Department of Anaesthesia, Glasgow Royal Infirmary, Glasgow, UK
[4]Department of Anaesthesia and Critical Care, Queen Elizabeth University Hospital, Glasgow, UK
[5]Golden Jubilee National Hospital West of Scotland Regional Heart and Lung Centre, Clydebank, UK
[6]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[7]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK
[8]Department of Anaesthesia and Perioperative Medicine, Barts Health NHS Trust, Royal London Hospital, London, UK

Twitter Philip McCall @philipmccall

Contributors All authors contributed significantly to the submitted work. TK and JM wrote the initial draft of the protocol. BS and PM conceived the study and BS is the grant holder. CB contributed to study design and initial funding application. RK and SM are co-principal investigators at Glasgow Royal Infirmary and contributed to study design. MW is principal investigator and IR co-investigator at the Queen Elizabeth University Hospital, both contributed to study design. GA is coinvestigator at the Royal London Hospital and contributed to study design. KER is a coinvestigator and lead interventional cardiologist for the study and was involved in study design. NG advised on statistical analyses for the study. All authors read and approved the final manuscript.

Funding This study is supported by the National Institute of Academic Anaesthesia/Royal College of Anaesthetists British Oxygen Company Chair of Anaesthesia Research Grant. CB is supported by the BHF Centre of Research Excellence grant (reference number RE/18/6/34217). GA is supported by the NIHR Advanced Fellowship (NIHR300097).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
James McErlane http://orcid.org/0000-0002-0490-8425
Benjamin Shelley http://orcid.org/0000-0001-6771-9659

REFERENCES

1 Writing Committee for the VISION Study Investigators, Devereaux PJ, Biccard BM, *et al*. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2017;317:1642.
2 Puelacher C, Gualandro DM, Glarner N, *et al*. Long-term outcomes of perioperative myocardial infarction/injury after non-cardiac surgery. *Eur Heart J* 2023;44:1690–701.
3 Rodseth RN, Biccard BM, Chu R, *et al*. Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: systematic review and individual patient meta-analysis. *Anesthesiology* 2013;119:270–83.
4 Lafferty B, McCall P, Shelley B. BNP for prediction of outcome following lung resection surgery (PROFILES); an interim analysis. *J Cardiothorac Vasc Anesth* 2020;34:S6–7.
5 Markin NW, Gmelch BS, Griffee MJ, *et al*. A review of 364 perioperative rescue echocardiograms: findings of an anesthesiologist-staffed perioperative echocardiography service. *J Cardiothorac Vasc Anesth* 2015;29:82–8.
6 Murphy E, Shelley B. Clinical presentation and management of right ventricular dysfunction. *BJA Educ* 2019;19:183–90.
7 Chou J, Ma M, Gylys M, *et al*. Preexisting right ventricular dysfunction is associated with higher postoperative cardiac complications and longer hospital stay in high-risk patients undergoing nonemergent major vascular surgery. *J Cardiothorac Vasc Anesth* 2019;33:1279–86.
8 McCall PJ, Arthur A, Glass A, *et al*. The right ventricular response to lung resection. *J Thorac Cardiovasc Surg* 2019;158:556–65.
9 Modin D, Møgelvang R, Andersen DM, *et al*. Right ventricular function evaluated by tricuspid annular plane systolic excursion predicts cardiovascular death in the general population. *J Am Heart Assoc* 2019;8:e012197.
10 Murphy E, Shelley B. The right ventricle-structural and functional importance for anaesthesia and intensive care. *BJA Educ* 2018;18:239–45.
11 Grobben RB, van Waes JAR, Leiner T, *et al*. Unexpected cardiac computed tomography findings in patients with postoperative myocardial injury. *Anesth Analg* 2018;126:1462–8.
12 Glass A, McCall P, Arthur A, *et al*. Pulmonary artery wave reflection and right ventricular function after lung resection. *Br J Anaesth* 2023;130:e128–36.
13 Sheth T, Chan M, Butler C, *et al*. Prognostic capabilities of coronary computed tomographic angiography before non-cardiac surgery: prospective cohort study. *BMJ* 2015;350:h1907.

14 Ackland GL, Abbott TEF, Cain D, *et al*. Preoperative systemic inflammation and perioperative myocardial injury: prospective observational multicentre cohort study of patients undergoing non-cardiac surgery. *Br J Anaesth* 2019;122:180–7.
15 Murphy E, Glass A, McCall P, *et al*. Myocardial inflammation after major non-cardiac thoracic surgery. *Br J Anaesth* 2021;126:e80–1.
16 Robinson S, Rana B, Oxborough D, *et al*. A practical guideline for performing a comprehensive transthoracic echocardiogram in adults: the British society of echocardiography minimum dataset. *Echo Res Pract* 2020;7:G59–93.
17 Lang RM, Badano LP, Mor-Avi V, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr* 2015;28:1–39.
18 Zaidi A, Oxborough D, Augustine DX, *et al*. Echocardiographic assessment of the tricuspid and pulmonary valves: a practical guideline from the British society of echocardiography. *Echo Res Pract* 2020;7:G95–122.
19 Addetia K, Miyoshi T, Citro R, *et al*. Two-dimensional echocardiographic right ventricular size and systolic function measurements stratified by sex, age, and ethnicity: results of the world alliance of societies of echocardiography study. *J Am Soc Echocardiogr* 2021;34:1148–57.
20 Rudski LG, Lai WW, Afilalo J, *et al*. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American society of echocardiography endorsed by the European association of echocardiography, a registered branch of the European society of cardiology, and the Canadian society of echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713;
21 Lahm T, Douglas IS, Archer SL, *et al*. Assessment of right ventricular function in the research setting: knowledge gaps and pathways forward. an official American thoracic society research statement. *Am J Respir Crit Care Med* 2018;198:e15–43.
22 Focardi M, Cameli M, Carbone SF, *et al*. Traditional and innovative echocardiographic parameters for the analysis of right ventricular performance in comparison with cardiac magnetic resonance. *Eur Heart J Cardiovasc Imaging* 2015;16:47–52.
23 McCall P, Soosay A, Kinsella J, *et al*. The utility of transthoracic echocardiographic measures of right ventricular systolic function in a lung resection cohort. *Echo Res Pract* 2019;6:7–15.
24 Lang RM, Badano LP, Mor-Avi V, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233–70.
25 Myles PS, Shulman MA, Heritier S, *et al*. Validation of days at home as an outcome measure after surgery: a prospective cohort study in Australia. *BMJ Open* 2017;7:e015828.
26 Jerath A, Austin PC, Wijeysundera DN. Days alive and out of hospital: validation of a patient-centered outcome for perioperative medicine. *Anesthesiology* 2019;131:84–93.
27 Beattie WS, Lalu M, Bocock M, *et al*. Systematic review and consensus definitions for the standardized endpoints in perioperative medicine (step) initiative: cardiovascular outcomes. *Br J Anaesth* 2021;126:56–66.
28 Abbott TEF, Fowler AJ, Pelosi P, *et al*. A systematic review and consensus definitions for standardised end-points in perioperative medicine: pulmonary complications. *Br J Anaesth* 2018;120:1066–79.
29 McIlroy DR, Bellomo R, Billings FT, *et al*. Systematic review and consensus definitions for the standardised endpoints in perioperative medicine (step) initiative: renal endpoints. *Br J Anaesth* 2018;121:1013–24.
30 Barnes J, Hunter J, Harris S, *et al*. Systematic review and consensus definitions for the standardised endpoints in perioperative medicine (step) initiative: infection and sepsis. *Br J Anaesth* 2019;122:500–8.
31 Haller G, Bampoe S, Cook T, *et al*. Systematic review and consensus definitions for the standardised endpoints in perioperative medicine initiative: clinical indicators. *Br J Anaesth* 2019;123:228–37.

List of References

1. Shelley B, McAreavey R, McCall P. Epidemiology of perioperative RV dysfunction: risk factors, incidence, and clinical implications. *Perioperative medicine (London, England)* 2024; **13**(1).
2. Grignola JC, E D. Acute Right Ventricular Dysfunction in Intensive Care Unit. *BioMed research international* 2017; **2017**.
3. Wanner PM, Filipovic M. The Right Ventricle-You May Forget it, but It Will Not Forget You. *Journal of clinical medicine* 2020; **9**(2).
4. Bleeker GB, Steendijk P, Holman ER, et al. Assessing right ventricular function: the role of echocardiography and complementary technologies. *Heart (British Cardiac Society)* 2006; **92 Suppl 1**(Suppl 1).
5. Murphy E, Shelley B. Clinical presentation and management of right ventricular dysfunction. *British Journal of Anaesthesia Education* 2019; **19**(6).
6. Ventetuolo CE, Klinger JR. Management of acute right ventricular failure in the intensive care unit. *Annals of the American Thoracic Society* 2014; **11**(5).
7. Subramani S, Sharma A, Arora L, Hanada S, Krishnan S, Ramakrishna H. Perioperative Right Ventricular Dysfunction: Analysis of Outcomes. *Journal of cardiothoracic and vascular anesthesia* 2022; **36**(1).
8. Vos M, Cox E, Schagen M, et al. Right ventricular strain measurements in critically ill patients: an observational SICS sub-study. *Annals of intensive care* 2022; **12**(1).
9. Hiraiwa H, Kasugai D, Ozaki M, et al. Clinical impact of visually assessed right ventricular dysfunction in patients with septic shock. *Scientific reports* 2021; **11**(1).
10. Zhang H, Huang W, Zhang Q, Chen X, Wang X, Liu D. Prevalence and prognostic value of various types of right ventricular dysfunction in mechanically ventilated septic patients. *Annals of intensive care* 2021; **11**(1).
11. ten Wolde M, Söhne M, Quak E, Mac Gillavry MR, Büller HR. Prognostic value of echocardiographically assessed right ventricular dysfunction in patients with pulmonary embolism. *Archives of internal medicine* 2004; **164**(15).
12. Sato R, Dugar S, Cheungpasitporn W, et al. The impact of right ventricular injury on the mortality in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Critical care (London, England)* 2021; **25**(1).
13. Zochios V, Parhar K, Tunnicliffe W, Roscoe A, Gao F. The Right Ventricle in ARDS. *Chest* 2017; **152**(1).
14. McCall PJ, Willder JM, Stanley BL, et al. Right ventricular dysfunction in patients with COVID-19 pneumonitis whose lungs are mechanically ventilated: a multicentre prospective cohort study. *Anaesthesia* 2022; **77**(7).
15. Bleakley C, Singh S, Garfield B, et al. Right ventricular dysfunction in critically ill COVID-19 ARDS. *International Journal of Cardiology* 2021; **327**.
16. Li Y, Li H, Zhu S, et al. Prognostic Value of Right Ventricular Longitudinal Strain in Patients With COVID-19. *Journals of the American College of Cardiology: Cardiovascular Imaging* 2020; **13**(11).
17. Bauchmuller K, Condliffe R, Southern J, et al. Critical care outcomes in patients with pre-existing pulmonary hypertension: insights from the ASPIRE registry. *ERJ open research* 2021; **7**(2).
18. Huynh TN, Weigt SS, Sugar CA, Shapiro S, Kleerup EC. Prognostic factors and outcomes of patients with pulmonary hypertension admitted to the intensive care unit. *Journal of critical care* 2012; **27**(6).
19. Mitaka C, Nagura T, Sakanishi N, Tsunoda Y, Amaha K. Two-dimensional echocardiographic evaluation of inferior vena cava, right ventricle, and left

ventricle during positive-pressure ventilation with varying levels of positive end-expiratory pressure. *Critical care medicine* 1989; **17**(3).
20. Schulman DS, Biondi JW, Matthay RA, Barash PG, Zaret BL, Soufer R. Effect of positive end-expiratory pressure on right ventricular performance. Importance of baseline right ventricular function. *The American journal of medicine* 1988; **84**(1).
21. D'Andrea A, Martone F, Liccardo B, et al. Acute and Chronic Effects of Noninvasive Ventilation on Left and Right Myocardial Function in Patients with Obstructive Sleep Apnea Syndrome: A Speckle Tracking Echocardiographic Study. *Echocardiography (Mount Kisco, NY)* 2016; **33**(8).
22. Murphy E, Shelley B. The right ventricle-structural and functional importance for anaesthesia and intensive care. *BJA education* 2018; **18**(8).
23. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Critical care (London, England)* 2010; **14**(5).
24. Vieillard-Baron A, Prigent A, Repessé X, et al. Right ventricular failure in septic shock: characterization, incidence and impact on fluid responsiveness. *Critical care (London, England)* 2020; **24**(1).
25. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Critical care medicine* 2011; **39**(2).
26. Beattie WS, Lalu M, Bocock M, et al. Systematic review and consensus definitions for the Standardized Endpoints in Perioperative Medicine (StEP) initiative: cardiovascular outcomes. *British journal of anaesthesia* 2021; **126**(1).
27. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. *JAMA* 2017; **317**(16).
28. Ruetzler K, Smilowitz NR, Berger JS, et al. Diagnosis and Management of Patients With Myocardial Injury After Noncardiac Surgery: A Scientific Statement From the American Heart Association. *Circulation* 2021; **144**(19).
29. Devereaux PJ, Szczeklik W. Myocardial injury after non-cardiac surgery: diagnosis and management. *European heart journal* 2020; **41**(32).
30. Chou J, Ma M, Gylys M, et al. Preexisting Right Ventricular Dysfunction Is Associated With Higher Postoperative Cardiac Complications and Longer Hospital Stay in High-Risk Patients Undergoing Nonemergent Major Vascular Surgery. *Journal of cardiothoracic and vascular anesthesia* 2019; **33**(5).
31. Chou J, Ma M, Gylys M, et al. Preexisting right ventricular systolic dysfunction in high-risk patients undergoing non.emergent open abdominal surgery: A retrospective cohort study. *Annals of cardiac anaesthesia* 2021; **24**(1).
32. Markin NW, Gmelch BS, Griffee MJ, Holmberg TJ, Morgan DE, Zimmerman JM. A review of 364 perioperative rescue echocardiograms: findings of an anesthesiologist-staffed perioperative echocardiography service. *Journal of cardiothoracic and vascular anesthesia* 2015; **29**(1).
33. Reed C, Spinale F, Crawford F. Effect of pulmonary resection on right ventricular function. *The Annals of thoracic surgery* 1992; **53**(4).
34. McCall PJ, Arthur A, Glass A, et al. The right ventricular response to lung resection. *The Journal of thoracic and cardiovascular surgery* 2019; **158**(2).
35. Urban M, Sheppard R, Gordon M, Urquhart B. Right ventricular function during revision total hip arthroplasty. *Anesthesia and analgesia* 1996; **82**(6).
36. Kozian A, Schilling T, Fredén F, et al. One-lung ventilation induces hyperperfusion and alveolar damage in the ventilated lung: an experimental study. *British journal of anaesthesia* 2008; **100**(4).

37. Corp A, Thomas C, Adlam M. The cardiovascular effects of positive pressure ventilation. *BJA education* 2021; **21**(6).
38. Elliott CG. Pulmonary physiology during pulmonary embolism. *Chest* 1992; **101**(4 Suppl).
39. Grobben RB, van Waes JAR, Leiner T, et al. Unexpected Cardiac Computed Tomography Findings in Patients With Postoperative Myocardial Injury. *Anesthesia and analgesia* 2018; **126**(5).
40. Murphy E, Glass A, McCall P, B S. Myocardial inflammation after major non-cardiac thoracic surgery. *British Journal of Anaesthesia* 2021; **126(2); E80-1.**
41. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation* 2008; **117**(11).
42. Grocott MP, Browne JP, Van der Meulen J, et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *Journal of clinical epidemiology* 2007; **60**(9).
43. Wang J, Rai R, Carrasco M, et al. An anatomical review of the right ventricle. *Translational Research in Anatomy* 2019; **17**.
44. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. 2nd ed: Cambridge University Press; 2019.
45. Farrer-Brown G. Vascular pattern of myocardium of right ventricle of human heart. *British heart journal* 1968; **30**(5).
46. Sanz J, Sánchez-Quintana D, Bossone E, Bogaard HJ, Naeije R. Anatomy, Function, and Dysfunction of the Right Ventricle: JACC State-of-the-Art Review. *Journal of the American College of Cardiology* 2019; **73**(12).
47. Buckberg G, Hoffman JI. Right ventricular architecture responsible for mechanical performance: unifying role of ventricular septum. *The Journal of thoracic and cardiovascular surgery* 2014; **148**(6).
48. Trip P, Westerhof N, Noordegraaf AV. Function of the Right Ventricle. In: Gaine, S., Naeije, R., Peacock, A. (eds). The Right Heart. : Springer; 2014.
49. Madamanchi A. Beta-adrenergic receptor signaling in cardiac function and heart failure. *McGill journal of medicine : MJM : an international forum for the advancement of medical sciences by students* 2007; **10**(2).
50. Klabunde R. Cardiovascular physiology concepts: Lippincott Williams & Wilkins; 2011.
51. Haddad F, Vrtovec B, Ashley EA, Deschamps A, Haddad H, Denault AY. The concept of ventricular reserve in heart failure and pulmonary hypertension: an old metric that brings us one step closer in our quest for prediction. *Current opinion in cardiology* 2011; **26**(2).
52. Brener MI, Masoumi A, Ng VG, et al. Invasive Right Ventricular Pressure-Volume Analysis: Basic Principles, Clinical Applications, and Practical Recommendations. *Circulation Heart failure* 2022; **15**(1).
53. Vonk Noordegraaf A, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. *The European respiratory journal* 2019; **53**(1).
54. Lahm T, Douglas IS, Archer SL, et al. Assessment of Right Ventricular Function in the Research Setting: Knowledge Gaps and Pathways Forward. An Official American Thoracic Society Research Statement. *American journal of respiratory and critical care medicine* 2018; **198**(4).
55. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The Relationship Between the Right Ventricle and its Load in Pulmonary Hypertension. *Journal of the American College of Cardiology* 2017; **69**(2).
56. Hein M, Roehl AB, Baumert JH, Rossaint R, Steendijk P. Continuous right ventricular volumetry by fast-response thermodilution during right ventricular

ischemia: head-to-head comparison with conductance catheter measurements. *Critical care medicine* 2009; **37**(11).
57. Swan HJ, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *The New England journal of medicine* 1970; **283**(9).
58. Chatterjee K. The Swan-Ganz catheters: past, present, and future. A viewpoint. *Circulation* 2009; **119**(1).
59. Hadian M, Pinsky MR. Evidence-based review of the use of the pulmonary artery catheter: impact data and complications. *Critical care (London, England)* 2006; **10 Suppl 3**(Suppl 3).
60. Robin E, Costecalde M, Lebuffe G, Vallet B. Clinical relevance of data from the pulmonary artery catheter. *Critical care (London, England)* 2006; **10 Suppl 3**(Suppl 3).
61. Surkova E, Cosyns B, Gerber B, Gimelli A, La Gerche A, Ajmone Marsan N. The dysfunctional right ventricle: the importance of multi-modality imaging. *European heart journal Cardiovascular Imaging* 2022; **23**(7).
62. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2015; **28**(1).
63. Torlasco C, Castelletti S, Soranna D, et al. Effective Study: Development and Application of a Question-Driven, Time-Effective Cardiac Magnetic Resonance Scanning Protocol. *Journal of the American Heart Association* 2022; **11**(1).
64. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2010; **23**(7).
65. Zaidi A, Knight DS, Augustine DX, et al. Echocardiographic assessment of the right heart in adults: a practical guideline from the British Society of Echocardiography. *Echo research and practice* 2020; **7**(1).
66. Morcos P, Vick GW, Sahn DJ, Jerosch-Herold M, Shurman A, Sheehan FH. Correlation of right ventricular ejection fraction and tricuspid annular plane systolic excursion in tetralogy of Fallot by magnetic resonance imaging. *The international journal of cardiovascular imaging* 2009; **25**(3).
67. Mertens LL, Friedberg MK. Imaging the right ventricle--current state of the art. *Nature reviews Cardiology* 2010; **7**(10).
68. Augustine DX, Coates-Bradshaw LD, Willis J, et al. Echocardiographic assessment of pulmonary hypertension: a guideline protocol from the British Society of Echocardiography. *Echo research and practice* 2018; **5**(3).
69. Glass A, McCall P, Arthur A, Mangion K, B S. Pulmonary artery wave reflection and right ventricular function after lung resection. *British journal of anaesthesia* 2022.
70. Leong DP, Grover S, Molaee P, et al. Nonvolumetric echocardiographic indices of right ventricular systolic function: validation with cardiovascular magnetic resonance and relationship with functional capacity. *Echocardiography (Mount Kisco, NY)* 2012; **29**(4).
71. Lu KJ, Chen JX, Profitis K, et al. Right ventricular global longitudinal strain is an independent predictor of right ventricular function: a multimodality study of

cardiac magnetic resonance imaging, real time three-dimensional echocardiography and speckle tracking echocardiography. *Echocardiography (Mount Kisco, NY)* 2015; **32**(6).
72. Focardi M, Cameli M, Carbone SF, et al. Traditional and innovative echocardiographic parameters for the analysis of right ventricular performance in comparison with cardiac magnetic resonance. *European heart journal Cardiovascular Imaging* 2015; **16**(1).
73. Pavlicek M, Wahl A, Rutz T, et al. Right ventricular systolic function assessment: rank of echocardiographic methods vs. cardiac magnetic resonance imaging. *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology* 2011; **12**(11).
74. McCall P, Soosay A, Kinsella J, Sonecki P, Shelley B. The utility of transthoracic echocardiographic measures of right ventricular systolic function in a lung resection cohort. *Echo research and practice* 2019; **6**(1).
75. Hosmer DW, Lemeshow S. Applied Logistic Regression. 2nd ed. New York: John Wiley and Sons; 2000.
76. Orde S, Huang SJ, McLean AS. Speckle tracking echocardiography in the critically ill: enticing research with minimal clinical practicality or the answer to non-invasive cardiac assessment? *Anaesthesia and intensive care* 2016; **44**(5).
77. Blessberger H, Binder T. Two dimensional speckle tracking echocardiography: basic principles. *Heart (British Cardiac Society)* 2010; **96**(9).
78. Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. *Circulation* 2000; **102**(10).
79. Leitman M, Lysyansky P, Sidenko S, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2004; **17**(10).
80. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2004; **17**(6).
81. Hoit BD. Strain and strain rate echocardiography and coronary artery disease. *Circulation Cardiovascular imaging* 2011; **4**(2).
82. Sjøli B, Ørn S, Grenne B, Ihlen H, Edvardsen T, Brunvand H. Diagnostic capability and reproducibility of strain by Doppler and by speckle tracking in patients with acute myocardial infarction. *JACC Cardiovascular imaging* 2009; **2**(1).
83. Houghton A. Making Sense of Echocardiography : A Hands-on Guide. 2nd ed: CRC Press; 2014.
84. Johnson C, Kuyt K, Oxborough D, Stout M. Practical tips and tricks in measuring strain, strain rate and twist for the left and right ventricles. *Echo research and practice* 2019; **6**(3).
85. Badano L, Kolias T, Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *European heart journal Cardiovascular Imaging* 2018; **19**(6).
86. Fine NM, Shah AA, Han IY, et al. Left and right ventricular strain and strain rate measurement in normal adults using velocity vector imaging: an assessment of reference values and intersystem agreement. *The international journal of cardiovascular imaging* 2013; **29**(3).

87. Chia EM, Hsieh CH, Boyd A, et al. Effects of age and gender on right ventricular systolic and diastolic function using two-dimensional speckle-tracking strain. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2014; **27**(10).
88. Muraru D, Onciul S, Peluso D, et al. Sex- and Method-Specific Reference Values for Right Ventricular Strain by 2-Dimensional Speckle-Tracking Echocardiography. *Circulation Cardiovascular imaging* 2016; **9**(2).
89. Wang TKM, Grimm RA, Rodriguez LL, Collier P, Griffin BP, Popović ZB. Defining the reference range for right ventricular systolic strain by echocardiography in healthy subjects: A meta-analysis. *PloS one* 2021; **16**(8).
90. Antoni ML, Scherptong RW, Atary JZ, et al. Prognostic value of right ventricular function in patients after acute myocardial infarction treated with primary percutaneous coronary intervention. *Circulation Cardiovascular imaging* 2010; **3**(3).
91. Guendouz S, Rappeneau S, Nahum J, et al. Prognostic significance and normal values of 2D strain to assess right ventricular systolic function in chronic heart failure. *Circulation journal : official journal of the Japanese Circulation Society* 2012; **76**(1).
92. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *European heart journal Cardiovascular Imaging* 2015; **16**(1).
93. Farsalinos KE, Daraban AM, Ünlü S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2015; **28**(10).
94. Chamberlain R, Shiino K, Scalia GM, Sabapathy S, Chan J. Advantage and validation of vendor-independent software for myocardial strain analysis compared to vendor-specific software. *Australasian journal of ultrasound in medicine* 2020; **24**(1).
95. Il'Giovine ZJ, Mulder H, Chiswell K, et al. Right Ventricular Longitudinal Strain Reproducibility Using Vendor-Dependent and Vendor-Independent Software. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2018; **31**(6).
96. Roediger V. AutoStrain LV/RV/LA – automated strain measurements. Philips Ultrasound Whitepaper ed: Philips; 2019.
97. Peng GJ, Luo SY, Zhong XF, et al. Feasibility and reproducibility of semi-automated longitudinal strain analysis: a comparative study with conventional manual strain analysis. *Cardiovascular ultrasound* 2023; **21**(1).
98. Sirico D, Spigariol G, Mahmoud HT, et al. Acute Changes in Right Ventricular Function in Pediatric Patients with Pulmonary Valve Stenosis Undergoing Percutaneous Valvuloplasty: A Speckle-Tracking Study. *Journal of clinical medicine* 2023; **12**(13).
99. Li Y, Sun C, Zhang L, et al. Feasibility, Reproducibility, and Prognostic Value of Fully Automated Measurement of Right Ventricular Longitudinal Strain. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2022; **35**(6).
100. Chamberlain R, Scalia GM, Wee Y, et al. The Learning Curve for Competency in Right Ventricular Longitudinal Strain Analysis. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2020; **33**(4).

101. Chan J, Shiino K, Obonyo NG, et al. Left Ventricular Global Strain Analysis by Two-Dimensional Speckle-Tracking Echocardiography: The Learning Curve. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2017; **30**(11).
102. Nagata Y, Kado Y, Onoue T, et al. Impact of image quality on reliability of the measurements of left ventricular systolic function and global longitudinal strain in 2D echocardiography. *Echo research and practice* 2018; **5**(1).
103. Wilke L, Abellan Schneyder FE, Roskopf M, Jenke AC, Heusch A, Hensel KO. Speckle tracking stress echocardiography in children: interobserver and intraobserver reproducibility and the impact of echocardiographic image quality. *Scientific reports* 2018; **8**(1).
104. Muraru D, Niero A, Rodriguez-Zanella H, Cherata D, Badano L. Three-dimensional speckle-tracking echocardiography: benefits and limitations of integrating myocardial mechanics with three-dimensional imaging. *Cardiovascular diagnosis and therapy* 2018; **8**(1).
105. Li Y, Wan X, Xiao Q, et al. Value of 3D Versus 2D Speckle-Tracking Echocardiography for RV Strain Measurement: Validation With Cardiac Magnetic Resonance. *JACC Cardiovascular imaging* 2020; **13**(9).
106. Chetan IM, Gergely-Domokos B, Beyer R, et al. The role of 3D speckle tracking echocardiography in the diagnosis of obstructive sleep apnea and its severity. *Scientific reports* 2022; **12**(1).
107. Prabhu MR, George A. Transesophageal Monitoring in Anaesthesia: An Update. *Curr Anesthesiol Rep* 2014; **4**: 261–73
108. Tousignant C, Desmet M, Bowry R, Harrington AM, Cruz JD, Mazer CD. Speckle tracking for the intraoperative assessment of right ventricular function: a feasibility study. *Journal of cardiothoracic and vascular anesthesia* 2010; **24**(2).
109. Kurt M, Tanboga IH, Isik T, et al. Comparison of transthoracic and transesophageal 2-dimensional speckle tracking echocardiography. *Journal of cardiothoracic and vascular anesthesia* 2012; **26**(1).
110. Addetia K, Miyoshi T, Citro R, et al. Two-Dimensional Echocardiographic Right Ventricular Size and Systolic Function Measurements Stratified by Sex, Age, and Ethnicity: Results of the World Alliance of Societies of Echocardiography Study. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2021; **34**(11).
111. Espersen C, Skaarup KG, Lassen MCH, et al. Normal age- and sex-based values of right ventricular free wall and four-chamber longitudinal strain by speckle-tracking echocardiography: from the Copenhagen City heart study. *Clinical research in cardiology : official journal of the German Cardiac Society* 2023.
112. Beyls C, Bohbot Y, Caboche M, et al. Preload Dependency of 2D Right Ventricle Speckle Tracking Echocardiography Parameters in Healthy Volunteers: A Prospective Pilot Study. *Journal of clinical medicine* 2021; **11**(1).
113. Jategaonkar SR, Scholtz W, Butz T, Bogunovic N, Faber L, Horstkotte D. Two-dimensional strain and strain rate imaging of the right ventricle in adult patients before and after percutaneous closure of atrial septal defects. *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology* 2009; **10**(4).
114. Schlangen J, Petko C, Hansen JH, et al. Two-dimensional global longitudinal strain rate is a preload independent index of systemic right ventricular contractility in hypoplastic left heart syndrome patients after Fontan operation. *Circulation Cardiovascular imaging* 2014; **7**(6).

115. Missant C, Rex S, Claus P, Mertens L, Wouters PF. Load-sensitivity of regional tissue deformation in the right ventricle: isovolumic versus ejection-phase indices of contractility. *Heart (British Cardiac Society)* 2008; **94**(4).
116. Ewalts M, Dawkins T, Boulet LM, Thijssen D, Stembridge M. The influence of increased venous return on right ventricular dyssynchrony during acute and sustained hypoxaemia. *Experimental physiology* 2021; **106**(4).
117. Pezzuto B, Forton K, Badagliacca R, Motoji Y, Faoro V, Naeije R. Right ventricular dyssynchrony during hypoxic breathing but not during exercise in healthy subjects: a speckle tracking echocardiography study. *Experimental physiology* 2018; **103**(10).
118. Goebel B, Handrick V, Lauten A, et al. Impact of acute normobaric hypoxia on regional and global myocardial function: a speckle tracking echocardiography study. *The international journal of cardiovascular imaging* 2013; **29**(3).
119. Yang Y, Liu C, Tian J, et al. Preliminary Study of Right Ventricular Dyssynchrony Under High-Altitude Exposure: Determinants and Impacts. *Frontiers in physiology* 2020; **11**.
120. Yuan F, Liu C, Yu S, et al. The Association Between Notching of the Right Ventricular Outflow Tract Flow Velocity Doppler Envelope and Impaired Right Ventricular Function After Acute High-Altitude Exposure. *Frontiers in physiology* 2021; **12**.
121. Wright L, Negishi K, Dwyer N, Wahi S, Marwick TH. Afterload Dependence of Right Ventricular Myocardial Strain. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2017; **30**(7).
122. Sunbul M, Kivrak T, Durmus E, Yildizeli B, Mutlu B. Evaluation of right and left heart mechanics in patients with chronic thromboembolic pulmonary hypertension before and after pulmonary thromboendarterectomy. *The international journal of cardiovascular imaging* 2015; **31**(6).
123. Yuchi Y, Suzuki R, Kanno H, et al. Influence of heart rate on right ventricular function assessed by right heart catheterization and echocardiography in healthy anesthetized dogs. *BMC veterinary research* 2022; **18**(1).
124. Di Terlizzi V, Barone R, Manuppelli V, et al. Influence of Heart Rate on Left and Right Ventricular Longitudinal Strain in Patients with Chronic Heart Failure. *Applied Sciences* 2022; **12**(2): 556.
125. Yang HS, Mookadam F, Warsame TA, Khandheria BK, Tajik JA, Chandrasekaran K. Evaluation of right ventricular global and regional function during stress echocardiography using novel velocity vector imaging. *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology* 2010; **11**(2).
126. Mamazhakypov A, Sartmyrzaeva M, Kushubakova N, et al. Right Ventricular Response to Acute Hypoxia Exposure: A Systematic Review. *Frontiers in physiology* 2022; **12**.
127. Noble M. An introduction to modern work on the Bowditch phenomenon. *Cardiovascular research* 1988; **22**(8): 586-.
128. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation* 2013; **128**(8).
129. Claessen G, La Gerche A, Dymarkowski S, Claus P, Delcroix M, Heidbuchel H. Pulmonary vascular and right ventricular reserve in patients with normalized resting hemodynamics after pulmonary endarterectomy. *Journal of the American Heart Association* 2015; **4**(3).
130. Lewis GD, Bossone E, Naeije R, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation* 2013; **128**(13).

131. Skytioti M, Søvik S, Elstad M. Respiratory pump maintains cardiac stroke volume during hypovolemia in young, healthy volunteers. *Journal of applied physiology (Bethesda, Md : 1985)* 2018; **124**(5).
132. Burton D, Stokes K, Hall G. Physiological effects of exercise. *BJA Education* 2004; **4**(6): 185-8.
133. Lin AC, Strugnell WE, Seale H, et al. Exercise cardiac MRI-derived right ventriculo-arterial coupling ratio detects early right ventricular maladaptation in PAH. *The European respiratory journal* 2016; **48**(6).
134. Okada M, Ota T, Okada M, Matsuda H, Okada K, Ishii N. Right ventricular dysfunction after major pulmonary resection. *The Journal of thoracic and cardiovascular surgery* 1994; **108**(3).
135. Ireland CG, Damico RL, Kolb TM, et al. Exercise right ventricular ejection fraction predicts right ventricular contractile reserve. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2021; **40**(6).
136. Claeys M, Claessen G, Claus P, et al. Right ventricular strain rate during exercise accurately identifies male athletes with right ventricular arrhythmias. *European heart journal Cardiovascular Imaging* 2020; **21**(3).
137. Chia EM, Hsieh CH, Pham P, et al. Changes in Right Ventricular Function with Exercise in Healthy Subjects: Optimal Parameters and Effects of Gender and Age. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2015; **28**(12).
138. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *American journal of respiratory and critical care medicine* 2003; **167**(2).
139. Swain DP, Abernathy KS, Smith CS, Lee SJ, SA B. Target heart rates for the development of cardiorespiratory fitness. *Medicine and science in sports and exercise* 1994; **26**(1).
140. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and science in sports and exercise* 2011; **43**(7).
141. Lord RN, George K, Jones H, Somauroo J, Oxborough D. Reproducibility and feasibility of right ventricular strain and strain rate (SR) as determined by myocardial speckle tracking during high-intensity upright exercise: a comparison with tissue Doppler-derived strain and SR in healthy human hearts. *Echo research and practice* 2014; **1**(1).
142. Sanz-de la Garza M, Giraldeau G, Marin J, et al. Influence of gender on right ventricle adaptation to endurance exercise: an ultrasound two-dimensional speckle-tracking stress study. *European journal of applied physiology* 2017; **117**(3).
143. Sanz-de la Garza M, Giraldeau G, Marin J, et al. Should the septum be included in the assessment of right ventricular longitudinal strain? An ultrasound two-dimensional speckle-tracking stress study. *The international journal of cardiovascular imaging* 2019; **35**(10).
144. Stewart GM, Yamada A, Haseler LJ, et al. Altered ventricular mechanics after 60 min of high-intensity endurance exercise: insights from exercise speckle-tracking echocardiography. *American journal of physiology Heart and circulatory physiology* 2015; **308**(8).
145. Wu XP, Li YD, Wang YD, et al. Impaired Right Ventricular Mechanics at Rest and During Exercise Are Associated With Exercise Capacity in Patients With

Hypertrophic Cardiomyopathy. *Journal of the American Heart Association* 2019; **8**(5).
146. Kinoshita M, Inoue K, Higashi H, et al. Impact of right ventricular contractile reserve during low-load exercise on exercise intolerance in heart failure. *ESC heart failure* 2020; **7**(6).
147. Cobra SB, Rodrigues MP, de Melo FX, Ferreira NMC, Melo-Silva CA. Right ventricular contractility decreases during exercise in patients with non-advanced idiopathic pulmonary fibrosis. *Medicine* 2021; **100**(27).
148. Voilliot D, Huttin O, Schwartz J, et al. Normal parameters of right ventricular mechanics during exercise in healthy individuals: A 2D speckle imaging study. *Archives of Cardiovascular Diseases* 2011; **104**(4): 287.
149. Chia EM, Lau EM, Xuan W, Celermajer DS, Thomas L. Exercise testing can unmask right ventricular dysfunction in systemic sclerosis patients with normal resting pulmonary artery pressure. *International journal of cardiology* 2016; **204**.
150. D'Andrea A, Limongelli G, Baldini L, et al. Exercise speckle-tracking strain imaging demonstrates impaired right ventricular contractile reserve in hypertrophic cardiomyopathy. *International journal of cardiology* 2017; **227**.
151. Vizzardi E, Bonadei I, Sciatti E, et al. Quantitative analysis of right ventricular (RV) function with echocardiography in chronic heart failure with no or mild RV dysfunction: comparison with cardiac magnetic resonance imaging. *Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine* 2015; **34**(2).
152. Li YD, Wang YD, Zhai ZG, et al. Relationship between echocardiographic and cardiac magnetic resonance imaging-derived measures of right ventricular function in patients with chronic thromboembolic pulmonary hypertension. *Thrombosis research* 2015; **135**(4).
153. Park SJ, Park JH, Lee HS, et al. Impaired RV global longitudinal strain is associated with poor long-term clinical outcomes in patients with acute inferior STEMI. *JACC Cardiovascular imaging* 2015; **8**(2).
154. Motoki H, Borowski AG, Shrestha K, et al. Right ventricular global longitudinal strain provides prognostic value incremental to left ventricular ejection fraction in patients with heart failure. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2014; **27**(7).
155. Park JH, Park MM, Farha S, et al. Impaired Global Right Ventricular Longitudinal Strain Predicts Long-Term Adverse Outcomes in Patients with Pulmonary Arterial Hypertension. *Journal of cardiovascular ultrasound* 2015; **23**(2).
156. Mokkink LB, Boers M, van der Vleuten CPM, et al. COSMIN Risk of Bias tool to assess the quality of studies on reliability or measurement error of outcome measurement instruments: a Delphi study. *BMC medical research methodology* 2020; **20**(1).
157. Rubenfeld GD. Epidemiology of acute lung injury. *Critical care medicine* 2003; **31**(4 Suppl).
158. Barros Filho ACL, Moreira HT, Dias BP, et al. Feasibility and reference intervals assessed by conventional and speckle-tracking echocardiography in normal hamsters. *Physiological reports* 2021; **9**(5).
159. Reardon L, Scheels WJ, Singer AJ, Reardon RF. Feasibility and accuracy of speckle tracking echocardiography in emergency department patients. *The American journal of emergency medicine* 2018; **36**(12).
160. Bunting KV, Steeds RP, Slater LT, Rogers JK, Gkoutos GV, Kotecha D. A Practical Guide to Assess the Reproducibility of Echocardiographic

Measurements. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2019; **32**(12).
161. Popović ZB, Thomas JD. Assessing observer variability: a user's guide. *Cardiovascular diagnosis and therapy* 2017; **7**(3).
162. Cecconi M, Rhodes A, Poloniecki J, Della Rocca G, Grounds RM. Bench-to-bedside review: the importance of the precision of the reference technique in method comparison studies--with specific reference to the measurement of cardiac output. *Critical care (London, England)* 2009; **13**(1).
163. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet (London, England)* 1986; **1**(8476).
164. Reed GF, Lynn F, Meade BD. Use of coefficient of variation in assessing variability of quantitative assays. *Clinical and diagnostic laboratory immunology* 2002; **9**(6).
165. Holm C, Mayr M, Hörbrand F, et al. Reproducibility of transpulmonary thermodilution measurements in patients with burn shock and hypothermia. *The Journal of burn care & rehabilitation* 2005; **26**(3).
166. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of chiropractic medicine* 2016; **15**(2).
167. Hazra A, Gogtay N. Biostatistics Series Module 6: Correlation and Linear Regression. *Indian journal of dermatology* 2016; **61**(6).
168. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *Journal of clinical epidemiology* 2010; **63**(7).
169. De Vet H, Terwee C, Mokkink L, Knol D. Measurement in Medicine: Cambridge University Press; 2011.
170. Romagnoli E, Burzotta F, Trani C, et al. EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart (British Cardiac Society)* 2009; **95**(1).
171. Haeck ML, Scherptong RW, Marsan NA, et al. Prognostic value of right ventricular longitudinal peak systolic strain in patients with pulmonary hypertension. *Circulation Cardiovascular imaging* 2012; **5**(5).
172. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003; **289**(22).
173. Phillips SM, Summerbell C, Hobbs M, et al. A systematic review of the validity, reliability, and feasibility of measurement tools used to assess the physical activity and sedentary behaviour of pre-school aged children. *The international journal of behavioral nutrition and physical activity* 2021; **18**(1).
174. Sun W, Zhang Y, Wu C, et al. Incremental prognostic value of biventricular longitudinal strain and high-sensitivity troponin I in COVID-19 patients. *Echocardiography (Mount Kisco, NY)* 2021; **38**(8).
175. Xie Y, Wang L, Li M, et al. Biventricular Longitudinal Strain Predict Mortality in COVID-19 Patients. *Frontiers in cardiovascular medicine* 2021; **7**.
176. Zhang Y, Sun W, Wu C, et al. Prognostic Value of Right Ventricular Ejection Fraction Assessed by 3D Echocardiography in COVID-19 Patients. *Frontiers in cardiovascular medicine* 2021; **8**.
177. Bonizzoli M, Cipani S, Lazzeri C, et al. Speckle tracking echocardiography and right ventricle dysfunction in acute respiratory distress syndrome a pilot study. *Echocardiography* 2018; **35**(12).

178. Lemarié J, Maigrat CH, Kimmoun A, et al. Feasibility, reproducibility and diagnostic usefulness of right ventricular strain by 2-dimensional speckle-tracking echocardiography in ARDS patients: the ARD strain study. *Annals of Intensive Care* 2020; **10**(1).
179. Kim M, Nam J, Son J, et al. Cardiac Manifestations of Coronavirus Disease 2019 (COVID-19): a Multicenter Cohort Study. *Journal of Korean Medical Science* 2020; **35**(40).
180. Baycan O, Barman H, Atici A, et al. Evaluation of biventricular function in patients with COVID-19 using speckle tracking echocardiography. *The International Journal of Cardiovascular Imaging* 2021; **37**(1).
181. Bursi F, Santangelo G, Sansalone D, et al. Prognostic utility of quantitative offline 2D-echocardiography in hospitalized patients with COVID-19 disease. *Echocardiography* 2020; **37**(12).
182. Stockenhuber A, Vrettos A, Androschuck V, et al. A pilot study on right ventricular longitudinal strain as a predictor of outcome in COVID-19 patients with evidence of cardiac involvement. *Echocardiography* 2021; **38**(2).
183. Jain R, Salinas PD, Kroboth S, et al. Comprehensive Echocardiographic Findings in Critically Ill COVID-19 Patients With or Without Prior Cardiac Disease. *Journal of Patient-Centered Research and Reviews* 2021; **8**(1).
184. Khemasuwan D, Yingchoncharoen T, Tunsupon P, et al. Right ventricular echocardiographic parameters are associated with mortality after acute pulmonary embolism. *Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography* 2015; **28**(3).
185. Dahhan T, Siddiqui I, Tapson V, et al. Clinical and echocardiographic predictors of mortality in acute pulmonary embolism. *Cardiovascular Ultrasound* 2016; **14**(1).
186. Lindqvist P, Calcutteea A, Henein M. Echocardiography in the assessment of right heart function. *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology* 2008; **9**(2).
187. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research synthesis methods* 2010; **1**(2).
188. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56**(2).
189. Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to Meta-Analysis.: John Wiley & Sons, Ltd; 2019.
190. Main AB, Braham R, Campbell D, Inglis AJ, McLean A, Orde S. Subcostal TAPSE: a retrospective analysis of a novel right ventricle function assessment method from the subcostal position in patients with sepsis. *The ultrasound journal* 2019; **11**(1).
191. Dalla K, Hallman C, Bech-Hanssen O, Haney M, Ricksten S. Strain echocardiography identifies impaired longitudinal systolic function in patients with septic shock and preserved ejection fraction. *Cardiovascular ultrasound* 2015; **13**.
192. Dalla K, Bech-Hanssen O, Ricksten S. Impact of norepinephrine on right ventricular afterload and function in septic shock-a strain echocardiography study. *Acta Anaesthesiologica Scandinavica* 2019; **63**(10).
193. Garcia-Montilla R, Imam F, Miao M, Stinson K, Khan A, Heitner S. Optimal right heart filling pressure in acute respiratory distress syndrome determined by strain echocardiography. *Echocardiography (Mount Kisco, NY)* 2017; **34**(6).
194. Park J, Kim Y, Pereira J, et al. Understanding the role of left and right ventricular strain assessment in patients hospitalized with COVID-19. *American heart journal plus : cardiology research and practice* 2021; **6**.

195. Orde S, Pulido J, Masaki M, et al. Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function. *Critical Care* 2014; **18**(4).
196. de Braga Lima Carvalho Canesso M, Borges IN, de Deus Queiroz Santos T, et al. Value of speckle-tracking echocardiography changes in monitoring myocardial dysfunction during treatment of sepsis: potential prognostic implications. *The international journal of cardiovascular imaging* 2019; **35**(5).
197. L'Heureux M, Sternberg M, Brath L, Turlington J, Kashiouris M. Sepsis-Induced Cardiomyopathy: a Comprehensive Review. *Current cardiology reports* 2020; **22**(5).
198. Mercado P, Maizel J, Kontar L, et al. Moderate and Severe Acute Respiratory Distress Syndrome: Hemodynamic and Cardiac Effects of an Open Lung Strategy With Recruitment Maneuver Analyzed Using Echocardiography. *Critical care medicine* 2018; **46**(10).
199. Franchi F, Faltoni A, Cameli M, et al. Influence of positive end-expiratory pressure on myocardial strain assessed by speckle tracking echocardiography in mechanically ventilated patients. *BioMed research international* 2013; **2013**.
200. West J, Luks A. West's Respiratory Physiology: The Essentials. 10th ed: West's Respiratory Physiology: The Essentials; 2015.
201. Gibson L, Fenza R, Lang M, et al. Right Ventricular Strain Is Common in Intubated COVID-19 Patients and Does Not Reflect Severity of Respiratory Illness. *Journal of intensive care medicine* 2021; **36**(8).
202. Repessé X, Vieillard-Baron A. Right heart function during acute respiratory distress syndrome. *Annals of translational medicine* 2017; **5**(14).
203. Ranieri V, Rubenfeld G, Thompson B, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307**(23).
204. Hékimian G, Lebreton G, Bréchot N, Luyt CE, Schmidt M, Combes A. Severe pulmonary embolism in COVID-19 patients: a call for increased awareness. *Critical care (London, England)* 2020; **24**(1).
205. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis research* 2020; **191**.
206. Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. *Heart rhythm* 2020; **17**(9).
207. Perrier A, Desmarais S, Goehring C, et al. D-dimer testing for suspected pulmonary embolism in outpatients. *American journal of respiratory and critical care medicine* 1997; **156**(2 Pt 1).
208. Wei P. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). *Chinese medical journal* 2020; **133**(9).
209. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *American journal of respiratory and critical care medicine* 2019; **200**(7).
210. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive care medicine* 1996; **22**(7).
211. Kanar BG, Şahin A, Göl G, et al. Timing and magnitude of regional right ventricular function and their relationship with early hospital mortality in patients with acute pulmonary embolism. *Anatolian journal of cardiology* 2019; **22**(1).
212. Pérez-Terán P, Roca O, Rodríguez-Palomares J, et al. Influence of right ventricular function on the development of primary graft dysfunction after lung

transplantation. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2015; **34**(11).
213. Pérez-Terán P, Roca O, Rodríguez-Palomares J, et al. Prospective validation of right ventricular role in primary graft dysfunction after lung transplantation. *The European respiratory journal* 2016; **48**(6).
214. Kumaresan A, Shapeton AD, Yuan HM, Hess PE. Transthoracic echocardiographic assessment of the right ventricle before and after caesarean delivery: A preliminary investigation. *Anaesthesia and intensive care* 2020; **48**(2).
215. Simsek Z, Simsek E. Does Nasal Surgery Affect Right Ventricular Myocardial Functions at the Tissue Level in Patients with Nasal Septum Deviation? *Journal of clinical medicine* 2018; **7**(8).
216. Marston N, Brown JP, Olson N, et al. Right ventricular strain before and after pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension. *Echocardiography (Mount Kisco, NY)* 2015; **32**(7).
217. Giusca S, Dambrauskaite V, Scheurwegs C, et al. Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring. *Heart (British Cardiac Society)* 2010; **96**(4).
218. Khani M, Hamidzad M, Bayat F, et al. 2D Speckle Tracking of RV Function after Coronary Artery Bypass Grafting and Cardiopulmonary Bypass Time. 2020.
219. WHO. Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic. 2023. https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic.
220. Willder JM, McCall P, Messow CM, Gillies M, Berry C, Shelley B. Study protocol for COVID-RV: a multicentre prospective observational cohort study of right ventricular dysfunction in ventilated patients with COVID-19. *British Medical Journal Open* 2021; **11**(1).
221. Szekely Y, Lichter Y, Taieb P, et al. Spectrum of Cardiac Manifestations in COVID-19: A Systematic Echocardiographic Study. *Circulation* 2020; **142**(4).
222. Argulian E, Sud K, Vogel B, et al. Right Ventricular Dilation in Hospitalized Patients With COVID-19 Infection. *JACC Cardiovascular imaging* 2020; **13**(11).
223. D'Alto M, Marra AM, Severino S, et al. Right ventricular-arterial uncoupling independently predicts survival in COVID-19 ARDS. *Critical care (London, England)* 2020; **24**(1).
224. Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. *Intensive care medicine* 2016; **42**(5).
225. Jardin F, Vieillard-Baron A. Is there a safe plateau pressure in ARDS? The right heart only knows. *Intensive care medicine* 2007; **33**(3).
226. Huang S, Vignon P, Mekontso-Dessap A, et al. Echocardiography findings in COVID-19 patients admitted to intensive care units: a multi-national observational study (the ECHO-COVID study). *Intensive care medicine* 2022.
227. Robinson S, Rana B, Oxborough D, et al. A practical guideline for performing a comprehensive transthoracic echocardiogram in adults: the British Society of Echocardiography minimum dataset. *Echo research and practice* 2020; **7**(4).
228. Corica B, Marra AM, Basili S, et al. Prevalence of right ventricular dysfunction and impact on all-cause death in hospitalized patients with COVID-19: a systematic review and meta-analysis. *Scientific reports* 2021; **11**(1).
229. Chotalia M, Ali M, Alderman JE, et al. Cardiovascular Subphenotypes in Acute Respiratory Distress Syndrome. *Critical care medicine* 2023; **51**(4).

230. Evrard B, Goudelin M, Montmagnon N, Fedou AL, Lafon T, Vignon P. Cardiovascular phenotypes in ventilated patients with COVID-19 acute respiratory distress syndrome. *Critical care (London, England)* 2020; **24**(1).
231. Mueller C, Giannitsis E, Jaffe AS, et al. Cardiovascular biomarkers in patients with COVID-19. *European heart journal Acute cardiovascular care* 2021; **10**(3).
232. McCall PJ, Willder JM, Stanley BL, et al. Right ventricular dysfunction in patients with COVID-19 pneumonitis whose lungs are mechanically ventilated: a multicentre prospective cohort study. *Anaesthesia* 2022.
233. (NICE) NIfHaCE. COVID-19 rapid guideline: reducing the risk of venous thromboembolism in over 16s with COVID-19 NICE guideline [NG186]. 2020. https://www.nice.org.uk/guidance/ng191/documents/review-questions.
234. Chotalia M, Ali M, Alderman JE, et al. Right Ventricular Dysfunction and Its Association With Mortality in Coronavirus Disease 2019 Acute Respiratory Distress Syndrome. *Critical care medicine* 2021; **49**(10).
235. Hjortrup PB, Butt W. Cardiac manifestations in critically ill patients with COVID-19: do we really know what hit us? *Intensive care medicine* 2022.
236. Chaouat A, Sitbon O, Mercy M, et al. Prognostic value of exercise pulmonary haemodynamics in pulmonary arterial hypertension. *The European respiratory journal* 2014; **44**(3).
237. Sharma T, Lau EM, Choudhary P, et al. Dobutamine stress for evaluation of right ventricular reserve in pulmonary arterial hypertension. *The European respiratory journal* 2015; **45**(3).
238. D'Andrea A, Stanziola AA, Saggar R, et al. Right Ventricular Functional Reserve in Early-Stage Idiopathic Pulmonary Fibrosis: An Exercise Two-Dimensional Speckle Tracking Doppler Echocardiography Study. *Chest* 2019; **155**(2).
239. Sarna L, Evangelista L, Tashkin D, et al. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. *Chest* 2004; **125**(2).
240. Pelletier C, Lapointe L, LeBlanc P. Effects of lung resection on pulmonary function and exercise capacity. *Thorax* 1990; **45**(7).
241. Larsen KR, Svendsen UG, Milman N, Brenøe J, Petersen BN. Cardiopulmonary function at rest and during exercise after resection for bronchial carcinoma. *The Annals of thoracic surgery* 1997; **64**(4).
242. Shelley B, Glass A, Keast T, et al. Perioperative cardiovascular pathophysiology in patients undergoing lung resection surgery: a narrative review. *British journal of anaesthesia* 2022.
243. Okada M, Okada M, Ishii N, et al. Right ventricular ejection fraction in the preoperative risk evaluation of candidates for pulmonary resection. *The Journal of thoracic and cardiovascular surgery* 1996; **112**(2).
244. Leibowitz AB. Pulmonary artery catheter determined right ventricular ejection fraction and right ventricular end-diastolic volume: another case of "The Emperor Has No Clothes". *Critical care medicine* 2009; **37**(11).
245. Senoner T, Velik-Salchner C, Tauber H. The Pulmonary Artery Catheter in the Perioperative Setting: Should It Still Be Used? *Diagnostics (Basel, Switzerland)* 2022; **12**(1).
246. Gershengorn HB, Wunsch H. Understanding changes in established practice: pulmonary artery catheter use in critically ill patients. *Critical care medicine* 2013; **41**(12).
247. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of

Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *European heart journal* 2016; **37**(1).
248. Larsen AH, Clemmensen TS, Wiggers H, Poulsen SH. Left Ventricular Myocardial Contractile Reserve during Exercise Stress in Healthy Adults: A Two-Dimensional Speckle-Tracking Echocardiographic Study. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2018; **31**(10).
249. Orlowska M, Bézy S, Ramalli A, Voigt JU, D'hooge J. High-Frame-Rate Speckle Tracking for Echocardiographic Stress Testing. *Ultrasound in medicine & biology* 2022; **48**(8).
250. Becher H, Chambers J, Fox K, et al. BSE procedure guidelines for the clinical application of stress echocardiography, recommendations for performance and interpretation of stress echocardiography: a report of the British Society of Echocardiography Policy Committee. *Heart (British Cardiac Society)* 2004; **90 Suppl 6**(Suppl 6).
251. Stenton C. The MRC breathlessness scale. *Occupational medicine (Oxford, England)* 2008; **58**(3).
252. Little B. *The Criteria Committee of the New York Heart Association.* Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed; 1994.
253. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2011; **20**(10).
254. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *Journal of the American College of Cardiology* 2001; **37**(1).
255. Falcoz PE, Conti M, Brouchet L, et al. The Thoracic Surgery Scoring System (Thoracoscore): risk model for in-hospital death in 15,183 patients requiring thoracic surgery. *The Journal of thoracic and cardiovascular surgery* 2007; **133**(2).
256. Harris P, Kuppurao L. Quantitative Doppler echocardiography. *BJA Education* 2023; **16**(2): 46-52.
257. Parasuraman S, Walker S, Loudon BL, et al. Assessment of pulmonary artery pressure by echocardiography-A comprehensive review. *International journal of cardiology Heart & vasculature* 2016; **12**.
258. Keast T, McErlane J, Kearns R, et al. Study protocol for IMPRoVE: a multicentre prospective observational cohort study of the incidence, impact and mechanisms of perioperative right ventricular dysfunction in non-cardiac surgery. *BMJ open* 2023; **13**(9).
259. Myles PS, Grocott MP, Boney O, Moonesinghe SR. Standardizing end points in perioperative trials: towards a core and extended outcome set. *British journal of anaesthesia* 2016; **116**(5).
260. Krishnamoorthy P, Croft L, Ro R, et al. Biventricular strain by speckle tracking echocardiography in COVID-19: findings and possible prognostic implications. *https://doiorg/102217/fca-2020-0100* 2020; **17**.