"Pressure & Flow relationships in the pulmonary circulation in man"

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Summary

Background: Current gold standard pulmonary artery pressure measurements (PAP) are not accurate using a fluid filled catheter. High fidelity micromanometer tipped catheters are more accurate both at rest and during exercise. They have been used to examine the pattern of pulmonary artery pressure waveforms under various physiological conditions.

A new thoracic impedance device has been developed, the Physioflow 1 (©Manatec, France), which has been shown to measure cardiac output (CO) accurately in a variety of respiratory conditions.

It is known that PAP varies with changes in posture, sleep and exercise, and may sometimes appear normal at rest in early disease. Resting pressures vary daily. However, pressure and flow is linearly related in physiological ranges and the relationship is relatively constant. Changes in pressure-flow relationships may be missed at rest. It has been shown that response to a given treatment may be missed if measurements are based solely on resting PAP. For this reason the slopes of pressure-flow plots, are more useful than spot measures of pressure and flow. This has not adequately been explored in humans.

Aims: To validate the use of the physioflow 1 cardiac output device, for use in subjects with pulmonary hypertension, and to develop a method of combining its data with high fidelity pulmonary artery catheter measurements, to produce pressure flow plots in a clinical context. The use of exercise or dobutamine, will be explored to achieve this, to then examine the effects on pressure–flow plots of the following:

1. The inhalation of oxygen or a nitric oxide/oxygen combination
2. Changing exercise posture
3. The response of different causes of pulmonary hypertension to the former two investigations
4. The response of pressure-flow curves to oxygen or nitric oxide/oxygen combination on vasodilator responders and non-responders (at rest).

Recruitment, Ethics and Methods Ethical approval was granted for all studies. All subjects who attended the Scottish Pulmonary Vascular Unit between April 2001 and August 2003, for invasive investigations, were offered to participate in the pressure–flow and other studies.

Whilst the subjects underwent routine right heart catheter investigations, measurement of cardiac output derived from the physioflow-1 cardiac output device was compared against thermodilutional derived cardiac output measurements concurrently measured during rest or during any physiological or pharmacological manoeuvres.

Those who agreed to the study had the micromanometer tipped catheter, inserted into their main pulmonary artery, and measurements were taken concurrently with thoracic impedance derived cardiac output measurements, during exercise or a dobutamine infusion under varying experimental conditions.

Results: We found that the physioflow 1 device, overestimated the cardiac output, compared to thermodilutional measurements 1.21 (± 1.85) L min^{-1}. The percentage

change from baseline however was similar between the two methods, and the physioflow 1 gave an overestimation of only 2.08 % (± 12.5), making it reliable in following the trends of changes in cardiac output in individuals.

In the reliable production of pressure- flow plots, both studies failed. The straight leg raising exercise studies, had a 20% equipment failure rate, and only achieved statistically linear plots in 45% of studies. The slope and intercepts had wide confidence intervals making them unsuitable for clinical comparisons (the 95% confidence interval < 20% baseline in 27% of studies). The dobutamine studies were unsuccessful, as the PAP seemed to plateau, as cardiac output continued to increase.

Pooled data of vasodilator responders and non-responders, demonstrated that when given air or nitric oxide/oxygen, the non-vasodilator responders slope significantly decreased from 10.2 to 6.9 respectively ($p < 0.001$), but for responders the slope did not significantly change from 8.6 to 8.9, and the 95 % confidence intervals overlapped (8.2-8.8 versus 8.7-9.2). For individual disease groups, chronic thromboembolic pulmonary hypertension and normal subjects responded in a similar fashion (decrease in the slope of pressure-flow plots) to non-vasodilator responders ($p = 0.004$ and <0.001 respectively), in response to oxygen and nitric oxide combined, whereas idiopathic pulmonary hypertensive and connective tissue disorder subjects had parallel shifts similar to vasodilator responders ($p = 0.237$ and 0.09 respectively).

Conclusion: The physioflow-1 not been shown to be accurate enough quantatively in general clinical practice in subjects with pulmonary hypertension when compared to

thermodilution cardiac output measurements. It does however follow trends fairly accurately and can thus be a useful research tool.

In conjunction with the high fidelity ambulatory pulmonary catheter, pressure flow plots can be produced with exercise. The quality of these plots in an individual, however, is not enough to be used to compare pressure-flows clinically. The data when pooled however is sufficient enough to discover other findings like the difference in response to vasodilators of so called vasodilator responders and non responders. It would seem that responders have a parallel shift and non-responders alter their pressure-flow gradient.

The use of straight leg raising exercise or dobutamine infusions does not lead to linear pressure flow plots of sufficient quality to be used in individuals clinically but pooled results may be a useful research tool.

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List Of Publications

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Syyed, R., Welsh, D., & Peacock, A. J. P62 The Physioflow 1 Thoracic Bioimepedance Device Follows Trends in Cardiac Output Changes in Patients with Pulmonary Hypertension. Thorax 62[Suppl 3], A85-A86. 2007.

List Of Abbreviations

η – coefficient of viscosity

λ – wavelength

μg – microgram

Δ – change in

6- MWT – six minute walk test

A- cross sectional area

BSA – body surface area

CaO_2-The amount of oxygen carried by a unit of arterial blood

CO – cardiac output

CO_{THERM} – thermodilutional derived cardiac output

CO_{PF}- physioflow derived cardiac output

COPD – chronic obstructive pulmonary disease

CI – cardiac index

CPET – cardiopulmonary exercise testing

CTEPH – chronic thromboembolic pulmonary hypertension

CTH – hypertension secondary to connective tissue disorder

CTI – contractility index

CvO_2- The mount of oxygen carried in a unit of blood venous blood

CVP – central venous pressure

DAP –systemic diastolic pressure

DE/dt- differential of ECG signal to time

dZ/dt –differential of impedance signal to time

DPAP – diastolic pulmonary artery pressure

DTT – Disease targeted therapy

dZ/dt – change in impedance during systole

E – voltage drop

ECG- electrocardiograph

f – frequency

F, f – female

f_c – heart rate

FiO_2 – fraction of inspired oxygen

Hep –PH – portopulmonary pulmonary hypertension

HPV – hypoxic pulmonary vasoconstriction

HR – heart rate

IPAH – idiopathic arterial pulmonary hypertension

k- constant

kg – kilogram

ILD – pulmonary hypertension secondary to interstitial lung disease

L, l – length

L - litre

LAP – Left atrial pressure

M, m - male

MAP – systemic mean arterial pressure

min – minute

MPAP – mean pulmonary artery pressure

n – number

N – No

N/A – not applicable

NO – nitric oxide

NYHA New York Heart Association

O_2 – oxygen

P – resistance of a material

P-Q – pressure-flow

$PaCO_2$ – partial pressure of carbon dioxide in arterial blood

PAH – pulmonary arterial hypertension

PaO_2 – partial pressure of oxygen in arterial blood

PAOP – pulmonary arterial occlusion pressure

PAP – pulmonary artery pressure

PAP-Q –(pulmonary artery) pressure-flow

PAPP – pulmonary artery pulse pressure

Pawp– Pulmonary artery wedge pressure

P_{in}–inflow pressure

pO_2 – partial pressure of oxygen

Portopulm – portopulmonary hypertension

P_{out} – outflow pressure

ppm – parts per million

PVH – pulmonary hypertension secondary to left heart disease

PCWP – pulmonary capillary wedge pressure

PVR – pulmonary vascular resistance

Q – blood flow

$\dot{\mathbf{Q}}$ - blood flow per unit time (cardiac output)

$\dot{\mathbf{Q}}$ Fick – Fick cardiac output

$\dot{\mathbf{Q}}$ PF, ($\dot{\mathbf{Q}}$ physioflow) -cardiac output Physioflow

$\dot{\mathbf{Q}}$ $\dot{\mathbf{Q}}$ Imp – impedance derived cardiac output

$\dot{\mathbf{Q}}$ $\dot{\mathbf{Q}}_{THERM}$– cardiac output via thermodilutional method

PC- personal computer

R – resistance or peripheral resistance

r - radius

r^2 , R^2 square of correlation coefficient

RAM – rapid access memory

RAP – Right atrial pressure

RV – Right Ventricle

SAP- systemic systolic arterial pressure

SaO_2 – oxygen saturation arterial blood

S.D., s.d. - standard deviation

SPVU – Scottish Pulmonary Vascular Unit

SV – stroke volume

Svi – stroke volume index

Svi_{cal}- calibrated stroke volume index

SvO_2 – venous blood oxygen saturation

T – left ventricular ejection time

v – wave velocity

VO_2 – body oxygen consumption

$\dot{\mathbf{V}}\mathbf{O}_2$ - oxygen consumption (total body) per unit time

$W(TFIT_{cal})$ - weighted time interval between the first zero value following the commencement of the cardiac cycle

WHO – World health organisation

Y - yes

Z – impedance

Z_0 – baseline impedance

Chapter 1

Introduction

1.1 A Brief History of the Science of the Pulmonary Vasculature & Pulmonary Hypertension

In ancient times there were numerous explanations of the working of the human body. Between 138 and 201 AD Galen summarised these ideas. It was thought that blood was formed in the liver and distributed around the body by the venous system, where it was consumed, whilst nourishing the body (Grover, R. F. et al 1983). It was thought that some of the blood flowed through the right side of the heart in order to nourish the lungs. Most of the blood it was thought passed into the left side of the heart via invisible pores. Galen believed that the lungs conveyed air to the left ventricle, where it became "Vital Spirit." (Fleming, D. 1955; Grover, R. F. et al 1983). 'Soot' produced by the ventricle was then transported back to the lungs and exhaled. This became church doctrine for 1400 years. It took William Harvey, a student of Padau, during the 17th century, to establish the idea in mainstream science, that blood follows a circuit, both through the systemic and pulmonary systems. (Grover, R. F. et al 1983).

Stephen Hales in the 17th and early 18th Centuries performed the first quantitative measures of the systemic circulation, where he measured the carotid pressure and the cardiac output of a goose. He also deduced that pulmonary artery resistance was likely to be less than systemic vascular resistance, due to the corresponding thickness of the vessel walls, and that the blood velocity must be greater through the lungs then the rest of the body. He estimated the capillary cross diameter, and total lung capillary volume (Grover, R. F. et al 1983).

In 1870, Fick described the measurement of cardiac output (CO) in animals and estimated that in man it was likely to be 4.6 L/min. The first direct measurements of

pulmonary arterial pressure was performed by Auguste Chauveau and Etienne Jules Marey (Grover, R. F. et al 1983). During the 19th and early 20th century, Otto Frank measured the outflow pressures allowing the calculation of pulmonary resistance, and Ernest Henry Starling heart-lung preparations allowed the experimental analysis of mechanical and physiological properties of the heart and lung (Fishman, A. P. 2004). In the early part of the 20th Century, Forssmann showed that right heart catheterisation was possible via a peripheral vein. (The experiments were performed on himself) (Fishman, A. P. 2004). This was taken up by Cournand and Richards, at the Bellevue laboratories. It was here moved from the laboratory to the bedside (Fishman, A. P. 2004). In 1953, Hermann Rahn used this catheter with a balloon tip to measure outflow pressure (Fishman, A. P. 2004). In 1970 William Ganz and Harold J. C. Swan introduced a balloon tipped catheter that could be advanced into the pulmonary artery under haemodynamic monitoring (Swan, H. J. et al 1970).

The first physiological studies into pulmonary hypertension were preceded by histopathological studies. In 1891, the first case report was published by Ernst von Romberg, calling the disease "pulmonary vascular sclerosis" (Fishman, A. P. 2004). Following this several other case series were published. In 1901, during a lecture Abel Ayerza described a syndrome categorised by pulmonary hypertension and right ventricular dilatation (Fishman, A. P. 2004). Until the 1940's, it was believed that the cause of primary pulmonary hypertension was syphilis, but Oscar Brenner in Birmingham reviewed 100 case reports and autopsy files of patients with pulmonary hypertension and found that through histological examination syphilis was not the cause (Fishman, A. P. 2004).

In 1951, Dresdale and his co-workers discovered that pulmonary vasoconstriction was involved in the pathogenesis of primary pulmonary hypertension (Dresdale, D. T. et al 1954). Since then there has interest in the scientific investigation of pulmonary hypertension, but the majority has been in the pathophysiology of the disease.

1.2 Clinical Pulmonary Hypertension

1.2.1 Definition & Epidemiology

Pulmonary arterial hypertension (PAH) accompanies nearly all heart and lung disease. Because of the difficulty of making measurements of pulmonary arterial pressure and flow, the morbidity associated with pulmonary hypertension is poorly understood. Pulmonary hypertension is said to exist if the mean pulmonary artery pressure is greater than 25mmHg at rest or 30mmHg with exercise (Rubin, L. J. 1993). A list of causes of pulmonary hypertension is shown in Table 1.1 (Simonneau, G. et al 2004).

1. Pulmonary Arterial Hypertension (PAH)
1.1 Idiopathic PAH
1.2 Familial PAH
1.3 Associated with (APAH)
1.3.1 Collagen Vascular Disease
1.3.2. Congenital systemic-to-pulmonary shunts
1.3.3. Portal Hypertension
1.3.4. HIV infection
1.3.5. Drugs & Toxins
1.3.6. Other
1.4 Associated with significant venous or capillary involvement
1.5 Persistent pulmonary hypertension of the newborn
2. Pulmonary Venous Hypertension
Left sided atrial, ventricular or valvular heart disease
3. Pulmonary hypertension associated with disorders of the respiratory system
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Sleep disordered breathing
3.4 Exposure to high altitude
3.5 Alveolar hypoventilation
3.6 Developmental abnormalities
4.Pulmonary hypertension due to chronic thromboembolic disease
5. Miscellaneous

Table 1.1: WHO Classification of pulmonary hypertension

Severity varies between different causes, however the histological changes seen in the vessels are similar and also there also appears to be similarity in responses to treatment, suggesting a common link that leads to vascular changes. Changes are seen in all three layers of the blood vessels, the intima, the media and the adventitia. It is now clear that the factors leading to pulmonary vasoconstriction also leads to remodelling of pulmonary vessels, (vasomotor cell growth coupling) (Barer, G. R. et al 1989; Cutaia, M. et al 1990; Peacock, A. J. 1999).

The incidence of idiopathic pulmonary arterial hypertension is 1-2 per million per annum (Rich, S. et al 1987). It causes disabling symptoms and left untreated leads to an early death. The incidence of other causes of pulmonary hypertension apart from COPD equal another 1-2 per million per annum (Gaine, S. P. et al 1998; Sanchez, O. et al 1999). The incidence of pulmonary hypertension amongst COPD patients has been calculated to be between 5-40% (Bchnka, R. H. et al 1971; Fishman, A. P. 1978; Flint, F. J. 1954; Report of an expert committee 1970). This may give prevalence amongst the general population of 0.3%. In the U.S. it has been estimated that up to 30% of hospital admissions with 'congestive cardiac failure' actually have fluid retention secondary to hypoxic lung disease (Flint, F. J. 1954; Report of an expert committee 1970; Weitzenblum, E. et al 1996).

1.2.2 Pathophysiology

It is likely that pulmonary hypertension develops as a consequence of a number of genetic and environmental influences (Humbert, M. et al 2004)which ultimately, at the level of the pulmonary arterioles and capillaries, can be divided into 3 pathophysiological facets.

As mentioned earlier, hypoxic vasoconstriction is one of the mechanisms behind pulmonary hypertension. The other two are destruction of the vascular bed and remodelling.

Over the past decade, the PPH1 gene has been mapped to the locus 2q31-32 (Deng, Z. et al 2000; Lane, K. B. et al 2000; Nichols, W. C. et al 1997).In idiopathic pulmonary arterial hypertension. This gene encodes for bone morphogenetic protein-II (BMPR-2) receptor. Carriers have a 10-20% chance of developing pulmonary hypertension(Newman, J. H. et al 2001), but the mutation is only found in 26% of sporadic pulmonary arterial hypertension(Thomson, J. R. et al 2000). A further gene the activin receptor-like kinase (ALK)-1 has been found to be associated with pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia (Trembath, R. C. 2001). Bone morphogenetic protein is part of the TGF-β superfamily and may either promote or inhibit cell growth(Loscalzo, J. 2001). Other patients, who do not have the PPH1 mutation, may have other abnormalities which interfere with BMPR-2 function. Angiopoietin-1 protein is involved in smooth muscle recruitment and vascular development is overexpressed in patients with pulmonary hypertension and down regulates BMPR2 mRNA. Angiopoietin-1 protein also is correlated with pulmonary vascular resistance (Du, L. et al 2003; Sullivan, C. C. et al 2003). The inability to regulate the proliferative response to injury may be the reason for endothelial cell proliferation found in plexiform lesions.

In pulmonary hypertensive subjects, there is often found an imbalance in many circulatory and tissue coagulation and other factors, and this may lead to in-situ thrombi. These factors include raised thromboxane A2 levels, reduced prostacyclin

levels, reduced nitric oxide synthase and raised endothelin-1 lung tissue levels, elevated serotonin and serotonin transporter levels (Presberg, K. W. et al 2003b).

Hypoxic pulmonary vasoconstriction has been known to exist since 1946 (von Euler, U. S. et al 1946) but is not yet fully understood. It will be further discussed in chapter 1.3.2.1. Destruction of the pulmonary vascular bed is often due to diseases which result in a loss of lung parenchyma but it take up to 50-75% of the vascular bed to be destroyed before the pulmonary artery pressure rises at rest. In addition to short-term autoregulatory changes in vascular tone, vessels can undergo profound fibrocellular changes, in various clinical conditions (Ryland, D. et al 1975; Semmens, M. et al 1974), termed vascular remodelling. Pulmonary vascular remodelling is important clinically because it renders the vessels relatively non-distensible to vasodilators.

The process of pulmonary vascular remodelling, adventitial changes, medial smooth muscle hypertrophy, distal smooth muscle hypertrophy, intimal proliferation, endothelial cell proliferation, in-situ thrombus and plexiform lesions (Presberg, K. W. et al 2003a).

As pulmonary hypertension develops, the thin walled right ventricle of the heart tends to slowly thicken, in response to an increase in afterload. As the right ventricle dilates, this causes a fall in CO as the right ventricle competes for space with the left ventricle in the pericardial sac. This in turn may lead to right ventricular ischaemia and a drop in right ventricle contractility, further reducing the CO (Carlson, E. B. et al 1985; Franciosi, R. A. et al 1968; Gold, F. L. et al 1982; Horan, M. et al 1981; Milnor, W. R. et al 1978).

1.2.3 Investigations

Following initial clinical assessment of pulmonary hypertension a multitude of investigations are arranged; however there is no single ideal investigation for diagnosis. The problems with less invasive tests are inaccuracy, and they measure surrogate markers of pulmonary hypertension and so cannot be relied upon to make a diagnosis. The most important investigation is right heart catheterisation. Right heart catheterisation is the diagnostic gold standard measuring mean pulmonary artery pressure (PAP) and cardiac output (CO) with the patient at rest and supine while performing a vasodilator challenge test. Even though this test is the gold standard it has its limitations as will be discussed later. There are several vasodilator substances used in this testing, and one of the most useful is nitric oxide (NO) (Pepke-Zaba, J. et al 1991; Ricciardi, M. J. et al 1998; Roberts, J. D., Jr. et al 2000). A positive vasodilator response is defined as a fall of 20% in either mean pulmonary artery pressure or pulmonary vascular resistance (Chemla, D. et al 2002).

1.2.4 Treatment

Treatment should be aimed at the underlying cause of pulmonary hypertension. Conventional treatments include oxygen therapy and anticoagulation.

In secondary pulmonary hypertension, hypoxia is a precipitating factor. There is evidence that oxygen improves symptoms in children with pulmonary arterial hypertension (1985; Kanemoto, N. et al 1989; Kral, H. et al 1993; Nagasaka, Y. et al 1978; Stark, R. D. et al 1973; Weitzenblum, E. et al 1985; Wuertemberger, G. et al 1990).

The other mainstay of treatment is vasodilator therapy. The theory behind the use of vasodilators in pulmonary hypertension is based on the importance of vasoconstriction in the development of pulmonary hypertension. These can be subdivided into calcium channel blockers and disease directed therapy. Disease Targeted Therapies (DTT) includes prostacyclin, endothelial antagonists and phosphodiestease 5 antagonists. Apart from vasodilatation, these agents may have other beneficial effects in pulmonary hypertension.

Calcium channel blockers are used in those deemed to be vasodilator responders (Rich, S. et al 1991; Rich, S. et al 1992), and disease targeted therapy in those who are not. Disease target therapy may double five year survival rates (Rubin, L. J. et al 1990). These beneficial effects may persist up to 10 years (Bush, A. et al 1987; Ewert, R. et al 2000; Galie, N. et al 2002; Hoeper, M. M. et al 2000; Jones, K. et al 1989; Machherndl, S. et al 2001; Olschewski, H. et al 2000; Olschewski, H. et al 2002; Oudiz, R. J. et al 2004; Rubin, L. J. 1997; Rubin, L. J. et al 2002; Simonneau, G. et al 2002). Combination therapy of disease targeted therapy may also be useful (Ghofrani, H. A. et al 2003; Hoeper, M. M. et al 2004; Lunze, K. et al 2006).

1.3 Introduction to Haemodynamics

1.3.1 Introduction

Optimal condition for exchange of mixed venous blood and inspired air is a low pressure high flow system with very little distance separating the air from the blood. The pulmonary circulation is a low pressure system and this prevents fluid from moving out of the vessels into the interstitial space and also allows the right ventricle to operate at a minimal energy cost. The pulmonary circulation operates at approximately 20 % of systemic pressures at rest. This means that the pressure-flow (P-Q) relationship is very sensitive to mechanical influences. The heart and pulmonary vasculature are situated in a pressure chamber – the thorax. Pressure measurements have to be interpreted relative to surrounding pressure as breathing effort can generate changes that override normal pulmonary vascular pressures.

Resistance can be described as the opposing force to a given constant flow. Pulmonary vascular resistance, (PVR), is used to evaluate the forces that oppose right ventricular ejection but can be misleading. PVR is calculated by

$$\mathbf{PVR} = \frac{\mathbf{MPAP - LAP}}{\mathbf{Q}}$$, and is the ratio of the mean pressure drop across the lung to cardiac output, where Q is blood flow per unit time (or cardiac output, CO, measured in L min^{-1}), MPAP is mean pulmonary artery pressure and LAP is left atrial pressure.

Pulmonary Artery Occlusion Pressure (PAOP) is the pressure measured when a balloon is inflated within the pulmonary artery and it gives an estimation of LAP under normal circumstances if the tip of the catheter is placed below the level of the left atrium. The

pulmonary circulation is affected by passive and active mechanisms and is altered by varying physiological activity.

1.3.2 Passive Regulation

The pulmonary circulation can be affected by lung volume, interstitial pressure or left atrial pressure (LAP). Blood vessels in the lung can be divided into alveolar vessels and extra-alveolar vessels. As lung volume increases (during inspiration), it has different affects on the different groups of pulmonary vessels (Graham, R. et al 1982). The transmural pressures of intra-alveolar vessels and extra-alveolar vessels also depend on changes in alveolar and interstitial pressure produced by changes in lung volume. (Fishman 1985; Naeije 1996)

It has been observed in experimental models of pulmonary hypertension with positive extrapolated intercepts of pulmonary artery pressure-flow (P-Q) plots, that LAP can be increased up to a certain point above normal without affecting pulmonary artery pressure (PAP). The exact level at which increases in LAP leads to an increased PAP varies from model to model of pulmonary hypertension. This shows that LAP can seldom be taken as the effective outflow pressure to calculate resistance of a hypothetical Poiseuillian flow within the pulmonary circulation (Naeije, R. 1996).

1.3.3. Active Regulation

1.3.3.1 Hypoxic Pulmonary Vasoconstriction (HPV)

Hypoxic pulmonary vasoconstriction (HPV) was first demonstrated in 1946 (von Euler, U. S. et al 1946). Describing the effects on the pulmonary circulation of acute (hours) or chronic (days-weeks) hypoxia is complicated, in view of the great amount of inter &

intra species variability. This can be demonstrated by the variable response of animals to changes in altitude. As altitude increases, the partial pressure of oxygen in the atmosphere decreases. Some animals, like the cow or cat, show a large increase in pulmonary arterial pressure to decreases in the partial pressure of oxygen, whereas others, like the rabbit or guinea pig show only a little response to decreases in Partial pressure in arterial blood (PaO_2). Most animals, including man, fall in the mid category (Reeves, J. T. et al 1979b)

Intra species variation also occurs. In adult humans, Reeves and Grover found that there was a large variation in pulmonary artery pressure in those living at high altitude, with a lesser degree of variation or range in those living at sea level (Reeves, J. T. et al 1979a). The variation in the pulmonary artery pressures noted in individuals at high altitude appears to be due to variations in arterial oxygen levels (Grover, R. F. et al 1983).

Hypoxic pulmonary vasoconstriction is intrinsic to the lung and does not require external neural or humoral stimulation. As the airway oxygen tension reduces below 100mmHg, the arterial pressure increases, until the response fails (Barer, G. R. et al 1970; Hauge, A. 1968). The onset of vasoconstriction is gradual over minutes, but the offset is rapid (McMurtry, I. F. et al 1976). The response can be affected by other factors, such as cardiac output, left atrial pressure, autonomic nerve stimulation and circulating vasoactive substances (Naeije, R. 1996). The exact biochemical mechanism of HPV is unknown (Fishman, A. P. 1985; Grover, R. F. et al 1983). Giving oxygen may reverse the effects of hypoxic vasoconstriction.

1.3.3.2. Nervous Control of Pulmonary Vascular Tone

The pulmonary Vasculature has both sympathetic & cholinergic innervation. α-adrenergic receptors produce vasoconstriction and β-adrenergic receptors vasodilation (Grover, Wagner et al. 1983; Fishman 1985). However, an increase or a change in sympathetic stimulation does not lead to HPV. Thus the α- adrenergic effects are either greater than or balanced with the β-adrenergic effects.

Studies have shown that in total autonomic block by chemical sympathectomy, pressure-flow plots in dogs move to a higher pressure (Murray, P. A. et al 1986; Naeije, R. et al 1989). This suggests that under certain circumstances the sympathetic system may produce a net vasodilatory response.

1.3.3.3 Humoral Control of the Pulmonary Vascular Tone

Many mediators have been proposed to modulate pulmonary vascular tone (Naeije, R. 1996), but only prostacyclin and nitric oxide have been shown to reduce normal vascular tone in experimental models.

1.4. Effects of Various Physiological Conditions on the Pulmonary Circulation

1.4.1. Hyperoxia

Pulmonary arteries have been shown to dilate in response to hyperoxia (Madden, J. A. et al 1985; Peake, M. D. et al 1981). During ventilation in the normal lung, the pulmonary vasculature is kept in a relatively relaxed state. Hyperoxia may lead to an acute fall in calculated pulmonary vascular resistance and pulmonary arterial pressure, but with no significant effect on the systemic circulation or cardiac output (Tucker, A. et al 1975). Hyperoxia selectively decreases the pulmonary vasoconstrictive response of prostaglandin $F_{2\alpha}$ (Lonigro, A. J. et al 1975) but does not affect the response to serotonin and noradrenaline (Archer, S. L. et al 1989).

1.4.2. Posture

When a human stands up, the intravascular pressure increases due to the force of gravity, leading to increased transmural pressure and dilation of the venous system. This leads to less venous return and reduced heart filling. Normally 400-500ml is shifted through the leg veins. Although the reservoir of pulmonary blood is decreased, the left heart can still be filled out of this reduced reserve for 10 beats. This is followed by an increased vascular resistance in the skeletal muscle and a reflex tachycardia, augmentation of the contractility of the ventricles, and a catecholamine release. In humans at rest, cardiac output may be up to 25% lower, stroke volume 40% lower and heart rate 30% higher when erect as compared to supine. The distribution of blood in the lungs can be split into 4 zones with regards to the source of pressures that alter flow, and these are partially gravity dependant, (Permutt, S. et al 1962; West, J. B. et al 1964). In the upright position, the blood volume is redistributed to the dependant parts of the body and lung, and thus cardiac return and filling is reduced (Bevegard, S. et al 1960;

Reeves, J. T. et al 1961b). In the lung, the blood distributes, preferentially perfusing the lower segments (Harf, A. et al 1978; West, J. B. 1999).

In the supine human lung, the whole lung is perfused (Reeves, J. T. et al 1988a). Pulmonary venous pressure is important for vascular recruitment, thus a higher LAP would allow more recruitment (Permutt, S. et al 1962; Wagner, W. W., Jr. et al 1979). In the erect lung at rest, there is higher pulmonary vascular resistance as there is a smaller lung vascular bed being perfused, and at rest PAP is too low to allow even distribution of blood (West, J. B. 1999). However, even moderate exercise is enough to reverse this and allows the recruitment of upper lobe vessels (Harf, A. et al 1978). An increase in the cardiac output is likely to be the major factor behind this but increasing ventilation may be a contributing factor (Bake, B. et al 1974).

1.4.3. Exercise

Reeves, Grover and Dempsey extensively reviewed the literature and reanalysed combined data with regards to exercise and the pulmonary circulation in normal humans (Reeves, J. T. et al 1988a). For supine exercise they analysed data on 91 subjects, (28 females), with 196 measurements from several studies (Bevegard, S. et al 1960; Bevegard, S. et al 1963; Bevegard, S. 1963; Dexter, L. et al 1951; Gurtner, H. P. et al 1975; Holmgren, A. et al 1960; Varnauskas, E. 1955). In erect subjects they analysed data on 24 subjects (1 female), with 104 measurements (Bevegard, S. et al 1963; Groves, B. M. et al 1987; Reeves, J. T. et al 1987). In the supine subjects, the workload was up to 1600 kg m min^{-1}. In mild exercise there was a two to three times increase in oxygen uptake, but there was no change in pulmonary vascular resistance. However

more significant amounts of exercise resulted in a slight decrease in pulmonary vascular resistance (Bevegard, S. A. et al 1963; Holmgren, A. et al 1960). When reviewing the paired data in individuals, there was a 1mmHg rise in PAP for every 1L rise in cardiac output (Reeves, J. T. et al 1988a). It was assumed that the outflow pressure was pulmonary artery wedge pressure (Pawp), and that the net driving force through the lungs was the difference between PAP and Pawp. Both the regression lines for PAP and Pawp, when paired with Q, had similar intercepts across the y-axis, and thus when the PAP-Pawp vs Q plot was produced, the intercept appeared to got though the origin (Reeves, J. T. et al 1988a). This would suggest that there is only a little change in the pulmonary vascular resistance.

In upright subjects, during mild exercise, they found a significant rise in Pawp from 5 ± 3 mmHg, to 9 ±2 mmHg. They also found that PVR also fell significantly, from 1.5 ± 0.5 to 0.8 ± 0.3 units. With heavier exercise, they found that PVR was only reduced slightly when compared to mild exercise, with values in these individuals of 2.1 ± 0.6 units at rest, to 0.8 ± 0.2 during mild exercise, and 0.5 ± 0.1 units during heavy exercise. They also found that in individuals, the PAP- Q relationship was linear, and the Pawp-Q relationship was linear, but the PAP-Pawp & flow relationship was not. This suggested that when changing from mild to moderate exercise, there is no increase in the pressure gradient, but the calculated PVR decreases (Reeves, J. T. et al 1988a). When the data for resting pressures whilst erect were removed from the linear regression calculations, the line went through the origin, and gave a PVR value of 0.63, which is close to the value of 0.61 obtained for the PVR during exercise at rest. This would suggest that the

main affect of posture is during rest, and even mild exercise takes away the influence of posture (Bevegard, S. A. et al 1960; Reeves, J. T. et al 1961a; Reeves, J. T. et al 1988a).

It is felt in general that lung vascular resistance acts passively during exercise, but during prolonged exercise there may be a drop in pulmonary vascular resistance (Ekelund, L. G. 1967).

1.5. Pulmonary Vascular Resistance

Since the Swan-Ganz catheter was introduced in 1970, pulmonary vascular resistance (PVR) has been measured worldwide. The catheter allows measurement of pulmonary arterial occlusion pressure (PAOP). However as it is a fluid filled catheter, it is inaccurate in the measurements of instantaneous pressures, due to inadequate frequency response, motion artefacts, errors in zero levelling and altered signal quality due to regular debubbling and frequent flushing. However, it is assumed that the measurement of mean vascular pressures is reliable. Thermodilutional flow measurements require several cycles (and are not simultaneous), thus this catheter imposes a simplification in which is the pulsatile nature of the pulmonary circulation is ignored.

In steady state flow haemodynamics, resistance is calculated as a pressure drop from an upstream point (inflow pressure, P_{in}) to a downstream point (outflow pressure, P_{out}) divided by the flow. In smooth-walled thin, non-distensible tubes, with a laminar flow of a Newtonian fluid, Poiseuille's law states that: $\mathbf{R = (P_{in} - P_{out})/Q = 8.l.\eta/ \pi.r^4}$

Where l is the length of the tube, η is the coefficient of viscosity, and r is the radius. In most clinical circumstances PAOP gives an estimation of LAP, provided the catheter tip is placed below the level of the left atrium. If pulmonary venous resistance is increased then PAOP is less then pulmonary arterial wedge pressure (PAWP), and PAWP will overestimate LAP. Poiseuille's law assumes that in the pulmonary circulation (PAP-LAP)/Q plots are both linear and cross the origin. Accordingly the PVR, the slope of (PAP-LAP)/Q is constant.

1.6 The Pressure-Flow Relationship & Limitations of PVR Calculations

There are several limitations to the use of PVR calculations. Pulmonary vessels are compliant and thus PVR should decrease as MPAP increases (by virtue of the effect of pressure on vessel calibre). Also, the pulmonary vessels may collapse as a result of outside forces at low PAP. These outside forces may include alveolar pressure on capillaries or elastic or muscular recoil of the vessel.

These limitations in PVR measurement or the (PAP-LAP)/Q relationship mean that, although the relationship may be linear at a physiological range, it may have a positive intercept (extrapolated) and in some subjects PVR decreases as blood flow increases.

Theoretically (PAP-LAP)/Q should not follow Poisseuille's law as pulmonary blood flow has a branching pattern and is not laminar as it is not a simple Newtonian fluid. However physiological experiments suggest that the relationship is linear with a positive intercept, both in animals and humans (Naeije, R. 1996). This is a constant observation in isolated lung preparations.

In well recruited, well oxygenated subjects who are healthy, the plots may intercept the origin. In hypoxia, increased alveolar pressure, vasoconstrictor drugs and a variety of pulmonary and cardiac diseases may shift the curves to a higher slopes and higher intercepts. (Fishman, A. P. 1985; McGregor, M. et al 1985a; Mitzner, W. et al 1989; Naeije, R. 1996).

1.6.1. Explanation for Higher Intercepts in Pressure Flow Plots

Linear curve shifts towards higher pressures with an increase in pressure intercepts have been explained by the vascular waterfall model (Permutt, S. et al 1962). According to this model, the pulmonary circulation is made up of parallel collapsible vessels, with different closing pressures. At low flow (and pressure) these vessels are derecruited. At higher flows within the normal physiological range, the P-Q curves are linear, and their extrapolated pressure intercept represents the mean of the individual vascular closing pressures. This mean closing pressure is the effective downstream pressure of the pulmonary circulation. The slope of the linear portion of the P-Q curves reflects the cross-sectional area of the perfused vessels and is interpreted as an incremental resistance upstream from the site of vascular closure.

There is however an alternative explanation based on the 'distensible vessel' model (Zhuang, F. Y. et al 1983). According to this model, the diameter of the pulmonary vessels increase, as their transmural pressure increases. This pressure/diameter ratio flattens progressively until a limiting diameter is attained. The resulting P-Q curves are markedly affected by small changes in compliance. Interestingly a parallel shift of P-Q curves is predicted by the model if both resistance and the compliance increases in small order arterioles (Mitzner, W. et al 1989)

1.6.2. Interpretation and Problems with Pressure-Flow plots

Interpretation of pulmonary vascular P-Q curves in intact animals must take into account major methodological difficulties. PAP can be affected at both the highest and lowest flows by changes in the mixed venous PO_2, neurohumoral activity and LAP (Fishman, A. P. 1985; McGregor, M. et al 1985a; Mitzner, W. et al 1989; Naeije, R.

1996). In addition, very low flows are impossible to study in intact animals. A slight overestimation of PAP at the highest Q leads to an increased slope and decrease the extrapolated pressure intercept of a P-Q plot. This can be avoided by limiting the analysis of data points to comparisons at a given level flow.

The ideal way to describe pulmonary vascular function is as a P-Q curve generated from as many points as possible. If the analysis is restricted to the effect of a pharmacological intervention at one single point, one may be mislead into believing that the intervention has improved the PVR, as seen in figure 1.1 (ie C to A), but all that has happened is the flow has decreased. Correspondingly, an improvement might be missed by single measurements (figure 1.1: B to A) but the pharmaceutical agent has decreased the P-Q plot. Thus, the use of a P-Q diagram allows a more reliable identification of changes in pulmonary vascular tone at different cardiac outputs.

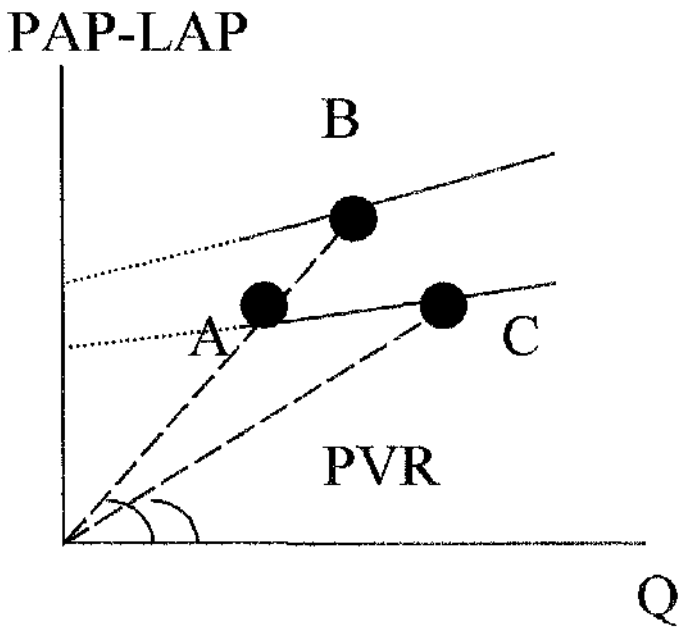


Figure 1.1: Pulmonary arterial and flow relationships and the mis-representation of resistance changes of the pulmonary vasculature from point A, when measuring classical pulmonary vascular resistance changes in respect of to two possible coordinate values, B & C.

The relationship of (PAP-LAP)/Q or PVR is only meaningful if LAP is the relevant downstream or outlet pressure (McGregor, M. et al 1985b; McGregor, M. et al 1985a; Sniderman, A. D. et al 1988). For instance in normal subjects the pressure flow ratio (PVR) decreases as blood flow increases using LAP as the outlet pressure, and this has been assumed to be secondary to flow induced dilatation or recruitment of new parallel vessels. Sniderman et al, (1984, 1988) found in animal studies that the mean pulmonary artery pressure to flow relationship is constant over a large range of flows (Sniderman, A. et al 1984; Sniderman, A. D. et al 1988), but they also found that the pressure flow relationship intercept was always positive. Its minimum intercept represents the critical

closing pressure (the pressure at which blood vessels collapse) (Burton, A. C. 1951; West, J. B. et al 1964), which was usually related to alveolar pressure rather then left atrial pressure. This slope represents resistance, but becomes misleading if LAP is less than the critical closing pressure, because LAP is no longer the appropriate downstream pressure, but critical closing pressure is. The critical closing pressure in normal man is 10mmHg (Brofman, B. H. et al 1957) but in subjects with COPD may as great as 30 mmHg (Charms, Brofman et al. 1958). To date no measurements have been made in pulmonary hypertension.

It is known that if a vasodilator is given in pulmonary hypertension, stroke volume will increase, but PAP changes little. Thus the PVR apparently decreases, as calculated from /Q. Figure 1.2 helps demonstrate the possible explanations for a change in PAP and CO to an pharmacological agent, where pressure-flow coordinates change from A to B. From the pressure-flow model there may be one or a combination of both of two alternative explanations.

1. It may be that critical closing pressure increases, but real PVR remains constant, (the vessels have the same cross sectional area as normal subjects). If critical closing pressure increases, PAP would be higher for any given level of flow.
Also, if critical closing pressure was reduced by vasodilator drug, and real resistance left unchanged, Q would increase without an increase in the apparent driving pressure, leading to an apparent decrease in calculated PVR
2. Increases in real PVR (the vessels have a reduced cross sectional area) associated with no change in critical closing pressure (Sniderman, A. D. et al 1988).

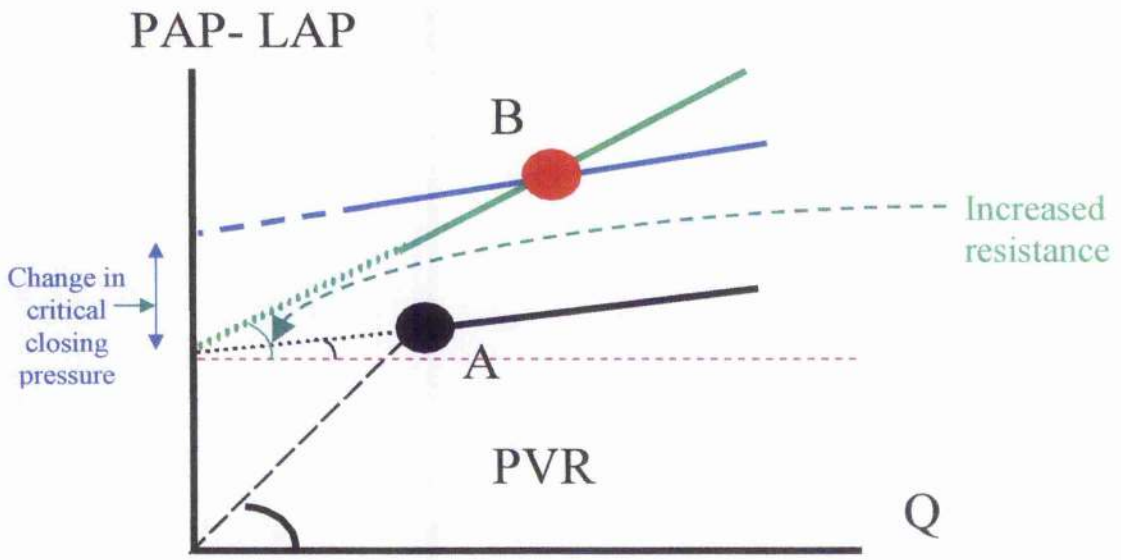


Figure 1.2: Possible explanations for change in pressure and flow in an individual subject

1.6.3. Pulmonary Vascular Pressure-Flow Relationships: Evidence from animal studies

The plots seen in animals vary. Hypoxia increases the slope of pressure-flow plots in both dogs and pigs, but with a greater increase in pigs (Maggiorini, M. et al 1998). Dogs MPAP have variable response to hypoxia (up to 50% non-hypoxia responders) (Lejeune, P. et al 1988). Minipigs & dogs have reduction in P-Q slopes to both hypoxia and hyperoxia when given nitric oxide. The shift of the slope up, to hypoxia, was reversed. Minipigs have a greater reduction in downstream resistance (as calculated by PaOP) (Maggiorini, M. et al 1998). Other chemicals and pharmacaeutical agents, in both normoxia and hypoxia were found to have variable effects on both the gradient and intercept (Lejeune, P. et al 1988).

1.6.4. Pulmonary Vascular Pressure-Flow Relationships: Human studies

1.6.4.1. Normal Values at Rest

The haemodynamic values in humans at rest are PAP 13mmHg (8-20), PAOP 9 mmHg (5-14), RAP 5mmHg (2-9). Q 6.5 l min^{-1} (4-8.3), Heart rate 69 bpm (40-100) (Naeije, R. 1996).

1.6.4.2 Methods of measuring P-Q

Pressure flow curves can be produced by several methods. Currently using exercise is the main method in use. In the past, unilateral pulmonary arterial occlusion and extracorporeal circulation were used to produce P-Q curves.

Unilateral pulmonary arterial occlusion relies on the assumption that flow is divided equally between the two lungs. If the artery of one lung is obstructed, then all the blood flows through the other lung. From the changes pre and post occlusion the P-Q can be plotted for the obstructed lung. Using this method, the average intercept pressure in normals is ~10mmHg (slightly higher than LAP), and the slope of the P-Q curve is 0.9-1 mmHg/l/min (Evans, P. et al 1971; McGregor, M. et al 1985a; Reeves, J. T. et al 1988a).

Physical exercise can be used for P-Q plots, but as discussed below, it is not ideal. However, so long as LAP, pleural and alveolar pressures are monitored, and excessive changes between different levels of flow are avoided, physical exercise is acceptable. An infusion of dobutamine at 10ng/kg/min may be an alternative method of studying passive P-Q relationships (Naeije, R. et al 1994).

1.6.4.3. Physical Exercise & Posture

An increase in cardiac output during exercise does not normally affect pulmonary vascular pressures (Fishman, A. P. 1985; Reeves, J. T. et al 1988a). In healthy supine young adults the P-Q plots during moderate exercise does not exceed 1mmHg/l/min, corresponding to a PAP of 25mmHg, for a Q of about 20 l/min (Reeves, J. T. et al 1988a) Exercise –induced PAP greater than 30 mmHg is considered diagnostic of pulmonary hypertension.

The P-Q plots during exercise may also be influenced by exercise induced changes in pleural pressure, alveolar pressure and left atrial pressure. PAOP increases to 12-15 mmHg during moderate exercise, but during strenuous exercise may increase to as much as 30-35 mmHg (i.e. in triathletes) (Naeije, R et al 1993; Reeves, J. T. et al 1988a). Interestingly these changes in PAOP does not seem to affect the slope of PAP-Q plots during exercise, probably because of vascular distension at high levels of Q and PAOP.

P-Q slopes have been reported to decrease when exercise is performed standing or sitting, as opposed to supine. This can be explained by vascular derecuitment at rest (Reeves, J. T. et al 1988a).

1.6.4.4. Age & Negative Intercept

In older subjects, exercise is associated with greater increases in PAP and PAOP at lower CO. In patients with cardiac and/or pulmonary disease, pulmonary hypertension at low levels is explained by early increases in LAP and intrathoracic pressure, and also by mixed venous blood hypoxemia which enhances hypoxic pulmonary

vasoconstriction (Naeije, R. 1996). All these changes account for the negative extrapolated pressure intercepts for P-Q plots produced by physical exercise in patients with pulmonary vascular disease of various origins (Janicki, J. S. et al 1985; Naeije, R. et al 1994).

These changes thus may make exercise not the ideal method to generate multipoint pulmonary vascular P-Q plots, which are only influenced by flow.

1.6.4.5. Hypoxia

Using the unilateral pulmonary arterial occlusion method, it has been shown that inspiratory hypoxia (FiO_2 9-12%) in normal subjects shifts P-Q plots in parallel towards higher pressures (Evans, P. et al 1971; McGregor, M. et al 1985a).

1.6.4.6. Pulmonary hypertension

It has been shown that improvements by treatment with prostacyclin may be missed by PVR alone but detected by P-Q changes (Castelain, V. et al 2002; Janicki, J. S. et al 1985). Depending on the underlying cause of pulmonary hypertension the P-Q relationship have varying slopes or intercepts (Evans, P. et al 1971; Janicki, J. S. et al 1985; Leeman, M. et al 1990; McGregor, M. et al 1985a; Naeije, R. et al 1994).

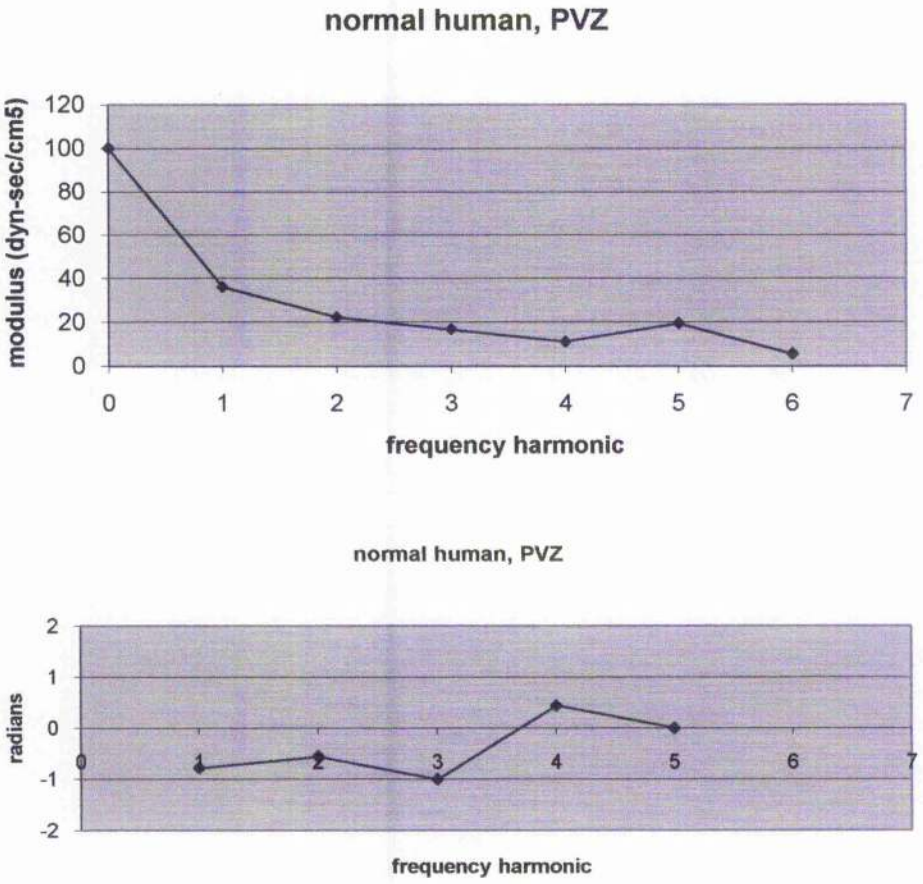
1.7. General Haemodynamics

The importance of impedance and hydraulic energy in the subject of pulmonary hypertension can be taken from the fact that even when vasodilators reduced PVR, it is the total right ventricular load (which includes a pulsatile component) and not changes inflow or resistance that will influence clinical outcome. Resistance would be more apt with constant flow (using an electrical analogy-D.C. current) whereas impedance is more apt for pulsatile flow (AC current).

1.7.1 Pulmonary Vascular Impedance

It is possible to measure PAP & Q instantaneously. Pulmonary Vascular Impedance (PVZ) is basically the instantaneous pulmonary artery P/Q changes, separated into separate harmonics. Each harmonic has its own modulis (amplitude) and phase delay. PVZ is calculated after comparing the instantaneous harmonic frequencies of PAP & Q. Pulmonary vascular impedance is the ratio of pressure oscillations to flow oscillations. It is most often measured in the main pulmonary artery ('input impedence'). It is expressed as two components : the ratio of pressure and flow moduli and a phase angle (whether the pressure changes come before or after flow changes, negative indicates flow before pressure wave. Both of these are compared against frequency (multiples of HR) (Milnor, W. R. 1982). Pulmonary vascular impedance at 0 hz (Z_o), is equivalent to pulmonary vascular resistance as calculated from PAP/Q.

Figure 1.3: Example of graphical representation of first 6 harmonics of pulmonary vascular impedance in a normal human subject, with pulmonary artery input impedance and phase.



Pulmonary vascular impedance at 0 hz (Z_o), is equivalent to pulmonary vascular resistance as calculated from PAP/Q.

The impedance decreases from this maximum to a minimum at 2-3 hz. Then increase to a smaller secondary maximum at 5-6 hz

At low frequencies, the phase angle is negative and this means that blood flow changes lead pressure flow changes (Naeije, R. 1996).

1.7.2. Models of the Pulmonary Circulation

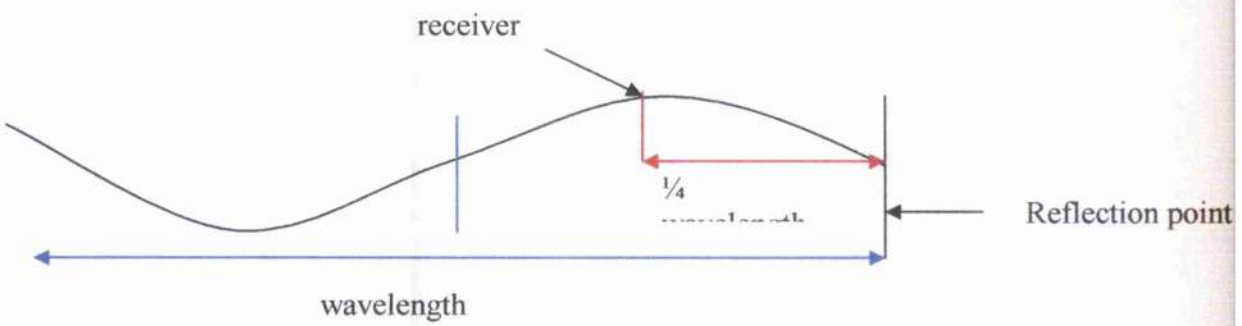
Various attempts have been made to try and mimic and explain the observed behaviour of the pulmonary vascular bed, and input impedance including early attempts by Engelberg and Dubois, the Fishman's transmission line theory and the Pollack's transmission line theory model (Engelberg, J. et al 1959; Pollack, G. H. et al 1968; Weiner, F. et al 1966). These models emphasise the differences compared to the systemic circulation in that: wave reflection is less in the pulmonary circulation and pulse transmission is decreased pulse wave velocity and differences of wave amplification.

1.7.3. Wave Reflection

In the systemic circulation, from the relationship of resistance to the minimum and the subsequent impedance modulii, we can deduce the coefficient of reflection in peripheral arteries. This is approximately 0.8 (ie the wave reflected from peripheral bed has an amplitude of 80% of incident wave) (O'Rourke, M. F. 1971). The point of reflection is equivalent to the point of minimums in frequency. Thus, the distance to point reflection $= \lambda/4 = (v/f)/4$,

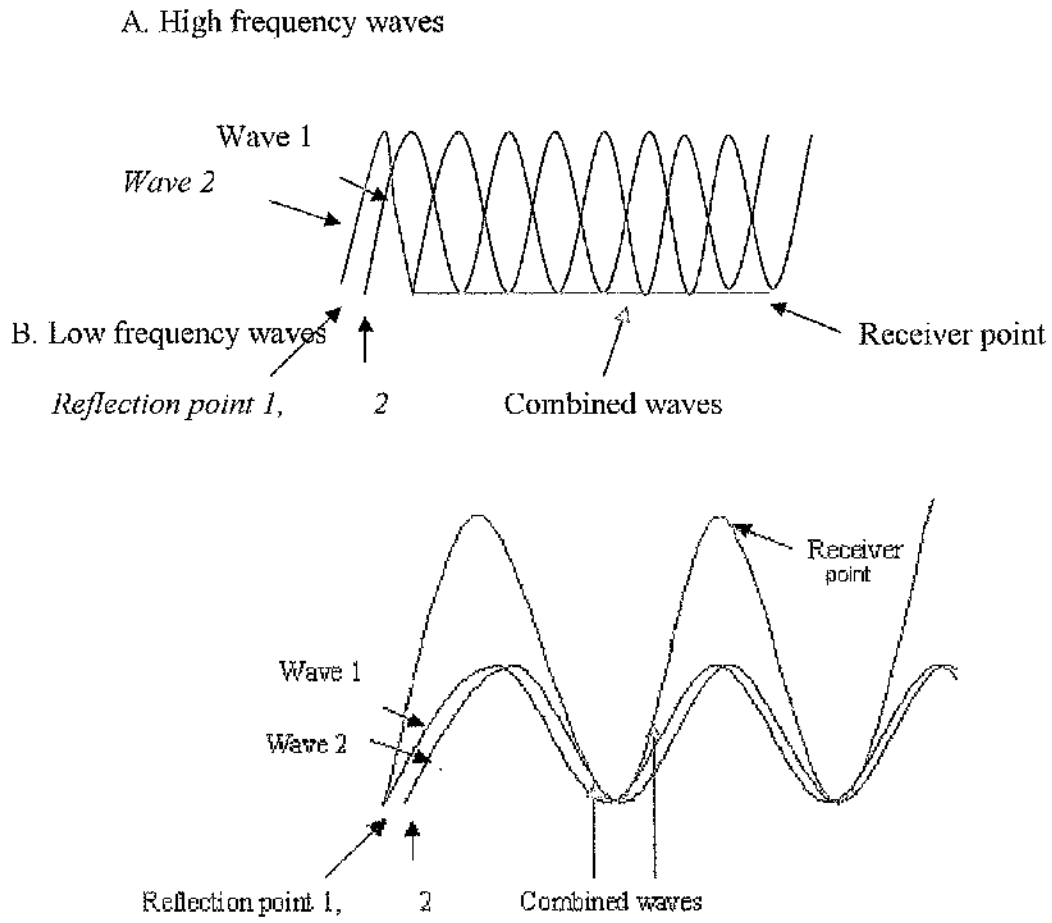
where, λ=wavelength, v = wave velocity, f =harmonic frequency & $v=\lambda$. (figure 1.4)

Figure 1.4: Example of single reflected wave, where only when the reflection point is ¼ of the wavelength, or a multiple of a wavelength and a ¼, will it register at the receiver.



A high frequency suggests a small wavelength. There are multiple waves of same frequency, but at different phases. Different phased waves have the ability to cancel each other out, especially if the wavelength is smaller than distance to receiver (catheter). A wave with wavelengths larger than the distance to the receiver have no opportunity to cancel each other out. Thus the higher the frequency found at the receiver, the smaller the wave's wavelength, and the more proximal the reflection point of the wave must be, as demonstrated in figure 1.5 (Westerhof, N. et al 1972).

Figure 1.5A & B: waves produced at two different reflection points. Wave 1 & 2 are in black, and combined wave produced is in red. A. Two high frequency waves, which when combined, cancel each other out B. Low frequency waves, which may be additive



In hypertension, the reflected wave velocity is faster than in normal subjects and thus the modulus and phase curves are shifted to right. This may be secondary to decreased vessel distensibility. Increased in PVR may change PVZ little (O'Rourke 1970) and vice a versa, decreases in PVZ may not be noted by measuring PVR.

Systemic central pulse pressure increases if there is an increased resistance and decreased distensibility of the blood vessels (O'Rourke 1970)

1.7.4. Aortic pressure waves

1.7.4.1. Contour of ascending aortic pressure wave

Hypertension leads to changes in pulmonary impedance, which increases in lower, as compared to higher, pressure harmonics. It also leads to changes in phase. This combination leads to increased amplitude of aortic pressure wave and alteration in its shape.

At low pressure there is a simultaneous peak flow and pressure wave. With increasing mean pressure the first peak of pressure wave becomes less prominent (becoming either a hump or change in slope of upstroke. The diastolic wave moves from diastole into late systole and contributes to late systolic pump. The diastolic wave falls in smooth and exponential fashion (O'Rourke 1970)

Figure 1.6: Changes in normal aortic pressure wave contour in rabbits subject to alteration in mean pressure

1.7.4.2. Synthesised aortic pressure waves

Normally diastolic wave is not apparent in the proximal aorta or brachiocephalic arteries. However if there is a reduction in pulse wave velocity, the diastolic wave becomes apparent. This is due to the late return of reflected wave before aortic valve closure compared to normal early return. As the pulse wave velocity increased the diastolic wave becomes less apparent and the amplitude of pressure wave increases in late systole (O'Rourke, M. F. et al 1980).

Ejection wave shortening leads to the diastolic wave becoming apparent due to the lower body reflection wave returning after aortic closure. (O'Rourke, M. F. et al 1980). This is found in hypertension, arterial degenerative disease, and aortic coarctation (O'Rourke, M. F. 1970). The mechanism is completely explicable from change in vascular bed and not the pattern of ventricular ejection.

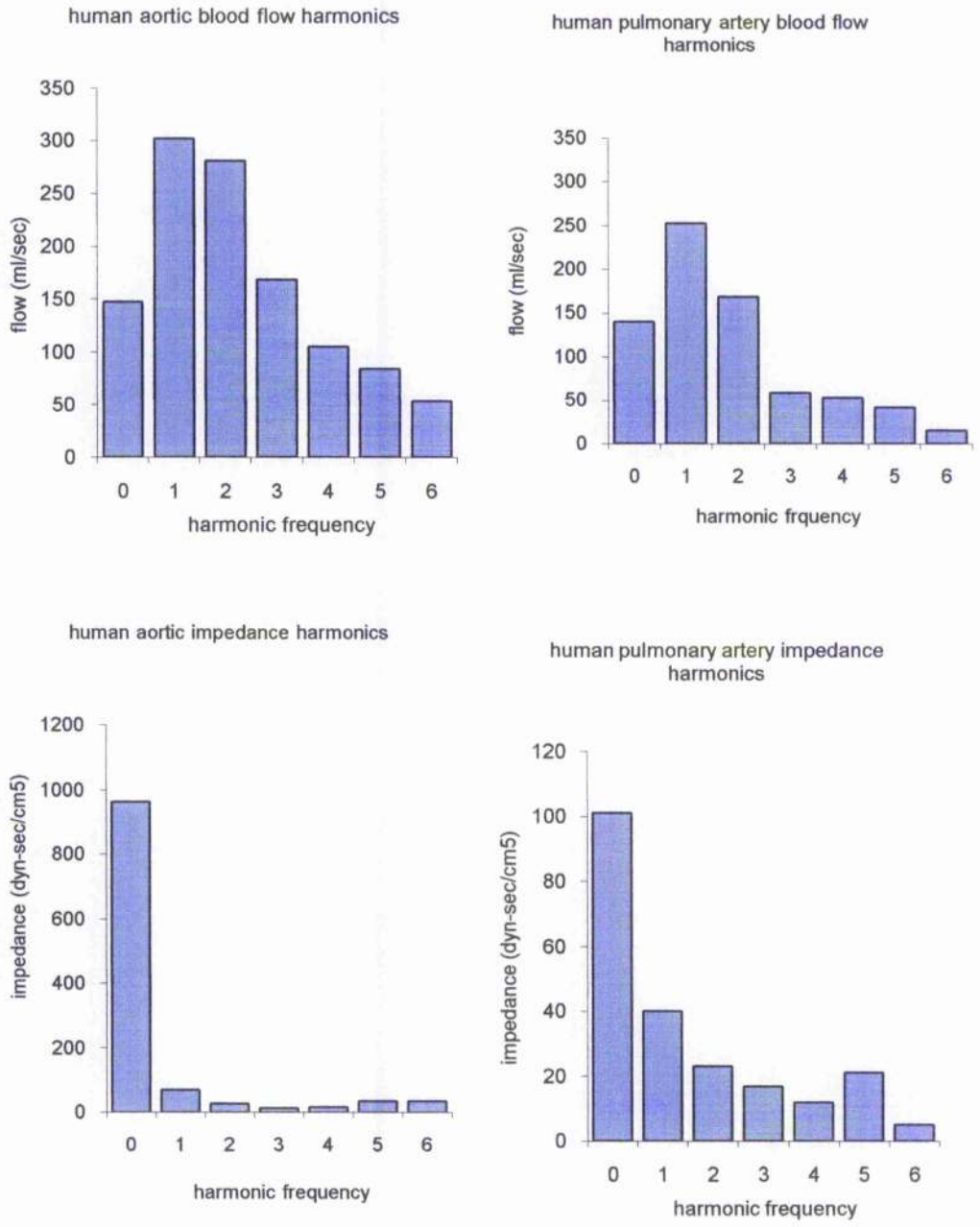
In children and animals, pressure wave contour in different systemic arteries can be explained from wave reflection (at upper and lower body) leading to a prominent diastolic wave. As age increases this disappears. It is attributable to a high wave velocity leading to reflected waves from the upper and lower body both fusing together and combining with the initial wave generation, from the ventricle. They become prominent when wave velocity falls or duration of ejection shortens, (ie shock or hypotension).

1.7.5. Pulmonary artery wave reflection

The oscillations in pulmonary vascular impedance result from wave reflection in animal studies (Bergel, D. H. et al 1965; Caro, C. G. et al 1961). Pressure wave reflections

originate from the pulmonary microcirculation but also from branch points in the large vessels (Piene, H. et al 1982). The timing of these reflections to the entrance of the pulmonary bed depends on the distance of the reflecting site and also the wave transmission velocity Distance of the reflecting site is much shorter in the pulmonary circulation compared to systemic circulation. The low pressure / high compliance nature of the pulmonary vasculature leads to a slower velocity compared to systemic circulation (O'Rourke, M. 1982; Westerhof, N. et al 1972). The matching of wave transmission velocity and arterial length results in the same pronounced impedance minimum seen in both circulations. Maximum flow amplitude occurs at the same frequencies where impedance is lowest.

Figure 1.7: Graphical example of matched pulmonary and aortic impedance and blood flow harmonics. (Matched for transmission velocity and arterial length)



Maximal flow amplitude with minimum impedance leads minimum expenditure of pulsatile power and thus optimal vascular-ventricular coupling. This relationship is

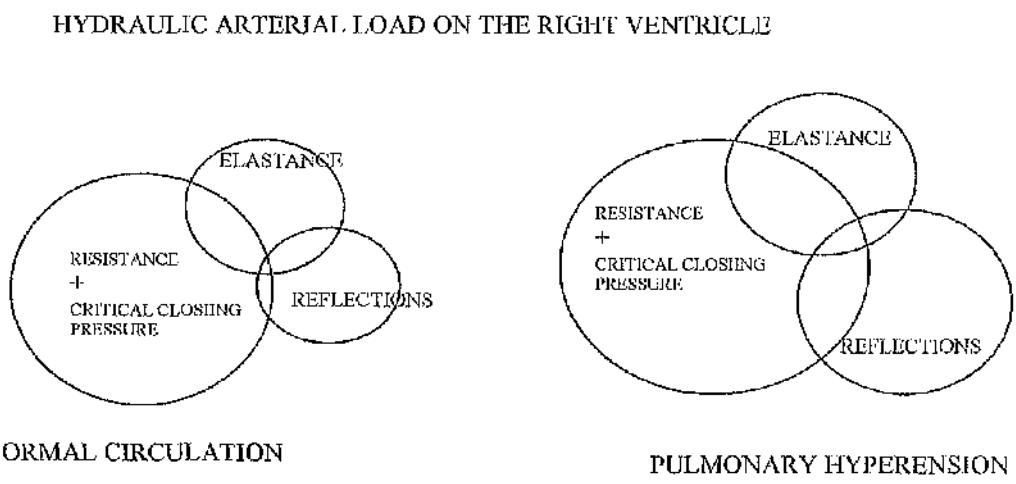
adjusted by the phase relationship between pressure and flow, power being proportional to the cosine of this angle (Kuusmaul, Noordergraaf et al. 1992). It is worth noting that the flow patterns at vascular junction are more affected compared to pressure from reflected waves as reflected waves subtract from flow in one direction of the branch and adds to it in the other but reflected waves add to pressure waves in all branches of the junction.

In pulmonary hypertension, lower compliance leads to a faster wave reflection velocity, which in turn leads means reflections occur earlier during systole and enhance the systolic pressure load on the right ventricle. This occurs in the systemic circulation but can be reduced by nitroglycerin (Fitchett, D. H. et al 1988). Effects of vasodilators on the pulmonary vascular impedance in hypertension, has not been adequately investigated.

Computer models of the pulmonary circulation suggest that, if large vessel compliance is unchanged, the usual vasodilator response, (increase flow and decreased ejection time) leads to a small decrease in mean pressure and little change in SPAP, and consequently pulse pressure increases and DPAP decreases. However, if vasodilators result in the opens previously closed vascular channels closed by pathological vasoconstriction they would reduce PVR and diminishes the contribution of reflected waves on the SPAP. Unless pulmonary artery compliance decreases or pulmonary artery resistance declines more than systemic vascular resistance there will not be a decrease in SPAP (Sniderman, A. D. et al 1988).

In summary, pressure generated by the right ventricle is determined by the flow output from the ventricle and the hydraulic arterial load.

Figure 1.8: Venn diagrams of relative contributions of elastance, reflections and resistance &critical closing pressures to hydraulic load on the right ventricle in normal humans and pulmonary hypetension



In the pulmonary circulation, elastance (compliance) and wave reflections may become more important to the overall hydraulic load compared to the normal pulmonary circulation. Thus PVR only describes part of the load on the heart.

Increasing CO is beneficial to the circulation as an increased SV reaching the systemic circulation will lead to a diuresis, less fatigue and more well being. But increasing CO could result in increase load on the right ventricle and lead to heart failure and death. The reason for the increased load on the right ventricle can be seen when considering the end-systolic pressure-volume relationship (Sagawa, K. 1978; Sagawa, K. 1981). If a vasodilator results in an increase in CO, this consequently leads to an effect on the right ventricle. The increased venous return leads to a right ventricular pressure change. If

SPAP & contractility do not change, an increased SV requires increased right ventricular end diastolic (RVED) volume. RVED volume increases result in an increased ejection fraction and increasing diastolic and systolic wall tensions. If RV already generating excessive power, this will be harmful.

If SPAP are reduced, an increase in SV can be achieved by a decrease in RVSD volumes and perhaps RVED volumes leading to reduced systolic and diastolic wall tensions and thus beneficial to the overworked RV.

Thus only if pulmonary pressures are reduced can the vasodilator be beneficial to RV performance. This occurs rarely (Rich, S. et al 1983).Calcium blockers can sometimes do this (Rich, S. et al 1985).

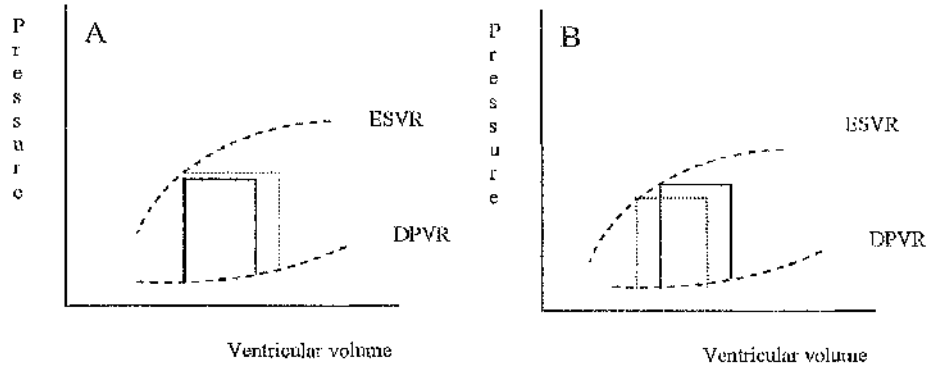
Figure 1.9: The pulmonary vasodilator effect on pressure volume relationship in the right ventricle, with increased CO.

A. When PAP unchanged, increased SV achieved by increased EDV

B. When decresed PAP, systolic volume and wall stress decrease, and if RV function improve, EDV and stress will decrease

ESPVR = end-systlic pressure-volume relationship

DPVR= diastolic pressure volume relationship



1.7.6 Animal Studies of Impedance and Hydraulics

Several studies have been performed in rabbits (Caro, C. G. et al 1961; Engelberg, J. et al 1959) and dogs (Bergel, D. H. et al 1965; Elkins, R. C. et al 1971; Pace, J. B. 1971; Patel, D. J. et al 1963; Reuben, S. R. et al 1971b), studying impedance and hydraulics in the pulmonary circulation. These had many differences in methodology, but similarity in results.

These studies showed that there was an overall similarity of the pulmonary input impedance pattern to that of the ascending aorta. Impedance moduli decreased rapidly from a high level at 0 hz (Z_o), to significantly lower levels at higher frequencies.

However there are several differences between the pulmonary and aortic impedances including an increased distensibility of pulmonary artery (slope of the decline related to pulmonary artery compliance). There are many differences in the pulmonary input impedance spectrum as compared to the systemic circulation which suggest diminished wave reflection in comparison to the systemic circulation. In some subjects, a clear early impedance minimum and secondary rise at twice its frequency point to a relatively discrete and symmetric effective reflection site. This may correspond to the major division of the main pulmonary artery into two branches (Kuusmaul, W. G. et al 1992). In hypoxia, it has been found that the impedance first minimum changes from 3.5 to 5.6, and with serotonin to 6.6 in dogs (Reuben, S. R. et al 1971b). With sympathetic nerve stimulation this moved to 7.5. This indicates a major change in the site of wave reflection, so the site was more proximal. Thus the site of vascular resistance moves more proximal.

1.7.8. Hydraulic Energy

One of the consequences of the pulsatile nature of blood nature of blood flow is that more energy is used to move blood per minute than if the heart somehow generated non-pulsatile flow.

The hydraulic energy associated with blood flow of two types, potential energy which is the product of flow and pressure, (E_p = Q.P) and kinetic energy which is calculated as the physical mass of blood and square of its velocity, (E_k = ½ m.v^2).

Both types of energy depend on instantaneous flow and velocities, and are underestimated when calculated from mean pressure, cardiac output or SV. The difference in estimated energy to actual energy can be regarded as a kind of 'extra' energy due to pulsations.

This pulsatile component normally makes up about one third of the total hydraulic power output of right ventricle and one tenth of left ventricular output (but can increase to approximately one third of left ventricular output in aortic coarctation) (Milnor, W. R. et al 1969).

Right ventricular pulsatile power is affected by a change in heart rate, the compliance of the branches of the large pulmonary arteries and by wave reflection (Milnor 1983). The System is most efficient when flow occurs during low impedance. As proximal portion of vasculature contains most pulse wave energy, it is most efficient to have low impedance here.

In normal humans PAPP is approximately 50% of PAP. Thus the pulsatile arterial power generated by the RV is an important proportion of total external power (30-40%).

An important issue is, do vasodilators reduce pulsatile pressure & thus power requirements.

An important component of pulsatile hydraulic load is the elasticity of the large and medium size arteries. Normal pulmonary arteries are thinner walled compared their systemic counterparts and the more distensible elastic vessels extend to arteries of 1mm in size (Sniderman, A. D. et al 1988). Consequently the pulsatile load in the pulmonary circulation is less (although a bigger proportion of total) compared to the systemic circulation. As pulmonary hypertension develops the distensibility (or compliance) of the elastic arteries decreases (Reuben, S. R. et al 1971a), partially due to structural changes in the pulmonary circulation, and also in part due to the higher pressures the arteries operating in the steeper portion of their pressure-volume relationship. Thus a larger amount of right ventricular energy must be expended to distend the stiff pulmonary arteries.

If vasodilators were able to decrease the PAP, it could be assumed that compliance would increase as the arteries move down their pressure-volume relationship. Were this to occur, we would find a disproportionate fall in the systolic pressure compared to mean pressure.

1.7.9. Right Ventricular Haemodynamics

Compared to the systemic circulation, pulmonary circulation is unique in its ability to transport an equivalent amount of flow with substantially lower pressures. In addition, the pulsatile nature of ventricular ejection and the homeostatic requirements for an equivalent amount of blood ejected per beat from each ventricle, place unique constraints upon the right ventricle and the opposition to forward flow in the pulmonary circulation (Kuusmaul, W. G. et al 1992).

There are several differences between normal right and left ventricles. The right ventricle is thin walled, with one third of the muscle is in continuity with the left ventricle. It has a bellow shape and inertial forces dominate the development of intracavity pressure (result in sufficient pressure for ejection).

The presence of low pulmonary vascular resistance minimises load on right ventricle by matching output impedance of pump with input impedance of pulmonary vascular system (Milnor, W. R. 1982).

1.7.10. Characteristics of the Pulmonary Artery

The external hydraulic components of opposition to forward flow in the pulmonary circulation must be different its systemic counterpart, in order to produce the same flow at such a reduced pressure. At the steady state, the term of opposition (resistive, PVR) to flow must be substantially less than systemic vascular resistance. The vascular distensibility in the pulmonary circulation must be greater than the systemic circulation. The intrapulmonary course of the vasculature has a radial distribution of perivascular

and interstitial pressure. It is subject to gravitational (postural) affects and has a distinct pattern of vascular division

But there are also similarities with the systemic circulation. The amount of blood ejected per beat and the size of the proximal vessels are similar in both the systemic and pulmonary vasculature.

The differences in the pulmonary circulation lead to certain features. There is increased distensibility and decreased resistance and thus a low PAP. If PAP was equal the systemic pressure then there would be transudation across the alveolar membrane and pulmonary oedema.

The proximal portions of the right and left circulation are both within the intrathoracic cavity. But only the pulmonary circulation has the rest of its vasculature in the intrathoracic cavity. This leaves it subject to variations in the intrathoracic pressure.

The remarkable pattern of vascular division in the pulmonary circulation leaves a rather short proximal elastic pulmonary artery and a complex pattern of distal branching and tapering. This has important implications for wave reflections and transmission (Kuusmaul, W. G. et al 1992).

1.7.10.1 Compliance

Decreased arterial compliance is unlikely to cause major impairment of large pulmonary and systemic arteries. For instance, aging decreases compliance but does not cause heart disease (Gonza, E. R et al 1974).

1.7.10.2. Resistance

Increased pulmonary vascular resistance leads to impaired right heart function. This causes increased pressure, causes decreased vascular compliance and increased load on the right ventricle This is associated with symptoms and death (Reeves, J. T. et al 1988b).

1.7.10.3. Pulmonary artery, resistance, compliance and the right ventricle

Reduced compliance of pulmonary arteries is associated with increased mortality (Gan, C. T. et al 2007). Pulmonary vascular resistance increases alone lead to PAP becoming narrow (animal studies). This is not seen in pulmonary hypertensive patients. They have an increase in PAPP as chronic increases in pulmonary vascular resistance leads to increases in the turgidity and the thickness of the walls of large pulmonary arteries. Both lead to decreases in the compliance in large Pulmonary artery (Milnor, W. R. et al 1978). A decrease in compliance affects the right ventricular load in the following way. If the changes that occur with decreased compliance and increased pulmonary vascular resistance in animals resemble those of patients, with decreased flow, right ventricular hypertrophy and increased pulmonary arterial pulse pressure then reduced compliance and increased pulmonary vascular resistance lead to a decrease in flow. This implies that low compliance imposed an additional load to the right ventricle.

Decreased lung vessel compliance by up to sixteen fold, with an unchanged pulmonary resistance leads to a reduction of blood flow but the reduction in flow is less than that caused by a fourfold increase in pulmonary vascular resistance. This leads to an increase in right ventricular systolic pressure. Pulmonary arterial diastolic pressure remains low but with an increase in PAPP. Thus decreased compliance of large pulmonary vessels

contributes to loading of the Ventricle & may be responsible for large PAPP in pulmonary hypertension. Even in mild pulmonary hypertension, where there is an absence of gross abnormalities in the right ventricle, the mechanical function of the right ventricle may be affected, leading to dyssynchrony (Lopez-Candales, A. et al 2007).

In the systemic circulation, there is an increased in systemic systolic and pulse pressures with increasing population age due to stiffened vessels and hypertension. The pressure wave has an increased amplitude, late peak and absence of norm diastolic wave (O'Rourke, M. F 1985).

The degree of Left ventricular hypertrophy is related to systemic systolic arterial pressure and to arterial pulse velocity, even at a constant systemic diastolic pressure, and thus decreased compliance, independent to left ventricular systolic load (Bothier, B. N. et al 1985).

In the isolated heart, reduced pulmonary artery compliance affects the right ventricular pressure, leading to a change shape of the pressure curve.

In normal subjects, the pressure contour resembles a square wave (high fidelity catheters). In pulmonary hypertension, the normal right ventricular pressure contour is followed by a secondary pressure rise. This is not seen in pulmonary valvular stenosis, but only when the obstruction to flow is distal (Reeves, J. T. et al 1988b). This suggests that a load that is imposed in late systole leads to a right ventricular response and

increasing pressure. Late pressure rises account for 30-40% of the total systolic pressure.

Hori et al (Hori, M. et al 1981) confirmed that a load suddenly imposed during ejection leads to a change in the pressure contour within a beat.

Imposing impedance on the left ventricle early in systole leads to an early increase in left ventricular pressure, similar to that seen in with that seen in the late introduction of impedance. Thus during a single contraction, the left ventricle can perceive a change in load and respond. No change in power is required if flow decreases and pressure increases.

Extrapolating to the pulmonary circulation, we can speculate that a late systolic load is behind the increases in pressure seen in pulmonary hypertension. We can also state that the pressure contour arises from an abnormal circulation, as obstruction at the outlet valve does not lead to a change in contour (Reeves, J. T. et al 1988b) and also Decreases in compliance lead to a late load rise (Elzinga, G. et al 1980).Thus, decreased Compliance lead to a late load rise, increased right ventricular pressure and pulmonary hypertension. In vitro flow and pressure contours are similar in normals but dissimilar if there is an increases in pulmonary vascular resistance and decreases in compliance.

In animal models flow is maximal during early systole and pressure maximal during late systole. This suggests that a late load leads to impaired output (especially when the load is maximum). Data from isolated heart model resembles humans as measured by echo. In normals, maximal flow is during mid systole. In pulmonary

hypertension, maximal flow is during early systole. Doppler measurements confirm that as pulmonary vascular resistance increases, maximal flow becomes earlier (Kitabatake, A. et al 1983). Thus the pressure maximum occurs after the flow maximum in pulmonary hypertension and pressure rises as flow falls (later in systole). Increased pulmonary vascular resistance and decreased compliance, lead to a late load, and late systolic augmentation occurs by early return of reflected wave (O'Rourke, M. F 1985).

In dogs with congenital pulmonary stenosis and raised right ventricular pressure, in response to occlusive hypereamia, the normal increase in systolic coronary artery blood flow is decreased (and is less than diastole). Total flow is approximately 100% of the normal, but a higher work load is required by the right ventricle due, to increased pulmonary vascular resistance, and thus flow not adequate. This leads to right ventricular ischaemia (Franciosi, R. A. et al 1968; Gold, F. L. et al 1982). At post mortem right venticular infarcts are reported in pulmonary hypertension with normal coronary arteries (Carlson, E. B. et al 1985; Horan, M. et al 1981).

It is observed – RV adepts variably to similar severities of pulmonary hypertension as assessed by PAP and PVR. Improved evaluation would come from using pulsatile haemodynamics and would allow a better understanding of right ventriculovascular coupling (Kuusmaul, W. G. et al 1992). The use of pulsatile haemodynamics could also explain the disappointing clinical results of vasodilators selected exclusively on the basis of PVR in patients with pulmonary hypertension (Sniderman, A. D. et al 1988).

1.8. Pharmacological Agents

1.8.1. Nitric Oxide

Following the identification of nitric oxide (NO) in 1986 as a factor known to be a mediator in the relaxation of blood vessels, there has been an exponential increase in the understanding if its biological role (Murad, F et al 1995; Murad, F. 2006). NO is an unstable radical, with a molecular weight of 30g/mol, and with a low blood-gas partition coefficient.

The affinity of haemoglobin for oxygen is 10^6 times less than that for NO (Borland, C. 1991). In the lungs, nitric oxide combines with oxygen and water and leads to methaemoglobin and nitrate entering the systemic circulation. This reactivity with oxygen and methaemoglobin, leads to a short half life and limits the effect of NO on the pulmonary circulation (Carlsen E & Comroe JH Jr 1958). The half life of NO has been estimated at between 0.05 to 1.8 milliseconds (Celermajer, D. S. et al 1994; Stamler, J. S. et al 1994) Because of this NO must be continuously produced.

1.8.1.1. Physiological Effects

Stamler et al (1994) & Celermajer (1994), demonstrated that there must be a continuous release of NO even at rest in normoxia, as when they infused a NO antagonist into the pulmonary circulation in both adults and infants respectively, they increased pulmonary vascular resistance and decreased pulmonary blood flow velocity.(Fagan, K. A. et al 1999). During hypoxia, it is likely that NO production is increased as with the endothelial NOS knockout mice, which develop pulmonary hypertension in hypoxia (Isaacson, T. C. et al 1994; Zhao, L. et al 1993). Experiments have also demonstrated that even in chronic hypoxia, there must be continuous production of NO. When NO is

inhibited under these conditions, there is an increase in basal vascular tone (Ignarro, L. J. et al 1987; Ignarro, L. J. et al 1999; Singh, S. et al 1997).

NO inhibits platelet aggregation and is also a potent inhibitor of smooth muscle cell migration and proliferation, and both of which would oppose the development of pulmonary hypertension, by reducing in-situ thrombi and remodelling (Borland, C. 1991).

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1.8.1.3. Toxicity

At the levels of NO used clinically, less than 80ppm, if used for only a few hours, NO has very few side effects.

1.8.1.4. Therapeutic Use

Compared to systemic agents, NO has several potential advantages in both the investigation and treatment of pulmonary hypertension. It has few of the systemic side effects (Pepke-Zaba, J. et al 1991) due to its short half life, and it is a potent and selective pulmonary vasodilator (Clark, R. H. et al 2000; Clark, R. H. et al 2003; Davidson, D. et al 1998; Journois, D. et al 1994). As mentioned earlier in this chapter, it is an ideal agent for the vasodilator test required in the assessment of pulmonary hypertension. Its is now routinely used in the treatment of persistent pulmonary hypertension of newborns and has been found to improve the outcome in this condition (Leier, C. V. et al 1983).

1.8.2. Dobutamine

Dobutamine was originally developed as a synthetic catecholamine for short term parenteral administration and became clinically available in 1978 (Leier, C. V. et al 1983). It is a powerful ionotrope, with relatively mild chronotropic and vascular effects. The predominant mechanism of action, augmentation of myocardial activity, is mediated through predominantly $beta_1$ adrenergic receptor stimulation. However, at standard doses, it also has $beta_2$ and $alpha_1$ agonist activity. The effects of these additional activities are normally balanced, and so have very little effect on the systemic vasculature (Leier, C. V. et al 1979).

The plasma concentration of dobutamine seems to be directly related to its haemodynamic effects (Kates, R. E. et al 1978) In clinical practice, dobutamine infusions use are commenced at 2-3 $\mu g\ kg^{-1}\ min^{-1}$ increments every 10-30 minutes until the desired effects are obtained. Usually at doses greater than 15 $\mu g\ kg^{-1}\ min^{-1}$ side effects such as headaches, tachycardias, arrythmias, headaches, anxiety, tremors and blood pressure changes may occur. The onset of action of a continuous infusion of dobutamine, usually occurs within 2 minutes, with maximal effects occurring after 10 or more minutes. Due to the short plasma half life of 2.37 ± 0.70 minutes (in cardiac heart failure) means that most of the drug will be metabolised within 10-12 minutes of the infusion being stopped.(Loeb, H. S. et al 1977; Stoner, J. D., III et al 1977). Its major metabolites are pharmacologically inactive. Unlike some other clinically used catecholamines, dobutamine does not alter ventricular pressures (Mishra, M. B. et al 1997).

In many cardiology departments, dobutamine is often used as a surrogate to exercise, in order to perform a cardiac stress test. A standard protocol for this, uses 3 minute stages, with incremental doses, and with the range of infusion being given, ranging from 5 to 40μg/kg/min (Mishra, M. B. et al 1997). Mishra et al, (1997) investigated the haemodynamic effects of dobutamine in 69 human subjects being investigated for ischaemic heart disease, and found that in these subjects mean stroke volume rose from 67.5ml pre test, to 82 ml on 20 $\mu g\ kg^{-1}\ min^{-1}$ dobutamine and 85ml on 40 $\mu g\ kg^{-1}\ min^{-1}$. Only 26% of subjects reached their maximal stroke volume, by using 10 $\mu g\ kg^{-1}\ min^{-1}$ of dobutamine (Vatner, S. F. et al 1972; Vatner, S. F. et al 1974). Studies in animals have shown that the prime action of dobutamine is on contractility, with myocardial contractility increasing by 82% in exercise compared with 125% with dobutamine (Cohen, J. L. et al 1993).

Another study, comparing dobutamine to exercise, found when using the standard dobutamine stress testing protocol, (with dobutamine used up to doses of 40 $\mu g\ kg^{-1}\ min^{-1}$), that none of the subjects investigated had any fatigue, versus 58% in the exercise group ($p<0.001$). 29% of patients had arrhythmias in the dobutamine group versus 8% in the cardiac group ($p<0.05$), the majority were clinically non-significant arrhythmias, like premature beats, but 4% of subjects had a supraventricular tachycardia. Only 4% had non-sustained ventricular tachycardias (Bradford, K. K. et al 2000; Jenkins, I. R. et al 1997; Murali, S. et al 1991; Schneider, A. J. et al 1987).

The effects of dobutamine on the pulmonary circulation are more difficult to ascertain. Studies suggest dobutamine reduces PVR. (Ducas, J. et al 1992; Furman, W. R. et al

1982; Hyman, A. L. et al 1985; Lejeune, P. et al 1987b; Light, R. B. et al 1988) However, these studies do not take account to flow affects on PVR. Where flow conditions have been controlled, pulmonary vascular resistance, as ascertained from the gradient of the difference of pulmonary arterial inflow and outflow pressure against flow, has been found to either remain static, increase or decrease.(Pagnamenta, A. et al 2003).

A study by Pagnamenta et al, of experimentally induced pulmonary hypertension in 10 anaesthetised and ventilated dogs, found that dobutamine up to a concentration of 10 μg kg^{-1} min^{-1} had no effect the pressure flow gradients produced in these animals (Pagnamenta, A. et al 2003). However, at higher doses, the effect is dependant on the existing tone. If the existing tone is high, dobutamine may reduce the pressure flow plots, and if the basal tone is low, it may increase the pressure flow gradient (Lejeune, P. et al 1987a). Previously, the same team demonstrated that in dogs, dobutamine at 10 μg kg^{-1} min^{-1} did not affect the pressure flow plots during hypoxia or hyperoxia. 20 μg kg^{-1} min^{-1} led to an increase in the difference between pulmonary arterial pressure and occlusion pressure at the lowest flows in hyperoxia, but in hypoxia decreased it at all levels (Lejeune, P. et al 1987a).

1.9. Pulmonary Artery Pressure: Methods of Measurements

1.9.1 Swan-Gantz Catheterisation: Brief overview

Right heart catheterisation is the most useful investigation in pulmonary hypertension as it allows the measurements of a number of important variables. The swan-gantz catheter allows the right atrial and ventricular pressures to be measured before it is placed in the pulmonary artery and an indirect measurement of the left atrial pressure can be made, by obstructing a branch of the pulmonary artery using a balloon. The catheter can also be used to measure pulmonary artery pressure and using the thermodilutional method, an indication of cardiac output can be made.

1.9.1.2. Measurements & Accuracy

Using a swan ganz catheter allows various measurements to be made but the accuracy of these is variable. As the pressure is measured using a fluid filled catheter, they are limited in accuracy as they are liable to artefacts such as overshooting and over dampening. An accurate estimation of the zero point is also required.

1.9.1.3. Disadvantages & Problems

Apart from the risk from an invasive intervention, the measurements can only be made in a supine position and that real life daily haemodynamic changes cannot be determined.

1.9.2. Ambulatory Pulmonary Artery Catheter: A Brief Overview

Attempts have been made to measure continuous pulmonary artery pressures by fluid filled catheters in a partially ambulatory subject (Levy, R. D. et al 1986). Although they managed to get a limited amount of data on ten patients, this method was fraught with

problems. There was a difficulty of localising the zero reference point, there was a requirement for anticoagulation, and there was a need for filtering for data retrieval. In addition Levy et al (1986) (Levy, R. D. et al 1986), found that a change in posture altered the zero reference point by 4 mm and that there were often substandard recordings due to repeated clotting of the catheter tip and dampening of the sine pressure wave. They were also problems with the equipment and a liability to artefacts. They were satisfactory in measuring stationary pressure, but have limitations in fidelity when they are used with varying pressure.

In order to measure it during daily activities of living and during exercise tests another method of measurement was required. Micro-manometer tipped pressure catheters were ideal. Levy et al (1986), validated these catheters against fluid filled catheters (Levy, R. D. et al 1986). The amplitude response, the method of measuring pressure, was constant over a selected band of frequencies and fell off at frequencies above and below this. If high frequency response was severely limited then the fastest moving components, the upstroke (systolic pressure) may have been underestimated. This was the case with fluid filled catheters which underestimate the systolic pressure by up to 20 % compared with the micromanometer tipped catheter.

1.9.2.1. Measurements, Accuracy & Risk

As mentioned earlier, the micromanometer tipped catheter has been validated by Levy et al, (1986) as well as Gibbs et al (1989,1992), when compared with fluid filled catheters (Gibbs, J. S. et al 1989; Gibbs, J. S. et al 1992). There are however a number of problems associated with these catheters. One problem with the micromanometer tipped catheters was zero drift. This has been overcome in the newer catheters, by

zeroing it during the in vivo measurements on several occasions and then using a computer program to readjust all the measurements to correct for this (Raeside, D. A. et al 1998; Raeside, D. A. et al 2000; Richards, A. M. et al 1990). In addition, the pressure transducer was placed at the catheter tip, making the tip its own zero reference point.

1.9.2.2. Use in Pulmonary hypertension

The micromanometer tipped catheter has been used to measure pulmonary artery pressure while lying flat, sitting, while asleep and during exercise. Raeside et al (1998, 2000) and Richards et al (1990), performed several studies using these catheters successfully (Donald, K. W. et al 1953; Fagard, R. et al 1990; Grenvik, A. 1966; Hillis, L. D. et al 1985; Reddy, P. S. et al 1976; Reeves, J. T. et al 1961a; Sekelj, P. et al 1958; Vissher, M. B. et al 1953; Warburton, D. E. et al 1999a).

1.10. Measurement of Cardiac Output

There are various methods of measurement cardiac output. These range from non-invasive methods like Doppler echocardiography, thoracic bio-impedance cardiography, semi invasive techniques like LIDDCO, and PICCO, (both of which have not been validated for exercise) and invasive techniques like thermodilutional cardiac output or Fick method. They have various problems including, accuracy, difficulty of implementation during exercise, reproducibility and risks. There may also be some difficulty in performing them during exercise.

1.10.1.Invasive

1.10.1.1. Gold Standard

Invasive techniques, namely the direct Fick and dye-dilutional methods, are still currently the gold standard methods for measuring cardiac output. A number of studies have been performed comparing these two methods, performed in the 1940's to 60's, showing that they give reliable and valid determinations of cardiac output at rest and submaximal exercise to an accuracy of within 5-10% (Doyle, J. T. et al 1953; Eliasch, H. et al 1920; Friedlich, A. et al 1950; Miller, D. E. et al 1962; Thomasson, B. 1957; Warburton, D. E. et al 1999a). The measurement of cardiac output via the Fick method relies on the measurement of oxygen from an artery and on mixed venous blood sampled centrally (pulmonary artery), along with a measure of oxygen consumption, by the body (lungs), during a steady state condition (Warburton, Haykowsky et al. 1999). This requires a pulmonary artery catheter to be inserted centrally, and then cardiac output, $\dot{\mathbf{Q}}$ is calculated by the Fick equation,

$$\dot{Q} = \frac{\dot{V}O_2}{CaO_2 - C\bar{v}O_2}$$

This gives an accurate measurement of cardiac output (Kopelman, H et al 1951; MacCanon, DM et al 1955; Warburton, D. E. et al 1999a), at rest or submaximal exercise, but becomes a problem in maximal exercise when a steady state of exercise for 2-3 minutes is not achievable. It also requires highly trained personnel to perform precisely and meticulously, and without this becomes more inaccurate (Clausen, J. P. et al 1970; Grenvik, A. 1966; Hillis, L. D. et al 1985; Mohammed, M. M. et al 1981; Warburton, D. E. et al 1999a). In addition there may be problems with cardiac catheterisation, including arrhythmias, and perforation of the artery or right ventricle (Ekblom, B. et al 1968; Strand, P. O. et al 1964).

1.10.1.2. Thermodilutional

The thermodilutional technique can be used to measure $\dot{Q}$ at both rest and exercise. It is based on the same technique as the dye-dilutional test, but replaces the dye with cold saline (or 5% dextrose) injected through a proximal port of a pulmonary artery catheter. This cools the blood and this blood is measured at the tip of the catheter by a thermistor. The amount of cooling is inversely proportional to $\dot{Q}$ (Nishikawa, T. et al 1993).

The advantages of thermodilution compared to the dye-dilutional method is that it produces no changes in the indicator baseline, allows numerous measurements to be made and recirculation is of little concern (Nishikawa, T. et al 1993).

Its disadvantage is that as heat is used as a marker, a proportion of it may be lost during handling of the syringes and in the catheter before it enters the circulation (Mackenzie, J. D. et al 1986; Russell, A. E. et al 1990). The error due to the temperature of the

injected water not being ice cold is that $\dot{Q}$ is approximately 2.86% overestimated for every 1°C that the injectate temperature is warmer (Nishikawa, T. et al 1982; Nishikawa, T. et al 1988; Nishikawa, T. et al 1990; Nishikawa, T. et al 1992). For every 13 seconds a glass filled syringe is held in a hand at 36°C, the 10ml of iced water will increase in temperature by 1°C, (Evonuk, E. et al 1961). Further more, physiological variations occur in blood temperature as a result of phasic heat exchange of air in the lungs (Kohanna, F. H. et al 1977; Nishikawa, T. et al 1993). Using iced fluid may also lead to a transient slowing of the heart and alterations in systemic and pulmonary arterial pressures, right atrial pressure, and right ventricular pressure (Cigarroa, R. G. et al 1989; Hillis, L. D. et al 1985; Nishikawa, T. et al 1993; Ohteki, H. et al 1981; Olsson, B. et al 1970; Rahimtoola, S. H. et al 1965; Samet, P. et al 1966a; Samet, P. et al 1966b),. These effects are greater the cooler the fluid is and the larger the volume (Cigarroa, R. G. et al 1989). In subjects with a low cardiac output, it may overestimate cardiac output due to recirculation of the indicator before analysis is complete (Konishi, T. et al 1992).

In patients with valvular heart disease, it has been found that thermodilution cardiac output is often unreliable (Hamilton, M. A. et al 1989). In tricuspid regurgitation, this may lead to an underestimate of cardiac output (Hoeper, M. M. et al 1999). Konishi et al (1992) found that a combination of a low cardiac output state and tricuspid regurgitation have opposing errors which may cancel out and lead to a more accurate result ($r = 0.98$, slope = 0.86). Similar results have been found in other studies (Branthwaite, M. A. et al 1968; Espersen, K. et al 1995; Mackenzie, J. D. et al 1986; Russell, A. E. et al 1990; van, Grondelle A. et al 1983). Hamilton et al (1989) also

reported little difference between Fick measurements and thermodilution measurements in subjects with heart failure and tricuspid regurgitation (r =0.8). Similar findings have been found by others (Hsia, C. C. et al 1995; van, Grondelle A. et al 1983).

In patients with pulmonary hypertension, Hoeper et al (1992) found an acceptable agreement between Fick and thermodilutional cardiac output measurements (mean ±95%, +0.01±1.1L/min), but with a large splay of single results of approximately ±1.1L/min (±30%). Similar findings have been found by others (Becklake, M. R. et al 1962; Chapman, C. B. et al 1950; Werko L et al 2006; Zeidifard, E. et al 1976)

The accuracy of the thermodilutional technique is debatable, and certainly it is not a gold standard method, but it has found widespread use in clinical practice. Many studies have reported that this measurement may overestimate the value of $\dot{Q}$ compared to Doppler echocardiography, CO_2 rebreathing, and direct Fick methods, during supine or upright rest and light exercise of up to 40% (Warburton, D. E. et al 1999a) and this error may be even greater during vigorous exercise (Clausen, J. P. et al 1970; Espersen, K. et al 1995).

1.10.2 Non-Invasive

Other methods of measuring cardiac output include the foreign gas method, indirect Fick method and Doppler echocardiography. The foreign gas method has been found to be less accurate during resting conditions and in subjects with pulmonary conditions (Clausen, J. P. et al 1970; Farhi, L. E. et al 1976).

The results of the indirect Fick method may vary from direct Fick by 0 to 31% at rest (Espersen, K. et al 1995; Gardin, J. M. et al 1984; Shaw, J. G. et al 1985) and 2 to 19% during exercise (Christie, J. et al 1987; Shaw, J. G. et al 1985).

Doppler echocardiography has several possible areas in which errors can be introduced resulting in a lot of inter and intra operator variability (Kubicek, W. G. et al 1966), and in studies, Doppler echocardiography has been found to often underestimate $\dot{Q}$ when compared to other methods of measuring cardiac output, by up to 21% (Sramek, B. et al 1983) or may overestimate in the supine posture (Bernstein, D. P. 1986).

1.11. Thoracic Bio-impedance

In 1966 Kubicek et al (Kubicek, W. G. et al 1966) described a method of calculating stroke volume, i.e. cardiac output ($\dot{\mathbf{Q}}$) , from thoracic impedance signal. However obtaining the results required special electrodes, a specific configuration, vigorous skin cleansing, and measurements of distances between electrodes were required. It was also assumed the thorax was like a cylinder. All these factors may lead to the introduction of errors into the assessment. Later, Sramek et al (1983)(Osypka, M. J. et al 1999) suggested an alternative equation likening the thorax to a truncated cone. This equation has been further modified by Benstein et al (1986) (Osypka, M. J. et al 1999) to improve accuracy. There are now a number of commercially available instruments available for the measurement of bioimpedance, incorporating these equations.

One of the more recent devices is the Physioflow® (Manatec Biomechanical, Macheren, Paris). This had further modified the equation to allow ease of use and a more accurate result.

1.11.1. Basic Principles & Theory

In electricity an analogous relationship exists to the biological relationship between cardiac output $(\dot{\mathbf{Q}})$, pressure gradient (**MAP – CVP**, where **MAP** is the mean arterial pressure and **CVP** is central venous pressure) and peripheral vascular resistance (**R**),

where $\dot{\mathbf{Q}} = \frac{\mathbf{MAP - CVP}}{\mathbf{R}}$. This is Ohm's law where the flow of a direct current, **I**, is analogous to $\dot{\mathbf{Q}}$, is equal to the voltage drop, **E**, between the two ends of circuit with resistance, **R**, giving us

$\mathbf{R} = \frac{\mathbf{E}}{\mathbf{I}}$, where **R** is measured in ohms (Ω).

If the current, **I**, remains constant then any change in resistance, **ΔR,** is proportional to any change in voltage **ΔE, i.e.**

$\mathbf{\Delta R \approx \Delta E}$, so any voltage drop would be due to a drop in resistance.

The resistance of an electrical object is dependent on the size, shape and resistivity of a material. For an alternating current, resistance is known as impedance, **Z**, and is frequency dependent. We would then obtain the equation,

$$\mathbf{Z} = \frac{\mathbf{E}}{\mathbf{I}}$$

Following the logic for the direct current, we get

$\mathbf{\Delta Z \approx \Delta E}$. **I** remains constant then any change in resistance, **ΔZ,** is proportional to any change in voltage **ΔE.**

The impedance of a simple cylindrical circuit, is equal to the specific resistance of the material, (ρ), times its length (**L**), divided by its cross sectional area, (**A**),

$$\mathbf{Z} = \rho \cdot \frac{\mathbf{L}}{\mathbf{A}}$$

Thus if both **L** and **ρ** remain constant, then **Z** is inversely proportional to the cross sectional area.

If like Kubicek et al(Kubicek, W. G. et al 1966) we assume that the thorax can be modelled like a cylindrical conductor, with length **L**, and which has embedded, within itself and in parallel with itself, a second smaller cylindrical conductor, the great vessels (Figure 1.10) (Osypka, M. J. et al 1999).

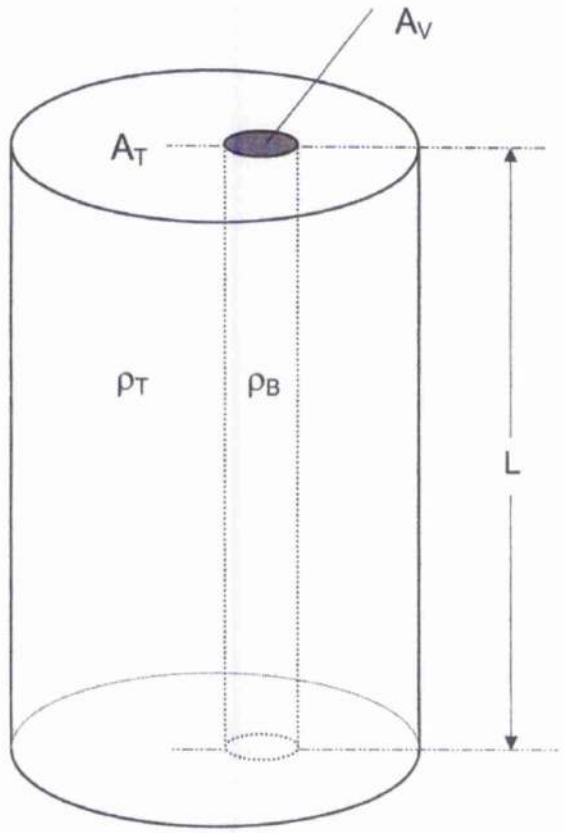


*Figure 1.10. Cylindrical conductor as a simple model of the human thorax. In this model, the great vessels (aorta, pulmonary artery) are considered as a smaller cylindrical conductor of cross-sectional area (A_V), length (**L**), and specific resistance (ρ_B) of blood, and the remaining thoracic volume is characterized by cross-sectional area A_T, length **L**, and specific resistance ρ_T ($\rho_B << \rho_T$). ©(Osypka, M. J. et al 1999)*

It is assume that with each beat-to-beat pulsation, the cross sectional area of the great vessels will alter, giving us an area, If ventilation is suspended, then it can be assumed that change in **Z**, (**ΔZ**), with each heartbeat, is caused mainly by changes in the cross sectional area of the great vessels.

By using all these assumptions and synthesising them with the theory of Ohm's law, the changes in the cross sectional area of the great vessels, in turn must lead to an inverse change in thoracic impedance. The impedance changes are directly proportional to the voltage and can be measured (Osypka, M. J. et al 1999) and varies directly and proportionally in time with changes in the pulmonary and aortic blood volume, (Khan, M. R. et al 1977), giving the following equation.

$$\Delta V(t) = \rho_B \cdot \frac{L^2}{Z_0^2} \cdot \Delta Z(t) \quad \text{or} \quad SV = \rho_B \cdot \frac{L^2}{Z_0^2} \cdot dZ/dt \cdot T$$

where Z_0, is the measured non pulsatile baseline impedance. This is the basis for thoracic bioimpedance and directly leads to the Kubicek equation (Osypka, M. J. et al 1999)where **SV** is stroke volume in ml, ρ is the resistivity of blood (135Ω cm), **L** is the measured distance between the neck and thoracic leads, **Zo** is baseline thoracic impedance (Ω) **dZ/dt** is the, maximum rate of change of impedance during systole (Ω/sec) and **T** is left ventricular ejection time (s).

Thus in practice a constant current is introduced across the chest and the voltage drop measured. This voltage measured is proportional to impedance across the chest. The major part of Zo does not change during beat to beat, only a small component due to the air to liquid ratio during breathing (Wang L. et al 1995).

In healthy adults Z_0 has a mean value of 30Ω (Bernstein, D. P. 1986; Kubicek, W. G. et al 1966; Sramek, B. et al 1983; Sramek, B. B et al 1983). Superimposed on this baseline impedance is change in impedance, ΔZ, which is due to both changes due to ventilation and due to blood flow, giving the following equation,

$$\mathbf{Z(t) = Z_0 + \Delta Z(t)}$$

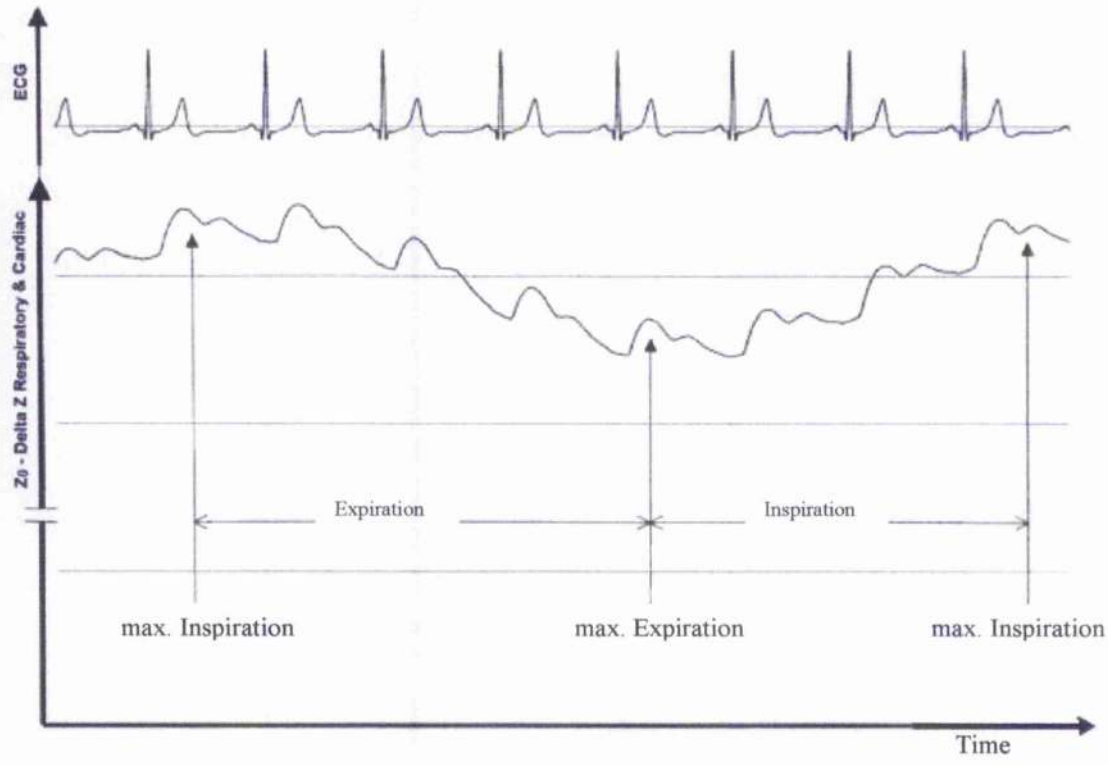


Figure 1.11. Variation of thoracic impedance Z(t) = Z_0 + [DELTA]Z(t) with a ventilation cycle and with each heart beat. The electrocardiogram on top is a reference for the impedance changes related to the cardiac cycle. © (Osypka, M. J. et al 1999)

The overall variations in impedance due to respiration are greater then the variation in impedance due to blood flow (Figure 1.11) (Appel, P. L. et al 1986; Goldstein, D. S. et al 1986).

If ventilation is suppressed or corrected for, only the cardiac component of thoracic impedance is left. This is usual about 0.1 to 0.2 Ω, (about 0.3% to 0.5% of total thoracic impedance). It was found in a theoretical model developed by Wang and Patterson (1995) (Gotshall, R. W. et al 1989), that blood vessel structural changes only contributed 4% to thoracic impedance.

1.11.2. Non-physioflow bio-impedance devices

Both the Kubicek, and the Sramek & Bernstein (Yakimets, J. et al 1995) methods of analysing bio–impedance derived cardiac output relies on sitting a set of two electrodes on the neck and two on the lower thorax, to inject and sense current, and four electrodes to sense an ECG.

These equations have been tested against each other and against invasive measurements on many occasions. In some diseases both these equations have performed adequately against thermodilutional measurements (Jensen, L. et al 1995).

Gotshall et al (1989) (Jensen, L. et al 1995) also compared the equations, using different equipment, against critically ill patients, (with additional thermodilutional measurements) and in normal subjects. They found in critical care patients there was no significant difference between either the equations or the thermodilutional

measurements. However the values in normals where found to be divergent. The Smarek-Bernstein equation was found to have higher values than the Kubriek equation, the latter being more compatible with previously published values of cardiac output in supine normal patients at rest. An extensive review by Jensen et al (1995) (Bernstein, D. P. 1986; Jensen, L. et al 1995; Kubicek, W. G. et al 1966; Penney, B. C. 1986; Sramek, B. B et al 1983), found that the Kubriek method when compared to the direct Fick method, had correlation values of between 0.63 - 0.93 and the modified Sramek-Bernstein equation method had correlation values ranging from 0.41 to 0.99 (Charloux, A. et al 2000; Jensen, L. et al 1995), when compared with thermodilutional methods. Analysis of ΔZ may also be problematic in subjects who are fluid overloaded, as this reduces baseline impedance to 20Ω or less (Warburton, D. E. et al 1999b). This suggests the value obtained for cardiac output may vary depending on the equation used and the equipment as well as the type of subject the measurements are taken on.

1.11.3. Physioflow Cardiac Output Monitoring Device: Theory

The physioflow (Physioflow, Type PF05L1, Manatec, France) bio-impedance cardiac monitoring device was developed after technical improvements occurred in the available hardware (a new generation of analog technology allows the Physio Flow to improve signal filtering and stability and provide better data processing), and the basic equation has been adjusted. The equation has been modified in order to overcome the difficulties in evaluating blood resistivity (ρ), the distance between recording electrodes (L) and Z_0 used in the Kubicek and Sramek-Bernstein equations.

Previously getting a precise measurement of Z_0, the distance between electrodes and a measurement of left ventricular ejections time was needed for measuring cardiac output

by thoracic impedance (Charloux, A. et al 2000; Hsu, A. et al 2006), but the physioflow avoids the need to know these values. The Physioflow equation was developed by the analysis of an extensive database. Impedance cardiography is based on the analysis of signal waveform and its variations. The database was collected on patients with a variety of cardiovascular conditions ranging from severe heart failure to hyperthyroidism, and taken at rest and exercise using the physioflow prototype. The haemodynamic status was assessed using echocardiography and angiography.

This equation has allowed the discarding of Z_0, thorax height, distance between sensing electrodes and blood resistivity in the calculation of SV (Charloux, A. et al 2000).

It uses the following formula:

$$\dot{\mathbf{Q}}_c = \mathbf{fc \times SVi \times BSA}$$

where $\dot{\mathbf{Q}}_c$ is cardiac output (l/min)), f_c is the heart rate (beats/min); [based on R-R interval measurement, determined on ECG first derivative, dECG/dt, (providing a more stable signal)], **BSA** (m^2) is body surface area, calculated according to Haycocks formula ($BSA = 0.24265 \times BM^{0.5378} \times H^{0.3964}$, where BM is body mass in kg and H is height in cm), and SVi is SV index (SV divided by BSA).

An evaluation of SVi is derived from SVi_{cal} which can be calculated by the following equation:

$\mathbf{SVi_{cal} = k \times [(dZ/dt_{max})/(Z_{max}-Z_{min})] \times W(TFIT_{cal})}$, where $W(TFIT_{cal})$ is the weighted thoracic flow inversion time. The explanation for the production of this equation is

given in Charloux et al (2000) (Charloux, A. et al 2000)SVi_{cal} represents the baseline reference. During the data acquisition phase, the variations of the parameters described above are analysed and compared to those obtained during the calibration phase.

$SV_i = SVi_{cal} \times \sqrt[3]{CTI / CTI_{cal} \times TFIT_{cal} / TFIT}$., where CTI is dZ/dt, or the contractility index

Charloux et al (Charloux, Lonsdorfer-Wolf et al. 2000) suggested that the physioflow thoracic impedance cardiac output device had several apparent advantages over other methods of non-invasive thoracic impedance cardiac output devices are, which were:

1. Multiple electrodes are not needed (only 4 impedance electrodes and two ECG electrodes) to obtain good quality signals
2. The SV results may have better reproducibility even under non-optimal conditions (different electrode positions, types or perspiration)
3. A greater range of applications (e.g. cyclo – ergometer)
4. No need to measure thorax morphology
5. Increased reliability of the whole acquisition procedure by introducing a calibration phase.

1.11.4. Physioflow Cardiac Output Monitoring Device: Validation & Reproducibility

There have only been a few studies examining the accuracy and reproducibility of the physioflow (Physioflow, Type PF05L1, Manatec, France) device. The reproducibility of the test was performed as part of a thesis submitted to the University Hospital in Angers, France by Dr R Trouve in his thesis (Trouve, R. 1997).

Two tests of reproducibility were performed. The first involved 25 haemodialysis patients, over 3 sessions providing 75 measurements of stroke volume. The results were a reproducibility correlation of, $r = 0.98$ $p < 0.0001$.

Similar results were obtained during another test of 7 patients, supine at rest, using 3 separate operators and with 3 consecutive measurements being made by each operator. The purpose was to evaluate reproducibility of stroke volume measurements under various measurement conditions and operators. The results were inter and intra-operator reproducibility of $r > 0.96$, $p<0.0001$. These results also demonstrated a remarkable reproducibility during cyclo-ergometer exercise, and under non-optimal measurement conditions (important modifications of electrode positions).

Hsu et al (Hsu, A. R. et al 2006) quoted unpublished results from their own laboratories, that in 20 young men (age 27 ± 4 years) the coefficient for variation for SV and Q at peak exercise using the Physio Flow during repeat exercise ergometer tests, spaced more than 2 days apart were 3.6% and 3.4% respectively.

There have only been three published studies comparing cardiac output results using the physioflow (Physioflow, Type PF05L1, Manatec, France) with invasive methods. Charloux et al (2000) (Charloux, A. et al 2000)evaluated the reliability and accuracy of the Physio Flow, at rest and during a mild constant effort performed in the supine position on 40 patients with either sleep apnoea syndrome or chronic obstructive pulmonary disease. The cardiac output was compared with results obtained by simultaneous direct Fick cardiac output measurements. Thirty-two patients were able to perform exercise, ranging from 10 to 50 watts. 72 cardiac outputs measurements were

taken at rest and during exercise, and ranged from 4.34 to 14.84 L/min for Physio Flow and from 3.60 to 15.03 L/min for "direct" Fick. Under linear regression analysis, a correlation coefficient of 0.89 ($p<0.001$) was obtained for resting values and of 0.85 ($p<0.001$) for exercising values of physioflow versus Fick cardiac output.

Comparison of the two techniques with the Bland and Altman method was also performed. At rest, the mean difference ($\dot{Q}$ Fick - $\dot{Q}$ PF) was 0.07 L/min (95% confidence interval: -0.23, +0.27 L/min), which represents 0.29% of the mean resting cardiac output. The ($\dot{Q}$ Fick - $\dot{Q}$ PF) difference did not vary significantly with the mean of ($\dot{Q}$ Fick, $\dot{Q}$ PF). The limits of agreement were (-1.18, +1.32 L/min) at rest. Thus, in 95% of paired measurements, the difference between $\dot{Q}$ Fick and $\dot{Q}$ PF was within a (-19%, +19%) interval. During a mild effort, the mean of the ($\dot{Q}$ Fick - $\dot{Q}$ PF) difference was 0.26 L/min (2.44% of mean exercising cardiac output) with a (-0.17, +0.69 L/min) 95% confidence interval. The limits of agreement during exercise were -2.16 and +2.68 L/min (-21%, +26% of cardiac output).

In the second study, Richard et al. (2001)(Richard, R. et al 2001) performed a study during which a 1-minute step incremental exercise test was performed from rest to maximal peak effort by a group of 12 subjects. Each subject performed two comparable tests while their $\dot{Q}$ was measured by impedance cardiography using the new device ($\dot{Q}$ Imp1, $\dot{Q}$ Imp2). In a subgroup of seven subjects $\dot{Q}$ was also determined by the direct Fick method ($\dot{Q}$ Fick) during the second test. The mean difference between the values obtained by impedance (i.e. $\dot{Q}$ Imp1-$\dot{Q}$ Imp2) was -0.009 $l.min^{-1}$ (95% confidence

interval: -4.2 l.min^{-1}, 4.2 l.min^{-1}), and $\dot{Q}$ ranged from 3.55 l.min^{-1} to 26.75 l.min^{-1} (n = 146). When expressed as a percentage, the difference ($\dot{Q}$ Imp1 - $\dot{Q}$ Imp2) did not vary with increasing cardiac output. The mean difference between the results obtained using direct Fick and the impedance method was not significant at rest (0.07 L·min^{-1}, i.e., 1%) and during steady state exercise [0.26 L·min^{-1}, i.e., 2.78% (95% confidence interval: -27.44%, 21.78%]. In addition, they also reported that the direct Fick method was highly correlated with the impedance method during steady state exercise ($r^2 = 0.79$, $P < 0.05$, N = 40 and during incremental testing ($r = 0.94$, $P < 0.01$, N = 50).

In a third study, Bougault et al (2006) examined whether the Physio Flow would still be reliable measuring cardiac output at maximal exercise in patients with COPD when compared to the direct Fick method. The difference found between Physioflow and direct Fick measurements were found to be 3.2 L/min ± 2.9 L/min (31 ± 21%) for maximal incremental exercise and 2.5 ± 2.1 L/min (25 ± 20%) for the strenuous intermittent work exercise test measurements, when analysed by the Bland Altman method (Bland, JM. et al 1986a)

Mourea et al (2001) presented data at an international meeting which analysed the results of measurements by the thermodilutional method and taken by the physioflow on 107 ITU patient. They found that the results had a linear regression factor of r = 0.88 (p<0,001), with an equation of $\dot{Q}$ physioflow =0.75 • $\dot{Q}_{THERM}$ +1.33. The Bland Altman analysis found a bias of –0.014 L/min.

1.11.5. Cardiac Output Conclusion

In essence, the most reliable method for measuring cardiac output in human subjects is the invasive method of Direct Fick cardiac output. The Fick method is more reliable at rest then exercise. It requires a steady state of exercise and is quite invasive and intensive. Thermodilutional cardiac output measurements are less intensive, but under several circumstances may be inaccurate when compared to the Fick method.

Non- invasive tests also have problems. Doppler echocardiography is hard to perform during exercise and the reliability of the Indirect Fick method is questionable.

Thoracic Bioimpedance may be an easy alternative non-invasive method of measuring cardiac output at both rest and exercise. It however requires several assumptions to made about the physiology of the thorax. The accuracy and reproducibility of the results obtained seem to depend on the equation and types of device used as well as any other pathological conditions the patient may have, and each impedance device has to be validated under varying physiological and pathological conditions.

The physioflow device has been validated under a few pathophysiological conditions. Under sub-maximal exercise it seems to perform well, but in certain patient groups may not be accurate. It has not yet been validated in patients with pulmonary hypertension at either rest or exercise but results in other patient groups suggest that it may be a useful device for the measuring of cardiac output, non-invasively.

1.12. Aims

The work relayed to this thesis was undertaken as a review of the literature found that pulmonary hypertensive subjects have important changes in their pressure- flow relationships when exposed to various pharmacological agents or physiological manoeuvres, which are not demonstrated at rest (as per PVR).

Performing exercise may be difficult in patients with respiratory conditions, hence dobutamine is routinely used as a substitute for exercise in order to increase cardiac output in patients with cardiac disease. There have been no investigations as to whether in the diseased pulmonary vasculature, the response of the pulmonary circulation to dobutamine follows a similar pattern to exercise and whether dobutamine could be a reasonable substitute for exercise.

The main aim of this thesis was, by using a combination of high fidelity micromanometer tipped catheters to measure pulmonary artery pressures (PAP), and non-invasive cardiac output (CO) derived from impedance plethsmography in subjects with pulmonary hypertension (PHT), to investigate the pulmonary circulation.

There has been a paucity of information relating to the pulmonary circulation under dynamic stress, in humans. This research would demonstrate the importance of investigating the pulmonary circulation under dynamic conditions and also the advantages of simultaneously measuring PAP and CO. It would also open further avenues of research, into whether subjects with different pressure-flow responses had differing prognoses and response to treatments.

This project aimed to:

1. Validate the use of the Physioflow 1 for measuring cardiac output in subjects with pulmonary hypertension.
2. Examine the viability of the production of pressure-flow plots by this method, for general clinical practice
3. Examine if in the subjects studied, whether there was any difference in pressure flow plots with respect to disease type or vasodilatory response
4. Examine if with cardiopulmonary exercise testing, we can discover a non-invasive surrogate of pressure-flow plots
5. Examine dobutamine as an alternative to exercise for pressure flow plots

Chapter 2

Methods

2. METHODS

2.1. Ambulatory Pulmonary Artery Pressure Monitoring

2.1.1. Equipment

The catheter was a 7 F micromanometer tipped catheter supplied by Gaeltec Ltd (Dunvegan, Isle of Skye) (Figure 2.1). This catheter is designed for multiple use and was gas sterilised in ethylene oxide. The data was recorded by a portable battery powered recorder, (Type MPR/2, Gaeltec Ltd, Dunvegan, Isle of Skye), (Figure 2.2.), before being downloaded into a Toshiba satellite 21 OCS laptop. Patients were supplied with a diary.

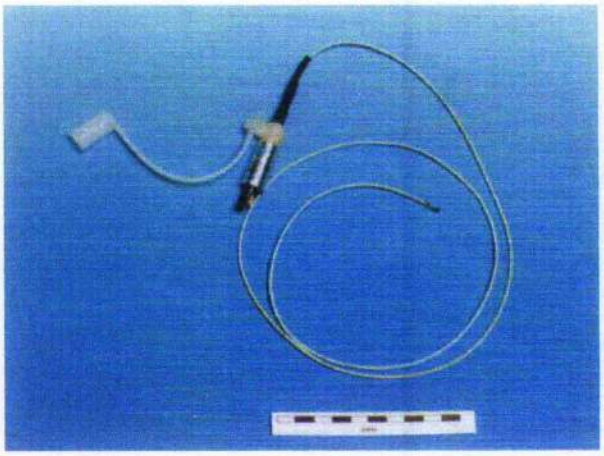


Figure 2.1: Gaeltec Pulmonary Artery 7F catheter

Figure 2.2. Gaeltec MPR/2 Portable Battery powered recorder

2.1.2. The Software

The ambulatory pulmonary artery pressure monitoring programme was supplied by Gaeltec Ltd (Dunvegan, Isle of Skye), and required a computer running a DOS and windows 3.1 operating systems

2.1.3. Making a Prolonged Pulmonary Artery Pressure Recording

The portable recording box had new batteries for every recording and catheters was sent to TSSU for ethylene glycol gas sterilisation a minimum of 10 days before the planned date of catheterisation. On the morning of the catheterisation, the patient had a 8G French sheath inserted in the right internal jugular vein in the cardiac pacing room.

The computer, catheter and recording box were taken to the catheterisation laboratory. Following completion of the routine right heart catheterisation on the subject, the ambulatory Gaeltec catheter was removed from its sterile packaging, coiled, and placed in sterile saline for a minimum of two minutes. 0.4mls of air was injected into the port using an insulin syringe with the needle removed and end of the catheter was observed under the sterile saline to check that there was no air leakage. The catheter was kept under the saline for a minimum of 2 minutes as the coating absorbed some fluid. The catheter was then connected to the recorder box that was then switched on and the programme started. On the monitor, the set up menu was entered and the legend "*calibrate pressure transducers*" selected.

This offered a positive or negative pressure calibration. A 'negative' pressure calibration was always be used. When this was selected, the menu required the recorder to be stopped. At this stage the non-sterile rubber tubing, stored with the computer, was

connected to the port on the catheter and via a 3-way tap, to the port on the rear of the recording box. The 3-way tap was opened to air and *return* pressed. The system was then opened to air before the pressure calibration was continued. *Return* was then pressured again and 0 mmHg was established. The programme required a negative pressure calibration to be performed in which the 20 ml syringe is connected to the 3-way tap in communication with the recording box and the catheter, and the syringe was *gently sucked* until the programme read "calibration complete" and the recording box likewise. At this stage the catheter was ready for insertion into the patient.

2.1.4. Cardiac Catheterisation using the Ambulatory Gaeltec Catheter

This was placed in the usual way in the proximal pulmonary artery. Care was taken not to advance the tip too far into the pulmonary circulation as wedging led to loss of trace as well as to complications. The tip of the ambulatory was placed no further distal than the transverse processes, preferably on the right.

Once the catheter was satisfactorily in place it was re-connected to the recording box then on the computer screen the "record" menu was selected and "start new real time recording" option selected. This showed a real time pressure tracing. There was no need to record at this stage. 0.4 mls of air was again injected into the port in the catheter to see if the preset 0 was satisfactory. So long as the value lay between plus or minus 32 the error was suitable to be corrected later.

The catheter was now in a satisfactory position making an adequate recording, and the sheath was pulled back over the catheter to its end and left in position. This tended to displace the catheter further into the pulmonary circulation, therefore the catheter

position was screened again before finally being secured with a suture at the point of insertion.

2.1.5. Starting a New Recording

The computer and recording box was required in order to start a new recording. The computer and the recording box were taken to the subject and were connected to the catheter. From the computer programme, "start real time recording" was selected from the "record" menu to check that the catheter continued to record satisfactorily. The recorder battery voltage was checked again at this stage using the selection from the same menu and if this was adequate, a new recording was started. The 4 megabyte RAM card was inserted in slot in the base of the recording box and " start recorder" selected from the record menu. This cleared the memory card for a new recording and gave the time on the liquid crystal display that the new recording was started. At this point, this recording was being recorded both on the memory card and on the hard disc of the computer.

It was possible to view the actual trace at any time during this on screen using the "start new real time" record option in the record display and during the early period of the trace this was done on a number of occasions to check that 0 calibrations are adequate.

2.1.6. Troubleshooting

When 0 calibrations were not accurate i.e. injection of 0.4 mls of air results in the trace reading a figure different from 0, an "in vivo" calibration was performed. To carry this out, under the 'record' menu, the recorder was stopped, the balloon on the catheter was inflated and kept inflated with 0.4 mls of air. The "enter terminal mode" selection was

then made from the record menu. At C prompt the instruction PZERO in continuous upper case was entered and return pressed. The programme instructed the user when the new 0 had been inserted into the catheter and at this stage the ambulatory PAP programme was re-entered. "Start new real time recording" was selected from the record menu and 0 rechecked viewing the screen trace. If this procedure was successful, the 0 calibration resulted in an adequate trace which records close to the actual 0 line when calibrated.

If the tracing was still not satisfactory, the above procedure was repeated (several times if necessary).

0 calibration was performed several times at beginning and end of the trace and intermittently throughout the recording.

The liquid Crystal display on the recording box indicated the time and the percentage of memory that had been used.

2.1.7. Event button

If the patient was put through a series of experiments, standing etc., the "event" button on the recording box was pressed at the beginning and end of these manoeuvres.

2.1.8. Completing a Trace

At the end of a ambulatory recording from the record menu the "stop recorder" option was selected and this selection confirmed using the mouse as requested by the program. The 4 megabyte RAM card was then removed from the recording box and inserted in the

card reader device which was connected to the computer via the printer port.

On the "record" menu the "read data from PC card slot" was then selected and the patient file was transferred from the RAM card to the hard disc of the PC. This was then saved to the hard drive and patient details entered as appropriate. Under "comments", the catheter used was recorded as subsequent problems that could have occurred during recordings, and which may have been specific to individual catheters, could have been identified.

At no time during transfer of data from the PC card to the hard disc of the computer was the bottom option on the menu entitled "Initialise Card in PC slot" selected, as this would have wiped the data from the RAM card. This data was backed up on floppy disc.

A section of the visible recorded tracing was highlighted on the screen, on the time scale covering a few hours. The program was then told to save the data first as a beat file, then as an average file and then finally the average file was saved as a comma delimited asc text file.

Windows 3.1 was started by typing in WIN and using excel the asc text file was imported as a delimited file. The comma delimits were selected when importing the file, and then the file was resaved as an excel file.

2.1.9. Ending the Catheterisation

The ambulatory catheter was removed and hand washed in warm soapy water. The balloon was re-checked by it being placed under water again, 0.4 ml of air was injected into the catheter port and the balloon at the end of the catheter was checked for the escape of any air bubbles. The catheter was then be dried and re-connected to the recording box and a "new real time recording" was started under the Record menu.

The end of the catheter was then placed in the grey top pressure chamber, the plastic tubing connected to the end of this chamber and, via a 3-way tap, to the sphygmomanometer. A syringe was then connected to the 3-way tap and a pressure (measured by the sphygmomanometer) was applied to the pressure chamber and hence the catheter. This pressure appeared on screen as a square wave trace with a given value at the side of the screen for the pressure being measured by the catheter. Thus for an applied pressure of 50 mmHg ideally the pressure wave on screen also recorded 50 mm.

2.1.10. Analyzing a Trace

The original pressure trace was viewed on screen. This was accomplished by entering the Amb.PAP. program and the "review"' option was selected.

"Review" menu - "list load recordings", "list load from Disc C" commands were entered in sequence, and the patient trace selected and loaded. At this point the trace required to be corrected for any 0 drift.

Using the "Select page" option at the foot of the screen, the cursor was dragged to the beginning of the trace and the time corresponding with that was noted as the start time

of the manoeuvre.

At this point, the trace was opened out to 1.03 min per page and using the page up/page down facilities the first of the 0 calibrations was brought onto the screen. The cursor was then placed on the middle of the 0 calibration and the value to the right of the screen was read, the actual measurement which was made at that time. At this stage, if there was any error inherent in the catheters calibration, revealed against the true pressure applied in the pressure chamber with the sphygmomanometer, then this was corrected.

2.1.10.1. Y axis change

The CTRL F9 keys were pressed simultaneously and a window appeared on screen, showing "Channel normalizing procedure". The carriage return was then pressed, and when "Enter value at cursor" appeared, 0 was entered. Return was then pressed and the computer would request, "Enter the output observed output observed for a thousand unit step". The error noted against the measured pressure of 50 was calculated for a unit step of 1000 (e.g. a reading of 40 mm against a measured pressure of 50 would require 800 to be entered). Carriage return was then pressed and the "continue" option on the bottom line selected and the channel normalized. The trace was then re-checked at the first and last 0 points to check that these were on the 0 line.

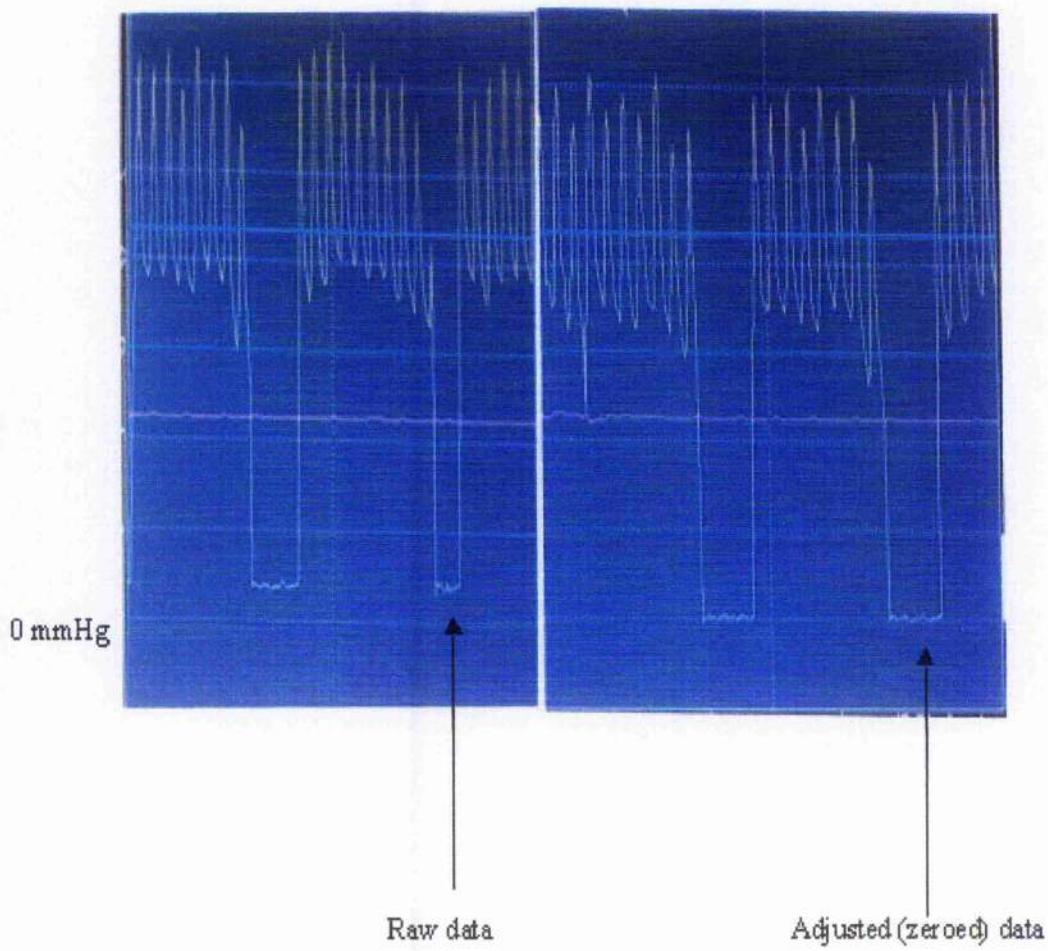


Figure 2.3: Example of Zero calibration points, on raw data and after adjustment

If this was not the case, then in addition to the **correction** being inserted, the trace was also required to be **levelled.** The cursor should once again be placed on the first 0 calibration, and the F9 key pressed. The box on screen indicated that the channel leveling procedure was being used and that the cursor indicated the first point to be included. Carriage return was then pressed and the cursor moved to the next 0 point, F9 was pressed again and so on until the end of the trace. Once the last 0 had been

selected using F9, **Shift F9** was pressed and the entire trace was levelled. At this stage the trace had been corrected and levelled and was ready for further analysis.

2.1.11. Further Analysis

The "analyse" option was selected and from the review menu make "beat by beat" file selected. The programme analysed the entire trace beat by beat removing any artefacts. At the end of this procedure the beat file had been created and this was stored on the hard drive using the patient's name followed by the suffix BT.

Once the beat-by-beat file had been created, the next option "Start new average file" was selected and the procedure was repeated. The programme selected every 16 beats of information and created a new average file. This again was stored on the hard disc with the patient's name and suffix AV. To analyse the trace further the "use average data file" option was selected.

2.1.11.1. Creating an ASCII File

The "use average data" file was selected and the average data appeared on screen. The trace was opened out to, 1.4 minutes per page and using the select page option the cursor dragged to the beginning of the trace. Using the mouse the trace was then marked as close to the beginning as possible. The screen then read that the trace has been marked for analysis and a 2nd point was selected. Using the select page option the cursor was dragged to the end of the file and the 2nd point marked at the end of the trace. Under the "analyse" option Create ASCII file appeared and was selected. The programme created an ASCII file for the entire average trace and this was stored again to the hard drive with the patient's name and suffix ASC.

For statistical analysis the ASCII files were imported into an Excel file, as a delimited file, and comma's selected as the delimiter.

On Excel, The first column was time (1.0= 24hours), 2nd DPAP, 3rd MPAP, 4th SPAP, 5th Heart rate, 6th SaO_2, 7th HR from SaO_2 monitor, and the 8th was an ECG and 9th EVENTS.

Time was converted to hrs min secs by changing cell format on excel.

Each set of data was a 16 sec average. The time was as a decimal fraction of a day but was converted to hours, minutes and seconds by changing the format of the cell to 00:00:00.

2.1.11.2. Backup

This data was backed up using the Windows 3.1.

Windows 3.1 was started by typing in WIN. A back up of the excel, ASCII and the raw data files was made. The raw data was found in the subdirectories in the directory PAPECGO

2.2. Physioflow

2.2.1. Physioflow Set-up and Use

The following is a very brief summary of the manual and details from correspondence with the designer of the physioflow 1, with regards to the calibration phase, assessing adequacy of signal acquisition and trouble shooting to improve results.

Device: Physio Flow PF-05 Lab1, Manatec, France

Software: software version PF-1.05 for Windows 95/98/Me/XP/2000 (32-bits)

Laptop: Sony HEP R600P Pentium IV 850MHz

Figure 2.4a & b: (a) Physioflow device, connected to computer and leads

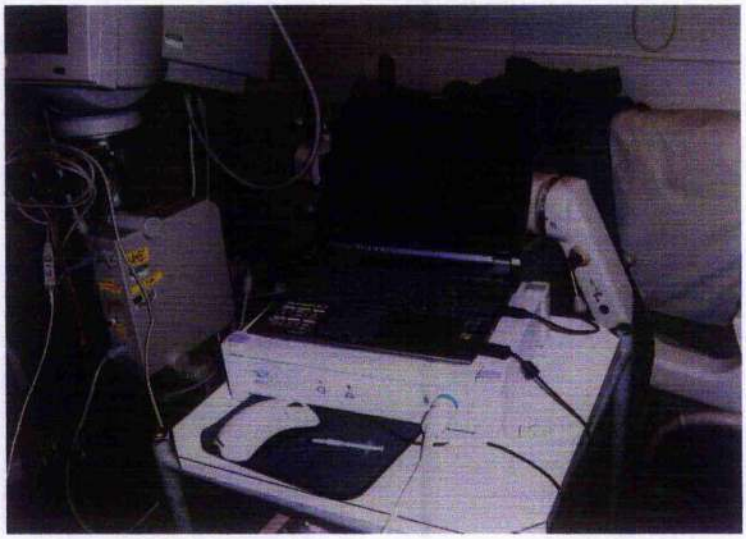
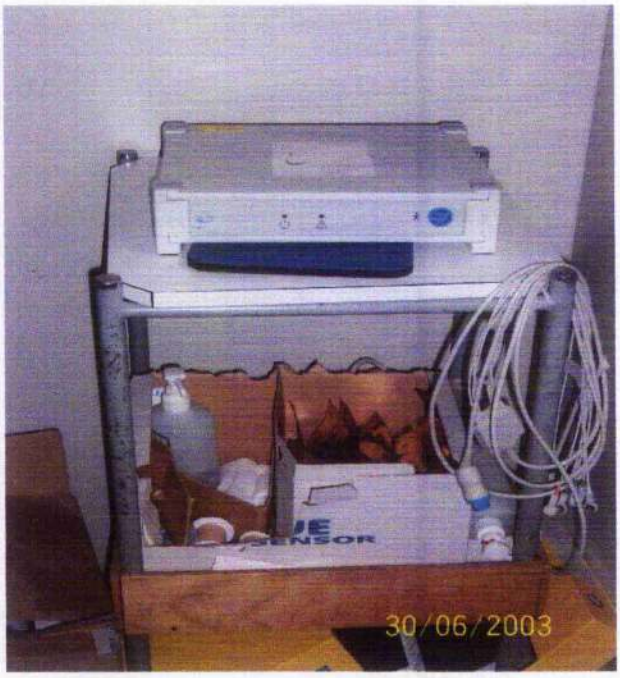


Figure 2.4a & b: (b)Device alone



The Physio Flow 1 is a non-invasive cardiac output measurement device that can be used in patients at rest or under exercise.

The user manual is available to download form the World Wide Web at http://www.physioflow.com/download/free/enman104.zip.

2.2.2. Connections, Device & Subject

The subject was connected, using pre-gelled ECG electrodes. The ambu Blue sensor SP (Ambu, Copenhagen, Denmark), was an Ag/Al wet gel electrode, ideal for medium term stress testing.

The electrodes were placed on the thorax in the shown figure 2.5. Two electrodes are used to monitor ECG in order to measure the heart rate. Four electrodes were used to monitor the impedance signal.

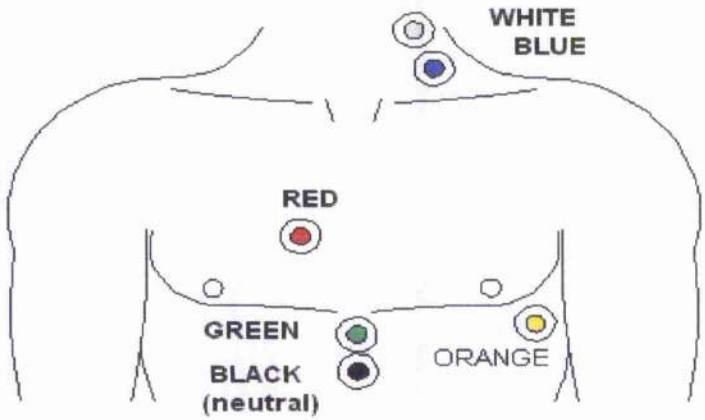


Figure 2.5: Electrode positions for Physioflow 1 device

The exact position of the impedance electrodes was not supposed to be critical provided that one pair is on neck base, and one on thorax base. Adjustments, as mentioned later, were often found to be useful.

During bicycle exercise, V1 ECG electrode was positioned on the manubrium sterna, the upper impedance electrodes were not placed on the sternocleidomastoid muscle (neck basis), and the lower electrodes were not placed over the over abdominal muscle. Cable wires were fixed on patient's skin with adhesive tape.

2.2.3. Pre calibration requirements

Pre calibration is described in detail in the manual.

2.2.4. Calibration Phase

Instructions appeared on the Calibration Wizard screen, which were followed. Calibration was particularly important as reliability and reproducibility depended on it. After the best signal stability possible was achieved, it was performed on 60 cycles (the standard profile is 30 cycles). The subject was requested to remain still and to breath normally. A simultaneous blood pressure reading was taken for basal reference values.

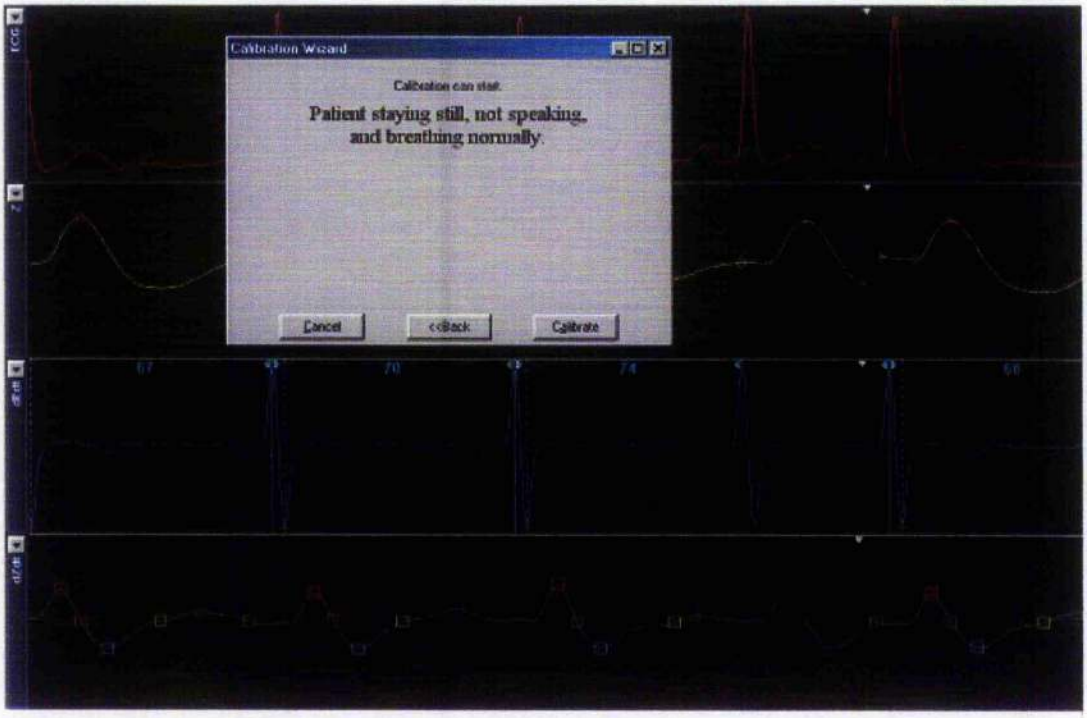


Figure 2.6: Calibration Phase

ECG and impedance metric signals were displayed on the screen from the start of this phase and it was important to ensure that they are reproducible, stable, and without artefacts or interference (figure 2.6).

It was also vitally important that the heart rate results were accurate, by reviewing the cycle beat by beat on the dE/dt signal (light blue digits corresponding to heart rate and a dark blue signal waveform). Similarly, it was important that verification that the characteristic points of the dZ/dt (green) signal were correctly detected, represented by the presence of red and yellow squares on the signal, the red at the maximal peak and the yellow a little time after the maximal trough in the waveform. The yellow square in dZ/dt was also checked to ensure that it did not appear at the end of the heart cycle.

If signal was satisfactory, then " Calibration " was clicked in order to proceed

When calibration was completed (60 heartbeats), systolic and diastolic blood pressure was entered. Once the calibration results were verified, they were accepted and monitoring was started.

If the calibration looked wrong (bad quality of signal, aberrant values), calibration was restarted by entering (« Retry »).

In order to improve calibration and signal, other adjustments were possible. It was possible to increase the calibration cycle to include a larger number of cycles, by entering the profile menu, and entering calibration window. By using this menu, it was also possible to adjust the acquisition signal from a default of 20 cycles before acquisition of data, to 1 cycle (which was required for the pressure-flow experiments). When necessary, entering the analysis menu and entering the signal setup submenu allowed the increase or decrease of sensitivity of both the analysis of the ECG and the impedance (Z) signals.

2.2.5. Monitoring/Recording Phase

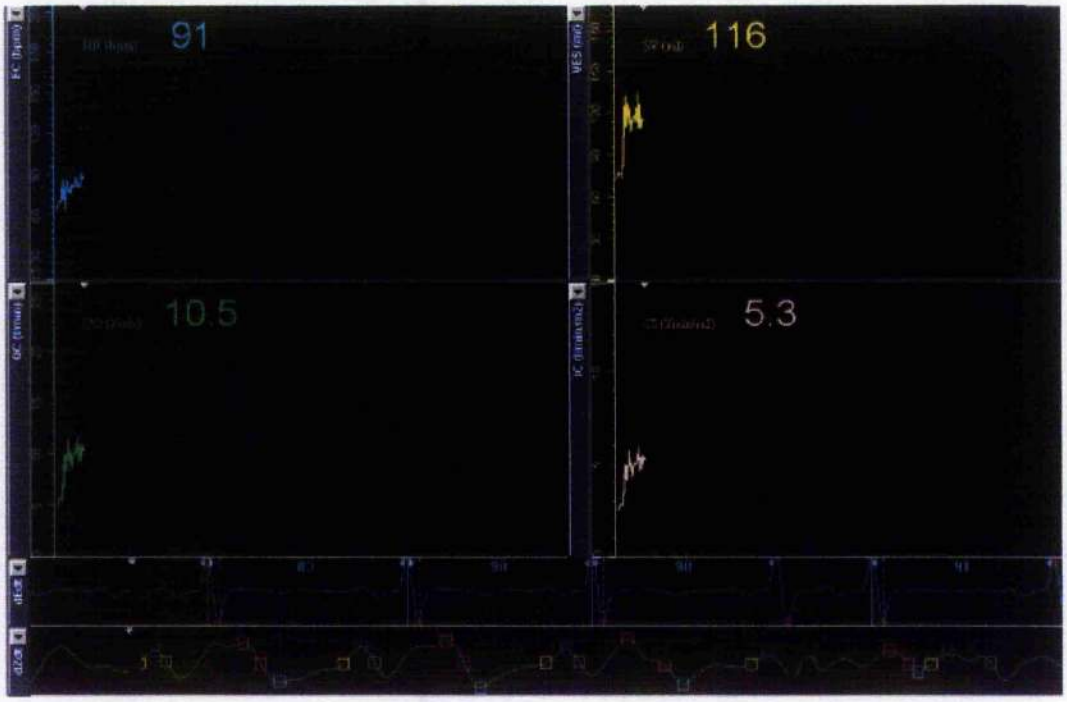


Figure 2.7: An example of the 'Monitoring Screen', with the current values for heart rate (HR, bpm), stroke volume (SV, ml), cardiac output (CO, L/min) and cardiac index (CI, L/min/m^2), as well as graphical representations of these values on the y axis against time on the x axis. Also on this monitoring screen is dE/dt (differential of the ECG signal versus time) and dZ/dt (differential of impedance signal versus time)

The default monitoring screen (HR = Heart Rate, SV = Stroke Volume, CO CI = Cardiac Output/Index (cardiac index is cardiac output divided by body surface area), SAP, MAP, DAP (systolic/mean/diastolic arterial blood pressure)) was left for the studies as in figure 2.7.

During the monitoring, events were marked by pressing SPACEBAR. A window appeared in which details of commencement or discontinuation of an experimental

protocol were noted. Pressing "enter" validated this event and a vertical line appears on the screen. The recording was completed by clicking on " End of acquisition " .

The colour squares on the dZ/dt signal (red to yellow) were checked to see if one could draw a curve oriented downwards (during systolic phase), as shown in figures 2.8 a, b & c.

Figure 2.8a

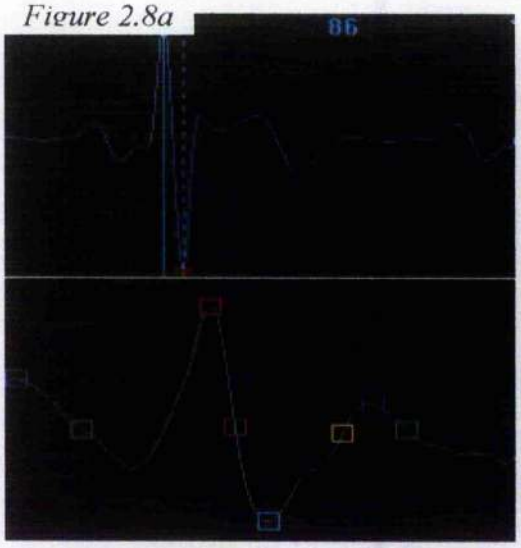


Figure 2.8b

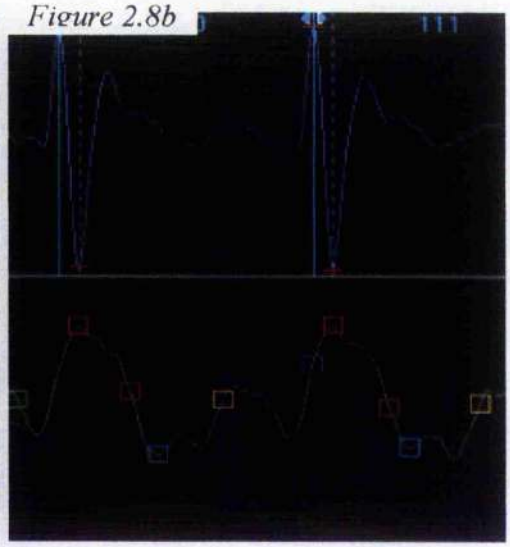
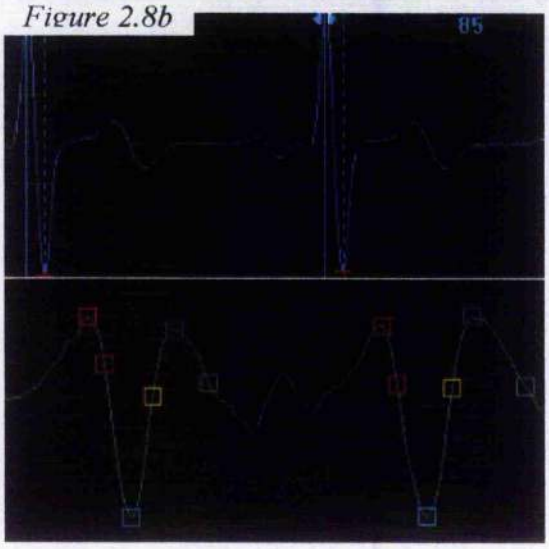


Figure 2.8b



Figures 2.8 a, b &c: Examples of acceptable signal for physioflow cardiac output measurements, showing dE/dt (differential of the ECG signal versus time) and dZ/dt (differential of impedance signal versus time).

2.2.7. Poor Signal & Possible solutions

Despite the measures taken, often the acquisition signals were of poor quality. The following are examples, with the solutions used.

In figure 2.9a, there was no systolic curve during dZ/dt and the colour squares were not regularly plotted. The possible solutions were to clean and shave the skin again, replace impedance electrodes, and reposition impedance electrodes (on the same horizontal level).

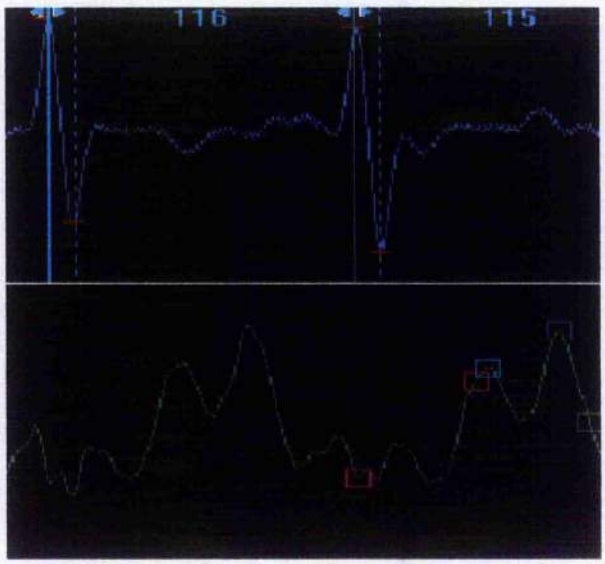


Figure 2.9a:Poor quality signal received by physioflow device

In figure 2.9b, there was an artefact on dZ/dt curve occurring during QRS. The possible solution to this was to clean and shave the skin again was to replace impedance electrodes, and reposition impedance electrodes (on the same horizontal level).

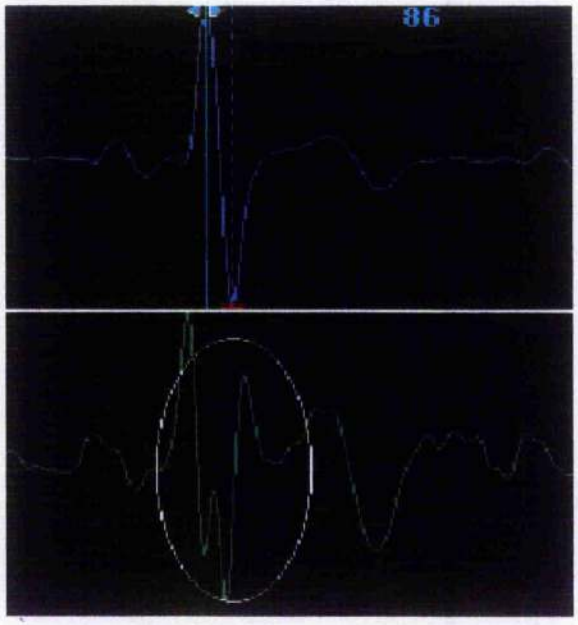


Figure2.9b: Another example of a poor quality signal received by the physioflow device

Figure 2.9c demonstrated a trace which had electrical interference with static electricity on the ECG.

The solution to this was if possible turn off source of static electricity. In addition, it was important to check that no physioflow wires were crossing other wires (e.g. the micromanometer catheter).

In figure 2.9d, the majority of QRS were no properly detected and heart rate was wrong. This problem could often occurs in case of bundle branch block or pacemaker patients (QRS large and of low dynamic, and in this case the solution was to increase ECG sensitivity as previously mentioned. An alternate solution would have been to reverse the ECG leads.

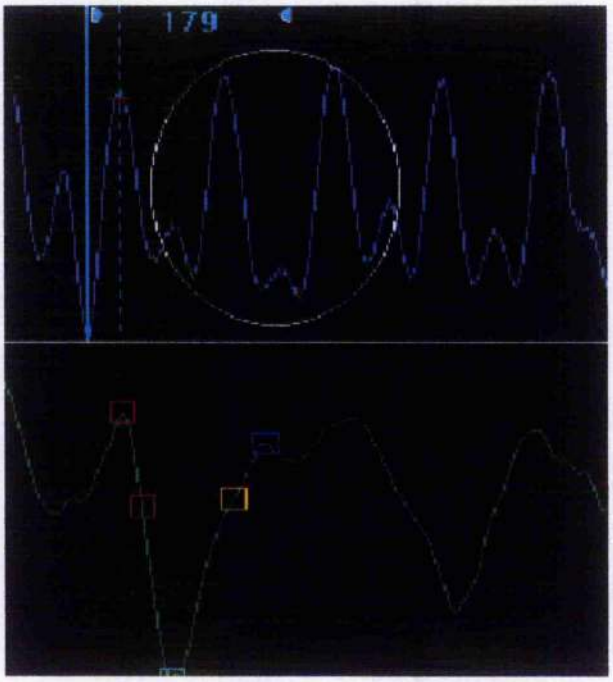


Figure 2.9c: third example of poor quality signal from physioflow device

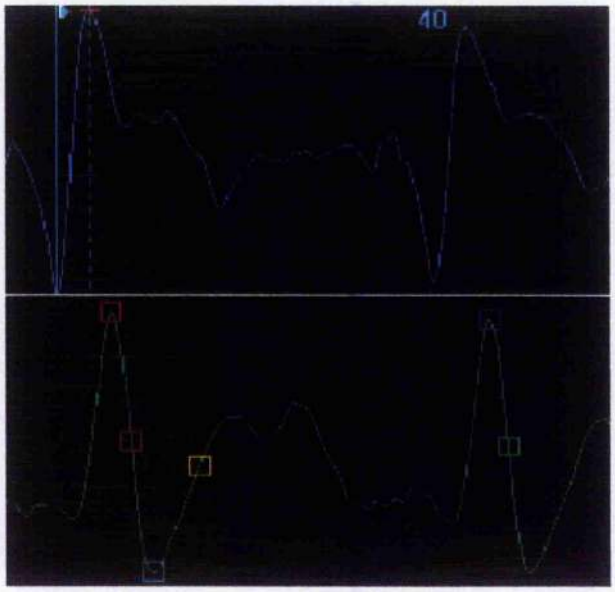


Figure 2.9d: Final example of poor quality signal

2.2.8. Other tips and signal ways of improving signal quality

During the studies, one came across other problems and solutions

1. It was found that the use of Q & SP blue sensor electrodes or other short & medium term electrodes, were inadequate for the study. We switched to using long term silver oxide gel electrodes.
2. Avoiding pressing down on gel part of electrode during placement
3. When the ECG downward peak was HIGH the ECG electrodes were inverted
4. When ECG recognised too many points, the threshold was DECREASED, & if too few it was INCREASED.
5. The most important points was to review waveform were the red and yellow boxes on the dZ /dt. These should have been in systole ie after QRS (as shown in figure 7) with the curves of the dZ/dt falling after the red box, before going up to the yellow box.
6. To improve signal occasionally electrode placement on the back of the neck was tried (less skin folds).
7. Occasionally the electrodes were placed onto the lower rib cage (esp during exercise as less muscle interferance).
8. The blood pressure measured during calibration was as accurate as possible, as any error here would have been square rooted for cardiac output. (ie error blood pressure error 5%, cardiac output error will be 10% error (1.05 x 1.05) in cardiac output.
9. Entering the analysis menu and entering the signal setup submenu allows the increased or decreased of sensitivity of both the analysis of the ECG and the impedance (Z) signals.

10. We improved initial calibration by calibrating over more cycles, as mentioned previously (60 compared to 30).
11. And finally if due to time constraints it was not possible to adjust analysis for reliable analysis (red and yellow box placements), but the dE/dt & dZ/dt signals were reliable, it was possible to run the physioflow simulator as described later and an adjust analysis parameters at a later time.

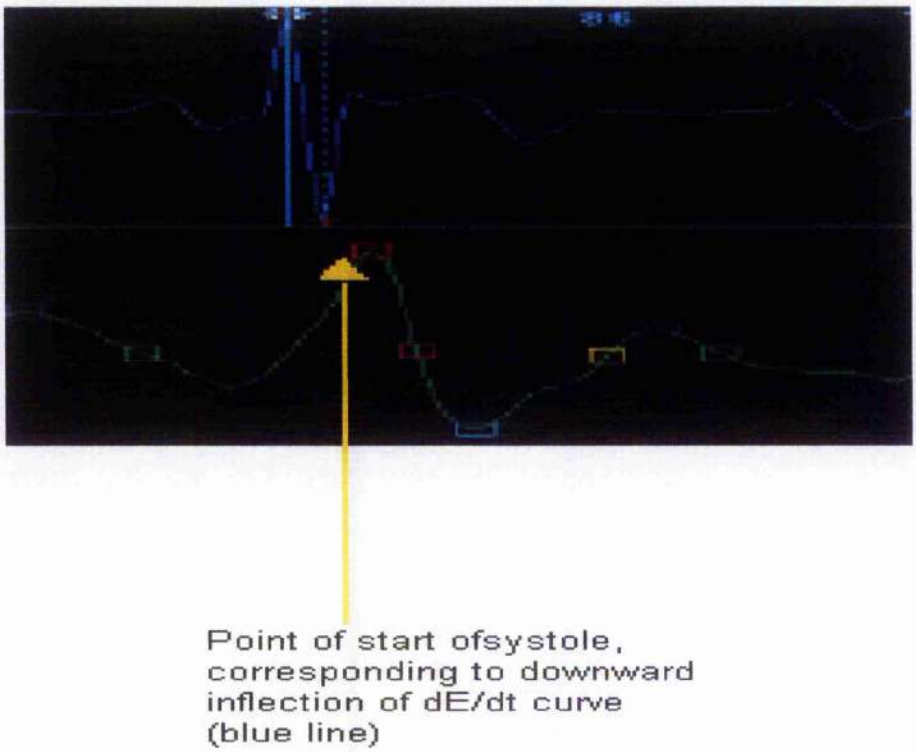


Figure 2.10:Point of start of systole of dZ/dt signal, corresponding to the maximum point of the negative inflection of dE/dt signal

Also note if right ventricular hyperterophy, this may lead to changes in the Z curve with the systolic wave being smaller then the diastolic wave (figure 2.11)

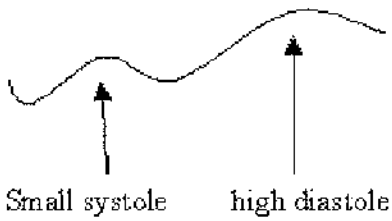


Figure 2.11: Change in Z curve seen with right ventricular hypertrophy, with small systole and large diastole peaks.

2.2.9 Reviewing acquisition

Instructions are as per the manual available on http://www.physioflow.com/download/frcc/cnman104.zip.

2.2.10. Physioflow Simulator Operation

If the impedance wave analysis had been sub optimal due to difficulties in adjusting the wave form analysis parameters during the experiment the entire recording could have be reanalysed under different settings by using two computers, one playing the recorded information and the other analysing it. However there were two problems with this, the computers would analyse this as a continuing loop and the initial calibration data was not recorded, so calibration had to be performed on the actual previously recorded data and thus making it difficult to ascertain what time periods in the new analysis correspond to the old analysis. This process was not undertaken during this study. Instructions on how to perform this were obtained at the time this additional software was obtained.

2.3. Pressure-Flow Experiments

The experiment was explained to the patient. As previously described the APAP catheter was inserted into the right (or left if not possible) pulmonary artery via a main central vein.

The ambulatory catheter was attached to the ambulatory box and this to the laptop computer. The computer is APAP programme was switched to real time mode, in which the pulmonary artery wave form can be monitored. Several zero calibration manoeuvres were performed (as described previously). The physioflow electrodes were then attached and the machine underwent a calibration period (as described previously). The machine's parameters were adjusted to save data for each cardiac cycle and were adjusted in order to optimise the impedance waveform

Then several readings of the time on the physioflow computer, the laptop for APAP and the APAP box were taken in order to later match the data from the APAP and physioflow devices.

The subject was placed the gas inhalation mouthpiece in their mouth. The gas delivery system was as described in chapter 2.5. The subject was given time to become comfortable with the device, whilst on air. Once comfortable, the experiment began, with the patient inhaling a gas whilst at rest, either air, Oxygen at 15l/min or a combination of NO at 40ppm and oxygen at 15l/min.

After 5 minutes of acclimatization, the patient was asked to start raising their legs alternately, at a rate of 1 leg rise per second, and for a total of 3 minutes or until they

tired out. Then prior to the next exercise test, the subject rested whilst inhaling air or oxygen as desired for 3 minutes, before repeating the entire procedure again, until all three sets of gases were given. The order in which the gases were given was selected at random prior to the experiment.

The data was then analysed as described in chapter 2.7.

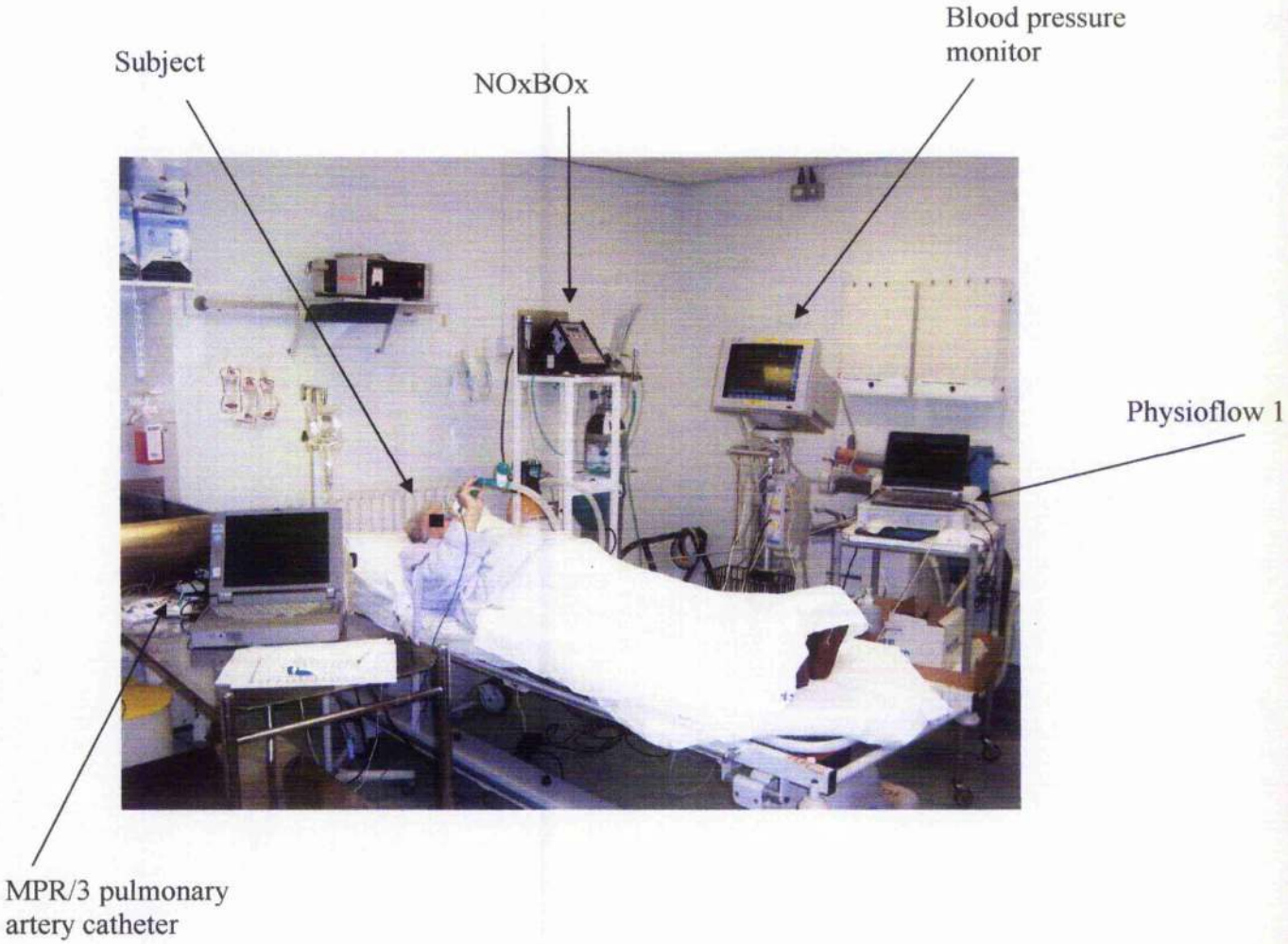


Figure 2.12:Pressure-Flow experiments. Patient inhaling experimental gas, whilst attached to the physioflow cardiac output monitor, a blood pressure monitor and the micromanometer tipped pulmonary artery catheter and recorder.

2.4. Gas Delivery System

2.4.1. Materials

Magill-Mapelson A 1.6m with 2L reservoir bag (Intersugical Ltd, Berkshire, UK).

Assorted Male to female connectors of 22 & 30 sizes, with T junctions and adaptors from Nitric oxide monitoring kit (Intersugical Ltd, Berkshire, UK).

Flextube (Elephant tubing) 22mm (Intersugical Ltd, Berkshire, UK).

Oxygen bubble tubing (UN 881) 3mm, (UHS, Enfield, UK)

NoxBOx II (Bedfont Scientific, Kent, UK).

Nitric oxide gas cylinder (LindeGas, UK Ltd)

Air gas cylinder (LindeGas, UK Ltd)

Oxygen via piped hospital oxygen supply, (BAC Ltd)

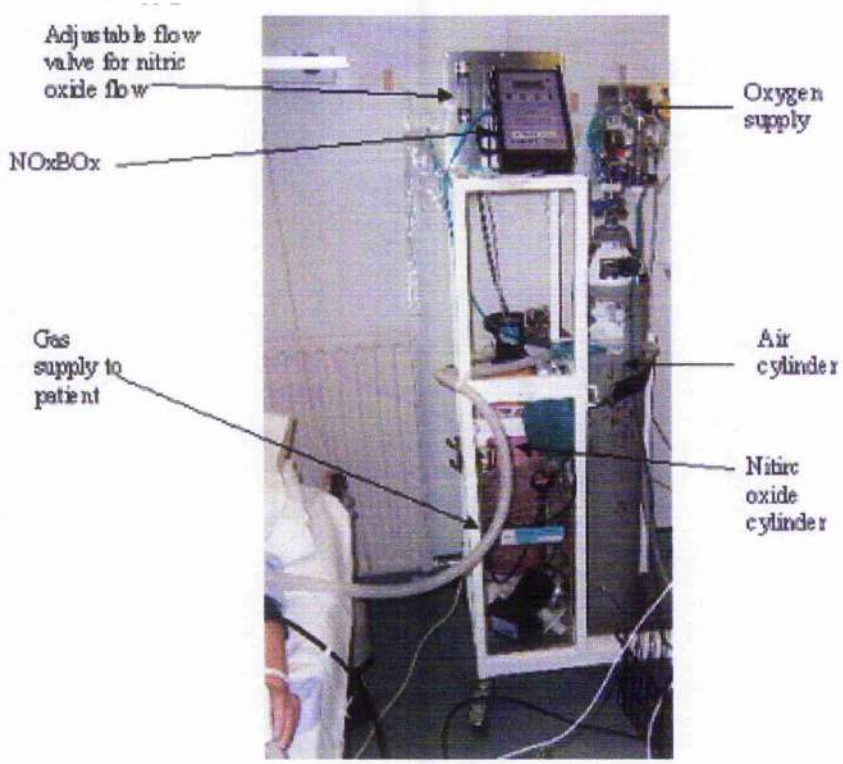
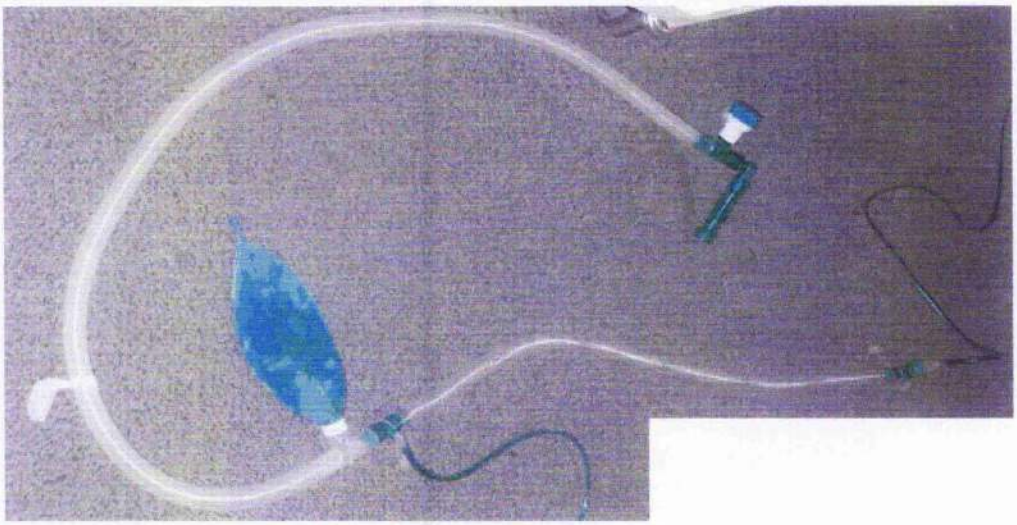
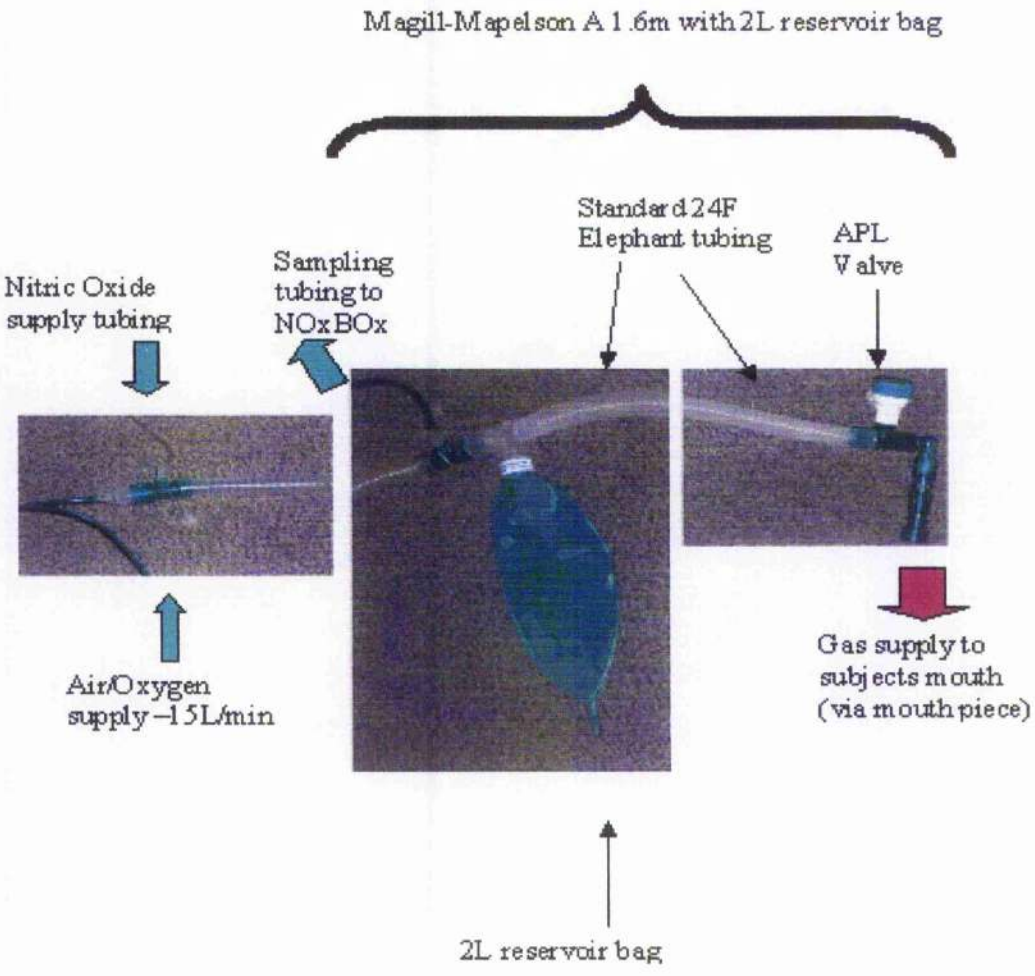


Figure 2.13a: Gas delivery system, used to deliver nitric oxide & air. Or air alone, or when attached to hospital oxygen supply, oxygen or nitric oxide and oxygen

Figure2.13b: Gas delivery system. The entire supply piping



. *Figure 2.13c: Gas delivery system. The supply piping*



The gas delivery system, was the same system used clinically at the Scottish Pulmonary Vascular Unit between 2001 & 2004, and was made up of a basic Magill-Mapelson A 1.6m with 2L reservoir bag system, attached to a further 22mm flextube, via a nitric oxide adaptor kit (Figure 2.14 a-c). Air or oxygen was supplied at the tail end of the system, at 15 L min^{-1}. Nitric oxide was also supplied here. The mixture of gases was thoroughly mixed when it reaches the middle section, with the 2L reservoir bag. The concentration of NO is sampled here. A further 1.6m downstream, the subject inhaled the mixture. They also exhaled through the system, and the gas escaped through the escape port of the APL 60cm^2 relief valve. The valve was set at mid pressure in order to cause some back flow through the system, and mixing of gases at the reservoir bag point.

The sampled gas was tested by the NoxBOx II, and after a few minutes of calibration time, the flow of NO was adjusted by the adjustable flow valve, in order to obtain the desired NO concentration (figure 2.14a-c). The Patient inhaled the gases, via a rubber reusable mouthpiece (sterilised by Milton sterilisation solution). This mouthpiece fitted tightly in the mouth, between the teeth and the lips, to form a secure seal, whilst nasal breathing was prevented by the use of standard nasal prongs. Between the mouth piece and the main delivery system was a standard microbial filter.

2.5 Matching APAP and Physioflow data

During an experiment, on at least three occasions the corresponding time points for the APAP machine and the physioflow machines were noted.

Using this information of equivalent time points noted down during the experiment, the difference between the times were calculated, and the average of this was then used to allow conversion of APAP times to physioflow times.

For instance if 09:33:22 (Hours:minutes:seconds) was the APAP time, and 00:01:02 was the physioflow time, the difference would have been 09:33:22 - 00:01:02 giving 09:32:20. This would then be used to convert all other APAP times to physioflow times (ie APAP = 09:33:38 the equivalent physioflow time would be = 09:33:38- **09:32:20** giving 00:01:18.

Then the time periods corresponding to the APAP data was marked on the physioflow data, and the averages from this time period until the next time period were calculated for the physioflow data (as previously mentioned the APAP data time period correspond to the average data over the preceding 16 seconds). For instance data over the time period 00:01:02 to 00:01:18 would be averaged.

This data would be then added to the corresponding APAP data and would allow further analysis to be undertaken.

2.6 Study groups, Recruitment and Data gathering

Subjects were recruited from all patients attending the Scottish Pulmonary Vascular Unit, (Western Infirmary, Glasgow, UK), between October 2001 and July 2003, all of which were due to undergo invasive investigations for suspected pulmonary hypertension. Bioimepedance data (n=30, for chapters 3-9) and those with combined bioimpedance data and micromanometer tipped data (n=24, from 2001-2003, for chapters 4-8). Figures 2.14a & b demonstrate the recruitment pool for the studies, and the other studies patients were being recruited for simultaneously.

The inclusion and exclusion criteria were as follows.

Inclusion criteria

1) Primary or secondary pulmonary hypertension at echocardiography and/or right heart catheterisation
2) Listed for right heart catheterisation for purposes other than this study
3) Age 18 - 80
4) Informed consent

Exclusion criteria

1) Exercise capacity limited by disease other than pulmonary hypertension
   (e.g. musculoskeletal disorder)
2) Prostacyclin infusion via Hickman line.
3) Left-sided heart disease including significant aortic or mitral valve disease, cardiomyopathy, left ventricular failure or coronary artery disease limiting exercise tolerance.
4) Nursing or pregnant women.

The 'normal' patients recruited, were all symptomatic, and initial investigations at referring hospitals were suggestive of pulmonary hypertension but after investigating at the unit, they were found to have no obvious disease pathology.

All studies, as well as routine clinical tests were performed over a period of a week, as demonstrated in figure 2.15. Spirometry, CT scanning, echocardiography and 6-minute walk test were all performed by the regular NHS staff. The right heart catheterisation and routine haemodynamic measurements were performed either by Dr R. Syyed, Professor A.J. Peacock or Dr H. Mortimer. The simultaneous thoracic bioimpedance and thermodilutional cardiac output data were noted by either, Dr R. Syyed, Dr H. Mortimer or Sister A. Crozier. The thoracic bioimpedance device setup and the insertion of the ambulatory pulmonary artery catheter were performed by Dr R Syyed. The thoracic bioimpedance device was left to run during the routine haemodynamic tests. If Dr Syyed was performing the routine haemodynamic investigations, and the thoracic bio-impedance signal was lost, it was not possible to re-set this device. All other experiments were performed by Dr R. Syyed. All data processing and analysis was performed by Dr R. Syyed.

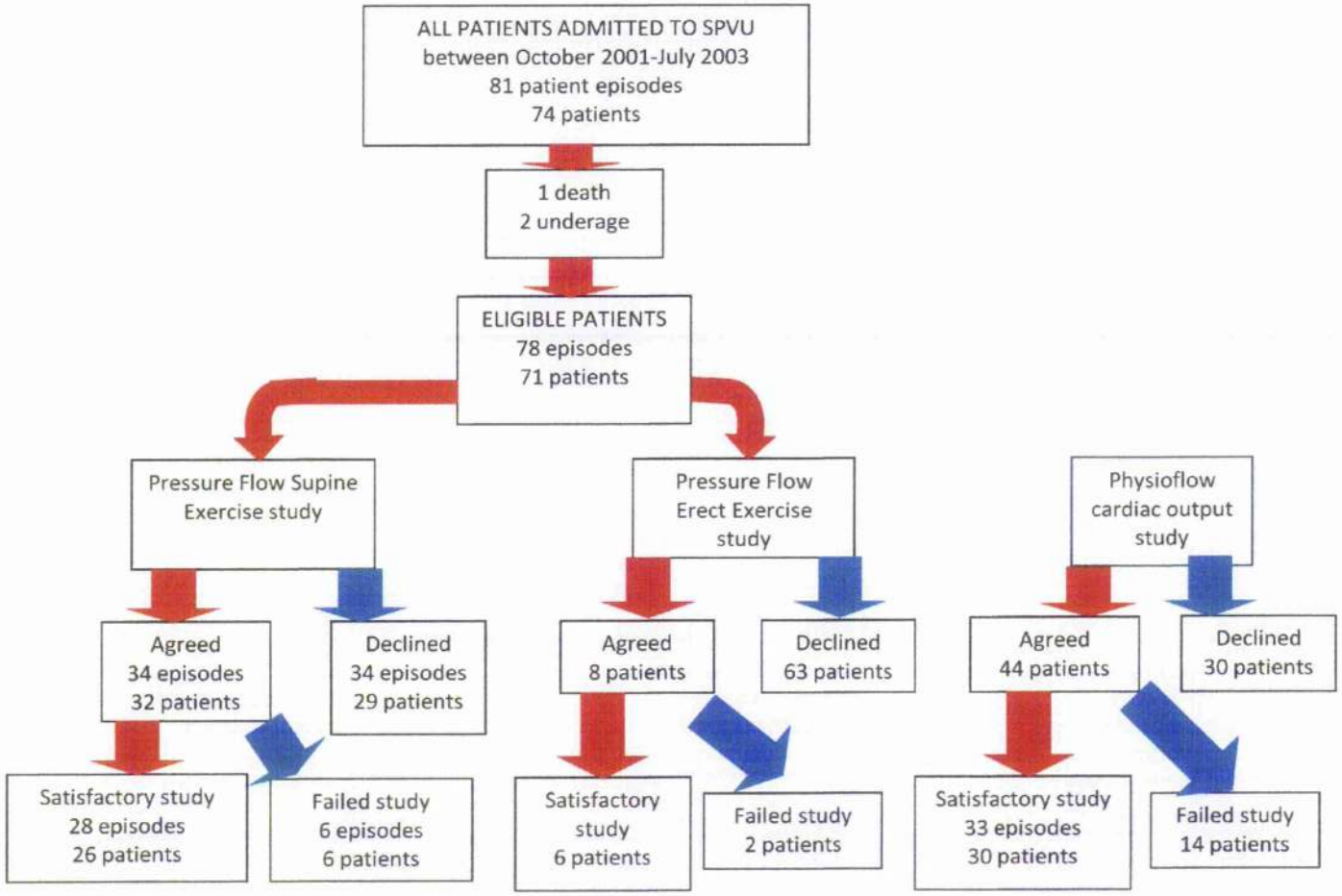


Figure 2.14a: Recruitment of patients to research studies. The subjects were offered to participate in a number of research studies simultaneously, over a period of a week.

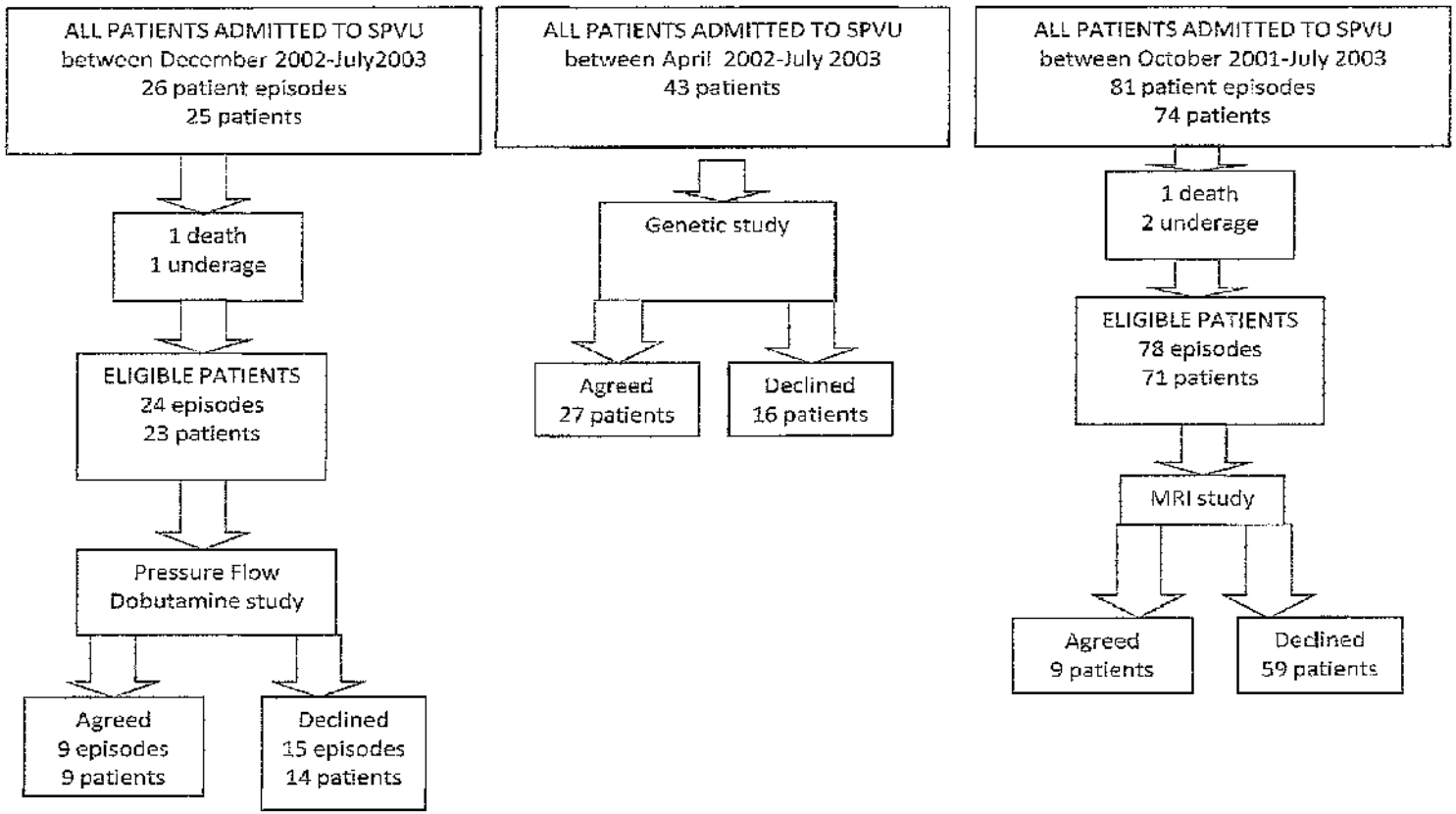


Figure 2.14b: Recruitment of patients to research studies. The subjects were offered to participate in a number of research studies simultaneously, over a period of a week. Study titles in blue were not part of this thesis.

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
AM	Admission from any part of Scotland	Blood tests Pulmonary function tests 6-minute walk test	Further discussion of research +/- consent MRI scan Genetic blood tests	Insertion of catheter sheath into right internal jugular Test set up of cardiac output measurements	Pressure-Flow Study/ Dobutamine pressure-flow study/ other studies* (Removal of catheter) Commencement of treatment
PM	Clerk in / / first discussion of research	HR-CT & CT-PA Further discussion of research +/- consent	Echocardiography	Routine haemodynamic measurements & vasodilator study Non-invasive cardiac output measurements	(Cardiopulmonary Exercise Test)/ erect pressure-flow study (removal of catheter) HOME
				Discussion of results with patient Pressure-Flow Study/ Dobutamine pressure-flow study/ other studies* Overnight ambulatory catheter study	

Figure 2.15: Timetable of procedures for subjects during their 1 week admission. Routine clinical tests are labelled in black, and research in red

2.7 Data analysis

Data are expressed as mean ± S.D. The tests used varied between experiments. The student t-test was used for chapter 3. using SPSS-Vs 14.0, Bland Altman analysis (Bland, JM. et al 1986b) for Chapter 4. Multivariate analysis was performed in chapter 3, but due to heterogeneity and small number of subjects recruited, and the interrelated variables like pressure variables, the analysis may not be statistically robust.

For chapters 5-8, the Poon test to combine data was used (Poon, C. S. 1988) and this data was further analysed by general linear regression analysis (SPSS vs 14.0). Linear

regression analysis was used to produce histograms and normality plots, as well as the values and confidence intervals of the slopes and intercepts of the lines obtained. Initial assessment of the probability of the linearity of the plots was done by visually reviewing the scattergrams of the plots and the histogram and normality plots of the residuals. Further assessment of the whether the likelihood of the linearity of the plots of paired data was by the ANOVA test of linearity where possible. A test of the usefulness of the plots was attempted by performing the ANCOVA test, a test of likelihood of parallelism, on the data, comparing air with nitric oxide / oxygen combination, air with oxygen and oxygen with the nitric oxide / oxygen combination.

2.8 Ethics

Ethical approval was provided by the West Ethics committee, North Glasgow NHS University Trust. All subjects gave informed consent for thoracic bioimpedance cardiac output measurements as part of their clinical evaluation for suspected pulmonary hypertension.

Chapter 3

A Comparison of Cardiac Output Measured by Thermodilutional Methods & by the Physioflow 1 Thoracic Bioimpedance Device in subjects being investigated for Pulmonary Hypertension

3.1 Introduction

For years, the clinical gold standard test for measuring cardiac output has been by the thermodilutional method. This has been widely validated against gold standard experimental methods.

With regards to the use of the thermodilutional method in subjects with pulmonary hypertension, its accuracy has been questioned, but it is now in routine use. In a number of studies, it has been shown to overestimate cardiac output as compared to Fick and dye dilutional methods, the experimental gold standards (Branthwaite, M. A. et al 1968; Hsia, C. C. et al 1995; Mackenzie, J. D. et al 1986; Russell, A. E. et al 1990; van, Grondelle A. et al 1983) at rest and during exercise.

Since 1966, (Kubicek, W. G. et al 1966) cardiac output has been monitored experimentally by measuring the electrical impedance changes across the thorax. There have been several equations and devices developed over the past 30 years to measure this, with varying but improving accuracy (Bernstein, D. P. 1986; Sramek, B. B et al 1983). The accuracy, reliability and reproducibility of these devices in clinical practice, however have not been good enough to contemplate their use either as a replacement or an adjunct to current clinical gold standard methods (Warburton, D. E. et al 1999).

Recently a new device, the Physioflow 1 (Physioflow, Type PF05L1, Manatec, France) bioimpedance device, was developed after technical improvements occurred in the hardware (a new generation of analog technology allows the Physio Flow to improve signal filtering and stability and provide better data processing), and the basic equation has been adjusted. The equation has been modified in order to overcome the difficulties

in evaluating blood resistivity (ρ), the distance between recording electrodes (L) and baseline impedance (Z_0) used in the Kubicek and Sramek-Bernstein equations. There have been several studies investigating the accuracy and reproducibility of the physioflow in clinical practice. Charloux et al (2000), investigated a number of subjects with respiratory conditions (COPD, n=26, sleep apnoea, n=14) at rest and during exercise, and found that a strong correlation was obtained between the physioflow determined cardiac output and the Fick derived cardiac output values, of 0.89 ($p<0.001$) at rest and of 0.85 ($p<0.001$) during exercise. Similar results have been found by both Bougault et al (2005) and Richards et al (2001). The physioflow seems to be more accurate in a clinical practice when used in a number of clinical conditions and situations compared to older devices.

This device has not been validated for use in subjects with pulmonary hypertension, and a study to investigate its usefulness in this was undertaken.

3.2 Methods

3.2.1. Data Subjects

All the subjects were patients at the Scottish Pulmonary Vascular Unit between October 2001 and July 2003, who had been admitted for routine investigations, which included measurement of thermodilutional cardiac output, of their suspected pulmonary hypertension. There were 30 subjects examined on 33 occasions, and with 32 sets of 3 cardiac output measurements undertaken whilst breathing air, (table 3.1, n=33), 7 whilst breathing oxygen, 12 breathing a nitric oxide and oxygen combination (NO/O_2) and 7 whilst exercising (table 3.2). There were 13 males & 17 females. The mean (±S.D.) age was 58.2 (± 13.8) years. The general demographics are seen in table 3.1 & 3.4.

4 subjects were normals without pulmonary hypertension and the other 26 had pulmonary hypertension due to the following causes, 3 with COPD, 6 with Connective tissue disease (CTD), 1 due to portopulmonary (portopulm.) hypertension, 7 due to idiopathic pulmonary arterial hypertension (IPAH), 6 due to chronic thromboembolic pulmonary hypertension (CTEPH) and in one subject, at the time of the study the exact cause of pulmonary hypertension was still to be established. The demographics for the disease groups, and for the activity undertaken are given in tables, 3.1 and 3.4a & b.

Pulmonary and right heart haemodynamic data obtained via the right heart catheterisation, was available for all the subjects (table 3.4a), and spirometry data available in 14 patients (table 3.4b)

Table 3.1

Subject Number	Initials	Age	Sex	Cardiac Output on Air Thermodilutional ($L \cdot min^{-1}$)	Cardiac Output on Air Bioimpedance ($L \cdot min^{-1}$)	Diagnosis
1	M,C	55	F	8.1	7.6	normal
2	L,C	40	F	3.7	5	normal
3	B,R	37	F	5.6	5.8	normal
4	L,G	52	F	5.8	6.5	normal
5	G,C	49	M	5.5	10.2	IPAH
5	G,C	50	M	4.6	4.9	IPAH
5	G,C	50	M	4.2	5.1	IPAH
6	W,F	67	M	3.3	3.8	IPAH
7	E,M	73	F	3.7	8.7	IPAH
9	S,S	45	F	4.5	8.1	IPAH
10	D,H	64	F	3.3	3.5	IPAH
11	H,C	37	F	4.3	4.6	IPAH
12	M,Y	37	F	3.4	4.3	IPAH
13	R,C	54	F	3.6	3.6	CTD
15	I,P	46	F	4.4	5.1	CTD
16	J,P	59	M	2.4	3.8	CTD
17	K,S	62	F	3.9	4.1	CTD
18	J,R	74	F	2.6	4.4	CTD
19	E,K	73	F	2.6	2.7	CTD
20	J,F	71	M	3.7	5.1	CTEPH
21	S,O	74	M	5	9.1	CTEPH
22	A,C	62	M	4.8	4.4	CTEPH
23	A,T	35	F	5.3	6.25	CTEPH
24	C,A	46	M	4.4	5.5	CTEPH
25	E,R	67	F	3.6	4.3	CTEPH
28	W,F	71	M	2.6	4.1	ILD
29	D,B	72	M	5.1	6.4	ILD
31	R,McD	60	M	2.2	5.1	COPD
32	M,T	81	F	4.1	5.2	COPD
33	H,J	77	M	2.6	4.4	COPD
34	S,C	48	F	10.7	5.1	portopulm
35	M,E	76	F	3.6	2.7	unknown
Mean		58.2		4.3	5.3	
S.D.		13.8		1.7	1.8	

Table 3.1: Details of subjects studied concurrently with both the thoracic impedance cardiac output Physioflow 1 (Mantanec, France) device and a standard swan-gantz thermodilutional pulmonary artery catheter (n=30). All subjects for the thesis have been allocated an individual number, 1 to 37. Details of age, sex and underlying cause of pulmonary hypertension, as well as cardiac output measurements ($L \cdot min^{-1}$) for both methods measurements of subjects at rest, supine inhaling air are listed

Table 3.2

Number	Cardiac Output on Oxygen ($L\ min^{-1}$)		Cardiac Output on Nitric Oxide ($L\ min^{-1}$)		Cardiac Output on Exercise ($L\ min^{-1}$)	
	Thermo-dilutional	Bio-impedance	Thermo-dilutional	Bio-impedance	Thermo-dilutional	Bio-impedance
1					9	9.9
3					11.3	11.6
4					10.8	11
6			4.5	4.5		
7			4.1	8.1		
9			4.8	8.9		
10	3.2	3.3				
13			3.8	4		
15					4.8	6.8
16			2.4	4.1		
17	3.3	4.3	4	4.5		
19					2.7	3
20	3.5	4.8	3.4	4.8		
21					7.5	16.4
22			4.5	4.6		
23			5.7	7.1	6.7	7.6
24	4.6	5.7	4.5	5.5		
28			3.1	4.1		
29	4.7	6	5.1	6.5		
32	3.7	3.8				
33	3.1	5.3				
Mean	4.72	4.74	4.16	5.56	7.54	9.47
S.D.	0.66	1.00	0.90	1.69	3.12	4.23

Table 3.2: Details of cardiac output measurements ($L \cdot min^{-1}$) studied concurrently whilst inhaling oxygen, nitric oxide and during exercise, from both the thoracic impedance cardiac output Physioflow 1 (Mantanec, France) device and a standard swan-gantz thermodilutional pulmonary artery catheter. All subjects were supine. Subject numbers corresponds with subjects in table 3.1.

Table 3.3a

Number	Initials	Change in Cardiac Output from Baseline (Baseline is Cardiac Output on air) ($L \cdot min^{-1}$)					
		Oxygen		Nitric Oxide		Exercise	
		Thermo-dilutional	Bio-impedance	Thermo-dilutional	Bio-impedance	Thermo-dilutional	Bio-impedance
1	M,C					0.9	2.3
3	B,R					5.7	5.8
4	L,G					5	4.5
6	W,F			1.2	0.7		
7	E,M			0.4	-0.6		
9	S,S			0.3	0.8		
10	D,H	-0.1	-0.2				
13	R,C			0.2	0.4		
15	I,P					0.4	1.7
16	J,P			0	0.3		
17	K,S	-0.6	0.2	0.1	0.4		
19	E,K					0.1	0.3
20	J,F	-0.2	-0.3	-0.3	-0.3		
21	S,O					2.5	7.3
22	A,C			-0.3	0.2		
23	A,T			0.4	0.85	1.4	1.35
24	C,A	0.2	0.2	0.1	0		
28	W,F			0.5	0		
29	D,B	-0.4	-0.4	0	0.1		
32	M,T	-0.4	-1.4				
33	H,J	0.5	0.9				
Mean		-0.14	-0.14	0.22	0.23	2.29	3.32
S.D.		0.38	0.70	0.40	0.43	2.24	2.58

Table 3.3b

Number	Initials	Percentage change in Cardiac Output from Baseline (Baseline is Cardiac Output on air) (%)					
		Oxygen		Nitric Oxide		Exercise	
		Thermo-dilutional	Bio-impedance	Thermo-dilutional	Bio-impedance	Thermo-dilutional	Bio-impedance
1	M,C					11	30.3
3	B,R					101.7	100
4	L,G					87	69.2
6	W,F			33.7	4.5		
7	E,M			9.9	-6.9		
9	S,S			6.7	8.9		
10	D,H	-4.8	-5.7				
13	R,C			6.7	11		
15	I,P					9.9	33.3
16	J,P			0	7.9		
17	K,S	-15.5	4.9	2.9	9.7		
19	E,K					2.3	11.1
20	J,F	-6.1	-5.9	-8.1	4.8		
21	S,O					51	80.2
22	A,C			-4.9	4.6		
23	A,T			6.3	7.1	25	21.6
24	C,A	4.5	3.6	3	0		
28	W,F			17.3	0		
29	D,B	-8.4	-6.3	-0.7	1.6		
32	M,T	-9.8	-26.9				
33	H,J	19.2	20.5				
Mean		-2.99	-2.26	6.07	4.43	41.12	49.38
S.D.		11.50	14.44	10.99	5.09	39.83	33.57

Table 3.3a & b: Details of change (a) and percentage change (b) in cardiac output measurements studied concurrently whilst inhaling oxygen, nitric oxide and during exercise, from both the thoracic impedance cardiac output Physioflow 1 (Mantanec, France) device and a standard swan-gantz thermodilutional pulmonary artery catheter as compared to baseline values at rest, supine, breathing room air. Actual cardiac values are listed in tables 3.1 and 3.2. Subject numbers corresponds with subjects in table 3.1.

Table 3.4a

Number	Initials	MPAP (mmHg)	SPAP (mmHg)	DPAP (mmHg)	PAPP (mmHg)	RAP (mmHg)	PVR (mmHg /L min^{-1})	PAWP (mmHg)
1	M,C	17	23	11	12	47	2	
2	B,R	15	24	3	21	9	0.5	12
3	L,G	14	26	3	23	5	1	7
4	I,C	8	14	2	12	14	0	1
5	G,C	57	91	37	54	6	9	7
6	W,F	79	137	48	89	11	20	14
7	E,M	63	115	23	92	14	13	15
9	S,S	60	103	60	43	10	13	3
10	D,H	46	80	23	57	5	11	9
11	H,C	33	55	17	38	2	7	
12	M,Y	48	79	33	46	0	14	1
13	R,C	49	77	27	50	8	12	5
15	I,P	36	62	17	45	5	7	6
16	J,P	99	130	82	48	4	37	9
17	K,S	36	61	22	39	2	4	
18	J,R	42	70	25	45	11	15	
19	E,K	48	86	26	60	6	18	2
20	J,F	63	100	36	64	20	12	20
21	S,O	46	79	27	52	8	11	
22	A,C	55	90	40	50	20	8	
23	A,T	60	103	36	67	8	9	
24	C,A	25	40	19	21	15	3	15
25	E,R	40	66	21	45	4	9	
28	W,F	39	54	28	26	18	5	12
29	D,B	33	50	20	30	1	5	7
31	R,McD	43	74	26	48	11	16	8
32	M,T	30	50	10	40	4	4	13
33	H,J	49	90	30	60	19	16	22
34	S,C	19	31	9	22	15	0.4	10
35	M,E	36	65	17	48	2	9	
Mean		43.8	72.5	26.4	46.0	8.9	9.96	9.4
S.D.		19.4	30.4	16.8	18.6	6.0	7.55	5.8

Table 3.4b

Number	Initials	FEV_1 (L)	% predicted FEV_1	FVC (L)	% predicted FVC	FEV1/FVC Ratio (%)	KCO	% Predicted KCO
1	M,C	2.67	119	3.25	123	103		
2	B,R							
3	L,G							
4	I,C							
5	G,C	3.57	99	4.98	112	72	1.21	81
6	W,F							
7	E,M							
9	S,S							
10	D,H							
11	H,C	3.57	99	4.98	112	72	1.21	81
12	M,Y	2.84	100	3.24	99	88	1.82	101
13	R,C	3.02	119	4.07	137	74	0.25	15
15	I,P							
16	J,P							
17	K,S							
18	J,R							
19	E,K							
20	J,F	3.41	113	4.58	116	75	1.03	81
21	S,O							
22	A,C							
23	A,T	3.57	97	4.1	97	87	1.26	74
24	C,A	3.24	89	4.54	102		0.91	60
25	E,R							
28	W,F	2.29	89	2.61	78	88		20
29	D,B							
31	R,McD	2.16	64	3.9	92	55	0.34	24
32	M,T	1.16	75	2.19	115	53	0.5	36
33	H,J	1.34	50	2.48	69	73	0.32	26
34	S,C							
35	M,E							
Mean		2.74	92.7	104.3	76.4	0.88	0.88	54.5
S.D.		.84	21.2	0.97	19.0	14.8	0.52	30.8

Tables 3.4a & 3.4b: Table 3.4a is giving haemodynamic values of the individual subjects in the study. The values are obtained through a standard swan-ganz fluid filled

pulmonary artery catheter. Table 3.4b spirometic values available for individual subjects. Subject numbers corresponds with subjects in table 3.1.

3.2.2. Procedure

The physioflow 1, cardiac output bio-impedance device, was set up and calibrated before the patient commenced right heart catheterisation. Blood pressure was initially inputted at this time. Thereafter, a designate operator for the physioflow-1 cardiac output bio-impedance device was only then allocated, if staffing levels permitted. Further adjustments to the device, and further blood pressure adjustments were only made in 10 subjects. During the clinical procedure three sets of thermodilutional cardiac output measurements (CO_{THERM}) were taken when felt to be clinically relevant, and bio-impedance cardiac output data was noted at the same time (CO_{PF}). The bio-impedance device was set to give measurements over a 15 second interval. Several sets of thermodilutional cardiac output data were made until three values matched within 10% or 0.5L/min of each other. This was then averaged to obtain a single value. Only the bioimpedance measurements taken at the same time as the selected thermodilutional measurements were noted and averaged.

During the right heart catheterisation, pulmonary artery pressures (Diastolic, mean and systolic pulmonary artery pressure, DPAP, MPAP, SPAP), right atrial pressure, (RAP), and pulmonary artery wedge pressure, (PAWP) were measured.

Spirometry results (forced expiratory volume in 1 second, FEV_1, Forced vital capacity FVC, & diffusion coefficient, KCO) were obtained by a vitalograph, in 14 patients.

3.2.3 Ethics

Ethical approval was provided by the West Ethics committee, North Glasgow NHS University Trust. All subjects gave informed consent for thoracic bioimpedance cardiac output measurements as part of their clinical evaluation for suspected pulmonary hypertension.

3.2.3. Statistics

Population data was analysed to give values +/- standard deviations. Comparisons between the measurements obtained by both methods was initially performed by linear regression, and then analysed by the Bland Altman method. This was done for all the results, and sub-analysed for the results whilst receiving air, oxygen, nitric oxide, or during exercise, and also for the subjects with IPAH, CTD, & CTPEH individually.

The actual change, as well percentage change, from baseline (on air) to receiving oxygen, nitric oxide, or with exercise were compared between thermodilutional results and bio-impedance results.

These actual and percentage differences between the thermodilutional results and bio-impedance results were compared with spirometry and right heart catheterisation data for the subjects in order to ascertain whether there was any underlying reason for the differences in cardiac output data obtained.

3.3. Results

The correlation coefficient squared of the two techniques was $r^2 = 0.463$ ($p < 0.001$) when all the data was analyzed, and gave a regression equation of $CO_{PF} = 1.924 + CO_{THERM} \bullet 0.844$ ($L \bullet min^{-1}$), for all 57 sets of measurements, as shown in figure 3.1a. & 3.1c. A comparison (by the Bland-Altman method) of the two techniques was made for all 57 measurements, as shown in figures 3.1b & 3.1d, and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 1.21 (± 1.85) $L \bullet min^{-1}$, (giving 95% confidence intervals of between –2.44 and 4.86 $L \bullet min^{-1}$). The total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 23.35 (± 35.9) %.

If, to avoid overrepresentation of individuals, only the first result of subject 5 was taken as well as only measurements taken on air at rest, the correlation coefficient squared of the two techniques was $r^2 = 0.152$ ($p < 0.019$) when all the data was analyzed, and gave a regression equation of $CO_{PF} = 3.38 + CO_{THERM} \bullet 0.451$ ($L \bullet min^{-1}$), for the 35 sets of measurements. A comparison (by the Bland-Altman method) of the two techniques was made for the 35 measurements, and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 1.03 (± 1.93) $L \bullet min^{-1}$, (giving 95% confidence intervals of between –2.83 and 4.89 $L \bullet min^{-1}$). The total mean difference (CO_{PF} - CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 21.5 (± 40.2) %.

Figure 3.1a

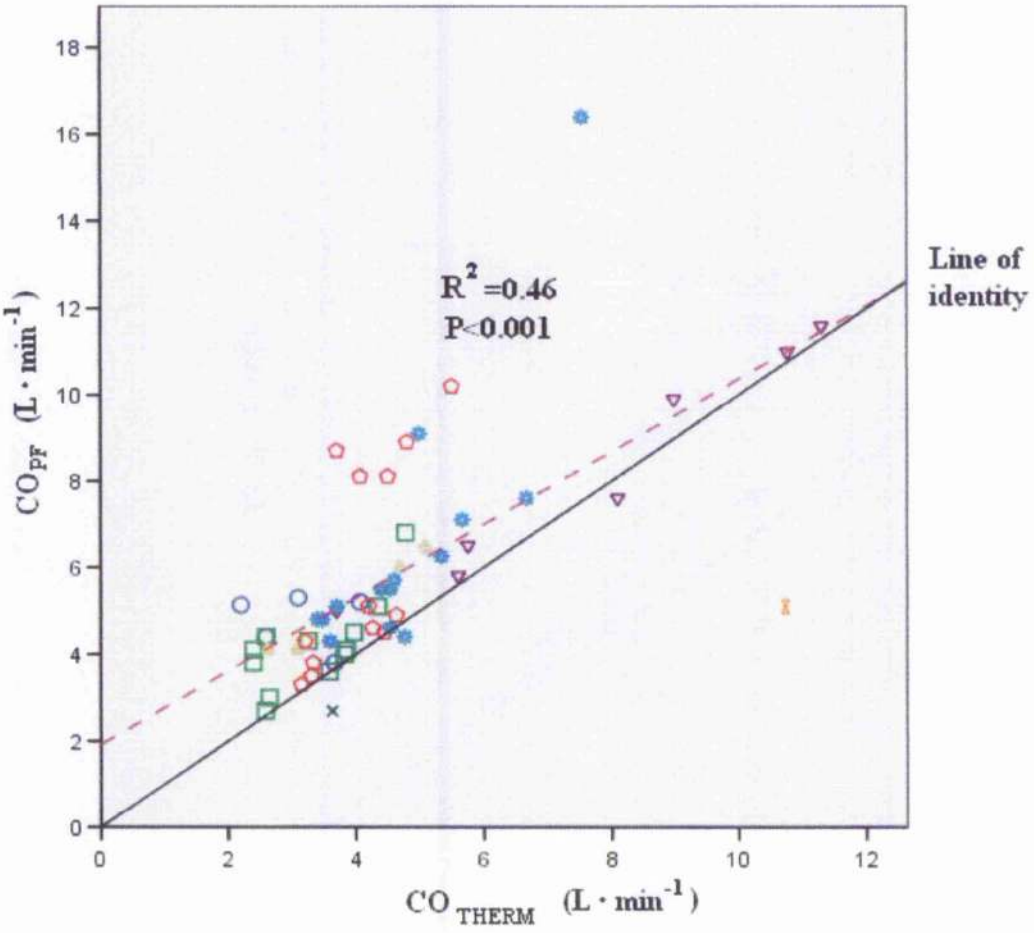


Figure 3.1a: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) in the 30 individuals (n=57 the line of identity given by the continuous black line, and the regression line for the combined paired data, by the broken purple line. Individual diseases shown in ***a****, with the paired data of normal subjects represented by an inverse purple triangle, Idiopathic pulmonary arterial hypertension (IPAH) by a red hexagon, Connective tissue disorders (CTD) by a green square, Chronic obstructive pulmonary disease (COPD) by a dark blue circle, interstitial lung disease shown with a tanned upright triangle, Chronic thromboembolic pulmonary hypertension by a light blue star, Portopulmonary hypertension by an orange hour glass and the unknown subject by a green cross.*

Figure 3.1b

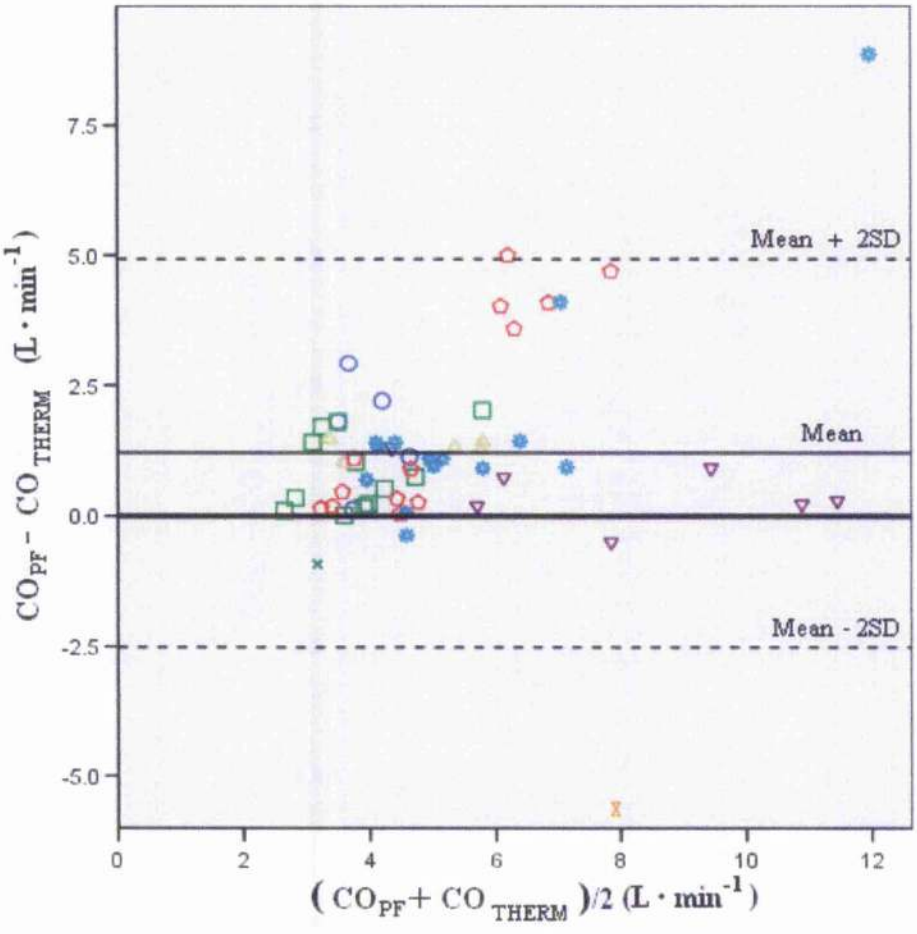


Figure 3.1b: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) in the 30 individuals (n=57) as a graphical representations of the differences between the two measurements (CO_{PF} - CO_{THERM} vs. the mean of the two measurements [(CO_{PF} + CO_{THERM})/2] for each measure, according to the Bland and Altman method. The continuous thick horizontal line represents the line of origin of the x-axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ± 2S.D.). The paired data of a normal subjects by an inverse purple triangle, Idiopathic pulmonary arterial hypertension (IPAH) by a red hexagon, Connective tissue disorders (CTD) by a green square, Chronic obstructive pulmonary disease (COPD) by a dark blue circle, interstitial lung disease shown with a tanned upright triangle, Chronic thromboembolic pulmonary hypertension by a light blue star, Portopulmonary hypertension by an orange hour glass and the unknown subject by a green cross.

Figure 3.1c

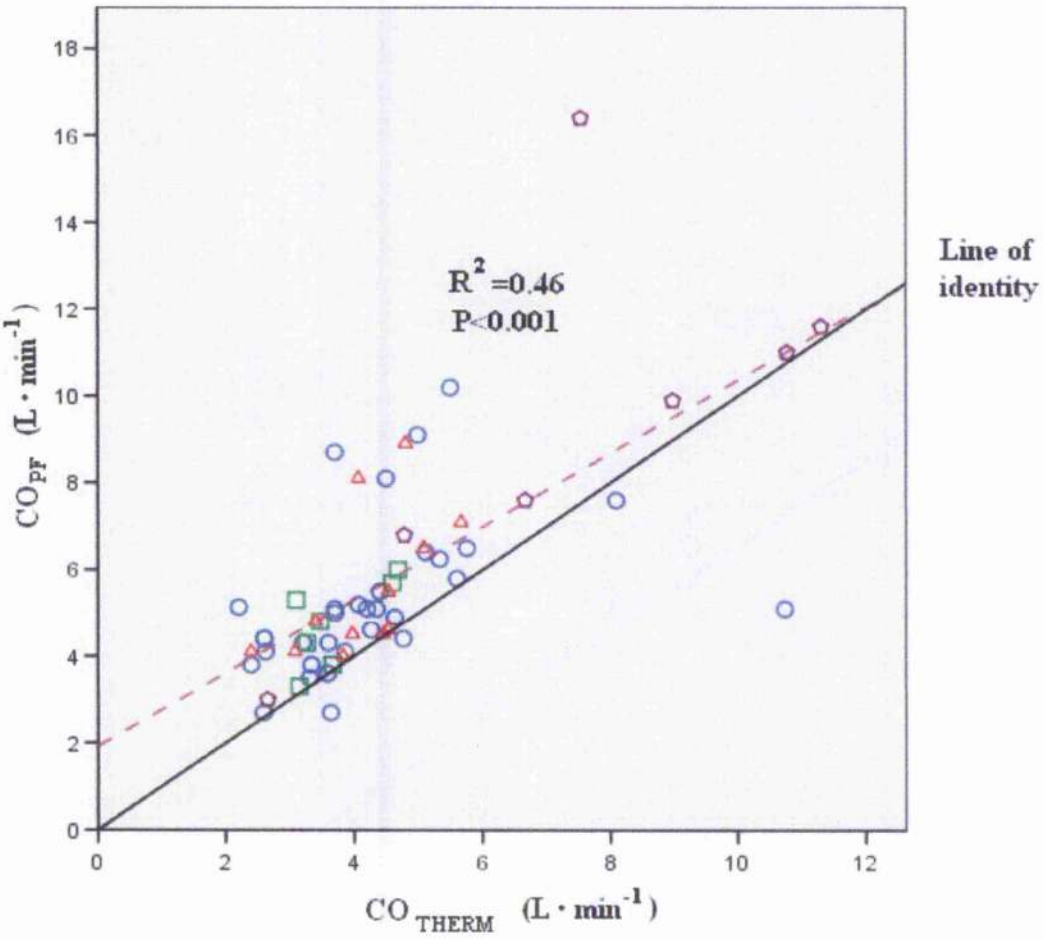


Figure 3.1c: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) in the 30 individuals (n=57) the line of identity given by the continuous black line, and the regression lines for the combined paired data, by the broken purple line. . The paired data for the individual physiological circumstances are shown, with inhalation by air shown by a dark blue circle, oxygen by a green square, nitric oxide by a red upright triangle, and during exercise with a purple hexagon.

Figure 3.1d

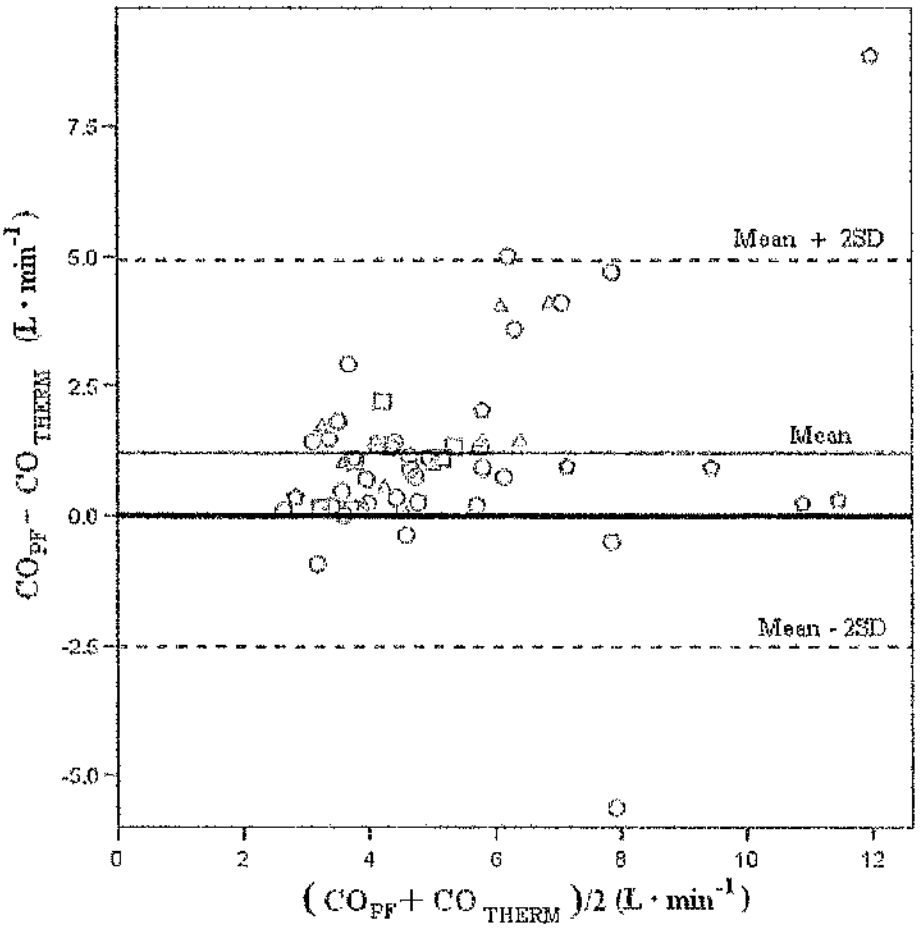


Figure 3.1d: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) in the 30 individuals (n=57) as a graphical representations of the differences between the two measurements ($CO_{PF} - CO_{THERM}$ vs. the mean of the two measurements [($CO_{PF} + CO_{THERM}$)/2] for each measure, according to the Bland and Altman method. The continuous thick horizontal line represents the line of origin of the x axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ± 2S.D.). The paired data for the individual physiological circumstances are shown, with inhalation by air shown by a dark blue circle, oxygen by a green square, nitric oxide by a red upright triangle, and during exercise with a purple hexagon.

When analyzed the individual subgroups of the paired data on air, oxygen, nitric oxide/oxygen combination and during exercise, the following results were obtained.

The correlation coefficient squared of the two techniques whilst inhaling air was r^2 = 0.179 (p = 0.085) when all the data was analyzed, and gave a regression equation of CO_{PF} = 3.385 + CO_{THERM} • 0.447 ($L \bullet min^{-1}$), for all 32 sets of measurements, as shown in figure 3.1c. A comparison (by the Bland-Altman method) of the two techniques was made for the 32 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 1.02 (± 1.87) $L \bullet min^{-1}$, (giving 95% confidence intervals of between –2.66 and 4.69 $L \bullet min^{-1}$). The total mean difference (CO_{PF} - CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 22.89 (± 39.1)%.

The correlation coefficient squared of the two techniques whilst inhaling oxygen was r^2 = 0.479 (p = 0.085) when all the data was analyzed, and gave a regression equation of CO_{PF} = 0.92 + CO_{THERM} • 1.032 ($L \bullet min^{-1}$), for all 7 sets of measurements, as shown in figure 3.1c. A comparison (by the Bland-Altman method) of the two techniques was made for the 7 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 1.04 (± 0.72) $L \bullet min^{-1}$, (giving 95% confidence intervals of between –0.38 and 2.45 $L \bullet min^{-1}$). The total mean difference (CO_{PF} - CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 24.45 (± 17.09) %.

The correlation coefficient squared of the two techniques whilst inhaling nitric oxide was r^2 = 0.347 (p = 0.044) when all the data was analyzed, and gave a regression equation of CO_{PF} = 0.969 + CO_{THERM} • 1.105 ($L \bullet min^{-1}$), for all 12 sets of measurements, as shown in figure 3.1c. A comparison (by the Bland-Altman method)

of the two techniques was made for the 12 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 1.41 (± 1.37) L•min^{-1}, (giving 95% confidence intervals of between –1.27 and 4.08 L•min^{-1}). The total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 29.08 (± 28.16) %.

The correlation coefficient squared of the two techniques during straight leg raising exercise was r^2 = 0.463 (p = 0.09.) when all the data was analyzed, and gave a regression equation of CO_{PF} = 2.553 + CO_{THERM} • 0.919 (L•min^{-1}), for all 5 sets of measurements, as shown in figure 3.1c. A comparison (by the Bland-Altman method) of the two techniques was made for the 5 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 1.95 (± 3.11) L•min^{-1}, (giving 95% confidence intervals of between –4.16 and 8.04 L•min^{-1}). The total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 29.01 (± 28.16)%.

Several of the individual disease subgroups were sub-analysed, IPAH, CTEPH, normals, CTD and ILD.

The correlation coefficient squared of the two techniques in the four subjects without pulmonary hypertension, was r^2 = 0.96 (p < 0.001) when all the data was analyzed, and gave a regression equation of CO_{PF} = 1.165 + CO_{THERM} • 0.909 (L•min^{-1}), for all 7 sets of measurements, as shown in figure 3.2a. A comparison (by the Bland-Altman method, figure 3.2b) of the two techniques was made for the 7 measurements and the

total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 0.45 (± 0.58) L•min^{-1}, (giving 95% confidence intervals of between –0.69 and 1.60 L•min^{-1}). The total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 5.68 (± 7.34) %.

If, to avoid overrepresentation of individuals, only the measurements taken on air at rest were analysed the correlation coefficient squared of the two techniques, was $r^2 = 0.95$ ($p = 0.02$) when all the data was analyzed, and gave a regression equation of $CO_{PF} = 2.76 + CO_{THERM} \bullet 0.60$ (L•min^{-1}), for the 4 sets of measurements, as shown in figure 3.2a. A comparison (by the Bland-Altman method), of the two techniques was made for the 4 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 0.42 (± 0.76) L•min^{-1}, (giving 95% confidence intervals of between –1.1 and 1.95 L•min^{-1}). The total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 7.06 (± 12.70) %.

Figure 3.2a

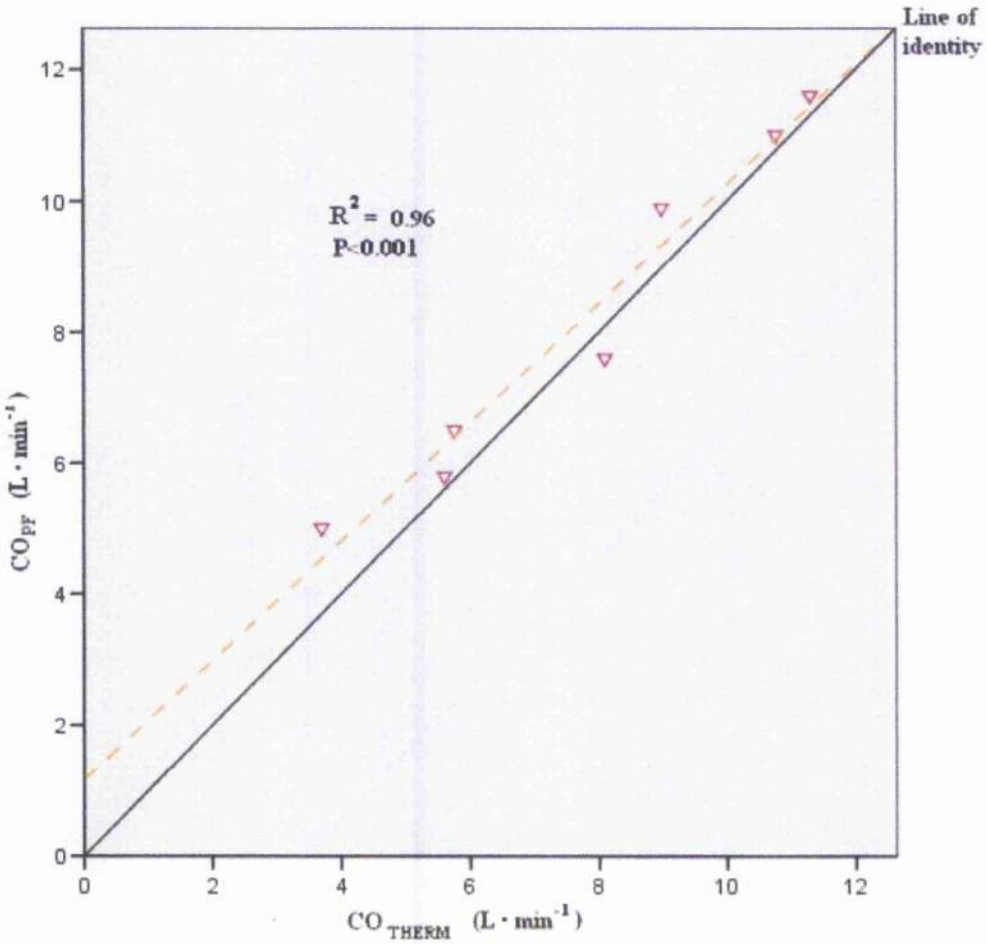


*Figure 3.2a: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) for individuals with no pulmonary hypertension (normals)(n=7) are shown in **a**, with the paired data of a normal subjects by purple inverse triangle, the line of identity given by the continuous black line, and the regression lines for the combined ordinate, by the broken purple line.*

Figure 3.2b

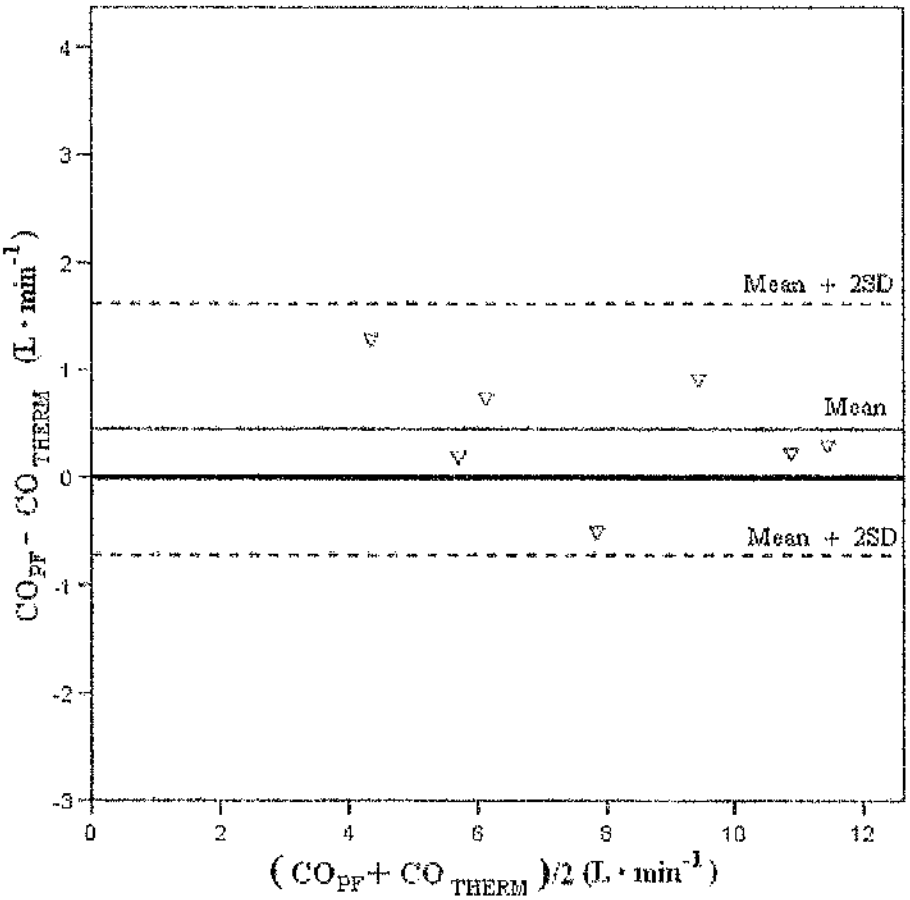


Figure 3.2b: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) for individuals with no pulmonary hypertension (normals)(n=7) are shown in a, with the paired data of subjects by a purple inverse triangle in figure 3.2b as a graphical representations of the differences between the two measurements (CO_{PF} - CO_{THERM} vs. the mean of the two measurements [(CO_{PF} + CO_{THERM})/2] for each measure, according to the Bland and Altman method. The continuous thick horizontal line represents the line of origin of the x-axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ±2S.D.).

The correlation coefficient squared of the two techniques in the 7 subjects with IPAH was $r^2 = 0.453$ ($p = 0.12$) when all the data was analysed, and gave a regression equation of $CO_{PF} = -3.273 + CO_{THERM} \bullet 2.269$ (L•min^{-1}), for all 13 sets of measurements, as shown in figure 3.3a. A comparison (by the Bland-Altman method,

figure 3.3b) of the two techniques was made for the 13 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 1.19 (± 2.00) $L \bullet min^{-1}$, (giving 95% confidence intervals of between –2.00 and 5.83 $L \bullet min^{-1}$). The total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 37.8 (± 39.7) %.

If, to avoid overrepresentation of individuals, only the measurements taken on air at rest the correlation coefficient squared of the two techniques in the 7 subjects with IPAH was $r^2 = 0.60$ ($p = 0.041$) when all the data was analysed, and gave a regression equation of $CO_{PF} = -4.201 + CO_{THERM} \bullet 2.594$ ($L \bullet min^{-1}$), for the 7 sets of measurements, A comparison (by the Bland-Altman method) of the two techniques was made for the 7 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 2.17 (± 2.17) $L \bullet min^{-1}$, (giving 95% confidence intervals of between –2.17 and 6.51 $L \bullet min^{-1}$). The total mean difference (CO_{PF} - CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 42.7(± 42.7) %.

Figure 3.3a

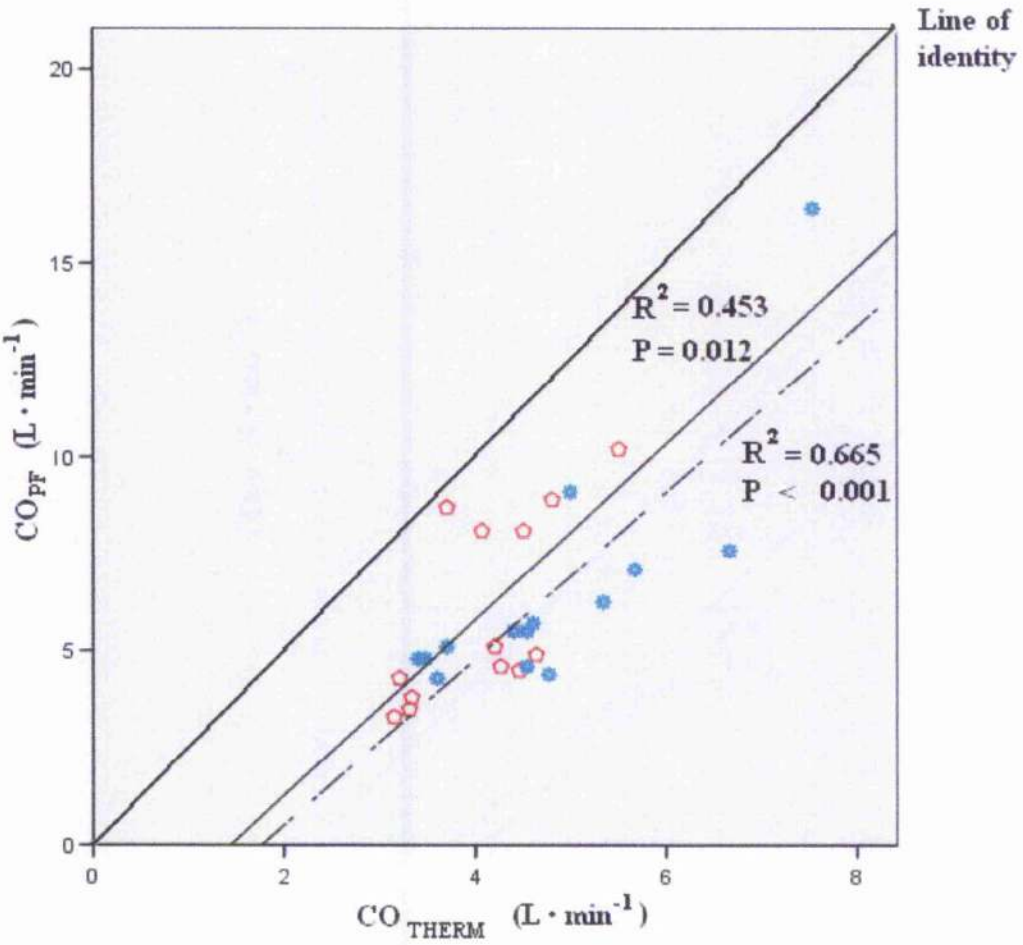


Figure 3.3a: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) in seven individuals with idiopathic pulmonary hypertension (IPAH)(n=9), the paired data of a shown by a red hexagon and in six individuals with chronic thromboembolic pulmonary hypertension (n=14), the paired data shown by blue stars. The line of identity given is by the continuous black line. The regression lines for the combined paired data, of IPAH and CTEPH, are given by the thin black line, and the broken black line respectively.

Figure 3.3b

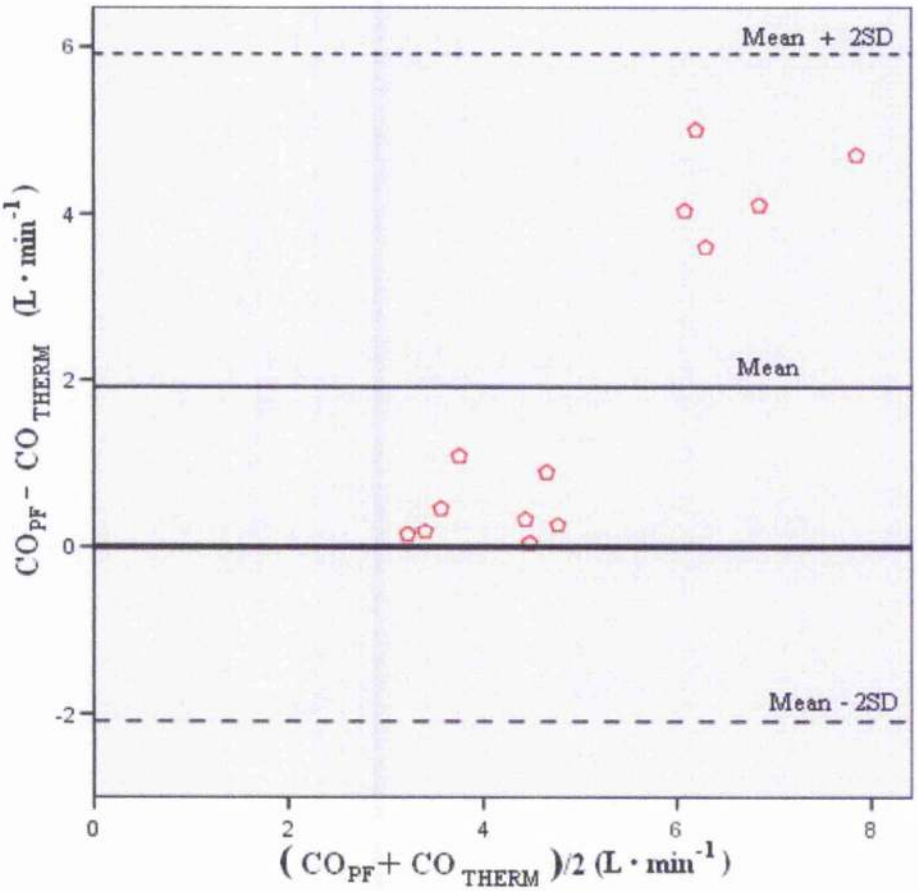


Figure 3.3b: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) by the Bland and Altman method during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) in seven individuals with idiopathic pulmonary hypertension (IPAH)(n=13), are shown), the paired data of which are shown by a red hexagon. The differences between the two measurements (CO_{PF} - CO_{THERM} vs. the mean of the two measurements [(CO_{PF} + CO_{THERM})/2] for each measure, are represented graphically. The continuous thick horizontal line represents the line of origin of the x-axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ± 2S.D.).

Figure 3.3c

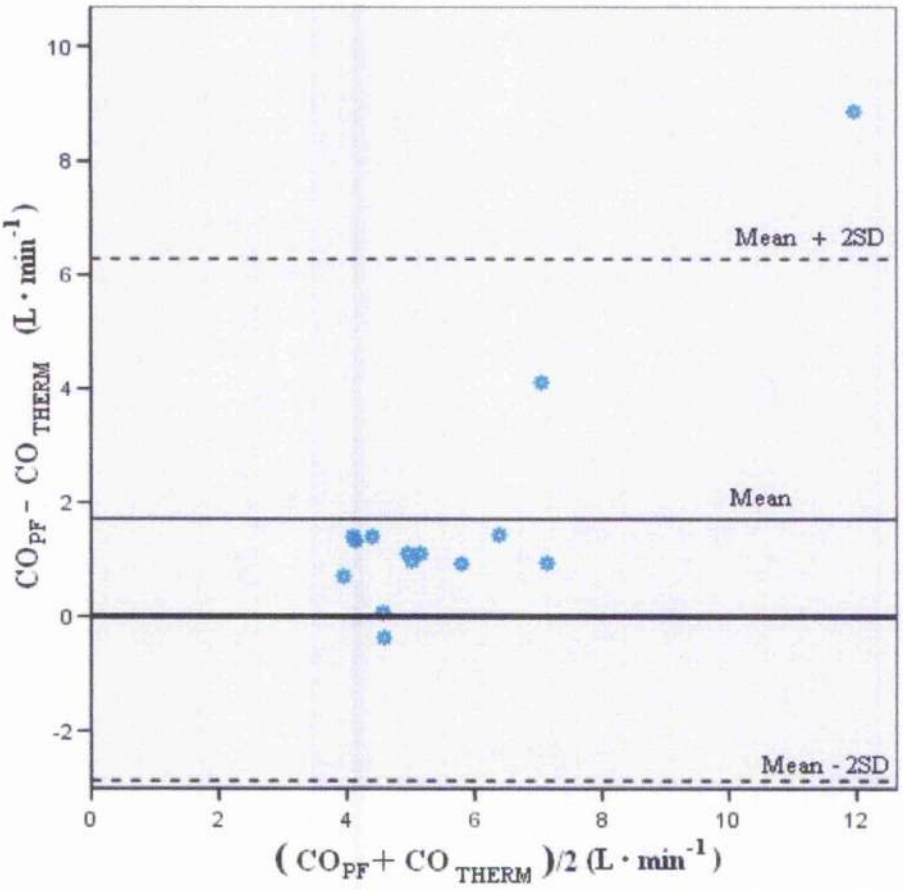


Figure 3.3c: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) by the Bland and Altman method during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) in six individuals with chronic thromboembolic pulmonary hypertension (n=14), the paired data shown by blue stars. The differences between the two measurements (CO_{PF} - CO_{THERM} vs. the mean of the two measurements [(CO_{PF} + CO_{THERM})/2] for each measure, are represented graphically. The continuous thick horizontal line represents the line of origin of the x-axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ± 2S.D.).

The correlation coefficient squared of the two techniques in the 6 subjects with CTEPH was $r^2 = 0.665$ ($p < 0.001$) when all the data was analyzed, and gave a regression equation of $CO_{PF} = -3.789 + CO_{THERM} \bullet 2.446$ (L•min^{-1}), for all 14 sets of measurements, as shown in figure 3.3a. A comparison (by the Bland-Altman method,

figure 3.3c) of the two techniques was made for the 13 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 3.95 (± 2.01) L•min^{-1}, (giving 95% confidence intervals of between –2.76 and 6.19 L•min^{-1}). The total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 30.3 (± 40.8) %.

The correlation coefficient squared of the two techniques in the 6 subjects with CTD was r^2 = 0.522 (p = 0.008) when all the data was analyzed, and gave a regression equation of CO_{PF} = 1.122 + CO_{THERM} • 0.917 (L•min^{-1}), for all 12 sets of measurements, as shown in figure 3.4a. A comparison (by the Bland-Altman method, figure 3.4b) of the two techniques was made for the 12 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 0.84 (± 0.72) L•min^{-1}, (giving 95% confidence intervals of between –0.58 and 2.26 L•min^{-1}). The total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 22.3 (± 19.2) %.

If, to avoid overrepresentation of individuals, only the measurements taken on air at rest the correlation coefficient squared of the two techniques in the 6 subjects with CTD was r^2 = 0.338 (p = 0.226) when all the data was analyzed, and gave a regression equation of CO_{PF} = 2.10 + CO_{THERM} • 0.57(L•min^{-1}), for the 6 sets of measurements. A comparison (by the Bland-Altman method), of the two techniques was made for the 6 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 0.70 (± 0.75) L•min^{-1}, (giving 95% confidence intervals of between –0.80 and 2.20 L•min^{-1}). The total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) as

expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 19.4 (± 20.8) %.

Figure 3.4a

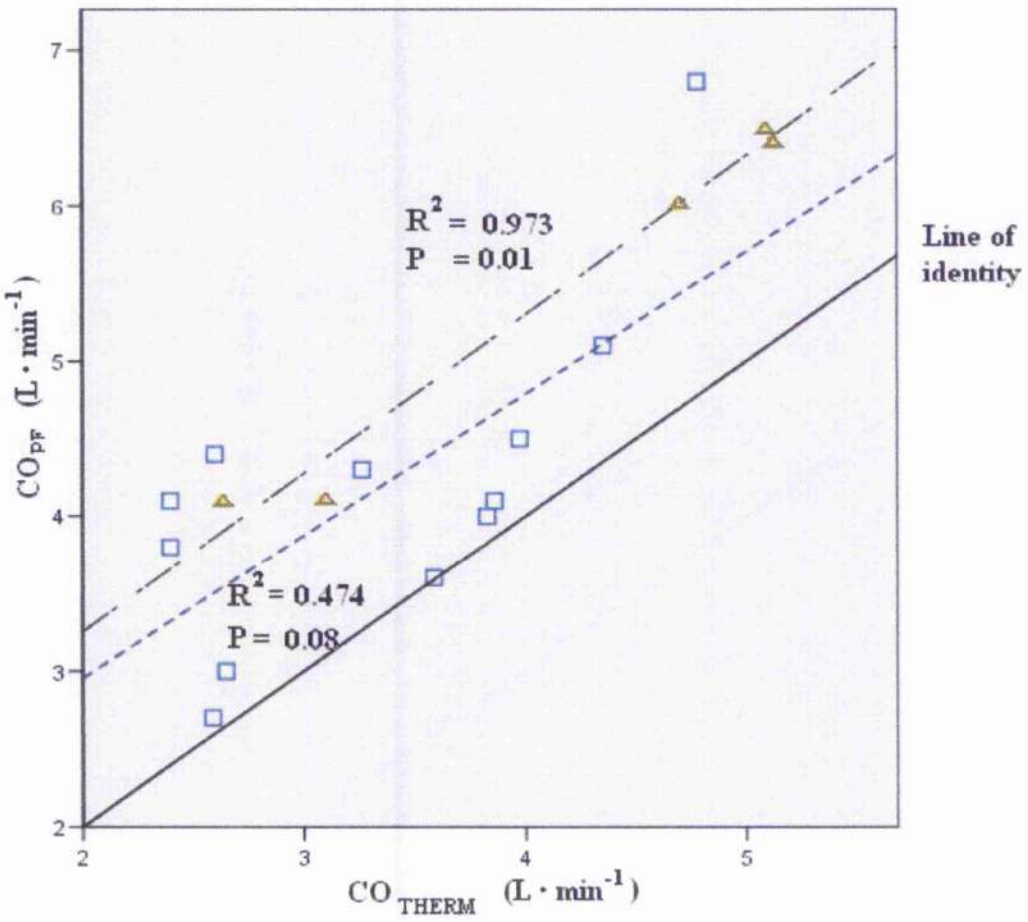


Figure 3.4a: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) in six individuals with connective tissue disease (CTD)(n=12) are shown in ***a****, with the paired data of a shown by a square and in the two individuals with interstitial lung disease (ILD)(n=5), the paired data shown by brown triangles. The line of identity given is by the continuous black line. The regression lines for the combined paired data, of CTD and ILD are given by the broken black line respectively and the broken black line differing line and space lengths respectively.*

Figure 3.4b

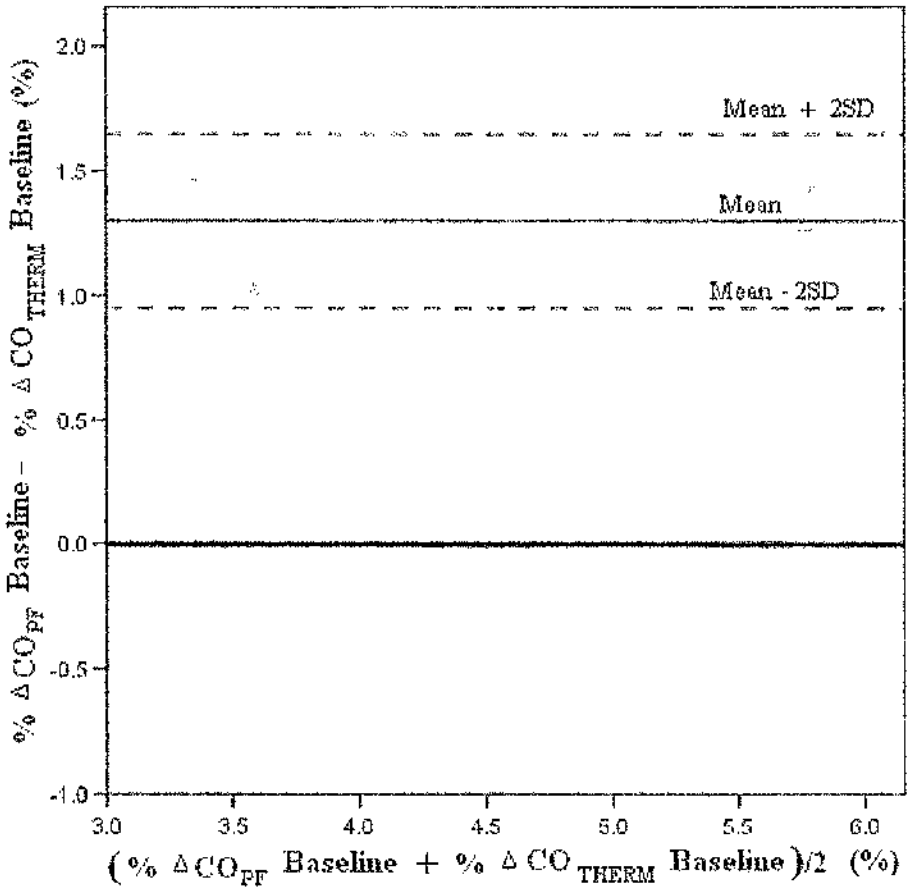


Figure 3.4b: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) by the Bland and Altman method during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) in the two individuals with interstitial lung disease (ILD)(n=5), the paired data shown by brown triangles. The differences between the two measurements (CO_{PF} - CO_{THERM} vs. the mean of the two measurements [(CO_{PF} + CO_{THERM})/2] for each measure, are represented graphically. The continuous thick horizontal line represents the line of origin of the x-axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ± 2S.D.).

Figure 3.4c

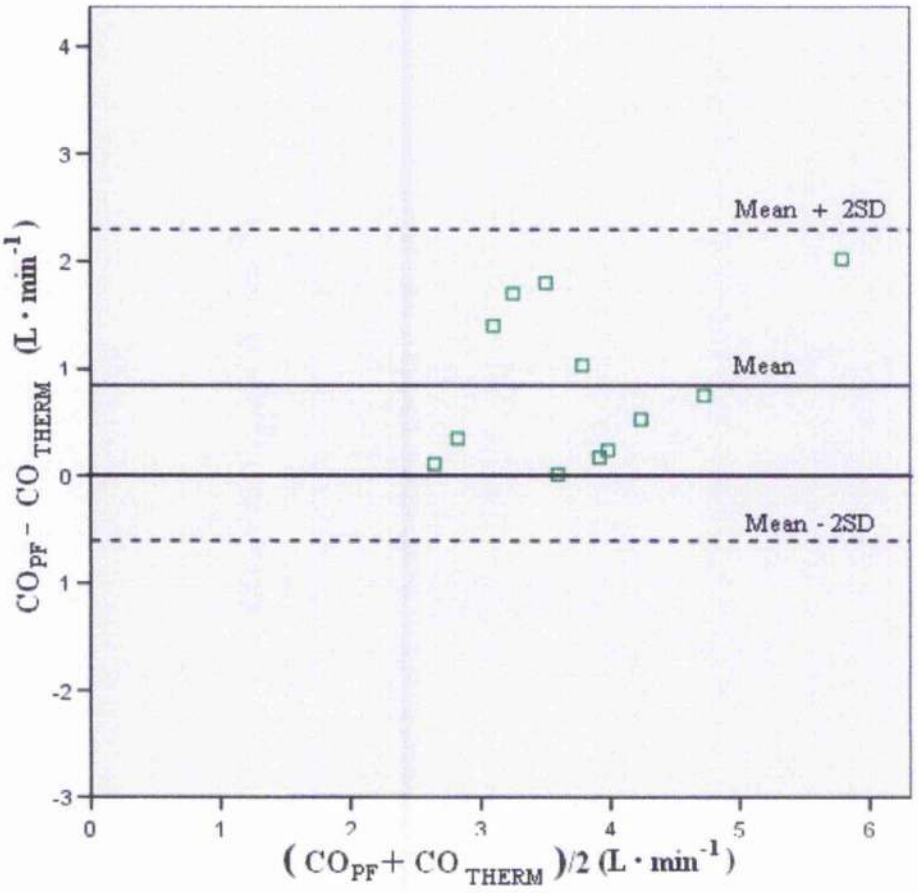


Figure 3.4c: Comparison of cardiac output (CO) obtained using the impedance method (CO_{PF}) by the Bland and Altman method during all the physiological situations compared with that of the cardiac output obtained by the thermodilutional method (CO_{THERM}) in six individuals with connective tissue disease (CTD)(n=12), are shown), the paired data of which are shown by a square. The differences between the two measurements (CO_{PF} - CO_{THERM} vs. the mean of the two measurements [(CO_{PF} + CO_{THERM})/2] for each measure, are represented graphically. The continuous thick horizontal line represents the line of origin of the x-axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ± 2S.D.).

The correlation coefficient squared of the two techniques in the 2 subjects with ILD was $r^2 = 0.98$ ($p = 0.001$) when all the data was analyzed, and gave a regression equation of $CO_{PF} = 1.203 + CO_{THERM} \bullet 1.024$ (L•min^{-1}), for all 5 sets of measurements, as shown in

figure 3.4a. A comparison (by the Bland-Altman method, figure 3.4b) of the two techniques was made for the 5 measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 1.30 (± 0.17) L•min^{-1}, (giving 95% confidence intervals of between 0.95 and 1.64 L•min^{-1}). The total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) as expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 22.4 (± 3.0)%.

An analysis was also undertaken reviewing the change occurring in the subjects, when taking the baseline to be supine subjects at rest, and comparing with the difference to values inhaling oxygen, nitric oxide/oxygen combined or during exercise. These differences were expressed in L min^{-1}, change of physioflow derived cardiac output from baseline, ΔCO_{PF}Baseline, and change from baseline of thermodilutional derived cardiac output, ΔCO_{THERM}Baseline). The correlation coefficient squared of the two techniques in the 21 subjects, 26 paired data, $r^2 = 0.71$ ($p < 0.001$) when all the data was analyzed, and gave a regression equation of ΔCO_{PF}Baseline = 0.22 + ΔCO_{THERM}Baseline • 1.1 (L min^{-1}), for all 26 sets of measurements, as shown in figure 3.5a. A comparison (by the Bland-Altman method, figure 3.5b) of the two techniques was made for the 26 measurements and the total mean difference (ΔCO_{PF}Baseline - ΔCO_{THERM}Baseline) (± standard deviation) was found to be 0.29 (± 1.05) L min^{-1}, (giving 95% confidence intervals of between –0.79 and 1.97 L min^{-1}). The total mean difference (ΔCO_{PF}Baseline -ΔCO_{THERM}Baseline) (± standard deviation) as expressed as a percentage of mean of ΔCO_{PF}Baseline and ΔCO_{THERM}Baseline was found to be 35 (± 131)%.

If, to avoid overrepresentation of individuals, only the measurements taken under individual physiological circumstances, we get the following results.

The correlation coefficient squared of the two techniques in the 7 subjects, receiving oxygen at rest, $r^2 = 0.40$ ($p = 0.13$) when all the data was analyzed, and gave a regression equation of $\Delta CO_{PF}Baseline = 0.024 + \Delta CO_{THERM}Baseline \bullet 1.71$ (L min^{-1}), for the 7 sets of measurements. A comparison (by the Bland-Altman method) of the two techniques was made for the 7 measurements and the total mean difference ($\Delta CO_{PF}Baseline - \Delta CO_{THERM}Baseline$) (± standard deviation) was found to be 0.00 (± 0.55) L min^{-1}, (giving 95% confidence intervals of between -1.10 and 1.10 L min^{-1}). The total mean difference ($\Delta CO_{PF}Baseline - \Delta CO_{THERM}Baseline$) (± standard deviation) as expressed as a percentage of mean of $\Delta CO_{PF}Baseline$ and $\Delta CO_{THERM}Baseline$ was found to be 0 (± 385)%.

The correlation coefficient squared of the two techniques in the 14 subjects, receiving nitric oxide at rest, $r^2 = 0.24$ ($p = 0.14$) when all the data was analyzed, and gave a regression equation of $\Delta CO_{PF}Baseline = 0.15 + \Delta CO_{THERM}Baseline \bullet 0.40$ (L min^{-1}), for the 14 sets of measurements. A comparison (by the Bland-Altman method) of the two techniques was made for the 14 measurements and the total mean difference ($\Delta CO_{PF}Baseline - \Delta CO_{THERM}Baseline$) (± standard deviation) was found to be 0.02 (± 0.47) L min^{-1}, (giving 95% confidence intervals of between —0.92 and 0.96 L min^{-1}). The total mean difference ($\Delta CO_{PF}Baseline - \Delta CO_{THERM}Baseline$) (± standard deviation) as expressed as a percentage of mean of $\Delta CO_{PF}Baseline$ and $\Delta CO_{THERM}Baseline$ was found to be 9 (± 207)%.

The correlation coefficient squared of the two techniques in the 9 subjects, exercising, r^2 = 0.53 (p = 0.06) when all the data was analyzed, and gave a regression equation of $\Delta CO_{PF}Baseline = 1.14 + \Delta CO_{THERM}Baseline * 0.84$ (L min^{-1}), for the 9 sets of measurements. A comparison (by the Bland-Altman method) of the two techniques was made for the 9 measurements and the total mean difference ($\Delta CO_{PF}Baseline$ - $\Delta CO_{THERM}Baseline$) (± standard deviation) was found to be 1.04 (± 1.80) L min^{-1}, (giving 95% confidence intervals of between –2.56 and 4.63 L min^{-1}). The total mean difference ($\Delta CO_{PF}Baseline$ -$\Delta CO_{THERM}Baseline$) (± standard deviation) as expressed as a percentage of mean of $\Delta CO_{PF}Baseline$ and $\Delta CO_{THERM}Baseline$ was found to be 37 (± 64)%.

Figure 3.5a

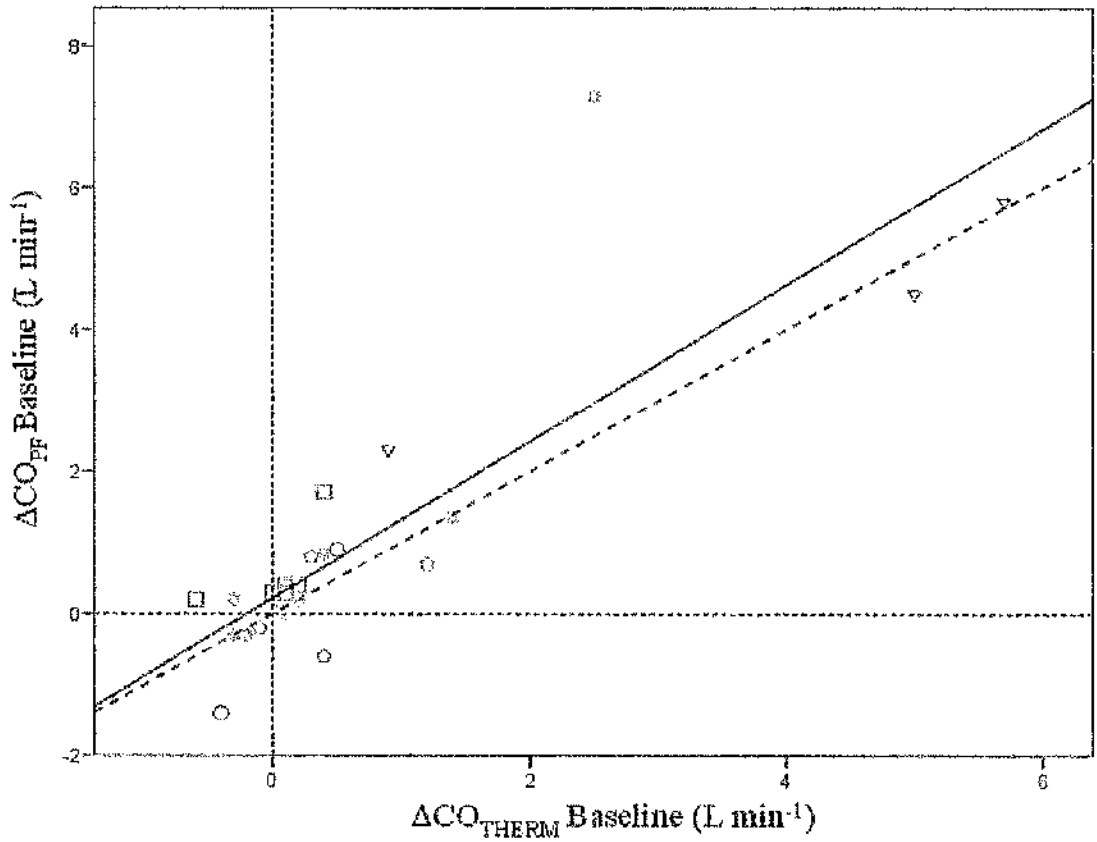


Figure 3.5a: Comparison change of physioflow derived cardiac output from baseline, ΔCO_{PF}Baseline (L min^{-1}), during all the physiological situations compared with that of the change from baseline of thermodilutional derived cardiac output, ΔCO_{THERM}Baseline (L min^{-1}), in the 21 individuals (n=26). The individual diseases with the paired data of normal subjects shown by an inverse purple triangle, idiopathic pulmonary arterial hypertension (IPAH) by a red hexagon, Connective tissue disorders (CTD) by a green square, Chronic obstructive pulmonary disease (COPD) by a dark blue circle, interstitial lung disease shown with a tanned upright triangle and Chronic thromboembolic pulmonary hypertension by a light blue star. The line of identity given by the broken black line, and the regression line for the combined paired data sets, by the continuous black line.

Figure 3.5b

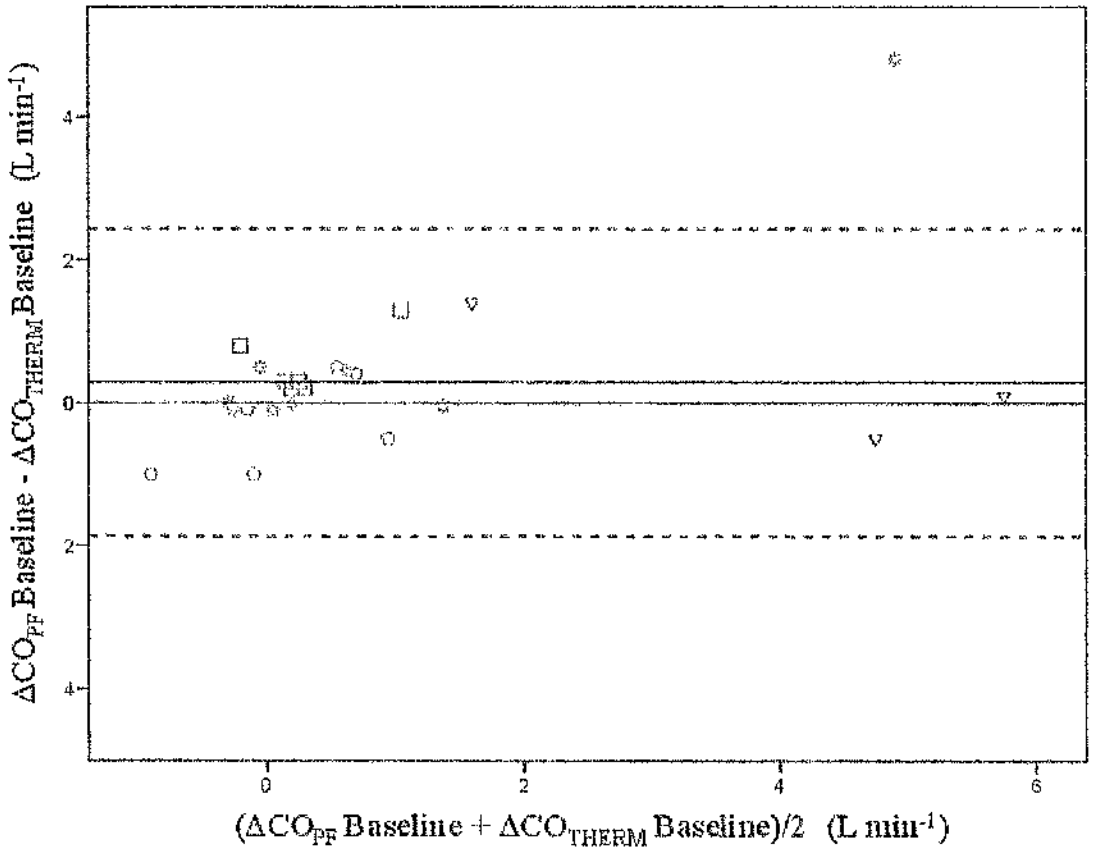


Figure 3.5b: Comparison change of physioflow derived cardiac output from baseline, ΔCO_{PF}Baseline (L min^{-1}), during all the physiological situations compared with that of the change from baseline of thermodilutional derived cardiac output, ΔCO_{THERM}Baseline (L min^{-1}), in the 21 individuals (n=26) by the Bland and Altman method. The individual diseases with the paired data of a normal subjects shown by an inverse purple triangle, Idiopathic pulmonary arterial hypertension (IPAH) by a red hexagon, Connective tissue disorders (CTD) by a green square, Chronic obstructive pulmonary disease (COPD) by a dark blue circle, interstitial lung disease shown with a tanned upright triangle and Chronic thromboembolic pulmonary hypertension by a light blue star. The differences between the two measurements (CO_{PF} - CO_{THERM} vs. the mean of the two measurements [(CO_{PF} + CO_{THERM})/2] for each measure, are represented graphically. The continuous thick horizontal line represents the line of origin of the x-axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ± 2S.D.).

Figure 3.5c

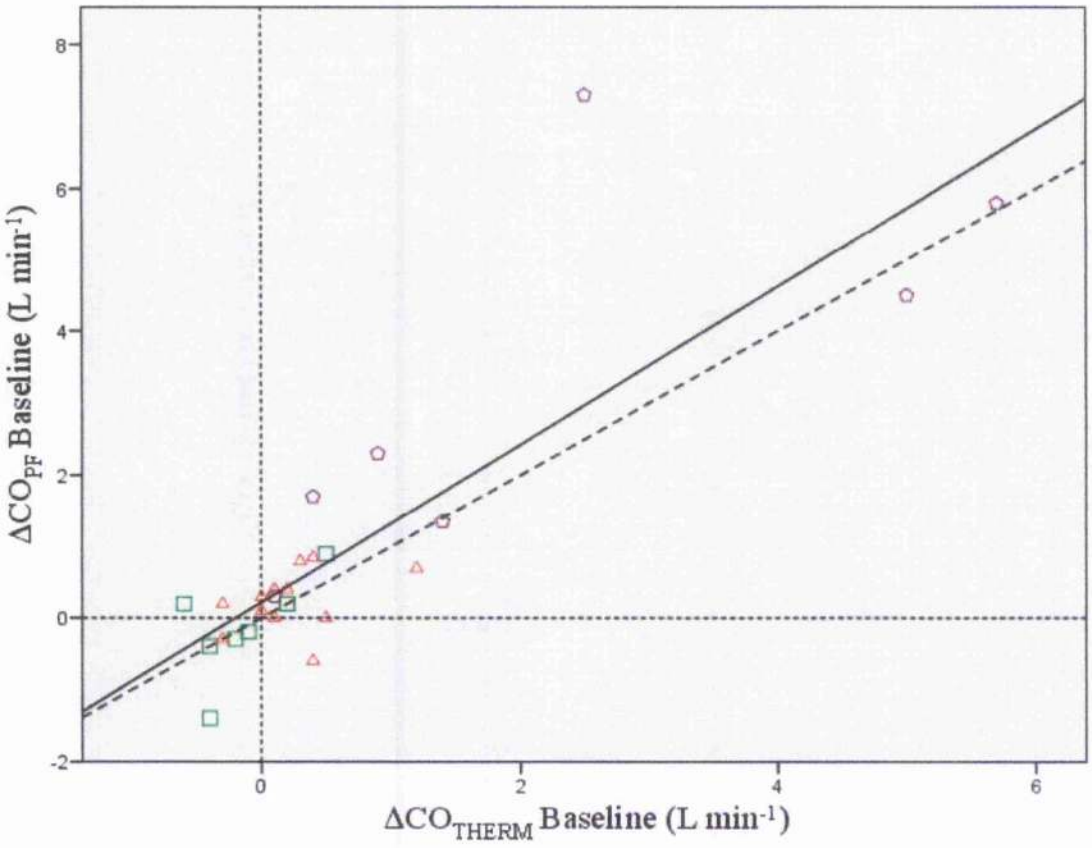


Figure 3.5c: Comparison change of physioflow derived cardiac output from baseline, ΔCO_{PF}Baseline (L min^{-1}), during all the physiological situations compared with that of the change from baseline of thermodilutional derived cardiac output, ΔCO_{THERM}Baseline (L min^{-1}), in the 21 individuals (n=26). The paired data for the individual physiological circumstances are shown, with inhalation by air shown by a dark blue circle, oxygen by a green triangle, nitric oxide by a red upright triangle, and during exercise with a purple hexagon. The line of identity given by the continuous black line, and the regression line for the combined paired data sets, by the broken black line.

Figure 3.5d

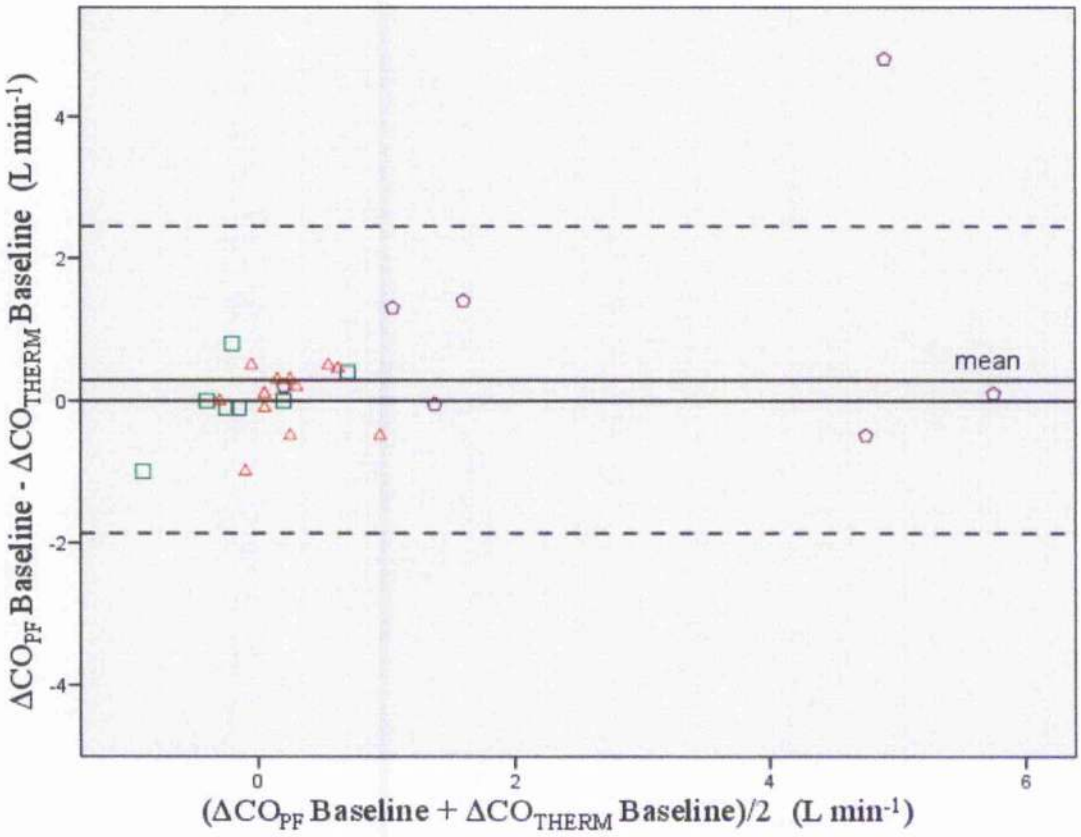


Figure 3.5d: Comparison change of physioflow derived cardiac output from baseline, ΔCO_{PF}Baseline (L min^{-1}), during all the physiological situations compared with that of the change from baseline of thermodilutional derived cardiac output, ΔCO_{THERM}Baseline (L min^{-1}), in the 21 individuals (n=26) by the Bland and Altman method. The paired data for the individual physiological circumstances are shown, with inhalation by air shown by a dark blue circle, oxygen by a green triangle, nitric oxide by a red upright triangle, and during exercise with a purple hexagon. The differences between the two measurements (CO_{PF} - CO_{THERM} vs. the mean of the two measurements [(CO_{PF} + CO_{THERM})/2] for each measure, are represented graphically. The continuous thick horizontal line represents the line of origin of the x-axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ± 2S.D.).

An analysis was also undertaken reviewing the change in cardiac output which occurred in the subjects, from baseline, (the baseline taken to be the cardiac output of the subject, at rest, inhaling air), and comparing with the difference to values inhaling oxygen, nitric oxide/oxygen combined or during exercise. These differences were expressed as a percentage of the value at baseline (percentage change of physioflow derived cardiac output from baseline, $\%\Delta CO_{PF}$Baseline, and percentage change from baseline of thermodilutional derived cardiac output, $\%\Delta CO_{THERM}$Baseline). The correlation coefficient squared of the two techniques in the 21 subjects, 26 paired data, $r^2 = 0.81$ ($p < 0.001$) when all the data was analyzed, and gave a regression equation of $\%\Delta CO_{PF}$Baseline = 3.16 + $\%\Delta CO_{THERM}$Baseline • 0.916 (%), for all 26 sets of measurements, as shown in figure 3.6a. A comparison (by the Bland-Altman method, figure 3.6b) of the two techniques was made for the 26 measurements and the total mean difference ($\%\Delta CO_{PF}$Baseline -$\%\Delta CO_{THERM}$Baseline) (± standard deviation) was found to be 2.08 % (± 12.5), (giving 95% confidence intervals of between –23.0 and 27.1 %). The total mean difference ($\%\Delta CO_{PF}$Baseline -$\%\Delta CO_{THERM}$Baseline) (± standard deviation) as expressed as a percentage of mean of $\%\Delta CO_{PF}$Baseline and $\%\Delta CO_{THERM}$Baseline was found to be 14.7% (± 90.7).

If, to avoid overrepresentation of individuals, only the measurements taken under individual physiological circumstances, we get the following results.

The correlation coefficient squared of the two techniques in the 7 subjects, receiving oxygen at rest, was $r^2 = 0.45$ ($p = 0.101$) when all the data was analyzed, and gave a regression equation of $\%\Delta CO_{PF}$Baseline = 0.25 + $\%\Delta CO_{THERM}$Baseline • 0.84 (%), for

the 7 sets of measurements. A comparison (by the Bland-Altman method) of the two techniques was made for the 7 measurements and the total mean difference ($\%\Delta CO_{PF}$Baseline -$\%\Delta CO_{THERM}$Baseline) (± standard deviation) was found to be 0.728 % (± 10.89), (giving 95% confidence intervals of between –22.1 and 22.5%). The total mean difference ($\%\Delta CO_{PF}$Baseline -$\%\Delta CO_{THERM}$Baseline) (± standard deviation) as expressed as a percentage of mean of $\%\Delta CO_{PF}$Baseline and $\%\Delta CO_{THERM}$Baseline was found to be -27.8% (± 415.0).

The correlation coefficient squared of the two techniques in the 12 subjects, receiving nitric oxide/oxygen at rest, was $r^2 = 0.02$ ($p = 0.63$) when all the data was analyzed, and gave a regression equation of $\%\Delta CO_{PF}$Baseline = 4.87 + $\%\Delta CO_{THERM}$Baseline • -0.07 (%), for the 12 sets of measurements. A comparison (by the Bland-Altman method) of the two techniques was made for the 12 measurements and the total mean difference ($\%\Delta CO_{PF}$Baseline -$\%\Delta CO_{THERM}$Baseline) (± standard deviation) was found to be -1.6 % (± 12.8), (giving 95% confidence intervals of between -27.3 and 24.0%). The total mean difference ($\%\Delta CO_{PF}$Baseline -$\%\Delta CO_{THERM}$Baseline) (± standard deviation) as expressed as a percentage of mean of $\%\Delta CO_{PF}$Baseline and $\%\Delta CO_{THERM}$Baseline was found to be -31.1% (± 244.0).

The correlation coefficient squared of the two techniques in the 9 subjects, whilst exercising, was $r^2 = 0.82$ ($p = 0.005$) when all the data was analyzed, and gave a regression equation of $\%\Delta CO_{PF}$Baseline = 17.89 + $\%\Delta CO_{THERM}$Baseline • 0.766(%), for the 12 sets of measurements. A comparison (by the Bland-Altman method) of the two techniques was made for the 12 measurements and the total mean difference

(%ΔCO_{PF}Baseline -%ΔCO_{THERM}Baseline) (± standard deviation) was found to be 8.26 % (± 16.8) , (giving 95% confidence intervals of between --25.5 and 42.0%). The total mean difference (%ΔCO_{PF}Baseline -%ΔCO_{THERM}Baseline) (± standard deviation) as expressed as a percentage of mean of %ΔCO_{PF}Baseline and %ΔCO_{THERM}Baseline was found to be 18.2% (± 37.2).

Figure 3.6a

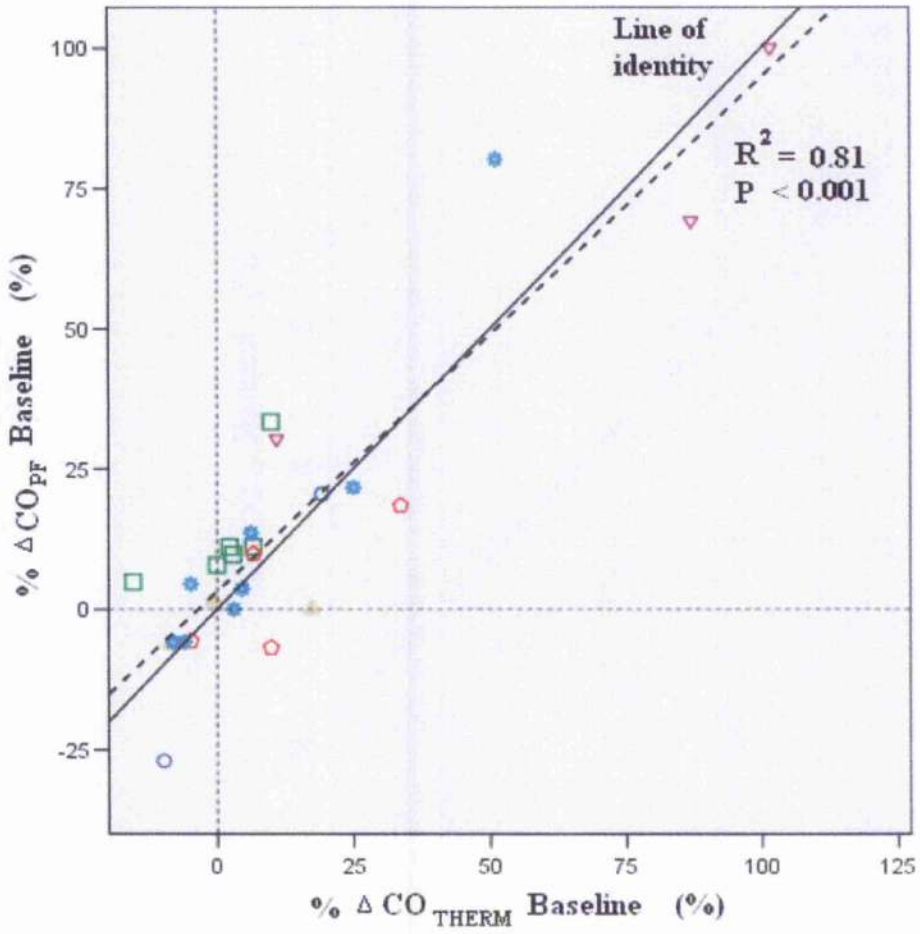


Figure 3.6a: Comparison change of physioflow derived cardiac output from baseline, $\%\Delta CO_{PF}$Baseline, during all the physiological situations compared with that of the change from baseline of thermodilutional derived cardiac output, $\%\Delta CO_{THERM}$Baseline in the 21 individuals (n=26). The individual diseases with the paired data of a normal subjects shown by an inverse purple triangle, Idiopathic pulmonary arterial hypertension (IPAH) by a red hexagon, Connective tissue disorders (CTD) by a green square, Chronic obstructive pulmonary disease (COPD) by a dark blue circle, interstitial lung disease shown with a tanned upright triangle and Chronic thromboembolic pulmonary hypertension by a light blue star. The line of identity given by the continuous black line, and the regression line for the combined ordinate, by the broken black line.

Figure 3.6b

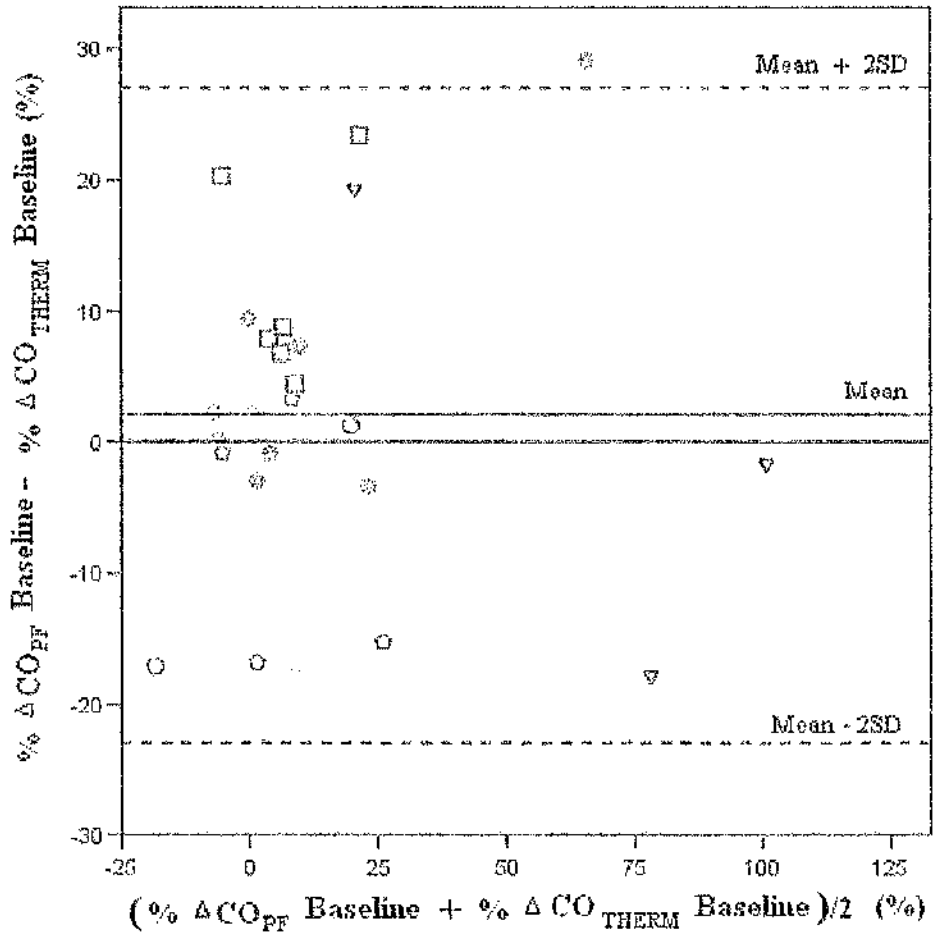


Figure 3.6b: Comparison change of physioflow derived cardiac output from baseline, $\%\Delta CO_{PF}$Baseline, during all the physiological situations compared with that of the change from baseline of thermodilutional derived cardiac output, $\%\Delta CO_{THERM}$Baseline, in the 21 individuals (n=26) by the Bland and Altman method. The individual diseases with the paired data of a normal subjects shown by an inverse purple triangle, Idiopathic pulmonary arterial hypertension (IPAH) by a red hexagon, Connective tissue disorders (CTD) by a green square, Chronic obstructive pulmonary disease (COPD) by a dark blue circle, interstitial lung disease shown with a tanned upright triangle and Chronic thromboembolic pulmonary hypertension by a light blue star. The differences between the two measurements (CO_{PF} - CO_{THERM} vs. the mean of the two measurements [(CO_{PF} + CO_{THERM})/2] for each measure, are represented graphically. The continuous thick horizontal line represents the line of origin of the x-axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ±2S.D.).

Figure 3.6c

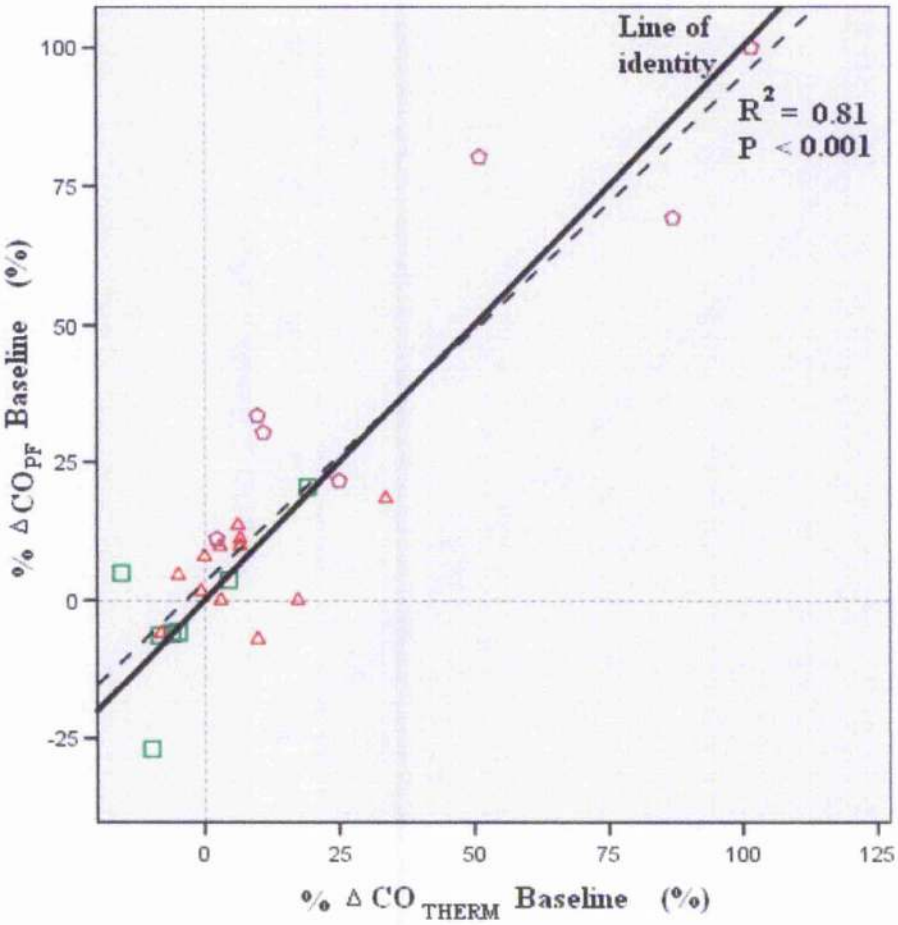


Figure 3.6c: Comparison change of physioflow derived cardiac output from baseline, %ΔCO_{PF}Baseline, during all the physiological situations compared with that of the change from baseline of thermodilutional derived cardiac output, %ΔCO_{THERM}Baseline, in the 21 individuals (n=26). The paired data for the individual physiological circumstances are shown, with inhalation by air shown by a dark blue circle, oxygen by a green triangle, nitric oxide by a red upright triangle, and during exercise with a purple hexagon. The line of identity given by the continuous black line, and the regression line for the combined ordinate, by the broken black line.

Figure 3.6d

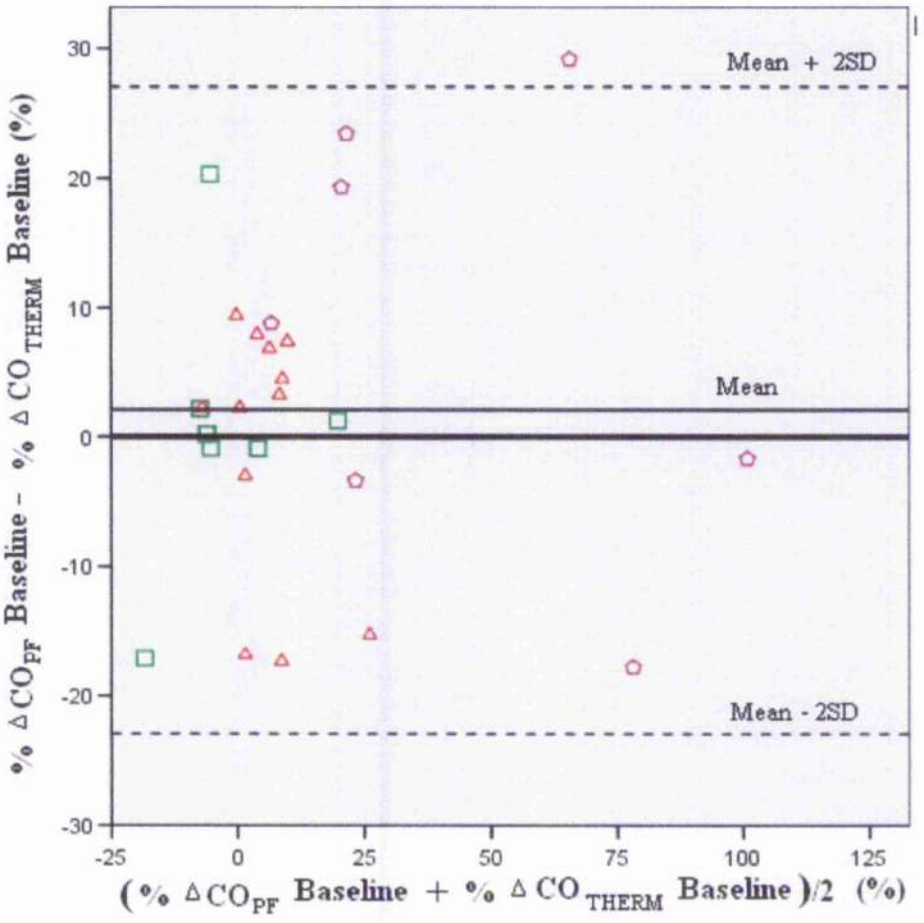


Figure 3.6d: Comparison change of physioflow derived cardiac output from baseline, $\%\Delta CO_{PF}$Baseline, during all the physiological situations compared with that of the change from baseline of thermodilutional derived cardiac output, $\%\Delta CO_{THERM}$Baseline, in the 21 individuals (n=26) by the Bland and Altman method. The paired data for the individual physiological circumstances are shown, with inhalation by oxygen by a green triangle, nitric oxide by a red upright triangle, and during exercise with a purple hexagon. The differences between the two measurements (CO_{PF} - CO_{THERM} vs. the mean of the two measurements [(CO_{PF} + CO_{THERM})/2] for each measure, are represented graphically. The continuous thick horizontal line represents the line of origin of the x-axis, the thin continuous line indicate the means difference or bias and the broken lines, the limits of agreement (defined as mean ± 2S.D.).

Stepwise regression analysis was performed on the mean difference of the two methods

(CO_{PF} -CO_{THERM}) to investigate whether other haemodynamic or lung function parameters may have been responsible for the difference in results between the two methods. This was only performed where the results were available, on 25 subjects with regards to mean pulmonary arterial pressure, (MPAP), systolic pulmonary arterial pressure (SPAP), diastolic pulmonary arterial pressure (DPAP), pulmonary arterial pulse pressure (SPAP-DPAP, PAPP), pulmonary artery wedge pressure (PAWP), Right atrial pressure (RAP) and pulmonary vascular resistance, (PVR), and on 13 subjects with respect to forced expiratory volume in 1 second, (FEV_1), forced vital capacity (FVC), percent of predicted FEV_1, and FVC, ratio of FEV_1/FVC, carbon dioxide transfer coefficient, (KCO) and percent predicted KCO. No correlations were found.

The small number of subjects, the large number of covariates and the inter-correlation of some of the covariates, the stepwise regression analysis should have been biased towards positive results. The results of this analysis, being negative, suggests that none of these variables were related to the mean difference of the two methods (CO_{PF} - CO_{THERM}). In order to minimise errors, the stepwise regression analysis was repeated, with only MPAP, PAWP, RAP and PVR for 25 subjects and no correlation was still found.

3.4. Discussion

The results of this study found that the physioflow bioimpedance (Physioflow, Type PF05L1, Manatec, France) device overestimates cardiac output when compared to thermodilutional results. When all the results were analysed, the overestimation was estimate to be on average 1.21 (± 1.85) $L \bullet min^{-1}$, and the total mean difference (CO_{PF} - CO_{THERM}) (± standard deviation), expressed as a percentage of mean of CO_{PF} and CO_{THERM} was found to be 23.35 (± 35.9) %. This latter result is similar to results obtained when evaluating other methods of now validated clinical cardiac output devices in the statistical variation, except with a positive bias (Bein, B. et al 2004; Durkin, R. J. et al 1994; Hoeper, M. M. et al 1999). Positive and negative errors in measurement are often be seen under certain clinical conditions, in routinely used clinical devices, for instance the positive bias often seen with thermodilutional methods in the people with low output states (Kohanna, F. H. et al 1977; Nishikawa, T. et al 1993) or negative bias in valvular heart disease (Cigarroa, R. G. et al 1989).

There are several areas of introducible errors in the measurement of cardiac output by thoracic bioimpedance in this study, which may explain the overestimate. These may include operator error and procedural differences, and that the other studies compared the bioimpedance cardiac output obtained against results obtained by Fick's method or by echocardiography rather than thermodilutional derived cardiac output. With regards to operator error, all results obtained during the early period of the learning curve have been included. Further error may have been introduced in those subjects where the device was left unadjusted during the right heart catheterisation, even when signal difficulties may have developed. A further issue was that in those subjects in whom the

physioflow (Physioflow, Type PF05L1, Manatec, France) device was left unattended, further blood pressure measurements, just prior to the thermodilutional measurements, were not inputted.

During the straight leg raising, the cardiac output derived by the thermodilutional method, measures cardiac output over on average 30 seconds. If repeated 3 times for accuracy, the cardiac output obtained would be an average over 1-2 minutes. This would be satisfactory, if cardiac output was constant, but in a clinical context, with ill subjects, the work load achieved, and thus the cardiac output would also vary. The physioflow (Physioflow, Type PF05L1, Manatec, France), however took measurements over 15 seconds, and so may be checking a different cardiac output timescale (value) as opposed to the thermodilutional cardiac output timescale. Furthermore, the accuracy of the results obtained by the thermodilutional method, when testing subjects with tricuspid regurgitation and thus pulmonary hypertension, has been questioned after a number of studies (Hoeper, M. M. et al 1999).

When sub-analysed by underlying disease condition, we found that the correlations for normals was better than previous studies, with a correlation coefficient squared of the two techniques of $r^2 = 0.96$ ($p < 0.001$) and measurements and the total mean difference (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 0.45 (± 0.58) $L \bullet min^{-1}$. However in all the pulmonary hypertensive subgroups analyzed, the total mean difference between the methods had a positive bias, [IPAH, 1.19 (± 2.00) $L \bullet min^{-1}$, CTEPH 3.95 (± 2.01) $L \bullet min^{-1}$, CTD 0.84 (± 0.72) $L \bullet min^{-1}$, ILD 1.30 (± 0.17) $L \bullet min^{-1}$]. Unfortunately, the numbers of individual subjects in each group were small, and it may

be that one or two individuals in each group may have biased the result.

With regards to the initial correlation of the combined data, $CO_{PF} = 1.924 + CO_{THERM} \bullet 0.844$ ($L \bullet min^{-1}$), the strong correlation is largely driven by the good correlation found in the normal subjects $CO_{PF} = 1.165 + CO_{THERM} \bullet 0.909$ ($L \bullet min^{-1}$), as in most of the pulmonary hypertensive patients, the correlation was weaker.

The resting data whilst inhaling air was used in an attempt to comparing both techniques, without the pooling of variable amounts of data from individuals, leading to bias. This demonstrated that the correlation in the various subgroups of patients, was similar, but usually weaker, than when all the data was combined [in IPAH subjects, (CO_{PF} -CO_{THERM}) (± standard deviation) was found to be 1.19 (± 2.00) $L \bullet min^{-1}$ when all the data is used and 2.17 (± 2.17) $L \bullet min^{-1}$] as compared to only using measurements at rest on air. When analysing percentage change in cardiac output data for either oxygen, nitric oxide/oxygen inhalations and exercising, the correlation was found to be particular poor in the pulmonary hypertensive disease subgroup data of inhaling nitric oxide and oxygen. The poor correlation may have been as a result of the data from 4 individuals having the difference in percentage changes in cardiac output between the physioflow and thermodilutional methods being greater than 10%.

Critchley & Critchley (1998) found that in subjects with large lung fluid content, cardiac output measured by a thoracic impedance device underestimated CO. This is consistent with the results of subject 34 who had portopulmonary hypertension. This was felt to be secondary to the differential of the aorta's change in impedance with

respect to time (dZ/dt) being minored by the pulmonary's dZ/dt (the lung resistance is usually higher, and conductivity lower, than mediastinal tissues, but this is reversed if there is a large fluid content in the lungs). Bougault et al (2005) found that in subjects with COPD during maximal exercise, the results obtained by thoracic impedance, underestimated cardiac output, and speculated that for the opposite reasons in COPD, the values obtained by thoracic bioimpedance methods may overestimate the levels in their COPD subjects. In subjects with pulmonary hypertension due to arterial disease or emboli, it is likely that the lung water volume would be reduced, especially compared to normals during exercise, and that the lung impedance would increase as compared to aortic, so we can speculate that the findings are consistent with those found in other studies.

Bougault et al found in their study in 2005, that in subjects with mild to moderate COPD, during upright exercise, the physioflow overestimated SV and thus cardiac output when compared with Fick derived measurements. However, the trend of change in cardiac output followed changes in cardiac output trends.

The percentage changes from baseline seen with the physioflow (Physioflow, Type PF05L1, Manatec, France) device were better correlated then actual values and this may suggest that the physioflow 1 derived cardiac output may be adequate to observe changes in CO within individual subjects. The correlation coefficient squared of the two techniques in the 21 subjects, 26 paired data, $r^2 = 0.81$ ($p < 0.001$) and gave a regression equation of $\%\Delta CO_{PF}Baseline = 3.16 + \%\Delta CO_{THERM}Baseline \bullet 0.916$ (%), (figure 3.4a.) The Bland-Altman comparison (figure 3.4b) of the two techniques ($\%\Delta CO_{PF}Baseline$ -

$\%\Delta CO_{THERM}$Baseline) (± standard deviation) was found to be 2.08 (± 12.5) %, (giving 95% confidence intervals of between –23.0 and 27.1 %). The total mean difference ($\%\Delta CO_{PF}$Baseline -$\%\Delta CO_{THERM}$Baseline) (± standard deviation) as expressed as a percentage of mean of $\%\Delta CO_{PF}$Baseline and $\%\Delta CO_{THERM}$Baseline was found to be 14.7 (± 90.7) %. Unfortunately, unlike Bougault et al (2005), we do not have data on stepwise exercise, demonstrating the physioflow 1 (Physioflow, Type PF05L1, Manatec, France) follows the cardiac output changes seen by the Fick method, in subjects with pulmonary hypertension.

Our study demonstrates that the physioflow (Physioflow, Type PF05L1, Manatec, France) gave slightly more positive values as compared to thermodilutional values. Assuming that the thermodilutional methods are accurate, the Physioflow (Physioflow, Type PF05L1, Manatec, France) could not be recommended from this study as a method of getting accurate results for absolute CO in clinical situations. However, the thermodilutional method of cardiac output measurement has been reported to underestimate the cardiac output in comparison the Fick method, when subjects have tricuspid regurgitation (Hoeper, M. M. et al 1999). The results of this study, however, demonstrate that the physioflow device is probably accurate in measuring changes in trends in cardiac output within an individual. The degree of accuracy, under various physiological, pathological and pharmacological states may vary. This will allow the physioflow (Physioflow, Type PF05L1, Manatec, France) to be a useful device in measuring CO changes during exercise or pharmacological interventions.

Chapter 4

Viability of Pulmonary Pressure Flow Plots During Routine Clinical Investigations of Subjects with Possible Pulmonary Hypertension

4.1 Introduction

Pulmonary hypertension is defined as a condition in which mean pulmonary arterial pressure at rest is elevated above 25mHg or 30mmHg. In its purest form, idiopathic pulmonary arterial hypertension, is a condition with a historically poor prognosis, but which more recently a number of new therapeutic options have been developed (British Cardiac Society Guidelines 2001).

Traditionally, haemodynamic assessment has been made whilst the subject is at rest and supine, with a change in 'pulmonary vascular resistance' (PVR) being one of the most important parameters measured. However, it has been shown that changes in PVR can be misleading as the pulmonary arterial pressure, although linearly related to cardiac output (CO) in the physiological range usually has a positive extrapolated intercept (McGregor, M. et al 1985; Sniderman, A. D. et al 1988). This means that if there is a passive increase in CO, there will be a corresponding increase in pulmonary arterial pressure, without any change in the underlying pulmonary vascular state. Therefore, the calculated PVR would seem to fall, without any real change in the resistance, compliance or dilatation of the blood vessels.

This can be resolved this by plotting pressure flow curves, created from paired data of mean pulmonary arterial pressure and cardiac output (McGregor, M. et al 1985; Sniderman, A. D. et al 1988). The change in cardiac output can be generated via exercise, or diverting blood through one lung (Naeije, R. 1996). This has been performed experimentally in animals, and in a few human studies, but only in very few subjects with pulmonary hypertension (Evans, P. et al 1971; Janicki, J. S. et al 1985; Leeman, M. et al 1990; McGregor, M. et al 1985; Naeije, R. et al 1994), and has not

been used clinically. Changes in the slope of the plot, or the intercept reflect changes in the resistance of the pulmonary vasculature.

The object of this study was to assess the feasibility of producing pressure flow plots via exercise in a clinical context, and whether clinical effects pharmacologically on the true pulmonary vasculature could be detected clinically on an individual basis.

4.2 Methods

4.2.1. Patient group & Ethics

The study was approved by the ethics committee of the West Glasgow's NHS trust, and informed consent was obtained from all the patients. Thirty consecutive patients consented, but only twenty-four were successfully studied (11 males and 13 females) (Table 4.1). In six subjects, the study was unsuccessful, due to equipment failure, 2 due to the micromometer tipped pulmonary artery catheter and 4 due to problems with the thoracic bioimpedance device. The mean (±S.D.) age of the studied subjects was 56.6 years (± 13.5), but ranged from 33 to 81. Three turned out to be normal subjects, five had idiopathic pulmonary arterial hypertension (IPAH), five pulmonary hypertension secondary to connective tissue disorder (CTD), four had chronic thromboembolic pulmonary hypertension (CTEPH), two pulmonary hypertension due to interstitial lung disease (ILD), two due to chronic obstructive pulmonary disease (COPD), one found to have portopulmonary hypertension and two as a consequence of left sided heart disease (PVH). Ten had more than a 20% drop in pulmonary vascular resistance (PVR) to nitric oxide (NO, a pulmonary vasodilator) nine did not, and 4 were not studied. Mean pulmonary artery pressure (MPAP) ranged from 15 mmHg to 99 mmHg, with a mean (±S.D.) of 48.9 (± 19.5) mmHg, right atrial pressure, 0 to 47 mmHg, mean 11.0 (± 9.4) mmHg, pulmonary artery wedge pressure 1 to 28 mmHg with a mean of 10.8 (± 7.5) mmHg and PVR ranging from 0.5 to 37 $\mathbf{mmHg \bullet L^{-1} min}$, with a mean of 11.1 (± 8.6) $\mathbf{mmHg \bullet L^{-1} min}$. In total 86 studies were performed, 30 each whilst inhaling air or a nitric oxide/ oxygen combination, and 26 whilst inhaling oxygen.

Table 4.1: Subject demographics and haemodynamic supine resting

Subject Number	Study Number	Initials	MPAP	SPAP	DPAP	RAP	PAWP	CO	PVR	Age	Sex	Diagnosis	Vaso-dilator Response
			(mmHg)					(L.min^{-1})	(mmHg / L.min^{-1})				
1	1	M,C	17	23	11	47		8.1	2	55	F	normal	N/A
2	2	L,C	8	14	2	1	14	3.7	0.0	40	F	normal	
3	3	B,Ri	15	24	3	12	9	5.6	0.5	37	F	normal	N/A
5	4	G,C	57	91	37	6	7	5.5	9	49	M	IPAH	N
5	5	G,C	56	90	32	5	8	4.6	10.4	50	M	IPAH	N
5	6	G,C	55	85	34	11	10	4.2	10.7	50	M	IPAH	N
6	7	W,F	79	137	48	11	14	3.3	20	67	M	IPAH	Y
7	8	E,M	63	115	23	14	15	3.7	13	73	F	IPAH	Y
8	9	W,O'H	51	82	28	4	2	3.0	16.3	61	M	IPAH	Y
8	10	W,O'H	51	82	28	4	2	3.0	16.3	61	M	IPAH	Y
8	11	W,O'H	51	82	28	4	2	3.0	16.3	61	M	IPAH	Y
9	12	S,S	60	103	60	10	3	4.5	13	45	F	IPAH	N
13	13	R,C	49	77	27	8	5	3.6	12	54	F	CTD	Y
14	14	Y,McB	48	79	33	0	1	2.6	14	48	F	CTD	Y
15	15	I,P	36	62	17	6	5	4.4	7.3	46	F	CTD	Y
16	16	J,P	99	130	82	9	4	2.4	37.1	59	M	CTD	Y
17	17	K,S	36	61	22	2		3.9	4	62	F	CTD	N
17	18	K,S	37	62	23	3		3.9	5	63	F	CTD	N
17	19	K,S	38	63	24	4		3.9	6	64	F	CTD	N
20	20	J,F	63	100	36	20	20	3.7	12	71	M	CTEPH	N
21	21	S,O	46	79	27	8		5	11	74	M	CTEPH	N/A
26	22	G,S	66	107	40	14	23	4.1	10.6	50	M	CTEPH	N
27	23	G,W	56	98	33	9	7	3.3	14.9	37	M	CTEPH	N
28	24	W,F	39	54	28	18	12	2.6	5	71	M	ILD	Y
30	25	B,Ra	57	81	44	3	4	2.0	26.1	33	F	ILD	Y
31	26	R,McD	43	74	26	11	8	2.2	16	60	M	COPD	N
32	27	M,T	30	50	10	4	13	4.1	4	81	F	COPD	N
34	28	S,C	19	31	9	10	15	10.7	0.4	48	F	portopulm	N/A
36	29	F,B	43	60	26	9	22	4.9	4.2	65	F	PVH	N
37	30	J,B	52	86	32	19	28	5.4	4.2	73	M	PVH	Y

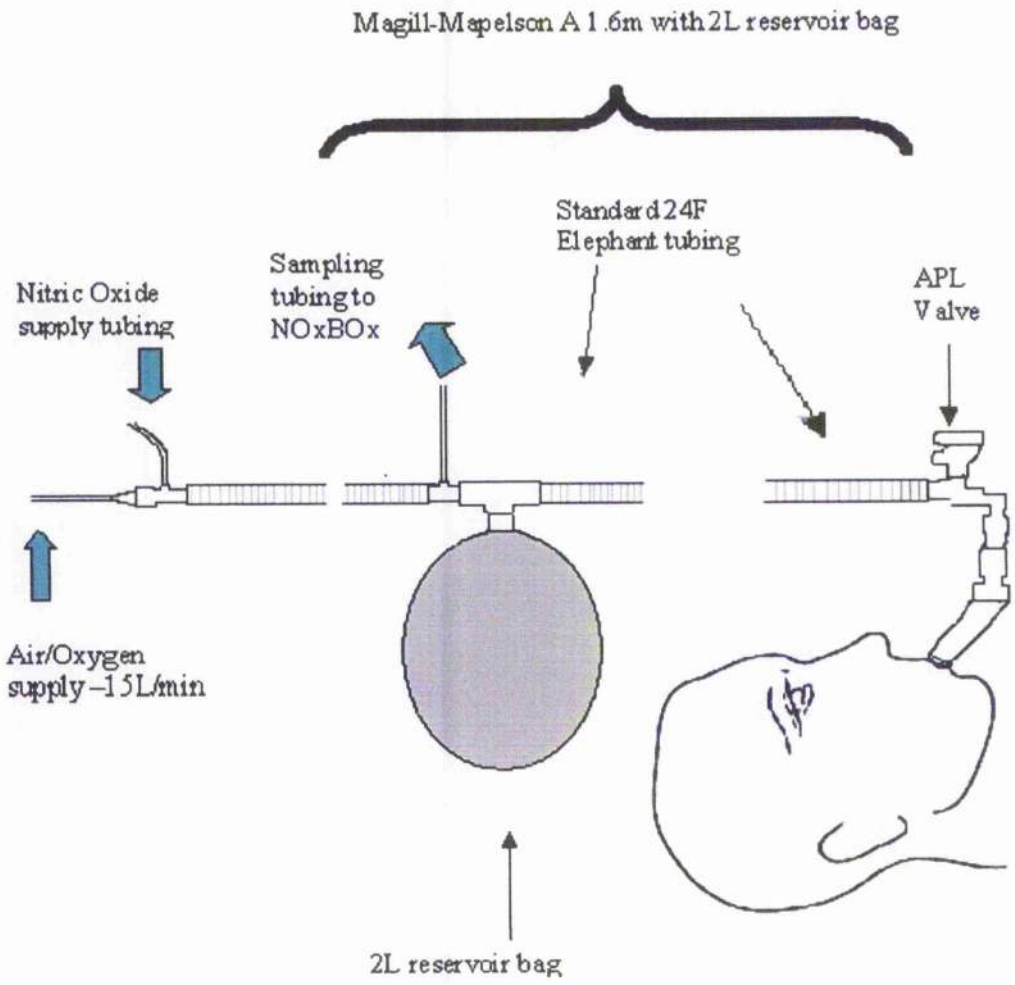
4.2.2. Equipment and Experiments

Initial haemodynamic evaluation was performed with the patient supine and breathing room air, according to our standard protocol as described in chapter 2.3. The inhaled gas was delivered to the patient, as described in chapter 2.5.1, and shown in Figures 2.14 a-

c and Figure 4.1. The right heart catheter (Gaeltec, Dunvegan, Isle of Skye), its insertion storage and processing are described in chapter 2.1. Cardiac output was measured non-invasively by thoracic electrical bioimpedance (PhysioFlow 1, Manatec, France) as described in chapter 2.2 and the pulmonary pressure and cardiac output data combined as in chapter 2.5. Between 4-18 sets, [mean (± S.D.) of 14 (± 3.2), on air mean (± S.D.) 12.1 (± 3.7), with oxygen 14.6 (± 2.5), and with the nitric oxide oxygen combination, 14.9 (± 2.6)] of paired of data were collected at rest and exercise respectively on each subject. The exercise consisted of a maximum of 3 minutes, or less if the subjects could not manage it, of alternate straight leg raising. All subjects had almost a full resting haemodynamics performed within 24 hours of the exercise test during routine right heart catheterization with a swan-gantz catheter, when MPAP, Svo2, PWCP and CO were initially measured.

The nitric oxide was supplied by a pure NO source cylinder (BOC, UK) and delivered via a mouth piece (figure 4.1). The mixture of O2/NO was sampled by a NO sampling device (NOXBOX II, Bedford scientific Ltd, Kent, England).

Figure 4.1:Inhalation gas delivery system



4.2.3. Analysis

Analysis of the data obtained was performed using the SPSS 13.0 package as described in chapter 2.7.

4.3. Results

All the sets of paired data for all the studies underwent regression analysis with confidence intervals for slope and intercept (tables 4.2, and table 4.3). Scattergrams were reviewed for predicted- actual MPAP versus actual MPAP, and were all found to be reasonable. An anova test of non-linearity (table 4.3), the visual assessment of histograms of frequency of standardized residuals and normal probability plots of standardized residuals were reviewed, to assess the linearity or suitability for linear regression of the produced lines. An ancova test of parallelism (table 4.4) as well as comparing the confidence intervals of the slope and intercept were undertaken to assess if the slopes (or intercepts) were statistically different.

Figure 4.2a

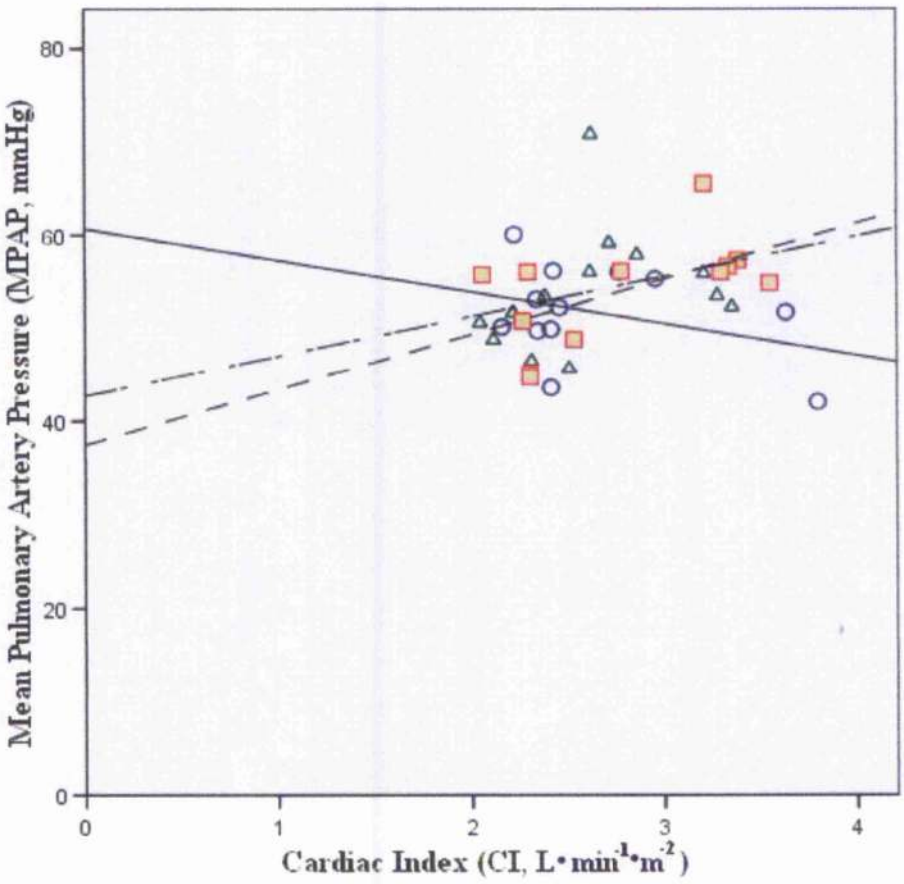
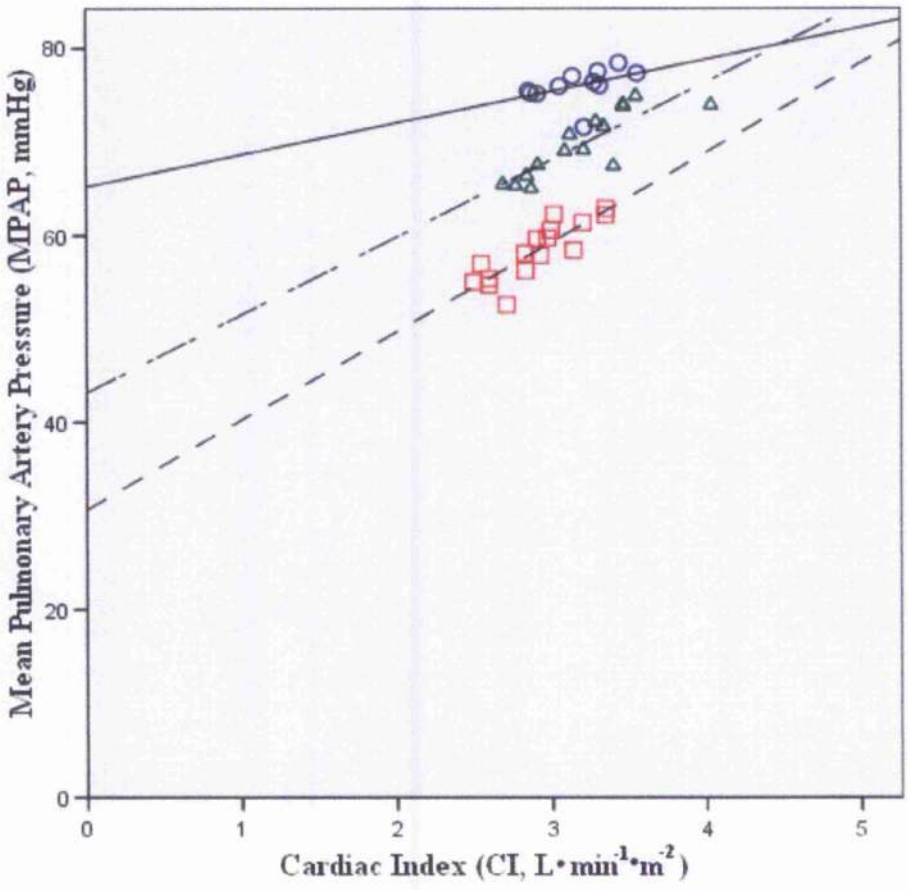


Figure 4.2b



Figures 4.2a & b: Examples of regression plots produced from individual subjects, using data derived during a 3 minute straight leg raising exercise test, and from a micromanometer tipped pulmonary artery catheter and thoracic bio-impedance (a) example of poor quality plots (b) example of good quality plots.

Examples of the variable quality of plots produced are shown in figures 4.2a & b.

The combined number of subjects was 24, and they underwent sets 30 studies, producing 86 linear regression lines (a single line for each exercise test). Of these lines, only forty two were able to be tested for non-linearity and 3 were statistically found to be non-linear. The histograms of frequency of residuals and the normal probability plot

of residuals, in more than 50% of the lines, were also visually poor, with either a poor normal distribution or deviation from the line of identity. The combination of these three tests despite all the scattergrams being reasonable, suggest that about a third of the plots could produce lines which were satisfactorily straight.

The analysis of differences in slope, performed by the ancova test of parallelism, (covariance) found only a significant difference in only 26 pairing of slopes, out of 86. The confidence intervals for slopes did not overlap in only 9 pairs of slopes.

The intercept had a standard error that was on average 51% of intercept, (± 109%) but with a median of 26.52% and range of 5.38%- 966.67%. Seven of the 86 intercepts had a standard error of greater than 100% of baseline, and if these were excluded the mean standard error would have been 30.1% of intercept, (± 21.0%) but with a median of 25.7% and range of 5.38% to 99.07%. Only 32 of the 86 lines had a standard error of less than 20% of baseline. The slope had a standard error that was on average 105% of baseline, (± 359%) but with a median of 15.1% and range of 1.4 to 2767%. Ten of the 86 slopes had a standard error of greater than 100% of baseline, and if these were excluded the mean standard error would have been 20.0% of baseline slope, (± 20.7%) but with a median of 14.27% and range of 1.4% to 98.6%. Only 49 of the 85 lines had a standard error of the slope less than 20% of baseline. In addition, only 65 of the of the linear regression analysis were significant (Table 4.3).

STUDY	GAS		constant	Sig.	95% Confidence Interval for constant	
					Lower	Upper
1	AIR	Intercept	-6.57	0.215	-17.394	4.255
		Slope	5.74	<0.001	3.635	7.854
	OXYGEN	Intercept	-12.62	0.003	-20.071	-5.176
		Slope	6.05	<0.001	4.645	7.455
	NO & OXYGEN	Intercept	-2.86	0.326	-8.864	3.139
		Slope	3.64	<0.001	2.546	4.742
2	AIR	Intercept	-0.35	0.801	-3.233	2.541
		Slope	1.62	<0.001	1.196	2.035
	OXYGEN	Intercept	4.31	0.001	2.019	6.599
		Slope	1.80	<0.001	1.441	2.150
	NO & OXYGEN	Intercept	7.74	<0.001	4.540	10.935
		Slope	1.48	<0.001	0.940	2.025
3	AIR	Intercept	18.07	<0.001	13.921	22.226
		Slope	1.96	0.001	0.968	2.950
	OXYGEN	Intercept	-2.51	0.738	-18.215	13.192
		Slope	7.33	0.002	3.120	11.538
	NO & OXYGEN	Intercept	12.69	<0.001	9.126	16.255
		Slope	2.82	<0.001	1.820	3.817
4	AIR	Intercept	60.32	0.001	33.079	87.559
		Slope	3.45	0.237	-2.856	9.751
	OXYGEN	Intercept	45.72	<0.001	38.899	52.540
		Slope	7.95	<0.001	6.244	9.648
	NO & OXYGEN	Intercept	64.80	<0.001	56.045	73.547
		Slope	2.80	0.018	0.552	5.039
5	AIR	Intercept	39.55	<0.001	34.120	44.981
		Slope	7.56	<0.001	6.234	8.877
	OXYGEN	Intercept	52.96	<0.001	47.238	58.686
		Slope	4.57	<0.001	3.080	6.063
	NO & OXYGEN	Intercept	44.85	<0.001	42.121	47.584
		Slope	6.69	<0.001	5.925	7.453
6	AIR	Intercept	28.86	0.002	12.715	45.002
		Slope	10.89	<0.001	6.727	15.057
	OXYGEN	Intercept	41.47	<0.001	28.443	54.494
		Slope	7.38	<0.001	3.929	10.839
	NO & OXYGEN	Intercept	45.87	<0.001	33.915	57.818
		Slope	5.96	0.002	2.483	9.437
7	AIR	Intercept	72.72	<0.001	48.842	96.595
		Slope	3.38	0.548	-8.891	15.657
	OXYGEN	Intercept	62.46	<0.001	52.838	72.082
		Slope	6.85	0.011	1.826	11.874
	NO & OXYGEN	Intercept	53.90	<0.001	49.639	58.156
		Slope	5.06	0.002	2.267	7.846

Table 4.2a: The value of the constant for the Slope, intercept with the y-axis of the linear regression equation for each study, as well as the significance and the 95% confidence interval for each value, for studies 1-7

STUDY	GAS		constant	Sig.	95% Confidence Interval for constant	
					Lower Bound	Upper Bound
8	AIR	Intercept	23.03	0.238	-18.575	64.635
		Slope	7.98	0.059	-0.390	16.346
	OXYGEN	Intercept	99.24	0.002	48.332	150.151
		Slope	-8.55	0.119	-19.772	2.669
	NO & OXYGEN	Intercept	31.13	0.055	-0.731	62.989
		Slope	5.92	0.072	-0.613	12.457
9	AIR	Intercept	46.26	<0.001	40.079	52.433
		Slope	9.44	<0.001	7.432	11.445
	OXYGEN	Intercept	15.46	0.008	4.771	26.153
		Slope	17.00	<0.001	13.187	20.803
	NO & OXYGEN	Intercept	23.28	0.011	6.349	40.213
		Slope	11.98	0.001	6.126	17.838
10	AIR	Intercept	20.31	0.034	2.088	38.539
		Slope	15.44	0.001	8.882	21.993
	NO & OXYGEN	Intercept	-9.83	0.541	-43.472	23.817
		Slope	22.87	0.001	10.973	34.776
11	AIR	Intercept	40.43	0.010	13.182	67.677
		Slope	15.07	0.006	5.846	24.296
	NO & OXYGEN	Intercept	15.12	0.117	-4.282	34.520
		Slope	16.07	<0.001	9.236	22.909
12	AIR	Intercept	40.42	0.049	0.239	80.601
		Slope	8.55	0.078	-1.290	18.381
	OXYGEN	Intercept	39.84	0.038	2.773	76.907
		Slope	7.88	0.108	-2.153	17.922
	NO & OXYGEN	Intercept	36.60	0.026	5.506	67.702
		Slope	6.25	0.100	-1.503	14.012
13	AIR	Intercept	65.20	<0.001	48.536	81.868
		Slope	3.40	0.176	-1.841	8.636
	OXYGEN	Intercept	43.28	<0.001	33.411	53.154
		Slope	8.26	<0.001	5.200	11.329
	NO & OXYGEN	Intercept	30.67	<0.001	20.582	40.761
		Slope	9.54	<0.001	6.081	13.001
14	AIR	Intercept	37.31	0.003	17.174	57.455
		Slope	6.49	0.017	1.535	11.444
	OXYGEN	Intercept	44.70	0.001	23.592	65.813
		Slope	4.34	0.127	-1.470	10.141
	NO & OXYGEN	Intercept	49.18	<0.001	41.161	57.207
		Slope	2.53	0.028	0.335	4.720

Table 4.2b: The value of the constant for the Slope, intercept with the y-axis of the linear regression equation for each study, as well as the significance and the 95% confidence interval for each value, for studies 8-14

STUDY	GAS		CONSTANT	Sig.	95% Confidence Interval for Constant	
					Lower Bound	Upper Bound
15	AIR	Intercept	23.66	<0.001	14.951	32.366
		Slope	5.66	<0.001	3.447	7.873
	OXYGEN	Intercept	29.90	<0.001	25.193	34.609
		Slope	4.14	<0.001	2.875	5.408
	NO & OXYGEN	Intercept	27.22	<0.001	23.638	30.795
		Slope	3.89	<0.001	2.889	4.888
16	AIR	Intercept	94.79	<0.001	91.860	97.721
		Slope	2.13	<0.001	1.327	2.934
	OXYGEN	Intercept	80.00	<0.001	74.136	85.868
		Slope	5.92	<0.001	4.206	7.638
	NO & OXYGEN	Intercept	59.46	<0.001	54.209	64.702
		Slope	9.67	<0.001	7.886	11.448
17	AIR	Intercept	35.69	0.001	22.712	48.662
		Slope	4.35	0.067	-0.424	9.116
	NO & OXYGEN	Intercept	41.37	<0.001	36.052	46.680
		Slope	1.42	0.132	-0.516	3.350
18	AIR	Intercept	47.59	<0.001	39.922	55.249
		Slope	1.09	0.367	-1.542	3.725
	NO & OXYGEN	Intercept	43.82	<0.001	39.956	47.685
		Slope	1.23	0.061	-0.068	2.523
19	AIR	Intercept	41.59	<0.001	33.839	49.345
		Slope	1.48	0.199	-0.990	3.949
	OXYGEN	Intercept	40.01	<0.001	35.912	44.109
		Slope	1.74	0.021	0.343	3.146
	NO & OXYGEN	Intercept	43.80	<0.001	41.804	45.787
		Slope	-0.03	0.912	-0.703	0.636
20	AIR	Intercept	13.97	0.415	-21.841	49.781
		Slope	15.43	0.018	3.067	27.786
	OXYGEN	Intercept	17.53	0.113	-4.734	39.801
		Slope	15.09	0.001	6.970	23.214
	NO & OXYGEN	Intercept	30.58	<0.001	24.397	36.769
		Slope	9.37	<0.001	7.044	11.687
21	AIR	Intercept	-6.71	0.067	-13.970	0.541
		Slope	12.17	<0.001	9.916	14.414
	OXYGEN	Intercept	0.60	0.919	-11.658	12.867
		Slope	9.89	<0.001	6.026	13.751
	NO & OXYGEN	Intercept	2.39	0.749	-12.886	17.668
		Slope	7.40	0.008	2.100	12.705

Table 4.2c: The value of the constant for the Slope, intercept with the y-axis of the linear regression equation for each study, as well as the significance and the 95% confidence interval for each value, for studies 15-21

STUDY	GAS		CONSTANT	Sig.	95% Confidence Interval for constant	
					Lower Bound	Upper Bound
22	AIR	Intercept	86.98	<0.001	75.044	98.925
		Slope	4.18	0.002	1.793	6.575
	OXYGEN	Intercept	97.79	<0.001	94.513	101.067
		Slope	1.75	<0.001	1.124	2.366
	NO & OXYGEN	Intercept	104.09	<0.001	97.757	110.423
		Slope	0.46	0.401	-0.684	1.603
23	AIR	Intercept	38.54	<0.001	21.748	55.325
		Slope	9.63	0.005	3.636	15.629
	OXYGEN	Intercept	45.31	<0.001	41.848	48.766
		Slope	5.56	<0.001	4.231	6.895
	NO & OXYGEN	Intercept	52.32	<0.001	47.124	57.514
		Slope	3.19	0.004	1.262	5.116
24	AIR	Intercept	35.71	<0.001	27.835	43.577
		Slope	4.20	0.021	0.860	7.530
	OXYGEN	Intercept	45.23	<0.001	38.362	52.102
		Slope	0.49	0.710	-2.461	3.448
	NO & OXYGEN	Intercept	22.59	0.014	5.993	39.191
		Slope	7.87	0.030	0.985	14.745
25	AIR	Intercept	21.26	0.088	-3.948	46.462
		Slope	17.59	0.002	8.650	26.534
	OXYGEN	Intercept	43.64	<0.001	29.876	57.397
		Slope	5.13	0.074	-0.593	10.847
	NO & OXYGEN	Intercept	27.14	<0.001	18.600	35.675
		Slope	10.57	<0.001	6.692	14.451
26	AIR	Intercept	60.68	<0.001	43.662	77.692
		Slope	-3.38	0.258	-9.661	2.901
	OXYGEN	Intercept	42.71	0.003	17.696	67.727
		Slope	4.30	0.335	-5.086	13.681
	NO & OXYGEN	Intercept	37.44	0.001	19.922	54.955
		Slope	5.96	0.058	-0.241	12.163
27	AIR	Intercept	0.98	0.888	-14.131	16.089
		Slope	9.22	<0.001	5.555	12.882
	OXYGEN	Intercept	-0.31	0.972	-19.005	18.382
		Slope	9.82	0.003	4.155	15.483
	NO & OXYGEN	Intercept	4.32	0.244	-3.293	11.940
		Slope	7.78	<0.001	5.588	9.978

Table 4.2d: The value of the constant for the Slope, intercept with the y-axis of the linear regression equation for each study, as well as the significance and the 95% confidence interval for each value, for studies 22-27

Study	gas		CONSTANT	Sig.	95% Confidence Interval for constant	
					Lower Bound	Upper Bound
28	AIR	Intercept	21.69	<0.001	16.351	27.034
		Slope	0.33	0.520	-0.758	1.414
	OXYGEN	Intercept	-4.22	0.656	-24.007	15.575
		Slope	10.15	0.011	2.707	17.593
	NO & OXYGEN	Intercept	24.30	0.001	11.743	36.857
		Slope	-0.80	0.667	-4.657	3.065
29	AIR	Intercept	28.88	<0.001	15.559	42.198
		Slope	5.42	0.002	2.263	8.580
	OXYGEN	Intercept	31.94	<0.001	22.395	41.495
		Slope	4.19	0.001	1.918	6.458
	NO & OXYGEN	Intercept	43.13	<0.001	35.710	50.554
		Slope	1.16	0.205	-0.688	3.017
30	AIR	Intercept	23.56	0.102	-8.590	55.717
		Slope	12.84	0.039	1.250	24.428
	OXYGEN	Intercept	1.10	0.949	-35.344	37.554
		Slope	19.71	0.004	7.224	32.203
	NO & OXYGEN	Intercept	35.74	<0.001	26.887	44.584
		Slope	4.65	0.001	2.393	6.914

Table 4.2e: The value of the constant for the Slope, intercept with the y-axis of the linear regression equation for each study, as well as the significance and the 95% confidence interval for each value, for studies 28-30

Study	gas	Linear regression statistics			test of deviation from linearity	
		F	Sig.	R^2	F	Sig.
1	AIR	33.68	<0.001	0.692	16.78	0.19
	OXYGEN	85.34	<0.001	0.859	1.26	0.61
	NO & OXYGEN	50.07	<0.001	0.769	8.03	0.27
2	AIR	68.23	<0.001	0.830		
	OXYGEN	117.87	<0.001	0.894	0.99	0.55
	NO & OXYGEN	34.38	<0.001	0.711	5.28	0.33
3	AIR	17.75	0.001	0.542	1.81	0.30
	OXYGEN	13.78	0.002	0.479	4.40	0.20
	NO & OXYGEN	36.19	<0.001	0.707	4.49	0.20
4	AIR	1.67	0.237	0.193	1.51	0.55
	OXYGEN	100.30	<0.001	0.878		
	NO & OXYGEN	7.14	0.018	0.338	17.17	0.02
5	AIR	150.31	<0.001	0.915	5.96	0.31
	OXYGEN	41.82	<0.001	0.711		
	NO & OXYGEN	348.02	<0.001	0.959		
6	AIR	2.01	.199(a)	0.692	0.75	0.66
	OXYGEN	8.24	.021(a)	0.600		
	NO & OXYGEN	0.01	.912(a)	0.491	10.11	0.02
7	AIR	4.52	0.078	0.041	2.01	0.49
	OXYGEN	3.28	0.108	0.400		
	NO & OXYGEN	3.46	0.100	0.519		
8	AIR	31.46	<0.001	0.377		
	OXYGEN	21.01	<0.001	0.248		
	NO & OXYGEN	13.52	0.002	0.245		
9	AIR	0.39	0.548	0.926		
	OXYGEN	8.68	0.011	0.858	12.95	0.21
	NO & OXYGEN	15.11	0.002	0.579		
10	AIR	4.83	.059(a)	0.816	1.88	0.39
	NO & OXYGEN	2.97	.119(a)	0.548		
11	AIR	3.90	.072(a)	0.681	1.26	0.61
	NO & OXYGEN	113.21	<0.001	0.626		

Table 4.3a: Linear regression statistics, and test of linearity statistics, for studies 1-11

Study	gas	Linear regression statistics			test of deviation from linearity	
		F	Sig.	R^2	F	Sig.
12	AIR	90.50	<0.001	0.430	1.67	0.55
	OXYGEN	19.26	0.001	0.291		
	NO & OXYGEN	31.01	0.001	0.302		
13	AIR	16.99	0.001	0.193		
	OXYGEN	14.92	0.006	0.723		
	NO & OXYGEN	25.11	<0.001	0.714		
14	AIR	2.15	0.176	0.578		
	OXYGEN	33.94	<0.001	0.217		
	NO & OXYGEN	34.99	<0.001	0.430		
15	AIR	9.59	.017(a)	0.721		
	OXYGEN	2.77	.127(a)	0.825		
	NO & OXYGEN	6.80	.028(a)	0.882	0.16	0.96
16	AIR	31.06	<0.001	0.800		
	OXYGEN	51.80	<0.001	0.825	20.32	0.17
	NO & OXYGEN	75.09	<0.001	0.906	29.04	0.03
17	AIR	35.95	<0.001	0.453		
	NO & OXYGEN	56.54	<0.001	0.234		
18	AIR	135.58	<0.001	0.102		
	NO & OXYGEN	4.97	.067(a)	0.244		
19	AIR	2.75	.132(a)	0.223	1.72	0.42
	OXYGEN	0.91	.367(a)	0.507	0.09	0.99
	NO & OXYGEN	4.19	.061(a)	0.002	2.89	0.28
20	AIR	7.27	.018(a)	0.359		
	OXYGEN	16.12	0.001	0.553	4.85	0.34
	NO & OXYGEN	74.86	<0.001	0.842	1.95	0.51
21	AIR	131.45	<0.001	0.891	2.01	0.51
	OXYGEN	28.93	<0.001	0.616	0.52	0.81
	NO & OXYGEN	8.38	.008(a)	0.276	4.87	0.18
22	AIR	14.29	.002(a)	0.524	191.99	0.06
	OXYGEN	36.82	<0.001	0.739	1229.92	0.02
	NO & OXYGEN	0.75	.401(a)	0.055	21.30	0.17

Table 4.3b: Linear regression statistics, and test of linearity statistics, for studies 12-22

study	gas	Linear regression statistics			test of deviation from linearity	
		F	Sig.	R^2	F	Sig.
23	AIR	12.81	.005(a)	0.562		
	OXYGEN	80.21	<0.001	0.851		
	NO & OXYGEN	13.01	.004(a)	0.520		
24	AIR	8.84	.021(a)	0.558		
	OXYGEN	0.15	.710(a)	0.018	17.22	0.18
	NO & OXYGEN	6.95	.030(a)	0.465		
25	AIR	20.58	.002(a)	0.720		
	OXYGEN	3.99	.074(a)	0.285		
	NO & OXYGEN	34.16	<0.001	0.709	6.83	0.28
26	AIR	1.44	.258(a)	0.126		
	OXYGEN	1.02	.335(a)	0.085		
	NO & OXYGEN	4.59	.058(a)	0.314	0.38	0.86
27	AIR	31.43	<0.001	0.759		
	OXYGEN	14.27	.003(a)	0.543		
	NO & OXYGEN	57.85	<0.001	0.805		
28	AIR	0.44	.520(a)	0.039	146.07	0.06
	OXYGEN	8.45	.011(a)	0.360	5.01	0.34
	NO & OXYGEN	0.19	.667(a)	0.013	5.68	0.32
29	AIR	12.82	.002(a)	0.391		
	OXYGEN	14.72	0.001	0.412	1.28	0.53
	NO & OXYGEN	1.72	.205(a)	0.079	0.21	0.96
30	AIR	12.43	.039(a)	0.806		
	OXYGEN	11.46	.004(a)	0.450	4.23	0.37
	NO & OXYGEN	19.49	0.001	0.582	0.76	0.70

Table 4.3c: Linear regression statistics, and test of linearity statistics, for studies 23-30

study	F (air vs O2)	Sig.(air vs O2)	F (Air vs NO)	Sig. (air vs NO)	F (O2 vs NO)	Sig. (O2 vs NO)
1	0.062	0.805	3.855	0.059	8.146	0.008
2	0.495	0.488	0.168	0.685	1.031	0.319
3	8.062	0.008	1.387	0.248	6.785	0.014
4	3.991	0.059	0.068	0.797	15.633	<0.001
5	10.079	0.003	1.390	0.248	6.472	0.016
6	1.689	0.204	3.808	0.061	0.354	0.556
7	0.424	0.522	0.133	0.719	0.482	0.493
8	7.280	0.015	0.145	0.707	5.565	0.028
9	14.847	0.001	0.876	0.359	2.455	0.128
10	.	.	1.465	0.240	.	.
11	.	.	0.035	0.853	.	.
12	0.011	0.916	0.178	0.680	0.089	0.769
13	2.955	0.100	4.769	0.039	0.344	0.562
14	0.379	0.546	2.409	0.140	0.251	0.622
15	1.770	0.196	2.111	0.160	0.099	0.757
16	18.198	<0.001	66.598	<0.001	10.705	0.003
17	.	.	1.322	0.268	.	.
18	.	.	0.009	0.925	.	.
19	0.039	0.846	2.574	0.129	7.087	0.017
20	0.002	0.961	1.301	0.264	2.263	0.144
21	1.187	0.284	3.251	0.079	0.597	0.444
22	6.088	0.021	9.946	0.004	4.552	0.042
23	3.324	0.081	6.799	0.016	4.804	0.038
24	2.602	0.128	17.749	0.001	0.219	0.646
25	6.164	0.023	3.413	0.078	2.326	0.140
26	2.320	0.143	5.561	0.029	0.110	0.743
27	0.028	0.868	0.541	0.469	0.616	0.440
28	6.652	0.016	0.304	0.586	7.856	0.009
29	0.449	0.507	6.207	0.017	4.632	0.037
30	0.558	0.465	1.294	0.271	6.751	0.015

Table 4.4.: F values and significance for comparison of slopes of equations produced by linear regression analysis for individual studies whilst inhaling air, oxygen of nitric oxide and oxygen.

4.4. Discussion

The results of the study showed some variability. Of the 62 subjects asked to participate in the study, only 30 agreed. Of this cohort, due to equipment failure, only 24 underwent successful studies (80%), 4 failed due to complete failure of the impedance cardiac output monitor (13% of those studied) and 2 (7%) due to a failure of the micromanometer tipped catheter to measure or record accurately the pulmonary artery pressures.

86 sets of paired data were successfully performed, whilst supine at rest and exercising, as part of 30 experiments. From the 86 sets of paired data, only 42 could be tested statistically for linearity and 3 failed the test of linearity, leaving only 45 % successful. Furthermore, the confidence intervals for the slope & the intercept were so wide, that only 32 of 86 obtained had slopes that had 95% confidence intervals that were within 20% of the base levels, and 65 with intercepts that had 95% confidence intervals that were within 20% of the base levels.

These results indicate that at least on an individual basis, reliable Pressure-Flow (P-Q) plots generated by a combination of a micromanometer tipped catheter, thoracic bioimpedance, and supine straight leg raising exercise is not feasible in clinical practice in subjects investigated for pulmonary hypertension.

Experimentally, however, cumulative effects in individual patient groups may still be detectable, if the results from several individuals were pooled. This method may still be useful in the investigation of effects of diseases and pharmaceuticals in human experiments.

The thoracic bioimpedance Cardiac index seemed to be the less reliable of the two devices. If the cardiac index and the pulmonary arterial pressure values obtained during each episode of exercise were plotted against time, the measured mean pulmonary artery pressures followed more closely the exercise periods, with less variability than the increase in cardiac output measurements. It may be that another method of measurement for continuous cardiac output, like pulse contour continuous cardiac output (PiCCO) or continuous lithium dilutional cardiac output (LiDCO) (Warburton, D. E. et al 1999), or another exercise mechanism, like a supine cycle ergometer, may give better results. It is however worth noting that the LiDCO and PiCCO devices have not been validated for use during exercise. Simminou et al (2002), used a supine cycle ergometer to produce the exercise, and states that in all seven subjects the plots produced were recto-linear, but the statistical evidence to back up this statement was not produced.

It is also worth noting that although we aimed to collect a total of 15-17 sets of paired data, 4 during rest and 11/12 during 3 minutes exercise, a large percentage of subjects could not maintain this exercise regime. In only 46 out of 86 studies, were 15 or more sets of paired data collected, and of these only 9 out of 30 of the studies completed the full regime whilst inhaling air, during exercise. The fraction of incomplete studies, in which the full term of exercise was not completed, when divided into disease categories, was as follows, 6 of 26 studies in IPAH subjects, 8 out of 12 studies in subjects with CTEPH, 12 out of 19 studies in subjects with CTD, and 9 out of 10 studies in subjects with COPD or ILD. The average time exercising achieved in those who did not complete the exercise was 110 secs (100 seconds in the 19 air inhalation studies, and

120 seconds in the 25 incomplete studies inhaling O_2 or NO/O_2).

The linear regression analysis of sets of paired data include 4 taken just prior to exercise, as it was assumed that the anticipation of exercise, would lead to a slight increase in cardiac output. This was not always seen. The importance of this is that the resting values may be too contiguous, and alter the weighting of the linear regression equation. Furthermore, with the large numbers of incomplete exercise studies, the influence would be even greater.

Possible methods of increasing the number of sets of paired data would be to do repeated exercise tests or to continue monitoring pressure flow data after exercise. The problem with the former method is the fact that we were dealing with sick individuals. If an individual study is performed, without any problems, and with the pressure and flow values returning to baseline within the six-minute rest period, excluding set up time, the study lasted a minimum of 1/2 hr. In practice, the study would last at least an hour or more, from start to finish, and the individuals in whom repeated values are most required, were those who were unable to exercise for the full 3 minutes as they were fairly exhausted. Repeating the tests on the same day in such cases is clearly not feasible and other factors may change if the study was to be repeated on another occasion. With the latter possible method, to continue monitoring pressure flow data after exercise, the subjects in our study were detached from the gas delivery apparatus immediately post exercise, often at their own request, especially when inhaling air, and so the experimental conditions were altered. Furthermore, even if this had not been the case, the fact that the subject was not exercising, may also have altered the conditions.

The importance of attempts to continue to develop a method of producing pressure flow plots clinically, can be demonstrated by the paper by Simminou et al (2002) , as well as chapters 1.6. Simminou et al (2002) demonstrate that there are clear differences in subjects at baseline and at 3 months after prostacyclin treatment, without a significant difference in traditional haemodynamic outcomes, which may be the reason for improved exercise tolerance. Future research might demonstrate differences in response to treatments or prognosis.

Finally, a study investigating the use of dobutamine as a method of producing pressure flow plots clinically would be useful (Naeije, R. et al 1994)..

Chapter 5

Analysis of the Pulmonary Pressure-Flow Response in Man during Exercise whilst inhaling Pharmacological Agents, & a Sub-analysis of the Response within Disease Subsets

5.1 Introduction

As previously mentioned, the term and calculation of pulmonary vascular resistance, (PVR), which is the calculation in common usage in both the literature, and medical practice, is misleading. It is only correct where the pulmonary arterial wedge pressure (PAWP), which is a surrogate marker for left atrial pressure, is also the critical closing pressure. The critical closing pressure is the pressure at which blood flow ceases, and this may be at a higher pulmonary arterial pressure than left atrial pressure (McGregor, M. et al 1985). This may be due to alveolar pressure (on pulmonary capillaries (West, J. B. et al 1965)) or other factors external to the blood vessels, or due to elastic recoil of the blood vessel wall (Burton, A. C. 1951). However, by ignoring the critical pressure, an error is introduced in the analysis of any change in 'resistance', in that the 'resistance' as taken by PVR, may seem to decrease as cardiac output increases, without any change in the vasomotor, compliance, elasticity or any other physical properties of the pulmonary vasculature (Chapter 1.6) (McGregor, M. et al 1985).

Several authors have now published data, demonstrating that pressure-flow plots, which demonstrate more accurately the state of the pulmonary vasculature, could be produced in both animals and humans, by various mechanisms (Evans, P. et al 1971; McGregor, M. et al 1985; Naeije, R. et al 1994; Naeije, R. 1996; Reeves, J. T. et al 1988).

In our previous studies, (Chapter 4), we have shown that it is possible to produce such pressure-flow plots, in humans, using a combination of a micromanometer tipped pulmonary arterial catheter, and a non-invasive, thoracic bioimpedance cardiac output, during straight leg raising exercise, under clinical conditions in 'diseased' humans, with

a varying degree of success. An analysis of the pooled data of all the studied subjects, to review the response to the pressure-flow plots to receiving air, oxygen (O_2) or a nitric oxide/oxygen combination (NO/O_2), and a further sub-analysis of the data, was undertaken, to review whether differing disease subgroups responded in different ways.

5.2 Methods

5.2.1. Patient group & Ethics

Recruitment and Ethics are described in Chapter 2. In total, twenty four were successfully studied (Table 4.1). The data was pooled for all the studies, and where there were sufficient numbers of subjects, in a patient disease group, and then further analyzed. For the subgroup analysis, only the normal subject group (n=3), the idiopathic pulmonary arterial hypertension (PAH) group (n=5), the pulmonary hypertension secondary to connective tissue disorder (CTD) group (n=5), and the chronic thromboembolic pulmonary hypertension (CTEPH) (n=4) (Table 5.1) were there sufficient subjects. In the 3 normal subjects, all 3 were females, the mean (± S.D.) age was 44 (± 9) years. The idiopathic pulmonary arterial hypertension (IPAH) group, consisted of 3 males and 2 females, 3 of which were vasodilator responders, and whose mean (± S.D.) age was 59 (± 11) years. The five pulmonary hypertension secondary to connective tissue disorder (CTD) group consisted of 4 females and 1 male, 4 vasodilator responders and 1 non responder, with an mean age of 54 ± 7 years. The four subjects in the chronic thromboembolic pulmonary hypertension (CTEPH) group, were all males, 3 were vasodilator non-responders, and their mean (± S.D.) age was 58 (± 18) years. The details are shown in table 5.1

Subject Number	Study Number	Initials	MPAP	SPAP	DPAP	RAP	PAWP	CO	PVR	Age	Sex	Diagnosis	Vasodilator Response
			(mmHg)					(L.min^{-1})	(mmHg / L.min^{-1})				
1	1	M,C	17	23	11	47		55	2	55	F	normal	N/A
2	2	I,C	8	14	2	1	14	40	0.0	40	F	normal	
3	3	B,Ri	15	24	3	12	9	37	0.5	37	F	normal	N/A
5	4	G,C	57	91	37	6	7	49	9	49	M	IPAH	N
6	7	W,F	79	137	48	11	14	67	20	67	M	IPAH	Y
7	8	E,M	63	115	23	14	15	73	13	73	F	IPAH	Y
8	9	W,O'H	51	82	28	4	2	61	16.3	61	M	IPAH	Y
9	12	S,S	60	103	60	10	3	45	13	45	F	IPAH	N
13	13	R,C	49	77	27	8	5	54	12	54	F	CTD	Y
14	14	Y,McB	48	79	33	0	1	48	14	48	F	CTD	Y
15	15	I,P	36	62	17	6	5	46	7.3	46	F	CTD	Y
16	16	J,P	99	130	82	9	4	59	37.1	59	M	CTD	Y
17	17	K,S	36	61	22	2		62	4	62	F	CTD	N
20	20	J,F	63	100	36	20	20	71	12	71	M	CTEPH	N
21	21	S,O	46	79	27	8		74	11	74	M	CTEPH	N/A
26	22	G,S	66	107	40	14	23	50	10.6	50	M	CTEPH	N
27	23	G,W	56	98	33	9	7	37	14.9	37	M	CTEPH	N
MEAN			54.9	89.7	34.4	8.9	8.8	55.5	13.0	55.5			
S.D.			21.0	32.3	19.0	10.7	6.9	12.1	8.7	12.1			

Table 5.1: List of subjects and studies used to pool data for assessment of individual disease subgroups.

5.2.2.Equipment and Experiments

Initial haemodynamic evaluation was performed with the patient supine and breathing room air, according to our standard protocol as described in chapter 2.3. The inhaled gas was delivered to the patient, as described in chapter 2.5.1, and shown in Figures 2.14 a-c and Figure 4.1. The right heart catheter (Gaeltec, Dunvegan, Isle of Skye), its insertion

storage and processing are described in chapter 2.1. Cardiac output was measured non-invasively by thoracic electrical bioimpedance (PhysioFlow 1, Manatec, France) as described in chapter 2.2 and the pulmonary pressure and cardiac output data combined as in chapter 2.5. Between 4-18 sets, [combined mean (± S.D.) of 14 (± 3.2), on air mean (± S.D.) 12.1 (± 3.7), with oxygen 14.6 (± 2.5), and with the nitric oxide/oxygen combination 14.9 (± 2.6)] of paired of data were collected at rest and exercise on each subject. All subjects had almost a full resting haemodynamics performed within 24 hours of the exercise test during routine right heart catheterization with a swan-gantz catheter, when MPAP, PWCP and CO were initially measured.

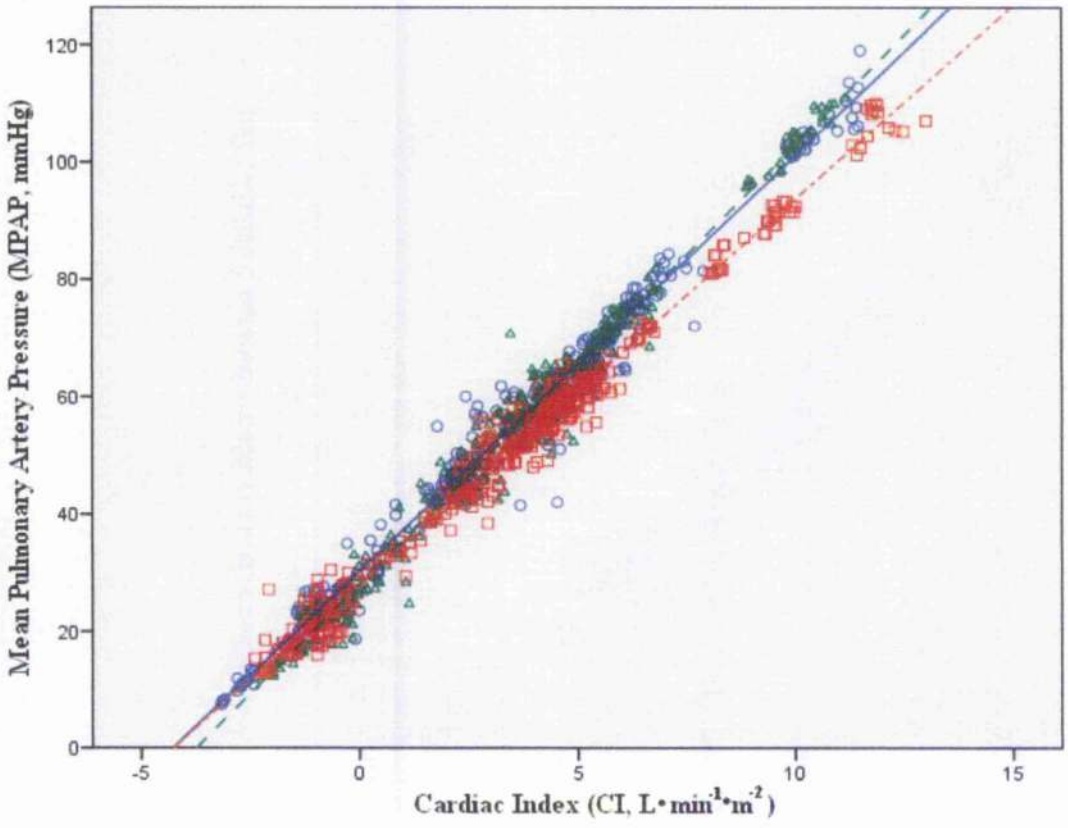
The nitric oxide was supplied as previously described (chapter 4.2, figure 4.1).

5.2.3. Analysis

Analysis of the data obtained was performed using the SPSS 13.0 package as described in chapter 2.7.

5.3 Results

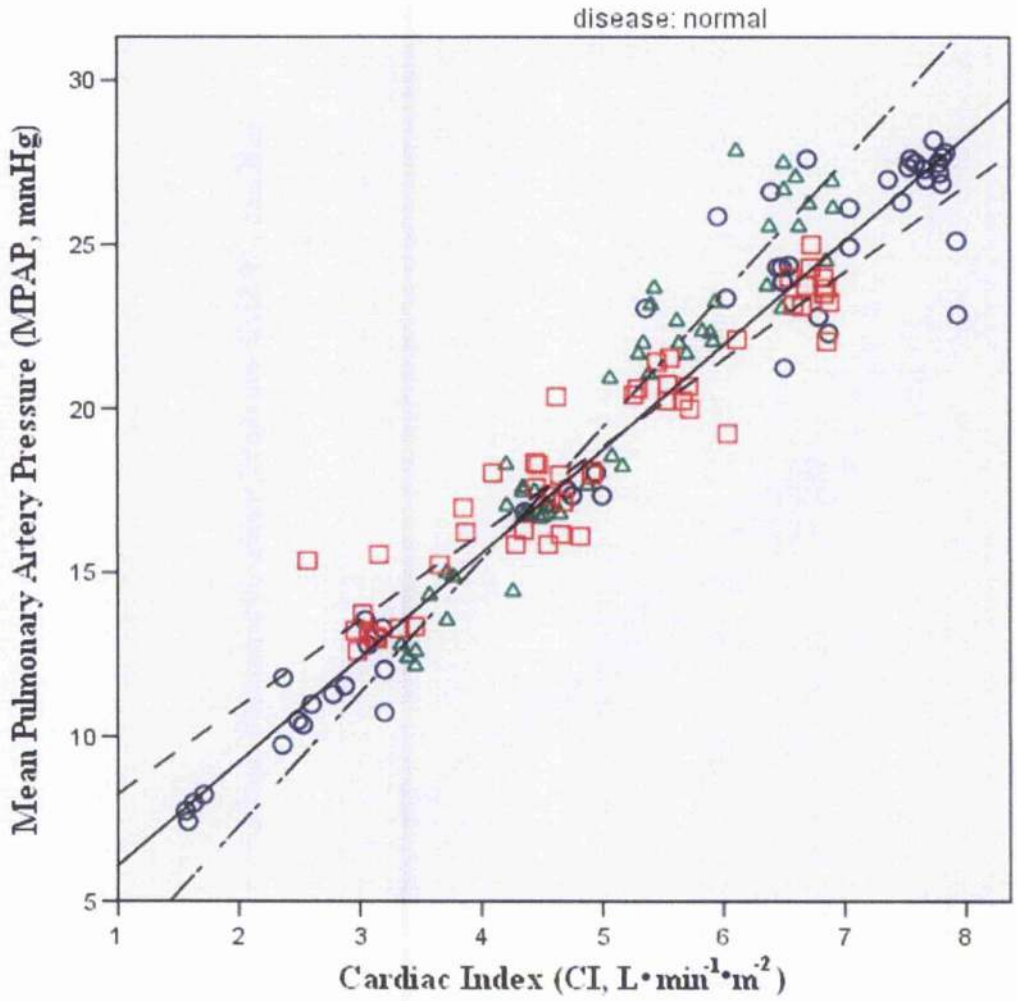
The combined data of all 24 subjects produced 308 sets of paired sets of data for inhaling oxygen, 357 for inhaling oxygen and 372 for inhaling the nitric oxide/oxygen combination. The data, the slope was significantly different for between all three inhaled gas groups, ($p<0.001$, $p=0.001$, $p<0.001$, for air compared to oxygen, air compared to nitric oxide/oxygen, and oxygen compared to nitric oxide and oxygen combined, respectively) (Tables 5.4, Figure 5.1).



Figures 5.1: Shows the linear regression plot of the data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of the entire pooled data set. A blue circle indicates the air plots, a green triangle for the oxygen (O_2) plots and a red square for the nitric oxide and oxygen inhalation plots (NO/O_2). The continuous line is the line of regression for the air plots, the evenly broken dashed line for the oxygen plots and the unevenly dashed line for the nitric oxide and oxygen plots.

The linear regression equations for the combined exercise data of the all the subjects, for inhalation of air, oxygen (O_2) and the nitric oxide/oxygen combination (NO/O_2), were respectively [MPAP = 7.1 •CI + 30.2] mmHg, ($R^2 = 0.98$, $p < 0.001$), [MPAP =7.5 • CI + 28.0] mmHg, ($R^2 = 0.98$, $p < 0.001$), [MPAP = 6.6 • CI + 28.0] mmHg, ($R^2 = 0.99$, $p < 0.001$) (Tables 5.2 & 5.3).

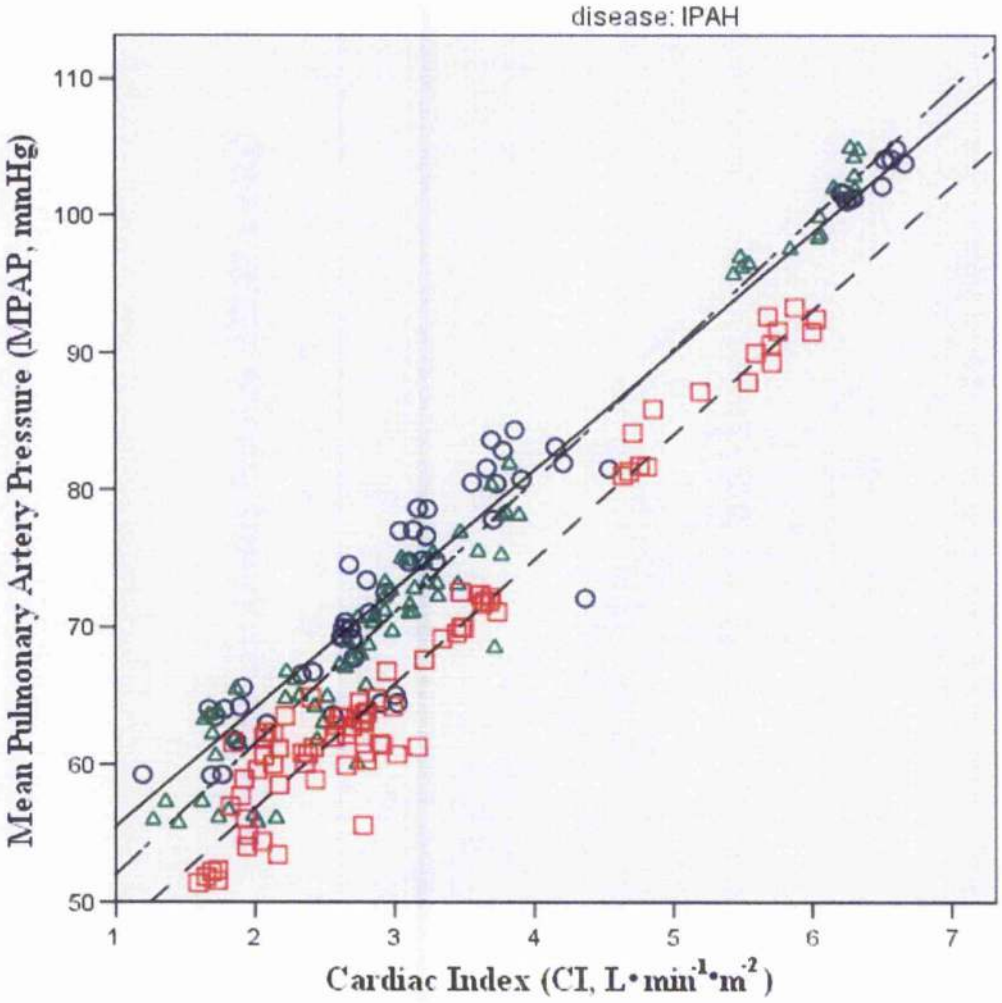
In the normal group, subjects 1-3, the data, the slope was significantly different for between all three inhaled gas groups, ($p<0.001$, $p=0.004$, $p<0.001$, for air compared to oxygen, air compared to nitric oxide/oxygen, and oxygen compared to nitric oxide and oxygen combined, respectively) (Tables 5.4, Figure 5.2).



Figures 5.2: Shows the linear regression plot of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of the pool data of the study disease subgroup of normals. A blue circle indicates the air plots, a green triangle for the oxygen (O_2) plots and a red square for the nitric oxide and oxygen inhalation plots (NO/O_2). The continuous line is the line of regression for the air plots, the evenly broken dashed line for the oxygen plots and the unevenly dashed line for the nitric oxide and oxygen plots.

The linear regression equations for the combined exercise data of the three normal subjects, for inhalation of air, oxygen (O_2) and the nitric oxide/oxygen combination (NO/O_2), were respectively [MPAP = 3.1 •CI + 2.9] mmHg, (R^2 = 0.95, p <0.001), [MPAP =4.0 • CI 0.8] mmHg, (R^2 = 0.92, p <0.001), [MPAP = 2.6 • CI + 5.6] mmHg, (R^2 = 0.90, p <0.001) (Tables 5.2 & 5.3).

The slope of the NO/O_2 group, was the shallowest (slope = 2.6 mmHg •min • m^2• L^{-1}), indicating that in this group, true resistance increased the least with exercise in this group (table 5.4).



Figures 5.3: Shows the linear regression plots of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of the pool data of the study disease subgroup of Idiopathic pulmonary arterial hypertension (IPAH). A blue circle indicates the air plots, a green triangle for the oxygen (O_2) plots and a red square for the nitric oxide and oxygen inhalation plots (NO/O_2). The continuous line is the line of regression for the air plots, the evenly broken dashed line for the oxygen plots and the unevenly dashed line for the nitric oxide and oxygen plots.

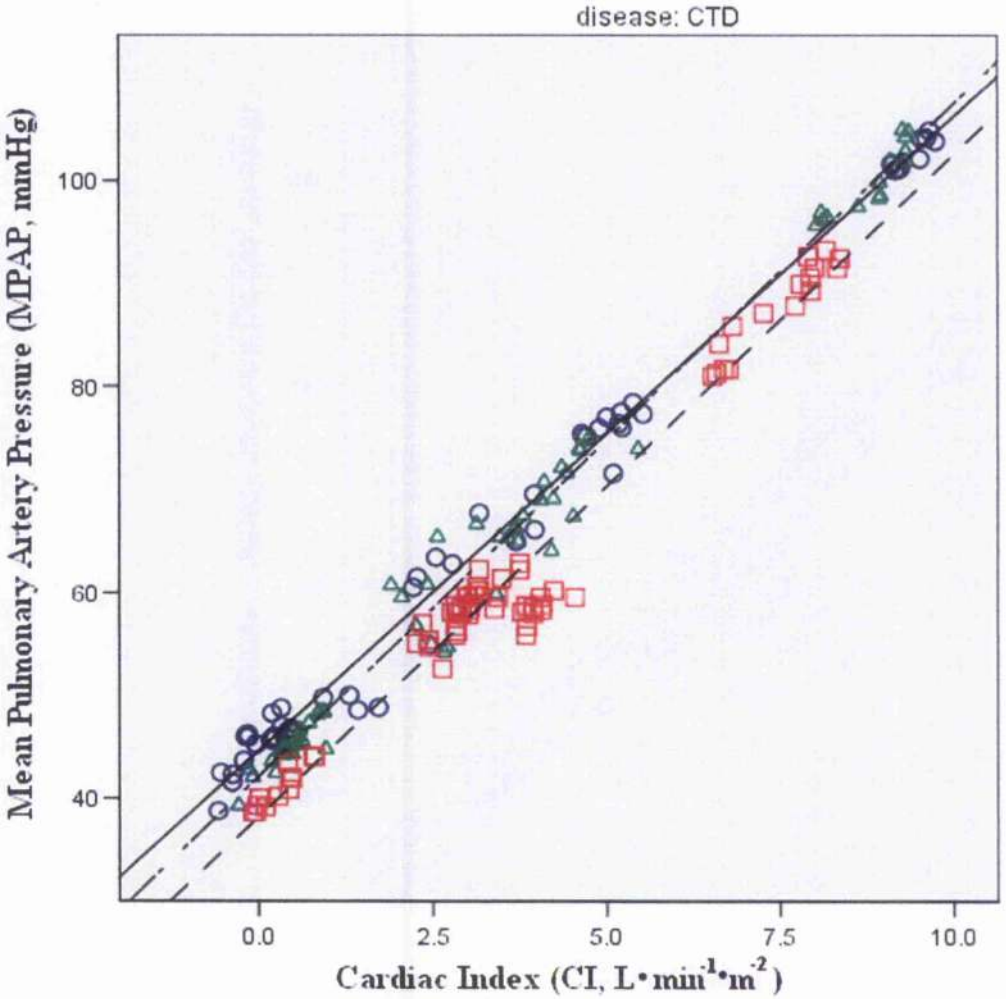
The linear regression equations for the combined exercise data of the five IPAH subjects during the inhalation of air, oxygen (O_2) and the nitric oxide/oxygen combination (NO/O_2), were respectively [MPAP = 8.6 •CI + 47] mmHg, ($R^2 = 0.94$, p

<0.001), [MPAP = 9.6 • CI + 42] mmHg, (R^2 = 0.96, p <0.001), and [MPAP = 9.0 • CI + 38] mmHg, (R^2 = 0.95, p <0.001) (Tables 5.2 & 5.3, Figure 5.3).

In the IPAH group, the data, the slope was significantly different for between only the air and the oxygen subgroup, (p= 0.01) (Table 5.4).

The linear regression equations for the combined exercise data of the five CTD subjects during the inhalation of air, oxygen (O_2) and the nitric oxide/oxygen combination (NO/O_2), were respectively [MPAP = 6.2 •CI + 44] mmHg •min • m^2• L^{-1}, (R^2 = 0.99, p <0.001), [MPAP = 6.5 • CI + 42] mmHg, (R^2 = 0.99, p <0.001), and [MPAP = 6.4 • CI + 38] mmHg, (R^2 = 0.97, p <0.001) (Tables 5.2 & 5.3, Figure 5.4).

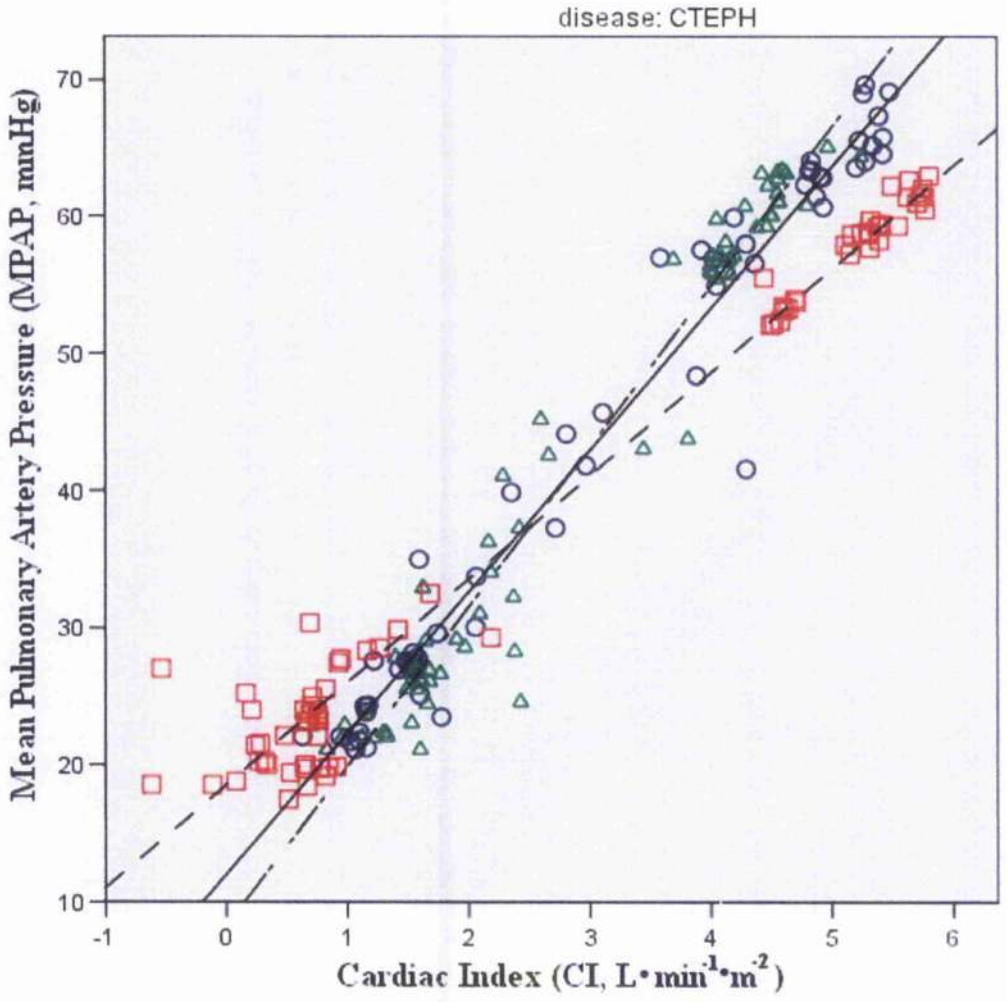
In the CTD group, the data, the slope was significantly different for between only the air and the oxygen subgroup, (p = 0.003) (Table 5.4).



Figures 5.4: Shows the linear regression plot of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of the pool data of the study disease subgroup of pulmonary arterial hypertension secondary to connective tissue disease (CTD). A blue circle indicates the air plots, a green triangle for the oxygen (O_2) plots and a red square for the nitric oxide and oxygen inhalation plots (NO/O_2). The continuous line is the line of regression for the air plots, the evenly broken dashed line for the oxygen plots and the unevenly dashed line for the nitric oxide and oxygen plots.

The linear regression equations for the combined exercise data of the four CTEPH subjects during the inhalation of air, oxygen (O_2) and the nitric oxide/oxygen combination (NO/O_2), were respectively [MPAP = 10.3 •CI + 12] mmHg, ($R^2 = 0.98$, p

<0.001), [MPAP = 11.7 • CI + 8.2] mmHg, (R^2 = 0.97, p <0.001), and [MPAP = 7.5 • CI + 18] mmHg, (R^2 = 0.96, p <0.001) (Table 5.2 & 5.3, Figure 5.5).



Figures 5.5: Shows the linear regression plot of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of the pool data of the study disease subgroup of Chronic thrombo-embolic pulmonary hypertension (CTEPH). A blue circle indicates the air plots, a green triangle for the oxygen (O_2) plots and a red square for the nitric oxide and oxygen inhalation plots (NO/O_2). The continuous line is the line of regression for the air plots, the evenly broken dashed line for the oxygen plots and the unevenly dashed line for the nitric oxide and oxygen plots.

In the CTEPH group, the data, the slope was significantly different for between all three inhaled gas groups, (p = 0.001, p < 0.001, p < 0.001, for air compared to oxygen, air

compared to nitric oxide/oxygen, and oxygen compared to nitric oxide and oxygen combined, respectively) (Table 5.4).

The slope of the NO/O_2 group, was the shallowest (slope = 7.5 mmHg •min • m^2• L^{-1}), indicating that in this group, true resistance increased the least with exercise in this group (Table 5.4).

		Linear regression			Test of deviation from linearity	
study	gas	F	Sig.	R Square	F	Sig.
All	AIR	4,037	<0.001	0.972	0.339	0.977
	Oxygen	5,011	<0.001	0.975	26.197	0.001
	NO + O2	8,622	<0.001	0.985	2.579	0.114
normal	AIR	955	<0.001	0.952	3.622	0.398
	Oxygen	563	<0.001	0.923	1.604	0.566
	NO + O2	443	<0.001	0.902		
IPAH	AIR	965	<0.001	0.944		
	Oxygen	1,770	<0.001	0.96		
	NO + O2	1,573	<0.001	0.953		
CTD	AIR	5,705	<0.001	0.991		
	Oxygen	4,980	<0.001	0.988		
	NO + O2	2,023	<0.001	0.969		
CTEPH	AIR	1,798	<0.001	0.968	0.105	1
	Oxygen	1,589	<0.001	0.96	42.91	0.001
	NO + O2	2,661	<0.001	0.975	1.564	0.364

Table 5.2: Linear regression statistics, standardised residual statistics and test of linearity statistics, for pooled data of individual disease subgroups

DISEASE	gas		Constants of slope or intercept	Sig.	95% Confidence Interval for B	
					Lower Bound	Upper Bound
ALL	AIR	Intercept	24.67	<0.001	23.4	26.0
		Slope	10.17	<0.001	9.9	10.5
	Oxygen	Intercept	32.74	<0.001	31.8	33.7
		Slope	7.79	<0.001	7.6	8.0
	NO + O2	Intercept	34.66	<0.001	34.0	35.3
		Slope	6.89	<0.001	6.7	7.0
normal	AIR	Intercept	2.90	<0.001	1.7	4.1
		Slope	3.17	<0.001	3	3.4
	Oxygen	Intercept	-0.81	0.373	-2.6	1
		Slope	4.05	<0.001	3.7	4.4
	NO + O2	Intercept	5.62	<0.001	4.3	6.9
		Slope	2.65	<0.001	2.4	2.9
IPAH	AIR	Intercept	46.83	<0.001	44.7	49
		Slope	8.64	<0.001	8.1	9.2
	Oxygen	Intercept	42.40	<0.001	40.8	44
		Slope	9.56	<0.001	9.1	10
	NO + O2	Intercept	38.65	<0.001	37.1	40.2
		Slope	9.07	<0.001	8.6	9.5
CTD	AIR	Intercept	44.62	<0.001	43.8	45.4
		Slope	6.17	<0.001	6	6.3
	Oxygen	Intercept	42.13	<0.001	41.2	43
		Slope	6.54	<0.001	6.4	6.7
	NO + O2	Intercept	38.15	<0.001	36.9	39.4
		Slope	6.44	<0.001	6.2	6.7
CTEPH	AIR	Intercept	12.00	<0.001	10.3	13.7
		Slope	10.31	<0.001	9.8	10.8
	Oxygen	Intercept	8.24	<0.001	6.4	10.1
		Slope	11.66	<0.001	11.1	12.2
	NO + O2	Intercept	18.54	<0.001	17.5	19.5
		Slope	7.52	<0.001	7.2	7.8

Table 5.3: Slope, intercept of the linear regression equation for each study, as well as the standard errors and significance and confidence interval for each value, for pooled data of individual disease subgroups

study	F (air vs O2)	Sig.(air vs O2)	F (Air vs NO)	Sig. (air vs NO)	F (O2 vs NO)	Sig. (O2 vs NO)
All Combined	30.6	<0.001	59.3	<0.001	199.6	<0.001
Normal	16.962	<0.001	8.833	0.004	44.771	<0.001
IPAH	6.669	0.011	1.411	0.237	2.308	0.131
CTD	9.157	0.003	2.928	0.09	0.35	0.555
CTEPH	12.447	<0.001	102.437	<0.001	172.915	<0.001

Table 5.4.: F values and significance for comparison of slopes of equations produced by linear regression analysis for individual studies whilst inhaling air, oxygen (O2), or nitric oxide and oxygen (NO), for pooled data of individual disease subgroups.

5.4 Discussion

Pooled data and sub analysis of individual disease groups turned up some interesting findings. The slopes produced in the group of 'normal' patients ranged from 2.6-4.1 mmHg •min •m^2• L^{-1}, which is higher than that previously noted for normal individuals (previously noted at ~1.5 mmHg•min•m^2•L^{-1}). Other studies have found that the slope in normals was 1 mmHg • L^{-1} in fit young men (Reeves, J. T. et al 1988), and assuming an average B.S.A. of 1.9, this would give a slope of 2.85 mmHg •min •m^2• L^{-1}. There are several possible explanations for any discrepancies between our result in normals and findings from previous studies.

Firstly, most of the studies looking at pulmonary pressure flow responses in man obstructed one of the main pulmonary arteries thereby doubling the flow of blood down the other artery. This avoided the possible error introduced of increasing left arterial pressure during exercise, which may alter the resultant slope. A second error is the action of straight leg raising exercise, which may alter the alveolar effects on the vasculature, as with this form of exercise, the abdominal muscles are often involved, increasing intra-abdominal pressure and thus splinting the diaphragm and altering thoracic pressure. As, the data in Chapter 3 demonstrated, the measurement of cardiac output by thoracic impedance may give reasonable trends, but the actual values of cardiac output derived from this method did not match accurately those derived from thermodilutional methods. Finally, in subject 1, the slope was significantly steeper than subjects 2 & 3 (Table 4.2a), and this may have biased the pooled result.

In the 'normal' subgroup, the NO/O_2 combination seemed to reduce the slope, and thus the resistance by the most.

In the IPAH subgroup, the slopes whilst inhaling air or O_2 or NO/O_2 combinations, were all similar, (8.6, 9.6, 9.0 mmHg •min • m^2• L^{-1} respectively), but analysis found a statistically difference between the air and the oxygen subgroups, with a suggestion that with high flow oxygen, the resistance actually increased. This is not what was expected. Both subjects 4 & 5 demonstrated a steeper individual slope for O_2 as opposed to air. Although not statistically significant, the slope of the air group was less than the NO/O_2 group, but the latter had a lower critical closing pressure (47 mmHg with air as opposed to 38 mmHg with NO/O_2).

Again in the CTD group of patients, all the slopes were similar (6.2 mmHg •min • m^2• L^{-1} for air, 6.5 mmHg •min • m^2• L^{-1} for O_2, 6.4 mmHg •min • m^2• L^{-1} for the NO/O_2 group), but the slope was significantly different when comparing air with oxygen, ($p=0.003$). Again, both O_2 and NO/O_2 results seem to suggest that resistance is increased when inhaling these gases. The critical closing pressure however seems to be lower when giving the O_2 or NO/O_2 mixture (closing pressure of air was 45mHg, O_2 42mmHg, and NO/O_2 38mmHg).

In the final subgroup, of four CTEPH patients, there was a significant drop in slope (or resistance) from the baseline when inhaling air (slope of 10.3 mmHg •min • m^2• L^{-1}) to both O_2 inhalation (slope 8.2 mmHg •min • m^2• L^{-1}, $p= 0.001$) and NO/O_2 inhalation study (slope 7.5 mmHg •min • m^2• L^{-1}, $p<0.001$) and also between the O_2 study and the NO/O_2 study of pooled data ($p<0.001$), which is what was expected in all the patient subgroups.

As mentioned earlier, the slope of the 'normal' subgroup was twice that which was expected. As previously demonstrated by other authors, the slope (or real resistance) of the IPAH group, was greater than the normal subgroup (Castelain, V. et al 2002; Janicki, J. S. et al 1985), but the slope produced here was less than noted in these other studies. The slope in the CTD group was also elevated but less compared to the IPAH group, and the CTEPH group was steeper, suggesting that the baseline resistance was greatest with CTEPH and least with CTD in the pulmonary hypertensive group. The reduction in resistance on giving NO/O_2 was greatest for the CTEPH group but seemed to not occur in the other disease groups. In the idiopathic pulmonary arterial hypertensive group, although the test for parallelism (or lack of difference) between slopes was non-significant (Table 5.4), the confidence intervals between the air and the NO/O_2 slopes overlap (8.1-9.2 an 8.6-9.5 respectively). In this group the NO/O_2 slope had a lower intercept (or closing pressure, air 46.83 mmHg (± 2.17) compared to NO/O_2 38.65 mmHg (± 1.55).

One of the weaknesses of this study was that due to low numbers of subjects, the data could not be split further into vasodilator responders and non-vasodilator responders. Both the IPAH and CTD groups had a preponderance of vasodilator responders (3 out of 5 and 4 out of 5, and the CTEPH group, non-vasodilator responders (at least 3 out of 4). It may be that there is a difference between the vasodilator responders and the non-vasodilator responders, but a larger number of subjects would be required for to divide each of the disease subgroups into differing vasodilator properties.

Chapter 6

Pulmonary hypertension, vasodilator non-responders: Fact or Fiction

6.1 Introduction

The majority of patients with pulmonary hypertension have a thickened non-responsive vasculature. This was demonstrated by a non-reduction of pulmonary vascular resistance (PVR) or mean pulmonary arterial pressure (MPAP) to an acute trial of inhaled nitric oxide (NO), one of the most potent and specific pulmonary vasodilators (Peacock, AJ 1996; Zapol, W. M. et al 1994). If a subject was shown to have no response at rest, then it was felt that the pulmonary vasculature could not be affected pharmacologically. However as demonstrated by Castelain et al (2002), PVR measurements alone may not reflect the effects of pharmacological agents on the pulmonary circulation. This is because the extrapolated pressure –flow (P-Q) plot has a positive intercept in patients with primary pulmonary hypertension and other respiratory conditions (Castelain, V. et al 2002; Harris, P. et al 1968; Janicki, J. S. et al 1985). Consequently changes in PVR, which is (MPAP-Left Atrial Pressure [LAP])/CO), may not actually reflect changes to the underlying physiology of the pulmonary circulation but simply reflect changes in cardiac output, pushing the pressure up or down a static P-Q plot.

The haemodynamic response of a subject to a vasodilator, at rest, on first presentation, is used to divide all patients into vasodilator responders and non-responders, the former having a greater than 20% improvement in either MPAP or PVR (2001), which allows patients to be selected for long term vasodilator therapy or disease targeted therapy (Rubin, L. J. 1997).

The purpose of this study was to ascertain whether no response of pulmonary haemodynamics to a vasodilator at rest, (essentially PVR), meant that there was no

change in the P-Q profile, and hence no change in the nature of the pulmonary vasculature. In addition, if any change in the pressure-flow profiles was found, was it found in both vasodilator responders and non-responders. The measurements were performed with inhaled air, oxygen and a nitric oxide/oxygen (NO/O_2) combination.

6.2 Methods

6.2.1. Patient group & Ethics

The ethics and recruitment are described in chapters 2.8 and 2.6 respectively. There were 9 subjects in the vasodilator non-responder subgroup, of which 6 were male, 3 female, 2 had Idiopathic pulmonary hypertension (IPAH), one pulmonary hypertension secondary to connective tissue disorder (CTD), 4 secondary to chronic thromboembolic disease (CTEPH), and 2 due to chronic obstructive pulmonary disease (COPD), and the mean (± S.D.) age was 58 (± 15) years (Table 6.1a). The diagnosis of pulmonary hypertension was made from the criteria from the 2002-WHO symposium (Simonneau, G. et al 2004). Patients with right-to-left shunting were excluded.

Subject Number	Initials	MPAP	SPAP	DPAP	RAP	PAWP	CO	PVR	Age	Sex	Diagnosis	Vasodilator Response
		(mmHg)					$L.min^{-1}$	(mmHg / $L.min^{-1}$)				
5	G,C	57	91	37	6	7	4.6	9	49	M	IPAH	N
9	S,S	60	103	60	10	3	4.5	13	45	F	IPAH	N
17	K,S	36	61	22	2		3.9	4	62	F	CTD	N
20	J,F	63	100	36	20	20	3.7	12	71	M	CTEPH	N
21	S,O	46	79	27	8		5	11	74	M	CTEPH	N
26	G,S	66	107	40	14	23	4.1	10.6	50	M	CTEPH	N
27	G,W	56	98	33	9	7	3.3	14.9	37	M	CTEPH	N
31	R,McD	43	74	26	11	8	2.2	16	60	M	COPD	N
32	M,T	30	50	10	4	13	4.1	4	81	F	COPD	N
Mean		50.8	84.8	32.3	9.3	11.6	3.9	10.5	58.8			
S.D.		12.6	27.6	13.1	5.9	6.9	1.2	4.0	21.0			

Table 6.1a: List of subjects and studies used to pool data for assessment vasodilator non responder subgroup.

There were 9 subjects in the vasodilator responder subgroup, of which 4 were male, 5 female, 3 had Idiopathic pulmonary hypertension (IPAH), 4 pulmonary hypertension

secondary to connective tissue disorder (CTD), 2 secondary to interstitial lung disease (ILD), and the mean (± S.D.) age was 57 (± 13) (Table 6.1b).

Subject Number	Initials	MPAP	SPAP	DPAP	RAP	PAWP	CO	PVR	Age	Sex	Diagnosis	Vasodilator Response
		(mmHg)					$L.min^{-1}$	(mmHg / $L.min^{-1}$)				
6	W,F	79	137	48	11	14	3.3	20	67	M	IPAH	Y
7	E,M	63	115	23	14	15	3.7	13	73	F	IPAH	Y
8	W,O'H	51	82	28	4	2	3	16.3	61	M	IPAH	Y
13	R,C	49	77	27	8	5	3	12	54	F	CTD	Y
14	Y,McB	48	79	33	0	1	3	14	48	F	CTD	Y
15	I,P	36	62	17	6	5	3.6	7.3	46	F	CTD	Y
16	J,P	99	130	82	9	4	2.6	37.1	59	M	CTD	Y
28	W,F	39	54	28	18	12	4.4	5	71	M	ILD	Y
30	B,Ra	57	81	44	3	4	2.4	26.1	33	F	ILD	Y
Mean		57.9	90.8	36.7	8.1	6.9	3.2	16.8	56.9			
S.D.		20.1	29.5	19.6	5.6	5.3	0.6	9.9	13.0			

Table 6.1b: List of subjects and studies used to pool data for assessment vasodilator responder subgroup.

6.2.2. Study Protocol

Initial haemodynamic evaluation was performed with the patient supine and breathing room air, according to our standard protocol as described in chapter 2.3. The inhaled gas was delivered to the patient, as described in chapter 2.5.1, and shown in Figures 2.14 a-c and Figure 4.1. Cardiac output was measured non-invasively by thoracic electrical bioimpedance (PhysioFlow 1, Manatec, France) and Cardiac Index (CI) calculated from CO divided by body surface area. This thoracic electrical bioimpedance device has previously been described (Chapter 1.11, 2.2 and 3) (Charloux, A. et al 2000). The results were transferred to Microsoft Excel, and then processed to produce 16-second averages compatible in time with the MPAP. Between 9-19 sets, [vasodilator combined

mean (± S.D.) of 12.5 (± 2.5), on air mean (± S.D.) 10.7 (± 1.5), with oxygen 12.6 (± 2.5), and with the nitric oxide oxygen combination, 14.4 (± 2.1), and non-vasodilator responder combined mean (± S.D.) of 13.3 (± 3.5), on air mean (± S.D.) 12.6 (± 3.3), with oxygen 13.1 (± 4.3), and with the nitric oxide oxygen combination, 14.1 (± 3.1)] of paired of data were collected at rest and exercise respectively on each subject. The exercise consisted of a maximum of 3 minutes, or less if the subjects could not manage it, of alternate straight leg raising. All subjects had almost a full resting haemodynamics performed within 24 hours of the exercise test during routine right heart catheterization with a swan-gantz catheter, at which time MPAP, PWCP and CO were initially measured, except subject 21, who had previously had a vasodilator study, in which he was not a responder, and in whom total pulmonary vascular resistance (MPAP/CO) also had a less than 20% drop with the NO/O_2 combination.

The nitric oxide was supplied as previously described (chapter 4.2, figure 4.1).

6.2.3. Analysis

Analysis of the data obtained was performed using the SPSS 13.0 package as described in chapter 2.7.

6.3 Results

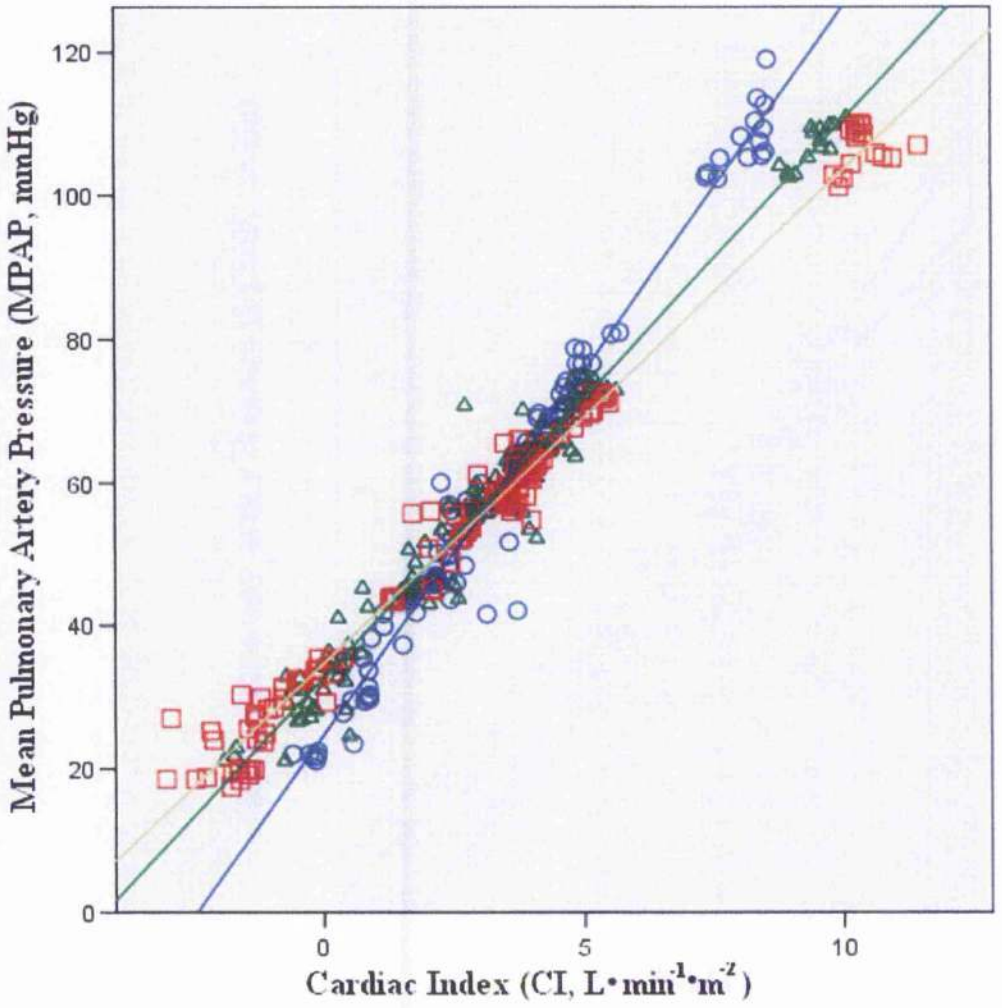
The haemodynamic variables and patient groups are shown in Table 6.1 a & b. In the vasodilator non-responder group, the air and NO/O_2 recto-linear lines, did not significantly deviate from linearity. The oxygen recto-linear plot, statistically deviated from linearity ($F = 262$, $p = 0.001$). However, on reviewing the scattergrams, histograms of residuals, and normal probability plots of the residuals, all three lines seem to meet the criteria for linearity.

The regression lines for vasodilator responders, were not able to be tested statistically for linearity, due to small study numbers, however on reviewing the scattergrams, histograms of residuals, and normal probability plots of the residuals, all three lines seem to meet the criteria for linearity.

4 data points, in the 64 seconds prior to exercise and 5-13 data points, during exercise, were recorded on each patient, producing reasonable visually recto-linear plots in the majority of studies.

The slope of the MPAP/CI plot tended to decrease but was not statistically significant in all patients on the NO/O_2 mixture as compared to the slope on air. When the data points from the nine patients who were non-vasodilator responders, were pooled the relations between MPAP and CI were rectilinear (Figure 6.1) with the following equations produced, on air MPAP = 10.1•CI + 24.1, $R^2 = 0.97$, $p< 0.001$, with oxygen, MPAP = 7.8•CI +32.7, $R^2 = 0.97$, $p< 0.001$ and NO/O_2 mixture, MPAP = 6.9•CI+ 34.6, $R^2 = 0.98$, $p<0.001$). The slope of the MPAP/CI plot was significantly decreased from air to

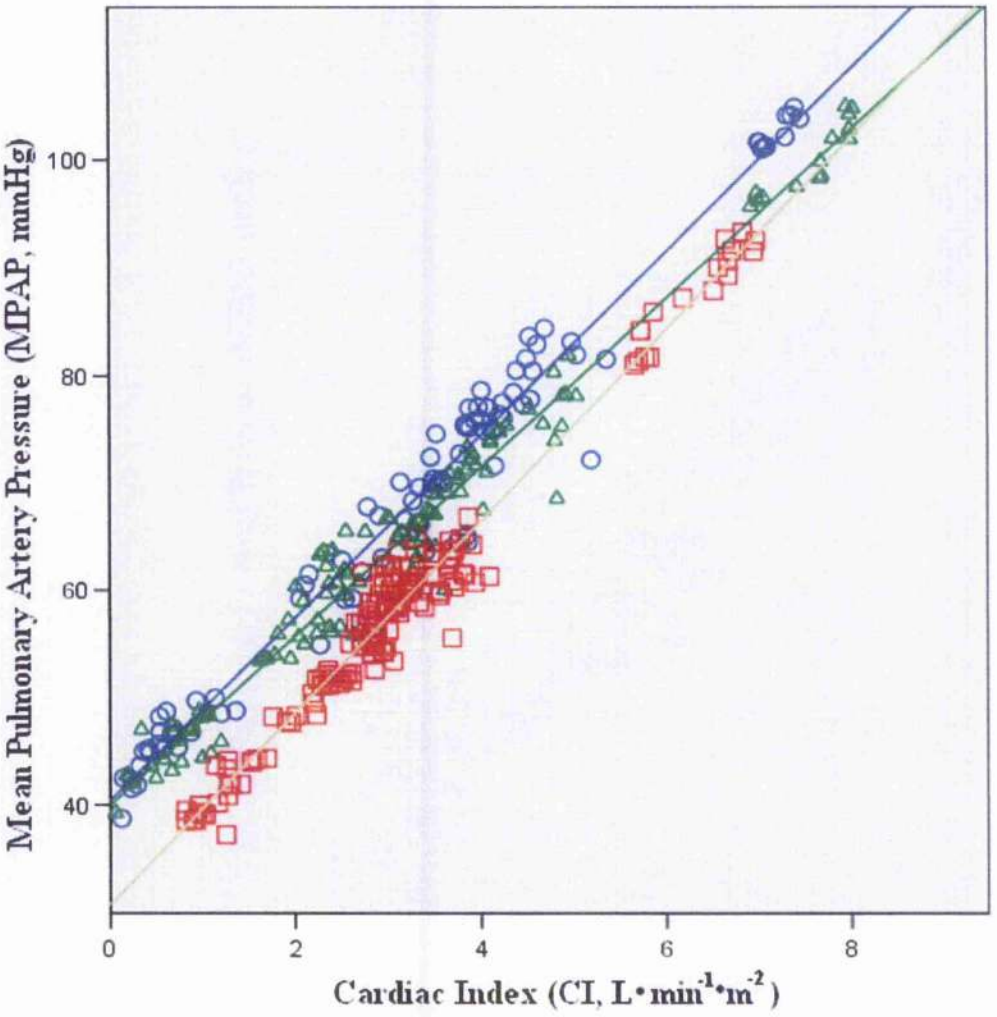
oxygen and the to the NO/O_2 mixture (Figure 6.1, Table 6.2 & 6.3) (10.1 vs. 7.8 vs. 6.9 mmHg/L/min/m2; $p<0.001$) suggesting that in these non-vasodilator responder subjects, there is a decrease in true resistance after inhaling oxygen and a further decrease with the addition of nitric oxide.



Figures 6.1: Shows the linear regression plots of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of the pool data of the study non-vasodilator responder subgroup. A blue circle indicates the air plots, a green triangle for the oxygen (O_2) plots and a red square for the nitric oxide and oxygen inhalation plots (NO/O_2). The blues line is the line of regression for the air plots, green line for the oxygen plots red for the nitric oxide and oxygen plots.

When the data points from the nine patients who were vasodilator responders, were pooled the relations between MPAP and CI were rectilinear (Figure 6.2) with the following equations produced, on air MPAP =8.5•CI + 40.4, R^2 = 0.97, p< 0.001, with oxygen, MPAP = 7.8•CI +40.1, R^2 = 0.97, p< 0.001 and NO/O_2 mixture, MPAP = 8.9•CI+ 30.1, R^2 = 0.97, p<0.001). The slope of the MPAP/CI plot on testing by ANCOVA was significantly decreased from air to oxygen, and increased form the air to the NO/O_2 mixture, and oxygen to the NO/O_2 mixture (Figure 6.2, Table 6.2 & 6.3) (8.5 vs. 7.8 vs. 8.9 mmHg/L/min/m2; p = 0.001, p= 0.044, p<0.001).

However the 95% confidence intervals for the slopes of the air and the NO/O_2 groups overlapped, which may actually suggest that there is no significant decrease in resistance in vasodilator responders.



Figures 6.2: Shows the linear regression plot of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of the pooled data of the study vasodilator subgroup. A blue circle indicates the air plots, a green triangle for the oxygen (O_2) plots and a red square for the nitric oxide and oxygen inhalation plots (NO/O_2). The blues line is the line of regression for the air plots, green line for the oxygen plots red for the nitric oxide and oxygen plots.

VASODILA-TION	Gas	Linear regression			Test of deviation from linearity	
		F	Sig.	R^2	F	Sig.
Non Responder	AIR	4036.73	<0.001	0.97	0.34	0.977
	Oxygen	5011.19	<0.001	0.97	26.20	0.001
	NO + O2	8621.66	<0.001	0.99	2.58	0.114
Responder	AIR	3302.97	<0.001	0.97		
	Oxygen	4201.17	<0.001	0.97		
	NO + O2	4481.89	<0.001	0.97		

Table 6.2: Linear regression statistics, standardised residual statistics and test of linearity statistics, for pooled data of vasodilator responder and non-responder subgroups

Vasodilator responder	Gas		Constants of slope or intercept	Sig.	95% Confidence Interval for B	
					Lower Bound	Upper Bound
Non Responder	AIR	Intercept	24.672	<0.001	23.345	25.999
		Slope	10.174	<0.001	9.856	10.491
	Oxygen	Intercept	32.737	<0.001	31.789	33.685
		Slope	7.786	<0.001	7.568	8.004
	NO + O2	Intercept	34.660	<0.001	33.997	35.324
		Slope	6.890	<0.001	6.744	7.037
Responder	AIR	Intercept	40.41631	<0.001	39.26813	41.56449
		Slope	8.506524	<0.001	8.212599	8.800448
	Oxygen	Intercept	40.01696	<0.001	39.09567	40.93826
		Slope	7.850533	<0.001	7.610573	8.090492
	NO + O2	Intercept	30.77414	<0.001	29.87121	31.67708
		Slope	8.910249	<0.001	8.646919	9.173579

Table 6.3: Slope, intercept of the linear regression equation for each study, as well as the standard errors and significance and confidence interval for each value, for pooled data of vasodilator responder and non-responder subgroups

VASODILATION	F (air vs. O2)	Sig. (air vs. O2)	F (Air vs. NO)	Sig. (air vs. NO)	F (O2 vs. NO)	Sig. (O2 vs. NO)
NON RESPONDER	155.302	<0.001	47.316	<0.001	47.316	<0.001
RESPONDER	11.984	0.001	4.114	0.044	32.977	<0.001

Table 6.4.: F values and significance for comparison of slopes of equations produced by linear regression analysis for individual studies whilst inhaling air, oxygen (O2) or nitric oxide and oxygen (NO), for pooled data of vasodilator responder and non-responder subgroups

6.2 Discussion

Pulmonary vascular tone in animals and humans is commonly evaluated by PVR calculated as MPAP minus PAOP (assumed equal to left atrial pressure) divided by CO. This approach is misleading in many clinical and experimental circumstances (Ahmed, T. et al 1983; Graham, R. et al 1983; Lodato.R.J. et al 1985; McGregor, M. et al 1985) and does not change with changes in the patients clinical condition (Castelain, V. et al 2002). In both isolated lung and *in vivo* the MPAP/ flow relationship is rectilinear over the physiological range of flow (Castelain, V. et al 2002; Janicki, J. S. et al 1985). In young normal humans this MPAP-LAP/CO line when extrapolated towards the y axis, may cross through the origin (Ekelund, L. G. et al 1967). However disease processes or pharmacological interventions can alter both the intercepts, making it either positive or negative, across the pressure axis, or to alter the slope, (Castelain, V. et al 2002; Harris, P. et al 1968; Janicki, J. S. et al 1985; Leeman, M. et al 1988; Murray, P. A. et al 1986; Naeije, R. et al 1987). When closing pressure is greater than PCWP and flow varies, the discrimination of passive (or flow dependant) and active changes to PAP cannot be determined from single PVR calculations. The correct approach would be to determine P-Q over several levels of flow (McGregor, M. et al 1985).

The extrapolated intercept is felt by most to represent the mean closing pressure of the pulmonary vessels. The slope is felt to represent the average cross sectional area of the opened vessels, (Dawson, C. A. et al 1988; Mitzner, W. et al 1987).

We felt it important that the techniques used in this study could be easily replicated in a normal clinical setting. However, the method of increasing cardiac output does present problems and inaccuracies in the study. Straight leg raising is a difficult exercise to

perform and many subjects were unable to complete the exercise period. Secondly, straight leg raising uses abdominal muscles, leading to increased intra abdominal and intra thoracic pressures. It was hoped that the averaging of the pressures and cardiac outputs over 16 seconds would eradicate any swing in pressures form this source. A future study, repeating the studies using a supine cycle ergometer may reduce this error.

The changes in the slopes of the recto-linear plots produced on linear regression analysis of the individual inhalational studies suggest that in the subjects reported to be vasodilator 'non-responders', that the NO/O_2 combination, far from having no effect on the pulmonary vasculature, may decrease the actual resistance or effect the distensibility and compliance of the pulmonary vessels, (slope of the air plot 10.1 [95% confidence interval 9.8-10.5] compared with NO/O_2 slope of 6.9 [95% confidence interval 6.7-7.0]). It was noted that 4 out of the 9 subjects in this group had CTEPH, but this fall in slope remained true, even when data from the remaining 5 subjects was pooled and analyzed separately.

More surprisingly, although statistically the recto-linear plots of the 'vasodilator responsive' pooled subjects were all different under ANCOVA analysis, and indeed the slope of the NO/O_2 plot was greater than the air plot, it was noted that visually, the air and the NO/O_2 inhalational plots seemed to run parallel. Indeed the 95% confidence interval of the air and the NO/O_2 groups for their individual slopes, overlapped (95% confidence interval for the slope of the air plot, 8.2-8.8 and for the NO/O_2 plot, 8.6-9.1). In only the oxygen group, was the slope decreased, compared to baseline on air. What was startlingly obvious was the overlap of the intercept between the air and the oxygen group, but the reduction of the intercept in the NO/O_2 group (for air, 40.4, 95%

confidence interval 39.3-41.6, for oxygen, 40.0, 95% confidence interval 39.1-40.9, and for NO/O_2 30.1, 95% confidence interval 29.9-31.7). As the ANCOVA analysis of the plots suggested a change in the slopes, further analysis of the intercepts was not undertaken, but this study suggests that in 'vasodilator responsive' subjects, the effect of the vasodilator is to the reduce the mean opening pressure of the vessels, but to leave the resistance of the vessels intact.

The method of measuring cardiac output by thoracic bioimpedance has been validated in subjects with several respiratory conditions, but the accuracy in subjects with pulmonary hypertension during exercise had not been previously investigated. This analysis (chapter 3) suggests that although the actual values of cardiac output in an individual were not as accurate when compared to the thermodilutional method, but the percentage change in cardiac output, in an individual, were statistically comparable.

Another problem has been that the subjects received between 40-80 ppm of NO in the NO/ O2 mixture. It has been shown that at 20 ppm, NO exclusively affects small arterioles. At 50 ppm and above, venules and small veins may be affected. This however should not be a major problem in this patient group as the expected main site of resistance would be before the venous system (Shirai, M. et al 1996).

Hypoxia during exercise in subjects with cardiorespiratory disease may account for the increased steepness of the air P-Q plots. A reduction in the slopes the pressure-flow plots was seen in both the non-vasodilator and vasodilator groups, when inhaling oxygen alone. It was noted that the slope of the plots with oxygen in both groups was 7.8.

A further problem may be that the change to the P-Q plot is secondary to either changes in LAP, intrathoracic pressure, or lung volumes. Although no attempt was made to assess lung volumes or intrathoracic pressures, by averaging over 16s (several respiratory cycles) we hoped to eradicate any changes, which would be due to changes in the respiratory rate or depth. It is hoped that in the near future, thoracic bioelectrical impedance will be able to give an accurate estimation of LAP.

Due to the heterogeneous nature of the subjects studied, subjects with pulmonary venous hypertension were excluded. It would be useful, if further studies were performed, to repeat this sub analysis of vasodilator responsive and non-responsive subjects, within individual disease subgroups. A separate study, looking at the effects of various concentrations of NO, with and without oxygen would also be useful.

Apart from the limitations of this study, there may be several reasons, other than actual direct vasodilating effects of vasodilators, to why the NO/O_2 group had a reduced P-Q slope. During exercise, the subject may become hypoxic. The addition of oxygen may reduce this effect and thus reduce hypoxic vasoconstriction. In addition, during exercise there is adrenergic stimulation. Research has previously shown in dogs that blockade of β receptors leads to a parallel shift of the P-Q plot up and α blockade leads to a parallel shift down (Murray, P. A. et al 1986). It is known that NO affects the receptors, and may be possible that some NO diffuses to nerve endings. This infiltration of nerve endings may have differing effects in our vasodilator responsive and non-responsive groups.

Finally, the point of action of the vasodilator may not necessarily be at the point of maximum resistance. It has been postulated that the change of slope reflects change in Starling resistance and that resistance is mostly upstream from the point of obstruction. Thus, the vasodilatation may all be upstream from the pathological regions of obstruction.

More research is required to see if the individual variations within subjects in their slopes or intercepts of their P-Q plots correlate with patient's morbidity, mortality or other haemodynamic or clinical values.

In conclusion, giving nitric oxide and oxygen to subjects who have no vasodilatory response at rest, does have an effect on the P-Q slopes, leading to a reduction in the slope and indicates that the vasculature is still responsive to vasodilators. In vasodilator responders, the effect of nitric oxide seems to be to reduce the critical closing pressure. To our knowledge, this is the first time that these differences have been found. This demonstrates that it is important to measure P-Q plots and responses to vasodilators at baseline. Differences in the extent of response in P-Q plots may be found in the future to be responsible for differences in morbidity and mortality, or demonstrate affects of vasodilator responses.

In light of the results of this study, it would have been interesting to see whether in the Castilian et al (2002) study of the effects of prostacyclin at 3 months in non-vasodilator responders, whether these subjects had a reduction in resistance with NO or prostacyclin at the commencement of the study, and whether the resistance actually altered with long term treatment with prostacyclin. Another study of interest would be to assess the

vasodilator responders, who seem to reduce their critical closing pressure, and to follow them to discover if their pressure-flow plot response changes, in non-responders, on treatment, become more like responders.

Chapter 7

Postural Effects on Pressure Flow gradients measured by Micromanometer tipped Pulmonary Artery Catheter and Thoracic Impedance Cardiac output in subjects being investigated for Pulmonary hypertension

7.1 Introduction

It has been demonstrated that changes in pulmonary vascular resistance (PVR) as defined by the difference between mean pulmonary artery pressure (MPAP) and left atrial pressure (LAP) divided by cardiac output (CO), may not truly reflect any changes in the vasomotor tone of the pulmonary vasculature. The production of pressure flow plots of MPAP vs CO, leads to a more accurate way of following changes in vasomotor tone (Castelain, V. et al 2002; Harris, P. et al 1968; Janicki, J. S. et al 1985).

We have performed a series of studies looking at the usefulness of producing pressure flow plots in clinical practice of subjects being investigated for possible pulmonary hypertension (Chapters 4-6). It was the intention of this part of the study that as part of the investigations the subjects would be offered cardiopulmonary exercise testing (CPET), whilst measuring their pressure flow gradients. The intention was to investigate whether any of the CPET measurements were related to the pressure-flow slope or the intercept and could be used as surrogates. Unfortunately, there was a poor level of consent and recruitment amongst potential subjects, hence this was not possible to perform.

7.2 Methods

7.2.1. Patient group & Ethics

Recruitment and Ethics are described in Chapter 2. Six patients consented, but only four were successfully studied (2 males and 2 females) (Table 7.1). In two subjects, the study was unsuccessful due to problems with the thoracic bioimpedance device. The mean age (± S.D.) of the studied subjects was 55.5 years (± 17.9), but ranged from 33 to 74. The disease groups very heterogeneous, with one normal, one with chronic thromboembolic pulmonary hypertension, one with pulmonary hypertension secondary to interstitial disease and one secondary to chronic obstructive pulmonary disease.

Subject Number	Initials	MPAP	SPAP	DPAP	RAP	PAWP	PVR	Age	Sex	CO	Diagnosis	Vasodilator Response
		(mmHg)					(mmHg / L.min^{-1})			(L min^{-1})		
1	M,C	17	23	11	47		2	55	F	8.1	normal	N/A
21	S,O	46	79	27	8		11	74	M	5.0	CTEPH	N/A
31	R,McD	43	74	26	11	8	16	60	M	2.2	COPD	N
36	F.B	43	60	26	9	22	4.2	65	F	4.9	PVH	N
Mean		37.3	59.0	22.5	18.8	15.0	8.3	63.5		5.1		
S.D.		15.9	27.6	8.5	15.9	7.7	6.0	26.7		2.4		

Table 7.1: List of individual subjects with demographics and baseline haemodynamic results

7.2.2.Equipment and Experiments

Initial haemodynamic evaluation was performed with the patient supine and breathing room air, according to our standard protocol as described in chapter 2.3. The inhaled gas was delivered to the patient, as described in chapter 2.5.1, and shown in Figures 2.14 a-c and Figure 4.1. The right heart catheter (Gaeltec, Dunvegan, Isle of Skye), was as described in Chapter 2.1. Cardiac output was measured non-invasively by thoracic electrical bioimpedance (PhysioFlow 1, Manatec, France) as described previously

(Chapter 1.11, 2.2 and 3) (Charloux, A. et al 2000). The results were transferred to Microsoft Excel, and then processed to produce 16 second averages compatible in time with the MPAP as described in chapter 2.5.

Between 12-19 sets, [mean (± S.D.) of 16.2 (± 2.9)], of paired data were measured in these subjects whilst supine, breathing air performing straight leg raising exercises (chapter 4), and between 18-40 sets of paired data [mean (± S.D.) 30.8 (± 11.0)] were taken one minute prior, and during the cardiopulmonary exercise test. The cardiopulmonary exercise test was a standard ramp test, with an estimation of incremental work sufficient to allow 6-7 minutes before maximal exercise. All subjects had almost a full resting haemodynamics performed within 24 hours of the exercise test during routine right heart catheterization with a Swan-Gantz catheter, where MPAP, Svo2, PWCP and CO were initially measured.

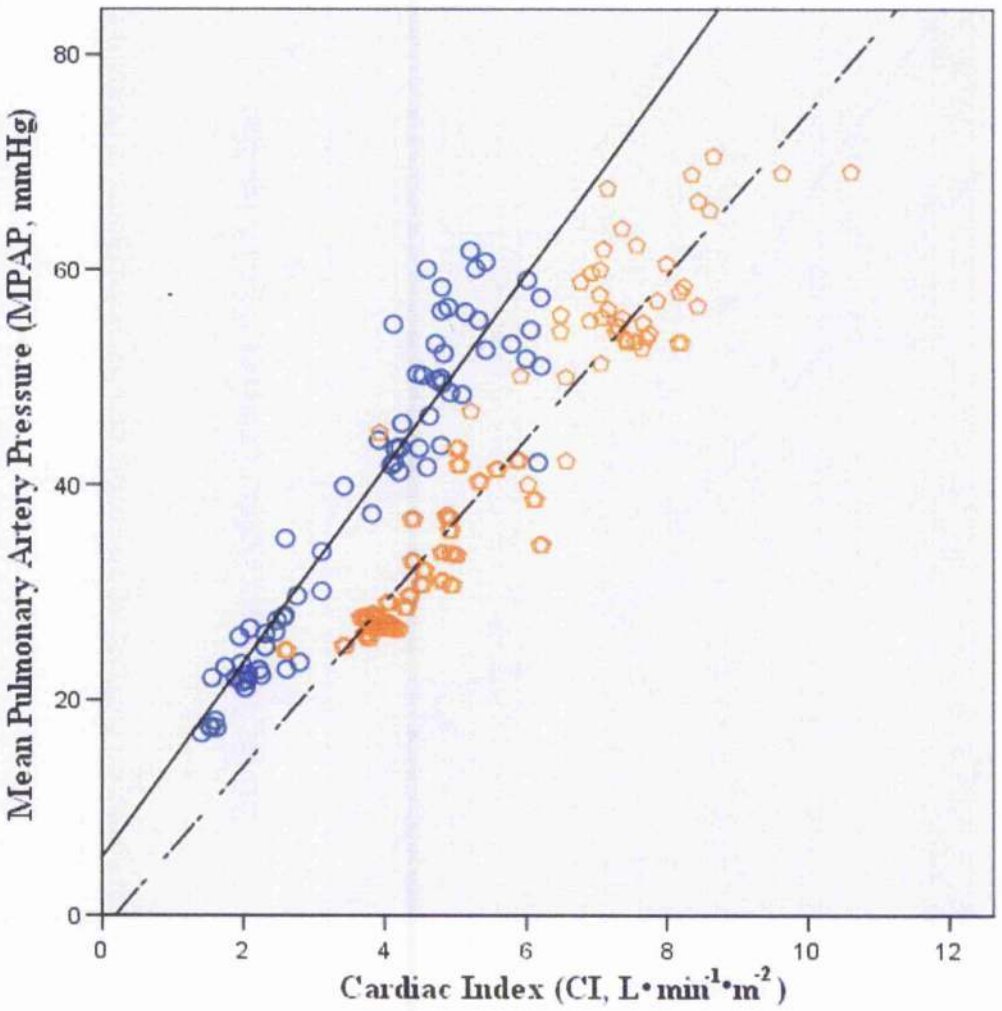
All subjects were exercised using the "Sensormatics V-max system" (Sensormatics, Yorba Linda, CA, USA) wearing an adult face mask (Hans Rudolph, inc. 72000, Kansas City, USA).

7.2.3. Analysis

Analysis of the data obtained was performed using the SPSS 13.0 package as described in chapter 2.7.

7.3 Results

The linear regression plots for the pooled data was MPAP = 7.6•CI - 1.46 mmHg, for the semi-erect study, and MPAP = 9.0•CI + 5.7 mmHg, for the supine study, and the slopes were significantly different (F=9.0, =0.003).



Figures 7.1: Shows the linear regression plot of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of the pooled data of differing posture. A blue circle indicates the air plots taken whilst supine and, an orange pentagram for the air plots taken whilst semi-erect. The continuous line is the line of regression for the air plots, whilst supine the evenly broken dashed line whilst semi-erect.

The equations for the individual subjects were as follows. Subject 1, MPAP = 5.2 • CI – 8.8 mmHg, for the semi-erect study, and MPAP = 5.7 • CI -6.6 mmHg, for the supine study. Subject 21, MPAP = 12 • CI – 5.7 mmHg, for the semi-erect study, and MPAP = 6.8 • CI -8.7 mmHg, for the supine study. Subject 31, MPAP = 9.4 • CI + 27.4 mmHg, for the semi-erect study, and MPAP = -3.4 • CI + 60.1 mmHg, for the supine study. Subject 36, MPAP = 2.4 • CI + 35.8 mmHg, for the semi-erect study, and MPAP = 5.4 • CI + 28.9 mmHg, for the supine study. Subjects 21 and 36 had slopes that statistically differed ($F = 17.4$, $p<0.001$, $F = 10.3$, $p=0.003$), whereas the slopes of subject 1 and 31 did not differ.

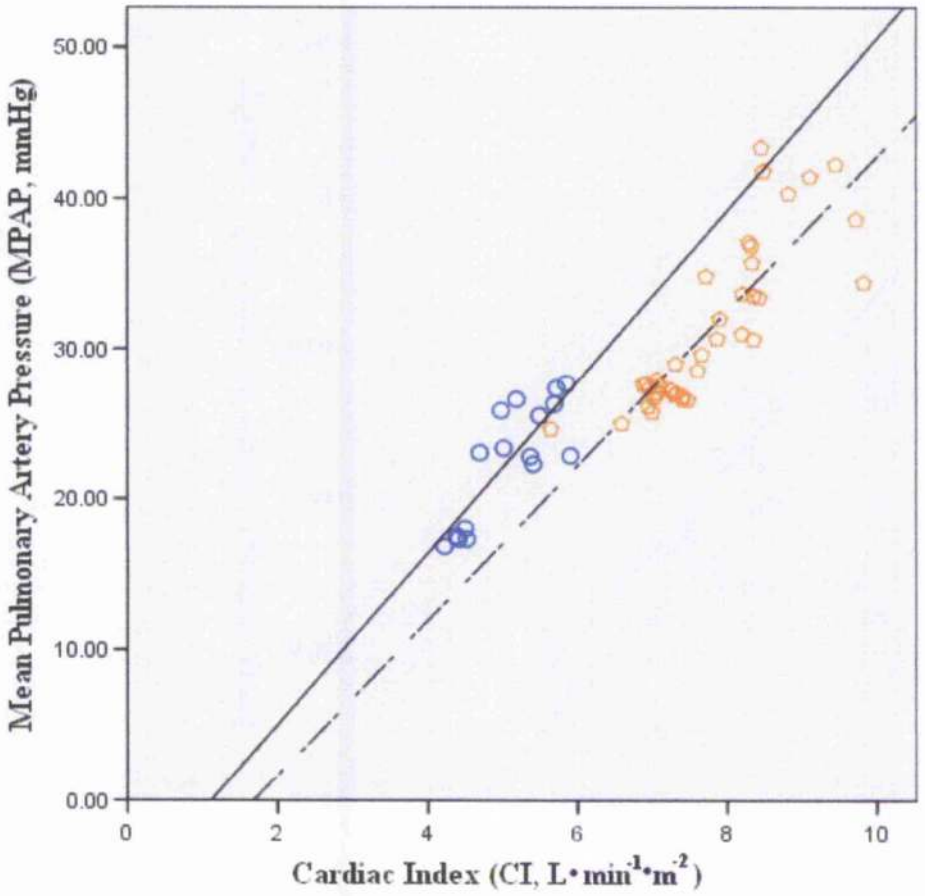


Figure 7.2a: Shows the linear regression plot of paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of subject 1 of differing posture. A blue circle indicates the air plots taken whilst supine and, an orange pentagram for the air plots taken whilst semi-erect. The continuous line is the line of regression for the air plots, whilst supine the evenly broken dashed line whilst semi-erect.

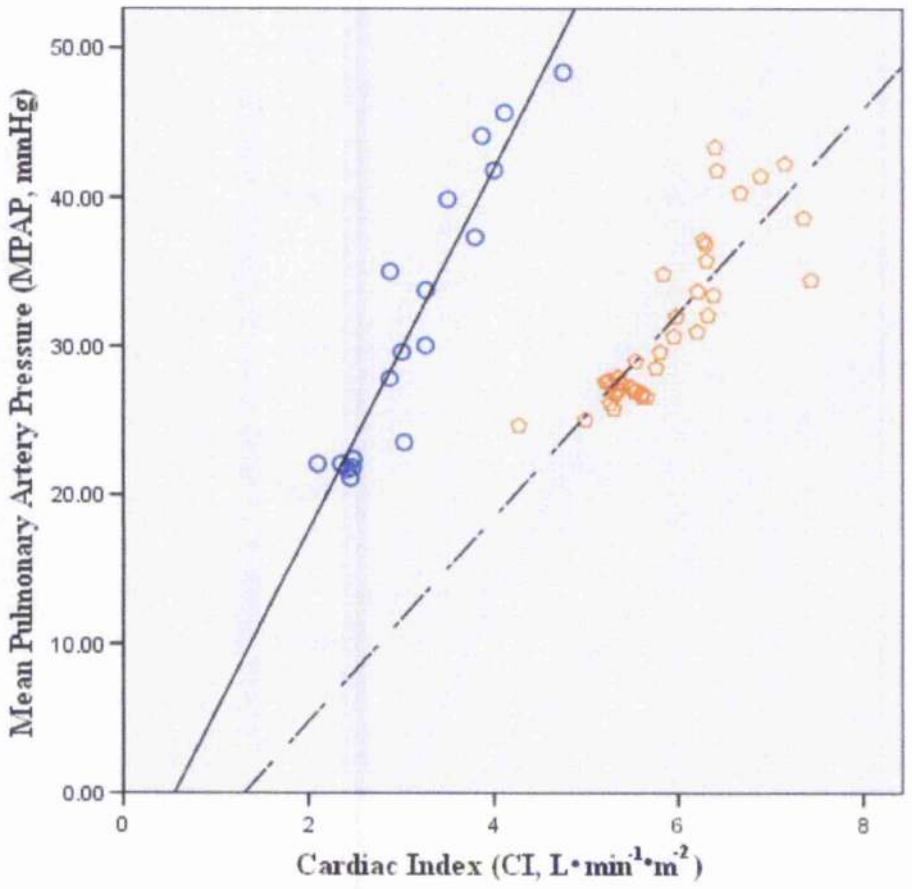


Figure 7.2b: Shows the linear regression plot of paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of subject 21 of differing posture. A blue circle indicates the air plots taken whilst supine and, an orange pentagram for the air plots taken whilst semi-erect. The continuous line is the line of regression for the air plots, whilst supine the evenly broken dashed line whilst semi-erect.

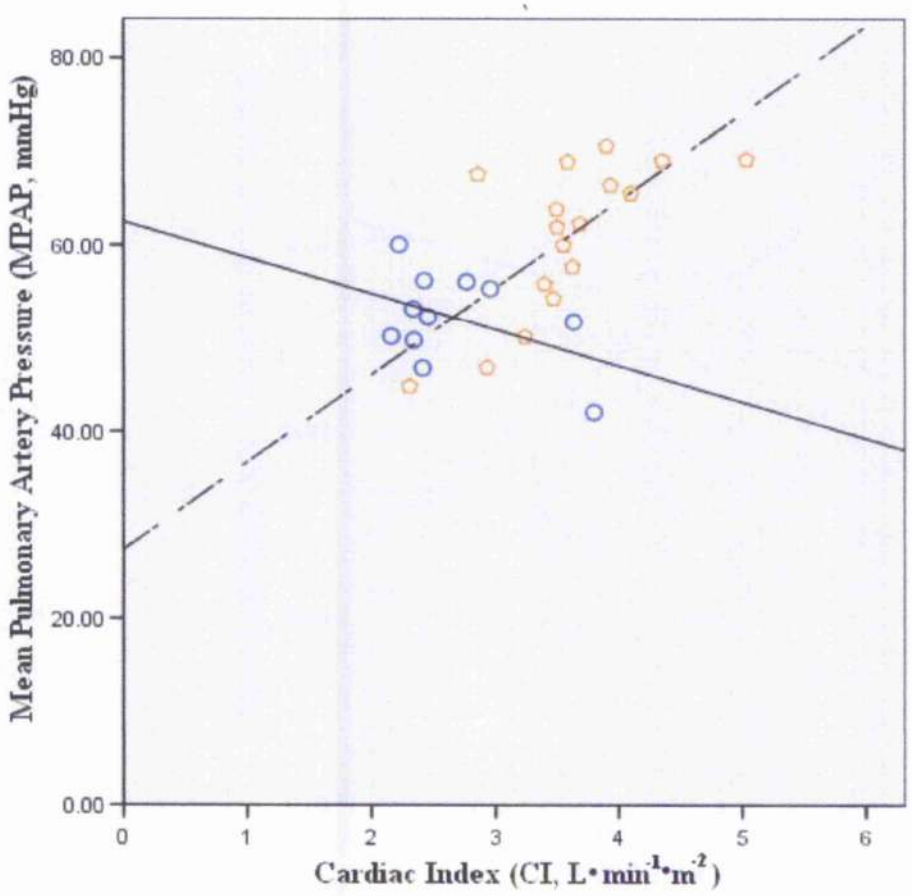


Figure 7.2c: Shows the linear regression plot of paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of subject 31 of differing posture. A blue circle indicates the air plots taken whilst supine and, an orange pentagram for the air plots taken whilst semi-erect. The continuous line is the line of regression for the air plots, whilst supine the evenly broken dashed line whilst semi-erect.

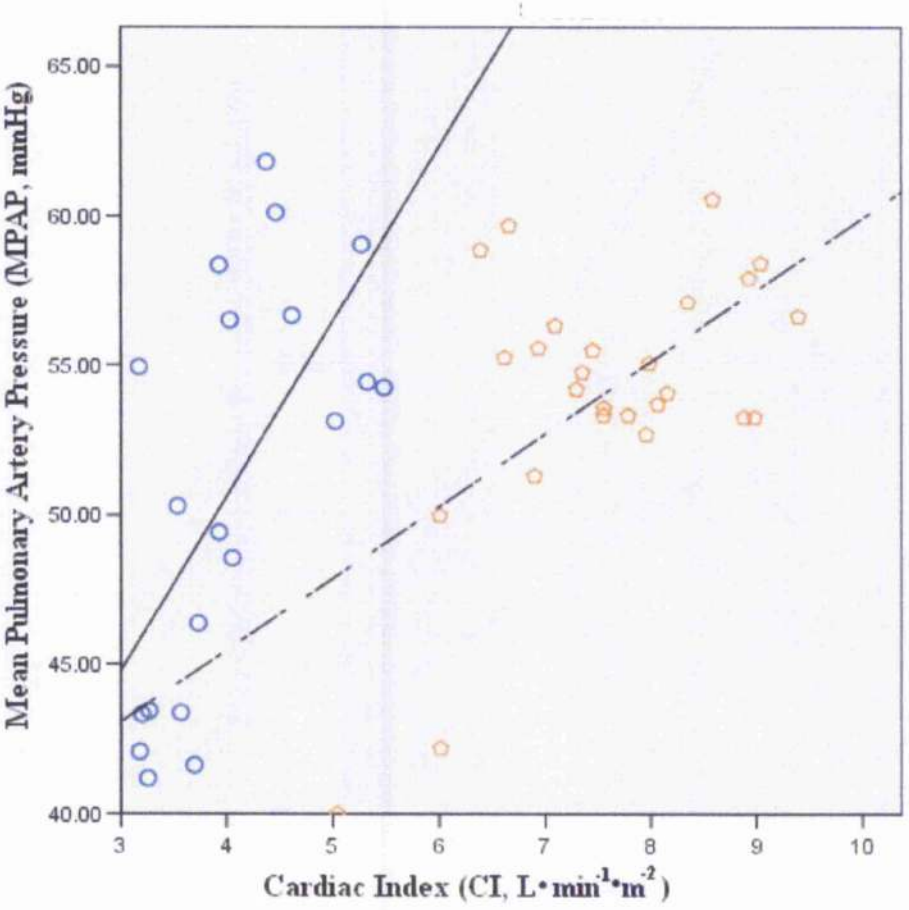


Figure 7.2d: Shows the linear regression plot of paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, of subject 36 of differing posture. A blue circle indicates the air plots taken whilst supine and, an orange pentagram for the air plots taken whilst semi-erect. The continuous line is the line of regression for the air plots, whilst supine the evenly broken dashed line whilst semi-erect.

SUBJECT	POSTURE		Constants of slope or intercept	Sig.	95% Confidence Interval for B	
					Lower Bound	Upper Bound
POOLED	SUPINE	Intercept	5.361	0.002	2.016	8.706
		Slope	9.026	<0.001	8.195	9.857
	SEMI-ERECT	Intercept	-1.457	0.313	-4.301	1.388
		Slope	7.606	<0.001	7.11	8.103
1	SUPINE	Intercept	-6.569	0.215	-17.394	4.255
		Slope	5.745	<0.001	3.635	7.854
	SEMI-ERECT	Intercept	-8.782	0.053	-17.694	0.129
		Slope	5.168	<0.001	4.029	6.308
21	SUPINE	Intercept	-6.714	0.067	-13.970	0.541
		Slope	12.165	<0.001	9.916	14.414
	SEMI-ERECT	Intercept	-8.782	0.053	-17.694	0.129
		Slope	6.830	<0.001	5.324	8.336
31	SUPINE	Intercept	60.677	<0.001	43.662	77.692
		Slope	-3.380	0.258	-9.661	2.901
	SEMI-ERECT	Intercept	27.400	0.008	8.437	46.363
		Slope	9.339	0.002	4.121	14.558
36	SUPINE	Intercept	28.879	<0.001	15.559	42.198
		Slope	5.422	0.002	2.263	8.580
	SEMI-ERECT	Intercept	35.819	<0.001	24.575	47.063
		Slope	2.413	0.002	0.942	3.883

Table 7.2: Slope, intercept of the linear regression equation for each study, as well as the standard errors and significance and confidence interval for each value, supine and erect, for pooled data of and individual subjects

SUBJECT	POSTURE	Linear regression			test of deviation from linearity	
		F	Sig.	R^2	F	Sig.
POOLED	SUPINE	470.066	<0.001	0.689	1.406	0.413
	ERECT	921.037	<0.001	0.689	5.523	0.031
1	SUPINE	33.683	<0.001	0.692	7.427	0.281
	ERECT	84.270	<0.001	0.689	2.474	0.329
21	SUPINE	131.446	<0.001	0.891	2.439	0.253
	ERECT	84.270	<0.001	0.689		
31	SUPINE	1.438	0.258	0.126		
	ERECT	14.550	0.002	0.492	2.439	0.253
36	SUPINE	12.818	0.002	0.391		
	ERECT	11.471	0.002	0.323	1.130	0.570

Table 7.3: Linear regression statistics, standardised residual statistics and test of linearity statistics, supine and erect, for pooled data of and individual subjects

study	F (supine vs semi-erect)	Sig.(supine vs semi-erect)
POOLED	9.062	0.003
1	0.175	0.677
21	17.44	<0.001
31	10.33	0.003
36	3.767	0.059

Table 7.4.: F values and significance for comparison of slopes of equations produced by linear regression analysis supine and erect, for pooled data of and individual subjects

7.4. Discussion

In all but one of the subjects, as well as in the pooled result, the slope pulmonary pressure flow response supine was greater than the slope erect. However the critical closing pressure (the slopes' intercept) was reduced in the semi-erect position. The latter change was expected, as when a human subject is erect, the left atrial pressure, initially is lower than then the supine pressure (Reeves, J. T. et al 1988). However, in an analysis of pooled data of other studies performed by Reeves et al (1988), found that although the pulmonary artery pressure starts at a lower level when at rest semi-erect, the rate of increase thereafter (the slope of the P-Q plot or the true resistance) in young healthy subjects is actually equal in both the supine and semi-erect exercise (Reeves, J. T. et al 1988). The subjects for which the semi-erect data was analysed were not all fit and young subjects (Bevegard, S. et al 1963; Groves, B. M. et al 1987; Reeves, J. T. et al 1987). In this study, of the 4 subjects tested, the results were not as expected. A possible explanation for this is that the type of supine exercise performed was different to that performed in other studies (straight leg raising, as opposed to supine bicycle ergometry), and that the inhalation of air at rest in this study was through a gas delivery system. Both of these changes may have combined to increase intrathoracic pressure. If this increase in intrathoracic pressure resulted in a steady increase in alveolar pressure, the result might be a continual rise in the outflow pressure, and a continual rise in the total or mean pulmonary artery pressure.

Another source of error may have been the method used to monitor cardiac output, namely the Physioflow (Manatec, France) thoracic impedance device. This however has been validated in both COPD, and normal subjects at rest and in chapter 3,

demonstrating changes in cardiac output in an individual with pulmonary hypertension adequately. Another possible explanation is the heterogeneity of the disease group, and degrees of pulmonary hypertension. The slope of the only normal subject, was as expected, but that of the other 3 subjects, with COPD, CTEPH, and PVH, varied, with the former having a more shallow slope whilst supine and the latter two subjects, having more shallow slopes whilst semi-erect.

The purposes of performing this study, namely comparing the differences in slope produced with varying posture in different disease groups, and comparing the slope and intercept of these produced pressure and flow plots, with variables obtained from cardiopulmonary exercise testing, was not able to be investigated, due to the relatively low number of studies achieved. This was because this study was the final investigation of a week of clinical and research procedures in subjects who were already feeling tired and ill. It may be possible however, by removing other parts of the studies performed on each of these subjects, to recruit greater numbers in the future, and complete this study in the future.

Chapter 8

Pressure -Flow plots:
Use of Dobutamine as a Surrogate for Exercise.

8.1. Introduction

Traditionally, the main method of assessing haemodynamically the success of any treatment in subjects with pulmonary hypertension was to review the changes to pulmonary vascular resistance, mean pulmonary artery pressure, and cardiac output. This is satisfactory if all three components improve, but may be misleading under other circumstances. As previously discussed, an increase in cardiac output, may lead to a small passive increase in mean pulmonary artery pressure, and an apparent decrease in pulmonary vascular resistance as traditionally calculated. This would erroneously then suggest that a pharmacological agent had led to some vasodilation of the pulmonary vascular circulation, when in effect its only real effect was to increase cardiac output, (McGregor, M. et al 1985).

A more sound way of assessing the effects on the pulmonary circulation, would be to plot the pressure -flow plots of a series of paired data of mean pulmonary artery pressure and cardiac output (or index) produced by altering the flow through the lungs (Castelain, V. et al 2002; Harris, P. et al 1968; Janicki, J. S. et al 1985).

There are several possible methods to achieve this. Traditionally, extra-corporal membrane oxygenation (ECMO) by-pass has been used in children in a clinical context. This is no longer in regular clinical use. Another method would be to measure the pressure and flow before and after obstructing one of the two main branches of the pulmonary arteries (right or left) and effectively doubling the flow through the other artery (Lategola, M. T. 1958). With regards to subjects with pulmonary hypertension, such a sudden rise in pulmonary artery pressure may be dangerous, and might have catastrophic haemodynamic consequences.

The final two options used are to increase cardiac output from the heart, either pharmacologically or via exercise (Kafi, S. A. et al 1998). The latter has seen numerous experimental studies in humans (Castelain, V. et al 2002; Janicki, J. S. et al 1985; Reeves, J. T. et al 1988), but as shown earlier in chapter 4, is unlikely to be useful in an individual basis for the majority of patients.

Dobutamine has been used in a number of experimental animal and human studies (Ducas, J. et al 1992; Furman, W. R. et al 1982; Hyman, A. L. et al 1985; Lejeune, P. et al 1987b; Lejeune, P. et al 1987a; Light, R. B. et al 1988; Naeije, R. et al 1994; Pagnamenta, A. et al 2003). It is the intention of this study, to examine the feasibility of dobutamine as an alternative to exercise, to produce pressure flow plots in a clinical context, and to examine any differences to pressure flow plots produced by this method, and by exercise.

8.2. Method

8.2.1. Patient group & Ethics

The study was approved by the ethics committee of the West Glasgow's NHS trust, and informed consent was obtained from all the patients. Subjects were recruited from all patients attending the Scottish Pulmonary Vascular Unit (SPVU) between January 2003 and July 2003, for invasive investigations. Five consecutive patients consented (2 males and 3 females) (Table 8.1). The mean age (± S.D.) of the studied subjects was 55.2 years (± 12.6), but the age ranged from 40 to 73. One turned out to be a normal subject, three had idiopathic pulmonary arterial hypertension (IPAH) and one pulmonary hypertension secondary to connective tissue disorder (CTD). Three had more than a 20% drop in pulmonary vascular resistance (PVR) to nitric oxide (NO, a pulmonary vasodilator), one did not, and one was not studied. Mean pulmonary artery pressure (MPAP) ranged from 8 mmHg to 79 mmHg, with a mean (± S.D.) of 48.6 (± 24.5) mmHg. The range, mean and 95% confidence intervals for the other measured values were, right atrial pressure, 1 to 14 mmHg, mean 7.6 (± 4.5) mmHg, pulmonary artery wedge pressure 5 to 15 mmHg with a mean of 11.0 ± 4.1 mmHg and PVR, ranging from 0.5 to 20 $\mathbf{mmHg \bullet min \bullet L^{-1}}$ with a mean of 9.9 ± 6.6.

Subject Number	Initials	MPAP	SPAP	DPAP	RAP	PAWP	CO	PVR	Age	Sex	Diagnosis	Vasodilator Response
		(mmHg)					$L.min^{-1}$	mmHg / $L.min^{-1}$)				
2	I,C	8	14	2	1	14	3.7	0	40	F	normal	
5	G,C	57	91	37	6	7	4.6	9	50	M	IPAH	N
6	W,F	79	137	48	11	14	3.3	20	67	M	IPAH	Y
7	E,M	63	115	23	14	15	3.7	13	73	F	IPAH	Y
15	I,P	36	62	17	6	5	4.4	7	46	F	CTD	Y
Mean		58.8	101.3	31.3	9.3	10.3	3.9	12.3	55.2			
S.D.		24.6	43.2	15.8	4.5	4.5	1.0	8.2	16.0			

Table 8.1: List of subjects who received a 10 minute dobutamine infusion, at a rate of 5 micrograms per kg weight per minute for 5 minutes, and then at a rate of 10 micrograms per kg weight per minute for 5 minutes whilst inhaling air or a nitric oxide/ oxygen combination through a gas delivery system.

8.2.2. Equipment and Experiments

Initial haemodynamic evaluation was performed with the patient supine and breathing room air, according to our standard protocol as described in chapter 2.3. The inhaled gas was delivered to the patient, as described in chapter 2.5.1, and shown in Figures 2.14 a-c and Figure 4.1. The right heart catheter (Gaeltec, Dunvegan, Isle of Skye), its insertion storage and processing are described in chapter 2.1. Cardiac output was measured non-invasively by thoracic electrical bioimpedance (PhysioFlow 1, Manatec, France) as described in chapter 2.2 and the pulmonary pressure and cardiac output data combined as in chapter 2.5. Between 41-45 sets, [mean (± S.D.) of 43 (± 1.6), on air and with the nitric oxide oxygen combination, mean (± S.D.) 42.6 (± 0.55)] of paired of data were collected at rest (4 sets) and during the dobutamine intravenous infusion, on each subject. The infusion lasted for a maximum of 10 minutes. All subjects had almost full resting haemodynamics performed within 24 hours of the exercise test during routine right heart catheterization with a swan-gantz catheter, when MPAP, PWCP and CO were initially measured.

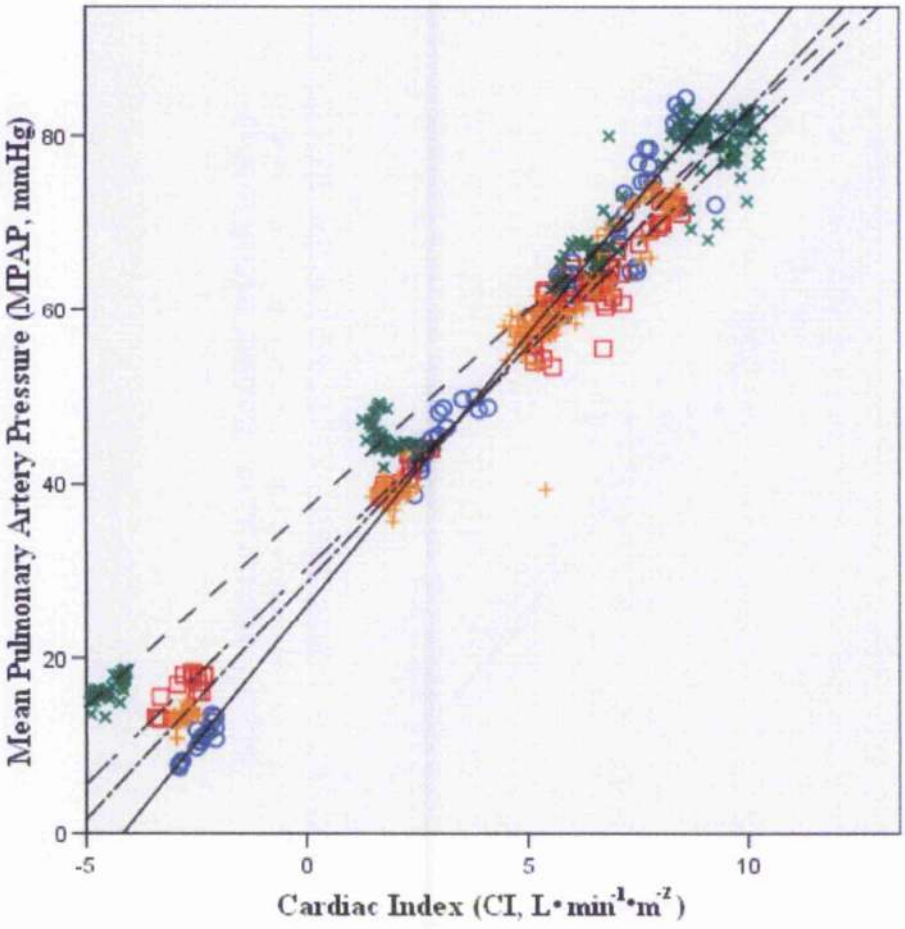
The exercise protocol was performed as described in chapter 2.3 The number of data plots collected for the exercise part of the study ranged between 10-16 sets, [mean (± S.D.) of 13.4 (± 2.8), on air and with the nitric oxide oxygen combination, mean (± S.D.) of 14.8 (± 1.8)]. The nitric oxide was supplied as previously described (chapter 4.2, figure 4.1).

8.2.3. Analysis

Analysis of the data obtained was performed using the SPSS 13.0 package as described in chapter 2.7.

8.3 Results

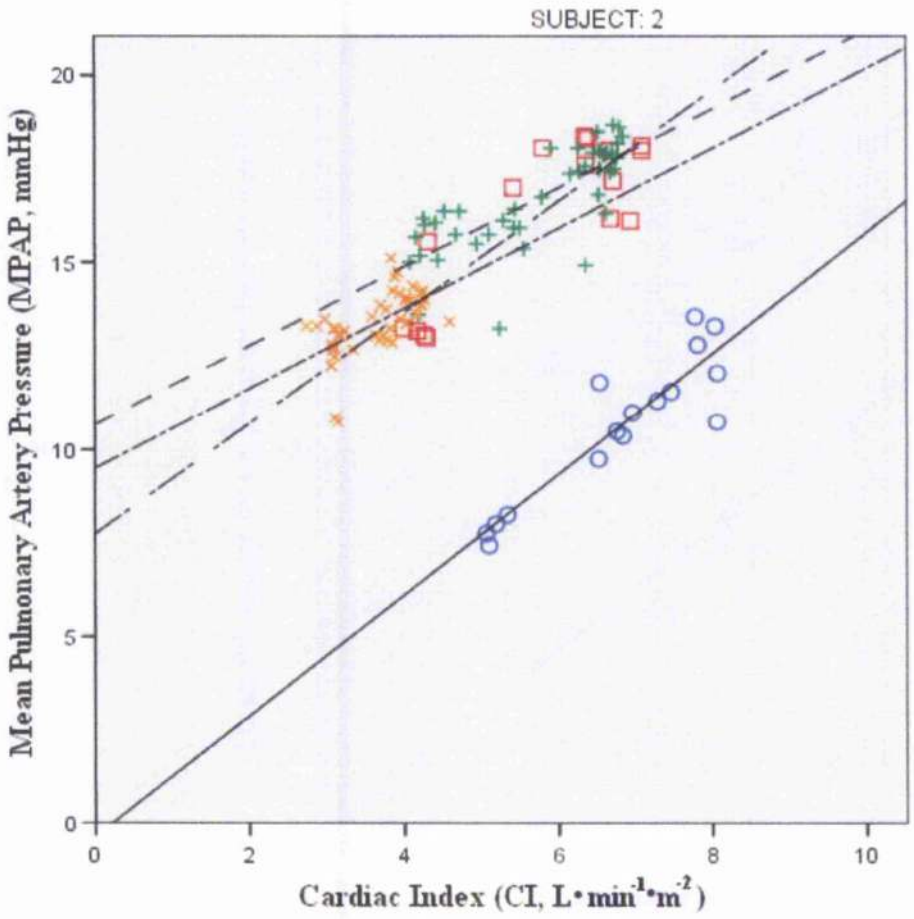
The results of the study, was variable in individual subjects. In the pooled data, the slope of the regression line was greatest in the study, if inhaling air (6.23 with 95% confidence intervals of 6.0-6.42). As expected, the slope of the NO/O_2 pooled study



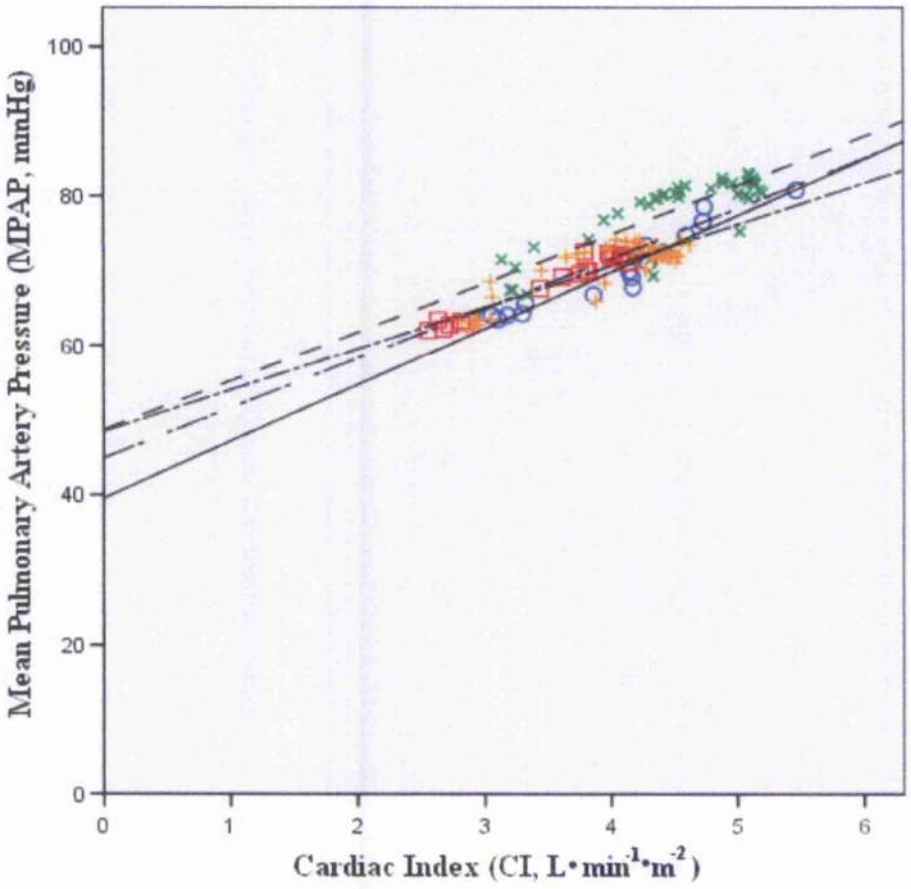
Figures 8.1: Shows the linear regression plot of all the pooled paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, or during a 10 minute intravenous dobutamine infusion (of 5-10 micrograms/kg/min). A blue circle indicates the exercise inhaling air plots, a red square for the exercise inhaling nitric oxide and oxygen inhalation plots (NO/O_2, 40-80 ppm and 15L respectively), with an unbroken line, and a long and short broken line with wide gaps, representing the lines of regression respectively. A green cross indicates a plot of dobutamine whilst inhaling air, and an orange plus, dobutamine whilst inhaling the NO/O_2 combination, with lines of regression respectively given by a broken line and by a line with long and short breaks and small gaps.

during exercise was shallower (lower resistance), with a value of 4.97 (95% confidence interval of 4.84-5.09). However, the slopes of the dobutamine pressure-flow lines were not as expected. The air inhalation pooled data had a slope of 4.54 (95% confidence interval of 4.47-4.62), which indicated that it had the lowest resistance of all the studies. The slope of the NO/O_2 inhalation dobutamine group was 5.42 (95% confidence interval of 5.35-5.50) (Figure 8.1, Tables 8.2). Comparison of the slopes by ANCOVA analysis found that there was a significant difference between the slopes of the air studies (exercise versus dobutamine, F 290, P<0.001), the NO/O_2 studies (exercise versus dobutamine, F = 38, P <0.001), and between the studies of dobutamine (air versus NO/O_2 slope, F = 218, P<0.001)(Table 8.2). Other analyses were not performed.

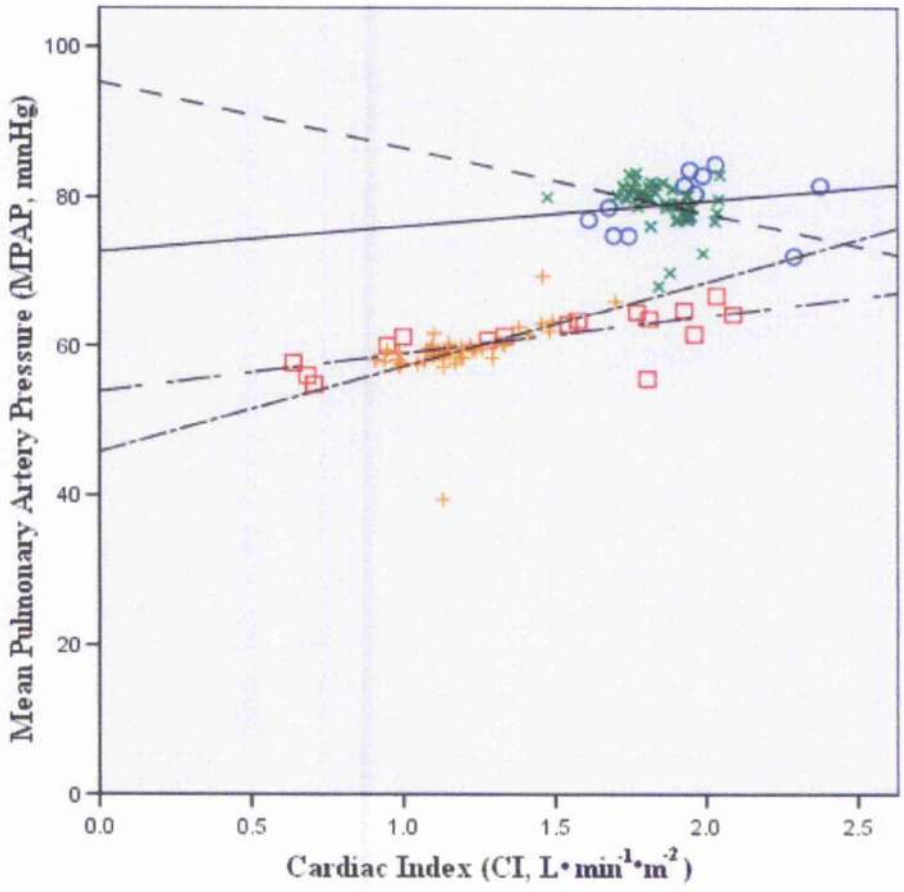
The results of the individual subjects were more variable (Figures 8.2 a-e, and Table 8.2). In four subjects, the slopes of the dobutamine infusion studies were lower than the exercise study, (Table 8.2, figures 8.2a, b, d, e) (statistically true by ANCOVA analysis in 6 out of these 8 comparisons, Table 8.3). In two subjects, 5 & 11 (Figures 8.2c & e), the pressure – flow slope was found to be negative for the inhalation of air whilst receiving dobutamine. Conversely, in subject 5, the NO/O_2 & dobutamine pressure-flow slope was significantly steeper (11.42, with a 95% confidence interval of 5.08-17.76) compared to the other studies in that subject (Table 8.2).



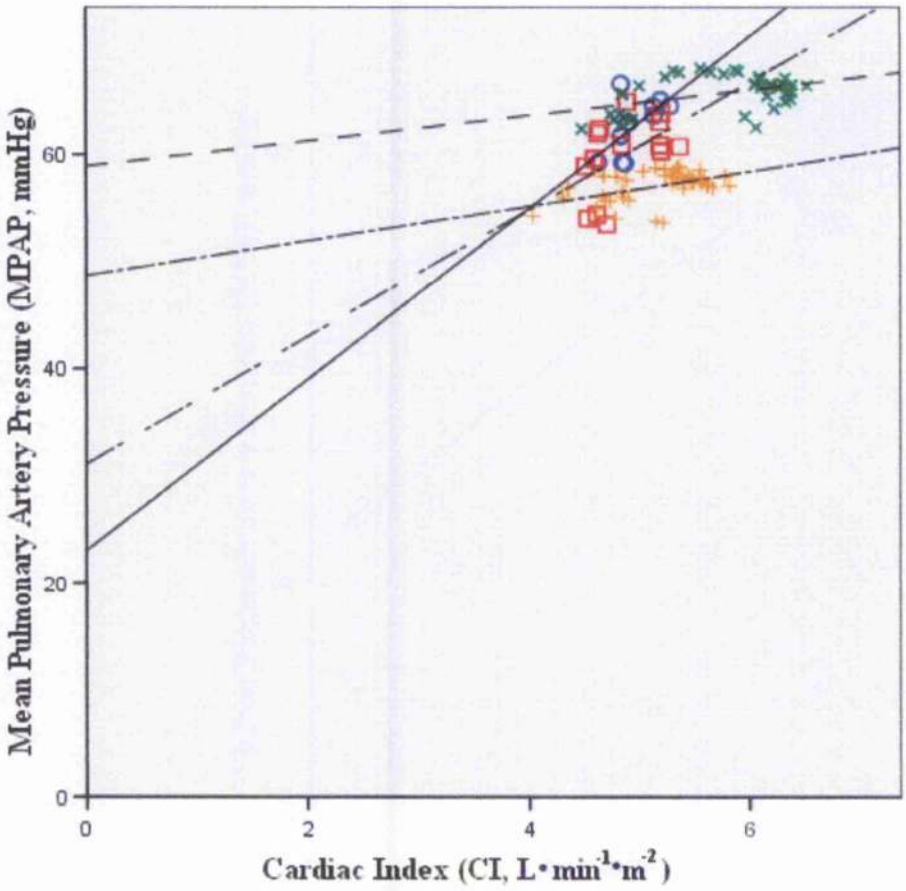
Figures 8.2a: Shows the linear regression plot of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, or during a 10 minute intravenous dobutamine infusion (of 5-10 micrograms/kg/min), in subject 2. A blue circle indicates the exercise inhaling air plots, a red square for the exercise inhaling nitric oxide and oxygen inhalation plots (NO/O_2, 40-80 ppm and 15L respectively), with an unbroken line, and a long and short broken line with wide gaps, representing the lines of regression respectively. A green cross indicates a plot of dobutamine whilst inhaling air, and an orange plus, dobutamine whilst inhaling the NO/O_2 combination, with lines of regression respectively given by a broken line and by a line with long and short breaks and small gaps.



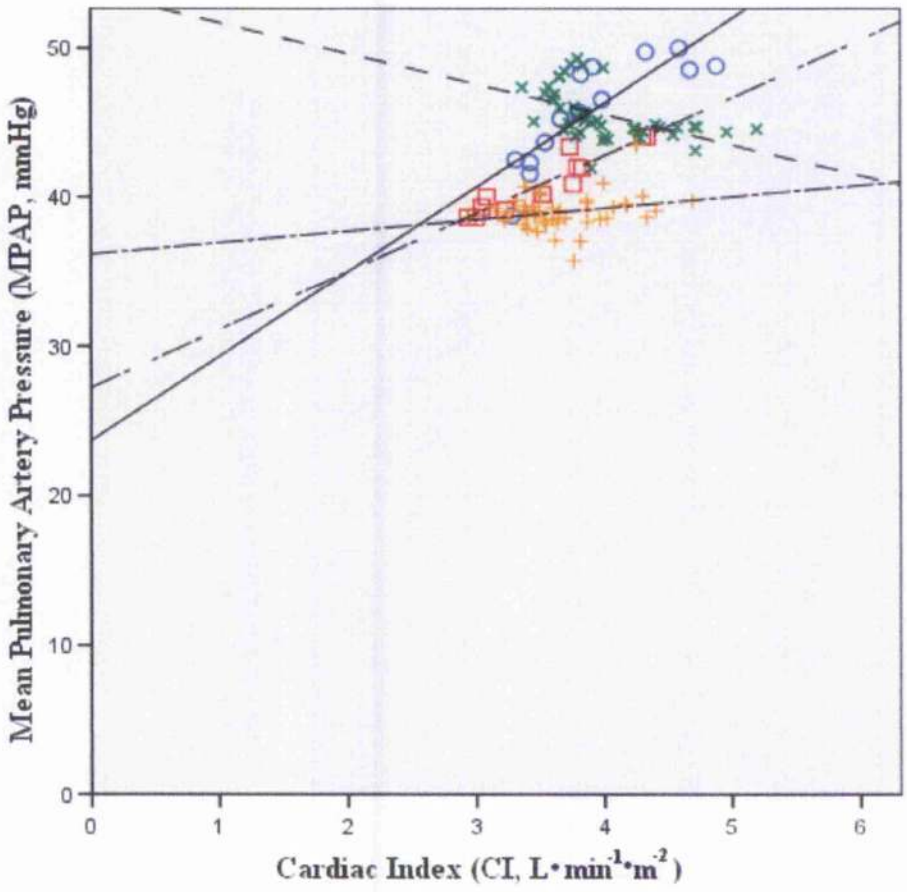
Figures 8.2b: Shows the linear regression plot of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, or during a 10 minute intravenous dobutamine infusion (of 5-10 micrograms/kg/min), in subject 5. A blue circle indicates the exercise inhaling air plots, a red square for the exercise inhaling nitric oxide and oxygen inhalation plots (NO/O_2, 40-80 ppm and 15L respectively), with an unbroken line, and a long and short broken line with wide gaps, representing the lines of regression respectively. A green cross indicates a plot of dobutamine whilst inhaling air, and an orange plus, dobutamine whilst inhaling the NO/O_2 combination, with lines of regression respectively given by a broken line and by a line with long and short breaks and small gaps.



Figures 8.2c: Shows the linear regression plot of paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, or during a 10 minute intravenous dobutamine infusion (of 5-10 micrograms/kg/min), in subject 6. A blue circle indicates the exercise inhaling air plots, a red square for the exercise inhaling nitric oxide and oxygen inhalation plots (NO/O_2, 40-80 ppm and 15L respectively), with an unbroken line, and a long and short broken line with wide gaps, representing the lines of regression respectively. A green cross indicates a plot of dobutamine whilst inhaling air, and an orange plus, dobutamine whilst inhaling the NO/O_2 combination, with lines of regression respectively given by a broken line and by a line with long and short breaks and small gaps.



Figures 8.2d: Shows the linear regression plot of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, or during a 10 minute intravenous dobutamine infusion (of 5-10 micrograms/kg/min), in subject 7. A blue circle indicates the exercise inhaling air plots, a red square for the exercise inhaling nitric oxide and oxygen inhalation plots (NO/O_2, 40-80 ppm and 15L respectively), with an unbroken line, and a long and short broken line with wide gaps, representing the lines of regression respectively. A green cross indicates a plot of dobutamine whilst inhaling air, and an orange plus, dobutamine whilst inhaling the NO/O_2 combination, with lines of regression respectively given by a broken line and by a line with long and short breaks and small gaps.



Figures 8.2e: Shows the linear regression plot of the paired data of cardiac index (CI, L min^{-1} m^{-2}) and mean pulmonary artery pressure (MPAP, mmHg) produced during exercise, or during a 10 minute intravenous dobutamine infusion (of 5-10 micrograms/kg/min), in subject 15. A blue circle indicates the exercise inhaling air plots, a red square for the exercise inhaling nitric oxide and oxygen inhalation plots (NO/O_2, 40-80 ppm and 15L respectively), with an unbroken line, and a long and short broken line with wide gaps, representing the lines of regression respectively. A green cross indicates a plot of dobutamine whilst inhaling air, and an orange plus, dobutamine whilst inhaling the NO/O_2 combination, with lines of regression respectively given by a broken line and by a line with long and short breaks and small gaps.

It can be seen from figure 8.3, that the cardiac output increase for the individual subjects, whilst receiving dobutamine, was variable. In subjects 15 (whilst inhaling air) and 7 (whilst inhaling NO/O_2) it may have actually decreased in the 1st minute following the commencement of the dobutamine infusion, before subsequently increasing (figure 8.3). Taking the last minute of the dobutamine infusion to represent the maximal increase in Cardiac index (CI), the mean (± S.D.) increase in, as a percentage of baseline was 137 (± 19) % for air (range 116-161) and 135 (± 14) % for NO/O_2 (range 118-154). More startling, was the relatively little increase in mean pulmonary artery pressure (MPAP), the mean (± S.D.) for dobutamine whilst inhaling air was 106 (± 14) %, (range 90-123), and whilst inhaling NO/O_2 107 (± 7) %, (range 103-115). There was no statistically difference between the percentage increases in the air and the nitric oxide/ oxygen for neither CI nor MPAP. There was also no statistical difference between the percentage MPAP pressure increase and baseline MPAP. The response to dobutamine in the individual subjects with respect to MPAP was again variable. Subject 15 has an apparent decrease in MPAP initially in both studies, followed in the NO/O_2 with a late increase. Subject 5, seemed to initially have an increase in MPAP, but later, this was followed by a decrease. Subject 4 had an early and large increase in MPAP under both studies. Subject 2 has either a steady or late increase in MPAP under both studies, and in subject 7, the MPAP seemed relatively static. (Figure 8.3)

SUBJECT	PHARMACOLOGY		Constants of slope or Intercept	Sig.	95% Confidence Interval for B	
					Lower Bound	Upper Bound
POOLED	AIR	Intercept	25.97	<0.001	24.90	27.04
		Slope	6.23	<0.001	6.04	6.42
	NO/O2	Intercept	30.35	<0.001	28.67	31.02
		Slope	4.97	<0.001	4.84	5.09
	DOBUTAMINE & AIR	Intercept	37.15	<0.001	36.63	37.68
		Slope	4.54	<0.001	4.47	4.62
	DOBUTAMINE & NO/O2	Intercept	28.67	<0.001	28.27	29.07
		Slope	5.42	<0.001	5.35	5.50
2	AIR	Intercept	-0.35	0.801	-3.23	2.54
		Slope	1.62	<0.001	1.20	2.03
	NO/O2	Intercept	7.74	<0.001	4.54	10.93
		Slope	1.48	<0.001	0.94	2.03
	DOBUTAMINE & AIR	Intercept	10.67	<0.001	9.01	12.33
		Slope	1.05	<0.001	0.77	1.34
	DOBUTAMINE & NO/O2	Intercept	9.50	<0.001	7.83	11.17
		Slope	1.07	<0.001	0.61	1.52
5	AIR	Intercept	39.55	<0.001	34.12	44.98
		Slope	7.56	<0.001	6.23	8.88
	NO/O2	Intercept	44.85	<0.001	42.12	47.58
		Slope	6.69	<0.001	5.92	7.45
	DOBUTAMINE & AIR	Intercept	48.62	<0.001	42.98	54.27
		Slope	6.55	<0.001	5.30	7.80
	DOBUTAMINE & NO/O2	Intercept	48.40	<0.001	44.27	52.54
		Slope	5.55	<0.001	4.52	6.58

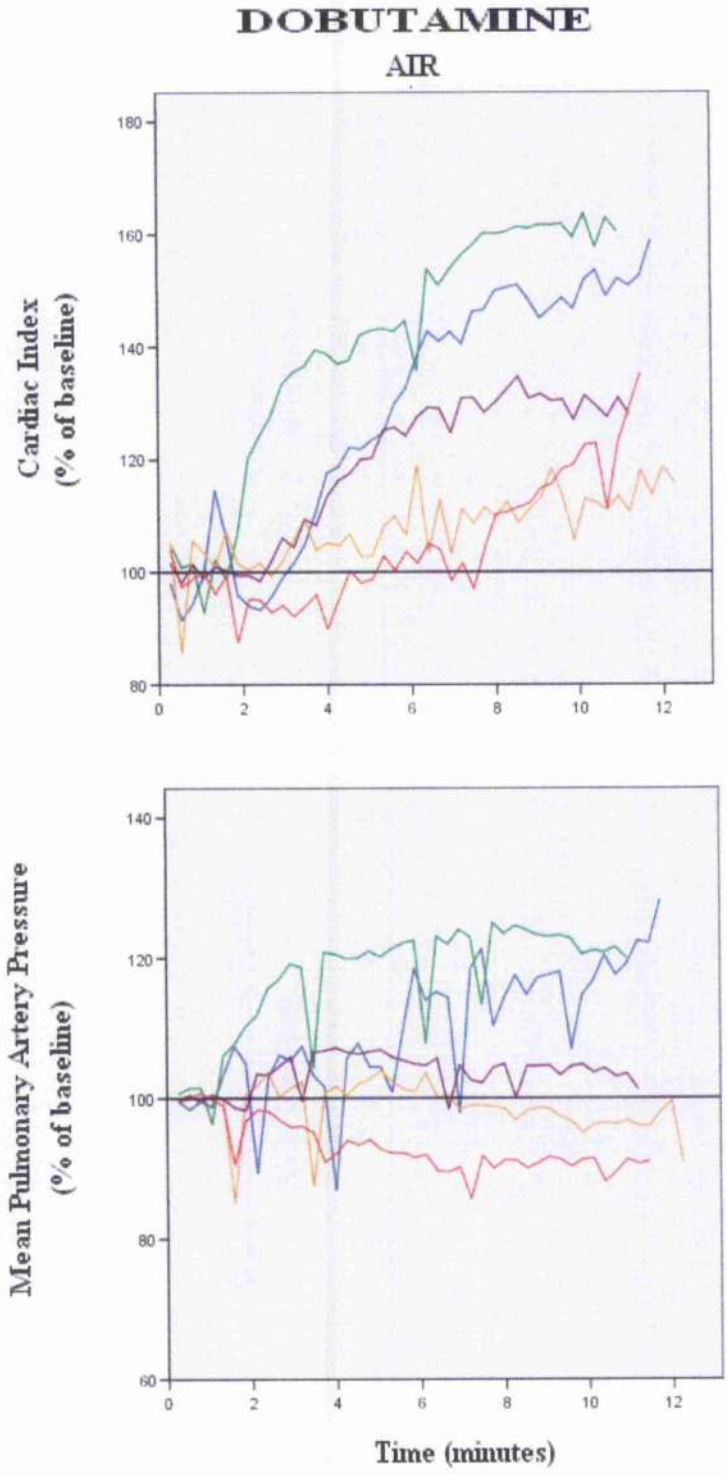
Table 8.2a: Slope, intercept of the linear regression equation for each subject and study, as well as the standard errors and significance and confidence interval for each value, supine, for pooled data of and individual subjects during exercise, or during a 10 minute intravenous dobutamine infusion (of 5-10 micrograms/kg/min), whilst inhaling air or the nitric oxide/ oxygen combination

SUBJECT	PHARMACOLOGY		Constants of slope or intercept	Sig.	95% Confidence Interval for B	
					Lower Bound	Upper Bound
6	AIR	Intercept	72.72	<0.001	48.84	96.60
		Slope	3.38	0.548	-8.89	15.66
	NO/O2	Intercept	53.90	<0.001	49.64	58.16
		Slope	5.06	0.002	2.27	7.85
	DOBUTAMINE & AIR	Intercept	92.19	<0.001	80.02	104.35
		Slope	-1.43	0.034	-2.76	-0.11
	DOBUTAMINE & NO/O2	Intercept	45.79	<0.001	38.20	53.39
		Slope	11.42	0.001	5.08	17.76
7	AIR	Intercept	23.03	0.072	-2.24	48.30
		Slope	7.98	0.004	2.90	13.06
	NO/O2	Intercept	31.13	0.004	10.71	51.55
		Slope	5.92	0.007	1.73	10.11
	DOBUTAMINE & AIR	Intercept	58.91	<0.001	54.55	63.27
		Slope	1.18	0.003	0.42	1.93
	DOBUTAMINE & NO/O2	Intercept	48.66	<0.001	43.95	53.37
		Slope	1.62	0.001	0.72	2.53
15	AIR	Intercept	23.66	<0.001	14.95	32.37
		Slope	5.66	<0.001	3.45	7.87
	NO/O2	Intercept	27.22	<0.001	23.64	30.79
		Slope	3.89	<0.001	2.89	4.89
	DOBUTAMINE & AIR	Intercept	53.75	<0.001	49.22	58.28
		Slope	-2.05	0.001	-3.17	-0.93
	DOBUTAMINE & NO/O2	Intercept	36.18	<0.001	32.62	39.74
		Slope	0.77	0.114	-0.19	1.73

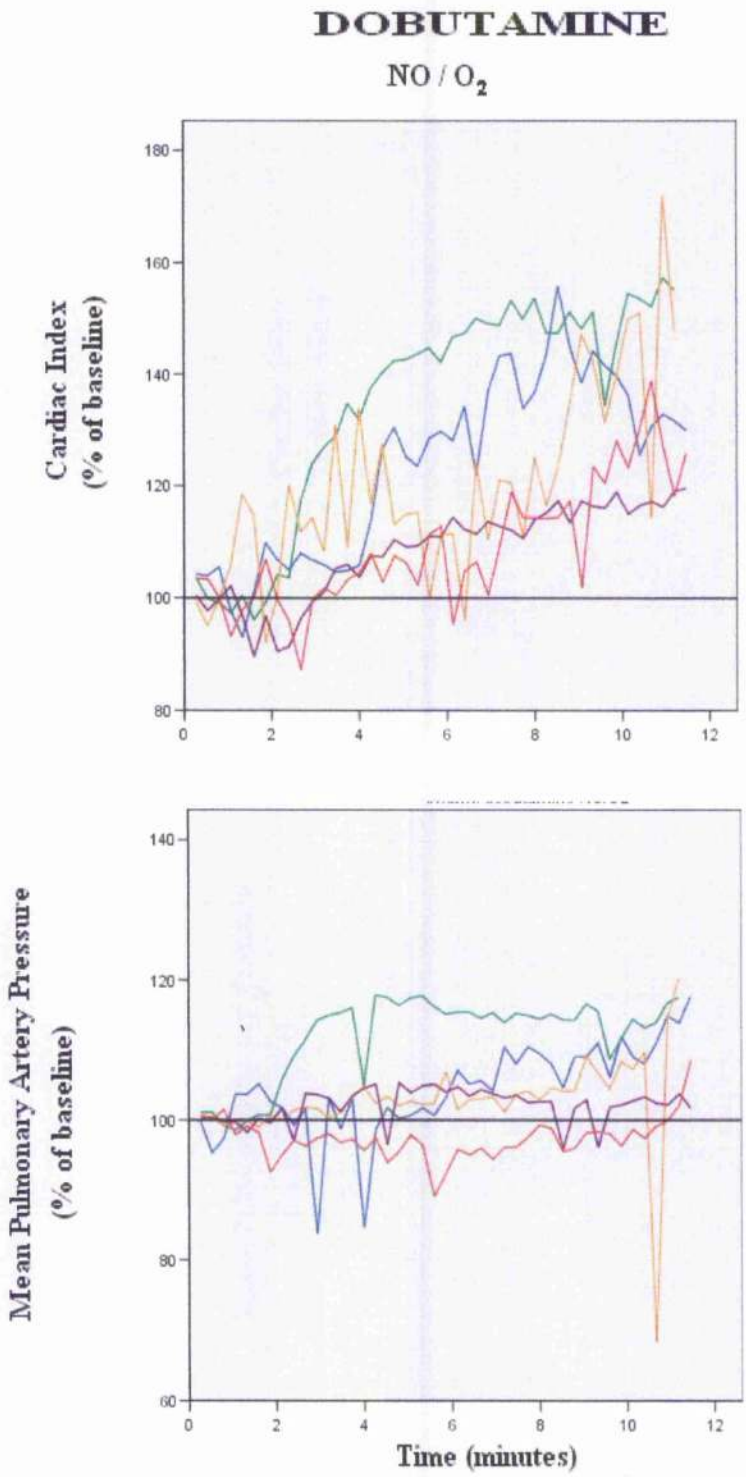
Table 8.2b: Slope, intercept of the linear regression equation for each subject and study, as well as the standard errors and significance and confidence interval for each value, supine, for pooled data of and individual subjects during exercise, or during a 10 minute intravenous dobutamine infusion (of 5-10 micrograms/kg/min), whilst inhaling air or the nitric oxide/ oxygen combination

STUDY	F (AIR:Exercise vs dobutamine)	Sig.(AIR:Exercise vs dobutamine)	F (NO/O2:Exercise vs dobutamine)	Sig. (NO/O2:Exercise vs dobutamine)	F (Dobutamine: air vs NO/O2)	Sig. (Dobutamine:air vs NO/O2)
Pooled	290.50	<0.001	38.30	<0.001	218.40	<0.001
2	5.30	0.025	1.60	0.211	<0.001	0.966
5	8.97	0.004	3.35	0.073	1.50	0.225
6	6.86	0.011	2.86	0.096	18.80	<0.001
7	7.79	0.008	11.83	0.001	0.54	0.465
15	54.64	<0.001	14.98	<0.001	14.40	<0.001

Table 8.3.: F values and significance for comparison of slopes of equations produced by linear regression analysis, for pooled data of and individual subjects in the dobutamine study



Figures 8.3a: Shows the plot of the mean pulmonary artery pressure (MPAP, %) and cardiac index (CI, %) from baseline (64 seconds resting values or pre-infusion values) against time, produced during a dobutamine infusion (5-10 micrograms/kg/min), of the individual subjects whilst inhaling air. The blue line represents for subject 2, the green line subject 5, orange line subject 6, purple line subject 7 and the red line subject 15.



Figures 8.3b: Shows the plot of the mean pulmonary artery pressure (MPAP, %) and cardiac index (CI, %) from baseline (64 seconds resting values or pre-infusion values) against time, produced during a dobutamine infusion (5-10 micrograms/kg/min), of the individual subjects whilst inhaling NO/O_2 (40-80 ppm/15L respectively) on the right. The blue line is for subject 2, the green line for subject 5, orange line for subject 6, purple line for subject 7 and the red line for subject 15.

8.4. Discussion

Over the past two decades, the inadequacies of our current clinical investigation of the pulmonary circulation have become apparent. The in-vivo investigation that would give the most information with regards to the pulmonary vasculature would be investigations to determine pulmonary impedance. As this requires surgically implanted devices, it is difficult to determine in humans, and is impractical in a clinical context. Thus, the next level of information would be to obtain more about the non-pulsatile component of the pulmonary circulation.

It has been shown that pressure-flow plots avoid the errors generated in reviewing PVR and other static haemodynamic parameters, in assessing the state of dilatation and compliance of the pulmonary vasculature. Castelain et al (2002) found that in IPAH, those patients in whom there was no improvement in conventional haemodynamic measurements 3 month after commencement of intravenous prostacyclin, showed changes in pressure-flow gradients. This, they speculated, may account for the improved exercise tolerance found in this group. As demonstrated in chapter 6, the pressure flow response to vasodilators may be different in responders as opposed to non-responders.

The majority of pressure flow plots produced in recent years in man, were produced by exercise or by the artery occlusion technique. They have investigated subjects with heart failure, ischaemic heart disease, idiopathic pulmonary hypertension, connective tissue disorders, pulmonary embolic disease and normals (Castelain, V. et al 2002; Janicki, J. S. et al 1985; Reeves, J. T. et al 1988). They also pooled data obtained from several subjects to obtain their conclusions. However, studies have not been performed to discover changes in individual subjects. Our study of 24 subjects who were being

investigated for pulmonary hypertension, demonstrated that for individuals, pressure-flow plots produced by exercise are impractical, due to the poor success of achieving linearity and the wide confidence intervals for slopes and intercepts. Although changes in the exercise protocol and in the cardiac output measuring system might improve this, many of the subjects had significantly reduced exercise ability and this would lead to inadequate clinical test for these individuals.

Dobutamine is an ionotropic agent that has been in use since the 70's. It has combined alpha and beta adrenoreceptor activity. Alpha receptors and ß receptors are found in the peripheral systemic vasculature, and it seems that at standard doses the effects of dobutamine on the systemic vasculature seems to cancel itself out. Its main effect is on the beta-$_1$ receptors in the myocardium (Leier, C. V. et al 1983) and leads to increase myocardial contractility (Vatner, S. F. et al 1972; Vatner, S. F. et al 1974). It is often used in cardiac patients in order to increase cardiac output. With regards to the pulmonary circulation, receptors are present, but are not thought to have any clinical relevance.

This study used dobutamine as an alternative mechanism for producing pressure-flow plots. As with other studies in animals using dobutamine (Pagnamenta, A. et al 2003), we found that the steepness of the slopes of the recto-linear plots produced by the use of dobutamine rather than exercise, varied significantly between subjects. However, where there was a change in slope seen after inhaling a NO/O2 combination during exercise, this was only replicated in only two of the five subjects, during the dobutamine infusion.

The differences in the slopes produced from dobutamine as compared to exercise may be due to several reasons. It may be that during exercise autonomic stimulation actually has an effect on the pulmonary circulation. There is some evidence to back this up, in that following prolonged exercise, pulmonary vascular resistance may actually fall to below pre- exercise levels (Ekelund, L. G. 1967; Reeves, J. T. et al 1988). Furthermore, during exercise the respiratory rate and flow increases six fold. This increases the alveolar pressure and the intrathoracic pressure in normal humans and results in an increase in the critical closing pressure. In some of our subjects, with underlying lung disease the effect may be exaggerated.

It was interesting to note the varying effects on MPAP despite a universal increase in cardiac index (CI). Pagnamenta et al (2003) noted that in dogs with experimentally induced pulmonary hypertension, at doses higher than 10 $\mu g\ kg^{-1}\ min^{-1}$ the effect of dobutamine on the pressure-flow curves depended on the resting tone. It may be in humans, depending on the underlying cause of pulmonary hypertension, the concentration of dobutamine required to be affective by resting tone may actually decrease. Other possible explanations for the reduction in MPAP noted, is that the dobutamine part of the study was performed 20 minutes after 3 sets of 3 minute straight leg raising exercises were performed (over a 33 minute period). Although the exercise was mild, in chronically ill subjects with pulmonary hypertension who are haemodynamically restricted, this exercise may have led to an alteration of basal tone, which changed during the dobutamine study. Performing the dobutamine study several hours after the exercise study may resolve this possibility.

It was also noted that the CI only increased by a third in this study. It was decided to not

exceed 10 μg kg^{-1} min^{-1} in this initial study for safety concerns. It would be useful to repeat this study using the routine cardiac protocol for dobutamine stress tests. This would involve increasing the dobutamine concentration in 5 μg kg^{-1} min^{-1} increments every few minutes, until the desired result, or a 40 μg kg^{-1} min^{-1} maximal threshold is achieved (Mishra, M. B. et al 1997). Mishra et al (1997) found that only 25% of subjects with possible ischaemic heart disease reached their maximal stroke volume on a 10 μg kg^{-1} min^{-1} infusion of dobutamine. In the pulmonary hypertensive subjects, a doubling of the CI might be appropriate.

A further pressure-flow study with dobutamine should be performed looking at the effects of dobutamine, at various concentrations, on CI and MPAP in humans with various diseases.

From the results of this current study, dobutamine, at least under the current protocol cannot be recommended as a method for producing pressure flow plots in humans for routine clinical evaluation. Further studies, into its effect on humans, with pulmonary hypertension from a variety of causes need to be performed.

Chapter 9

General Discussion

9.1 Summary of results

Although this thesis has been limited by subject recruitment, and equipment failures, it has added information in several areas, but also brought up several new questions that require further studies. In some of the studies we performed, it would be useful to continue collecting subjects in order to get sufficient numbers to assess statistically.

9.1.1. Non invasive cardiac output measurements in subjects with pulmonary hypertension

The gold standard measurement of cardiac output is by the Fick method. In clinical practice, the thermodilutional method is the main method of obtaining cardiac output, but its accuracy with respect to pulmonary hypertension is questionable for several reasons, and the blood flow results are not instantaneous (Cigarroa, R. G. et al 1989; Kohanna, F. H. et al 1977).

The physioflow 1, (© Manatec, France), in several previous studies seemed to have a higher accuracy then other thoracic impedance systems at measuring cardiac output, and it avoided the need for measuring plasma viscosity or distance between electrodes, it also benefited from an easy calibration system (Charloux, A. et al 2000). This device was potentially useful in subjects with pulmonary hypertension, but had not been previously validated in subjects with pulmonary hypertension.

Our study, the results of which are in chapter 3, demonstrate that with regards to the use of the physioflow 1 (© Manatec, France), in subjects with pulmonary hypertension, in general clinical practice, it did not produce results consistent with results produced by the thermodilutional method. The correlation with the thermodilutional results was r^2 =

0.463, with a regression equation of $CO_{PF} = 1.924 + CO_{THERM} \bullet 0.844$ ($L \bullet min^{-1}$). Assessment by the Bland- Altman method demonstrated that the physioflow overestimated cardiac output by 1.21 (± 1.85) $L \bullet min^{-1}$ when comparing the values with thermodilutional values, giving a mean difference (± S.D.) of 23.35 (± 35.9) %. A similar result was obtained during exercise. An overestimation could be expected, as previous findings have found excessive thoracic fluid, leads to a drop in estimated pressures, and in subjects with COPD and pulmonary hypertension, using other impedance devices, an overestimate was noted (Bougault, V. et al 2005). There is evidence that thermodilutional results in subjects with tricuspid regurgitation (and thus pulmonary hypertension), may be an underestimation (Hoeper, M. M. et al 1999).

With regards to changes of cardiac output within an individual, the physioflow was much more promising. In an analyses of 21 subjects, whilst either exercising or receiving oxygen or nitric oxide, the percentage change from baseline gave a correlation, $r^2 = 0.81$ ($p < 0.001$), with a regression equation of,

$$\%\Delta CO_{PF}Baseline = 3.16 + \%\Delta CO_{THERM}Baseline \bullet 0.916\ (\%).$$

Assessment by the Bland Altman method found that the change was a small overestimation of 2.08 (± 12.5) %, (giving 95% confidence intervals of between –23.0 and 27.1 %). Of the 21 subjects analysed, 3 did not have pulmonary hypertension, and 9 were pulmonary arterial hypertensive (WHO group I) subjects. The study, when sub-analysed, to avoid over-representing individual subjects, found a much poorer correlation for the oxygen and the nitric oxide group. In the nitric oxide group the percentage change from baseline gave a correlation, $r^2 = 0.02$ ($p = 0.63$), with a regression equation of,

$$\%\Delta CO_{PF}Baseline = 4.87 + \%\Delta CO_{THERM}Baseline \bullet -0.07(\%).$$

The number of subjects studied was small, and if more subjects were obtained, better results may have been obtained.

Our study had several areas of weaknesses. The first was the lack of any data of reproducibility of measurements on an individual when measurements are days apart. This was due to the limitation regarding ethics, but with this device potentially being an important tool in the future, a study looking into this would be useful.

Another weakness was that the method being used to compare the physioflow with was the thermodilutional technique, which in itself has been suggested to be inaccurate, especially in the context of pulmonary hypertension or severe tricuspid regurgitation. Unfortunately, echocardiographic data for severe tricuspid regurgitation was only retrospectively available in 13 of the 25 individuals. The Fick technique, at least amongst the pulmonary hypertensive subjects, would be a more fair technique to make a comparison, to evaluate the physioflow's usefulness in a clinical situation.

Two other weaknesses in the study were the small number of subjects in individual disease subgroups, making an individual disease sub-analysis difficult. In the exercise comparison, straight leg raising involves the intra-abdominal muscles more than other types of exercise, and is more likely to produce a poor signal for the physioflow than other methods of increasing cardiac output.

9.1.2. Pressure flow plots

With regards to the production of pressure-flow plots, several areas were explored. Our aim for the project was to develop an easy and repeatable way of producing such plots in individual subjects in clinical practice. In order to do this, a combination of a micro-manometer tipped pulmonary artery catheter placed in the right pulmonary artery and the use of a continuous cardiac output monitor, in the guise of the physioflow 1 thoracic impedance device was used in order to measure pulmonary artery pressure and cardiac output respectively. The first method used to change the individual subjects cardiac output was straight leg raising exercise. The first problem that arose, was the high level of equipment failure with either the catheter failing to be placed adequately, measurement recordings failing to be stored, or the failure to get adequate signals from the physioflow. The failure rate was in 20% of subjects.

The second problem, as found in chapter 3, was the discrepancy in cardiac output measurements taken by the physioflow 1 and by thermodilutional methods. Although in an individual, the changes in percentage from baseline were accurate, the lack of accurate quantitation mean that the slopes and intercepts produced in an individual subject would not be able to be compared with other individuals. Another problem is that no studies have been performed using the physioflow 1 to demonstrate reproducibility within an individual with pulmonary hypertension in terms of either cardiac output or pressure flow plots, over time.

With regards to the successful production of linear pressure-flow plots, 86 sets of paired data were produced in these studies, whilst supine and performing straight leg exercises. The results of chapter 4 found that of the 86 plots of paired data, all had an acceptable

scattergram, but only 56 of the 86 (65%) had adequate histograms of frequency versus regression standardized residuals and plots of cumulative probability of regression standardised plots. With regards for the ANOVA test of non-linearity, only 3 failed that test, but the test could not be performed on over half the linear regression plots, giving only 39 of 86 lines, achieved statistical linearity. When reviewing the confidence intervals of the slopes, only 38% of the slopes and 20% of the intercepts had confidence intervals which were within 20% of the linear equation slope or intercept, making comparisons of small differences in the slopes or intercepts difficult.

When the data was sub-analysed, by pooling subject data into their respective disease groupings, there was very little difference in the slope between inhaled gases, except in the subjects with chronic thromboembolic hypertension (CTEPH) (and normals). Excluding the chronic thromboembolic and normal subjects, the slopes in the disease subgroups all seemed to show a parallel shift in the pressure flow plots. In the chronic thromboembolic group, there was a significant reduction in the slope from air to nitric oxide. In both the IPAH and CTEPH group, oxygen seemed to increase resistance.

An unexpected but interesting finding, which may explain the differences seen in chapter 5, was that non- vasodilator responders had a reduction in the slope of the pressure flow plot when given nitric oxide and oxygen combined, whereas vasodilator responders had a shift in their critical closing pressure (intercept) rather than a fall in their resistance. It may be that the effect of a high concentration of nitric oxide led to vasodilation of the pulmonary venules, and this may somehow altered the mean closing pressure.

Our attempt to use dobutamine for the production of pressure flow plots (chapter 8) was not successful. It was found that despite a gradually increasing cardiac output in all 5 subjects throughout the study, the mean pulmonary artery pressure either increased within the first few minutes of the study and then reached a plateau, or in the case of one subject actually decreased. Its possible that the exercise performed at least 20 minutes earlier (chapter 4), resulted in an alteration of the basal tone of the pulmonary vasculature (Ekelund, L. G. 1967; Reeves, J. T. et al 1988). This may also be due to the effect of dobutamine on either the alpha or beta receptors in blood vessels in the pulmonary vasculature. In the systemic circulation, these effects on the blood vessels normally cancel each other out, (Leier, C. V. et al 1983) but this may not necessarily be the case in the pulmonary circulation. It had also been previously noted that the effects of dobutamine on the pulmonary vasculature in dogs, at concentrations higher than used in our study, depended on the underlying resting tone (Pagnamenta, A. et al 2003).

9.2. Future Work

There are several areas, in which the results of this thesis indicate future studies may be useful. With regards to the physioflow device, it would be useful to study whether a given cardiac output at rest, and changes of cardiac output from baseline, by exercise or dobutamine, are reproducible when measured within individuals, when the measurements are separated by a gap of several days. The pressure flow gradients produced, should also be repeated after several days to assess whether the results in an individual subject remains constant, which would mean the device would be able to be used to track changes in individuals.

When the studies were initiated, the nitric oxide group was given additional oxygen, irrespective of whether they were hypoxic at rest. This was in order to maximise the vasodilatory effects. However, as was noted in chapter 5, oxygen inhalation in the idiopathic pulmonary hypertensive subjects, seem to increase the slope and thus vascular resistance in some patients. During these studies, a direct comparison made between nitric oxide alone and nitric oxide/oxygen combination was not performed. It was noted that in chapter 5, in the IPAH subgroup, the slope of the pressure-flow plot actually increased with oxygen, and in the CTD group increased to 6.4 with the NO/O_2 combination, and 6.5 with oxygen alone. It may be the effects of oxygen on the pulmonary vasculature may differ depending on whether a subject is exercising. This would be a future avenue to pursue. Furthermore, Shirai et al (1996) found that nitric oxide at concentrations of 20ppm were sufficient to dilate pulmonary arterioles. At concentrations above 40ppm, the pulmonary venules start to be affected. A study comparing various dosages of nitric oxide and its effect on pressure-flow plots in individuals would be useful. This would be particularly interesting to see if by altering

the nitric oxide concentration, the effect on critical closing pressure alters, as the pulmonary venules vasodilate and outflow pressure alters. Using the pressure decay curve following pulmonary artery occlusion (Kafi, S. A. et al 1998), might help to partition the pulmonary vascular resistance. Finally, once the reproducibility of cardiac output measurements over time in an individual with pulmonary hypertension when measured by the physioflow 1 device is established long term studies, looking for changes in the response to vasodilators in subjects treated with disease modifying drugs, may be of interest.

Additionally a pilot study, using other methods of exercise, for instance a supine bicycle ergometer, is needed, to see whether the plots produced are more linear. A study comparing the effects of breathing air with or without the use nitric oxide delivery system would also be useful.

The use of dobutamine in these subjects, in order to produce pressure-flow plots, needs to be further investigated and ideally on separate days to any exercise studies. Further studies, using varying dosing regimes, also need to be performed, (either steady state or incremental up to 40 $\mu g\ kg^{-1}\ min^{-1}$), to discover the optimum regime.

An unpublished review of high fidelity pulmonary artery pressure data, obtained over the past several years at the Scottish Pulmonary Vascular Unit, suggest that there is a linear relationship between systolic, diastolic, mean and pulse pressure, in the sense that knowing one pressure will allow the calculations of other pressures, through several derived equations. However, with regards to pulse pressure, the equation obtained, PAPP = 1.1 + 0.79 SAPP (mmHg), had the greatest variance, giving a standard

deviation of 6.61 mmHg. A further study of unpublished data, found that pulmonary artery pulse pressure was related to survival, in all cause pulmonary hypertension. The 2 year survival probability was 95 % for a pulse pressure of <55mmHg, but only 60% for a pulse pressure >70mmHg. Pulse pressure differences may be a reflection of differences in compliance or distensibility of the pulmonary vasculature. This is because pulse pressure is basically affected by four components. Compliance of the vessels that the blood is flowing through, the point of wave reflection (branch points), the volume of blood passed into the vasculature (stroke volume), and the frequency of flow pulsation (heart rate). It would be hoped, but not necessarily true, that when comparing the effects of pharmacological agents on a subject, the wave reflection sites would remain static. Thus further analysis of the pulmonary artery pressure data collected via the high fidelity pulmonary artery catheters and corresponding stroke volume and heart rate data from the physioflow 1 thoracic impedance device would be useful to investigate changes in compliance in individual disease groups. This would be especially be true when looking at changes in posture and in respect of vasodilator responses to oxygen or nitric oxide. (Data chapters 5-6).

All the evidence suggests that the pulsatile nature of the pulmonary circulation is important in determining the amount of stress placed on the right ventricle, as the hypertrophy of the right ventricle is a major contributor to death. The ideal situation would be to look at pulmonary vascular impedance, but in humans, under normal clinical conditions, this would be impractical. Studying the pulmonary artery pulse pressure alone and in conjunction with stroke volume or heart rate would go some way in looking at this pulsatile component to blood flow.

9.3 Conclusions

As a consequence of these studies, we have come to several conclusions, but the study has resulted in many more questions needing to be answered. It has been known for some years, that our current haemodynamic measurements of the pulmonary circulation are inadequate. This thesis attempted to look into several aspects of pulmonary circulation in order to improve our basic clinical investigations of all subjects.

The thesis relates to the validation of the non-invasive cardiac output device, the physioflow 1, and its use in the production of pressure flow plots in subjects with pulmonary hypertension. With regards to this, we found, at least when compared with thermodilution cardiac output, the physioflow overestimated cardiac output by 1L, and had a wide confidence intervals. It did, however, follow trends in cardiac output much more readily. Thus, it may be useful experimentally with the pooling of data, but it cannot currently be a clinical substitute for invasive measurement. If further reproducibility studies are performed and found to be accurate within an individual, it may then become a method of following changes in cardiac output in an individual over a period of time.

The pressure-flow response to nitric oxide, varies from 'vasodilator' responders and non-responders, in an unexpected manner, and may also vary between disease actiologies. Further investigations to understand this difference, may open up novel therapeutic options.

Studies in both normal and pulmonary hypertensive humans with regards to the pulmonary circulations response to dobutamine are also necessary. Understanding this may help in allowing dobutamine to be used as a surrogate for exercise.

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