Resuscitative Endovascular Haemorrhage Control in Wartime Injury

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Abstract

Non-compressible haemorrhage from within the torso and junctional regions constitutes the leading cause of potentially preventable death on the battlefield. It can be defined as haemorrhagic shock arising from injury to named torso vessels, pulmonary parenchyma, high grade solid organ injury and/or disruption of the bony pelvis.

Data from the US Department of Defence Trauma Registry demonstrate a torso injury rate of 12.7% with 17.1% of casualties exhibiting torso injury and shock. The overall mortality is 18.7%, with major arterial injury and pulmonary injury identified as independent predictors of mortality on multivariate analysis. The UK Joint Theatre Trauma Registry reports similar findings with the greatest burden of mortality occurring prior to hospital admission (75.0%), a rate that has remained unchanged over a decade of war. Injury from improvised explosive devices (IEDs) in particular are associated with non-compressible haemorrhage, frequently causing traumatic lower extremity amputation in combination with torso injury.

Contemporary surgical strategy relates to early operative haemorrhage control in patients presenting with shock. In patients sustaining a circulatory arrest, resuscitative thoracotomy and aortic cross clamping can be used to control inflow and increase cardiac afterload. The UK experience over 5 years at Camp Bastion demonstrated a mortality of 78.5%, with greatest survival observed in patients with the shortest time to thoracotomy. In patients sustaining lower extremity amputation following IED injury, 1 in 5 require a laparotomy for proximal vascular control, with less than half requiring further intra-abdominal intervention. There is a pressing need for a haemorrhage control and resuscitation adjunct in non-compressible haemorrhage that can be deployed prior to or as an adjunct to operative haemorrhage control.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a technique that can occlude the aorta without the need for an operating theatre. It is an experimental technique, so its effect on survival and physiology is unknown. In a porcine model of uncontrolled pelvic haemorrhage, infra-renal REBOA was shown

to be as effective as chitosan gauze in the setting of normal coagulation. However, REBOA was associated with a significantly greater survival in a coagulopathic setting. Similar results were obtained when using a porcine model of abdominal haemorrhage in conjunction with thoracic REBOA. In both studies, balloon occlusion demonstrated a significant improvement in systolic blood pressure and other haemodynamic measures compared to the no-occlusion control groups.

Having demonstrated a survival and haemodynamic benefit in uncontrolled haemorrhage models, the metabolic and inflammatory consequences of thoracic REBOA were characterised in further detail using a porcine model of controlled hypovolaemic shock. Occlusion for 30 and 90 minutes was associated with a significant lactate burden when compared to animals undergoing shock alone. However, following resuscitation with blood and intravenous fluid, normal physiology was restored within 6 hours. The inflammatory sequelae were studied following 30, 60 and 90 minutes of shock and occlusion. Increasing occlusion time resulted in an escalating release of interleukin-6 which manifest clinically as an increase in ARDS and need for vassopressor support.

In order to develop a fluoroscopy free REBOA system, a series of human studies were undertaken to examine the relationship between an external measure of torso height and aortic length in order to guide insertion length. A retrospective examination of computed tomography in male trauma patients demonstrated a correlation between torso height and aortic length. This was confirmed by a prospective study which was also used linear regression to develop equations predictive of insertion length.

Finally, the UK Joint Theatre Trauma Registry was used to determine the need for REBOA in a population of UK military personnel injured over 10 years of conflict. Of 1317 severely injured patients 70.2% had no indication, 11.2% had a contra-indication and 18.5% had an injury pattern indication for REBOA. Of those with an indication for REBOA, 66 (27.0%) patients died en-route to hospital and 29 (11.9%) died in-hospital.

In conclusion, non-compressible haemorrhage constitutes a significant burden of potentially preventable battlefield mortality. REBOA is a technique that can be

used in the thoracic or infra-renal aorta as a haemorrhage control and resuscitation adjunct, prior to operative haemorrhage control. While associated with a significant survival advantage in models of uncontrolled haemorrhage, it is associated with a significant metabolic penalty, although with resuscitation this can be ameliorated successfully.

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Thesis Declaration

I, Jonathan Morrison, declare that, except where explicit reference is made to the contribution of others in Appendix A, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Signature 

Printed name Jonathan Morrison

Date 01/08/2014

List of Common Abbreviations

AIS	Abbreviated Injury Scale
AUC	Area Under the Curve
CO	Cardiac Output
CNS	Central Nervous System
CFR	Case Fatality Rate
DOW	Died of Wounds
DoDTR	Department of Defence Trauma Registry
DCBI	Dismounted Complex Blast Injury
DCR	Damage Control Resuscitation
ED	Emergency Department
EP	Extra Peritoneal
GCS	Glasgow Coma Score
ISS	Injury Severity Score
ICU	Intensive Care Unit
IED	Improvised Explosive Device
IP	Intra Peritoneal
JTTR	Joint Theatre Trauma Registry
JTS	Joint Trauma System
KIA	Killed in Action
MAP	Mean Arterial Pressure
MTF	Medical Treatment Facility
MCAP	Mean Central Aortic Pressure
NCTH	Noncompressible Torso Haemorrhage
NCTI	Noncompressible Torso Injury
NISS	New Injury Severity Score
OR	Operating Room
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
RT	Resuscitative Thorsacotomy
ROC	Receiver Operator Characteristic
RTS	Revised Trauma Score
ROSC	Return of Spontaneous Circulation
SBP	Systolic Blood Pressure
SVR	Systemic Vascular Resistance

Chapter 1: Introduction

The UK and US military have been engaged in continuous combat operations for over a decade, involving deployments in Iraq and Afghanistan. This has come at a significant cost in terms of personnel: in the period from 2001 to 2013, there have been 626 UK and 6788 US combat deaths (1). As a consequence, there has been a concerted effort to better characterise mortal injury patterns in order to drive improvements in clinical care that will reduce battlefield mortality.

One of the first studies to systematically examine the cause of battlefield death was by Holcomb et al. who reviewed the autopsy findings of special operations forces personnel killed early in the wars in Afghanistan and Iraq, between 2001 – 2004 (2). A panel of experts reviewed the clinical records of fatalities and categorised them as non-survivable (severe head or cardiac injuries) or potentially survivable (haemorrhage, tension pneumothorax and airway obstruction). Of the 82 patients examined, 16 were deemed potentially survivable, with the greatest burden of death from exsanguination (81.3%).

This study went on to divide bleeding patients into two groups based upon whether they can be controlled by compression or not in the pre-hospital setting. Compressible haemorrhage is from anatomical regions such as the extremity, where bleeding can be controlled by simple manual pressure or tourniquet application (3). Non-compressible haemorrhage encompasses the torso and junction regions such as axillae and groin. Over half of the deaths considered potentially preventable were due to non-compressible bleeding arising from within the torso (2).

These findings have been reaffirmed by a recent study by Eastridge et al. who used the same methodology as Holcomb, but applied to 10 years or 4596 US military deaths (4). A quarter of deaths (24.3%) were identified as having a potentially survivable injury, of which 90.9% were due to haemorrhage. The largest focus was truncal (67.3%) followed by junctional (19.2%) and extremity (13.5%) sources. Importantly, nine out of 10 deaths occurred prior to admission to a hospital.

Strategies to control compressible sources of haemorrhage have seen great development over the last decade, with numerous types of bandage, novel

haemostatic compound and tourniquet being developed and deployed (5). This has seen a significant reduction in the mortality rate from compressible haemorrhage (3).

However, non-compressible haemorrhage has not seen the same level of innovation despite a pressing need for a haemorrhage control and resuscitation adjunct for use in the pre-hospital setting. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is a recently described technique which may fulfil this requirement (6).

REBOA uses aortic balloon occlusion to provide inflow control and cardiac afterload support in haemorrhagic shock (3). It can either be inserted prophylactically in patients at risk of haemorrhage and then inflated in the event of a deterioration, or as a substitute to open cross clamping in the moribund patient. REBOA is designed as a proactive manoeuvre, which can be inserted in austere circumstances, providing a physiological bridge to definitive haemorrhage control.

The clinical use of this technique was first described in the 1950s (7), with further reports in the 1980s (8,9). Despite some favourable outcomes, technological limitations relating to arterial access, balloon construction and placement meant its adoption was not widespread. However, following the evolution of endovascular surgery and the experience with aortic balloon occlusion during endovascular aneurysm repair, many of these constrains can be overcome (10).

To facilitate REBOA deployment, the aorta has been characterised into three functional zones: zone I extends from the origin of the left subclavian to the coeliac trunk, zone II is from the coeliac trunk to the lowest renal artery and the infra-renal aorta constitutes zone III (6). Zone I and III serve as "landing zones" for occlusion in specific injury patterns. Zone I occlusion provides resuscitation in circulatory arrest and control for abdominal exsanguination and zone III occlusion is for ileo-femoral junctional pelvic haemorrhage.

1.1 Thesis Aims and Objectives

The aim of this thesis is to use UK and US military trauma registries to characterise patterns of injury associated with non-compressible haemorrhage. Following this, current surgical strategies used in non-compressible haemorrhage and their outcomes will be examined, also using these registries. This will be followed by a programme of experiments using large animal models of controlled and uncontrolled haemorrhage in order to assess the efficacy of REBOA in hypovolaemic shock and its associated metabolic consequences. Finally, a mixture of human and animal studies will be used to demonstrate the development and clinical need for a fluoroscopy free REBOA system.

Chapter 2: The Epidemiology of Non-Compressible Torso Haemorrhage in the Wars in Iraq and Afghanistan

2.1 Introduction

Vascular injury with concomitant haemorrhage is the leading cause of potentially preventable death in both civilian and military trauma patients (2,4,11-17). Studies from the wars in Afghanistan and Iraq have suggested that up to 80% of potentially survivable patients expire as a result of exsanguination (15,16). These studies categorise bleeding broadly in this context as *compressible* or *non-compressible* depending upon whether the haemorrhage control measures can be applied soon after the point of injury.

Compressible haemorrhage originates from extremity injury and can be managed by direct application of pressure or a tourniquet. The reemphasis on wartime tourniquet use has increased survival from compressible extremity haemorrhage to greater than 90% (5,18-20). In contrast, methods to manage bleeding from sites within the torso, recently referred to as non-compressible torso haemorrhage (NCTH) (2), remain largely limited to the use of conventional operative techniques (3).

Until recently, despite the intuitive use of the term "non-compressible", NCTH has lacked a consistent definition with which to characterise the epidemiology of this morbid injury complex. US and UK military surgeons have proposed a definition of NCTH which includes vascular disruption within the thorax, abdomen and pelvis, linked to physiological indices of shock and/or the need for operative haemorrhage control (3).

The objective of this study was to characterise the prevalence of NCTH in a large population of wartime casualties using this contemporary definition. In that context, an additional objective was to characterise the mortality of this injury pattern within a population of combat wounded and identify sites of vascular disruption within the torso associated with the highest mortality.

2.2 Methods

This study was conducted under approval from the US Army Medical Research and Material Command Institutional Review Board. The investigation used the Department of Defence Trauma Registry (DoDTR) to examine the prevalence of non-compressible torso haemorrhage between 2002 and 2010. The DoDTR is housed within the US Army Institute of Surgical Research (ISR) and is used by the Joint Trauma System (JTS) as a process improvement tool to benchmark trauma care (21). Patient data is entered on all US service personnel injured while on operations, who are admitted to a Medical Treatment Facility (MTF). In this context, the prevalence of NCTH was examined in troops who survived to receive care at an MTF and not those who died as a result of wounds prior to reaching medical treatment, also referred to as killed in action (KIA) (22).

2.2.1 Definition of Non-compressible Torso Vascular Injury and Haemorrhage

Using Abbreviated Injury Scale (AIS) Scores, the JTTR was queried for US service personnel sustaining an injury within one of four categories (Table 2.1): Category I Main axial torso vessel; Category II: Grade 4 or 5 solid organ (liver, kidney or spleen) injury (23); Category III: Massive haemothorax from pulmonary parenchymal injury; and Category IV: Open ring pelvic fractures with vascular disruption. Within Category I, the injuries were subdivided into major and minor. Major arterial injury was defined as that to the aorta or named primary branch vessel (e.g. celiac, superior mesenteric or renal artery) whereas minor injury was defined as that to any tertiary arterial branch (e.g. gastric, gluteal, gonadal arteries). Venous injuries were similarly defined as major or minor based on the vena cava as the primary axial vessel. Because of their high lethality in the wartime setting, cardiac injuries were not included in the definition of NCTH (3).

Table 2.1: Definition of non-compressible torso haemorrhage

Non-Compressible Torso Haemorrhage is defined as vascular disruption in one or more of:		
1) Named axial torso vessel 2) Solid organ injury ≥ grade 4 (liver, kidney, spleen) 3) Thoracic cavity (including lung) 4) Pelvic fracture with ring disruption	PLUS	Concomitant Shock*; or Immediate Operation

* defined as a systolic blood pressure < 90 mmHg

For purposes of the study, two groups were formed from the overall cohort. The non-compressible torso injury (NCTI) group consisted of casualties who were identified as having sustained one or more of the *anatomical* vascular injury categories by the DoDTR search. In contrast, the NTCH group consisted of patients identified within the overall cohort who also had a physiological indicator of shock and/or the need for operative haemorrhage control.

Shock was defined as a blood pressure of <90mmHg on admission to a Role III Medical Treatment Facility (equivalent to a US level one trauma centre). The need for operative haemorrhage control was defined as the need for an immediate laparotomy, thoracotomy or pelvic fixation, identified by ICD-9 procedure codes. Information collected included demographic, injury and physiologic data as well as 30-day mortality.

2.2.2 Statistical Analysis

The demographic data, mechanism of injury, admission physiology, injury pattern and mortality was compared between the NCTI and NCTH groups. Continuous variables were compared using the Student t-test or Mann-Whitney log rank test; categorical variables were compared using the chi-squared test. The injury pattern subdivisions were compared between survivors and non-survivors in the NCTH group. Any univariate comparison within the NCTH group where $p \leq 0.20$ was included in a step-wise logistic regression in order to identify independent predictors of mortality. The strength of the logistic regression model was examined by the area under the receiver operator characteristic curve. Analysis was performed using SPSS 19 software (IBM®, New York).

2.3 Results

Of 15,209 battle injuries reported within the JTTR during the study period, 12.7% (n=1936) sustained an injury within one or more of the categories defined in Table 2.1. The majority of patients (97.6%; n=1920) in the overall cohort were male and the mean age (± standard deviation) was 25.8 ± 6.6 years. The mean ISS of the overall cohort was 26.0±12.6 with 57.0% (n=1122) of patients injured by blast, 26.1% (n=514) by gunshot and the remainder by blunt mechanisms (e.g. helicopter or vehicle crash). Of patients in the overall cohort 17.1% (n=331) met

physiological and/or operative criteria indicating active haemorrhage (Table 2.1) and formed the NCTH group. The remaining 1605 patients formed the NCTI group.

When comparing the NCTI and NCTH groups (Table 2.2), there were more males in the NCTH group ($p=0.043$), who also had sustained significantly more blast related injuries ($p<0.001$). The NCTH group also had a lower mean admission SBP (a selection criteria), a lower GCS and higher mean ISS ($p<0.001$). When comparing severe injury per body region (defined as an AIS≥3), the NCTH group had a greater proportion of abdominal and extremity injury than the NCTI group ($p<0.001$).

Among the NCTI group, the most common injury involved the pulmonary parenchyma (53.1%) followed by a solid organ injury (21.3%), named torso vessel (16.0%) and finally complex pelvic fracture (12.3%) (Figure 2.1). The most commonly injured solid organ was the spleen (10.5%) followed by liver (6.7%) and kidney (3.9%).

A similar distribution of injuries was observed within the NCTH group, although the relative proportions were greater, with the exception of pulmonary injury (41.7%). Solid organ injury occurred in 29.3%, named vessel injury in 25.7% and pelvic injury in 15.1%. Again the spleen was the most commonly injured solid organ (12.4%) followed by the liver (10.0%) and kidney (15.1%) (Figure 2.1).

In terms of operative intervention, consistent with an increased injury severity, a greater number of interventions were performed on the NCTH group (Table 2.2). Over half of the NCTH group required tube thoracostomy or laparotomy, compared to less than half in the NCTI group. There was a ten-fold increase in the need for thoracotomy in the NCTH group compared to the NCTI group. The greater injury burden is also reflected in the mortality, with the NCTH group sustaining more than twice the number of deaths than the NCTI group (18.7% vs. 8.8%; $p<0.001$).

Table 2.2: demographic, mechanism, admission physiology, injury pattern, operative intervention and mortality of patients with non-compressible torso injury (NCTI) vs non-compressible torso haemorrhage

Parameter	NCTI	NCTH	P value
n	1605	331	
male, % (n)	1560 (97.2%)	328 (99.1%)	0.043
age, mean ± SD	25.8 ± 6.6	25.8 ± 6.4	0.851
GSW, n (%)	435 (27.1%)	79 (23.9%)	< 0.001
Explosion, n (%)	892 (55.6%)	230 (69.5%)	
Other, n (%)	278 (17.3%)	22 (6.6%)	
SBP/mmHg, mean ± SD	134 ± 24.8	82.7 ± 26.1	< 0.001
GCS, mean ± SD	12.0 ± 4.4	6.6 ± 4.9	< 0.001
GCS < 8, n (%)	319 (19.9%)	183 (55.3%)	< 0.001
ISS, mean ± SD	25.1 ± 12.2	30.1 ± 13.3	< 0.001
Head/Neck AIS ≥ 3, n (%)	317 (19.8%)	77 (23.3%)	0.148
Face AIS ≥ 3, n (%)	76 (4.7%)	11 (3.3%)	0.259
Chest AIS ≥ 3, n (%)	1115 (69.5%)	223 (67.4%)	0.452
Abdomen AIS ≥ 3, n (%)	609 (37.9%)	183 (55.3%)	< 0.001
Extremity AIS ≥ 3, n (%)	718 (44.7%)	206 (62.2%)	< 0.001
External AIS ≥ 3, n (%)	52 (3.2%)	17 (5.1%)	0.090
Torso Vessel Injury, n (%)	257 (16.0%)	85 (25.7%)	< 0.001
Chest Injury, n (%)	853 (53.1%)	138 (41.7%)	< 0.001
Solid Organ Injury, n (%)	342 (21.3%)	97 (29.3%)	< 0.001
Pelvic Injury, n (%)	197 (12.3%)	50 (15.1%)	0.010
Laparotomy	336 (20.9%)	215 (65.0%)	< 0.001
Thoracotomy	41 (2.6%)	67 (20.2%)	< 0.001
Pelvic Ex-Fix	64 (4.0%)	37 (11.1%)	0.057
Tube Thoracostomy	643 (40.1%)	185 (55.9%)	< 0.001
Mortality	142 (8.8%)	62 (18.7%)	< 0.001

Abbreviation: NCTI – Non-Compressible Torso Injury, NCTH – Non-Compressible Torso Haemorrhage, GSW – Gun Shot Wound, SBP – Systolic Blood Pressure, GCS – Glasgow Coma Score, AIS – Abbreviated Injury Scale.

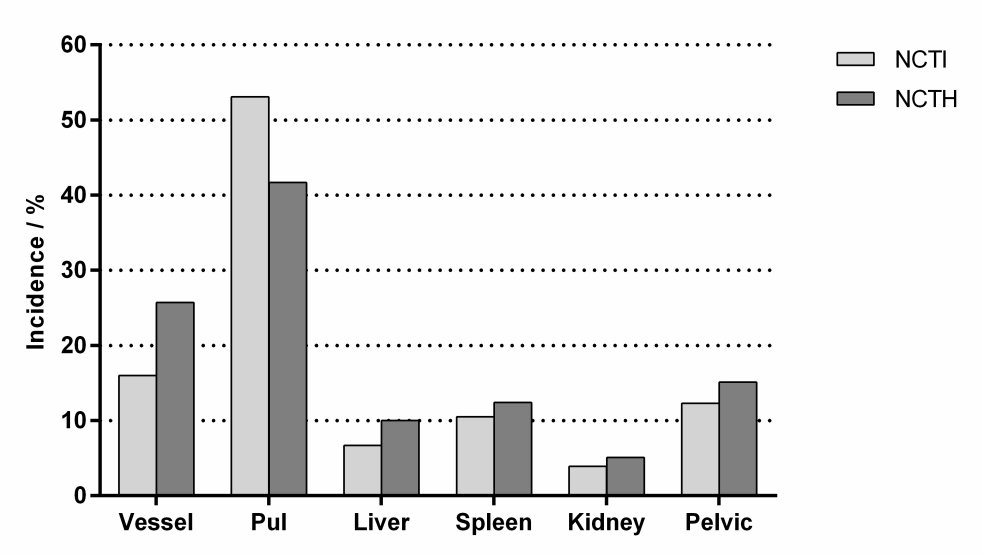

Figure 2.1: The incidence of specific injury complexes for patients with non-compressible *injury* and *haemorrhage* as a percentage

Table 2.3: Comparison of injury patterns in patients with NCTH, survivors vs non-survivors

Injury Type	Survivor	Non-Survivor	P value
n	269	62	
Major Arterial	25 (9.3%)	16 (25.8%)	< 0.001
Minor Arterial	13 (4.8%)	4 (6.5%)	0.603
Major Venous	23 (8.6%)	11 (17.1%)	0.032
Minor Venous	8 (3.0%)	2 (3.2%)	0.917
Pulmonary Injury	103 (38.3%)	35 (56.5%)	0.026
Liver	23 (8.6%)	11 (17.7%)	0.349
Spleen	38 (14.1%)	3 (4.8%)	0.032
Kidney	13 (4.8%)	4 (6.5%)	0.817
Pelvic Fracture	42 (15.6%)	8 (12.9%)	0.591

Table 2.4: Multivariate regression analysis of significant univariate parameters for mortality in patients with NCTH

Parameter	Odds Ratio	95% Confidence Interval	P Value
Major Arterial Injury	3.38	(1.17 - 9.74)	0.024
Pulmonary Injury	2.23	(1.23 - 4.98)	0.050
Splenic Injury	0.82	(0.67 - 0.98)	0.047
Systolic Blood Pressure	0.97	(0.96 - 0.99)	< 0.001
Glasgow Coma Scale	0.92	(0.83 - 1.00)	< 0.001

Table 2.3 represents a comparison of the injury pattern of survivors compared with non-survivors within the NCTH group. There are a greater proportion of major arterial, major venous and pulmonary parenchymal injuries in non-survivors. In contrast, the survivor group had a higher percentage of splenic injuries, with no difference between the other solid organs or pelvic injuries.

When univariate parameters had a $p \leq 0.20$, they were entered into a multivariate logistic regression to determine factors associated with mortality (Table 2.4). The following parameters were entered into the model: admission systolic BP, admission GCS, major arterial, major venous, pulmonary and splenic injury. Systolic blood pressure and GCS were significant physiological parameters ($p<0.001$). In terms of injury pattern, major arterial and pulmonary injuries were significantly associated with mortality, whereas survival from NCTH was significantly associated with splenic injury. The area under the ROC curve was 0.774.

2.4 Discussion

This study utilises a new definition of non-compressible torso haemorrhage based on specific anatomic, physiologic and procedural indices reflective of haemorrhage. Findings from this study demonstrate that 12.7% of wounded in combat sustain an anatomical injury pattern that is at risk for NCTH, and of these, 17.1% had evidence of ongoing haemorrhage. Casualties with this injury pattern and indicators of non-compressible haemorrhage have twice the mortality compared to those with the at risk injury pattern alone. Major arterial and pulmonary are the injury patterns associated with the highest mortality while injury to the spleen is associated with survival.

This current study confirms and extends the work of Holcomb et al. who published one of the first studies to recognise the importance of uncontrolled truncal haemorrhage (2). The autopsy findings of 82 special operations forces personnel killed early in the wars in Afghanistan and Iraq, between 2001 - 2004, were reviewed by a panel of experts and judged as non-survivable (e.g. lethal head or cardiac wounds) or potentially salvageable. While there were subjective aspects to the methodology of this study, it was one of the first studies to

specifically use the term "non-compressible truncal haemorrhage", although it was not specifically defined. Truncal haemorrhage was found to be the cause of death in 50% of patients judged to have sustained potentially survivable injuries.

Kelly at al used a similar methodology to analyze 997 US military deaths that occurred within two time periods: 2003-2004 and 2006 (15). Haemorrhage was the leading cause of death in those with otherwise survivable injuries and accounted for 87% and 83% of deaths during these respective periods. Airway problems, head injury and sepsis constituted the remaining causes of death. Interestingly, these figures remained unchanged when Eastridge et al. expanded this analysis to US military personnel who died of wounds 2001-2009 (16) and all deaths 2001-2011 (4). While lethal head injury was the dominant pattern of trauma in the non-survivable cases; haemorrhage again accounted for 80-90% of potentially survivable deaths with truncal haemorrhage accounted for 48-67% deaths in these analyses.

The publication of these studies provided an important characterisation of battlefield injury and illustrated the high and early lethality of NCTH in those who could have otherwise survived their injuries. These studies are largely responsible for the institution of tourniquets and other Tactical Combat Casualty Care manoeuvres, many, of which have been shown to improve survivability following wartime injury (5,20). The current study extends these findings to enable a characterisation of the contribution of specific injury patterns within the umbrella of NCTH.

The finding that pulmonary injury followed by major vascular injury contributes the greatest to the mortality burden is supported by several clinical studies examining the incidence of haemorrhage in particular organ systems (17,24). Propper et al. examined wartime thoracic injury from 2002-2009 (24). The authors found that thoracic injury of any type occurred in 5% of wartime casualties, with a mean ISS of 15 and crude mortality of 12%. The most common thoracic injury pattern in Propper’s study was pulmonary contusion (32%), followed by haemopneumothorax (19%).

In a separate study, White et al. reported the incidence of vascular injury in US troops between 2002-2009 (17). The authors of this study observed a specific vascular injury rate of 12% (1570 of 13 075) which was 5 times higher than that described in previous wartime reports. Large vessel injury accounted for 12% of the torso vascular injuries in White's study, with iliac, aortic and subclavian vessels being the most commonly injured. These findings were later extended to a comparison of military patients to a propensity matched cohort from the national trauma databank (25). For non-compressible arterial injury, the military had a significantly lower mortality compared to a civilian population (10.8% vs. 36.4%; p=0.008).

The low mortality associated with splenic injury in this study is not surprising in comparison to other injury patterns. While the control of splenic haemorrhage can be challenging, definitive haemorrhage control via splenectomy is relatively more straightforward in contrast to the complex management of torso vascular or pulmonary haemorrhage. Recently, Zonie and Eastridge reported 10 years of wartime splenic trauma management with a series of 393 patients with only 11 out 36 deaths due to uncontrolled splenic haemorrhage (2.8%) (26).

This study has a number of limitations, inherent to any retrospective study from a combat zone. The US DoDTR is designed as a performance improvement tool and not as a clinical record; thus it cannot be viewed as such. However, injury pattern data is collected prospectively, and frequently updated, although this does not include cause of death. A further consideration is that data collection commences upon admission to a medical treatment facility and thus patient initially treated at lower echelons of care may not have been included.

2.4.1 Conclusions

Ultimately, NCTH has been identified as a significant burden of mortality in patients sustaining battlefield injury, with highest mortality found in axial vessel and pulmonary injury. Novel methods of haemorrhage control and resuscitation, which can be initiated in the pre-hospital setting, are required to reduce the high mortality of this injury pattern.

Chapter 3: Injury Pattern and Mortality of Non-Compressible Torso Haemorrhage in UK Combat Casualties

3.1 Introduction

Haemorrhage is the leading cause of potentially preventable death on the battlefield, with the torso identified as the primary focus in 80% of cases (2,4,15,16). Deaths from extremity haemorrhage now constitute a minority of deaths due to the effective pre-hospital use of haemorrhage control adjuncts such as tourniquets (5,18,19).

These observations have generated renewed interest in non-compressible torso haemorrhage (NCTH) which is the disruption of a named axial vessel or vessels within the pulmonary parenchyma of the chest, the solid organs of the abdomen or those of the bony pelvis (3). This definition has recently been applied to a US population of wartime injured who survived to medical treatment facility (MTF) admission (defined as a NATO role III facility) and identified vascular and pulmonary injury as the most mortal injury complexes (27). The in-hospital mortality rate of patients sustaining NCTH was 18.7%, which is considerably greater than the overall in-hospital mortality (or died of wounds rates), of 4.8%, demonstrating the lethality of NCTH (28).

Furthermore, a recent US Joint Trauma System study reviewed 4596 US military deaths and identified that nine out of ten battlefield deaths occurred prior to MTF admission (4). Using previously established criteria to define catastrophic injury, 24.3% of the cohort were considered potentially survivable, of which haemorrhage constituted 90.9% of deaths. The torso constituted the largest source of haemorrhage (67.3%), followed by junctional (19.2%) and extremity (13.5%).

It is unclear whether the injury pattern of patients with NCTH who die in the pre-MTF phase of care is different to patients surviving to MTF admission. This is important to understand in order to direct research strategies into the pre-hospital management of NCTH. The aim of this study is to examine a complete

population of patients with NCTH, injured in wartime, in order to characterise the injury pattern pre- and post- MTF admission.

3.2 Methods

This study was conducted with the approval from the Royal Centre for Defence Medicine (RCDM) Academic Unit. The prospectively collected UK Joint Theatre Trauma Registry (JTTR) was used to retrospectively identify all UK military personnel sustaining NCTH between August 2002 through July 2012 in Iraq or Afghanistan.

NCTH was defined using a previously published definition based upon anatomical injury accompanied by physiological or procedural indices of shock (3). Anatomical - injury to a named torso vessel, pulmonary injury (massive haemothorax or hilar), grade 4 or more solid organ injury (liver, kidney or spleen), or pelvic fracture associated with ring disruption and haemorrhage. Named torso vessel was further sub-divided into major/minor arteries/veins depending on whether they were a direct branch/tributary of the aorta/IVC. Physiological - a systolic blood pressure less than 90 mmHg or procedurally - the need for an immediate laparotomy, thoracotomy or pelvic fixation in order to control haemorrhage.

The UK JTTR is a performance improvement tool which captures clinical data on casualties admitted to UK MTF's (29). In the case of UK personnel, this includes data from the point of wounding through to discharge from a UK mainland hospital facility. Patients who died prior to reaching an MTF are classified as Killed in Action (KIA) and patients who survive to admission, but ultimately succumb to their injuries, are termed Died of Wounds (DOW). Surviving patients are considered Wounded in Action (WIA). Post-mortem data from patients who are KIA and DOW is also entered into the UK JTTR, permitting the comprehensive analysis of a population of wartime injured. This system of classification enables the calculation of Case Fatality Rates (CFR), a metric of lethality, expressed as a percentage: CFR = [KIA + DOW] / [KIA + DOW + WIA] (22).

Information retrieved from the JTTR included patients demographic data, month of injury, injury pattern, outcome, cause and location of death. The 2005 Military Abbreviated Injury Scale (AIS) Scores (30) were used to calculate both the Injury Severity Score (ISS) (31) and the New Injury Severity Score (NISS) (32). In patients surviving to MTF admission, admission systolic blood pressure (SBP), heart rate (HR), Glasgow Coma Scores (GCS) and any operative intervention was also retrieved.

3.2.1 Statistical Analysis

Initially, the demography of the KIA, DOW and WIA groups was compared using chi squared tests for categorical data and analysis of variance (ANOVA) for continuous data. In patients surviving to hospital, admission physiology and rates of operative intervention was compared. CFR data were then presented based on operational theatre, temporal trend and NCTH injury domains (named vessel, pulmonary, solid organ injury and pelvic injury). The injury pattern was compared between the following patient groups: patients surviving to admission (WIA + DOW) versus patients dying prior to admission (KIA) and survivors (WIA) versus non-survivors (KIA + DOW). Multivariate analysis was then used to control for multiple injuries in order to identify which injury patterns were most lethal.

3.3 Results

Over the 10 year study period, 296 patients were identified from the UK JTTR having sustained NCTH (Table 3.1). The majority of patients (n=222, 75.0%) had died prior to MTF admission and were classified as KIA. Of the 74 patients (25.0%) surviving to admission, there were 43 WIA and 31 DOW generating an overall CFR for NCTH of 85.5%. The distribution of gender, age, theatre of operations (Iraq vs Afghanistan) and mechanism of injury between the WIA, DOW and KIA groups were similar ($p > 0.05$). However, there was a significant increase in injury burden observed across the WIA, DOW and KIA groups respectively, as measured by both ISS and NISS ($p < 0.001$).

Of the patients admitted to hospital, those who survived presented with a higher median (interquartile range) systolic blood pressure (108 (43) vs. 89 (46); $p = 0.123$) and GCS (14 (12) vs. 3 (0); $p < 0.001$) (Table 3.1). In terms of operative

intervention, resuscitative thoracotomy was used significantly more in the DOW group (51.9% vs. 9.5%; < 0.001), although thoracotomy, laparotomy and pelvic fixation was used similarly between the WIA and DOW groups (p > 0.1)

When examining the location of the 253 deaths, the majority (87.7%) occurred in the pre-MTF setting, with 7.9% in the emergency/operating room and 4.3% in the intensive care unit (Figure 3.1). In terms of cause of death, while all patients had sustained NCTH, it was not the primary focus of injury in all patients. Torso haemorrhage accounted for 60.1% of deaths, but central nervous system (CNS) disruption (brain or spinal cord injury) accounted for 30.8%, total body destruction (severe blast injury) for 5.1% and multi-organ failure for 4.0% (Figure 3.2).

The CFR was independent of operation theatre with a rate of 89.7% for Iraq and 84.5% for Afghanistan (p = 0.407) (Table 3.2). When analysing the temporal trend across the decade of study, the cohort was divided into three equal tertiles (n=99) covering the following time periods: August '02 - May '08, May '08 - Dec '11 and Dec '11 to July '12. The CFR demonstrated a decreasing trend of 90.9%, 83.3% and 81.6% across the respective groups, but this did not achieve statistical significance (p = 0.155).

When comparing the CFR of the major anatomical NCTH domains, vascular injury is significant higher when compared to non-vascular injury (p < 0.001), but remains similar for the remaining domains (p > 0.1).

Table 3.1: General demographic characteristics, trauma scores, admission physiology and operative intervention of patients with NCTH

	Survivors	Non-Survivors		
	WIA	DOW	KIA	*p*
n	43	31	222	
Male, n (%)	43 (100%)	31 (100%)	218 (98.2%)	0.509
Age, median (IQR)	23 (8)	23 (8)	26 (9)	0.088
Theatre of Operations				
Iraq, n (%)	6 (10.3%)	3 (5.2%)	49 (84.5%)	0.160
Afghanistan, n (%)	37 (15.5%)	28 (11.8)	173 (72.7%)	
Mechanism of Injury				
Explosion, n (%)	27 (62.8%)	21 (67.7%)	155 (69.8%)	0.789
Gun Shot, n (%)	13 (30.2%)	9 (29.0%)	52 (23.4%)	
Other, n (%)	3 (7.0%)	1 (3.2%)	15 (78.9%)	
Trauma Scores				
ISS, median (IQR)	26 (21)	57 (33)	75 (18)	< 0.001
NISS, median (IQR)	34 (28)	75 (18)	75 (0)	< 0.001
Physiology				
Systolic Blood Pressure	108 (43)	89 (46)	n/a	0.123
Heart Rate	100 (52)	100 (128)	n/a	0.025
Glasgow Coma Score	14 (12)	3 (0)	n/a	0.001
Operative Intervention				
Resus Thoracotomy, n (%)	4 (9.5%)	14 (51.9%)	n/a	< 0.001
Thoracotomy, n (%)	7 (16.7%)	4 (14.8%)	n/a	0.838
Laparotomy, n (%)	27 (64.3%)	15 (55.6%)	n/a	0.468
Pelvic Ex-Fix, n (%)	9 (21.4%)	5 (18.5%)	n/a	0.769

Abbreviations: WIA - Wounded in Action; DOW - Died of Wounds; KIA - Killed in Action

Table 3.2: The casualty fatality rate for the overall cohort, operational theatre, time and non-compressible torso haemorrhage anatomical domain

		CFR	*p*
	Overall	85.5%	
Operational Theatre			
	Iraq	89.7%	0.407
	Afghanistan	84.5%	
Time Period			
	Aug 2002 - May 2008	90.9%	0.155
	May 2008 - Dec 2011	83.8%	
	Dec 2011 - July 2012	81.6%	
NCTH Domain			
	Vascular	93.0%	< 0.001
	Pulmonary	85.9%	0.534
	Solid Organ	90.0%	0.124
	Pelvis	88.4%	0.210

Abbreviations: CFR - Case Fatality Rate; NCTH - Non-Compressible Torso Haemorrhage

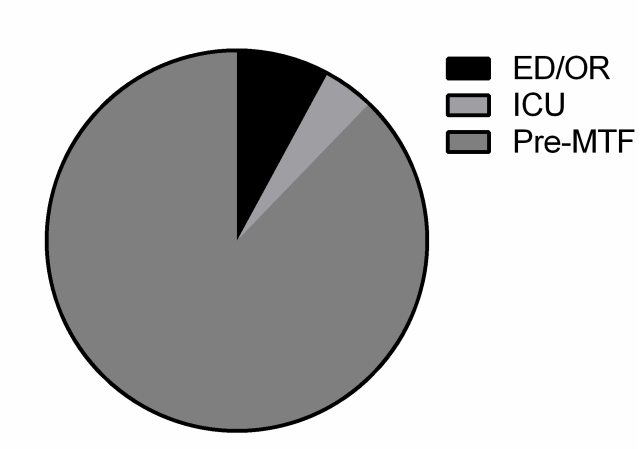

Figure 3.1: Location of death

Abbreviations: ED/OR – emergency department/operating room, ICU – Intensive care unit, Pre-MTF – pre-medical treatment facility.

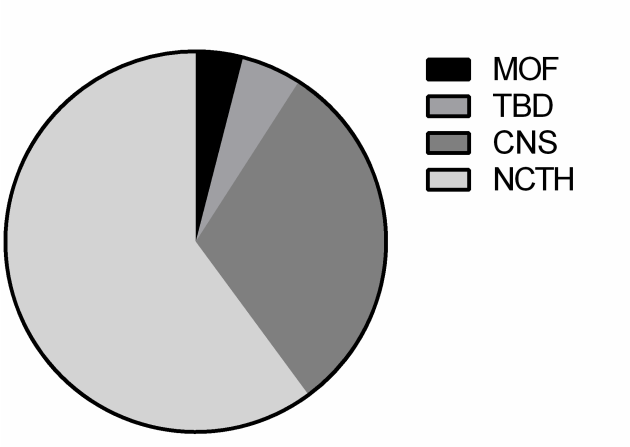

Figure 3.2: Cause of death

Abbreviations: CNS – central nervous system disruption, TBD – total body disruption, MOF – multiple-organ failure, NCTH – non-compressible torso haemorrhage

In terms of injury pattern using a AIS≥3 as a marker of severe injury, as previously alluded by the ISS and NISS scores, there is a globally higher injury burden in non-survivors (Table 3.3). The biggest contributors to mortality on univariate analysis are severe head (7.0% vs. 39.9%; $p<0.001$) and chest (46.5% vs. 80.6%; $p<0.001$) injuries. This pattern is broadly similar when comparing patients who survived to MTF admission (WIA + DOW) versus those who died pre-MTF (i.e. KIA).

When considering the four major NCTH anatomical domains, vascular injury was the most lethal (30.2 vs. 68.0%; $p<0.001$) when comparing survivors with non-survivors. This is also apparent in the MTF versus no-MTF admission comparison, with the addition that a greater proportion of solid organ injuries die prior in the field (28.4% vs. 39.6%; $p=0.053$). When analysing the NCTH sub-domains in greater detail, major arterial and liver injury are identified in both groups as significant contributors to mortality.

In order to adjust for multiple interactions, injury parameters which had a $p<0.2$ on univariate testing of survivors versus non-survivors were entered into a logistic regression. The following parameters were used to build the regression model: severe head, neck, major arterial, minor arterial, pulmonary hilar, liver spleen and extremity injury (Table 3.4). Several independent predictors of mortality in NCTH were identified and presented using odds ratios and 95% Confidence Intervals. Major arterial and pulmonary hilar injury were the most lethal NCTH domains with a lesser contribution from liver trauma. Severe head, neck and extremity injury were major non-torso domains of injury.

Table 3.3: Injury pattern, survivors versus non-survivors.

	Survivor	Non-Survivor	p	MTF	No MTF	*p*
n	43	253		74	222	
AIS ≥ 3						
Head	3 (7.0%)	101 (39.9%)	< 0.001	13 (17.6%)	91 (41.0%)	< 0.001
Face	0 (0)	19 (7.5%)	0.087	1 (1.4%)	18 (8.1%)	0.040
Neck	1 (2.3%)	42 (16.6%)	0.010	2 (2.7%)	41 (18.5%)	< 0.001
Chest	20 (46.5%)	204 (80.6%)	< 0.001	39 (52.7%)	185 (83.3%)	< 0.001
Abdomen	27 (62.8%)	181 (71.5%)	0.280	51 (68.9%)	157 (70.7%)	0.769
Upper Extremity	3 (7.0%)	74 (29.2%)	0.001	10 (13.5%)	67 (30.2%)	0.005
Lower Extremity	17 (39.5%)	151 (59.7%)	0.014	36 (48.6%)	132 (59.5%)	0.107
NCTH Domains						
Vascular	13 (30.2%)	172 (68.0%)	< 0.001	31 (41.9%)	154 (69.4%)	< 0.001
Pulmonary	11 (25.6%)	67 (26.5%)	0.901	18 (24.3%)	60 (27.0%)	0.648
Solid Organ	11 (25.6%)	98 (38.7%)	0.124	21 (28.4%)	88 (39.6%)	0.053
Pelvic	11 (25.6%)	84 (33.2%)	0.322	24 (32.4%)	71 (32.0%)	0.525
NCTH Sub-Domains						
Major Arterial	5 (11.6%)	152 (60.1%)	< 0.001	17 (23.0%)	140 (63.1%)	< 0.001
Minor Arterial	4 (9.3%)	7 (2.8%)	0.059	7 (9.5%)	4 (1.8%)	0.003
Major Venous	6 (14.0%)	55 (21.7%)	0.243	11 (14.9%)	50 (22.5%)	0.158
Minor Venous	1 (2.3%)	5 (2.0%)	0.881	2 (2.7%)	4 (1.8%)	0.634
Pul Hilar	1 (2.3%)	26 (10.3%)	0.071	4 (5.4%)	23 (10.4%)	0.249
Pul Parenchyma	10 (23.3%)	48 (19.0%)	0.513	14 (18.9%)	44 (19.8%)	0.507
Renal	6 (14.0%)	38 (15.0%)	0.856	10 (13.5%)	34 (15.3%)	0.706
Liver	4 (9.3%)	73 (28.9%)	0.008	12 (16.2%)	65 (29.3%)	0.032
Spleen	3 (7.0%)	42 (16.6%)	0.104	4 (5.4%)	41 (18.5%)	0.005
Pelvic	11 (11.6%)	84 (33.2%)	0.322	24 (32.4%)	71 (32.0%)	0.525

All values are n with percentage in parentheses

Abbreviations: MTF - Medical Treatment Facility; AIS - Abbreviated Injury Score; NCTH - Non-Compressible Torso Haemorrhage; Pul – Pulmonary.

Table 3.4: Logistic regression

Injury Region	OR	95% Confidence Interval	p
Head	6.46	1.78 - 23.42	0.005
Neck	9.00	0.98 - 82.35	0.052
Major Arterial	16.44	5.50 - 49.11	< 0.001
Minor Arterial	0.430	0.081 - 2.30	0.324
Pulmonary Hilar	9.61	1.06 - 87.00	0.044
Liver	6.00	1.71 - 21.04	0.005
Spleen	3.78	0.73 - 19.58	0.114
Extremity	4.22	1.72 - 10.34	0.002

Hosmer-Lemeshow Statistic = 3.448, $p = 0.841$, $df = 7$

AUC = 0.892

3.4 Discussion

This study is the first to comprehensively examine a population of wartime injured (including pre-MTF fatalities) using a contemporary definition of NCTH. The current study has demonstrated that 9 out of 10 deaths in patients with NCTH occur in the pre-MTF phase of care, although the in-hospital mortality is also substantial. Furthermore, while NCTH directly contributes to the bulk of deaths, there are other primary foci, the largest of which is concomitant CNS injury. The independent predictors of mortality from torso injury were major arterial, pulmonary hilar and liver injury.

The current study confirms and extends the findings from a number of studies analysing data from the wars in Iraq and Afghanistan. Holcomb et al. first coined the specific term "non-compressible truncal haemorrhage" in a cause of death analysis of 82 US military personnel killed between 2001 and 2004 (15). The cohort was reviewed by an expert panel, and patients were judged as having a potentially survivable or non-survivable injury. Of the potentially survivable deaths, 67% were due to haemorrhage originating from the torso, only amenable to surgical control in the OR. This landmark study provided a fresh perspective on classifying the cause of death from haemorrhage, which was largely based on the method of pre-MTF control. As experience from the war evolved, deaths from "tourniquetable" haemorrhage have decreased due to improved pre-MTF haemostasis, specifically the deployment of haemostatic gauze and tourniquets (5,18).

This approach to classifying haemorrhage was expanded upon in a study by Kelly et al. who compared the cause of death in US military personnel killed during two time periods (15). The rates of truncal haemorrhage did not differ across the time periods and accounted for the majority cause (50%) of potentially survivable deaths. This has been further confirmed most recently by Eastridge et al. who examined the cause of death in US forces over 10 years of war (4). In total, there were 4596 fatalities, with 87.3% occurring in the pre-MTF phase of care. There were 976 potentially survivable deaths of which 67.3% were as a consequence of truncal haemorrhage.

The cause of in-hospital combat-related death has also been examined within a clinical context, looking for opportunities for improvement. Martin et al. examined 151 deaths admitted to an MTF where haemorrhage was the leading cause of non-expectant death (33). There were 76 non-expectant deaths, with at least one opportunity for improvement identified in 59 patients (78%). The largest region noted for improvement was in pre-hospital transport time and pre-hospital haemorrhage control. These findings add clinical context to the results from the current study, where the pre-hospital environment was the most common location of death.

Following these consistent findings, military surgeons from the UK and US set out to formalise a definition of NCTH in terms of anatomical and physiological parameters in order to be able to characterise this highly lethal, yet potentially survivable, injury complex. Morrison and Rasmussen proposed the definition used in the current study, which was designed to be inclusive of all major foci of torso haemorrhage, yet exclusive to patients presenting with shock or the need for immediate haemorrhage control (3). This definition was designed to be practical and to enable the comparison of populations or interventions used in the management of NCTH.

This definition has been applied by Stannard et al. to US military personnel admitted to MTFs over an 8 year period (27). They identified an incidence of 12.7% of patients sustaining the anatomical injury pattern, with 17.1% of those patients demonstrating evidence of shock or the need for urgent haemorrhage control. Following adjustment using multivariate analysis, the most mortal injury complexes were major arterial injury (OR 3.38; 95% CI: 1.17-9.74) and pulmonary injury (OR 2.23; 95% CI: 1.23-4.98).

The current study extends these findings to include a military population who died in the pre-MTF phase of care. Almost 9 out of 10 deaths occur prior to MTF admission and again, major arterial injury and pulmonary hilar injury were identified as independent predictors of mortality, along with traumatic liver injury. It is useful to know that the NCTH injury patterns are consistent across populations that die pre- or post-MTF admission as this has implications for future haemorrhage control and resuscitation strategies. Importantly, any novel

device or treatment can be tested and refined in an MTF, prior to projecting forward, with the knowledge that although overall injury severity may increase, the major injury patterns are similar.

A further important finding from the current study is from the cause of death analysis. While all patients had sustained NCTH, death from uncontrolled haemorrhage only accounted for 60.1% of the primary cause of death. In almost a third of cases, CNS injury was graded as more severe than the haemorrhagic component, further supported by the regression finding that severe head injury was a strong independent predictor of mortality. While many of these patients likely sustained an unsurvivable CNS injury, this highlights the multi-system nature of modern combat injury and the need for a pre-MTF haemorrhage control strategy that includes a neuro-protective component. The current paradigm of hypotensive resuscitation in haemorrhage may compound secondary brain injury in patients with concomitant neuro-trauma.

The current study has a number of important limitations to note. Despite the largest burden of mortality occurring in the pre-MTF phase of care, little is known regarding the physiology or care rendered during this crucial time. Furthermore, despite a population of almost 300 patients, due to the volume of poly-trauma, it is difficult to analyse sub-groups in isolation. Regression was used to overcome the issue of multiple injuries; however, it is conceivable that some lesser injuries may be overshadowed by the dominant injury patterns.

3.4.1 Conclusions

This study demonstrates that the majority of patients sustaining NCTH die in the pre-MTF phase of care. Major arterial, pulmonary and liver trauma are independent predictors of mortality. Injury pattern does not change significantly between patients surviving to MTF admission compared to patients dying prior to MTF admission, although overall injury burden does increase. The majority cause of death is from uncontrolled haemorrhage, although CNS disruption is an important contributor. Future haemorrhage control and resuscitation strategies must be forward deployed and incorporate a neuro-protective component in order to reduce the mortality from NCTH.

Chapter 4: Prevalence of Torso and Head Injuries in Casualties with Traumatic Lower Extremity Amputations Caused by Improvised Explosive Device Injury

4.1 Introduction

Traumatic lower extremity amputation caused by improvised explosive devices (IEDs) has become the signature injury of the conflict in Afghanistan (Figure 4.1). Media sources report that IED strikes accounted for 42.4% of fatalities in 2007, rising to 58.4% in 2010 (34). United States military casualty statistics record 209 major limb amputations for operations in Afghanistan between 2001 and September 2010 (35) and British records show 163 amputations and 32 significant multiple amputations (survivors only) between 2006 and September 2010 (36). The initial treatment of these injuries is focused on controlling haemorrhage. Distal amputations are managed with tourniquets, but when injuries are too proximal to permit the application of tourniquets, operative control of the femoral or iliac vessels, or even aorta, may be required. Pelvic fractures are managed with extraperitoneal packing and external fixation. Subsequent treatment includes the debridement of necrotic and contaminated tissue, and the management of associated injuries. Even if performed concurrently by several surgeons, operative treatment may take several hours.

Concern regarding clinically occult torso and intracranial injury has led to a practice of “intra-operative” CT scanning, once vascular control has been attained. This approach has been rationalised as a contracted damage control sequence, comprising initial haemorrhage control and restoration of physiology, followed by secondary survey and imaging, and immediate further surgery, such as debridement, completion of amputations and formation of stomas.

Figure 4.1: A proximal bilateral above-knee traumatic amputation, which necessitated immediate laparotomy for vascular control, and associated upper limb injuries. The patient had no thoracic or brain injury.

The prevalence or severity of associated torso and neurological injuries in combat casualties with traumatic lower extremity amputations is not known. If uncommon, of little immediate consequence, or clinically obvious from the outset, a strategy of deferring cross-sectional imaging until the end of the procedure might be more appropriate. We therefore decided to conduct a study of torso and neurological injuries associated with traumatic lower extremity amputations inflicted by IEDs, to guide clinicians managing this complex and devastating injury complex.

4.2 Materials and Methods

This study was conducted using the prospectively recorded UK Joint Theatre Trauma Registry (JTTR). Registry data are mined from clinical records and – in the case of fatal injury – post-mortem reports, supplemented by discussions with the forensic pathologist. Injury pattern reporting is thus comprehensive, and case ascertainment is complete. Permission for the study was obtained from Joint Medical Command and Her Majesties Coroner, Oxfordshire.

A retrospective search was performed to identify all UK service personnel who sustained a lower extremity amputation, proximal to the ankle, following an IED strike in Afghanistan between Jan 2007 and December 2010. The Role 3 (UK) Medical Treatment Facility at Camp Bastion, Afghanistan, receives the majority of combat casualties from the Helmand region. It has a multinational staff consisting of General and Orthopaedic Trauma Surgeons, Anaesthetists, Intensivists and Emergency Medicine Physicians. Extracted data included demographic details, injury severity scoring, level of traumatic amputation, associated injuries, operative interventions and 28-day mortality.

Levels of traumatic amputation were classified using Abbreviated Injury Scale (AIS) coding as hind-quarter (HQ) when at the hip or buttock level, above knee (AK) and below knee (BK) (31). Patients were classified as killed in action (KIA) where death occurred at scene, died of wounds (DOW) if attended hospital, but ultimately died, and wounded in action (WIA). This enabled the calculation of the casualty fatality rate (CFR = [KIA + DOW] / [KIA + WIA + DOW]) for IED injuries overall, and by amputation type (22). AIS scores were also used to

describe injury pattern (31). Severe injury was defined as an AIS ≥ 3. Data were analysed by group, using ANOVA for continuous and chi squared tests for categorical variables. Risk ratios were generated for severe head, chest and abdominal injury and the need for laparotomy, per highest level of amputation.

4.3 Results

Over a four year period, there were 656 IED casualties: 138 (21.0%) were KIA, 31 (4.7%) DOW and 487 (74.2%) were WIA, translating into an overall IED CFR of 26%. Of these 656 casualties, 169 sustained 278 traumatic lower extremity amputations: 69 were KIA, 16 DOW and 84 were WIA.

4.3.1 Injury patterns

The demographics, injury severity and injury patterns of the three groups are summarised in Tables 4.1, 4.2 and 4.3. Those who were killed in action had suffered a higher injury burden – both in terms of lower extremity injury extent, and associated abdominal, thoracic and neurological injuries – than those who died of wounds, or those who survived (Tables 4.2 and 4.3). As expected, more proximal lower extremity amputation levels were associated with reduced survival: 12 (7.1%) casualties suffered bilateral hindquarter amputations, all of whom died. Unilateral hindquarter amputation, plus another lower level amputation, was sustained by 27 (16.0%) of patients, 2 (1.2%) of whom survived to 28 days. The bilateral above-knee amputation level is the point where more patients survive to reach hospital as demonstrated by the halving in CFR (Table 4.2). The relative risk of dying as a result of hindquarter, above-knee and below-knee traumatic amputation compared to any lower extremity amputation, and the association between traumatic amputation level and associated injuries to other body regions, is shown in Table 4.4.

Table 4.1: Baseline characteristics of study cohort, by outcome group

	Total	KIA	DOW	WIA	P (KIA vs DOW vs WIA)	p (DOW vs WIA)
n	169	69	16	84		
Median Age, (IQR)	24.0 (7.0)	24.5 (9.0)	27.0 (8.0)	24.0 (5.0)	0.219	0.149
Male, n (%)	168 (99.4%)	68 (98.6%)	16 (100%)	84 (100%)	0.482	n/a
Median ISS, (IQR)	41 (43)	75 (21)	46 (23)	29 (12)	< 0.001	< 0.001
Median NISS, (IQR)	66 (30)	75 (0)	71 (18)	45 (23)	< 0.001	< 0.001
Median RTS, (IQR)	0 (6.38)	0 (0)	0 (5.97)	6.9 (3.80)	< 0.001	0.003

Abbreviations: KIA – Killed in Action, DOW – Died of Wounds, WIA – Wounded in Action, IQR – Interquartile Range, ISS – Injury Severity Score, NISS – New Injury Severity Score, RTS – Revised Trauma Score

Table 4.2: Distribution of amputation levels, by outcome group, and casualty fatality rate

Amputation Type	CFR (%)	Total n (%)	KIA n (%)	DOW n (%)	WIA n (%)	p (KIA vs DOW vs WIA)	p (DOW vs WIA)
HQ / HQ	100%	12 (7.1%)	11 (15.9%)	1 (6.3%)	0 (0.0%)		
HQ / AK	93%	14 (8.3%)	13 (18.8%)	0 (0.0%)	1 (1.2%)		
HQ / BK	86%	7 (4.1%)	5 (7.2%)	1 (6.3%)	1 (1.2%)		
HQ / -	100%	6 (3.6%)	5 (7.2%)	1 (6.3%)	0		
AK / AK	40%	40 (23.7%)	11 (15.8%)	5 (31.1%)	24 (28.6%)	< 0.001	0.022
AK / BK	35%	20 (11.8%)	4 (5.8%)	3 (18.8%)	13 (15.5%)		
AK / -	55%	20 (11.8)	10 (14.5%)	1 (6.3%)	9 (10.7%)		
BK / BK	41%	22 (13.0%)	5 (7.2%)	4 (25%)	13 (15.5%)		
BK / -	18%	28 (16.6%)	5 (7.2%)	0 (0.0%)	23 (27.4%)		

Abbreviations: KIA – Killed in Action, DOW – Died of Wounds, WIA – Wounded in Action, HQ – Hindquater, AK – Above Knee, BK – Below Knee, CFR – Casualty Fatality Rate

Table 4.3: Distribution and severity of associated injuries, by outcome group

AIS Region	Total	KIA	DOW	WIA	p (KIA vs DOW vs WIA)	p (DOW vs WIA)
Median Head AIS, (IQR)	0 (2.0)	2 (6.0)	0 (3.5)	0 (0)	< 0.001	0.004
Head AIS ≥ 3, n (%)	37 (21.9%)	29 (42.0%)	4 (25.0%)	4 (4.8%)	< 0.001	0.006
Median Chest AIS, (IQR)	0 (3.0)	3.0 (4.0)	0 (2.0)	0	< 0.001	0.023
Chest AIS ≥ 3, n (%)	49 (29.0%)	41 (59.4%)	3 (18.8%)	5 (6.0%)	< 0.001	0.084
Median Abdominal AIS, (IQR)	2.0 (4.0)	4.0 (3.0)	4.0 (2.5)	1.0 (2.0)	< 0.001	< 0.001
Abdominal AIS ≥ 3, n (%)	70 (41.4%)	49 (71.0%)	12 (75.0%)	9 (10.7%)	< 0.001	< 0.001

Abbreviations: KIA – Killed in Action, DOW – Died of Wounds, WIA – Wounded in Action, IQR – Interquartile Range, ISS – Injury Severity Score, NISS – New Injury Severity Score, RTS – Revised Trauma Score, AIS – Abbreviated Injury Score, HQ – Hindquater, AK – Above Knee, BK – Below Knee, CFR – Casualty Fatality Rate

Table 4.4: Mortality and relative risk of death, and prevalence and relative risk of associated severe head, chest or abdominal injury, pelvic fracture, and need for laparotomy (by highest amputation level, with reference to all casualties who have sustained any battlefield lower extremity amputation).

	n	**HQ**		**AK**		**BK**	
n		39		80		50	
		n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Death	85	37 (94.9%)	31.6 (7.3,137.0)	34 (42.5%)	1.0 (0.5,1.8)	14 (28.0%)	0.3 (0.2,1.6)
Head AIS ≥ 3	37	15 (38.5%)	3.1 (1.4,6.8)	16 (20.0%)	1.4 (0.7,3.0)	6 (12.0%)	0.4 (0.2,0.9)
Chest AIS ≥ 3	49	25 (64.1%)	7.9 (3.6,17.4)	16 (20.0%)	0.8 (0.4,1.5)	8 (16.0%)	0.3 (0.2,0.7)
Abdominal AIS ≥ 3	70	28 (71.8%)	5.3 (2.4,11.7)	28 (35.0%)	0.8 (0.4,1.4)	14 (28%)	0.7 (0.4,1.3)
Unstable Pelvic Fracture	52	19 (48.7%)	2.8 (1.3,5.9)	23 (28.8%)	1.0 (0.5,2.0)	10 (20.0%)	0.9 (0.5,1.8)
Need for Laparotomy*	39	3 (7.7%)	2.5 (0.4,15.4)	25 (31.3%)	2.0 (0.9,4.8)	11 (20.0%)	0.3 (0.1,0.7)

Abbreviations: HQ – Hindquater, AK – Above Knee, BK – Below Knee, AIS – Abbreviated Injury Score, RR – Relative Risk

* Excluding KIA

4.3.2 Management

Of the 100 casualties (DOW + WIA) who were not killed in action, twelve did not have a palpable central pulse on admission. Nine underwent resuscitative thoracotomy (Figure 4.2). The injury patterns of the remaining 88 patients are shown in Table 4.5. Six suffered severe (AIS ≥ 3) traumatic brain injuries. Only one required craniotomy, for a clinically obvious penetrating brain injury. The remaining five patients had sustained closed head injuries, which required no operative intervention. Five patients sustained a severe (AIS ≥ 3) thoracic injury; four developed pulmonary contusions and one sustained a flail chest, but none required a thoracotomy.

Of the three patients who survived resuscitative thoracotomy; two had sustained bilateral above-knee amputations and one bilateral below-knee amputations. None had suffered serious head or torso injury. Of the six patients who died despite resuscitative thoracotomy; five had sustained unstable pelvic fractures, four had a high grade solid abdominal organ injury, three had severe blunt head injuries and one had a superior vena cava injury. The three patients who only underwent CPR all had unstable pelvic fractures with bilateral below and above knee amputations and died of their wounds.

4.4 Discussion

This study adds to our understanding of current injury patterns in combat casualties who sustain traumatic amputations as a result of the evolving IED threat in Afghanistan. Analyses of previous conflicts have predominantly focused on the role of amputation in the management of the mangled extremity following landmines and unexploded ordinance (37,38). Similar analyses have been performed in civilian patients exposed to landmines (39,40). These injuries are generally limited to a unilateral below-knee extremity and not comparable to the frequent bilateral, transfemoral level amputations seen in Afghanistan, and described in this current study.

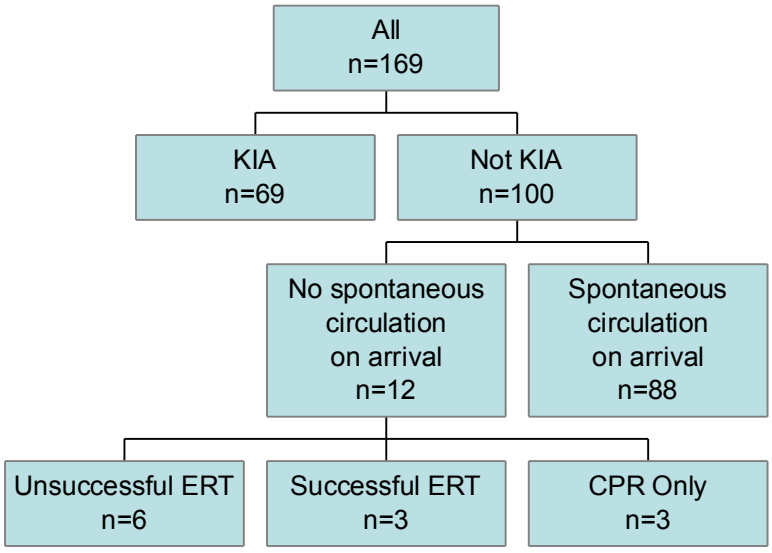

Figure 4.2: Flow diagram of cohort selection

Abbreviations: KIA – killed in action, ERT – emergency resuscitative thoracotomy, CPR – cardiopulmonary resuscitation.

Table 4.5: Injury pattern in patients with a central pulse (Laparotomy vs No-Laparotomy).

	Total	Lap	No-Lap	p
n	88	34	54	
Demographic				
Median Age, (IQR)	24.0 (6.0)	25.0 (8.0)	24.0 (4.0)	0.162
Male, n (%)	88 (100%)	34 (100%)	54 (100%)	N/A
Injury Severity				
Median ISS, (IQR)	29 (14)	33 (13)	26 (11)	< 0.001
Median NISS, (IQR)	45 (23)	57 (19)	41 (26)	< 0.001
Median RTS, (IQR)	6.38 (3.75)	4.09 (2.29)	7.84 (3.75)	< 0.001
Associated injuries				
Median Head AIS, (IQR)	0 (0)	0 (0)	0 (0)	0.531
Head AIS ≥ 3, n (%)	6	3	3	0.554
Median Chest AIS, (IQR)	0 (0)	0 (0.5)	0 (0)	0.022
Chest AIS ≥ 3, n (%)	5	5	0	0.004
Median Abdominal AIS, (IQR)	1.0 (2.0)	2.0 (2.0)	0 (2.0)	< 0.001
Abdominal AIS ≥ 3, n (%)	14	11	0	< 0.001
Amputation Type				
HQ / BK, n (%)	1	0	1 (1.9%)	0.055
AK / AK, n (%)	26	14 (41.2%)	12 (22.2%)	
AK / BK, n (%)	15	6 (17.6%)	9 (16.7%)	
BK / BK, n (%)	13	7 (20.6%)	6 (11.1%)	
AK / - , n (%)	10	4 (11.8%)	6 (11.1%)	
BK / - , n (%)	23	3 (8.8%)	20 (37.0%)	

Abbreviations: IQR – Interquartile Range, ISS – Injury Severity Score, NISS – New Injury Severity Score, RTS – Revised Trauma Score, AIS – Abbreviated Injury Score, HQ – Hindquater, AK – Above Knee, BK – Below Knee.

More relevant, in terms of wounding mechanism, is a case series from Iraq, comprising 18 patients exposed to close proximity blast injury from IEDs (41); 4 patients were dead on arrival, 5 had long bone fractures, 2 penetrating head injuries and 1 laparotomy. However, no patients sustained traumatic amputation, suggesting a different type of IED threat to that experienced in Afghanistan.

Our results confirm that traumatic lower extremity amputation caused by IED strikes is associated with high mortality, which broadly correlates with the extent of the traumatic amputation (HQ vs AK vs BK). Our study also confirms that these injuries are frequently associated with other, often severe injuries to the abdomen, thorax and head. However, most of these injuries occur in those killed in action. In casualties who survive to the Role 3 facility at Camp Bastion, thoracic and traumatic brain injuries which are not clinically obvious, and thus require CT for diagnosis, appear to be rare. This finding has important implications for practice: Casualties who require laparotomy, either for proximal vascular control, or clinically obvious abdominal injuries, and who have no apparent thoracic or head injuries on clinical examination or plain chest x-ray, do not require “intra-operative” CT scanning. Instead, these patients should have CT scan on completion of their surgery, en route to the intensive care unit.

4.4.1 Conclusions

Injury from IEDs constitutes a significant threat to coalition forces in Afghanistan. Highest amputation level can serve as a surrogate marker of injury severity. “Intra-operative” CT appears to have little value and may unnecessarily prolong surgery.

Chapter 5: Resuscitative Thoracotomy following Wartime Injury

5.1 Introduction

Resuscitative thoracotomy (RT) is performed on trauma patients who have either no central pulse or are peri-arrest (42,43). It is a dramatic manoeuvre, intended to facilitate the release of pericardial tamponade, control massive haemorrhage and air-leaks, or allow open cardiac massage and aortic control, in order to restore spontaneous circulation. RT has been thoroughly evaluated in civilian practice, with best survival rates observed in penetrating trauma to the thorax (8.8% to 33.0%), with least favourable outcomes noted in blunt injury (0.5% to 1.4%) (44-48).

Despite a significantly different wounding pattern, currently UK and US military Clinical Practice Guidelines (CPG's) are largely based upon civilian practice due to a limited evidence base (49,50). Military patients are predominantly injured by explosive and high energy gunshot mechanisms (51). These wounds are often sustained in austere circumstances with lengthier pre-hospital evacuation times in comparison to civilian Emergency Medical Service (EMS) systems (52).

However, within these constraints, there have been a number of reports of successful outcomes following RT in the combat environment (53), but only a single large series reporting 101 consecutive combat-related RTs performed between 2003-2007 with an overall survival rate of 12% (54). Specifically, there is limited data on the location and timing of cardiac arrest in combat wounded undergoing RT.

Since 2006, the UK Defence Medical Service (DMS) has been providing trauma care in Helmand Province, Southern Afghanistan at the Role 3 Hospital in Camp Bastion. Within this time there have been significant developments in combat casualty care, such as balanced resuscitation strategies, forward critical care and the use of tourniquets. The UK and US military has incorporated such developments into a paradigm of damage control resuscitation (DCR) beginning at the point-of-wounding through to discharge (55). The aim of this study is to analyse survival, and the causes and times of death in patients undergoing RT

within the context of modern battlefield resuscitation. This study aims to inform clinicians dealing with the complex decision making surrounding RT in the pulseless combat trauma patient.

5.2 Methods

A retrospective cohort study was performed on consecutive admissions to a Field Hospital in Southern Afghanistan following approval from the United Kingdom's Joint Medical Command Academic Unit and the United States Army's Institute for Surgical Research. All patients, both local nationals and NATO personnel, in circulatory arrest (i.e. no palpable central pulse), undergoing resuscitative thoracotomy (RT) were identified using the UK Joint Theatre Trauma Registry (JTTR). We defined RT as thoracotomy performed in hospital, in a pulseless patient, with the intention to restore spontaneous circulation.

Data retrieved included the mechanism and severity of injury, admission physiology, blood product use, surgical interventions, survival up to 30 days and causes of death. We were specifically interested in the location of the arrest (in the field, during evacuation or in the Emergency Department (ED)) and time from circulatory arrest to thoracotomy, where available. Admission respiratory rate, systolic blood pressure and Glasgow Coma Scale (GCS) were used to generate a Revised Trauma Score which is inversely proportion to survival (56). The Abbreviated Injury Scale was used to describe injury pattern and calculate an Injury Severity Score (ISS) and New Injury Severity Score - the greater the score, the greater the injury burden (31). A severe injury to a body region was defined as an AIS score of 3 or greater.

The UK JTTR records the complete follow-up for all UK military patients, however, the day of discharge accounts for the last day of follow-up for all other patients. Thus, in order to maximise cohort follow-up, all US patients were identified and cross referenced with the US Joint Theatre Trauma Registry. This enabled the 30-day follow-up of UK and US patients admitted to Camp Bastion.

The cohort was divided into survivors and non-survivors. Comparisons were made using the chi-squared test for categorical data and differences in means assessed using t-test's or Mann-Whitney rank-sum test for continuous variables.

5.3 Results

Between April 2006 and March 2011, there were 8402 consecutive trauma admissions to the Role 3 Hospital, Camp Bastion following combat related injury. Of these patients, 65 (0.7%) underwent RT following circulatory arrest. The arrests occurred in the field in 10 (15.4%) patients, during evacuation in 28 (43.1%) and in the ED in 26 (40.0%). The mean (± SD) age was 25 ± 7 with one female patient within the cohort. There were 19 (29.2%) local nationals, 28 (43.1%) UK military, 14 (21.5%) US military, and four (6.2%) from other NATO countries. The mean (± SD) RTS was 1.25 ± 2.0, ISS was 34 ± 20 and NISS was 47 ± 21 in the overall cohort. Of the 65 patients, return of spontaneous circulation (ROSC) was achieved in 33 (51%) patients but was not sustained in 19 (57.7%) of those; the overall survival rate was 14 (21.5%).

The age, gender distribution and mechanism of injury were similar in the survivor and non-survivor groups (Table 5.1). There is an inclination towards a greater injury burden and severity in the fatalities, however, no parameter achieves statistical significance (Table 5.1). Of note, there were no severe head injuries in the survivor group with nine (17.6%) in the non-survivor group. Survivors proportionally tended to have less severe thoracic injury ($p = 0.352$), with a greater proportion of severe extremity injury ($p = 0.253$).

Table 5.1: Demographic and injury pattern data of patients undergoing resuscitative thoracotomy at The Role 3 Hospital, Camp Bastion

	Dead	Alive	*P*
n	51	14	
Demographic Data			
Age/years, mean ± SD	25.6 ± 7.6	23.6 ± 5.4	0.314
Male, n (%)	50 (98.0%)	14 (100.0%)	1.000
Mechanism of Injury			
GSW, n (%)	22 (43.1%)	5 (35.7%)	0.618
Explosion, n (%)	29 (56.9%)	9 (64.3%)	
Trauma Scoring			
Mean ISS	36.0 ± 22.1	27.3 ± 7.6	0.636
Mean NISS	47.5 ± 22.9	43.4 ± 12.9	0.419
Head AIS ≥ 3, n (%)	9 (17.6%)	0	0.090
Neck AIS ≥ 3, n (%)	2 (3.9%)	0	0.452
Chest AIS ≥ 3, n (%)	29 (56.9%)	6 (42.9%)	0.352
Abdominal AIS ≥ 3, n (%)	18 (35.3%)	5 (35.7%)	0.977
Extremity AIS ≥ 3, n (%)	21 (41.2%)	9 (64.3%)	0.253
RTS, mean ± SD	0.98 ± 1.82	2.67 ± 2.32	0.126
Injury Burden			
Number of Injuries, mean ± SD	6.6 ± 5.8	5.6 ± 2.3	0.596
Number of Regions Injured, mean ± SD	2.8 ± 1.6	2.6 ± 1.4	0.960
Injuries Per Body Region, mean ± SD	2.3 ± 1.8	2.3 ± 0.7	0.202
Number of Severe* Injuries, mean ± SD	1.6 ± 1.0	1.4 ± 0.5	0.888

GSW, Gunshot Wound; ISS, Injury Severity Score; NISS, New Injury Severity Score; AIS, Abbreviated Injury Scale; RTS, Revised Trauma Score. *Severe injury is defined as an AIS Organ Score ≥ 3.

Comparing survivors with non-survivors, there was no difference in the time (minutes) from incident to hospital admission (70.0 ± 28.5 vs. 72.0 ± 35.4; p = 0.741). However, the time from loss of pulse to thoracotomy was significantly less in the survivor group (6.15 ± 5.8 vs. 17.7 ± 12.63; p < 0.001). The longest time between circulatory arrest and thoracotomy in a patient to survive to 30 days was 24 minutes. None of the 10 patients who arrested in the field ever had their cardiac output restored, whilst of the 29 patients who arrested en-route, 13 (44.8%) had a transient ROSC with three (10.3%) 30-day survivors. There were 26 patients who arrested in the ED, 20 (76.9%) of whom had their cardiac output restored; however, it was only sustained in 11 (42.3%) patients to 30-days (Table 5.2).

At thoracotomy, open cardiac massage was used significantly less in patients who survived to 30 days (64.3% vs. 92.2%; p 0.007) - of the five patients undergoing thoracotomy without cardiac massage, their hearts were considered contractile but empty at pericardiotomy. Aortic control - either cross clamping or manual compression - was employed similarly in both groups, to enhance cerebral and myocardial perfusion. One survivor required release of a cardiac tamponade and repair of the right ventricular outflow tract following fragmentation injury and ED arrest. Several thoracic haemorrhage control manoeuvres (pulmonary tractotomy, non-anatomical lung resection, vascular repair) were employed in both groups evenly. A greater proportion of survivors required a concomitant laparotomy for haemorrhage control in the abdomen although this only trended towards statistical significance (57.1% vs. 31.4%; p = 0.077). Table 5.3 includes a summary of operative procedures within the groups.

There were significantly more blood products utilised in the resuscitation of patients who ultimately survived (p < 0.001; Table 5.3). The mean FFP:PRBC ratio was also higher in the survivor group (0.9 ± 0.1 vs 0.7 ± 0.4; p = 0.051). There was no significant difference in the use of Tranexamic acid or Recombinant Factor 7a.

Table 5.2: Location of circulatory arrest, presenting cardiac rhythm and timeline data of patients undergoing resuscitative thoracotomy at Camp Bastion

	Dead	Alive	*P*
n	51	14	
Circulatory Arrest Location			
In the Field, n (%)	10 (19.6%)	0	0.001
Evacuation, n (%)	26 (51.0%)	3 (21.4%)	
Emergency Department, n (%)	15 (29.4%)	11 (78.6%)	
Arrest Rhythm			
Asystole, n (%)	7 (13.7%)	0	0.002
Pulseless Electrical Activity, n (%)	18 (35.3%)	13 (92.9%)	
Ventricular Fibrillation, n (%)	2 (3.9%)	0	
Unknown, n (%)	24 (47.1%)	1 (7.1%)	
ROSC at any time, n (%)	19 (37.3%)	14 (100.0%)	< 0.001
Timeline Data/Mins			
Incident to Admission, mean ± SD	70.0 ± 28.5	72.0 ± 35.4	0.741
Time from Arrest to Thoracotomy, mean ± SD	17.7 ± 12.63	5.54 ± 3.8	< 0.001

Abbreviations: ROSC, Return of Spontaneous Circulation

Table 5.3: Operative maneuvers and resuscitation data of patients undergoing resuscitative thoracotomy at Camp Bastion

	Dead	Alive	*P*
n	51	14	
Surgical Intervention			
Cardiac Massage, n (%)	47 (92.2%)	9 (64.3%)	0.007
Aortic Control, n (%)	51 (100.0%)	12 (85.7%)	0.682
Lobectomy, n (%)	2 (3.9%)	2 (14.3%)	0.153
Release of Tamponade, n (%)	0	1 (7.1%)	0.054
Bronchial Repair, n (%)	1(2.0%)	0	0.597
Vascular Repair, n (%)	2 (3.9%)	1 (7.1%)	0.611
Laparotomy, n (%)	16 (31.4%)	8 (57.1%)	0.077
Resuscitation			
PRBC, mean ± SD / units	10.3 ± 12.2	36.1 ± 38.6	< 0.001
FFP, mean ± SD / units	7.8 ± 10.9	33.1 ± 32.3	< 0.001
Cryoprecipitate, mean ± SD / units	0.45 ± 1.14	2.79 ± 2.97	< 0.001
Platelets, mean ± SD / units	0.81 ± 1.84	5.29 ± 5.36	< 0.001
Fresh Whole Blood, mean ± SD / units	0	2.5 ± 5.7	0.003
Tranexamic Acid, n (%)	9 (17.6%)	3 (21.4%)	0.711
Recombinant Factor 7a, n (%)	10 (19.6%)	6 (42.9%)	0.090

Abbreviations: PRBC, Packed Red Blood Cells; FFP, Fresh Frozen Plasma.

The majority of deaths (45 patients or 88.2%) occurred intra-operatively with a mean time from admission to death of 33 ± 33 minutes. Only 13 (28.9%) of these patients had ROSC, although none were sustained for a significant period of time. All 45 patients died from haemorrhage and irretrievable cardiovascular collapse, although nine patients had also sustained a severe head injury. Nineteen patients were successfully resuscitated, achieving sufficient cardiovascular stability to be transferred to the ICU. Ultimately, three patients died within 24 hours following refractory hypotension, fulminate multi-organ failure and coagulopathy. Two patients had sustained hypoxic brain injuries, dying on post-operative days 1 and 2 respectively. The mean time from admission to death in patients surviving to ICU was 19.8 ± 26.8 hours.

Of the remaining 14 patients, one local national was discharged ambulatory from intensive care on day 14 and onwards to a local Afghan facility on day 22. Seven UK and six US patients underwent strategic aeromedical evacuation to their respective countries for continued care, with follow-up available for all patients to 30-days.

5.4 Discussion

We report a series of 65 patients undergoing emergency resuscitative thoracotomy for circulatory arrest following combat injury with 14 survivors (21.5%). The majority of survivors arrested in the ED, with a minority occurring during medical evacuation. No patient arresting in the field achieved a return of spontaneous circulation and no patient with a severe head injury survived beyond 24 hours. Of the patients in whom cardiac output was restored long enough to be transferred to the ICU, a quarter ultimately died of either physiological exhaustion or hypoxic brain injury within three days of injury. In the remaining 14 patients, 13 have been followed-up to 30 days and one local national to discharge at 22 days.

This registry study is limited by its retrospective nature in that we may not have identified all eligible patients and are unable to report detailed neurological outcomes. We are also unable to comment on the use of cardio-pulmonary resuscitation in the field as this pre-hospital data is not recorded within the JTTR. However we are confident that we have captured all relevant cases by

extensive cross-checking databases with operating surgeons. Additionally, we have derived causes of death from the registry data, which is not as comprehensive as a formal autopsy.

Factors associated with survival, in the civilian literature, include injury pattern and length of warm ischaemia (42,43). Survival rates have been reported as high as 38% in subgroup analyses of patients who presented with thoracic stab wounds and tamponade (57-59). However, a review by the trauma sub-committee of the American College of Surgeons (44) identified an overall survival rate of 7.8% in 7035 thoracotomies: 11.2% for penetrating and 1.6% for blunt injury. Best results have been found in patients with cardiovascular collapse from cardiac tamponade following isolated cardiac chamber injury (59,60). Time between arrest and restoration of cardiac output is variable in survivors (61), although a maximum of 30 minutes is generally accepted (45,62).

However, military trauma is significantly different from civilian in both mechanism and anatomical wounding pattern (51). In the current conflict, there is a preponderance towards blast injury and high energy transfer ballistic injury yielding heavily contaminated wounds with substantial tissue destruction (16). Thus, the civilian experience of RT has limited applicability to military wounded. The evidence for the use of resuscitative thoracotomy in the military is currently limited to case series (53) and cohort studies (54,63).

Our results are comparable to the best civilian outcomes, despite an injury pattern dominated by extra-thoracic injury and exsanguination. These outcomes have been achieved by several components related to the treated population and system of treatment. Firstly our patients were generally young and fit with a significant physiological reserve permitting a degree of resilience to major insults. In terms of care, the treatment of patients commenced at the point of wounding, which while in this cohort did not prevent any patients arresting, it may have extended time with a spontaneous circulation. Furthermore, upon admission to the Field Hospital, all patients received aggressive DCR to restore volume and achieve surgical haemostasis, combined with field critical care.

The largest series to date looks at the outcomes following emergency thoracotomy from a US combat support hospital in Iraq in 2003-2007 (54). Edens and colleagues reported a 12% survival rate in a consecutive series of 101 patients injured by all mechanisms (blunt and penetrating). There were no survivors in the seven patients injured by a blunt mechanism. The primary location of wounding was the thorax (40%), abdomen (30%), extremities (22%) and the head/neck (2%).

Our series extends these findings to the Afghan theatre although there are differences in injury pattern and resuscitation. We report a higher proportion of patients with severe extremity injury (46.2%), which is characteristic of the dismounted complex blast injury, a signature injury of the war in Afghanistan (Figure 5.1) (64). Patients who are hypovolaemic from a severe limb injury may be more likely to achieve a ROSC if the circulating volume is rapidly restored. Our study reports more than twice the average PRBC (36U versus 15U) and four times the average FFP (33U versus 7U) used per survivor than in Edens' study. Balanced resuscitation is associated with improved outcomes (65).

Our results are further complimented by a prospective observational study of 52 patients with military traumatic circulatory arrest at Camp Bastion performed by Tarmey and co-workers (63). They reported 14 (27%) patients exhibiting ROSC, although only sustained in 4 (8%). RT was performed in 12 patients, including the 4 who survived to discharge. The majority of deaths (79%) occurred within an hour and the longest duration of arrest associated with survival was 24 minutes. It is important to note that our study overlaps with their work, although we have only examined the sub-group of patients undergoing resuscitative thoracotomy.

They concluded that despite higher ISS scores than contemporary civilian studies and the high prevalence of exsanguination, outcomes were similar. They identified short arrest times, presence of electrical activity and cardiac movement on ultrasound to be associated with successful resuscitations. Unfortunately, we are unable to report the role of ultrasound and although we do not know the presenting rhythm of 38.5% of our cohort, 92.9% of survivors were in a PEA rhythm.

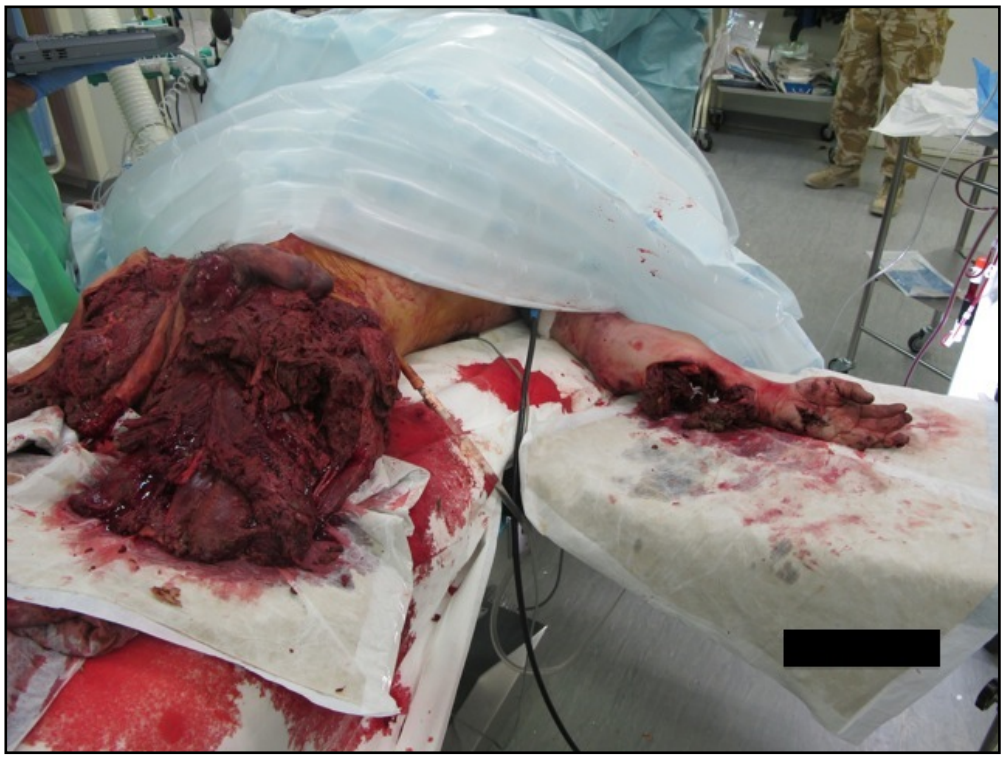

Figure 5.1: A typical example of a patient sustaining a dismounted complex blast injury with bilateral traumatic lower extremity amputation

The UK and US military have both published CPG's for the use of RT, of which we are able to comment on the penetrating component of the guidelines. The UK DMS CPG starts with an assessment for the presence of "signs of life" - absence in the field suggests that RT is futile contra- indicated in such circumstances (49). The guideline goes on to suggest that RT should only be performed if it can be accomplished within 5 minutes from the loss of "signs of life". The US military's CPG is similar, but specifies that RT should only be performed within 10 minutes from the loss of a pulse in patients without an isolated head injury (50).

Our data largely support these guidelines which recognise the time critical nature of RT and the futility in the presence of head injury and arrest in the field. However, the data presented suggest that the time limits proposed within current CPG's are too conservative - the longest time from arrest to RT in a survivor within this series was 24 minutes. Clearly military surgeons are performing RT beyond these times - this may be due to a lack of pre-hospital information or the exercising of clinical judgment. We would suggest amending the UK and US CPG's to increase the length of time to 30 minutes within which RT may be of benefit to pulseless combat casualties.

However, it is important to recognise the dynamic nature of warfare, especially when in an expeditionary phase. Our data demonstrate that ROSC was possible in half of our patients, but only sustained in a fifth, requiring significant operative and critical care resources. These outcomes were achieved in a mature facility, with significant resources and personnel and may not extend to further forward austere locations.

The importance of a short arrest time would suggest that earlier pre-hospital thoracotomy (PHT) may be sensible. The facility for PHT exists within the DMS on the Medical Emergency Response Team (MERT) aeromedical platform and several have been performed with no survivors to date (UK JTTR, unpublished data). A previous analysis suggested that military wounding is not amenable to such an approach due to the multi-cavity nature of high energy transfer military projectiles (66). Our study highlights the importance of haemostatic resuscitation in military circulatory arrest - it is likely that a thoracotomy performed without aggressive DCR, is probably limited in its effectiveness.

We have reported 3/19 (16%) patients who had a sustained ROSC, but died of fulminate multiple organ failure in ICU. These types of patients, who ultimately die despite correction of their physiological instability, are becoming increasingly recognised as a specific sub-group. Recently the term "exsanguination shock" has been used to describe this group; however, the mechanism of this process remains elusive (67). Undoubtedly, there are multiple, complex cellular processes evolving in these severely injured patients, which if understood may assist in directing the future care of trauma patients.

5.4.1 Conclusions

Resuscitative thoracotomy is a procedure that surgeons deployed in conflict zones need to be comfortable performing as appropriate application can yield unexpected survivors. Survival rates are similar to well performing civilian centers, although the injury pattern is significantly different. Haemorrhage is the leading cause of arrest, often from abdominal and extremity trauma, with head injuries carrying a very poor prognosis. Short arrest times and in-hospital or en-route arrest locations are associated with greater survival. RT for patients arresting at the point-of-wounding appears to be futile. Survivors require significant operative, critical care and transfusion resources.

Chapter 6: Utilisation and Complications of Operative Control of Arterial Inflow in Combat Casualties with Traumatic Lower Extremity Amputations Caused by Improvised Explosive Devices

6.1 Background

Traumatic lower extremity amputation from Improvised Explosive Devices (IEDs) blasts has become the one of the most complex, challenging injuries faced by military surgeons in Afghanistan (68). Survival is largely dependent upon prompt haemorrhage control, which in the setting of distal amputation can usually be accomplished with tourniquets. However, as the amputation level ascends, haemorrhage control becomes more challenging, both in the pre-hospital and hospital setting. The case fatality rate for high transfemoral bilateral amputation exceeds 90% and junctional bleeding accounts for 20% of overall combat deaths from haemorrhage (15,68).

Several devices, pneumatic and mechanical, have been developed for the pre-hospital control of junctional haemorrhage; in contrast, hospital control has evolved little beyond conventional operative management. In general, the current approach is to obtain control of the terminal aorta or proximal iliac segments via an intra- or extra-peritoneal approach. The use of laparotomy is further rationalised, as there may also be a need to concomitantly manage intra-abdominal hollow or solid organ injury.

However, the use of proximal control, the incidence of intra-abdominal injuries and complications has yet to be characterised in a population of wartime injured. The aim of the study is evaluate the use of immediate operative control of arterial inflow and its complications.

6.2 Methods

This study was approved by the Royal Centre for Defence Medicine (RCDM) Academic Unit. All patients who sustained a traumatic lower extremity amputation and required supra-inguinal vascular control were identified from the UK Joint Trauma Registry (JTTR). The search used a combination of body

region and surgical procedures coding to identify patients injured between July 2008 and December 2010. The UK JTTR is a prospective registry recording data on casualties who trigger trauma team activation (29).

Data on patient demographics, injury severity and patterns, mechanism of injury, timeline, admission physiology, blood products and surgical procedures were retrieved. Overall injury burden was quantified using the Injury Severity Score (ISS) and New Injury Severity Score (NISS) (31). The Abbreviated Injury Scale (AIS) was used to classify anatomical injury patterns. A severe injury was defined as an AIS ≥ 3 (56).

Patients' charts were reviewed to identify the method of supra-inguinal vascular control and complications that arose. In cases where multiple levels of control were used, data on all vessels were collected. Extra-peritoneal approach (EP) was defined as control of the iliac vessels via midline or Pfannenstiel incisions without breach of the peritoneum. Intra-peritoneal (IP) approach was defined as control of vessels via the midline laparotomy incision that opened the peritoneum.

Patients were categorised as survivors or fatalities (30 day mortality) and all statistical analyses performed using SPSS 19 software (IBM®, New York). T-tests were used for continuous data, Mann-Whitney rank-sum test for ordinal data and categorical data were analysed using chi-squared test.

6.3 Results

Between July 2008 and December 2010, 260 patients were identified as having sustained traumatic lower extremity amputations, of which 51 also required proximal control (Figure 6.1). The majority (80.4%) of patients had intra-peritoneal control. Both groups (IP versus EP) were comparable in age and all patients were male (Table 6.1). Mortality was higher in the IP group than in the EP group, although this result was not statistically significant (29.3% vs 10.0%; p = 0.210).

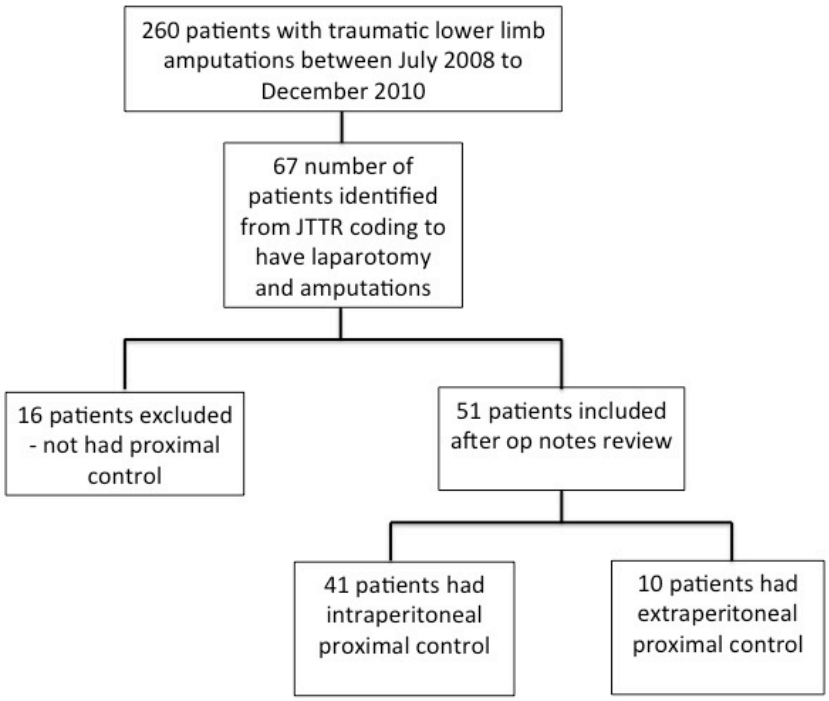

Figure 6.1: Flow diagram of the cohort selection

Table 6.1: Baseline characteristics and injury pattern of patients requiring proximal control

	IP control	EP control	*P* value
n	41	10	
Gender (%)	41 (100)	10 (100)	-
Age (years)* †	25 (6)	28 (5)	0.448
Fatalities	12 (29.3)	1 (10.0)	0.210
Trauma Scores			
Median ISS (IQR)	30 (14)	30 (12.5)	0.090∞
Median NISS (IQR)	54 (17)	54 (17)	0.777∞
Median RTS (IQR)*	4.09 (2.29)	4.09 (3.20)	0.981∞
Injury Pattern			
Head AIS ≥ 3	3 (7.3)	0 (0)	0.378
Chest AIS ≥ 3	5 (12.2)	1 (10)	0.847
Abdomen AIS ≥ 3	14 (34.1)	0 (0)	0.030
Upper Extremity AIS ≥ 3	8 (19.5)	5 (50)	0.047
Lower Extremity AIS ≥ 3	41 (100)	10 (100)	-

Values in parentheses are percentage unless otherwise stated.
*Missing data in 17 patients. ISS, Injury Severity Score; NISS, New Injury Severity Score; RTS, Revised Trauma Score; TRISS, Trauma Injury Severity Score; AIS, Abbreviated Injury Score. IP, intraperitoneal; EP, extraperitoneal. Intraperitoneal versus extraperitoneal (chi-square test, except ∞ Mann-Whitney Rank sum test).

6.3.1 Trauma Scoring and Injury Pattern

The overall median ISS was 30 and NISS was 54. There were no significant differences in ISS, NISS, RTS and TRISS between the IP and EP groups (Table 6.1). In the analysis of AIS body region scoring, the IP group had sustained a greater proportion of severe abdominal injury (p=0.03) and upper extremity trauma (p=0.047) compared to the EP group. All groups had a similar distribution of lower extremity injuries, reflective of the inclusion criteria.

The distribution of the levels of bilateral lower extremity amputees in the IP and EP group were similar with the majority of patients had sustained at least one transfemoral amputation (Table 6.2). In the IP group, a significantly greater proportion of patients had pelvic fractures compared to EP group (43.9% vs 10%; p = 0.047).

6.3.2 Type of Vascular Control

Eight patients initially required aortic control, which was released once more distal control had been established in five cases. In the IP group (n=41), the majority (73.2%) patients had bilateral control along the length of their iliac segments, and unilateral control in 19.6%. Right sided iliac segment control was more common in IP group (12.5% vs 7.3%). In the EP group (n=10), half of the patients had bilateral control of iliac segments, followed by 30% that had left sided control. There is no statistical significance observed in the various lateralities (Table 6.3, Figure 6.2).

Table 6.2: Amputation pattern in patients requiring proximal control

	IP control	EP control	*P*
n	**41**	**10**	
Amputation Number			
Single lower extremity	5 (12.2)	1 (10)	0.448
Bilateral lower extremity	28 (68.3)	6 (50)	
Triple	7 (17.1)	4 (40)	
Quadruple	1 (2.4)	0 (0)	
Lower Extremity Amputation Configuration			
Bilateral PTF	9 (22)	1 (10)	0.561
Bilateral DTF	9 (22)	3 (30)	
Bilateral BK	2 (4.9)	0 (0)	
Unilateral PTF + Other	11 (26.8)	5 (50)	
Unilateral DTF + Other	5 (12.2)	0 (0)	
Others	5 (12.2)	1(10)	

Values in parentheses are percentage unless otherwise stated. IP, intraperitoneal; EP, extraperitoneal. PTF, proximal transfemoral; DTF, distal transfemoral; TK, through knee; BK, below knee. Others include: single PTF, single DTF, single TK, single BK, TK/BK. Intraperitoneal versus extraperitoneal (chi-square test).

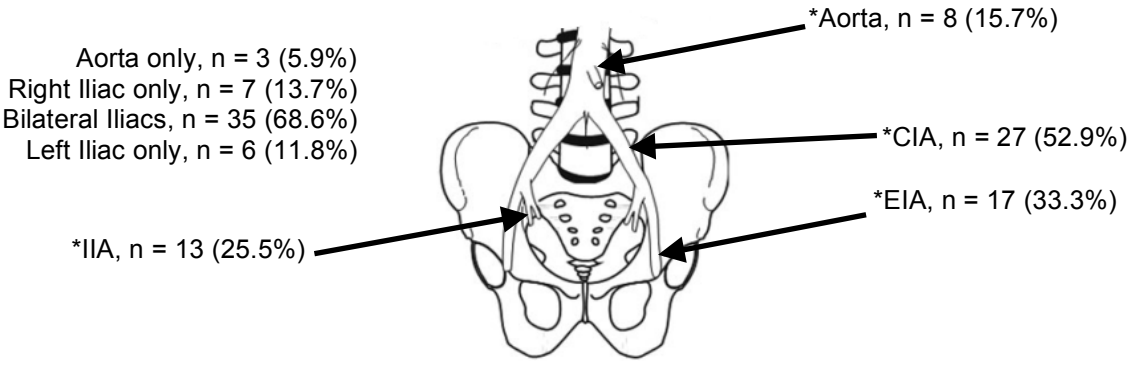

Figure 6.2: Line drawing of the pelvic vasculature with relative proportions of the regions used for control

Values in parentheses are percentage. IP, intraperitoneal; EP, extraperitoneal. *Multiple vessels allowed for. CIA, common iliac artery; IIA, internal iliac artery; EIA, external iliac artery.

Table 6.3: Breakdown of vessel control

	IP control	EP control	*P*
n	41	10	
Laterality			
Right iliac segment only	5 (12.2)	2 (20)	0.155
Left iliac segment only	3 (7.3)	3 (30)	
Bilateral iliac segments	30 (73.2)	5 (50)	
Aorta control only	3 (7.3)	0 (0)	
Named vessels			
Aorta controlled	8	-	
In isolated	3 (37.5)	-	
No CIA control	17 (41.5)	7 (70)	0.026
Right CIA	4 (9.8)	0 (0)	
Left CIA	1 (2.4)	2 (20)	
Bilateral CIA	19 (46.3)	1 (10)	
No IIA control	30 (73.2)	8 (80)	0.012
Right IIA	0 (0)	2 (20)	
Left IIA	3 (7.3)	0 (0)	
Bilateral IIA	8 (19.5)	0 (0)	
No EIA control	31 (75.6)	3 (30)	0.002
Right EIA	1 (2.4)	3 (30)	
Left EIA	1 (2.4)	2 (20)	
Bilateral EIA	8 (19.5)	2 (20)	

Values in parentheses are percentages. IP, intraperitoneal; EP, extraperitoneal. Intraperitoneal versus extraperitoneal (chi-square test). CIA, common iliac artery; IIA, internal iliac artery; EIA, external iliac artery.

The common iliac artery (CIA) was the most common vessel controlled in the IP group; amongst the 19 patients (46.3%) that had bilateral CIA control, one patient subsequently had bilateral internal iliac artery (IIA) control. In the EP group, one patient (10%) had bilateral CIA control. The control of the IIA was utilised more commonly via the IP approach compared to EP (p=0.012). External iliac artery (EIA) was the most common vessel controlled via the EP approach. (Table 6.3, Figure 6.2)

6.3.3 Indications of Abdominal Surgery

In the cohort of patients who had IP control, the indication for laparotomy was mainly for proximal control (46.3%) followed by haemodynamic instability (29.3%) and clinical suspicion of intra-abdominal injuries (24.6%). Hollow organ intervention was performed in 13 of the laparotomies, mainly for formation of colostomy (Table 6.4). Solid organ haemorrhage control manoeuvres such as liver packing or splenectomy was performed in four patients in this cohort. Over half of the patients only had proximal control from the laparotomy, 41.5% of patients had proximal control and other intra-abdominal intervention (Table 6.4).

One negative trauma laparotomy was performed in the IP group, with initial suspected abdominal injury hence laparotomy which showed no intra-operative findings, however the patient proceed to have IP proximal vascular control for superficial femoral artery and vein through and through injury.

Three patients underwent a laparotomy in the EP group; one patient had EP vascular control followed by computed tomography (CT), which demonstrated free air and the patient proceeded to a laparotomy which was negative. The remaining two patients in this group underwent formation of colostomy.

6.3.4 Complications

One patient, who had undergone IP control, suffered an injury to the common iliac vein, which was repaired. There were no other immediate complications reported.

Table 6.4: Abdominal surgery: indications and interventions

		Laparotomy
	n	41
Indications		
Proximal Control		19 (46.3)
Haemodynamic Instability		12 (29.3)
Clinical Suspicion		10 (24.4)
Imaging Directed		0 (0)
Interventions		
Proximal Control		40
Solid Organ		4
Hollow Organ		13
Vascular Repair		1
Category		
Proximal Control, *in isolation*		23 (56.1)
Proximal Control, *plus intervention*		17 (41.5)
No Proximal Control, *intervention only*		0 (0)
Non-Therapeutic Laparotomy		1 (2.4)

Values in parentheses are percentage unless otherwise stated.

6.4 Discussion

This study reports a consecutive series of 51 patients with traumatic lower extremity amputation in wartime who required supra-inguinal inflow control. The majority (80.4%) of patients had their peritoneum explored through a midline laparotomy and over half (56.1%) of patients undergoing laparotomy required no other abdominal intervention.

Traumatic amputation in wartime carries a significant burden of mortality: 40.8% of patients die prior to hospital admission, with an in-hospital mortality of 16.0% (68). Haemorrhage constitutes the leading cause of death - bilateral proximal hindquarter amputations are almost universally fatal, decreasing to a case fatality rate of 18.0% for unilateral below-knee amputations (68).

The mortality from isolated extremity injury has decreased, largely attributed to the introduction of tourniquets (18,19). However, ileo-femoral junctional and pelvic bleeding remains highly lethal (4,15) and challenging to manage (69,70). The devastating soft tissue injury associated with perineal blast injury often results in the disruption of vessels in hard to reach places. For example, gluteal artery haemorrhage is difficult to control by direct means, such as gauze packing, thus proximal control of the internal iliac becomes a key haemostatic manoeuvre. There is a higher mortality in the IP group, compared to the EP, although this does not achieve statistical significance, likely due to a lack of power within the study.

The war in Afghanistan has become characterised by the use of IEDs, which are associated with high, often bilateral, lower extremity amputations, and pelvic and genital injuries. This constellation has been termed the "Dismounted Complex Blast Injury (DCBI)" as it is generally sustained by military personnel on foot (71). Care in-hospital consists of concomitant resuscitation and haemorrhage control (69,70), often necessitating General and Orthopaedic surgeons working synchronously, as well as massive transfusion and haemostatic resuscitation, administered by the anaesthetic team. Most of the vascular injuries in our cohort were blast related, with disruption of lower extremity vasculature, where the use of proximal control is used to control bleeding and facilitate amputation.

The current study demonstrates that proximal control is felt necessary in one in five patients who sustain a traumatic lower extremity amputation, and appears to be associated with few complications. A greater number of patients had proximal control achieved by an intra-peritoneal route, which may reflect the rapidity with which infra-aortic control can be achieved. Furthermore, over half of these patients do not require any other abdominal intervention, which asks the question if control can be achieved by less invasive means.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a recently described endovascular concept where a compliant balloon is placed in the aorta to support central pressure while also providing inflow control (6). Infra-renal balloon occlusion has been demonstrated to improve survival from pelvic haemorrhage in both animal and clinical studies (72,73). Such an approach may become more feasible as endovascular capabilities become more common place in deployed operations (74).

The current study has a number of limitations that are important to recognise. The retrospective nature of this study's methodology may mean that not all eligible patients were identified and that use of proximal control has been underestimated. Furthermore, we are unable to comment on whether supra-inguinal vascular control was clinically necessary or not. We are also unable to collect reliable and consistent data on the time of control required and its effectiveness. It is also well known that documentation of complications is poor, so despite a comprehensive chart review, not all morbidity may have been captured.

Despite these limitations, this study provides insight into the utilisation of proximal control in wartime. One in five patients with a traumatic amputation requires laparotomy for proximal control, which appears to be associated with little morbidity. However, over half of patients require no other intra-abdominal intervention, suggesting that less invasive techniques of proximal control may have a role in the future. Further prospective study is required to determine the need and effectiveness of proximal control in couple with exploration of novel methods of pre-hospital and hospital haemorrhage control.

Chapter 7: Aortic Balloon Occlusion is Effective in Controlling Pelvic Haemorrhage

7.1 Introduction

Vascular disruption with concomitant haemorrhage is the leading cause of potentially preventable death following military and civilian trauma (14-16). Vascular injury within the pelvis and proximal femoral region is particularly challenging, as it exists within a junctional zone between the torso and the extremities (75,76). In this anatomic location, pelvic and proximal femoral vascular injury is not readily amenable to direct pressure or tourniquet application and generally requires control to be obtained within the abdomen.

The issue of vascular control in the setting of pelvic and junctional femoral haemorrhage has become particularly relevant to surgeons treating patients injured by improvised explosive devices (IEDs) (68). Frequently these patients have sustained bilateral high lower extremity amputations with pelvic disruption and present *in extremis* requiring significant resuscitation and immediate operation (70). Often, the first surgical manoeuvre required is occlusion of the terminal aorta through a laparotomy in order to reduce bleeding and enhance central aortic pressure.

An alternative method of aortic control is the use of endovascular aortic balloon occlusion, a technique which has been used in the setting of elective and emergent aneurysm repair for many years (10,77). When used in the trauma context, this technique has been termed resuscitative endovascular balloon occlusion of the aorta or REBOA (6). The technique of REBOA does not require an operative room (OR) and has been used to salvage patients with pelvic trauma who are too unstable to move from the emergency room (ER) (72). Recently, three aortic zones have been proposed for consideration with the use of REBOA. Zone I: an occlusion zone of the descending thoracic aorta; Zone II: a non-occlusion zone consisting of the paravisceral aorta; and Zone III: an occlusion zone of the infrarenal aorta (6). The aim of this study is to evaluate the effectiveness of Zone III REBOA in a porcine model of pelvic arterial haemorrhage.

7.2 Materials and Methods

7.2.1 Study Overview

This study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) and was undertaken at an accredited facility (Lackland Air Force Base, San Antonio, TX) under the supervision of licensed veterinary staff. Female Yorkshire swine (*Sus Scrofa*), aged between 5-6 months, weighing between 75-100 kg were studied. Animals were physically fit and free of pathogens having undergone a quarantine and acclimatisation phase in the facility 7 days prior to the protocol.

The study consisted of two phases, each comparing the effectiveness of the haemostatic interventions Combat Gauze and Zone III REBOA (Figure 7.1). In Phase I, the clotting profile was unaltered and included a control group with no intervention (NI) and a Combat Gauze™ (CG) and a Zone III REBOA (REBOA) group. Phase II of the study was performed in the setting of an induced dilutional coagulopathy testing the effectiveness of Combat Gauze (CG-C) and Zone III (REBOA-C).

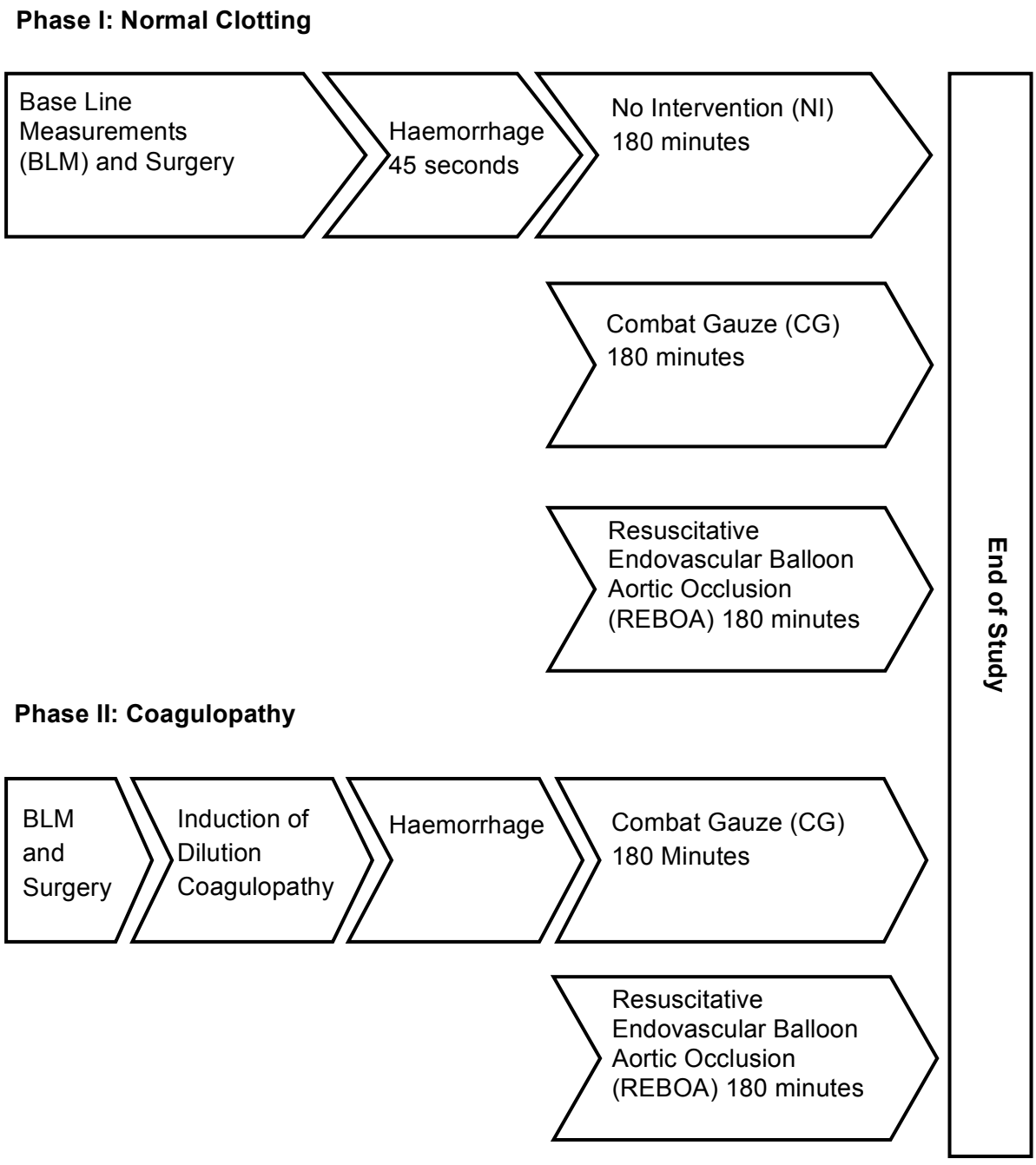

Figure 7.1: Schematic representation of experimental groups and timelines

Following induction of anaesthesia, all groups were entered into three consecutive stages of the protocol: injury (distal iliac artery injury), haemorrhage (45 seconds) and haemostatic intervention (180 mins). Following the haemostatic intervention phase the animals were euthanised for post-mortem analysis and the terminal aorta harvested for histological examination.

7.2.2 Animals Preparation

Following cannulation of an ear vein, anaesthesia was induced with intravenous Ketamine and maintained with Isoflurane (range: 2 - 4%) following oro-tracheal intubation and mechanical ventilation. All animals underwent cannulation of the internal jugular vein and common carotid artery with a large bore cannula through a midline surgical exposure using a modified Seldinger technique. This permitted large intra-venous volume infusion using a Belmont fluid infuser and transduction of the arterial cannula enabled continuous blood pressure monitoring. Throughout the protocol, heart rate (HR), blood pressure (BP), end tidal carbon dioxide (CO_2), core temperature (rectal) and urine output (UOP) were continuously monitored. Maintenance intravenous fluid was infused through the ear-vein with Lactated Ringers Solution at a rate of 100ml/hr as soon as practicable. Prior to commencement of the injury stage, baseline blood tests were drawn from the arterial line and physiological measurements recorded.

7.2.3 Induction of Dilutional Coagulopathy

The technique used has been described in a previous publication (78) and was utilised in Phase II of this study. Following pre-peritoneal surgical exposure, the iliac artery is cannulated with a 14 F sheath. This enabled the removal of 60% of the animals circulating volume at a rate of 60 ml/min. This is accompanied by concomitant replacement with a colloid (Hextend™) at the same rate and volume. The animal does not undergo any active warming in order to exacerbate the coagulopathy. All blood tests and baseline monitoring are repeated post-dilution with a target INR of between 1.4 and 1.6.

7.2.4 Surgical Injury and Haemorrhage

A standard model of non-compressible junctional pelvic arterial haemorrhage was developed. A midline incision was used to access the right sided pre-peritoneal space. Using blunt dissection, the distal external iliac artery was

identified and controlled with silastic vessel loops. The vessel was dissected free of adventitial tissue 5 cm proximal to the distal bifurcation. Following proximal and distal control, a small arteriotomy was performed to enable the deployment of a 6 mm arterial punch to create a standard arterial defect. All clamps and loops were then removed to permit 45 seconds of uncontrolled arterial haemorrhage. Blood was evacuated from the wound by surgical suction applied to the periphery of the wound (as not to disrupt any clot formation) into graduated containers to record volume.

7.2.5 Haemostatic Intervention

Common to all groups was a IV bolus of 500 ml of colloid (Hextend™) following the conclusion of the haemorrhage stage. Subsequent IV fluid administration with Lactated Ringers Solution at 100 ml/min (to a maximum of 10l) is triggered when the MAP is less than 65 mmHg. Recordings of all physiological parameters were made at 15 minute intervals throughout the protocol. The NI group underwent no further intervention.

The CG and CG-C groups underwent packing of the wound with Combat Gauze (packaged as a 3 inch by 12 foot roll) and the application of pressure for 2 minutes. At the end of 2 minutes, should bleeding have persisted around or through the gauze, it was replaced with a new roll of Combat Gauze™. A maximal of 2 rolls was permitted and the wound was left undisturbed after the second roll. Surgical suction was applied to the periphery of the wound to record losses.

The REBOA and REBOA-C groups had a 0.035' wire pre-positioned in the left femoral artery following an ultrasound guided puncture and Seldinger insertion. A Cook® Medical Coda® Balloon Catheter was mounted on the wire, but not advanced beyond the skin of the animal. An angiogram was obtained to ensure correct wire position and to delineate the aortic anatomy. Following conclusion of the haemorrhage stage, the wire was advanced into the aorta and the balloon catheter delivered into the region of the terminal aorta and inflated to resistance under fluoroscopic guidance.

The experiment was concluded at 180 minutes post haemorrhage or sooner if the animal died (defined as a MAP < 20 mmHg and ET CO_2 < 15 mmHg). At the end-

of-study point, final laboratory blood samples were drawn and physiological recordings made. Total blood loss was calculated from the volume in the surgical suction reservoir and weight of surgical sponges and combat gauze (if used).

7.2.6 Study End-Points

The primary end point of the study was mortality within 180 minutes. Secondary end-points were the MAP at 15, 60 and 180 mins, rate of haemorrhage (ml/min), volume of resuscitation fluid, measures of acidosis and tissue ischemia (pH, BE and lactate) and evidence of histological damage to the terminal aorta.

7.2.7 Statistical Analysis

Data were analysed using SPSS® 19.0 (SPSS, Chicago, Illinois, USA). Chi-square tests were used to compare categorical data, analysis of variance (ANOVA) and t-tests for normally distributed continuous variables and Mann-Whitney rank-sum tests for non-normally distributed variables. Kaplan-Meier rank-sum test in conjunction with survival plots were used for survival analysis.

7.3 Results

Thirty-eight consecutive animals were entered into the investigation; 3 model development and 35 study animals. All animals had similar pre-injury physiologic and laboratory indices (Table 7.1) except for weight. The animals in the NI group where heaviest with animals in the GC group the lightest. There was no difference among groups when comparing the volume of blood loss during the 45 second haemorrhage phase ($p = 0.366$).

In Phase I (normal coagulation profile) the rate of haemorrhage (ml/min) during the intervention phase was greatest in the NI group (822 ± 415 ml/min) compared to the REBOA (9.5 ± 12.1 ml/min) and the CG groups (0.2 ± 0.4 ml/min) (Table 7.2). All of the animals in NI died within 15 min with no deaths in either the CG or AB groups (Figure 7.2). During the Phase I experiments, there was no difference between the MAP (mmHg) in the CG vs REBOA groups at 15 mins (70 ± 4 vs 70 ± 11; $p = 0.955$), 60 mins (71 ± 7 vs 63 ± 15; $p = 0.209$) or 180 minutes (71 ± 9 vs 56 ± 27; $p = 202$) (Figure 7.4).

Table 7.1: Baseline characteristics of study groups

	NI	CG	REBOA	CG-C	REBOA-C	*P*
n	7	7	7	7	7	
Weight / Kg	93.1 ± 10.7	71.7 ± 7.2	74.5 ± 10.8	86.3 ± 3.9	75.9 ± 12.5	0.001
Female	7 (100%)	7 (100%)	7 (100%)	7 (100%)	7 (100%)	1.000
MAP / mmHg	67 ± 11	61 ± 12	59 ± 7	66 ± 18	59 ± 7	0.569
HR / beats per min	85 ± 21	85 ± 17	69 ± 10	82 ± 18	81 ± 8	0.287
ET CO_2 / mmHg	35 ± 4	40 ± 2	38 ± 4	36 ± 4	37 ± 4	0.167
Temp / ^{o}C	36.0 ± 3.7	37.8 ± 0.5	36.4 ± 1.4	36.1 ± 2.1	35.8 ± 3.1	0.723
pH	7.46 ± 0.06	7.31 ± 0.04	7.45 ± 0.03	7.48 ± 0.04	7.44 ± 0.04	0.400
Base Excess	1.8 ± 2.8	3.1 ± 2.5	2.6 ± 1.4	3.7 ± 2.1	6.1 ± 6.4	0.222
Lactate / mmol/L	2.0 ± 1.6	2.1 ± 1.6	1.7 ± 1.7	1.0 ± 0.3	1.6 ± 0.3	0.583
Haemoglobin / g/dL	10.2 ± 1.3	10.0 ± 0.7	10.2 ± 0.8	10.0 ± 0.5	9.0 ± 0.7	0.090
Hemtocrit	32.0 ± 3.7	31.5 ± 2.0	32.2 ± 2.3	31.5 ± 1.7	28.7 ± 2.1	0.076
Platelet Count / 10^{10}/L	271 ± 51	318 ± 72	308 ± 80	359 ± 37	312 ± 34	0.126
PT / Seconds	13.8 ± 0.5	13.6 ± 0.3	28.5 ± 0.3	13.6 ± 0.4	14.0 ± 0.5	0.518
aPTT / Seconds	32.7 ± 8.8	31.1 ± 3.9	31.8 ± 7.5	30.6 ± 5.0	30.0 ± 9.2	0.965
INR	1.0 ± 0.1	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.1 ± 0.0	0.070
Fibrin / mg/dL	187 ± 30	193 ± 26	210 ± 40	218 ± 24	173 ± 14	0.042

Abbreviations: NI - No Intervention, CG - Combat Gauze, REBOA - Resuscitative Endovascular Balloon Aortic Occlusion, MAP - Mean Arterial Pressure; HR - Heart Rate; ET CO_2 - End Tidal Carbon Dioxide; PT - pro-thormbin time; aPTT - activated partial thromboplastin time; INR - International Normalised Ratio.

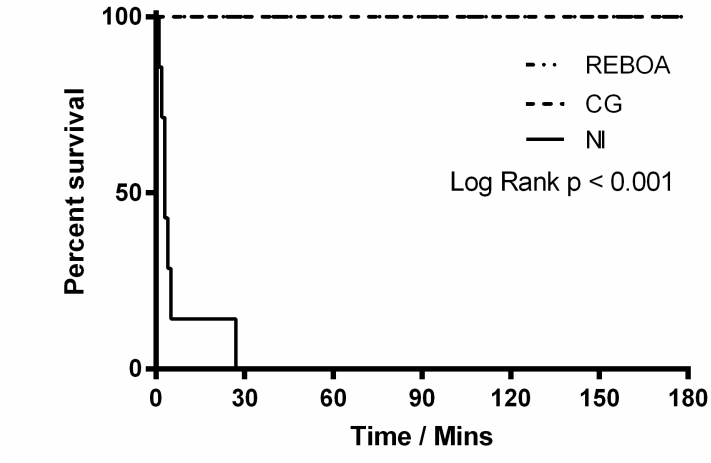

Figure 7.2: Kaplan-Meier survival curve of animals with no coagulopathy.

Treated with either no intervention (NI), combat gauze (CG) or resuscitative endovascular balloon occlusion aortic (REBOA)

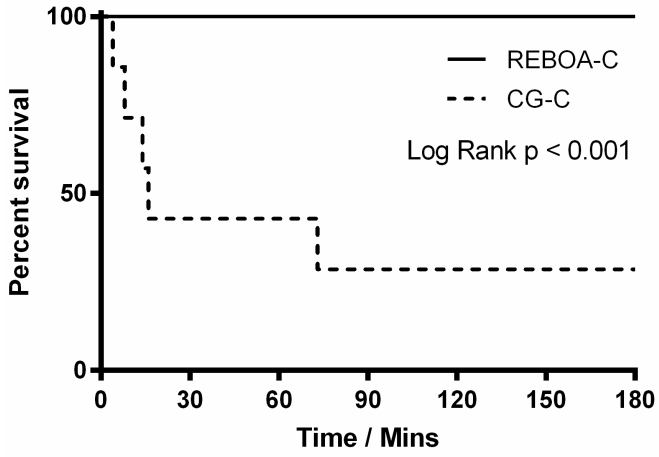

Figure 7.3: Kaplan-Meier survival curve of animals with dilution coagulopathy

Treated with either combat gauze (CG-C) or resuscitative endovascular balloon occlusion aortic (REBOA-C)

Table 7.2: Comparison of end-of-study laboratory, blood loss and meab survival length between groups

	NI	CG	REBOA	*P* *	*P* **	CG-C	REBOA -C	*P* ***
n	7	7	7					
pH	7.56 ± 0.04	7.48 ± 0.04	7.43 ± 0.06	0.001	0.152	7.54 ± 0.07	7.43 ± 0.05	0.008
Base Excess	-2.6 ± 3.0	5.5 ± 1.2	2.2 ± 5.6	0.003	0.040	0.6 ± 2.6	1.7 ± 3.0	0.491
Lactate / mmol/L	5.5 ± 1.9	2.0 ± 1.2	3.8 ± 4.6	0.125	0.281	6.1 ± 2.5	5.6 ± 1.1	0.653
Hemoglobin / g/dL	9.2 ± 2.5	7.5 ± 1.1	5.8 ± 2.2	0.015	0.121	4.8 ± 2.6	3.5 ± 1.6	0.284
Hematocrit	29.1 ± 7.4	23.8 ± 3.2	18.9 ± 6.7	0.016	0.094	15.7 ± 7.9	11.8 ± 5.0	0.288
Platelet Count / 10^{10}/L	217 ± 62	254 ± 69	203 ± 64	0.314	0.281	88 ± 32	104 ± 30	0.342
PT / Seconds	14.5 ± 1.0	13.8 ± 0.3	15.9 ± 3.3	0.186	0.040	24.3 ± 5.7	34.3 ± 9.7	0.037
aPTT / Seconds	24.3 ± 5.3	24.6 ± 2.4	21.2 ± 4.8	0.258	0.072	24.9 ± 12.8	43.2 ± 32.6	0.199
INR	1.1 ± 0.1	1.0 ± 0.0	1.2 ± 0.3	0.193	0.040	2.1 ± 0.6	3.3 ± 1.2	0.038
Fibrin / mg/dL	133 ± 31	158 ± 20	124 ± 38	0.119	0.054	70 ± 28	60 ± 1.9	0.401
Hemorrhage Phase BL	957 ± 264	786 ± 225	1031 ± 385	0.307	0.164	943 ± 341	1043 ± 321	0.582
Intervention Phase BL	3207 ± 2354	32 ± 74	1709 ± 2177	0.017	0.064	2536 ± 1234	3579 ± 1169	0.130
Blood Loss / min	822 ± 415	0.2 ± 0.4	9.5 ± 12.1	< 0.001	0.001	274 ± 104	20 ± 7	0.041
Total IV Fluid / ml	703 ± 887	3250 ± 1841	6679 ± 4243	0.002	0.070	5359 ± 2565	8459 ±3286	0.073
Rate of IV Fluid / ml/min	133 ± 59	18 ± 10	37 ± 24	< 0.001	0.066	257 ± 237	47 ± 18	0.037
Mortality, n (%)	7 (100%)	0	0	< 0.001	n/a	5 (71.4%)	0	0.010
Length of Survival, min	6.4 ± 9.2	180 ± 0	180 ± 0	< 0.001	1.000	68 ± 80	180 ± 0	0.003

Abbreviations: NI - No Intervention, CG - Combat Gauze, REBOA - Resuscitative Endovascular Balloon Aortic Occlusion; min - minutes; PT - pro-thormbin time; aPTT - activated partial thromboplastin time;INR - International Normalized Ratio; BL - Blood Loss.
* NI vs GC vs REBOA, ** GC vs REBOA, *** GC-C vs REBOA-C

The REBOA group required an apparent but not significantly higher resuscitation rate and total volume during the protocol than the CG group. At the termination of the protocol the CG group had a higher BE (5.5 ± 1.2 vs 2.2 ± 5.6; p = 0.040) and lower INR (1.0 ± 0.0 vs 1.2 ± 0.3; p = 0.040) than the REBOA group (Table 7.2).

Similar and effective coagulopathy during Phase II of the study was confirmed with INR measurements post-dilution in the CG-C (INR 1.4 ± 0.3) and REBOA-C (1.5 ± 0.3) groups (p=0.507). There were no differences between the baseline physiologic or laboratory measurements (Table 7.2) or the post-dilution measurements (Table 7.3) in either the CG-C or REBOA-C groups during Phase II of the study.

Mortality during Phase II of the study was 71.4% (5 of 7) in the CG-C group compared to 0.0% in the REBOA-C group (p=0.010) (Figure 7.3). The REBOA-C group required a larger volume of IV fluid than the CG-C group (p = 0.073), however, when comparing the rate of administration, the REBOA-C group required a significantly lower rate of infusion (47±18 vs. 257 ± 237; p 0.037) (Table 7.3).

During Phase II of the study, the MAP at 15 mins was greater in the REBOA-C (71±12) than the CG-C and group (28±31; p=0.005) a finding that was sustained through to the end of the protocol (Figure 7.5). There was no difference in the histological appearance of the terminal aorta between any of the groups.

7.4 Discussion

This study describes a novel translatable model of pelvic vascular injury resulting in a consistent rate of haemorrhage and mortality. Findings from this study demonstrate that in the setting of normal coagulation, Zone III REBOA is equally effective at controlling haemorrhage as manual pressure with a known topical haemostatic agent (Combat Gauze™) but results in greater resuscitative fluid requirements. In the setting of dilutional coagulopathy, Zone III REBOA provides better haemorrhage control, improved central aortic pressure and lower mortality than the established topical haemostatic agent. In this model, Zone III REBOA was technically feasible and resulted in no adverse aortic injury.

Table 7.3: Physiological and laboratory indices post induction of dilutional coagulopathy

	CG-C	REBOA-C	P value
n	7	7	
Physiology			
MAP	75 ± 14	88 ± 13	0.103
HR	101 ± 21	129 ± 28	0.055
ET CO_2	33 ± 3	38 ± 4	0.032
Temp	35.1 ± 2.3	35.4 ± 0.3	0.737
Laboratory			
pH	7.44 ± 0.04	7.40 ± 0.02	0.058
Base Excess	1.7 ± 1.8	2.0 ± 0.4	0.718
Lactate / mmol/L	6.5 ± 9.5	2.9 ± 0.4	0.383
Haemoglobin / g/dL	3.2 ± 0.7	2.9 ± 0.7	0.339
Haematocrit	10.7 ± 2.2	9.5 ± 2.3	0.358
Platelet Count / 10^{10}/L	109 ± 30	79 ± 30	0.086
PT / Seconds	17.9 ± 2.4	18.9 ± 3.0	0.507
aPTT / Seconds	18.8 ± 2.3	17.9 ± 1.3	0.351
INR	1.4 ± 0.3	1.5 ± 0.3	0.507
Fibrin / mg/dL	89 ± 27	78.9 ± 27	0.491

Abbreviations: CG - Combat Gauze, REBOA - Resuscitative Endovascular Balloon Aortic Occlusion, MAP - Mean Arterial Pressure; HR - Heart Rate; ET CO_2 - End Tidal Carbon Dioxide; PT - pro-thrombin time; aPTT - activated partial thromboplastin time; INR - International Normalised Ratio.

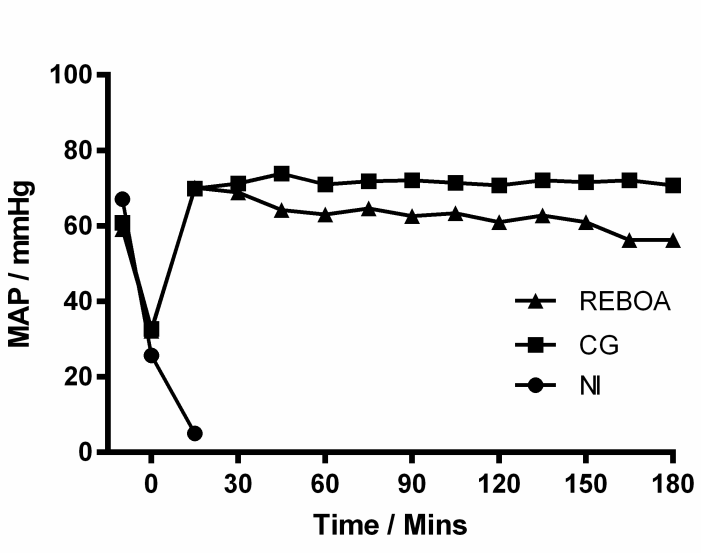

Figure 7.4: Mean MAP in animals with normal coagulation

Undergoing treatment with either no intervention (NI), combat gauze (CG) or resuscitative endovascular balloon occlusion aortic (REBOA)

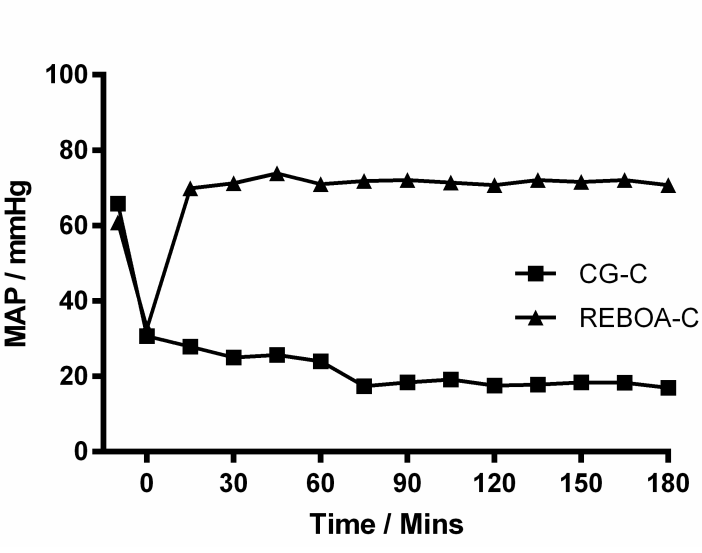

Figure 7.5: Mean MAP in animals with dilution coagulopathy

Undergoing treatment with either combat gauze (CG-C) or resuscitative endovascular balloon occlusion aortic (REBOA-C)

Findings from the current study confirm and extend previous work by White et al. who utilised a porcine model of haemorrhagic shock (79) to demonstrate the superiority of Zone I REBOA to emergency thoracotomy in class IV shock (80). Animals that underwent Zone I REBOA had a higher pH, lower lactate and required less fluid and inotropic support during resuscitation than animals undergoing thoracotomy and aortic clamping. These findings are further supported by the recent work by Avaro et al. who demonstrated that 40 minutes of Zone I occlusion increased the 2 hour survival of animals in hypovolaemic shock compared to those treated with saline (7/16 vs 0/9; $p = 0.03$). All studies demonstrated an improvement in mean blood pressure following REBOA. Importantly, the current study is the first to examine Zone III occlusion in the context of a specific vascular injury model.

Interestingly, REBOA has been previously examined by studies undertaken in the 1950s and 1970s, although in a less formalised manner (15,16). Studies undertaken in dogs found that Zone I occlusion in shock was associated with a rise in central blood pressure and a reduction in traumatic abdominal haemorrhage (81,82). However, the technique was not recommended for practice due to the high incidence of hind limb paralysis in survived subjects, although this could be eliminated with the use of hypothermia (83).

The current study also extends the findings from groups which have studied the effectiveness of the procoagulant topical haemostatic agent Combat Gauze™ in porcine models of femoral arterial injury (78,84-86). Results from the current investigation demonstrate that the haemostatic effect of CG is present even in the setting of an injury to a larger artery such as the iliac. Furthermore, this study confirms the observation by Kheirabadi et al. that the effectiveness of CG is reduced in the setting of a dilutional coagulopathy (78). Dilutional coagulopathy reduces all components required in the circulation to form a stable clot: red blood cells, platelets, coagulation factors and fibrinogen (Table 7.2). As such, dilutional coagulopathy effectively eliminates the procoagulant action of the Kaolin which is impregnated into the GC with the intent of activating the prothrombin complex.

Importantly, the current study supports the clinical findings from a study describing the use of zone III REBOA. Martinelli and co-workers described a series of 13 patients with pelvic fracture following blunt injury who were in refractory hypovolaemic shock with a mean systolic blood pressure of 41 ± 26 mmHg (72). Blind deployment of a balloon catheter to effect Zone III REBOA resulted in a significant increase in SBP (70 mmHg; p = 0.001). The mean ISS of the cohort was 48 ± 15.5 and had an overall survival rate of 6/13 (46%). The clinical report from Martinelli and the current study are the first report on the specific effectiveness of Zone III REBOA. However, the utility of endovascular balloon occlusion as a pre-emptive or resuscitation adjunct has been demonstrated in the elective and emergent repair of abdominal aortic aneurysms (10,77). A recent technical note from this group provided a fuller description of the technique of compliant balloon selection, insertion, inflation, deflation and removal while proposing a series of aortic zones (or landing sites) in order to facilitate the consistent use and reporting of REBOA (6).

The current study has limitations worth noting. Foremost, the two methods of haemorrhage control used in this study, CG and REBOA, have inherent differences and may not be fully comparable. As a topical haemostatic, CG is designed to be applied with an element of manual pressure to a junctional or extremity soft tissue wound while endovascular balloon control works under the premise of halting inflow from within the vessel proximal to the site of bleeding. The model of injury in the current study was to the distal iliac artery located within the pelvis and therefore not inherently suited (i.e. not directly accessible or compressible) for CG application in the clinical setting. However, because the technique of REBOA for haemorrhage control is in early stages of re-evaluation and may be well suited for instances of junctional iliac or femoral injury, its comparison in this model against a known standard such as GC is sensible. In this context, REBOA and CG should not be viewed as mutually exclusive forms of haemorrhage control but instead complimentary. It is the authors' viewpoint that improvements in haemorrhage control will require not one but a combination of techniques (e.g. tourniquets, manual pressure with and without haemostatic agents and endovascular balloon control) to manage a wide array of complex injury patterns.

Another limitation relates to the artificial nature of the induced coagulopathy. Specifically, the model of coagulopathy in this study may not be as severe as that which is encountered clinically following vascular injury and shock. As such the effectiveness of REBOA in the current study may not reflect its usefulness in the setting of more profound physiologic derangement in the clinical setting. Finally, as an initial study examining the feasibility of REBOA this study did not make observations during a survival phase. Consequently any adverse effect of Zone III REBOA on the distal circulation of the hind limbs was not accounted for in this study. Despite these limitations, this set of experiments was based on established models and demonstrated Zone III REBOA to be effective compared to a recognised standard. As such, the current report provides an important foundation from which to perform additional study of this technique including observations in a survival model.

7.4.1 Conclusions

In the setting of normal coagulation, Zone III REBOA is equally effective at controlling haemorrhage as manual pressure with a known topical haemostatic agent but results in greater resuscitative fluid requirements. In the setting of coagulopathy, Zone III REBOA provides improved control of bleeding, higher central aortic pressure and lower mortality than the established topical haemostatic agent. In the current model, Zone III REBOA had high rates of technical success and resulted in no adverse aortic injury. The technique of Zone III REBOA should be further developed as an adjunct to manage non-compressible pelvic and junctional femoral haemorrhage.

Chapter 8: Physiologic Tolerance of Descending Thoracic Aortic Balloon Occlusion in a Swine Model of Haemorrhagic Shock

8.1 Introduction

Vascular disruption within the torso with concomitant haemorrhage remains a leading cause of death in military and civilian trauma (2,13,15,16,87). Patients often present *in extremis* with profound cardiovascular collapse. Occlusion of the thoracic aorta can be used to improve after-load, supporting the myocardial and cerebral circulations (88), while controlling arterial inflow to the distal circulation where vascular disruption has occurred. This is most commonly performed via a thoracotomy and aortic cross-clamp; however, this technique requires significant resources and yields few survivors (43,47,89). Recognition of these limitations has motivated investigators to explore other methods of achieving aortic occlusion earlier and by less invasive means (6,9,72).

One such alternative is endovascular balloon occlusion, which is practiced by vascular surgeons to control the inflow of abdominal aortic aneurysms during the placement of stent-grafts (10,77). Interestingly, the use of balloon occlusion of the aorta in trauma is not a new concept having been reported as early as the 1950's during the Korean War (7), but has never gained widespread acceptance. With refinements in surgical technology and improved critical care, this technique is now being revisited clinically (72).

A recent publication from our group has characterised the method of insertion of resuscitative endovascular balloon occlusion of the aorta (REBOA) for trauma patients (6). The authors described 3 aortic zones: I - left subclavian to celiac trunk, II - celiac trunk to the lowest renal artery and III - the infrarenal aorta. Zone I occlusion was described as optimal for torso haemorrhage and zone II for pelvic and lower extremity haemorrhage. However, while REBOA appears to have clear application for haemorrhage control in patients *in extremis*, the physiological sequelae following balloon deflation after extended periods of aortic occlusion remain un-quantified. The aim of this study was to assess the physiological tolerance of Zone I REBOA for 30 and 90 minutes compared to

untreated class IV shock in a survivable porcine model of controlled haemorrhage.

8.2 Materials and Methods

8.2.1 Study Approval and Overview

Institutional Animal Care and Use Committee (IACUC) approval was obtained in accordance with all applicable laws, regulations and policies. Procedures were performed at an accredited facility (Lackland Air Force Base, San Antonio, TX) in compliance with IACUC policies and under the supervision of a licensed veterinary staff. Female Yorkshire–Landrace crossbred swine (John Albert, Cibolo, TX) (age range, 5–6 months; weight range 70-90 kg) were housed at the facility 7 days before the protocol to allow for quarantine and acclimation.

There were 4 study groups, each with 6 animals: 30 mins of shock and Zone I REBOA (30-REBOA), 30 mins of shock alone (30-Shock), 90 mins of shock and Zone I REBOA (90-REBOA) and 90 mins of shock alone (90-Shock). Animals were exposed to 5 study phases: surgical preparation, haemorrhage, intervention, resuscitation and critical care phases (Figure 8.1). Physiological and biochemical parameters were recorded throughout the protocol and animals were euthanised at the end of the 48 hour critical care phase where necropsy was performed, gross pathology assessed and tissue was taken for histology.

8.2.2 Preparation of Animals

Following cannulation of an ear vein, anaesthesia was induced with intravenous Ketamine to facilitate oro-tracheal intubation and mechanical ventilation where anaesthesia was maintained with Isoflurane (range: 2 - 4%). All animals underwent cannulation of the common carotid artery, and the internal and external jugular veins by midline surgical exposure using a modified Seldinger technique. This permitted transduction of the carotid arterial catheter to enable carotid-flow monitoring, intra-venous fluid replacement via the internal-jugular catheter and measurement of cardiovascular indices via a Swan-Ganz catheter in the external-jugular.

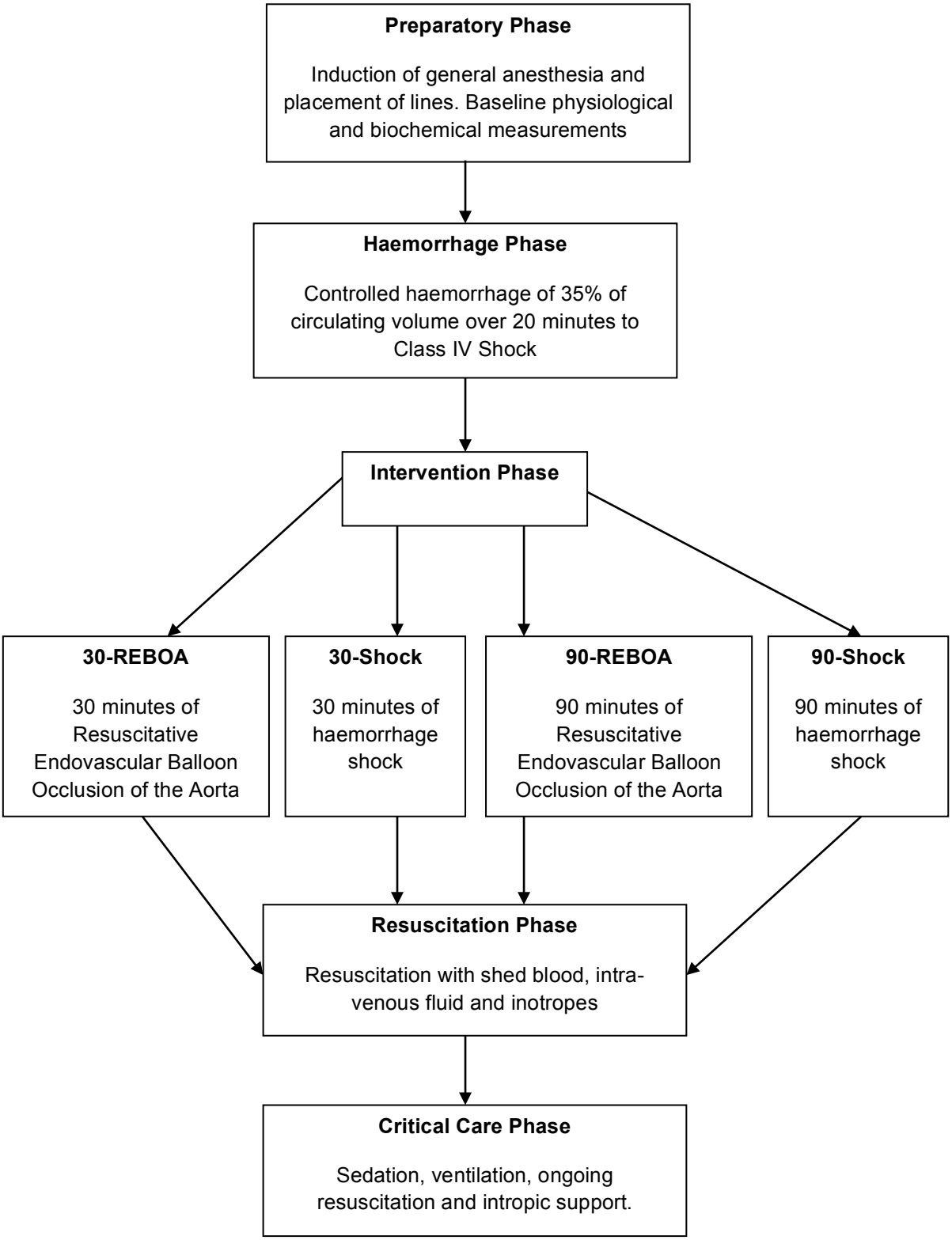

Figure 8.1: Flow diagram of the study protocol

The right brachial artery was operatively exposed and a cannula was fluoroscopically guided into the aortic arch to measure central aortic pressure. The right iliac artery was exposed via retroperitoneal approach and cannulated with a 15 fr sheath to permit a controlled haemorrhage and access for endovascular aortic balloon placement. The animals' cranium was also trephined to permit the placement of a brain oximeter (Licox; Integra NeuroSciences, Plainsboro, NJ).

At the conclusion of surgical procedures and catheter placements, baseline laboratory and physiological recordings were performed. Throughout the protocol, heart rate (HR), mean central aortic pressure (MCAP), brain oxygenation ($PbrO_2$), carotid flow (CF), end tidal carbon dioxide (CO_2), core temperature (rectal), and urine output (UOP) were continuously monitored.

8.2.3 Haemorrhage (30 minutes)

To achieve a controlled haemorrhage and class IV shock, a method for blood and volume estimation and rate of haemorrhage was used as previously described (79). In brief, over 20 mins, 35% of total blood volume (total porcine intravascular volume: 66 ml/kg) was withdrawn through the sheath in the iliac artery; half of this volume was taken over 7 mins and the remaining over 13 mins. As swine possess a contractile spleen and can readily autotransfuse in response to haemorrhagic shock, animals were subjected to ongoing haemorrhage at a rate of 0.15ml/kg/min for an additional 10 minutes to ensure class IV shock was maintained. Shed blood was stored in citrated bags (Terumo, Japan) for later transfusion during the resuscitation phase. If mean arterial pressure (MCAP) decreased below 30 mm Hg, haemorrhage was stopped until arterial pressure was consistently greater than 30 mmHg, and then the haemorrhage was resumed until completion.

The start of the haemorrhage phase was considered time zero; the reference points for all other experimental timings. The 30 min time period also served to simulate the pre-hospital time, prior to admission to a trauma centre. At the conclusion of the haemorrhage phase, labs were drawn and physiological recordings made.

8.2.4 Intervention (30 or 90 minutes)

Following the haemorrhage phase, animals were randomised into one of four groups: 30-Shock, 30-REBOA, 90-Shock or 90-REBOA. Animals in either REBOA group underwent aortic occlusion with an endovascular balloon (Coda Balloon; Cook Medical Inc, Bloomington, IN), inflated distal to the left subclavian artery orifice under fluoroscopic guidance. Successful occlusion was confirmed by loss of an arterial waveform from a catheter transduced distal to the balloon. Animals in the shock groups were observed throughout their study period (30 or 90 minutes) without any intervention taking place.

8.2.5 Resuscitation (6 hours)

A 6 hour resuscitation phase began immediately subsequent to the intervention phase with animals receiving transfusion of previously shed whole blood. Following withdrawal of the iliac arterial sheath (with or without balloon), the artery was ligated and the midline incision closed. The resuscitation strategy differed slightly between the REBOA groups and the shock groups.

Resuscitation in the REBOA groups was initiated 10 minutes prior to the end of 30 or 90 minute intervention period. Whole blood was slowly infused until the MCAP was raised by 25%, to avoid precipitous cardiovascular collapse, prior to deflation of the aortic balloon. The aortic balloon deflation was accomplished incrementally over a 3-minute period and the remainder of the blood was given after complete deflation. The resuscitation in the shock groups began immediately upon completion of the 30 or 90-minute period of shock with whole blood.

Blood pressure was titrated to a goal mean pressure of 60 mm Hg using 1 litre intravenous fluid boluses once the previously collected whole shed blood was exhausted. When animals failed fluid challenges, norepinephrine was administered for haemodynamic support. Norepinephrine doses were titrated to maintain the targeted MCAP.

8.2.6 Critical Care (48 hours)

The final component of the protocol was a 48 hour critical care phase where the animals remained sedated (Isofluane, Ketamine and Midazolam) and

mechanically ventilated. The haemodynamic support commenced during the resuscitation phase was continued and was designed to replicate the support that trauma patients would receive in the intensive care unit post damage control surgery. Blood samples were taken and physiological parameters recorded throughout this phase. At conclusion of the ICU phase, the animals were euthanised and underwent necropsy and gross pathology. Tissue samples from brain, spinal cord, liver, lung, heart and kidney were collected for histological analysis.

8.2.7 Study End Points

Study end-points were separated into three categories: perfusion, organ dysfunction and resuscitation requirements. Markers of perfusion included mean central aortic pressure (MCAP), cerebral oxygen partial pressure ($PBrO_2$) and lactate measurements. These samples were taken from the brachial arterial line at Q15 minutes until 2 hours and then Q30 minutes until the end of the resuscitation phase, then at 24 and 48 hours.

Markers of cardiac, renal, hepatic and muscle dysfunction were analysed at 24 and 48 hours and included cardiac Troponin I (cTnI), Aminotransferases, Blood Urea Nitrogen (BUN), Creatinine, Potassium and Creatine Kinase. Brain, spinal cord, heart, lung, kidney and liver were also examined histologically at the conclusion of the study. Tissues were examined by a Veterinary Pathologist and subjectively graded as having no, minimal, mild, moderate, marked or severe necrosis using a nominal scale of zero to five. Resuscitation requirement consisted of total norepinepherine dose and total volume of intra-venous fluid (blood and crystalloid) administered over 48 hours.

8.2.8 Statistical Analysis

Statistical analyses were performed using SAS Version 9.2 for Windows (SAS Institute, Cary, North Carolina) and R Version 2.13.1 (R Foundation for Statistical Computing). Continuous data were tested with a mixed effect repeated measures analysis of variance (ANOVA). Nominal data were tested with contingency tables using Fisher's exact test and ordinal data were tested with

the Kruskal-Wallis test. The Bonferroni method was used to correct the level of significance for post hoc multiple comparison tests to investigate effects.

8.3 Results

8.3.1 Baseline Characteristics and Mortality

The baseline characteristics of the 4 study groups (n = 6 / group), are shown in Table 8.1. Time zero occurred at the start of the haemorrhage phase, and serves as the reference point for all reported time points and values. There was no significant difference in weight or volume of haemorrhage (per kg) used to induce shock. Measures of perfusion and organ function were also similar amongst the groups. There were two deaths: one animal died in the 30-Shock group during the haemorrhage phase and another animal in the 90-Shock group died during the resuscitation phase. Necropsy did not identify an obvious cause of death, although cardiovascular collapse was thought likely.

8.3.2 Measures of Organ Perfusion

Immediately post haemorrhage, all four groups had a similar mean MCAP (±SD) of 33±8 mmHg, indicating class IV shock had been attained (Figure 8.2). In the 30 minute arm, the 30-REBOA group had a significantly greater MCAP upon initiation of aortic occlusion (91±16 vs 31±4; $p<0.001$) compared to the 30-Shock group. The MCAP remained significantly elevated throughout the intervention phase in the 30-REBOA group compared to the 30-Shock group. This observation was also recorded in the 90 minute group where the MCAP was significantly greater in the 90-REBOA compared to the 90-Shock group (89±22 vs 38±13; $p=0.001$). This increased MCAP was maintained throughout the 90 minute intervention phase in the REBOA group. In all groups, the MCAP's returned to their respective baselines during the resuscitation and critical care phases.

Table 8.1: Baseline characteristics

	30-Shock	30-REBOA	90-Shock	90-REBOA	*p*
N	6	6	6	6	
Weight/Kg	79.3±4.3	81.3±7.5	87.5±6.7	88.0±11.3	0.171
Female, % (n)	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	n/a
Haemorrhage, ml/Kg	21.7±4.0	24.6±2.3	23.2±3.1	25.8±0.7	0.104
MCAP, mmHg	73±11	68±11	67±17	72±8	0.752
HR, bpm	83±8	80±4	82±17	76±15	0.775
$PBrO_2$, mmHg	53±37	49±51	43±25	56±24	0.937
Temp, ℃	36.4±1.0	35.3±0.9	36.2±0.9	35.6±0.9	0.230
pH	7.49±0.04	7.47±0.04	7.47±0.04	7.44±0.05	0.387
Lactate, mmol/l	0.9±0.3	1.3±0.4	1.3±0.5	1.2±0.4	0.355
Troponin, ng/ml	0.00±0.00	0.00±0.00	0.22±0.53	0.00±0.00	0.413
AST, U/L	29.5±6.1	36.8±4.9	34.5±5.2	39.0±7.4	0.068
LDH, U/L	437±138	395±117	309±58	339±80	0.170
BUN, mg/dL	11.2±2.0	10.2±2.4	12.3±7.6	11.5±4.6	0.884
Creatinine, mg/dL	1.6±0.3	1.4±0.2	1.7±0.6	1.7±0.4	0.613
K^+, mmol/l	4.4±0.3	4.3±0.2	4.6±0.7	4.6±0.5	0.548
CK, U/L	1176±624	1051±452	1131±396	1121±253	0.971

Values are mean ± SD unless otherwise stated.

Abbreviations: REBOA – Resuscitative Endovascular Balloon Occlusion of the Aorta, MCAP – Mean Central Aortic Pressure, HR – Heart Rate, AST – Aspartate Transaminase, LDH – Lactate Dehydrogenase, Blood Urea Nitrogen, CK – Creatine Kinase.

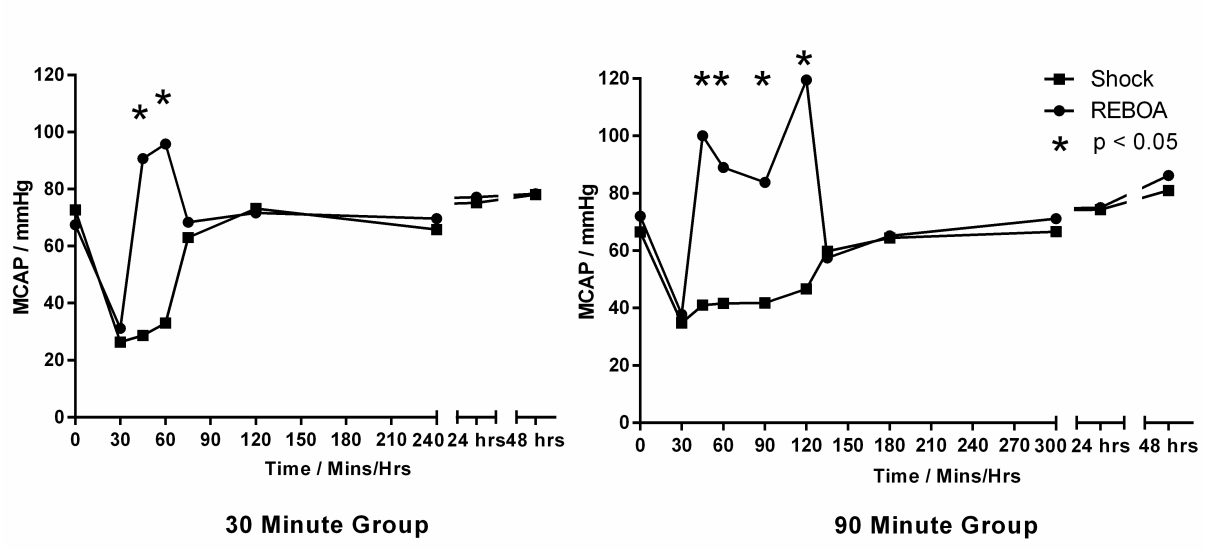

Figure 8.2: Mean Central Aortic Pressure measurements against time

The partial pressure of brain tissue oxygenation ($PBrO_2$) was noted to increase significantly from post-haemorrhage levels in both the REBOA groups ($p<0.001$), but not in either of the shock only groups. There was a significantly greater PBrO2 in the 90-REBOA compared to the 90-Shock group (66±35 vs 30±14; p=0.042); however, despite a rise in the 30-REBOA PBrO2 compared to the 30-Shock, there was no statistically significant difference (45±37 vs 22±17; p=0.225) (Figure 8.3).

There was a significantly elevated lactate concentration measured in the REBOA groups compared to the shock alone groups at 15 minutes into the intervention phase (Figure 8.4). This rise in lactate peaked at 75 minutes in the 30-REBOA and at 150 minutes in the 90-REBOA group. Lactate levels were no longer elevated, when compared to the shock only groups, by 150 minutes in the 30-REBOA and 320 minutes in the 90-REBOA group.

8.3.3 Measures of Organ Dysfunction

There was no difference in cTnI measurements across all four groups at either 24 or 48 hrs (Table 8.2 and Table 8.3).We observed a statistically significant rise in AST level in the 30-REBOA group compared to the 30-Shock at 24 hrs, although there was no detectable difference by 48 hrs (Table 8.2). The 90-REBOA group had a greater AST level at both 24 and 48 hours, although it was not statistically significant (Table 8.3).

LDH was noted to rise in all groups at 24 hours but began to decrease by 48 hrs. The reduction in LDH between the 24 and 48 hr time points was significantly greater in the Shock groups than in the REBOA groups.

There were no significant differences detected in Creatinine level amongst all groups; however, BUN was noted to be significantly higher in the 30-Shock group than the 30-REBOA group by 48 hrs. This trend was reversed by 90 minutes group, where the 90-REBOA group had a significantly greater BUN than the 90-Shock by 48 hrs. There was no difference in potassium or CK measurements by 48 hrs in either group.

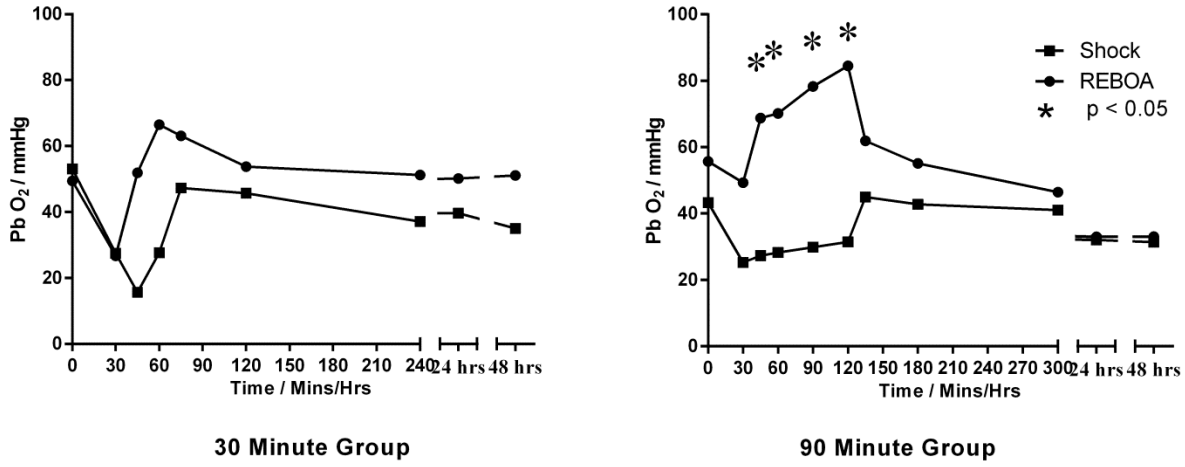

Figure 8.3: Cerebral Oxygenation measurements against time

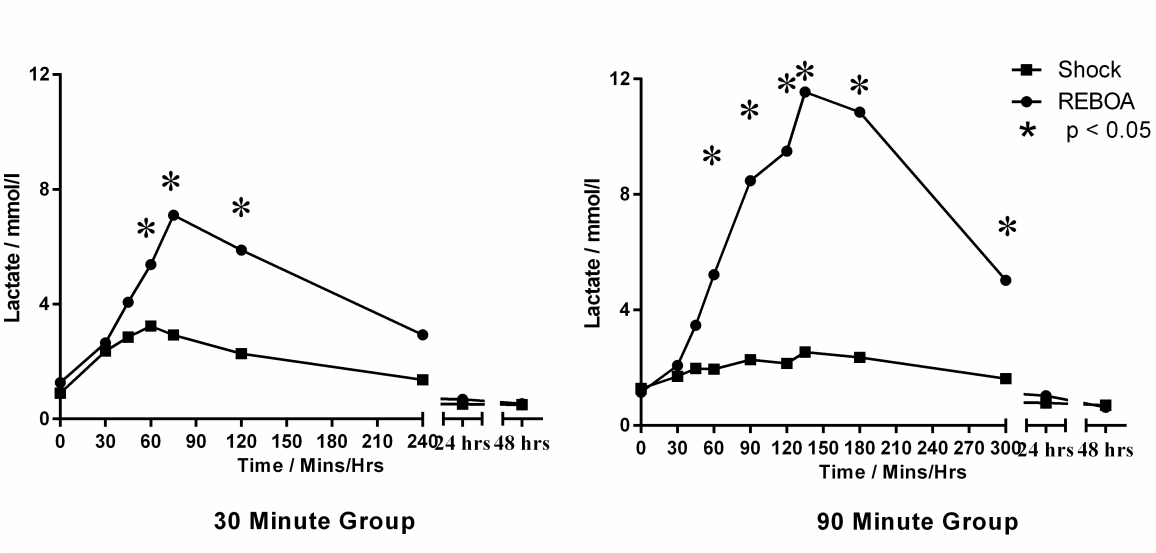

Figure 8.4: Lactate measurements against time

Table 8.2: Markers of end-organ dysfunction for the 30 minute groups

	24 Hours			48 Hours		
	30-Shock	**30-REBOA**	***P***	**30-Shock**	**30-REBOA**	***P***
Troponin, ng/ml	0.09±0.10	0.28±0.24	0.114	0.04±0.05	0.13±18	0.288
AST, U/L	288±70	560±180	0.011	379±224	641±329	0.165
LDH, U/L	1924±391	2625±623	0.058	1462±175	2427±702	0.016
BUN, mg/dL	21.2±3.1	18.2±2.6	0.110	22.4±2.9	18.2±1.8	0.016
Creatinine, mg/dL	0.9±0.4	1.1±0.4	0.266	0.9±0.4	1.1±0.4	0.363
K+, mmol/l	3.5±0.3	3.6±0.3	0.610	3.8±0.4	3.6±0.2	0.340
CK, U/L	23804±6651	39881±8161	0.006	36032±27750	45545±17359	0.504

Abbreviations: REBOA – Resuscitative Endovascular Balloon Occlusion of the Aorta, AST – Aspartate Transaminase, LDH – Lactate Dehydrogenase, Blood Urea Nitrogen, CK – Creatine Kinase.

Table 8.3: Markers of end-organ dysfunction for the 90 minute groups

	24 Hours			48 Hours		
	90-Shock	**90-REBOA**	***P***	**90-Shock**	**90-REBOA**	***P***
Troponin, ng/ml	0.60±1.14	0.38±0.49	0.681	0.16±0.30	0.19±0.27	0.852
AST, U/L	879±131	1292±466	0.089	1006±173	1360±330	0.060
LDH, U/L	8462±5453	9693±4487	0.690	7468±4724	9673±5501	0.499
BUN, mg/dL	24.2±7.3	28.0±2.6	0.263	24.8±7.3	37.3±5.3	0.009
Creatinine, mg/dL	1.7±0.3	1.8±1.1	0.847	1.2±0.2	1.5±0.6	0.400
K+, mmol/l	4.1±0.6	4.6±1.1	0.344	4.0±0.5	4.2±0.5	0.559
CK, U/L	85706±33920	76580±41352	0.703	78334±30713	58797±27659	0.296

Abbreviations: REBOA – Resuscitative Endovascular Balloon Occlusion of the Aorta, AST – Aspartate Transaminase, LDH – Lactate Dehydrogenase, Blood Urea Nitrogen, CK – Creatine Kinase.

Histologically, there was no significant difference in the numerical rates of necrosis, inflammatory infiltrates or oedema observed in cerebral, spinal cord or myocardial tissue amongst the four groups (Figure 8.5). There was a suggestion of greater renal damage and regeneration in the 90-REBOA group compared with the 90-Shock group, though neither achieved statistical significance. There was, however, significantly higher observed rate of centrilobular liver necrosis in the 90-REBOA group compared with the 90-Shock group. Significant necrosis was not observed in any other group's organs (Figure 8.5).

8.3.4 Resuscitation Requirements

Cumulative intravenous fluids (IVF) and vasopressor requirements during the resuscitation and critical care phases are shown in Table 8.4. The 90-REBOA group required a greater mean total fluid (ml) resuscitation than the 90-Shock group (2667±931 vs 1000±1225; p = 0.034). The total mean dose of Norepinepherine (mg) was also greater in the 90-REBOA group (2381.2±2316.3 vs 494.2±1171.7; p=0.068), although this only trended towards significance. There was no difference in IVF and norepinepherine dose between the 30 minute groups.

8.4 Discussion

This study characterises the physiological sequelae of Zone 1 REBOA in the setting of class IV shock compared to shock alone for either 30 or 90 minutes. Following the controlled haemorrhage, both REBOA groups had a significantly greater central aortic pressure and cerebral oxygen delivery than in shocked animals alone. This was achieved at the expense of a greater lactate rise observed following balloon deflation, as a consequence of visceral and lower extremity reperfusion. However, lactate measurements returned to control level by 150 mins in the 30-REBOA group and 320 mins in the 90-REBOA group. There was also evidence of limited organ dysfunction following 90 minutes of REBOA which manifested as an elevated indices of renal dysfunction and histological evidence of centilobular liver necrosis.

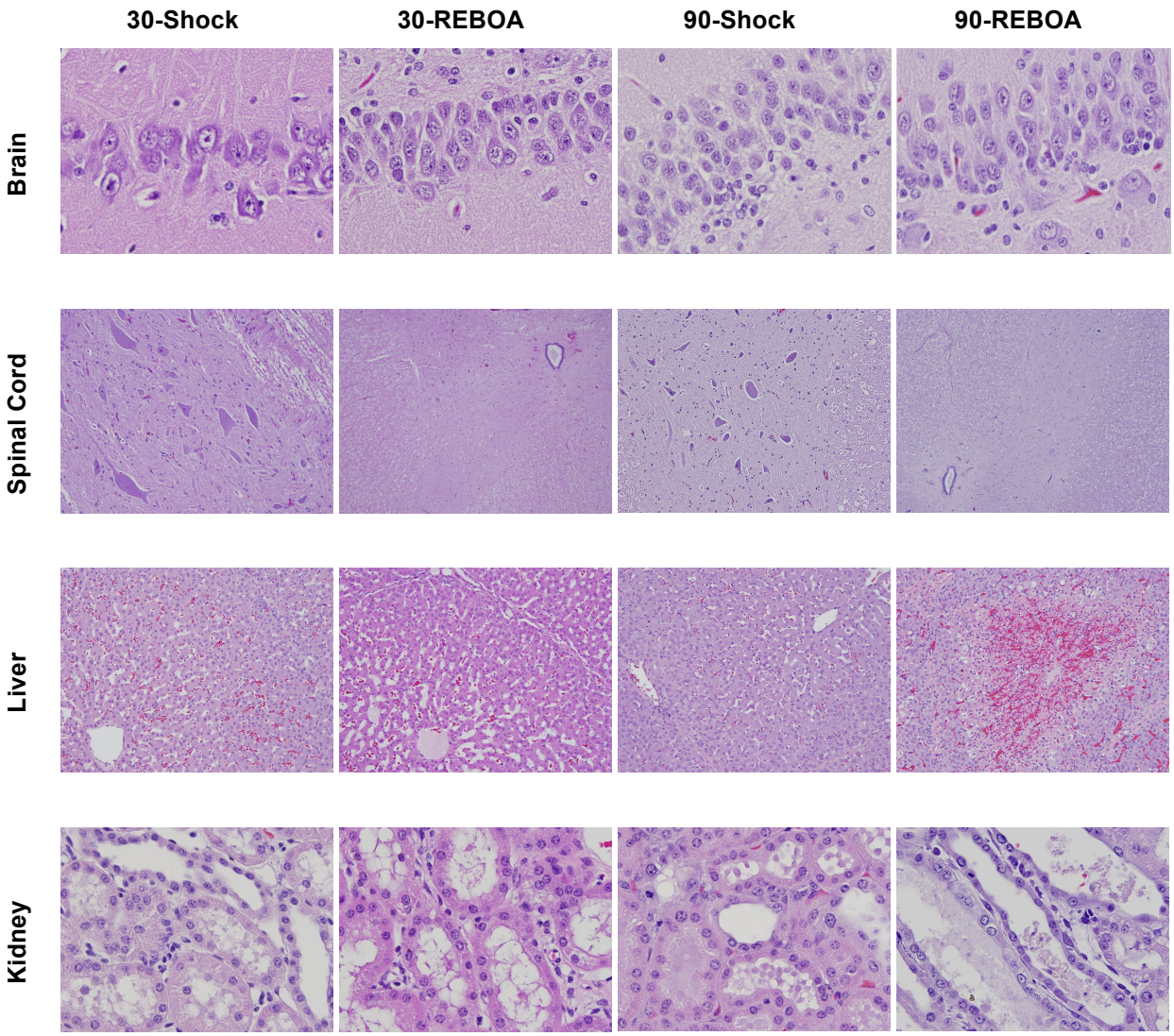

Figure 8.5: Representative histological samples of brain, spinal cord, liver and kidney tissue from all groups

The 90-REBOA liver sample shows centrilobular necrosis and the kidney sample shows some tubular debris. All remaining samples were unremarkable.

Table 8.4: Total resuscitation requirements

	30 Minute Groups			90 Minute Groups		
	30-Shock	30-REBOA	p	90-Shock	90-REBOA	p
IV Fluid, ml/24hrs	400±652	833±817	0.336	1000±1225	2667±931	0.034
Norepi Dose, mg/24hrs	0.0±0.0	57.6±91.0	0.176	494.2±1171.7	2381.2±2316.3	0.068

This study confirms and extends the findings of earlier work performed by our group and by others (80,90). White et al. demonstrated that the physiological burden of Zone I REBOA was significantly less than that of resuscitative thoracotomy in a porcine model of 50 minutes of haemorrhagic shock (80). Animals treated with REBOA were less acidotic with a lower serum lactate, requiring less resuscitation than animals treated with thoracotomy and aortic cross clamping.

Avaro et al. examined the role of Zone I REBOA in a porcine model of uncontrolled splenic haemorrhage compared to resuscitation with normal saline in combination with damage control surgery (DCS). The use of REBOA, followed by DCS, significantly increased mean arterial pressure and the proportion of 2 hour survivors while reducing overall haemorrhage and resuscitation volumes. When examining the REBOA groups that underwent either 40 or 60 minutes of occlusion, 40 minutes appeared to be optimal by incurring a lower lactate and potassium than the 60 minute group.

These studies prompted the current study to examine the temporal profile of the physiological burden incurred with REBOA. Ultimately, while there are physiological penalties, as also described by other investigators, the current study demonstrates that these can be ameliorated with proficient resuscitation and critical care, yielding zero mortality from re-perfusion injury in the REBOA groups by 48 hours.

The physiological burden must be weighed against the improvements seen in central aortic pressure and brain oxygenation - indices of vital importance in trauma patients presenting *in extremis*. This is especially important in patients who have sustained concomitant traumatic brain injury (TBI). REBOA may be able to preserve cerebral perfusion in the context of haemorrhage, although it is unclear whether this would reduce the effects of secondary brain injury, or dangerously raise intra-cranial pressure.

Clinical experience with Zone I REBOA is currently limited despite the concept's genesis over half a century ago. The first published report was by Hughes who deployed it in two combat casualties during the Korean War (7). Despite both

patients succumbing to their wounds, he felt it effective in restoring blood pressure and controlling intra-abdominal haemorrhage. Interestingly, this report pre-dated Ledgerwood's original description of the pre-laparotomy thoracotomy and aortic clamping in patients with a tense haemoperitoneum and shock (91).

The largest case series of Zone I REBOA comes from Gupta and co-workers who in 1989 deployed the technique in 21 patients in cardiac arrest or profound shock (9). Haemorrhage control was achieved in 11 patients, although ultimately only seven survived to be discharged. Failure was most commonly seen in major venous injuries and patients in cardiac arrest - challenging injury complexes for any surgeon.

The current study demonstrates the importance of resuscitation and organ support post REBOA use; however, there are a number of limitations to note. The animal model of shock consisted of a controlled haemorrhage; rather than an organ injury *per se*. This may reduce the inflammatory component and sequelae seen in trauma patients immediately post-injury. However, the study was designed to examine the physiological response to shock, thus a survivor model was essential where the volume of haemorrhage could be precisely controlled. While the study was able to demonstrate a difference in measures of perfusion; it could not demonstrate a statistical difference in organ dysfunction, which may relate to insufficient study power.

Furthermore, there were also important differences in the methods of resuscitation between the REBOA and shock alone groups. The "pre-loading" of blood, ten minutes prior to balloon deflation was essential to avoid precipitous cardiovascular collapse following balloon deflation, as noted in the model development phase of the study. While this may appear to favour the REBOA group, it is important to note that the balloon remained inflated for the full duration of the intervention phase and as already noted, a survival model was essential in order to study the physiological changes. As shed blood was the only oxygen carrying fluid available, it is also likely that animals were under resuscitated and the use of further blood would have reduced the inotropic support required.

8.4.1 Conclusions

Zone I REBOA can be used for up to 90 minutes in a porcine model of class IV shock without mortality as a consequence of the reperfusion injury. REBOA incurs a significant physiological burden, although this can be ameliorated with resuscitation and critical care. Central aortic pressure and cerebral oxygen delivery is significantly improved by the use of REBOA. Further study is required in a model of uncontrolled torso haemorrhage in order to further assess the clinical potential of REBOA.

Chapter 9: The Inflammatory Sequelae of Aortic Balloon Occlusion in Haemorrhagic Shock

9.1 Introduction

Haemorrhage remains the leading cause of potentially preventable death in civilian (11,12) and military (2,4) trauma, with a significant proportion occurring prior to hospital admission (92,93). Haemorrhages arising from the non-compressible regions in the torso and junctional regions have been consistently identified as particularly lethal with a mortality of 18-50% (27,94,95).

Definitive haemorrhage control and resuscitation is crucial to survival from exsanguinating injury (96). Despite advances in damage control resuscitation (97), the majority of torso haemorrhage control interventions require hospital-based facilities. However, the delivery of such care is both time dependent and capability-driven; a patient must survive long enough to access such a facility.

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is a proactive haemorrhage control adjunct designed to sustain vital perfusion until definitive haemostasis can be achieved (3,6). In the setting of non-compressible torso haemorrhage (NCTH), a balloon is inflated in the thoracic aorta. This augments cardiac afterload improving myocardial and cerebral perfusion while simultaneously controlling arterial inflow. Importantly, unlike resuscitative thoracotomy and aortic clamping, REBOA can be initiated without the need for general anaesthesia and applied in resource poor environments.

Translational large-animal work and early clinical series have shown REBOA to have significant promise as a bridge to definitive haemostasis (72,98-100). However, this technique is known to incur a lactate penalty that is proportional to the length of occlusion. While up to 90 minutes of occlusion has been demonstrated to be survivable in a swine model of haemorrhagic shock, the systemic inflammatory response and the cardiopulmonary sequelae have yet to be characterised (99). The aim of this study is to quantify the inflammatory response to different occlusion times and their effect on cardiopulmonary function.

9.2 Methods

9.2.1 Overview

This study represents the analysis of previously unpublished data from three experimental groups (30-REBOA, n=6; 60-REBOA, n=8 and 90-REBOA, n=6) drawn from two previously published studies (99,100). These two studies shared a common experimental design but realised different end-points. All experiments were conducted at a single accredited large animal facility under the supervision of an Institutional Animal Care and Use Committee supported by licensed veterinary staff. All animals were in good health and housed for at least 7 days prior to study enrolment to allow for acclimation.

Female Yorkshire swine (*Sus scrofa*) weighing 70-90kg were entered into a study protocol consisting of 5 phases: animal preparation, induction of haemorrhagic shock (30 mins), balloon occlusion (30, 60 or 90 mins), resuscitation (6 hours) and critical care (48 hours) (Figure 9.1). Indices of haemodynamic performance were recorded throughout the study, along with blood sampling at specific time points. Animals were euthanised at the end of the critical care phase and necropsy performed.

9.2.2 Animal Preparation

General anaesthesia was induced using IV ketamine and maintained followed orotracheal intubation with isoflurane (range 2 – 4%). Animals were ventilated using a volume controlled mode of 6 – 8 ml/kg with an FiO_2 of 40-80% sufficient to maintain an SpO_2 of >96%. Surgical exposure and cannulation of the common carotid, internal and external jugular vein was performed via a midline neck incision. This facilitated invasive blood pressure monitoring, IV fluid resuscitation and the placement of a Swan-Ganz catheter. A 14 Fr sheath was placed in the external iliac artery via a retroperitoneal surgical exposure in the 30-REBOA and 90-REBOA groups, whereas this was accomplished in the 60-REBOA group by an ultrasound guided percutaneous technique.

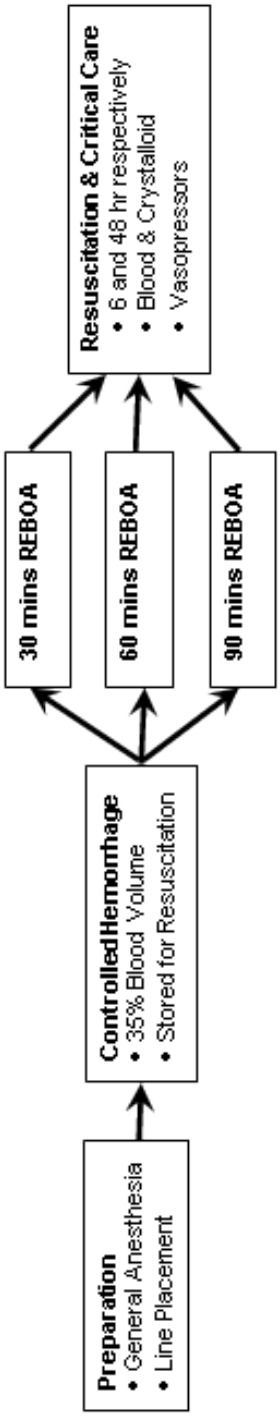

Figure 9.1: An overview of the experimental design.

A cerebral oximetry probe (LICOX, Integra Life Sciences, Plainsboro, NJ) and carotid flow probe (Transonic Systems Inc., Ithaca, NY) were also placed; the data from these devices have been reported previously and will not be discussed further.

9.2.3 Induction of Haemorrhagic Shock (30 mins)

Class IV haemorrhagic shock was induced using a standardised technique previously described (79). Over 20 mins, 35% of the animal's blood volume (total porcine blood volume: 66 ml/kg) was removed from the iliac arterial sheath: half over 7 minutes and the remaining over 13 minutes. As the swine has a contractile spleen, animals underwent a further haemorrhage of 0.15 ml/kg/min for 10 minutes to minimise the effect of autotransfusion. Whole blood was collected in citrated bags for re-infusion during the resuscitation phase.

9.2.4 Balloon Occlusion (30, 60 or 90 mins)

Following the conclusion of the controlled haemorrhage, REBOA was performed for either 30, 60 or 90 minutes. A stiff Amplatz wire was passed through the 14 Fr sheath into the thoracic aorta guided by fluoroscopy. A Coda® balloon catheter (Cook Medical, Bloomington, IN) was advanced to the midpoint of the thoracic aorta using an "over the wire" technique and inflated with a mixture of saline and contrast medium observed under fluoroscopy.

9.2.5 Resuscitation (6 hrs) and Critical Care (48 hrs)

Fluid resuscitation was initiated 10 minutes prior to commencing balloon deflation at the end of the occlusion period (30, 60 or 90 minutes). Shed whole blood was slowly infused in order to raise the Mean Arterial Pressure (MAP) by around 25%. This was to avoid precipitous cardiovascular collapse once balloon deflation was commenced, which was performed gradually over 3 minutes in parallel with the rapid infusion of shed whole blood. Once the balloon was fully deflated, the catheter and wire were withdrawn from the sheath.

Whole blood resuscitation continued and was titrated to a MAP of 60 mmHg. Once these reserves were exhausted, boluses of 1.0 L of 0.9% Saline were used to achieve the target blood pressure. When animals became refractory to fluid challenges, an infusion of norepinephrine was commenced at 4 µg/h and titrated

to a MAP of 60 mmHg. Animals were also transitioned from inhaled isoflurane to intravenous ketamine and midazolam sedation once considered sufficiently stable.

9.2.6 Study End-Points, Data Collection and Analysis

The primary outcome of this study related to the rise in the pro-inflammatory cytokines: Interleukin-6 (IL-6) and Tumour Necrosis Factor Alpha (TNF-α). Serum samples were analysed using an Enzyme Linked Immunosorbent Assays (ELISA) technique. IL-6 and TNF-α were run on porcine-specific kits obtained from R&D Systems (Minneapolis, MN). Plates were set-up following manufacturer's instructions, read on a BIO-TEK Synergy H4 microplate reader and data analysed using GEN5 software from Bio-Tek.

Secondary outcomes related to measures of inflammation-mediated cardiopulmonary dysfunction manifest as failure of vascular tone and the development of Acute Respiratory Distress Syndrome (ARDS). Failure of vascular tone was quantified by the need for vasopressor medication (norepinephrine). Evidence of ARDS was made using the Berlin definition which describes a mild, moderate and severe pattern based upon an PaO_2:FiO_2 ratio of 201-300, 100-200 and <100 mmHg respectively (101). A pulmonary arterial wedge pressure (PAWP) of less than 18 mmHg was used as an objective measure of the absence of cardiac failure and histologic evidence of pulmonary oedema was used in lieu of chest radiography.

Indices of haemodynamic performance (Cardiac Output – CO, Systemic Vascular Resistance – SVR, MAP and PAWP) were recorded continuously throughout the study. Inflammatory cytokines were measured at 8 hours and 24 hours. At the end of study, animals were euthanised, lungs removed, weighted and submitted for blinded histologic evaluation by a veterinary pathologist.

Data were analysed using SPSS v20.0 (IBM, Chicago, Il). Chi^2 tests were used to compare categorical data and analysis of variance (ANOVA) with *post-hoc* testing for continuous variables using a Bonferroni correction.

9.3 Results

9.3.1 Baseline Characteristics and Induction of Haemorrhagic Shock

There was no significant difference in baseline measures of weight, haemodynamic or metabolic parameters between the 30-REBOA, 60-REBOA or 90-REBOA groups (Table 9.1). The induction of shock was successful, with all animals tolerating the controlled haemorrhage well, achieving their predicted volume. Importantly, all animals demonstrated an appropriate tachycardia along with profound hypotension consistent with severe hypovolaemic shock (Table 9.1). There was no unexpected mortality during the study protocol.

9.3.2 Haemodynamic Performance and Resuscitation

All groups responded to aortic occlusion with a substantial rise in MAP, which was sustained throughout each groups' respective occlusion period (Figure 9.2A). A similar trend was noted with the SVR which demonstrated a modest increase during the haemorrhage phase, but more than doubled following aortic balloon occlusion (Figure 9.2B). This is in contrast to CO which decreased during the haemorrhage phase entering a plateau during the balloon occlusion phase (Figure 9.2C). It was only during the resuscitation phase did the CO increase, achieving similar values to the baseline recordings.

At the end-of-study, there was no difference amongst the groups in the final HR, MAP, SV, CO, MPAP, PAWP, temperature, pH or lactate measurements (Table 9.2). The SVR was significantly elevated in the 90-REBOA group when compared to the 60-REBOA group (1189 ± 391 vs. 623 ± 113; p = 0.024). There were no differences in cardiac Troponin-I measured at 8 and 24 hrs (Table 9.2).

Regarding fluid resuscitation, all animals had their previously shed whole blood returned. The 60-REBOA group went on to receive a larger volume of crystalloid than the 30-REBOA group (12014 ± 6699 vs. 6535 ± 2517; p = 0.043) and the 90-REBOA group (12014 ± 6699 vs. 10341 ± 7231; p = 0.089) although the latter was not statistically significant (Table 9.2).

Table 9.1: Baseline characteristics of the three study groups and physiology following a 35% controlled haemorrhage

Data is presented as mean and standard deviation or proportions (percentages).

	30-REBOA	**60-REBOA**	**90-REBOA**	***p****
n	6	8	6	
Weight, Kg	81.3 ± 7.5	77.5 ± 5.9	88.0 ± 11.3	0.143
Female, %	6 (100.0%)	8 (100%)	6 (100.0%)	n/a
Haemodynamic				
HR, bpm	80 ± 4	81 ± 8	76 ± 15	0.647
MAP, mmHg	68 ± 11	65 ± 10	72 ± 8	0.447
SV, ml/min	91 ± 15	97 ± 22	73 ± 25	0.138
CO, l/min	7.2 ± 1.3	7.9 ± 1.6	6.4 ± 1.2	0.190
SVR, dynes.sec/cm^5	683 ± 120	607 ± 91	918 ± 125	< 0.001
MPAP, mmHg	17 ± 6	17 ± 4	20 ± 3	0.419
PAWP, mmHg	11 ± 6	11 ± 4	12 ± 3	0.785
FiO_2:PaO_2 Ratio, mmHg	507 ± 130	467 ± 33	430 ± 188	0.571
Metabolic				
Temp, ℃	35.3 ± 0.9	34.9 ± 1.3	35.6 ± 0.9	0.437
pH	7.47 ± 0.04	7.50 ± 0.03	7.44 ± 0.05	0.032
Lactate, mmol/L	1.3 ± 0.4	0.8 ± 0.2	1.2 ± 0.4	0.052
Haemorrhage				
Predicted Volume, mL	2145 ± 197	2072 ± 174	2323 ± 300	0.144
Actual Volume, mL	1996 ± 193	1942 ± 278	2264 ± 283	0.082
HR Post-Haemorrhage, mmHg	151 ± 26	167 ± 15	140 ± 23	0.073
MAP Post-Haemorrhage, mmHg	31 ± 4	35 ± 8	38 ± 13	0.433

Abbreviations: REBOA – Resuscitative Endovascular Balloon Occlusion of Aorta; HR – Heart Rate; MAP – Mean Arterial Pressure; SV – Stroke Volume; CO – Cardiac Output; SVR – Systemic Vascular Resistance; Mean Pulmonary Arterial Pressure; PAWP – Pulmonary Arterial Wedge Pressure

*Statistical Test – Analysis of Variance.

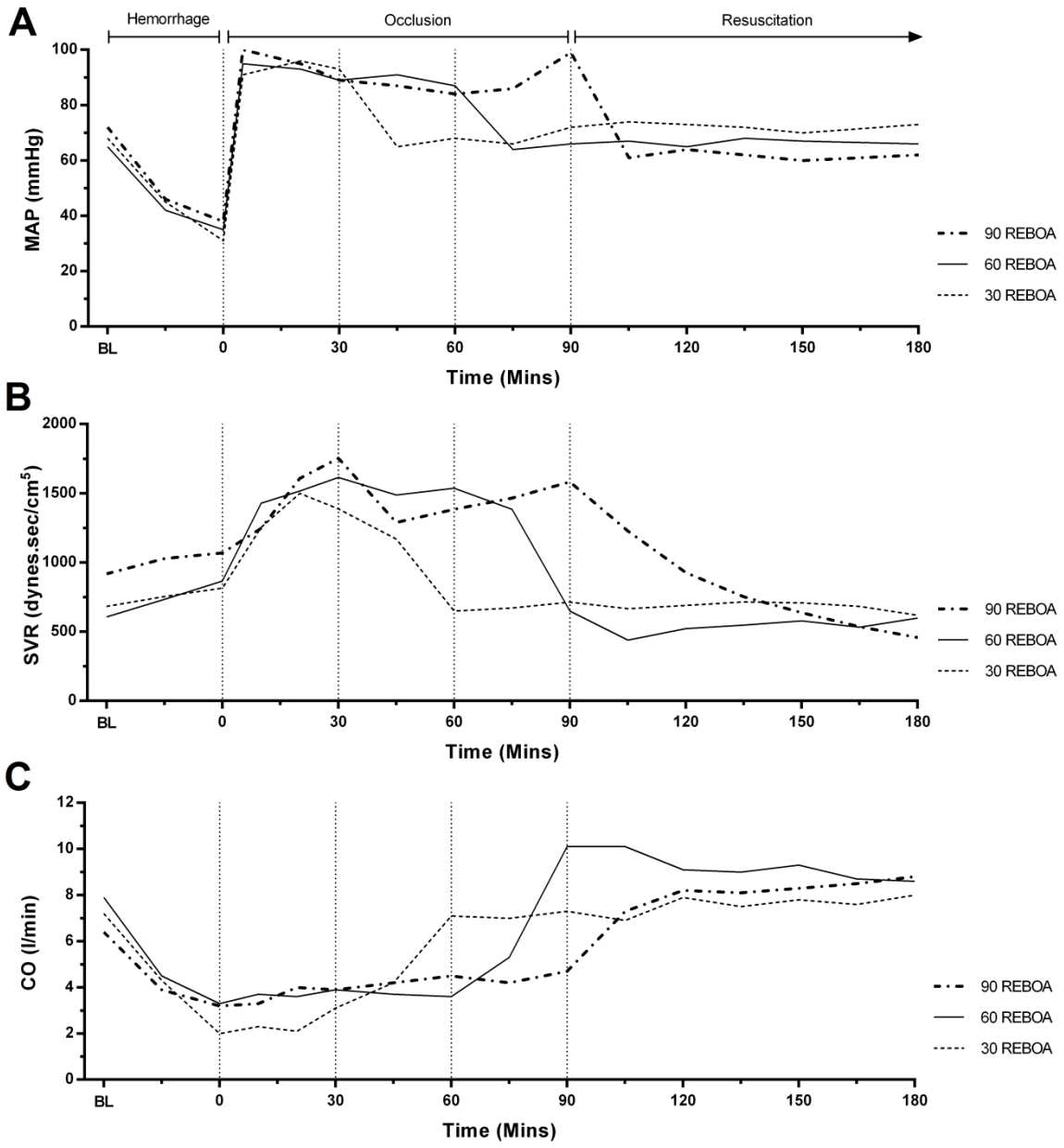

Figure 9.2: The haemodynamic performance of swine undergoing a controlled haemorrhage (35% circulating volume) and 30, 60 or 90 minutes of REBOA

Data is plotted as mean value. A. Mean Arterial Pressure – MAP; B. Systemic Vascular Resistance – SVR; C. Cardiac Output – CO.

Table 9.2: End of study resuscitation volumes, haemodynamic indices, metabolic and troponin measurements following 30, 60 or 90 minutes of aortic balloon occlusion.

Data is presented as mean and standard deviation.

	30-REBOA	60-REBOA	90-REBOA	*p**
n	6	8	6	
Haemodynamic				
HR, bpm	79 ± 18	102 ± 28	92 ± 10	0.163
MAP, mmHg	78 ± 13	68 ± 14	86 ± 9	0.057
SV, mL/min	75 ± 22	87 ± 22	57 ± 6	0.129
CO, L/min	5.5 ± 1.6	6.0 ± 2.5	5.0 ± 1.0	0.765
SVR, dynes.sec/cm^5	977 ± 176	623 ± 113	1189 ± 391	0.003
MPAP, mmHg	18 ± 7	21 ± 3	26 ± 6	0.096
PAWP, mmHg	13 ± 7	10 ± 4	13 ± 9	0.666
FiO_2:PaO_2 Ratio, mmHg	516 ± 122	412 ± 124	313 ± 137	0.043
Metabolic				
Temp, ℃	37.8 ± 1.3	37.8 ± 0.5	36.9 ± 1.2	0.268
pH	7.46 ± 0.02	7.40 ± 0.10	7.43 ± 0.04	0.298
Lactate, mmol/L	0.5 ± 0.1	0.6 ± 0.2	0.6 ± 0.1	0.440
Cardiac Troponin-I				
8 hrs, ng/mL	0.65 ± 0.46	0.87 ± 0.72	0.96 ± 0.80	0.719
24 hrs, ng/mL	0.28 ± 0.24	0.44 ± 0.38	0.38 ± 0.49	0.759
Total Fluid Resuscitation				
Whole Blood, mL	1996 ± 193	1942 ± 278	2264 ± 283	0.082
Crystalloid, mL	6535 ± 2517	12014 ± 6699	10341 ± 7231	< 0.001

Abbreviations: REBOA – Resuscitative Endovascular Balloon Occlusion of Aorta; HR – Heart Rate; MAP – Mean Arterial Pressure; SV – Stroke Volume; CO – Cardiac Output; SVR – Systemic Vascular Resistance; Mean Pulmonary Arterial Pressure; PAWP – Pulmonary Arterial Wedge Pressure.
*Statistical Test – Analysis of Variance.

9.3.3 Inflammatory Cytokines

There was no difference in baseline IL-6 (Figure 9.3A; p = 0.095) or TNF-α (Figure 9.4A; p = 0.597) within the three groups. There was no significant increase in IL-6 compared to baseline value for the 8 and 24 hr samples in the 30-REBOA group. By contrast, both the 60-REBOA and 90-REBOA groups saw a rise in IL-6 (pg/mL) at 8 hrs compared to baseline values: 289 ± 258 vs. 10 ± 5; p = 0.018 and 630 ± 348; p = 0.007 respectively. This had returned to baseline in the 60-REBOA group by 24 hrs (36 ± 36 vs. 9 ± 6; p = 0.083), but was still elevated in the 90-REBOA group (89 ± 45 vs. 19 ± 20; p = 0.028).

When examining between groups at 8 hrs the 90-REBOA group has a significantly elevated IL-6 compared to the 30-REBOA group (630 ± 348 vs. 53 ± 37; p = 0.003) (Figure 9.3B). At 24 hrs IL-6 in the 90-REBOA group was significantly greater when compared to both the 30-REBOA and 60-REBOA groups: 89 ± 45 vs. 16 ± 15; p = 0.006 and 89 ± 45 vs. 36 ± 36; p = 0.040 respectively (Figure 9.3C).For TNF-α, there was no significant elevation across the time points or amongst the groups (Figure 9.4A-C).

9.3.4 Cardiopulmonary Dysfunction

There was no statistical difference in either the total dose of norepinephrine or proportion of animals requiring vasopressor support. These measures did however demonstrate a trend towards a stepwise increase in the vasopressor requirements across the 30-REBOA, 60-REBOA and 90-REBOA groups. This was demonstrated by total dose (mg) of norepinephrine administered (0.06 ± 0.09 vs. 1.16 ± 2.58 vs. 2.38 ± 2.31; p = 0.183) and the proportion of animals requiring vasopressor support (2 (33.3%) vs. 4 (50.0%) vs. 5 (83.3%); p = 0.205) respectively (Figure 9.5A and B).

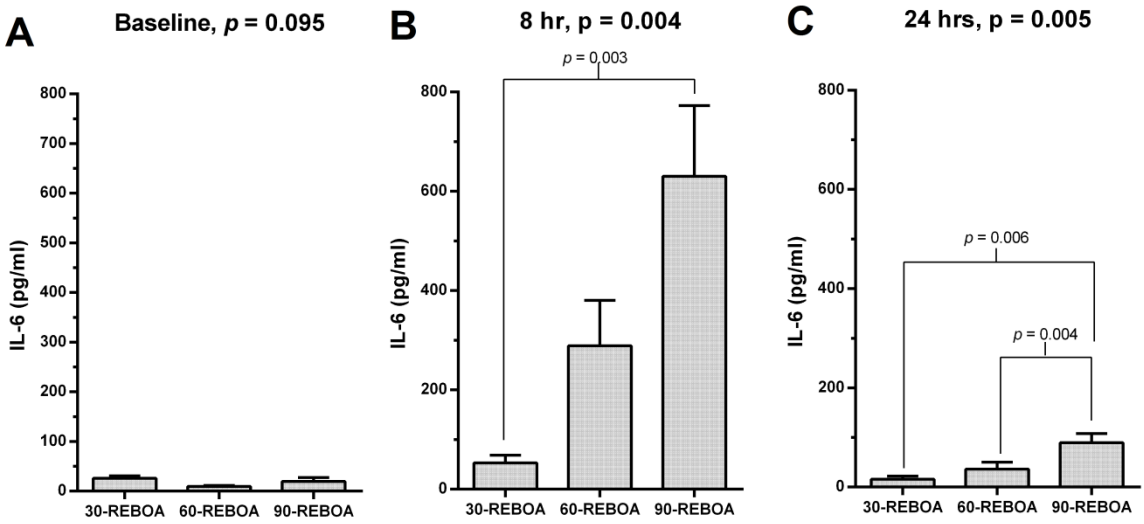

Figure 9.3: Interleukin-6 measurements (mean and standard error) following 30, 60 and 90 minutes of haemorrhagic shock

A. Baseline, B. 8 hours and C**.** 24 hours. *ANOVA, ***post-hoc* testing between groups.

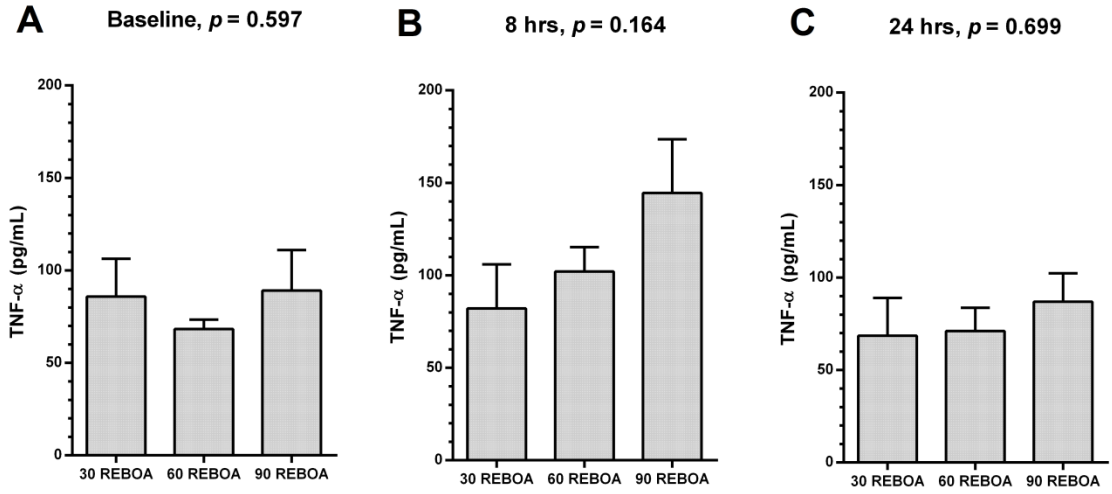

Figure 9.4: Tumour Necrosis Factor Alpha measurements (mean and standard error) following 30, 60 and 90 minutes of haemorrhagic shock

A. Baseline, B. 8 hours and C. 24 hours. *ANOVA.

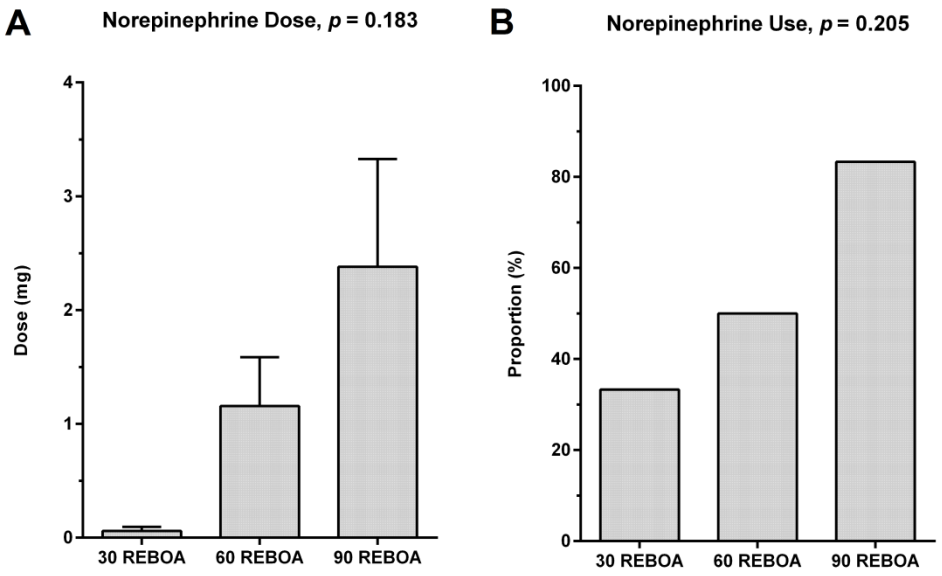

Figure 9.5: Total dose of norepinephrine (mean and standard deviation) and the proportion of animals requiring vasopressor support (percentage)

A. Total Dose and B. Proportion. *ANOVA.

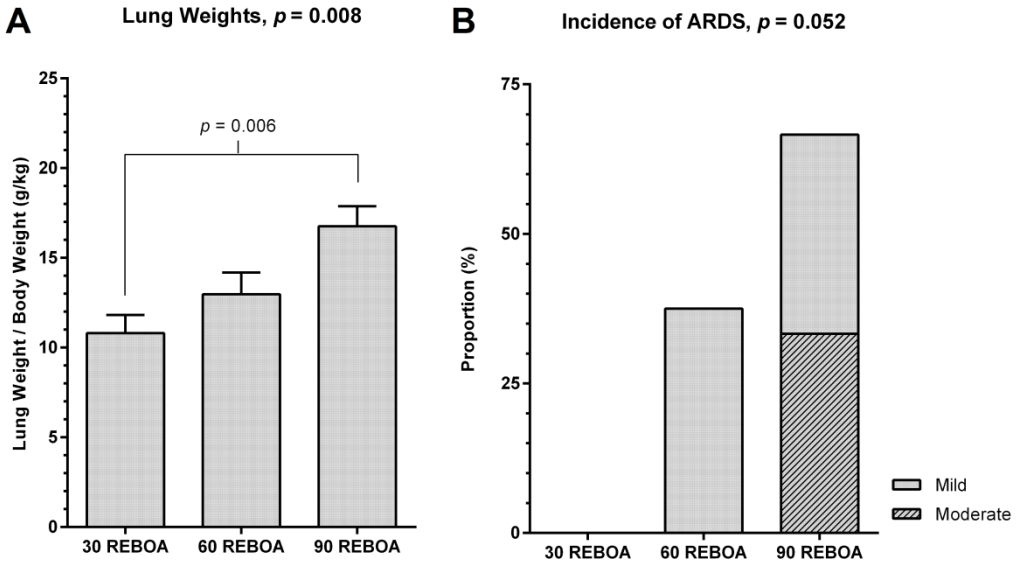

Figure 9.6: Measures of pulmonary congestion.

A. Lung weight per body weight (mean and standard error) and B. Incidence of Acute Respiratory Distress Syndrome. *ANOVA, ***post-hoc* testing between groups.

There was a significant stepwise increase in the wet lung weight to body weight ratio between the three groups (10.8 ± 2.5 vs. 13.0 ± 3.4 vs. 16.8 ± 2.7; p = 0.008) (Figure 9.6A). The lung weight ratio of the 90-REBOA group was significantly greater than the 30-REBOA group; p = 0.006. The inverse of this trend was observed in the end-of-study FiO_2:PaO_2 ratio which reduced as occlusion time increased (Table 9.2). The 90-REBOA FiO_2:PaO_2 ratio was significantly less than that of the 30-REBOA group (313 ± 137 vs. 516 ± 122; p = 0.040) (Table 9.2).

The incidence in ARDS trended towards an increase across the groups (p = 0.052) (Figure 9.6B). No animals in the 30-REBOA group had an FiO_2:PaO_2 ratio suggestive of ARDS. There were 3 (37.5%) animals in the 60-REBOA group with a reduced FiO_2:PaO_2 ratio and histology (Figure 9.7A and B) consistent with mild ARDS. There were 4 (66.7%) animals in the 90-REBOA group with evidence of ARDS: two with mild and two with medium grade ARDS.

9.4 Discussion

The current study is the first characterisation of the systemic inflammatory response following aortic balloon occlusion and haemorrhagic shock. As the occlusion time increased, a greater release of IL-6 as measured at 8 and 24 hrs was observed. This was associated with a trend towards an increase in vasopressor use and incidence of ARDS, which was unrelated to cardiac function as measured by a normal end-of-study PAWP and CO. The relationship between occlusion time and inflammatory sequelae is important in the understanding of the critical care challenges faced by the post-REBOA patient.

The current study is an examination of previously unpublished data amalgamated from three groups from two previously published studies (99,100). Markov et al. examined 30 and 90 minutes of haemorrhagic shock with and without balloon occlusion (99). Those investigators explored the influence of occlusion on measures of perfusion and demonstrated superior central pressures with balloon occlusion. This was associated with a significant metabolic burden as measured by serum lactate; however, with suitable resuscitation, this returned to baseline levels within 6 hours of occlusion.

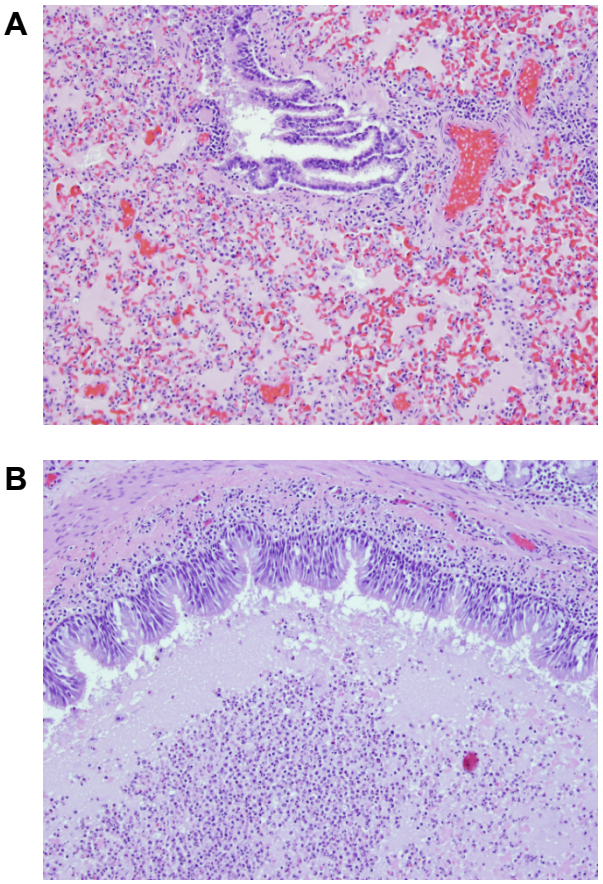

Figure 9.7: A representative histological section of an animal that underwent 90 minutes of REBOA

Haematoxylin and Eosin Stain, 10x Magnification. A. Diffuse severe alveolar oedema. B. Bronchial exudates. These features, in conjunction with an FiO_2:PaO_2 ratio less than 300 mmHg, are suggestive of Acute Respiratory Distress Syndrome.

Scott et al. used an occlusion time of 60 minutes with which to evaluate a novel, self-centring, low-profile, prototype REBOA catheter compared to a conventional balloon system (100). This demonstrated the reproducibility of fluoroscopy-free placement while examining the consequence of 60 minutes of occlusion. This also reaffirmed the favourable haemodynamic performance of balloon occlusion in shock upon central perfusion.

The lactate burden reported in these studies demonstrates that REBOA was associated with a significant ischemia-reperfusion injury. The current study is able to explore this phenomenon in more detail, both using molecular markers, as well as clinically relevant secondary endpoints. Importantly, by using a similar methodology in earlier studies, this has been achieved without the need for further animal experimentation. However, due to the nature of how the current study was constructed, there are some important limitations to discuss.

Several secondary endpoints did not achieve statistical significance, specifically, the total dose and proportion of animals requiring vasopressor support. The finding that the majority (80%) of animals undergoing 90 minutes of occlusion required vasopressor support is clinically very important, although not reflected statistically. This likely relates to sample size.

Furthermore, there are some subtle differences in methodology between the groups. Iliac arterial access was obtained percutaneously in the 60-REBOA group, whereas an operative approach was used in the 30 and 90-REBOA groups. The latter approach could increase soft tissue injury and artificially add to the inflammatory release, although the data presented here does not suggest that to be the case.

It is also important to discuss the resuscitation employed, which was predominantly crystalloid-based following the infusion of shed whole blood. A more “haemostatic” resuscitation (i.e. more blood products and less synthetic fluid) would have been preferable; however, this would have required a porcine blood bank and the complexities inherent to such a capability. This is important, as significant crystalloid use has been associated with an increase in ARDS in trauma patients (102). However, the IL-6 increase did not correlate with

resuscitation volumes, suggesting that shock and aortic occlusion time contributes more to the generation of the systemic inflammatory response.

There was a greater volume of fluid resuscitation administered to the 60-REBOA group, which is surprising in the context of a common resuscitation protocol. This is likely reflective of differences between laboratory staff who performed the experiments. It appears that the investigators in 60-REBOA group were more liberal in their fluid administration.

Finally, the current study does not include “control” groups consisting of hypovolaemic shock without REBOA or normovolaemia with REBOA. This was deliberate, as the aim of the study was to explore the inflammatory burden associated with increasing occlusion times, not the effect of shock or REBOA alone. The effect of shock is already well characterised in the literature and the use of REBOA in normovolaemia is not a clinically realistic scenario. Importantly, as REBOA is already in limited clinical use (98), it is crucial to examine relevant models.

Cytokines are well established mediators of inflammation and their excessive release is associated with multiple organ failure following trauma and sepsis (103-105). The results noted in the current study support and extend the literature relating to cytokine release and traumatic injury. IL-6 and TNF-α has been noted to be elevated in both haemorrhage and tissue injury, although different mechanisms and time courses prevail (106,107).

TNF-α has been associated with an early rise at 45 minute, persisting up to 4 hours in haemorrhage, whereas although IL-6 rises similarly, it tends to persist for longer and is more associated with tissue injury (106). This may explain the discrepancy in trend between IL-6 and TNF-α in the above study. Unfortunately, due to the *post-hoc* way in which the current study is constructed, serum for analysis from early post-REBOA time points is unavailable. Further study is required to assess the role of other cytokine at different time points.

Within the context of the current study, IL-6 has been linked to the development of ARDS (108-112). Several small animals studies have demonstrated that IL-6

produced in response to haemorrhage induces the sequestration of polymorphic neutrophils in the pulmonary capillary beds (113,114). Interestingly, no animal in the current study demonstrated severe ARDS, suggesting that this may be a self-limiting phenomenon although further investigation is required.

REBOA is a proactive method of circulatory support designed to salvage patients with end-stage hypovolaemic shock, bridging their physiology until definitive haemorrhage control. It is now being gradually introduced into clinical practice with formalised protocols established in several civilian and military trauma systems. A number of successful case series have already been published regarding the use of this novel adjunct clearly demonstrating the favourable haemodynamic profile of REBOA in haemorrhagic shock (72,98).

However, as the use of REBOA increases in clinical practice, clinicians need to be aware of the association between occlusion time and inflammatory burden. While clearly providers need to strive for the minimum occlusion time possible, the reality is that some patients with complex injuries will push that envelope. It is important that the use of REBOA does not simply transition the place of death from the Emergency Department to the Intensive Care Unit. It will be vital to anticipate the critical care needs of all patients who undergo REBOA, but especially so for those with extended occlusion time of 60 minutes and beyond.

Several promising lines of research have opened up that could potentially be combined with REBOA systems to help ameliorate the inflammatory burden of occlusion in shock. Technologies that can eliminate pro-inflammatory mediators, such as haemoadsorption filters (115), could be included within an extra-corporeal circuit merged with a REBOA system. Equally, a perfusion capable REBOA catheter (116) could be used to prophylactically deliver an anti-inflammatory perfusate such as a statin suspension (117).

9.4.1 Conclusions

The current study reaffirms that in severe haemorrhagic shock, REBOA can help sustain central perfusion, despite a low cardiac out, by increasing systemic vascular resistance. Importantly, there appears to be minimal direct cardiac injury as a result of this haemodynamic mechanism. There is a proportional

relationship between the length of shock and the resultant pro-inflammatory IL-6 release. This is associated with a trend towards an increase in vasopressor use and the incidence of ARDS, suggestive of a clinically important systemic inflammatory response. Clinicians must anticipate the need for organ support when managing patients where REBOA has been employed as a haemorrhage control adjunct.

Chapter 10: Use of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) in a Highly Lethal Model of Non-Compressible Torso Haemorrhage

10.1 Introduction

Haemorrhage is the leading cause of potentially preventable death in trauma accounting for 90% of military (4) and 26-40% of civilian (11,12) deaths. Non-compressible torso haemorrhage (NCTH) is vascular disruption to axial torso vessels, solid organs, pulmonary parenchyma and/or the bony pelvis, when accompanied by shock (3). This injury complex constitutes the great burden of haemorrhage-related deaths in both military (27,95) and civilian (94) trauma with mortality rates of 43% and 42% respectively. Importantly, many patients exsanguinate prior to definitive haemorrhage control, either dying prior to hospital admission or in the emergency department (4,92,93).

Patients with NCTH, especially those presenting *in extremis*, require resuscitation and haemorrhage control (96). Thoracic aortic occlusion is a manoeuvre that addresses both by augmenting cardiac afterload and providing torso inflow control (3). This can be a life-saving intervention in patients with end-stage haemorrhagic shock; however, it is generally performed as part of a resuscitative thoracotomy (RT) as a reactive manoeuvre following the loss of a central pulse. As a consequence, the survival rate following circulatory arrest and RT is dismal, with rates in military and civilian practice of between 0.5 - 20% (44,54,59,118). A preferable solution is the proactive use of aortic control, expanding the physiological window of salvage, thereby bridging critical physiology to definitive haemorrhage control.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a technique which provides proactive circulatory support in a hypotensive patient at risk of cardiovascular collapse (6). The effectiveness of REBOA has been established as a resuscitative adjunct in the setting of ruptured abdominal aortic aneurysm, another pathology characterised by uncontrolled haemorrhage (119). Despite its usefulness in this setting, the use of REBOA in end stage haemorrhagic shock from trauma has not been well characterised. The aim of this study is to

examine the impact of REBOA on mortality as an adjunct to damage control resuscitation (DCR) in the setting of catastrophic torso trauma.

10.2 Methods

10.2.1 Study Design and Overview

This study was undertaken at an American Association for Laboratory Animal Science accredited large animal research facility following protocol approval by the Institutional Animal Care and Use Committee. The study used Male Yorkshire-Landrace swine (*Sus scrofa*) weighing between 70 and 90 kg, which were housed at the facility for 7 days, under the supervision of licensed veterinary staff, prior to experimentation.

At total of 24 animals were divided into three groups which are named continuous REBOA (cREBOA), intermittent REBOA (iREBOA) and no REBOA (nREBOA). These groups were then entered into a study protocol consisting of 5 phases - Preparation, Injury, Intervention, Damage Control Surgery and Critical Care (Figure 10.1).

10.2.2 Preparation

Following induction with ketamine, animals were intubated and ventilated with oxygen (FiO_2 0.3) and isoflurane (1.5 - 4.0%) sufficient to maintain general anaesthesia. Large bore 8.5 Fr sheaths were placed in both external and right internal jugular veins to permit placement of a pulmonary artery catheter and establish central venous access. A transonic flow-probe was placed around the left carotid artery (Transonic Systems Inc., Ithaca, NY) and the right carotid artery was cannulated for invasive blood pressure monitoring. Infra-diaphragmatic arterial access was also secured in both femoral arteries to permit blood sampling and REBOA deployment.

As swine possess a contractile spleen that can readily autotransfuse in response to haemorrhagic shock, a splenectomy was performed through a small upper midline laparotomy. Prior to closure of the abdomen in three layers, three 12 mm and one 5 mm laparoscopy ports were placed under direct vision to facilitate subsequent laparoscopy during the injury phase.

10.2.3 Injury

This injury was designed to replicate a lethal Grade V liver injury and is based on a previously described model which utilises a laparoscopic liver resection method (120). Carbon dioxide was insufflated in order to attain a 12 mmHg pneumoperitoneum; concomitantly, the FiO_2 was titrated to 0.21 to simulate atmospheric conditions. The left lobe of the liver was divided using laparoscopic scissors, following a line 2 cm medial to the hilum, in order to resect approximately 80% of the left lobe. The goal was to accomplish the transection within 2 minutes, following which the pneumoperitoneum was rapidly evacuated, the ports removed and the skin wounds closed. The animal then underwent a 10 minute free bleed period in which no treatment was administered.

10.2.4 Intervention

At the conclusion of the 10 minute free bleed period, all animals had a 0.035" Lunderquist® (Cook Medical, Bloomington, IN) wire placed into the thoracic aorta under fluoroscopic guidance through the sheath in the right superficial femoral artery. Animals in the cREBOA and iREBOA groups had a 14Fr Coda® Balloon (Cook Medical, Bloomington, IN) placed over the wire through this sheath into the thoracic aorta. The balloon was positioned cephalad to the diaphragm and inflated with contrast medium (Figure 10.2). Animals were transitioned to an FiO_2 of 100% and received 250 mL boluses of IV colloid (Hextend™) if Mean Arterial Pressure (MAP) decreased to less than 50 mm Hg, up to total of 1500 ml. For the animals in the cREBOA group, the aorta was occluded continuously for 60 minutes. Animals in the iREBOA group had the balloon gradually deflated over the course of one minute with the balloon completely deflated for 60 seconds; early re-inflation was performed if the MAP decreased to less than 30mm Hg. The balloon was deflated at both 20 and 40 minutes after initial inflation of balloon. The animals in the control group (nREBOA) only received colloid boluses (Hextend™) during the 60 minute intervention phase.

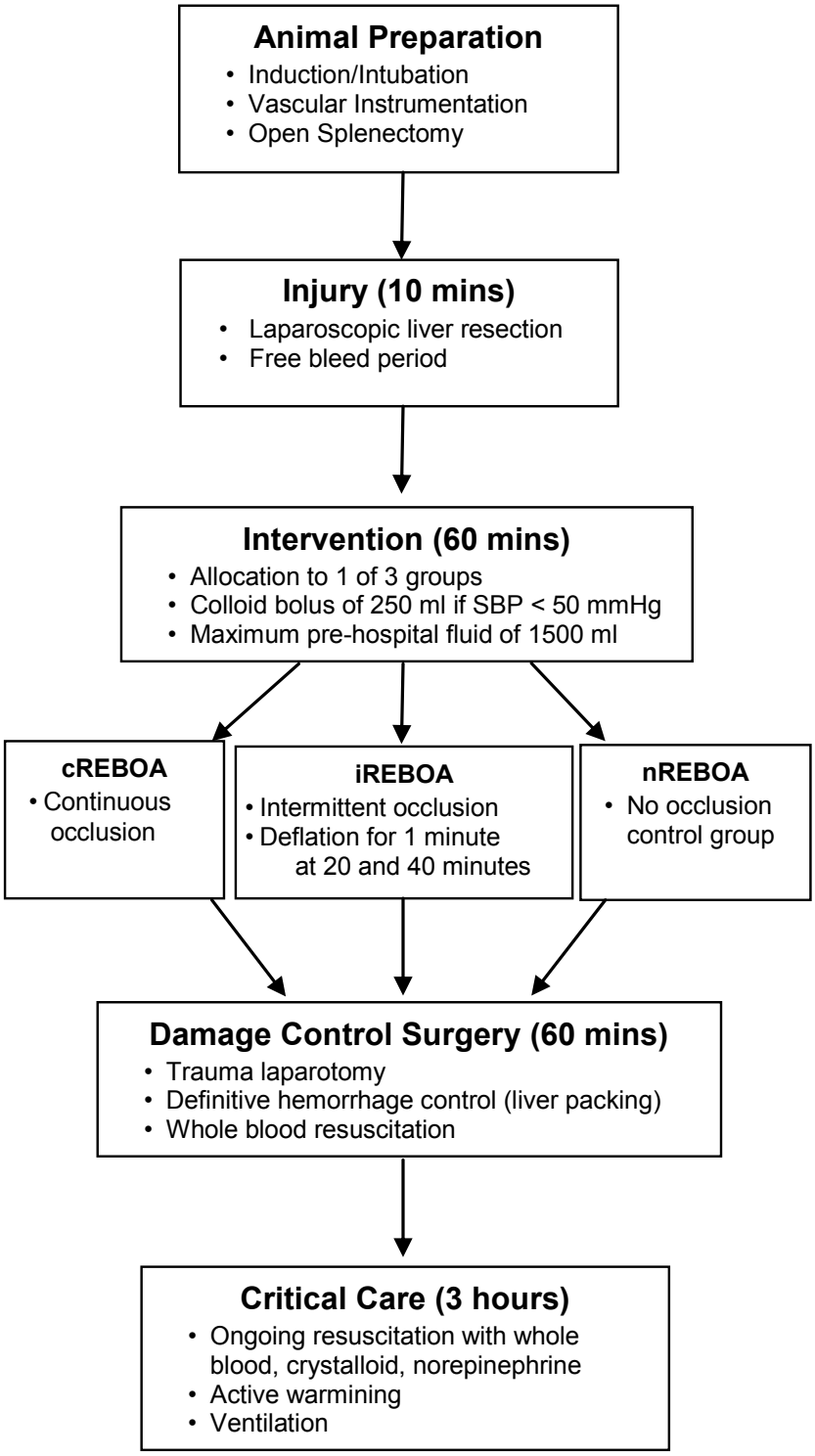

Figure 10.1: Experimental design

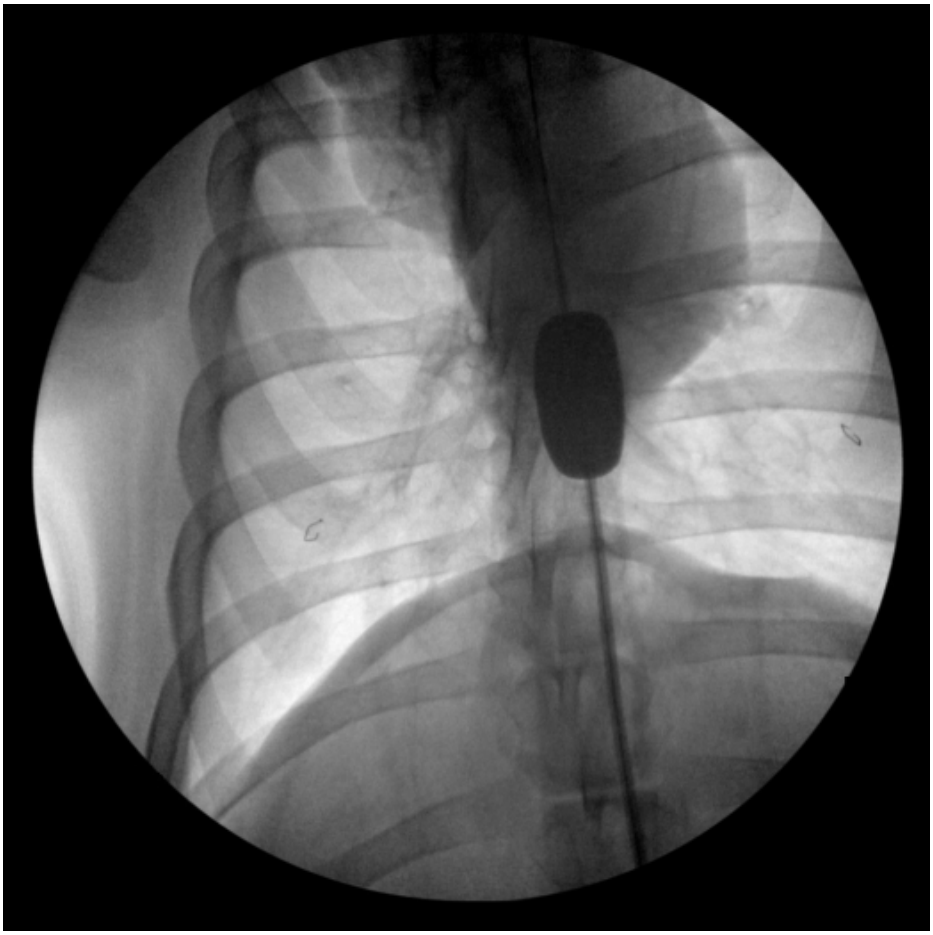

Figure 10.2: Fluoroscopy image of resuscitative endovascular balloon occlusion of the aorta

10.2.5 Damage Control Surgery

Following the 60 minute intervention phase, the 3 groups of animals underwent concomitant whole blood (WB) resuscitation and damage control surgery.

WB was banked from non-study animals, stored in citrated bags, refrigerated for up to one week, with a unit comprising approximately 500 ml. Provision was made for the availability of between 6 and 8 units of WB per study animal. A Belmont Rapid Infuser (Belmont Instrument Corporation, Billerica, MA) was used to warm and administer the WB through a large bore central venous catheter. Resuscitation was titrated to a MAP of 60 mmHg and a haemoglobin of 10 g/dl. Hypocalcaemia, as measured by arterial blood gas sampling, was treated with 1g IV infusions of Calcium Chloride solution.

The damage control laparotomy was performed in the 3 groups via a full midline incision and the first surgical manoeuvre was application of the Pringle manoeuvre (clamping of the hepatic artery and portal vein) and manual control of the cut edge of the liver. The haemoperitoneum was evacuated and the volume of evacuated blood recorded. Definitive liver haemostasis was then achieved through a combination of selective vessel ligation, diathermy and multi-axial packing.

Once hepatic haemorrhage control was obtained and a sufficient volume of WB had been infused to achieve a MAP consistently greater than 70 mmHg, balloon deflation was commenced. This was performed by the incremental withdrawn of 1-2 mL over five to ten minutes. The balloon was re-inflated in response to hypotension or liver haemorrhage. Once balloon deflation and liver haemostasis was complete, a Foley catheter was placed in the urinary bladder and the midline wound closed.

10.2.6 Critical Care

Post-operatively, resuscitation was continued in a critical care environment. Further WB and crystalloid were used to maintain a MAP of 60 mmHg or greater. Animals refractory to volume repletion were administered norepinephrine for haemodynamic support. Hyperkalaemia was treated with intravenous insulin administration and 50% Dextrose. Active re-warming was performed using a

forced air heating blanket (Bair Hugger™, Arizant Healthcare Inc, Eden Prairie, MN). The end of study (EOS) was 6 hours post injury at which point the animals were euthanised according to institutional protocol.

10.2.7 Study End Points

The primary end point of this study was mortality which was defined as the onset of asystole on electrocardiography. Secondary end points were divided into measures of haemodynamic performance, metabolic burden, laboratory parameters of organ function and resuscitation volumes.

Haemodynamic parameters included systemic SBP, pulmonary SBP, cardiac output (CO; L/min), central venous oxygen saturation (SVO_2; %), and carotid flow rates (CFR; mL/min) were measured throughout the study. Metabolic burden was quantified by pH and lactate measured at 30 minute intervals. Laboratory parameters of organ function included potassium (K^+), blood urea nitrogen (BUN), creatinine, hepatic aminotransferases and cardiac Troponin I (cTnI). Inflammatory burden was measured using Interleukin-6 (IL-6), Tumour Necrosis Factor Alpha (TNF-α) and Interleukin-8 (IL-8) assays. Laboratory and cytokine assays were measured at baseline (BL) and EOS. Total volumes and doses of intravenous fluids (blood, crystalloid, and colloid) and drugs (norepinephrine, calcium and insulin) were collated at the EOS. Following euthanasia, the liver was excised with measurements obtained of total liver mass, resected liver mass, and total mass of the left lobe.

10.2.8 Statistical Analysis

Data were analysed using SPSS v20.0 (IBM, Chicago, Il). Chi^2 tests were used to compare categorical data, analysis of variance (ANOVA) and t-tests for continuous variables. Log rank test in conjunction with Kaplan-Meier survival plots were used for survival analysis.

10.3 Results

10.3.1 Baseline Characteristics and Splenectomy

Baseline characteristics are presented in Tables 10.1, 10.2 and 10.3 Physiological baseline values were statistically similar across the groups, with the exception of

heart rate (HR, bpm) which was significantly higher in the nREBOA group compared to the cREBOA and iREBOA groups (98 ± 22 vs. 77 ± 16 and 75 ± 12; p = 0.030) (Table 10.1). There were no differences in laboratory baseline values (Table 10.3).

There was no difference in the time taken to perform the splenectomy across the three groups with an overall mean time (mins) of 29 ± 14 (Table 10.1). Splenic weight was also consistent amongst the groups, with a mean weight (g) of 535 ± 150. There was no difference in post-splenectomy haemodynamic or laboratory parameters (Table 10.3).

The liver injury was accomplished within 2 minutes in all animals, resecting a consistent segment of the left lobe across the groups, with a mean overall weight (g) of 286 ± 71 and percentage (%) resection of 75.0 ± 7.5 (Table 10.1).

10.3.2 Haemodynamic Performance

Following liver injury, all animals underwent a precipitous cardiovascular collapse during the 10 minute free bleed period (Figure 10.3). Systolic blood pressure (SBP, mmHg) at the end of free bleed period for the cREBOA, iREBOA and nREBOA groups was 31 ± 14, 48 ± 28 and 28 ± 17 respectively; p = 0.125 (Figure 10.3A).

The initiation of balloon occlusion in the cREBOA and iREBOA groups during the intervention phase resulted in restoration of SBP to values significantly higher than baseline (79 ± 12 vs. 107 ± 19; p = 0.015 and 85 ± 9 vs. 117 ± 20; p = 0.023 respectively). However, the SBP in the nREBOA control group continued to decrease with all animals progressing to asystolic cardiac arrest by 25 minutes of the intervention phase (35 mins post-injury) (Figure 10.3A).

A similar trend was observed for pulmonary SBP, SVO_2 and carotid flow among the groups (Figure 10.3B, D and E). Following a significant decrease in each parameter during the free bleed period, the deployment of REBOA resulted in the restoration of supra-normal values; this was not observed in the nREBOA group.

Table 10.1: Baseline physiology, splenectomy, liver injury, operative and resuscitation data. Values are mean and standard deviation

	cREBOA	iREBOA	nREBOA	*p* value*
n	8	8	8	
Weight, kg	74.4 ± 2.1	76.5 ± 6.6	79.8 ± 3.7	0.079
Baseline Physiology				
Heart Rate, bpm	77 ± 16	75 ± 12	98 ± 22	0.030
Systemic SBP, mmHg	79 ± 12	85 ± 9	91 ± 18	0.262
Pulmonary SBP, mmHg	22 ± 6	24 ± 3	26 ± 5	0.309
Carotid Flow, mL/min	318 ± 75	360 ± 82	473 ± 324	0.335
CVP, mmHg	8 ± 3	10 ± 2	12 ± 6	0.426
Splenectomy				
Operation Time, mins	31 ± 8	32 ± 20	21 ± 8	0.328
Weight of Spleen, g	559 ± 195	510 ± 123	536 ± 140	0.821
Liver Injury				
Total Liver, g	1529 ± 216	1553 ± 283	1664 ± 322	0.592
Left Lobe, g	373 ± 36	358 ± 77	405 ± 101	0.122
Resection, g	273 ± 31	244 ± 59	309 ± 82	0.117
Resected Lobe, %	74 ± 6	74 ±8	78 ± 8	0.397
Operative				
Total Haemoperitoneum, mL	3285 ± 813	3005 ± 865	2767 ± 614	0.419
Pringle Time, mins	18 ± 5	12 ± 3	n/a	0.095
Total Intra-Operative REBOA Time, mins	20 ± 9	15 ± 8	n/a	0.293
REBOA Re-inflations, n (%)	2 (25.0%)	4 (50.0%)	n/a	0.608
Trauma Laparotomy Time, mins	36 ± 11	32 ± 8	n/a	0.611
Need for Re-Laparotomy, n (%)	1 (12.5%)	1 (12.5%)	n/a	1.000
Resuscitation Fluids and Drugs				
Intervention Phase Colloid, mL	569 ± 493	813 ± 438	1144 ± 306	0.039
Critical Care Phase Crystalloid, mL	1922 ± 1745	1392 ± 1534	n/a	0.529
Whole blood, units	6.8 ± 2.9	7.9 ± 3.6	n/a	0.561
Norepinephrine, mg	4.7 ± 12.3	3.2 ± 7.8	n/a	0.774
Calcium, g	10.8 ± 5.1	10.3 ± 8.7	n/a	0.892
Insulin, units	3.8 ± 7.4	5.0 ± 7.6	n/a	0.744
50% Glucose, mL	32 ± 41	21 ± 44	n/a	0.615

Abbreviations: REBOA – Resuscitative Endovascular Balloon Occlusion of the Aorta, c – continuous, i – intermittent, n – no.

*Analysis of Variance

Table 10.2: End of study laboratory parameter analysis

	cREBOA			iREBOA			EOS
	BL	EOS	BL vs. EOS *p* value*	BL	EOS	BL vs. EOS *p* value*	cREBOA vs. iREBOA *p* value*
Hb, g/dl	9.6 ± 0.6	10.5 ± 0.2	0.633	9.9 ± 1.0	9.1 ± 2.6	0.859	0.574
PT, sec	13.4 ± 0.5	15.5 ± 1.5	0.049	13.5 ± 0.5	15.5 ± 2.4	0.170	0.963
PTT, sec	35.0 ±11.6	33.4 ± 6.6	0.919	30.4 ± 6.8	37.1 ± 10.9	0.218	0.531
Platelets, x10^9/L	288 ± 124	209 ± 66	0.373	292 ± 119	152 ± 98	0.027	0.273
Fibrinogen, mg/dL	204 ± 55	125 ± 57	0.110	185 ± 34	146 ± 26	0.238	0.483
BUN, mg/dL	9.0 ± 2.5	12.0 ± 1.6	0.011	9.1 ± 5.3	11.0 ± 3.2	0.002	0.553
Creatinine, mg/dL	1.84 ± 0.34	2.6 ± 0.5	0.014	1.48 ± 0.30	2.4 ± 0.4	0.006	0.497
K^+, mmol/l	3.7 ± 0.3	5.2 ± 0.8	0.017	3.6 ± 0.3	4.4 ± 0.6	0.102	0.121
ALT, U/L	32 ± 6	58 ± 23	0.149	32 ± 5	59 ± 44	0.242	0.981
AST, U/L	20 ± 9	403 ± 133	0.001	21 ± 4	466 ± 633	0.188	0.816
LDH, U/L	415 ± 72	1342 ± 415	0.004	381 ± 43	1593 ± 1143	0.078	0.627
CK, U/L	1846 ± 1792	5502 ± 2191	0.048	959 ± 636	4920 ± 3848	0.053	0.759
C Tn-I, ng/mL	0 ± 0	2.9 ± 1.5	0.005	0 ± 0	1.8 ± 1.5	0.033	0.218
Il-6, pg/mL	33 ± 14	1188 ± 279	0.001	27 ± 15	834.6 ± 287	0.003	0.084
TNF-α, pg/mL	105 ± 48	205 ± 92	0.124	69 ± 37	109.8 ± 36	0.236	0.063
IL-8, pg/mL	41 ± 15	329 ± 505	0.280	36 ± 25	226.8 ± 296	0.211	0.710

Values are mean ± SD.

Abbreviations: REBOA – Resuscitative Endovascular Balloon Occlusion of the Aorta, c – continuous, i – intermittent, n – no, EOS – end of study. Hb – Hemaglobin, PT – Prothrombin Time, PTT – Partial Thromboplastin Time, ALT – Alanine Aminotransferase, AST – Aspartate Aminotransferase, LDH – Lactate Dehydrogenase, CK – Creatine Kinase, C Tn-I – Cardiac Troponin I.

*t-test

Table 10.3: Physiological and laboratory parameters at baseline and post-splenectomy
Values are mean and standarddeviation

	Baseline				Post-Splenectomy			
	cREBOA	**iREBOA**	**nREBOA**	***p* value***	**cREBOA**	**iREBOA**	**nREBOA**	***p* value***
n	8	8	8		8	8	8	
Weight, kg	74.4 ± 2.1	76.5 ± 6.6	79.8 ± 3.7	0.079	n/a	n/a	n/a	
Physiological								
Heart Rate, bpm	77 ± 16	75 ± 12	98 ± 22	0.030	78 ± 23	77 ± 15	99 ± 24	0.076
Systemic SBP, mmHg	79 ± 12	85 ± 9	91 ± 18	0.262	78 ± 10	93 ± 14	88 ± 15	0.113
Pulmonary SBP, mmHg	22 ± 6	24 ± 3	26 ± 5	0.309	18 ± 4	23 ± 4	26 ± 4	0.008
Carotid Flow, mL/min	318 ± 75	360 ± 82	473 ± 324	0.335	315 ± 71	393 ± 94	579 ± 563	0.318
CVP, mmHg	8 ± 3	10 ± 2	12 ± 6	0.426	5 ± 3	9 ± 3	11 ± 6	0.069
Laboratory								
Hb, g/dL	9.6 ± 0.6	9.9 ± 1.0	9.6 ± 1.0	0.848	10.8 ± 0.8	11.0 ± 1.1	10.3 ± 0.9	0.475
PT, sec	13.4 ± 0.5	13.5 ± 0.5	13.8 ± 0.7	0.411	13.6 ± 0.6	13.4 ± 0.4	13.5 ± 0.5	0.776
PTT, sec	35.0 ±11.6	30.4 ± 6.8	34.6 ± 6.7	0.521	32.7 ± 11.1	31.9 ± 6.2	36.5 ± 6.5	0.589
Platelets, $x10^9$/L	288 ± 124	292 ± 119	270 ± 94	0.931	278 ± 92	286 ± 110	285 ± 99	0.987
Fibrinogen, mg/dL	204 ± 55	185 ± 34	201 ± 63	0.739	191 ± 53	192 ± 38	208 ± 64	0.820
BUN, mg/dL	9.0 ± 2.5	9.1 ± 5.3	10.4 ± 2.3	0.761	9.0 ± 2.5	9.1 ± 5.1	11.1 ± 2.3	0.520
Creatinine, mg/dL	1.8 ± 0.3	1.5 ± 0.3	1.5 ± 0.4	0.094	1.9 ± 0.3	1.5 ± 0.3	1.5 ± 0.4	0.070
K^+, mmol/L	3.7 ± 0.3	3.6 ± 0.3	3.7 ± 0.2	0.650	3.8 ± 0.4	3.7 ± 0.5	3.8 ± 0.3	0.726
ALT, U/L	32 ± 6	32 ± 5	33 ± 11	0.948	32 ± 5	33 ± 5	34 ± 11	0.909
AST, U/L	20 ± 9	21 ± 4	29 ± 19	0.315	24 ± 7	26 ± 8	35 ± 17	0.166
LDH, U/L	415 ± 72	381 ± 43	432 ± 91	0.377	429 ± 63	398 ± 39	426 ± 84	0.577
CK, U/L	1846 ± 1792	959 ± 636	2621 ± 2483	0.215	1836 ± 1697	990 ± 591	1766 ± 1756	0.221

Abbreviations: REBOA – Resuscitative Endovascular Balloon Occlusion of the Aorta, c – continuous, i – intermittent, n – no, PT – Prothrombin Time, PTT – Partial Thromboplastin Time, ALT – Alanine Aminotransferase, AST – Aspartate Aminotransferase, LDH – Lactate Dehydrogenase, CK – Creatine Kinase.
*Analysis of Variance

Throughout the 60 minute intervention phase, the cREBOA and iREBOA groups both maintained SBP following the initial elevation post injury. This is in contrast to CO, which decreased during the injury phase in the cREBOA and iREBOA groups to 3.2 ± 1.3 and 5.1 ± 1.2 respectively (Figure 10.3C). CO made little recovery during the intervention phase decreasing to the lowest value of 2.5 ± 0.5 at 30 mins in the cREBOA group and 4.6 ± 1.6 at 10 mins in the iREBOA group. Following resuscitation during the damage control surgery phase, CO increased to levels higher than baseline, with a peak of 7.6 ± 2.5 at 110 mins in the cREBOA group and 7.7 ± 1.3 at 150 mins in the iREBOA group. All indices of haemodynamic performance were maintained through to the EOS.

10.3.3 Metabolic Burden

Throughout the free bleed and intervention phase, there was an increase in lactate and a commensurate decrease in pH (Figure 10.4). In the nREBOA group, the lactate peaked at 14.4 mmol/l prior to the demise of the last animal in the group at 35 minutes post injury. The lactate trend was similar for both the cREBOA and iREBOA groups with peaks of 13.7 ± 2.2 at 90 mins and 13.5 ± 3.3 at 105 mins respectively. Similarly, the lowest pH occurred at 105 mins for both the cREBOA and iREBOA groups with measurements of 7.17 ± 0.09 and 7.17 ± 0.10.

Lactate measurements continued to decline from their peak measurement during the critical care phase to a lowest measurement at 4.5 hrs of 7.7 ± 2.4 and 6.6 ± 2.9 for the cREBOA and iREBOA groups. The pH peaked at this time point with values 7.39 ± 0.83 and 7.31 ± 0.13 respectively. The EOS values saw a small increase in lactate to 9.0 ± 4.5 and 7.8 ± 4.5 and a decrease in pH of 7.22 ± 1.45 and 7.28 ± 0.18 for the cREBOA and iREBOA groups.

10.3.4 Laboratory Parameters

A comparison of BL and EOS laboratory parameters for the cREBOA and iREBOA groups is presented in Table 10.2. Measures of haemoglobin, clotting time (Prothrombin and Partial Thromboplastin Time) and fibrinogen did not differ between BL and EOS. There was a significant decrease in platelet count observed between BL and EOS samples in the iREBOA group (292 ± 119 vs. 152 ± 98; $p = 0.027$).

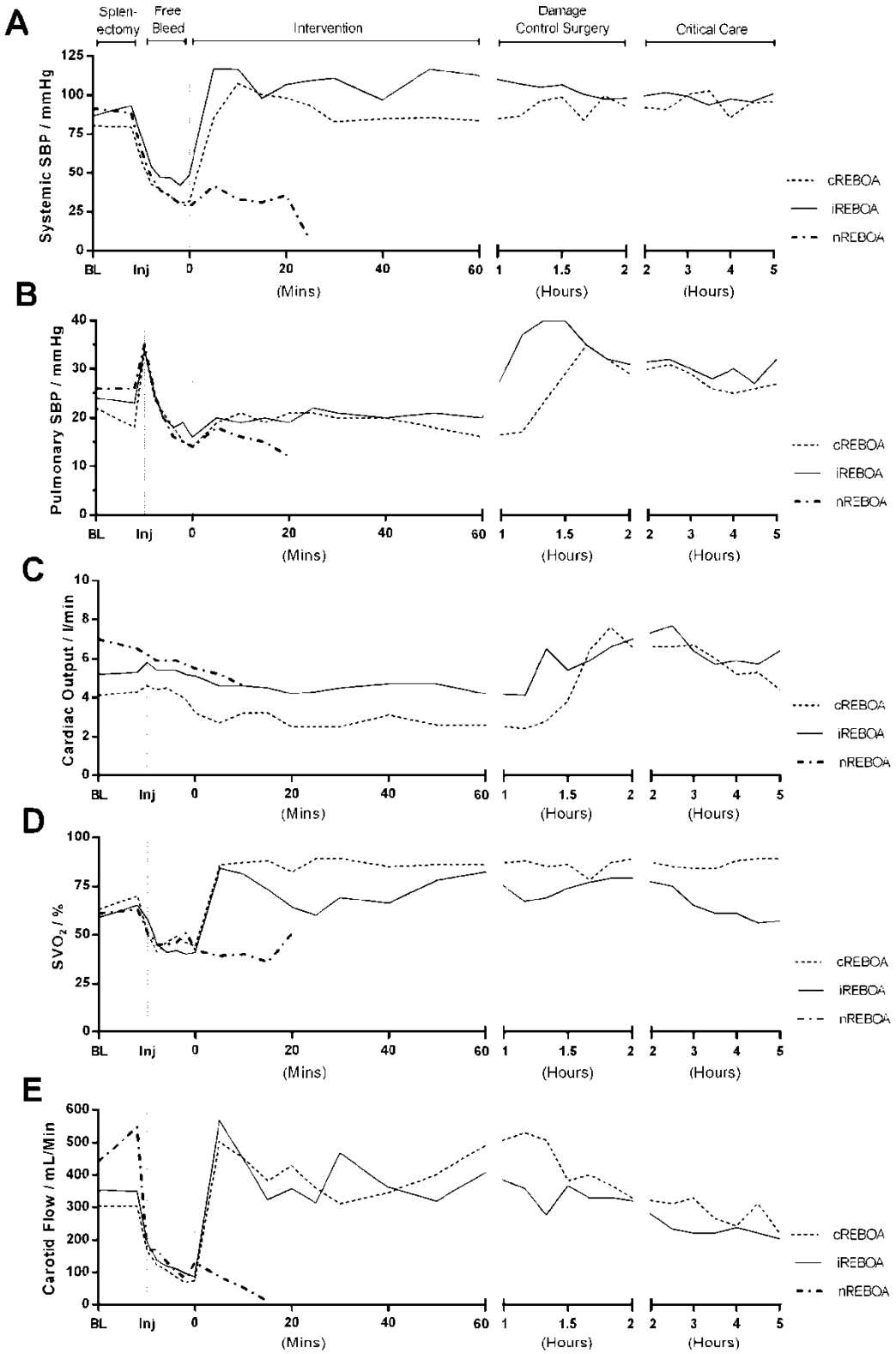

Figure 10.3: Haemodynamic response to balloon occlusion

As measured by A. systemic systolic blood pressure (SBP), B. pulmonary SBP, C. cardiac output, D. mixed central venous oxygen saturation, E. carotid flow. Data is plotted as mean values.

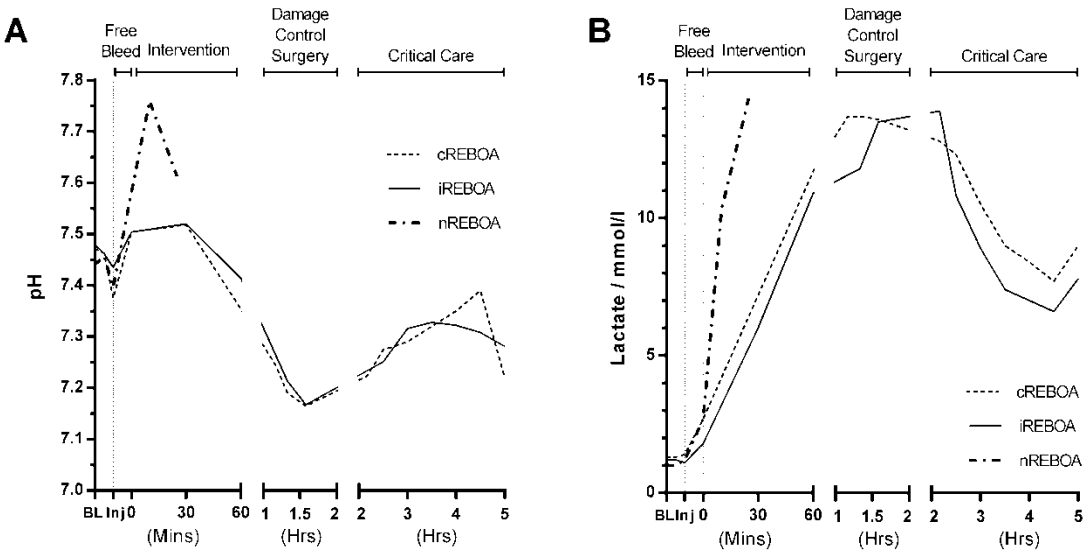

Figure 10.4: Metabolic changes in response to balloon occlusion

As measured by A. pH and B. lactate. Data is plotted as mean values.

An increase was observed in laboratory measures of end organ damage including renal, hepatic and cardiac parameters. BUN increased significantly in the cREBOA and iREBOA groups to 12.0 ± 1.6 and 11 ± 3.2 respectively. A similar trend was observed in creatinine. There was a non-significant increase in ALT across both groups and a significant rise in AST in the cREBOA group (20 ±9 vs. 403 ± 133; p = 0.001). Significant cardiac troponin-I increases were also observed, greatest in the cREBOA group (0 vs. 2.9 ± 1.5; p = 0.005) but also in the iREBOA group (0 vs. 1.8 ± 1.5; p = 0.033).

10.3.5 Inflammatory Burden

Only data from the cREBOA and iREBOA groups are presented as no animal in the nREBOA group survived to the EOS (Table 10.2). There was no difference in baseline measurements between the cREBOA and iREBOA groups for IL-6, TNF-α or IL-8. A significant increase from BL to EOS was noted in IL-6 measurements in both the cREBOA (32 ± 14 vs. 1188 ± 279; p = 0.001) and iREBOA (36 ± 26 vs. 227 ± 296; p = 0.003) groups.

While an increase in EOS compared to BL TNF-α and IL-8 was observed, it was not significant in either group (Table 10.2). In terms of EOS values between the groups, cREBOA had a incurred a greater IL-6 (1187 ± 279 vs. 834 ± 287; p = 0.084), TNF-α (205 ± 92 vs. 110 ± 36; p = 0.063) and IL-8 (329 ± 505 vs. 227 ± 296; p = 0.708) release than the nREBOA group, although again, none achieved statistical significance.

10.3.6 Operative Intervention and Resuscitation

Damage control surgery was performed in the cREBOA and iREBOA groups as no animal in the nREBOA group survived beyond the intervention phase (Table 10.2). Total Pringle time was similar between the cREBOA and iREBOA groups (18 ± 5 vs. 12 ± 3; p = 0.095) as was the intra-operative REBOA time (min) (20 ± 9 vs. 15 ± 8; p =0.293). Emergent re-inflation was required for two animals in the cREBOA and four in the iREBOA groups, predominantly for control of hypotension. All laparotomies were performed within the allocated 60 minutes with an overall mean time of 35 ± 10 mins.

Both groups received similar volumes of WB and crystalloid. Insulin and 50% dextrose was used in five animals to treat a K^+ greater than 5.5 mmol/l, two required 50% dextrose for hypoglycaemia and inotropic support was necessary in five cases. One animal developed a tension pneumothorax which was treated with tube thoracostomy.

There were two unplanned re-laparotomies. One animal in the cREBOA group had a rising lactate despite resuscitation and re-exploration identified global small bowel ischemia which improved following withdrawal of the REBOA catheter from the thoracic aorta. The second re-laparotomy occurred in an iREBOA animal, in response to haemodynamic instability and falling haemoglobin suggestive of ongoing bleeding. There was evidence of gross coagulopathy with no surgically remedial solution; despite exhaustion of WB reserves, the animal survived to the end of study.

10.3.7 Mortality

There were 11 early deaths from exsanguination that occurred during the intervention phase (Figure 10.5). All of the nREBOA animals died within 35 minutes of injury. Deployment of REBOA was unable to salvage two animals in the iREBOA group (11 and 15 mins post-injury) and one animal in the cREBOA group (12 mins post-injury).

There was one intra-operative death in the iREBOA group (80 minutes post injury). This animal tolerated balloon deflation during the intervention phase poorly, requiring emergent re-occlusion during both attempts. The animal displayed gross haemodynamic instability ten minutes prior to damage control laparotomy, deteriorating into cardiac arrest with pulseless electrical activity 3 minutes prior to damage control surgery. Despite aggressive resuscitation attempts, including internal cardiac massage and rapid whole blood infusion, there was no return of spontaneous circulation. One death was observed during the critical care phase in the cREBOA group (5 hours post injury). This animal developed cardiogenic shock refractory to inotropic support.

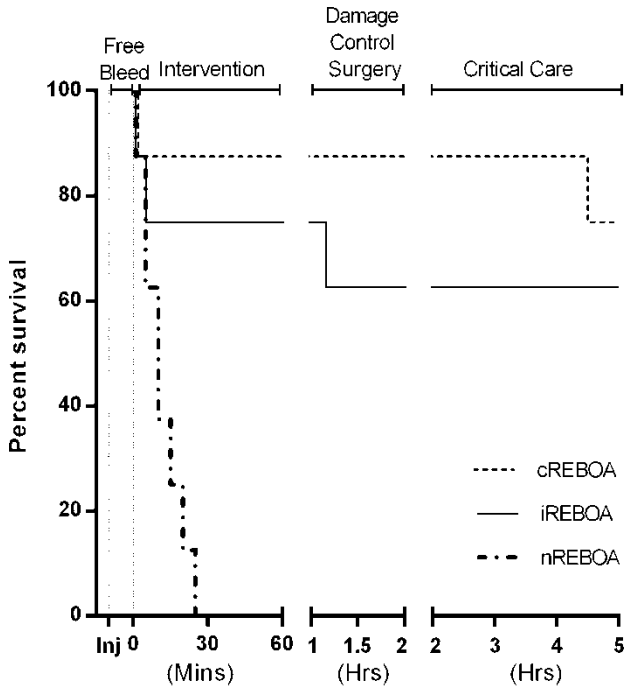

Figure 10.5: Survival following balloon occlusion

Log Rank Test, $p = 0.001$.

The overall survival for the cREBOA, iREBOA and nREBOA groups to EOS was 75.0%, 62.5% and 0.0% respectively. A pairwise log rank (Mantel-Cox) comparison between the groups demonstrated a significant difference in survival when comparing nREBOA to cREBOA ($p = 0.001$) and nREBOA to iREBOA ($p = 0.007$). There was no difference comparing cREBOA to iREBOA ($p = 0.572$).

10.4 Discussion

The current study examines the effectiveness of REBOA as a haemorrhage control adjunct in a highly lethal porcine model of non-compressible torso haemorrhage. It is the first study to evaluate this adjunct in conjunction with modern damage control resuscitation (DCR). REBOA was used to successfully salvage 13/16 (81.3%) animals from imminent circulatory arrest and to sustain the circulation of 12/16 (75.0%) animals until definitive haemorrhage control. This is in contrast to the control animals, all of whom died of rapid exsanguination. Furthermore, the current study also examined outcomes between intermittent and continuous occlusion, in an effort to assess whether transient reperfusion reduced the metabolic or inflammatory burden. No difference was detected in these outcomes between the continuous and intermittent REBOA groups.

This study confirms and extends previous work characterising the haemodynamic and metabolic sequelae of balloon occlusion in haemorrhagic shock. White et al. used a porcine model of controlled haemorrhage to demonstrate that REBOA had a comparably favourable haemodynamic profile to open clamp occlusion of the thoracic aorta, but resulted in less of a metabolic burden than resuscitative thoracotomy (80). Markov et al. used a similar model to evaluate the physiologic tolerance of 30 and 90 minutes of occlusion (25). A lactic acidosis was incurred with both occlusion times, greatest in the 90 minute group, but ultimately survivable with the restoration of normal physiology following balloon deflation.

Most recently, Scott et al. used an occlusion time of 60 minutes with which to assess the performance of a newly developed, self-centring, low-profile, prototype REBOA catheter (100). Results from that study demonstrated the reproducibility of blind or fluoroscopy-free placement, with physiological results

that complemented Markov's work. While this body of literature demonstrates the haemodynamic advantages of REBOA and the survivability following balloon deflation, more clinically relevant models of uncontrolled haemorrhage have been required to assess the practical application of REBOA.

Avaro et al. used a porcine model of open splenic trauma, resuscitated with saline, to evaluate a control group with 40 or 60 mins of REBOA followed by splenectomy (90). The control group all exsanguinated within 80 minutes of injury and 9/12 (75.0%) of the 60 minute group died upon balloon deflation due to metabolic derangement. All animals in the 40 minute group in the Avaro study survived, suggesting that 40 minutes constitutes an optimum physiologic threshold for resuscitative aortic occlusion.

The current study builds on Avaro's work, by incorporating DCR (including whole blood administration) that successfully extends this physiological threshold to 60 minutes. This approach results in a greater overall survival (68.8%), despite a longer occlusion time and a more lethal model. The combination of WB resuscitation, prompt correction of electrolyte derangement, active warming and haemodynamic support can successfully ameliorate the metabolic consequences of balloon deflation and reperfusion.

However, it is important to acknowledge that the current study's resuscitation was by no means comprehensive. Whole blood reserves were limited and adjuncts such as Tranexamic Acid (121) or specialised blood products like cryoprecipitate (122) were not employed. This was reflected by the ongoing acidosis during the critical care phase which is frequently corrected intra-operatively using contemporary DCR (97).

There are further limitations that are important to discuss. The use of intermittent REBOA was an attempt to permit a degree of ischemic pre-conditioning that would enhance resilience to the reperfusion injury. The time of one minute was used, as during the model development phase, it was clear that animals would not tolerate prolonged deflation without resuscitation. It is likely that the period of minute is too brief and therefore conclusions relating to

the iREBOA group should be cautious. Further work examining techniques to ameliorate reperfusion injury should be explored.

The use of REBOA has not been limited to animal studies, with the earliest reported human use during the Korean War in 1953 by Lt Col Hughes (7). He described two casualties with exsanguinating truncal injuries, both of whom responded to balloon occlusion, but ultimately died of their wounds. Despite its attractions, balloon occlusion was surpassed by the experience of open clamp occlusion which became the standard of care (91).

Resuscitative aortic balloon occlusion was explored again in the 1980s; however, success was limited by patient selection and insertion technique (8,9). The majority of patients were either in established cardiac arrest or moribund and the method of arterial access was generally by cut-down, frequently unsuccessful. REBOA may be most successful as a proactive intervention (i.e. aortic pressure monitoring with capacity to inflate a balloon) in patients with a spontaneous circulation, at risk of circulatory arrest.

Following the refinement of both catheter technology and Seldinger insertion techniques during the 1990s, along with the developments in trauma resuscitation, the re-evaluation of this technology is a logical step (6). Brenner and colleagues recently report a series of 6 trauma patients, injured by a mixture of blunt and penetrating trauma treated using REBOA as an adjunct to DCR (98). The mean admission SBP was 59 ± 27 mmHg which was increased to 114 ± 20 mmHg following the deployment of REBOA. While one patient died of traumatic brain injury and another of multi-organ failure, there were no REBOA related complications. Ultimately, this adjunct was used as a haemostatic and resuscitative bridge to definitive haemorrhage control, incurring no haemorrhage related mortality.

Resuscitative endovascular balloon occlusion of the aorta can temporise exsanguinating haemorrhage and restore life-sustaining perfusion, bridging critical physiology to definitive haemorrhage control (i.e. surgical haemostasis). In the current study, intermittent compared to continuous REBOA offered no additional benefit, although different schedules of occlusion should be explored

in future studies. Importantly, the physiologic penalty incurred by 60 minutes of occlusion could be ameliorated with aggressive DCR. Prospective observational studies of REBOA as a haemorrhage control adjunct should be undertaken in appropriate groups of human trauma patients.

Chapter 11: Morphometric Analysis of Torso Arterial Anatomy with Implications for Resuscitative Aortic Occlusion

11.1 Introduction

In the setting of haemorrhagic shock, maintenance of central aortic pressure is critical to sustain myocardial and cerebral perfusion until resuscitation can be initiated and bleeding controlled (96). Resuscitative aortic occlusion at locations between the origin of the left subclavian artery and the aortic bifurcation can be a life sustaining procedure, which maintains central pressure and mitigates distal haemorrhage (3). Currently this manoeuvre is achieved with an aortic clamp at the time of thoracotomy or laparotomy or with an endovascular balloon introduced through the femoral artery (6,42).

Despite the potential for resuscitative aortic occlusion to sustain life and control haemorrhage there is little quantitative information on the morphometry of the aorta or the iliac or femoral arteries. Morphometry, in this context, refers to the diameters at various locations along the aorta and distances between the femoral vessels and major aortic side branches. The current understanding of torso arterial anatomy is mostly based on cadaveric dissection and medical illustration. Even when computed tomography (CT) provides detailed arterial measurements, the imaging is per individual and obtained post injury. For significant advances to occur in the management of haemorrhage, including the use of resuscitative aortic occlusion, a more complete knowledge of aortic and access vessel morphometry is necessary.

The common use of CT following injury has resulted in repositories of imaging data in trauma populations (123,124). These collections of data include imaging of the aorta, iliac and femoral arteries stored on systems with software to perform detailed vessel diameter and centre line length measurements. Structured collection and analysis of torso arterial measurements from large numbers of CT imaging studies may allow the quantification of morphometric norms. Knowledge of such norms prior to injury stands to facilitate new techniques in resuscitation and haemorrhage control without the need for fluoroscopy.

The objective of this study is to quantify torso arterial morphometry in a trauma population using a volume of archived CT images. An additional objective is to characterise the correlation of arterial lengths or distances with a novel measure of torso extent.

11.2 Material and Methods

Following Institutional Review Board approval, consecutive trauma patients over a 12 month period, who underwent CT scanning, were retrospectively identified from the Wilford Hall United States Air Force Medical Center database (Lackland Air Force Base (San Antonio), Texas). For inclusion, CT scans were those performed on male patients between the ages of 18 and 45. All CT scans were contrast-enhanced, 64-slice continuous examinations of the chest, abdomen, pelvis and femoral vessels.

The individual scans were loaded on to a CT workstation running Volume Viewer™ software (General Electric, Waukesha, WI). Three-dimensional reconstructed angiograms permitted the measurement - in millimetres (mm) - of the distance between vessel origins and diameters (Figure 11.1).

The aorta was divided into and examined as three previously described zones (Figure 11.2) (6). Aortic Zone I extended from the origin of the left subclavian artery to the celiac trunk. Aortic Zone II extended from the celiac trunk to the origin of the lowest renal artery and the infra-renal aorta (lowest renal to the aortic bifurcation) comprised Aortic Zone III.

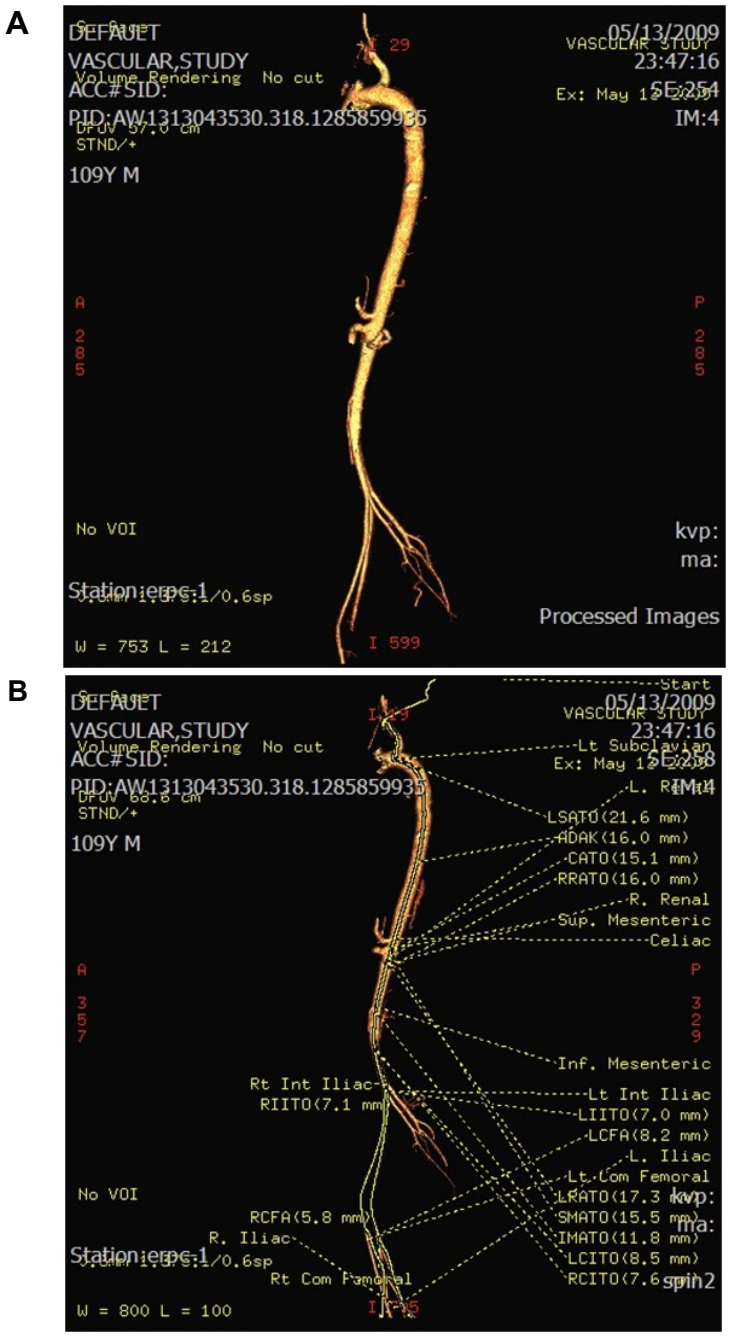

Figure 11.1: A. CT 3-D rendering of the aorta, iliac and femoral arteries; B. Same image with superimposed centre line measurements

The centre line length (mm) of each zone was measured and the luminal diameter of the aorta at the proximal and distal most extent of each of the zones was recorded. Additionally, the distance from left and right common femoral artery at the midpoint of the femoral head to the aortic bifurcation and the origin of the left subclavian artery was recorded. The common femoral artery landmark was chosen as a plausible site for arterial access. For purposes of the study the external measure of torso extent was defined as the straight line distance (mm) from the suprasternal notch of the manubrium to the mid-pubic symphysis, parallel to the patient's cranio-caudal axis.

CT images were examined by a single reader, with 10 scans reassessed *de novo* and measured at different sessions to assess intra reader variability. Data were collected in an Excel spreadsheet (Microsoft, Redmond, Washington, USA) and imported to SPSS version 20 (IBM®, New York) for analysis. Distances and diameters were reported as medians, accompanied by interquartile range and maximum/minimum values for distribution. Scatter plots were generated plotting aortic zone length against torso extent or height and a best fit line was drawn using linear regression analysis. The correlation of determination (R^2) was reported as measures of the strength of the linear regression.

11.3 Results

Two hundred male patients underwent CT imaging following traumatic injury between April 1, 2009 and March 31, 2010. There were 112 (56%) exclusions with 102 (51%) removed because of a low quality contrast bolus or a non-contiguous chest, abdomen, pelvis and femoral imaging. Eight scans (4%) were excluded due to inadequate anatomic exposure and 2 (1%) were excluded due to abnormal vascular anatomy. The final cohort comprised 88 patients with a mean (±SD) age of 28±4 years and a median (interquartile range or IQR) torso extent or height of 521mm (500-536).

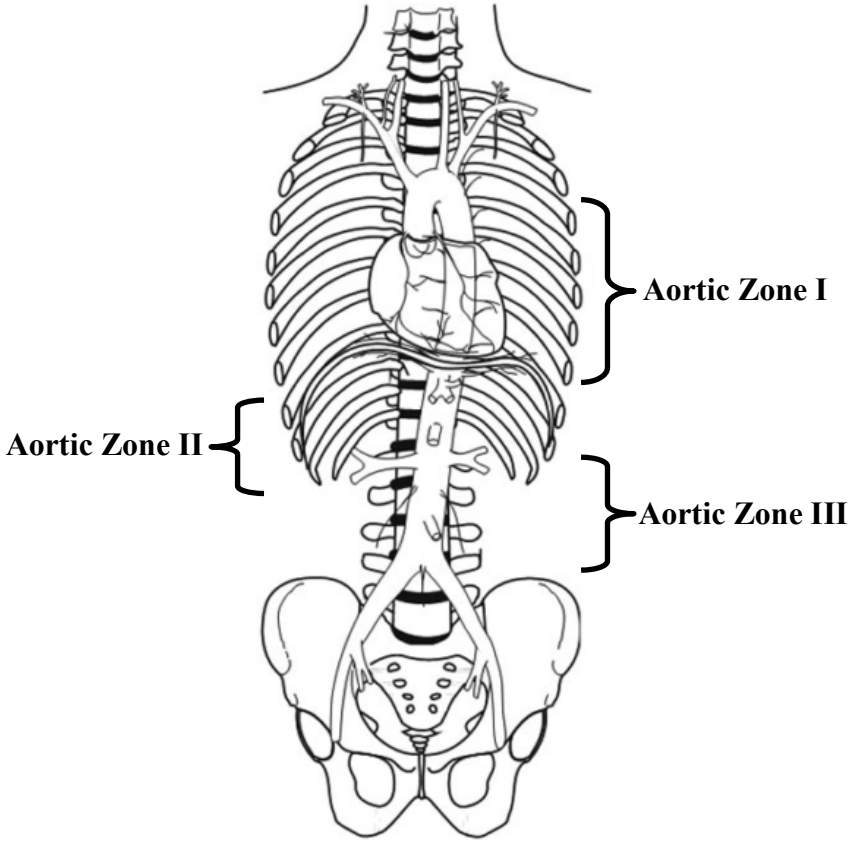

Figure 11.2: Line drawing demonstrating the three aortic zones

11.3.1 Distances or Lengths

The distances (mm) from skin to the left or right common femoral artery (CFA) was similar, with a median distance of 35mm and IQR of 29-41mm Table 11.1. The distance from the CFA to the aortic bifurcation was longer by 30 mm on the right than the left side. The median (IQR) distance for the right and left were 197mm (182-213) and 206mm (195-219) respectively. The total length of the aorta from the left subclavian to the aortic bifurcation was 340mm (323-360). Aortic zone I was the longest with a median length of 211mm (202-223). The length of Zone III was 97mm (91-103) and the length of Zone II was 33mm (28-38).

11.3.2 Diameters

The diameters of the left and right CFA were the same measuring 8mm (7-9) (Table 11.2). Aortic diameter was the smallest (14mm (13-15)) at the bifurcation. Aortic diameter increased to 15mm (14-16) at the lowest renal artery, 18mm (16-19) at the celiac trunk and 21mm (20-23) at the level of the left subclavian artery (Table 11.2).

11.3.3 Linear Regression

Length measurements of the descending aorta were plotted against the measurements of torso extent or height (Figure 11.3) and linear regression was used to apply a best fit line. An R^2 of 0.454 demonstrated torso extent alone was able to explain over 45 percent of the variability in aortic length. This method was repeated for the individual aortic zones (Figure 11.4) with both aortic zone I and zone III resulting in an R^2 of 0.294 and 0.212 respectively indicating other explanatory variables may be involved Zone II had a low R^2 of 0.065 suggestive of a poor linear relationship to torso height.

Table 11.1: Measurements of key vascular distances

Distance (mm)	Minimum	25th Percentile	Median	75th Percentile	Maximum
Aortic Zone I	96	202	211	223	260
Aortic Zone II	16	28	33	38	129
Aortic Zone III	66	91	97	103	123
Left CFA to AB	146	182	197	213	241
Right CFA to AB	163	195	206	219	244
Skin to Left CFA	10	29	35	41	76
Skin to Right CFA	11	29	35	40	78

Abbreviations and definitions: Aortic Zone I - left subclavian to celiac trunk; Aortic Zone II - celiac trunk to lowest renal artery; Aortic Zone III - lowest renal artery to aortic bifurcation; CFA - common femoral artery; AB - aortic bifurcation.

Table 11.2: Vessel diameters at key vascular landmarks.

Diameter (mm)	Minimum	25th Percentile	Median	75th Percentile	Maximum
Aorta at Left SCA	16	20	21	23	27
Aorta at CT	12	16	18	19	23
Aorta at LRA	11	14	15	16	19
Aortic Bifurcation	10	13	14	15	18
Left CFA	5	7	8	9	11
Right CFA	4	7	8	9	12

Abbreviations and definitions: SCA - subclavian artery; CT - celiac trunk; LRA - lowest renal artery; CFA - common femoral artery.

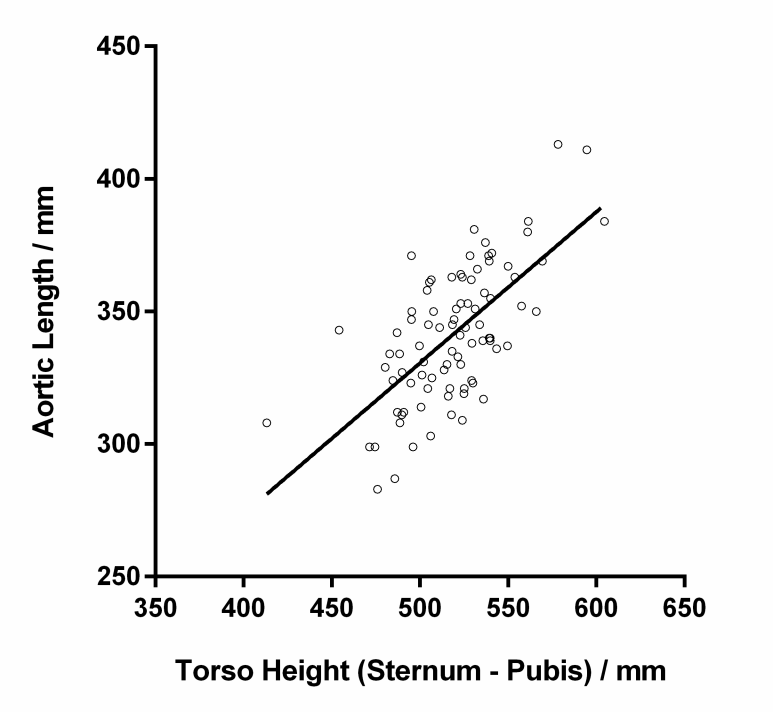

Figure 11.3: Scatter plot of torso height against descending aortic length with accompany best fit line.

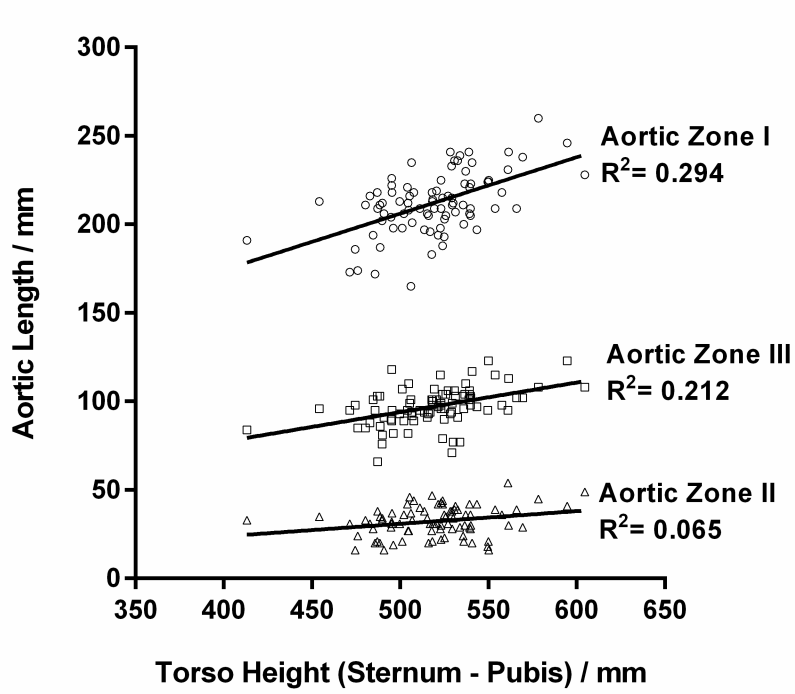

Figure 11.4: Scatter plots of torso height against the three aortic zones with accompany best fit lines

11.4 Discussion

This study is the first to report numerical characterisation of the aorta, iliac and femoral arteries using stored CT images of male trauma patients. Additionally, this analysis reports the morphometric measures of three clinically relevant aortic zones and demonstrates a correlation between aortic length and torso height. This capability has largely come about due to scanning techniques and software originally designed for the planning of endovascular intervention, but the commonality of CT imaging in trauma extends the applicability (123,124).

This study compliments our group's previous work in torso trauma, where the aorta has been characterised into three zones (6). Zone I extends from the origin of the left subclavian artery to the celiac trunk and has a median length of 211 mm. Zone II is from the origin of the celiac trunk to the lowest renal artery and has the smallest median length of 33 mm. The infra-renal aorta is Zone III and is 97 mm in median length.

Aortic Zones I and III were described as regions of occlusion, in order to achieve inflow control and afterload support of patients *in extremis* with NCTH (6). Zone I is the suggested region of occlusion for patients with abdominal exsanguination and/or circulatory collapse/arrest. Zone III occlusion provides terminal aortic control for patients with exsanguinating pelvic and/or inguino-femoral junctional haemorrhage. Zone II or the para-visceral segment, is a zone of no-occlusion and is conveniently the shortest zone.

Aortic occlusion can be achieved by a number of methods - open and endovascular. Open aortic cross clamping following resuscitative thoracotomy is well described in both military (118) and civilian (125) settings. However, this is only generally possible in appropriately resourced facilities, and is often performed as a reactive manoeuvre following the loss of a central pulse and is associated with poor outcome (42,118).

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a minimally invasive, proactive technique designed to be used in patients with haemorrhagic shock, that can support the circulation until definitive haemorrhage control (6).

Critical to this adjunct is correct balloon placement, of which radiographic imaging may not always be possible. Morphometric analyses, such as the one presented in the current study, will help guide the deployment of such devices.

This study has a number of important limitations relating to design, population and technical issues. This study is retrospective in nature, which may mean that not all eligible patients were identified; although, by using a computerised radiology database, rather than case records, this should be minimal. The current study also only examined a male population which limits the reported findings to men, as women do have morphological differences. The male gender was chosen as there were insufficient female subjects available for an adequately powered analysis. The analysis of this relatively homogeneous population has the effect of producing a narrow interquartile range of values. However, the study population is reflective of most trauma populations which are dominated by young men.

The biggest limitation is that 56% of the originally identified cohort were excluded - the majority (91%) due to poor contrast quality. It is unclear whether this introduces a bias to the distribution of measurements. It may be the case that a larger sample size, with fewer exclusions, will improve the strength of the linear regression.

11.4.1 Conclusions

The current study is the first numerical characterisation of aortic zones demonstrating correlation to torso height, using a CT data repository. First, this demonstrates both the feasibility and limitations of this methodology, which may be applicable to other morphometric analyses. Second, these results permit the application of numeric planning to future resuscitative interventions for NCTH. This has particularly relevant to the emerging use of endovascular technology, which is an exciting new development in torso haemorrhage control. Further study in a broader population, that includes female torso anatomy, is warranted in order to develop the application of morphometric analysis in torso trauma.

Chapter 12: Prospective Evaluation of the Correlation between Torso Height and Aortic Anatomy in Respect of a Fluoroscopy Free Aortic Balloon Occlusion System

12.1 Introduction

Haemorrhage is the leading cause of potentially preventable death in military trauma (2,15,16). The majority of haemorrhagic foci originate in non-compressible regions such as the torso and junctional zones (groin and axilla), accounting for 86.5% of haemorrhage related combat deaths (4). Furthermore, almost nine out of 10 deaths occur in the pre-hospital setting (4). Current management is reliant on operative haemorrhage control which is contingent on patients surviving to hospital admission (3). Even then, many patients arrive *in extremis* with circulatory collapse, where reactive manoeuvres such as resuscitative thoracotomy and aortic cross clamping yields few survivors (118).

Resuscitative endovascular balloon occlusion of the aorta (REBOA) provides inflow control and afterload support to patients with circulatory collapse from haemorrhage (6). It can either be inserted prophylactically in patients at risk of haemorrhage and then inflated in the event of a deterioration, or as a substitute to open cross clamping in the moribund patient (80). REBOA is designed as a proactive manoeuvre, which can be inserted in austere circumstances, providing a physiological bridge to definitive haemorrhage control.

The clinical use of this technique was first described in the 1950s (7), with further reports in the 1980s (8,9). Despite some favourable outcomes, technological limitations relating to arterial access, balloon construction and placement meant its adoption was not widespread. However, following the evolution of endovascular surgery and the experience with aortic balloon occlusion during endovascular aneurysm repair (10,77), many of these constrains have been overcome. The use of REBOA in traumatic haemorrhagic shock is currently being revisited clinically using “off-the-shelf” devices (98), but there is also active research into trauma-specific catheters (100).

To facilitate REBOA deployment, the aorta has been characterised into three functional zones: zone I extends from the origin of the left subclavian to the

celiac trunk, zone II is from the celiac trunk to the lowest renal artery and the infra-renal aorta constitutes zone III (Figure 12.1) (6). Zone I and III serve as "landing zones" for occlusion in specific injury patterns. Zone I occlusion provides resuscitation in circulatory arrest and control for abdominal exsanguination and zone III occlusion is for ileo-femoral junctional haemorrhage (3).

Current technology requires fluoroscopy for precision placement, which limits the deployment of REBOA systems in the pre-hospital or emergency department setting. Unassisted blind insertion is fraught with potential complications, varying from aortic arch placement precipitating cerebral ischemia to iliac artery occlusion inadequately controlling inflow.

A potential solution to aid fluoroscopy free placement is to use an external anatomical measure to predict internal vascular length. A linear relationship has been previously demonstrated between aortic length and torso height (126). The aim of this study is to develop predictive models of REBOA insertion distance, based upon an external measure of torso height (EMTH) correlated with internal vascular distance. The accuracy of which will then be assessed using prospective EMTH data, collected in a realistic clinical setting.

12.2 Methods

This prospective observational study was performed following approval from the UK Royal Centre for Defence Medicine Academic Unit and the US Medical Research and Material Command. The study was conducted at the Combat Support Hospital in Camp Bastion, Helmand Province, Southern Afghanistan. This hospital is unique in the theatre of Afghanistan as it is a joint UK and US facility, staffed by clinicians from each nation’s military amongst others. It is also the busiest coalition medical facility in the region, providing comprehensive trauma care for both military and civilian patients (127). The infrastructure includes two 64-slice CT scanner, in addition to an emergency department, operating suite and critical care facilities (123). Data were collected over two time periods (July 2011 - September 2011 and November 2011 - January 2012), during the deployments of two authors (AS and JJM).

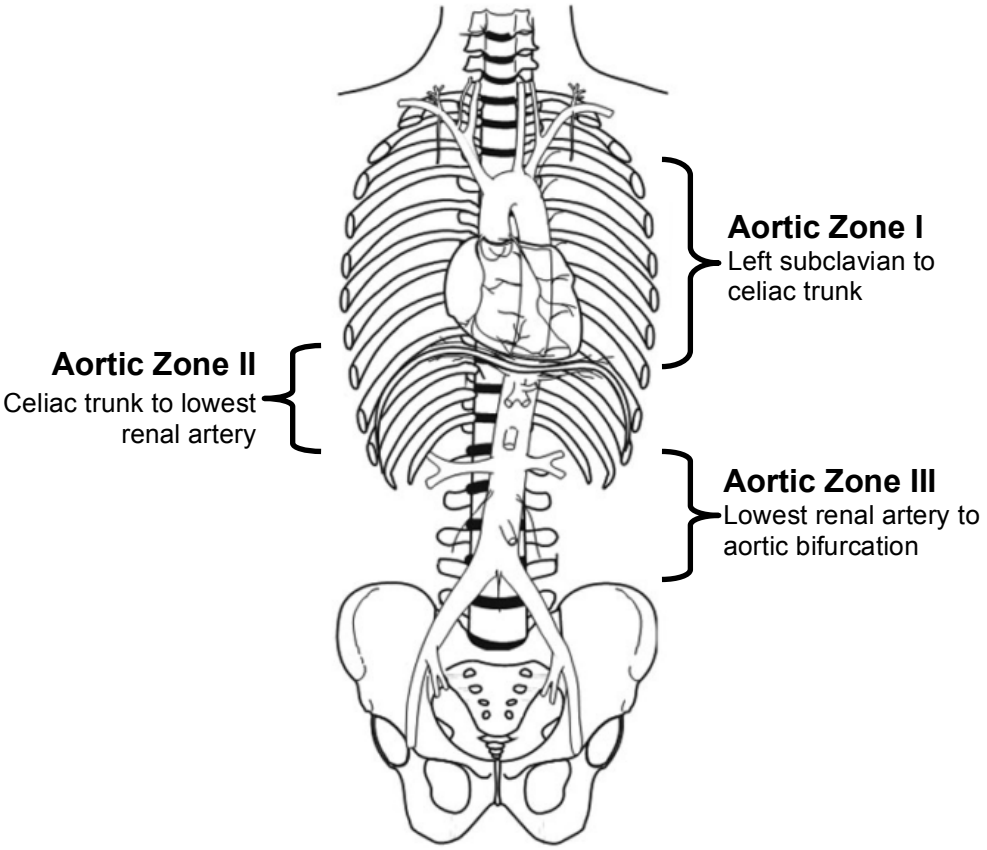

Figure 12.1: Line drawing demonstrating the three aortic zones.

12.2.1 Study Population

A non-random, non-consecutive (convenience) sample of male patients aged between 18 and 50 years, who underwent contrast enhanced CT imaging of the chest, abdomen and pelvis as part of their care, were included in the study. A convenience sample was used, rather than consecutive patients, due to the brisk operational tempo and single handed nature of the data collection. Nation status was dichotomised into patients of Afghan origin (military or civilian) termed "Host National", and the remaining patients were termed "Coalition Military". Enemy combatants were not included in the study.

Once patients had been identified as requiring CT imaging, an external measure of torso height (EMTH) was recorded prior to discharge. This was performed using a tape measure, held parallel to the subject's cranio-caudal axis, to obtain the distance from the jugular notch to the pubic symphysis (Figure 12.2). All tape measurements were performed by one of two individuals (AS or JJM) to the nearest centimetre (cm).

Using a CT workstation, the centre line distances from the left and right common femoral artery (CFA), at the level of the mid-point of the femoral head, to several key aortic landmarks (bifurcation, take off of the lowest renal artery, celiac and left subclavian) were calculated. This technique takes into account vessel tortuosity and angulation providing for precision measurements. The CFA landmark was chosen as a possible site of arterial access for the insertion of a REBOA system. The EMTH was also repeated using the CT callipers on the sagittal view of the scout film. All CT measurements were to the nearest millimetre (mm).

12.2.2 Statistical Analysis

Initially, the measurements of key vascular landmarks and torso height by CT and tape measure were reported for the entire cohort. Specifically, the distance from the left and right CFA insertion points to the mid-points of zones I and III were calculated. These distances represent the insertion length required for a REBOA system to occlude the aorta at the mid-point or "landing zone" of each respective zone.

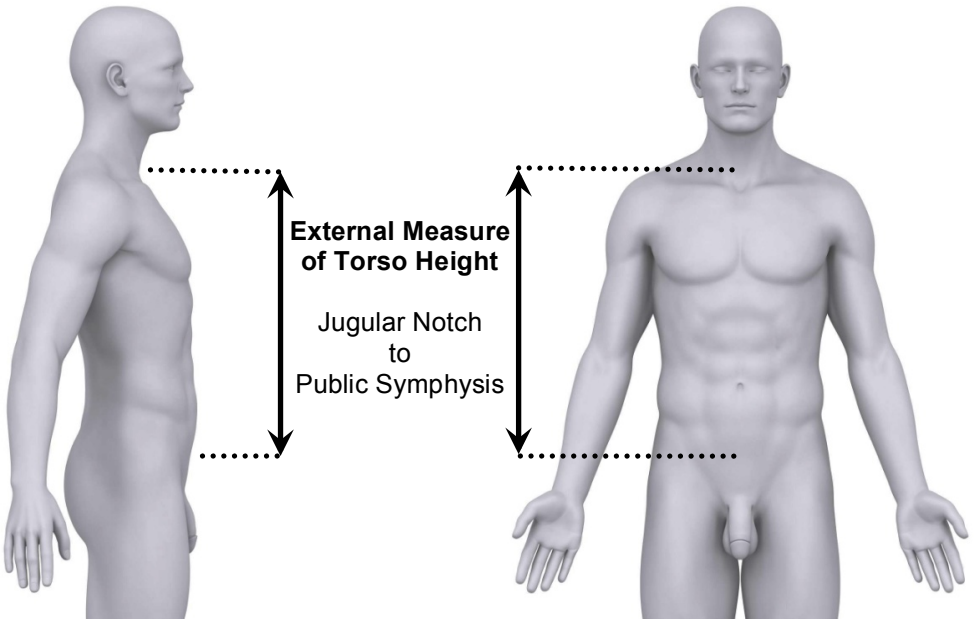

Figure 12.2: Landmarks demonstrating the external measure of torso height

Following this, a 20% sample of the study group was selected at random and used as a development cohort to generate linear regression models of insertion using the CT EMTH as the dependant variable. Model group 1 included both insertion length and nation status (Host National or Coalition Military) as covariates, whereas model group 2 only utilised insertion length. Models were generated for insertions through both left and right CFAs and for the mid-points of zones I and III; 4 in total. The strength of each regression model was presented using the coefficient of determination adjusted for sample size (adjusted R^2). Analysis of variance (ANOVA) was used to test the null hypothesis. Model group 3 consisted of a constant which was the median insertion distance for the population, without adjustment for any parameter.

Following the development of the insertion models, the remaining 80% of the study group were used as a validation cohort. The tape EMTH was used in conjunction with the model equations, to generate predicted insertion lengths. These predicted lengths were then correlated with the observed lengths and the strength of the linear dependence reported using Pearson's correlation coefficient. Accuracy was also assessed by the proportion of subjects “landing” both within the zone and within the middle 60% of the zone. The latter was chosen, as this leaves a 20% safety margin at either end of the zone to accommodate a theoretical balloon "foot-print". Box and whisker plots were used to graphically demonstrate the accuracy of the models within the proximal and distal extent of the aortic zones, expressed as a proportion.

Data were recorded and organised in an Excel spreadsheet (Microsoft®, Redmond, Washington, USA) and then imported into SPSS version 20 (IBM®, New York) which was used to perform the statistical analysis. Data which was not normally distributed was presented as medians, with 25th and 75th quartiles, minimum and maximum values. Statistical significance was defined as a $p < 0.01$.

12.3 Results

Data were collected on 80 and 97 patients during the two time periods, providing a total cohort for analysis of 177 patients. The median (IQR) age of the

cohort was 23 (8) with 104 (58.8%) of Host National origin. There was no missing data.

Table 12.1 provides a summary of the measurements of key vascular landmarks for the total cohort, measured in mm. The median distance from the right CFA to the aortic bifurcation was longer than from the left CFA by a distance of 5 mm. Zone I was the longest of the aortic zones with a median (IQR) measurement of 222 (24), followed by zone III with 92 (15). Zone II was the shortest zone, with a median (IQR) distance of 31 (9).

Correspondingly, the insertion length from the CFA to the mid-point of each zone was longer from the right side compared to the left. For occlusion of the mid-point of zone I, the median insertion from the right CFA was 423 (27) and from the left CFA was 418 (29). For zone III occlusion, the insertion distance was considerably shorter than zone I, with a median distance from the right of 232 (21) and from the left of 228 (22). The EMTH by CT and tape measure were in similar agreement with respective values of 533 (34) and 540 (30).

A 20% (n = 36) model development cohort was selected at random and compared to the remaining 80% (n = 141) model validation cohort for key measurements. There was no significant difference in EMTH values and respective insertion lengths ($p > 0.01$) between the groups using a Mann-Whitney rank sum test.

Linear regression was used to develop several models to predict insertion length (Table 12.2). Model group 1 used the CT EMTH as the dependent variable and the zone insertion length and nation status as the independent variables. The models generated for zone I occlusion had adjusted coefficient of determination values of 0.803 and 0.824 for left and right insertions respectively. Zone III demonstrated a lower coefficient of determination with values of 0.613 and 0.642 respectively.

Table 12.1: Measurements of key vascular landmarks (n = 177)

Distance (mm)	Minimum	25th Percentile	Median	75th Percentile	Maximum
Vessel Lengths					
Left CFA to AB	116	174	182	194	223
Right CFA to AB	121	178	187	199	242
Left CFA to Lowest RA	179	264	275	287	312
Left CFA to CA	198	296	307	319	357
Left CFA to Left SCA	348	514	530	548	590
Zone Lengths					
Zone I	141	209	222	233	255
Zone II	16	27	31	36	70
Zone III	63	84	92	99	123
Insertion Lengths					
Right CFA Mid-Zone I	280	409	423	436	488
Left CFA Mid-Zone I	277	404	418	433	468
Right CFA Mid-Zone III	152	223	232	244	286
Left CFA Mid-Zone III	148	218	228	240	268
Torso Height					
Measured by CT	366	517	533	552	590
Measured by Tape	370	530	540	560	610

Abbreviations and definitions: CFA - common femoral artery; AB - aortic bifurcation; RA - renal artery; SCA - subclavian artery; Aortic Zone I - left subclavian to celiac trunk; Aortic Zone II - celiac trunk to lowest renal artery; Aortic Zone III - lowest renal artery to aortic bifurcation.

Table 12.2: Linear regression models, developed with and without regard to nation status, from 20% (n = 36) of the overall cohort.

	Equation	Adjusted Coefficient of Determination	p-value
*Model Group 1			
R CFA to Mid Zone I	$E(Y) = \beta_0 + \beta_1X_1 + \beta_2X_2$	0.803	< 0.001
L CFA to Mid Zone I		0.824	< 0.001
R CFA to Mid Zone III		0.613	< 0.001
L CFA to Mid Zone III		0.642	< 0.001
**Model Group 2			
R CFA to Mid Zone I	$E(Y) = \beta_0 + \beta_1X_1$	0.806	< 0.001
L CFA to Mid Zone I		0.828	< 0.001
R CFA to Mid Zone III		0.620	< 0.001
L CFA to Mid Zone III		0.642	< 0.001
***Model Group 3			
Any CFA to Mid Zone I	E(Y) = median (insertion length)	n/a	n/a
Any CFA to Mid Zone III		n/a	n/a

*Model Group1 - Incorporates nation status as a covariate.

** Model Group 2 - Developed with no regard to nation status.

***Model Group 3 - Insertion to the median population zone insertion length.

E(Y) = Predicted insertion length; X_1 = Torso height; X_2 = Nation status.

Model group 2 utilised the CT EMTH as the dependent variable and zone insertion length as the independent variable. The models in group 2 performed similarly to group 1, with the strongest models observed in zone 1 with adjusted correlation of determination values of 0.803 and 0.824 for right and left insertion respectively. Zone III models for the right and left insertion scored 0.620 and 0.642 respectively. No correlation was determined for model group 3 as the insertion distance was a constant: 418 for zone I and 229 for zone III.

The tape EMTH from the validation cohort (n = 141) was used in conjunction with the 3 model groups to calculate predicted insertion distances (Table 12.3). Model group 1 demonstrated a good correlation for the zone I insertion with a Pearson's correlation of 0.740 for each side. This was reflected by 100% of predicted insertion lengths landing within zone 1 and almost 100% of patients within the middle 60% of the zone (Table 12.3 and Figure 12.3). For zone III insertion, Pearson's correlation was fell to 0.504 and 0.491 for right and left insertion, although all but one patient landed within the desired zone. When assessing accuracy to within the middle 60% of zone III, the left and right insertion were 89.4% and 90.0% accurate respectively (Table 12.3 and Figure 12.4).

Table 12.3: Predicted versus observed values, correlation and accuracy of placement (i.e. within zone boundaries) from the remaining 80% (n = 141) of the cohort

Distance (mm)	Observed Length Median (95% CI)	Predicted Length Median (95% CI)	Correlation		Accuracy	
			Pearson's	p-value	Total Zone	Middle 60% of Zone
Model Group 1						
R CFA to Mid Zone I	423 (418 - 427)	432 (429 - 435)	0.740	< 0.001	141 (100%)	140 (99.3%)
L CFA to Mid Zone I	419 (414 - 422)	427 (424 - 431)	0.740	< 0.001	141 (100%)	141 (100%)
R CFA to Mid Zone III	232 (231 - 236)	241 (238 - 242)	0.504	< 0.001	141 (100%)	126 (89.4%)
L CFA to Mid Zone III	228 (226 - 232)	238 (234 - 238)	0.491	< 0.001	140 (99.3%)	127 (90.0%)
Model Group 2						
R CFA to Mid Zone I	423 (418 - 427)	431 (429 - 436)	0.741	< 0.001	141 (100%)	140 (99.3%)
L CFA to Mid Zone I	419 (414 - 422)	426 (425 - 431)	0.741	< 0.001	141 (100%)	140 (99.3%)
R CFA to Mid Zone III	232 (231 - 236)	238 (238 - 241)	0.523	< 0.001	141 (100%)	128 (90.8%)
L CFA to Mid Zone III	228 (226 - 232)	234 (233 - 237)	0.517	< 0.001	141 (100%)	131 (92.9%)
Model Group 3						
R CFA to Mid Zone I	423 (418 - 427)	418 (n/a)	(n/a)	(n/a)	140 (99.3%)	138 (97.9%)
L CFA to Mid Zone I	419 (414 - 422)	418 (n/a)	(n/a)	(n/a)	139 (98.6%)	138 (97.9%)
R CFA to Mid Zone III	232 (231 - 236)	229 (n/a)	(n/a)	(n/a)	138 (97.9%)	127 (90.0%)
L CFA to Mid Zone III	228 (226 - 232)	229 (n/a)	(n/a)	(n/a)	138 (97.9%)	129 (91.5%)

Abbreviations and definitions: CFA - common femoral artery; Aortic Zone I - left subclavian to celiac trunk; Aortic Zone III - lowest renal artery to aortic bifurcation.

A similar pattern was observed for model group 2, albeit with a slightly higher Pearson's value across all zones (Table 12.3). Zone I scored 0.741 for both insertion sides, with a 100% and 99.3% accuracy for total zone and middle 60% zone accuracy respectively (Figure 12.3). Zone III achieved correlations of 0.523 and 0.517 for the right and left insertion. This translated to 100% of patients landing within the zone and 90.8% and 92.9% of the right and left insertions landing within the middle 60% of the zone (Figure 12.4).

Pearson's correlations could not be generated for model group 3 as this used a fixed insertion distance (Table 12.3). The majority of patients were landed within their desired zone: 99% for zone I and 98% for zone III. When assess the proportion of patients landing within the middle 60% of the zone, 97.9% accuracy was achieved for zone I and greater than 90% for zone III (Figures 12.3 and 12.4).

12.4 Discussion

The current study represents the first prospective evaluation of aortic morphometry in the development of a fluoroscopy free REBOA system for use in non-compressible haemorrhage. A strong correlation exists between torso height and torso arterial morphometry. This is important as torso height can be easily measured in the emergent setting and used to consistently predict the insertion length required for occlusion of aortic zones I and III by a REBOA system. A reliable and reproducible method to predict insertion length is essential in order to avoid incorrect placement, which could have potentially lethal consequences.

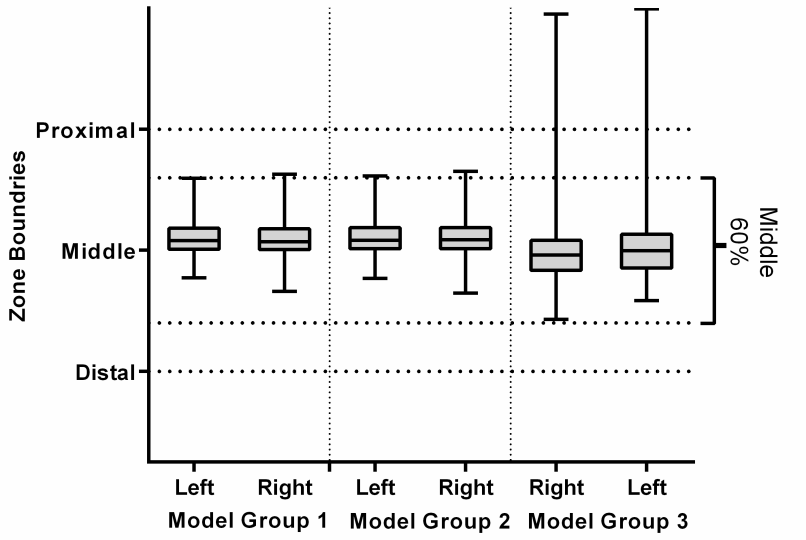

Figure 12.3: Box and whisker plot of the median, interquartile, maximum and minimum range of predicted placement within zone I, as a proportion of zone extent

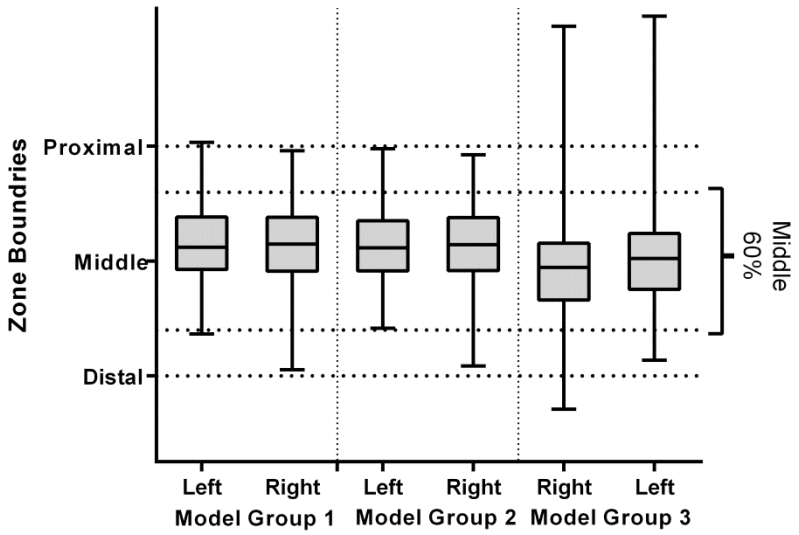

Figure 12.4: Box and whisker plot of the median, interquartile, maximum and minimum range of predicted placement within zone III, as a proportion of zone extent

This study is an extension of our group's previous morphometric analyses characterizing the external-internal relationship between torso extent and aortic length. Stannard et al. retrospectively analysed a CT data repository of 200 scans to identify a cohort of 88 which were suitable for inclusion (126). That study also examined a male only population and their reported median zones lengths are in agreement with the current study. Those investigators correlated descending aortic length with torso height (sternum to pubis) and described a correlation of determination of 0.454. Importantly, the current study represents a progression of Stannard et al.'s work by using a more robust prospective methodology. The acquisition of more data points and subjects has enabled the analysis of ethnicity and a more detailed mathematic exploration of the relationship between torso height and vascular length.

Accurate placement is essential to avoid complications; occlusion proximal to zone 1 could cover the origin of one or both carotid arteries, theoretically precipitate an ischemic stroke and dangerously elevate cardiac afterload. Inadvertent zone II placement and occlusion of the celiac trunk or mesenteric arteries could induce visceral ischemia, adding to the patient's metabolic burden. The concern with placement in an iliac artery is that contralateral inflow control is not established which could be driving pelvic or junctional haemorrhage.

The current study yields some interesting results that are important to discuss. The finding that the inclusion of nation status as a covariate adds little to the accuracy of the models is at first surprising. However, military personnel are drawn from numerous ethnic backgrounds - Caucasian, Hispanic, African-American, Samoan, and Nepalese - to name but a few. This means that the binary categorisation of nation status is likely an over simplification of a complex issue. To understand the impact of ethnicity on aortic morphometry, a much larger population, with more detailed ethnic origin data will be required.

The current study reports three insertion models, two of which were derived from linear regression and third used the median population measurement as an insertion length. Interestingly, the use of population medians (model group 3) performed almost as well as either of the regression models. This result may

lead to the suggestion that the use of regression modelling is overly complicated and therefore redundant. However, while the cohort's ethnicity may be fairly heterogeneous, their torso dimensions are relatively homogenous. For example, the interquartile range for torso height, zone I and III are only 35, 24, 15 mm respectively. This, combined with the relatively large lengths of the zones, means that insertion to the population median, without adjustment, will have a significant chance of accurate placement.

However, the regression models are essential for guiding the placement of patients who lie out-with population norms. This is best demonstrated by examining the whisker range plots in Figures 12.3 and 12.4. While the majority of patients in model group 3 are within the zone boundaries, the range extends significantly out-with the proximal and in some cases, the distal extent of the zone. Following the use of regression in Model Groups 1 and 2, essentially all are within the zone boundary.

Furthermore, it is important to acknowledge that the blind deployment of a REBOA system requires more than just an insertion equation; the catheter is required to remain with the aorta and be resistant to deviation down side-branches. This challenge is being met with novel catheter designs that incorporate a low-profile construction with novel self-centring technology to ensure minimal deviation out with the aorta during insertion (100).

The current study has a number of limitations that are important to understand. The reported dataset is limited and does not include other important factors which may affect torso measurements and arterial lengths, such as body habitus, gender and age. A larger number of subjects with a greater number of variables would allow for better modelling and more rigorous evaluation of predicted insertion lengths. Importantly, future populations must also be relatively heterogeneous in order to best understand the impact of variation. For example, the tortuosity of vasculature increases with age (128,129), something vital to understand for the successful deployment of REBOA systems in older patients.

These limitations have largely come about due to the circumstances of the current studies data collection. Data were collected by two military surgeons,

deployed in an operational Combat Support Hospital and therefore the data parameters collected were minimalist. Furthermore, due to the nature of combat operations, the study population was male, with a bias towards patients in their second and third decades of life.

Despite these limitations, this prospective observational study demonstrates the feasibility of this methodology in the development of a fluoroscopy free REBOA system. The relatively large size of zones I and III lend themselves well as functional zones of occlusion. The use of linear regression modelling has led to almost 100% accurate prediction of insertion distances. The influence of ethnicity on aortic morphometry requires further study along with additional variables such as age, body habitus and gender.

Chapter 13: A Novel Fluoroscopy-Free, Resuscitative Endovascular Aortic Balloon Occlusion System in a Model of Haemorrhagic Shock

13.1 Background

Haemorrhage is the leading cause of death in civilian and military trauma (2,4,11,12,15,16). In the military setting, 70% percent of deaths are due to exsanguination from truncal injuries, of which nine out of ten occur prior to hospital admission (4). The civilian experience is similar, with bleeding shown as a major contributor to trauma deaths and the leading cause of potentially preventable death (11,12). Non-Compressible Torso haemorrhage (NCTH) has recently been defined as haemorrhage arising from trauma to the torso vessels, pulmonary parenchyma, solid abdominal organs and disruption of the bony pelvis resulting in hypotension or shock (3,27).

Haemorrhage leads to cardiovascular collapse and death unless myocardial and cerebral perfusion can be maintained. In the setting of NCTH resuscitative aortic occlusion mitigates haemorrhage and increases afterload and central aortic pressure until haemostasis can be achieved. For decades however this manoeuvre has required thoracotomy and aortic clamping relegating it as a reactive procedure performed after the loss of pulses (3). In the endovascular era there has been a reappraisal of resuscitative endovascular balloon occlusion of the aorta (REBOA) as an alternative to resuscitative thoracotomy (6). Unlike thoracotomy, REBOA is performed in a series of less invasive steps beginning with transfemoral arterial access and pressure monitoring. As such REBOA may facilitate a proactive approach to aortic control ready to support the central circulation of patients at imminent risk of cardiovascular collapse (6,80).

Emerging animal evidence demonstrates the benefits of REBOA in shock, with occlusion time of up to 90 minutes generating a significant, but survivable metabolic penalty (90,99). However, today's technology requires that this adjunct be performed with a large calibre balloon catheter passed over a wire through a large sheath. Additionally REBOA is currently constrained by the requirement of fluoroscopy to guide the wire and balloon positioning. Characteristics of existing technology limit the ability of this manoeuvre to be

performed in the emergent setting (6). The objective of this study is to report a new, low-profile REBOA system designed to be placed without fluoroscopic guidance. An additional objective is to compare this system to existing endovascular technology in accuracy of placement and effectiveness in supporting central aortic pressures upon balloon inflation. Finally, this study aims to characterise the physiologic consequence and survivability following 60 minutes of aortic occlusion with these systems in a model of haemorrhagic shock.

13.2 Methods

13.2.1 Overview

This study was performed at an accredited facility (Clinical Research Division, Lackland Air Force Base, TX) under supervision of a veterinary staff with Institutional Animal Care and Use Committee approval. Female Yorkshire swine (*Sus scrofa*), (70-90 kg) in shock were randomised in groups of 8 to either Conventional Balloon System (CBS) or Prototype Balloon System (PBS). The CBS consisted of commercially available devices including a stiff 0.035”Amplatz wire with an 8cm flexible tip (Cook Medical, Bloomington IN) and a 14Fr, 120cm Coda® Balloon (Cook Medical, Bloomington, IN).

13.2.2 Fluoroscopy-free, endovascular aortic balloon occlusion system

The Prototype Balloon System (PBS) was a fused wire and balloon catheter scheme (Pryor Medical, Arvada, CO) (Figure 13.1). This uni-body construct allowed the PBS to be passed through an 8 Fr femoral artery sheath into the abdominal aorta and positioned in the thoracic aorta using a “one-pass”, fluoroscopy-free method. The main body was 100cm, consisting of a semi-stiff 0.035” core wire extending 20 cm beyond the trail end of the device. The lead or insertion end consisted of a curved or floppy tipped wire fused inside a compliant balloon catheter alleviating traditional “over the wire” insertion steps. At the insertion end of the PBS was a collapsible, self-centring, nitenol rail system (Figure 13.1A). This system was positioned between the wire tip and the compliant balloon for purposes of centring the system in the arterial lumen during advancement (Figure 13.1C).

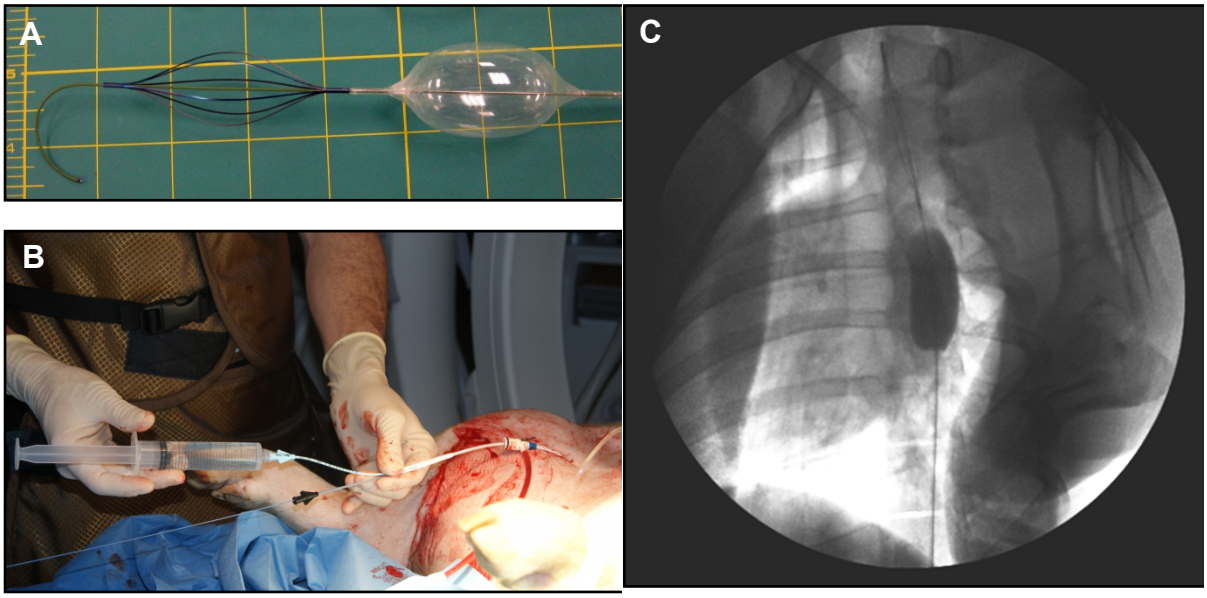

Figure 13.1: A single component prototype balloon system

A, Single component prototype balloon system (PBS) designed to be positioned and inflated without fluoroscopy. The lead or insertion end is a floppy tipped 0.035” wire fused to the compliant balloon catheter. A collapsible nitenol rail system is positioned between the floppy tip of the wire and the compliant balloon for the purpose of centring the system within the axial arterial lumen as the device is inserted and positioned. B, Photograph of the PBS having been inserted through an 8 French right femoral artery sheath. The syringe is filled with a mixture of contrast agent and saline for balloon inflation. C, Fluoroscopic image of the PBS inflated in the thoracic aorta with the floppy wire tip and flexible nitenol rail system proximal to the inflated balloon.

13.2.3 Study Design and Baseline Phase

The study had four phases: Baseline, Haemorrhage, REBOA and Resuscitation (Figure 13.2). After induction of anaesthesia with ketamine and isoflurane, animals underwent cannulation of the jugular vein through an open incision. The carotid artery was encircled with a transonic probe (Transonic Systems Inc., Ithaca, NY) to monitor flow. Ultrasound-guided access to the brachial artery was achieved using a microcatheter (Cook Medical, Inc., Bloomington, IN) which was advanced into the aortic arch for pressure monitoring. The femoral artery opposite the device sheath was cannulated for blood pressure measurement in the distal aorta. Ultrasound-guided access to the femoral artery (device side) was achieved and a sheath (8 or 14 French) was positioned. A cerebral oximetry probe (LICOX, Integra Life-Sciences, Plainsboro, NJ) was placed to monitor cerebral oxygenation.

13.2.4 Haemorrhage Phase

Haemorrhagic shock was established over a 30 minute period using a previously described method of rate and volume controlled haemorrhage (80,99). In brief, 35% of blood volume (total circulatory volume of the pig calculated as 66 mL/kg) was withdrawn through the catheter in the femoral artery; half taken over 7 minutes and the remaining half over 13 minutes. To avoid splenic autotransfusion animals were subjected to ongoing haemorrhage at a rate of 0.15mL/kg/min for an additional 10 minutes to ensure haemorrhagic shock was maintained. Shed blood was banked in citrated bags for transfusion during the resuscitation phase. If mean arterial pressure (MAP) decreased below 30 mmHg, haemorrhage was stopped until the pressure was greater than 30 mmHg, at which point haemorrhage was resumed.

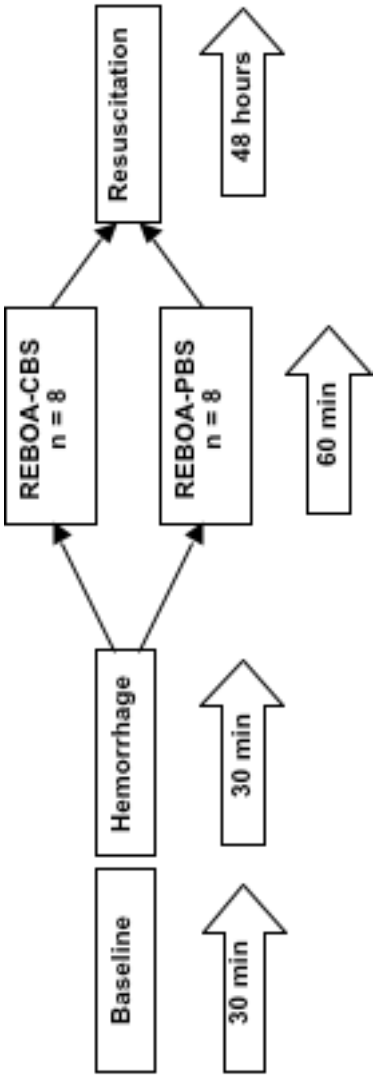

Figure 13.2: Consort diagram of the study protocol which included Baseline, Haemorrhage, REBOA and Resuscitation phases.

13.2.5 REBOA Phase

Following haemorrhage, REBOA was performed with either the prototype or the conventional system. In the PBS group, devices were inserted through the femoral sheath (8 French) without fluoroscopic guidance (Figure 13.1). The depth of insertion was determined using an estimated external measure of torso extent which spanned a line from the inguinal crease to the mid-sternum. This distance was used as the estimated transfemoral insertion distance or depth for the PBS device. PBS devices were advanced to this depth or distance without fluoroscopy and inflated with a mixture of saline and contrast agent. Placement was confirmed with fluoroscopy and recorded as accurate if in the thoracic aorta (Figure 13.1). If resistance was met during insertion, the PBS was stopped and the catheter position checked with fluoroscopy; placement was not adjusted post-imaging. Inaccurate positioning was defined as placement of the PBS within a branch vessel of the aorta or in the abdominal aorta. In the CBS group, the Amplatz wire was advanced into the thoracic aorta through the femoral artery sheath (14 French) using fluoroscopic guidance. The wire was pinned in place while the Coda® balloon catheter was advanced into position in the thoracic aorta using conventional “over the wire” manoeuvres. The Coda® was inflated under fluoroscopic visualisation using a mixture of saline and contrast agent.

13.2.6 Resuscitation Phase

Following 60 minutes of REBOA with CBS or PBS, the balloon was deflated and a 6-hour resuscitative phase initiated. Gradual balloon deflation was performed to avoid sudden cardiovascular collapse. Specifically, attention was given to blood pressure during and after balloon deflation with whole shed blood and vasopressor medications given to maintain a goal mean arterial pressure (MAP) of 60mmHg or greater. After shed whole blood was transfused, 1L boluses of saline were administered to maintain MAP until a threshold of 20 cc/kg of crystalloid was reached. Persistent hypotension was treated with vasopressor norepinephrine starting at 4mcg/hr and titrated to MAP of 60mmHg; animals which were refractory and nearing cardiovascular collapse received a 10mcg bolus of norepinephrine until an infusion could be established. Following resuscitation, animals were transitioned from isoflurane to ketamine and versed

infusion and survived in an intensive care phase for 48 hours. At the conclusion of the Resuscitation Phase animals were euthanised and underwent necropsy.

13.2.7 Data Acquisition, Timeline and Outcome Measures

Systolic blood pressure (SBP), heart rate (HR), core temperature, partial pressure of brain oxygen ($PBrO_2$) and carotid flow were monitored and circulating markers of perfusion and end-organ injury were measured. After baseline observations, data were recorded at 30, 45, 60 minutes and 3, 6, 24, 48 hours post haemorrhage. The primary outcome measure was accurate, placement of either the CPS or BPS in the thoracic aorta. Secondary outcome measures included mortality, carotid flow, partial pressure of brain tissue oxygenation, central or mean arterial pressure, serum pH, base deficit, lactate, fluid volume and vasopressor requirement and histological analysis of aorta, heart, lung, kidney, brain and spinal cord.

13.2.8 Statistical Analysis

Data were analysed with SAS version 9.2 (SAS Institute Inc., Cary, NC). Normally distributed measures were compared with t-test while Wilcoxson rank-sum method was used for non-parametric measures. Proportions were compared by either chi-square or Fisher's Exact as appropriate. For repeated measures, comparisons were conducted using a model with autoregressive first-order covariance structure treating time as a categorical factor. A *p* value less than 0.05 was considered significant.

13.3 Results

13.3.1 Baseline Characteristics and Haemorrhagic Shock

Sixteen animals were randomised to the PBS or the CBS group (n=8 per group) and baseline characteristics are shown in Table 13.1. There were no differences between groups with respect to weight, baseline vital statistics and laboratory values. The induction of class IV shock was achieved with a mean shed blood volume of 1904 ± 280 mL (predicted of 2058±160.4mL, p=0.17). At the end of haemorrhage phase, immediately prior to balloon inflation (t_{30}), SBP was equally reduced in both groups (PBS vs. CBS; 46 ±7 vs. 46±11mmHg, p=0.91) and HR was equally elevated (PBS vs. CBS; 167±15 vs. 148±46mmHg, p=0.91).

13.3.2 Balloon Deployment, Inflation and Resuscitation

Accurate balloon positioning and inflation rate was 87.5% in the PBS and 100% in the CBS group. One aberrant placement in the PBS group occurred when the device entered a right renal artery which had a cephalad angle or take-off at its origin from the abdominal aorta. REBOA resulted in similar increases in mean arterial pressure, carotid blood flow and partial pressure of brain oxygenation in the PBS and CBS groups while there was no increase in cardiac output following balloon inflation in either group (Figure 13.3). Balloon occlusion times were the same in PBS and CBS (77.0±11.3 vs. 70.3±12.3 min, p=0.30) as were times to complete balloon deflation (17.6±11.6 vs. 13.1±10.2 min, p=0.46). Animals in the PBS and CBS groups required similar volumes of saline over 48 hours (14,301±6,197mL vs. 12,014±6,699mL, p=0.46). Norepinephrine was the only vasopressor administered during resuscitation and there was no difference between PBS and CBS with respect to total requirements (5,733±8,129 mcg vs. 1,157±2,579 mcg, p=0.21).

13.3.3 Physiologic Derangement, Mortality and Histologic Examination

During resuscitation the PBS and CBS groups demonstrated similar trends in serum lactate which peaked between 2 and 3 hours following balloon deflation and returned to normal by 24 hours and 48 hours (Figure 13.4). A similar trend was observed in serum pH between the PBS and CBS groups. Other measures of end-organ dysfunction were elevated 24 hours following balloon deflation (Table 13.2). The same circulating markers remained elevated at 48 hours just prior to termination of the study with a higher potassium level in the CBS compared to the PBS group (7.7 ± 1.5 vs. 6.1 ± 3.3mmol/L, p=0.007) and a higher creatine kinase (CK) level in PBS than CBS (144,290 ± 138,363 vs. 68,876 ± 57,291U/L, p,0.001) (Table 13.2). Mortality was similar between groups (PBS vs. CBS; 25% vs. 12.5%, p=0.50) with each of the deaths occurring during resuscitation due to cardiac arrest from physiologic disturbances. There were no histologic differences observed among end organs examined (brain, heart, kidney and spinal cord) in the PBS and CBS groups.

Table 13.1: Baseline measurements and haemorrhage volumes of the study groups

(mean and standard deviation)

Variable	CBS Group	PBS Group	*P*
n	8	8	
Weight (kg)	77.5 ± 5.9	78.5 ± 6.6	0.755
Female	8 (100%)	8 (100%)	n/a
Physiological			
SBP (mmHg)	94 ± 37	81 ± 10	0.180
MAP (mmHg)	65.1 ± 10.4	64.3 ± 6.4	0.895
HR (bpm)	81 ± 8	93 ± 13	0.270
Temp (℃)	34.9 ± 1.3	35.5 ± 1.2	0.300
$PBrO_2$ (mmHg)	18.7 ± 14.4	49.6 ± 78.4	0.209
Carotid Flow (mL/min)	346.8 ± 87.4	375.9 ± 87.8	0.548
Lab Measures			
pH	7.50 ± 0.03	7.51 ± 0.05	0.853
pCO_2 (mmHg)	38 ± 4	38 ± 5	0.910
pO_2 (mmHg)	247 ± 47	209 ± 33	0.077
K+ (mmol/L)	3.39 ± 0.02	3.36 ± 0.13	0.951
Glucose (mg/dL)	84 ± 13.7	98.8 ± 27.2	0.526
Lactate (mmol/L)	0.84 ± 0.15	1.18 ± 0.41	0.710
Base Excess (mEq/mL)	6.45 ± 2.12	6.63 ± 1.20	0.917
HCO_3 (mmol/L)	30.4 ± 1.9	30.6 ± 1.3	0.929
Hb (gm/dL)	9.4 ± 1.0	8.2 ± 1.1	0.076
Haemorrhage			
Predicted Volume (mL)	2072 ± 174	2044 ± 156	0.741
Actual Volume (mL)	1942 ± 278	1867 ± 294	0.609
SBP Post Haemorrhage (mmHg)	46 ± 11	46 ± 7	0.940
HR Post Haemorrhage (mmHg)	167 ± 15	148 ± 46	0.571

Abbreviations: CBS, Conventional Aortic Balloon Occlusion System; PBS, Prototype Balloon System;

p value less than 0.05 considered significant

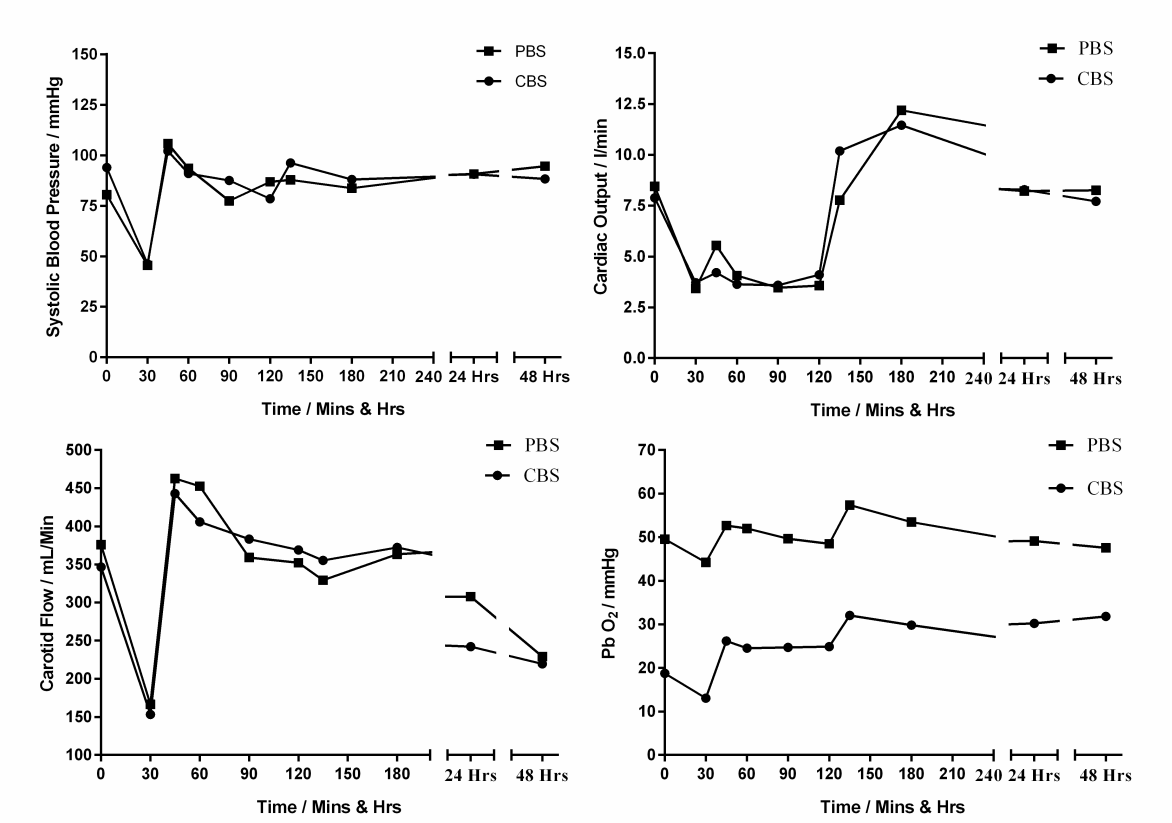

Figure 13.3: Haemodynamic measurements performed over the course of the study

There was no difference in the haemodynamic response to REBOA between the prototype (PBS) and the conventional (CBS) groups.

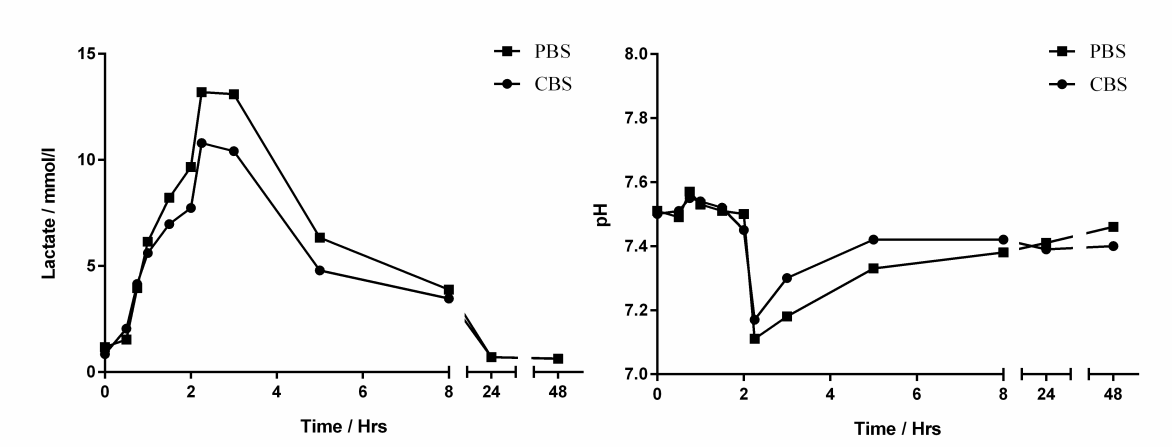

Figure 13.4: Serum lactate and pH over the course of the study

There was no difference in lactate or pH between the prototype (PBS) and the conventional (CBS) groups.

Table 13.2: Markers of end-organ dysfunction

mean and standard deviation

	24 Hours			48 Hours		
	CBS	**PBS**	**p**	**CBS**	**PBS**	**p**
Lactate (mmol/L)	0.70 ± 0.28	0.70 ± 0.07	0.522	0.63 ± 0.21	0.62 ± 0.08	0.693
AST (U/L)	970 ± 626	881 ± 433	0.790	1198 ± 984	1065 ± 403	0.628
LDH (U/L)	10527 ± 12915	10392 ± 7995	0.989	7259 ± 7216	8742 ± 5423	0.452
Cre (mg/dL)	2.3 ± 1.2	1.7 ± 0.4	0.029	1.7 ± 0.8	1.5 ± 0.2	0.418
K+ (mmol/L)	7.49 ± 1.72	7.60 ± 1.28	0.845	7.66 ± 1.45	6.10 ± 3.27	0.007
CK (U/L)	47031 ± 14109	70152 ± 32362	0.228	68876 ± 57291	144290 ± 138363	<0.001

Abbreviations: AST - Aspartate Aminotransferase; LDH - Lactate Dehydrogenase; Cr – Creatine, K+ - Potassium; CK - Creatine Kinase.

13.4 Discussion

This report describes a new resuscitative endovascular balloon occlusion system designed to be placed into the thoracic aorta without the aid of radiographic imaging. Findings demonstrate the feasibility of this uni-body system to be positioned and inflated in the thoracic aorta without fluoroscopy. REBOA using the new prototype results in increased central aortic pressure and cerebral perfusion which are equivalent to those observed with the use of existing endovascular technology. Finally, results from this study demonstrate that 60 minutes of resuscitative endovascular balloon occlusion of the aorta with either system is associated with a recoverably metabolic acidosis and acceptable short-term survival.

13.4.1 Context of Previous Research

This research confirms and extends a series of studies characterising temporary resuscitative aortic occlusion as a manoeuvre used in the setting of end stage haemorrhagic shock. In an experiment which compared the efficacy of resuscitative thoracotomy with aortic clamping to REBOA, White et al. demonstrated both approaches to be effective at restoring central aortic pressure and myocardial and cerebral perfusion (80). White and colleagues also demonstrated a more severe metabolic derangement during the recovery or resuscitation phase in the resuscitative thoracotomy group compared to the endovascular balloon occlusion group.

Markov et al. recently characterised the ischemic threshold of REBOA in the setting of shock comparing 30 to 90 minutes of aortic occlusion in a 48 hour survival model (99). Using circulating markers, mortality and histology Markov demonstrated that 90 minutes of REBOA was survivable although it was associated with severe physiologic derangement and non-reversible end organ damage. In that same study Markov found that 30 minutes of REBOA was well tolerated, recoverable and required no additional organ support during the resuscitation phase. Based on these findings it was proposed that the maximum REBOA is 60 or fewer minutes (99). Findings from the current study confirm that 60 minutes of REBOA with either the commercially available or the newly

designed device is recoverable in this model with a normalisation of acidosis within 24 hours of balloon deflation.

Others have demonstrated the effectiveness of REBOA in the setting of uncontrolled haemorrhage and shock (90). Avaro et al. subjected pigs to splenic disruption and compared control animals to groups of 40 and 60 minutes of REBOA. Animals were resuscitated with normal saline and not shed whole blood for a two hour recovery phase. Avaro and colleagues demonstrated a mortality benefit in both REBOA groups compared to controls and all animals in the 40 minute occlusion time group survived. From that study, the authors observed a more severe physiologic derangement in the 60 versus the 40 minute occlusion time group and postulated 40 minutes to be the maximum REBOA time. However, in contrast to the current study the Avaro report used normal saline as a resuscitation fluid which may have limited the resiliency of their cohorts to reperfusion injury and introduced conservative bias to their findings.

13.4.2 Endovascular Technology for Proactive Aortic Control

The most significant aspect of the current study is introduction of a new, low profile REBOA technology able to be positioned and inflated without radiographic imaging. To date, REBOA has been studied using commercially available balloons designed to be used in the setting of complex vascular operations with support of an operating room and fluoroscopy (8,119,130). As such, existing balloon technology is typically large diameter (12-14Fr) and better suited for the management age-related vascular disease. As an example, the compliant Coda® (Cook Medical, Bloomington, IN) balloon used in this study has a diameter of 32-40 mm and requires large sheath (14 French) access for placement. Although well suited for dilated or ectatic aortas in elderly patients with aneurysm disease, this device is too large to be routinely used for REBOA in younger trauma patients. Other occlusion balloons have similarly large diameters and require “over the wire” fluoroscopic guidance for positioning and inflation.

In this context the Prototype Balloon System (Pryor Medical, Arvada, CO) represents technology designed with haemorrhage control and resuscitation for trauma as the originating premise. The most important characteristic of this and future technologies for REBOA in trauma is liberation from radiographic imaging.

Although a lower insertion profile is imperative, the ability to accurately introduce, position and inflate REBOA devices without fluoroscopy represents the paradigm shift which would allow this manoeuvre to be performed in urgent settings. If REBOA devices also included the ability to monitor central aortic pressure before, during and following inflation of the balloon, one could envision proactive access and control of the aorta in patients prone to cardiovascular collapse. In this context resuscitative aortic occlusion could move from a reactive and terminal operation to a proactive, less invasive manoeuvre. Other favourable characteristics of future REBOA devices may include pressure regulated inflation to guard against aortic wall injury and catheters designed to resist balloon egress or 'retreat' with the return of central aortic pulse pressure. Although not all of these characteristics are present in the prototype used in this study, the current technology introduces the concepts and demonstrates feasibility in a live tissue model.

13.4.3 Limitations

This study has limitations worth considering. Foremost, the prototype balloon catheter in this study was designed for this translational model and these results do not necessarily translate to human aortic anatomy or shock physiology. It should be pointed out that one of the balloon insertions in the PBS group inadvertently entered a renal artery. While the renal arteries in the quadruped are directed cephalad and more easily accessed from a transfemoral approach, this aberrant placement should not be overlooked. Misplacement of the PBS in this one case underscores the preliminary nature of this prototype and suggests that a "self-centring" mechanism requires modification and further study.

The results of this study were in a model with limited survival without assessment of lower extremity strength. As such the deleterious effects of 60 minutes of REBOA may not have been fully ascertained. Although spinal cord ischemia was not present on histology, a longer survival would be required to examine the effects of REBOA on cord and extremity function. Another limitation is the controlled nature of haemorrhage and what was ostensibly artificial haemorrhagic shock. In this context the model did not assess REBOA in the most extreme cases of free haemorrhage but was chosen instead to assess

the technical deployment of these devices and basic haemodynamic consequences of balloon inflation. Future studies are underway in models of free haemorrhage and high mortality to assess life-saving benefits of these devices.

13.4.4 Conclusions

In conclusion, this study reports a newly designed resuscitative endovascular balloon occlusion system able to be placed without radiographic imaging. This uni-body system is able to be positioned and inflated in the thoracic aorta without fluoroscopy, although additional design and study is required to assure consistent positioning. Resuscitative endovascular balloon occlusion of the aorta with this prototype is an effective adjunct in this model, equivalent to existing endovascular technology. Future development of lower profile, fluoroscopy-free endovascular balloon catheters may allow for proactive aortic control in patients at risk for haemorrhagic shock and cardiovascular collapse.

Chapter 14: Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA): A Gap Analysis of Severely Injured UK Combat Casualties

14.1 Introduction

Haemorrhage is the leading cause of potentially preventable death following both civilian and military trauma (4,13). The last decade of war in Iraq and Afghanistan has seen significant innovation in the management of compressible haemorrhage – extremity bleeding amenable to control by simple pressure – which has translated to improved survival (5). However, bleeding from non-compressible sites within the torso and junctional regions (groin and axilla) remains a significant cause of mortality (27,68,95).

A recent review of 10 years' of US military deaths identified 24.3% of casualties as having a potentially survivable injury, of which 90.9% were due to haemorrhage (4). The largest focus was truncal (67.3%) followed by junctional (19.2%) and extremity (13.5%) sources. Importantly, nine out of 10 deaths occurred prior to admission to a medical treatment facility (MTF). There is a pressing need for a haemorrhage control and resuscitation adjunct that can be deployed prior to MTF admission in order sustain life until definitive haemorrhage control can be attained.

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) is a technique which has demonstrated promise in both large animal and early clinical case series, as an adjunct that supports central perfusion and controls arterial inflow (6,73,98,131). Two functional aortic zones of occlusion have been described: thoracic (zone I) and infra-renal (zone III), for exsanguinating abdominal and pelvic haemorrhage respectively (6).

However, despite compelling evidence demonstrating the favourable haemodynamic profile of aortic occlusion in haemorrhage, it is unknown what proportion of combat casualties have an injury pattern and clinical course that would be amenable to REBOA deployment. The aim of this study is to evaluate 10 years' of consecutive UK combat casualties in order to identify patients that might have benefitted from REBOA.

14.2 Methods

This study was conducted following approval from the Royal Centre for Defence Medicine Academic Unit. The prospectively collected UK Joint Theatre Trauma Registry (JTTR) was used to retrospectively identify all UK military personnel sustaining a severe combat injury in one or more body region, in Iraq or Afghanistan, between August 2002 and July 2012. Severe injury was defined as a military Abbreviated Injury Scale (AIS) score of three or greater in any AIS body region. The 2005 Military AIS Scores were used to calculate both the Injury Severity Score (ISS) and the New Injury Severity Score (NISS).

The UK JTTR is a performance improvement tool which captures data on all casualties admitted to UK MTF's. It is most detailed in the case of UK military personnel, as the JTTR has visibility of this population from the point-of-wounding to either discharge or post-mortem examination. Importantly, the JTTR includes data pertaining to casualties who do not survive to MTF admission, permitting the comprehensive analysis of a consecutive population of wartime injured.

Suitability for REBOA was initially determined by injury pattern using AIS coding. Three categories were defined: indicated, contra-indicated and not-indicated (Table 14.1). In general terms, Zone I REBOA was deemed indicated in the setting of abdominal haemorrhage: high grade (AIS ≥ 4) solid organ, mesenteric disruption or injury to a named vessel proximal to the aortic bifurcation. Zone III REBOA was deemed indicated in pelvic/groin haemorrhage: pelvic fracture with ring disruption, traumatic amputation at/near the hip or injury to a named vessel proximal to the femoral segments.

Contra-indication to REBOA was defined as a focus of non-compressible haemorrhage proximal to the zone of occlusion. This included thoracic aortic disruption, and arterial injury located within the superior mediastinum, neck and axillary regions. Patients with both an indication and contra-indication for REBOA were only included in the contra-indicated group and patients with neither were placed in the no-indication group.

Table 14.1: Indications and contra-indication to for the use Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA)

Indications		Contra-Indications
Zone I	**Zone III**	
High Grade (AIS ≥ 4) Injury to:	High Grade (AIS ≥ 4) Injury to:	Non-Compressible Haemorrhage in:
● Liver/Kidney/Spleen	● Pelvic Fracture with Ring Disruption	● Superior Mediastinum
● Mesenteric Disruption	● Named Pelvic Vessel Injury	● Axilla
● Named Abdominal Vessel Injury	● Traumatic Amputation at/near Hip	● Neck
		● Face

Abbreviations: AIS – Abbreviated Injury Scale

Patients with an injury pattern indication for REBOA then underwent a detailed review of their registry record including examination of pre-hospital and in-hospital free-text description fields. This enabled the identification of patients who had signs-of-life (SOL) at the point of wounding, but lost cardiac output en-route to an MTF. This is important, as the purpose of this study is to identify a population where REBOA has a realistic window of opportunity for deployment. Patients with catastrophic wounding and cardiac arrest at the point of wounding will not benefit from REBOA. Categorisation of signs of life was deliberately conservative; in the absence of documentation to that effect, patients were assumed to have died at the point of wounding.

The operative indications for patients undergoing thoracotomy and laparotomy were also retrieved. Thoracotomy indications were divided into three categories: thoracic haemorrhage control (control of bleeding vessels, lung parenchyma), non-haemorrhage control (control of air leaks, release of tamponade) and resuscitation (aortic cross clamping, cardiac massage). Laparotomy indications were similarly classified: abdominal haemorrhage control (packing, organ removal), non-haemorrhage control (management of hollow organ injury) and proximal control (control of lower extremity inflow via the abdomen).

This permits not only an analysis of types of surgical manoeuvres required, but also the identification of a population of patients who only required arterial control in isolation. For example, patients with very proximal traumatic amputations can require a laparotomy to obtain vascular inflow control of the iliac arteries, but no other abdominal intervention. The intra-operative use of REBOA may have a role in avoiding cavity surgery for isolated arterial control (132).

14.3 Results

During the decade of war between August 2002 and July 2012, there were a total of 1317 UK military personnel who sustained one or more severe combat injury and were entered into the UK JTTR (Figure 14.1). This was associated with a high burden of injury as indicated by a mean ISS (SD) of 40 (27) and a mortality

rate of 569 (43.2%). In terms of injury pattern, 925 (70.2%) patients had no indication for REBOA, 148 (11.2%) had a contra-indication and 244 (18.5%) had an injury pattern that might have been amenable to REBOA.

Of the 244 with an injury pattern indication for REBOA, 145 (59.4%) patients died prior to MTF admission – 79 patients were considered to have died at the point-of-wounding and 66 died en-route to an MTF. Of the 99 admitted to an MTF, 29 patients subsequently died of their injuries, with 70 survivors. The indicated zone of occlusion was consistent across these four groups ($p = 0.791$), with zone I indicated in 147 (60.2%) and zone III in 97 (39.8%) of the cohort (Figure 14.2).

Only the patients who survived beyond the point-of-wounding ($n = 165$) will be analysed further and are considered in three groups: en-route deaths, MTF deaths and survivors.

The gender, age and mechanism of injury were consistent across en-route deaths, MTF deaths and survivors (Table 14.2). The cohort could be characterised as largely male, in their mid-20s, predominantly injured by an explosive event. As per the selection criteria, there was a high preponderance of abdominal and lower extremity injuries across all three groups. There was a stepwise increase in injury burden across the groups as measured by both ISS and NISS ($p < 0.001$).

Patients who died en-route to an MTF had the greatest injury burden, followed by MTF deaths, with survivors sustaining the lowest injury burden. This pattern was mirrored when considering anatomical injury pattern with patients dying en-route sustaining a significantly greater proportion of severe head and chest injuries compared to the other groups.

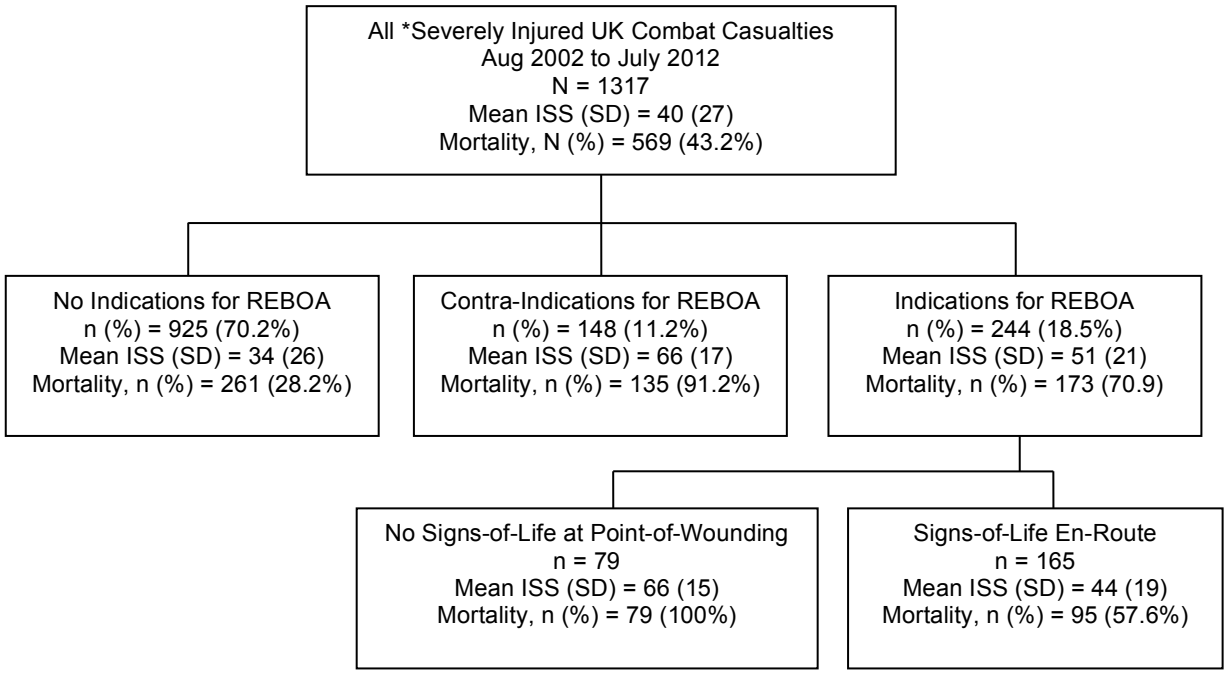

Figure 14.1: Breakdown of the groups

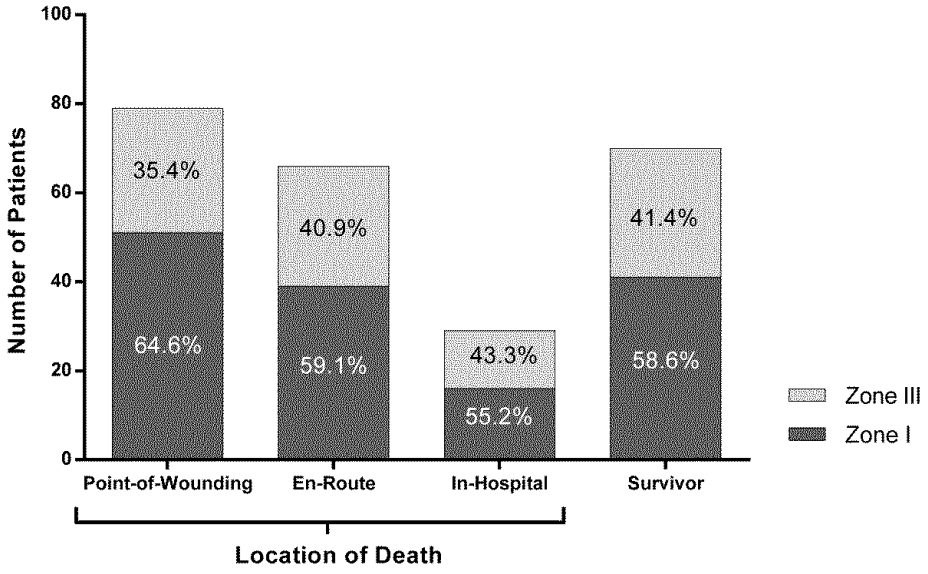

Figure 14.2: The numbers and proportions of patients requiring Zone I and Zone III occlusion

Table 14.2: Demography, trauma burden and injury pattern compared between UK military casualties, with an indication for REBOA, who either die en-route, in-hospital or survived

	Group			
	***En-route* Deaths**	**MTF Deaths**	**Survivor**	***p****
n	66	29	70	
Demography				
Male, n (%)	66 (100.0%)	27 (93.1%)	69 (98.6%)	0.065
Age/Yrs, Mean (SD)	26.2 (6.7)	26.0 (6.2)	25.5 (6.1)	0.828
Mechanism of Injury				
Blast, n (%)	47 (71.2%)	21 (72.4%)	44 (62.9%)	0.804
GSW, n (%)	15 (22.7%)	6 (20.7%)	19 (27.1%)	
Blunt, n (%)	4 (6.1%)	2 (6.9%)	7 (10.0%)	
Trauma Scores				
ISS, Mean (SD)	56.5 (16.4)	49.9 (15.4)	29.5 (12.2)	< 0.001
NISS, Mean (SD)	66.5 (12.3)	62.6 (12.8)	37.7 (16.7)	< 0.001
Injury Pattern				
Head, n (%)	25 (37.9%)	10 (34.5%)	6 (8.6%)	< 0.001
Face, n (%)	1 (1.5%)	1 (3.4%)	0 (0.0%)	0.346
Neck, n (%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0.470
Chest, n (%)	43 (65.2%)	16 (55.2%)	22 (31.4%)	< 0.001
Abdomen, n (%)	60 (90.9%)	2 (93.1%)	55 (78.6%)	0.056
Upper Extremity, n (%)	22 (33.3%)	6 (20.7%)	2 (2.9%)	< 0.001
Lower Extremity, n (%)	51 (77.3%)	21 (72.4%)	35 (50.0%)	0.003

Abbreviations: MTF – Medical Treatment Facility, GSW – Gun Shot Wound, ISS – Injury Severity Score, NISS – New Injury Severity Score. * Analysis of Variance

Table 14.3: Hospital intervention data

	MTF Deaths	**Survivors**	***p****
n	29	70	
Admission Physiology			
SBP, Mean (SD)	52 (54)	113 (38)	< 0.001
Pulse, Mean (SD)	65 (61)	103 (33)	0.011
GCS, Mean (SD)	5 (4)	12 (5)	< 0.001
Indications for Thoracotomy			
Haemorrhage Control, n (%)	1 (4.3%)	1 (2.1%)	0.589
Non-Haemorrhage Control, n (%)	0 (0.0%)	1 (2.1%)	0.679
Resuscitation, n (%)	12 (52.2%)	4 (8.3%)	< 0.001
Resuscitation *in isolation*, n (%)	12 (52.2%)	4 (8.3%)	< 0.001
Indications for Laparotomy			
Abdominal Haemorrhage Control, n (%)	13 (56.5%)	35 (72.9%)	0.167
Abdominal Non-Haemorrhage Control, n (%)	5 (21.7%)	19 (39.6%)	0.137
Proximal Control, n (%)	9 (39.1%)	11 (22.9%)	0.155
Proximal Control *in isolation*, n (%)	3 (10.3%)	8 (11.4%)	0.592
Pelvic Stabilisation			
External Fixation	5 (21.7%)	12 (25.0%)	0.763

Abbreviations: MTF – Medical Treatment Facility, SBP – Systolic Blood Pressure, GCS – Glasgow Coma Scale. * Analysis of Variance

Of the 66 patients who died en-route to an MTF, reliable time of death was recorded in 36 (54.5%) patients with median (IQR) time of 75 (67) minutes. While all patients had a focus of non-compressible haemorrhage, traumatic brain injury (TBI) was felt to be the greater contributor to mortality in 19 (28.8%) patients.

Of the 99 patients who survived to MTF admission (i.e. MTF deaths and survivors), pre-hospital time was available in 57 (57.6%) of cases, with a median (IQR) time of 61 (55) minutes. MTF deaths had a lower admission systolic blood pressure, pulse rate and Glasgow coma score compared to survivors (Table 14.3). Of the 29 MTF deaths, all had a focus of haemorrhage, but the primary cause of death was non-compressible haemorrhage in 14 (48.3%), TBI in 9 (31.0%) and multiple-organ failure in 6 (20.7%).

The use of thoracotomy, laparotomy and pelvic fixation for haemorrhage control was employed similarly between fatalities and survivors (Table 14.3). However, resuscitative thoracotomy was used in a greater proportion of fatalities (52.2% vs. 8.3%; $p < 0.001$). Interestingly, within the 70 survivors, 4 (8.3%) required a thoracotomy and 8 (11.4%) required a laparotomy for aortic/iliac control in isolation, i.e. no other thoracic or abdominal intervention was required.

14.4 Discussion

This study is the first to examine a consecutive population of wartime wounded in order to evaluate the potential role of REBOA as a haemorrhage control and resuscitative adjunct. The current study demonstrates that one in five patients sustaining a severe injury have an injury pattern that is potentially amenable to this manoeuvre, although 79 (32.3%) had no signs-of-life at the scene and REBOA is unlikely to change their outcome. However, 89 (36.5%) of patients have a spontaneous circulation that deteriorates into circulatory arrest prior to, or upon MTF admission. REBOA may have utility in this group, by sustaining central perfusion until definitive haemorrhage control can be attained.

Patients with critical bleeding require concomitant resuscitation and haemorrhage control (96). The last decade has seen significant advances in the field of resuscitation with formalised Damage Control Resuscitation (DCR) algorithms capable of correcting even profound physiological abnormality intra-operatively (97). This has resulted in the lowest died-of-wounds rate in

contemporary conflict (28); however, this is dependent upon a casualty surviving to an MTF and it is now well established that the majority of deaths occur prior to admission (4,68,95).

The fundamental problem is how to get an exsanguinating patient to definitive haemorrhage control before they undergo a circulatory arrest. Definitive haemorrhage control is generally achieved using either operative or angio-embolic techniques (3). This requires trained personnel working with well-maintained infrastructure, support by an appropriate logistical chain and as such is only really practical in a formal MTF. Clearly one solution is to move the MTF closer to the point-of-wounding; however, this is rarely practical in dynamic and kinetic military operations. An alternative solution is the deployment of an adjunct that can support the spontaneous circulation until definitive haemorrhage control.

Aortic balloon occlusion, as achieved by REBOA, results in a haemodynamic profile which is highly beneficial to trauma patients as demonstrated in both animal (99,131) and human studies (98). Firstly, provided the haemorrhagic focus is perfused distal to the balloon, inflation will control arterial inflow slowing the rate of exsanguination. Second, the increase in afterload will enhance both myocardial and cerebral perfusion. This may be of particular importance in the setting of TBI where the maintenance of cerebral perfusion helps to reduce secondary brain injury. The current study reports that around a third of patients had sustained a TBI in addition to their haemorrhagic focus. However, this neuroprotective effect is strictly theoretical and currently there is no supporting human evidence.

Furthermore, REBOA may have a role as a surgical adjunct by reducing the need for cavity surgery in patients requiring arterial control in isolation. The current study demonstrates that of the 70 patients who survived, 14 required a laparotomy or thoracotomy purely for proximal control of the aorta or iliac segments. The operating room use of REBOA could have theoretically eliminated the need for open surgery, reducing the associated physiological penalty. This has the greatest potential for patients sustaining a dismounted complex blast

injury where the control of pelvic and proximal extremity haemorrhage often necessitates a laparotomy (70,132).

While the concept of REBOA may appear attractive, it is important to acknowledge the practical challenges involved in the deployment of this adjunct, especially in the pre-MTF setting. The main issues relate to obtaining arterial access and the "blind" insertion of a catheter system without fluoroscopic assistance. Arterial access in hypotensive patients is challenging and this step has limited the effectiveness of aortic balloon occlusion in the historic literature (9). However, with the refinement of endovascular technology and the availability of portable ultrasound imaging devices, the chances of successful arterial cannulation can be optimised (98).

Furthermore, the risks of blind insertion are also being minimised with a number of technical innovations combined with an improved understanding of aortic morphometry. Novel REBOA systems have been designed that combine a low-profile, uni-body construction with self-centring capability to maintain aortic travel (100). CT based morphometric analysis has permitted the characterisation of the internal-external relationship between the aorta and torso height (126,133)). This has enabled the development of equations that can reliably predict the insertion length required to occlude the desired aortic zone (133).

With these challenges in mind, the deployment of a REBOA system is only really practical during the en-route phase of evacuation, where care can be delivered in a more permissive environment. Advanced medical retrieval (AMR) platforms such as the UK Medical Emergency Response Team and the USAF Tactical Critical Care Evacuation Team are ideally placed to deploy REBOA (134,135).

These platforms already deliver a suite of advanced interventions such as drug assisted intubation, central venous access and the administration of blood products (135). Importantly, the skill-set required to perform these interventions is similar to those required to deploy a REBOA catheter. Clinicians need to be familiar and well-practiced with Seldinger vascular access techniques and the use of invasive monitoring. These practical skills need to be combined with prompt injury pattern recognition and decisive decision making (98).

Furthermore, the current study reports a median (IQR) time to death in patients with signs of life en-route, that expire prior to MTF admission of 75 (67) minutes. This, theoretically, may be a long enough window in which an AMR platform could retrieve a patient and deploy a REBOA system en-route to an MTF and definitive haemorrhage control.

The current study has a number of important limitations that require discussion. The most important caveat is that the reported analysis is strictly theoretical. The reality is that the majority of patients who die prior to MTF admission have sustained a high burden of injury and that even with immediate operative intervention and resuscitation, salvage is not assured.

Furthermore, the current study does not report comprehensive time of death data and it is unknown if the window for REBOA deployment is actually shorter than reported. However, within the deployed experience of the authors, these figures are not incongruous.

It is also important not to overstate the case for REBOA as other mechanical adjuncts for resuscitation and haemorrhage control have come and gone. Pneumatic anti-shock garments (PASG) is such an example which generated much interest through the 1970s and 1980s, but ultimately, there has been no demonstrable reduction in mortality, length of stay hospital or ICU stay (136). A key difference with REBOA is that it combines both haemorrhage control and resuscitation, setting it apart from many other mechanical adjuncts. With these points in mind, the current study makes a compelling case for the pre-MTF deployment of REBOA in torso and pelvic haemorrhage.

In conclusion, one-in-five severely injured UK combat casualties have a focus of haemorrhage in the abdomen or pelvic junctional region. This is associated with a high burden of mortality and there exists a discreet and definable group of patients that undergo exsanguination en-route to an MTF. These patients would theoretically benefit from the deployment of a REBOA system, ideally on board an AMR platform that is clinically well supported. The UK Defence Medical Service should explore the use of REBOA during the en-route phase of care for

patients with evidence of non-compressible haemorrhage that are at risk of exsanguinating prior to definitive haemorrhage control.

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Appendix A: Author Contribution

Chapter 2: The Epidemiology of Non-Compressible Torso Haemorrhage in the Wars in Iraq and Afghanistan.

Contribution: The Principle Investigator was Dr Rasmussen, who conceived the study. Mr Stannard obtained approval for the study from the US military authorities and I collected the data from the registry. I performed the statistical analysis and wrote the manuscript taking into account comments and edits from my co-authors.

Reference: Stannard A, Morrison JJ, Scott DJ, Ivatury RA, Ross JD, Rasmussen TE. The epidemiology of noncompressible torso hemorrhage in the wars in Iraq and Afghanistan. J Trauma Acute Care Surg. 2013;74:830-4.

Chapter 3: Injury Pattern and Mortality of Non-Compressible Torso Haemorrhage in UK Combat Casualties.

Contribution: The Principle Investigator was Prof Midwinter, who in conjunction with myself conceived the study. I obtained approval for the study from the UK military authorities and collected the data from the registry. I performed the statistical analysis and wrote the manuscript taking into account comments and edits from my co-authors.

Reference: Morrison JJ, Stannard A, Rasmussen TE, Jansen JO, Tai NR, Midwinter MJ. Injury pattern and mortality of noncompressible torso hemorrhage in UK combat casualties. J Trauma Acute Care Surg. 2013;75:S263-8.

Chapter 4: Associated Injuries in Casualties with Traumatic Lower Extremity Amputations Caused by Improvised Explosive Devices.

Contribution: The Principle Investigator was Mr Jansen, who in conjunction with myself conceived the study. I obtained approval for the study from the UK military authorities and collected the data from the registry. I performed the statistical analysis and wrote the manuscript taking into account comments and edits from my co-authors.

Reference: Morrison JJ, Hunt N, Midwinter MJ, Jansen JO. Associated injuries in casualties with traumatic lower extremity amputations caused by improvised explosive devices. Br J Surg. 2012;99:362-6.

Chapter 5: Resuscitative Thoracotomy Following Wartime Injury.

Contribution: The Principle Investigator was Prof Midwinter, who in conjunction with myself conceived the study. I obtained approval for the study from the UK military authorities and collected the data from the registry. I performed the statistical analysis and wrote the manuscript taking into account comments and edits from my co-authors.

Reference: Morrison JJ, Poon H, Rasmussen TE, Khan MA, Midwinter MJ, Blackbourne LH, Garner JP. Resuscitative thoracotomy following wartime injury. J Trauma Acute Care Surg. 2013;74:825-9.

Chapter 6: Use and Complications of Operative Control of Arterial Inflow in Combat Casualties with Traumatic Lower-Extremity Amputations Caused by Improvised Explosive Devices.

Contribution: The Principle Investigator was Mr Jansen, who in conjunction with myself conceived the study. I obtained approval for the study from the UK military authorities and collected the data from the registry. Miss Poon and I collected data from patients notes, performed the statistical analysis and wrote the manuscript jointly, taking into account comments and edits from my co-authors.

Reference: Poon H, Morrison JJ, Clasper JC, Midwinter MJ, Jansen JO. Use and complications of operative control of arterial inflow in combat casualties with traumatic lower-extremity amputations caused by improvised explosive devices. J Trauma Acute Care Surg. 2013;75:S233-7.

Chapter 7: Aortic Balloon Occlusion is Effective in Controlling Pelvic Hemorrhage.

Contribution: The Principle Investigator was Dr Rasmussen who conceived the study idea and the initial proposal was drafted by Dr Percival. I completed the proposal, secured approval for the study from the Lackland Institutional Animal

Care and Use Committee (IACUC) and acquired US Air Force General Medical Education (GME) funding. I led the experimental phase and collected the data with support from my co-authors. I performed the statistical analysis and wrote the submitted manuscript taking into account comments and edits from my co-authors.

Reference: Morrison JJ, Percival TJ, Markov NP, Villamaria C, Scott DJ, Saches KA, Spencer JR, Rasmussen TE. Aortic balloon occlusion is effective in controlling pelvic hemorrhage. J Surg Res. 2012;177:341-7.

Chapter 8: Physiologic Tolerance of Descending Thoracic Aortic Balloon Occlusion in a Swine Model of Hemorrhagic Shock.

Contribution: The Principle Investigator was Dr Rasmussen who devised the study idea and Dr Markov wrote the study proposal. He acquired both approval from the IACUC and GME funding for the study. Dr Markov led the experimental phase and data collection; the listed co-authors and I assisted with the execution of the experiments. I performed the statistical analysis and wrote the submitted manuscript taking into account comments and edits from my co-authors.

Reference: Markov NP, Percival TJ, Morrison JJ, Ross JD, Scott DJ, Spencer JR, Rasmussen TE. Physiologic tolerance of descending thoracic aortic balloon occlusion in a swine model of hemorrhagic shock. Surgery. 2013;153:848-56.

Chapter 9: The Inflammatory Sequelae of Aortic Balloon Occlusion in Haemorrhagic Shock.

Contribution: The Principle Investigator was Dr Rasmussen, who between myself and Dr Ross jointly conceived the study. No additional funding was required. The cytokine assays were performed by Mrs Dickson, assisted by myself. I collected the data, performed the statistical analysis and wrote the manuscript taking into account comments and edits from my co-authors.

Reference: Morrison JJ, Ross JD, Spencer JR, Rasmussen TE. The Inflammatory Sequelae of Aortic Balloon Occlusion in Hemorrhagic Shock. J Surg Res. 2014 *In Press*

Chapter 10: Use of Resuscitative Endovascular Balloon Occlusion of the Aorta in a Highly Lethal Model of Non-Compressible Torso Haemorrhage.

Contribution: The Principle Investigator was Dr Rasmussen, who along with myself and Dr Ross jointly conceived the study. I wrote the study proposal and obtained the IACUC approval and GME funding. I led the experimental phase and collected the data, supported by my co-authors. I performed the statistical analysis and wrote the manuscript taking into account comments and edits from my co-authors.

Reference: Morrison JJ, Ross JD, Houston IV R, Watson JDB, Sokol KK, Rasmussen TE. Use of Resuscitative Endovascular Balloon Occlusion of the Aorta in a Highly Lethal Model of Non-Compressible Torso Hemorrhage. Shock. 2014;41:130-7.

Chapter 11: Morphometric Analysis of Torso Arterial Anatomy with Implications for Resuscitative Aortic Occlusion.

Contribution: The Principle Investigator was Dr Rasmussen and Mr Stannard obtained the necessary IRB permissions to perform the study. Mr Stannard collected the data from the CT data repository. This was analysed jointly by Mr Sharon and myself, whereupon I wrote the manuscript taking into account comments and edits from my co-authors.

Reference: Stannard A, Morrison JJ, Sharon DJ, Eliason JL, Rasmussen TE. Morphometric analysis of torso arterial anatomy with implications for resuscitative aortic occlusion. J Trauma Acute Care Surg. 2013;75:S169-72.

Chapter 12: Prospective Evaluation of the Correlation Between Torso Height and Aortic Anatomy in Respect of a Fluroscopy Free Aortic Occlusion System.

Contribution: The Principle Investigators were Dr Rasmussen and Prof Midwinter. Mr Stannard wrote the IRB proposal and obtaining permission from both US and UK military authorities with input from myself. Both Mr Stannard and myself collected the data. I performed the statistical analysis with advise

from Mr Sharon and wrote the manuscript taking into account comments and edits from my co-authors.

Reference: Morrison JJ, Stannard A, Midwinter MJ, Sharon DJ, Eliason JL, Rasmussen TE. Prospective Evaluation of the Correlation Between Torso Height and Aortic Anatomy in Respect of a Fluroscopy Free Aortic Occlusion System. Surgery. 2014;155:1044-51.

Chaper 13: A Novel Fluoroscopy-Free, Resuscitative Endovascular Aortic Balloon Occlusion System in a Model of Hemorrhagic Shock.

Contribution: The Principle Investigator was Dr Rasmussen who conceived the study concept and in conjunction with Dr Eliason, developed the prototype catheter. Dr Scott wrote the animal proposal and secured IACUC permission and GME funding. Dr Scott led the experimental phase and data collection; the listed co-authors and I assisted with the execution of the experiments. I performed the statistical analysis and wrote the submitted manuscript in conjunction with Drs Rasmussen and Eliason taking into account comments and edits from the other co-authors.

Reference: Scott DJ, Eliason JL, Villamaria C, Morrison JJ, Houston IV R, Spencer JR, Rasmussen TE. A novel fluoroscopy-free, resuscitative endovascular aortic balloon occlusion system in a model of hemorrhagic shock. J Trauma Acute Care Surg. 2013;75:122-8.

Chapter 14: Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA): A Gap Analysis of Severely Injured UK Combat Casualties.

Contribution: The Principle Investigator was Mr Jansen, who in conjunction with myself conceived the study. I obtained approval for the study from the UK military authorities and collected the data from the registry. I performed the statistical analysis and wrote the manuscript taking into account comments and edits from my co-authors.

Reference: Morrison JJ, Ross JD, Rasmussen TE, Midwinter MJ, Jansen JO. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA): A Gap Analysis of Severely Injured UK Combat Casualties. Shock. 2014;41:388-393.