Endovascular Resuscitation

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Abstract

Haemorrhage is the leading cause of preventable death in trauma. The key in management of patients with haemorrhagic shock is timely haemorrhage control before the patient dies from exsanguination. However, this can be challenging, particularly in non-compressible torse haemorrhage leading to delays and eventual exsanguination and death. Despite significant advances in trauma care and resuscitation strategies over the past few decades, mortality related to traumatic haemorrhage remains very high.

Endovascular resuscitation is an emerging concept of catheter-based techniques designed to control haemorrhage, support central blood pressure, and tissue perfusion. While Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) and related endovascular techniques present optimistic treatment solutions, early clinical data do not show a clear benefit and there are significant risks related to these techniques such as arterial access complications and ischaemia reperfusion injury. It is unknown who would most benefit from these techniques and there is limited knowledge of precise physiology of exsanguination to allow optimal management strategies.

The aims of this thesis are to analyse the effectiveness and safety of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) and explore the physiology of exsanguination.

We used data from a local trauma registry to study outcomes in trauma patients treated with REBOA at a high-volume centre. We applied propensity score matching to compare patients treated with REBOA to those who were not. Our study demonstrated improved in- hospital, and 30- day survival in REBOA patients.

Using a local REBOA registry data from a large volume centre we also compared trauma patients who were treated with partial and complete occlusion REBOA as well as total occlusion time less than and more than 30 min. This study showed that prolonged REBOA was associated with increased mortality. Surviving patients treated with partial occlusion required less need for vasopressors.

With safety concerns of blind REBOA inflation, ex-vivo porcine aortic tissues were used to compare inflation parameters of compliant and semi-compliant balloons. We found that the latter allows for concomitant use with a safety valve which would prevent any overinflation.

Finally, a swine model of controlled haemorrhage was used to define two distinct physiological phases of exsanguination cardiac arrest which have implications for treatment: preload support or coronary perfusion. This model was later used to study the relationship between the duration of cardiac arrest and the likelihood of successful resuscitation with Selective Aortic Arch Perfusion (SAAP). This showed that SAAP can accomplish return of spontaneous circulation even after 10 minutes of unsupported cardiac arrest due to haemorrhage.

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Equations

List of Abbreviations

AAST	American Association for the Surgery of Trauma
ABG	Arterial Blood Gas
AIS	Abbreviated Injury Scale
AO	Aortic Occlusion
AORTA	Aortic Occlusion for the Resuscitation in Trauma
atm	atmosphere unit
AV	Aortic Valve
BE	Base Excess
BUN	Blood Urea Nitrogen
BP	Blood Pressure
bpm	beats per minute
°C	Centigrade
Ca^{2+}	Calcium
$CaCl_2$	Calcium Chloride
CB	Compliant Balloon
CB-CT	Cone Beam Computed Tomography
CI	Confidence Interval
cm	centimetre
CO	Cardiac Output
CO_2	Carbon Dioxide
CPP	Coronary Perfusion Pressure
CPR	Cardiopulmonary Resuscitation
C-REBOA	Complete Occlusion Resuscitative Endovascular Balloon Occlusion of the Aorta
CRYO	Cryoprecipitate
CSR	Circumferential Stretch Ratio
DBP	Diastolic Blood Pressure

dL	decilitre
ECA	Exsanguination Cardiac Arrest
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ECPR	Extracorporeal Cardio-pulmonary Resuscitation
EF	Ejection Fraction
EMR	Electronic Medical Records
EPR	Emergency Preservation Resuscitation
$ETCO_2$	End- tidal carbon dioxide
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
FO2Hb	Fraction of Oxyhaemoglobin
Fr	French unit
G	Gauge
GCS	Glasgow coma scale
Hb	Haemoglobin
HBOC-201	bovine derived haemoglobin oxygen carrier
HCO_{3-}	Bicarbonate
Hct	Haematocrit
HR	Heart rate
Hr	Hour
IACUC	Institutional Animal Care and Use Committee
iCa^{2+}	Ionized Calcium
ICU	Intensive Care Unit
IL	Interleukin
INR	international normalized ratio
IQR	interquartile range
IRI	Ischaemia Reperfusion Injury

IRB	Institutional Review Board
ISS	Injury Severity Score
IU	International unit
IV	Intravenous
J	
K^+	Potassium
kg	kilogram
L	Litre
LV	Left Ventricle
LAD	Left anterior descending artery
MAP	Mean Arterial Pressure
mcg	microgram
mEq	milliequivalent
mg	milligram
Mg^{2+}	Magnesium
$MgSO_4$	Magnesium Sulphate
min	Minute
mL	millilitre
mM	millimoles
mmHg	millimetres of mercury
mmol	millimoles
N	number
Na^-	Sodium
NaCl	Sodium Chloride
NADPH	Nicotinamide adenine dinucleotide phosphate
NCTH	Non- compressible torso haemorrhage
O_2	Oxygen

OR	Operating Room
PACS	Patient Archive and Communication System
pCO_2	Partial Pressure of Carbon Dioxide
PEA	Pulseless Electrical Activity
PLT	Platelets
pO_2	Partial Pressure of Oxygen
PRC	Packed Red Cells
P-REBOA	Partial Resuscitative Endovascular Balloon Occlusion of the Aorta
pg	picograms
pH	potential hydrogen
PV	Pressure Volume
RAP	Right Atrial Pressure
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
ROSC	Return of spontaneous circulation
RR	respiratory rate
RT	Resuscitative thoracotomy
RV	Right Ventricle
RVP	Right Ventricular Pressure
SAAP	Selective Aortic Arch Perfusion
SaO_2	Oxygen saturation
SBP	Systolic Blood Pressure
SCB	Semi- Compliant Balloon
SD	standard deviation
sec	second
SOFA	Sequential Organ Failure Assessment
SV	Stroke Volume
TBI	Traumatic Brain Injury
TNF	Tumour Necrosis Factor
TnT	Troponin T

TQIP	Trauma Quality Improvement Program
U	Unit
USA	United States of America
VA-ECMO	Veno-Arterial Extracorporeal Membrane Oxygenation
WL	Working Length
Year	yr

Aims and Objectives

The aims of this thesis are:

1. To assess mortality and complications in civilian trauma patients with haemorrhagic shock managed with REBOA in a large volume level one trauma centre in the United States.
2. To assess clinical outcomes in trauma patients treated with REBOA with focus on degree of aortic occlusion (partial versus complete), and duration of aortic occlusion.
3. To explore the technical characteristics of a prototype, new REBOA catheter design with potential implications on the safety profile and ability to deliver partial occlusion.
4. To explore the pathophysiology of exsanguination cardiac arrest in a large animal model of controlled haemorrhage to define the point of myocardial failure with a focus for optimising treatment opportunities.
5. To assess survival after exsanguination cardiac arrest treated with Selective Aortic Arch Perfusion using a large model of exsanguination cardiac arrest, and to define the window for survival following the application of SAAP.

Chapter 1. Introduction

1.1 Background

Patients who present *in extremis* with profound hypotension or cardiac arrest have a high mortality rate (Andreka and Frenneaux, 2006; Girotra *et al.*, 2012; Morrison and Rasmussen, 2012). While many of these patients have a terminal pathology, a sub-group have a potentially survivable aetiology, provided the underlying problem can be reversed and their physiological derangement corrected. Examples of potentially survivable pathologies include haemorrhagic shock, cardiac tamponade, and pulmonary embolism.

Haemorrhage results in death or significant morbidity though a complex of mechanisms which are consequence of hypoperfusion and insufficient oxygen delivery (Cannon, 2018). Reduced blood flow to cells results in inadequate oxygen delivery to injured tissues with increased metabolic demands (Barbee *et al*., 2010). As a result, cells transition from aerobic to anaerobic metabolism which in return leads to accumulation of lactate, inorganic phosphates, and oxygen radicals. In addition, there are alterations in mitochondrial function. With ongoing decrease in supply of ATP, cells eventually die. With persistent hypoperfusion, there is end organ damage due to ischemia. All these mechanisms take hours to days eventually leading to which lead to a systemic inflammatory response (SIRS) and multiorgan failure (MOF) (Chaudry *et al.*, 1983; Zhang *et al*., 2010). However, in extreme cases of haemorrhage where blood loss is rapid, exsanguination ensues with overwhelming loss of volume leading to loss of palpable pulse inciting cerebral and myocardial hypoperfusion which quickly lead to anoxic brain injury and cardiac arrest (Tisherman *et al.,* 2017). Despite it being a major, preventable cause of death, on a physiological level, exsanguination cardiac arrest is poorly understood and little improvement has been achieved in outcomes over the last several decades despite significant advances in healthcare (Jenkins *et al.*, 2016) .

The last two decades have seen the introduction of the concept of “endovascular resuscitation”, where catheter-based therapies are used to manipulate a patient’s physiology. The goals of these interventions include the support of central blood pressure (BP), haemorrhage control, as well as oxygenation and tissue perfusion. Examples of endovascular resuscitation techniques include Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA), Selective Aortic Arch Perfusion (SAAP), Veno-Arterial

Extracorporeal Membrane Oxygenation (VA-ECMO) and Emergency Preservation Resuscitation **(**EPR) (Chen *et al.*, 2008; Barnard *et al.*, 2017; Brenner, Teeter, *et al.*, 2018).

Endovascular resuscitation is in its nascent stages and is far from being widely accepted into clinical practice. However, elements are gaining significant momentum with compelling pre-clinical studies and technological advancements. This chapter aims to discuss and summarise the field of endovascular resuscitation, with a focus on background, current evidence, and the obstacles limiting current clinical application.

1.2 Resuscitative Endovascular Balloon Occlusion of Aorta (REBOA)

1.2.1 Overview

REBOA is a technique whereby a compliant balloon is inflated in the aorta, interrupting perfusion to the distal circulation, and increasing cardiac afterload (figure 1.1). REBOA is a haemorrhage control adjunct in non-compressible torso haemorrhage designed to improve central aortic pressure in order to bridge to definitive haemostasis (Martinelli *et al.*, 2010; Stannard, Eliason and Rasmussen, 2011; Morrison *et al.*, 2012).

Aortic balloon occlusion was first described during the Korean war in the 1950s to control haemorrhage in combat trauma (Hughes, 1954); however, endovascular technology was relatively immature before the 1990s and the technique was not consistently used in ruptured aortic abdominal aneurysm management until endovascular repair become mainstream (Greenberg *et al.*, 2000; Malina *et al.*, 2005). Non- compressible torso haemorrhage (NCTH) is defined as high grade vascular disruption in 1 of 4 anatomical domains – solid organ, named blood vessel, pulmonary injury and pelvic ring fracture associated with bleeding – and physiological instability or the need for emergent haemorrhage control (Dutton *et al.*, 2010; Eastridge *et al.*, 2012; Morrison and Rasmussen, 2012). Typical management centres around damage control surgery; however, some patients suffer circulatory collapse before definitive surgical haemorrhage control can be attempted. In this setting, resuscitative measures which include blood product transfusion, and resuscitative thoracotomy (RT) to facilitate cardiac massage, aortic cross clamping, and intrathoracic haemorrhage control are required.

REBOA has emerged as an alternative to RT and aortic cross clamping, which eliminates the need for thoracotomy in the absence of a chest injury (Morrison and Rasmussen, 2012). The initial reports on aortic balloon occlusion, combined with the experience gained from the recent military conflicts in Iraq and Afghanistan, have led to the re-evaluation of the concept in trauma to limit non-compressible, abdominal, and pelvic haemorrhage. This has resulted in significant pre-clinical and clinical research in order to define the optimal use of the technique.

1.2.2 Technique

Establishing arterial access is essential to REBOA and most other forms of endovascular resuscitation. Vascular access for placement of the REBOA catheter is typically achieved via the common femoral artery (Stannard, Eliason and Rasmussen, 2011; Eastridge *et al.*, 2012), mainly due to its large calibre, consistent location, and convenience of manual pressure for haemostasis. Early reports described other access sites but these have largely been abandoned (Heimbecker, 1964; Ng and Ochsner, 1977; Matsuoka *et al.*, 2001; Matsuda *et al.*, 2003). Common femoral artery cannulation can be achieved via a percutaneous puncture, open cutdown, or if there is a pre-existing arterial line, upsizing to a larger sheath using a guidewire. Blind puncture using anatomical landmarks is possible although difficult in a hypotensive or pulseless patient, thus use of ultrasound guidance has been accepted as a reliable method for percutaneous access (Stannard, Eliason and Rasmussen, 2011; Qasim *et al.*, 2015; Morrison *et al.*, 2016). Alternatively, direct surgical cutdown is a reliable method for obtaining access (Ordoñez *et al.*, 2020), which can be particularly useful in a pulseless patient with a challenging body habitus (Brenner, Teeter, *et al.*, 2018). The femoral access for REBOA can be obtained at either groin and the decision should be made according to the injury pattern and the preference of the person obtaining the access and positioning of equipment and personnel.

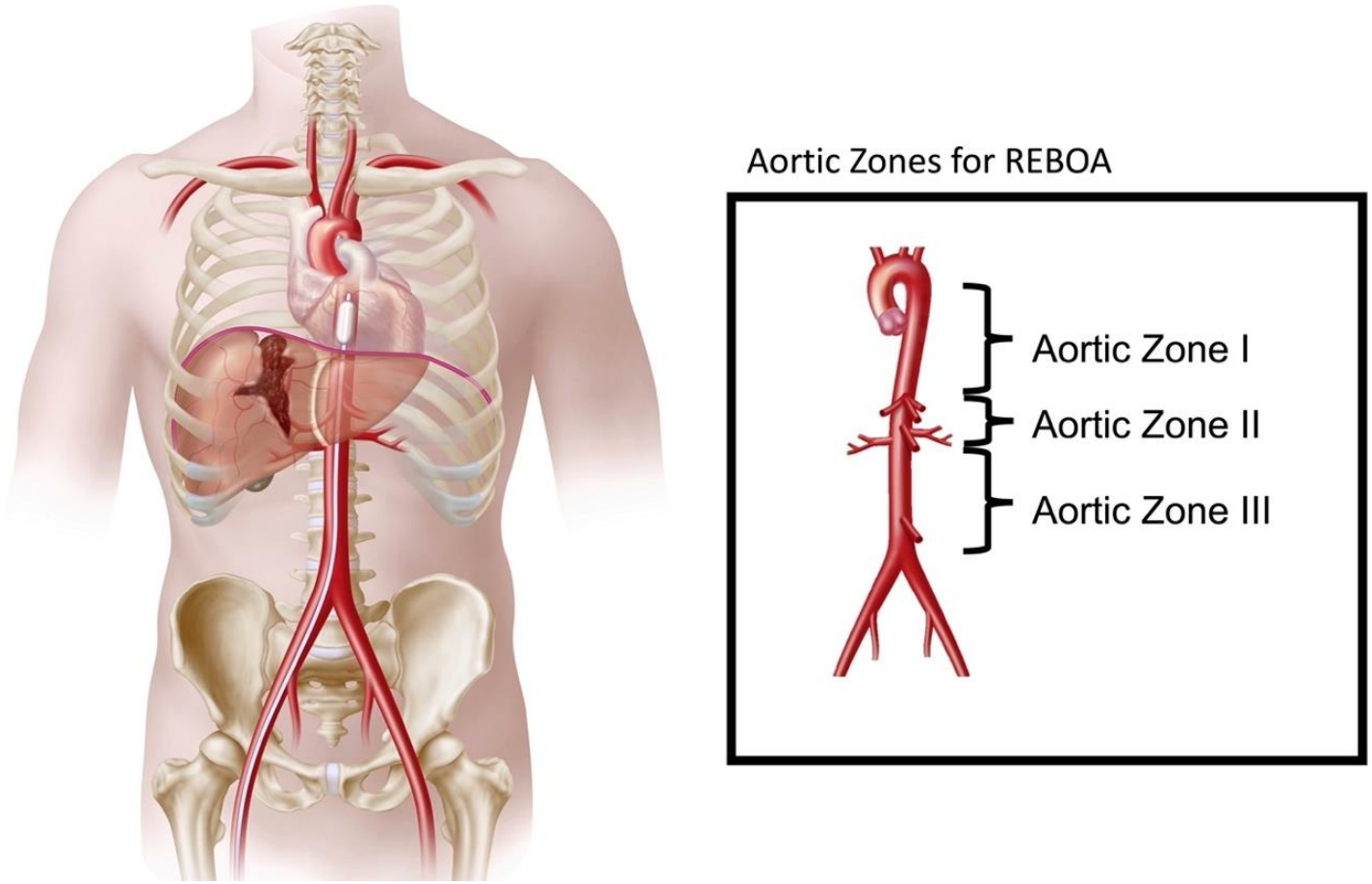

Figure 1.1 Resuscitative endovascular balloon occlusion of the aorta (REBOA), where an aortic occlusion balloon is inflated in Zone I. Insert demonstrating aortic zones for REBOA. Zone I is limited by the left subclavian artery superiorly, and the celiac artery inferiorly. Zone II extends from the celiac trunk to the lowest renal artery and occlusion should be avoided in this region. Zone III extends from the lower renal artery superiorly to the aortic bifurcation. Source: (Madurska, Ross, *et al.*, 2020)

REBOA technology had advanced considerably in the last decade, with devices available which are wire- free and 7 French (Fr) sheath compatible. The smaller sheath diameter is associated with reduced risk of ischaemic limb and can be safely removed without the need for surgical repair (Teeter *et al.*, 2016). Guidewire placement necessitates use of fluoroscopy and adds more procedural steps, this in turn increases procedural complexity, time to aortic occlusion (AO) and resource demands in the form of a fluoroscopy unit. Moreover, placing a stiff wire in the aorta carries the risk of traumatic vascular injury and stroke (Kessel and Robertson, 2010). Thus, wire-free devices may have an improved safety profile and reduce the complexity of REBOA.

Once vascular access is obtained, catheter deployment does not take more than a few minutes. A retrospective analysis of patients who have undergone resuscitative AO at the R Adams Cowley Shock Trauma Centre demonstrated time to REBOA deployment to be about 4 minutes (Romagnoli *et al.*, 2017). Importantly, this was including the use of guidewire, thus it is expected that time to deployment is significantly shorter in wire- free devices. The balloon is inflated with saline or a contrast saline mix to occlude the aorta. Correct placement is traditionally confirmed with fluoroscopy, x-ray or ultrasound although it can also be guided purely by clinical signs (Morrison *et al.*, 2016). Once REBOA has been deployed, definitive control of haemorrhage must be obtained as soon as possible to minimize the risk of distal ischaemia before gradual deflation and removal of the catheter- ideally still in the operating room (OR) once definitive control of bleeding has been obtained. Current guidelines recommend that AO is no longer than 30 min (Bulger *et al.*, 2019).

The location of balloon placement depends on the source of bleeding and is guided by the functional aortic zones described by Stannard et al. (Stannard, Eliason and Rasmussen, 2011). Typically, in patients with non-traumatic cardiac arrest or abdominal haemorrhage REBOA is placed in zone I (descending aorta between the origin of the left subclavian artery and the celiac artery), while zone III occlusion (infrarenal aorta between the lowest renal artery and the bifurcation) is usually utilized in bleeding in the pelvis or below (Stannard, Eliason and Rasmussen, 2011; Brenner, Teeter, *et al.*, 2018) (figure 1.1).

1.2.3 Experimental Evidence

REBOA has been investigated as an adjunct in cardiopulmonary resuscitation (CPR) and the management of torso haemorrhage. The physiological principle behind both these applications relates to afterload augmentation and inflow control.

Morrison and colleagues used a swine model with uncontrolled torso haemorrhage to demonstrate a significant increase in systolic BP in animals treated with REBOA vs no REBOA (96 mmHg vs 42 mmHg respectively) in addition to improved mortality (37.5 % vs 100 %) (Morrison, Ross, Houston, *et al.*, 2014). Another swine study comparing REBOA to RT in the setting of non-compressible torso haemorrhage showed similar increase of central aortic pressure and cerebral perfusion, however, the REBOA group had less metabolic acidosis (lactate (mmol/L) 4.27 vs 6.55, and pH 7.35 vs 7.24) and reduced volume requirements compared to RT (White *et al.*, 2011). Nonetheless, several studies support the finding of metabolic ischaemia associated with prolonged REBOA, particularly detrimental in occlusion times exceeding 60 min (Markov *et al.*, 2013; Scott *et al.*, 2013).

In patients with non-traumatic cardiac arrest, coronary perfusion pressure - a result of a gradient between aorta and right atrium - must be maintained above at least 15 mmHg in order to achieve return of spontaneous circulation (ROSC) (Paradis *et al.*, 1990). Conventional advanced cardiovascular life support measures are often unable to maintain the optimum circulation necessary for ROSC (Cunningham *et al.*, 2012). Animal studies of non-traumatic cardiac arrest demonstrated that REBOA as an adjunct to CPR resulted in significant increases in mean arterial BP (114 %) and cerebral perfusion (50 %) compared to CPR alone (Spence *et al.*, 1990), as well as improved coronary perfusion and ROSC rates (Rubertsson, Bircher and Alexander, 1997; Gedeborg, Rubertsson and Wiklund, 1999; Sesma *et al.*, 2002).

1.2.4 Clinical Evidence

A number of observational studies have shown that REBOA can successfully elevate the central BP in haemorrhagic shock (Borger van der Burg *et al.*, 2018), and reported survival ranging between 9.6 % and 83.4 % (Martinelli *et al.*, 2010; Moore *et al.*, 2015; Abe *et al.*, 2016; Brenner, Inaba, *et al.*, 2018). Based on current evidence, the benefit for use of REBOA skews towards patients with haemorrhagic shock. A single centre retrospective study on patients with haemorrhage reported that 58 % of those who were treated with REBOA for a traumatic cardiac arrest had ROSC and only 10 % survived 30 days. This is in contrast to trauma patients with haemorrhagic shock and no cardiac arrest who demonstrated a 61 % survival at 30 days, and non- traumatic haemorrhage patients who had an overall survival of 64 % (Brenner, Teeter, *et al.*, 2018).

Large population studies have not consistently shown a benefit in the use of REBOA. A significant source of data has come from the Japanese trauma databank, where reported outcomes vary according to analysis technique. Norii et al. used propensity score matching to compare trauma patients who were treated with REBOA with those who did not receive REBOA as part of their management. These investigators reported that REBOA patients were three times more likely to die (odds ratio = 0.3) (Norii, Crandall and Terasaka, 2015). Interestingly, Yamamoto and colleagues used the same database, but a different propensity model to demonstrate that severely injured trauma patients (mean ISS 35) had a higher rate of survival to discharge than those with no REBOA (45.5 % vs 32.5 %, odds ratio = 1.75) (Yamamoto *et al.*, 2019). However, an analysis of the United States of America (US) trauma quality improvement program (TQIP) revealed almost double the mortality rate for REBOA vs no- REBOA patients (35.7 % vs 18.9 % respectively) (Joseph *et al.*, 2019).

Despite the existing evidence, REBOA remains a controversial therapeutic intervention, with lack of high- quality clinical evidence demonstrating a clear mortality benefit. Fundamentally, current evidence is based on retrospectively collected data with small samples and potential bias limiting the conclusions that can be drawn- highlighting the need for more prospective randomized trials. Moreover, despite the improvements in catheter design, there are risks of over inflating the balloon. Smaller diameter catheters

provide limited tactile feedback when the balloon is inflated, increasing the over inflation risk. This, coupled with the small diameter of non-diseased aortas observed within the younger trauma population, further increasing this risk (Stannard *et al.*, 2013; Morrison, Stannard, *et al.*, 2014). Although these reports describe a small number of cases, all of the ruptured aortas due to REBOA reported within the literature have involved small vessels and over inflation (Søvik *et al.*, 2012; Davidson *et al.*, 2018).

At present, there are several clinical trials underway which investigate use of REBOA. The UK REBOA trial is a prospective, randomized controlled trial which commenced in 2017, recruiting patients from 17 major trauma centres across the United Kingdom. It aims to use Bayesian statistics (Jansen *et al.*, 2017) to compare standard major trauma centre treatment alone to that with REBOA as an adjunct. The study aims to assess 90-day mortality, late complications, and cost- effectiveness. At the time of writing this thesis 90 of 120 adult patients have been recruited with suspected or confirmed life- threatening torso haemorrhage thought to be amendable to adjunctive REBOA treatment (*UK-REBOA*, 2022). The results of this trial will hopefully elucidate the role of REBOA and help define the selection criteria for its use. Investigators in Bern, Switzerland are currently enrolling 15 patients to study outcomes in patients who were treated with REBOA for refractory, non-traumatic cardiac arrest in an out of hospital setting (University Hospital Inselspital, Berne, 2021). Also, investigators in Trondheim, Norway are currently enrolling 200 patients into a prospective, randomised, multicentre clinical trial to study the efficacy of REBOA as an adjunct treatment to ACLS for patients with non- traumatic cardiac arrest in a pre- hospital setting (Brede *et al.*, 2021; St. Olavs Hospital, 2021). While the completion of this trial is expected in 2025, preliminary data on 10 patients showed 100 % success of cannulation, 6 patients had ROSC, and one patient survived more than 30 days (Brede Jostein Rødseth *et al.*, 2019). Preliminary results are also awaited from phase I of the Resuscitative Endo Vascular AO for Maximal Perfusion trial at Yale University, which enrolled 5 patients to assess safety and practicality of delivering REBOA as an adjunct to advanced cardiac life support in patients undergoing non-traumatic cardiac arrest in a hospital setting (Daley, 2021).

1.2.5 Specific Limitations

With increased use and interest in the use of REBOA there are concerns associated with REBOA placement. These include haemodynamic, metabolic, haemodynamic, and vascular complications.

1.2.5.1 Metabolic complications

Aortic Occlusion caused by REBOA, can cause ischaemic injury to organs distal to the balloon, this includes renal, hepatic, intestinal ischaemia, as well as spinal cord ischaemia which may culminate in paralysis and limb ischaemia (Russo, Neff, Johnson, *et al*.,2016; Stannard, Eliason and Rasmussen, 2011)

A major limitation of REBOA is the ischaemia- reperfusion injury (IRI) observed with prolonged AO which leads to distal organ ischaemia. Balloon occlusion and resulting ischaemic injury is followed by balloon deflation resulting in a significant reperfusion injury as the ischaemic metabolites are washed into the systemic circulation (Abu-Nema *et al.*, 1988; Markov *et al.*, 2013).

Ischaemic hypoxia leads to a series of events including altered production of bioactive agents and de- regulation of gene expression, which eventually cause impaired cytoskeletal organization, electrolyte imbalance, and increased intracellular volume. This endothelial cell damage is further exacerbated by reperfusion through production of reactive oxygen metabolites and nitric oxide which cause cell swelling, loss of pinocytotic vesicles, lifting of endothelial cells from basement membrane and neutrophil adherence. The microvascular changes are reflected by arteriolar dilation, capillary plugging and increased vascular permeability leading to oedema. The local inflammatory endothelial dysfunction lasts for several hours before the ischaemia- reperfusion elicited sequalae begin affecting distant organs (Carden and Granger, 2000).

Extensive basic science research has been carried out to define inflammatory mediated pathways in ischaemia, while animal and clinical studies analysing the effects of AO in aortic aneurysm repair have been used to characterize the sequalae in IRI. High levels of TNF-a, IL-6, IL-8 and IL-1b have been found during ischaemia elicited by AO studies

(Casey, Balk and Bone, 1993; Roumen *et al.*, 1993; Holmberg *et al.*, 1999; Morrison, Ross, Markov, *et al.*, 2014). Moreover, IL-10 has been implied as a driving factor in the development of systemic inflammatory response syndrome in severe trauma patients (Sherry *et al.*, 1996), while the cytokines released into the systemic circulation were found to activate resident neutrophils in distant sites leading to inflammatory mediated reactions in distant organ systems (Bown *et al.*, 2001; Morrison, Ross, Markov, *et al.*, 2014). In post ischaemic tissues, cytokine release stimulates production of reactive oxygens species which cause endothelial barrier dysfunction, and thrombosis by means of increased expression of endothelial cell adhesion molecules, enhanced leukocyte-endothelial cell adhesion, and increased production of mediators such as platelet activating factor (Granger and Kvietys, 2015). These processes are initially expressed by signs of systemic inflammation before progressing to multi-organ failure. The sequential failure of organs usually begins with lungs as seen with acute respiratory distress syndrome before development of renal, central nervous system, hepatic and cardiac dysfunction and finally culminating in death (Bown *et al.*, 2001).

Since implication of reactive oxygens species into reperfusion injury and inflammation, much research has been done to further characterize these pathways and identify key mediators. The responsible enzyme systems have been pinpointed to xanthine oxidase, NADPH oxidase, mitochondria and uncoupled nitric oxide synthase. However, these exist in various concentrations in different species and different organs, in addition to varying tissue response depending on its state (e.g. inflammation) (Gelman, 1995; Granger and Kvietys, 2015). Consequently, therapies which target reactive oxygens species have so far shown limited benefit.

There is limited data characterizing IRI pathways and mediators specific to REBOA; however, animal studies have been conducted to assess the physiologic effects of aortic balloon occlusion and reperfusion. An early study of aortic balloon occlusion in a haemorrhagic shock model in sheep demonstrated that a 30 min AO resulted in worse lactic acidosis, and acute renal failure, in addition to increased mortality (Abu-Nema *et al.*, 1988). Further studies demonstrated that prolonged REBOA is associated with organ failure and metabolic acidosis. A swine model of uncontrolled haemorrhage comparing 40 min and 60 min REBOA demonstrated significantly higher potassium (K^+) and lactate

levels (mmol/L) following 60 min REBOA (6.29 and 11.39 respectively) as compared with 40 min REBOA (5.2 and 4.83 respectively) and controls (4.16 and 6. 43 respectively) (Avaro *et al.*, 2011).

These findings are supported by another study using an ovine haemorrhagic shock model, where 60 min REBOA resulted in significantly higher increases in serum K^+ and lactate than 30 min REBOA or no REBOA (V. A. Reva *et al.*, 2018). Morrison et al studied inflammatory response in swine with haemorrhagic shock who received REBOA over 30, 60- and 90- min. Animals in the prolonged occlusion groups (60 and 90 min) demonstrated significantly increased levels of IL-6 (pg/mL) from baseline at 8 hours REBOA (289 and 630 respectively versus 10 at baseline) (Morrison, Ross, Markov, *et al.*, 2014).

Moreover, prolonged REBOA was associated with higher incidence of ARDS and a greater trend in vasopressor use during the 48- hr critical care period (Morrison, Ross, Markov, *et al.*, 2014). Markov and colleagues used a swine model of haemorrhagic shock to compare 30 and 90 min REBOA with shock with no AO. The results showed delayed liver and renal dysfunction in the 90 min REBOA as demonstrated by Aspartate aminotransferase (U/L) (1,360 vs 1,006 in control) and blood urea nitrogen (BUN) levels (mg/dL) (37.3 vs 25 in control) at 48 hours. Prolonged REBOA occlusion group also required higher resuscitation fluid volumes (mL) (2,667 vs 1,000) in the 48 critical care period (Markov *et al.*, 2013).

While IRI can be well characterized in controlled animal studies, clinically, it is more challenging as patients have already incurred cellular injury from their original trauma (Avaro *et al.*, 2011; Markov *et al.*, 2013; V. A. Reva *et al.*, 2018). It may be difficult to elucidate exact contribution of the aetiology to IRI from clinical data because trauma patients are typically highly heterogenous in their injury pattern. There is currently little data to define significance of the initial injury in development of ischaemia reperfusion injury.

Overall, there is a demonstrated time dependent detrimental sequalae of REBOA, with significant metabolic derangements following AO of more than 30 min. This time

restriction limits the usefulness of REBOA to an in- hospital setting. The next frontier is prolonging safe REBOA intervention while reducing the IRI. This could potentially expand the applicability of REBOA to pre- hospital settings with prolonged transport time to damage control surgery and allow inter- hospital patient transfers before definitive haemorrhage control has been achieved.

1.2.5.2 Haemodynamic complications

Aortic occlusion causes increased afterload, supraphysiologic arterial hypertension proximal to the occlusion, increased carotid blood flow as well as increase in preload due to redistribution of blood from distal to proximal vasculature (Gelman, 1995; Johnson, Davidson, *et al.*, 2017). Whilst these changes are pursued in a hemodynamically unstable patient, increased preload and afterload may lead to cardiac dysfunction in those with pre-existing cardiac disease (Gelman, 1995; Russo, Neff, Johnson, *et al*.,2016), and supraphysiologic hypertension may further exacerbate brain injury in trauma patients (Russo, Neff, Johnson, *et al*. ,2016, Davidson *et al*., 2018). Moreover, balloon deflation may lead to a rapid shift of volume between proximal and distal vascular beds, washout of vasoactive ischemic metabolites, and as a result cause significant reactive hypotension and myocardial dysfunction (Gelman, 1995, Russo, Neff, Johnson, *et al*., 2016; Davidson *et al*., 2018).

1.2.5.3 Vascular complications

Vascular site complications due to iatrogenic injury associated with placement of large calibre endovascular sheaths are well described in literature (Stone and Campbell, 2012) and reported in REBOA placement. These usually include thrombosis, pseudoaneurysm formation and intimal flap dissection which lead to acute limb ischaemia (DuBose *et al.*, 2016, Morrison *et al.*, 2016) and tend to be associated with larger sheath use (Teeter *et al.*, 2016). Vascular complications from transcatheter procedures may require further surgical procedures for limb salvage or a major limb amputation. Other vascular complications related to REBOA, albeit rare, have been reported as balloon overinflation leading to aortic or iliac injury balloon displacement or balloon rupture (Davidson *et al.*, 2016; Hörer *et al.*, 2016; Okumura *et al.*, 2016; de Schoutheete *et al.*, 2018).

Taylor et al reported one of the largest case series from Colorado, USA on 48 patients who underwent REBOA for NCTH. N=38 received were treated via a 14 Fr sheath. Of the 28 patients who had a 14 Fr sheath and survived to sheath removal, 19 had primary closure of arteriotomy without vascular complications and 5 needed additional procedures to achieve arteriotomy closure; 2 patients had a thrombectomy with a dissection flap repair and patch angioplasty, 1 patient required thrombectomy with patch angioplasty, 1 patient had an interposition graft and prophylactic fasciotomies and 1 had a thrombectomy with repair of a dissection flap. 8 of 10 patients who had REBOA via a 7Fr sheath survived to sheath removal, and none of these had any vascular complications. (Taylor *et al*., 2017).

1.2.5.4 Partial Occlusion

A method which could address the haemodynamic and metabolic complications of complete AO, as well as potentially allow prolonged occlusion, beyond the recommended maximum 30 min, has been described as partial REBOA (P-REBOA) where low volume aortic flow is permitted distal to the occlusion, through a partially deflated balloon. This technique aims to balance the blood flow past the balloon with some permitted haemorrhage but reduced distal ischaemia and reperfusion (Russo, Neff, *et al.*, 2016).

A swine model studied by Russo et al. demonstrated that P-REBOA can be used to effectively elevate the mean arterial pressure (MAP) proximal to the balloon, whilst keeping it within physiological limits compared to supraphysiological levels for complete occlusion REBOA (+ 13.5 mmHg from baseline vs + 69 mmHg respectively). Moreover, this model demonstrated preserved visceral perfusion as demonstrated by higher MAP (mmHg) in the jejunal branch of the superior mesenteric artery (45 in P-REBOA vs 10 in REBOA), and lower lactate levels (mmol/L) (3.2 vs 9.3 in standard REBOA) (Johnson *et al.*, 2016).

Sadeghi and colleagues used a swine model to compare haemodynamic and metabolic indices between P-REBOA and total occlusion REBOA and found that 3 hr post reperfusion, intraperitoneal lactate and pyruvate were almost half in the P-REBOA arm

compared to REBOA (129- and 2.8-mM vs 295 and 2.5 mM respectively) (Sadeghi *et al.*, 2018). These findings should be considered with some scepticism as inflammatory markers of reperfusion might take well over 12 hr to accumulate, while the study allowed only 3 hr of critical care post- reperfusion before the end of the protocol. Another study compared P-REBOA to REBOA with intermittent full occlusion, following 15 min complete occlusion in a swine haemorrhage model. This demonstrated that P-REBOA was associated with a reduced time of total occlusion (20 vs 70 min, p=0.008), and allowed for a greater amount of distal flow (20.9 L vs 9.8 L p=0.03) despite equivalent blood loss (Johnson *et al.*, 2020).

Another animal study by Johnson and colleagues using a traumatic brain injury (TBI) model showed that compared with standard REBOA, P-REBOA resulted in more physiologic proximal MAP (92.7 vs 105.3 mmHg in complete occlusion) as well as carotid blood flow (464.2 vs 673.1 mL/min in complete occlusion) (Johnson, Williams, *et al.*, 2017). Importantly, these findings suggest that P-REBOA is less likely to aggravate concomitant TBI, although actual progression of TBI has not been demonstrated in this study. The limitations of the large animal cranial anatomy make it difficult to effectively study TBI (Vink, 2018) and a reliable model is needed to explore the true effects of REBOA on TBI.

The P-REBOA technique is poorly described and there are no formally accepted standards which would define optimal partial occlusion with the available catheters. Nevertheless, some clinicians use the technique, and apply a staged approach by gradually deflating the initially fully inflated balloon using the distal arterial pressure as a guidance (Johnson *et al.*, 2016; DuBose, 2017; Viktor A. Reva *et al.*, 2018).

Clinical evidence is limited to a few case reports where clinicians were able to titrate the balloon volume and achieve P-REBOA (Davidson *et al.*, 2016; Hörer *et al.*, 2016). Despite promising results, haemodynamic stability with partial occlusion using currently available devices is extremally difficult to achieve as even minimal balloon deflation leads to large fluctuations in aortic blood flow and proximal BP (Russo, Neff, *et al.*, 2016; Johnson, Davidson, *et al.*, 2017). Device improvements will have to take place before widespread application of P-REBOA.

1.3 Selective Aortic Arch Perfusion (SAAP)

1.3.1 Overview

SAAP is a catheter-based technique consisting of an AO balloon and a capability of infusing oxygenated resuscitation fluid and drugs directly into the aorta proximal to the balloon. SAAP was initially developed to address the inadequacy of CPR during non-traumatic cardiac arrest has also shown promising results in delivering resuscitation in an exsanguination cardiac arrest (ECA) model. (Manning *et al.*, 2001).

Coronary perfusion is driven by the coronary perfusion pressure (CPP), a result of a pressure gradient between the aorta and the right atrium. During cardiac arrest when there is no organized, cardiac contractility, circulation is dependent on chest compressions. Paradis et al. demonstrated that during CPR, ROSC rate is directly proportional to CPP, with at least 15 mmHg necessary for any chance of ROSC (Paradis *et al.*, 1990). Even with good quality CPR, optimal CPP often isn't adequately maintained (Cunningham *et al.*, 2012). However, SAAP has been shown to effectively deliver adequate coronary flow in animal models with CPP of 62 mmHg, resulting in increased ROSC rates (86 % vs 20 % respectively) (Paradis, Rose and Gawryl, 1994).

1.3.2 Technique

SAAP, like REBOA, begins with femoral arterial access, followed by placement of a balloon-tipped catheter in the proximal descending thoracic aorta. The balloon is inflated to occlude the thoracic aorta, essentially isolating the head, neck, and upper extremity circulation from the rest of the body. This is followed by intra- aortic delivery of oxygenated resuscitation fluid and drugs, which facilitates ROSC and supports cerebral and coronary circulation whilst increasing afterload and limiting sub- diaphragmatic haemorrhage (Manning *et al.*, 1992) in the case of exsanguination (figure 1.2).

A catheter with a working length (WL) of 55- 60 cm has an internal lumen of 6.3 to 7.5 Fr to support perfusate infusion rates in the range of 10 mL/kg/min (Manning *et al.*, 2016; Barnard *et al.*, 2017). The remaining SAAP circuit elements include: an infuser- reservoir

for up to 3 L of fluid, an oxygenator, a pump, and 3/8" tubing with the possibility to accommodate extra ports for recirculation, sampling, co- infusions, etc. (Barnard *et al.*, 2017).

A variety of perfusates have been explored including Lactated Ringer's solution, perfluorocarbons, bovine derived haemoglobin oxygen carrier (HBOC-201), and whole blood (Manning *et al.*, 1992; Manning, Batson, Gansman, *et al.*, 1997; Manning *et al.*, 2000, 2016). Haemoglobin (Hb) based oxygen carriers were found to be most effective when infused at a rate of 10 mL/kg/min (Manning *et al.*, 2001).

SAAP is still in a pre-clinical phase and no SAAP specific catheter has yet been approved for clinical use. The optimal perfusate also poses a technical challenge. A variety of oxygen carrying fluids have been explored including: perflubron emulsion (fluorocarbon-based oxygen carrier) (Manning, Batson, Gansman, *et al.*, 1997), oxygenated lactated Ringer's solution (Manning *et al.*, 2016), HBOC-201 (Manning *et al.*, 2001, p. 201) oxygenated whole blood as well as packed red cells (PRC) diluted with normal saline or lactated Ringer's solution (Manning *et al.*, 2016).

Currently, there is no synthetic or homologous oxygen carrier which is approved for clinical use by the Food and Drug Administration, however, HBOC-201 is currently under investigation, and is available in some centres under expanded access for compassionate use (*HBOC-201 Expanded Access Protocol for Life-threatening Anemia for Whom Allogeneic Blood Transfusion is Not an Option - Full Text View - ClinicalTrials.gov*, 2022). Whole blood and PRC are stored in citrate, which ionizes intravascular calcium stores leading to severe hypocalcaemia and dysrhythmias, requiring a co-infusion of 10% calcium gluconate at 11.1 mL/min to prevent calcium chelation (Manning *et al.*, 2016). Lactated Ringers used to dilute PRCs has shown to initiate thrombosis in a porcine model (Manning *et al.*, 2016).

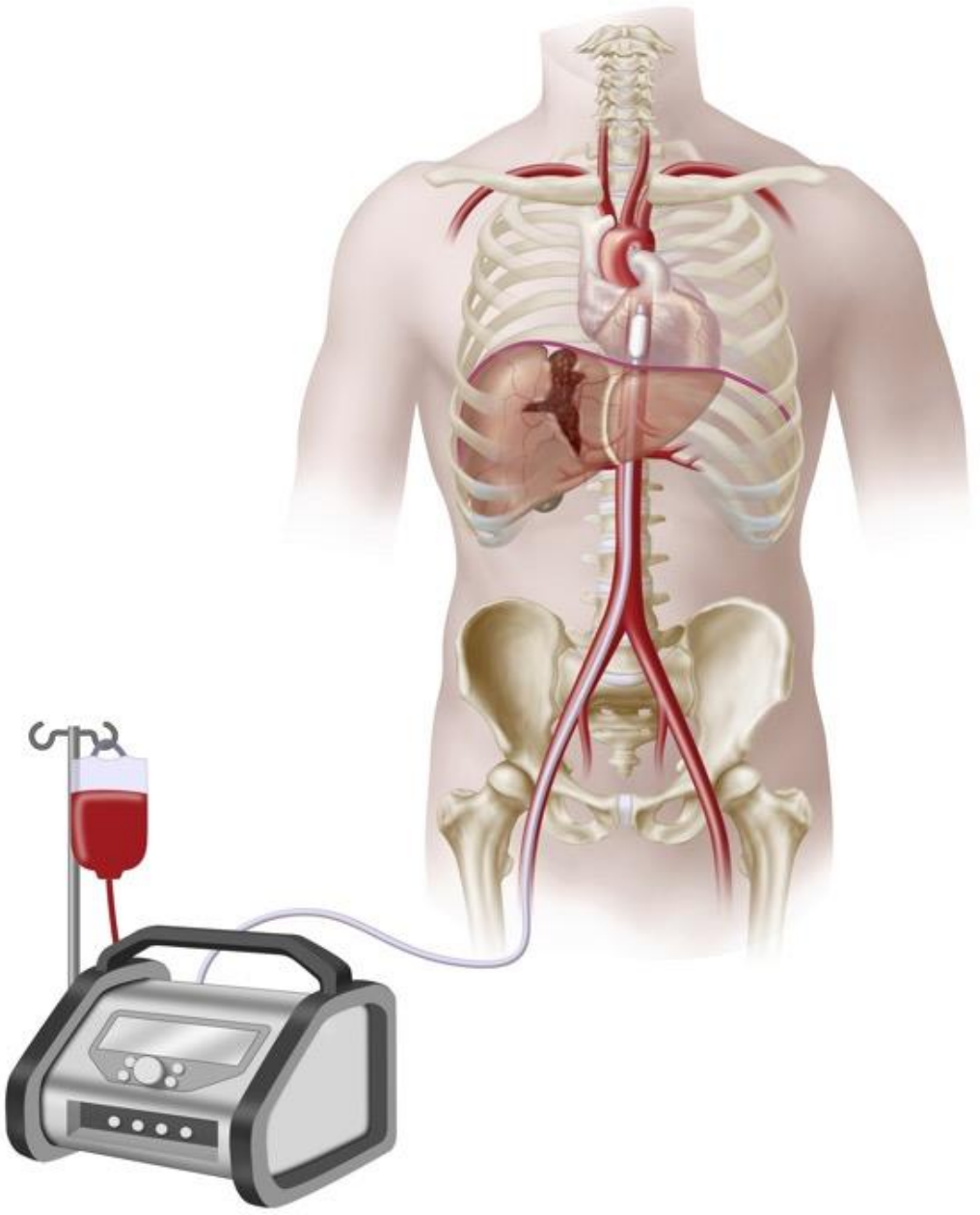

Figure 1.2 Selective aortic arch perfusion (SAAP). An occlusive aortic balloon is inflated in aortic Zone I, with direct, retrograde perfusion of oxygenated blood into the aortic arch. Source: (Madurska, Ross, *et al.*, 2020)

The perfusate and other products given via SAAP must be delivered with precision in terms of timing and volume. Translational studies report using a modified ECMO circuit (Barnard *et al.*, 2017; Hoops *et al.*, 2019), but a specialized unit which can readily deliver oxygenated blood at precise pressures and volumes in a resuscitation bay according to each patient's need is not yet commercially available.

Moreover, a rapid, retrograde injection of large volume of perfusate to achieve closure of the aortic valve (AV) and optimal coronary blood flow, may lead to left to right heart shunting and pulmonary oedema, particularly in patients with an incompetent AV (Manning *et al.*, 1992). Although optimal volumes of perfusate have been tested on animals in order to maintain cerebral and coronary perfusion (Manning, Batson, Payne, *et al.*, 1997), clinical studies are awaited.

1.3.3 Experimental Evidence

The first published study on SAAP demonstrated the use of the device in a canine model with ventricular fibrillation cardiac arrest using a range of infusion approaches. It demonstrated that SAAP can deliver adequate coronary flow resulting in CPP of 50 mmHg, and that direct intra- aortic infusion of adrenaline doubled the mid- aortic pressure compared to infusion of perfusate alone. Moreover, perfusate volumes and flow rates were optimized to prevent retrograde flow through the pulmonary system (Manning *et al.*, 1992). Manning expanded on these findings by adding intra- aortic adrenaline resulting in significant increase in CPP (mmHg) (10 to 40) and reducing time to ROSC (min) (11 to 6) compared to SAAP with peripheral adrenaline (Manning, Batson, Payne, *et al.*, 1997).

SAAP without perfusate is effectively REBOA; the inflated aortic balloon can increase afterload but without direct perfusion of the coronary vessels. Early SAAP studies used conventional CPR as control groups to demonstrate superior ROSC rates in canine ventricular fibrillation cardiac arrest model (Manning *et al.*, 1992; Barton, Manning and Batson, 1996; Manning, Batson, Payne, *et al.*, 1997). Paradis used a similar study design to demonstrate that adequate coronary perfusion in SAAP with CPP reaching above 60 mmHg – was needed for ROSC (Paradis, Rose and Gawryl, 1994). However, Barnard

and colleagues demonstrated the benefit of perfusate use with an AO balloon by comparing REBOA with concomitant peripheral blood transfusion to SAAP with central perfusion using blood and Lactated Ringer's solution in an uncontrolled haemorrhage model in swine. ROSC was not achieved in any of the REBOA animals in contrast to the SAAP groups, where 6/10 animals had ROSC following SAAP + Lactated Ringer's solution as perfusate, and 10/10 which had SAAP with whole blood as a perfusate (Barnard *et al.*, 2017).

Use of an oxygen carrier as a perfusate in a haemorrhagic cardiac arrest model was investigated in a study where all swine (n=6) treated with SAAP with HBOC-201 had ROSC vs only 1/3 of those treated with SAAP with Lactated Ringer's solution as a perfusate (Manning *et al.*, 2001). A follow up study demonstrated excellent ROSC rates in animals who received blood products (whole blood and red blood cells) as a perfusate with a co- infusion of 10% calcium chloride, interestingly the only two animals with no ROSC did not receive a calcium chloride and developed refractory ventricular fibrillation (Manning *et al.*, 2016).

A study which used a porcine haemorrhagic cardiac arrest model, compared three resuscitation strategies: REBOA with peripheral whole blood infusion, SAAP with oxygenated Lactated Ringer's solution as a perfusate, and SAAP with oxygenated whole blood as a perfusate (Barnard *et al. 2017)*. None of the animals in the REBOA arm had ROSC, while in the SAAP groups, ROSC was achieved in 60 % of those who were perfused with Lactated Ringer's solution and 100% in those with oxygenated whole blood (95 % CI 0- 30.9, 26.2-87.8 and 69.2-100 respectively). Moreover, following ROSC in the SAAP cohorts, survival after 60 min of resuscitation was 90 % in the oxygenated whole blood group vs 10 % in the Lactated Ringer's solution (95 % CI 55.5-97 vs 0.25- 44.5) demonstrating that an oxygen carrying molecule was crucial in effective SAAP therapy. This was further supported with a follow-up study by Hoops et al., which advanced the concept to include HBCO-201. The study demonstrated similar outcomes between groups using SAAP with whole blood and HBCO-201 in terms of ROSC rates (100 % vs 86 %, $p = 0.483$) and survival after 5.5 hr (92 % vs 67 %, $p = 0.120$), confirming equal efficacy of both Hb- based oxygen carriers in SAAP therapy (Hoops *et al.*, 2019).

Several clinical trials were being conducted on the use of HBOC-201, including a feasibility study in trauma patients in South Africa (*A Single Site Safety and Tolerability Study of HBOC-201 in Trauma Subjects*, 2008). However, following reports of potential increased mortality due to toxicity (Natanson *et al.*, 2008) all trials and development of HBOC have been halted (Silverman and Weiskopf, 2009). Due to ongoing need for alternatives to blood products, new and amended trail protocols are anticipated (Mackenzie *et al.*, 2019).

1.3.4 Specific Limitations

1.3.4.1 Training

SAAP would be a natural bridge between resuscitation and ECMO in the event further physiological support is required. This raises questions of who would need to be trained to deliver this procedure (emergency physicians, surgeons, pre-hospital providers, etc.), and what the training delivery format would be. While practicing access techniques could be done with artificial simulation trainers, resuscitation itself might require an animal model with a cardiac arrest which can be resuscitated. Currently, Oregon Health and Science University offers a training course on SAAP therapy to trauma surgeons and critical care physicians. The program consists of didactic lectures, simulation session and hands-on sessions using a live model of porcine haemorrhagic cardiac arrest.

1.4 Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) and Extracorporeal Cardiopulmonary Resuscitation (ECPR)

1.4.1 Overview

ECMO involves the placement of two cannulae- one for drainage and another one for return of blood which is pumped around a circuit that includes an oxygenator and heat exchanger. The most common configuration of the ECMO system utilizes venous cannulae and exclusively provides oxygenation support for patients in respiratory therapy. This technique is called veno- venous ECMO and was introduced in the 1960s (Kennedy, 1966). As it is primarily used as a rescue therapy for patients who are failing mechanical ventilation (Peek *et al.*, 2009), rather than resuscitation, it will not be discussed further in this work. VA-ECMO is aimed at cardiac or cardio- respiratory support and involves

systemic venous blood draining via a venous cannula with passage through a pump where gas exchange takes place before returning back to the circulation via an arterial cannula (Sidebotham *et al.*, 2010) (figure 1.3).

VA-ECMO is used for circulatory support in refractory haemorrhagic or cardiogenic shock with reversible aetiologies or in pulmonary embolism with circulatory arrest. In cases of refractory cardiac arrest where VA-ECMO is used for resuscitation - this is termed Extracorporeal Cardio-pulmonary Resuscitation (ECPR) (Chen *et al.*, 2008; Arlt *et al.*, 2010; Pasrija *et al.*, 2018). Depending on the aetiology, VA-ECMO can be used as a bridge to definitive care including catheter- based therapy, systemic thrombolysis, or surgical intervention (Lamhaut, Hutin, Puymirat, *et al.*, 2017; Pasrija *et al.*, 2018).

Moreover, in limited clinical use is the combination of VA-ECMO with therapeutic hypothermia in the form of EPR (Safar *et al.*, 2000). This discussion focuses primarily on resuscitation in circulatory collapse and will focus on VA-ECMO while ommiting discussion on VV or other ECMO modalities.

1.4.2 Technique

The circuit used in VA-ECMO consists of arterial and venous cannulae, surface- coated tubing, a membrane oxygenator, and a centrifugal pump (Safar *et al.*, 2000; Arlt *et al.*, 2010). In addition to haemodynamic support the system allows for temperature control and direct delivery of drugs and blood products.

Arterial and venous cannulation is achieved using the Seldinger technique, either via cutdown or percutaneously. With ongoing mechanical CPR, a large, 21- 23 Fr outflow cannula is placed in the femoral vein with the tip inserted into the inferior vena cava. For inflow, a 15- 17 Fr cannula is inserted into the femoral artery with the tip in the common iliac artery or distal aorta (Arlt *et al.*, 2010). Transthoracic Echocardiography can be used to confirm the correct placement of the cannulae (Lamhaut *et al.*, 2013).

Once cannulation has been achieved and primed tubing is connected, the pump flow is initially set at 2.5- 4 L/min and adjusted to maintain target MAP of > 60 mmHg (Lamhaut

et al., 2013). In non-traumatic cardiac arrest, unfractionated heparin is typically administered to avoid coagulation in the membrane oxygenator, however in trauma patients who are bleeding this can be delayed until after damage control surgery (Arlt *et al.*, 2010). A variety of anti- thrombotic surface coatings are applied in contemporary circuits precluding absolute need for systemic anticoagulation (Ontaneda and Annich, 2018).

1.4.3 Experimental Evidence

Several animal studies have demonstrated a survival benefit and improved ROSC rates following ECPR in porcine and canine ventricular fibrillation cardiac arrest models (Kano *et al.*, 1993; Ao *et al.*, 2001; Ichinose *et al.*, 2006; Liakopoulos *et al.*, 2010). An ovine cardiac arrest model showed a significant CPP (mmHg) increase with ECPR (17.84 +/- 2 to 22.94 +/- 3, pre and post ECPR respectively) (Stub *et al.*, 2013). A similar model confirmed the raised CPP (< 15 to 68) and demonstrated > 80 % increase in coronary and cerebral blood flow with use of ECPR (Bělohlávek *et al.*, 2012). Menegazzi used a swine model to demonstrate the possibility of using a portable device to initiate VA-ECMO during active CPR (Menegazzi *et al.*, 2012).

Recent studies of haemorrhagic shock show promising outcomes. A study using a rabbit model with prolonged haemorrhagic shock found that resuscitation using VA-ECMO resulted in higher arterial BP (mmHg) compared to standard fluid resuscitation (60 vs 40). Moreover, animals treated with VA-ECMO had a reduced inflammatory response (Zhao *et al.*, 2014). Another study using a rabbit haemorrhagic shock model comparing VA-ECMO to standard transfusion protocol showed improvements in clot formation time (111 vs 1770 sec), and reduction in acidosis (pH 7.08 vs 6.90), as well as serum lactate (7.8 vs 14.3 mmol/L) (Larsson *et al.*, 2017).

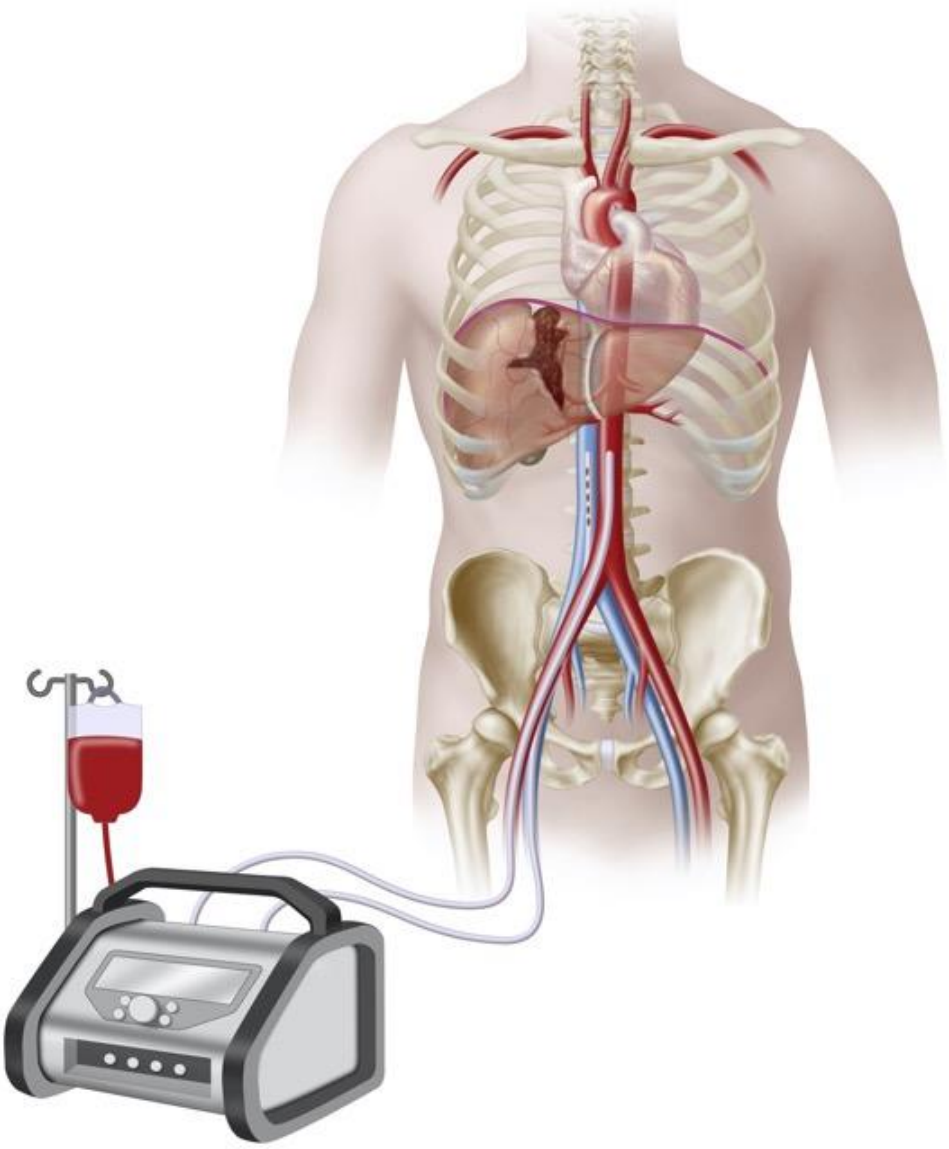

Figure 1.3 Venous arterial extracorporeal membrane oxygenation (VA- ECMO)/ Extracorporeal Cardiopulmonary Resuscitation (ECPR). Both aorta and inferior vena cava (IVC) are cannulated via the femoral vessels allowing venous drainage via the circuit, and recirculation of oxygenated blood back to the aorta. Source: (Madurska, Ross, *et al.*, 2020)

1.4.4 Clinical Evidence

Initial reports of survival benefit of rescue ECPR following failed CPR in patients with in-hospital cardiac arrest were published in the early 2000s (Chen *et al.*, 2003; Massetti *et al.*, 2005). A landmark study from Taiwan used propensity score matching to compare 59 patients who had undergone ECPR to 113 who had conventional CPR. The investigators observed improved survival in the ECPR group at discharge, 30 days, and 1 yr (hazard ratio = 0.51, 0.47 and 0.53 respectively) (Chen *et al.*, 2008). Another study form Korea confirmed these findings along with improved neurological outcomes following ECPR (Shin *et al.*, 2011).

The reported success in ECPR prompted development of a pre- hospital system in Paris in 2013, with introduction of mobile intensive care units. An initial 7 patient case series described modest results with only 1 survivor from a non- traumatic cardiac arrest (Lamhaut *et al.*, 2013). However, a more recent study from the same group including 156 patients with cardiac arrest showed that earlier ECPR and strict patient selection resulted in a significant survival improvement (8 % to 29 %) (Lamhaut, Hutin, Puymirat, *et al.*, 2017). Another French cohort study of 131 patients reported a 10.4 % survival to discharge (Pozzi *et al.*, 2019). Interestingly, a Korean study on 110 patients who received ECPR in the emergency department reported 18.9 % survival to discharge and good neurological outcomes in 81 % of the survivors (Lee *et al.*, 2017).

VA-ECMO has also been used in the management of massive pulmonary embolism with haemodynamic instability, although the current evidence base is limited to case series. The earliest publication from Japan reported on 4 out of 7 patients surviving to hospital discharge (Kawahito *et al.*, 2000). A series from Paris on 17 patients treated with rescue VA-ECMO, 7 of whom were cannulated during CPR, reported a 47 % survival at 90 days (Corsi *et al.*, 2017). Similarly, 53.1 % of 32 patients survived to hospital discharge as reported by a group from the University of Kentucky (George *et al.*, 2018). A recent study from the University of Maryland on 20 patients reported 95% survival at 90 days, and 80% for those who needed CPR before cannulation, moreover VA-ECMO was used to bridge all patients to definitive treatment (thrombolysis or invasive therapy) (Pasrija *et al.*, 2018).

VA-ECMO as an adjunct in circulatory support in trauma is a new concept. The current evidence base consists of a few case series (Arlt *et al.*, 2010; Bonacchi *et al.*, 2013; Gatti *et al.*, 2014). The earliest report by Arlt et al. described 3 patients with exsanguinating shock, who were treated with VA-ECMO without systemic heparinization, 2 of whom survived to discharge (Arlt *et al.*, 2010). Another series from Italy, reported 13 trauma patients who underwent VA-ECMO for haemorrhagic shock with or without cardiac arrest; whilst implementation of ECLS was successful in 9 patients, only 2 survived to discharge, but in 5 brain-dead patients ECLS supported organ perfusion to donation (Bonacchi *et al.*, 2013).

At present there are 24 registered clinical trials assessing outcomes of VA-ECMO in pre-hospital or in hospital cardiac arrest, three of which are now complete with preliminary results awaited (*Search of: ECMO | Cardiac Arrest - List Results - ClinicalTrials.gov*, 2022).

1.4.5 Specific Limitations

VA-ECMO and ECPR are associated with significant complications, the most common of which is bleeding occurring in about 7% patients (Ganslmeier *et al.*, 2011). Bleeding is related to the need for systemic anticoagulation, and although this can be temporarily avoided, provided heparin coated tubing is used in the circuit, it comes with risk of circuit thrombosis. Other cannulation related risks include vascular and cardiac injury, limb ischaemia (3.2 %) and cannula migration (Alam *et al.*, 2008; Swol *et al.*, 2018).

Other complications include thromboembolism, haemolysis, inadequate perfusion, pump or circuit failure, left ventricular distension and pulmonary oedema (Swol *et al.*, 2018). Cannulation during ongoing CPR is significantly challenging and can increase the severity of cannulation related complications, however chest compressions should continue uninterrupted at the best possible quality to maintain central perfusion. Appropriate choice of cannula size should be made considering the size of patient and their vasculature as well as the flow rates needed to obtain. Formal definitions of optimal flow rates for many specific ECMO indications are lacking (Swol *et al.*, 2018).

Optimal patient selection remains a significant issue in ECMO (Lamhaut, Hutin, Puymirat, *et al.*, 2017). Absolute contraindications include unwitnessed cardiac arrest, inadequate CPR for a prolonged period of time, irreversible, severe brain injury and conditions incompatible with life or associated terminal illness such as advanced malignancy (Swol *et al.*, 2018). Improved survival in ECPR has been suggested with aggressive patient selection and timely access to ECPR (Lamhaut, Hutin, Puymirat, *et al.*, 2017), however, decision- making has to be made real- time, emergently, often with limited information about the patient's background and limited prediction of their neurological outcome.

Other important challenges to ECMO based interventions are related to logistics and resources. Access and circuit management requires trained providers. If performed pre-hospital, challenges include suboptimal conditions (poor lighting, limited space, disruptive presence of members of the public) as well as obstacles in moving the patient to the extraction vehicle (stairs, limited space, traffic) as described by the experience from Paris (Lamhaut *et al.*, 2013; Lamhaut, Hutin, Deutsch, *et al.*, 2017). Following out- of- hospital ECMO initiation, the patient requires transport to a unit with appropriate specialist facilities, as further management might involve ongoing ECMO, coronary intervention or complex surgical and critical care. This needs an organized, protocolized system including specialized transport modalities, well- resourced units within optimal distance, and reliable communication channels, all of which need significant cost and effort to develop.

1.5 Emergency Preservation Resuscitation (EPR)

1.5.1 Overview

Emergency preservation of resuscitation is a novel concept which was pioneered in the 1980s by a group led by Dr Peter Safar and Col Ronald Bellamy (Kochanek, 2009). EPR aims to support patients with exsanguinating cardiac arrest by induction of temporary, profound hypothermia by means of injecting cold saline into the aorta to produce "a state of suspended animation", allowing time for damage control intervention and delayed resuscitation (Kochanek *et al.*, 2004; True, Siler and Manning, 2013)

1.5.2 Technique

EPR involves infusing a large volume of cold saline into the aorta resulting in rapid cooling to 10 °C for up to 3 hr (Wu *et al.*, 2008). Access can be achieved via a femoral catheter (Kochanek, 2009), or cardiopulmonary bypass cannula inserted directly into the descending thoracic aorta during a RT (Tisherman *et al.*, 2017) (figure 1.4). An aortic flush is delivered retrograde, and a bypass circuit can be established by cannulating the right atrium. The patient undergoes damage control surgery during the state of hypothermia, before being gradually rewarmed to 34 °C. Mild hypothermia is maintained for a further 12 hr, unless there is significant coagulopathy (Tisherman *et al.*, 2017).

1.5.3 Experimental Evidence

This technique is new with current evidence limited to pre-clinical data only. Kochanek initially studied hypothermia (8 to 34 °C) with delayed resuscitation using cardio-pulmonary bypass on a canine model of prolonged haemorrhagic cardiac arrest (90 min) and consistently demonstrated promising outcomes with preserved neurologic function (Safar *et al.*, 2000; Kochanek *et al.*, 2004). A further study developed the technique by continuing prolonged mild hypothermia following resuscitation (34 °C for 12 or 36 hr) (Wu *et al.*, 2006). And a follow up study demonstrated that supplementing glucose and oxygen during the induction allowed to extend the duration of EPR from 2- 3 hr with preserved neurological function (Wu *et al.*, 2008). Furthermore, studies on swine with polytrauma and haemorrhagic shock, where deep hypothermic bypass (10 °C) was used for 90- 120 min, demonstrated not only preserved neurological function, but also 75- 90 % survival at 6 weeks (Sailhamer *et al.*, 2007; Alam *et al.*, 2008). The first clinical trial on EPR for cardiac arrest in trauma is currently enrolling at Shock Trauma Centre at the University of Maryland in Baltimore (Tisherman *et al.*, 2017).

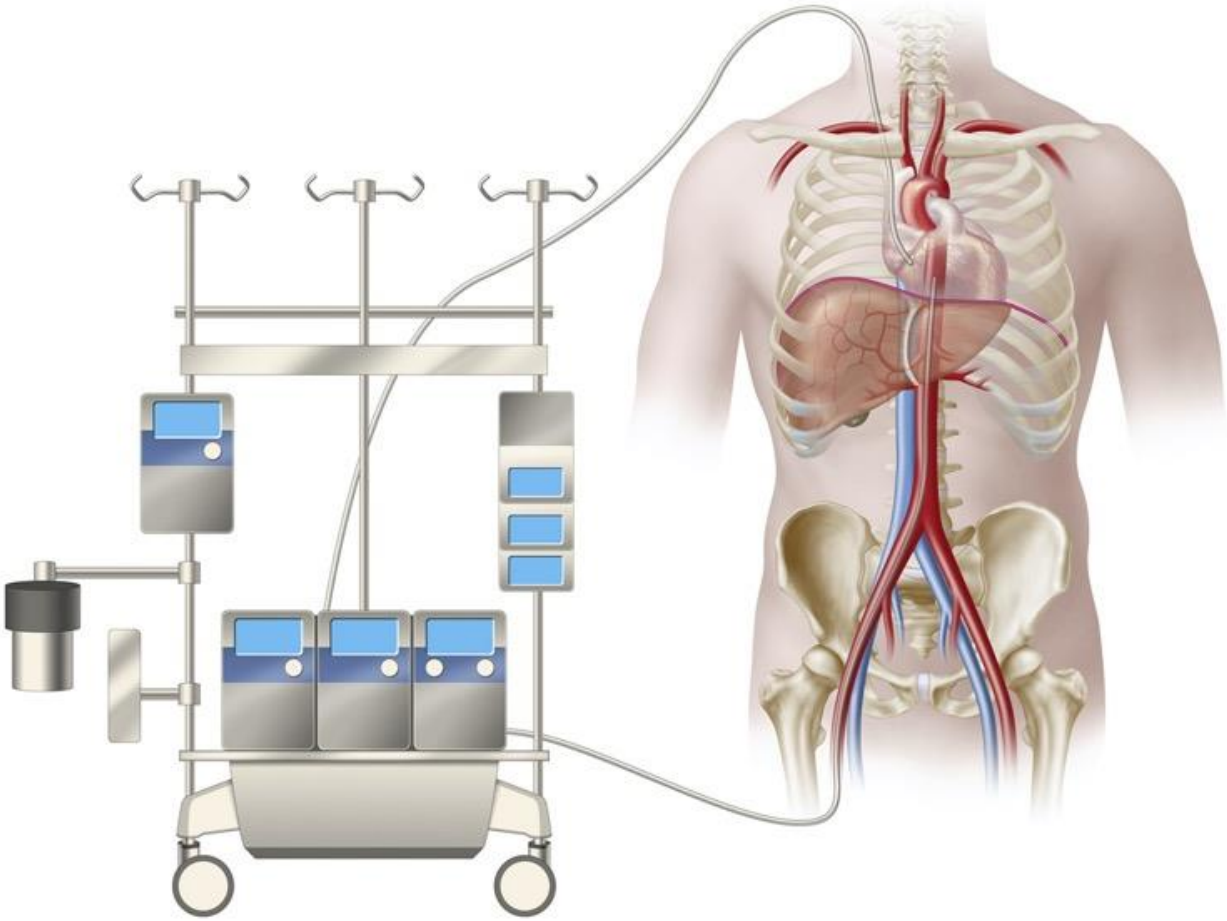

Figure 1.4 Emergency preservation resuscitation (EPR). Aorta is cannulated to allow infusion of cold saline, then followed by venous cannulation and establishing cardiopulmonary bypass once damage control has been achieved. Source: (Madurska, Ross, *et al.*, 2020)

1.5.4 Specific Limitations

A major limitation is that the technique is complex to execute and requires orchestrated co-operation of a team with ready access to instruments and devices as well as large volumes of cold saline. In addition to immediate access to theatre and post- operative critical care facilities for management of the physiological challenges compounded by the injury and hypothermia.

There is a significant amount of evidence suggesting detrimental effects of crystalloid resuscitation. Aggressive crystalloid resuscitation has been shown to cause dilutional coagulopathy which is characterized by reduced platelet count and fibrinogen polymerization (Nienaber *et al.*, 2011). Rapid saline infusion has been associated with hyperchloremic acidosis which can lead to reduced cardiac contractility through negative ionotropic effects (Scheingraber *et al.*, 1999). Hypothermia is known to be associated with poor outcomes in trauma patients (Chen *et al.*, 2003) with coagulopathy being one of the most notorious complications (Eddy, Morris and Cullinane, 2000; Leibner *et al.*, 2020). Moreover, large infusions of crystalloids will result in extracellular fluid shifts contributing to oedema (Frost, 2015). Although animal studies demonstrated promising outcomes in EPR, the detrimental effects of large volume, cold crystalloid infusion will inevitably have to be addressed before successful clinical implementation of this technique.

1.5.5 Targets for application

The tools described in the previous sections are evolving catheter-based techniques designed to support patients' physiology in extremis. They provide circulatory support to patients in severe shock and inflow control to mitigate ongoing haemorrhage while being minimally invasive in controlling non- compressible torso haemorrhage.

With ongoing technological development, a new era of resuscitation is soon to emerge where a dynamic system of catheter- based resuscitation strategies could be used as

dictated by the patient's changing physiology. For example: following early access for monitoring a patient at risk, REBOA can be used when a patient becomes hypotensive, with maintained spontaneous circulation, this can be escalated to SAAP when circulation has been lost but there is cardiac activity. SAAP can be further progressed to VA-ECMO if there is poor ROSC or to EPR when cardiac activity is lost (figure 1.5).

There are current limitations to these techniques being widely implemented. Access site complications, ischaemia reperfusion injury, lack of optimal oxygen carrier needed for SAAP or device specific issues such as lack of FDA approved catheter or complex implementation requiring significant training and resources. There is lack of evidence to define optimal patient population and clinical environment for use of REBOA and related techniques and more expertise is needed to safely implement these.

In the context of uncontrolled bleeding, worsening haemorrhagic shock will eventually lead to cardiac arrest- where the key issues are dismal prognosis and very high mortality despite current strategies in trauma management. Undoubtedly, there is point in the patient's physiology during shock where doe to global malperfusion of the heart, cardiac failure ensues leading to eventual cardiac arrest. This could serve as a target for treatment. However, currently, there is limited knowledge of physiology of exsanguination to elucidate this point, and a potential target for optimal application of the endovascular resuscitation techniques.

The work presented in this thesis aims to elucidate the physiology of exsanguination cardiac arrest with potential to defining optimal target for treatment using endovascular resuscitation techniques. Other aims of the work included in this work is to describe clinical outcomes in an experience trauma centre with use of REBOA and explore balloon properties with view for technological improvement of current devices.

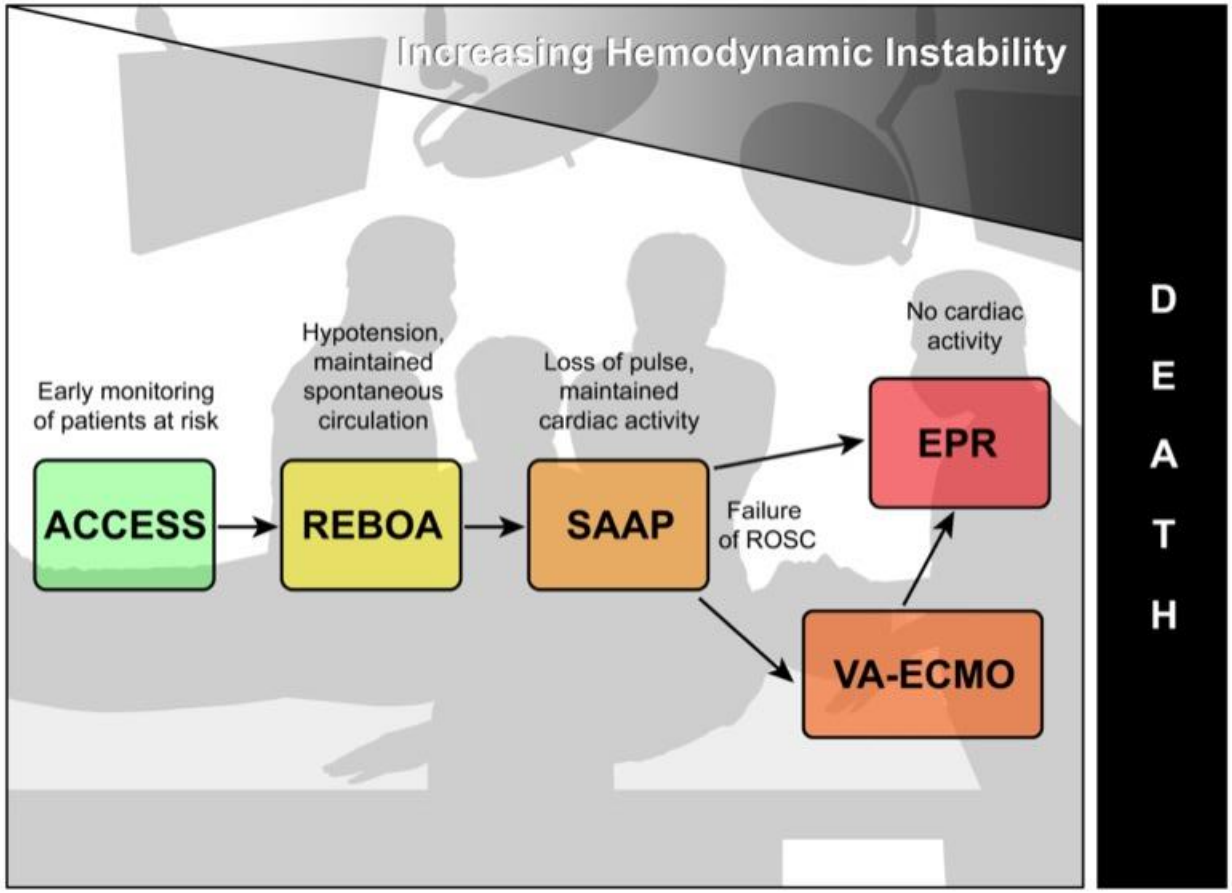

Figure 1.5 Endovascular resuscitation algorithm which proposes the integration of endovascular techniques into resuscitation, where with worsening haemodynamic instability, early arterial access can be upgraded to REBOA: resuscitative endovascular balloon occlusion of the aorta. After loss of peripheral pulse (but with maintained cardiac activity) this can be further upgraded to SAAP: selective aortic arch perfusion, and with failure of return of spontaneous circulation (ROSC), SAAP can be further upgraded to extracorporeal life support (ECLS), and extended preservation resuscitation (EPR). Source**:** (Madurska, Ross, *et al.*, 2020)

Chapter 2. Methods

2.1 Ethical Considerations

2.1.1 Clinical Studies

Full approval of the study protocol was obtained from the University of Maryland, Baltimore Institutional Review Board (IRB), prior to commencement of each clinical study described in chapter 3. Approval documents can be found in appendix 1.

2.1.2 Ex- Vivo study

The study of balloon compliance described in chapter 4 uses post-mortem porcine tissues. Due to the post- mortem design of the study Institutional Animal Care and Use Committee (IACUC) approval was not required.

2.1.3 Experimental Studies

The animal studies were conducted following approval by the by the IACUC at the University of Maryland Medical School. Approval documents can be found in appendix 1.

2.2 Institutional setting

All clinical studies were performed at The R Adams Cowley Shock Trauma Centre, which serves as the primary adult resource centre for the state of Maryland, USA, holding a capability analogous to an enhanced level 1 trauma centre. The institution admits between 6000 and 7000 trauma patients annually.

2.3 Animal Housing/ Husbandry

Animals utilized in the experimental studies were sexually mature male Yorkshire swine (Sus Scrofa) weighing between 60- 90 kg. These were obtained from approved research animal vendors following institutional approval. Prior to experimentation, animals were housed in communal pens, under veterinary supervision, with free access to food and water for at least 72 hr to allow acclimatization. Animals were fasted for 12 hr prior enrolment in the study. Animals were housed singly in cages placed next to one another to allow interaction. The light cycle was 12 hr on and 12 hr off. The swine were fed a

standard Tekland 7037 pellet diet (Envigo, Indianapolis IN). The experiments started at approximately 7:00 am and lasted for up to about 5 hr.

2.4 General Anaesthesia

2.4.1 Sedation and Induction of general anaesthesia

Animals were sedated with Telazol (4.5 mg/kg)/ Xylazine (2 mg/kg) via an intramuscular injection using a 20 gauge (G) or smaller bore needle placed into the gluteal region or caudal to the ear. General anaesthesia was induced with 2- 4 % Isoflurane in 100 % O_2 inhaled via a veterinary facemask until full relation of the jaw tone.

2.4.2 Intubation

Orotracheal intubation was performed following spraying 1 mL of Lidocaine (2 %) in the posterior pharynx for topical anaesthesia to the vocal folds. Whilst holding the jaws open and extending the head, the epiglottis was visualised, and the tip of the laryngoscope was passed into the oropharyngeal cavity to displace the epiglottis from the soft palate. The endotracheal tube was advanced 10-14 cm into the trachea whilst rotating it to avoid entrapment in the ventral laryngeal sacculae distal to the vocal folds. Once the correct placement of the endotracheal tube was confirmed with chest auscultation, the tube was secured to the animal's snout using tape.

2.4.3 Maintenance of General Anaesthesia

Following intubation, general anaesthesia was maintained with 2% isoflurane in 100% Oxygen using volume control mechanical ventilation. Mechanical ventilation consisted of respiratory rate (RR) of 10- 15 breaths/min and tidal volumes of 7-10 mL/kg (Fabius GS ventilator, Dräger, Lübeck, Germany).

2.5 Animal Instrumentation and surgical procedures

2.5.1 Positioning

The animals were placed supine on a warming blanket set at 39 °C to prevent hypothermia. The front hooves were retracted cephalad, and the rear hooves were retracted caudally with a slight flexion of the hip joint. The animal was secured to the table with straps attached to front and rear hooves (figure 2.1).

2.5.2 Vital signs transducer placement

A pulse oximetry probe (Cardiocap 5, Datex-Ohmeda, Madison, WI, USA) was attached to the animal's earlobe and connected to the anaesthetic machine. A research grade large animal rectal transducer was inserted about 5 cm into the rectum and connected to the digital integrated data acquisition system via the temperature pod (AD Instruments, Sydney, Australia). 5 lead ECG adhesive electrodes (AD Instruments, Sydney, Australia) were placed on the animals': the right forelimb, left forelimb, right hindlimb and left hindlimb as well as a precordial lead placed on the xiphoid. These were connected to a transducer, and data acquisition system via a research grade biological amplifier (AD Instruments, Sydney, Australia). End- tidal CO_2 ($ETCO_{2)}$. A research grade in- line filter and a drying tube (AD Instruments, Sydney, Australia) were connected to the sidearm device of the endotracheal tube to collect respiratory gasses, the distal end of the drying tube was connected to a gas analyser and to the integrated data acquisition system.

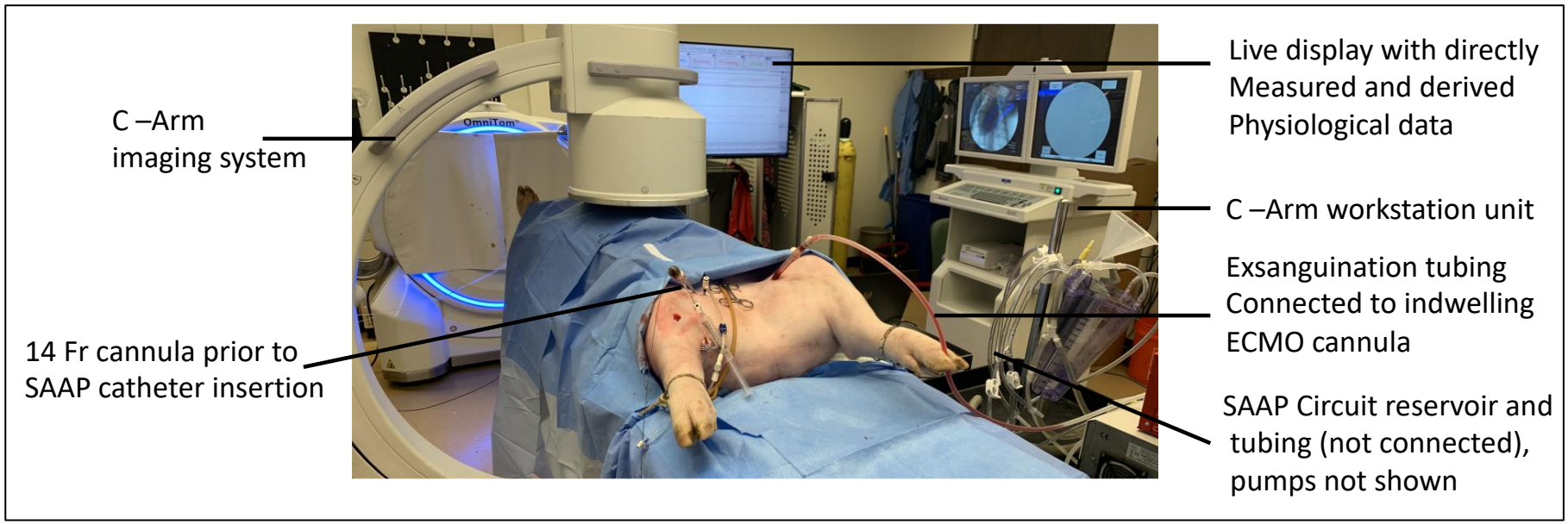

Figure 2.1 Animal positioning and laboratory set up during the experimentation.

2.5.3 Vascular access

2.5.3.1 Cervical Vessels

The neck vasculature was accessed percutaneously using the Seldinger technique for the placement of haemodynamic measurement instruments as described below. All percutaneous access was achieved with ultrasound guidance using a handheld device with a vascular transducer (Phillips Lumify, Amsterdam, Netherlands). The external jugular vein was visualized with ultrasound in the jugular furrow about 2- 3 cm deep to the skin. The carotid artery was identified about 3 cm deep to the skin and just lateral to the trachea. The internal jugular vein was visualized adjacent to the carotid artery. Compression of the veins with the ultrasound probe allowed to differentiate these structures from arteries. All cervical vessels were accessed percutaneously using a 19 G needle placed under ultrasound vision at 45 degrees to the skin followed by introduction of an 0.018- inch platinum - tipped microwire through the needle before upsizing the wire using a dilator, to a standard 0.035- inch guidewire (Cook Medical, Bloomington, Indiana, USA). Finally, a 10 cm long, 7 Fr introducer sheath (Terumo Pinnacle, Tokyo, Japan) was threaded over the guidewire, and secured to the skin with a silk suture before removal of the guidewire. All sheaths were flushed with sterile NaCl via a sidearm to confirm intra-vascular placement and prevent thrombosis. In the event of failed percutaneous access, internal jugular veins and carotid arteries were accessed using an open cutdown technique where a 10 cm longitudinal incision was made in the midline of the neck, a self-retaining retractor was placed, and a dissection was made in the plane between the strap and the sternocleidomastoid muscles to facilitate exposure of the jugular vein and the carotid artery in the carotid sheath.

2.5.3.2 Femoral Vessels

The femoral artery and vein were identified in the femoral canal using ultrasound, with the femoral vein lying posteromedially to the artery. Femoral vessels were accessed percutaneously using the same technique as described above for the cervical vessels. If percutaneous access failed, direct cutdown was used to access the femoral vessels. A longitudinal, 10 cm incision was made in the skin folds between the gracilis and sartorius

muscles, and the subcutaneous tissues were dissected. A self- retaining retractor was placed in the wound and the femoral artery and adjacent vein was isolated by blunt dissection.

2.5.4 Laparotomy

Using diathermy, a 20 cm midline laparotomy starting a point 5 cm caudal to the xiphisternum was made. Splenectomy was performed to prevent autotransfusion in response to exsanguination (Chien *et al.*, 1973; Horton *et al.*, 1984; Vnuk *et al.*, 2010). The spleen was gently delivered into the wound. The left gastroepiploic and splenic arteries and veins were identified, clamped, suture- ligated (1'0 silk) and transected. The deeper lying short gastric vessels (arteries and veins) were gently suture- ligated *in situ* and transected. Careful inspection of the ligated vessels was made to ensure haemostasis and any bleeding vessels were suture ligated. The spleen was removed and weighed. A cystostomy was performed to allow urine collection and measurement. A purse- string suture (1'0 silk) was placed in the anterior wall of the bladder and a cystostomy was performed in the centre of the suture using diathermy. A 12 Fr urinary catheter tip was placed in the bladder via the cystostomy, the catheter balloon was inflated with 10 mL of NaCl and the purse- string was tightened around the catheter to avoid urine leaking around it. The urinary catheter was connected to a standard urometer- collection bag. The abdomen was closed using towel clips placed around the catheter.

2.5.5 Thoracotomy

In order to facilitate access to the heart and mediastinal contents, an extended, left antero-lateral thoracotomy was performed. A 10 cm skin incision along the line from the dorso-caudal aspect of the scapula towards the first rib was made. Subcutaneous tissues were dissected to expose 4- 6^{th} ribs. 5^{th} intercostal space was dissected, taking care not to damage the underlying lung. The internal mammary vessels were identified running along the edge of the sternum, before being ligated and divided. The sternum was divided horizontally using a bone cutter to extend the thoracotomy, and a self-retaining rib retractor was used to expose the mediastinum. The left lung was retracted ventrally using moist laparotomy sponges to expose the heart. The pericardial sac was opened by

making a 1 cm incision at the apex using scissors, and extending it cranially to expose the underlying myocardium, coronary vessels, and proximal thoracic aorta (figure 2.2).

2.5.6 Instrumentation

Following animal preparation as described above, percutaneous instrumentation was performed for data collection and exsanguination for each of two animal studies described in Chapter 5.

2.5.6.1 Study defining the Physiology of Exsanguination cardiac arrest

Following appropriate calibration according to the manufacturer instructions the cardiac pressure volume (PV) loop catheter and the solid- state pressure catheters were positioned in the following structures via indwelling 7 Fr intravascular sheaths. Under fluoroscopic guidance, a PV loop catheter (Transonic Corporation, Ithaca, NY) was introduced into the left ventricle (LV), and solid-state pressure catheters (Transonic Corporation, Ithaca, NY) were positioned in the right ventricle (RV), right atrium (RA), and aortic arch via the neck vessels (figure 2.3). The position of the solid- state pressure catheters was confirmed with fluoroscopy and by visualizing the shapes of the pressure waveforms as displayed on the computer using a data collection software (LabChart, AD Instruments, Sydney, Australia). A 14 Fr sheath (Gore DrySeal, Newark, DE, USA) was percutaneously introduced into the right femoral artery to permit controlled exsanguination.

Following thoracotomy as described in section 2.4.5, the left coronary artery was identified, and a 1 cm segment of the main trunk was dissected circumferentially to allow placement of a perivascular flow probe (figure 2.3 B) for continuous blood flow measurement. A 2 - 4 mm perivascular flow probe (PS series, Transonic, Ithaca, NY, USA) was placed around the dissected segment of the left coronary artery, the flow probe window was filled with ultrasonic gel as per manufacturer's instructions for optimization of signal conduction. A miniature, suturable laser Doppler surface probe (Transonic, Ithaca, NY, USA) was placed on the epicardium of the apex and secured to the

epicardium with 3 x 3’0 Prolene sutures. This was used for measurement of the regional microvascular blood flow in the epicardium (figure 2.3 B).

2.5.6.2 Study of Myocardial Tolerance to Exsanguination and Retrieval Using Whole Blood-Selective Aortic Arch Perfusion

Instrumentation for this study is demonstrated in figure 2.4. The right carotid artery and external jugular vein were cannulated with a 10 cm 7 Fr sheath (Terumo, Tokyo, Japan) each. Solid-state pressure catheters (Transonic Corporation, Ithaca, NY) were positioned in the right atrium, and aortic arch via the indwelling 7 Fr vascular access sheaths. Correct placement of the solid-state catheters was confirmed with fluoroscopy and pressure waveform visualization. The left external jugular vein was cannulated with a double lumen central venous catheter (Arrow, Teleflex, Wayne, PE, USA) for drug delivery. The right femoral vein was cannulated with a 9 Fr central venous catheter (Cordis, Miami, FL, USA) this was to allow additional central venous access for fluid resuscitation. A 14 Fr sheath was placed in the left femoral artery (DrySeal, Gore Medical, Newark, DE, USA) to accommodate the SAAP catheter.) A 15 cm long, 15 Fr ECMO cannula (Maquet, Rastatt, Germany) was placed in the right femoral artery to allow controlled exsanguination. Prior to SAAP resuscitation, a SAAP catheter was advanced via the femoral artery 14 Fr sheath (DrySeal, Gore Medical, Newark, DE, USA) with the tip of the catheter inserted into the proximal descending aorta. Position of the catheter was confirmed with fluoroscopy.

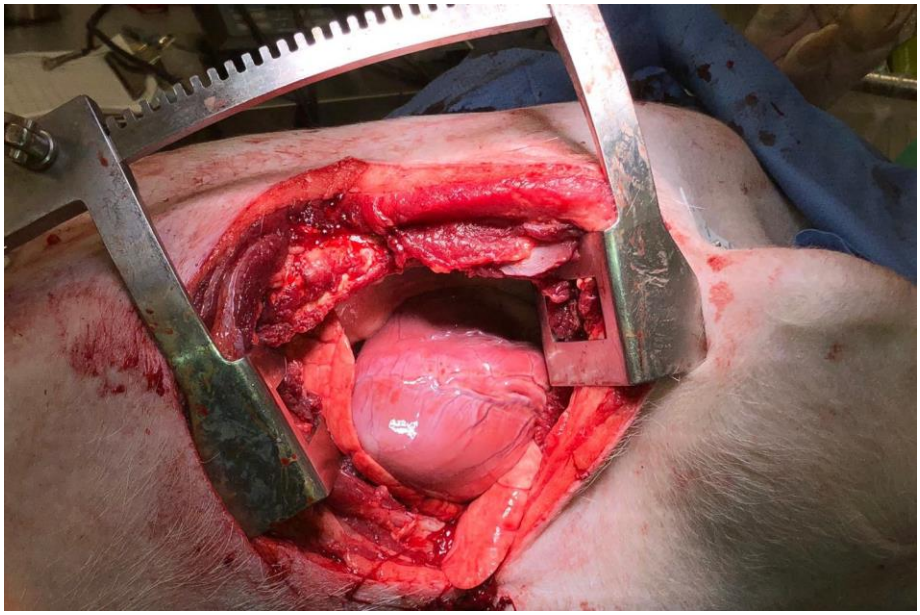

Figure 2.2 Antero- lateral thoracotomy with a self-retaining rib retractor exposing the anterior heart with the pericardial sac opened.

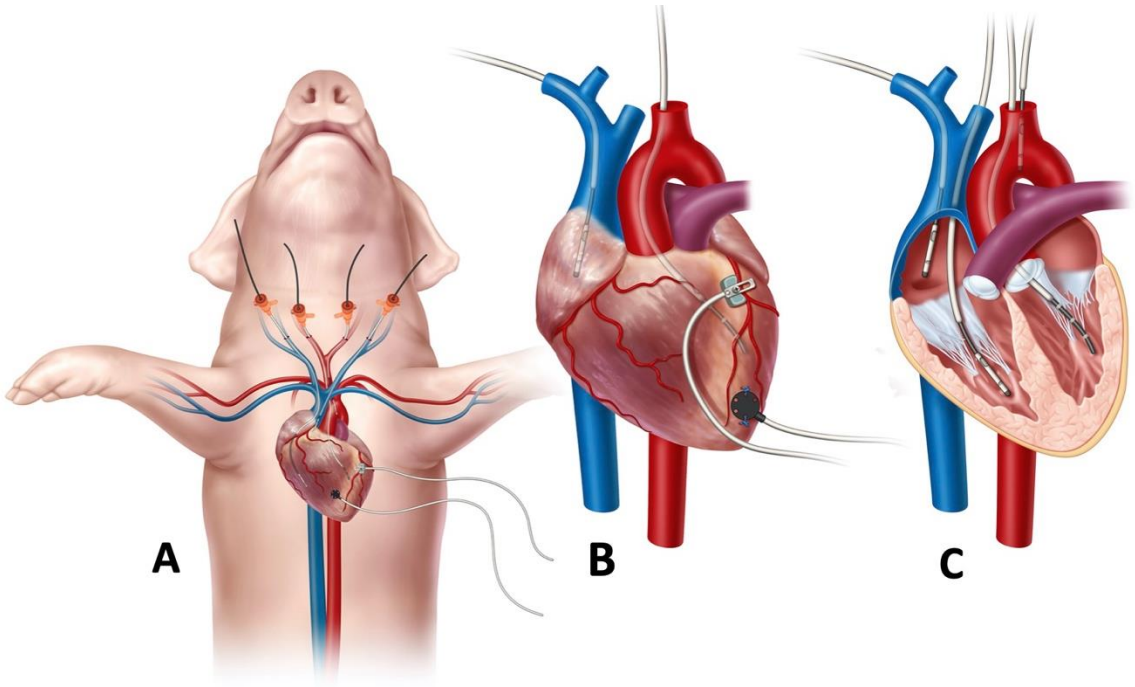

Figure 2.3 Schematic diagram representing vascular access and data collection transducers for collecting hemodynamic data in the study to define the physiology of exsanguination cardiac arrest. A. Vascular Access. B. Left anterior descending coronary artery flow probe and laser Doppler probe placement. C. Position of the PV loop and pressure catheters in the cardiac chambers and aortic root.

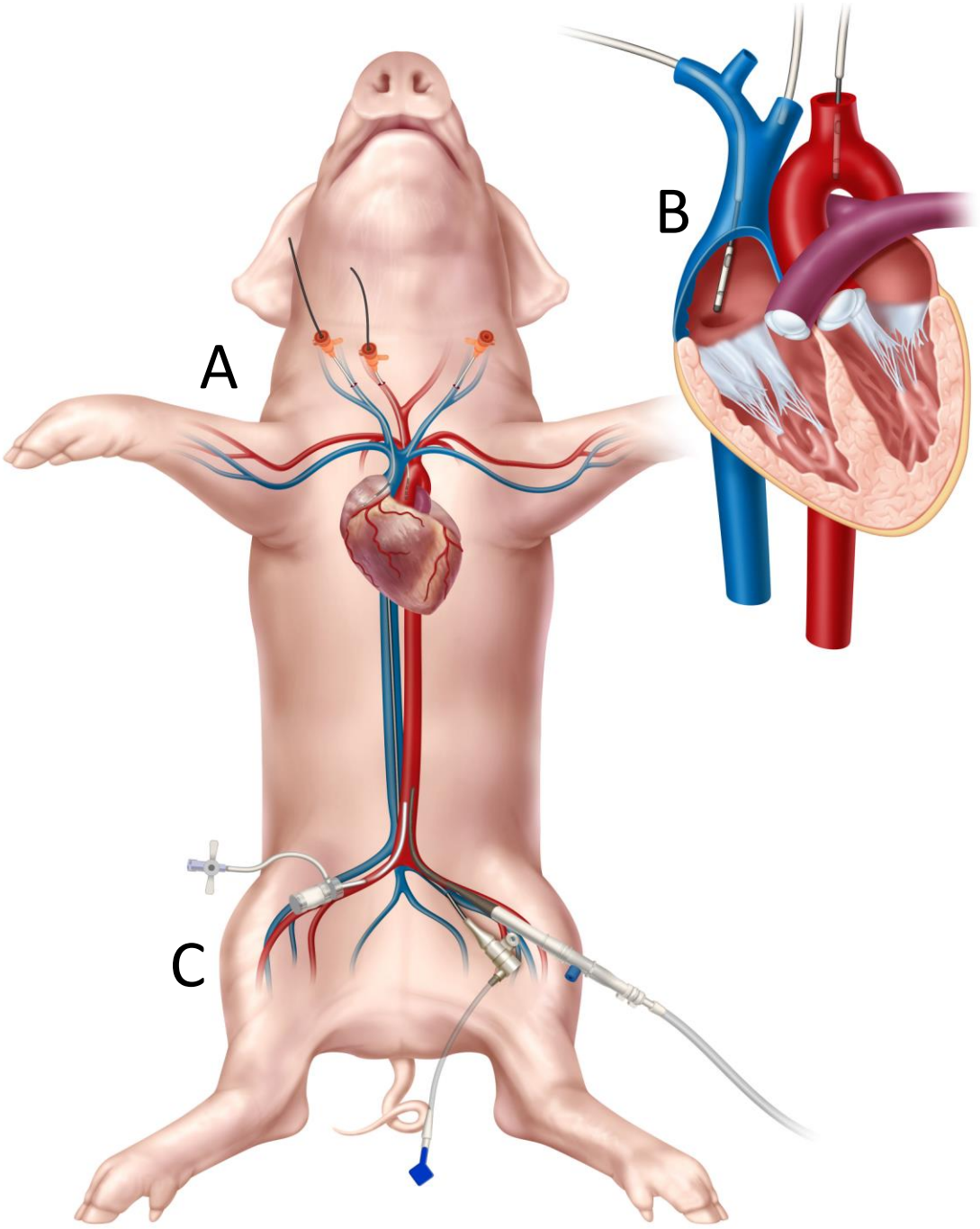

Figure 2.4 Schematic diagram of the animal instrumentation in the study of Myocardial Tolerance to Exsanguination and Retrieval Using Whole Blood- Selective Aortic Arch Perfusion. A. Instrumentation of cervical vessels with indwelling sheaths in both internal jugular veins and one of the carotid arteries. B. Indwelling pressure catheters in the right atrium and aortic root. Central venous catheter in the internal jugular vein C. Instrumentation of the femoral vessels with the 14 Fr Catheter in the right femoral artery. ECMO cannula in the left femoral artery. Central venous catheter in the left femoral vein.

2.6 Exsanguination

Following administration of 25,000 IU (International Units) of Heparin intravenously (IV) to prevent coagulation of the exsanguination tubing, a controlled, logarithmic exsanguination was commenced until cardiac arrest as defined per each study protocol. The exsanguination was performed using a peristaltic pump via tubing connected to an access cannula placed in the femoral artery. The exsanguination rate was calculated assuming the total blood volume for adult swine is 66 mL/kg (Bush *et al.*, 1955; Swindle and Smith, 2016). The logarithmic flow rates were adjusted to the animal weight with decreasing flow at specific time increments and were calculated to achieve 50 % blood loss at a prespecified time. The time increments and time to achieve 50 % blood loss was set according to each study protocol and the logarithmic exsanguination rates were calculated using a formula:

$$f_i = \frac{f_{i-1}}{\left(\left[\frac{\log\left(\frac{(L+x)-t_{i-1}}{x}\right)}{\log\left(\frac{(L+x)-t_i}{x}\right)}\right]\beta + b\left(\frac{5x-t_i}{t_i-3}\right)\right)}$$

$$x = length\ of\ time\ in\ each\ increment$$

$$L = Estimated\ time\ to\ 50\%\ blood\ volume\ loss$$

$$t_i = current\ time\ increment$$

$$f_i = \ flow\ rate\ solved\ for\ at\ time\ increment\ i$$

$$i-1 = previous\ step\ function\ increment$$

Equation 2.1 Logarithmic exsanguination rate calculation.

2.6.1 Study Defining the Physiology of Exsanguination cardiac arrest

The logarithmic flow rate increments were calculated to reach a target of 50 % blood loss by 45 mins using 5 min increments. The exsanguination continued until asystole as defined by the lack of discernible electrical activity on the ECG monitor (*Asystole and its treatment | ACLS-Algorithms.com*, 2022). The blood was shed using a pre-programmable peristaltic pump (Masterflex, Gelsenkirchen, Germany), which was connected to the femoral access sheath.

2.6.2 Study of Myocardial Tolerance to Exsanguination and Retrieval Using Whole Blood-Selective Aortic Arch Perfusion

The logarithmic flow rate increments were calculated to reach a target of 50 % blood loss by 15 mins using 1 min flow increments. The blood was shed using a pre- programmable peristaltic pump (New Era Pump Systems, Farmingdale, NY, USA), which was connected to the 15 Fr ECMO cannula in the femoral sheath. The shed blood was stored in a reservoir connected to the SAAP circuit (figure 2.6). The exsanguination continued until ECA as defined by a sustained MAP < 20 mmHg, a critical threshold previously defined by the Study Defining the Physiology of ECA described in section 4.2.

2.7 SAAP circuit

2.7.1 SAAP Catheter

The SAAP catheter used (figure 2.5) was a prototype model (described in section 1.3.2) provided by Dr James E Manning – the co-founder of Resusitech Inc (Menlo Park, CA, USA), which holds the patent for the device. This catheter has been previously used in SAAP translational research (Barnard *et al.*, 2017; Hoops *et al.*, 2019). The catheter used is not commercially available and is not FDA approved but is being applied as an investigative tool for rescuing animals in severe haemorrhagic shock.

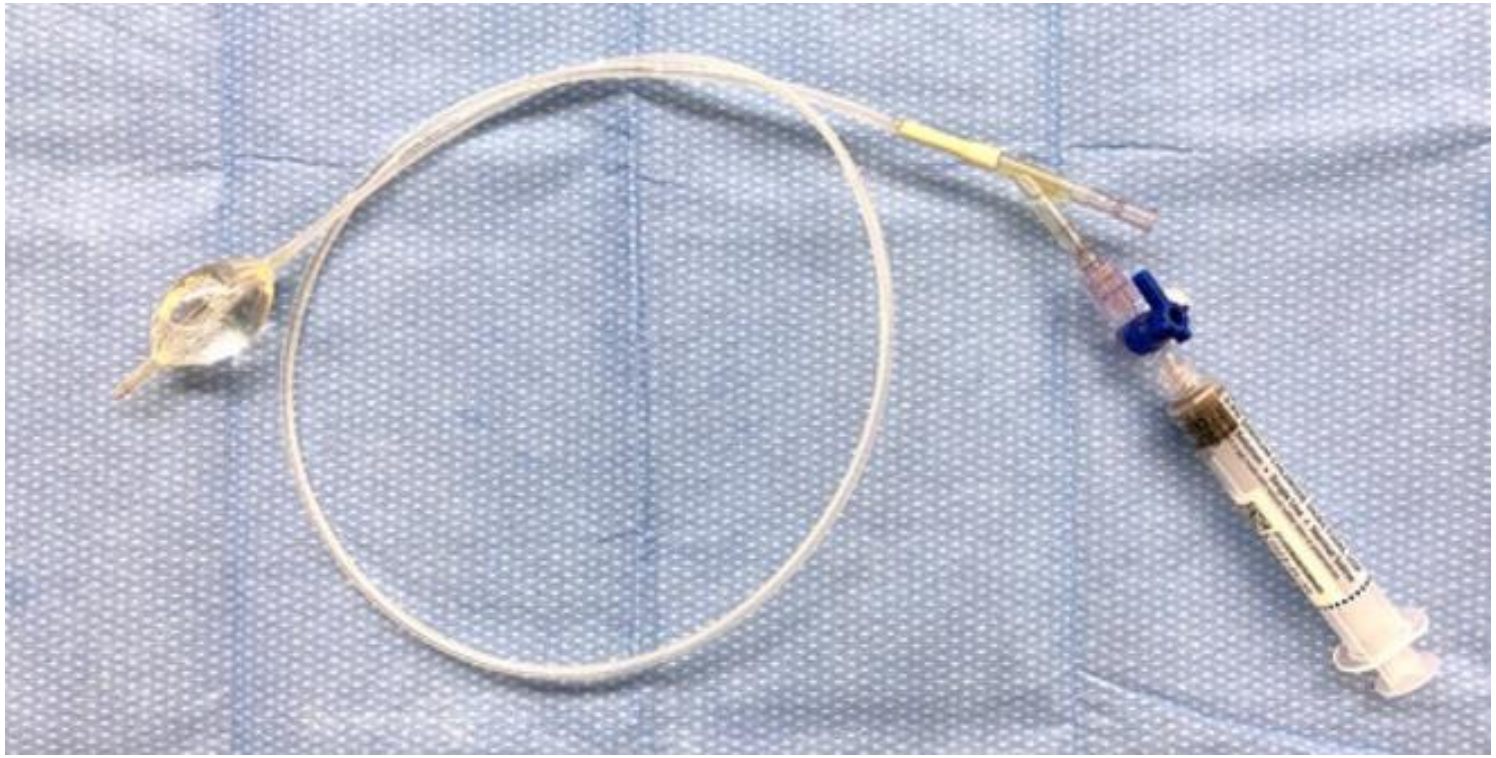

Figure 2.5 SAAP catheter, which has an internal diameter of 10 Fr, and 13 Fr external diameter, contains a compliant balloon near the tip which can hold up to 50 mL of volume. The catheter has two ports: a balloon port and an arterial lumen port, both of which can accommodate standard IV tubing connectors.

2.7.2 Perfusion Circuit

The SAAP perfusion circuit was custom built with the capabilities to store the previously shed blood for perfusion, adequately oxygenate the blood, and efficiently deliver the blood at a specific flow rate through the SAAP catheter to provide resuscitation with limited risk of thrombosis (Madurska, Abdou, *et al.*, 2020). The key elements include a blood reservoir, tubing, oxygenator, a centrifugal pump, and a peristaltic pump (figure 2.6). The materials used for assembly of the perfusion circuit are presented in appendix B. Prior to SAAP resuscitation the circuit was primed with 500 mL of 0.9 % NaCl and heparinised (5000 IU of unfractionated heparin) to prevent thrombosis. The perfusion system was tested prior to the study, during the model development stage and was demonstrated to deliver appropriate perfusion rates in an animal model (Madurska, Abdou, *et al.*, 2020).

2.8 Resuscitation

2.8.1 Selective Aortic Arch (SAAP) Perfusion

Resuscitation with SAAP was performed using a standard technique validated by previous studies by Manning and colleagues (Manning, Batson, Payne, *et al.*, 1997; Manning *et al.*, 2016). An initial 60 mL bolus of 0.9 % NaCl mixed with 100 mcg of Adrenaline and 20 mL iodinated contrast was injected via the SAAP catheter and observed using fluoroscopy to confirm closure of the AV, to prevent left ventricular distension (figure 2.7). Following valve closure, the SAAP perfusion was commenced using oxygenated shed blood at a rate of 10 mL/kg for 1 min. The aortic pressure catheter trace was observed for pulsatility (figure 29 B), indicating ROSC or otherwise. In the absence of ROSC, further SAAP boluses could be delivered up to a maximum of three. If ROSC was successful, the SAAP circuit was used to deliver blood to the venous side of the circulation via a femoral venous cannula. Specific steps for SAAP delivery using the above animal model have been described by Madurska et al. (Madurska, Abdou, *et al.*, 2020). A diagram of the SAAP circuit with specific focus on the swine set up is presented in figure 2.8.

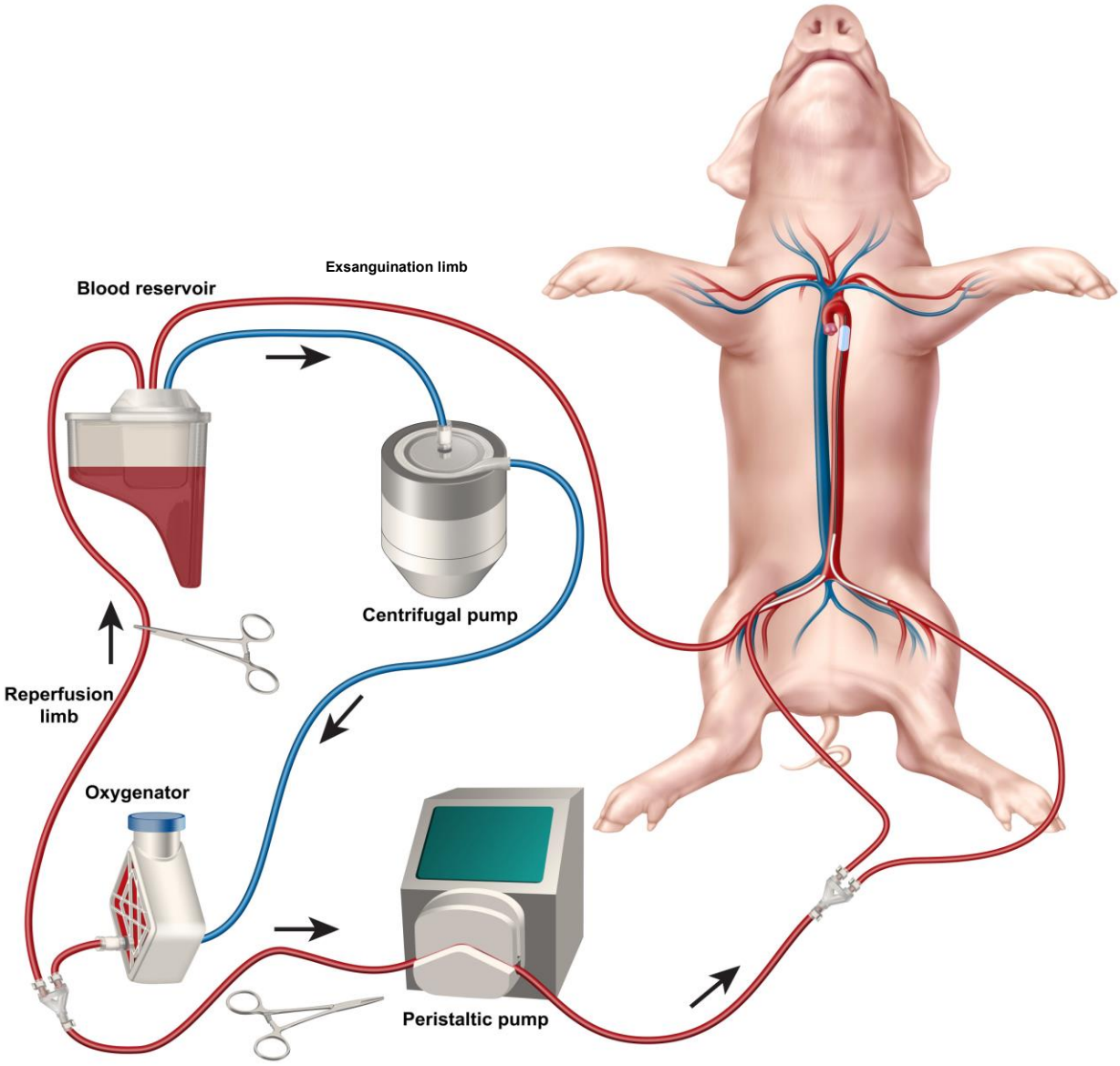

Figure 2.6 Schematic diagram of the SAAP circuit demonstrating the set-up of the circuit elements including blood reservoir, oxygenator, centrifugal and peristaltic pumps as well as the reperfusion, main perfusion, SAAP, peripheral and exsanguination limbs. Source: (Madurska, Abdou, *et al.*, 2020)

2.8.2 Defibrillation

In the event of a shockable arrythmia, external defibrillation was delivered with up to 3 shocks at 150, 200, 200 Joules respectively using a biphasic defibrillator (Lifepak, Physio-Control, Redmond, WA, USA). During the defibrillation the electrical transducers used to collect data were temporarily disconnected to protect the electrical circuits.

2.9 Critical Care Period

Following ROSC, critical care treatment was delivered. Remaining shed blood in the SAAP circuit reservoir and 0.9 % NaCl were infused to correct hypovolemia and maintain baseline SBP while monitoring right atrial pressure. Blood and 0.9 % NaCl were infused rapidly via the SAAP circuit connected to the indwelling femoral vein catheter (figure 2.6). In the event of hypotension unresponsive to IV fluid, pharmaceutical cardiovascular support was commenced, initially using Noradrenaline (up to 0.4 mcg/kg), then Dobutamine (up to 20 mcg/kg). These drugs were infused into the external jugular vein via a double lumen central venous catheter using a digital syringe pump (DigiPump, Digicare Animal Health, Daytona Beach, FL).

Normal PO_2 was maintained by titrating the FIO_2 based on the arterial blood gas (ABG) sample analysis results. Ventilation parameters were maintained as per algorithms depicted in appendix C. Hypocalcaemia ($iCa^{2+} < 0.9$ g/dL) was treated with 1 g of 10 % $CaCl_2$ IV. Hypokalaemia ($K^+ < 3.5$ mEq/L) was managed with IV infusion of 10 mmol/L of KCl. Hyperkalaemia ($K^+ > 5.5$ mEq/L) was treated with a 50 mL solution of 50 % Dextrose and 10 IU of Insulin. Hypoglycaemia (serum glucose < 3 mmol/L) was treated by 50 mL of 50 % Dextrose IV. Significant acidosis (pH < 7.10) was treated with 50 mL of 8.5% Sodium Bicarbonate solution IV. Hypomagnesemia ($Mg^{2+} < 1.46$ mg/dl) was treated with 1 gram of Magnesium Sulphate ($MgSO_4$) IV. Detailed drug delivery instructions for the critical care protocol are provided in appendix D.

2.10 Euthanasia

At the end of the experiment animals were using IV K^+ (> 2 mmol/kg). Animal was pronounced dead when ECG indicated asystole for > 2 min in addition to absence of corneal and pain reflexes.

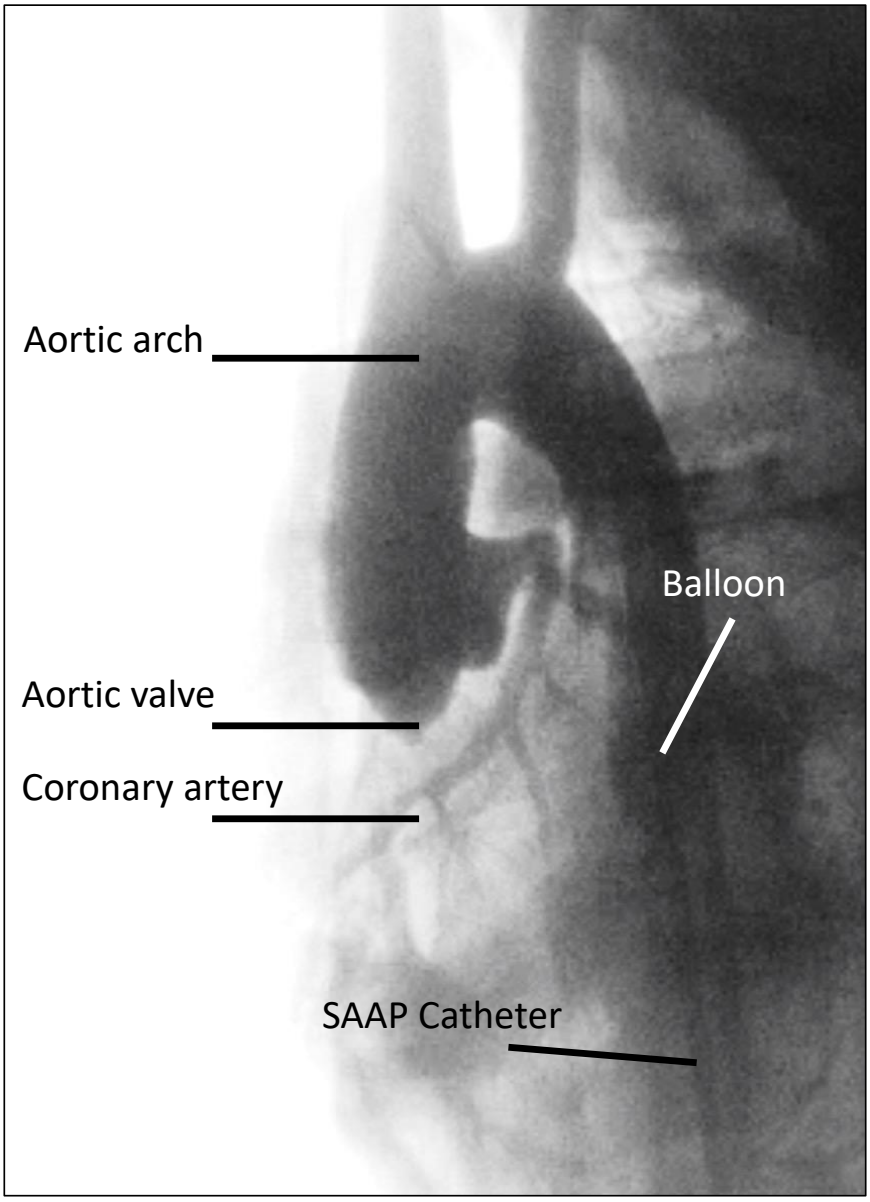

Figure 2.7 Fluoroscopy image during SAAP demonstrating contrast volume in the aortic arch and coronary artery with the aortic valve (AV) closed.

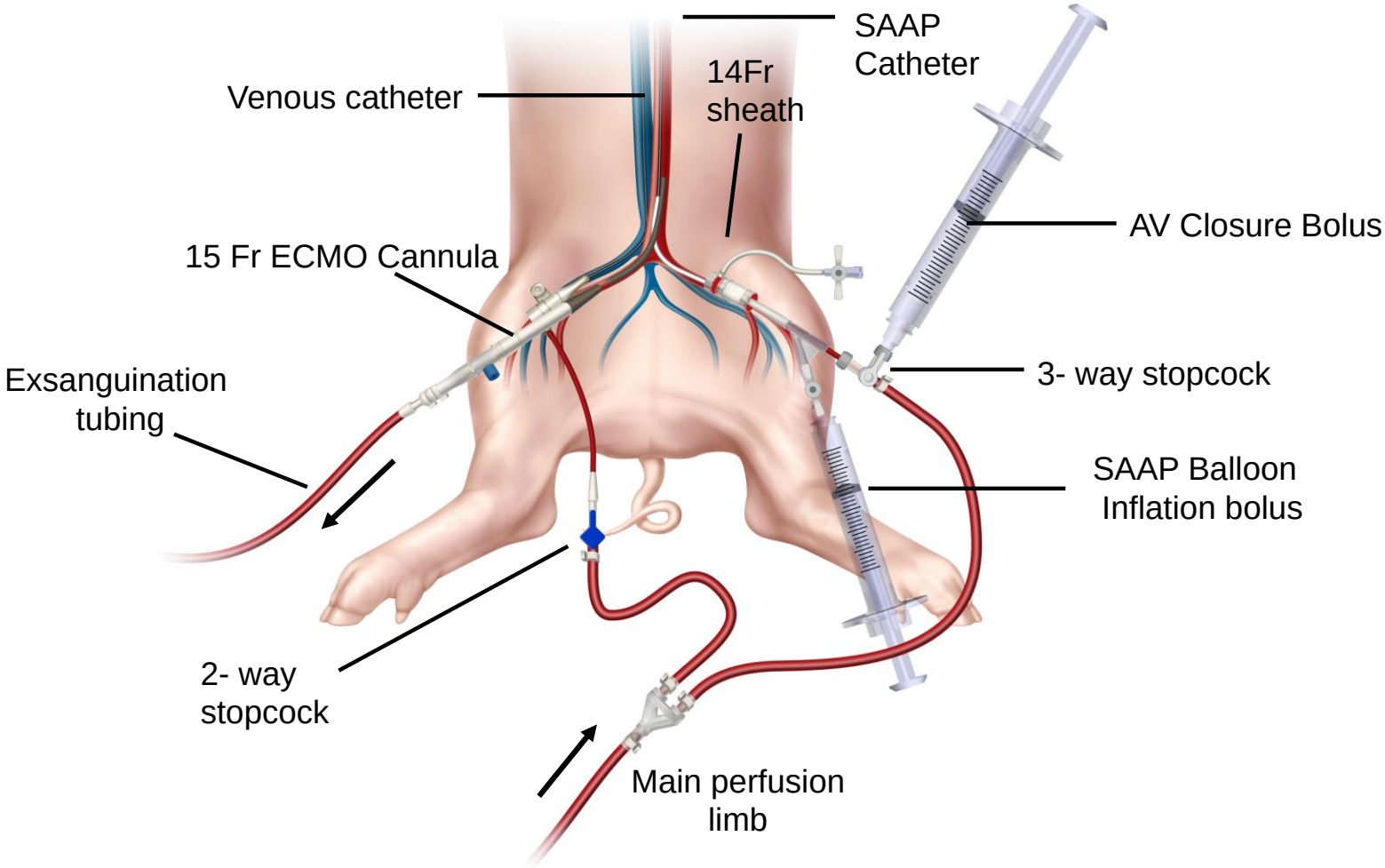

Figure 2.8 Diagram demonstrating the SAAP circuit elements with focus on swine set-up: SAAP perfusion limb and peripheral perfusion limbs with percutaneous access and SAAP catheter set up in a swine model. Aortic Valve (AV) Closure bolus and SAAP Balloon inflation bolus syringes are demonstrated to be connected to the corresponding ports in the SAAP catheter. A 15 Fr ECMO cannula placed in the right femoral artery is connected to exsanguination tubing. Source: (Madurska, Abdou, *et al.*, 2020)

2.11 Data collection

2.11.1 Clinical studies

Data used in the clinical studies were collected from the patients' electronic medical records (EMR) and patient archive and communication system (PACS) at R Adams Cowley Shock Trauma Centre. The patients were identified using name, date of birth, medical record number and hospital admission number. These identifiers allowed linkage to the EMR, PACS systems and the trauma registry. Data collected included: demographic information, Glasgow coma scale (GCS), injury severity score (ISS), body region abbreviated injury scale (AIS), mechanism of injury (blunt or penetrating), admission vital signs, admission blood results including Hb, haematocrit (Hct), INR, pH, and Base Excess. Admission systolic BP measurements were obtained from a standard BP cuff or continuous data signs monitoring derived from the arterial line waveform. Data on volumes of estimated surgical blood loss and blood product transfusion as well as use of vasopressors were also collected.

2.11.1.1 Trauma Registry

The trauma registry accessed has been developed for purposes of quality improvement and data monitoring and is a requirement for Level 1 trauma verification by the American College of Surgeons. It is a prospectively collected database that captures hundreds of variables ranging from demographic information to clinical presentation and outcomes. The findings are merged with databases from other trauma centres and used for national trauma outcomes reporting (Stewart, Rotondo and Nathens, 2016). The patients' demographic details, admission physiology, and injury, as well as outcome data, are included in this registry.

2.11.2 Animal studies

During animal studies, recorded animal data included: total weight, exsanguinated blood volume and splenic weight. Physiologic data collected are presented in table 2.1. ABG samples were obtained from the carotid artery and analysed using an iSTAT analyser

(Abbott, Chicago, IL, USA). Venous blood samples were taken at: baseline, beginning of the critical care period and end of study. Haematological and biochemical variables included: pH, pCO_2, pO_2, FO2Hb %, K^+, Na^-, Ca^{2+}, Glucose, Lactate, Base Excess, HCO_{3-}, BUN, Troponin T (TnT), Hct and Hb. During the critical care period, total amount of each drug given as well as total volume infused, and the urine output were recorded.

2.11.2.1 Coronary perfusion pressure

CPP was used as one of the outcomes in the animal studies described in this thesis. Although typically this is defined as: Coronary Perfusion Pressure (CPP) = Aortic Diastolic Pressure – Left Ventricular end-diastolic Pressure (LVEDP) (Nguyen et al., 2018), we derived this measure by subtracting measured RAP from DBP as described in table 2.1. Paradis used the latter equation in his work (Paradis *et al.*, 1990; Paradis, Rose and Gawryl, 1994). Moreover, we also used the simpler equation as obtaining reliable RAP and DBP was more likely than reliable measurements of LVEDP. LVEDP would have to be measured by the PV loop catheter. However, the constantly changing blood volume in protocol for our animal studies- could have affected the reliablility of measurements obtained by the PV loop catheter.

2.11.3 Data Acquisition System

An integrated data collection system was used to measure, calculate, and derive the physiologic data continuously. Mean values were set at 60 second intervals for data capture and analysis. The data collection system consisted of various transducers (described in section 2.4.2) used to convert biological signals into electrical signals; signal conditioners (AD Instruments, Sydney, Australia) - which received the signals from transducers and conditioned the signals using amplification, voltage or current limiting and anti- aliasing filtering, and PowerLab Data acquisition device (AD Instruments, Sydney, Australia) – used to record analogue data and digitize it. The physiologic data acquisition system described is certified research grade equipment for use in animal haemodynamic and cardiovascular experiments. The data collection hardware set up used for the studies included in this work is presented in figure 2.9. Sampling methods for physiologic data using the digital data collection system are described in table 2.1.

Collected physiologic data were displayed in waveforms, analysed, and calculated using the LabChart physiological data analysis software (AD Instruments, Sydney, Australia). During the experiments live data were displayed on a monitor in a waveform and calculated value forms (figure 2.9).

2.12 Statistical Analysis

All data were amalgamated in an Excel spreadsheet (Microsoft, Redmond, WA.). GraphPad Prism (version 8) (San Diego, CA, USA) was used to display the results graphically. Statistical analyses were performed using SPSS version 26 (IBM, Chicago, IL), R (version 3.5.2) and RStudio (version 1.1.463) (R Foundation for Statistical Computing, Vienna, Austria). All statistical analysis using SPSS was performed by Marta J Madurska. Statistical analysis using RStudio was performed by and by Dr Melike Harfouche for the study described in section 3.3. Normality testing was employed to determine the distribution of continuous variables. Continuous data are presented as means with standard deviation (SD), or as median and interquartile range (IQR) depending on distribution. Categorical data are presented as proportions (%).

Categorical data were assessed using a Chi^2 test. Fisher's exact test was applied when assumptions weren't met including a small sample size. Comparisons between two independent continuous observations were made using the 2- tailed student t- test or Mann- Whitney test depending on data distribution. Two paired observations were compared using paired sample t- test for normally distributed data and Wilcoxon-signed rank test for data that was not normally distributed. When comparing more than 2 groups, outcomes were analysed using one-way ANOVA test for normally distributed data or Kruskal Wallis test for not normally distributed data. Comparisons between more than 2 repeated observations were made using repeated measures ANOVA test with *post hoc* testing for continuous variables using a Bonferroni correction. Survival analysis was performed using Kaplan-Meier curves and differences were tested using Log- rank (Mantel-Cox) testing using individual rank tests. Statistical significance was set at $p = 0.05$. Statistical support was provided retrospectively by Ms Kim Pearse- a statistician at Newcastle University.

Sampling Method		Metric
Measured Data		SaO2, ETCO2, Temp, ECG, cardiac PV loop parameters (Pressure, Volume, Phase, Magnitude), aortic root pressure, RAP, RVP, left coronary blood flow
Derived Data		
	PV loop parameters	CO, SV, LV diastolic volume, LV pressure, EF
	ECG	HR
	Aortic Root Pressure	MAP, SBP, DBP
	DBP and RAP Gradient*	CPP

Abbreviations: SaO2- Oxygen saturation, $ETCO_2$- end- tidal carbon dioxide, temp- Core temperature, ECG- Electrocardiogram, PV- Pressure Volume, CO- Cardiac Output, SV- Stroke Volume, LV- Left Ventricle, EF- Ejection Fraction, HR- Heart Rate, MAP- Mean Arterial Pressure, SBP- Systolic Blood Pressure, DBP- Diastolic Blood Pressure, CPP- Coronary Perfusion Pressure, RAP – Right Atrial Pressure, RVP – Right Ventricular Pressure

* as defined by Paradis et al (Paradis *et al.*, 1990)

Table 2.1 Physiologic data collected using the integrated data collection system. Metrics measured directly using the transduced signals and those derived by using measured data.

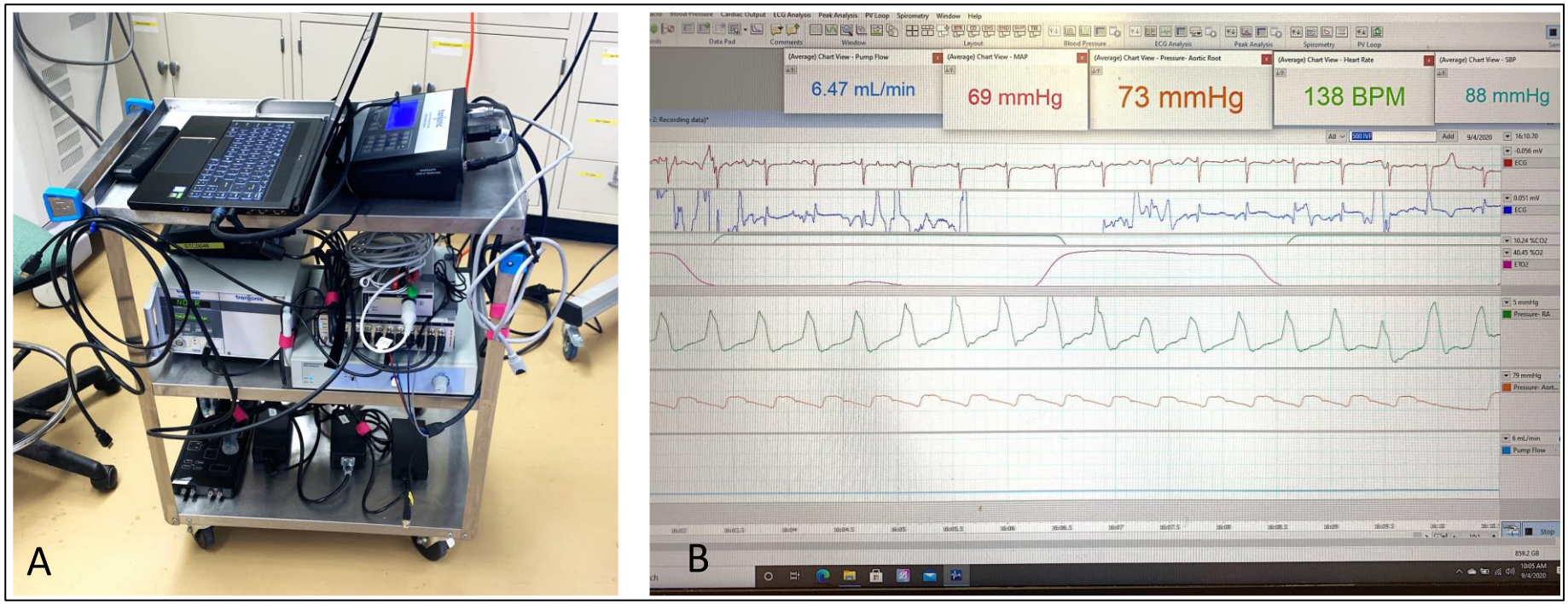

Figure 2.9 A. Workstation with the data collection hardware including a computer, signal conditioners, and PowerLab Data acquisition device. B. Monitor displaying live waveforms and calculated values during animal experimentation.

Chapter 3. Clinical Studies

3.1 Introduction

The current lack of compelling outcome -related evidence for catheter- based resuscitation techniques in clinical practice are highlighted in sections 1.2.5.1 and 1.2.5.2. The clinical studies described in this chapter aim to explore these issues.

3.2 Clinical study of REBOA vs No-REBOA

3.2.1 Author contribution

This study has been conducted in collaboration with other researchers. Researcher contributions are as described:

- **Conceptualization:** Melike N. Harfouche, Marta J. Madurska, Noha Elansary, Hossam Abdou, Eric Lang, Joseph J. DuBose, Rishi Kundi, David V. Feliciano, Thomas M. Scalea, Jonathan J. Morrison.
- **Data curation:** Noha Elansary, Joseph J. DuBose.
- **Formal analysis:** Melike N. Harfouche, Marta J. Madurska, Noha Elansary, Hossam Abdou, Eric Lang, Joseph J. DuBose, Rishi Kundi.
- **Methodology:** Melike N. Harfouche, Noha Elansary, Hossam Abdou, Eric Lang, Joseph J. DuBose, David V. Feliciano, Jonathan J. Morrison.

3.2.2 Background

REBOA has been gaining popularity over the past decade as an endoluminal adjunct to resuscitation in NCTH. Despite promising evidence that it can provide circulatory support in patients with haemorrhagic shock, the use of REBOA has proven to be controversial as there is a lack of high-quality evidence of clear survival benefit as described in sections 1.2.4 and 1.8. With current ongoing clinical equipoise and lack of reported data with a suitable control group from a mature Level 1 Trauma Centre, the aim of this study was to use the local trauma registry to compare outcomes between trauma patients who were managed with REBOA and those who received standard treatment without REBOA.

3.2.3 Study Population and Data Management

All trauma patients In R Adams Shock Trauma Centre, between 2000 and 2019 were identified and reviewed retrospectively using the local trauma registry as described in section 2.11.1.1. Patients were stratified into two groups: the REBOA group and the no-

REBOA group. Within the no-REBOA group, historic (H = 2000 to 2012) and contemporary (C = 2013 to 2019) subgroups were created. The no-REBOA patients were divided into historic and contemporary groups to control for any bias associated with improvements in resuscitation and critical care management that would not have been available to the patients in the historic group but were available to the ones in the contemporary and REBOA groups. Although REBOA has been used locally since 2013, REBOA patients were included in the study starting in the year 2015 to reduce bias due to a learning curve after the device was initially introduced. Patients < 16 yrs old, as well as those in cardiac arrest upon arrival to the hospital, and those with missing significant clinical data or covariates were excluded. The REBOA service is provided as described in section 3.3.3.

3.2.3.1 Inclusion Criteria

Trauma patients who were 16 years of age and over who received REBOA as part of treatment for haemorrhagic shock. These included zone I and zone III REBOA placement. Patients who had a cardiac arrest on admission or those who were missing significant clinical data or covariates were excluded.

3.2.4 Endpoints

The primary outcomes of interest were 24 hr and 30- day survival. Secondary outcomes were length of hospital stay, total blood products transfused, and systemic and lower limb complications.

3.2.5 Statistical Analysis

Univariate analyses comparing demographic and clinical factors between the REBOA and no-REBOA groups (historic and contemporary) were performed using statistical techniques described in section 2.12. In addition, propensity score matching was used to compare the groups using the Matchit package version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). A logistic regression model was used to assign a propensity score for each patient based on pre- treatment variables that were found to be significant

on univariate comparison of REBOA to no-REBOA patients. These variables were: age, sex, race, mechanism of injury, ISS, body region AIS score (brain, thorax, abdomen/pelvis, and upper and lower extremities), and lowest SBP and GCS within one hour of arrival to the hospital. Patients in the historic and contemporary groups were propensity matched 2:1 to the REBOA group (R = 2015 - 2019), using the nearest neighbour method, to give the closest possible match in pre-specified criteria. A match tolerance of 0.001 was used. The Kaplan-Meier estimate was used to assess 30 - day survival in each group form the day that REBOA was used. Post-match univariate analyses were performed between the REBOA and no-REBOA groups for primary and secondary outcomes.

3.2.6 Results

A total of 130,651 patients from the registry within the study period were identified (H = 105,134, C = 25,410, R = 107). Patients were excluded due to age < 16 (n = 2,518), arrival in cardiac arrest (n = 6,985) and incomplete data (n = 18,667). A total of 102,481 patients were included in the study (H = 88,545, C = 13,879, R = 57). Comparison of the REBOA group to the no-REBOA contemporary and historic groups by demographic, injury and physiology data is presented both pre- and post-match in table 3.1 and table 3.2, respectively. Prior to matching, the REBOA group was significantly more likely to be male (R = 90 % versus C = 67 % and H = 70 %), have a higher body-region AIS and overall ISS (R = 34 versus C = 10 and H = 11), lower SBP (R = 67 mmHg versus C = 113 and H=127) and lower GCS (R = 5 versus C = 14 and H = 14) than the no-REBOA groups. When compared to the no-REBOA patients, the REBOA patients tended to be younger (R = 37 yr versus C = 47 yr, H = 40 yr, $p < 0.001$), and were more likely to have a penetrating mechanism of injury (R = 23 % versus C = 13 %, H = 13 %, $p < 0.001$).

114 patients each in the contemporary and historic groups were matched to 57 REBOA patients. To determine if patients had been appropriately matched, baseline characteristics were compared. As demonstrated in tables 3.4 and 3.5, patients in both the contemporary and historic groups did not differ in pre- treatment variables when compared to patients in the REBOA group after matching was complete. Post matching,

in- hospital mortality was significantly lower in the REBOA group (19.3 %) when compared to the contemporary (35.1 %, p = 0.024) and historic (44.7 %, p = 0.001) groups. Kaplan-Meier estimates of survival over time to 30 days (log rank) demonstrated higher survival in the REBOA group compared to the historic (p = 0.035) and contemporary (p = 0.020) groups (figure 3.1). Chi-square comparison of mortality at 24 hr between the REBOA and no-REBOA historic group demonstrated lower mortality in the REBOA group (12 % versus 28 %, p = 0.014). There were no differences in 24 hr mortality when compared to the contemporary group (table 3.3). Total length of hospital stay was longer in the REBOA group by 20 days when compared to the historic group (p < 0.001) and by 9 days when compared to the contemporary group (p = 0.03). There were no differences in acute kidney injury and total transfusions of PRCs between groups, but platelet transfusions were higher in the REBOA group when compared to the no-REBOA groups (table 3.3).

The overall incidence of lower extremity complications was low. A review of lower extremity complications associated with patients who underwent REBOA placement did not show any difference in rates of lower extremity amputation, exploration, fasciotomy or thrombectomy when compared to no-REBOA patients (table 3.4).

	Before Matching			After Matching		
Variable	**Contemporary No-REBOA *n* = 13,879**	**REBOA *n* = 57**	***p***	**Contemporary No-REBOA *n* = 114**	**REBOA *n* = 57**	***p***
Age (years)/ median (IQR)	47 (21)	37 (14)	<0.001*	42 (20)	37 (14)	0.194
Sex (M)/ n (%)	9326 (66.9)	51 (89.5)	<0.001*	83 (72.8)	51 (89.5)	0.050
Race/ n (%)						
White	4814 (34.5)	24 (42.1)	<0.001*	36 (31.6)	24 (42.1)	0.050
African- American	7917 (56.8)	23 (40.4)		72 (63.2)	23 (40.4)	
Other	1205 (8.6)	10 (17.5)		6 (5.3)	10 (17.5)	
Mechanism of injury/ n (%)						
Blunt	11509 (80.8)	38 (66.7)	<0.001*	81 (73)	38 (66.7)	0.764
Penetrating	1806 (12.8)	13 (22.8)		18 (16.2)	13 (22.8)	
Unknown	564 (6.4)	6 (10.6)		12 (10.8)	6 (10.6)	
ISS/ median (IQR)	10 (10)	34 (15)	<0.001*	38 (14)	34 (15)	0.420
Lowest SBP (mmHg)/ median (IQR)	113 (22)	67 (18)	<0.001*	67 (21)	67 (18)	0.382
Lowest GCS (mmHg)/ median (IQR)	14 (1)	5 (3)	<0.001*	4 (2)	5 (3)	0.399
Body Region AIS/ median (IQR)						
Brain	1 (1)	2 (2)	0.003*	2 (2)	2 (2)	0.100
Thorax	1 (1)	2 (1)	<0.001*	2 (1)	2 (1)	0.222
Abdominal	0 (1)	3 (2)	<0.001*	3 (2)	3 (2)	0.600
Upper Extremity	1 (1)	1 (1)	<0.001*	1 (1)	1 (1)	0.709
Lower Extremity	1 (1)	2 (1)	<0.001*	2 (1)	2 (1)	0.587

Table 3.1 Baseline measurements. REBOA vs No-REBOA Contemporary Group before and after propensity-matching. SBP - Systolic Blood Pressure, GCS - Glasgow Coma Scale, AIS - Abbreviated Injury Scale.

Variable	Before Matching			After Matching		
	Historic No-REBOA ***n* = 88,545**	**REBOA** ***n* = 57**	***p***	**Historic No-REBOA** ***n* = 114**	**REBOA** ***n* = 57**	***p***
Age (years)/ median (IQR)	40 (19)	37 (14)	<0.001*	38 (17)	37 (14)	0.969
Sex (M)/ n (%)	62,161 (70.2)	51 (89.5)	<0.001*	80 (70.2)	51 (89.5)	0.050
Race/ n (%)						
White	52,352 (59.1)	24 (42.1)	<0.001*	31 (27.2)	24 (42.1)	0.313
African- American	29,746 (33.6)	23 (40.4)		72 (63.2)	23 (40.4)	
Other	6,447 (7.3)	10 (17.5)		11 (9.6)	10 (17.5)	
Mechanism of injury/ n (%)						
Blunt	71,166 (80.4)	38 (66.7)	<0.001*	80 (70.2)	38 (66.7)	0.236
Penetrating	11,380 (12.9)	13 (22.8)		18 (15.8)	13 (22.8)	
Unknown	5,999 (6.6)	6 (10.6)		16 (14.1)	6 (10.6)	
ISS/ median (IQR)	11 (10)	34 (15)	<0.001*	33 (16)	34 (15)	0.553
Lowest SBP (mmHg)/ median (IQR)	127 (18)	67 (18)	<0.001*	69 (21)	67 (18)	0.636
Lowest GCS (mmHg)/ median (IQR)	14 (3)	5 (3)	<0.001*	4 (2)	5 (3)	0.479
Body Region AIS/ median (IQR)						
Brain	0 (0)	2 (2)	<0.001*	2 (2)	2 (2)	0.589
Thorax	0 (0)	2 (1)	<0.001*	2 (2)	2 (1)	0.178
Abdominal	0 (0)	3 (2)	<0.001*	3 (2)	3 (2)	0.498
Upper Extremity	0 (0)	1 (1)	<0.001*	1 (1)	1 (1)	0.992
Lower Extremity	0 (0)	2 (1)	<0.001*	2 (1)	2 (1)	0.773

Table 3.2 Baseline measurements. REBOA vs No-REBOA Historic Group before and after propensity-matching. SBP - Systolic Blood Pressure, GCS - Glasgow Coma Scale, AIS- Abbreviated Injury Scale

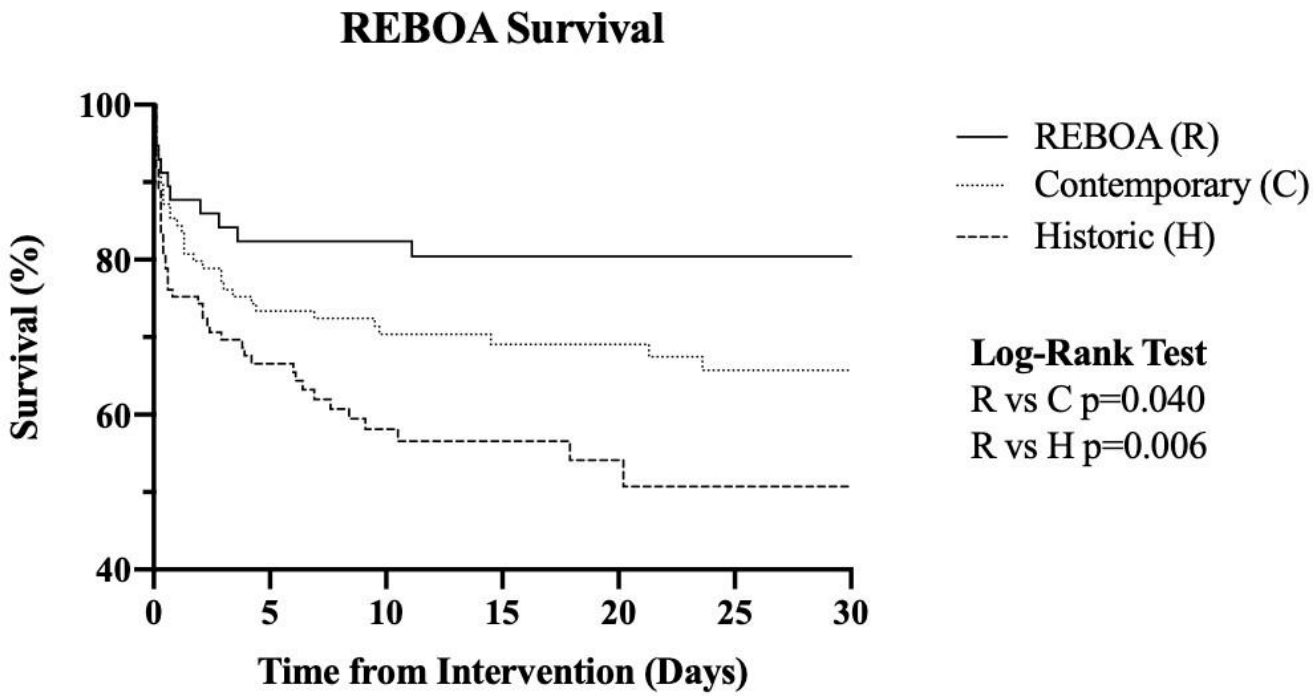

Figure 3.1 Kaplan- Meier 30- day survival Analysis between REBOA (R), No- REBOA Historic (H) and No-REBOA Contemporary (C) groups.

Variable	Contemporary No-REBOA	REBOA	*p*	Historic No-REBOA	REBOA	*p*
	***n* = 114**	***n* = 57**		***n* = 114**	***n* = 57**	
24 hr mortality/ n (%)	22 (19.3)	7 (12.3)	0.249	32 (28.1)	7 (12.3)	0.014*
In-hospital mortality/ n (%)	40 (35.1)	11 (19.3)	0.024*	51 (44.7)	11 (19.3)	0.001*
Total length of stay- (days) / mean (SD)	20 (20)	29 (29)	0.030*	9 (9)	29 (29)	< 0.001*
Total transfusions (Units)						
PRC/ median (IQR)	19 (18)	18 (18)	0.533	17 (14)	18 (18)	0.498
Platelets/ mean (SD)	0.5 (0.2)	2.9 (3.2)	< 0.001*	0.2 (1.2)	2.9 (3.2)	< 0.001*
Acute Kidney Injury/ n (%)	28 (25)	13 (22.8)	0.455	27 (23.7)	13 (22.8)	0.530

Table 3.3 Outcomes in REBOA and No-REBOA contemporary and No-REBOA Historic groups in the post- match cohort. PRC- Packed Red Cells.

Variable	Contemporary No-REBOA	REBOA	*p*	Historic No-REBOA	REBOA	*p*
	***n* = 114**	***n* = 57**		***n* = 114**	***n* = 57**	
Lower Extremity Amputation/ n (%)	1 (0.9)	3 (5.3)	0.075	2 (1.8)	3 (5.3)	0.203
Lower Extremity Exploration/ n (%)	8 (7.1)	8 (14.0)	0.143	8 (7.0)	8 (14.0)	0.143
Fasciotomy/ n (%)	3 (2.6)	4 (7.0)	0.181	8 (7.1)	4 (7.0)	0.976
Thrombectomy/ n (%)	1 (0.9)	3 (5.3)	0.075	2 (1.8)	3 (5.3)	0.203

Table 3.4 Lower extremity complications in REBOA vs no-REBOA group (contemporary and historic) in the post-match cohort.

3.2.7 Discussion

This study, from an experienced, high-volume trauma centre in the USA, compares REBOA outcomes to a suitable, well-matched control group. The findings demonstrate a lower rate of overall mortality and improved 30- day survival in patients who underwent management with REBOA as compared to both historical and contemporary cohorts of those who received standard trauma care without REBOA matched on injury severity, injury pattern and physiology. REBOA patients had significantly longer length of hospital stay and higher platelet transfusion requirements, but no differences with regards to acute kidney injury and lower extremity complications.

Considerations must be taken regarding the methodology of the above study. Although a prospective, randomised, blinded, controlled trial is the best study design for assessing treatment outcomes, it is not always suitable due to ethical, economical, or practical reasons. Therefore, an observational study design with propensity score matching or multivariate analysis can provide a feasible alternative, however, is not without disadvantages (Nuttall *et al*., 2008). Neither of the statistical methods (propensity score matching and multivariate analysis) can control for the specific method of the treatment provided, including patient selection, physician experience or in case of REBOA exact technical aspects such as timing of placement, access type, or type of catheter used. Propensity score matching has been designed to account for all considered co-variates where the treatment and control groups are matched according to scores based on the confounders with the aim for both groups to be similar in terms of co-variates (Rubin and Thomas 1996). However, propensity score matching can only take into the account measured co-variates, while unmeasured characteristic will not be accounted for- this can skew the results (D'Agostino 1998; Cepeda *et al*., 2003). Another problem with propensity score matching is that subjects with missing values on covariates are excluded from the study. This means that the excluded data could contain co-variates that may have influenced the results. In this study, a high proportion of patients were removed due to missing data. This can unduly influence the results, as the characteristics of the study population are biased towards individuals that have all data available. Multivariate logistic regression is a commonly used study design with the aim to simultaneously control for multiple differences between treatment groups in an observational study. However, in a

setting where many variables have to be considered relative to the number of events, the estimate produced by the model may be false (Cepeda *et al*., 2003). REBOA is a relatively infrequent event, even in high volume centres, often yielding small study numbers. Using multivariate analysis in studying REBOA outcomes makes these studies vulnerable to biased results.

There are other limitations that must be considered. As this is an observational study and no formal REBOA practice guidelines exist, there is likely selection bias. Locally patients are treated with REBOA according to a well-established institutional algorithm (Brenner, et al., 2014), although ultimately decision to treat lies with the on call attending physician. There is no data on hemodynamic response after REBOA placement. Lower extremity complications can pose a significant morbidity in patients receiving REBOA. Locally, all hypotensive patients who do not respond to initial resuscitation have a femoral arterial access attempted, which can serve for arterial blood pressure monitoring or upsized to a 7 Fr catheter for REBOA access if needed. No patients have a catheter placed prophylactically, once the decision is made for REBOA the device is placed using the access sheath and deployed. The rate of lower limb complications in the REBOA cohort presented in this study is low. Although there were no statistically significant differences between REBOA and No-REBOA groups (table 3.4), there is a signal that these may be higher in the REBOA group. The sample size is small and there is a risk of a type II statistical error potentiating a false negative result. Moreover, there may be a survival bias in the REBOA group where only a small number of patients who survived were able to be observed for lower extremity complications.

The study cannot determine the institution-specific characteristics that may have contributed to improved outcomes with REBOA, as these were not captured in the retrospective data. Hence, we can only cautiously conclude that high-volume REBOA users at our institution may have played a role in improved survival in the REBOA group. However, the study results may not be applicable to centres with a different patient population, operator experience, and resource availability.

3.2.8 Conclusion

This single-institution, propensity-matched, retrospective study demonstrated lower in-hospital mortality and improved 30-day survival for REBOA when compared to both contemporary and historic no-REBOA groups, and lower 24-hour mortality when compared to the historic group. In a high-volume centre where its use is part of a coordinated haemorrhage control strategy, REBOA may improve survival in patients with noncompressible torso haemorrhage.

3.3 A Clinical study of P-REBOA

3.3.1 Background

Prolonged AO related to REBOA can lead to significant morbidity and mortality, as described in sections 1.2.3 and 1.2.5.1. Evidence outlined in section 1.2.5 suggests that P-REBOA can potentially mitigate the negative consequences of traditional REBOA. However, P-REBOA remains poorly described in clinical practice, with the literature limited to a few case reports (Davidson *et al.*, 2016; Hörer *et al.*, 2016; Okumura *et al.*, 2016; de Schoutheete *et al.*, 2018). The aims of this study are to present the initial clinical experience of P-REBOA in a high-volume institution and to compare the outcomes of patients based on type of REBOA treatment (partial occlusion (P-REBOA) vs complete occlusion (C-REBOA)), and duration of occlusion (brief or prolonged).

3.3.2 Study Population

Patients considered were those who underwent REBOA between January 2016 and May 2019. The inclusion criteria consisted of patients treated with complete or partial REBOA in zone I for infra- diaphragmatic haemorrhage who underwent attempted haemorrhage control in the OR. Exclusion criteria included: age < 18 yrs, zone III occlusion, non-traumatic haemorrhage, overt signs of TBI (blown pupil after blunt injury or penetrating head injury), or death prior to attempted operative haemorrhage control.

Although REBOA has been practiced locally since 2013, the chosen date range was to allow for the institutional learning curve and the introduction of the current generation catheter in 2015 (ER REBOA, Prytime Medical, Boerne, TX, USA). This allowed for the

reporting of a standardized approach to REBOA in an experienced institution using a single catheter type.

3.3.3 REBOA Service

The institutional setting has been described in section 2.2. As per section 3.3.2, REBOA has been introduced into clinical practice locally in 2013 (Brenner, Teeter, *et al.*, 2018) and is performed either by a consultant trauma surgeon or a fellow who has completed the “Basic Endovascular Skills for Trauma” (BEST) course (Brenner *et al.*, 2014). The procedure typically takes place either in the Trauma Resuscitation Unit or the Operating Room (OR). The type of REBOA treatment (C-REBOA, vs P-REBOA) is a matter of judgement, depending on clinician preference and familiarity with the procedure. REBOA use at Shock Trauma Centre is guided by a locally developed, institutional algorithm (Brenner, *et al*., 2014) whereby trauma patients who are hypotensive (SBP < 90 mmHg) and either do not or only partially respond to fluid resuscitation have a femoral artery access established. The femoral artery access is used either as arterial access for support of resuscitation or for REBOA placement. In the absence of obvious thoracic injury, a plain chest x ray is performed to exclude possible aortic injury. In the event of suspected chest injury REBOA is not attempted. If chest injury is not suspected, a FAST Ultrasound examination (Inaba *et al*., 2015) is performed and if positive, Zone I REBOA is placed. If FAST is negative, a pelvic X ray is performed to rule out pelvic fracture. If pelvic fracture is confirmed, REBOA is placed in Zone III, if there is no pelvic fracture but patient is hypotensive with a negative FAST, REBOA is placed in Zone III.

3.3.4 Partial Occlusion Technique

The technique for P-REBOA in this study typically involves a set up with two arterial lines- one proximal to the balloon (can be transduced through the REBOA catheter) and one distal to the balloon, where the arterial line is attached to the side arm of the 7 Fr sheath through which the REBOA catheter is placed (DuBose, 2017) (figure 3.2). An initial period of complete occlusion for up to 10 min is applied to allow for haemodynamic assessment and time for clot stabilization. This is followed by careful introduction of distal flow which consists of a dynamic process which involves gradual, incremental deflation and

reinflation to achieve a targeted systolic BP of ≥ 90 mmHg. This is to maintain perfusion proximal to the balloon whilst allowing some perfusion beyond the REBOA. There is no specific target for distal flow in this setting, as the primary goal is to maintain proximal target pressure, but a noticeable difference in distal pressure following gradual balloon deflation is a marker for obtaining partial occlusion. Due to the unique physiological response of each patient requiring careful, targeted balloon manipulation, the P-REBOA technique in this setting cannot be standardized with strict inflation/ deflation parameters.

3.3.5 Data Collection

Patients who have undergone REBOA treatment were identified using a prospectively led local REBOA registry. Clinical data were collected as described in section 2.11.1. In addition, REBOA specific data were extracted from the REBOA registry, these included inflation time since admission, duration of inflation, type of inflation (continuous or partial), and pre- and post- balloon inflation systolic BP.

3.3.6 Data Management

Patients were divided into two groups based upon REBOA technique (P-REBOA and C-REBOA) and occlusion duration (prolonged or brief). Prolonged occlusion was defined as > 30 min, brief occlusion was defined as ≤ 30 min.

3.3.7 Study Outcomes

The primary outcome was in- hospital survival and secondary outcomes were length of hospital stay, number of ICU days, ventilator days and need for organ support. Multi-organ failure was assessed using a SOFA (Sequential Organ Failure Assessment) score. This was calculated at 24, 48 and 72 hr based upon measure of ventilation, coagulation, hepatic, neurological, cardiovascular and renal functions (Fröhlich *et al.*, 2016). SOFA is a scale between 0 and 24, with a 90 % mortality in patients with a SOFA > 15 (Vincent *et al.*, 1998; Ferreira *et al.*, 2001). For the purposes of the current study, the SOFA score was dichotomized into low- SOFA (< 9) and high-SOFA (≥ 9). This cut-off was chosen to reflect the evidence that mortality abruptly increases beyond a SOFA of 9 to greater than 20 % (Vincent *et al.*, 1998; Ferreira *et al.*, 2001).

3.3.8 Results

3.3.8.1 Baseline characteristics

A total of 46 patients who had met the inclusion criteria were identified. P-REBOA was used in n = 14 patients and C-REBOA in n = 32. The demographic and admission characteristics and outcomes are presented in table 3.5. There were no significant differences between the C-REBOA and P-REBOA patients in terms of sex, age, injury type, ISS, GCS, admission vital signs, estimated blood loss at damage control surgery or admission blood results (Hb, Hct, INR, pH, BE, Lactate).

3.3.8.2 Duration of Occlusion

When analysing groups according to duration of REBOA, n = 20 patients had prolonged C-REBOA and n = 12 had prolonged P-REBOA. Overall, the mortality in patients who received REBOA, regardless of technique, was significantly higher in the prolonged group (0 vs 32 %, p = 0.044, Fisher's exact test) (figure 3.3). Furthermore, a subgroup analysis of the REBOA type by occlusion duration demonstrated an increased use of vasopressors (30 %, vs 72.7 %, p = 0.049), need for dialysis (0 vs 36.4 %, p = 0.035), and higher SOFA scores at 48 hrs (median 6.00 (IQR 7) vs 6.50 (6), p = 0.031) in prolonged as compared to ≤ 30 min C-REBOA.

3.3.8.3 Type of Occlusion

Table 3.6 represents outcomes between C-REBOA and P-REBOA. When comparing all C-REBOA and P-REBOA patients, there were no statistically significant differences. When C-REBOA and P-REBOA groups were compared exclusively in patients who had prolonged inflation time (> 30 min), the C-REBOA group had increased vasopressor requirements compared to P-REBOA (72.7 % vs 33.3 % respectively, p = 0.026), and only 6.7 % of C-REBOA vs 57.1 % of P-REBOA patients were discharged home rather than a rehabilitation facility (p = 0.009). In the prolonged occlusion cohort, the C-REBOA group demonstrates a trend towards more organ failure as reflected by high SOFA scores at 24 hr (43.8 % vs 12.5 % in P-REBOA, p = 0.126) and 48 hr post admission (40 % vs 12.5 %, p = 0.172). Similarly, 54.5 % of prolonged occlusion C-REBOA patients had acute renal failure, compared to 33.3 % of P-REBOA (p = 0.236). 36.4 % of C-REBOA group required renal replacement therapy as opposed to 16.7 % (p = 0.228).

Variable	All	C-REBOA *n* = 32	P-REBOA *n* = 14	*p*
Demography				
Male/ n (%)	40 (87 %)	28 (87.5 %)	12 (85.7 %)	0.869
Age/ mean (SD)	37.04 (13.7)	34.74 (13.9)	42.29 (12.1)	0.087
Injury Data				
ISS high (>24)/ n (%)	25 (54.3 %)	19 (59.4 %)	6 (42.9 %)	0.278
GCS low (<9)/ n (%)	21 (45.7 %)	14 (43.8 %)	7 (50 %)	0.695
Blunt Injury/ n (%)	28 (60.9 %)	20 (62.5 %)	8 (57.1 %)	0.732
EBL (mL)/median (IQR)	2600 (3825)	2500 (3850)	3000 (2875)	0.796
Admission Physiology				
SBP (mmHg)/ median (IQR)	98 (68)	99.5 (72)	95.5 (73)	0.481
HR/ median (IQR)	92 (51)	94 (59)	92 (33)	0.659
RR/ median (IQR)	20 (14)	20 (20)	21 (8)	0.480
Temp (°C)/ mean (SD)	35.91 (1.1)	35.92 (1.2)	35.90 (0.9)	0.955
Admission Lab Tests				
Hb/ mean (SD)	10.94 (11.2)	10.85 (2.3)	11.14 (2.3)	0.693
HCT/ mean (SD)	33.40 (34.5)	33.37 (6.9)	33.48 (7.6)	0.962
INR/ median (IQR)	1.40 (0.7)	1.40 (0.6)	1.25 (0.7)	0.990
pH/ median (IQR)	7.15 (0.3)	7.15 (0.3)	7.20 (0.4)	0.201
BE/ mean (SD)	-12.87 (8.5)	-13.27 (8.7)	-11.98 (8.4)	0.642
Lactate/ median (IQR)	8.25 (9.6)	8.25 (10.9)	7.95 (9.4)	0.932

Legend: ISS – Injury Severity Score, GCS- Glasgow Coma Score, EBL- Estimated Blood Loss, SBP- Systolic Blood Pressure, HR- Heart Rate, RR- Respiratory Rate, Hb- Haemoglobin, HCT- Haematocrit, BE- Base Excess

Table 3.5 Admission characteristics and baseline physiology of the study population

Variable	All Occlusion			> 30 min Occlusion		
	C-REBOA *n* = 32	P-REBOA *n* = 14	*p*	C-REBOA *n* = 20	P-REBOA *n* = 12	*p*
SOFA Score						
24 hr/ median (IQR)	7 (5)	5.5 (4)	0.442	7 (7)	6 (5)	0.183
48 hr/ median (IQR)	6 (5)	6 (5)	0.782	6.5 (6)	5.5 (4)	0.162
72 hr/ median (IQR)	6 (5)	5.5 (4)	0.660	6.5 (6)	5.5 (3)	0.581
Severe organ failure (SOFA > 8)						
24 hr/ n (%)	8 (30.8 %)	1 (10 %)	0.197	7 (43.8 %)	1 (12.5 %)	0.126
48 hr/ n (%)	8 (32 %)	2 (20 %)	0.478	6 (40 %)	1 (12.5 %)	0.172
72 hr/ n (%)	6 (24 %)	4 (40 %)	0.344	6 (40 %)	3 (37.5 %)	0.907
Organ Support						
ICU Days/ median (IQR)	21 (24)	17.03 (16)	0.400	27 (38)	18.99 (23)	0.419
Ventilator Days/ median (IQR)	17 (18)	7 (10)	0.294	19 (11)	5.5 (9)	0.483
Vasoactive Support/ n (%)	19 (59.4 %)	6 (42.9 %)	0.301	16 (72.7 %)	4 (33.3 %)	0.026*
Acute Renal Failure/ n (%)	16 (50 %)	4 (28.6 %)	0.177	12 (54.5 %)	4 (33.3 %)	0.236
Renal Replacement Therapy/ n (%)	8 (25 %)	2 (14.3 %)	0.418	8 (36.4 %)	2 (16.7 %)	0.228
Mortality						
Hospital Mortality/ n (%)	7 (21.9 %)	4 (28.6 %)	0.624	7 (31.8 %)	4 (33.3 %)	0.928
Discharge Data						
GCS on Discharge/ median (IQR)	15 (2)	15 (0)	0.676	15 (4)	15 (0)	0.571
Discharged Home/ n (%)	5 (20 %)	4 (44.4 %)	0.154	1 (6.7 %)	4 (57.1 %)	0.009*

Table 3.6 Outcomes between patients treated with C-REBOA and P-REBOA.

Figure 3.2 Photograph of an operating room monitor where two arterial lines are employed to deliver partial resuscitative endovascular balloon occlusion of the aorta in a trauma patient with a hemoperitoneum and zone 1 occlusion. The red trace is transduced proximal to the balloon (ie: central aortic pressure) and the white trace is transduced from the arterial sheath distal to the balloon (ie: iliac pressure).

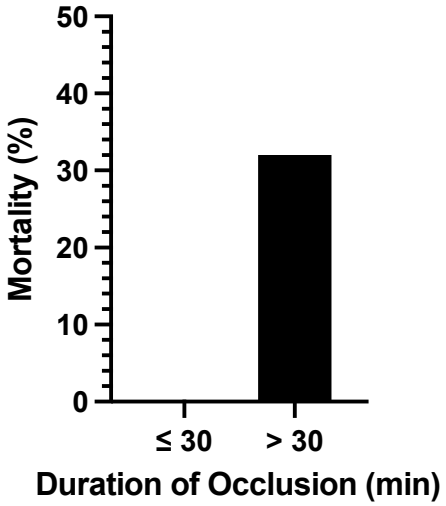

Figure 3.3 Overall REBOA mortality per occlusion duration (≤ 30 min, vs > 30 min), (p = 0.044).

3.3.9 Discussion

This is the first clinical study which demonstrates increased mortality and organ failure in prolonged REBOA and validates current clinical practice guidelines for maximal occlusion time (Glaser *et al.*, 2017; Bulger *et al.*, 2019). The current study also examines the clinical use of P-REBOA, reporting no additional procedural morbidity, but suggests that this technique may be associated with less end-organ dysfunction than C-REBOA. The purpose of this study was to compare trauma patients with infra- diaphragmatic haemorrhage who were treated with P-REBOA to those with C-REBOA. Our cohort showed no significant complications associated with P-REBOA.

The current study has several limitations. The study is retrospective, observational and the sample size is small and from a single institution. The quality of the data is dependent on the quality of the patient's medical records. Although the time of the catheter placement, beginning of inflation and complete deflation and removal were documented, the exact duration of partial inflation was difficult to determine. The exact technique of partial occlusion was poorly documented for each patient. Moreover, due to the nature of P-REBOA, requiring specific balloon manipulation depending on each patient's unique haemodynamic response, it is impossible to standardize it or to control for the deflation/ inflation profile. Ultimately a prospective study with an adequate sample size is needed to appropriately guide clinical practice.

3.3.10 Conclusion

This study demonstrates that REBOA > 30 min is associated with increased mortality and need for organ support, whilst prolonged P-REBOA appears to be associated with less organ failure than C-REBOA. P-REBOA may be a useful tool in safely prolonging REBOA, whilst avoiding the detrimental consequences of prolonged complete occlusion. More clinical data is needed to inform on the benefit of partial occlusion REBOA.

Chapter 4. *Ex- Vivo* Balloon Compliance Study

4.1 Introduction

Blind intra-aortic balloon inflation remains a potential safety problem during REBOA deployment. Despite improvements in catheter design since the advent of REBOA, there is an ongoing fear of balloon overinflation and resulting iatrogenic aortic injury as highlighted in section 1.2.4 of this thesis. The study described in this chapter aims to explore the problem of overinflation in the light of emerging advancements in catheter design.

4.2 *Ex- Vivo* Balloon Compliance Study

4.2.1 Background

Currently, first- generation REBOA technology incorporates the use of a compliant balloon (CB) which is designed to expand and accommodate for inflated volume (Mehta *et al.*, 2014). Although this design aims to optimise safety, it does not eliminate the possibility of iatrogenic injury due to over inflation. Apart from fluoroscopy, there are no techniques which are feasible in clinical practice to effectively alert over inflation. REBOA is typically performed in an emergent setting with blind balloon inflation, where the risk of over- inflation may be an issue.

The aims of this study were to compare the inflation characteristics of a compliant versus semi-compliant balloon REBOA catheters in an *ex vivo* swine model and to characterize the over inflation profile. Another aim was to determine whether an addition of a pressure relief valve can be practically applied to a semi- compliant balloon (SCB) catheter as a safety device.

4.2.2 Methods

The study was conducted in two phases: a pressure inflation comparison (CB versus SCB) and an assessment of the pressure- relief valve in the SCB catheter.

4.2.2.1 Specimen Preparation and Experimental Set-Up

All aortic specimens were harvested from adult Yorkshire swine (Sus Scrofa) weighing 60 - 100 kg. Specimens were no more than 48 hr post-mortem and had been refrigerated

prior to use, without any fixative or preservative that could have altered the tissue architecture or structural integrity. Each specimen was dissected free of any redundant tissue and all branches were ligated.

The aortic segments were mounted on a flow loop system, which allowed non-pulsatile pressurization at 128 mmHg with a 9:1 ratio of 0.9 % NaCl to contrast. This allowed for the measurement of baseline aortic diameters using a cone- beam computed tomography (CB-CT) imaging system (Artis Zeego, Siemens, Malvern, PA). A side- port was available on the flow-loop for pressure measurements using a digital pressure gauge (Omega Engineering Inc, Norwalk, CT).

4.2.2.2 Balloon Catheter Designs

The CB catheter used in the experiments was the commercially available ER-REBOA™ catheter (Prytime Medical Inc, Boerne, TX) (figure 4.1). This catheter consists of a balloon manufactured from polyurethane and is expandable with a maximum volume of 24 mL to a diameter of 32 mm. The working length (WL) is 10 - 70 mm, depending on vessel diameter.

The SCB catheter is a final pre- clinical prototype pREBOA-PRO™ catheter (Prytime Medical Inc, Boerne, TX) (figure 4.1), inflated with a maximum volume of 25 mL to a diameter of 26 mm. The intended WL is 54 mm for zone I total occlusion – this can vary with vessel diameter.

Balloon compliance refers to the ability of the balloon material to expand with pressure. CB can expand and change their shape significantly to accommodate additional balloon volume, conforming to the surrounding anatomy, while SCB do not elongate significantly and thus result in a more abrupt increase in balloon pressure once occlusion has occurred.

4.2.2.3 Balloon Inflation Comparison

Balloon catheters were inserted into an aortic segment and inflated at 1 ml increments with a 3:1 NaCl/ contrast solution. No aortic segment was re- used, and no balloon

catheter had been previously inflated. Pressure within the balloon was measured at each mL increment and a CB-CT image obtained at every 5 mL. Incremental balloon inflation continued until aortic or balloon failure.

4.2.2.4 Semi-Compliant Balloon Inflation Plus Safety Valve

SCB catheters, with the addition of a safety valve set at 0.45 atmospheres (atm), placed between the inflation manifold and balloon, were inflated with a volume of 3:1 NaCl/ contrast solution until the valve release was observed. An additional 30 mL NaCl/contrast solution was then instilled in an effort to deliberately overinflate the balloon. Pressure and volume were recorded, and fluoroscopy images obtained at the time of the initial valve release and after additional volume injection attempted.

4.2.2.5 Data and Image Analysis

The CB-CT images were processed and read using openly available viewing software (Horos, version 3.0, Purview, Annapolis, MD) and interrogated for balloon diameter, WL and circumference measurements. Circumference measurements were divided by the baseline measurement to generate the circumferential stretch ratio (CSR), which is a previously described measure of over inflation (Teeter *et al.*, 2016). These data along with the pressure and volume data were stored and analysed according as described in 2.11. Mean and SD were displayed using a box plot. Pressure (normalized for baseline pressure value) was plotted against balloon volume and curves were fitted to understand the relationship between variables. The goodness of fit was determined by the R^2 value.

4.2.3 Results

4.2.3.1 Baseline Characteristics

A total of n = 12 aortic segments were used; these were 20 cm in length and when pressurized to 128 mmHg had a minimum and maximum diameter range between 14.06 mm and 25.34 mm at the midpoint of the aortic segment length. Six aortic segments were used per each group (CB and SCB). Average aortic diameter (mm) was 21.51 ± 2.45 for

CB group and 18.78 ± 4.29 for SCB group with no statistically significant difference between the groups (p = 0.206).

4.2.3.2 Incremental inflation without safety valve

Comparing CB and SCB catheters, when inflated incrementally until failure, 66 % (4/6) of balloons failed in each group before aortic rupture. Figure 4.2 represents findings prior to failure in each group. The CB group demonstrated almost double the volume in the balloon as compared to the SCB group (49.83 ± 23.25 vs 25.16 ± 8.93; p = 0.004). The WL was significantly higher in the CB (81.17 ± 19.11) than in the SCB group (59.49 ± 4.86, p = 0.023). When comparing pressure, diameter and CSR prior to failure, there were no significant differences between the groups.

4.2.3.3 Pressure-Volume Relationship

The pressure-volume curves were fitted for CB and SCB groups (figure 4.3). The pressure- volume relationship for the CB group fit a linear model (p = 0.313), $R^2 = 0.522$, and the SCB group fit a quadratic model (p < 0.001), $R^2 = 0.759$.

4.2.3.4 Semi-compliant balloon (SCB) Inflation with safety valve

Six aortic segments were used. The mean (SD) diameter of the aortic segments was 19.16 ± 4.33 mm. The mean (SD) volume injected into the balloon before the pressure valve release was 15.33 ± 5.35. Following initial valve release, an additional 30 ml was injected into the balloon lumen of the catheter; however, since the safety valve was installed in- line with the balloon, most of the additional volume was seen leaking out of the valve, rather than filling the balloon. Upon measuring the inflation parameters of the balloon before and after the additional injection of a 30 mL bolus, there were no significant differences between pressure, measured diameter, WL, and CSR (figure 4.4).

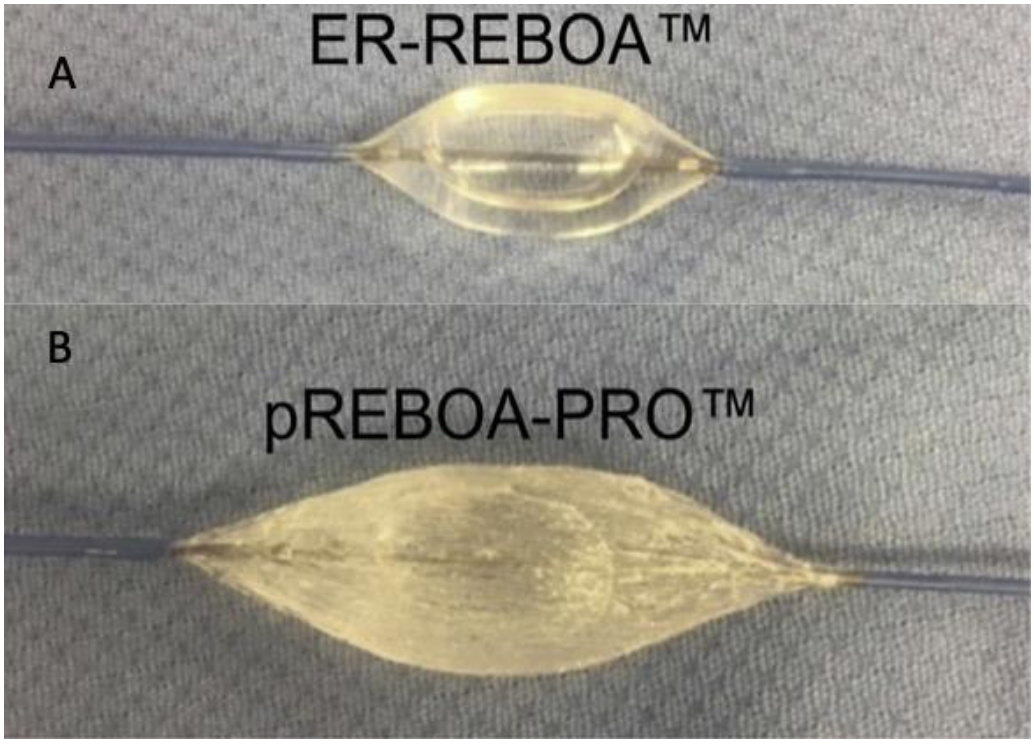

Figure 4.1 Endo-aortic occlusion balloon catheters. A. ER-REBOA™. B. pREBOA-PRO™ Source: (White *et al.*, 2020)

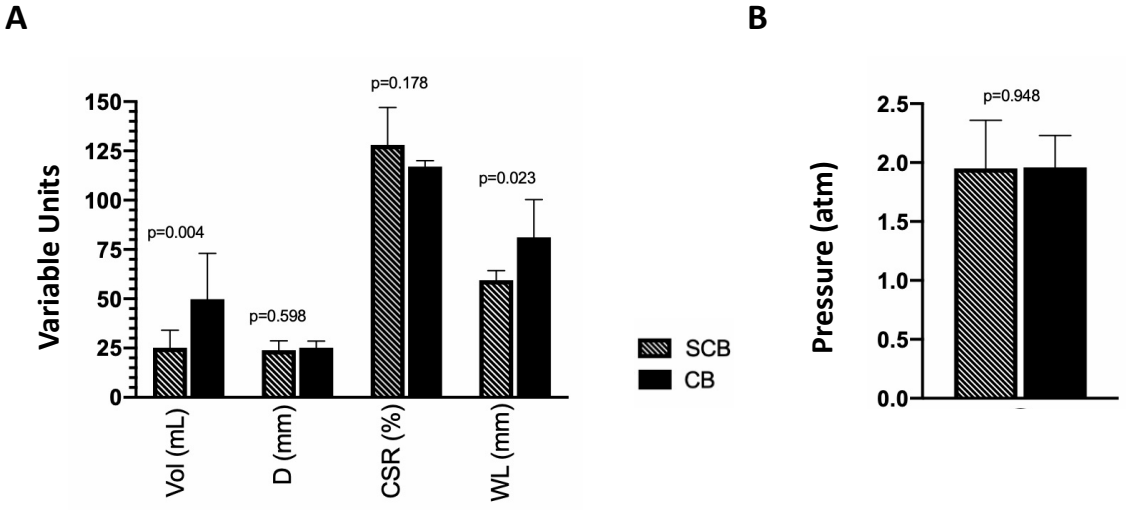

Figure 4.2 Inflation parameters comparing CB and SCB (no pressure valve) groups just before failure. A. variable units – each described below the corresponding bar: volume (Vol), measured diameter (D), circumferential stretch ratio (CSR), and working length (WL). B pressure (P).

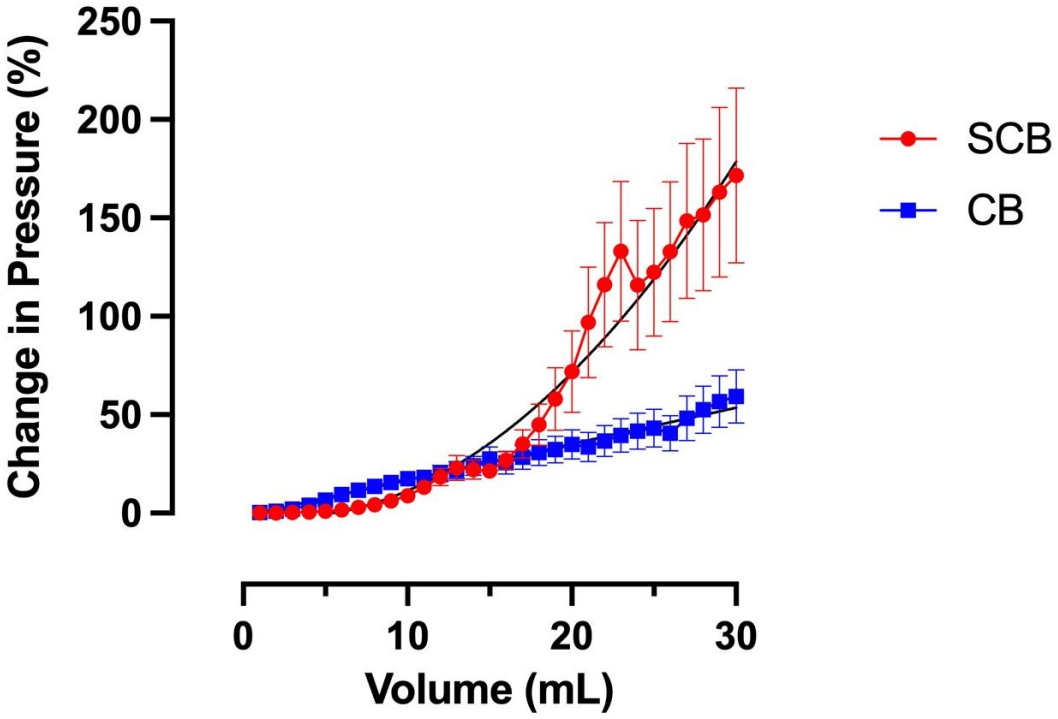

Figure 4.3 Relationship between pressure and volume for CB and SCB with incremental balloon inflation.

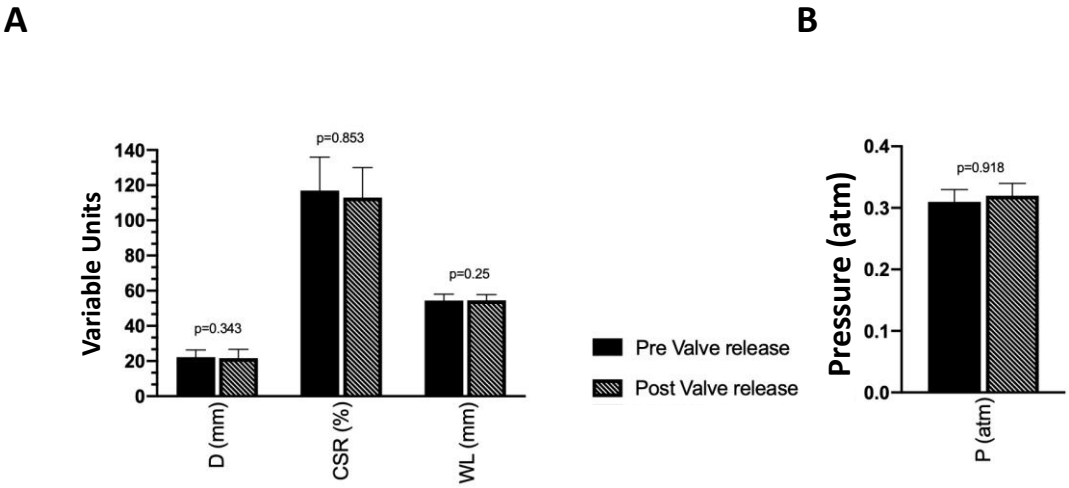

Figure 4.4 Inflation parameters for SCB balloons with pressure valve. Comparing parameters immediately before and after valve release. A. variable units – each described below the corresponding bar: measured diameter (D), circumferential stretch ratio (CSR) and working length (WL). B pressure (P).

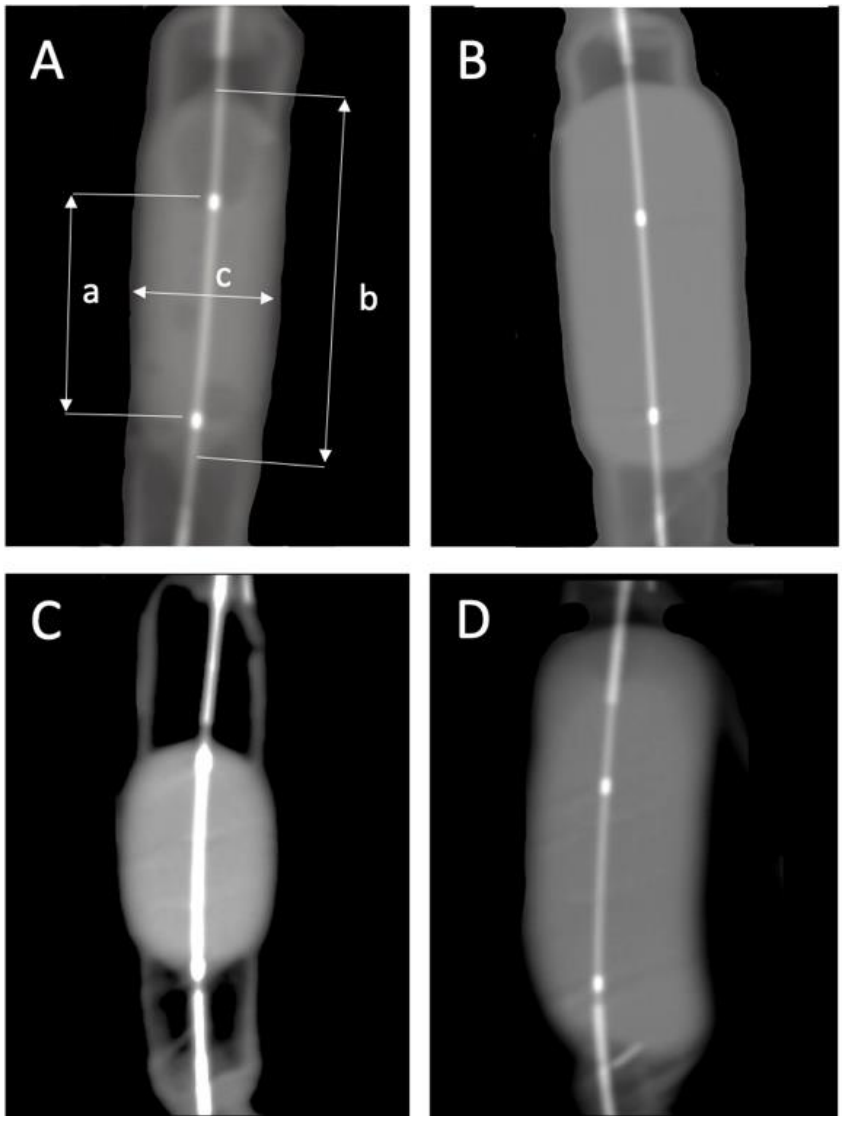

Figure 4.5 Cone-beam computed tomography image representing compliant balloon at baseline inflation (A) and significantly overinflated (B), semi-compliant balloon at baseline inflation (C) and at over inflation (D). Length ‘a’ is the intended working length, ‘b’ is total balloon length, and ‘c’ is the diameter of the balloon.

4.2.4 Discussion

This study suggests that an AO catheter design with a semi- compliant balloon in conjunction with a safety valve may be able to provide a safer blind aortic inflation profile and potentially reduce the risk of iatrogenic aortic injury.

This study demonstrates that there are significant differences between inflation characteristics between the standard compliant and semi- compliant balloon designs. The relationship between pressure and volume varies between CB and SCB catheters. While the SCB demonstrates a quadratic model when pressure against volume is plotted, the CB plot of pressure vs volume represents a linear model. Without the safety valve, CB has a higher threshold of failure. However, the quadratic relationship of pressure to volume demonstrated by the SCB plot includes a transition point where there is a rapid rise in pressure with ongoing inflation, this allows application of a safety valve to prevent overinflation. In the CB such valve is not applicable.

This study has several limitations. The design consists of a relatively small sample of swine aortic specimens which will differ from human aortas in composition. There was no histopathological assessment which could demonstrate presence of microscopic endothelial injury in the segments which did not rupture. Moreover, the design of this study also precludes assessing possible late onset changes associated with microscopic endothelial injury – such as myointimal hyperplasia- which can occur days to months after injury (Tediashvili *et al.*, 2018; Sterpetti *et al.*, 2019). The *ex vivo* design of this study might elicit different endothelial responses on a microscopic level than an *in vivo* model.

The design of the current study allowed a pressurized fluid model during the baseline measurement phase of the experiment, whilst the incremental inflation and the valve testing was performed without pressurised flow in the vessel segment. It is conceivable that a pressurized model may result in a change in the interaction between the aortic wall and balloon. The lack of pressurized flow and pulsatility potentially affect identification of optimal occlusion point. To address this, future research would ideally include the use of a SCB *in vivo*, with a detailed histological examination.

Our model uses exclusively healthy aortic tissues, this reflects the clinical setting of REBOA use, where patients are typically young without underlying aortic disease. However, the different aortic wall compliance associated with vascular disease and ageing may play a role in the relationship with varying balloon material, and this should be explored in future studies.

4.2.5 Conclusion

This study demonstrates that the inflation profile differs between balloon designs. In contrast to semi-compliant balloons, compliant ones will accommodate more volume to mitigate increase in pressure. This does not eliminate the risk of over inflation. However, the inflation characteristics of the semi-compliant balloon permit pairing it with a safety valve, which could lead to a development of a safer balloon technology in the future.

Chapter 5. Response to exsanguination and resuscitation in a porcine model.

5.1 Introduction

A few endovascular resuscitation strategies including SAAP and EPR are still in preclinical stages of development. Despite a body of evidence demonstrating promising outcomes as described in sections 1.3.3 and 1.5.3, more research is needed to explore the efficacy and limitations of these techniques. The animal studies described in this chapter focus on understanding the physiology of cardiac arrest from haemorrhage to best apply and incorporate SAAP and other endovascular resuscitation techniques.

5.2 Laboratory facilities

Animal studies described in this chapter have been conducted in the department of Comparative Medicine at the University of Maryland School of Medicine, which consists of animal laboratories and animal housing facilities accredited by the American Association for Laboratory Animal Science.

5.3 Defining the Physiology of Exsanguination Cardiac Arrest

5.3.1 Background

Currently, ECA is associated with an exceptionally poor prognosis and constitutes to be the leading cause of civilian and military preventable death (Dutton *et al.*, 2010; Eastridge *et al.*, 2012). Although haemorrhagic shock has been studied extensively (Cannon, 2018), the physiological underpinnings of the terminal stages are less well understood (Sarnoff *et al.*, 1954; Crippen *et al.*, 1991). Until recently, detailed knowledge of the pathophysiology of the late stages of exsanguination carried little relevance as therapy largely remained limited to RT and IV transfusion. However, this is changing with the advent of more sophisticated endovascular resuscitation techniques as described in section 1.6, thus warranting a more detailed characterization of physiology of cardiac arrest from haemorrhage.

This study aims to explore the pathophysiology of ECA and define the natural history and optimal opportunity for deployment of SAAP and other endovascular resuscitation tools.

5.3.2 Study Design

This study utilized animals as described in section 2.2. The study consisted of a single cohort and was conducted in two phases: animal preparation followed by controlled exsanguination where cardiac and haemodynamic indices were recorded continuously with arterial blood sampling at baseline and every 15 minutes until asystole. Following the end of protocol, the animals were euthanized. Figure 5.1 shows the study overview.

5.3.3 Methods

Animals were instrumented as described in section 2.4.6 before pump- controlled exsanguination was performed according to section 2.5.

5.3.4 Data Collection

Data collection was performed according to section 2.10.2. Blood gas sampling was performed every 15 minutes.

5.3.5 Experimental Outcomes

The primary outcomes of this study were cardiac and hemodynamic trends over the period of progressive exsanguination up to death, these included: RAP, RVP, aortic root pressure, HR, CO, SV, LV diastolic volume and pressure, EF, CPP, and coronary blood flow. The secondary outcomes were metabolic and biochemical trends including: $ETCO_2$, lactate, pH, pCO_2, pO_2, K^+, Na^-, Ca^{2+}, Cl^-, Glucose, lactate, BE, HCO_3-.

5.3.6 Statistical Analysis

In addition to statistical methods described in section 2.11. A linear regression analysis was performed to determine the relationship between EF and left anterior descending artery (LAD) flow. A non- linear regression curve was fitted to determine the relationships between MAP and LAD flow. A power calculation was performed which assumed the following parameters: 80 % power, 5 % alpha, using a repeated measures ANOVA with 5 time points (0, 15, 30, 45, 60 minutes), modelling previously published MAP data (Burns *et al.*, 2011), yielded an N of 9 animals.

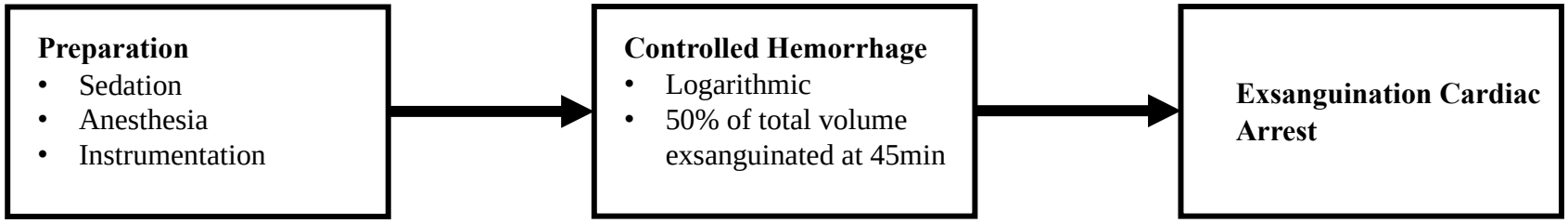

Figure 5.1 Overview of the experimental design.

5.3.7 Results

5.3.7.1 Baseline Characteristics

10 animals were used, with 9 animals surviving to the end of the protocol. One animal died following coronary artery injury during the placement of the flow probe. Baseline measurements including metabolic, haemodynamic, and biochemical parameters are presented in table 5.1. The mean weight (kg) ± SD was 69 ± 15.1, with an estimated total blood volume (mL) of 4769 ± 828. The time (min) from start of exsanguination to asystole was 53 ± 13, and 2538 ± 682 (mL) of blood were shed, comprising of 52 ± 11 (%) of total volume. No arrythmias were recorded, with organized cardiac activity present until asystole.

5.3.7.2 Biochemical Trends

Figure 5.2 represents serum lactate and K^+ trends throughout exsanguination. There was a significant raise in lactate overall (One way ANOVA. $p < 0.001$). Post hoc analysis revealed an increase from 2.17 ± 0.20 mmol/L at baseline to 3.78 ± 0.35 mmol/L at 30 min, ($p = 0.004$), and with every 15 min increment thereafter 6.68 ± 0.51mmol/L ($p < 0.001$) and 9.11 ± 0.53 mmol/L, ($p = 0.039$) at 45 and 60 min respectively. Similarly, for BE and HCO_3-, there was a trend demonstrating a gradual reduction overtime with 6.07 ± 0.95 mmol/L at baseline to - 0.58 ± 0.62 mmol/L at 45 min ($p < 0.001$), and 29.38 ± 0.80 mmol/L at baseline to 21.00 ± 1.48 mmol/L at 60 min ($p < 0.001$).

There were statistically significant changes in trends for pO_2 ($p < 0.001$), K^+ ($p < 0.001$) and Na^- ($p = 0.017$). Post- hoc analysis demonstrated a decrease in pO_2 from 528 ± 16.85 mmHg at baseline to 220 ± 62.23 mmHg at 60 min, ($p = 0.010$), an increase in K^+ from 4.26 ± 0.15 mmol/L at baseline to 5.71 ± 0.16 mmol/L at 30 min, ($p < 0.001$), and a reduction in Na^- from 137.42 ± 0.99 mmol/L at baseline to 132.85 ± 1.06 mmol/L at 45 min, ($p < 0.001$). There were no statistically significant differences in pCO_2 ($p = 0.146$), Ca^{2+} ($p = 0.311$), or Glucose ($p = 0.127$) throughout the exsanguination as determined by repeated measures ANOVA.

Parameter		N=9
Weight (kg)		69 (15.1)
Male, (%)		11 (100 %)
Estimated total blood volume (mL)		4769 (828)
Spleen weight (g)*		588 (194)
Baseline Metabolic		
	pH	7.44 (0.06)
	pCO_2 (mmHg)	45.61 (5.95)
	pO_2 (mmHg)	540.73 (46.00)
	Lactate (mmol/L)	1.99 (0.56)
	BE	6.20 (2.70)
	Bicarbonate (mEq/L)	29.67 (2.66)
	Temp (°C)	38.21 (0.92)
	$ETCO_2$ (%)	352 (0.51)
Baseline Biochemistry		
	K^+ (mmol/L)	4.21 (0.38)
	Na^-(mmol/L)	136.9 (1.52)
	Ca^{2+}(mmol/L)	1.39 (0.05)
	Cl^- (mmol/L)	99.2 (1.75)
	Glucose (mg/dL)	89.4 (44.71)
	BUN (mg/dL)	6.78 (2.91)
	Creatinine (mg/dL)	1.34 (0.25)
Baseline Haematology		
	Hct (%)	28.25 (2.82)
	Hb (g/dL)	9.61 (0.96)
Hemodynamic		
	RAP (mmHg)	2.84 (1.30)
	RVP (mmHg)	15.45 (5.74)
	Aortic Root SBP (mmHg)	77.38 (9.65)
	Aortic Root Pressure DBP (mmHg)	57.33 (10.54)
	HR (bpm)	86 (6)
	CO (L/min)	3.10 (0.49)
	SV (mL)	36.43 (7.02)
	LV End Diastolic Volume (mL)	118.26 (32.98)
	LV End Diastolic Pressure (mmHg)	4.22 (0.97)
	EF (%)	29.69 (12.47)
	CPP (mmHg)	56.07 (10.06)
	Coronary flow (mL/min)	29.36 (10.96)
Exsanguination		
	Time to ECA (min)	53 (13)
	Volume exsanguinated (mL)	2538 (682)
	% total volume exsanguinated	52 (11)

Legend: Hct- Haematocrit, Hb- Haemoglobin, BUN- Blood Urea Nitrogen, RAP- Right Atrial Pressure, RVP- Right Ventricular Pressure, SBP- Systolic Blood Pressure, DBP- Diastolic Blood Pressure, HR- Heart Rate, CO- Cardiac Output, SV- Stroke Volume, LV- Left Ventricle, EF- Ejection Fraction, CPP- Coronary Perfusion Pressure

Table 5.1 Baseline characteristics of the study group. Presented as mean and standard deviation (*median and IQR) or proportions (percentages).

5.3.7.3 Hemodynamic, Cardiac and Coronary Trends

Figure 5.3 represents hemodynamic changes which occur during the exsanguination. A drop in MAP was demonstrated ($p < 0.001$). Following the start of exsanguination there was a sudden reduction in aortic BP in the first 15 minutes, followed by a more gradual decrease until asystole. The reduction of aortic MAP during the hemorrhage was demonstrated using repeated measures ANOVA ($p < 0.001$) with a significant drop from 70 ± 3 mmHg at baseline to 39 ± 4 mmHg at 15 minutes, ($p = 0.036$). The following 15 min incremental reductions in MAP were not statistically significant: 35 ± 3 mmHg, ($p = 0.622$), 24 ± 3 mmHg, ($p = 1.000$), and 12 ± 5 mmHg, ($p = 0.121$).

A similar trend was demonstrated with CPP although not statistically significant ($p = 0.475$). A trend in the cardiac output (CO), (figure 5.4 A) also demonstrates a sudden reduction in the first 15 min followed by a plateau between 15 - 30 min before a final gradual descent until asystole although these changes are not statistically significant ($p = 0.142$). Likewise, similar findings are demonstrated for left ventricular end diastolic volume ($p = 0.067$), and SV ($p = 0.085$), with a rapid drop in indices in the first 15 min of hemorrhage followed by a plateau until a final deterioration at about 60 min.

Coronary flow was maintained at a constant plateau ($p = 0.208$) during the exsanguination until a sudden reduction at about 55 min. Similar trend over time was demonstrated with EF ($p = 0.355$). Coronary flow was correlated against EF using a simple linear regression, with $R^2 = 0.6567$, $p < 0.001$ (figure 5.5 D). When plotted against MAP, coronary flow is preserved throughout at 23 ± 5 mL/min until a decline once MAP reached 20 mmHg leading to asystole (figure 5.5 C). $R^2 = 0.8178$ and a maximal inflexion point of 22.50.

5.3.8 Discussion

This study describes the hemodynamic changes observed during a logarithmic exsanguination in fluid naïve animals. Two distinct phases are apparent – an initial fall in BP and CO, with relative preservation of coronary flow, until a critical blood pressure threshold, whereupon coronary flow fails, and asystole ensues. The critical pressure at which that occurred was 20 mmHg MAP.

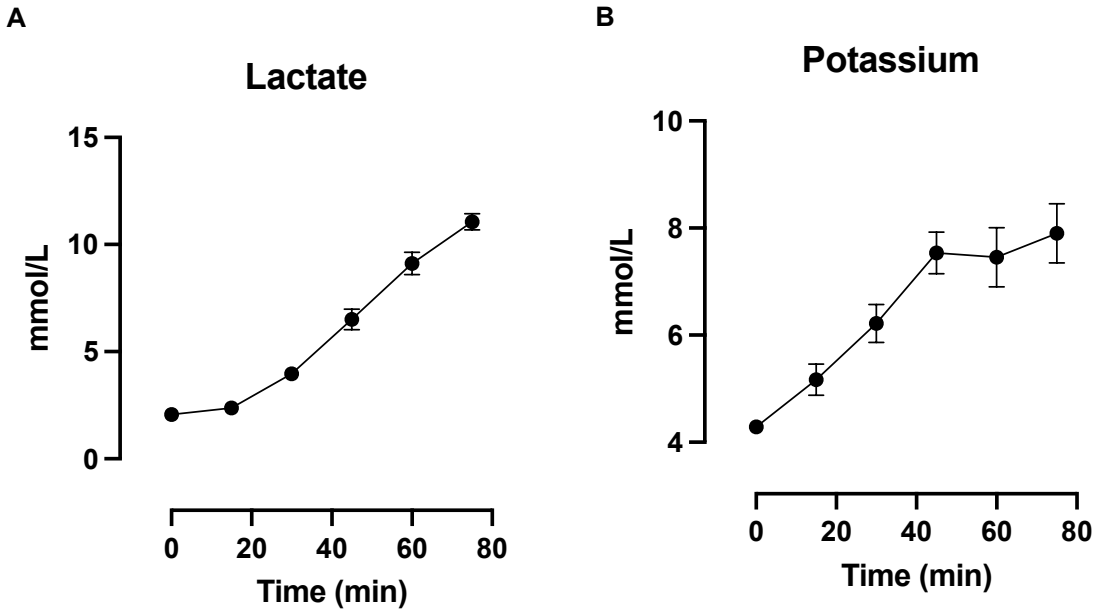

Figure 5.2 Lactate (A) and Potassium (B) trends showing a significant increase ($p < 0.001$, one-way ANOVA) during a logarithmic exsanguination of fluid naïve swine, where 45 minutes correlated with 50 % circulating volume. Presented as mean and standard error of mean.

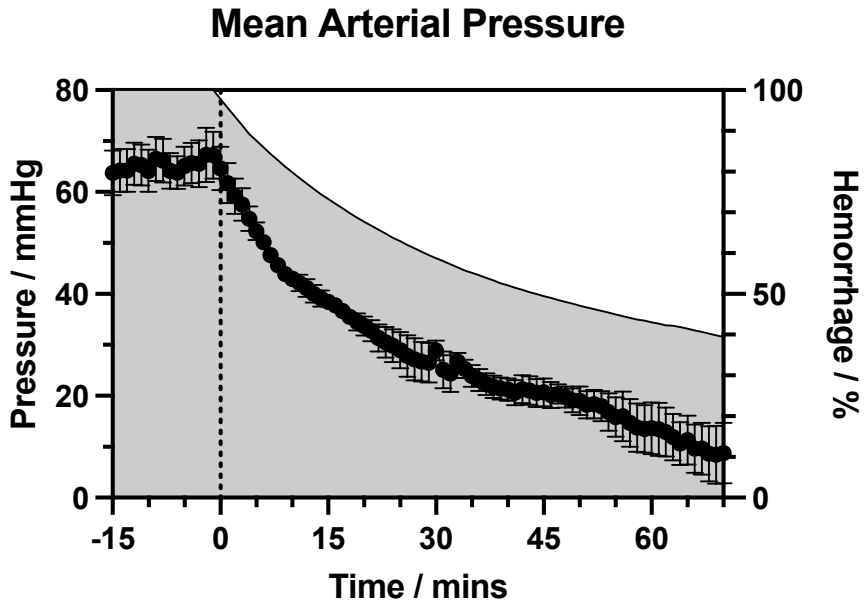

Figure 5.3 Hemodynamic changes during a logarithmic exsanguination of fluid naïve swine, where 45 minutes correlated with 50% circulating volume. Reducing trend in mean arterial pressure over time ($p = 0.005$, one-way ANOVA) presented as mean and standard error of mean.

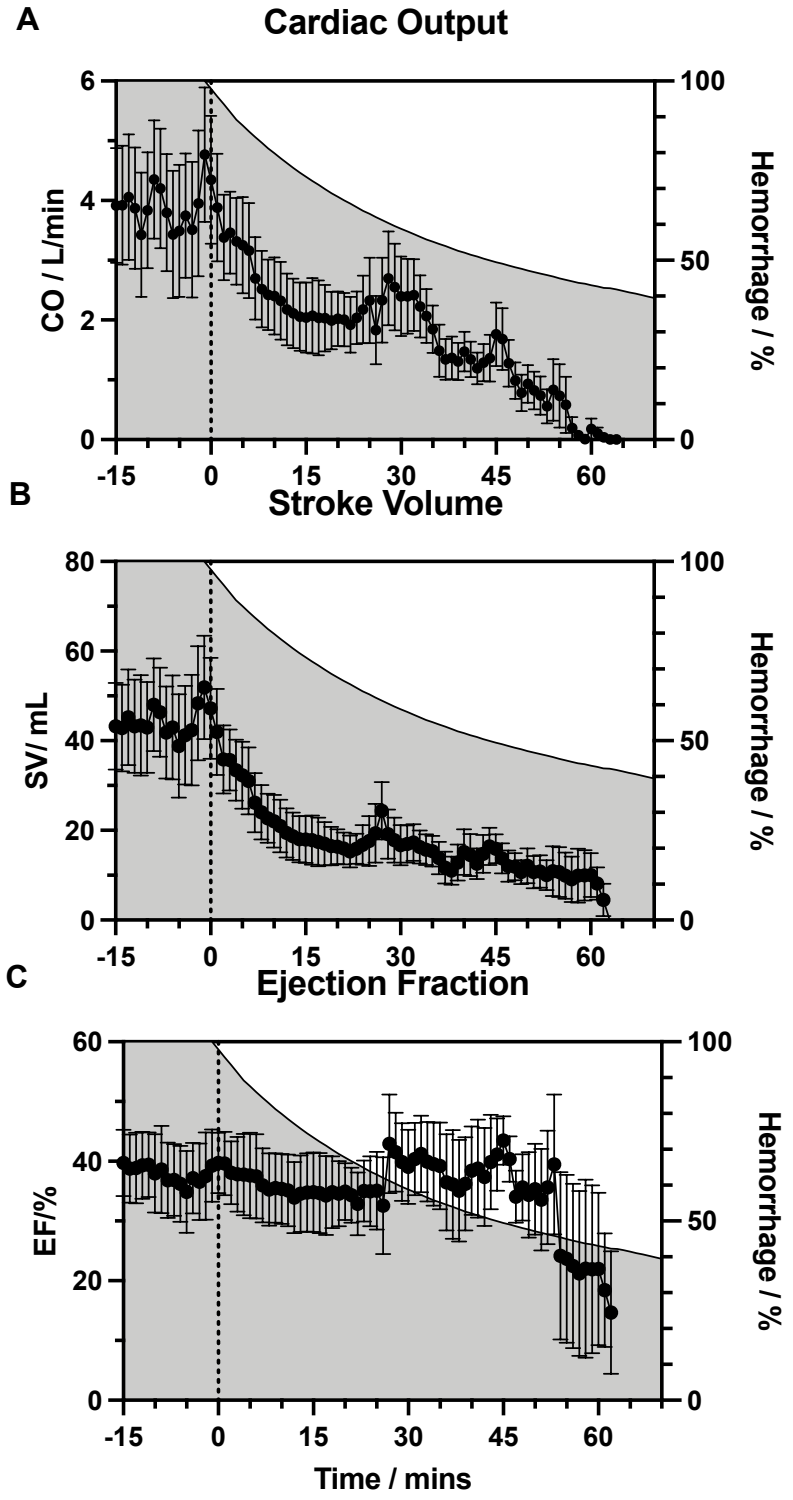

Figure 5.4 Trends representing changes in cardiac indices during the logarithmic exsanguination of fluid naïve swine, where 45 minutes correlated with 50% circulating volume. A Cardiac Output (p = 0.142, one- way ANOVA). B Stroke Volume (p = 0.085, one- way ANOVA). C Ejection Fraction (p = 0.355, one- way ANOVA). Presented as mean and standard error of mean.

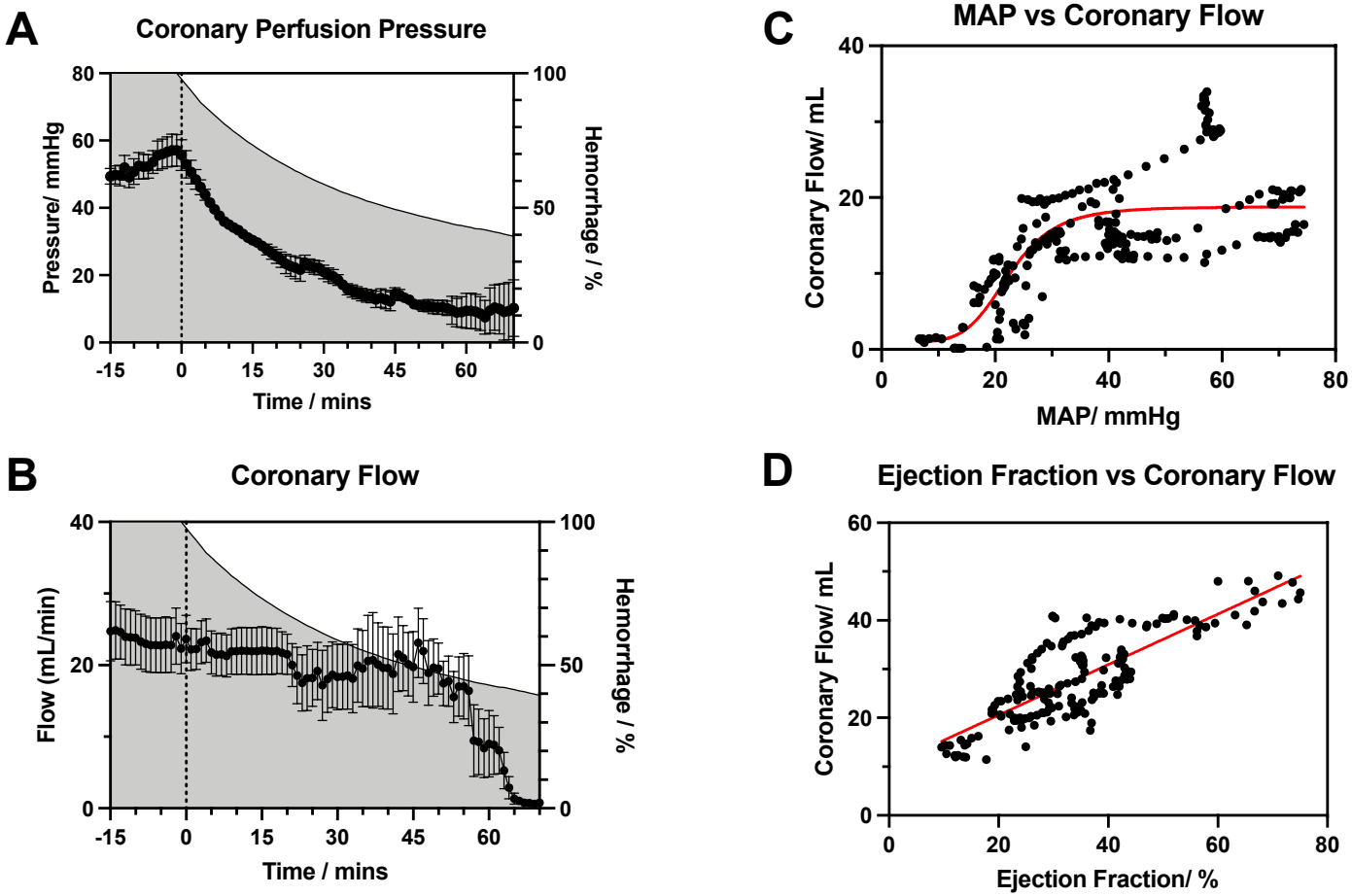

Figure 5.5 Trends representing changes in coronary indices during the logarithmic exsanguination of fluid naïve swine, where 45 minutes correlated with 50% circulating volume. A Coronary Perfusion Pressure (p =0.474, one- way ANOVA). B Coronary Flow (p = 0.208, one-way ANOVA) presented as mean and standard error of mean. C A scatterplot of coronary flow versus Mean Arterial Pressure with a nonlinear curve fitted. D A scatterplot of coronary flow versus Ejection Fraction with a linear curve fitted.

There are several limitations to this study. Only one model of exsanguination was chosen to represent the processes that occur during haemorrhage until asystole. The non- linear model applied in this work has been shown to reflect the physiological changes that occur during bleeding (Frankel *et al.*, 2007). Real life clinical scenarios, vary in terms of rate of haemorrhage and accompanying factors such as co-morbidities, injury pattern or environmental influences which are unique to every patient. The exsanguination model applied may not reflect all these factors. Swine have been studied extensively in cardiovascular research due to physiological similarities to humans, however, interspecies variations may still exist- confounding the results. The data presented in this work is limited to haemodynamic changes, other complex physiological mechanisms such as activation of inflammatory or haemostatic pathways may take place during exsanguination, but this is beyond the scope of this study. Another limitation relates to data accuracy. The PV conductance catheter used in this study has been shown to be a reliable method of measuring beat to beat cardiac indices (Baan *et al.*, 1984). However, the accuracy of data obtained by the conductance catheter depends on its position within the left ventricle relative to the apex and ventricular walls. There is the possibility of relative change in the catheter position due to ongoing hypovolemia and reduced ventricular filling resulting which could reduce the accuracy of data obtained. Moreover, there was a failure of the LDF probe early in the experiment, and reliable data for this were only obtained for 3 animals. Thus, we have elected to exclude LDF data from analysis. Although this was deemed to have limited impact in the current findings, future analysis of regional cardiac tissue perfusion may add further knowledge to exsanguination physiology and impact future management options.

5.3.9 Conclusions

This study demonstrates that initial haemodynamic instability relates to preload failure, but late changes resulting in asystole relate to failure in coronary perfusion. Current therapies do not address coronary perfusion specifically, which likely explains the poor clinical outcomes following ECA. Future resuscitative therapies need to directly address coronary perfusion failure if effective attempts are to be made to salvage these patients.

5.4 Myocardial Tolerance to Exsanguination and Retrieval Using Whole Blood-Selective Aortic Arch Perfusion

5.4.1 Background

SAAP is an emerging catheter-based resuscitation technique consisting of aortic occlusion and selective perfusion of the coronary and cerebral circulation with an oxygen carrier (Manning *et al.*, 2001; Madurska, Abdou, *et al.*, 2020; Madurska *et al.*, 2021). The resulting coronary flow is crucial to obtaining ROSC as described in sections 1.3.1 and 1.3.2. Translational research outlined in section 1.3.3 has demonstrated encouraging outcomes in animal models of ECA. Conventional resuscitative measures such as RT and open cardiac message or REBOA are known to be futile after only a few minutes of arrest (Ivatury *et al.*, 1991; Blake *et al.*, 1992; Mazzorana *et al.*, 1994; Hunt, Greaves and Owens, 2006; Søreide *et al.*, 2007; Van Waes *et al.*, 2012; Lockey, Lyon and Davies, 2013; Millin *et al.*, 2013; Inaba *et al.*, 2015; Braz *et al.*, 2020). Many centres do not perform RT for ECA if it has been more than 10 or 15 minutes of downtime, depending on the clinical scenario and mechanism of injury (Burlew *et al.*, 2012). It is, however, not known what length of arrest, before initiation of SAAP, the myocardium will tolerate before outcomes deteriorate and intervention become futile. The aim of this study is to define the temporal relationship between the length of ECA and the ability to obtain ROSC with a whole blood SAAP system on a large animal cardiovascular model system.

5.4.2 Study Design

This study utilized animals as described in section 2.2. The study enrolled 24 animals in 3 groups, based upon untreated ECA time: 5 min (5-SAAP), 10 min (10-SAAP) or 15 min (15-SAAP). The experimental protocol consisted of five phases: preparation, baseline, ECA, SAAP resuscitation and a 60-min critical care period (figure 5.6). The animals were euthanized at the end of the study protocol. The animals were randomly allocated into one of three groups: 5-SAAP, 10-SAAP and 15-SAAP just before SAAP resuscitation using the sealed envelope allocation concealment system. The development of this protocol has been previously published (Madurska, Abdou, *et al.*, 2020). Cardiac arrest was defined as a sustained MAP < 20 mmHg, a critical threshold previously defined by

work from our laboratory (Madurska, Abdou, *et al.*, 2020; Abdou *et al.*, 2021; Madurska *et al.*, 2021).

5.4.3 Methods

Animal preparation was conducted as described in sections 2.3 and 2.4. Animals were instrumented according to section 2.4.6 and following 15 min of baseline data collection, pump- controlled exsanguination was performed according to sections 2.5 and 2.5.2.

5.4.4 Cardiac Arrest and Resuscitation

Once ECA was achieved, the animals were maintained in cardiac arrest without intervention for 5, 10 or 15 minutes - depending on the study arm. During this time, an 11 Fr balloon catheter was advanced via the 14 Fr femoral sheath under fluoroscopic guidance into the proximal thoracic aorta where the balloon was inflated to occlude the aorta. The ECMO cannula used for exsanguination was clamped, the indwelling SAAP catheter was connected to the circuit, and the syringes containing AV closure bolus and Adrenaline were attached to the syringe hub of the catheter (figure 2.5). At the time of intervention SAAP resuscitation was initiated as described in section 2.7.1, (Madurska, Abdou, *et al.*, 2020).

The aortic pressure catheter trace was observed for pulsatility, indicating ROSC which was defined as central MAP ≥ 50 mmHg sustained for > 1 min following initiation of SAAP. This was based on the rationale that clinically, a central pulse would not be palpable below this threshold (Deakin and Low, 2000). In the absence of ROSC, further SAAP boluses could be delivered up to a maximum of three. In the event of a shockable arrythmia, defibrillation was performed according to section 2.7.2. If ROSC was successful, the SAAP circuit was used to deliver blood to the venous side of the circulation via the femoral venous cannula. Following successful ROSC, 60 minutes of

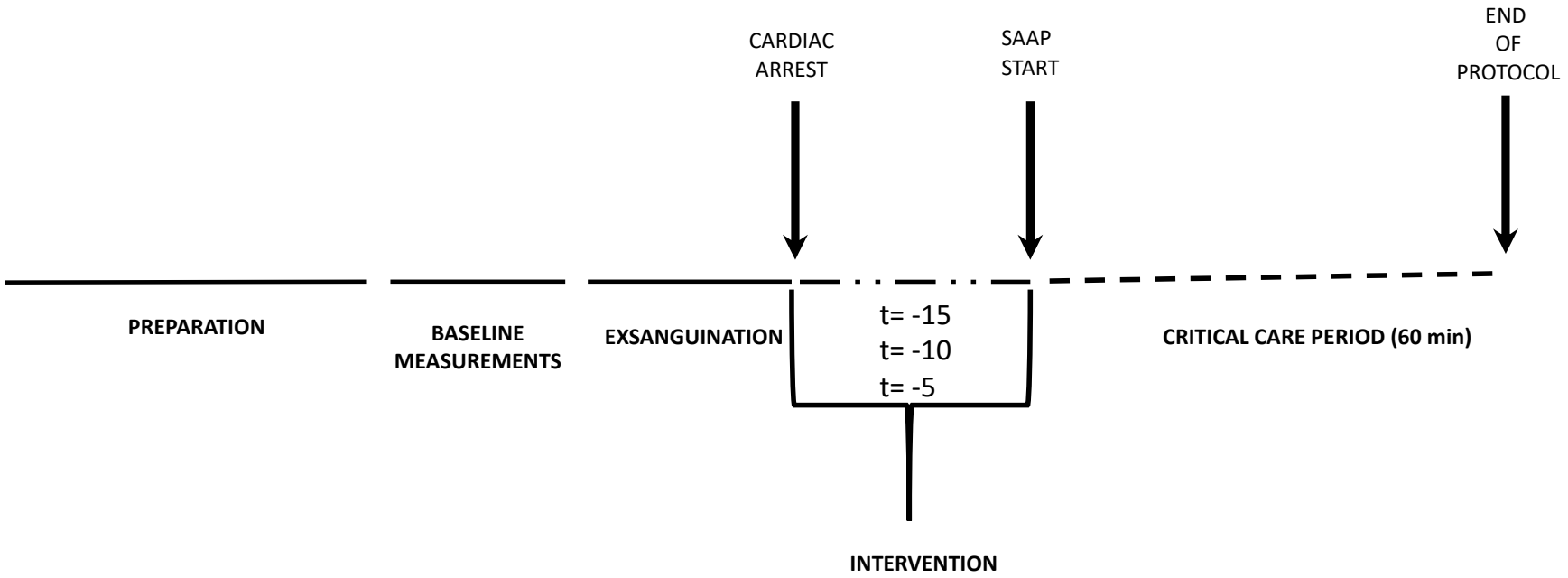

Figure 5.6 Study Protocol Timeline. After the animals were instrumented and prepared, a 15-minute window was observed for baseline data collection. Animals were then exsanguinated to 50 % blood loss followed by a 5-, 10- or 15-min ECA time, at which time SAAP was started, and the animal is resuscitated.

critical care period was commenced where animals were observed, and supportive management was applied as described in section 2.8. After the critical care period, the animals were euthanized as per section 2.10.

5.4.5 End of study

The study concluded when either the animal died or survived to the end of the 60- min critical care period. At the end of the study blood samples were drawn, and the animal was euthanized as described in section 2.9.

5.4.6 Data Collection

Data collection was performed according to sections 2.10.2 and 2.10.3. Physiologic data collected included: SaO2, $ETCO_2$, core body temperature, electrocardiography monitoring, aortic root pressure and RAP, MAP, HR. Blood gas sampling was performed at baseline and every 15 minutes during the critical care period (Radiometer, Copenhagen, Denmark). Venous blood samples were taken at baseline, beginning and end of the critical care period.

5.4.7 Experimental Outcomes

The primary outcome was survival. Secondary outcomes consisted of the hemodynamic data, resuscitation requirements, and metabolic findings.

5.4.8 Statistical Analysis

Statistical analysis was performed as described in section 2.11.

5.4.9 Results

5.4.9.1 Baseline Characteristics

A total of 24 animals were enrolled into the study and were randomized into three groups. Baseline measurements were obtained after instrumentation and prior to the start of exsanguination (figure 5.6). One animal sustained a myocardial infarction during the

exsanguination and was excluded from the study. The final groups were made up: 5-SAAP n = 8, 10-SAAP n = 8 and 15-SAAP n = 7. All animals were of a similar weight and baseline physiological parameters as presented in table 5.2.

5.4.9.2 ROSC and Overall Survival

Following SAAP, the proportion of animals achieving ROSC per group was: 8/8 (100 %) 5-SAAP, 6/8 (75 %) 10-SAAP, and 3/7 (43 %) 15-SAAP group; p = 0.042. In terms of the number of SAAP runs given to provide adequate ROSC, in both 5- SAAP and 10-SAAP groups 2/8 (25 %) animals received 2 runs and in the 15-SAAP group 1/7 (14 %) received 2 runs (p = 0.725), while all the other animals only had 1 run. Not all animals achieving ROSC survived to the end of the study, with 60 -minute survival per group: 6/8 (75 %) 5-SAAP, 50 % (4/8) 10-SAAP and 1/7 (14.3 %) 15-SAAP; p = 0.015 (figure 5.7). *Post-hoc* testing between groups demonstrated that the 5-SAAP group had a significantly higher survival compared to 15-SAAP (p = 0.032), but other comparisons did not achieve significance.

5.4.9.3 Hemodynamic Outcomes

Hemodynamic trends are presented in figure 5.9. All Animals responded similarly to controlled exsanguination with a sustained drop in BP and CPP to under 20 mmHg. HR was maintained with tachycardia until ECA whereupon the animals became profoundly bradycardic. RAP was relatively preserved through the exsanguination until ECA. During ECA, just prior to resuscitation, all groups were similar in terms of SBP, DBP, MAP, HR, and RAP (table 5.2).

During SAAP, the highest aortic blood pressure achieved per groups were: 127 ± 36 mmHg in 5-SAAP, 87 ± 45 mmHg in 10-SAAP, and 61 ± 41 mmHg in 15-SAAP (p = 0.016). This was reflective of the improved ROSC rate observed in the groups. The highest coronary perfusion pressure during 1 min of SAAP, measured prior to ROSC, was consistent between the 3 groups: 34 ± 10 mmHg, 34 ± 10 mmHg and 26 ± 13 mmHg (p > 0.05) (figure 5.9).

In animals that survived to the end of protocol, BP indices were significantly lower at the end of the critical care period compared to baseline (pairwise data), with MAP 78 ± 9.6 mmHg vs 58 ± 9.4 mmHg, ($p = 0.002$), SBP 94 ± 11.5 mmHg vs 81 ± 8.8 mmHg, ($p = 0.006$), and DBP 70 ± 8.7 mmHg vs 47 ± 11.8 mmHg ($p = 0.008$). HR was 93 ± 17 bpm at baseline compared to 144 ± 11 bpm at the end of the protocol ($p < 0.001$). RAP remained unchanged between baseline and end of protocol 3 ± 3 mmHg vs 2 ± 3 mmHg ($p = 0.394$). There were no differences in the study groups in hemodynamic indices at baseline or at end of the study.

5.4.9.4 Resuscitation Requirements

Four animals (n = 2 10-SAAP, and n = 2 15-SAAP) developed ventricular fibrillation (VF) and required defibrillation. Both animals in 10-SAAP group achieved ROSC but only one survived to the end of the protocol, while neither of the 15-SAAP group animals were successfully defibrillated.

Regarding transfusion and vasoactive medication, only groups with two or more animals surviving to the end-of-study were included in this analysis, no animals in the 15-SAAP group were eligible for analysis, thus this analysis included only 5-SAAP and 10-SAAP animals. The volume transfused was 2033 ± 1289 mL and 1875 ± 1250 mL for 5-SAAP and 10-SAAP respectively, ($p = 0.91$); urine output was 195 ± 183 mL and 170 ± 60 mL for 5-SAAP and 10-SAAP respectively, ($p = 0.25$). 10-SAAP required significantly more Noradrenaline (1.31 ± 0.83 mg vs 0.76 ± 0.24 mg) compared to 5-SAAP ($p = 0.008$). There were no differences in dobutamine, $CaCl_2$, dextrose, $MgSO_4$, or HCO_3- administration between the groups.

5.4.9.5 Metabolic Outcomes

There were no differences in metabolic indices demonstrated between the study groups at baseline compared to the end of the study. All animals that survived to the end of the protocol developed metabolic acidosis at the end of the critical care period as evidenced by changed in pH, Lactate, BE, and HCO_3- (table 5.3). There was a significant drop in Hb, Hct as well as arterial pO_2 at the end of the critical care period compared to baseline

measurements. Moreover, animals who survived to the end of the study had significantly increased serum TnT levels at the end of the protocol compared to baseline.

5.4.10 Discussion

This study demonstrates the temporal relationship between warm ischaemic time during ECA and the resuscitation potential of the myocardium using a whole blood SAAP system. In this swine model using non-diseased hearts and a weight based SAAP resuscitation protocol, 87.5 % of subjects achieved ROSC if the ischaemic time did not exceed 10 minutes, with a 75 % overall survival at 1- hour post- ROSC. Longer ischaemic time was also associated a greater vasopressor need in surviving subjects.

This study has some limitations. The experiments were performed on animals in laboratory conditions. SAAP resuscitation performed in the laboratory conditions was complex logistically and the set up would need more development before being feasible in a clinical realm. The researchers were not blinded to the study group, and this may have contributed to selection bias. This was due to limited personnel allowed in the laboratory during the COVID-19 pandemic. Restrictions related to the pandemic also limited the length of post-SAAP monitoring that was feasible due to limitations with veterinary resources and staffing. The study was performed using a controlled haemorrhage model- this allowed standardization but would not translate easily to a clinical realm where trauma cases and the rate of bleeding are highly heterogenous. The animals were instrumented *a priori*, including SAAP catheter placement- in a clinical scenario, in a patient in extremis catheterisation would likely be more complicated. Furthermore, this model does not assess long term outcomes including neurological sequalae of resuscitation after a prolonged cardiac arrest, nor cerebral perfusion directly during ECA or SAAP. Another major barrier to clinical application currently is lack of FDA approved catheter and circuit for the delivery of SAAP; however, devices and circuits used in cardiac surgery have been used in animal studies. To re- role such devices for SAAP would require investigational device exemptions from the FDA (Barnard *et al.*, 2017; Hoops *et al.*, 2019). Human blood, in most clinical scenarios, is the only available perfusate and its prompt availability carries logistical and immunological implications, but no more than a conventional massive transfusion protocol. Finally, expansion to humans

for post-cardiac arrest clinical trials would need careful ethical consideration as subjects would be unable to consent to enrolment in a trial, so an exempt community mechanism would have to be considered (Sanders, 2011).

5.4.11 Conclusion

In a swine model of controlled hemorrhage followed by cardiac arrest, whole blood SAAP can be used to restore spontaneous circulation at high rates even after 10 minutes of unsupported cardiac arrest, with some viability beyond to at least 15 minutes. Additional work is needed to fully optimize SAAP, with a focus on improving coronary and cerebral perfusion, and selecting medical adjuncts and perfusates to sustain myocardial recovery.

Baseline Characteristics				
Variable	**5 min** ***n* = 8**	**10 min** ***n* = 8**	**15 min** ***n* = 7**	***P***
Body weight/ kg	61.5 (9.8)	63.8 (13.2)	59.3 (6.9)	0.704
Spleen weight/g	397.6 (94.1)	407.5 (175.3)	380.9 (165.3)	0.703
Volume Shed/ mL	1549.8 (314.5)	1789.8 (495.2)	1750.1 (235.8)	0.402
Asystole/ %	0	3 (37.5 %)	2 (28.6 %)	0.032*
Arterial Blood Gas				
pH	7.5 (0.6)	7.5 (0.1)	7.5 (0.1)	0.653
pCO2/ mmHg	37 (3.5)	39.4 (8.3)	34.4 (7.2)	0.380
pO2/ mmHg	231.3 (50.3)	198.4 (86.5)	291.0 (47.4)	0.039*
sO2/ %	99.6 (0.2)	97.6 (5.2)	99.7 (0.1)	0.061*
FO2/ %	98.8 (0.2)	96.8 (5.1)	99.0 (0.1)	0.061*
FHHb/ %	0.4 (0.2)	2.4 (5.1)	0.2 (0.1)	0.061*
Lactate/ mmol/L	1.9 (0.8)	2.5 (1.5)	2.9 (1.4)	0.397
BE/ mmol/L	4.5 (3.1)	3.7 (5.2)	3.2 (2.4)	0.787
Bicarbonate/ mmol/L	28.9 (3)	28.0 (5.1)	27.9 (2.2)	0.851
Serum Biochemistry				
K+/ mmol/L	3.8 (0.3)	3.9 (0.2)	4.0 (0.3)	0.405
Na^-/ mmol/L	134.5 (3.8)	133.9 (3.0)	313.0 (3.5)	0.151
Ca^{2+}/ mmol/L	1.3 (0.0)	1.3 (0.1)	1.3 (0.6)	0.164
Cl^-/ mmol/L	100.6 (3.9)	100.4 (4.1)	98.1 (4.8)	0.357
Glucose/ mg/dL	97.0 (44.0)	93.9 (71.9)	117.7 (29.3)	0.641
BUN/ mg/dL	5.1 (2)	4.7 (1.6)	5.5 (3.1)	0.799
Creatinine/ mg/dL	1.3 (0.2)	1.3 (0.3)	1.4 (0.3)	0.645
Htc/ %	30.3 (3.7)	27.3 (4.5)	29.0 (2.7)	0.318
Hb/ g/dL	10.3 (1.3)	9.3 (1.5)	9.9 (0.9)	0.330
TnT/ ng/mL	0.1 (0.1)	0.0 (0.0)	0.1 (0.1)	0.212
Hemodynamic				
SBP/ mmHg	102 (13.6)	93 (10.9)	90 (12.4)	0.406
DBP/ mmHg	74 (12)	68 (10.4)	63 (11.5)	0.212
MAP/ mmHg	84 (12.4)	76 (10.4)	72 (11.4)	0.499
HR/ bpm	89 (21.0)	92 (13)	92 (9.3)	0.635
RAP/ mmHg	0 (3.8)	4 (3.4)	3 (4.3)	0.618
CPP/ mmHg	70 (12)	68 (9)	61 (10)	0.215
Hemodynamic during ECA/ Pre SAAP				
SBP/ mmHg	18 (10)	11 (7)	7 (8)	0.061
DBP/ mmHg	12 (3)	6 (6)	5 (9)	0.100
MAP/ mmHg	12 (8)	7 (6)	4 (6)	0.126
HR/ bpm	75 (80)	37 (18)	45 (16)	0.707
RAP/ mmHg	-2 (-2)	0 (2)	2 (3)	0.774

Legend: Hct- Haematocrit, Hb- Haemoglobin, BUN- Blood Urea Nitrogen, TnT- troponin T, RAP- Right Atrial Pressure, RVP- Right Ventricular Pressure, SBP- Systolic Blood Pressure, DBP- Diastolic Blood Pressure, MAP- Mean Arterial Pressure, HR- Heart Rate, CPP- Coronary Perfusion Pressure

Table 5.2 Baseline characteristics of the study groups.

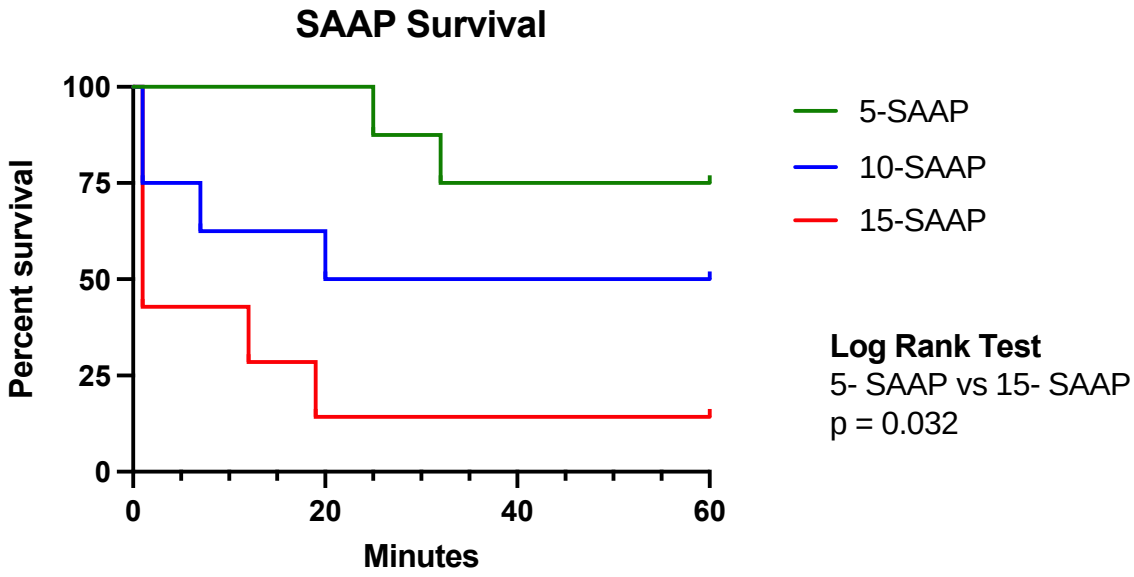

Figure 5.7 Overall percent survival (1- hour post ROSC) of 5-SAAP group (n = 6),10-SAAP group (n = 4) and 15-SAAP group (n = 1).

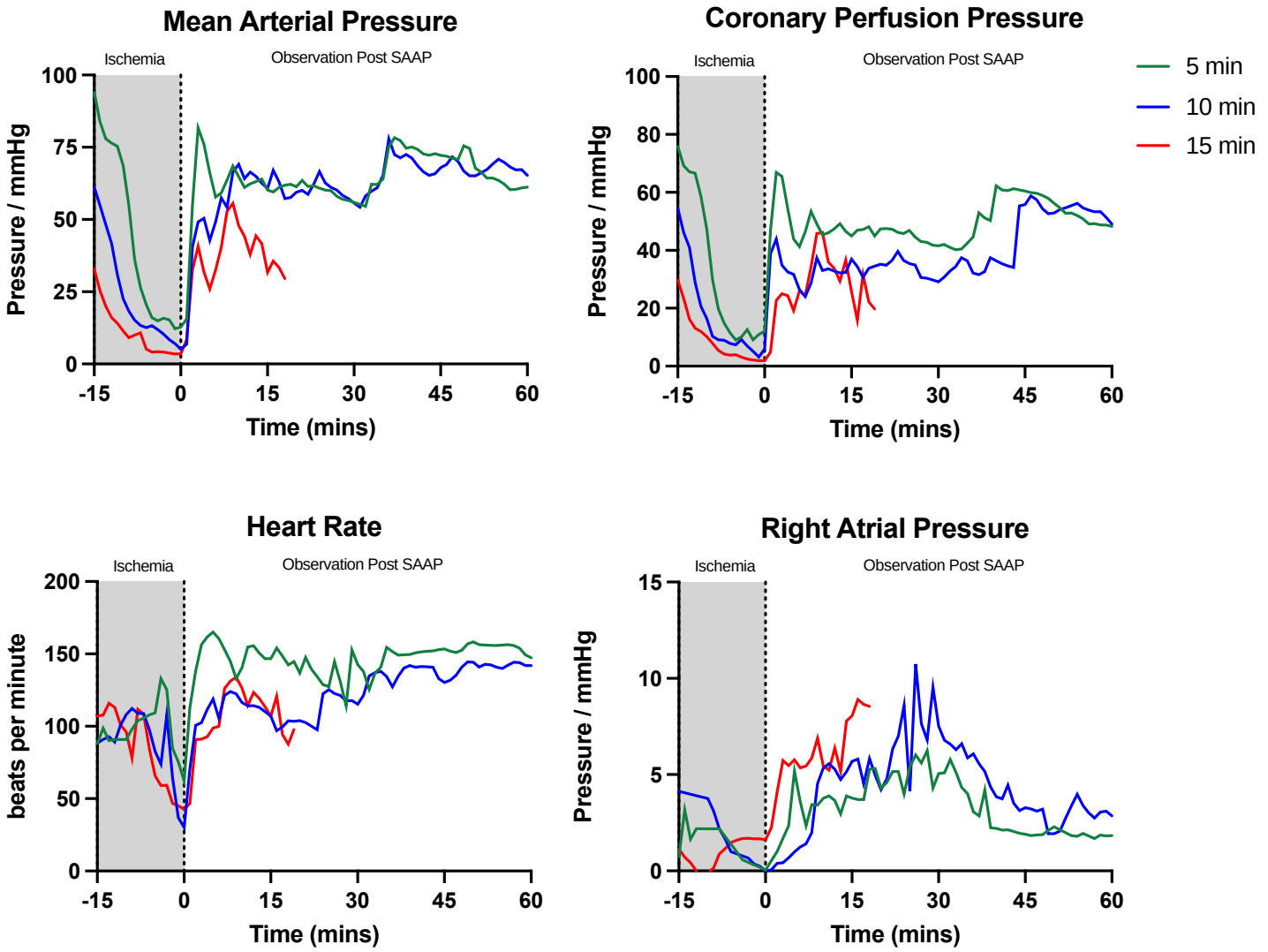

Figure 5.8 Secondary Outcomes. Mean Arterial Pressure, Coronary Perfusion Pressure, Heart Rate, Right Atrial Pressure trends throughout the experimental phase. The graphs are normalized to the initiation of SAAP at time = 0 min

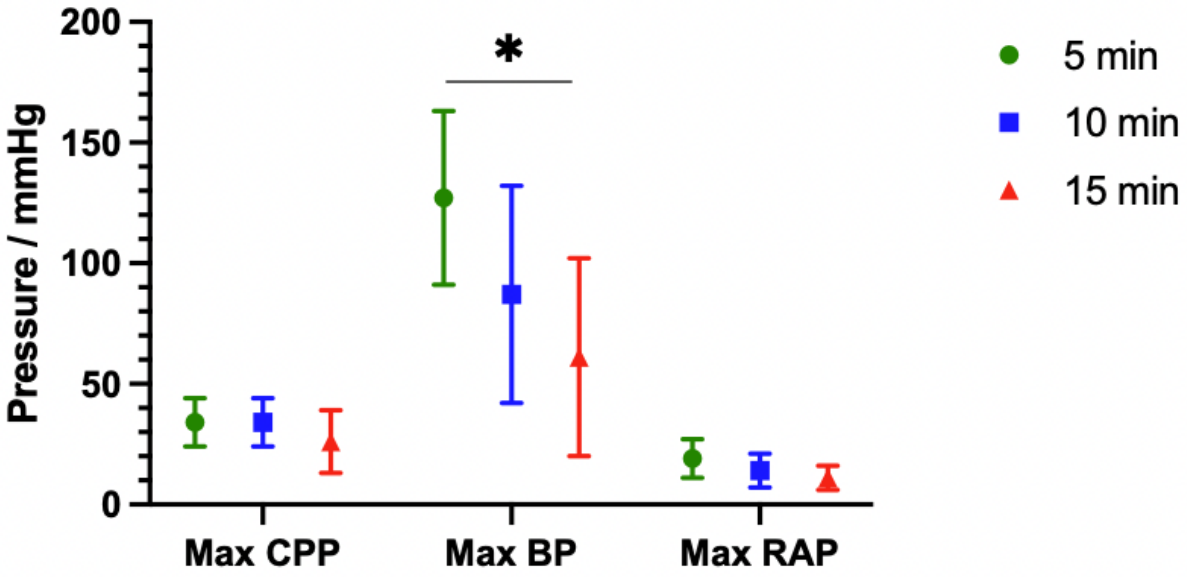

Figure 5.9 Hemodynamic indices during SAAP delivery. Maximal measured coronary perfusion pressure (Max CPP), maximal central aortic systolic blood pressure (Max BP) and maximal right atrial pressure (Max RAP). (*) Indicates differences between groups ($p < 0.05$).

	5- SAAP n = 6/8			10- SAAP n = 4/8		
Physiology	**Baseline**	**End of protocol**	***P***	**Baseline**	**End of protocol**	***P***
pH	7.49 (0.06)	7.19 (0.18)	0.005*	7.48 (0.12)	7.22 (0.12)	<0.001*
pCO_2	36.98 (3.25)	51.63 (17.78)	0.073	37.00 (3.39)	44.00 (11.58)	0.274
pO_2	231.25 (50.30)	181.80 (196.23)	0.542	233.40 (65.67)	126.60 (44.41)	0.034*
Lactate	1.94 (0.80)	6.14 (1.83)	0.012*	2.45 (1.46)	5.66 (1.02)	0.043*
BE	4.51 (3.06)	-8.24 (5.43)	0.001*	4.06 (6.31)	-8.40 (7.26)	0.001*
Bicarbonate	28.85 (2.95)	16.86 (5.32)	0.001*	28.58 (6.06)	17.30 (5.23)	0.001*
K^+	3.86 (0.31)	3.98 (1.12)	0.865	3.89 (0.18)	3.10 (0.45)	0.043*
Ca^{2+}	1.33 (0.04)	1.46 (0.19)	0.106	1.28 (0.05)	1.38 (0.18)	0.226
Glucose	97.00 (44.00)	147.88 (74.31)	0.123	93.86 (71.89)	156.40 (64.01)	0.225
BUN	5.12 (1.98)	5.13 (2.13)	1.000	4.70 (1.62)	4.11 (1.70)	0.180
Creatinine	1.28 (0.19)	1.20 (0.28)	0.334	1.29 (0.31)	1.14 (0.26)	0.336
Hct	30.25 (3.69)	26.71 (5.35)	0.075	27.27 (4.46)	20.43 (6.58)	0.043*
Hb	10.28 (1.30)	9.09 (1.82)	0.075	9.27 (1.52)	7.90 (2.05)	0.138
TnT	0.06 (0.05)	0.88 (0.84)	0.027*	0.02 (0.03)	0.65 (0.88)	0.108

Legend: BE- Base Excess, BUN- Blood Urea Nitrogen, Hct- Haematocrit, Hb- Haemoglobin, TnT- Troponin T

Table 5.3 Secondary outcomes comparing 5-SAAP baseline to end of protocol and 10-SAAP baseline to end of protocol. Metabolic indices before the experiment and at the end of 1-hour critical care period in animals that survived to the end of the study.

Chapter 6. General Discussion

6.1 Clinical study of REBOA in a large volume high experience centre

This study aimed to compare trauma patients treated with REBOA to those who did not undergo REBOA at a high- volume centre. We attempted to match the two groups of patients as well as possible- given the data constraints in the propensity score matching design. Our analysis showed that in a high volume, experienced centre., the use of REBOA is associated with a survival benefit in trauma patients.

Although the concept of aortic balloon occlusion for controlling intraabdominal haemorrhage was initially described during the war in Korea in the 1950s (Hughes, 1954), it was not readily adopted for another six decades due to limited availability (Osborn *et al.*, 2019). Since 2011, when it was re-introduced into clinical practice (Stannard, Eliason and Rasmussen, 2011), its use has grown across trauma centres and its role in the management of NCTH has been met with both praise (Moore *et al.*, 2015; Brenner, Inaba, *et al.*, 2018) and criticism (Norii *et al.*, 2015; Joseph *et al.*, 2019). Despite the growth in utilization of the technique, there is a paucity of evidence evaluating REBOA from high-volume centres within the United States with an adequate control group. Much of the literature that exists to date is from international sites (Yamamoto *et al.*, 2019), national databases that include both low and high-volume centres (Joseph *et al.*, 2019) and national registries that do not provide a suitable control group, if any (DuBose *et al.*, 2016; Brenner, Teeter, *et al.*, 2018).

The importance of evaluating REBOA outcomes in experienced centres to determine its true benefit cannot be overstated. A recent review of the American Association for the Surgery of Trauma (AAST) Aortic Occlusion for the Resuscitation in Trauma (AORTA) registry found that low- volume centres had a longer time to initiation of REBOA placement, longer time to AO and lower odds of successful placement when compared to high-volume centres (Theodorou *et al.*, 2020). Early and expedient common femoral artery access is critical to successful deployment of REBOA (Romagnoli *et al.*, 2017), but can be challenging in a hypovolemic patient, and is a technique that must be practiced regularly. Although REBOA patient volume by centre has yet to be directly liked to clinical outcomes, the relationship between experience and performance has been demonstrated

in several other procedural techniques. Given the introduction of the technique into the trauma landscape only 10 yrs prior, worldwide experience with REBOA is still building, and most centres are low- volume and still on the steep part of the learning curve.

Recent reviews of REBOA have been conducted using large database analyses and/or in other countries, which has yielded results that are not highly applicable to high-volume centres in the United States. The study by Joseph et. al has demonstrated worse outcomes using REBOA used the TQIP database from 2015- 2016, which draws information from hundreds of Level I- III trauma centres across the US, many of which only recently started using REBOA (Joseph *et al.*, 2019). Reports from the Japan Trauma Data Bank have been mixed regarding outcomes using REBOA, but the database used includes a large rural population with trained Emergency Department providers deploying REBOA (Norii *et al.*, 2015; Abe *et al.*, 2016).

The institution where the current study was conducted is a Level I trauma centre located in an urban setting with a high volume of penetrating trauma and high acuity blunt trauma, providing a vastly different setting for REBOA use as compared to those described in other observational studies either in the US or Japan. In this setting, REBOA is a part of a coordinated haemorrhage- control strategy that utilizes endovascular or open haemorrhage control techniques, with a 24/7 endovascular coverage by trauma-trained, vascular surgeons as part of an Endovascular Trauma Service. Service provision with dedicated trauma endovascular surgeons has shown reduced time to endovascular intervention and haemorrhage control (Morrison *et al.*, 2019). Local institutional set up includes a dedicated hybrid OR for trauma which allows for rapid access to concomitant endovascular and open procedures on patients who have undergone REBOA placement, if needed (Harfouche *et al.*, 2021). These resources ensure that REBOA is used in quick succession with other haemorrhage control techniques.

It has to be noted that the patients in the current study had very different selection criteria from the clinical study on Partial Occlusion REBOA described in section 3.3. The current study comparing REBOA to NO- REBOA included trauma patients aged 16 and over who

had both Zone I and Zone III occlusion, while the Partial REBOA study included patients 18 years and older in whom only Zone I occlusion was applied. Moreover, the current study comparing REBOA to No REBOA had excluded all patients who had a cardiac arrest prior to REBOA placement, but included all patients regardless to whether they made it to theatre or not. The P-REBOA study cohort on the other hand included patients who had a cardiac arrest prior to REBOA insertion but excluded all patients who had died before they had made to the operating room for damage control surgery.

There is selection bias related to patient inclusion to the studies as well to patients in whom the decision has been made to place REBOA in the first place and it must be recognised that outcomes in both studies may be affected by these biases.

6.2 Partial Occlusion REBOA

This is the first study comparing continuous and partial occlusion REBOA in a clinical setting. The study is underpowered and has a small sample but signals that continuous occlusion REBOA is associated with organ failure. There results also show increased need for vasoactive support in prolonged (> 30 min) complete occlusion REBOA compared with P-REBOA. This study demonstrates the feasibility and safety of P-REBOA in a trauma population with NCTH.

The important implication is that P-REBOA may avoid the detrimental consequences of prolonged total AO. The reduced need for vasopressors demonstrated in prolonged P-REBOA cohort could be explained by reduced ischaemia/ reperfusion injury. Moreover, although not statistically significant, this study demonstrates trends in lower SOFA scores in the first 48 hr as well as lower rates of renal failure and need for dialysis in prolonged P-REBOA.

Our findings confirm and extend previous published work. P-REBOA technique was first described by Johnson and colleagues in 2016 (Johnson *et al.*, 2016), who, using a porcine haemorrhagic shock model, demonstrated that P-REBOA is associated with a more

physiological haemodynamic profile than C-REBOA (Johnson, Williams, *et al.*, 2017). Moreover, another study demonstrated doubled survival time in swine treated with partial occlusion vs complete occlusion (163 min vs 86 min respectively) (Russo, Williams, *et al.*, 2016). The studies were further expanded to show that after 90 min, animals treated with C-REBOA had lactate levels three times higher than those managed with P-REBOA (3.2 vs 9.3), and signs of bowel ischaemia at necropsy (compared to none in P-REBOA) (Russo, Neff, *et al.*, 2016). Similarly, another swine model study showed that P-REBOA was associated with higher interstitial mucosal perfusion and three times lower tissue lactate/ pyruvate ratio compared to C-REBOA (Sadeghi *et al.*, 2018). With regards to occlusion duration, Markov and colleagues used a haemorrhagic swine model to demonstrate significantly higher fluid resuscitation needs (1,000 vs 2,667 ml/24hrs IV fluids ($p = 0.034$)), and higher level of renal dysfunction (BUN 32.3 vs 25 mg/dL, $p = 0.009$) in the 48 hr following 90 min REBOA than control group; these differences were not shown in 30 min occlusion (Markov *et al.*, 2013). Although 90 min occlusion employed by Markov is excessive given the current standards, it clearly demonstrates the detrimental outcomes of prolonged occlusion compared to haemorrhagic shock alone.

Although REBOA has been shown to improve survival in comparison to RT in the setting of NCTH (Moore *et al.*, 2015), large population studies using propensity score matching suggested that trauma patients treated with REBOA had increased mortality (Norii, Crandall and Terasaka, 2015), as well as higher rates of acute kidney injury (Joseph *et al.*, 2019). These studies do not report on duration or type of occlusion, but there is a suggestion of ischaemia/ reperfusion as an underlying cause of the mortality. A report from Japan, where P-REBOA has been practiced since 2011, includes 75 patients whose mortality was comparable to those treated with C-REBOA (Matsumura *et al.*, 2017), however, morbidity was not analysed. Furthermore, the current evidence base for P-REBOA is limited to several case reports with little evidence regarding outcomes (Davidson *et al.*, 2016; Hörer *et al.*, 2016; Okumura *et al.*, 2016; de Schoutheete *et al.*, 2018). Moreover, there are no clinical reports on patient outcomes depending on the duration of REBOA occlusion in contemporary literature, the current study being the only one.

The study showed that REBOA occlusion longer than 30 min, is associated with significantly higher mortality and increased need for organ support. These data have important potential implications for practice, and could explain increased mortality in REBOA patients observed in large studies by Joseph et al and Norii et al (Norii, Crandall and Terasaka, 2015; Joseph *et al.*, 2019). Our findings support the current clinical practice guidelines which recommend that Zone I REBOA is not inflated for more than 30 min (Glaser *et al.*, 2017; Bulger *et al.*, 2019). P-REBOA could potentially ameliorate the metabolic effects of occlusion and allow prolongation of REBOA without detrimental effects on mortality and morbidity.

The current study shows that prolonged P-REBOA patients required significantly less vasopressor support, and patients were more likely to be discharged home, rather than for ongoing rehabilitation. However, the numbers analysed to give this result were very small. We speculate that, with larger numbers of study subjects, significant differences in the need for organ support between prolonged P-REBOA and C-REBOA groups would be more evident. Moreover, the signal of reduced rates of organ failure in P-REBOA in prolonged use suggests that this technique may be able to prolong the beneficial effects of REBOA without the detrimental side effects of complete AO.

Despite growing clinical reports of P-REBOA, actual manual achievement of effective partial occlusion with REBOA is challenging. A study using an animal model demonstrated that even small changes in balloon volume, cause exponential variance in aortic flow past the balloon (Johnson, Davidson, *et al.*, 2017). In fact, optimal partial occlusion is not solely a product of the relationship between the aortic diameter and balloon volume but is influenced by a complex interplay of multiple, dynamic factors including volume status, catecholamine response, cardiac performance, and individual patient physiology. Whilst balloon inflation and resuscitation are the only variables subject to manipulation, the resulting aortic flow across the balloon, may not be sustainable (Johnson *et al.*, 2016). Difficulty in obtaining partial occlusion may also be related to the design of the balloon and currently there are ongoing developments in catheter design to address this (Forte *et al.*, 2019). Balloon technology in contemporary practice utilizes a

compliant design, which allows the balloon material to stretch and change shape to accommodate more inflated volume and mitigate the risks of arterial damage. Depending on the volume inflated and the diameter of the surrounding aorta, the balloon surface may have varying degrees of contact with the aortic wall. In a clinical scenario it is impossible to judge how much balloon volume should be removed to precisely reduce to the surface of balloon and aortic wall apposition to effectively transform balloon occlusion from complete to partial. Moreover, small changes in balloon volume may result in significant differences in blood flow across the balloon, effectively making it very difficult to standardize the technique and study it clinically.

6.3 *Ex- Vivo* study - Opportunities for technology improvement in REBOA balloon design.

The current *ex vivo* study is one where inflation characteristics for standard compliant and semi-compliant balloons are compared in the context of aortic balloon over inflation. The relationship between pressure and volume varies significantly between the two designs of balloon catheters. In the semi- compliant balloon, the plot of pressure against volume is optimally fitted using a quadratic model, demonstrating that due to limited compliance of the balloon material, once inflated past a certain threshold, the pressure in the balloon suddenly raises dramatically with ongoing inflation. The compliant balloon plot on the other hand, represents a linear model, where because of compliance, the relationship between volume and pressure remains constant throughout the inflation process. Both compliant and semi- compliant balloons have a maximum volume threshold at which point failure occurs, and this threshold is higher in the compliant balloons.

The quadratic relationship between pressure and volume in the semi- compliant balloon models a transition where there is a significant rise in pressure with ongoing inflation, lending itself to the addition of a safety valve to prevent over inflation. This may be a safer way to perform blind aortic balloon inflation.

Aorto-iliac injury due to balloon over inflation has been recognized since the advent of endovascular interventions. Most of the reported arterial rupture cases are associated

with non- compliant balloons designed to deliver excessive pressures and used in angioplasty in patients with underlying atherosclerotic vascular disease- predisposing them to injury (Berger, Sorensen and Konrad, 1986; Wu *et al.*, 2012; Mehta *et al.*, 2014; Yashima, Hayashida and Fukuda, 2016).

However, aorto- iliac ruptures have been reported with the use of semi- compliant balloons used for AO in postpartum haemorrhage, or during stent moulding in abdominal aneurysm endovascular repair (EVAR) (Moskowitz *et al.*, 1999; Lee *et al.*, 2011; Søvik *et al.*, 2012). Reports of aortic rupture with compliant balloons are scarce, but radiographic images of balloons taken post- inflation often show gross over inflation of the balloon. This concern has provoked efforts to improve the safety profile of the balloon catheters during blind inflation.

The relationship of the aortic diameter and rupture risk has been recognized, stressing the importance of exercising caution in high-risk patients who may have smaller vessels: women, children, and young adults (Kamenskiy *et al.*, 2015; Norii *et al.*, 2017; Davidson *et al.*, 2018). However, apart from “caution” there is no objective measure of preventing over inflation in this group in an emergency setting. Similarly, monitoring for change of balloon shape (elongation and “shouldering”) (Wasicek *et al.*, 2018) which can signify over inflation and is a feature of compliant balloons only, requires bedside fluoroscopy, and is subjective. Thus, blind inflation has been adopted by the centres which routinely perform REBOA (Teeter *et al.*, 2016).

Cross sectional imaging is essential in precise assessment aortic size but is not feasible in an emergency scenario where a REBOA balloon would be typically applied. Moreover, data that provide precise knowledge on aortic size according to each patient demographic is limited. However, Stannard et al and Morrison et al have conducted morphometric torso arterial anatomy studies including correlation with external torso anatomical landmarks that demonstrate consistency of aortic thoracic diameter with the length of the descending aorta in the AO inflation zones I and III (Stannard *et al.*, 2013; Morrison, Stannard, *et al.*, 2014). Moreover, the studies demonstrate that catheter insertion distances based on

external torso anatomical landmarks (sternal notch, pubis) correlate with correct zone I or zone III balloon placement. These studies, however, only assessed young males who are physically fit soldiers and did not inform on other demographics including gender, age or body habitus.

The concept of CSR has been established to delineate an objective measure of the maximal vessel distention before rupture (Wasicek *et al.*, 2018). Several studies analysing tension in post- mortem human or swine arteries found the CSR before failure to be 1.7- 1.8 (Mohan and Melvin, 1982; Teng *et al.*, 2009; Chen *et al.*, 2013; Wasicek *et al.*, 2018). Our study demonstrated a CSR of 1.17 (± 0.03) and 1.28 (± 0.19) for CB and SCB respectively ($p = 0.178$); however, these measurements were calculated before up to 4 ml of additional volume was injected prior to rupture, thus actual CSR at rupture could have been higher for both groups. Nevertheless, although CSR can be demonstrated in a lab setting, its application in clinical practice is limited, particularly in a trauma setting where time is of the essence, and it is impractical to obtain aortic measurement in time to control haemorrhage.

Compliant balloons are designed to stretch and expand as the inflation pressure increases, accommodating more volume, resulting in lower burst pressures (Seyithanoglu *et al.*, 1998). Semi- and non- compliant balloons will expand up to a pre- set target size and not much beyond that. The current study confirms this by demonstrating significantly higher inflation volume and WL in the compliant cohort. Semi- compliant balloons on the other hand are stiffer, do not accommodate their shape or size to added volume, and are more likely to burst or cause arterial damage if inflated in small vessels or overinflated beyond their target size (Seyithanoglu *et al.*, 1998). As a result, the compliant balloons have traditionally been perceived as a safer alternative in the context of blind aortic inflation. However, they can still exert damage when over- inflated in relatively small vessels.

Recent technological advances led development of a simple, safety adjunct to prevent over inflation in AO balloons in a form of a safety valve, which is in- line with the balloon

inflation lumen. This valve is designed to release any added volume that causes the balloon pressure to exceed the valve crack pressure, thus preventing further inflation. The current study demonstrates this as beyond the pressure valve threshold, any added fluid was released resulting in no observed increase in balloon pressure, diameter, CSR or WL of the balloon (figure 4.4). Moreover, despite attempted over inflation in a range of vessel diameters, the balloons reached CSR far below 1.7.

Compliant balloons can accommodate increasing volumes of fluid, with minimal pressure increase, because the balloon material stretches. This reduces the efficacy of a safety valve because actuation may occur after significant over inflation. The pressure- volume relationship of a semi- compliant balloon is more predictable across a range of vessel sizes, allowing application of a pressure safety valve. As a result, in the absence of imaging, when paired with the safety valve, a semi- compliant balloon may present a much safer option than a compliant balloon without a safety valve.

Crucially, the predictability of relationship between the volume and pressure in semi-compliant balloon design demonstrated in our work, may allow a more predictable relationship between the balloon volume, and return of blood flow past the balloon during gradual deflation, thus allowing a greater level of control in partial occlusion – something that is not possible to reliably achieve in a compliant design as highlighted in section 6.2. White et al demonstrated a more controllable deflation profile of a semi- compliant balloon compared to a compliant one using an animal model of haemorrhagic shock, where during the controlled continuous balloon deflation, the distal aortic flow strongly correlated with % of balloon volume in a semi- compliant design- suggesting a more precise control of distal perfusion (White *et al.*, 2020). The device improvement described here could allow for precise titration of the REBOA balloon to achieve reliable partial occlusion REBOA. With the recent FDA approval of the pREBOA – PRO^{TM} catheter (Prytime Medical, Boerne, Texas), future clinical studies with the use of this catheter are highly anticipated.

6.4 Pathophysiology of exsanguination

This study presents the first large animal model that uses controlled, logarithmic exsanguination to closely study the physiology of progressive shock and cardiac arrest due to exsanguination. This model demonstrates two distinct haemodynamic phases, before asystole ensues, that have not been previously described. In cardiac physiology terms, the initial hemodynamic upset relates to pre-load failure with the loss of intravascular volume signifying a period of *"warm myocardial ischaemia"*. The later phase represents intrinsic myocardial failure due to coronary hypoperfusion and myocardial ischaemia resulting in loss of cardiac inotropy representing a phase of *"failure of myocardial contraction"*. Our findings suggest that cardiac activity is preserved throughout the entire exsanguination, without dysrhythmias, until asystole. While these observations may seem obvious, there are important clinical implications associated with these mechanisms.

Many patients who present to the hospital following exsanguination undergo RT and manoeuvres such as internal massage and AO. These patients have a dismal prognosis, with an overall survival of less than 10 % (Moore *et al.*, 2015). Best outcomes are observed in patients who are profoundly hypotensive with reported survival of 15 – 59 % (Brenner, Inaba, *et al.*, 2018; Brenner, Teeter, *et al.*, 2018). Patients who present with prolonged cardiac arrest time have much worse outcomes with survival of 3 % (Brenner, Inaba, *et al.*, 2018; Brenner, Teeter, *et al.*, 2018). A single centre retrospective study from Shock Trauma centre reported that even with REBOA only 58% of n=50 trauma patients who presented with haemorrhagic cardiac arrest had ROSC and only 10% of those (n=5) survived 30 days (Brenner, Teeter, *et al.*, 2018). It is almost certain that these patients have coronary hypoperfusion and that their poor survival is in part due to a failure in restoring coronary perfusion by existing interventions.

Exploration of this area of physiology has been partly hindered by poor clinical terminology. Despite being used for decades in trauma surgery, the concept: "Pulseless Electrical Activity" (PEA) has been misleading when used in reference to patients in haemorrhagic shock.

The definition of PEA remains obscure and involves patients with a vast variety of aetiologies (Kloeck, 1995). It has been demonstrated that the majority of patients deemed to be in PEA have a preserved myocardial function (Bocka, Overton and Hauser, 1988), and that bleeding patients have fundamentally different aetiology from those with primary cardiac causes of arrest (Luna *et al.*, 1989; Jeffcoach *et al.*, 2016). Despite this, PEA is a poorly studied subject due to lack of an applicable model (Myerburg Robert J. *et al.*, 2013). The result is that PEA is a very broad and vague category which includes anyone in whom a palpable pulse is not detected. This in turn, has significant implications on the clinical management of patients included in this category. The current study demonstrates preserved cardiac activity and associated gradually diminishing, uninterrupted aortic pressure until final descent into asystole. A new term should be devised to describe patients in the late stages of the haemorrhagic shock to appropriately reflect their physiological state and to help guide appropriate management strategy.

The evidence base in the area of exsanguination is limited to a couple of studies from 1940s and 1950s which used a canine model. One of the earliest studies by Werle and colleagues demonstrated that initially, during haemorrhagic shock, there is a temporary response in arterial pressure to volume replacement, however, with ongoing bleeding eventually BP fails to respond to preload support- signifying ultimate cardiovascular failure. Further evidence for myocardial failure in the late stages of hemorrhage in that model was demonstrated by bradycardia and rising venous pressure (Werle, Cosby and Wiggers, 1942). In a similar canine model, Sarnoff found increasing left atrial pressures in the advanced stages of hemorrhage. Interestingly, these pressure alterations responded to augmentation in coronary flow, thus supporting the theory of need for perfusion support in the final stages of shock (Sarnoff *et al.*, 1954).

Coronary autoregulation has been studied extensively, but questions remain about the precise interplay of the mechanisms involved in it (Goodwill *et al.*, 2017). Studies using swine models with euvolemic haemodilution or pharmacologic central aortic pressure manipulation demonstrated that coronary autoregulation is maintained between MAP of

127 and as low as 40 - 50 mmHg (Kiel *et al.*, 2018; Guensch *et al.*, 2019) - which correlates with our findings.

The findings presented in our model may offer significant implications on the treatment approach, particularly considering the emerging endovascular resuscitation techniques such as REBOA, SAAP and EPR. Currently available resuscitation methods such as volume replacement or AO (whether by REBOA or direct aortic clamping), can augment preload or afterload, but do not support coronary perfusion, and are likely to be ineffective in the late stages of exsanguination. Cardiac massage aims to support cardiac perfusion by driving CPP (Paradis *et al.*, 1990) but with limited effectiveness. Novel techniques such as SAAP and EPR have demonstrated promising outcomes with haemorrhagic cardiac arrest in animal models (Kutcher, Forsythe and Tisherman, 2016; Barnard *et al.*, 2017). SAAP predominantly works by augmenting coronary perfusion (Paradis *et al.*, 2012). EPR aims to temporarily suspend metabolic demands as a bridge to definitive treatment (Kutcher, Forsythe and Tisherman, 2016). Our findings suggest that resuscitation efforts during the "*warm myocardial ischaemia*" phase, when myocardial failure has not occurred, should focus on preload and afterload support. However, when "*failure of myocardial contraction*" ensues, preload and afterload support alone will not suffice without perfusion augmentation- which is where SAAP may be effective.

This study demonstrates a linear correlation between coronary flow and EF. As normal EF lies between 50 and 70 %, values higher than this suggest a hyperdynamic state where the ventricle is emptying more completely in order to compensate for a reduced CO. Values lower than 40 % suggest some level of decompensation, assuming a non-diseased heart with acute changes. This finding could represent a diagnostic target or resuscitation endpoint in critically shocked patients. With the ubiquity of point-of-care ultrasonography and validated measurements of cardiac function such as the velocity time integral (Atkinson *et al.*, 2017), the bedside assessment of EF could be a useful and practical bedside marker of coronary flow. This should be explored in future studies.

6.5 Optimal window for application and survival following SAAP Resuscitation.

This study utilises the novel animal model of ECA described above to establish a temporal relationship between the warm ischaemic time during ECA and the resuscitation potential of the myocardium using whole blood SAAP.

The findings of this study support and extend previous reports which explored the use of SAAP in ECA. Barnard et. al used an animal model of uncontrolled haemorrhagic cardiac arrest to study resuscitation in three groups: REBOA with fresh oxygenated blood delivered IV, SAAP with oxygenated Lactated Ringer's solution, and SAAP with oxygenated whole blood. The authors demonstrated 100 % ROSC rates with SAAP and whole blood, and 60 % in animals treated with SAAP using Lactated Ringer's solution, while no animals in REBOA group had ROSC (Barnard *et al.*, 2017). This demonstrates that passive afterload support (REBOA) in isolation does not meaningfully increase ROSC rates following ECA, whereas active perfusion (SAAP) of the coronary circulation can achieve a 100 % ROSC following 3 min of ECA. This likely relates to the generation of CPP; however, this metric was not reported by the authors.

Data from the cardiac arrest literature suggest that CPP needs to be greater than 15 mmHg to have any possibility of ROSC (Paradis *et al.*, 1990; Edwards *et al.*, 2021). This threshold appears to also hold importance in ECA as demonstrated in the study defining the exsanguination cardiac arrest (section 5.3) As discussed in the previous section, while BP fell throughout the bleed, coronary flow was well preserved until a MAP of 20 mmHg which was associated with a precipitous fall in flow and failure of myocardial contractility.

Edwards et. al has explored CPP generation in the context of two resuscitation paradigms: internal cardiac massage with aortic cross clamping and SAAP. Open chest cardiac massage only achieved a CPP over 15 mmHg for 17 % of the cycle time, whereas SAAP exceeded this threshold 97 % of its cycle time. As this study used post- mortem swine to purely examine pressure dynamics, it was unable to comment on ROSC rates, but suggested that SAAP should be explored further as a resuscitation adjunct for ECA (Edwards *et al.*, 2021).

The current study aimed to quantify the temporal relationship between ischaemic time and the resuscitation potential of the myocardium. Based on clinical experience, we hypothesized that longer ischaemic time would be associated with a lower ROSC rate. Our data indeed do demonstrate a relationship between length of ECA, and likelihood of both ROSC and 1-hr survival following ROSC.

This study also establishes a baseline ROSC rate for whole blood SAAP at each of three studied time points, with excellent ROSC and survival in animals who had less than 10 minutes of ECA and promising 43 % ROSC outcomes for those that were in cardiac arrest for 15 minutes. This is significantly higher than rates reported in the literature using conventional measures in humans, where beyond 15 min, the Western Trauma Guidelines, would consider a RT in a human patient futile (Burlew *et al.*, 2012). This, coupled with the positive results in the 5- and 10- min groups, is promising and provokes several further questions: first, are there changes we could make to the SAAP procedural techniques to further increase the ROSC rate? Are there alternative perfusates or adjuncts other than whole blood that can further improve myocardial recovery following ischaemia and make ROSC more durable? And lastly, do there exist medical adjuncts or strategies to further optimize outcomes as we transition onto or off SAAP? This work lays a foundation for additional translational research that will have clinically relatable resuscitation timelines to optimize outcomes following ECA using SAAP and other adjuncts by providing baseline survival with whole blood.

A natural follow-up question is does this make SAAP applicable to prehospital care? And would this be feasible in a trauma bay for applications shortly after arrest? While more data are needed to assess prehospital implementation, this would be technically easier than prehospital ECMO, which is being investigated and used in some locations (Ottanapanich *et al.*, 2021), but more technically challenging than REBOA. In a hospital setting this requires equipment availability but can be applied quickly and with procedural times likely similar to thoracotomy and vascular access. With the data presented here, these patients meeting resuscitative thoracotomy guidelines would also quality for SAAP,

and may have at least comparable survival outcomes (Inaba *et al.*, 2015; Ottanapanich *et al.*, 2021).

In this study we opted to give noradrenaline and dobutamine, after providing shed blood and once reaching fluid non-responsiveness. Other protocols even in our lab have used adrenaline only, but we were hoping to separate out the effects of need for inotropy versus need for global vasoconstriction. Our result was ultimately that the longer SAAP groups needed more noradrenaline, but the amount of dobutamine was not different, providing cursory evidence that the primary driver of post- ROSC injury was not the myocardial ischaemia and need for inotropic support, but is related to the warm ischaemia and reperfusion and correction thereof. Adrenaline only would be another viable strategy for resuscitation but using adrenaline only may not have provided this insight.

6.6 Implications for delivery of care

Although the concept of endovascular resuscitation may appear attractive, there are important systemic implications of the work in this thesis that should be considered. The studies presented here have all been conducted in the USA with clinical data drawn from level one trauma centre experience. This must be acknowledged when considered the practical implications of translating trauma care delivery to the United Kingdom or other regions of the world. The USA ultimately presents a unique setting of trauma care to other healthcare systems with implications on patient characteristics, funding, hospital networks and access to specialist care adjuncts. The provision of trauma care in the USA also varies compared to the UK in terms of surgical specialist training (Herrold *et al.*, 2021), as well as training and availability of allied health practitioners fundamental to delivery of specialist care with best outcomes. Delivery of some of the endovascular techniques presented in this thesis would require complex logistical and financial considerations in order to provide optimal care as suggested by the model of pre- hospital ECPR developed in Paris (Lamhaut, Hutin, Puymirat, *et al.*, 2017). REBOA was initially developed as a haemorrhage control adjunct in the pre- hospital, combat environment. The studies presented here focus on in – hospital delivery, but this does not preclude future widespread application in the pre- hospital environment. Similarly, SAAP could

potentially be delivered in the pre- hospital setting but this has implications in training, equipment design and human resources as well as access to centres of definitive care. Moreover, I have approached this thesis from a civilian perspective, but military implications exist- particularly with pre- hospital development and funding for future studies.

6.7 Potential Future Work

Endovascular resuscitation techniques are beginning to translate into clinical practice with REBOA and VA-ECMO having been employed in patients with haemorrhagic shock and non-traumatic cardiac arrest for the past decade. Timely intervention and reliable access to facilities are crucial for continuing care (Arlt *et al.*, 2010; Morrison *et al.*, 2016; Yannopoulos *et al.*, 2017) and clinicians must be aware of possible limitations to applying these interventions. Several obstacles which prevent wide acceptance into clinical practice range from physiologic consequences to service- based factors. Even for REBOA and VA- ECMO there is clinical equipoise and despite initial enthusiasm, it is important to highlight that current evidence base is weak. Further studies and prognostic tools are needed to clearly delineate and select the patients who would benefit from these interventions.

Currently, there are five registered clinical trials investigating the feasibility of REBOA use in refractory cardiac arrest; four focus specifically on non-traumatic cardiac arrest and two involve pre-hospital use (Azienda Usl di Bologna, 2020; University Hospital Inselspital, Berne, 2020, 2020; Daley, 2021; Norwegian University of Science and Technology, 2021; St. Olavs Hospital, 2021). There is one ongoing clinical trial on the use of REBOA in trauma. The UK REBOA Trial is a UK based randomised controlled trial which applies Bayesian statistics (Jansen *et al.*, 2017) to compare outcomes in trauma patients treated with standard major trauma centre measures with use of REBOA as an adjunct. The study is currently recruiting across 10 Major Trauma UK Centres (*UK-REBOA*, 2022).

A non- randomized controlled trial is underway at the University of Maryland and the University of Pittsburgh comparing EPR to standard resuscitation during RT for cardiac arrest from trauma. This phase 2 trial aims to establish feasibility of EPR in exsanguinating cardiac arrest as well as measure survival and functional neurological outcomes and multiple organ system dysfunction (Tisherman, 2021).

With regards to ECPR, there are presently 6 clinical trials registered, evaluating outcomes of ECPR in management of refractory out of hospital cardiac arrest (Henriques, 2018; Maastricht University Medical Center, 2019; Barts & The London NHS Trust, 2020; Miranda, 2020; MD, 2021; Neumar, 2021).

If implemented, endovascular resuscitation techniques can only be used in facilities which provide a comprehensive level of care in terms of surgery and critical care. This includes adequately trained practitioners collaborating across multiple disciplines, rapid, 24 hr access to facilities including a hybrid theatre and critical care units with ECMO capabilities. Implementation of endovascular resuscitation techniques requires significant financial capital with high volumes of patients and well-established service networks in order to deliver optimal care.

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Appendix A- Study Approval

A.1 Study approval for the study “Endovascular Service in Trauma”

University of Maryland, Baltimore
Institutional Review Board (IRB)
Phone: (410) 706-5037
Fax: (410) 706-4189
Email: hrpo@umaryland.edu

APPROVAL OF RESEARCH NOTIFICATION

Date: November 6, 2018

To: Jonathan Morrison
RE: HP-00082909
Type of Submission: Initial Review
Type of IRB Review: Expedited

Approval for this project is valid from 11/6/2018 to 11/5/2019

This is to certify that the University of Maryland, Baltimore (UMB) Institutional Review Board (IRB) approved the above referenced protocol entitled, “*Acute Care Surgeons Performing Endovascular Interventions in Trauma*”.

The IRB has determined that this protocol qualifies for expedited review pursuant to Federal regulations 45 CFR 46.110, 21 CFR 56.110, & 38 CRF 16.110 category(ies):
(5) - Research involving materials (data, documents, records, or specimens) that have been collected for any purpose, or will be collected solely for non-research purposes.

The IRB made the following determinations regarding this submission:
- A waiver of consent has been approved per 45 CFR 46.116(d).
- A waiver of HIPAA authorization for release of the PHI identified in the CICERO application has been reviewed and approved for this research study.

This study is approved to enroll 180 local participants.

This study is approved to enroll 180 worldwide participants.

Below is a list of the documents attached to your application that have been approved:
Eligibility Checklist for HP-00082909 v9-18-2018-1537323636627
References
HP-00082909 Collection Fields.xlsx
HP-00082909 Collection Fields.xlsx

In conducting this research you are required to follow the requirements listed in the INVESTIGATOR MANUAL. Investigators are reminded that the IRB must be notified of any changes in the study. In addition, the PI is responsible for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103(4)(iii)). The PI must also inform the IRB of any new and significant information that may

impact a research participants' safety or willingness to continue in the study and any unanticipated problems involving risks to participants or others.

DHHS regulations at 45 CFR 46.109 (e) require that **continuing review** of research be conducted by the IRB at intervals appropriate to the degree of risk and **not less than once per year.** The regulations make **no provision for any grace period extending the conduct of the research beyond 11/5/2019.** You will receive continuing review email reminder notices prior to this date; however, it is your responsibility to submit your continuing review report in a timely manner to allow adequate time for substantive and meaningful IRB review and assure that this study is not conducted beyond **11/5/2019**. Investigators should submit continuing review reports in the electronic system at least six weeks prior to this date.

Research activity in which the VA Maryland Healthcare System (VAMHCS) is a recruitment site or in which VA resources (i.e., space, equipment, personnel, funding, data) are otherwise involved, must also be approved by the VAMHCS Research and Development Committee prior to initiation at the VAMHCS. Contact the VA Research Office at 410-605-7000 ext. 6568 for assistance.

The UMB IRB is organized and operated according to guidelines of the International Council on Harmonization, the United States Office for Human Research Protections and the United States Code of Federal Regulations and operates under Federal Wide Assurance No. FWA00007145.

If you have any questions about this review or questions, concerns, and/or suggestions regarding the Human Research Protection Program (HRPP), please do not hesitate to contact the Human Research Protections Office (HRPO) at (410) 706-5037 or HRPO@umaryland.edu.

A.2 Study approval for the studies: “Clinical study of REBOA vs No-REBOA” and “Clinical study of P-REBOA”.

University of Maryland, Baltimore
Institutional Review Board (IRB)
Phone: (410) 706-5037
Fax: (410) 706-4189
Email: hrpo@umaryland.edu

APPROVAL OF RESEARCH NOTIFICATION

Date: May 9, 2018

To: Jonathan Morrison
RE: HM-HP-00055545-25
Protocol Version and ID #: N/A
Type of Submission: Modification
Type of IRB Review: Expedited
Modification request dated: 4/23/2018

Modification Approval Date: 5/9/2018
Approval for this project is valid until 1/11/2019

This is to certify that the University of Maryland, Baltimore (UMB) Institutional Review Board (IRB) approved the above referenced modification request for the protocol entitled, “*Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA): Observational study of the Endovascular Skills in Trauma and Resuscitative Surgery (ESTARS) Working Group*”.

The IRB approved this modification via expedited review pursuant to Federal regulations 45 CFR 46.110(b)(2)/21 CFR 56.110(b)(2).

The IRB made the following determinations regarding this submission:
- No specific determinations made.

This study is approved to enroll 700 local participants.

This study is approved to enroll 3000 worldwide participants.

Below is a list of the documents attached to your application that have been approved:
Eligibility Checklist for HP-00055545_2 v9-25-2013-1380108078905
AORTA study proposal - Draft 28 Februar 2013 DuBose.doc
Study Schedule.docx
UMB-WellSpan IRB Agreement.pdf
White article.pdf
Avaro article.pdf
Sesma article.pdf
REBOA article.pdf
10-10-15 AAST AORTA data collection tool Revised.docx
AORTA study proposal - Draft 28 Februar 2013 DuBose.doc

In conducting this research you are required to follow the requirements listed in the INVESTIGATOR MANUAL. Investigators are reminded that the IRB must be notified of any changes in the study. In addition, the PI is

responsible for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103(4)(iii)). The PI must also inform the IRB of any new and significant information that may impact a research participants' safety or willingness to continue in the study and any unanticipated problems involving risks to participants or others.

Research activity in which the VA Maryland Healthcare System (VAMHCS) is a recruitment site or in which VA resources (i.e., space, equipment, personnel, funding, data) are otherwise involved, must also be approved by the VAMHCS Research and Development Committee prior to initiation at the VAMHCS. Contact the VA Research Office at 410-605-7000 ext. 6568 for assistance.

The UMB IRB is organized and operated according to guidelines of the International Council on Harmonization, the United States Office for Human Research Protections and the United States Code of Federal Regulations and operates under Federal Wide Assurance No. FWA00007145.

If you have any questions about this review or questions, concerns, and/or suggestions regarding the Human Research Protection Program (HRPP), please do not hesitate to contact the Human Research Protections Office (HRPO) at (410) 706-5037 or HRPO@umaryland.edu.

A.3 Study approval for the study “Defining the Physiology of Exsanguination Cardiac Arrest”.

UNIVERSITY OF MARYLAND
SCHOOL OF MEDICINE
Office of Animal Welfare Assurance

655 W. Baltimore Street
BRB, Mezzanine Ste. M023
Baltimore, MD 21201-1559

email: iacuc@som.umaryland.edu
voice: (410) 706-7859/ 8470
Assurance Number: A3200-01

DATE: February 14, 2019

TO: Jonathan Morrison, PhD
Department of Surgery
22 S.Greene St., Rm T1R66

FROM: Institutional Animal Care and Use Committee

RE: IACUC PROTOCOL #0119011
"Characterizing the Pathophysiology of Exsanguination Cardiac Arrest and Defining Opportunity for Intervention"

This is to certify that the Institutional Animal Care and Use Committee received your response to their queries and that your response was considered sufficient to grant FULL APPROVAL to your protocol.

An annual report must be submitted to the IACUC one month before each anniversary of the protocol. Please note that your protocol will expire on January 25, 2022. If you need to extend the protocol beyond this date, you must submit a new animal use protocol at least 3 months prior to the expiration.

If you have any questions, please do not hesitate to contact the Office of Animal Welfare Assurance by email (iacuc@som.umaryland.edu) or by phone (706-7859 / 8470).

John B. Sacci, Jr., Ph.D.
IACUC Chair

A.4 Study approval for the study “Myocardial Tolerance to Exsanguination and Retrieval Using Whole Blood – Selective Aortic Arch Perfusion”.

UNIVERSITY OF MARYLAND
SCHOOL OF MEDICINE
Office of Animal Welfare Assurance

655 W. Baltimore Street
BRB, Mezzanine Ste. M023
Baltimore, MD 21201-1559

email: iacuc@som.umaryland.edu
voice: (410) 706-7859/8470
Assurance Number: A3200-01

DATE: October 30, 2019

TO: Jonathan Morrison, PhD, FRCS,FEBVS
Department of Surgery
22 S.Greene St., Rm T1R66

FROM: Institutional Animal Care and Use Committee

RE: IACUC PROTOCOL #0919015
"Myocardial Tolerance to Exsanguination Cardiac Arrest"

This is to certify that the Institutional Animal Care and Use Committee received your response to their queries and that your response was considered sufficient to grant FULL APPROVAL to your protocol.

An annual report must be submitted to the IACUC one month before each anniversary of the protocol. Please note that your protocol will expire on September 20, 2022. If you need to extend the protocol beyond this date, you must submit a new animal use protocol at least 3 months prior to the expiration.

If you have any questions, please do not hesitate to contact the Office of Animal Welfare Assurance by email (iacuc@som.umaryland.edu) or by phone (706-7859 / 8470).

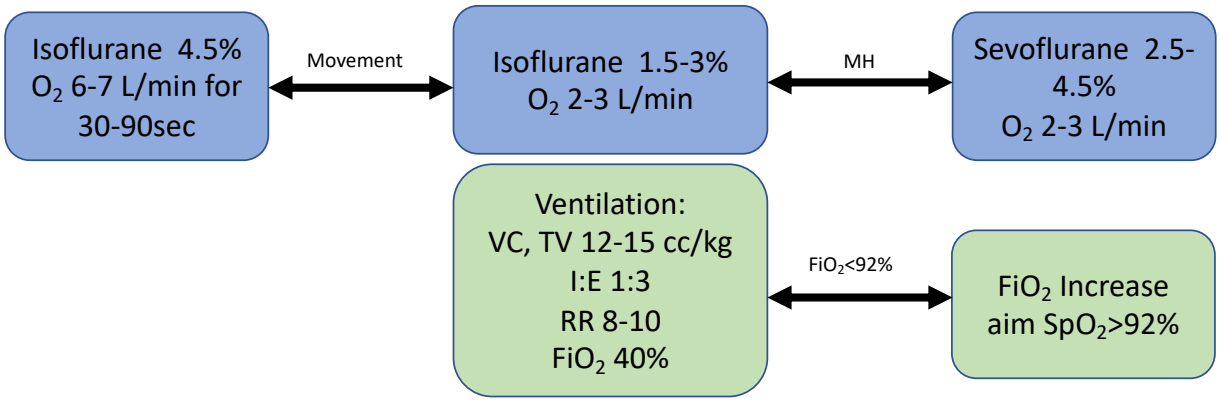
John B. Sacci, Jr., Ph.D.
IACUC Chair

Appendix B- Materials used to build the exsanguination/ perfusion system

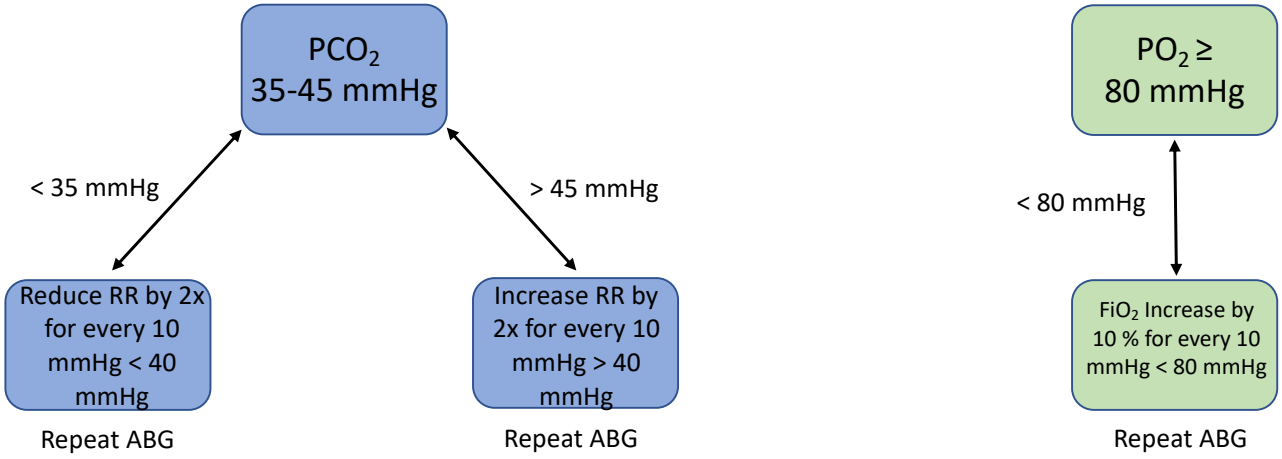
Name of Material/ Equipment	Company	Catalog Number	Comments/ Description
3/8” ID tubing	Saint-Gobain	E-3603	used throughout the circuit.
2-way stopcocks	Harvard Apparatus	72-2650	standard stopcock
3-way stopcocks	Harvard Apparatus	72-2658	standard stopcock
Barbed Connectors	Harvard Apparatus	72-1587	Y connectors
Barbed Connectors	Harvard Apparatus	72-1575	straight connectors
Blood Reservoir	LivaNova	50715	sold together with the oxygenator
Cable ties	Commercial Electric	GT-200ST	Standard cable ties.
Centrifugal pump BVP-Z	ISMATEC	ISM 446	centrifugal pump used for recirculation of blood
Gas tubing	AirLife	1302	standard oxygen tubing
Oxygen source	AirGas	OX USP300	standard oxygen tank with flowmeter
Oxygenator	LivaNova	50715	sold together with the reservoir
Peristaltic pump 1 MCP	ISMATEC	ISM 405	SAAP peristaltic pump
Controlled Peristaltic Dispensing Pump	New Era Pump Systems	NE-9000B	peristaltic pump used for exsanguination
SAAP catheter	n/a	n/a	proprietary catheter designed by Dr. Manning
Venous catheter	Teleflex	CDC-29903-1A	9 French single lumen catheter
1/4" tubing	Tygon	E-3603	2" segment for a connector between Exsanguination tubing and ECMO cannula
ECMO Cannula	Medtronic	96570-015	exsanguination cannula

Appendix C- Ventilation parameters

Appendix C.1 Maintenance Anaesthesia



Appendix C.2 Respiratory Parameters



Appendix D- Drugs Used in the Critical Care Period

Drugs	*Preparation*	*Infusion Site*	*Infusion Mode*
Adrenaline	32 mcg/mL of NaCl	Catheter in External Jugular Vein Sheath	DigiPump start 0.5 mcg/kg/min/hr titrate
Dobutamine	1000 mg/250 mL of 5% Dextrose (4000 mcg/mL)	Catheter in External Jugular Vein Sheath	DigiPump start 5 mcg/kg/min/hr titrate
50 % Dextrose	50 mL- neat	Femoral Vein Cordis	Syringe Bolus
Insulin	1 U/mL of NaCL	Femoral Vein Cordis	Syringe / Titrate
10% Calcium Chloride	1g/10 mL Pre-prepared syringe	Femoral Vein Cordis	Syringe Bolus
Potassium Chloride	10 mmol/ 100ml of NaCL	Femoral Vein Cordis	IV infusion bolus over 30 min pump
8.5% Sodium Bicarbonate	50 mL	Femoral Vein Cordis	Syringe Bolus
Magnesium Sulfate	1g/10 mL Pre-prepared syringe	Femoral Vein Cordis	Syringe Bolus