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Ultrasound-Guided Resuscitation in Open Aortic Surgery - The AORTUS Trial

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Abstract

Introduction: Major abdominal aortic surgery requires significant fluid resuscitation in the post-operative phase. Patients are at significant risk of perioperative morbidity and mortality which can be affected by the approach to post-operative fluid resuscitation. Point of care ultrasonography (POCUS) has evolved as a tool to perform whole-body assessments at the bedside to augment the physical exam and guide the resuscitation of the critically ill. This study will aim to explore the value of rigorous goal-directed resuscitation in aortic surgery using point of care ultrasonography (POCUS).

Methods: In an open-label, randomized, feasibility trial we enrolled 17 patients to receive resuscitation guided by either POCUS or usual care

Results: We observed that the trial protocol as designed met all of our pre-specified feasibility metrics

Conclusion: The use of POCUS in guiding post-operative fluid resuscitation is feasible and utilizing this protocol to design a study powered to detect statistically significant differences in clinical outcomes is warranted.

Keywords

Aortic surgery, resuscitation, ultrasound, point-of-care ultrasonography, echocardiography

Summary for Lay Audience

Open abdominal aortic surgery for aortic aneurysms (an abnormal bulge that occurs in the wall of the main major blood vessel that carries blood from your heart to the rest of the body) or occlusive disease (a buildup of plaque that causes decreased blood flow from the aorta to the rest of the body) represents a major surgery for patients. The care of patients after surgery includes administration of intravenous (IV) fluids to support the blood pressure and perfusion to the body's major organs. There are risks that come with administering too much IV fluid or too little in the post-operative period. This includes the risk of kidney injury from giving too little fluid, or the risk of pulmonary edema (fluid accumulation in the tissue and air spaces of the lungs) or congestive heart failure (fluid overwhelms the heart and causes it to pump inefficiently) from giving too much fluid. The standard practice is for doctors to use a combination of physical examination, urine output, and blood tests to guide the administration of IV fluids after abdominal aortic surgery.

Portable ultrasound can be routinely used to assess heart and lung function at the bedside to add additional information about a patient's fluid balance and response to fluid administration. This study used a protocol that compared the use of routine ultrasound of the heart and lungs versus standard practice for the first 48 hours after open abdominal aortic surgery. Since this is an innovative approach to taking care of post-operative patients this study first examined whether the protocol we designed was both safe and feasible to carry out. After enrolling 17 patients into the study, we found that all measures of safety and feasibility were met. This now allows us to proceed with the design of a larger trial which uses this same protocol to compare the ultrasound-guided care approach to the standard care approach and see if we can detect any measurable difference in patient outcomes between the two approaches.

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List of Abbreviations

AAA – Abdominal aortic aneurysm

AKI – Acute kidney injury

CAD – Coronary artery disease

COPD – Chronic obstructive pulmonary disease

CHF – Congestive heart failure

CHFe – Congestive heart failure exacerbation

CRP – C-reactive protein

CVP – Central Venous Pressure

ECG - Electrocardiogram

EVAR – Endovascular aneurysm repair

FFP – Fresh Frozen Plasma

HFpEF – Heart failure with preserved ejection fraction

HFrEF – Heart failure with reduced ejection fraction

ICU – Intensive Care Unit

IV – Intravenous

IVC – Inferior vena cava

LV – Left ventricle

MI – Myocardial infarction

NICOM – Non-invasive cardiac output monitor

OSR – Open surgical repair

PACS – Picture archiving and communications system

POCUS – Point of care ultrasound

PPV – Pulse Pressure Variation

PVD – Peripheral vascular disease

QA – Quality Assurance

SBP – Systolic Blood Pressure

SPV – Systolic pressure variation

SVV – Stroke volume variation

RV – Right ventricle

VT – ventricular tachycardia

Chapter 1

1 Introduction

Open abdominal aortic surgery for reconstruction of aneurysmal and occlusive disease imparts significant physiological stress which must be managed in the intraoperative and post-operative period. One of the mainstays of postoperative management involves judicious fluid administration in order to minimize the morbidity and mortality that accompanies both over-resuscitation and under-resuscitation. A number of invasive and noninvasive hemodynamic monitors have been used in this patient population to try and augment decision making to effectively maximize the benefits and minimize the harms during the post-operative resuscitation phase. The practice of critical care medicine has recently seen a significant increase in the use of bedside Point-of-Care Ultrasound (POCUS) for real-time hemodynamic assessments to gather both subjective and objective data to aid diagnosis and management of the critically ill; however, this technology has not been explored in the post-operative resuscitation of surgical patients.

1.1 Open Abdominal Aortic Surgery

Aneurysmal degeneration and occlusive atherosclerotic disease are two common pathologies of the abdominal aorta requiring surgical intervention. While initially treated with open surgical reconstruction[1,2], the development of endovascular techniques has introduced minimally invasive treatment options for both of these disease states. Regardless, there continues to remain a role for open surgery in the treatment of aneurysmal and occlusive disease of the abdominal aorta in modern vascular surgical practice in patients with anatomy not suitable for endovascular therapy.

The incidence of abdominal aortic aneurysm (AAA) is approximately 2% in women and 5% in men over the age of 65, and the incidence increases by 6% for each additional decade of life.[3] In addition to gender and age the development of AAA is associated with smoking history, hypertension, hypercholesterolemia, family history of AAA, coronary artery disease (CAD), and peripheral vascular disease (PVD).[4] As the diameter of an aneurysm increases, the risk of rupture increases. For this reason, patients are offered

surgery when the risk of rupture exceeds the risk of surgery. A number of studies have adequately described the natural history of unrepaired AAA's,[5,6] and based on this natural history data and the general perioperative risk of major complications, consideration for repair is given for AAA's greater than or equal to 5.5cm in size.[7] Since the introduction of Endovascular Aneurysm Repair by Dr. Juan Parodi in 1990[8] the use of Endovascular Aneurysm Repair (EVAR) has been increasing and the use of open surgical repair (OSR) has been decreasing in both the United States and Canada.[9,10] Despite this, recent long-term data from high-quality randomized controlled trials has shown a mortality advantage to open surgery after 8 years of post-operative follow-up[11] leading many to reinforce their belief that open surgical repair of AAA will continue to play a role in the future.

Aortoiliac occlusive disease represents a proximal anatomic location of peripheral vascular disease. PVD is associated with smoking, hypertension, hypercholesterolemia, and diabetes, though gender does not increase risk as it does in aneurysmal disease.[12,13] The anatomic diagnosis of PVD ranges from 1-22% depending on the population, risk factors, and diagnostic techniques that are used.[14] Anatomic disease may be asymptomatic, or it may present with claudication and critical limb ischemia (rest pain or lower extremity tissue loss and gangrene). Traditionally, patients are offered surgery for lifestyle-limiting claudication or critical limb ischemia provided they are suitable operative candidates. While recent developments in minimally invasive endovascular techniques have resulted in improved long-term patency for high grade aortoiliac occlusions,[15,16] open surgical treatment with aortobifemoral bypass remains the gold standard even in the modern endovascular era.[17]

1.2 Complications in Open Aortic Surgery

Open surgical reconstruction of the abdominal aorta results in significant impact on a patient's physiology both intraoperatively and post-operatively. In large population studies, overall perioperative mortality for open aortic aneurysm repair approaches 4%. Large cohorts assessing mortality of direct reconstruction of aortoiliac occlusive disease also demonstrate mortality approaching 4%.[18] Perioperative morbidity also remains high in open aortic surgery, with the incidence of both minor and major perioperative complications exceeding 20%.[19,20] The effects of aortic cross-clamping on cardiovascular

physiology[21], the anatomic disruption of blood supply to the lower half of the body, and the global effects of ischemia-reperfusion can manifest in multisystem insult. [19,22] Furthermore, a combination of intraoperative blood loss, pre-operative fasting, and accumulation of fluid in extravascular spaces contribute to significant post-operative fluid requirements. For this reason, post-operative fluid resuscitation plays a significant role in minimizing the risks of morbidity derived from over and under-resuscitation of these patients. Many of these complications are exacerbated by either too much or too little fluid resuscitation immediately following open aortic surgery. Appropriate fluid resuscitation to maintain adequate macrovascular perfusion of vital organs while avoiding excess intra-cellular and interstitial edema is critical to preserving organ function and avoiding these complications following aortic surgery.

Below is a list of some of the common complications of open aortic surgery for both aneurysmal and occlusive disease:

1.2.1 Acute Kidney Injury

The risk of acute kidney injury (AKI) in open aortic surgery is related to the physiologic derangement suffered by the patient during the post-operative recovery phase, as well as technical and anatomic factors of the conduct of the operation itself.

The physiologic basis for acute kidney injury caused by transperitoneal open aortic reconstruction occurs due to intravascular volume depletion from the cumulative effects of multiple factors. Dissection of the retroperitoneal structures during the process of aortic exposure results in disruption of lymphatic vessels as well as the release of inflammatory mediators from local tissue injury. During the course of the operation the viscera are exposed to the air resulting in measurable third space losses. Intraoperative blood loss causes direct depletion of circulating blood volume. The effect of aortic cross-clamping, as well as the resultant ischemia-reperfusion injury that follows has deleterious effects on both myocardial function and the microcirculatory function of the renal parenchyma. A decrease in intravascular volume activates neuroendocrine mechanisms which ultimately lead to the decrease in the renal excretion of both sodium and free water. The ultimate microcirculatory effects of these changes causes a net movement of

water out of cells and capillaries to the interstitium which can lead to pre-renal acute kidney injury.[23,24]

In addition to the physiologic factors mentioned above, there are several anatomic and technical factors which can contribute to the incidence of AKI during open aortic surgery. The level of aortic cross-clamping is directly related to the incidence of post-operative AKI, with increasingly high rates of AKI seen when progressing from standard infrarenal repair to thoracoabdominal aortic replacement.[25,26] For aortic cross-clamping above the level of the renal arteries, the duration of aortic cross-clamping and interruption of renal blood flow is directly correlated to the rate of post-operative AKI.[25] Exposure of the aorta at the level of the renal arteries sometimes requires division of the left renal vein, and this can contribute to rates of post-operative AKI.[27,28] Manipulation of the aorta and renal arteries in the presence of significant atherosclerotic disease can result in atheroembolism causing post-operative AKI.[29,30]

The combined effects of these physiologic and anatomic contributors leads to an incidence of post-operative AKI between 1 and 15% in contemporary series of open infrarenal aortic surgery.[9,17,19,31–35] Acute kidney injury is not always permanent as many patients show renal recovery, and a minority of patients with acute kidney injury progress to requiring permanent dialysis. More importantly, there is an association between higher post-operative mortality in those experiencing post-operative renal failure[25,31–37,37,38], and as a result meticulous operative technique and judicious use of post-operative fluid resuscitation are paramount to reducing both AKI and perioperative mortality.

1.2.2 Bowel Ischemia

Intestinal ischemia may occur after aortic surgery as a result of both patient and technical factors. Ligation of the inferior mesenteric artery or internal iliac arteries, iliofemoral or mesenteric occlusive disease, previous colonic resection, and a combination of pre-operative comorbidities and post-operative hypotension and shock are known to be associated with perioperative intestinal ischemia. The rates of bowel ischemia after elective aortic surgery range from 1-3% in contemporary case series,[39,40] though the perioperative mortality of patients suffering bowel ischemia can be as high as 50%.[41,42]

The rate of subclinical disease is higher, with rates of endoscopic and histologic findings of 13% and 30% in the absence of clinical symptoms.[43,44] For those patients that have partial thickness ischemic colitis in the absence of intestinal gangrene and multiorgan failure, broad spectrum antibiotics and aggressive correction of shock with volume resuscitation and cardiac support are required for successful medical treatment to prevent progression to full-thickness ischemia requiring bowel resection.

1.2.3 Limb Ischemia

Acute limb ischemia may occur as a result of open aortic reconstruction for aneurysmal or occlusive disease. Routine assessment of lower extremity pulses both pre and post-operatively is important to monitor for the occurrence of this complication. Technical anastomotic complications, vessel clamp injury, and acute thrombosis or thromboembolism can all result in acute limb ischemia around the time of surgery. In contemporary case series the rate of perioperative acute limb ischemia in open aortic surgery approaches 2%.[45] Similarly to the renal and mesenteric ischemia, patients experiencing perioperative acute limb ischemia have overall higher rates of mortality. Subclinical microscopic atheroembolic events are more common, but they are clinically silent and can only be detected by hemodynamic vascular lab studies.[46] Meticulous operative technique and appropriate use of intraoperative anticoagulation are important in the prevention of limb ischemia. In addition, the avoidance of significant post-operative hypotension through appropriate resuscitation is important in avoiding thrombosis of lower extremity arteries that have recently been manipulated during surgery.

1.2.4 Cardiac Complications

The major perioperative cardiac complications in patients receiving open aortic surgery are myocardial infarction, arrhythmias, and congestive heart failure. Major randomized trials of open vs. endovascular aneurysm repair demonstrate rates of major perioperative cardiac morbidity of 2-3% in the open surgery group,[47–49] but examination of registry data and population studies show rates as high as 15%.[50,51]

The burden of cardiac disease is high in this patient population, with a historical cohort of vascular surgery patients receiving pre-operative coronary angiography demonstrating

that only 8% of patients were free of coronary artery disease.[52] Intraoperatively, application of an aortic cross-clamp causes a significant increase in myocardial oxygen demand, and there is a significant increase in left ventricular (LV) afterload which escalates the more proximal the clamp is applied. Subsequent ischemia-reperfusion of the lower body causes myocardial suppression as the anaerobic metabolic byproducts are released back into the systemic circulation. Resultantly, the incidence of perioperative myocardial infarction in patients receiving open aortic surgery is as high as 10%.[53] If troponin rise is used as the definition alone, the rate of perioperative myocardial infarction (MI) in patients receiving vascular surgery is as high as 24%.[54]

Congestive heart failure (CHF) is a common occurrence after open aortic surgery as well. Both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) are common in this population as a result of the burden of ischemic heart disease or prolonged hypertension respectively. Patients are at risk of CHF exacerbation (CHFe) in the perioperative period, as significant volume resuscitation is often required to support the intravascular volume depletion and third-spacing of intravascular volume that occurs as a result of the physiologic and anatomic insult of the operation. Subsequently, the mobilization of body water from the third space back into the intravascular circulating volume can sometimes overwhelm the heart in a patient with pre-existing CHF leading to CHFe. CHF has been shown to be an independent predictor of mortality in open aortic surgery.[55] Furthermore, significant volume shifts can often result in arrhythmias, such as atrial fibrillation from atrial stretch, which contribute to the burden of perioperative morbidity.

Arrhythmias after vascular surgery are also common, and occur in up to 35% of patients after open aortic surgery.[55] Not all of these are benign electrocardiographic findings; one study demonstrating an incidence of perioperative ventricular tachycardiac (VT) of 30% in patients receiving open AAA repair, which was shown to be independently associated with both cardiovascular events and sudden cardiac death during 24 months of post-operative follow-up.[56] The rate of new-onset atrial fibrillation ranges from 3-10% in this patient population, and it has been associated with longer hospital stay and higher 1-year post-operative mortality.[57–59] Arrhythmias such as VF and higher-degree AV blocks do

occur and are often in the setting of acute myocardial ischemia/infarction as seen in the general population.[59]

1.2.5 Respiratory Failure

Respiratory failure after open aortic surgery occurs as a result of both patient and procedure-related factors. A recent systematic review and meta-analysis shows the incidence of post-operative pulmonary complications to be 10%, with the most common etiologies of respiratory failure being hypoxia, prolonged mechanical ventilation, and pneumonia.[60] Post-operative pulmonary complications have been shown to be associated with higher rates of perioperative mortality in this study.

The most commonly contributing comorbidities are smoking and chronic obstructive pulmonary disease (COPD) in this patient population. Among patients receiving open aortic surgery 30-70% are current smokers, and over 90% of them have a history of smoking at some point in their lifetime.[17,61–63] The rates of COPD are correspondingly high at 18-30%.[17,62,63] Other patient-related risks for post-operative respiratory failure include obstructive sleep apnea, congestive heart failure, and advanced age.[60]

Procedure-related risks also contribute to the likelihood of developing post-operative respiratory failure. Known risks include open transabdominal aortic surgery,[64,65] incisions that extend close to the diaphragm,[66] operative time >2 hours, emergency surgery, perioperative blood transfusions, and prolonged post-operative intubation.[65] These are commonly applicable to patients receiving open abdominal aortic surgery. The use of epidural analgesia intraoperatively as well as in the post-operative phase for analgesia may be protective against the development of respiratory failure, but results are heterogeneous.[67–69] Consideration must be taken to avoid over-resuscitation in the post-operative phase, as iatrogenic volume overload can cause pulmonary edema resulting in a risk for development of pneumonia and respiratory failure.

1.3 Point of Care Ultrasound

There are many tools available to assess hemodynamics to guide resuscitation; however, tools such as central venous pressure and mixed central venous oxygen saturation[70],

pulmonary artery catheters[3], and esophageal doppler probes[71] are all invasive monitors that carry with them a non-zero risk of complication during insertion and use. Non-invasive cardiac output monitors are also available, but some require peripheral arterial lines for pulse contour readings, and non-invasive thoracic bioimpedance devices are expensive and not readily accessible for use outside of operating rooms and intensive care units.[72]

Point of Care Ultrasound (POCUS) involves the use of ultrasound at the bedside to rapidly evaluate patient hemodynamics and diagnose cardiac, pulmonary, and intra-abdominal pathology. Studies have successfully identified POCUS as a tool to narrow the differential diagnosis in patients presenting with shock[73], and to direct the approach for resuscitation in critically ill patients in shock[74,75,76]. Furthermore, protocols have been developed to explore a "whole-body" approach to bedside ultrasonography, which involves ultrasound interrogation of the whole patient to augment data obtained by history, physical exam, and laboratory investigations.[77] A significant advantage inherent in POCUS is the scalability of the examination; significant information can be obtained from simple 2D images, and advanced hemodynamic data can be obtained using color doppler, M-mode, and pulse-wave or continuous-wave doppler techniques as indicated[78,79].

In the post-operative patient, this approach to rapid, multi-system evaluation of the patient with bedside ultrasonography has the potential to augment clinical data available at the bedside. Often traditional endpoints of resuscitation such as vital signs, urine output, and biochemistry can be misleading from confounders such as the use of epidural catheters for post-operative analgesia[80], ß-blockers and calcium-channel blockers[81], and pre-operative comorbid disease states. A focused examination of cardiac function, IVC diameter, and lung function has the potential to diagnose patient volume status to help guide post-operative resuscitation with fluids, vasopressors, and inotropes; furthermore, it has the potential to diagnose pathology associated with over-resuscitation and under-resuscitation, and guide patient management and the need for further investigation.

1.3.1 Cardiac POCUS

Cardiac point of care ultrasound generally involves a 4-view focused cardiac ultrasound to assess cardiac function. With these four basic views the scope of the exam can be as limited or detailed as necessary to adequately answer the clinical question at hand. This can range from simple 2D B-mode assessment for ventricular function or pericardial effusion to full pulse-wave doppler assessment of stroke volume, cardiac output, and valvular function. The complexity of the examination is flexibly scalable to the features of the equipment used, the abilities of the operator, and the clinical question being answered by the exam. The basic four views include the Parasternal long axis (Figure 1), the Parasternal short axis (Figure 2), the Apical four chamber (Figure 3), and the subcostal four chamber (Figure 4).

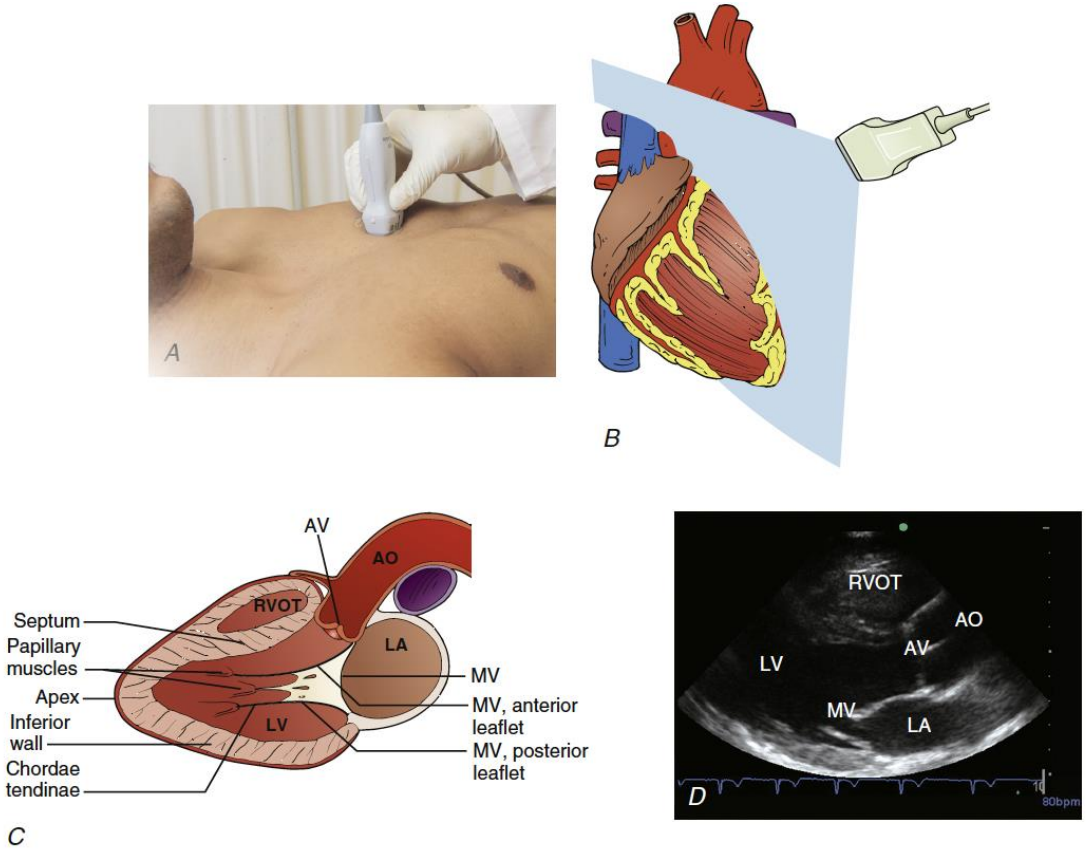

Figure 1: Parasternal long-axis view. **A.** Transducer Position. **B.** Imaging Plane. **C.** Cross-sectional anatomy. **D.** Ultrasound image. AO, aorta; AV, aortic valve; LA, left atrium; LV, left ventricle; RVOT, right ventricular outflow tract; MV, mitral valve

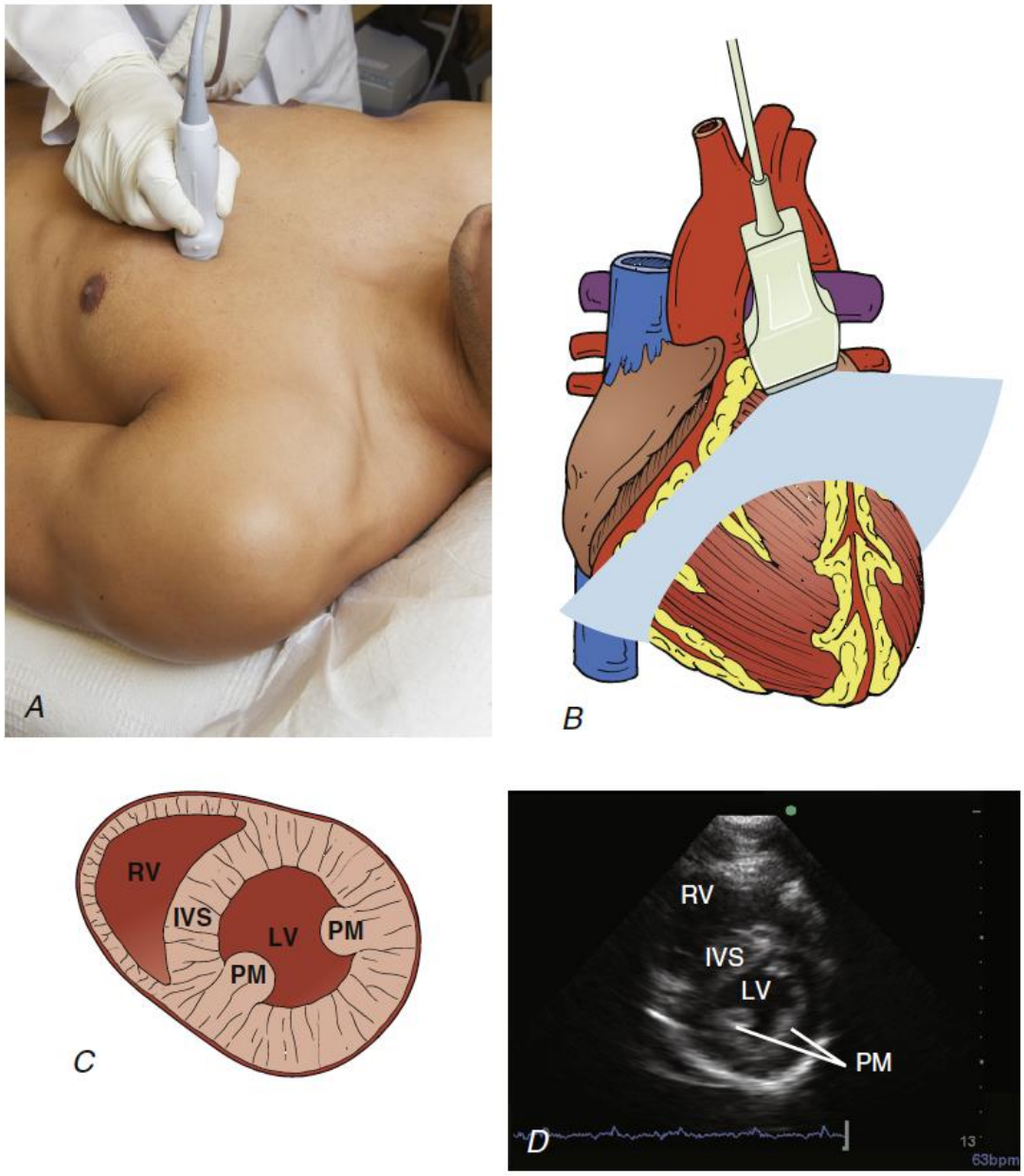

Figure 2: Parasternal short-axis view. **A**, Transducer position. **B**, Imaging plane. **C**, Cross-sectional anatomy. **D**, Ultrasound image. IVS, interventricular septum; LV, left ventricle; PM, papillary muscle; RV, right ventricle.

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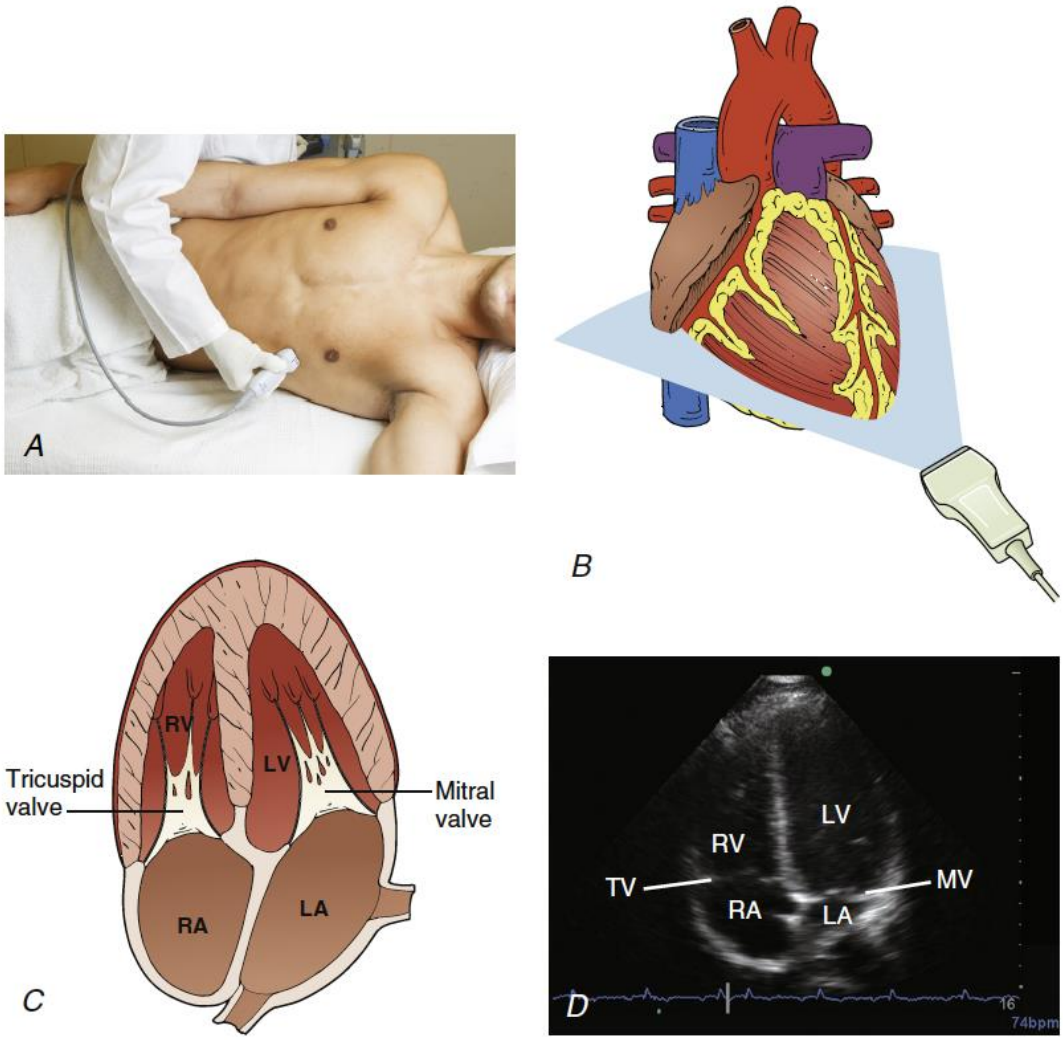

Figure 3: Apical 4-chamber view. **A,** Transducer position. **B,** Imaging plane. **C,** Cross-sectional anatomy. **D,** Ultrasound image. LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.

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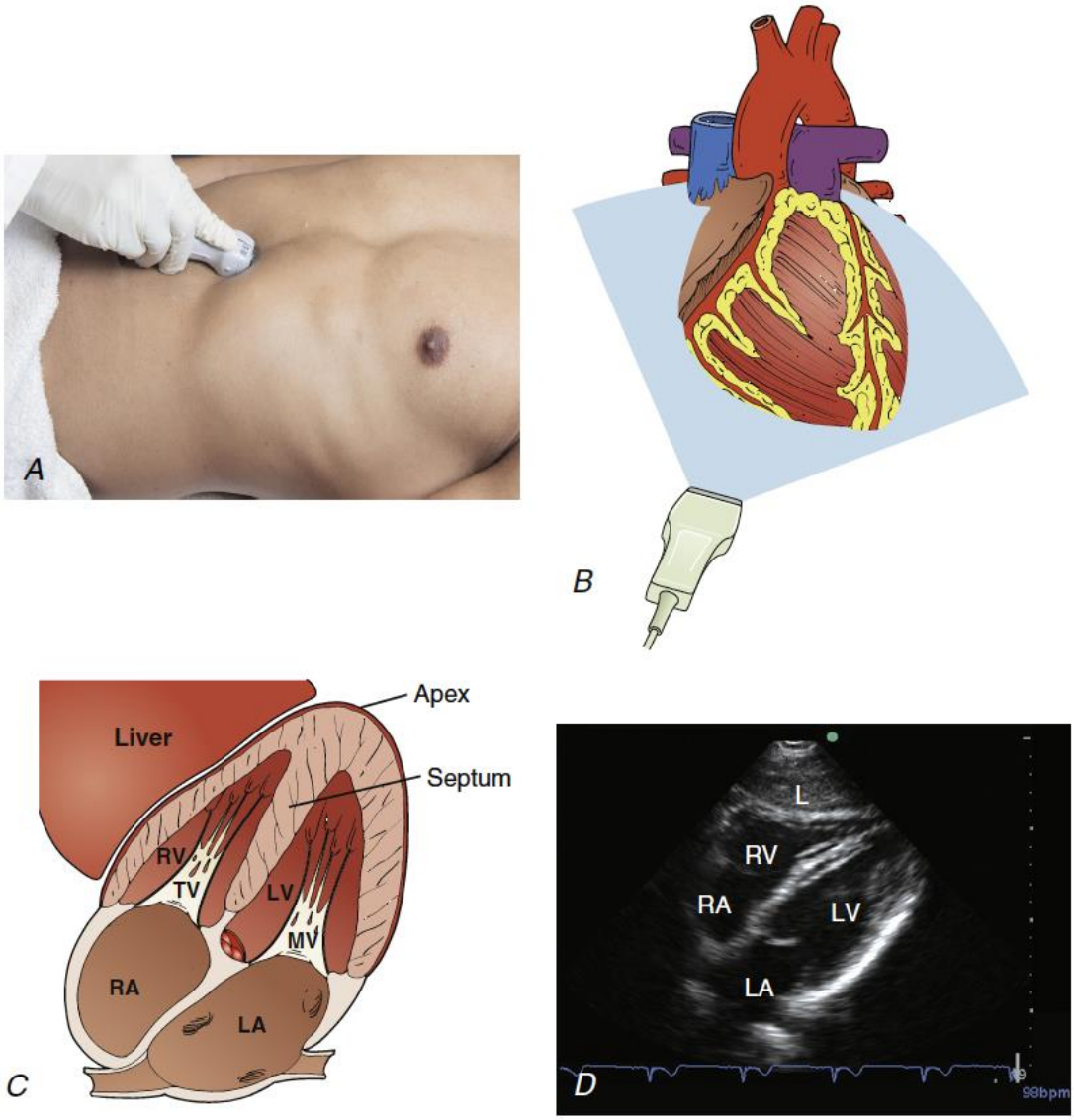

Figure 4: Subcostal 4-chamber view. **A,** Transducer position. **B,** Imaging plane. **C,** Cross-sectional anatomy. **D,** Ultrasound image. L, liver; LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve

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1.3.2 Lung POCUS

Lung ultrasound provides utility in rapidly assessing the pleura, parenchyma, and intrathoracic cavity at the bedside without the need for plain film x-ray, CT scan, or magnetic resonance imaging (MRI). Similar to targeted cardiac POCUS exams, lung pocus can serve to answer specific questions about the presence or absence of clinically suspected pathology, or to help aid in diagnosis of someone with undifferentiated respiratory failure. The BLUE protocol originally defined the four points of interrogation of the chest wall to aid in identifying pleural and parenchymal pathology in a systematic, organized fashion.[82] (Figure 5) Using simple 2D B-mode ultrasound image interpretation, a synthesis of the etiology of respiratory failure can be created from the images acquired (Figure 6).

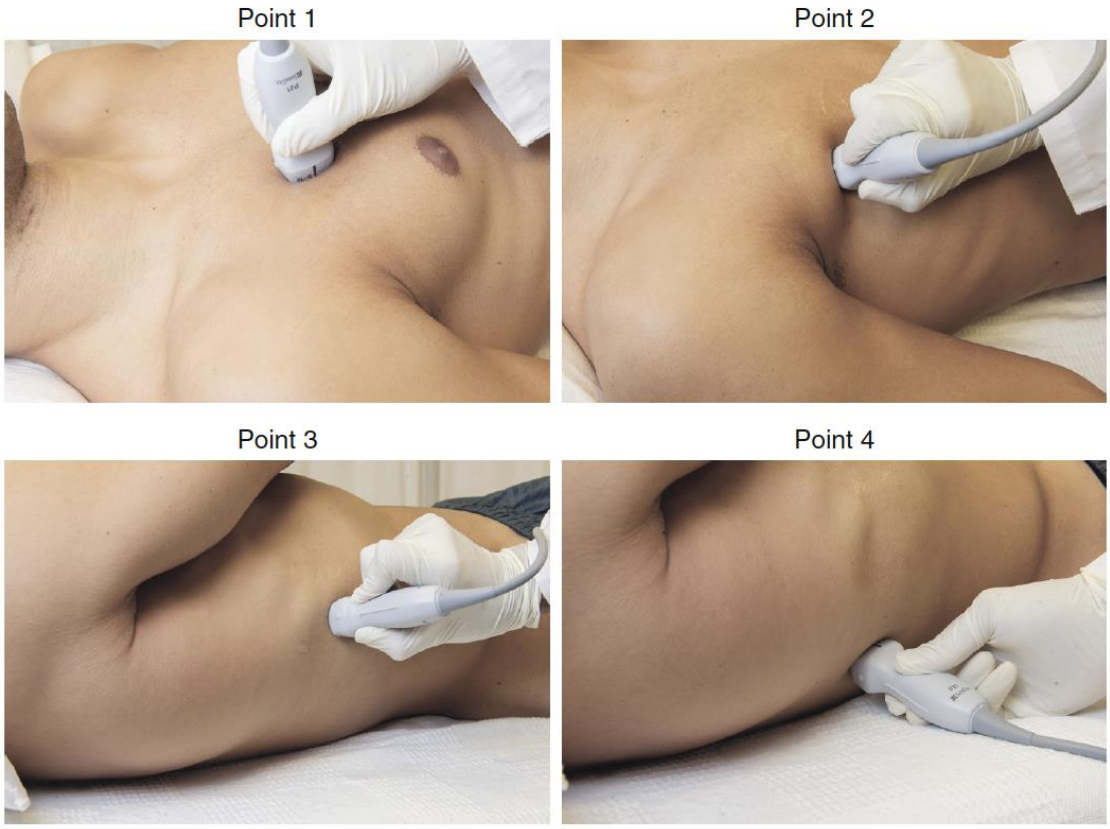

Figure 5: BLUE lung exam points. Point 1 is located on the mid-clavicular line at approximately the second intercostal space. Point 2 is located on the anterior axillary line at approximately intercostal space 5, usually just lateral to the nipple in men. Point 3 is located along the diaphragm in mid-axillary line. Point 4 is also called the posterolateral alveolar pleural syndrome (PLAPS) point and is the most posterior point along the diaphragm. Note the probe face is pointing to the sky with patient back rotated off the bed.

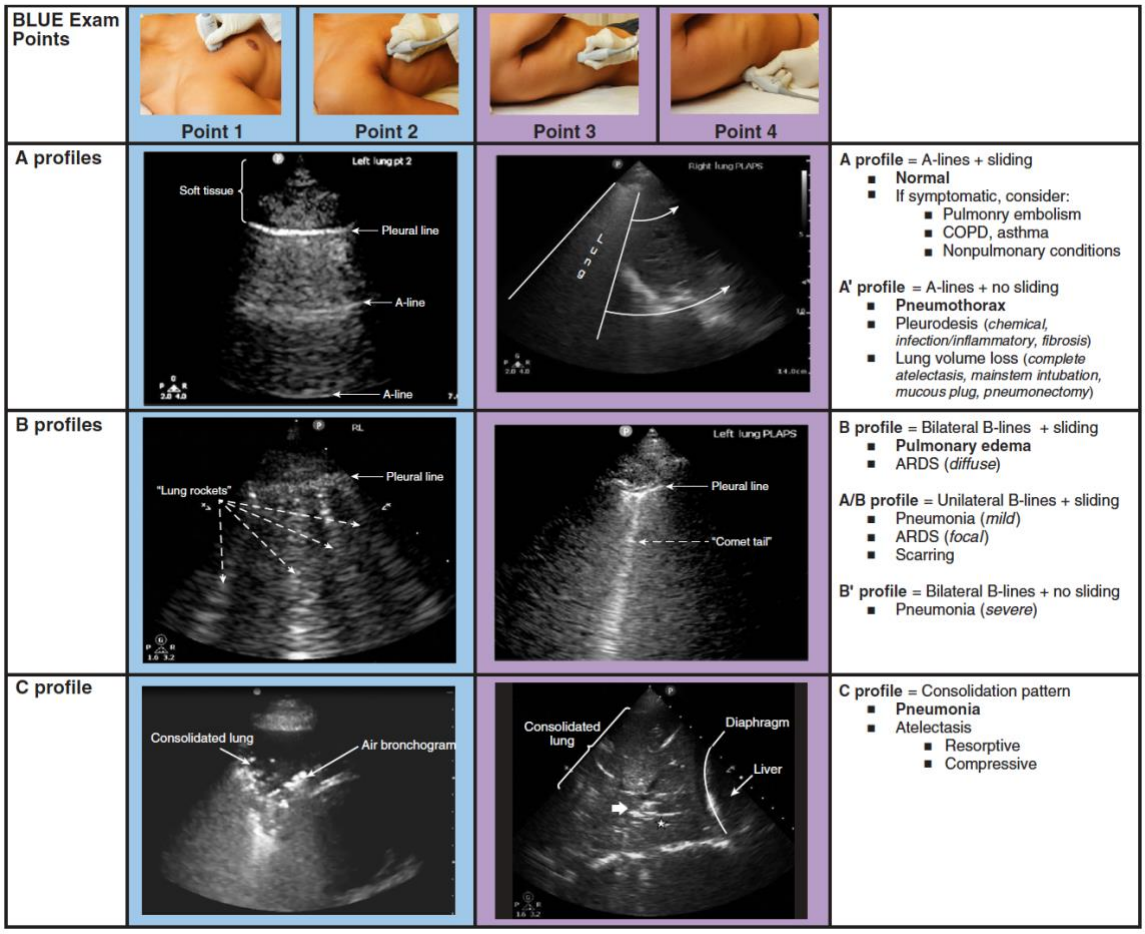

Figure 6: A sample of the correlation of specific findings on lung ultrasound to their respective disease states.

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1.3.3 Inferior Vena Cava POCUS

The inferior vena cava (IVC) can be viewed with POCUS to aid in synthesizing information about a patient's volume status. Those with obviously low intravascular volume will have a flat, depleted IVC whereas those that are volume replete or overloaded will have a dilated, plethoric IVC. It can also aid in the diagnosis of other disease states such as pericardial effusion causing tamponade, or right heart failure depending on the IVC findings in the context of heart and lung POCUS studies. The transverse diameter of the IVC can be easily measured from either a subcostal (Figure 7) or transhepatic position (Figure 8).

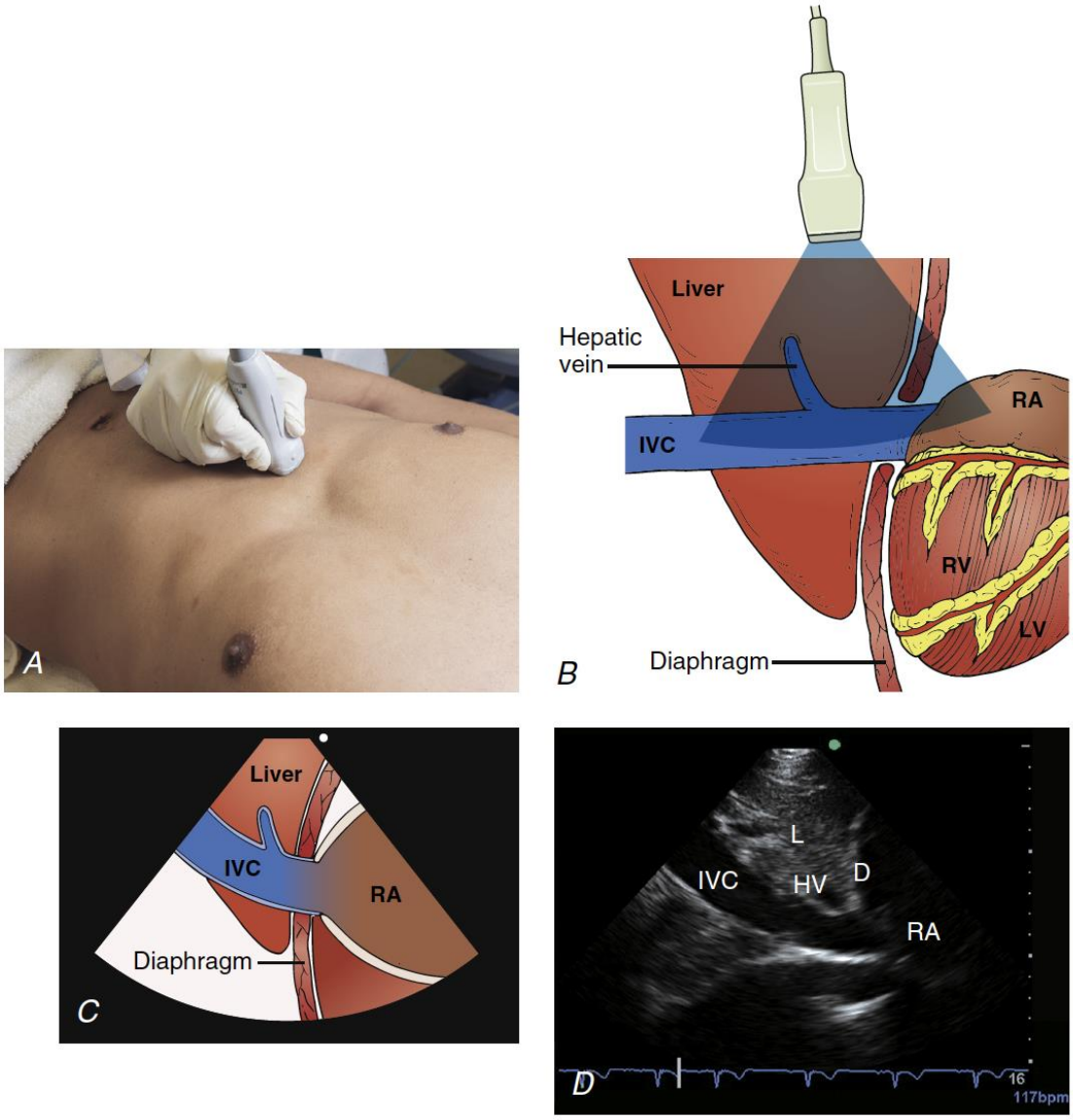

Figure 7: Subcostal inferior vena cava view. **A,** Transducer position. **B,** Imaging plane. **C,** Cross-sectional anatomy. **D,** Ultrasound image. D, diaphragm; HV, hepatic vein; IVC, inferior vena cava; L, liver; LV, left ventricle; RA, right atrium; RV, right ventricle.

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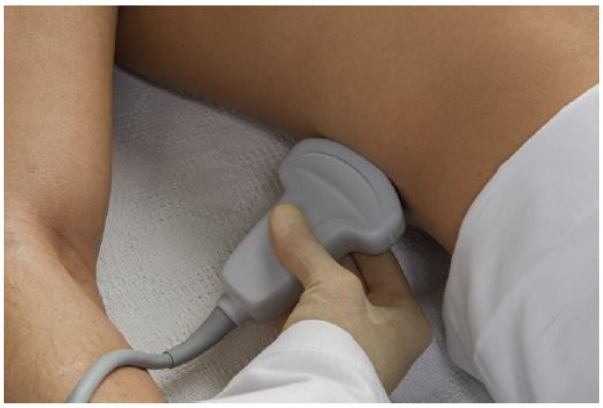

Figure 8: Transducer position to acquire a transhepatic coronal view of the inferior vena cava

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1.4 Goal-Directed Resuscitation

The resuscitation and care of patients after open aortic surgery has historically involved combining history, physical exam, vital signs, urine output, and laboratory biochemistry to guide fluid resuscitation strategies and triage the need for further investigations.[7] While studies have taken place in this patient population to determine whether fluid liberal or fluid restrictive resuscitation strategies represent the ideal approach to post-operative care, the results have been largely heterogeneous.[83,84,85,86,87,88] More recently, this question was explored with a high quality randomized control trial when the RELIEF trial examined the effects of liberal vs restrictive fluid administration in patients receiving major abdominal surgery, which included patients receiving major vascular surgery.[89] When considering the heterogeneity of results in this patient population, one can consider if it is appropriate to group all patients into a single resuscitation strategy. The concept of "goal-directed resuscitation", first popularized by Rivers et al in the management of septic shock[90], has also been explored in the resuscitation of patients receiving major open aortic surgery. Utilizing such tools as central venous pressure and mixed central venous oxygen saturation[70], cardiac output monitors with pulse contour to assess stroke

volume variation[72], pulmonary artery catheters[3], and esophageal doppler probes[71], benefit has been shown in individualizing resuscitation strategies towards objective goals that ensure balanced resuscitation without volume overload or excessive fluid restriction. Larger systematic reviews have demonstrated potential benefit of goal-directed therapy in a more generalized population of patients receiving major abdominal surgery.[91,92]

1.5 Determinants of Fluid Responsiveness

Post-operative management of patients receiving major abdominal aortic surgery frequently includes the challenge of managing hypotension and intravascular volume. While the goal of fluid resuscitation is to augment stroke volume in patients who are in the early part of the Frank-Starling curve[93], studies have demonstrated that only about half of patients that are hemodynamically unstable and critically ill respond appropriately to volume boluses[94]. Additionally, evidence suggests that over-resuscitation and volume overload can lead to significant morbidity and mortality in multiple patient populations[95,96,97,98]. In an attempt to appropriately identify patients that are volume responsive and avoid the morbidity of continued fluid resuscitation in unresponsive patients, clinical tools that predict volume responsiveness have been a subject of significant clinical and academic interest.[99]

1.5.1 Central Venous Pressure

One of the earliest metrics for determining fluid responsiveness involved using a central venous catheter to transduce a patient's central venous pressure (CVP). Transducing both the CVP in mmHg as well as a trend of the waveform provide information about venous circulation and right heart function. CVP became widely used based on the assumption that it was an adequate predictor of right ventricular (RV) preload, allowing clinicians to approximate a patient's trajectory on the frank-starling curve and subsequently predict fluid responsiveness.[100] While CVP has been explicitly explored in the goal-directed resuscitation of patients receiving open abdominal aortic surgery[70], there is robust evidence suggesting it is a poor predictor of fluid responsiveness and therefore unreliable to guide post-operative fluid management.[101]

1.5.2 Pulmonary Artery Catheters

Pulmonary artery catheters similarly have been widely used in the past as real-time beat-to-beat measures of right heart function with the ability to measure pulmonary artery occlusion pressures and cardiac output by thermodilution. While these have been used in goal-directed resuscitation of patients undergoing aortic surgery[3], they have fallen out of favor as regular monitors for post-operative hemodynamics owing to multiple studies showing no difference in mortality as well as the potential for significant morbidity or mortality with complications arising from their use.[102]

1.5.3 Systolic Pressure Variation, Pulse Pressure Variation, and Stroke Volume Variation

Dynamic changes in an invasive arterial line waveform have also been used to assess preload responsiveness, which are based on physiologic principles of the heart-lung interactions during the respiratory cycle. Systolic pressure variation (SPV), pulse pressure variation (PPV), and stroke volume variation (SVV) are three of these dynamic indices, which are derived through computer-assisted analysis of different elements of the arterial waveform throughout the cardiac cycle. A systematic review demonstrated that all three are accurate predictors of fluid responsiveness with PPV being the most accurate metric.[94] Stroke volume variation has been examined as a metric of goal directed therapy in patients receiving open abdominal aortic surgery with reasonable results.[72] Pitfalls of this technique include the fact that it requires patients to have an indwelling arterial catheter which carries with it the risk of complications, commercial devices are required to process the waveform to establish the desired index which carries with it an associated cost, and the accuracy of a given index can be confounded by arrythmias, heart or lung disease, and changes in ventilator mechanics.[99]

1.5.4 Non-Invasive Cardiac Output Monitors

The NICOM™ (Cheetah Medical, Portland, OR, USA) is a Non-invasive cardiac output monitor relying on the principle of thoracic biorectance to measure cardiac output, and has been shown to correlate with measurements obtained by pulse contour and thermodilution.[103] When combined with maneuvers such as a passive leg raise or a fluid

bolus, the NICOM device has been shown to adequately predict volume responsiveness.[104] Like dynamic indices of arterial waveform variation, the NICOM device requires special equipment for bioreactance measurements and analysis, although it has the benefit of being noninvasive. It has yet to be evaluated in goal-directed fluid resuscitation in patients receiving major aortic surgery.

1.5.5 Passive Leg Raise

The passive leg raise is a maneuver that can be performed at the bedside as a means of assessing fluid responsiveness.[105] The underlying principle involves consideration of the venous volume present in the lower extremities as a reversible autotransfusion. Assessment of hemodynamic effects after one minute of passive elevation of the legs can provide insight into the patient's fluid responsiveness, and ending the leg elevation reverses the volume augmentation associated with the maneuver. It is often used in conjunction with other monitoring devices such as arterial lines, PPV or SVV, or a NICOM device to dynamically assess for the presence of hemodynamic changes during the maneuver.[99] The utility of the passive leg raise is limited by patients who do not have intact lower extremities, those that cannot tolerate elevation of the legs to perform the maneuver, and the effects of intra-abdominal hypertension restricting the ability of venous return to reach the heart.

1.5.6 The Role of Ultrasound in Determining Fluid Responsiveness

Assessment of the IVC with ultrasound has been another metric of great interest in assessing both volume status and fluid responsiveness. Both absolute diameter of the IVC, as well as respiratory variation in the diameter of the IVC can be used as metrics.[74] The IVC can be used to obtain dynamic metrics of collapsibility of the IVC in spontaneously breathing patients[106] and distensibility of the IVC in mechanically ventilated patients with positive pressure ventilation[107]. Assessment of these variations in IVC have been proposed as a surrogate for fluid responsiveness, although there has been some heterogeneity in the literature and varied degrees of acceptance as to the utility of this metric in varying patient populations.[108]

Transthoracic ultrasonography of the lung can elucidate a number of different pathological states including pneumothorax, pleural effusion, pulmonary infection, and pulmonary edema from volume overload.[109] While the application of lung ultrasound for identification of etiology of undifferentiated respiratory failure is well described [82], it can also serve as a useful adjunct for decision making about volume status. In patients with sonographic findings of extravascular lung water in the form of pulmonary edema or pleural effusion based on the presence of "B-lines" suggesting parenchymal pathology, and pleural fluid at dependent areas, synthesis of volume overload can be enhanced through assessment of the lung fields with ultrasound.[74]

Routine assessment of left ventricular function can be performed using point of care ultrasound to integrate a picture of volume status and volume responsiveness at the bedside. Using a focused point-of-care qualitative assessment of LV function examining endocardial excursion, myocardial thickening, and septal motion of the anterior leaflet of the mitral valve, one can broadly categorize LV function as being hyperdynamic, normal, reduced, or severely reduced.[110,111] This data can be synthesized into an assessment of volume status, volume responsiveness, and identifying patients whose hypotension would be better treated with vasopressors or inotropes.

While the landscape of assessment of volume responsiveness has explored many techniques and tools, the pitfalls associated in the limitations of their accuracy and the invasive or expensive nature of the tools used to assess hemodynamics has limited their widespread adoption. Ultrasound provides the potential for a comparatively cheap, readily available, portable device that allows for a whole-body assessment of volume status and fluid responsiveness to augment the ability for physicians to make timely, insightful, and goal-directed resuscitation decisions at the bedside.

1.6 Study Rationale

There are numerous different post-operative complications associated with open abdominal aortic surgery, and the rate of complications is high given the nature of the surgery and the high-risk patient population involved. While attention to intraoperative approach and technique is an important part of minimizing complications, attention to

appropriate post-operative resuscitation and medical management of these patients is important as well in working toward minimizing the myriad of complications contributing to their perioperative morbidity and mortality. This combination of relatively high-risk surgery in high-risk patients makes an ideal population to develop a resuscitation strategy aiming to minimize the iatrogenic sequelae of over and under-resuscitation in the post-operative phase.

Instead of contemplating fluid liberal versus fluid restrictive resuscitation strategies, a more objective and clinically sound approach is to consider individualized resuscitation strategies for each patient. While this has been historically attempted with older and more invasive devices such as pulmonary artery catheters and esophageal doppler probes, these devices are costly, disposable, and limited to use in the operating room or intensive care unit.

To date no one has attempted a goal-directed resuscitation strategy guided by point of care ultrasound in surgical patients. Ultrasound as a tool has become progressively more democratized with the passing of time as devices have become less costly and more affordable, culminating in personal ultrasound probes that attach to a smartphone or digital tablet which are currently available on the market today. This has expanded the role of ultrasound for use in regular bedside assessments as a more high-tech stethoscope. POCUS has the potential to significantly augment the ability to perform personalized, goal-directed resuscitation at the bedside in this patient population by virtue of being cost-effective, non-invasive, easily reproducible, and its ability to rapidly synthesize information about the heart, lungs, and IVC together with a bedside clinical assessment with an aim to more accurately gauge intravascular volume and cardiac function.

1.7 Aim of the Study

This study will aim to examine the utility of using POCUS to assess cardiac function, pulmonary function, and volume status via Inferior Vena Cava assessment as a tool to provide individualized, goal-directed resuscitation after open aortic surgery. The potential benefits of this approach to post-operative care would include optimizing use of fluid liberal or fluid restrictive strategies when appropriate, selectively utilizing vasopressors

or inotropes when appropriate, and personalizing resuscitation strategies to prevent morbidity from over-resuscitation such as CHF, MI, and pulmonary edema, in addition to preventing morbidity from under-resuscitation such as acute kidney injury, limb ischemia, and bowel ischemia. To serve as a foundation for this investigation, we designed a feasibility study using an open label, randomized controlled trial. The first group received routine post-operative care guided by vital signs, biochemistry, and patient physical exam to guide resuscitation. The second group received regular POCUS assessments over the first 48 hours after surgery with a protocol designed to adjust the resuscitative strategy from either fluid restrictive or fluid liberal depending on the on the ultrasound findings.

1.8 Research Questions

The following research question was posed in conducting this study:

1. Is the protocol for goal-directed resuscitation using point-of-care ultrasound in patients receiving open abdominal aortic surgery feasible to execute in the clinical environment of our tertiary care Vascular Surgery program at Victoria Hospital, London Health Sciences Center.

Answering this research question will allow us to determine whether it is appropriate to consider further expanding this study into a trial adequately powered to detect a difference in key clinical endpoints, or whether modifications will be necessary before doing so.

1.9 Hypothesis

We hypothesize that the protocol for goal-directed resuscitation outlined in this trial will be feasible to implement at our tertiary care center.

Chapter 2

2 Study Design and Methodology

Patients assessed for elective open abdominal aortic surgery for both aneurysmal and occlusive disease either as inpatients or in the outpatient vascular surgery clinic were screened for eligibility at the time of initial consultation. Once the patient had been screened for eligibility, participants were enrolled on the basis of informed consent with a letter of information. The study was designed as an open-label 1:1 feasibility trial with the primary endpoints reflecting feasibility of executing the trial protocol. Randomization was performed in the REDCap™ database software using permuted block randomization with block sizes of 2 and 4. Randomization took place after the completion of the operation before the patient was transferred to the post-operative recovery area. Patient baseline characteristics were reviewed and input into REDCap™, and patients were only randomized if they met the inclusion criteria and did not meet any of the exclusion criteria.

The intervention arm involved randomization to POCUS-based management for goal-directed post-operative resuscitation for the first 48 hours of admission, whereas the control group received management by usual care for the first 48 hours of admission (figure 9). Patients randomized to POCUS received a focused cardiac, thoracic, and IVC study performed post-operatively in the surgical recovery room, as well as scheduled assessments on the inpatient ward in the morning and afternoon of post-operative day one and two.

The protocol for the intervention group included a 4-view transthoracic echocardiogram including the following views: Parasternal long axis, parasternal short axis, apical 4-chamber, and supplemental subcostal short-axis and subcostal 4-chamber if parasternal views were limited. Color Doppler was permitted for qualitative valvular assessment if indicated. A longitudinal IVC view was attempted in the usual subcostal transabdominal position, or the transhepatic position if the transabdominal view was not technically

feasible. A thoracic lung ultrasound study assessed the left and right anterior chest wall, anterior axillary regions, as well as the costophrenic angle and posterolateral regions.

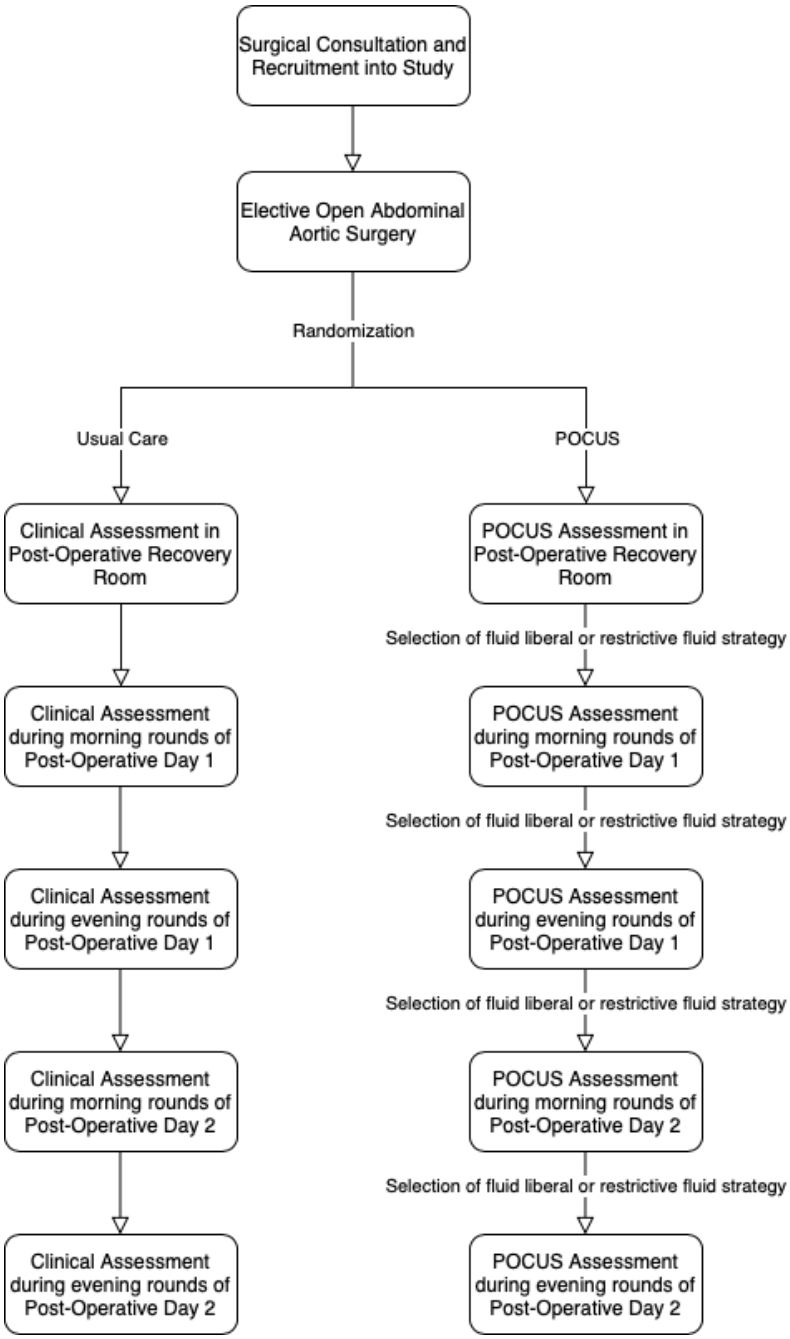

Figure 9: Flow diagram of participants in the study after randomization

Participants randomized to the point of care ultrasound arm also had access to routine avenues of patient assessment which included review of vital signs, biochemistry, and urine output as well as bedside physical exam. Images acquired were reviewed for quality assurance by sonographic experts with expertise in bedside point of care echocardiography through a central image reporting system.

Point of care studies synthesized cardiac, thoracic, and IVC views to elucidate whether patients were fluid deplete or fluid replete and if ventricular dysfunction was contributing to hypotension or end-organ dysfunction. Based on this conclusion patients were allocated to either a fluid restrictive or fluid liberal management strategy at each time interval. The fluid liberal strategy consisted of fluid infusion of 2ml/kg/hr of balanced crystalloid solution. For patients with a body weight greater than 100kg, fluid volumes were calculated based on a maximum body weight of 100kg. The fluid restrictive strategy consisted of a fluid infusion of 0.8ml/kg/hr of balanced crystalloid solution designed to approximate euvolemia. IV boluses of crystalloid were permitted to treat hypotension with Systolic Blood Pressure (SBP) <90mmHg with clinical signs of hypovolemia, but oliguria was not used as a trigger for fluid bolus or titration of fluid infusion rates. Blood transfusions were permitted to treat post-operative bleeding or anemia as clinically indicated, with indication for transfusion set at a hemoglobin of 70g/L. Those with severely decreased LV function who were presumed to be hypotensive secondary to poor cardiac output were transferred to an appropriate level 1 care monitored bed to receive vasopressors or inotropes to manage their hypotension. In addition to vasopressors they would receive fluid restrictive resuscitation with an infusion rate of 0.8 ml/kg/hr of balanced crystalloid solution. A visual summary of the goal-directed protocol is provided in figure 10.

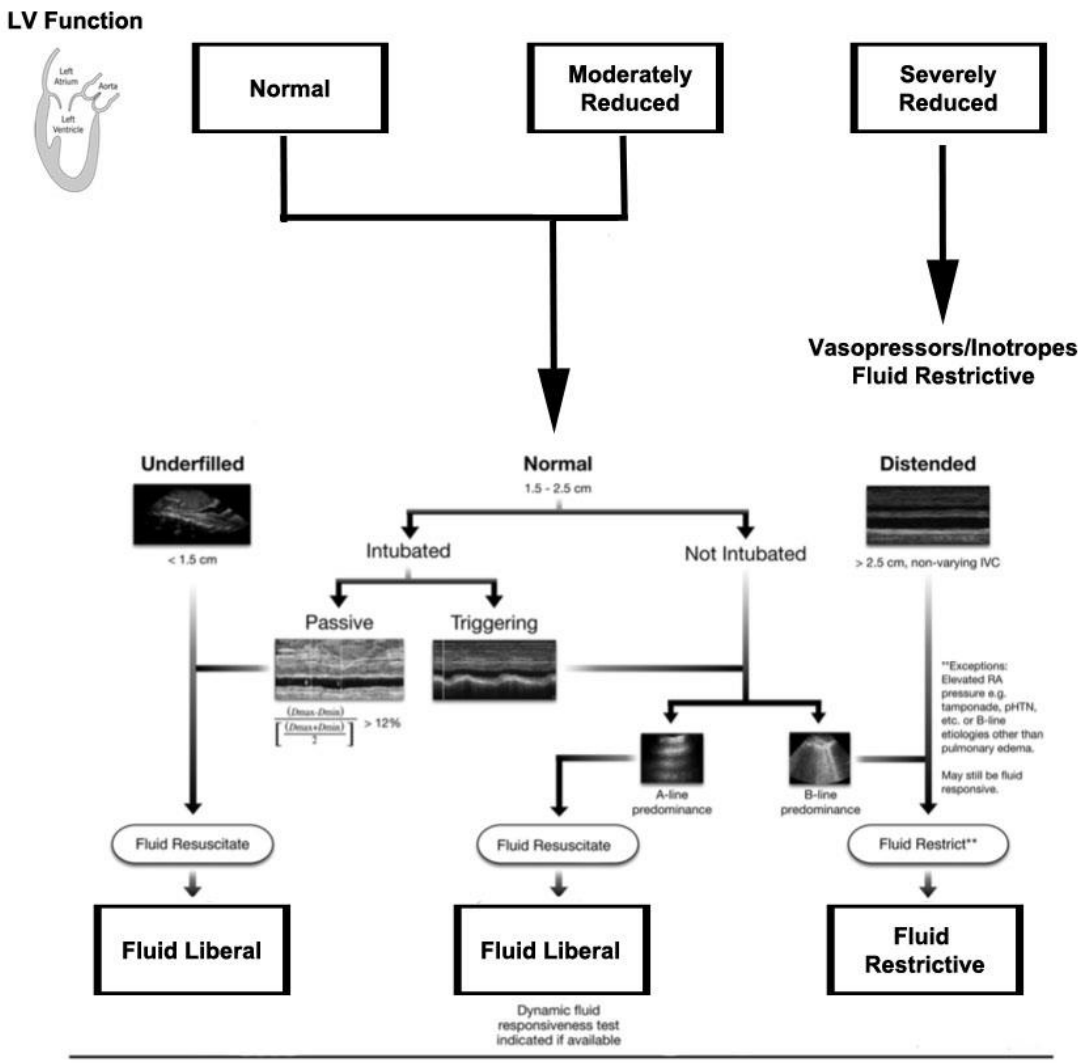

Figure 10: Protocol for POCUS goal-directed resuscitation

*Adapted from C. Lee et all, 2016 [74]

Participants randomized to the control group for usual care underwent resuscitation guided by conventional means which included both static and dynamic measures such review of vital signs, biochemistry, and urine output as well as the bedside physical exam. In this arm patients did not undergo POCUS during their admission. IV fluid infusion rates as well as targets for IV boluses were left to the discretion of the attending physician and included hypotension, hypovolemia, as well as oliguria. Blood transfusion was permitted for post-operative bleeding or anemia as clinically indicated, with indication for transfusion set at a hemoglobin of 70g/L.

The protocol did not restrict formal radiographic or ultrasound studies such as plain film x-rays, CT, MRI, echocardiography, abdominal ultrasonography, and duplex ultrasound of lower extremity veins in patients in the intervention or control groups with appropriate clinical indications.

Given that the point of care ultrasound arm involved using a portable ultrasound machine to directly acquire images and the usual care arm involved physical examination and interpretation of vital signs, urine output, and biochemistry, it was not be possible to blind participants. It was also not possible to blind practitioners in this trial. Data acquisition, interpretation, and implementation of a care plan based on the interventions of the trial was done by the surgical team as well as the POCUS practitioners. As a result, medical practitioners involved in patient care were aware of the allocation of their patients. After the initial two days both groups were treated equally based on the trajectories established during their first two post-operative days.

The inclusion criteria were focused to a specific patient population, which was intentional in its design to augment its external validity. We anticipated that randomization would balance the etiology of the aortic disease, patient comorbidities, and nature of surgical reconstruction adequately.

Inclusion Criteria:

- Patients must be 18 years of age or older.

    - There is no upper age limit for eligibility in this study.
- Elective surgical procedures
- Patients enrolled must be receiving open abdominal aortic surgery for either occlusive disease (aortobifemoral bypass, transaortic endarterectomy) or aneurysmal disease (infrarenal, juxtatrenal abdominal aortic aneurysms).
- Patients must be deemed suitable operative candidates for open abdominal aortic surgery as decided upon by the surgical and perioperative medicine assessments.

Exclusion Criteria:

- Thoracoabdominal aneurysms (Type IV or larger extent)
- Hybrid procedures (Requiring both endovascular and open surgical reconstruction)
- American Society of Anesthesiologists physical status class 5 identified
- Chronic renal failure requiring dialysis
- Inability of patient or substitute decision maker to consent to study

2.1 Feasibility Study Rationale

A feasibility trial was selected for this study design given the gap in knowledge with this specific research question, the infrastructure required to execute the protocol as designed, and the multi-disciplinary nature of the protocol.

While the previous literature review outlined the body of evidence characterizing the use of goal-directed resuscitation in the care of patients receiving open abdominal aortic surgery as well as the use of point-of-care ultrasound as a tool for guiding patient care decision in critical care, the synthesis of POCUS, goal-directed resuscitation, and the care of post-operative patients has not been explored in the literature previously. Assumptions being made in addressing this knowledge gap include presumption that using a goal-directed protocol of POCUS-guided resuscitation would be similar to goal-directed approaches using metrics from invasive monitors, that the utility of POCUS in the care of patients in critical care and emergency medicine suggests POCUS as a tool has similar potential in the care of the post-operative patient, and that the integration of POCUS in the daily workflow and clinical care of patients in critical care and emergency medicine

implies this model will also be successful in the surgical inpatient care setting. In an effort to explore the validity of these assumptions before embarking upon a study powered to detect clinical significance, a feasibility trial was selected to evaluate these assumptions objectively.

In addition to addressing the knowledge gap present with this clinical question, there existed some uncertainty about the technology and infrastructure required to support this study. While in isolation there may have been clinical utility to performing a POCUS exam on these patients in the post-operative setting, the reality of executing these exams in a clinical scenario carries with it certain specific challenges. Would the patients have adequate anatomical windows to obtain ultrasound images in the post-operative period? Would post-operative pain prohibit complete ultrasound examinations? Would the ultrasound devices be reliable enough to work consistently? Could the studies be completed in a reasonable amount of time such that obtaining the additional ultrasound information would not disrupt clinical workflow? Would the protocol as designed produce images that were actionable or clinically meaningful in this patient population? Would the central image reporting system function as expected in a timely and efficient manner? A feasibility trial was best equipped to answer these questions before embarking on a larger study powered to detect clinical significance.

Finally, the multi-disciplinary nature of executing a study such as this warranted a preliminary exploration with a feasibility trial in order to identify barriers to success at the provider level. Even if the physiologic principles of the protocol were found to be sound, it depended on the successful adherence to the protocol from surgeons, surgical trainees, intensive care staff, and nurses working to take care of these patients in surgical recovery, inpatient wards, and intensive care. In successfully examining barriers to protocol adherence in a feasibility trial, the impact of non-adherence could be objectively evaluated and strategies could be established to overcome these barriers before proceeding with a larger study. This study also looked at any changes that may need to be made to the protocol and POCUS assessments to make them as clinically meaningful and parsimonious as possible before implementation in a larger evaluative trial.

In addition to addressing the aforementioned issues, two important questions remained when designing this study: What sample size is adequate to explore the feasibility outcomes selected, and what are the criteria or thresholds for success for these outcomes? Answers to these questions were found in the work of health research methodologists. While guidance exists to estimate sample size based on effect size estimated from a main trial's design or from previous literature[112], the novel nature of this intervention in this population limited this more objective approach to sample size estimation. There exists evidence that the precision about the mean and variance plateaus at a sample size of 12 per group in a feasibility study [113]. With this in mind, coupled with the fact that papers assessing goal-directed resuscitation in patients receiving aortic surgery demonstrated statistical significance with sample sizes between 50 and 100, we conservatively selected a sample size of 20 patients per arm in our study for a sample size of 40.

2.2 Primary Feasibility Endpoints

The primary outcomes centered around 30-day outcomes assessing the feasibility of executing the trial protocol in this patient population. The pre-defined threshold for feasibility is identified for each metric below.

- Recruitment – consent rate of eligible patients as per inclusion/exclusion criteria - ≥80% of patients
- Successful randomization – Patients appropriately subjected to randomization at the completion of operation - ≥80% randomized
- Point of Care Ultrasound Completion – Studies successfully completed at intervals defined by trial protocol – ≥80% completed
    - Image Acquisition Adequate - Summary of quality review of images labelled as "No concerns, standards met with improvement suggestions, standards met with concerns, standards not met with serious concerns". Agreement defined by studies that meet targets of "standards met with improvement suggestions" or greater. - ≥80% adequate
    - Image Interpretation Adequate - Summary of quality review of images labelled as "No concerns, standards met with improvement suggestions,

standards met with concerns, standards not met with serious concerns". Agreement defined by studies that meet targets of "standards met with improvement suggestions" or greater. ≥80% adequate

- Protocol adherence – Patients appropriately receive fluid liberal or restrictive resuscitation as defined by the protocol in response to POCUS findings - ≥80% adherence
- Successful Data Collection – All required data points are collected as defined in the trial protocol - ≥80% of patients with complete data points
- Contamination rate – Patients are withdrawn from the study protocol or crossed over into the opposite arm of the study based on patient or physician motivators - ≤20% contamination

2.3 Secondary Outcomes

Secondary outcomes of interest included the following clinical endpoints measured up to 30 days post operation. While the trial was not be adequately powered to detect differences in these endpoints, they were collected to assist in development of further phases of this study in the event of successful execution of the feasibility trial.

- Myocardial infarction – Troponin elevation + Electrocardiogram (ECG) changes
- Pneumonia – Symptoms + Chest x-ray/Lung Ultrasound findings
- Surgical site infection – Purulence, positive wound culture
- Pulmonary edema – Chest x-ray/Lung US findings + increasing oxygen requirement in the absence of pneumonia
- Acute kidney injury (RIFLE stage 2 – creatinine doubling from baseline)
- Cardiac arrhythmia – as defined by bedside telemetry or ECG
- Ischemic bowel – Radiographic, endoscopic or surgical findings
- Unplanned admission to an Intensive Care Unit (ICU)
- Death
- Renal replacement therapy (Peritoneal dialysis or Hemodialysis)
- Limb ischemia requiring anticoagulation or re-operation – defined clinically or radiographically
- Unplanned re-operation

- Total volume of crystalloid received during admission
- Use of vasopressors or inotropes
- Length of hospital stay
- Length of ICU stay
- Number of ventilator days
- Inflammatory markers (C-reactive protein (CRP) at 24 hours post-operative)
- Tissue perfusion markers (peak plasma lactate within 24 hours of operation – taken at 6 and 24 hours)
- Post-operative blood product transfusions (Packed cells, platelets, Fresh frozen plasma (FFP), cryoprecipitate)

2.4 Statistical Analysis

The feasibility outcomes will be analyzed using descriptive statistics as follows:

Recruitment – Overall proportion of eligible patients successfully entered into the study divided by the total number of eligible patients consented and retained to full data completion

Successful randomization – Overall proportion of consented patients successfully receiving randomization at the completion of operation divided by the total number of consented patients

POCUS study completion – Overall proportion of completed studies divided by expected studies

Image quality – Proportion of agreement between physicians performing POCUS and experts auditing studies will be measured for both image acquisition and interpretation – threshold for quality ≥80% for acquisition and interpretation, measured separately

Protocol Adherence – Overall proportion of patients adequately receiving treatment as defined by the trial protocol divided by the total number of patients enrolled

Successful Data Collection – Proportion of patients with no absent data points in the database divided by the total number of patients enrolled

Contamination rate – The number of patients withdrawn or crossed over into the opposite arm of the study based on patient or physician motivators divided by the total number of patients enrolled

Clinical outcome data will be collected as defined in the secondary outcomes with an understanding that the trial will not be adequately powered to detect a difference in these metrics, but to assist in developing the future trial should this protocol be feasible. No data analysis will be performed on these metrics as a result.

2.5 Ethics Approval

This study received approval from the Western University Research Ethics Board. All patients involved in the study received a consent form and letter of information with specific attention paid to their freedom to withdraw from the study at any time with no adverse effects on the care they were receiving.

Chapter 3

3 Results

After obtaining ethics approval and successfully registering the study with clinicaltrials.gov (NCT #04180553) recruitment actively began in January of 2020. The duration of recruitment of the study was three months from January to March of 2020. At this time the global Covid-19 pandemic resulted in temporary cessation of recruitment of further patients into the study. The reasons for this were twofold: All research activity at our institution was halted to limit unnecessary exposure of research personnel to the hospital environment and to allocate resources for clinical investigation into Covid-19 patients, and also because elective surgery was put on hold thus rendering our patient population unavailable for clinical investigation during the pandemic. As a result data available on the 17 patients successfully recruited into the study will be reported in aggregate with plans to continue recruitment to the planned cohort of 40 patients once full clinical and research duties resume at our institution (figure 11). Demographic data of the cohort to date is outlined in table 1.

Expected rate of recruitment was 2 patients per week, with an estimated recruitment period of 5 months to achieve a cohort of 40 patients. Up until the time of the Covid-19 pandemic, the observed rate of recruitment matched this estimate and study completion was expected to meet the planned timeline (figure 12).

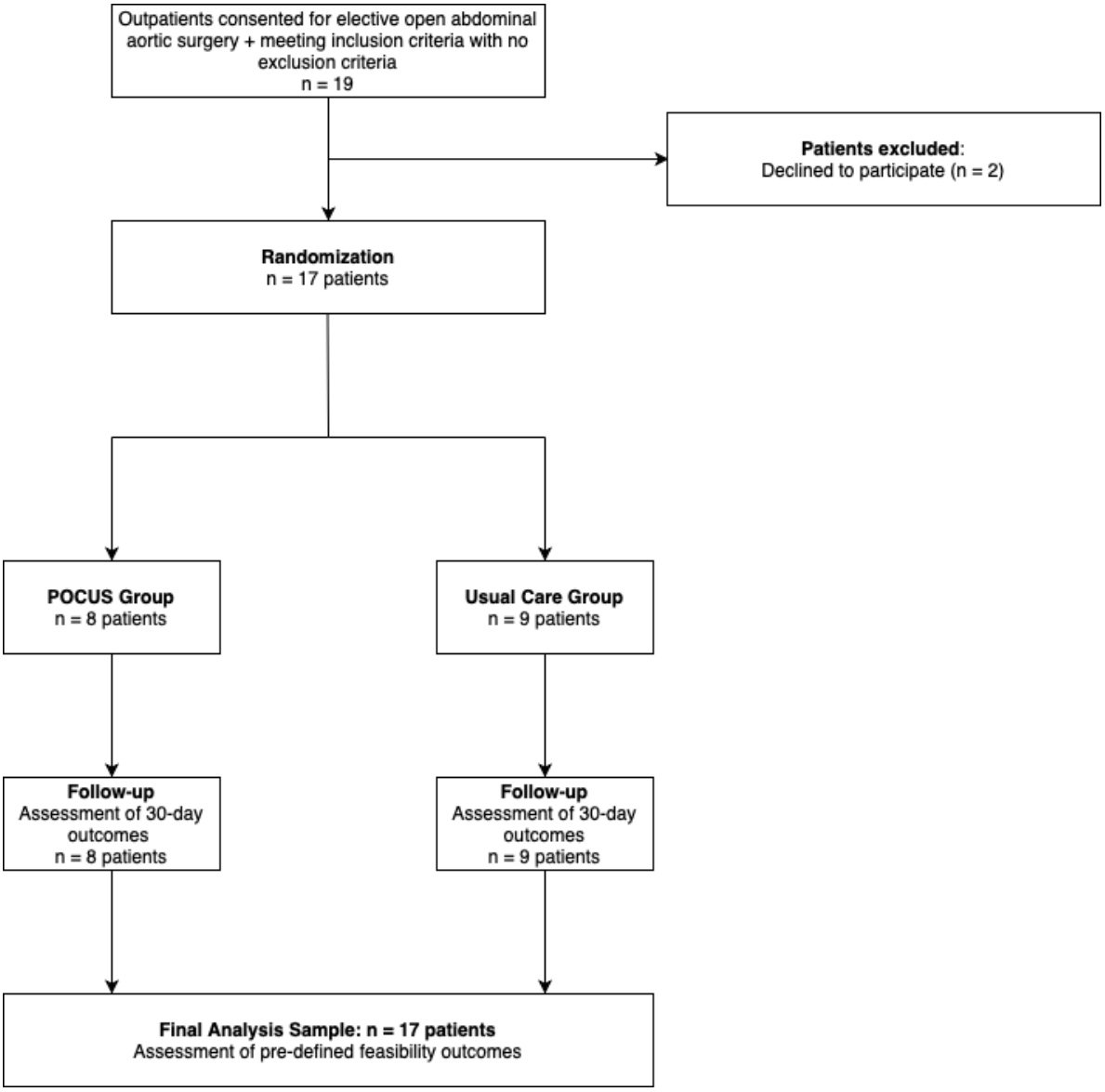

Figure 11: Timeline of patient involvement from the time of recruitment to final data analysis

Characteristic	Total Cohort (n = 17)
Median age (years)	67 (Range 55-92)
Sex	
Male	14 (82%)
Female	3 (18%)
Mean BMI (kg/m^2)	28 (± 6.6)
ASA Score	
1	0
2	0
3	2 (12%)
4	15 (88%)
Hypertension	9 (59%)
Heart Failure (LVEF < 35%)	1 (6%)
CKD Stage 3-5	0
Diabetes	3 (18%)
COPD	7 (41%)
Stroke/TIA	5 (29%)
Coronary Artery Disease	4 (21%)
Previous Coronary Artery Bypass	1 (6%)
Previous Coronary Artery Stenting	9 (59%)
Current Smoker	3 (18%)

Table 1: Baseline patient characteristics of the recruited patient cohort.

Figure 12: Rate of observed recruitment plotted against rate of expected recruitment of two patients per week. Cessation of observed recruitment coincided with initiation of covid-19 pandemic planning at our center.

3.1 Primary Feasibility Endpoints

Examining the primary endpoints of the cohort recruited to date demonstrates generally favorable metrics of feasibility (table 2). To date all metrics have met the pre-defined thresholds of feasibility. While definitive comments on the success of the feasibility trial will await the full cohort, commentary on trends or implications of the interim cohort accompany the analysis of each individual metric in the discussion below.

Feasibility Metric	Result
Recruitment	17 (89%)
Successful Randomization	17 (100%)
Ultrasound Studies Completed	40 (100%)
Ultrasound Image Quality Adequate	39 (98%)
Ultrasound Image Interpretation Adequate	40 (100%)
Protocol Adherence	14 (82%)
Successful Data Collection	16 (94%)
Contamination Rate	0

Table 2: Summary of outcomes of the primary feasibility endpoints of the recruited cohort

3.1.1 Recruitment

Generally, the patients had favorable reception to the proposed investigation. Patients were given adequate time to review the letter of information, and they were assured that it was not mandatory for them to come to a decision at the time of initial consultation for surgery. Out of a total of 19 patients who met the pre-defined inclusion criteria without meeting any exclusion criteria, 17 were successfully recruited into the study to its completion for a recruitment rate of 89%. Of the two patients who declined to consent for the study, one cited their anxiety at the seriousness of the operation and their desire to just see it through with as uncomplicated a plan of post-operative care as possible, and the other expressed hesitation at "being part of an experiment" with an untested protocol.

Once patients were recruited into the study, none asked to be withdrawn during the course of their inpatient stay after completion of their elective surgery. Despite our concerns that perioperative discomfort and disruption of patient rest and recovery would possibly affect patients' desire to remain in the study, it did not have an adverse effect on this interim cohort.

3.1.2 Successful Randomization

All 17 patients that were recruited into the study were successfully randomized at the completion of their operation. Because of the integration of the randomization process into the REDCap^{TM} database management software, physicians and trainees who were responsible for ensuring randomization occurred at the correct time at the completion of surgery found the process to be minimally disruptive to the workflow of clinical care in the operating room.

3.1.3 Point of Care Ultrasound Studies

Point of care ultrasound studies performed at the bedside were stored on a central picture archiving and communications (PACS) system. Attached to each set of images was a synoptic reporting form ensuring image assessment addressed each of the findings defined in the protocol (figure 13). Review of three discrete metrics allowed for an

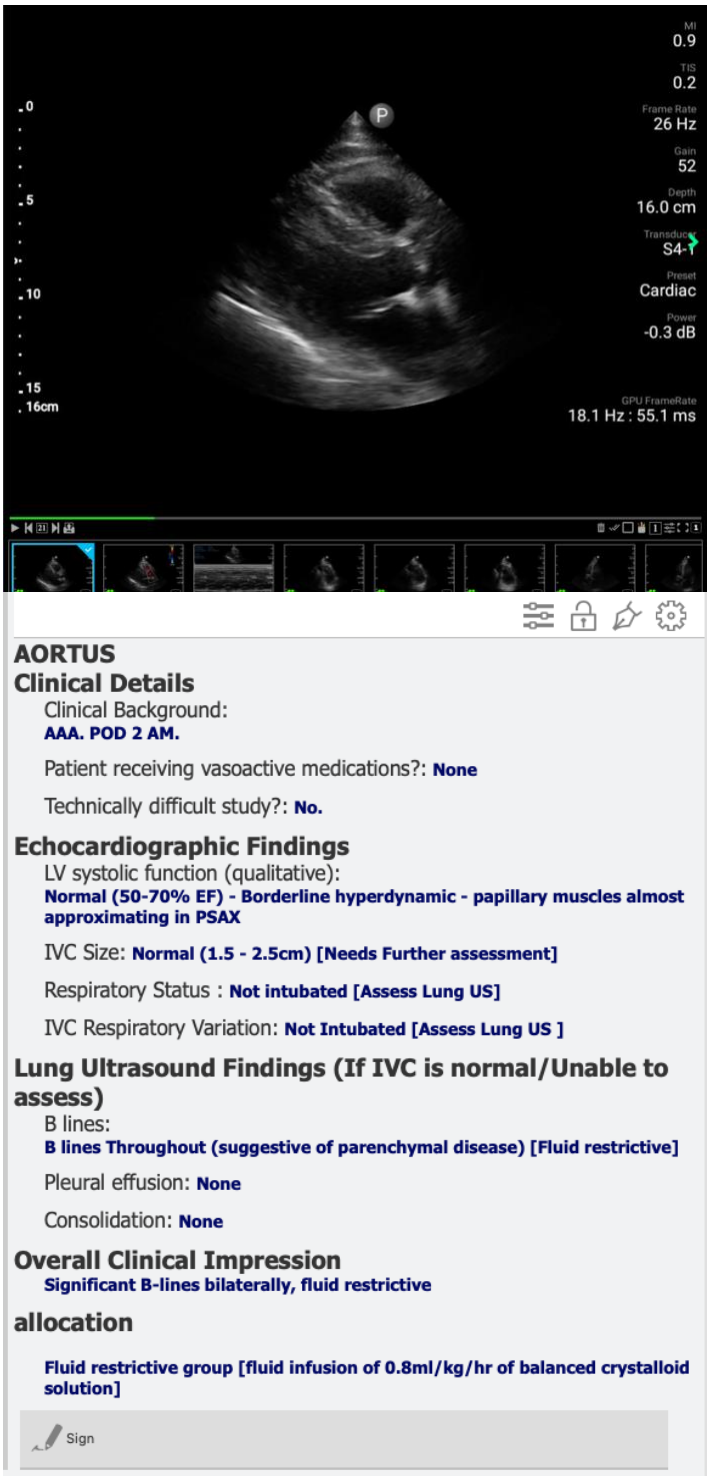

Figure 13: Sample POCUS study and accompanying synoptic reporting form identifying discrete metrics in the study to ensure completeness of image acquisition, interpretation, and patient allocation.

assessment of the feasibility of different aspects of executing the POCUS studies. Successful image completion required adequate physician availability, patient cooperation, and properly functioning ultrasound devices and information technology infrastructure. Appropriate image acquisition required that patients have anatomic ultrasound windows suitable for obtaining the information defined in the protocol, suitable patient comfort to tolerate ultrasound examinations, as well as physicians suitably facile in POCUS techniques to acquire the correct images. Finally, successful image interpretation required an understanding of the physiologic implications of ultrasound findings and selection of the appropriate fluid resuscitation strategy based on these findings.

Image Completion

Eight patients in total received POCUS-guided care. Given the trial protocol of five discrete ultrasound studies, this resulted in forty total ultrasound studies which should have been completed for this cohort. All forty studies were successfully completed. Completion was recorded in the PACS system database which allowed for identification of operator, ultrasound device, study duration, and subsequent quality assurance (QA) of image acquisition and interpretation (figure 14). Assessment of study duration of these 40 entries showed times ranging between 10 and 20 minutes per study, with longer times seen at the beginning of the cohort and shorter times seen at the end of the cohort.

ACCOUNT	DATE	EXAM TYPE	OPERATOR	REVIEWER	QA STATUS	INSTITUTION	GENDER
442299316	2020-01-15	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442299316	2020-01-15	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442299316	2020-01-16	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442299316	2020-01-16	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442299316	2020-01-16	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442299316	2020-01-17	AORTUS	Gottschalk, Byron	Alaifan, Thamer	Completed	VH-CCTC	Male
442299316	2020-01-17	AORTUS	Gottschalk, Byron	Alaifan, Thamer	Completed	VH-CCTC	Male
442403739	2020-01-24	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442403739	2020-01-24	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442403739	2020-01-25	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442403739	2020-01-25	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442403739	2020-01-26	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442403739	2020-01-26	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442466614	2020-01-31	AORTUS	Scallan, Oonagh	Alaifan, Thamer	Completed	VH-CCTC	Male
442466614	2020-02-01	AORTUS	Gottschalk, Byron	Alaifan, Thamer	Completed	VH-CCTC	Male
442466614	2020-02-01	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442466614	2020-02-02	AORTUS	Gottschalk, Byron	Alaifan, Thamer	Completed	VH-CCTC	Male
442466614	2020-02-02	AORTUS	Gottschalk, Byron	Alaifan, Thamer	Completed	VH-CCTC	Male
442339488	2020-02-10	AORTUS	Scallan, Oonagh	Alaifan, Thamer	Completed	VH-CCTC	Male
442339488	2020-02-11	AORTUS	Scallan, Oonagh	Alaifan, Thamer	Completed	VH-CCTC	Male
442522006	2020-02-11	AORTUS	Scallan, Oonagh	Alaifan, Thamer	Completed	VH-CCTC	Male
442522006	2020-02-11	AORTUS	Scallan, Oonagh	Alaifan, Thamer	Completed	VH-CCTC	Male
442339488	2020-02-11	AORTUS	Scallan, Oonagh	Alaifan, Thamer	Completed	VH-CCTC	Male
442339488	2020-02-12	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442522006	2020-02-12	AORTUS	Landau, John	Alaifan, Thamer	Completed	VH-CCTC	Male
442569517	2020-02-12	AORTUS	Scallan, Oonagh	Alaifan, Thamer	Completed	VH-CCTC	Male
442339488	2020-02-12	AORTUS	Scallan, Oonagh	Alaifan, Thamer	Completed	VH-CCTC	Male

Page 1 of 1 1 - 46 of 46 items

Figure 14: The PACS database identifying study dates, POCUS operators, and reviewer with ultrasound expertise providing QA. The database records 46 studies instead of 40 due to occasional duplicate study uploads from the portable ultrasound device.

Image Acquisition

POCUS images were acquired for assessment of the heart, lungs, and IVC in accordance with the views defined in the study protocol. Review of the studies for quality assurance by POCUS experts involved grading the acquired images on the following scale: Quality standards not met, quality standards met with improvements suggested, or quality standards met with no concerns. 39/40 studies had adequate image acquisition with a grade of "quality standards met with improvements suggested" or higher. The one deficient study was in a patient with a pectus deformity who, at the time of the study, was tachycardic with a heart rate of 120 and experiencing difficulty with post-operative pain compromising their tolerance for repositioning to optimize image acquisition. As a result, IVC views obtained were interpretable but the cardiac and lung images were not of sufficient quality. Given the poor image quality, decisions were made not to alter patient management until the subsequent study to avoid interpretation errors of poor-quality images.

Image Interpretation

After image acquisition, studies were reported using a synoptic reporting form to comment on the findings outlined in the study protocol. Image interpretation was graded on the same scale used to assess image acquisition. Of the 40 sets of study images obtained, 40 of them had adequate image acquisition with a grade of "quality standards met with improvements suggested" or higher. Subjective feedback provided in addition to the grading of quality allowed POCUS practitioners to refine their understanding of their findings with the guidance of the QA expert (figure 15).

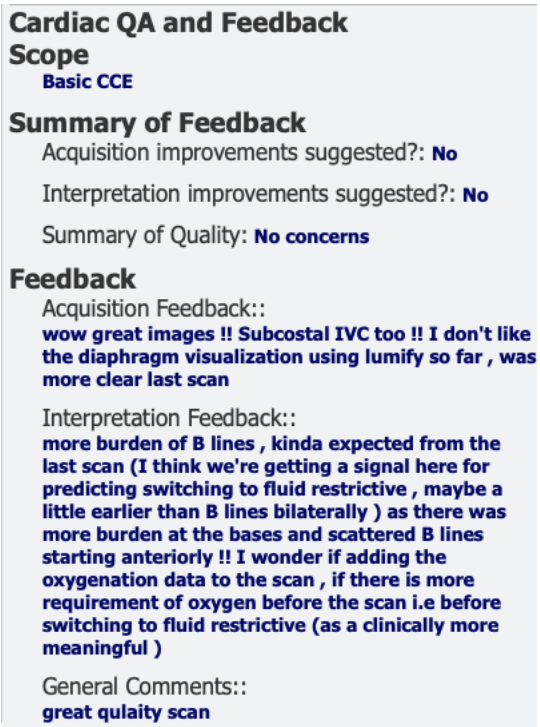

Figure 15: An example of the quality assessment and feedback form provided as an assessment of both the images acquired and the findings of the synoptic report for a given POCUS study.

3.1.4 Protocol Adherence

Of the cohort of 17 patients recruited, 14 of them had successful protocol adherence throughout their participation in the study. Three major protocol violations were identified at various time points in the study. All three violations occurred with patients randomized to the POCUS group. The first patient received a POCUS study on the afternoon of post-operative day two that suggested allocation to a fluid-liberal strategy despite having a trend of resuscitation that had already de-escalated from fluid liberal to restrictive (Table 3). This was likely the result of patient mobilization and reabsorption of third-space fluids leading to a decrease in pulmonary edema and ultrasound findings of fluid overload. As a result, the protocol was violated and the patient remained fluid restrictive as the POCUS-guided resuscitation strategy contradicted the clinical scenario otherwise.

The second patient, also allocated to the POCUS-guided resuscitation arm, received a fluid bolus in violation of the study protocol. This occurred early on in the study cohort when physicians were not yet adjusted to the study protocol. A physician responded to a page from the inpatient ward while in the operating room in the middle of a procedure and advised to give a fluid bolus to a patient with mild oliguria. The physician recognized the violation after the operation was complete and contacted research personnel to clarify the course of events and record the protocol violation.

The third and final protocol violation occurred in a patient who required unplanned admission to the intensive care unit. Prior to the initiation of the recruitment period, an extensive education campaign was undertaken with all relevant stakeholders to discuss the study, its rationale, and the effects it would have at the patient level. This included research personnel, nursing, leadership directors, and physicians in the intensive care unit. One group of stakeholders unaccounted for was the junior trainee house staff who rotated in and out of intensive care on a monthly basis. As a result, when a patient was transferred to intensive care in the evening the junior house staff were not aware of the patient's enrollment in the trial and their crystalloid resuscitation was changed from the rate as directed by the trial protocol to a different rate based on the junior physician's clinical assessment.

POCUS Study	Resuscitation Strategy
Post-operative recovery room	Fluid liberal
Post-operative day 1 - am	Fluid liberal
Post-operative day 1 - pm	Fluid restrictive
Post-operative day 2 - am	Fluid restrictive
Post-operative day 2 - pm	Fluid liberal – did not make sense given clinical course – protocol violated

Table 3: Illustration of the resuscitation strategy pathway for a patient allocated to POCUS-guided resuscitation which resulted in a protocol violation due to disagreement between ultrasound findings and the patient's clinical progress.

3.1.5 Successful Data Collection

A total of 16 out of the 17 patients recruited in the cohort to date had successful data collection and data entry into the REDCap™ database. One patient did not have their post-operative serum lactate and CRP lab values entered, which was the result of a clerical error made with the online ordering system that lead to the lab tests not being drawn during the required period.

3.1.6 Contamination Rate

None of the patients in this interim cohort had contamination of their allocation by withdrawal from the study before completion or by crossover from their assigned group up to final data collection at 30 days after their operation. This is a testament to the commitment of physicians enrolling their patients in the study, the commitment of research personnel, and the efforts made to fully inform patients and guide them through the consent process.

3.2 Clinical Data Collected

Clinical data of the cohort was collected at various times during their inpatient stay. Given the incomplete recruitment due to Covid-19 pandemic conditions, the data will be reported in aggregate here. Subsequent publication of the full cohort will display the full cohort broken down into each treatment group to assist in power and sample size calculations for a subsequent study examining clinical outcomes.

3.2.1 Intraoperative Data

The majority of patients in the cohort had operations done for aneurysmal disease (82%) as opposed to occlusive disease (18%). Most patients received epidurals (59%) for post-operative analgesia. Operations lasted an average of 223 minutes measured from first incision to skin closure. Aortic cross clamp time was an average of 84 minutes, which included time to placement of the proximal aortic clamp until the time the proximal and distal clamps were removed and the lower body was reperfused after the aortic

reconstructions were complete. The average estimated blood loss was 1124mL, but due to routine cell salvage an average of 441mL of salvaged blood was able to be returned to the patient by transfusion before the completion of the operation. No patients received intraoperative bank blood transfusions, and one patient received a bolus of 500mL of 5% albumin during the course of their operation. The average volume of crystalloid administered intraoperatively was 4100mL, and the average urine output during the conduct of the operation was 436mL. A summary of these intraoperative metrics is given below in table 4.

Intraoperative Metric	Value
Aortic Pathology	
- **Aneurysmal Disease**	14 patients (82%)
- **Occlusive disease**	3 patients (18%)
Epidural Use	10 patients (59%)
Surgery Duration (mean)	223 minutes
Aortic Crossclamp Time (mean)	84 minutes
Estimated blood loss (mean)	1124 mL
Cell Saver Blood Transfused (mean)	441 mL
Bank Blood Transfused (mean)	0 units
Crystalloid Volume Infused (mean)	0 mL
Colloid Administered (median)	1400 mL
Urine Output (mean)	436 mL

Table 4: Clinical data collected during the course of a patient's surgery in the operating room.

3.2.2 Post-operative Data

In analyzing patient post-operative course, metrics that may be related to altering the approach to crystalloid resuscitation were collected. Many of these metrics were collected within the first 48 hours after surgery as this was the time when the approach to resuscitation was guided by POCUS assessments or by usual care. The average crystalloid volume given over 48 hours was 9328mL. Assessing serum markers of inflammation and tissue perfusion, the average peak serum lactate was 2 mmol/L and the average peak CRP was 173 mg/L. The mean length of stay in hospital was 10 days. Three patients required vasopressors or inotropes for reasons other than as directed by the protocol based on POCUS findings. Five patients required post-operative blood product transfusions with packed red cells, platelets, fresh frozen plasma, or albumin. Four patients ultimately required unplanned ICU admission with one requiring emergency re-operation for ischemic bowel, and three requiring transfer for acute respiratory failure requiring invasive or non-invasive positive pressure ventilation. A summary of these post-operative findings is given below in table 5.

In addition to these clinical metrics, outcomes of major inpatient morbidity and mortality at 30 days were also collected. The most common morbidity was pulmonary edema in ten patients, and there was one major mortality at 30 days. A summary of the perioperative morbidity and mortality metrics is presented in table 6.

Post-Operative Metric	Value
Crystalloid Volume at 48 hours	9328 mL
Number of Patients Requiring Vasopressor or inotrope use	3 patients (18%)
Length of Hospital Stay (mean)	10 days
Peak CRP at 24 hours	173 mg/L
Peak Serum Lactate at 24 hours	2 mmol/L
Number of Patients Requiring Blood Product Transfusions	5 (29%)
Number of Patients Requiring Unplanned ICU Admission	4 (24%)

Table 5: Clinical data collected during the post-operative patient course. Unless otherwise specified metrics are collected from time of arrival in the post-operative recovery room until the time of patient discharge from hospital.

Major Morbidity/Mortality	Number of Patients (n=17)
Pulmonary Edema	10 (59%)
Cardiac Arrhythmia	5 (29%)
Myocardial Infarction	4 (24%)
Pneumonia	3 (18%)
Acute Kidney Injury	3 (18%)
Ischemic Bowel	2 (18%)
Unplanned Re-operation	2 (12%)
Ischemic Limb	1 (6%)
Death	1 (6%)
Surgical Site Infection	0
Renal Replacement Therapy	0

Table 6: Major inpatient morbidity and mortality metrics measured at up to 30 days after operation.

3.2.3 POCUS-Guided Resuscitation Pathways

The PACS system on which images were stored collected objective metrics of heart, lung, and IVC ultrasound findings on the synoptic reports (table 7). Cardiac views uniformly demonstrated left ventricular ejection fraction in the normal to moderately reduced range, with no studies demonstrating severely reduced ejection fraction. No cardiac studies had image quality poor enough to prevent suitable image interpretation. Lung views demonstrated a roughly equal mix of A-lines in 53% of studies and B-lines in 47% of studies. No lung studies yielded images poor enough to render them uninterpretable. IVC views proved to be the most problematic, with uninterpretable views 23% of the time. When views were adequate, IVC diameter in the normal range was the most common finding in 63% of studies, followed by distended diameter in 10% of studies, and reduced diameter 3% of the time. Of note, according to the protocol, this would imply that the IVC yielded a finding that influenced management in only 13% of the studies completed.

At each discrete time point the results of each organ system assessment were used to follow the ultrasound resuscitation protocol in figure 10 to determine if the patient should receive fluid liberal or fluid restrictive resuscitation at that time point. The results of each ultrasound metric for the eight patients randomized to POCUS-guided resuscitation are outlined in table 8.

POCUS Metric	Number of Results (n = 40)
Cardiac Findings	
- **Normal EF (50-70%)**	35 (88%)
- **Moderately Reduced EF (30-50%)**	5 (12%)
- **Severely Reduced EF (<30%)**	0
- **Indeterminate**	0
Lung Findings	
- **A-lines – suggested of well aerated lung**	21 (53%)
- **B-lines – suggestive of parenchymal disease, likely pulmonary edema**	19 (47%)
- **Indeterminate**	0
IVC Findings	
- **Distended (>2.5cm)**	4 (10%)
- **Normal (1.5 - 2.5cm)**	25 (63%)
- **Reduced size (<1.5 cm)**	1 (3%)
- **Intubated – Respiratory Variation assessed**	0
- **Indeterminate**	9 (23%)

Table 7: Ultrasound findings for heart, lung, and IVC assessments

Patient ID	Post-Operative Recovery Room	POD #1 - am	POD #1 - pm	POD #2 - am	POD #2 - pm
1	Liberal	Liberal	Restrictive	Restrictive	Restrictive
2	Liberal	Liberal	Liberal	Liberal	Restrictive
3	Liberal	Liberal	Liberal	Restrictive	Restrictive
4	Liberal	Liberal	Liberal	Restrictive	Restrictive
5	Liberal	Liberal	Restrictive	Restrictive	Restrictive
6	Liberal	Liberal	Restrictive	Restrictive	Restrictive
7	Liberal	Liberal	Restrictive	Restrictive	Restrictive
8	Liberal	Restrictive	Restrictive	Restrictive	Restrictive

Table 8: Resuscitation strategies chosen at each POCUS assessment for the patients randomized to POCUS-guided resuscitation.

Chapter 4

4 Discussion

Review of the feasibility outcomes to date have shown that the design of the study has potential to achieve feasibility in the full cohort, and clinical data have demonstrated results that show promise in informing development of clinical outcomes as well as power calculations and sample size estimates for future research studies. Furthermore, review of the instances where specific feasibility metrics were not met have identified areas for improvement in the protocol and execution of the study for future stages of this research program. Due to the Covid-19 pandemic this data set represents and interim analysis, and we anticipate further valuable insight will emerge with recruitment of the full cohort.

When considering the primary outcomes examining feasibility, it is important to evaluate them keeping in mind that the aim of a feasibility study is to determine the viability of executing a study as designed. Assessment of a given feasibility outcome can be grossly categorized as feasible with no modification, feasible but requires modification or adjustment, and not likely to be feasible. Review of the interim assessment of feasibility in the cohort recruited to date shows that the protocol as designed is generally feasible with some specific areas to consider revision pending the final cohort.

The recruitment consent rate of 89% shows that the rate of recruitment has potential to remain feasible in the final cohort. This speaks to the quality of informed consent obtained by the physicians and research personnel involved in the study, and it suggests the consent form and letter of information succeed in making patients feel comfortable participating in the study. Assuming this interim cohort is representative of the final population of 40 patients, this will result in a recruitment rate meeting the average expected recruitment rate estimated in the trial design (figure 11). If most candidates who meet the inclusion criteria and lack the exclusion criteria designed in the study are successful recruited into the study, this implies that yearly case volumes at a given center can be used in concert with sample size calculations as a reasonable estimation of

whether or not a full study can be completed at a single center in a reasonable amount of time or whether a multi-center trial would be needed to recruit the target cohort in a reasonable timeframe.

Successful randomization of 100% of the patients in the study recruited to date is a reassuring commentary on the design of the randomization process. Using digital tools accessible by computer or mobile device to randomize patients as opposed to a sealed envelope or other physical randomization tool allows for a decentralized and easily accessible process. Since randomization has been designed to take place at the end of an operation when room turnover, transfer of patients from the operating room to the post-operative recovery room, and finalization of post-operative orders are taking place, these tasks all have potential to divert attention away from initiation of randomization in a clinical trial. The trend of uniformly successful randomization suggests that the streamlined randomization process offered by our digital tool is suitable for convenient randomization in this clinical environment.

The POCUS metrics have shown trends toward feasibility in each component evaluated. Firstly, the successful completion of POCUS studies has been 100% successful in the interim cohort. This is a commentary on both human and technological factors in the study design. Given that these ultrasound assessments are done in a clinically busy environment with many competing demands, it is reassuring that the implementation of POCUS assessments into the clinical workflow of surgical trainees has not been so disruptive as to prohibit their completion in a suitable time. With study times starting at 30 minutes and eventually decreasing to as low as 10 minutes, this also reinforces the value of POCUS as a physician-lead augmentation of patient assessment at the bedside. Finally, the successful completion of studies also required the portable ultrasound technology to perform reliably in a consistent manner. Simple failures such as discharged batteries in portable ultrasound devices, network connectivity issues prohibiting transmission of information to the central PACS reporting system, or malfunction of ultrasound probes could potentially marginalize the successful execution of the study, and thankfully there have been no such technological barriers thus far.

POCUS image quality and image interpretation were judged to be adequate in 98% and 100% of studies respectively. This speaks to the design of the ultrasound protocol as well as the accessibility of POCUS skills to the personnel involved. These ultrasound examinations were performed by surgical trainees with previous experience in vascular ultrasound as well as the focused assessment with sonography in trauma (FAST) exam. With specific training and orientation including video modules, supervised practice ultrasound exams, and mentored POCUS exams on patients centered around the views of the heart, lung, and IVC used in the study they were able to successfully acquire and interpret images with extremely high rates of success. Limiting the study protocol to B-mode images without advanced doppler studies or quantitative hemodynamic assessments was done to decrease the amount of training required to acquire and interpret the images successfully while still being able to acquire information suitable to make clinical decisions about resuscitation. Beyond this specific feasibility metric, we did identify that the IVC diameter was the most frequently unreliable ultrasound metric, and it was a metric responsible for a change in resuscitation strategy only 13% of the time. It may be reasonable to consider eliminating the IVC diameter assessment in the trial protocol should this trend continue to be displayed in the final cohort.

The rate of protocol adherence was 82% in the interim cohort recruited to date, which represents three major protocol violations. These violations were due to three unique scenarios unanticipated in the design of the study and the preparation of its execution. With a metric close to the pre-defined threshold of feasibility, this suggests a trend toward feasibility requiring modification before execution of a final study. The specific adjustments that would aid in avoiding future protocol violations will be discussed in association with each protocol violation identified. The first violation occurred when the POCUS exam suggested the patient should receive fluid liberal resuscitation, despite the fact that their clinical trajectory saw de-escalating fluid requirements in the preceding 24 hours. This likely occurred as a result of the patient receiving appropriately targeted resuscitation with early de-escalation, and as a result their final POCUS exam in the afternoon of post-operative day 2 showed no signs of fluid overload. This discordance between the protocol's instruction and what was deemed clinically appropriate points out a flaw identified in the trial protocol. A revision to the protocol could be made such that

when patients transition from a fluid liberal to a fluid restrictive approach they continue on that trajectory until the need for IV fluids is no longer required. Further consideration could be given to the possibility of using the transition from fluid liberal to fluid restrictive resuscitation as a trigger to terminate future POCUS exams as the clinical likelihood of requiring a transition back to fluid liberal resuscitation as time progresses is very low. The second protocol violation occurred early on when a patient randomized to the POCUS arm received a fluid bolus in violation of the study protocol. This occurred very early on in the patient cohort before providers had grown accustomed to the protocol, and furthermore the order was given from a provider in the operating room with cognitive load from the operation being performed rendering them less available to recall the patient's involvement in the study. Making efforts to avoid contacting providers actively participating in operations to make clinical decisions about study patients would assist in minimizing repeat protocol violations of this kind. The last protocol violation occurred when a patient with unplanned admission to the ICU received resuscitation and management that were not in keeping with the study's protocol. This was a failure of education of all relevant stakeholders in execution of the study. Despite focusing on a hospital-wide education campaign prior to initiation of the study, intensive care unit junior house staff were not included in the relevant stakeholders involved in this education campaign. Preventing further protocol violations of this kind will be accomplished by explicit review of the trial protocol with ICU junior trainees upon transfer of patients, as well as a diligent review of any possible stakeholders in patient care to ensure other groups are not left uninformed of the study and its protocol.

Data collection was successful in 94% of the interim cohort. One patient did not have their post-operative serum lactate lab values entered due to a clerical error with the ordering system in the e-health record. This clerical error was addressed by revising the comprehensive care set of orders constructed for patients enrolled in the study, and no further issues with collection of lab samples occurred. The high rate of success of data collection is likely the result of the electronic health record as well as the electronic REDCap^{TM} database used in the design of the study. This allowed researchers to use any computer terminal or secure mobile device to review relevant clinical data and enter it

into the database, which negated the need for visits to a central health records location to manually review paper charts to abstract data.

The contamination rate was 0% in the interim cohort. This indicates that no patient or physician motivators resulted in patients being withdrawn from the study or crossed over from their randomized group to the opposite arm of the study. From a patient perspective, efforts made to set expectations during the initial consent process and by use of the consent form and letter of information likely helped to minimize patient desire to withdraw from the study. Additionally, it highlights a high degree of patient compliance with POCUS exams as factors such as patient discomfort or inconvenience would possibly contribute to patient desire to cease involvement in the study prematurely. From a physician perspective, it highlights the commitment of the vascular surgeons willing to enroll their patients in the study and allow an experimental protocol to deviate from their usual approach to patient care.

Beyond the feasibility metrics, the clinical data collected has been promising. Rates of perioperative morbidity and mortality approach those outlined in previous population studies. Although the data to date is reported in aggregate given the incomplete recruitment of this cohort, reporting the final cohort with clinical endpoints separated into the two arms of the study has the potential to identify multiple possible metrics to consider as primary and secondary outcomes.

4.1 Study Limitations

An obvious limitation of this study to date is the incompletely recruited cohort. This is an unfortunate side effect of the Covid-19 pandemic, and we are fully committed to final recruitment of the planned cohort once full clinical and research activities resume at our institution. Beyond this primary limitation, there are some other specific issues we have identified.

Feasibility studies carry with them their own specific limitations. While they make good methodological sense in a study such as this which explores a specific intervention that has a paucity of previously published studies and has potential for barriers to execution,

the only objective conclusions that can be drawn from them is whether or not the protocol itself is practical to execute as designed. Should this study prove to be feasible in the final cohort, this first step in the research program will in fact allow for a more effective successful implementation of a subsequent study designed to detect statistical significance in clinical endpoints.

There are also a number of limitations in the physiologic assumptions made by the POCUS metrics used in the trial protocol. Firstly, the simplicity of B-mode assessment of left ventricular ejection fraction is limited when compared to the more advanced and objective assessment of cardiac output using ultrasound pulse-wave doppler of the left ventricular outflow tract. In the absence of an objective metric of decreased cardiac output to connect hypotension to poor cardiac pump function, the assumption being made is that significant volume loading in a patient with a severely decreased left ventricular ejection fraction has significant risk of acute heart failure, and a volume-sparing approach with vasopressors and inotropes is a safer way to address hypotension in this population. Another assumption being made is that the accumulation of B-lines on lung ultrasound is a reasonable metric of volume overload in this patient population. While no studies have specifically examined this correlation, there is sound physiologic basis to the argument that sonographic identification of pulmonary edema should factor into the approach to crystalloid resuscitation.

The quality assurance process in reviewing POCUS studies also carries with it a potential limitation in that it is inherently subjective. While experts with certification in point of care ultrasound may generally agree on the findings of a given exam or set of images, the criteria for defining images as adequately acquired or interpreted is more subjective. We attempted to minimize the effect of this by designating a single expert with certification in both POCUS and advanced critical care echocardiography to grade the images for acquisition and interpretation. This may be more difficult to control if the study progresses to a trial designed for clinical significance if it is held at multiple sites or at a single site that requires a long period of recruitment. There is, however, potential for this limitation to be addressed with technology. Progression in portable POCUS technology has led to the development of artificial intelligence-based tools to grade the quality of an

image compared to a desired standard view a user is attempting to obtain (figure 16), and multiple providers have created remote tele-mentoring systems that allow a single centrally-located provider to directly observe live acquisition of POCUS exams to guide a user in real-time (figure 17). These technological advancements may allow for a more consistent centrally-located expert to remain the single provider of QA and study feedback.

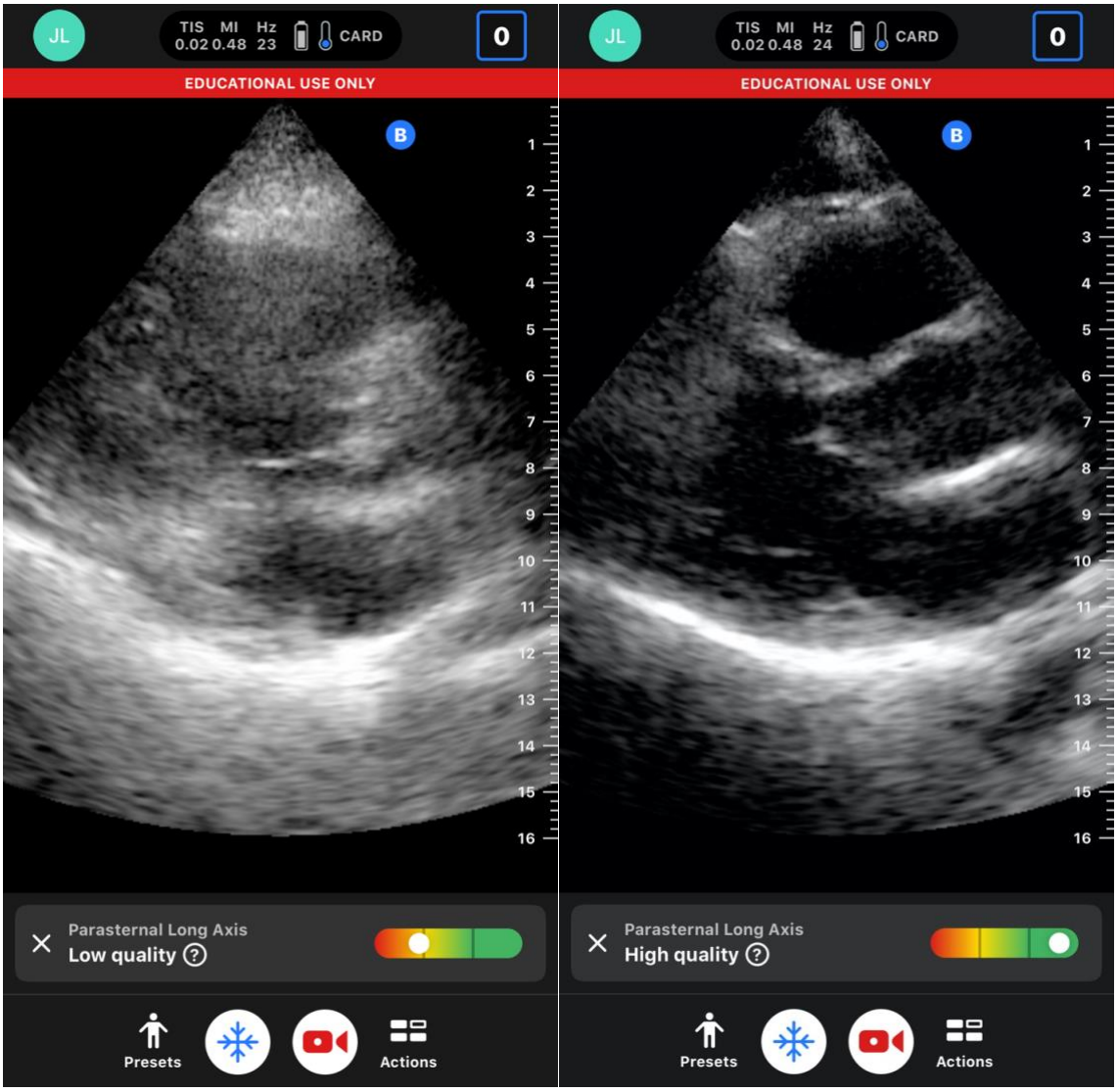

Figure 16: Artificial Intelligence (AI) interpretation of a parasternal long axis view of the heart. The left depicts a low-quality image as interpreted by the AI, and the right depicts a more optimized high-quality image.

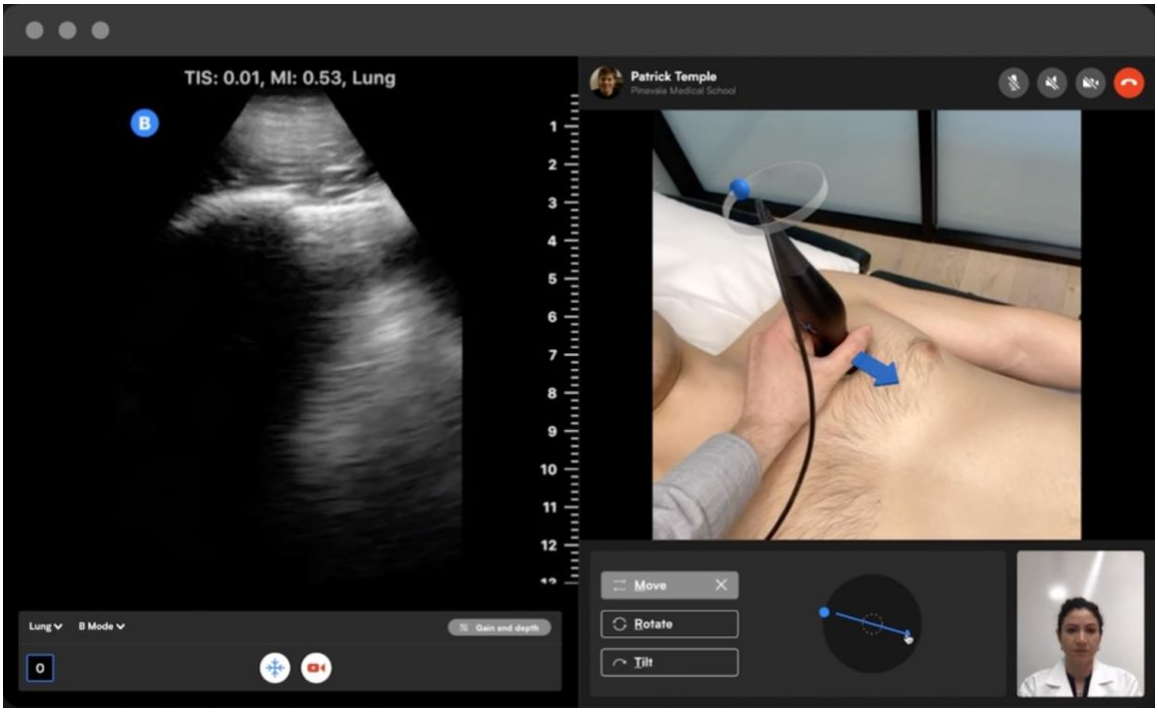

Figure 17: Remote teleguidance system provided by the Butterfly Network POCUS device platform. Real-time guidance is being given to optimize the location of the ultrasound probe to acquire lung ultrasound images.
Source: https://www.butterflynetwork.com/enca/teleguidance. Accessed July 31, 2020.

4.2 Conclusion

In conclusion, this study has used a novel approach of utilizing POCUS technology to establish a protocol for goal-directed resuscitation of patients receiving open abdominal aortic surgery. While the cohort has been incompletely recruited to due to the Covid-19 pandemic, early results are promising showing trends towards feasibility for all of the pre-defined primary outcomes. Lessons have been learned to date that will be valuable in modifying and streamlining implementation of the study in a subsequent trial powered to detect statistical significance in clinical outcomes. Pending final data from the full cohort, there may be revisions made to the trial to address concerns identified in the feasibility trial to date before proceeding with the next stage of this research program.

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Appendices

Appendix A: Research Ethics Board Approval Letter

Western Research

Date: 2 December 2019
To: Dr. Luc Dubois
Project ID: 113875
Study Title: Ultrasound-Guided Resuscitation in Open Aortic Surgery
Application Type: HSREB Initial Application
Review Type: Delegated
Meeting Date: 05/Nov/2019 13:00
Date Approval Issued: 02/Dec/2019 09:04
REB Approval Expiry Date: 02/Dec/2020

Dear Dr. Luc Dubois

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Aortic Surgery Pilot RCT Protocol - AORTUS Draft v3	Protocol	06/Nov/2019	3
AORTUS - LOI V3 Nov 6	Written Consent/Assent	06/Nov/2019	3
AORTUS REDCAP data points	Other Data Collection Instruments	06/Nov/2019	1
Protocol Image3	Other Data Collection Instruments	15/Sep/2019	1

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,
Nicola Geoghegan-Morphet, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix B: Letter of Information and Consent Form

LETTER OF INFORMATION AND CONSENT FORM

The AORTUS Trial
Ultrasound-Guided Resuscitation in Open Aortic Surgery
A single-center pilot study evaluating the use of point-of-care ultrasound (POCUS) for resuscitation after open abdominal aortic surgery

Sponsor: None

Primary Investigator: Dr. Luc Dubois, Division of Vascular Surgery

Co-Investigators: Dr. John Landau, Dr. Robert Arntfield, Dr. Ian Ball

INTRODUCTION

You are being invited to participate in a research study because you are scheduled to undergo open aortic surgery. Please read this document carefully and ask the investigator (study doctor) or research personnel to explain any words of information that is not clear to you. This will help to make sure you understand the details of your participation before you give your consent. The following sections will discuss the requirements of this study, and the details of your role as a participant. The investigator or other research personnel will answer any questions you may have about this consent form and the study.

You should be aware that Dr. Arntfield, one of the Co-Investigators of the study, has served as an educational consultant for Fujifilm, Sonosite Inc, a provider of ultrasound technology

PURPOSE OF THIS RESEARCH STUDY

Open abdominal aortic surgery for aneurysmal disease and occlusive disease represents a major abdominal surgery for patients. The care of patients after surgery involves administration of intravenous (IV) fluids to support the blood pressure and blood supply to the body's major organs. There are risks that come with administering too much fluid or too little fluid in the post-operative phase. Examples of this include the risk of kidney injury from giving too little fluid, or the risk of pulmonary edema (fluid accumulation in the tissue and air spaces of the lungs) or congestive heart failure (fluid backs up in the heart and causes it to pump inefficiently) from giving too much fluid. Physicians generally use a combination of physical examination, urine output, and blood tests to guide the administration of IV fluids. Portable ultrasound can be used to assess for heart failure and pulmonary edema at the bedside and add additional information about a patient's fluid balance and

response to fluid administration. It is not known whether receiving ultrasound guided care after surgery will be better, the same, or worse than usual care. This study will examine if the use of ultrasound of the heart and lungs for the first 48 hours after open abdominal aortic surgery will permit more optimal administration of IV fluids to reduce the risks that come with administering too much or too little fluid in the post-operative phase.

The study we are asking you to enroll in is a 'pilot' study, which aims to help us design a larger study that will involve hundreds of patients, which will help us better understand this issue. Future studies may determine whether ultrasound helps us to reduce the rates of post-operative complications in patients receiving major open abdominal aortic surgery at London Health Sciences Center (LHSC).

STUDY OUTLINE

This study will enroll approximately 40 patients from LHSC. Your participation in the study will span the first 48 hours after your surgery is complete. You will be randomly selected (assigned by chance like the flip of a coin)to receive the usual post-operative care or ultrasound-guided fluid therapy. Both groups will be monitored and treated as required to maintain optimal fluid levels. An AORTUS study personnel will contact you by phone 30 days after your surgery to check on your health status or if your first regular follow up appointment is at 30 days, study personnel will see you in the vascular surgery out-patient clinic.

If you agree to participate, you will:

- Be asked to sign the informed consent form at the end of this document.
- If allocated to the ultrasound group, you will receive 5 ultrasound examinations after your surgery is complete. One in the recovery room immediately after surgery, and then one study in the morning and evening of the first two days after surgery.
- Each ultrasound examination will take approximately 30 minutes to perform. A portable ultrasound machine will be brought to your bedside to examine your heart and lungs by placing an ultrasound probe on your chest over a number of areas.
- Be contacted by telephone 30 days after surgery or seen in the vascular surgery out- patient clinic if your regular appointment is within 30 days. You will be asked about any medical problems you have had since the surgery. The follow-up call will take approximately 15 minutes.

The ultrasound examinations you receive and the follow up calls are not part of your standard care. If any new clinically important information about your health is obtained as a result of your

participation in this study, you will be given the opportunity to decide whether you wish to be made aware of that information.

POSSIBLE RISKS OF TAKING PART IN THIS STUDY

This study requires regular ultrasound examinations. Ultrasound is a safe technology, and the use of diagnostic ultrasound itself does not impart any known risks to patients. It is not known whether receiving ultrasound-guided care after surgery will be superior, equivalent, or inferior to the usual approach to post-operative care. We are collecting personal health and identifiable information about you. As such,there is always risk of a privacy breach however measures are in place to decrease this risk. Your privacy will be protected as described in the Confidentiality section.

BENEFITS

There is no guarantee that you will receive any benefit from taking part in this study.

VOLUNTARY PARTICIPATION AND EARLY WITHDRAWAL FROM THE STUDY

Taking part in this research study is voluntary. You do not have to take part in this study. You can withdraw from the study at any time without giving a reason. This will not affect the standard medical care you receive. If you choose to take part in this study, you will be asked to sign this consent form. You will get a fully signed and dated copy of this letter of information and consent form.

Should you wish to not complete the study, please notify the investigator or research nurse at the telephone number listed on page 3 of this letter of information.

If you decide to not complete the study, the information about you that was collected as part of the research study will still be used to protect the quality of the study. The investigator will make their best effort to re-contact you (e.g., contacting your family physician, review available registries or health care database) to determine whether you experienced any major events such as heart attack, cardiac arrest, and kidney failure. All information will be kept completely confidential.

If any new findings or new information is learned about this study that may affect your willingness to continue, you will be told as soon as possible.

COSTS AND PAYMENT FOR PARTICIPATION

There will not be any monetary payment to you for participating in this study. In addition, you are not responsible for any costs for the required study visits and procedures.

CONFIDENTIALITY

Your collected data will be stored locally (paper data) in a secure location with limited access of authorized personnel only. The data will be stored for 15 years and securely disposed thereafter. The non paper data will be stored in an electronic data base, and, you will be identified only with a study number.A list linking your study number with your name and hospital medical records number will be kept separately by the study doctor on a secure password protected LHSC computer drive. Only the study doctor and study personnel will have access to these files. Data to be collected will include things like your date of birth, sex, height and weight, and past and current medical history. Your ultrasound examinations, details from your surgery, your in-hospital care after surgery, and discharge from hospital will also be collected.

To make sure the study is being done properly your research study file, as well as your hospital chart, could be checked by a person authorized by Western University Health Sciences Research Ethics Board, the institution, or the Lawson Health Research Institute Quality Assurance. This would only take place at LHSC.. These people and groups are obliged to respect your privacy. Your data will be kept confidential to the extent allowed by law, and you will not be identified in any presentations or reports dealing with this research. When the results of the study are published, your identity will not be revealed.

WHOM TO CONTACT

You are free to ask questions at any time. For answers to questions relating to this research study, to report a research related injury or for information about study procedures, contact: Principal Investigator: Dr. Luc Dubois, LHSC
Research Nurse/Coordinator: Teresa Novick, LHSC

If you feel you have a significant research-related injury that requires immediate or urgent medical attention, go to the closest emergency department. Medical care for research related injury will be provided at no cost.

If you have any questions about your rights as a research participant or the conduct of this study, you may contact the Patient Relations Office at LHSC or access the online form at: https://apps.lhsc.on.ca/?q=forms/patient-relations-contact-form. Do not sign this consent form unless you have had a chance to ask questions and have received acceptable answers to all of your questions. You do not waive any legal rights by signing the consent form.

CONSENT FORM

AORTUS Trial
Ultrasound-Guided Resuscitation in Open Aortic Surgery

This study has been explained to me and any questions I had have been answered. I know that I may leave the study at any time. I agree to take part in this study.

Printed Name of Participant	Signature of Participant	Date and Time

STUDY PERSONNEL STATEMENT

The person signing this consent form has had the study fully and carefully explained and has been given an opportunity to ask any questions regarding the nature, risks and benefits of the patient's participation in this research study.

Printed Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date and Time

If consent was presented orally,

Printed Name of Impartial Witness	Signature of Witness	Date and Time

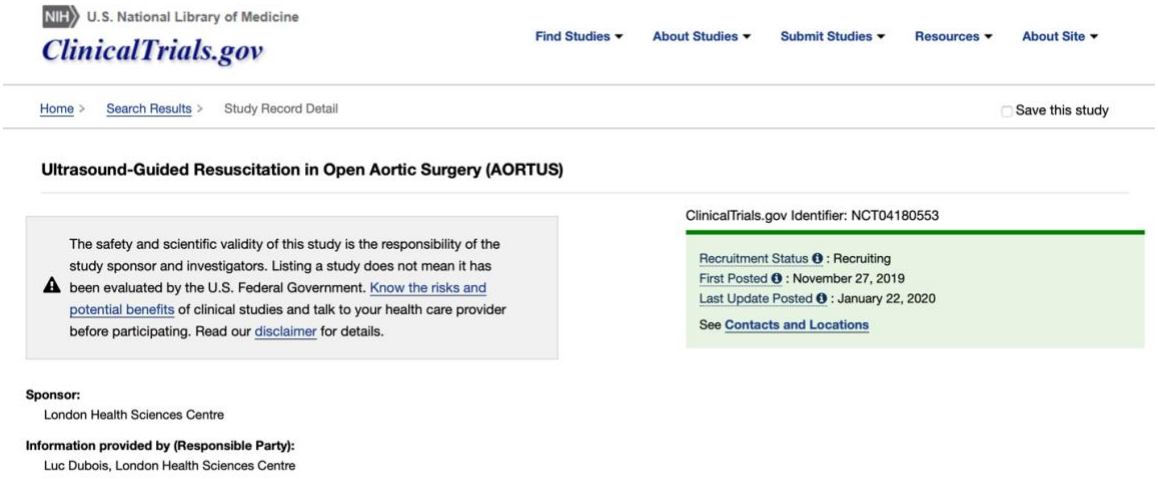
Signature of Translator in the event that the subject does not speak English

The person signing below acted as an independent translator for the participant during the consent process and attests that the study as set out in this form was accurately translated and the subject has had any questions answered.

Print Name of Translator	Signature	Date *(DD-MMM-YYYY)*

Language

Appendix C: Clinicaltrials.gov Registration



https://clinicaltrials.gov/ct2/show/NCT04180553

Curriculum Vitae

JOHN LANDAU

EDUCATION

Master of Science in Surgery 2019 - 2020
University of Western Ontario, Schulich School of Medicine & Dentistry, London ON
- Expected Graduation date Fall 2020

Critical Care Medicine Fellowship 2018 - 2020
University of Western Ontario, Schulich School of Medicine & Dentistry, London ON
- Graduated June 2020

Vascular Surgery Residency 2013 - 2018
University of Western Ontario, Schulich School of Medicine & Dentistry, London ON
- Graduated June 2018

Doctor of Medicine 2009 - 2013
University of Western Ontario, Schulich School of Medicine & Dentistry, London ON
- Graduated May 2013

Bachelor of Science With Honours 2003 - 2007
University of New Brunswick, Fredericton NB
- Major: Biology-Chemistry
- Graduated with First-Class Honours
- Completed an undergraduate honours thesis in computational drug design

ACADEMIC AWARDS AND HONOURS

Honour Society May 2013
Schulich School of Medicine, London ON
- Presented to final year students who, in the opinion of the honour society selection committee have distinguished themselves in rendering valuable extracurricular services to the medical school or the university as a whole

Kenneth A. Harris Vascular Surgery Award May 2013
Schulich School of Medicine, London ON
- Awarded annually to the undergraduate Doctor of Medicine (MD) program student at the completion of his/her fourth year who has excelled in Vascular Surgery during their clerkship rotation and/or the four years of undergraduate medical education.

Robert K. Annett Award October 2012
Schulich School of Medicine, London ON
- Awarded to a medical student during clerkship who best demonstrates awareness and concern for co-workers, as well as empathy and compassion for the physical and emotional needs of patients

RESEARCH AWARDS AND HONOURS

2nd Prize – Western-McMaster Critical Care Research Day June 2020
Schulich School of Medicine, London ON
- Awarded on the basis of podium presentation for AORTUS Trial interim data for critical care medicine scholar project

Travel and Research Principles Scholarships - SVS VAM - Washington DC, USA June 2012

Travel Scholarship – IAVS Conference, Tampa FL April 2012

3rd in prize poster competition - AMEE Annual Conference - Vienna, Austria June 2011
- Poster awarded 3rd prize out of 766 candidates

National Student Research Award - Canadian Society of Vascular Surgery May 2011
- 1 of 4 awards given annually

PUBLICATIONS AND CURRENT RESEARCH

Landau JH, Power AH, Leeper WR, Arntfield RT. Bedside identification of blunt thoracic aortic injury with point-of-care transesophageal echocardiography. Trauma. 2016 May;18(4): 287 - 290

Landau JH, Nagpal AD, Chu MW. Autologous Pericardial Reconstruction of Ruptured Salmonella Mycotic Aortic Arch Aneurysm. Can J Cardiol. 2016 Jan;32(1):136.e1-3

Landau JH, Power AH. "Isolated Mesenteric Artery Dissection - Results of Medical, Interventional, and Surgical Treatment". *Mesenteric Vascular Disease - Current Therapy*. Gustavo S. Oderich. New York, NY: Springer, 2015. 419-427. Print.

Landau JH, Novick TV, Dubois L, Harris JR, DeRose G, Forbes TL. Determination of Patient Preferences for Location of Elective Abdominal Aortic Aneurysm Surgery. Vasc Endovascular Surg. 2013 May;47(4):288-93.

ABSTRACTS AND PRESENTATIONS

Landau JH, Dubois LA, Power AH, Duncan A, Derose G, Chu MWA. Thoraflex Hybrid Endovascular Frozen Elephant Trunk Device for Treatment of Complex Aortic Arch Disease. Canadian Society of Vascular Surgery Annual Meeting, Banff Alberta, Sept. 15 2017 (Podium Presentation)

Landau JH. Thoracic Outlet Syndromes: Diagnosis and Management. Winnipeg Vascular and Endovascular Surgery Symposium, Fairmont Winnipeg, April 6, 2017 (Podium Presentation)

Landau JH, Power AH. Isolated Mesenteric Artery Dissection - Results of Medical, Interventional, and Surgical Treatment. Atlantic Vascular Society Annual Meeting, Fox Harb'r Nova Scotia, August 2014 (Podium Presentation)

Landau JH, Novick TV, Dubois L, Harris JR, DeRose G, Forbes TL. Endovascular Repair of Complicated Acute Aortic Dissections With Uncovered Stents. McMaster-Western Vascular Research Day, Hamilton Health Sciences Center, Nov. 2013. (Podium Presentation)

Landau JH, Novick TV, Dubois L, Harris JR, DeRose G, Forbes TL. Patient Preferences for Location of Abdominal Aortic Aneurysm Surgery With Implications for Regionalization. McMaster-

Western Vascular Research Day, Copetown Woods Golf Club, Oct. 12, 2012 (Podium Presentation)

Landau JH, Novick TV, Dubois L, Harris JR, DeRose G, Forbes TL. Patient Preferences for Location of Abdominal Aortic Aneurysm Surgery With Implications for Regionalization. Canadian Society for Vascular Surgery Annual Meeting, Quebec QC, September 2012. (Poster presentation)

Cristea O, **Landau J**, Moreland R, Johnson M, Ramage D, Browning D, Busato GM. CSTAR Interprofessional Surgery and Anaesthesia School: a novel program for pre-clinical medical and nursing students at the University of Western Ontario.

- Association for Medical Education in Europe, Vienna Austria, August 2011. (Poster presentation, 3rd prize)
- Canadian Association of General Surgeons - Canadian Surgery Forum, London ON, September 2011. (Poster presentation)
- London Health Research Day, London ON, March 2012 (Poster presentation)

Bodrogi A, **Landau J**, Staudt M, Ullah S, Luke PW. The Evolution of Medical Student Attitudes Towards Incentivized Kidney Donations. London Health Research Day, London ON, March 2012 (Poster presentation).

TEACHING AND EDUCATIONAL EXPERIENCE

Competency By Design Curriculum Committee for Vascular Surgery 2018 – 2019
Royal College of Physicians and Surgeons, Ottawa ON

- Participant in curriculum design and review for competency based education in vascular surgery residency

Surgical Foundations - Organ Failure and Surgical Complications in Intensive Care June 2019
Schulich School of Medicine, London ON

- Lecturer for critical care topics for junior residents in the surgical foundations course, and subsequent exam review sessions and mentorship

Anaesthesia and Perioperative Medicine - Spinal cord anatomy and blood supply May 2019
Schulich School of Medicine, London ON

- Lecturer for review of spinal cord anatomy and blood supply and perioperative strategies to mitigate spinal cord ischemia and paraplegia in cardiac and vascular surgery

Acute/Chronic limb ischemia clerkship teaching 2017 - 2019
Schulich School of Medicine, London ON

- Lecturer for select topics in vascular surgery for surgical clerkship curriculum

Basic Endovascular Skills in Trauma (BEST) Course August 2018
Schulich School of Medicine, London ON

- Instructor for AAST Course on the use of Resuscitative Endovascular Balloon Occulsion of the Aorta (REBOA)

PGY1 Surgical Nightmares - Vascular surgery July 2017
Schulich School of Medicine, London ON

- 1 Hour lecture given to PGY1 surgical foundations cohort on perioperative and inpatient surgical emergencies

Surgical Foundations workshop July 2015
Schulich School of Medicine, London ON
- Participated as an instructor in suturing and hand-tying workshops for the PGY1 surgical foundations cohort

Schulich Surgery Interest Group Surgery Symposium July 2015, 2016, 2017
Schulich School of Medicine, London ON
- Yearly participation in surgery interest group weekend including suturing, knot tying, and mentorship talks with Q&A

ADMINISTRATIVE INVOLVEMENT

Critical Care Medicine Chief Resident July 2019 - June 2020
Schulich School of Medicine, London ON
- Responsible for organizing call schedule, facilitating vacation requests, organizing teaching schedules, and holding M&M rounds for the Critical Care service

Vascular Surgery Chief Resident July 2016 - June 2017
Schulich School of Medicine, London ON
- Responsible for organizing call schedule, facilitating vacation requests, and organizing weekly resident schedules for the Vascular Surgery Service

Vascular Surgery PGME Committee Senior Representative July 2015 - June 2016
Schulich School of Medicine, London ON
- Senior Resident representative on the Vascular Surgery PGME committee

Vascular Surgery PGME Committee Junior Representative July 2013 - June 2014
Schulich School of Medicine, London ON
- Junior Resident representative on the Vascular Surgery PGME committee
- Responsible for taking and distributing meeting minutes