7-19-2023 7:00 AM

Malperfusion Syndrome in the Setting of Type A Aortic Dissection

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Surgery

Abstract

Background: Acute Type A aortic dissection (TAAD) patients who experience malperfusion syndrome (MPS) are at the greatest risk of major morbidity and mortality. However, the appropriate timing for open proximal aortic repair in the presence of MPS is still uncertain due to variations in clinical manifestations and diverse treatment approaches.

Methods: We conducted a comprehensive literature review to understand the importance of MPS in the setting of TAAD. Then, we conducted a national survey to understand the perception of cardiovascular surgeons across Canada and their approach for those patients. Furthermore, we performed a retrospective analysis of our local data to analyze the outcomes of TAAD with and without malperfusion syndrome from December 1999 to December 2021. Finally, we started a prospective pilot study to assess the feasibility and safety of using intravascular ultrasound (IVUS) to assess and early diagnose MPS in the setting of TAAD.

Results: The mortality of TAAD ranges from 17% to 31%, with a third of patients presenting with MPS. Mortality of TAAD patients increases significantly in the presence of MPS Specialized centers across the world have adopted new approaches to address malperfusion syndrome and have reported improved outcomes. From the national survey that we conducted, there is awareness of the significance of malperfusion syndrome in the setting of TAAD among the cardiac surgeons across Canada. From our local institution, the 30-day in-hospital mortality of TAAD is 13.6%. The mortality of patients with malperfusion is 36.2%, while without malperfusion is 6.2% (p

Conclusion: Adopting new approaches to address malperfusion syndrome in the setting of TAAD is critical to improving mortality and morbidity outcomes.

Summary for Lay Audience

Aortic dissection is a life-threatening condition that occurs when the internal layer of the aorta, a major artery that carries blood to all body organs, tears, causing the aortic wall layers to separate (dissect). This separation compromises blood flow to organs, leading to organ damage known as Malperfusion Syndrome. Despite repairing the aortic wall tear and restoring adequate blood flow through the true lumen, the presence of malperfusion syndrome remains a major risk factor associated with increased mortality rates, as well as long- and short-term damage to organs such as stroke, dead bowel, dialysis, or leg amputation.

To gain a better understanding of the disease and approaches taken by other centers worldwide, we conducted a comprehensive literature review. We also conducted a national survey of cardiovascular surgeons across Canada to analyze their understanding and approach to managing patients with malperfusion syndrome resulting from aortic dissection, including outcomes, deficits, and areas for potential improvement.

Furthermore, we reviewed the mortality and morbidity outcomes of acute aortic dissection cases previously managed at our center, London Health Sciences Center in London, Ontario, Canada. We focused on the presence of malperfusion syndrome and its effect on mortality and morbidity outcomes.

Finally, we are conducting a study to determine the feasibility of using Intravascular Ultrasound (IVUS) to assess in real-time and confirm any evidence of malperfusion syndrome after repairing the original aortic tear. IVUS is a small ultrasound wand attached

to the top of a thin tube, inserted into the aorta from the femoral artery in the groin. This device takes pictures of the aorta and its major branches to identify problems with blood flow. Having this real-time and dynamic assessment helps identify malperfused organs before leaving the operating room, potentially allowing us to address malperfusion syndrome quickly and limit complications. Without this technique, identifying the problem can take several days after surgery, by which point irreversible complications may have developed.

Co-Authorship Statement

Chapter 1

The thesis's introduction was written by Dr. Karama Bayamin and reviewed by Dr. Matthew Valdis and Dr. Luc Dubois, and Dr. Michael Chu

Chapter 2

The literature review was written by Dr. Karama Bayamin and reviewed by Dr. Matthew Valdis and Dr. Luc Dubois, Dr. Michael Chu, and Dr Adam Power.

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Keywords

Type A Aortic Dissection; Malperfusion Syndrome; National Survey; Intravascular Ultrasound Assessment

Acknowledgments

I would like to express my gratitude to Dr. Matthew Valdis, Dr. Luc Dubois, and Dr. Michael Chu for their support and supervision. I would like to give a special thanks to Dr. ML Myers, our program director for cardiac surgery, for her unwavering and continuous support that helped me achieve this milestone. I am also grateful to all the members of the cardiac surgery team for their support, which made it possible for me to prepare for this work. Additionally, I would like to thank and Dr. AbdelRahman Lawendy and Janice Sutherland from the MSc in Surgery program for their support and follow-up.

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Chapter 1: Introduction.

1.1 Thesis Rationale

An aortic dissection occurs when there is a tear in the intimal layer of the aortic wall. This results in blood flow being redirected through the intimal defect, creating a false lumen that often dissects through the media layer of the aortic wall. The dissected aortic wall is more prone to rupture and can lead to mortality. The dissection can also extend to involve the aortic branches that supply major organs with blood, causing end-organ damage and malperfusion syndrome (MPS). Type A aortic dissection (TAAD) is a life-threatening condition with a mortality rate of 1 to 2% per hour after the onset of symptoms and a mortality rate as high as 90% within 30 days[1]. The traditional surgical approach involves replacing the proximal aorta that contains the intimal tear with a tube graft, without addressing any possible distal malperfusion during the emergency proximal aorta surgery[2]. The current reported operative mortality rate ranges from 17 to 25%[3–5]. MPS has been reported in approximately 30% of patients with TAAD and is associated with significantly higher mortality rates[4,5]. Several centers of expertise around the world have adopted different approaches to address MPS in the setting of TAAD and have reported improved outcomes[6–8].

Using the integrated-article format, this thesis is divided into four chapters. In Chapter 2, we conduct a thorough literature review on malperfusion syndrome in the context of Type A aortic dissection. We review the outcomes reported by three major registries, including the International Registry of Acute Aortic Dissection (IRAD), the German Registry for Acute Aortic Dissection in Type A (GRAADA), and the Nordic Consortium for Acute Type A Aortic Dissection (NORACAAD)[3-5]. And explore various new approaches that have been developed to address MPS in TAAD with improved mortality and morbidity outcomes[6-8]. In Chapter 3, we present the results of a national survey that we conducted on cardiovascular surgeons across Canada, assessing their understanding and approach to managing MPS in TAAD. Chapter 4 reviews a retrospective analysis of the outcomes of managing patients with TAAD at our local institution from December 1999 to December 2021. In Chapter 5, we present our future plan to conduct a pilot study to evaluate the feasibility of using an intravascular ultrasound assessment device to early diagnose MPS in the setting of TAAD. Finally, we summarize all the thesis in chapter 6.

1.2 Thesis Objectives

1) To emphasize the significance of MPS in the context of TAAD, based on the literature.
    a) To review the outcomes reported by major registries on the management of TAAD.
    b) To examine the new approaches that have been adopted to address MPS and improve outcomes in the management of TAAD.
2) To investigate the understanding and practice of cardiovascular surgeons in Canada regarding the management of MPS in the context of TAAD.

3) To assess the mortality and morbidity outcomes of managing TAAD patients at our local institution and the impact of MPS on these outcomes.

4) Identify the potential areas for Improvements and propose a future plan.

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Chapter 2: Literature Review

A version of this chapter was published in the Journal of Cardiac Surgery

Bayamin K, Power A, Chu MWA, Dubois L, Valdis M. Malperfusion syndrome in acute type A aortic dissection: Thinking beyond the proximal repair. J Card Surg. 2022 Nov;37(11):3827-3834. doi: 10.1111/jocs.16872. Epub 2022 Aug 21. PMID: 35989530.

2.1 Abstract:

Background and Objective: Malperfusion syndrome is associated with the highest mortality and major morbidity risk in patients with acute Type A aortic dissection (TAAD). The timing of the open proximal aortic repair in the presence of malperfusion syndrome remains debatable given variability in clinical presentation and different local treatment algorithms. This paper provides an up to date and comprehensive overview of published outcomes and available techniques for addressing malperfusion in the setting of acute TAAD.

Methods: We have reviewed published data from the major aortic dissection registries, including the International Registry of Acute Aortic Dissection (IRAD), the German Registry for Acute Aortic Dissection In Type A (GERAADA), and the Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD), as well as the most up to date literature involving malperfusion in the setting of acute TAAD. This data highlights unique strategies that have been adopted at aortic centers internationally to address malperfusion in this setting pre-, intra-, and post-operatively, which are summarized here and may be of great clinical benefit to other centers treating this disease with more traditional methods.

Results: The review of the available data has definitively shown an increased mortality up to 43% and morbidity in patients presenting with malperfusion syndrome in the setting of acute TAAD. More specifically, preoperative malperfusion syndrome has been shown to be an independent predictor of mortality with mesenteric malperfusion associated with the worst mortality outcomes from 70% to 100%. Addressing malperfusion syndrome pre or intra- operatively is associated with significantly reduced mortality outcomes down to 4% to 13 %.

Conclusion: Adapting a dynamic and easily accessible diagnostic method for the comprehensive assessment of different forms of malperfusion (dynamic/static) and incorporating it within the surgical plan is the first step toward early diagnosis and prevention of malperfusion related complications.

As a review article, Institutional Review Board (IRB) approval, consent of human subjects, or clinical trial registration were not applicable for this chapter.

2.2 Type A Aortic Dissection

Acute Type A aortic dissection is a life-threatening condition with a reported mortality of approximately 1-2% per hour after symptoms onset and mortality as high as 90% within 30 days[1]. A recent report from the International Registry of Acute Aortic Dissection (IRAD) showed in-hospital mortality ranging between 22 to 31% and operative mortality between 18% and 25%[2]. Similarly, the German Registry for Acute Aortic Dissection in Type A (GERAADA 2015) recently showed an all-cause 30-day mortality of 16.9%[3]. Comparable results have also been reported in other large databases such as the Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD) group with a 30-day mortality of 17%[4].

2.3 Malperfusion Syndrome

In the setting of acute TAAD, the presence of malperfusion carries the greatest risk of mortality and major morbidity for these patients[2,3,5]. Malperfusion is defined as blood flow impairment to one or more end organs as a result of the extension of the intimal flap to that branching vessel[6].

According to multiple reports[2,7,8], malperfusion is found in almost a third of the patients presenting with acute Type A aortic dissection [2,7,8]. Over the past several years, emerging evidence has consistently demonstrated worsening outcomes of patients with acute TAAD presenting with malperfusion[2,3,5,6,9–13]. Geirsson et al. in 2007 reported in-hospital mortality as high as 30.5% in patients presenting with any malperfusion compared to only 6.2 % in patients presenting without MPS[14]. Patel et al. in 2008 reported in-hospital mortality of 89% in their historical control group of patients with acute type aortic dissection and malperfusion who underwent immediate surgical intervention for proximal aortic pathology[15]. In 2009, Girdauskas et al. demonstrated that multiple malperfused organ systems involved at the time of presentation with TAAD resulted in a higher risk of in-hospital mortality as compared with only single organ system malperfusion syndrome (44.4% versus 25.3%, p= 0.002)[16]. Similar data has been shown in the NORCAAD registry, where thirty-day mortality was 28.9% in patients with preoperative malperfusion and 12.1% in those without preoperative malperfusion[8]. They also reported a similar trend where more malperfused organ systems involved, resulted in an increase in 30-day mortality, one organ involved had an Odds Ratio of 2.562 (95% CI,1.745-3.761), two organs an OR of 2.723 (95% CI 1.438-5.155), and three or more organs an OR of 7.192 (95% CI 2.572-20.112). The GERAADA registry in 2015, also showed all-cause 30-day mortality of 16.9%, which increased thereafter substantially according to the number of organ systems affected by malperfusion (none - 12.6%, one system - 21.3%, two systems - 30.9%, three systems - 43.4%, P <0.001)[3].

For the purposes of patient management and clinical decision-making, it is essential to distinguish between malperfusion syndrome (MPS) and malperfusion alone. Malperfusion syndrome indicates blood flow impairment and end-organ failure in contrast to malperfusion alone, which is defined as only reduced blood flow without end-organ failure[6]. The diagnosis of MPS requires both clinical features (e.g., abdominal pain and tenderness to palpation, decreased urine output, absence of peripheral pulses, motor or sensory deficit of the extremity, neurological deficit, etc.) and laboratory findings that indicate inadequate end-organ perfusion (elevated lactate, liver or pancreatic enzymes, bilirubin, or creatinine) as well as radiographic findings demonstrating reduced or absent blood flow to organs[6].

2.4 Dynamic And Static Malperfusion

It is crucial to understand the difference between dynamic and static malperfusion in acute aortic dissection. Dynamic malperfusion describes the phenomena where there is an interruption of the intimal layer in an aortic dissection resulting in pressurization of the false lumen and collapse of the true lumen[17]. This form of malperfusion is considered to be the most common form, occurring in 80% of malperfusion cases[18]. The blood flow to branching vessels with a dynamic obstruction is intermittent in nature and mainly depends on factors such as blood pressure, heart rate, or the extension and location of the dissection flap[19]. Static malperfusion on the other hand, results from the extension of the intimal flap to branching vessels and subsequent thrombosis of the false lumen, causing a persistent obstruction regardless of the flow or the pressure gradient between the true and the false lumens[17]. Furthermore, with static malperfusion, even after the proximal repair of the aortic dissection is complete and flow has been reinstituted into the true lumen, the thrombosed branching vessels are still obstructed. This often goes unrecognized and further interventions are needed to identify and address this situation before end-organ damage occurs[20].

Patients who present with ongoing ischemia after surgery for TAAD may face challenges in accurately diagnosing the underlying cause. Standard labs and clinical examinations may not be sufficient to identify the underlying pathology, and the patient's instability may preclude the use of CT imaging. This can result in delayed diagnosis and treatment, leading to irreversible end-organ damage.

2.5 Integration Of Malperfusion in Aortic Dissection Classification

Giving the obvious clinical importance of malperfusion syndrome outlined by this data, identifying patients with MPS in the setting of acute aortic dissection has led to newer classification systems beyond the traditional Debakey[21] and Stanford[22] classifications.

Augoustides et al., in 2011, presented the Penn classification of acute Type A dissection, which focuses on ischemic profiles and malperfusion status in patients with acute Type A aortic dissection[23]. In this classification system, Class A represents hemodynamically stable patients with no evidence of circulatory collapse or branch vessel malperfusion. Class B represents patients with Type A aortic dissection and evidence of branch vessel or organ malperfusion, and Class C represents patients with evidence of circulatory collapse with or without cardiac involvement. Finally, a combination of both Class B and C (B/C) represent patients with both evidence of circulatory collapse and branch vessel malperfusion[23].

The clinical importance of this classification was reflected in the group's reported series of Type A aortic dissection patients, where patients with Class B/C had the highest in-hospital mortality of 40%, followed by Class B at 25.6%, Class C 17.6%, and finally Class A with only 3.1%[23]. These findings strongly demonstrate the increase in mortality and worsening outcomes with MPS that have been observed in the major three registries: IRAD[2], GERAADA[3], and NORCAAD[4].

2.6 Systemic Inflammatory Response to Maplerfusion Syndrome in Aortic Dissection

In addition to the negative impact on end-organ ischemia, malperfusion syndrome in acute TAAD can trigger an overwhelming inflammatory response[24–26]. In this setting, ischemic tissue has been shown to release oxygen-free radicals and elastase that cause direct endothelial damage[27,28], as well as indirect damage by increasing the level of tumor necrosis factor and interleukin-1, which eventually cause accumulation of polymorphonuclear monocytes (PMNs) by upregulating adhesion molecules on both PMNs and endothelial cells[29]. This results in the activation of more cytokines that ultimately draw more PMNs into the lungs[29]. Furthermore, this results in more free radical production and direct endothelial cell damage with subsequently increased permeability in the lungs and a higher risk of mortality[30]. Additionally, all these changes have been shown to be exacerbated by the stress of the cardiopulmonary bypass machine at the time of surgical repair[31], by activating the complement system and increasing serum levels of C3a and C5a, thromboxane, and cytokine levels[31]. In the surgical repair of these patients, prolonged cardiopulmonary bypass and need for massive transfusions have been shown to lead to the development of severe pulmonary capillary leak and worse mortality and morbidity outcomes[31]. Mitigating this lethal inflammatory cascade at the time of operation is an important reason why some highly specialized centers advocate for addressing malperfusion syndrome first, hemodynamically stabilizing the patient, and allowing for all these inflammatory and biochemical changes to resolve before addressing the proximal pathology surgically to improve patient outcomes[31].

2.7 Mortality and Morbidity Related to Malperfusion Syndrome

2.7.1 Independent Mortality Predictors:

As reported in the 2015 GERAADA Registry, independent predictors of mortality included age (OR, 1.02; 95% CI, 1.01-1.03), peripheral malperfusion (OR, 1.45; 95% CI, 1.01-2.01), involvement of supra-aortic branches (OR, 2.37; 95% CI, 1.34-4.17), coronary malperfusion, spinal malperfusion, primary entry in the descending aorta, and preoperative comatose state[3] (Table 1).

Table 2-1			
	GERAADA	**IRAD**	**NORCAAD**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Age >70 y	-	1.728 (1.060-2.816)[43]	-
Diabetes mellitus	-	-	3.650 (1.385-9.618)[8]
COPD	-	-	2.627 (1.411-4.888)[8]
Prior cardiac surgery		1.841 (1.013-3.343)[43]	
Hypotension & shock	-	3.211 (1.994 - 5.170)[32]	-
Cardiac arrest			3.242 (1.740-6.038)[8]
Coma and/or CVA	-	2.937 (1.410- 6.119)[32]	-
Preoperative ARF	-	2.468 (1.133 - 5.379)[32]	2.383 (1.231-4.613)[8]
Preoperative peripheral malperfusion	1.43 (1.01–2.01)[3]	1.75 (1.06–2.88) [33]	1.948 (1.262-3.007)[8]
Preoperative coronary malperfusion	1.61 (1.10–2.31)[3]	1.76 (1.02–3.03) [33]	2.366 (1.342-4.171)[8]
Preoperative spinal malperfusion	2.18 (1.11–4.28)[3]	-	-

Post-operative cerebral malperfusion	2.18 (1.45–3.24)[3]	-	-
Post-operative visceral malperfusion	3.24 (1.94–5.35)[3]	2.5[34]	-

Table 2-1: Independent predictors of early mortality in acute Type A aortic dissection

2.7.2 Visceral Malperfusion

The IRAD data reports a historical prevalence (1995-2010) of mesenteric malperfusion in 3.7% of 1809 patients presenting with acute TAAD[34]. Although this incidence is low, this presentation is associated with the highest rates of in-hospital mortality (63.2%, compared to 23.8% in patients without mesenteric malperfusion, $p<0.001$)[2]. Similarly, the GERAADA data also reported Visceral malperfusion in 6% of 2137 patients with acute TAAD[3]. In 2014, Perera et al. reviewed multiple registries and best evidence papers and detected a mortality rate of 70% to 100% for patients with TAAD complicated by mesenteric malperfusion [35]. Because of this, the authors recommended the initial management of these patients should include percutaneous procedures to reverse the malperfusion followed by delayed proximal aortic repair[35].

Diagnosing Visceral malperfusion in acute TAAD can be quite challenging[9]. From the IRAD data, patients with mesenteric malperfusion usually present with clinical signs such as abdominal and leg pain, but abdominal pain has been reported to not be present in up to

40% of patients with mesenteric ischemia[9]. Complicating this further, abdominal pain has been shown to be a presenting symptom reported in 20% of patients without mesenteric malperfusion [11]. Post-operative mesenteric malperfusion risk factors have been reported in the GERAADA data[3]. In this setting; renal malperfusion (OR 2.77; CI 1.52–4.96), preoperative visceral malperfusion (OR 9.40; CI 5.20–16.98), ascending aorta involvement (OR 0.29; CI 0.12–0.87), and descending aorta involvement (OR 2.24; CI 1.25–4.19) have all been identified as risk factors for post-operative visceral malperfusion[3]. The IRAD data has shown that male gender (OR 1.7; P = 0.002), age (OR 1.1/y; P =0,002), and renal failure (OR, 5.9; P= 0.020) were predictors of mortality in patients with mesenteric malperfusion[32].

The timing for surgical intervention on patients with mesenteric malperfusion is still controversial[34]. Despite the high mortality associated with mesenteric malperfusion, the IRAD data demonstrated better in-hospital mortality outcomes with surgical/hybrid therapy when compared with initial endovascular and medical treatment, respectively, 41.7% vs. 72.7% vs. 95.2% ($p<0.001$)[34]. This data however, showed a resistance of surgeons to proceed with upfront open surgery on these patients compared to uncomplicated patients (53% vs. 88%)[34].

2.7.3 Renal Malperfusion

The incidence of renal malperfusion has been reported to be between 2.8% and 9%[3,8]. In 2020, Kosaku et al. reported a series of 534 patients with TAAD, of which 64 patients

(12%) had preoperative renal malperfusion[36]. This was associated with a higher incidence of post-operative acute kidney injury compared to the group with no renal malperfusion (76.6% vs. 39.4%; $p<0.001$)[36]. Temporary dialysis was also significantly higher in this group as well (28.1% vs. 4.9%; $P < 0.001$)[36]. Furthermore, operative death was found to be significantly higher in the renal malperfusion group (12.5% vs. 3.8%; $P = 0.003$), and renal malperfusion was found to be an independent predictor of not only post-operative acute kidney injury (OR 4.32, 95% CI 2.25-8.67; $p <0.001$) but operative death as well (OR 3.08, 95% CI 1.02-8.86; $p <0.046$)[36]. The GERAADA data has also identified renal malperfusion as a risk factor for post-operative visceral malperfusion with an OR of 2.77 (1.52–4.96), which is a lethal complication as mentioned earlier[3].

2.7.4 Peripheral Malperfusion

In 2002, Bossone et al. described the clinical finding of a ‘pulse deficit’ as a marker for malperfusion after analyzing 154 IRAD patients, in which 30% were found to have pulse deficit upon presentation[37]. In this paper, they define the term ‘pulse deficit’ by a clinically documented weak or absent carotid, brachial, or femoral pulse. This clinical finding was further confirmed by imaging evidence of disrupted blood flow at the time of surgery or autopsy[37]. In this work, a pulse deficit was found to be an independent predictor of early mortality (Risk ratio 2.73, 95% CI 1.7 to 4.4; $p <0.0001$)[37]. Of those 154 patients with TAAD, a reduced or absent right brachial or common carotid pulse was found in 14.5% of patients, left common carotid in 6.0%, and left subclavian pulse in 11.7%[37]. In the lower body, right femoral pulsation was reduced in 14.5% and left femoral pulsation in 13.7%[37]. Of patients with pulse deficits, more than half (53.4%) had decreased pulsations in more than one vessel. Furthermore, the greater the number of vessels with a reduced pulse, the worse the risk of mortality (24.7% with no pulse deficit, and 36.2%, 48.9%, and 55.9% with 1, 2, and >/=3 vessels involved, respectively, $p < 0.0001$)[37]. Additionally, when the pulse deficit group was compared with the group without a pulse deficit, it was found to have more significant adverse events, neurological deficit (35% vs. 11%), coma (27% vs. 9.1%), renal failure (10% vs. 4.6%), and limb ischemia (29% vs. 2.1%)[37].

2.8 Different Surgical Approaches for Acute Type A Aortic Dissection

2.8.1 Traditional Approach

Given that MPS in acute TAAD carries the highest risk for mortality and major morbidity, there has been an emergence of novel techniques to deal with this problem that have yielded positive and exciting results[6,11]. The traditional surgical approach for acute TAAD has involved emergent repair of the proximal aorta with resection of the ascending aorta and replacement of the intimal tear [38]. The concept here is to reinstitute blood flow into the true lumen proximally to pressurize it and decompress the false lumen, leading to false lumen collapse, aortic remodeling, and the re-establishment of blood flow to all branching vessels. This approach mitigates the risk of proximal aortic complications such as aortic rupture, proximal extension into coronary arteries, cardiac tamponade, and aortic insufficiency.

However, only dealing with the proximal tear leaves a significant portion of patients at risk for complications from the inability to identify malperfusion of the spinal, visceral, renal, and limb vessels leading to end-organ ischemia, increased morbidity, and mortality[3,10]. Isolated emergent proximal repair may resolve dynamic obstructions, but as imaging techniques and our understanding of the disease process have evolved, we know that the presence of any static malperfusion will require further intervention to restore the blood flow[20]. In 2009, Girdauskas et al. reported series of 276 patients with acute TAAD, where 33.75% of patients presented with malperfusion syndrome, which was associated with higher in-hospital mortality (29% versus 13.9%p=0.002) and longer intensive care unit stays at 11.4 +/- 9.7 versus 7.7 +/- 6.9 days (p<0.04). As a result, the authors recommend percutaneous interventional procedures to treat the malperfusion and delayed surgery on those subgroups because of the dismal prognosis of immediate surgical repair[39]. Importantly, static malperfusion is often under-appreciated, under-investigated and under-treated.

2.8.2 Concomitant / Hybrid approach

The University of Duisburg-Essen group have published the results of their hybrid operating room concept for concomitant diagnostics, endovascular intervention, and open surgery for patients with acute TAAD[40]. In this model, all patients with TAAD are admitted directly to the hybrid operating room to be managed immediately by the aortic team, consisting of cardiac surgeons, cardiologists, and cardiac anesthesiologists. After obtaining invasive and noninvasive monitoring of the patient and after ensuring that the patient is hemodynamically stable, angiography is performed to assess four potential malperfusion sites (coronary, cerebral, visceral, and peripheral vascular branches) and for surgical planning[40]. Coronary angiography is done routinely in patients older than 50 years old[40]. In the case of static malperfusion of the visceral and peripheral arteries, endovascular restoration of end-organ perfusion is performed before surgery. Following this, endovascular intervention is decided upon either pre or post proximal surgical repair for dynamic malperfusion depending on the patient's hemodynamic stability[40]. With this hybrid model, the group published a series of 124 patients from 2004–2011, with lower in-hospital mortality in patients who had undergone preoperative invasive diagnostics and early diagnosis of malperfusion (12/90) compared to patients who had not due to hemodynamic instability (8/34)[40]. Visceral/peripheral malperfusion syndrome, requiring primary endovascular intervention occurred in 23% (16/71), and five post-operative endovascular interventions became necessary due to persistent malperfusion[40]. The authors reported a total of 32% (23/71) required coronary artery bypass grafting[40] during the open surgical repair and they found coexisting coronary artery disease in 27% of patients who underwent endovascular evaluation, and coronary revascularization was performed in 21% (15/71) of them[40]. This is an additional benefit of the hybrid model, where valuable preoperative information of the coronary anatomy can be obtained and addressed during the surgery when it is often unknown in most emergent cases and can lead to problems with myocardial protection and heart failure post-operatively[40].

2.8.3 Delayed proximal repair approach

In a 2018 Circulation paper published by Yang et al., the University of Michigan group outline a 20-year experience of a different approach to MPS in the setting of acute TAAD[6]. In this model, all stable patients with an acute TAAD presenting with evidence of malperfusion syndrome were managed first with endovascular revascularization followed by delayed open proximal aortic repair[6]. Those nonstable patients with signs of aortic tamponade or rupture will go for the open proximal aortic repair immediately. The authors reported that with this model, the overall mortality rate dropped from 21.0% to 10.7%[6]. With this approach, the authors outlined three major advantages compared to the traditional upfront open aortic repair for all. First, this approach allows for the resolution of any arterial obstruction, whether dynamic or static, in timely fashion before the open repair[6]. In their series, of the patients with suspected malperfusion syndrome, the majority (123/135) had undergone endovascular intervention, none of which would be achievable with the upfront surgical approach. After those patients recovered from malperfusion syndrome, mortality following the open aortic repair was very low at 3.7%[6]. Second, the delayed approach allows for the avoidance of a futile open aortic repair in borderline operative candidates with malperfusion syndrome who are not salvageable[6]. As the operative mortality of patients with malperfusion syndrome is reported to be as high as 45%, the upfront surgical approach (involving cardiopulmonary bypass, hypothermic circulatory arrest, etc.) potentiates the deleterious malperfusion effects and the related inflammatory response and organ dysfunction[6]. The authors report that 87% of deaths were attributed to organ failure from malperfusion syndrome even after fenestration and stenting[6]. Third, the authors reported favorable short and long-term outcomes with this approach[6]. In the short term, there is a significant reduction in mortality outcomes when this observed data is compared with expected mortality after upfront open aortic repair for all by prognostic models previously published in the literature, such as Verona[41], Leipzig-Halifax [42], Stockholm[43] (Table 2). As well as both in-hospital mortality and 30-day mortality after first intervention with the Penn[44] and GERAADA [3]models (Table 3).

Table 2-2		
In Hospital Mortality		
Expected with upfront surgical approach vs. Observed (University of Michigan)		
All patients (n=354)		
Verona model	24% vs. 11%	p<0.001
Leipzig-Halifax model	16% vs. 11%	p = 0.004
Stockholm	20% vs. 11%	p<0.001
Patients with malperfusion syndrome treated with IR + Delayed OR (n=26)		
Verona model	41% vs 4%	p<0.001
Leipzig-Halifax model	33% vs 4%	p = 0.001

Stockholm	33% vs 4%	p = 0.001

Table 2-2: In hospital mortality comparison between expected data from Verona, Leipzig-Halifax and Stockholm prognostic models vs, observed data from University of Michigan.

Table 2-3		
30-day mortality after first intervention		
Expected with upfront surgical approach vs. Observed (University of Michigan)		
All patients (n=354)		
Penn model	13% vs. 9%	p=0.03
GERAADA model	16% vs. 9%	p<0.001
Patients with malperfusion syndrome treated with IR + Delayed OR (n=26)		
Penn model	26% vs 4%	p=0.01
GERAADA model	30% vs 4%	p = 0.004

Table 2-3: in-hospital mortality and 30-day mortality after first intervention comparison between Penn and GERAADA models vs. University of Michigan results.

Skeptics of this approach have argued that the risk of leaving a patient with an acutely dissected aorta untreated for any length of time may lead to a higher incidence of rupture in the peri-operative hospitalization period[6]. However, in this series, the authors reported only a 4% risk of aortic rupture following fenestration and stenting prior to open surgical repair[6]. This finding indicates that malperfusion is a more significant cause of morbidity and mortality in these patients than aortic rupture[6].

In the long term, the authors reported a 5-year survival rate following primary endovascular revascularization of 80% and a 10-year survival rate of 63%, with no significant difference when compared to patients who originally presented without malperfusion syndrome[6].

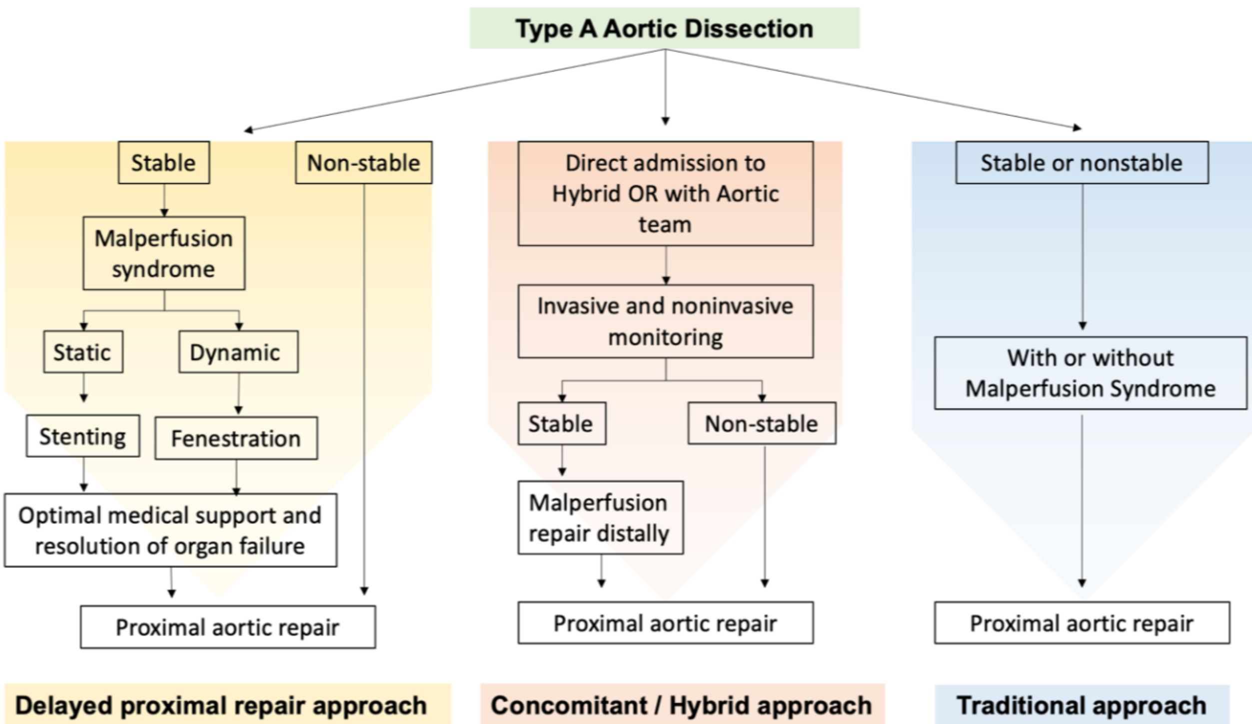

Figure 2-1: Comparison between different surgical approaches to manage acute type A aortic dissection. *Nonstable: cardiac arrest, cardiogenic shock, cardiac tamponade, or aortic rupture.*

2.8.4 Multi-disciplinary Approach to Malperfusion

Addressing malperfusion concurrently with hybrid approaches or first in delayed approaches requires an extremely collaborative model of care with a truly multi-disciplinary team of surgeons, interventionalists, anesthesiologists, intensivists, and cardiologists. Traditionally, it has been taught that the Type A should be treated first because of the high mortality of Type A dissection and leave the malperfusion to be addressed only if the patient survives and the malperfusion persists. With these newer treatment approaches, a nuanced and customized treatment plan is required for every patient. Only appropriate healthcare systems with adequate resources will be able to implement such innovative strategies.

2.9 Conclusion

Here we have combined data from the most up to date and extensive literature available that clearly demonstrates the significance of MPS in the setting of acute TAAD. The data published by University of Michigan and University of Duisburg-Essen groups have shown a significant improvement in mortality rates when the MPS has been addressed primarily prior to, or concomitant with surgical repair. Although these highly specialized programs are equipped with specialized teams and the infrastructure to provide comprehensive care to these patients, there is a significant opportunity to improve mortality outcomes at all cardiac surgical centers by addressing MPS in this setting.

Adapting a dynamic and easily accessible diagnostic method for the comprehensive assessment of different forms of malperfusion (dynamic/static) and incorporate it within the surgical plan is the first step toward early diagnosis and prevention of malperfusion related complications.

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Chapter 3: Canadian National Survey of Cardiovascular Surgeons' Approach and Understanding of Malperfusion Syndrome in the Setting of Acute Type A Aortic Dissection.

A version of this chapter will be submitted for publication at Canadian Journal of Cardiology.

3.1 Introduction

Acute type A aortic dissection (TAAD) is associated with a high mortality, approximately 1-2% per hour after the onset of symptoms and as high as 90% within 30 days without intervention[1]. A mortality of 17-31% within 30 days of surgery is reported from several major registries[2–5]. Approximately 30% of patients with TAAD present with Malperfusion Syndrome (MPS)[2,5,6]. Over the past several years, multiple reports have documented the increased mortality and morbidity outcomes of TAAD presenting with MPS[2,3,5,7,8]. Not surprisingly these reports demonstrate that the greater the number of malperfused organ systems at initial presentation, the higher the mortality[3,5,9,10]. Most significantly, in patients presenting with mesenteric malperfusion preoperatively, the mortality rate ranges from 70 to 100%[11].

The traditional approach to managing patients with TAAD is to address the proximal intimal tear in the ascending aorta and/or aortic arch[12]. This generally will prevent fatal complication such as aortic rupture, severe aortic regurgitation, tamponade, or myocardial infarction but does not necessarily address any remaining distal malperfusion. Different innovative approaches have been adopted and applied by several highly specialized centers to manage patients with TAAD presenting with MPS[13–16]. The main principle of these approaches is to diagnose MPS as early as possible so as to manage it either before or concomitantly with the proximal aortic repair. By doing this, there are reports of improved outcomes with decreased mortality rates ranging from 4 to13%[13,16]. However, a high level of multi-disciplinary collaboration, as well as specialized equipment is required to implement these potentially advantageous approaches.

The main objective of this national survey is to understand the available infrastructure and the current practice and approaches to patients with MPS in the setting of TAAD at cardiac surgery centers across Canada.

3.2 Materials And Methods

A questionnaire with both open ended and multiple choices questions was created. The questionnaire was designed and reviewed by the coauthors of this study. The web-based platform Western's Qualtrics was chosen and used through the University of Western Ontario. Western’s Qualtrics uses encryption technology and restricted access authorizations to protect all data collected. In addition, this platform does not allow multiple responses from the same individual.

3.2.1 Survey Distribution

The Cardiac Surgery Division Head at London Health Sciences Center, Dr. Michael Chu sent an invitation email incorporating the study web-based survey to Cardiovascular Surgery Division Heads across Canada. They were asked to distribute the invitation to division members carrying out TAAD surgery. The web-based survey was distributed with a two-month period for responses. A reminder email was then sent after the waiting period. As previously indicated, the survey was restrictively designed to limit responses to one per participant. Participation was restricted to practicing cardiovascular surgeons at Canadian centers who operate on patients with TAAD. No identifiable individual information was collected.

3.2.2 Ethics Approval

The study design and contents were approved by the University of Western Ontario’s Ethics board and the Lawson Health Research Institute (R-22-197). A letter of information was provided, and informed consent was obtained from all participants before proceeding to the study survey.

3.2.3 Statistical Analysis

All data and results of this survey are presented descriptively. Descriptive statistics were performed using mean ± standard deviation (SD) for normally distributed continuous variables and median for non-normally distributed variables. Skewness and normality were assessed using the Shapiro–Wilk test. The results are presented as absolute frequencies and percentages.

3.3 Results

A total of 53 cardiovascular surgeons across Canada responded to the survey request. Eight were excluded because of incomplete answers, leaving 45 fully completed responses. We communicated with 26 centers across Canada with a total number of 124 practicing cardiac surgeons, giving a response rate of 36.3%.

Centers' Experience and Available Resources:

The survey indicates that most cardiac surgeons (45.9%) in Canada reported performing 20-30 cases/year of TAAD in their respective centers with 35.6% reporting 10-20 cases/year. Thirteen percent reported that their center does more than 30 TAAD cases per year (Figure 3-1).

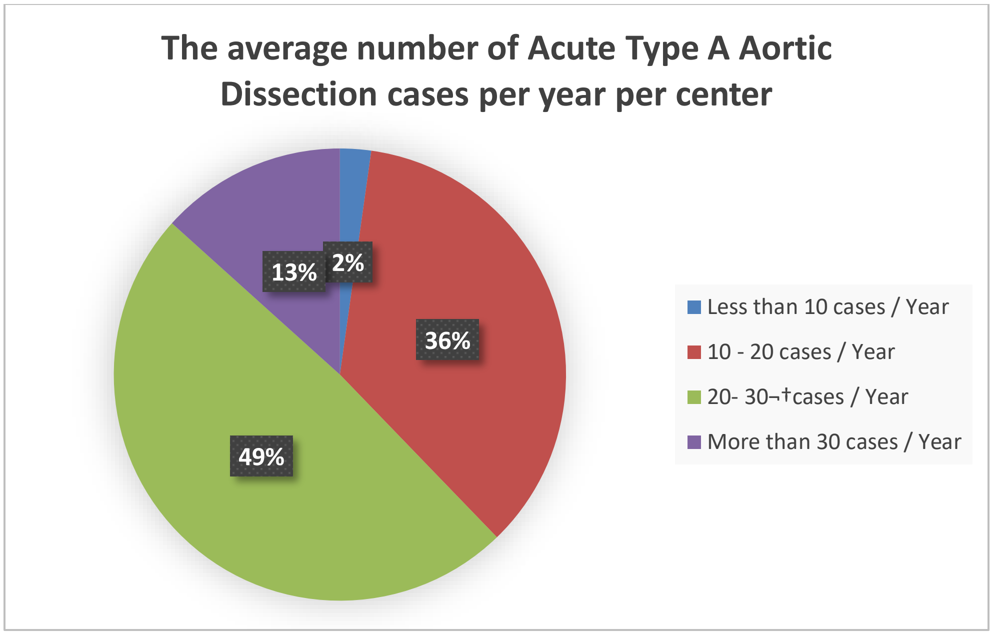

Figure 3-1: The average number of cases per year for each center in Canada.

Most of the respondents (88.9%) reported not having a dedicated aortic dissection team in their centers. Only a few of the respondents (11.1%) reported having a dedicated team that included vascular surgery and interventional radiology in addition to cardiac surgery. The majority (71.1%) reported access to a hybrid operating room. Although most of the respondents (71.1%) reported availability of Intravascular ultrasound assessment (IVUS) in their centers, only a limited number (28.9%) reported access to IVUS in the operating room.

<u>Diagnosis of Malperfusion Syndrome:</u>

There was general agreement on the importance of including clinical findings, imaging, and bloodwork to accurately diagnose MPS that associated with TAAD. Preoperative CT scan was reported by all as the most common imaging study. Essentially the same approach was reported for initial postoperative follow up. During surgery, the majority (84.4%) rely on clinical findings, e.g., low urine output or new absent pulse) and (88.9%) on bloodwork, e.g., rising serum lactate or creatinine. Only 31.1% rely on imaging and 76.9% of the those reported the use of intraoperative transesophageal echocardiography as an imagining study to assist in assessing intraoperative MPS. (Figure 3-2).

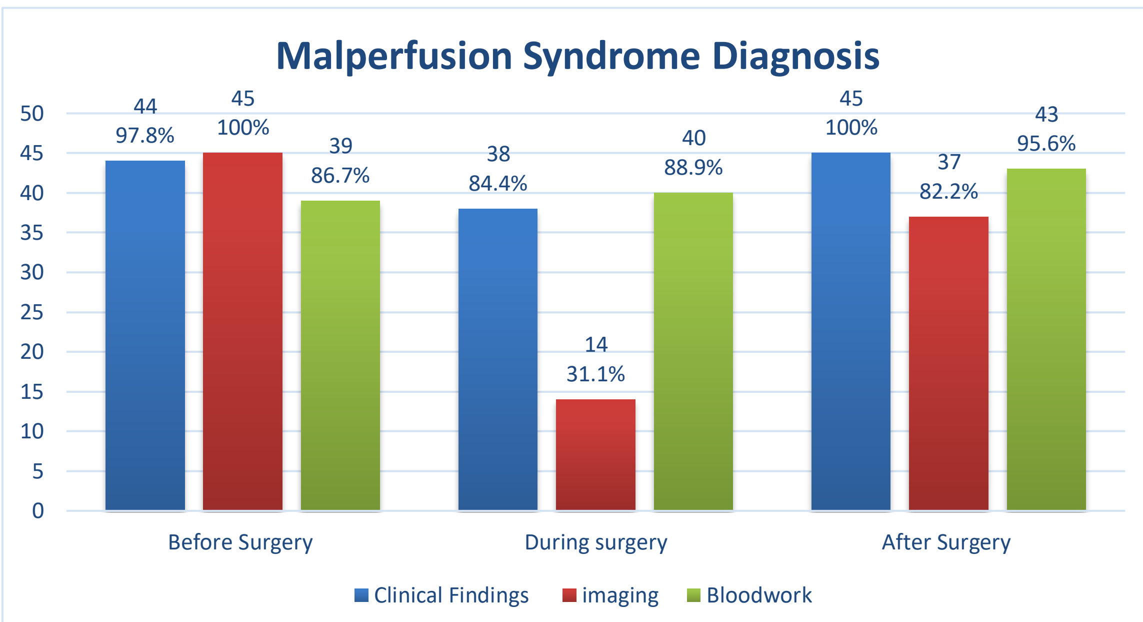

Figure 3-2: Methods of diagnosing malperfusion syndrome before, during and after the proximal aortic repair by cardiac surgeons in Canada.

Management of Malperfusion Syndrome:

Nineteen (42.2%) of the respondents reported that patients presenting with cerebral malperfusion/coma are less likely to be offered surgery. While 12 (26.7%) indicated a decreased likelihood of offering surgery to patients presenting with shock or aortic rupture. Thirteen (20.2%) of the respondents suggested that all patients should be offered emergency surgery regardless of their presentation.

The survey showed that approximately 5% of patients presenting with TAAD will be diagnosed with mesenteric malperfusion postoperatively. The respondents are almost equally divided with respect to their opinion on the timing of further management of mesenteric malperfusion in TAAD. Approximately one third advocated intervention to address the mesenteric maplerfusion prior to open aortic repair, one third concomitantly, and one third following aortic repair (Figure3-3).

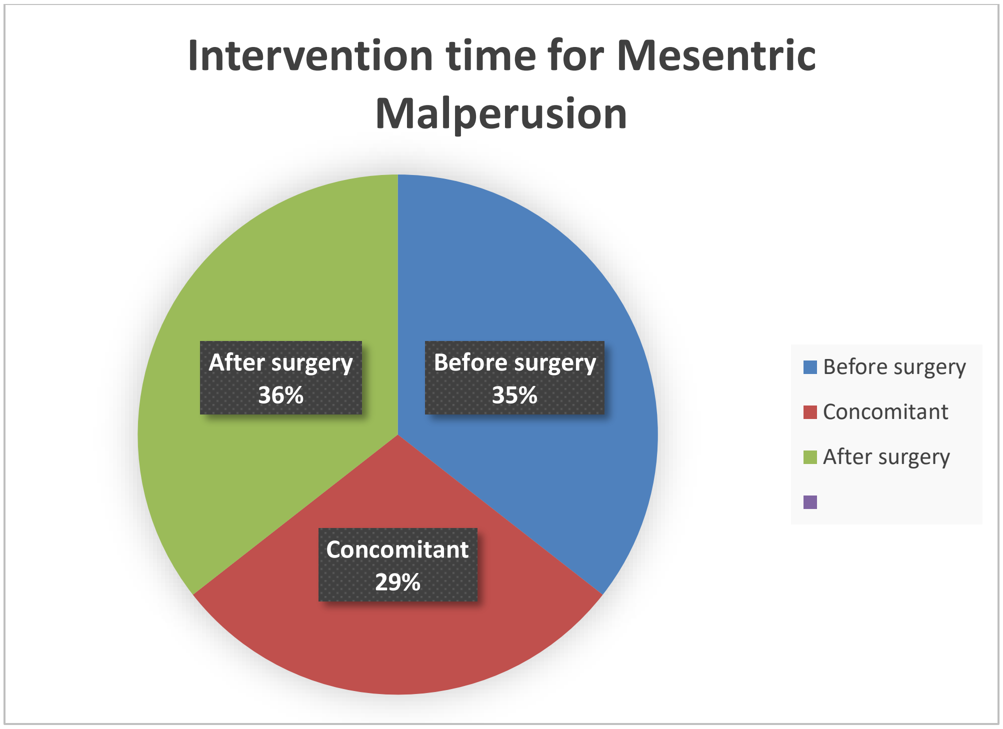

Figure 3-3: Cardiac surgeons' opinion on the ideal time for intervention to address mesenteric malperfusion in patients with type A aortic dissection.

The respondents predicted that approximately 20% of patients with TAAD will have acute kidney injury, and 5% of patients will likely need permanent dialysis. The survey estimated that approximately 5% of patients presenting with TAAD and limb malperfusion will require intervention. This would include fasciotomy, revascularization, or amputation.

Mortality Outcomes:

The respondents report a median of 13% as the approximate 30-day mortality of patients presenting with TAAD. Furthermore, they estimated a median of 30% of patients with TAAD presented initially also with MPS. The 30-day mortality of this subgroup of patients was estimated to be a median of 30%.

3.4 Discussion

Mortality Outcomes and Volume of Cases Per Center:

The annual incidence of TAAD is 4.2/100,000 patient-years as reported from a comprehensive national study[17]. Mortality in acute TAAD is related to a number of factors including the extent of the dissection, the presence of malperfusion, and the experience of the surgeon and center to which the patient presents. The IRAD registry showed operative mortality between 18% and 25% and in-hospital mortality ranging from 22 to 31% [2,18]. The GERAADA registry showed an all-cause 30-day mortality of 16.9%[3]. Comparable results have also been reported from the NORCAAD registry with a 30-day mortality of 17%[5]. The self-reported estimated 30-day mortality in our survey ranged from as low as 2% to 25%, with a median reported mortality of 13%. Interestingly, this estimated mortality is lower than that reported in the three major registries cited above[2,3,5,18]. The heterogeneity in the surgeons' perception of the mortality associated with TAAD can be explained to some extent by the individual surgeons' own experience, while the volume of cases carried out in each surgeons' respective center may also be a factor. Also, there is probably reporting or recall bias as surgeons might overestimate their survivability with treating TAAD[19].

Multiple reports suggest improved TAAD outcomes in centers with higher case volume[20–22]. A national study from the United State reported an operative mortality of 27.4% in centers performing 3 or fewer acute aortic dissections a year, compared with 16.4% in those performing more than 13 per year ($p < 0.001$)[22]. Another US study reported a mortality of 14.1% in high volume centers doing an average of 22.3 cases per year, compared with operative mortality of 24.1% in low volume centers with an average of 1.1 cases per year ($P=0.001$)[21]. In the United Kingdom, where the health care sector has a similar referral strategy as in Canada, surgeons with less than 4 cases per year over the study period had significantly higher in-hospital mortality rates in comparison with surgeons with a mean annual volume of 4 cases or more (19.3% vs 12.6%; $P = .015$)[20]. In our study approximately half of the surgeons reported that their center did 20-30 TAAD cases per year, with an additional third of surgeons reporting 10-20 cases per year. Forty of 45 surgeons reported that there was not a dedicated aortic dissection team at their center. From the Canadian Society of Cardiac Surgeons' website, there are 34 cardiac surgery centers across the country the majority of those centers accept referrals of patients with TAAD. There may be the potential to further improve outcomes by limiting TAAD surgery to centers with dedicated aortic teams. Unfortunately, there remains lots of work left to do in regard to organizing and developing dedicated aortic teams at most major cardiovascular centers in Canada.

Malperfusion syndrome:

There is emerging evidence of the importance of MPS as a cause of mortality in patients with TAAD. Our survey indicated that Canadian surgeons are aware of the significant of MPS in these patients. The survey reported that approximately one third of patients with TAAD present with MPS which is very similar to the Internationally reported data from

IRAD, GERAAD, and NORCAD[2,3,5,7]. The survey reported a 30-day mortality of approximately 30 % in patients with TAAD and MPS, which is approximately twice the predicted mortality of TAAD alone. Geirsson et al. in 2007 similarly reported in-hospital mortality as high as 30.5% in patients presenting with any malperfusion compared to only 6.2 % in patients presenting without MPS[23]. The GERAADA registry in 2015 showed a 30-day mortality of 16.9%, with a substantial increase in mortality according to the number of organ systems affected by malperfusion (none - 12.6%, one system - 21.3%, two systems - 30.9%, three systems - 43.4%, P <0.001)[3].

Malperfusion can be static or dynamic depending on the status of flow in the true and false lumens[24,25] and the CT scan carried out preoperatively may not reflect the dynamic changes that can occur subsequent to the scan. The majority of respondents agreed that clinical findings, imaging, and bloodwork would all be used to assess for MPS prior to surgery. During surgery, the survey showed that MPS is generally diagnosed by either new clinical findings such as low urine output, loss of a pulse, or change in blood work (e.g., increase in lactate or creatinine), but unfortunately those methods don’t necessarily reflect the severity of MPS or clearly direct further management. After surgery, most of the respondents agreed on monitoring for MPS by clinical findings, blood work, and imaging. Although those methods may detect MPS, much of the time extensive organ damage will have already occurred requiring invasive interventions to manage the consequences. This might include laparotomy with exploration for mesenteric ischemia, vascular intervention for renal malperfusion or surgery for limb malperfusion. The outcomes of such intervention are usually poor[11,26–29]. The respondents estimated approximately 5% of TAAD patients well require permanent dialysis after surgery. Furthermore, they estimated that approximately 5% of patients with TAAD are diagnosed with mesenteric malperfusion post-operatively. Multiple reports show mortality rates from 70 to 100% in TAAD patients with mesenteric malperfusion[11]. The IRAD registry reports an incidence of mesenteric malperfusion in 3.7% of 1809 patients presenting with acute TAAD[30], while the GERAADA registry reported visceral malperfusion in 6% of 2137 patients with acute TAAD[3].These registries also demonstrated that mesenteric malperfusion is an independent predictor of mortality.[3,29]

In our survey, the surgeons were divided about the appropriate time to address mesenteric malperfusion in the setting of TAAD (Figure 3). This highlights the current uncertainty with regards to the optimal management strategy for these complex patients. Along with developing a framework for dedicated, multidisciplinary, aortic teams there is an apparent need for guidelines and treatment protocols to help standardize approaches to these patients. As outlined in our literature review in Chapter 2, some centers have achieved much lower mortality rates when addressing malperfusion either before or during the intraoperative treatment of patients with type A dissection.

There is a heterogeneity among the respondents with respect to whether anything would prevent them from offering surgery to a patient with TAAD. Twenty percent (n=12) of the respondents suggested nothing should prevent emergency proximal aortic repair. Others 42.22% (n=19) wouldn't offer surgery for patients with cerebral malperfusion or coma. The IRAD registry suggested that surgery should even be offered even for patients in a comatose state[18]. The IRAD investigators showed that medical therapy was associated with dismal outcomes: 100% mortality in patients with coma and 76.2% in those with CVA. In contrast, surgery was found to be a protective factor against mortality (OR 0.058; P<0.001), leading to a 50% survival benefit over medical management[31]. A significant number (26.7%.) of the respondents would not offer surgery for patients presenting with shock or aortic rupture before surgery, which are considered as independent mortality predictors in the major registries[5,32]. Sacks et al conducted a behavior study about surgeons' perception of risk and benefit in the decision to operate. Given the same clinical scenarios, different surgeons' perceptions of the risks and benefits of treatment vary significantly and are highly predictive of their decision to operate[33]. The study also showed the process of surgical decision-making can be improved by collecting comprehensive data on the risks and benefits of all available treatment options. This data can then be used to explicitly incorporate risk and benefit assessments into the decision-making process, ultimately leading to better-informed and more effective treatment decisions.[33].

<u>Different approaches to address malperfusion syndrome in the setting of type A aortic dissection:</u>

Centers that apply new approaches to early diagnosis and management MPS during the initial presentation with TAAD report improved outcomes[13,16]. The University of Michigan group reported a 20-year experience using a different approach to MPS in the setting of acute TAAD[16]. With this approach, all stable patients with an acute TAAD presenting with evidence of MPS were first managed with endovascular revascularization followed by delayed open proximal aortic repair[16]. The overall mortality rate dropped from 21.0% to

10.7%[16]. The University of Duisburg-Essen group have published the results of their hybrid operating room concept for concomitant diagnostics, endovascular intervention, and open surgery for patients with acute TAAD[34]. Their in-hospital mortality was 13% (12/90) in patients who had undergone preoperative invasive diagnostics and 24% (8/34) in patients who had not[13]. Stanford University also reported mid-term improved survival in their hybrid approach cohort 96.7% (122/125) compared to the traditional approach cohort 87.2% (109/125) (p=0.002)[35]. These experiences reflect the importance and need for more multi-disciplinary collaboration. In this survey, most of the surgeons 71.1% (n=32) reported that they have access to a hybrid operating room, but only a few of them 11.1% (n=5) reported availability of a dedicated aortic dissection team. Although most of the respondents 71.11% (n=32) reported the availability of IVUS in their centers, primarily in the coronary angiography lab, most of them don't have access to IVUS in their operating rooms. This can be a helpful tool in the early diagnosing MPS[36]. There is a trend toward improved mortality outcomes in the IRAD registry over 17 years and that can be explained with different strategies that have been adopted by the participating centers[2]. The results of the survey thus suggest that there may be an opportunity for improving outcomes, which is also supported by the work of Andersen et al. which demonstrated a major decrease in mortality from 33.9% to 2.8% after implementing a multidisciplinary approach[37].

3.5 Conclusion

The survey reflected good awareness of cardiac surgeons across Canada about MPS in the setting of TAAD and its major negative impact on mortality and morbidity outcomes. It also indicates the lack of standardized approaches to TAAD patients with malperfusion and lack of dedicated multidisciplinary aortic teams at most major cardiovascular centers across Canada, despite recognition of the prevalence and severity of this clinical presentation. Encouraging more multidisciplinary collaboration would be helpful to utilize newer diagnostic resources to facilitate early diagnosis and management of MPS. Easily accessible and dynamic tools, such as IVUS, along with endovascular therapies should be investigated further in an effort to improve patient outcomes with MPS and to help create treatment protocols and to help manage patients with MPS and TAAD for all centers across Canada.

3.6 Limitations

It is likely that some of the estimates here are inaccurate due to recall bias and thus should be viewed as gross estimates only and as surgeons' perception of MPS in the setting of TAAD. We also only had a 36% response rate and, although this is acceptable for a survey of medical practitioners, we suspect the answers of the respondents may have differed from those of the non-respondents and thus may not be representative of the population as a whole.

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Chapter 4: Retrospective Mortality and Morbidity Analysis of Malperfusion Syndrome in the Setting of Type A Aortic Dissection.

4.1 Introduction

Type A aortic dissection (TAAD) is a life-threatening condition that can lead to high mortality rates, 90% within 30 days, if left untreated[1]. It is characterized by the separation of the aortic wall layers, resulting in the formation of a false lumen within the aorta. The traditional surgical approach for TAAD involves the repair of the proximal aorta with resection and replacement of the intima entry tear and aneurysmal tissue within the ascending aorta[2]. This approach aims to reduce the risk of complications such as aortic rupture, coronary artery extension, cardiac tamponade, and severe aortic valve insufficiency, all of which can lead to mortality[2].

However, there is emerging evidence suggesting that the traditional surgical approach may not be sufficient to reduce the high mortality rates associated with TAAD[3–6,15,16]. Malperfusion syndrome is a serious complication of TAAD that occurs when laminar blood flow is disrupted due to the interruption of the intimal layer, resulting in a gradient between the true and false lumen[6]. This can cause dynamic or static obstruction of the vessel, leading to end-organ damage and ischemia[6]. Approximately 30% of TAAD patients experience malperfusion syndrome[3,5,10].

Diagnosing and addressing malperfusion syndrome is essential for reducing mortality and morbidity rates in TAAD patients[6,7,50,61,64]. However, diagnosing malperfusion syndrome can be challenging, as traditional imaging techniques such as computed tomography (CT) scans may not accurately represent perfusion during and after proximal surgical repair[6]. This is because at the time of the initial CT scan, the intimal tear is still present, and flow may not be directed into the true lumen. In addition, patients' blood pressures may not be controlled, which can cause dynamic shifts in the intimal flap favoring either true or false lumen flow. Multiple distal re-entry tears can also form throughout the remaining aorta after surgical repair, which can alter arterial flow[21].

To improve outcomes for TAAD patients, innovative approaches have been developed by multiple experienced centers[6,8,14]. These approaches focus on early diagnosis and treatment of malperfusion syndrome[6–8,50].

4.2 Study Rationale

The introduction of the study highlights the severity of Type A aortic dissection (TAAD), which is a life-threatening condition that requires prompt surgical intervention to reduce mortality risk. Although emergent repair of the proximal extent of the TAAD is the current standard of care at the center under study, there is still a need to improve outcomes and reduce the risk of complications.

Reviewing local data of patients who presented with TAAD to their center will be a good starting point for improving outcomes and gaining a better understanding of MPS in the setting of TAAD. By analyzing the data from our own center, we hope to identify potential areas for improvement and determine if there are any differences in outcomes between patients with and without malperfusion. This can lead to the development of new strategies to reduce the incidence of malperfusion and improve overall patient outcomes.

4.3 Study Design

This is a single center retrospective cohort analysis of consecutive patients who underwent surgical repair of TAAD between December 1999 and December 2021.

4.4 Methodology

The methodology for this study involved a retrospective electronic chart review of a total of 235 consecutive patients who underwent aortic surgery for Type A aortic dissection (TAAD) at London Health Sciences Centre in London, Ontario, Canada, between December 1999 and December 2021. Total of 11 surgeons with different level of experience operated on patients with TAAD during the study period. The goal of this review was to identify the presenting anatomy, including the proximal and distal extent of the dissection, as well as any risk factors for aortic dissection, such as hypertension, family history, or connective tissue disorder. The operative procedure performed was also documented. The charts, imaging, and operative reports were examined for any evidence of malperfusion before and after surgery. The patients were then retrospectively classified into two groups based on the presence or absence of malperfusion.

The first group, the "Uncomplicated Type A Aortic Dissection cohort (non-MPS group)," included patients with no evidence of malperfusion before, during, or after aortic surgery repair. The second group, the "Complicated Type A Aortic Dissection cohort (MPS group)," included patients with evidence of malperfusion before or after aortic surgery repair. The two groups, the Non-MPS Group and MPS Group, were established to differentiate between patients with and without malperfusion, which allowed for a comparison of outcomes between the two groups.

All elements of this study were prospectively approved by The Western University Health Sciences Research Ethics Board and Lawson Health Research Institute (R-22-030)

4.4.1 Inclusion and exclusion criteria

Subject criteria were established for this study to identify patients who were eligible for inclusion in the study. Inclusion criteria consisted of patients who were diagnosed with Type A aortic dissection (TAAD), acute or acute on chronic aortic dissection, with or without evidence of malperfusion syndrome either before or after aortic surgery repair. Evidence of malperfusion syndrome was defined as meeting both of the following criteria. Imaging findings indicating reduced flow to the supra-aortic branches, celiac trunk, superior mesenteric artery, renal arteries, or iliac arteries. And clinical stigmata of end-organ ischemia (clinical neurological deficit, abdominal pain, distended abdomen, oliguria/anuria, reduced pulses, signs of limb ischemia) correlating with imaging findings. Or laboratory findings suggestive of end-organ ischemia (lactic acidosis, elevated LFTs, elevated creatinine, rhabdomyolysis, electrolyte derangements) correlating with imaging findings.

Exclusion criteria consisted of subjects who had not been diagnosed with TAAD or acute on chronic aortic dissection.

4.4.2 Primary and Secondary Outcomes

The outcomes of the study were established to measure the impact of malperfusion syndrome on patient outcomes. The primary outcome was 30-day in-hospital mortality, which was defined as death occurring within 30 days of hospital admission after the primary emergency proximal aorta surgery. Secondary outcomes included length of stay, acute kidney injury, ischemic bowel, new neurological deficit, and ischemic extremities.

Length of stay was defined as the number of days the patient spent in the hospital after the initial surgical repair for TAAD till discharge. Acute kidney injury was defined as the need for temporary or permanent dialysis after surgery. Mesenteric malperfusion was diagnosed by colonoscopy or radiological imaging with symptoms before or after surgery. New neurological deficit was defined as a new focal or global neurological deficit, such as stroke, confirmed by imaging and clinical examination. Limb malperfusion were defined as evidence of limb ischemia in imaging and clinical symptoms such as coolness, pallor, decreased capillary refill, or decreased pulses before surgery, or requiring surgical or endovascular intervention after surgery.

These outcomes were chosen to evaluate the impact of malperfusion syndrome on various organ systems and to measure the severity of the syndrome. The results of the study were used to identify potential interventions to improve patient outcomes and reduce mortality rates in TAAD patients with malperfusion syndrome.

4.4.3 Statistical analysis

Descriptive statistics were used to summarize the data in the study. Normally distributed continuous variables were reported as mean ± standard deviation (SD), while non-normally distributed variables were reported as median (interquartile range (IQR)). The Kolmogorov-Smirnov test was used to assess skewness and normality of the data. To determine differences between groups, the t-test was used for continuous variables, while the Chi-squared test was used for discrete variables. A p-value of less than 0.05 was considered statistically significant.

The statistical analysis was performed using the SPSS Version 29.0 software package.

4.5 Results

4.5.1 Patients Demographic and Clinical Characteristics

A total of 235 patients who underwent surgical repair for TAAD were included during the study period from December 1999 to December 2021. The mean age at presentation was 63 years ± 13.6, and 66% of them were male. The most common cardiovascular risk factor was hypertension (68%), followed by dyslipidemia (28%) and diabetes (9%). Six patients in this study had a previous history of chronic kidney disease (3%) and permanent dialysis (1%). A family history of aortic disease was found in 3% of the patients, and 5 patients (2%) had connective tissue disorder. Twenty-seven patients (11%) had a history of previous cardiac surgery. Upon initial presentation, 13 patients (6%) were intubated, 15 patients (6%) had circulatory arrest before arriving in the operating room, and 11 patients (5%) required infusion of hemodynamic medications for support (Table 4-1)

Table 4-1: Demographic and Clinical Characteristics				
Group; mean ± SD or no. (%)				
Characteristics	**Total (n=235)**	**Non-MPS Group**	**MPS Group**	**p value**
		177 (75.3)	58 (24.7)	
Age, years	63 ± 13.6	63 ± 13	63 ± 15.3	0.75
Male	155 (66)	113	42	0.232
Hypertension	159 (68)	122	37	0.468
Dyslipidemia	66 (28)	54	12	0.149
Diabetes	20 (9)	15	5	0.972
Heart Failure	3 (1)	2	1	0.726
Coronary Artery Disease	23 (10)	17	6	0.869
Valvular Heart Disease	6(3)	5	1	0.645
Previous Cardiac Surgery	27 (11)	23	4	0.206
Peripheral Vascular Disease	4 (2)	3	1	0.988
Chronic Kidney Disease	6 (3)	3	3	0.145
Permanent Dialysis	2 (1)	2	0	0.416
Family History	8 (3)	7	1	0.416
Connective Tissue Disorder	5 (2)	4	1	0.806

Marfan Syndrome	3			
Loeys-Dietz Syndrome	1			
Ehler Danlos Syndrome	1			
Intubated	13 (6)	4	9	<.001
Pre-Op Pressors	11 (5)	5	6	0.019
Arrested (CPR)	15 (6)	2	13	<.001
LOS, days	16.3 ± 21	14.1± 14.5	23.2 ± 33.1	<.001
In-hospital 30-day mortality	32 (13.6)	11 (6.2%)	21 (36.2%)	<.001

Table 4-1: Demographic and clinical characteristics of patients with type A aortic dissection who presented with and without malperfusion.

4.5.2 Operative Details

Of the total study papulation (235), 143 patients (61%) required supra coronary graft to address the proximal aortic pathology, while 86 patients (37%) required a root procedure. Ascending aorta/Hemi arch replacement was carried out in 164 patients (70%), while total arch replacement was carried out in 62 patients (26%). Twenty-eight patients (12%) required concomitant procedures, mainly coronary bypass surgery. In terms of arterial cannulation strategy, the axillary or subclavian approach was the most common in 75.9% of the patients, followed by femoral artery cannulation in 19.7%, and ascending aorta cannulation in only 2.5%. For venous cannulation, central cannulation with right atrium was the majority at 96.5%. The average cardiopulmonary bypass time was 251 minutes ± 83, and the cross-clamp time was 150 minutes ± 67 (Table 2).

Table 4-2: Operative Details

Group; mean ± SD or no. (%)		Non-MPS Group	MPS Group	p value
Characteristics	Total (n=235)			
Supracoronary Graft	142 (61)	113	29	0.55
Root Procedure	86 (37)	59	27	0.70
Ascending Aorta/Hemiarch	164 (70)	127	37	0.25
Total Arch	62 (26)	43	19	0.204
Concomitant Procedure	28 (12)	19	9	0.329
Arterial cannulation				
Ascending Aorta	5 (2.5)	5	0	0.68
Axillary	154 (75.9)	120	34	
Femoral	40 (19.7)	26	14	
Others	4 (2)	1	3	
Venous Cannulation				
Right Atrium	191 (96.5)	146	45	0.15
Femoral	7 (3.5)	45	2	
Cardiopulmonary bypass time, min n=187	251 ± 83	243.2 ± 79.7	275.2 ± 88.7	0.149

Aortic cross-clamp time, min n=184	150 ± 67	144.7 ± 64.3	166.1 ± 73.5	0.079

Table 4-2: Operative details of patients with type A aortic dissection with and without malperfusion.

4.5.3 Preoperative CT Imaging Findings

The majority of the patients with TAAD had evidence of an intimal tear on preoperative CT scans or during examination of the aorta intraoperatively, mostly in zone 0 (78.7%), followed by zone 1 (14%) (Table 3). The proximal extension of TAAD was found to be in zone 0 in 94% of the patients, while the distal extent of the dissection varied, with 35.3% in zone 10, 18.3% in zone 1, and 10.2% localized to zone 0 (Figure 1). The intimal flap extension in preoperative CT imaging was evident to involve the innominate artery in 92 patients (39.1%), the left common carotid artery in 57 patients (24.3%), and the left subclavian artery in 42 patients (18.9%). The coronary arteries involvement was seen only in only seven patients. The celiac artery was involved in 40 patients (17%) and the superior mesenteric artery in 37 patients (15.7%). The left renal artery was involved more frequently than the right renal artery, in 64 patients and 14 patients, respectively (Table 4-4).

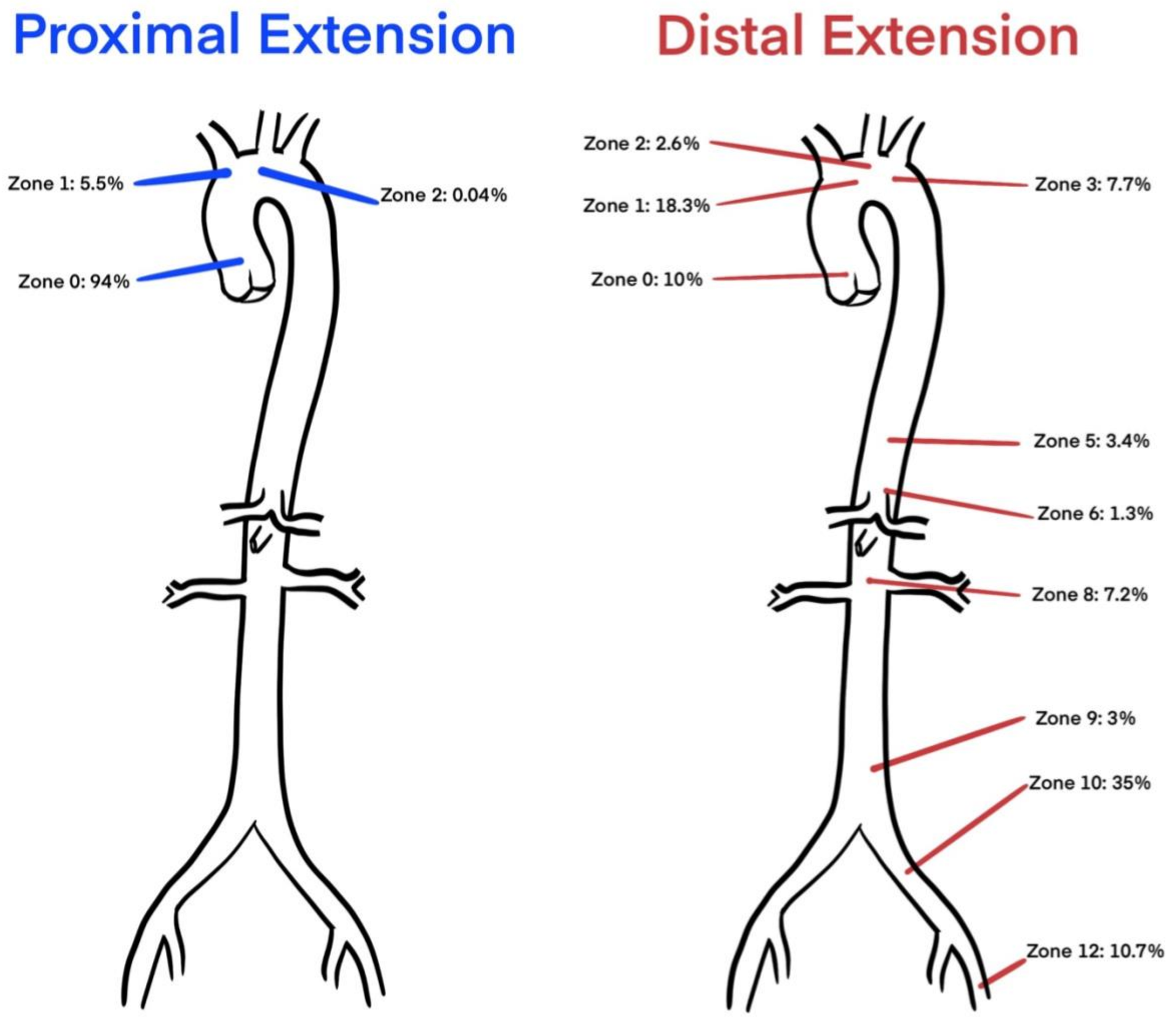

Figure 4-1: Proximal and distal extension the intimal flap of type A aortic dissection.

Table 4-3: Intimal Tear Location in Pre-Operative Imaging												
Total (n=235) no. (%)												
Z (0)	Z (1)	Z (2)	Z (3)	Z (4)	Z (5)	Z (6)	Z (7)	Z (8)	Z (9)	Z (10)	Z (11)	Z (12)
185 **(78.7)**	33 (14)	33 (14)	5 (2)	1 (0.04)	1 (0.04)	1 (0.04)	0 (0)	1 (0.04)	0 (0)	0 (0)	0 (0)	0 (0)
Z, Zone												

Table 4-3: Intimal tear location in pre-operative imaging of patients with type A aortic dissection.

Table 4-4: Extension of Dissected Intimal Flap to Aortic Branches	
	no. (%)
Rt coronary art	4 (1.7)
Lt coronary art	3 (1.3)
Innominate art	92 (39.1)
Lt common carotid art	57 (24.3)
Lt subclavian art	42 (17.9)
Celiac art	40 (17)
Sup mesenteric art	37 (15.7)
Rt renal art	14 (6)

Lt renal art	64 (27.2)
Rt common iliac art	6 (2.6)
Lt common iliac art	5 (2.1)
Rt external iliac art	6 (2.6)
Lt external iliac art	1 (0.04)
Rt femoral art	6 (2.6)
Lt femoral art	3 (1.3)

Table 4-4: Extension of dissected intimal flap to aortic branches of patients with type A aortic dissection

4.5.4 Malperfusion Syndrome

Evidence of malperfusion syndrome was found in 58 patients (24.7%) with TAAD during the study. MPS was present in 30 patients (12.8%) before surgery, including 13 patients with myocardial malperfusion and 15 patients with limb malperfusion. Four patients had mesenteric malperfusion, and three patients had cerebral malperfusion. Postoperatively, MPS were diagnosed in 42 patients. The majority was cerebral malperfusion with evidence of neurological deficit in 30 patients, followed by dialysis in 14 patients, limb malperfusion in four patients, and mesenteric malperfusion in six patients (Table 4-5).

Table 4-5: Pre and Post Operative Malperfusion Syndrome	no. (%)
Pre-Operative Malperfusion syndrome	30 (12.8)
Myocardial Malperfusion	13
Cerebral Malperfusion	3
Mesenteric Malperfusion	4
Limb Malperfusion	15
Post-Operative Malperfusion Syndrome	42 (17.9)
Dialysis	14
Ischemic bowel	6
Neurological deficit	30
Limb ischemia	4

Table 4-5: Pre and post operative malperfusion syndrome in patients with type A aortic dissection.

4.5.5 Mortality

The in-hospital 30-day mortality for all patients with TAAD was 13.6%. It was significantly higher in the malperfusion group at 36.2% compared to the no malperfusion group at 6.2% ($p < 0.001$). The mortality outcomes have improved over time. From December 1999 to December 2010, the mortality was 19.3%, and from December 2010 to December 2021, it was 11.8% but it is not statistically significant (Table 4-6).

Table 4-6: In Hospital 30-Day Mortality Comparison Between the First Half and Second Half of The Study Period			
	1999-2010 (n=57)	2011-2021 (n=178)	p value
In-hospital 30-day mortality	11 (19.3)	21 (11.8)	0.15

Table 4-6: In hospital 30-day mortality comparison between the first half and second half of the study period

4.6 Discussion

A retrospective review was conducted on 235 patients with TAAD who underwent surgical intervention from December 1999 to December 2021 at one institution, London Health Sciences Centre in London, ON, Canada. The traditional or surgery-first approach was applied to all these patients, regardless of the presence or absence of MPS. The mean age of patients with TAAD was 63 ± 13.6, and approximately two-thirds of them were male, which is similar to the reported data from major registries such as the International Registry of Acute Aortic Dissection (IRAD), the German Registry for Acute Aortic Dissection in Type A (GERAADA 2015), and the Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD)[4,5,12]. There were no significant differences between the malperfusion group and the non-malperfusion group regarding cardiovascular risk factors mentioned in Table 4-1. Thirteen patients (6%) with TAAD were intubated before surgery for various reasons, including loss of consciousness or hemodynamic instability. Furthermore, 11 patients required vasopressor medication support for resuscitation before surgery, and 15 patients required CPR for reasons mostly related to myocardial malperfusion. The last three factors were significantly different between the MPS group and the non-MPS group (Table 4-1). Patients with MPS needed to stay longer in the hospital after surgery compared to patients without MPS (Table 4-1).

From a surgical technique perspective, replacement of the intimal tear in the aorta with a supra-coronary graft was the most common technique, followed by the root procedure. Replacing the ascending aorta or hemiarch was performed more frequently than the total arch approach (70% vs. 26%). These findings are similar to the data from NORCAAD (91.9% vs. 5.9%) and GERAADA (84% vs. 16%)[4,11]. Similarly, axillary/subclavian approach was the most commonly used arterial cannulation strategy in this study, which is consistent with internationally reported data[4,5].

After reviewing the preoperative imaging of patients with TAAD, the majority of intimal tears were located within the ascending aorta (78.7%) and the proximal part of the arch (28%), which is similar to the data from GERAADA (75% and 15%, respectively)[4]. In the GERAADA data, only on third of the patients 37 % had an involvement of the supra-aortic arch vessels and similarly in this study, the dissection involved the innominate artery in 39.1% and left common carotid artery in 24.3% and left subclavian artery in 17.9%[4].

In this study preoperative MPS was found in 30 patients while 42 patients were diagnosed with MPS postoperatively. Thirteen patients presented with myocardial malperfusion. This group included all patients who presented with circulatory arrest due to either myocardial infraction or cardiac tamponade. Twenty-four patients required concomitant coronary surgery during the proximal aorta repair surgery. Five out of 13 patients died either intra operatively or after. The IRAD registry show that 10 to 15% of TAAD patients presented with myocardial malperfusion[15]. The GERAADA registry showed that pre-operative coronary malperfusion is a significant risk factor for mortality OR 1.61 (1.10–2.31)[4]. Also, the NORCAAD registry showed the same finding as early mortality predictor OR 2.366 (1.342-4.171)[11]. In this kind of malperfusion, surgery first approach can be the most reasonable option given the fact that the sooner the patient can get to the operating room and be stabilized, the better outcome.

Cerebral malperfusion was found in three patients preoperatively. All three patients survived after surgery, but each has a permanent neurological deficit. Interestingly, this data supports the IRAD group's advocacy for surgical intervention in patients with cerebrovascular accidents or comas, despite carrying a two- or three-fold higher mortality compared to patients without brain injury (CVA 40%; coma 60%; no brain injury 23%, $P<0.001$)[15]. The rationale behind this approach is that patients with conservative medical management alone have a mortality outcome of 100% for coma patients and 76.2% for CVA patients, while surgery has a 50% survival benefit over medical management (OR 0.058; $P<0.001$)[12]. Thirty patients in this study had a neurological deficit postoperatively.

Mesenteric malperfusion was diagnosed preoperatively in 4 patients. Half of them died (one intraoperatively and the other one died a few days later in the intensive care unit). Postoperatively, it was diagnosed in six patients, five of whom died - one intraoperatively and four who died days after. Only one patient who underwent surgical intervention for colectomy 8 days after surgery survived. This shows the challenging aspect of diagnosing mesenteric malperfusion and the timing of intervention. This data is supported by the IRAD data that showed, despite only 3.7% of patients with TAAD presenting with mesenteric malperfusion, the in-hospital mortality rate is 63.2% compared to 23.8% in patients without mesenteric malperfusion ($p<0.001$)[12]. Other reports showed a mortality rate of 70% to 100% in this group of TAAD patients[38].

The IRAD data revealed that mesenteric malperfusion is associated with high mortality rates[12]. However, the study found that surgical/hybrid therapy yielded better in-hospital mortality outcomes compared to initial endovascular and medical treatment, with mortality rates of 41.7%, 72.7%, and 95.2%, respectively ($p<0.001$)[12]. Despite these findings, the data indicated that surgeons were hesitant to perform upfront open surgery on these patients.

Renal malperfusion was defined in this study as the need of dialysis after surgery. Fourteen patients required dialysis post operatively and seven of them died after surgery (2 died more than 30 days after surgery). 2020, Kosaku et al. reported a statistically significant increase in operative mortality was observed in the group of patients with renal malperfusion compared to those without (12.5% vs. 3.8%; $P = 0.003$)[39]. Furthermore, renal malperfusion was identified as an independent predictor not only of acute kidney injury after surgery (odds ratio [OR] 4.32, 95% confidence interval [CI] 2.25-8.67; $p < 0.001$) but also of operative mortality (OR 3.08, 95% CI 1.02-8.86; $p < 0.046$)[39].

Interestingly, 15 patients presented in this study with limb malperfusion, and only four had persistent limb malperfusion post operatively. Two didn't need any surgical intervention, 1 needed a bypass surgery then died from mesenteric ischemia, and the last one required dialysis and had massive stroke. The NORCAAD data revealed that peripheral malperfusion is one of the 30-day mortality predictors OR 1.948 (1.262-3.007)[11].

The mortality outcome in this study is 13.6%, which is considered better than the average reported by major registries, including IRAD (18%), GERAADA (17%), and NORCAAD (17%)[4,5,12]. There was an improvement in mortality outcomes in the second half of the study period, from 19.3% to 11.8%. Multiple surgical techniques were used more frequently in the second half to improve distal perfusion, such as elephant trunk graft (2 vs 34) and uncovered stent (AMDS) (0 vs 18) respectively. Furthermore, there are recently more surgeons with additional training in aortic surgery involved in care of those patients. several experienced centers around the world have adopted different approaches not only to address malperfusion but also to early diagnose it. These approaches have resulted in significantly improved outcomes for patients with TAAD. Early recognition and treatment of malperfusion are critical in improving survival rates in these patients[6,7,50].

Mortality was significantly higher in the malperfusion group (36.2%) compared to the non-malperfusion group (6.2%, $p<0.001$), which is also supported by the major registries IRAD, GERAADA, and NORCAAD[3,4,11,12].

4.7 Conclusion:

This is a retrospective review of 235 patients with TAAD who underwent surgical intervention at London Health Sciences Centre in Canada between 1999 and 2021. The study found that patients with TAAD who had MPS had a higher mortality rate compared to those without MPS. Preoperative MPS was found in 30 patients, while 42 patients were diagnosed with MPS postoperatively. Myocardial malperfusion was the most common form of MPS, followed by cerebral malperfusion, mesenteric malperfusion, renal malperfusion, and limb malperfusion. The majority of intimal tears were located within the ascending aorta and the proximal part of the arch. The study also found that mortality rates improved in the second half of the study period due to the adoption of different approaches to address malperfusion and the involvement of more experienced and specialized surgeons in aortic surgery. The mortality rate was significantly higher in the malperfusion group (36.2%) than in the non-malperfusion group (6.2%, p<0.001). The findings of this study are consistent with those reported in major registries such as IRAD, GERAADA, and NORCAAD.

From the results of this study and the literature review, we appreciate the importance of MPS in patients with TAAD. Adopting innovative ways to address MPS have proven to improve outcomes. there is room to further improve the outcomes by not only addressing distal malperfusion but also with early diagnosis. It is essential to continue to explore new approaches to improve the diagnosis and management of MPS in patients with TAAD to further improve patient outcomes.

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Chapter 5: Intravascular Ultrasound Assessment of Malperfusion Syndrome in the Setting of Acute Type A Aortic Dissection (AAD-IVUS): A Pilot Study.

5.1 Introduction

Type A Aortic Dissection (TAAD) is a lethal condition that every cardiovascular surgeon will face at some point in their career. Although outcomes at our institution have been improving and are on par with, or better than, the existing International Registry of Acute Aortic Dissection (IRAD), the German Registry for Acute Aortic Dissection in Type A (GERAADA), and the Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD)[1–3]. There is still room to improve outcomes further by looking at other institutions with more advanced approaches to early diagnose and treat malperfusion syndrome (MPS)[4–6].

Intravascular Ultrasound (IVUS) has been used for real-time assessment of vascular anatomy in a variety of clinical settings for several decades. Since 1990s, IVUS has been used in patients undergoing endovascular aneurysm repair (EVAR)[7–9]. Also, it has been used to guide percutaneous coronary artery disease interventions[10].

In the setting of acute aortic dissection (AAD), IVUS can provide real-time data under physiologic conditions following open proximal repair to indicate the presence of distal re-entry tears, compression of the true lumen, and malperfusion to aortic branches. It can also be used intraoperatively to confirm resolution of malperfusion to the visceral segments and iliac arteries after proximal flow is reinstituted into the true lumen.

5.2 Study Objective

The objective of the AAD-IVUS study is to assess the safety and effectiveness of intraoperative IVUS for the immediate evaluation of malperfusion following emergent open repair of an TAAD.

5.3 Study Outcomes

5.3.1 Feasibility Endpoints

The feasibility endpoints for the study include three main aspects. Firstly, the ability to place an intravascular ultrasound (IVUS) catheter into the thoracoabdominal aorta during or immediately after an open TAAD repair in a hybrid operating room. Secondly, the ability to obtain and accurately interpret the status of the true lumen, false lumen, number and location of re-entry tears, and patency/status of branch vessels such as the mesenteric and renal arteries using the IVUS system. Finally, the study will track the percentage of cases where the surgical management or decision-making was influenced or altered due to the use of the IVUS system and document the reasons for any changes to the treatment plan.

5.3.2 Primary Safety Endpoint

The primary safety endpoint is a composite of all-cause in hospital mortality and major vascular complications related to using IVUS including bleeding, hematoma, pseudoaneurysm, or aortic rupture.

5.4 Ethics Approval

The Western University Health Sciences Research Ethics Board and Lawson Health Research Institute (R-22-356). The study protocol was shared with the public through ClinicalTrials.gov (NCT04907071).

5.5 Study Design and Sample Size.

The AAD-IVUS is a prospective, single-center pilot trial designed to evaluate the feasibility and safety intraoperative IVUS assessment during emergent TAAD repair to identify the presence or resolution of malperfusion. Up to 50 subjects will be enrolled at LHSC in London, Ontario, and all enrolled subjects are expected to be from Canada. The study cohorts for AAD-IVUS include the following:

A. **Malperfusion Cohort:**

A.1. Malperfusion Primary Cohort: This cohort consists of patients who present to the hospital with TAAD and meet the preoperative criteria for MPS, which includes two components. The first component is imaging findings that indicate reduced blood flow to the celiac trunk, superior mesenteric artery, renal arteries, or iliac arteries. The second component is either evidence of clinical stigmata of end-organ ischemia (e.g., abdominal pain, distended abdomen, oliguria/anuria, reduced pulses, or signs of limb ischemia), or evidence of laboratory findings that suggest end-organ ischemia (e.g., lactic acidosis, elevated liver function tests, elevated creatinine, rhabdomyolysis, or electrolyte abnormalities).

A.2. Malperfusion Secondary Cohort: This cohort consists of patients who develop new clinical signs or laboratory results indicating distal malperfusion after proximal repair of the TAAD is complete and proximal blood flow is redirected into the true lumen. The new clinical signs include loss of femoral pulses, distended abdomen, reduced urine output, and dusky extremities. The new laboratory signs include rising lactate (>50% above baseline), rising creatinine, metabolic acidosis, and rising LFTs.

B. No Malperfusion Cohort:

Patients presenting with TAAD with no evidence of malperfusion syndrome preoperatively and postoperatively.

The study design is summarized below in Figure 5.1.

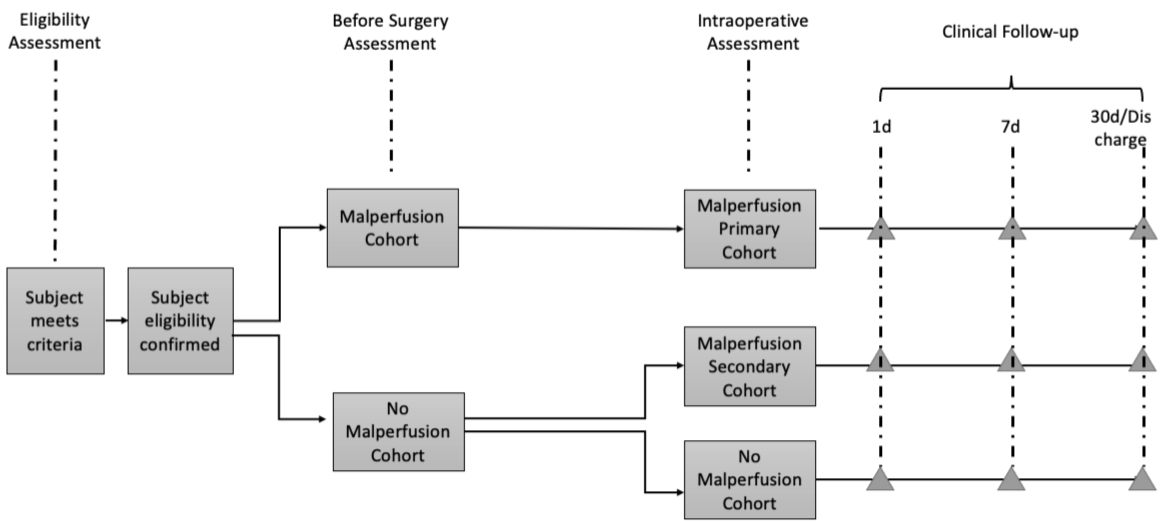

Figure 5-1: AAD-IVUS study design summery.

5.5.1 Inclusion And Exclusion Criteria

The study includes patients with a diagnosis of TAAD or acute on chronic aortic dissection who meet the following criteria for malperfusion syndrome: imaging findings indicating reduced flow to certain arteries and clinical or laboratory evidence of end organ ischemia correlating with the imaging findings. Additionally, patients who develop malperfusion syndrome due to dynamic flow changes after surgical repair of TAAD, as indicated by new clinical signs or laboratory results, are also included. Patients without evidence of malperfusion syndrome before or after surgical repair of TAAD are also included. Patients who do not have a diagnosis of TAAD or acute on chronic aortic dissection, are not hemodynamically stable for IVUS evaluation, have anatomy or pre-existing conditions that preclude safe use of IVUS evaluation, have a pre-existing condition that may explain evidence of malperfusion, or have a language barrier with no translator available during informed consent are excluded from the study.

5.5.2 Statistical Analysis

This study is a pilot prospective study. Descriptive analysis will be used to analyze the results. Normally distributed continuous variables will be reported as mean ± standard deviation (SD), while non-normally distributed variables will be reported as median (interquartile range (IQR)). The Kolmogorov-Smirnov test will be used to assess skewness and normality of the data. To determine differences between groups, the t-test will be used for continuous variables, while the Chi-squared test will be used for discrete variables. A p-value of less than 0.05 will be considered statistically significant.

5.5.3 Intervention Tool

The investigational 0.035 PV IVUS catheter (Volcano Therapeutics, Rancho Cordova, CA) is an over-the-wire catheter-based ultrasound with an 8.2-French profile at the transducer end and a 7.0-French shaft diameter. This catheter is run through a 9-French sheath placed under surface ultrasound guidance in the common femoral artery. The working length of this catheter is 90 cm, with the ability to image a diameter up to 60 mm.

5.5.4 Informed Consent

Prior to conducting any intraoperative assessments that are not part of the standard preparation and evaluation for emergent TAAD repair, informed consent must be obtained from either the potential subject or their substitute decision maker. Once a patient is diagnosed with acute aortic dissection and confirmed by the surgery team, the study team will be notified immediately. The principal investigator, co-investigators, or an authorized designee will then approach the patient or their substitute decision maker to obtain informed consent for the standard of care surgical repair. If time allows, the Investigator/designee will explain the nature and scope of the study, potential risks and benefits of participation, and answer any questions for the subject before obtaining written consent using the Research Ethics Board Approved Letter of Information and Consent. If emergency circumstances arise, the Investigator/designee will obtain verbal consent using the Research Ethics Board approved script, and a physical copy of the signed script will be kept in the subject's hospital chart. If during intraoperative assessments the subject is found to be ineligible for inclusion in the study, they will be notified postoperatively and receive appropriate treatment following standard of care. If the potential subject is unable to provide consent and no substitute decision maker is available, they will not be included in the study (Figure 5-2).

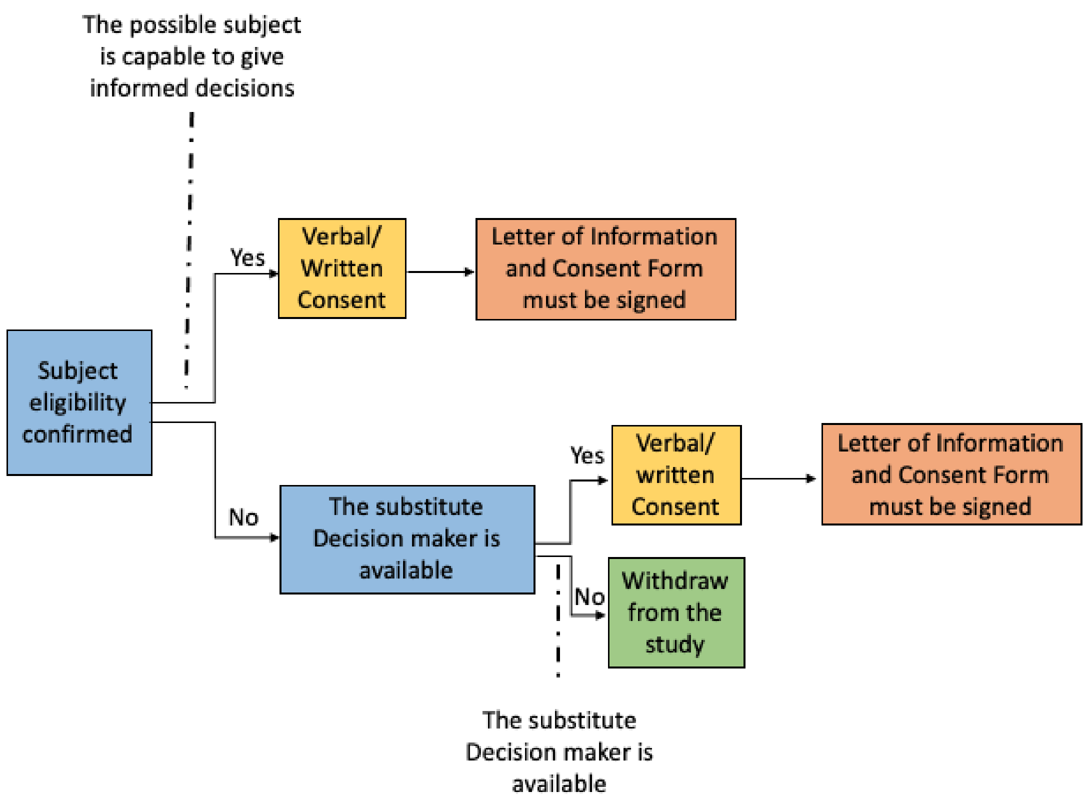

Figure 5-2: Algorithm for Informed Consent Process

5.6 Expected results:

This study is currently ongoing, having commenced patient enrollment in November 2022. Given that our center typically only sees around 10-15 cases of TAAD per year, patient recruitment for this study is expected to be challenging and may prolong the study period. However, we anticipate that our findings will demonstrate the safety and reproducibility of using IVUS. To ensure consistency, we will utilize the same standard of care femoral arterial access that usually used to monitor blood pressure to introduce the IVUS catheter. Additionally, we hope to promptly diagnose any malperfusion after standard of care emergent proximal aorta repair, allowing for the timely addressing of any potential MPS, or careful monitoring of the patient's condition post-surgery. And by doing that we expect a reduction in in mortality and morbidity outcomes.

5.7 Conclusion

The pilot AAD-IVUS pilot study is aimed at assessing the safety and feasibility of utilizing intraoperative IVUS assessment to detect malperfusion immediately after emergency open repair of a TAAD. The outcome of this trial is expected to yield significant insight into the application of IVUS in TAAD cases and potentially enhance outcomes for patients presenting with MPS. Once the trial proves successful and shows improved outcomes, we will consider expanding the study to more centers and conduct a larger clinical trial involving a larger study population. This larger trial would serve to confirm the potential benefits of IVUS in TAAD cases and could lead to its inclusion in clinical guidelines.

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Chapter 6: Thesis Summery

Chapter 2 of the thesis provides a comprehensive literature review on malperfusion syndrome (MPS) in the context of type A aortic dissection (TAAD). The study reviewed data from major registries such as the International Registry of Acute Aortic Dissection (IRAD), the German Registry for Acute Aortic Dissection in Type A (GERAADA), and the Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD)[1–3]. The mortality of type A aortic dissection ranges from 17% to 31%, and the mortality increases significantly in TAAD patients with MPS)[1–3]. The NORCAAD registry, reported a 30-day mortality of 28.9% in patients with preoperative malperfusion and 12.1% in those without preoperative malperfusion[3]. The GERAADA registry identified that there is a significant difference in mortality between patients with and without MPS, and the mortality worsens with the involvement of more malperfused organs (none - 12.6%, one system - 21.3%, two systems - 30.9%, three systems - 43.4%, $P < 0.001$)[1].

In this chapter we also highlighted the difference between dynamic and static malperfusion and how the traditional approach of addressing the proximal a word to intimal tear only addresses the dynamic malperfusion, leaving the distal static malperfusion unaddressed.

Specialized centers across the world are applying new approaches to manage TAAD patients with MPS. The University of Duisburg-Essen group manages TAAD patients with a concomitant/hybrid approach by using invasive diagnostic tests to diagnose any form of MPS and intervening with endovascular techniques concomitantly with the standard of care proximal aortic repair[4]. They reported in-hospital mortality for patients who underwent perioperative invasive diagnostics of 13% versus 24% in patients who had not[4]. Additionally, we reviewed the outcomes from the University of Michigan group, which took the delayed proximal aorta repair approach after addressing MPS with endovascular intervention and stabilizing the patients first[5]. They reported improved mortality outcomes from 21% to 10.7%[5].

In chapter 3, we conducted a national survey of cardiovascular surgeons in Canada to assess their understanding and approach towards MPS in the setting of TAAD. The survey showed that nearly half of the surgeons reported performing 20 to 30 cases per year in their respective centers, and a third reported performing 10 to 20 cases per year. However, most centers did not have a dedicated aortic dissection team. While these centers had access to hybrid operating rooms and intravascular ultrasound devices, the survey did not show evidence of their use to address or early detect MPS and TAAD. Most centers relied on transesophageal echocardiogram as an intraoperative imaging approach to detect MPS, which only monitors the proximal part of the aorta. In addition to the standard of care preoperative CT scan that only gives a static idea about a dynamic disease. The survey predicted that the same percentage of MPS presentations occur in TAAD patients as reported in from the previous discussed major registries, reflecting the awareness of this subgroup of patients. Furthermore, the survey predicted mortality rates of approximately 13% in TAAD patients and 30% in those with TAAD and MPS.

In Chapter 4, we reviewed our local mortality and morbidity outcomes in managing 235 TAAD patients with and without MPS from December 1999 until December 2021. The baseline characteristics are similar to the reported data from the major registries[1–3]. The preoperative CT scan showed an approximate extension of that intimal flap mostly to zone 0 in 94% of patients, and the majority of patients have a distal extension of the intimal flap down to zone 10 with 35%. MPS was found in 24.7% of patients with TAAD, 12.8% presented with MPS before surgery and 17.9% after. The 30-day in-hospital mortality of TAAD is 13.6%. Furthermore, in this study, the mortality of patients with malperfusion is 36.2%, and without malperfusion is 6.2% ($p < .001$), which is similar to the report from Geirsson et al. in 2007 with in-hospital mortality as high as 30.5% in patients presenting with any malperfusion compared to only 6.2 % in patients presenting without MPS[6]. Also similar to the data from the NORCAAD registry (28.9% vs. 12.1%)[7].

There is an improvement in overall mortality outcomes in our local data, the first half of the study compared to the second half, from 19.3% to 11.8%. This is a similar observation to the reported data by IRAD when they noticed an improvement in the mortality outcomes from 25% to 18%[2]. We believe the improvement in our mortality outcomes is because over the years, we started to implement different techniques to address distal malperfusion such as elephant trunk or uncovered stent implications. Furthermore, we have more experienced aortic surgeons that have been more involved in treating and operating on those patients. The improvement from the IRAD data was explained by recruiting centers adapting recently more approaches such as the hybrid approach or endovascular approaches[2].

In Chapter 5, after reviewing the current available literature, navigating through the new reported approaches of addressing MPS in patients with TAAD, and understanding the perception of cardiac surgeons across Canada about TAAD patient MPS and reviewing our own local data and outcomes, we concluded that early diagnosis of MPS will significantly reduce mortality outcomes. The challenge is to adapt an accessible and dynamic tool and study the feasibility and safety of that tool to detect MPS in TAAD patients. Having this dynamic tool to diagnose this dynamic disease will be helpful in reducing mortality.

Intravascular Ultrasound (IVUS) has been proven to improve outcomes and guide practice and management in different pathologies such as coronary artery disease and thoracoabdominal aneurysm[8–11]. The undergoing IVUS-AAD trial is a promising initiative that, after its success, can be expanded to involve a wider national collaboration to help recruit more patients and provide evidence of its benefit in guiding the management of MPS in the setting of TAAD. This can be part of the guideline and management protocol in the near future.

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Appendices

Appendix 1 The Canadian National Survey of chapter 3

Canadian National Survey of Cardiovascular Surgeons' Approach and Understanding of MPS in ATAAD

Q1 In your best estimate, what is the average number of Acute Type A Aortic Dissection cases per year at your center?

○ Less than 10 cases / Year (1)

○ 10 - 20 cases / Year (2)

○ 20- 30 cases / Year (3)

○ More than 30 cases / Year (4)

Q2 In your best estimate, what is the average number of Acute Type A Aortic Dissection cases per year at your center?

○ Less than 10 cases / Year (1)

○ 10 - 20 cases / Year (2)

○ 20- 30 cases / Year (3)

○ More than 30 cases / Year (4)

Q3 In you best estimate, what is the approximate 30 Day mortality of patients presenting with Type A Aortic Dissection at your center? (%)

____

Q4 In your best estimate, what is the percentage of Acute Type A Aortic Dissection cases per year which associated with Malperfusion Syndrome in your center? (%)

____

Q5 In your best estimate, what is the approximate 30 Day mortality of patients presenting with Type A Aortic Dissection and malperfusion syndrome? (%)

____

Q6 Does your center have a dedicated Aortic Dissection Team?

◯ No (1)

◯ Yes, please specify the involved teams: (2) ____

Q7 Do you have an access to Hybrid Operating Room at your center?

◯ No (1)

◯ Yes (2)

Q8 Do you have access to Intravascular Ultrasound assessment device **in your operating room?**

◯ No (1)

◯ Yes (2)

Q9 Do you have access to Intravascular Ultrasound assessment device **at your center?**

- ○ No (1)
- ○ Yes (2)

Q10 How would you diagnose Malperfusion Syndrome in the setting of Acute Type A aortic Dissection pre-operatively? (Choose all that apply)

- ☐ Clinical findings (ex. absent pulse, distended abdomen, decrease urine output, and neurological deficit) (1)
- ☐ Imaging (2)
- ☐ Bloodwork (ex. Serum Creatinine, Lactate, and liver enzymes) (3)
- ☐ Other (Please specify) (4) ____

Q11 If you chose pre-operative imaging, please specify: (Choose all that apply)

- ▢ Computed Tomography Scan (1)
- ▢ Ultrasound (2)
- ▢ Transesophageal echocardiogram (3)
- ▢ Transthoracic echocardiogram (4)
- ▢ Intravascular ultrasound assessment (5)
- ▢ Other (Please specify) (6) ____

Q12 Do you monitor patients with Acute Type A Aortic Dissection For Malperfusion Syndrome Intra-operatively ? (Choose all that apply)

- ▢ Clinical findings (ex. low urine output, new absent pulse, distended abdomen) (1)
- ▢ Bloodwork (ex. rising serum lactate, and serum creatinine) (2)
- ▢ Imaging (3)
- ▢ Other (Please specify) (4) ____

Q13 If you chose intra-operative imaging, please specify: (Choose all that apply)

▢ Computed Tomography Scan (1)

▢ Ultrasound (2)

▢ Transesophageal echocardiogram (3)

▢ Transthoracic echocardiogram (4)

▢ Intravascular ultrasound assessment (5)

▢ Other (Please specify) (6) ____

Q14 Do you monitor patients with Acute Type A Aortic Dissection For Malperfusion Syndrome Post-operatively ? (Choose all that apply)

▢ Clinical findings (ex. low urine output, new absent pulse, distended abdomen) (1)

▢ Bloodwork (ex. rising serum lactate, and serum creatinine) (2)

▢ Imaging (3)

▢ Other (Please specify) (4) ____

Q15 If you chose post-operative imaging, please specify: (Choose all that apply)

- ☐ Computed Tomography Scan (1)
- ☐ Ultrasound (2)
- ☐ Transesophageal echocardiogram (3)
- ☐ Transthoracic echocardiogram (4)
- ☐ Intravascular ultrasound assessment (5)
- ☐ Other (Please specify) (6) ____

Q16 What findings would prevent you from offering a surgical repair for Acute Type A Aortic Dissection? (Choose all that apply)

- ▢ Cerebral Malperfusion/Comtose Patient (1)
- ▢ Coronary Obstruction/STEMI (2)
- ▢ Mesenteric Ischemia (3)
- ▢ Renal Ischemia (4)
- ▢ Limb Ischemia (5)
- ▢ Shock/Hypotension/Aortic rupture (6)
- ▢ Nothing would prevent an emergent repair (7)
- ▢ Other (Please specify) (8) ____

Q17 In patients presenting with Acute Type A Aortic Dissection and confirmed mesenteric malperfusion syndrome (on Imagining and clinical findings/laboratory findings), When do you typically address the malperfusion?

- ☐ Prior the open proximal aortic repair. (1)
- ☐ Concomitantly with the open proximal aortic repair. (2)
- ☐ After the open proximal aortic repair. (3)
- ☐ Other (Please specify) (4) ____

Q18 In your best estimate, what is the percentage of patients with Acute Type A Aortic Dissection that complicated post-operatively with mesenteric ischemia ? (%)

____

Q19 In your best estimate, what percentage of patients with Acute Type A Aortic Dissection require new post-operative acute kidney injury or temporary dialysis ? (%)

____

Q20 In your best estimate, what percentage of patients with Acute Type A Aortic Dissection require new post-operative permanent dialysis? (%)

____

Q21 In your best estimate, what percentage of patients with Acute Type A Aortic Dissection have new post-operative Limb malperfusion that required fasciotomy / revascularization / amputation? (%)

____

Q22 Would you like to add any feedback or comments?

- ☐ No, thank you.
- ☐ Yes. ____

Appendix 2: Ethics approval for the Canadian National Survey of Cardiovascular Surgeons' Approach and Understanding of Malperfusion Syndrome in the Setting of Acute Type A Aortic Dissection

Western Research

Date: 14 April 2022

To: Matthew Valdis

Project ID: 119377

Study Title: Canadian National Survey of Cardiovascular Surgeons' Approach and Understanding of Malperfusion Syndrome in the Setting of Acute Type A Aortic Dissection.

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: 26/April/2022

Date Approval Issued: 14/Apr/2022 11:12

REB Approval Expiry Date: 14/Apr/2023

Dear Matthew Valdis

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 and mandated training must also be obtained prior to the conduct of the study**.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
MPS_ATAAD_National_Survey_V2_feb01_2022	Online Survey	01/Feb/2022	2
Study_Protocol_National_Survey_MPS_ATAAD_V4.0_April06_2022	Protocol	06/Apr/2022	4.0
First_Email_National_Survey_ V4.0_ April06_2022	Email Script	06/Apr/2022	4.0
Reminder_Email_National_Survey_ V4.0_ April06_2022	Email Script	06/Apr/2022	4.0
LOI_ National Survey_MPS_ATAAD_V4.0_April6_2022	Written Consent/Assent	06/Apr/2022	4.0

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,

Ms. Nicola Geoghegan-Morphet , Ethics Officer on behalf of Dr. Philip Jones, HSREB Chair

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

Appendix 3: Ethics approval for the Retrospective Mortality and Morbidity Analysis of Malperfusion Syndrome in the Setting of Type A Aortic Dissection

Date: 19 January 2022

To: Dr Matthew Valdis

Project ID: 118254

Study Title: Retrospective Mortality and Morbidity Analysis of Malperfusion Syndrome in the Setting of Acute Type A Aortic Dissection.

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: 08/February/2022

Date Approval Issued: 19/Jan/2022

REB Approval Expiry Date: 19/Jan/2023

Dear Dr Matthew Valdis

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 and mandated training must also be obtained prior to the conduct of the study**.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Retro_MMAAD_V3.0_december20_2021	Other Data Collection Instruments	20/Dec/2021	3.0
Retro_MMTAAD_T_V3.1_Jan10_2022	Protocol	10/Jan/2022	3.1
Retro_MMAAD_V3.1_Jan10_2022	Case Report Form	10/Jan/2022	3.1

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 Tri-Council 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,

Ms. Jhananiee Subendran, Ethics Coordinator on behalf of Dr. Philip Jones, HSREB Chair

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

Appendix 4:Ethics approval for Intravascular Ultrasound Assessment of Malperfusion Syndrome in the Setting of Acute Type A Aortic Dissection (AAD-IVUS): A Pilot Study

Western Research

Date: 18 February 2022

To: Dr Matthew Valdis

Project ID: 118233

Study Title: Intravascular Ultrasound Assessment of Malperfusion Syndrome in the Setting of Acute Aortic Dissection.

Application Type: HSREB Initial Application

Review Type: Full Board

Meeting Date: 21/Sept/2021; 11/Jan/2022

Date Approval Issued: 18/Feb/2022

REB Approval Expiry Date: 18/Feb/2023

Dear Dr Matthew Valdis

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 and mandated training must also be obtained prior to the conduct of the study**.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
AAD_IVUS_Master list_V1.0_December16_2021	Case Report Form	16/Dec/2021	1.0
AADIVUS_Study_Form_V2.0_ Feb01_2022	Case Report Form	01/Feb/2022	2.0
AAD_IVUS_DATA_V2.0_Feb01_2022	Case Report Form	01/Feb/2022	2.0
Study_Protocol_AADIVUS_V4.0_ Feb01_2022	Protocol	01/Feb/2022	4.0
Letter_of_Information_AADIVUS_ V5.0_Feb12_2022	Written Consent/Assent	12/Feb/2022	5.0
Verbal_Consent_AADIVUS_V3.0_Feb12_2022	Written Consent/Assent	12/Feb/2022	3.0

Documents Acknowledged:

Document Name	Document Type	Document Date
Philips IIVUS Agreement_University Hospital_Valdis	Study budget	13/Dec/2021

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,

Karen Gopaul , Ethics Officer on behalf of Dr. Philip Jones, HSREB Chair

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

Curriculum Vitae

Karama Bayamin. MBBS

Education and Training

Institution	Description	Start—End
Western University	Cardiac Surgery Residency	2018-2024 (Expected)
Western University	MSc in Surgery	2020-2023 (Expected)
University of Science and Technology-Yemen	Bachelor of Medicine and Bachelor of Surgery (MBBS)	2007-2015

Related Experience

Title	Dept./ Supervisor	Description	Start—End
Clinico-Patholgical Characteristics of Female Breast Cancer in Sanaa, Yemen.	Community Medicine / University of Science and Technology – Yemen	A descriptive retrospective study was conducted on patients who were admitted to surgical departments in 3 main hospitals in Sana'a, Yemen, from January 2010 through mid-December 2013. The research was presented in Graduate Medical Student Research Conference in Faculty of Medicine, University of Science and Technology, Yemen, 2013	2012-2013

Related Publications

Bayamin K, Power A, Chu MWA, Dubois L, Valdis M. Malperfusion syndrome in acute type A aortic dissection: Thinking beyond the proximal repair. J Card Surg. 2022 Nov;37(11):3827-3834. doi: 10.1111/jocs.16872. Epub 2022 Aug 21. PMID: 35989530.