Cause of Death Following Surgery for Acute Type A Dissection

Evidence from the Canadian Thoracic Aortic Collaborative

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Abstract

Background: Surgery confers the best chance of survival following acute Type A dissection (ATAD), yet perioperative mortality remains high. Although perioperative risk factors for mortality have been described, information on the actual causes of death is sparse. In this study, we aimed to characterize the inciting events causing death during surgical repair of ATAD.

Methods: Nine centers participated in the study. We included all patients who died following surgical repair for ATAD between January 2007 and December 2013. An aortic surgeon at each site determined the primary cause of death from seven predetermined categories: cardiac, stroke, hemorrhage, other organ ischemia (peripheral, renal, or visceral), multiorgan failure, sepsis, or other causes. Additional characteristics and variables were analyzed to delineate potential modifiable factors for mortality.

Results: Of the 692 surgeries for ATAD, there were 123 deaths (17.8% mortality rate). Mean age at death was 66 years. Events contributing to death were: cardiac (25%), stroke (22%), hemorrhage (21%), multiorgan failure (12%), other organ ischemia (11%), sepsis (4%), and other causes (5%). Neurologic injury at presentation was a predictor of stroke as the inciting cause of death (p = 0.04). Peripheral, renal, or visceral ischemia at presentation was highly predictive of death due to these presenting ischemic conditions (p = 0.004). We found no associations between cardiogenic shock, tamponade, or cardiopulmonary bypass duration and cardiac death.

Conclusion: Operative mortality for ATAD remains high in Canada. Nearly 70% of deaths arise from cardiac failure, stroke, or hemorrhage. Therefore, novel surgical, hybrid, and endovascular strategies should target these three areas.

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Aorta • Aortic dissection • Outcomes

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Introduction

The diagnosis of an acute Type A dissection (ATAD) is associated with a high mortality rate, near 50% at 48 hours without surgical intervention [1]. Despite surgery being the best treatment option, rates of in-hospital mortality following surgical repair remain quite sobering. Recent data from the International Registry of Acute Aortic Dissection (IRAD) show a decrease in operative mortality from 31% to 22% over a 17-year time period [2]. The German Registry for Acute Aortic Dissection Type A (GERAADA) recently reported a 30-day mortality of 17% for surgically treated ATAD [3]. To improve upon these results, modifiable factors need to be sought out and defined. Although preoperative risk factors predicting operative mortality are well described for ATAD [4–6], the inciting cause of death is not well understood. Therefore, characterizing the cause of death may guide modifications in surgical approach to improve outcomes. This study aimed to characterize the cause of death following surgical repair of ATAD in the current era.

Materials and Methods

The Canadian Thoracic Aortic Collaborative (CTAC) is a group of cardiovascular clinicians across Canada with specific interest and expertise in the management of thoracic aortic disease. Nine Canadian cardiac surgery centers in the collaborative participated in this study. Institutional Review Board approval was obtained from each site. Patient informed consent was waived, as the cohort of interest was comprised solely of patients who were deceased. The primary outcome of interest was cause of death following surgical repair of ATAD. Patients were included if they were 18 years of age or older and died either in-hospital or within 30 days of having undergone surgical repair for ATAD between January 1, 2007 and December 31, 2013. Patients who were diagnosed with an ATAD but did not undergo surgery were excluded. Cause of death was classified into one of seven predetermined categories: cardiac failure, stroke, hemorrhage, other organ ischemia (peripheral, renal, or visceral), multiorgan failure, sepsis, and other causes. Definitions of the seven predetermined categories are listed in Table 1. A single attending cardiac surgeon from each site reviewed the data and determined the primary cause of death for each case. In instances in which multiple categories may have contributed to the final outcome, the surgeon selected the single inciting event

Table 1. Definitions of the seven predetermined categories of cause of death.

Category	Description
Cardiac failure	Patient was in cardiogenic shock, requiring inotropes and/or intra-aortic balloon pump support with ventricular dysfunction noted in the operating room. Patient showed difficulties weaning from cardiopulmonary bypass, documented perioperative myocardial infarction, or low cardiac output state postoperatively resulting in death.
Stroke	Patient was clinically comatose or suffered profound neurological injury in the postoperative period with computer tomographic or magnetic resonance imaging to support diagnosis.
Hemorrhage	Patient required massive blood transfusion in the face of active bleeding. Despite volume resuscitation efforts, unrecoverable hemodynamic instability persisted, leading to cardiogenic shock or multiorgan failure.
Other organ ischemia	Clinical and supportive laboratory data showed peripheral, renal, or visceral end organ dysfunction.
Multiorgan failure	Patient died of multi-organ failure, with no specific inciting event beyond multiorgan failure identified.
Sepsis	Patient showed clinical signs of septicemia leading to multiorgan failure despite maximal medical support, with blood, urine, or sputum cultures supporting unrelenting bacterial infection.
All other causes	Any death that did not fit into one of the six other categories.

felt most likely to be responsible for death.

Surgical strategies and perioperative management at the time of aortic repair (e.g., arterial and venous access, myocardial and cerebral protection, anesthetic and intensive care unit protocols) were at the discretion of the operative surgeon and perioperative team. The conventional strategy of immediate operative repair and aortic reconstruction, removing aortic tissue at the site of injury to restore true lumen blood flow as expeditiously as possible, was used in all cases. Alternative treatment algorithms, such as delaying surgery for preferential percutaneous fenestrations or selective branch vessel stenting in the presence of malperfusion syndromes, were not utilized in this cohort.

Baseline characteristics, clinical status on presentation to the hospital, intraoperative variables, and postoperative complications were retrospectively reviewed from datasets at each hospital. In cases of missing data or dataset discrepancies, individual patient charts were reviewed to ensure accuracy.

Descriptive statistics for continuous variables were expressed as mean ± standard deviation (SD) or median and range, as appropriate. Independent t-tests were used to evaluate differences in normally distributed continuous variables. For non-normally distributed continuous data, Wilcoxon Signed rank tests were used. Chi-square tests were used to assess the association between presenting clinical characteristics and a specific cause of death for categorical variables. When a cell count was less than five in a 2×2 table, Fisher's exact tests were used. Statistical significance was determined by a two-sided $p < 0.05$. Statistical analyses were performed with SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Baseline characteristics for the cohort are shown in Table 2. The mean age at death was 65.9 ± 12.8 years. Women accounted for 50% of the cohort.

Results

During the 7-year study period, 692 patients underwent surgical repair for ATAD at the nine participating institutions. There were 123 deaths, for a mortality rate of 17.8%. Datasets were compiled and charts reviewed for these 123 non-survivors.

The most common causes of death were cardiac

Table 2. Baseline patient characteristics (n = 123).

Characteristic	Mean ± SD or n (%)
Age (years)	65.9 ± 12.8
Female	62 (50)
Diabetes	2 (17)
Dyslipidemia	36 (29)
Hypertension	75 (61)
Peripheral vascular disease	11 (9)
Cerebrovascular accident	13 (11)
COPD	10 (8)
Renal insufficiency	11 (9)
Renal failure (requiring dialysis)	1 (1)*
Congestive heart failure	7 (6)
Known CAD (MI, PCI, or CABG)	25 (20)
Previous cardiac surgery	9 (7)

CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention; SD = standard deviation.
*Due to missing data, the denominator was 90 patients.

failure (31 patients, 25.2%), stroke (27 patients, 22.0%), and uncontrollable hemorrhage (26 patients, 21.1%). Less common causes of death were multi-organ failure (15 patients, 12.2%), other organ ischemia (13 patients, 10.6%), sepsis (5 patients, 4.1%), and other causes (6 patients, 4.9%) (Figure 1).

Clinical status at the time of presentation to the treating hospitals is described in Table 3. Almost half of the patients were taken to the operating room with an emergent or salvage status. One-third of patients were in cardiogenic shock, and 31% either had a focal neurologic injury or were in a coma.

Operative characteristics are shown in Table 4. Adjunct antegrade cerebral perfusion was used for one-third of patients, and retrograde cerebral perfusion was used for 18% of patients. For patients without adjunct cerebral perfusion, median cerebral ischemic time was 22 min (range, 2–100 min). The median lowest systemic temperature for the cohort was 19°C (range, 13–34°C). Median cardiopulmonary bypass time was 3 h and 12 min. Of the 121 patients with data available regarding site of arterial cannulation, the femoral artery was used in just over half of patients. Right axillary cannulation was used in 37% of patients, the distal arch in 3% of
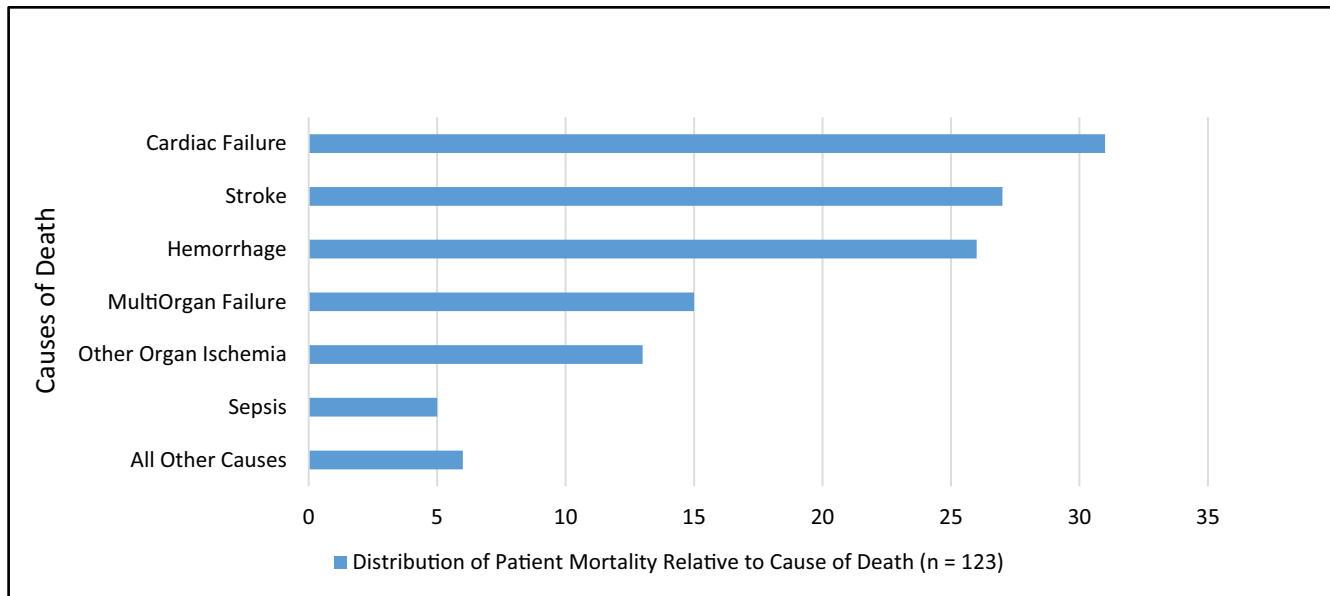
Figure 1. Distribution of patient mortality depending on cause of death during surgical repair for acute Type A dissection at nine surgical centers across Canada between 2007 and 2013.

Table 3. Clinical status on presentation to treatment hospital (n = 123).

Characteristic	n (%)
Neurological injury, focal	32 (26)
Neurological injury, coma	6 (5)
Limb ischemia	16 (13)
Visceral ischemia	8 (7)
Tamponade	33 (27)
Shock	41 (33)
Emergent salvage	59 (48)

patients, and alternative sites in 8% of patients. The extent of aortic replacement was conservative, with only 10% of patients receiving total arch replacement. Adjunct thoracic endovascular stent placement was used in only one patient.

Postoperative complications are shown in Table 5. Nearly half of the patients had some form of cardiac complication, although only 25% ultimately died from a cardiac cause. Nearly one-third of patients had a postoperative stroke, with 22% eventually succumbing to this cerebrovascular event. One-fifth of patients required re-exploration for bleeding or experienced multi-organ failure, and over 25% of patients experienced respiratory failure or renal failure requir-

ing dialysis.

We analyzed the relationship between cause of death and patients' preoperative clinical status and intraoperative surgical techniques. Patients presenting with focal neurologic injury or coma were more likely to have stroke as the inciting cause of death (34.3% vs. 17.2%, p = 0.04). Patients presenting with peripheral, renal, or visceral ischemia were more likely to have died from peripheral, renal, or visceral ischemia (28.6% vs. 6.9%, p = 0.004). There was a non-significant trend toward an association between peripheral, renal, or visceral ischemia at presentation and peripheral, renal, or visceral ischemia or multi-organ failure as the cause of death (38.1% vs. 19.8%, p = 0.07). Cardiac failure as the cause of death was not associated with a presenting status of tamponade (p = 0.37), cardiogenic shock (p = 0.33), or cardiopulmonary bypass time (p = 0.26).

We also analyzed potential associations between intraoperative protection strategies and stroke as the cause of death. No clear associations were identified. There was no association between circulatory arrest time and stroke as the cause of death. The median circulatory arrest time was 23.5 min (range, 1–65 min) for patients who died secondary to stroke and 25 min (range, 1–141 min) for patients who died from other causes (p = 0.93). Moreover, antegrade cerebral perfusion was

Table 4. Operative data.

Surgical Strategies, Operative Times, and Adjuncts	n	(%)	Denominator
Total arch replacement	12	9.8%	123
TEVAR or other stenting	1	0.8%	123
Cerebral perfusion			
Deep hypothermic circulatory arrest alone	57	49.1%	116
Retrograde cerebral perfusion	21	18.1%	116
Unilateral antegrade cerebral perfusion	32	27.6%	116
Bilateral antegrade cerebral perfusion	6	5.2%	116
Arterial cannulation site			
Femoral artery	62	51.2%	121
Right axillary artery	45	37.2%	121
Distal aortic arch	4	3.3%	121
Other	10	8.3%	121
Operative times			Mean ± SD
Lowest systemic temperature (°C)			20.4 ± 3.8
Cerebral ischemic time (min)			23.2 ± 16.0
Circulatory arrest time (min)			27.4 ± 23.0
Cardiac ischemic time (min)			101.9 ± 74.0
Cardiopulmonary bypass time (min)			227.2 ± 110.7
Intraoperative blood products and coagulopathy adjuncts			Mean ± SD
Packed red blood cells (units)			8.4 ± 7.5
Fresh frozen plasma (units)			11.1 ± 13.9
Platelets (units)			16.6 ± 33.2
Cryoprecipitate (units)			7.5 ± 11.4
Recombinant Factor VIIa (dose) (full dose 90 mcg/Kg)			0.8 ± 1.6

SD = standard deviation; TEVAR = thoracic endovascular aortic repair.

Table 5. Postoperative complications prior to death (n = 123).

Complication	n (%)
Cardiac complications	58 (47)
Respiratory failure	46 (37)
Stroke	37 (30)
Renal failure (requiring dialysis)	2 (26)
Gastrointestinal complications	30 (24)
Re-exploration for bleeding	25 (20)
Multiorgan failure	25 (20)
Sepsis	13 (11)
Paraplegia	9 (7)

not more protective against stroke as a cause of death compared to other cerebral management strategies. Of the 77 patients who received deep hypothermic circulatory arrest or retrograde cerebral perfusion as a cerebral management strategy, 26% (20/77) died of stroke, whereas of the 38 patients who received antegrade cerebral perfusion for cerebral protection, 18% (7/38) died of stroke (p = 0.36). There were no association between temperature and stroke as the cause of death (p = 0.54).

Discussion

In this study, we aimed to identify the inciting

events causing death during surgical repair of ATAD. With a more formal characterization of the cause of death in this patient population, operative variables and their associations with death may be better assessed. The 30-day mortality observed in this cohort was 17.8%. This mortality rate is consistent with those in larger worldwide registries such as IRAD (mortality = 20%) and GERAADA (mortality = 17%). These results highlight the high mortality associated with surgical repair of ATAD and the need for the international aortic community to improve upon this outcome. As cardiac failure, stroke, and uncontrollable bleeding were the primary causes of death in almost 70% of cases in the present series, focused efforts to improve management strategies specific to these three areas are likely to have the highest yield in improving outcomes.

Stroke is a frequent and major complication associated with ATAD [7]. In the present series, 26% of non-surviving patients presented with a focal neurological deficit, and 30% were diagnosed with a new postoperative stroke. Whether these strokes were due to embolic phenomena, dissection of the arch or distal intracranial vessels, or hypoperfusion at the time of surgery is not known. The impact of postoperative neurologic injury is significant, as 17% of deaths were due to new strokes not detected preoperatively, suggesting that they may be directly related to operative strategy or progression of the pathology. This study also highlights the variance in cerebral perfusion strategies employed across centers for surgical repair of ATAD, with 49% of non-survivors receiving deep hypothermic circulatory arrest as the lone protection strategy. Although data continue to accrue in support of antegrade cerebral perfusion for cerebral protection for all forms of aortic surgery [8–10], within this cohort of non-survivors, antegrade cerebral perfusion did not decrease the risk of death due to stroke. Choice of cerebral management strategy needs to be taken in context, as it may have more to do with the emergent status of the patients (48% of patients presented in an emergent or salvage state) than surgeon preference for or against adjunct cerebral management strategies. Extent of surgical repair may also be related to neurologic complications. Whereas the most common approach to repairing ATAD is conservative, as was the case in the present series, some data suggest that identification of resid-

ual dissection within the arch or head vessels warrants more aggressive total arch reconstruction at the time of surgery to decrease risk of stroke [11]. Such decisions need to be weighed against the physiologic reserve of the patient to withstand a more involved operation along with the comfort and expertise of the operative team.

Cannulation strategies were also variable, with arterial access achieved via the femoral artery in 51% of cases. Although antegrade perfusion is preferred when feasible, femoral access is an expedient option and often the preferred access point for hemodynamically unstable patients. Importantly, this study highlights two areas of significant variance, cerebral perfusion and cannulation strategies, where further refinements are within the hands of the operative surgeon and where modifications may yield disproportionate benefit.

With regard to cardiac failure, although general cardioprotective management strategies employ high potassium blood cardioplegia in conjunction with a degree of systemic cooling, the exact protocols utilized at each center were not captured in this study. The high proportion of death from cardiac failure may be reflective of prolonged periods of shock preoperatively. This should prompt the surgical team to carefully consider myocardial protection as a potential mode of death and ensure that the heart is well protected, that time for reperfusion is permitted, and that appropriate pharmacologic support is instituted.

Death from hemorrhage was another commonly identified inciting event. Uncontrolled hemorrhage may be due to the dissection process (e.g., aortic rupture, fragile tissues) but may also be secondary to a coagulopathic response [12, 13] or surgical mishap during the operation. Failure to resect a primary intimal tear in the arch or descending thoracic aorta may lead to hemorrhage. Similarly, failure to convert from retrograde perfusion with a cannula in the femoral artery to antegrade perfusion following distal aortic repair may lead to a pressurized false lumen and difficulty achieving hemostasis at the distal suture line. The actual cause of the uncontrollable bleeding was not captured in this study, and more detail regarding the location of and reasons for ongoing hemorrhage is beyond the scope of our dataset.

The impact of preoperative malperfusion on sur-

vival after surgical repair of ATAD is also highlighted by this study. Twenty percent of patients in this non-survivor series presented with limb or visceral ischemia. Although only 11% of patients were thought to subsequently die from peripheral, renal, or visceral ischemia, patients were four times more likely to die from malperfusion if they presented to the hospital with one of these malperfusing states. This is in line with a recent registry review reporting a significant increase in mortality, from 12.6% with no malperfusion at the time of surgery, up to 21.3% with one malperfused organ system, and up to 43.4% when three organ systems were affected [14]. Therefore, expeditious restitution of perfusion is absolutely paramount is such scenarios.

The timeframe from diagnosis to surgery also warrants discussion. Although treatment protocols call for immediate aortic reconstruction upon diagnosis, in the event that the diagnosis is identified at a smaller center without cardiac surgery services, time for transfer to a tertiary center could impact preoperative status and postoperative outcome. The Canadian health system is structured such that the vast majority of patients would have presented directly to a tertiary center, but for a small percentage of patients, transfer from smaller hospitals to more specialized centers would have been required. Many patients in this cohort presented in extremis conditions (33% were in shock at presentation). This could reasonably be attributed to the calamity of the aortic pathology, but the degree to which delayed intervention was also a contributing factor cannot be fully ascertained.

This study suggests that focused efforts to mitigate cardiac, cerebral, and bleeding complications may improve outcomes after surgical repair of ATAD. Patients presenting to the hospital in need of emergent life-saving aortic surgery bring forth unique challenges not encountered in elective scenarios. As the time delay from diagnosis to treatment is critical to survival, an organized algorithm of medical resuscitation, emergent investigations, and timely transfer to the operating room is necessary. The importance of timely transfer to the operating room negates the ability to modify preoperative risk factors prior to treatment. Therefore, quality initiatives to improve outcomes in the emergent setting need to focus on the betterment of intraoperative treatment strate-

gies in addition to early recognition and correction of operative or postoperative complications. These become the only truly modifiable factors when faced with an emergent condition such as ATAD. With this in mind, novel surgical practices, hybrid techniques, and incoming endovascular devices should either focus on cerebral or myocardial protection or facilitate a reduction in intraoperative blood loss in an effort to improve results.

With respect to novel surgical practices, the idea of dedicated aortic surgeons and a defined aortic team within the greater cardiac surgery division is likely a worthwhile endeavor. A dedicated aortic team facilitates repeated exposure and much-needed caseload experience to develop more mastery of the operation. In this sense, the surgeon, or more precisely the surgeon's experience, is the modifiable factor. Outcome data from cardiac centers committed to the aortic team philosophy demonstrate significant improvements to patient care with the implementation of such strategies [15–16]. Another surgical practice of likely benefit, as previously mentioned, is a more liberal use of total arch replacement in the face of cerebral malperfusion or a primary tear within the aortic arch [11]. Concerns about the potential increase in operative risk associated with this more aggressive approach could arguably be mitigated by greater expertise of the surgeon through an added caseload enabled by the aortic team concept.

Although not geared toward cerebral and myocardial protection, visceral malperfusion remains a lethal problem, and hybrid techniques to combat this issue with insertion of a frozen elephant trunk have shown early promise [17]. Alternatively, the delayed approach to surgery with initial endovascular interventions has also proved to be a useful strategy in the face of visceral malperfusion [18]. Each of these approaches has merit in select cases. Efforts to disseminate and more routinely implement such techniques should be promoted.

Building upon these techniques and projecting forward with this technology, it is conceivable that future technological advances in this area may spawn smaller devices for carotid artery deployment for cerebral protection. Such concepts and other "outside the box" research endeavors are needed if we are to make a sincere push toward improving outcomes of ATAD. This is an unchartered area in which future re-

search and development may have high yield.

Our study has some limitations. This is a retrospective review of 123 non-survivors from a larger cohort of 692 patients who underwent surgical repair of ATAD. This study focused on events that had significant impact on death, yet it did not capture similar events that may have occurred in the 569 surviving patients. Although a complete dataset on the total cohort of 692 patients would have been ideal, this was logistically unattainable. Recognizing this major limitation, due to the unique non-modifiable emergent status of ATAD patients, non-survivor data does, in and of itself, convey important information for the aortic team to discuss. Although it is possible that some findings within the non-survivor cohort would not hold true if assessed across the greater cohort, this does not lessen the importance of these findings to the surgeon and aortic team. As non-survivor cohorts highlight extremis conditions, they provide opportunities to develop strategies that mitigate such extremes. Moreover, because the data were captured retrospectively, they possess the inherent limitations of retrospective data. As it is possible that surgeons misclassified the cause of death, every effort was made to minimize such misclassifications by performing chart reviews in cases of discrepancy. Finally, this is a descriptive study with post-hoc analyses, and all observed associations should be considered exploratory.

Conclusion

Operative mortality following surgery for ATAD in the contemporary era remains high. Cardiac failure, postoperative stroke, and hemorrhage were the cause of death in nearly 70% of cases. In an effort to improve outcomes, emerging surgical, hybrid, and endovascular strategies should target these three areas.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

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