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IMPACT OF AORTIC ROOT AND ARCH MANAGEMENT ON LONG-TERM POSTOPERATIVE OUTCOMES FOR TYPE A AORTIC DISSECTION

by

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Degree to be awarded: Executive M.P.H.

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YANHUA WANG

Executive M.P.H., Emory University, 2023

Thesis Committee Chair: Jose N. Binongo, Ph.D.

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ABSTRACT

Objectives: Acute type A aortic dissection (ATAAD) is a life-threatening illness with fatal complications. It is considered a medical emergency that requires surgery. The reoperation rate and post-surgery mortality remain high. The purpose of this retrospective cohort study is to compare the long-term survival of patients who received different aortic operations at the root and arch.

Methods: Data were drawn from the medical records of patients with ATAAD from 2004 to 2019 at Emory University School of Medicine Department of Surgery. A total number of 529 ATAAD patients aged 20-86 who underwent root replacement, total arch replacement, hemiarch replacement, or valve resuspension were selected. Kaplan-Meier curves were plotted to describe graphically the survival experience of patients who underwent each surgical procedure. Univariable and multivariable Cox proportional hazards regression models were constructed to assess the statistical significance of the type of surgical procedure and also to identify the risk factors for long-term mortality. Multiple imputation was used to handle incomplete data, which were assumed to be missing at random.

Results: The mean age (± standard deviation) of patients was 55.4 ± 13.5 years, and the majority of patients were male (71.5%). The overall five-year and ten-year survival probabilities were 79.1% and 59.1%, respectively. Five-year and ten-year survival comparing root replacement versus valve resuspension were 77% vs 81%, and 60% vs 59%, respectively. Five-year and ten-year survival comparing total arch replacement versus hemiarch replacement were 70% vs 81%, and 59% vs 59%, respectively. In the univariable analysis, advanced age, large thoracic aortic maximum diameter, renal failure, aortic valve replacement, and respiratory failure were associated with an increased risk of death. In the multivariable analysis, advanced age, being female, large thoracic aortic maximum diameter, and a longer stay in hospitals were associated with a higher risk of death. Adjusting for age, thoracic aortic maximum diameter (42 mm), and length of stay in hospitals (9 days), the hazard ratio was not statistically significant: 1.03 (95% CI: 0.57-1.77) for root replacement vs valve resuspension, 1.50 (95% CI: 0.65-3.07) for total arch replacement vs hemiarch replacement.

Conclusion: When comparing root replacement to valve resuspension, and total arch replacement to hemiarch replacement, there was not a significant difference in long-term survival. When adjusting for age, thoracic aortic maximum diameter, and length of stay in hospitals, root replacement and total arch replacement were not significantly different in hazards when compared to valve resuspension and hemiarch replacement, respectively. In the multivariable analysis, advanced age, being female, larger thoracic aortic maximum diameter, and longer length of hospital stays significantly contributed to late mortality among ATAAD patients. In the univariable analysis, other predictors such as renal failure and aortic valve replacement were identified as additional risk factors.

Index Words: Acute type A aortic dissection Root replacement Total arch replacement

Hemiarch replacement Valve resuspension Long-term mortality Risk factors

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LIST OF ABBREVIATIONS

AAD	Acute aortic dissection
ATAAD	Acute type A aortic dissection
AVR	Aortic valve replacement
CI	Confidence Interval
CPB time	Cardiopulmonary bypass time
CT	Computed tomography
CVA	Cerebrovascular accident
FET	Frozen elephant trunk
MRI	Magnetic resonance imaging
OR	Odds ratio
PH	Proportional hazards
Post MI	Post myocardial infarction
TAAD	Type A aortic dissection
TBAD	Type B aortic dissection
Thoracic AMD	Thoracic aorta maximum diameter
TTE	Transthoracic echocardiography
VSRR	Valve sparing root replacement

Chapter I: Introduction

1.1 Problem Statement

Acute aortic dissection (AAD) is a serious condition in which a tear occurs in the intima (inner layer) of the aorta (the body's main artery). High-pressure blood rushes through the tear into the aortic wall and separates the intima and media. This separation is referred to as dissection. As blood continues to shear more of the intima off the media, a new lumen called the false lumen is created inside the aortic wall. Aortic dissection leads to an acute increase in the adventitia to adventitia diameter (aneurysm) of the aorta and may lead to aortic rupture (1) (Figure 1). When left untreated, about 33% of patients die within the first 24 hours, 50% die within 48 hours (2), and up to 90% of patients die within 30 days (3). Even with surgical treatment, in-hospital mortality is as high as 10-25% (4, 5). Therefore, acute aortic dissection is a medical emergency requiring immediate surgery which has a high mortality rate.

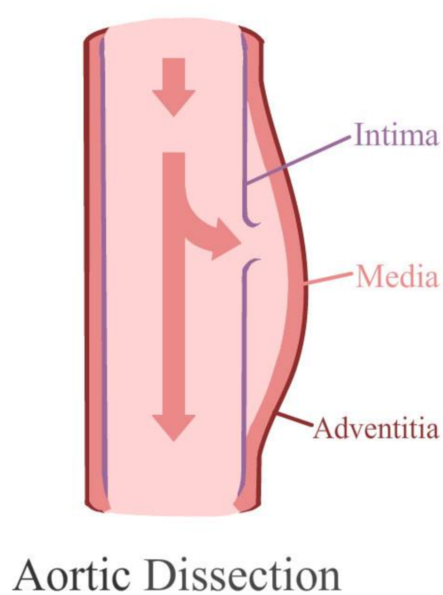


Figure 1: Schematic diagram showing aortic dissection (Drawn by Oliver Lee)

As the prevalence of aortic dissection risk factors such as uncontrolled hypertension, obesity, smoking, diabetes, and older age has been increasing in the United States, the aortic dissection mortality rate has almost uniformly increased among all demographic and regional groups by 2.5% from 2012 to 2019 (2). More than 13,000 people die from an aortic dissection each year. Using universal healthcare coverage data for Ontario, Canada, from 2003 to 2016, a total of $587.3 million has been spent on thoracic aortic dissection (6). Probably because aortic dissection has not gained sufficient public attention in the United States, no data have been collected on the healthcare utilization cost for the treatment of aortic dissection. But it is reasonable to assume that the treatment cost of the disease in this country is also high.

Because the mortality rate of aortic dissection is increasing, there is a need to provide optimized treatment plans to reduce reintervention rates and improve survival rates among patients with acute Type A aortic dissection (ATAAD) in the United States. For clinical purposes, aortic dissection is categorized into two types: Type A and Type B. Type A aortic dissection (TAAD) occurs in the first part of the aorta, closer to the heart than Type B aortic dissection (TBAD). As such, Type A is life-threatening and requires emergency surgery. TAAD carries higher mortality than TBAD; mortality rate increases by 1% to 2% per hour during the initial 48 hours (7). 75% of patients with undiagnosed ascending aortic dissection die in two weeks (8). In addition, TAAD contributes to 58–62% of all aortic dissections (9, 10) and is more common than Type B. Despite the improvement in diagnosis, medical management and surgical treatment, the hospital mortality of patients with ATAAD remains high and how this condition is treated varies from hospital to hospital. The optimal surgical approach is still unclear. For these reasons, it is important to formulate an evidence-based treatment plan for ATAAD. This pilot study aims to suggest an operative strategy that is best for patients with ATAAD.

1.2 Theoretical Framework

The survival of patients with aortic dissection is contingent on effectiveness of surgical intervention and identification of risk factors for postoperative mortality. Optimal surgical procedures result in low postoperative complications and high survival rates. Risk factors consist of demographic, social and medical factors. Evaluation of risk factors helps identify patients who are at a high risk of death after surgery. This study focuses on assessment of current surgical procedures and risk factors for mortality. The goal is to help provide guidance in designing a protocol that reduces mortality and complication rates.

1.3 Purpose Statement

To explore the optimal treatment plans for ATAAD, **this study was designed to compare the long-term survival probabilities among patients who received different initial aortic replacements at the root and arch for ATAAD at Emory hospitals between 2004 and 2019.** Arch management and root replacement/repair surgeries are standard treatments of ATAAD. However, large series of TAAD repairs in the literature have a 20-30% rate of reintervention, and overall long-term survival is poor. It is unknown whether a more aggressive approach at the initial operation (e.g. root/ascending/total arch replacement) would reduce reintervention on the distal aorta and improve long-term survival. In this study, we examined whether more aggressive approaches (total arch and root replacement/repair) at the initial operation increased long-term survival rate of patients with ATAAD. The null hypothesis was that there was no difference in survival probability among all procedures for the treatment of ATAAD.

1.4 Research Questions

This study aimed to address a number of research questions.

Objective I: Determine whether root replacement compared to valve resuspension was associated with increased survival probability of patients.

Objective II: Determine whether total arch replacement compared to hemiarch replacement was associated with increased survival probability of patients.

Objective III: Identify the preoperative variables that increased the risk of death among patients who underwent surgery.

Objective IV: Identify the intraoperative and postoperative variables associated with mortality.

1.5 Significance

Although ATAAD is uncommon, it is a highly lethal disease and can cause death within hours. The majority of patients die on the way to the emergency department. Estimates of hospital mortality ranges between 10% and 25% (4, 5). Therefore, identifying an optimal surgical procedure is beneficial for reducing the mortality associated with the disease. TAAD is closely related to other cardiovascular diseases such as hypertension and high blood cholesterol. Chronic hypertension has been reported as an important risk factor for aortic dissection (2). As the prevalence of hypertension and other cardiovascular diseases has increased over the past decades along with the increased diagnostic capacity to perform cross-sectional imaging of the aorta, aortic dissection is growing as a significant public health concern. Although there are surgical techniques available to treat this disorder, the optimal procedure for the treatment of

ATAAD remains controversial, and the worldwide mortality in high-volume centers remains around 18% (11). The high mortality rate and increasing TAAD prevalence highlight the significance of this study which aims to establish the optimal treatment for reducing the mortality of ATAAD. It is hoped that the study findings will suggest ways to improve patient health, save health resources, and advise medical education. Identification of risk factors in this study fills in the knowledge gap in public health practice and provides a direction for future intervention.

Chapter II: Review of the Literature

2.1 History

The study of aortic dissection was started by European anatomists in the sixteenth century. The Swiss surgeon, Maunoir, advanced the study by creating the term, dissection, in 1802. Dr. DeBakey and Dr. Morris made significant contributions to the understanding of the disease by performing the first successful surgical repairs of dissections in the descending aorta in 1955 and in the ascending aorta in 1963, respectively, which is considered a leap in the progress of treating aortic dissection. New technologies such as imaging techniques of echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) were introduced in the 1980s and significantly improve diagnosis of aortic dissection.

2.2 Classifications

Classifications of aortic dissection are evaluated from both temporal and anatomical perspectives. The temporal classification of aortic dissection is defined based on the time of symptom onset: acute and chronic dissections. Acute dissections are diagnosed when symptoms are present within the first two weeks. If symptoms lasted for more than two weeks, they are considered chronic dissections. The anatomical classification includes two systems: DeBakey and Stanford classifications (Figure 2). The Stanford classification is clinically useful for determining treatments. Under most conditions, type A dissections require urgent surgical operations, while type B dissections may be treated with medicines. In contrast, the DeBakey classification is anatomical and more informative in differentiating between proximal and distal aortic dissection for the long-term follow-up.

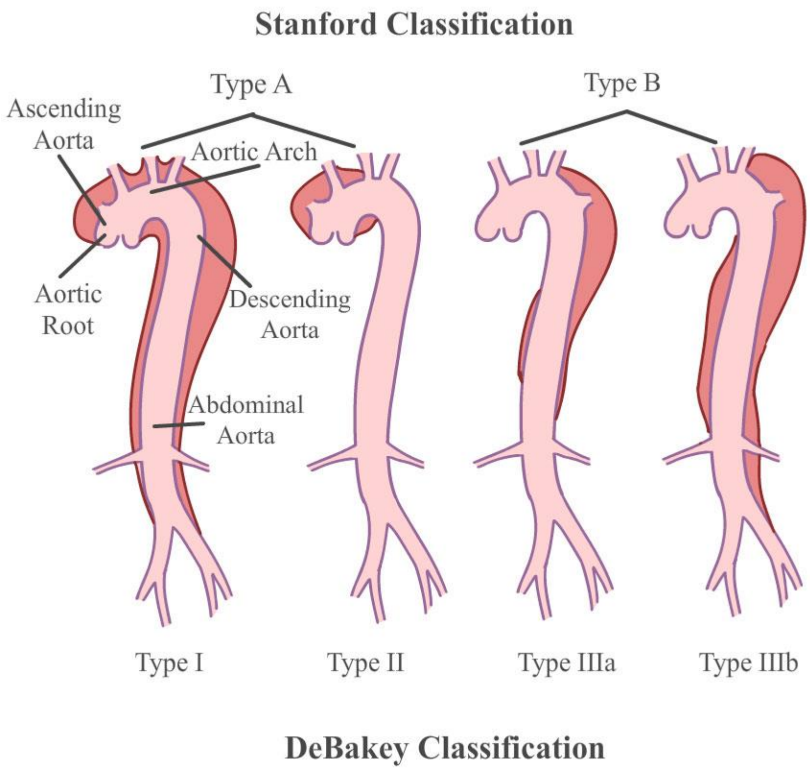


Figure 2: Classification of aortic dissection (pink: normal blood vessel; red: aortic dissection. Drawn by Oliver Lee)

The DeBakey classification comprises 3 types of dissection (8, 12). In Type I, the media dissects in the ascending aorta, aortic arch, descending aorta and may include the abdominal aorta. In contrast, Type II dissection happens exclusively in the ascending aorta. Type III dissections happen in the descending aorta at a distance from the left subclavian artery. Type III dissections are further categorized into IIIa and IIIb. Type IIIa dissections occur in the descending thoracic aorta mostly above the diaphragm and is at a distance from the left subclavian artery and close to the celiac artery. Type IIIb refers to dissections that originate the thoracic and abdominal aorta distal to the left subclavian artery and distal to the celiac artery and may extend below the diaphragm.

The Stanford classification divides dissections into two types: type A and type B. Type A (DeBakey types I and II) refers to any dissection that involves the ascending aorta, whether it involves the ascending aorta alone or both the ascending and descending thoracoabdominal aorta. This type of dissection usually involves the entire length of the aorta. Since the ascending aorta is close to the heart, this type of dissection is mostly acute and requires emergency open chest surgery to repair or replace the dissected segment of the aorta where the tear started. Type B (DeBakey types III) does not involve the ascending aorta. This type of tear begins farther down the aorta (descending aorta beyond the arch including the descending thoracic or thoracoabdominal aorta distal to the left subclavian artery), and farther from the heart. Whether an immediate surgery is required for fixing the dissection depends on exactly where the dissection happens and if it blocks blood flow to organs.

2.3 Epidemiology and Risk Factors

Aortic dissection is rare but can cause instant death, and its worldwide incidence is reported to be 5 to 30 cases per million people per year (13, 14). Type A accounts for two thirds of the cases and Type B contributes to one third of the cases. The incidence of acute dissection is 2-3.5 cases per 100,000 person-years, which is equivalent to 6000 to 10,000 cases annually in the United States (15). 40% of patients with aortic dissection die immediately before they reach an emergency department. Only 50% to 70% will be alive 5 years after surgery depending on age and underlying conditions (15). For untreated acute dissection of the ascending aorta the mortality rate is 1% to 2% per hour after onset. Even with surgical intervention, the mortality rate for type A dissection may be as high as 10% after 24 hours and nearly 20% 1 month after repair (15). Type B is less lethal than Type A. The 30-day mortality rate for an uncomplicated type B dissection is 10%. However, a complicated type B dissection has a 2-day mortality of

20%, which requires a prompt surgical intervention (15). The prevalence of aortic dissection appears to be increasing as noted by Nazir and colleagues (2), who found that the incidence of dissection among Americans has increased from 2012 to 2019 in a nationwide population-based analysis of death certificate data. The increase in prevalence may correlate with the increasing cardiovascular risk factors.

A variety of factors have been identified as increasing risk of aortic dissection. Such risk factors can be divided into two groups: those that contribute to medial degeneration of blood vessel walls such as Marfan syndrome and those that increase aortic wall stress such as hypertension. The risk factors include the following (8, 15, 16):

- **Hypertension**: 70% to 90% of patients with acute dissection have high blood pressure.
- **Aging**: Individuals aged 40-70 account for approximately 75% of dissections. In particular, age 50-65 is the peak period.
- **Atherosclerosis (hardened arteries)**: A hardening of arteries can weaken and cause tears within the intima layer.
- **Sex**: Males account for 65% of patients.
- **Physical Trauma (deceleration/torsional injury)**: The proximal descending aorta is commonly involved in blunt trauma and subjected to a tearing or shearing in sudden deceleration leading to a traumatic aortic dissection.
- **Congenital and inflammatory disorders**: Some inherited connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome, can also increase the risk for aortic dissection. Other associated congenital disorders include bicuspid aortic valve, Loeys-Dietz syndrome, aortic coarctation, Turner syndrome, and so on.

• **Pregnancy**: Pregnant women under age 40 tend to develop aortic dissection in the third trimester of pregnancy due to elevated cardiac output.

• **Iatrogenic**: Invasive procedures or surgeries on aorta and its branches such as cardiopulmonary bypass contribute to aortic dissection. These procedures may weaken the blood vessel wall since they are operated inside the aorta or cannulate its branches.

• **Unhealthy behaviors**: Aortic dissection can result from smoking, substance (cocaine) use, lack of exercise and a diet high in saturated fat.

• **Family history**: 11-19% of patients without a known genetic mutation have a first-degree relative with thoracic aortic disease.

2.4 Diagnosis and Surgical Treatment

Rapid diagnosis is necessary due to the potentially catastrophic complications of ATAAD such as aortic rupture, severe aortic insufficiency, coronary malperfusion, cardiac tamponade, and cerebrovascular accident. Aortic dissection must be considered if patients have chest pain, aortic regurgitation, neurological symptoms, or evidence of organ ischemia. The initial diagnostic approach is chest X-ray, which is not specific in diagnosis. Although lacking specificity, a chest radiograph detects abnormality in up to 90% of patients with aortic dissection (15). However, a negative radiograph must be confirmed by aortic imaging if patients are suspected to be at high risk for aortic dissection. Developments in highly accurate imaging technology including echocardiography, CT, and MRI improve diagnostic confirmation and treatment outcomes (17). CT has a sensitivity of 96% to 100% and a specificity of 96% to 100% (18, 19). MRI has both a sensitivity and specificity of 98% (19, 20). The sensitivity and specificity of transthoracic echocardiography (TTE) approaches 100% (21). However, each of these imaging technologies has limitations in diagnosis.   Patients with poor renal function or allergy to iodinated dye cannot be scanned by CT, and MRI can be used instead. MRI is too time-consuming and often unavailable. Compared to CT and MRI, TTE is a more powerful diagnostic tool and reveals more detailed information about the functional condition of the heart, valves and aortic root, but it provides poor visibility in the obese, in patients with chest deformities, and in patients on mechanical ventilation (21, 22). Surgeons decide the appropriate imaging approach depending on its availability in emergency situation as well as the experience of the staff. More than one imaging modality may be used to diagnose aortic dissection. Regardless, individuals with a suspected dissection should immediately request a diagnosis and surgical consultation. A delay in appropriate imaging detection increases mortality. For instance, a CT scan obtained within two hours yielded greater survival than MRI obtained after nine hours (23).

The best management for ATAAD is surgical therapy due to its being a medical emergency. The risk of death approaches 100% after a week without operating on a dissection of the ascending aorta. Surgical approaches excise dissected segments and reestablish blood flow in the true lumen of the aorta. The standard treatment of ATAAD involves emergent replacement of the dissected ascending aorta and a segment of the aortic arch using hypothermic circulatory arrest (24, 25). These surgical procedures replace the diseased aorta with artificial surgical grafts (Dacron graft). Management of the aortic arch consists of hemiarch or total arch replacement. Hemiarch replacement involves resection of the lesser curve of the arch from the base of the innominate artery to the level of the left subclavian artery while leaving the great vessels attached to the greater curve. Total arch replacement involves the replacement of the ascending aorta and entire aortic arch with reimplantation of the great vessels. Root replacement refers to the excision of the Sinus of Valsalva segments of the aorta, preservation or replacement of the aortic valve, and subsequent reattachment of the coronary arteries to the new aortic root graft. Valve resuspension preserves the patient' native valve while replacing the dissected aorta. The details of these surgical procedures are explained on the Emory Healthcare website (26).

Although surgical approaches reduce the lethal complications such as rupture/tamponade, myocardial ischemia, cardiac failure related to aortic regurgitation, end-organ malperfusion and ischemia, the mortality rate of ATAAD is still high and even worse in high-volume centers. The dissected segments of the aorta that are not replaced at the time of the initial surgery represent risk factors for aneurysmal degeneration and rupture. Indeed, large series of Type A dissection repairs in the literature have a 20-30% rate of reintervention, and overall long-term survival is poor. It is also unknown whether a more aggressive approach at the initial operation (e.g. root/ascending/total arch replacement) would reduce reintervention on the distal aorta and improve long-term survival. Without optimal treatments, the worldwide mortality of ATAAD in high-volume centers remains around 18% (11). The overall early mortality (30-day or in-hospital) in operated patients ranges from 5% to 24% (20-23). In addition, the mortality rates are not consistent among hospitals due to various treatment strategies used. The optimal surgical plan remains controversial. For instance, a meta-analysis shows that there is no difference in morbidity and mortality between hemiarch replacement and total arch replacement (27), whereas another meta-analysis shows that less aggressive ATAAD treatments are associated with lower early mortality but higher incidence of medium-long term aortic reoperation (28).

It is worth mentioning that every surgical choice involves a trade-off between risks and benefits. The average mortality, or risk of death, from repair of an aortic dissection is about 15% (29). Therefore, the risks involved in surgery are far lower than not operating for ATAAD. Many factors such as age and overall health status can also influence the effect of surgeries. It is common that complications, such as wound infection, stroke, kidney injury, bleeding, arrhythmias, occur after surgeries, which may also dampen the outcome of surgeries. The challenge confronting surgeons is that they need to adopt the appropriate management of the aorta based on patients' medical conditions and locations of dissection. Although expeditious surgeries improve outcomes and result in fewer complications, long-term follow-up monitoring is necessary for observing the development of complications or further dissections for patients with severe conditions.

In this study, the surgical procedures, aortic root replacement, arch management, and valve resuspension (preservation of native aortic valve) were evaluated based on the long-term survival probabilities. Next, the risk factors for the long-term mortality were identified using univariable and multivariable analyses. These findings add more to the current understanding of the treatment and prevention of ATAAD.

Chapter III: Methodology

3.1 Data Sources

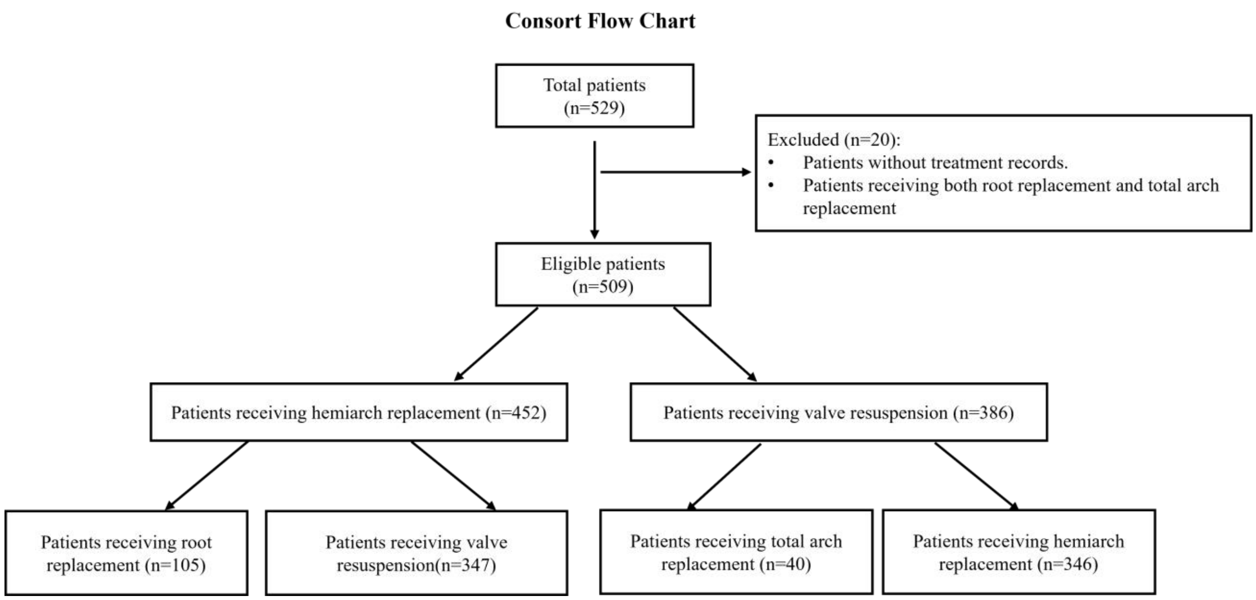
Data were drawn from the medical records on type A aortic dissection from 2004 to 2019 at Emory University School of Medicine Department of Surgery. The Institutional Review Board (IRB) at Emory University approved this retrospective study according to the Health Insurance Portability and Accountability Act regulations and the Declaration of Helsinki. The Institutional Review Board allowed for the use of data without individual patient consent.

3.2 Population and Sample

Aged 20-86, 529 patients with ATAAD were identified in the Society of Thoracic Surgeons database. The patients were treated with either root replacement, arch management, or valve resuspension for their Type A aortic dissection within Emory Healthcare–affiliated hospitals between 2004 and 2019. Two patients were excluded due to lack of treatment records.

3.3 Research Design

In this retrospective study, the survival probabilities of patients undergoing different surgical procedures (root replacement vs valve resuspension, and total arch replacement vs hemiarch replacement) were estimated to identify an optimal surgical strategy for type A aortic dissection. There were patients who received combinations of these surgical approaches. To address the research questions, the impact of root replacement on patient survival was compared to that of valve resuspension only among the hemiarch cohort (the hemiarch cohort contained the largest subcohorts of root replacement and valve resuspension) (Table 1). The influence of total arch replacement on patient survival was compared to that of hemiarch replacement only among the valve resuspension cohort which contained the largest subcohorts of total arch replacement and hemiarch replacement (Table 1). Patients receiving both root replacement and total arch replacement were excluded from the analysis. The association between the preoperative, intraoperative and postoperative variables and late mortality was also examined to determine the risk factors for late mortality.



3.4 Data Analysis

For each surgical procedure, groups were compared using preoperative, intraoperative and postoperative variables. Quantitative variables were summarized using mean ± standard deviation [or median (first quartile, third quartile), as appropriate]. Categorical variables were reported using frequency (percentage of the group). In the initial crude analyses, for continuous variables, two-sample t-tests were performed. For categorical variables, chi-square tests were conducted. Selected preoperative, intraoperative and postoperative variables were summarized in Tables 1-3. The Kaplan–Meier (KM) method was applied to estimate survival probabilities for each group and draw survival curves. To handle missing data, multiple imputation was used. The missing data were imputed 50 times, resulting in 50 imputed datasets for the subsequent univariable and multivariable analyses. The analysis results of the imputed datasets were combined to yield one set of hazard ratios.

Initially, single-predictor Cox regression (proportional hazards, PH) models were constructed to identify risk factors of late mortality (univariable analysis). Risk factors were also determined in the multivariable Cox PH model (multivariable analysis). Backward elimination was performed to remove variables that were not significant at the 0.05 level, one variable at a time, until all remaining predictors in the model were significant at the 0.05 level. All tests of hypotheses were two-sided and used a significance level of 0.05. All data analyses were performed using SAS 9.4 statistical software (SAS Institute Inc, Cary, NC).

Chapter IV: Results

4.1 Preoperative, intraoperative and postoperative characteristics

A total number of 529 patients were identified, of whom 128 patients were treated for aortic root replacement or repair, 60 patients were treated for total arch management, 467 patients were treated for hemiarch management, and 390 patients were treated for valve resuspension. Preoperative, intraoperative and postoperative patient variables are summarized in Tables 1-3, respectively. The mean ± standard deviation for age was 55.4 ± 13.4 years, and the majority of patients were male (71.5%). As for race, 52.8% were black and 44.8% were white. In regard to comorbidities, 94.4% of patients had hypertension; 8.1% of patients had congestive heart failure; 22.1% of patients presented with renal insufficiency; 5.2% of patients underwent hemodialysis; 12.8% of patients had diabetes; 11.7% of patients had stroke or cerebrovascular accident (CVA); 23.3% of patients developed malperfusion syndrome on admission of hospitals. For the maximum thoracic aorta diameter, the mean ± standard deviation was 44.5 ± 11.2 mm.

During surgery, the median (q_1-q_3) time when patients were placed on cardiopulmonary bypass (CPB), aortic crossclamp and circulatory arrest were 195 (157-255), 130 (96-192) and 36 (27-47) min, respectively. 23.7% of patients had prior aortic dissection surgeries. 10.6% of patients received the frozen elephant trunk treatment (FET) (Table 2).

Operative mortality was 14.6%. 19.0% of patients required reintervention. The post-surgery complications included CVA (10.5%), myocardial infarction (MI, 7.4%), pulmonary failure (11.8%), and renal failure (16.7%). The median length of stay in hospital was 9 days. Long-term mortality was 30.4% (Table 3).

Preoperative, intraoperative and postoperative variables were also compared between root replacement vs valve resuspension among the hemiarch cohort, and total arch replacement vs hemiarch replacement among the valve resuspension cohort (Table 1-3). Compared to valve resuspension (vrs) patients, patients with root replacement were younger [root mean ± standard deviation: 50.5 ± 13.5 years, vrs mean ± standard deviation: 56.7 ± 13.0 years, $p<0.001$], and had longer CPB time [root median (q_1-q_3): 254.0 (226.0, 298.0) minutes, vrs median (q_1-q_3): 170 (143.0, 199.0) minutes, $p<0.001$] and aortic crossclamp time [root median (q_1-q_3): 205 (172.0, 232.0) minutes, vrs median (q_1-q_3): 103 (86.0, 134.0) minutes, $p<0.001$]. Compared to patients receiving hemiarch replacement, more patients with total arch management underwent FET [total: 31.7%, hemi: 7.5%, $p<0.001$]. Patients with total arch treatment also experienced longer CPB time [total median (q_1-q_3): 253.0 (216.5, 289.5) minutes, hemi median (q_1-q_3): 170 (143.0, 199.0) minutes, $p<0.001$], aortic crossclamp time [total median (q_1-q_3): 157.5 (132.5, 196.5) minutes, hemi median (q_1-q_3): 103 (86.0, 134.0) minutes, $p<0.001$], and circulatory arrest time [total median (q_1-q_3): 54.5 (46.00, 80.0) minutes, hemi median (q_1-q_3): 34 (25.0, 44.0) minutes, $p<0.001$].

Table 1: Preoperative Characteristics.

Variable*	All (n=529)	Hemiarch Replacement (n=452)		*P*-value	Valve Resuspension (n=386)		*P*-value
		Root Replacement (n=105)	Valve Resuspension (n=347)		Total Arch Replacement (n=40)	Hemiarch Replacement (n=346)	
Age (years)	55.4 ± 13.4	50.5 ± 13.5	56.7 ± 13.0	**<0.001**	58.4 ± 12.9	56.6 ± 12.9	0.39
Sex (% Male)	377 (71.5%)	25 (23.8%)	105 (30.3%)	0.2	16 (39.0%)	104 (30.1%)	0.24
Race***				0.93			0.54
Black	218 (52.8%)	37 (50%)	140 (52.4%)		25 (61.0%)	139 (52.3%)	
White	185 (44.8%)	35 (47.3%)	120 (44.9%)		16 (39.0%)	120(45.1%)	
Other	10 (2.4%)	2 (2.7%)	7 (2.6%)		0 (0%)	7 (2.6%)	
Hypertension***	476 (94.4%)	93 (92.1%)	314 (95.7%)	0.15	38 (92.7%)	313 (95.7%)	0.42
Congestive heart failure***	10 (8.1%)	5 (16.7%)	5 (6.6%)	0.14	0 (0%)	5 (6.6%)	0.99
Renal insufficiency***	86 (22.1%)	20 (25%)	54 (20.6%)	0.40	7 (26.9%)	54 (20.7%)	0.46
Hemodialysis***	17 (5.2%)	3 (4.6%)	13 (5.9%)	0.99	0 (0.0%)	13 (5.9%)	0.62
Diabetes***	63 (12.8%)	12 (12.0%)	44 (13.6%)	0.68	5 (12.2%)	44 (13.7%)	0.80
Stroke/CVA***	57 (11.7%)	15 (15.3%)	36 (11.3%)	0.28	6 (14.6%)	35 (11.0%)	0.44
Malperfusion on admission**	123 (23.3%)	23 (21.9%)	75 (21.6%)	0.95	16 (39.0%)	75 (21.7%)	**0.01**
Thoracic maximum diameter (mm)***	44.5 ± 11.2	41.5 ± 9.0	45.1 ± 11.2	**0.03**	48.5 ± 14.3	45.1 ± 11.2	0.17

*Continuous variables are presented as mean ± standard deviation [or median (Q1, Q3)]. Categorical variables are summarized as frequency (%).
**Missing values are less than 5.
***Missing values are more than 10.

Table 2: Intraoperative Characteristics.

Variable*	All (n=529)	Hemiarch Replacement (n=452)		*P*-value	Valve Resuspension (n=386)		*P*-value
		Root Replacement (n=105)	Valve Resuspension (n=347)		Total Arch Replacement (n=40)	Hemiarch Replacement (n=346)	
Cardiopulmonary bypass (min)***	195.0 (157.0, 255.0)	254.0 (226.0, 298.0)	170.0 (143.0, 199.0)	**<0.001**	253.0 (216.5 289.5)	170.0 (143.0, 199.0)	**<0.001**
Aortic crossclamp (min)***	130.0 (96.0,192.0)	205.0 (172.0, 232.0)	103.0 (86.0,134.0)	**<0.001**	157.5 (132.5, 196.5)	103.0 (86.0, 134.0)	**<0.001**
Circulatory arrest (min)***	36.0 (27.0, 47.0)	35.0 (27.0, 43.0)	34.0 (25.0, 44.0)	0.75	54.5 (46.0, 80.0)	34.0 (25.0, 44.0)	**<0.001**
Reoperation	125 (23.7%)	19 (18.1%)	69 (19.9%)	0.68	6 (14.6%)	69 (19.9%)	0.42
FET**	56 (10.6%)	12 (11.4%)	26 (7.5%)	0.20	13 (31.7%)	26 (7.5%)	**<0.001**

*Continuous variables are presented as mean ± standard deviation [or median (Q1, Q3)]. Categorical variables are summarized as frequency (%).
**Missing values are less than 5.
***Missing values are more than 10.

Table 3: Postoperative Characteristics.

Variable*	All (n=529)	Hemiarch Replacement (n=452)		*P*-value	Valve Resuspension (n=386)		*P*-value
		Root Replacement (n=105)	Valve Resuspension (n=347)		Total Arch Replacement (n=40)	Hemiarch Replacement (n=346)	
Operative mortality	77 (14.6%)	11 (10.5%)	53 (15.3%)	0.22	10 (24.4%)	53 (15.3%)	0.14
Reintervention rate**	100 (19.0%)	19 (18.1%)	69 (19.9%)	0.68	6 (14.6%)	69 (20%)	0.41
CVA***	34 (10.5%)	8 (11.8%)	20 (9.4%)	0.57	2 (9.5%)	20 (9.4%)	0.99
MI***	24 (7.4%)	6 (8.8%)	15 (7.0%)	0.63	1 (4.8%)	15 (7.1%)	0.99
Pulmonary failure**	62 (11.8%)	17 (16.5%)	34 (9.8%)	0.06	8 (19.5%)	33 (9.5%)	0.06
Renal failure	88 (16.7%)	17 (16.2%)	54 (15.6%)	0.88	7 (17.1%)	54 (15.6%)	0.81
Length of stay***	9.0 (6.0, 15.0)	9.0 (6.0, 16.5)	9.0 (6.0, 15.0)	0.09	11.0 (6.0, 16.5)	9.0 (6.0, 15.0)	0.19
Late mortality	160 (30.4%)	36 (34.3%)	107 (30.8%)	0.51	11 (26.8%)	106 (30.6%)	0.62

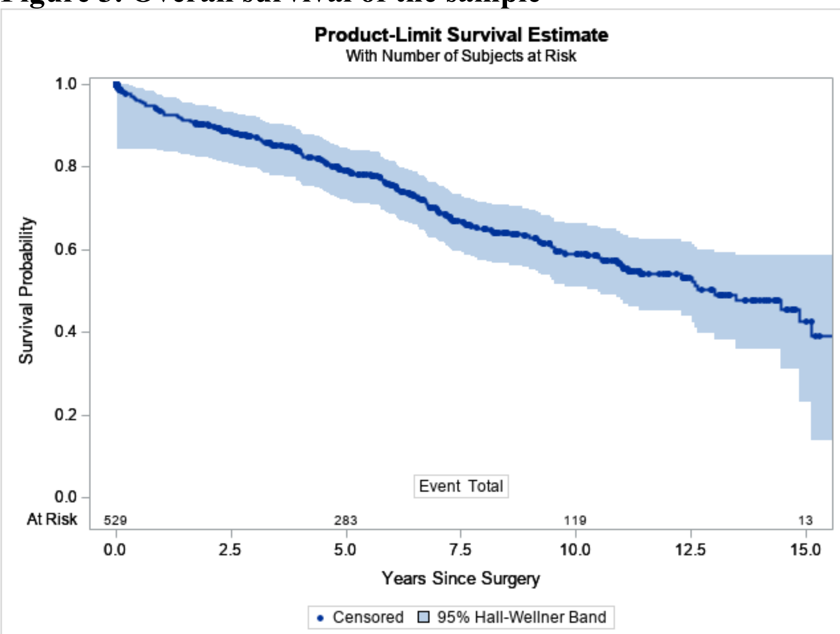
*Continuous variables are presented as mean ± standard deviation [or median (Q1, Q3)]. Categorical variables are summarized as frequency (%).
**Missing values are less than 5.
***Missing values are more than 10.

4.2 Long-Term Survival

4.2.1 Overall Survival of all patients

The overall survival was 79.1% at year 5, 59.1% at year 10, and 42.6% at year 15 (Figure 3 & Table 4). The median survival time was 13.0 years (95% CI: 11.0 – 15.0 years). 162 out of 529 patients in the cohort died. The median follow-up time was 5.6 years.

Figure 3. Overall survival of the sample



*The Kaplan-Meier method was used to estimate survival probabilities. 95% confidence bands are also provided in the figure.
● represents censored survival time.

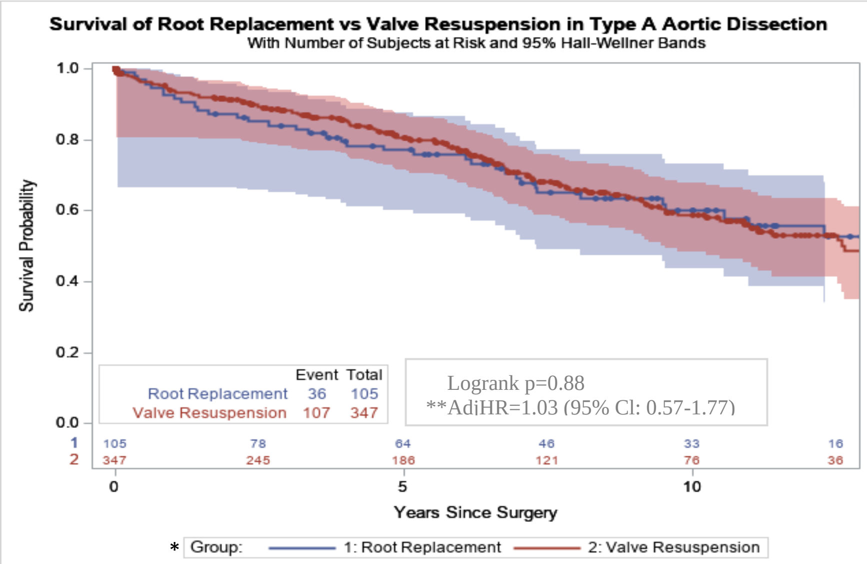
Table 4. Overall survival of the sample

Survival Probability (95% CI)			
Year 0	Year 5	Year 10	Year 15
1.00	0.79 (0.75-0.83)	0.59 (0.53-0.64)	0.43 (0.33-0.52)

4.2.2 Overall Survival of patients with root management

The impact of root replacement vs valve resuspension on patient survival was evaluated in the hemiarch cohort. The survival probability of hemiarch patients who also received root replacement was 77.0% at year 5, 60.0% at year 10, and 53.0% at year 15 (Figure 4 & Table 5). In contrast, the survival probability of hemiarch patients who also received valve resuspension was 81.0% at year 5, 59.0% at year 10, and 39.0% at year 15 (Figure 4 & Table 5). The median survival time for the root management group could not be determined since the survival curve did not reach 50%. The median survival time for the valve resuspension group was 12.7 years (95% CI: 10.5 – 15.1 years). 36 out of 105 patients died in the root management group. 107 out of 347 patients died in the valve resuspension group. For the root management group, the median follow-up time was 6.8 years; for the valve resuspension group, the median follow-up time was 5.7 years. The overall survival of patients with root management was not significantly different from that of patients with valve resuspension (p=0.88) (Figure 4).

Figure 4. Overall survival of patients with root management



***** Hemiarch patients with root repair/replacement were compared with hemiarch patients with valve resuspension. The Kaplan-Meier method was used to estimate survival probabilities. 95% confidence bands are also provided in the figure.
****** Hazard ratio of root vs valve resuspension adjusting for age (40 years), thoracic maximum aortic diameter (42 mm), and length of stay in hospitals (9 days).
● represents censored survival time.

Table 5. Survival of patients with root management

Treatment*	Survival Probability (95% CI)			
	Year 0	Year 5	Year 10	Year 15
Root Replacement	1.00	0.77 (0.67-0.84)	0.60 (0.48-0.70)	0.53 (0.39-0.64)
Valve Resuspension	1.00	0.81 (0.75-0.85)	0.59 (0.51-0.65)	0.39 (0.28-0.50)

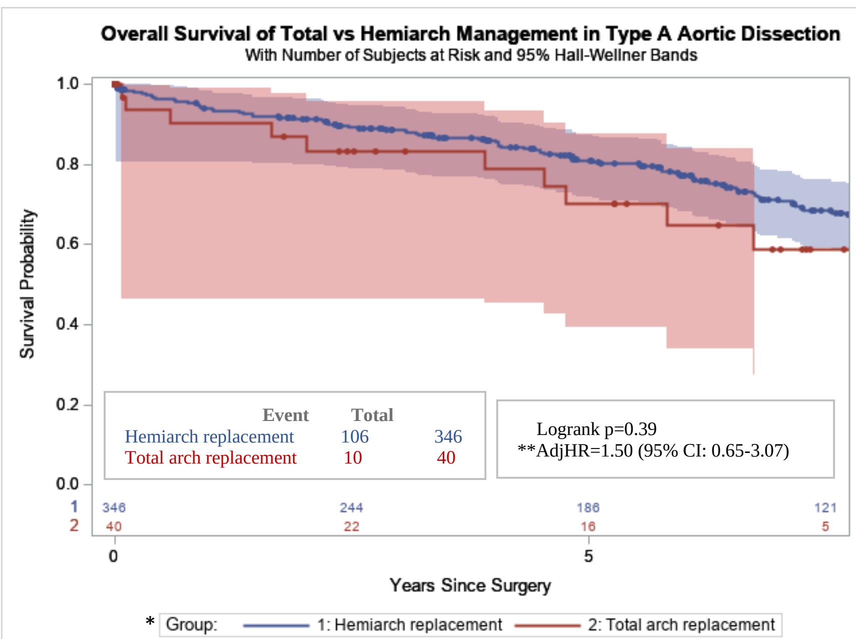
***** Root replacement group refers to hemiarch patients who also received root replacement. Valve resuspension group refers to hemiarch patients who also received valve resuspension.

4.2.3 Overall Survival of patients with arch management

The impact of total arch vs hemiarch replacement on patient survival was evaluated in the valve resuspension cohort. The survival probability of valve resuspension patients who also were treated with total arch replacement was 70.0% at year 5, 59.0% at year 10, and not estimable at year 15 (Figure 5 & Table 6). In comparison, the survival probability of valve resuspension patients who also were treated with hemiarch replacement was 81.0% at year 5, 59.0% at year

10, and 40% at year 15 (Figure 5 & Table 6). The median survival time for the total arch management group could not be determined since more than 50% of patients survived until the end of the study. The median survival time for the hemiarch group was 12.7 years (95% CI: 10.5 – 15.1 years). 10 out of 40 patients died in the total arch replacement group. 106 out of 346 patients died in the hemiarch replacement group. The median follow-up time was 2.9 years for the total arch group, and 5.7 years for the hemiarch group. The overall survival of patients who underwent total arch management was not significantly different from that of patients who underwent hemiarch management (p=0.39) (Figure 5).

Figure 5. Overall survival of patients with arch management



***** Valve resuspension patients with total arch replacement were compared with valve resuspension patients with hemiarch replacement. The Kaplan-Meier method was used to estimate survival probabilities. 95% confidence bands are also provided in the figure.
****** Hazard ratio of total vs hemi-arch replacement adjusting for age (40 years), thoracic maximum aortic diameter (42 mm), and length of stay in hospitals (9 days).
● represents censored survival time.

Table 6. Survival of patients with arch management

Treatment*	Survival Probability (95% CI)			
	Year 0	Year 5	Year 10	Year 15
Total Arch Replacement	1.00	0.70 (0.49-0.84)	0.59 (0.36-0.76)	-
Hemiarch Replacement	1.00	0.81 (0.76-0.85)	0.59 (0.52-0.66)	0.40 (0.29-0.50)

*****Total arch replacement group refers to valve resuspension patients who also received total arch replacement. Hemiarch replacement group refers to valve resuspension patients who also received hemiarch replacement.

4.3 Risk Factors for Long-Term Mortality

To determine risk factors for long-term mortality, hazard ratios (HRs) of predictors were calculated using, initially, univariable and, subsequently, multivariable analyses. Univariable analysis showed that malperfusion and valve-sparing root replacement (VSRR) had hazard ratios less than 1, suggesting that their presence is protective. On the other hand, older age, large thoracic aorta maximum diameter, renal failure, AVR, and respiratory failure had hazard ratios greater than 1, suggesting that they are risk factors for mortality (Table 7). In the multivariable analysis, older age, being female, large thoracic aorta maximum diameter, and longer surgery discharge (length of stay in hospitals) had hazard ratios greater than 1, suggesting that they are risk factors and malperfusion had a hazard ratio less than 1, suggesting it is a protective factor (Table 7).

Table 7. Risk factors for long-term mortality

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Age	**1.12 (1.05, 1.19)**	**<0.001**	**1.02 (1.00, 1.03)**	**0.01**
Female	1.39 (0.99, 1.92)	0.06	**1.47 (1.04, 2.07)**	**0.03**
Malperfusion	**0.55 (0.34, 0.89)**	**0.02**	**0.59 (0.36, 0.96)**	**0.03**
Thoracic AMD	**1.03 (1.01, 1.04)**	**<0.001**	**1.03 (1.01, 1.04)**	**<0.001**
Surgery Discharge	1.01 (1.00, 1.03)	0.06	**1.02 (1.00, 1.03)**	**0.03**
Reintervention	1.14 (0.81, 1.60)	0.46		
Race		0.47		
White vs. Black	1.06 (0.72, 1.55)			
Other Race vs. Black	0.48 (0.08, 1.55)			
Hypertension	0.94 (0.46, 1.91)	0.85		
Diabetes	0.67 (0.40, 1.12)	0.13		
Renal Insufficiency	0.85 (0.57, 1.26)	0.42		
Prior Heart Failure	1.70 (0.78, 3.68)	0.18		
Preop Hemodialysis	0.66 (0.30, 1.45)	0.30		
Postop Stroke (post CVA)	0.59 (0.31, 1.14)	0.11		
Post MI	0.43 (0.17, 1.10)	0.08		
Renal Failure (dialysis)	**1.50 (1.01, 2.22)**	**0.04**		
Preop Stroke/CVA	1.30 (0.84, 2.03)	0.25		
CPB Time	1.00 (1.00, 1.00)	0.34		
Crossclamp Time	1.00 (1.00, 1.00)	0.13		
Circulatory Arrest Time	1.00 (1.00, 1.00)	0.28		
Hemiarch	1.02 (0.59, 1.77)	0.95		
Valve Resuspension	1.05 (0.74, 1.49)	0.80		
Root	0.95 (0.66, 1.35)	0.79		
VSRR	**0.42 (0.22, 0.83)**	**0.01**		
AVR	**1.58 (1.04, 2.40)**	**0.03**		
FET	0.63 (0.28, 1.44)	0.27		
Respiratory Failure	**1.74 (1.13, 2.66)**	**0.01**		

Statistically significant results are shown in **boldface**. Hazard ratios were estimated using a Cox proportional harzard model. The values of hazard ratios and p values are rounded to the nearest hundredth. HR, hazard ratio; CI, confidence interval; Thoracic AMD, thoracic aorta maximum diameter; Post MI, post myocardial infarction; CPB Time, cardiopulmonary bypass time; VSRR, valve sparing root replacement; AVR, aortic valve replacement; FET, frozen elephant trunk; Surgery Discharge, length of stay in hospitals.

Chapter V: Discussion and Conclusion

ATAAD is one of the most challenging diseases that require immediate surgical treatment. Root replacement, arch management, and valve resuspension are among the most important surgical procedures for treating ATAAD. However, the post-surgery mortality of ATAAD remains high and differs by hospital due to concomitant complications. Appropriate surgical procedures are required to reduce both operative and long-term mortality. However, the optimal surgical approach remains unclear. To fill in this knowledge gap, this study compared the long-term outcome of ATAAD patients treated with one of the three aortic surgical approaches using KM curves, uni- and multivariable analyses in Cox PH models.

The data indicate that:

(1) median survival for root replacement was slightly higher than that of valve resuspension; however, the hazard was insignificant (p=0.88)

(2) total arch replacement was associated with a higher median survival time, but slightly decreased the long-term survival of patients compared to hemiarch replacement (p=0.39).

(3) Valve resuspension slightly increased patient survival within five years since surgery but decreased patient survival beyond five years. The difference in the impact of the three surgical approaches on the long-term survival was not statistically significant.

Aortic root management fixes dissection in the part of aorta attached to the heart. This approach either replaces the root of the aorta with a composite valve graft (aggressive root replacement) or repair the root of the aorta with a graft preserving the patient original aortic valve (valve-saving root replacement involving valve resuspension). Valve resuspension refers to preservation of normal native aortic valves while replacing the dissected aorta and arch. The advantages of valve resuspension over composite valve graft include reduced valve degeneration and valve-related complications, which is expected to avoid future reoperation. However, valve resuspension requires highly demanding expertise to succeed in an urgent situation. Whether aggressive root replacement results in better postoperative outcomes than more conservative valve resuspension is still unclear. There is evidence showing that aggressive root replacement improves the long-term clinical results (30-32) or at least maintains the same mortality as average (33). However, other studies show that valve resuspension yields a significantly higher survival probability than composite valve graft (34-36). Additional findings show that although valve resuspension improves valve competency, it does not change the long-term outcome (37, 38), and root repair involving valve resuspension increase the risk of reoperation (39).

In the current analysis, the effects of root replacement and valve resuspension on patient survival were evaluated among the hemiarch cohort, which excluded the confounding by arch management on root management and also maximize the sample size of root management. Our results showed that the median survival time for patients with valve resuspension was shorter than that for patients with root replacement. More than half of patients with root replacement were still alive at year 15. In comparison, half of patients receiving valve resuspension died at year 12.7. Patients with valve resuspension had a higher survival before year 5, and a lower survival after year 5 when compared to patients with valve replacement (Figure 4 & Table 5). However, the overall impact of root replacement on patient survival was not statistically different from that of valve resuspension. Compared to the average survival of the entire sample (Figure 3 & Table 4), root management was not associated with a higher mortality of patients throughout the entire study period. Our results seemed to support the conclusion that root replacement is not associated with higher patient mortality, and that valve resuspension is associated with higher survival probability earlier on but may increase mortality in the end.

Arch management comprises hemiarch replacement and total arch replacement. Total arch replacement is more aggressive than hemiarch replacement since it replaces the ascending aorta and entire aortic arch, which requires the reconnection of the great vessels (innominate, left carotid and left subclavian arteries) to the aortic arch graft. In contrast, hemiarch replaces the ascending aorta and the less curved portion of aortic arch, leaving the greater curved portion and the great vessels intact. Previous studies compare the advantages of the two approaches but a consensus regarding the optimal approach is not yet reached (40-43). A meta-analysis shows that there is no difference in mortality between hemi- and total-arch management (27). On the contrary, using a meta-analysis, Ma et al demonstrates that hemiarch replacement improves early survival, but increases late mortality compared to total arch replacement (44). The inconsistent conclusions may be due to non-randomized study designs and a lack of robust clinical data. Our results show that hemiarch replacement slightly promoted survival approximately within the initial 10 years since surgery compared to total arch replacement (Figure 5 & Table 6). We did not compare the survival beyond 10 years since the survival of the total arch replacement group after that time span cannot be estimated. Although the median survival time of patients with total arch replacement was longer than that of patients with hemiarch replacement, we cannot conclude that total arch replacement is more beneficial than hemiarch replacement since the number of patients in the total arch group was much smaller than that of patients in the hemiarch group (40 vs 346). The lack of events in addition to unbalanced sample sizes prevents us from making a more definitive conclusion.

Risk factors account for mortality and complications of ATAAD. Previous studies show that preoperative conditions such as hypertension (45), aging (45, 46), malperfusion syndrome (47, 48), massive blood transfusion (49, 50), surgical treatment such as CPB time (49, 50), and postoperative conditions such as renal failure (49, 50) contribute to the risk of mortality of ATAAD patients. We examined the hazard ratios of 21 preoperative, intraoperative, and postoperative variables in order to evaluate their influence on the long-term mortality. Our data showed that advanced age, large thoracic aorta maximum diameter, renal failure, aortic valve replacement, and respiratory failure were significantly associated with the mortality of ATAAD in the univariable analysis (Table 8), suggesting that they are risk factors for ATAAD. VSRR seemed to be protective against ATAAD. However, the sample size for VSRR was much smaller than that of the control patients (46 vs 481). Therefore, our data were not powerful enough to support the protective role of VSRR against ATAAD. Multivariable analysis identified advanced age, being female, large thoracic aorta maximum diameter, and long length of stay in hospitals as risk factors for mortality. Surprisingly, both uni- and multi-variable analyses showed that malperfusion syndrome reduced patient mortality, which contradicts findings from previous studies (47, 48) showing that malperfusion increases patient mortality. The reason that malperfusion did not contribute to higher risk of mortality is not well understood.

The adjusted hazard ratios of root replacement vs valve resuspension and total arch replacement vs hemiarch replacement were also calculated based on age (40 years), thoracic aorta maximum dimeter (45mm), and length of hospital stay (9 days). These three variables were selected since they are important risk factors for ATAAD. As age increases, the risk of ATAAD intensifies. Age 40 was selected since approximately 75% of dissections occur in patients aged 40-70 (8). Thoracic aorta maximum diameter is a critical indicator for diagnosing ATAAD.

Aortic aneurysms more than 40mm in diameter have a high chance of bursting. A diameter of 45mm was selected for adjusting hazard ratios since it was the mean aortic diameter of patients (Table 1). Generally, sicker patients have longer hospital stays. The mean length of stay in hospital (9 days) of patients was used to adjust hazard ratios. Our results showed that when adjusting for age, thoracic aorta maximum diameter, and length of hospital stay: 1) root replacement had a slightly higher hazard than valve resuspension (Figure 4); 2) total arch replacement showed a slightly higher hazard than hemiarch replacement (Figure 5); These findings suggest that aggressive surgical approaches including root replacement and total arch replacement do not lead to a significant higher mortality than conservative approaches such as hemiarch replacement and valve resuspension. Total arch replacement resulted in a relatively higher mortality compared to hemiarch replacement. Note that the sample size of total arch replacement was much smaller than that of hemiarch replacement (60 vs 467).

Our data suggest that patients including elders, females, those who have larger thoracic aorta adventitia-to-adventitia diameter, and those who stay at hospital for a longer time tend to have higher mortality. Males have a higher prevalence (71%, tables 1-3). Our findings verified that pre-, intra, and postoperative variables contribute to the risk of long-term mortality. In addition, our result showed that 94.4% of patients had hypertension, confirming that hypertension is a major risk factor for the prevalence of ATAAD. However, hypertension did not influence the long-term mortality rate in this cohort. Using this cohort, we cannot determine the role of hypertension in mortality since the control group (patients without hypertension) provided a much smaller sample size than the hypertension group. To ensure the accuracy of statistical analysis, the sample size of a control group should be greater than that of a treatment group.

This study was conducted based on a large sample size, yielding a more accurate evaluation on efficiency of the surgical procedures, and providing potential resources for improving technologies in treating ATAAD. Exhaustive risk factors were included and examined for their impact on the long-term mortality of ATAAD. However, it is worth mentioning that there are some limitations inherent in this study. This is a retrospective and single-center study. External validation requires the findings to be confirmed in other centers. This study had to use hospital controls who received multiple treatments since it is unethical to withhold patients from any treatments. It was not possible to assign patients to the treatments randomly. Surgeons decided the treatment plan based on patients' conditions. The non-randomized design might limit the efficacy in comparing the control and treatment groups. The dataset had a large number of missing values for some important factors, which limits the ability to evaluate their influence on mortality. Some subgroups possessed relatively small numbers of patients, which prevent certain important variables from being statistically significant in the uni- and multivariable analyses.

Although the current analyses do not yield a significant difference in efficacy of the four surgical procedures for ATAAD, this study highlights a trend favoring valve resuspension and hemiarch replacement. In addition to slightly higher survival within 10 follow-up years, patients with valve resuspension had shorter CPB time and aortic crossclamp time compared to patients with root replacement, and patients with hemiarch replacement had shorter CPB time and aortic crossclamp time compared to patients with total arch replacement (Table 2). More cases need to be collected to confirm the role of root replacement and total arch replacement on patient late mortality.

In conclusion, this study provides evidence that valve resuspension and hemiarch replacement are slightly more beneficial to the long-term survival of ATAAD patients. Our results assist in describing and summarizing the data of the different treatment strategies, but, unfortunately, these results fail to identify a particular surgical procedure as a primary approach. The appropriate approaches depend on patients' medical conditions and surgeon's experience. The current study has identified risk factors for long term mortality; it is hoped that the evidence provided in this thesis be taken into consideration in future investigations that aim to show the efficacy of interventions for ATAAD.

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