



## The Effect of Heparin Administration on In-Hospital Mortality in Patients with Aortic Dissection

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### Abstract

#### Objectives

Aortic Dissection (AD) and Acute Coronary Syndrome (ACS) have overlapping symptomatology that make differentiating them difficult. This sometimes results in patients with AD inadvertently receiving anticoagulation. The aim of this study was to determine if the administration of heparin to patients with AD increased in-hospital mortality.

#### Methods

A retrospective chart review of patients with AD admitted to a large academic hospital between 2010 and 2015 was performed. Patients with the diagnosis of type A AD or type B AD who were greater than or equal to 18 years were included. Exclusion criteria consisted of trauma, thrombolytic administration, and history of anticoagulant use. The in-hospital mortality of patients who received anticoagulation was compared to those who did not.

#### Results

A total of 131 patients were eligible for the study. 36 (27%) of the 131 patients received heparin; other comorbidities including Hypertension, Diabetes, and Hyperlipidemia were also studied. In-hospital mortality was found to be 9 times

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higher in patients with type A AD who received heparin compared to the non-heparin group. Patients with a diagnosis of type B AD who received heparin had a negative statistically non-significant correlation with mortality.

## Conclusion

Patients with type A AD who receive heparin are 9 times more likely to have in-hospital mortality than those who did not. This study advises a cautious utilization of anticoagulants in acute, undifferentiated chest pain in the emergency department. Such a finding is of great significance to our fellow emergency medicine physicians considering the similar manifestations of AD and ACS. Although, patients with type B AD who receive heparin showed lower in-hospital mortality compared with those who didn't receive Heparin, our data was not powerful enough to show a statistically significant outcome.

**Keywords:** Heparin; Aortic Dissection; Acute Aortic Syndrome; Anticoagulation; Acute Coronary Syndrome

## Introduction

Aortic Dissection (AD) is a potentially fatal aortic pathology classified according to the Stanford system into type A AD that involves the ascending aorta and possibly the descending aorta, and type B AD which only involves the descending aorta [1]. Type A AD are typically managed surgically, the mortality rate for type A AD managed surgically is around 22%, whereas in those managed medically, the mortality rate is 57%. Type B AD is typically managed medically, but in the last two decades, endovascular intervention has become an increasingly popular option [2]. Patients with type B AD who are managed medically have a mortality rate approaching 10%, whereas that undergoing endovascular repair is approximately 10.6%.

The classic presentation of AD involves ripping chest pain radiating into the back. More commonly in clinical practice the presentation is highly variable. The most common presenting symptom in type A AD is anterior chest pain, whereas abdominal pain and back pain were more common in type B AD [3]. Less common symptoms included syncope and stroke [3]. According to the Interna-

tional Registry of Acute Aortic Dissection (IRAD) database, 78.9% of patients with a Type A aortic dissection presented with chest pain [4]. Acute Coronary Syndrome (ACS) has a typical presentation of retrosternal pressure or heaviness radiating to the left arm, neck, or jaw. Atypical symptoms include stabbing chest pain, indigestion, syncope, diaphoresis, nausea, dyspnea, or pleuritic chest pain [5]. The overlap of symptomatology at presentation between ACS and AD makes clinical differentiation difficult. Furthermore, a study by Hagan et al in 2000 demonstrated that 42.6% of patients with a Type A aortic dissection and 42.8% of patients with a Type B aortic dissection demonstrated nonspecific ST-segment changes or T-wave changes on their electrocardiogram [3]. Such findings were also evident in a study in 2010 by Hirata et al where 49.7% of patients had electrocardiograms illustrating acute ST-segment changes [6]. Also, 8.2% of the patients had ST-segment elevation which could mimic ACS, specifically ST-elevated myocardial infarction (STEMI). The overlap of symptoms and Electrocardiography (ECG) patterns may result in patients with AD being treated as if they are experiencing ACS. The initial management of ACS includes consideration of administering anticoagulation to the patient, most commonly unfractionated heparin. This anticoagulant uses its cofactor, antithrombin III, to inhibit factor Xa, which will then inhibit the conversion of prothrombin to thrombin. Heparin also prevents further clot formation by inactivating thrombin and prevents the conversion of fibrinogen to fibrin. This mechanism is the basis of treatment behind the administration of heparin in ACS and STEMI. The efficacy of unfractionated heparin was examined in the 1990s and was reported in a meta-analysis by Oler et al, which showed heparin in addition to aspirin reduced myocardial infarction or death by 33% in patients with unstable angina [7]. Furthermore, the American Heart Association recommends unfractionated heparin in patients with a STEMI [8]. The decision to initiate heparin is often made in a timely fashion but can be limited by the potential for the patient presenting with symptoms concerning for ACS actually having AD. Heparin administration is often delayed until further workup can be done to rule out AD. This raises the question of do patients with AD have a higher mortality if they incidentally receive anticoagulation

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and should heparin administration be delayed in patients with suspected ACS until AD is ruled out?

To date, there has been sparse and conflicting evidence regarding the effects of anticoagulation on patients with aortic dissection. A retrospective study by Hansen et al in 2007 evaluated antithrombotic administration, including acetylsalicylic acid, clopidogrel, heparin, and fibrinolytic agents, in patients with misdiagnosis of ACS that actually had AD had a higher rate of major bleeding and mortality [9]. They found these patients had a higher primary endpoint of major bleeding and mortality combined if they received these agents but did not show an overall increase in mortality by itself [9]. However, a study by Pourafkari et al in 2016 found that patients who received anticoagulants did not have increased in-hospital mortality. However, they did find that patients who were inadvertently administered anticoagulants had a higher long-term mortality [10].

The early identification of AD necessitates judicious clinical assessment. However, similar presentations between AD and ACS can prove to be a diagnostic challenge due to the aforementioned reasons, leaving physicians in a potential dilemma about which treatment modality is best for acute undifferentiated chest pain. In this study we evaluate if heparin given to patients with AD increases their in-hospital mortality.

## Methods

This was a retrospective chart review of patients presenting to Charleston Area Medical Center (CAMC) between July 1, 2010 through July 1, 2015. All patients aged 18 and older with a diagnosis of AD were included in this study. Patients with trauma were excluded. The patients with the diagnosis of AD who met inclusion/exclusion criteria were divided into four cohorts based on the type of the dissection and Heparin administration during the same hospitalization. Group 1 is type B AD with no Heparin administration. Group 2 is type B AD that received Heparin during the same hospitalization. Group 3 is type A AD with no Heparin administration. Group 4 is type A AD that received Heparin during the same hospitalization. Group 1 was considered the reference category. The primary outcome measure was

In-hospital mortality. Additionally, age and comorbidities including hypertension, diabetes, and hyperlipidemia were evaluated. This study was approved by our Institutional Board Review.

## Data analysis

All analyses were performed using SPSS (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0 Armonk, NY: IBM Corp). Descriptive statistics are expressed in terms of frequencies, percentages, or means + one standard deviation (SD). Categorical variables were tested by chi-square or Fisher exact tests and continuous variables were tested by two-sample t-test or Mann-Whitney U where deemed appropriate. Multivariate backwards logistic regression model was used in a step-wise manner to identify the significant predictors of mortality. A 'p' value of 0.05 or less was considered significant.

## Results

133 patients were included in this retrospective study, 2 patients were excluded for incomplete data. 36 (27%) patients of the 131 received Heparin and 97 (74%) did not receive Heparin. Males accounted for 78 (59.5%) of the subjects and females were 53 (40.5%). 109 (83.2%) patients had hypertension which was the most common comorbidity; 59 (45%) patients had hyperlipidemia; and 19 (14.5%) patients had diabetes mellitus. Table (1).

Group 1 which is type B AD with no Heparin administration has 52 patients (39.6%). Group 2 is type B AD that received Heparin during the same hospitalization 27 (20.6%). Group 3 is type A AD with no Heparin administration 43 (32.8%). Group 4 is type A AD that received Heparin during the same hospitalization 9 (6.9%).

Patients in group 4 (type A AD and received Heparin) did show a statistically significant higher mortality Odds Ratio=9.0 (95% confidence interval, 1.81 to 44.85) ( $p=0.007$ ). Conversely, although patients in group 2 (Type B who were given Heparin) showed lower mortality but it was statistically not significant Odds Ratio=0.31 (95% confidence interval, 0.03 to 2.74) ( $p=0.290$ ). Table (2), Figure (1).

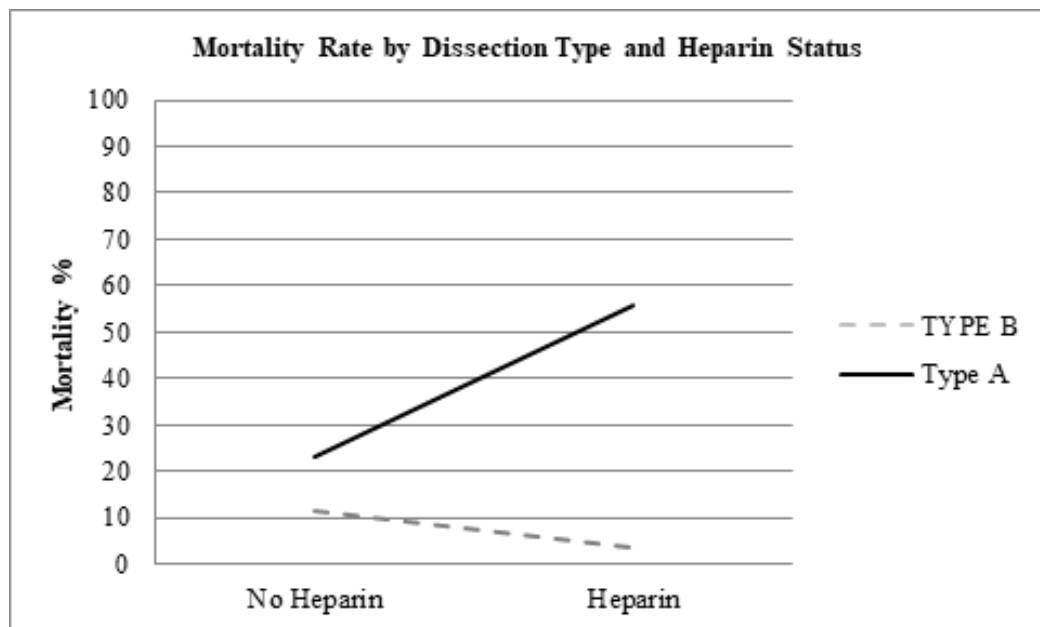
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**Table 1:** Comparing patients with aortic dissection in the emergency department with and without Heparin treatment in term of demographic information, comorbidities, and type of dissection. Results (n=131).

	Heparin		P-Value (Fisher's Probability)
	No (n=95)	Yes (n=36)	
Males	53 (55.8%)	25 (69.4%)	0.16
Female	42 (44.2%)	11 (30.6%)	
Age (average)	66	66	
Diabetes Mellitus	16 (16.84%)	3 (8.33%)	0.39
Hyperlipidemia	45 (47.37%)	14 (38.89%)	0.83
Hypertension	80 (84.21%)	29 (80.56%)	0.07
Tobacco use	50 (52.63%)	18 (50%)	0.83
Type A Aortic Dissection	43 (45.3%)	9 (25%)	<b>0.045</b>
Type B Aortic Dissection	52 (54.7%)	27 (75%)	

**Table 2:** Significant predictors of mortality.

Variables	Odds	95% C.I. for OR		p value
	Ratio	Lower	Upper	
Type B No Heparin	Reference			
Type B Heparin	0.31	0.03	2.74	.290
Type A No Heparin	2.51	0.80	7.83	.114
Type A Heparin	<b>9.00</b>	<b>1.81</b>	<b>44.85</b>	<b>.007</b>
Age (by decade)	1.63	1.08	2.45	.019



**Figure 1:** Mortality rate by Dissection type and Heparin.

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## Discussion

AD presents with varying symptomatology and ECG patterns that may make diagnosis difficult. As previously discussed, the features of ACS can mimic AD further complicating the diagnosis of these patients. AD and ACS have two very different treatment modalities. ACS treatment involves the administration of anticoagulation and has proven to be of remarkable benefit in terms of decreased morbidity and mortality. Most commonly the anticoagulant of choice in the treatment of ACS is unfractionated heparin which could potentially be detrimental to patients who are mistakenly diagnosed with ACS and actually have AD. Patients with type A AD are typically managed surgically, whereas type B AD have traditionally been treated medically, but endovascular management is becoming a popular modality. These differences in treatment combined with the overlapping symptomatology and early diagnostics leaves the emergency medicine physician faced with a treatment dilemma for acute, undifferentiated chest pain.

There has been sparse, yet conflicting evidence regarding anticoagulation use in AD. Hansen et al examined 66 patients with aortic dissection who presented to a tertiary care center over four years [9]. Twenty-six of these patients were initially misdiagnosed and received anticoagulation with either clopidogrel, aspirin, heparin, or fibrinolytic agents. Their study demonstrated a statistically significant higher rate of the combined primary outcome of in-hospital mortality and major bleeding ( $p=0.02$ ). However, when assessing in-hospital mortality by itself, there was not a statistically significant difference [9]. Furthermore, a study by Pourafkari et al looked at patients who were suspected of having aortic dissection versus those who were initially misdiagnosed and given antiplatelets/antithrombotics and compared in-hospital mortality and long-term mortality after hospital discharge [10]. This study demonstrated that the in-hospital mortality rate for those initially misdiagnosed was 48.9% versus 43.7% in patients with no initial misdiagnosis, and thus, there was no statistically significant difference ( $p=0.645$ ). However, there was a statistically significant difference in long-term mortality after

hospital discharge with a 55.6% mortality rate in those initially misdiagnosed and given antiplatelets/anticoagulants versus 21.2% in those that weren't ( $p=0.007$ ) [10].

These aforementioned studies highlight discrepancies regarding this topic. Our study set out to determine if patient mortality was influenced by the use of heparin in the setting of type A and type B AD. After adjusting for age and hyperlipidemia, patients with type A AD who received Heparin upon presenting in the ED had a statistically significant 9 times increase in mortality than those who did not receive heparin ( $p=0.007$ ); (CI: 1.81-44.85). One possibility for increased mortality in these patients is the activation of antithrombin III by heparin leads to clot prevention and promotes dissolution leading to thrombus breakdown and worsening dissection. Thus, the pharmacologic action of heparin may increase the mortality in AD by increasing proliferation of the false lumen. Such findings were demonstrated in a study by Sueyoshi et al where they looked at the growth rate of the aorta in relation to the patency of the false lumen in type B aortic dissections [11]. Their study demonstrated that in cases of completely patent false lumens, the diameter of the dissected aorta increased by an average of 4.9mm per year. However, if the false lumen was partially thrombosed, the enlargement increased only 4.0mm per year, and in cases of completely thrombosed false lumens, the size of the aorta actually decreased on average of 0.2mm in diameter per year [11].

In patients with type B AD who received heparin, only one patient expired out of twenty-five patients, correlating with a negative statistically significant mortality. The decrease in mortality in those with type B AD who received heparin might be related to a complication that occurs in 30% of type B AD: visceral ischemia [2-12]. Thrombosis of the false aortic lumen in type B AD causes subsequent ischemia via reduced blood flow to the renal, mesenteric, and iliac arteries, resulting in paralysis, end-organ dysfunction, and increased mortality [12, 13]. Some authors have suggested anticoagulation in the form of low dose intravenous heparin to prevent thrombosis and decrease mortality in patients with type B AD [13]. In our study, the decrease

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in mortality in patients with type B AD who received heparin may, in fact, suggest that anticoagulation is protective against thrombosis and visceral ischemia.

The initial symptoms and course of disease of aortic dissection is a potential mimicker of ACS, making chest pain in the Emergency Department a potentially complicated disease process. Use of anticoagulation in ACS has shown significant benefit in reduction of mortality, but to date, there have been limited studies with conflicting results examining the effects of anticoagulation in the setting of aortic dissection. With an increase in mortality in heparinized patients with type A AD, this retrospective study demonstrates that emergency medicine physicians should exercise caution when treating patients with acute, undifferentiated chest pain. However, our study also highlights and supports previous studies that the use of anticoagulation could prove beneficial in those with type B AD.

### Limitations

There are limitations associated with this retrospective study. The total number of patients in our study totaled 131; the number of patients that received anticoagulation was only 33, representing a small subset of patients that were diagnosed with AD who received heparin.

### Conclusion

Our study concludes that patients with type A AD who receive heparin are 9 times more likely to have in-hospital mortality than those who did not. This study advises a cautious utilization of anticoagulants in acute, undifferentiated chest pain in the emergency department. Such a finding is of great significance to our fellow emergency medicine physicians considering the similar manifestations of AD and ACS. Both of these medical emergencies necessitate prompt treatment and appropriate management, but our study clearly advocates that the administration of anticoagulants in the setting of type A AD could be catastrophic. Although, patients with type B AD who receive heparin showed lower in-hospital mortality compared with those who didn't receive Heparin, our data was not powerful enough to show a statistically significant outcome.

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