FIBRINOLYSIS PHENOTYPES DIFFER AMONGST CARDIAC SURGERY PATIENTS: ANTIFIBRINOLYTIC THERAPY FOR ALL?

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Abstract

The recognition of fibrinolysis phenotypes in trauma patients has led to a reevaluation of antifibrinolytic therapy (AF). Many cardiac patients also receive AF, however the distribution of fibrinolytic phenotypes in that population is unknown. The purpose of this study was to fill that gap. Methods: Data were retrospectively reviewed from 78 cardiac surgery patients. Phenotypes were defined as hypofibrinolytic (LY30 <0.8%), physiologic (LY30 0.8-3.0%) and hyperfibrinolytic (LY30 >3%). Continuous variables were expressed as M ± SD or median (interquartile range). Results: The study population was 65±10 yrs old, 74% male, average body mass index of 29±5 kg/m2. Fibrinolytic phenotypes were distributed as physiologic=45%, hypo=32% and hyper = 23%. There was no obvious effect of age, gender, race, or ethnicity on the distribution of fibrinolysis phenotypes; 47% received AF. The time with chest tube during post-operative recovery was longer in those who received AF (4[3,5] days) vs no AF (3[2,4] days), P=0.037). All cause morbidity occurred in 51% of patients who received AF vs 25% with no AF (p=0.017). However, with AF vs no AF, apparent differences in median chest tube output (1379 vs 820ml, p=0.075), hospital LOS (13 vs 10 days, P=0.873), estimated blood loss (1100 vs 775 ml, P=0.127), units of transfused RBCs (4 vs 2], P=0.152) or all-cause mortality (5.4% [2/37] vs 10% [4/41], P=0.518) were not statistically significant. Conclusion: This is the first description of three distinctly different fibrinolytic phenotypes in cardiac surgery patients. In this population, the use of AF was associated with increased morbidity.

INTRODUCTION:

Antifibrinolytics (AF) reduce bleeding and need for blood product transfusion in complex cardiac surgery and cardio-pulmonary bypass (CPB) cases[1,2]. The two most common AFs are Tranexamic acid (TXA) and Aminocaproic acid (ACA); both are lysine analogues that competitively inhibit conversion of plasminogen to plasmin[3-5]. AFs have demonstrated robust blood-loss reducing effects in a variety of settings without increased risk of thromboembolic events[6]. In 2011, The Society of Cardiovascular Anesthesiologists and Society of Thoracic Surgeons gave TXA their highest recommendation for use in blood conservation strategies although ACA is comparable in both efficacy and side effect profiles[7]. In the recent decade, use of AFs has expanded in both cardiac and non-cardiac surgery, with clinical applications in a wide range of surgical specialties[8].

The landmark CRASH-2 study concluded that early TXA reduced mortality in trauma patients[9]. Shortly thereafter, the MATTERs study reported similar benefits in the US military[10]. These compelling results led to an almost overnight paradigm shift and near worldwide incorporation of AF in trauma center resuscitation protocols, but questions soon followed. Why did less than half of the patients in CRASH-2 require PRBCs if they were bleeding to death?[11] Why did only 5% of CRASH-2 patients die from hemorrhage[11]? CRASH-2 was

also conducted in areas with underdeveloped rural trauma systems, leading to questions regarding application of CRASH-2 findings to mature urban trauma systems[12, 13]. Although TXA and ACA are generally well-tolerated, deleterious effects include increased risk of seizure and increased mortality in certain high-risk subpopulations[14, 15]. Concern over these findings and persistent questions about the mechanism of action have resulted in variable integration of AFs in US trauma centers[16-18].

Coagulopathy in cardiac and trauma surgery is diagnosed via a combination of conventional coagulation tests and viscoelastic assays such as the Thromboelastogram (TEG). TEG provides point-of-care evaluation of coagulation abnormalities and can guide coagulopathy treatment and decrease blood product use in cardiac surgery[19-21].

The TEG LY30 value has been used to stratify distinct fibrinolytic phenotypes among trauma patients. The physiologic phenotype is defined as LY30=0.8-3.0% and is associated with the lowest mortality[22]. However, if TXA was administered to trauma patients who present to the hospital with physiologic levels of fibrinolysis, they had the highest mortality[23]. At the very least, this suggests that some patients may benefit from TXA more than others and that the mechanism may be associated with fibrinolysis[24-28.]

While there is some evidence regarding distribution and functional consequences of fibrinolytic phenotypes in trauma patients, no studies to date have investigated these ideas in cardiac surgery patients. The aim of this study was to fill that gap.

METHODS:

Study Design

All open cardiac surgery patients at a single academic institution in 2018 were retrospectively reviewed. Those who did not receive an intraoperative TEG or had incomplete TEG data were excluded. TEG was used to group patients according to fibrinolysis phenotypes. Otherwise, there were no exclusions based on age, medical co-morbidities, or other demographic information. The retrospective study was approved by the institutional review board with waiver of consent.

Demographic, clinical, and outcomes data were compared between groups. Demographic data included age, sex, race, ethnicity, insurance status, and medical comorbidities. Clinical variables included specific cardiac operation, total operative time, any intra-operative or post-operative surgical complications, and all peri-operative and post-operative medications. Outcomes of interest included estimated blood loss (EBL), post-operative length of stay (LOS), chest tube days, total chest tube output, number of packed red blood cells (pRBCs) transfused, all cause morbidity, and mortality (defined as disability and/or death from, cardiac arrest, cerebrovascular accident, congestive heart failure, hemothorax, multiorgan failure myocardial infarction, pleural effusion, respiratory failure, sepsis, thromboembolism, valve dysfunction, and/or wound dehiscence/abscess).

Procedural and Statistical Analysis

Each TEG was processed and analyzed by a Computerized Thrombelastograph Coagulation Analyzer (CTEG model 3000, Haemoscope Corporation, Skokie, Ill) in the hospital pathology lab. The TEG for each patient was performed using Celite-activated whole blood at 37°C. The degree of fibrinolysis was defined by the LY30 value, which reflects the proportion of clot lysis 30 minutes after clot initiation. Three distinct fibrinolysis phenotypes were defined[24-28] 1) hypo-fibrinolytic (LY30 <0.8%), 2) physiologic fibrinolysis (LY30 0.8-3.0%), and 3) hyper-fibrinolytic (LY30 >3%).

Categorical variables are presented as counts (%) and continuous variables as mean ± standard deviation or median (interquartile range) based on the distribution of the corresponding variable. Outcomes of interest included hospital LOS, EBL, units of pRBCs, and all cause morbidity and mortality. Univariate analyses was performed using SPSS for Windows 6.0 (SPSS Corporation, Chicago, Ill) with significance assessed at $p<0.05$.

RESULTS

A total of 117 cardiac surgery patients were reviewed between January 2018 and December 2018 but 39 were excluded because of incomplete TEG data. The final study population was comprised of 78 cardiac surgery patients and was characterized as 58 male (74%) with a mean age of 65±10 years (range, 44-87 years). The mean body-mass-index (BMI) was 29±5 (range 20-43) kg/m^2. Patient race was categorized as 65% White (n = 51), 32% Black (n = 25), and 3% Asian (n = 2). The most common medical co-morbidity was hypertension (64%) followed by coronary artery disease (46%) and obesity (35%) There was a near equal distribution of on-pump (48%) and off-pump (51%) cardiac surgery . Median LOS was 12 [8,17] days. Overall mortality was 8%.

Fibrinolytic phenotypes were distributed as 45% physiologic, 32% hypo-, and 23% hyper-. There was no significant difference between age, gender, race, or ethnicity on the distribution of fibrinolysis phenotypes. There was a near equal distribution of fibrinolytic phenotypes between patients who received versus did not receive AF (P = 0.962).

Of the 78 patients included in the analysis, 47% (37/78) received AF and 53% (41/78) did not. When these two groups were further stratified by fibrinolytic phenotypes, the sub-group sizes were too small to make any meaningful determination of whether AF altered outcome .

Table 1 compares demographic and clinical data between groups. There were no statistically significant differences regarding: medical co-morbidities, including hypertension (84% vs 71%, P =0 .172), coronary artery disease (57% vs 37%, P =0 .074), and diabetes (35% vs 34%, P = 0.927), tobacco use (3% vs 12%, P = 0.116), preoperative hematocrit (34 ± 3 vs 33 ± 4, P =0 .430), Caprini score (9 ± 2 vs 9 ± 2, P =0 .201) Clopidogrel use (19% vs 24%, P = 0.559) or Aspirin use (60% vs 78%, P = 0.076).

For AF versus no AF (Table 2), median time with chest tube during post-operative recovery was longer (4 [3,5] vs 3 [2,4] days, p=0.037). Chest tube output was increased (1379 [945,1837] vs 820 [485,1400]), but this apparent difference did not reach statistical significance (P =0 .075). All-cause morbidity was the most significant outcome difference (P = .017), which occurred in 51% of patients who received AF versus 25% of patients who did not receive AF.

Other outcomes were similar, including hospital LOS (13 [8,17] vs 10 [8,17] days, P = .873), EBL (1100 [1000,1500] vs 775 [500,1050] ml, P = .127), transfused RBCs (4 [1,5] vs 2 [1,4] units, P = .152) or all-cause mortality (5.4% vs 10%, P = .518).

DISCUSSION

Fibrinolysis is a physiologic mechanism by which clots are degraded to maintain the patency of microvasculature. Pathologic over- or under-activation of fibrinolysis has significant clinical implications regarding optimal treatment interventions and patient outcomes in trauma patients[22-28] . This study is the first to categorize these fibrinolysis phenotypes in cardiac surgery patients. The data suggest that indiscriminate AF administration may have deleterious effects unless clinically indicated, but the sample size is too small to make definitive recommendations.

Hyper-, physiologic, and hypo-fibrinolytic phenotypes are well established among trauma patients. In theory, AF should have its most favorable effect in those with hyperfibrinolysis. In contrast, hypercoagulability associated with fibrinolytic shutdown is reported to occur in 46% to over 64% of trauma patients[22-32]. On this basis alone, it is reasonable to propose that all patients likely do not benefit from TXA[11]. Despite the high prevalence, it remains controversial if fibrinolytic shutdown is a physiological or maladaptive response to traumatic injury[33, 34]. Our study demonstrates a distribution of fibrinolytic phenotypes in cardiac surgery patients that is distinctly different than the established distributions among trauma patients. In particular, our data shows that cardiac surgery patients exhibited a rate of fibrinolytic shutdown of 32% compared to the reported range for trauma patients of 46-64%.

There are multiple proposed mechanisms by which fibrinolytic shutdown occurs, including: i) tissue plasminogen activator (t-PA) inhibition, ii) inadequate t-PA release in response to injury, iii) fibrinolytic resistance via cell free DNA, and iv) elevated plasmin to antiplasmin ratio[26, 30,32, 35, 36.] *In vivo* studies in animal models

have demonstrated that tPA release is predominantly driven by shock rather than by tissue injury and that altered clot formation has no correlation with altered clot degradation[22,36, 37]. Subsequent studies have yet to identify a correlation between injury severity score or injury mechanism and fibrinolytic phenotype[36, 38]. Nevertheless, changes in the fibrinolytic system after tissue injury have significant treatment implications regarding the treatment decision to administer or withhold AF therapy.

Although distinct fibrinolytic phenotypes are well-established in trauma patients, equivalent phenotypes are yet to be fully characterized in other surgical fields. Many studies have investigated the efficacy of empiric AF treatment across surgical groups; however, there is limited discussion of the prevalence or influence of distinct fibrinolytic phenotypes on treatment responsiveness and outcomes. In particular, there may be an increased potential for preventable harm if AF is administered to a patient who is already hypofibrinolytic (i.e. fibrinolysis shutdown=hypercoagulable), or if withheld from a patient who is hyperfibrinolytic (i.e. hypocoagulable).

In the United States, patients undergoing cardiac surgery demonstrate particularly high blood transfusion rates. In 2010, 34% of cardiac surgery patients received a perioperative transfusion despite the implementation of blood conservation guidelines in 2007[39-41]. Thus, AF is often used in this population to minimize perioperative blood loss [42]. It is well established that AF therapy reduces bleeding and allogeneic transfusion requirements[29]. Myles et al studied the effectiveness of TXA versus placebo in a randomized control study of 4631 coronary-artery surgical patients and demonstrated that death or thrombotic complication occurred in 18.1% of placebo patients versus 16.7% of TXA patients[43]. Transfusion requirements were reduced from 7,994 total units in placebo to 4,331 in the TXA group, with seizures reported in 0.1% of placebo versus 0.7% of TXA patients[43]. A recent metanalysis by Alaifan et al reported that TXA reduced bleeding in cardiac surgery, but surprisingly did not significantly impact overall mortality[49]. A randomized control trial by Leff at el comparing TXA and ACA in 114 cardiac surgery patients demonstrated that ACA was associated with less transfusions than TXA; though, both TXA and ACA significantly reduced perioperative bleeding and transfusions with no increase in adverse events[45]. The efficacy of AF in reducing perioperative bleeding and transfusion requirements has been reported by several others[46-48].

Our data demonstrated significant outcome differences in those who received AF versus those who did not. We show that cardiac surgery patients who received AF had significantly higher rate of all cause morbidity (n = 19, 51%) versus those who did not (n = 10, 25%, P = 0.017). Patients who received AF also had more days with a chest tube (P = 0.037) and an average of 559mL more output from the chest tube compared to patients who did not receive TXA (P = 0.075). Unfortunately, the sample size was not large enough to determine if these outcome differences were related to the fibrinolytic phenotype.

There was no obvious effect of age, gender, race, or ethnicity on the distribution of fibrinolysis phenotypes. There was a near equal distribution of physiologic, hyper-, and hypo-fibrinolytic phenotypes between patients who received AF (46% vs 30% vs 24%) and did not receive AF (45% vs 33% vs 22%, P = 0.962). This suggests that a patient's fibrinolytic phenotype was not a contributing factor in the decision to administer or withhold AF.

The use of AF in other surgical populations has generally been efficacious; though, there is significant heterogeneity across specialties. For instance, patients with hepatic dysfunction are at a markedly increased risk of excessive bleeding or coagulopathy during liver surgery or transplantation due to altered hepatic production of essential clotting factors[49]. Previously, AF were administered empirically in these patients; however, empiric therapy has since been questioned due an observed increase in rates of coagulopathy, venous thromboembolism, and mortality[49-51]. In current practice, the use of AF during hepatic operations is variable due to the considerable physiologic changes that occur pre- and post-liver transplantation. Accordingly, most liver transplant centers use TEG or viscoelastic monitoring with rotational thromboelastometry to guide AF administration if a patient exhibits hyperfibrinolysis[52-54]. Similarly, it has been established that only some trauma patients benefit from empiric AF therapy. Thus, the use of AF in trauma is generally informed and guided by TEG or comparable monitoring techniques.

The practical significance of fibrinolytic phenotype and therapeutic response has only recently been recognized. Even among the fields of liver and trauma surgery, where fibrinolytic variability has been consistently reported, there is still limited discussion of the relationship between AF and clinical outcomes across distinct fibrinolytic phenotypes.

Ultimately, further investigation is needed to assess the role of fibrinolytic phenotypes in modulating AF responsiveness and clinical outcomes, especially because AF therapy has a demonstrated utility in cardiac surgery. Ultimately, TEG -guided AF therapy might assure administration only when clinically indicated..

Our study is limited by its small sample size and retrospective methodology, which precluded subgroup analysis of AF outcomes across fibrinolytic phenotypes. Our small study size also hindered statistical significance of some outcome variables; though, we still observed clinically significant differences among patients who received AF, including an average of 325mL more EBL (P = 0.127) and 2 units more of RBCs transfused (P = 0.152) compared to patients who did not receive AF. Considering that fibrinolytic phenotypes and most demographic factors were relatively equal between patients who did and did not receive AF, these observed differences following AF may suggest a contributory role of fibrinolytic phenotype on patient outcomes. Therefore, a better understanding of fibrinolytic phenotypes may be especially significant in guiding the decision to administer or withhold AF in surgical patients.

In summary, this study is the first to describe three distinct fibrinolytic phenotypes in cardiac surgery patients. This distribution is different than the established distribution of fibrinolytic phenotypes in trauma patients. In most surgical specialties, intra-operative AF safely and effectively reduces bleeding complications, but there is on strong evidence from trauma patients that fibrinolytic phenotypes in modulating treatment responses to AF. In context with these current findings, we hope to open the dialog on whether it is safe to administer AFs to cardiac surgery patients who are normo- or hypofibrinolytic. Further studies are clearly indicated in cardiac surgery patients to investigate the clinical utility of pre- and post-operative TEG data to discern fibrinolytic phenotypes and guide AF use.

AUTHOR CONTRIBUTIONS:

MSS and ELR had full access to all the data and take responsibility for the accuracy of the analysis.

Study concept and design: MSS, TAS, DLG, KGP

Acquisition, analysis, or interpretation of data: MSS, TH, RI

Drafting of the manuscript: MSS, RI, TH, EMU, ACC, KGP

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: MSS, ELR

Administrative, technical, or material support: NN, TAS

Study supervision: KGP

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N (%), mean±SD	*N (%), mean±SD*	*No AF (n=41)*	*No AF (n=41)*	*AF (n=37)*	*AF (n=37)*	*P-value*	*P-value*
Age (years)			63 ± 10	63 ± 10	67 ± 10	67 ± 10	0.090
Gender	*Male*	*Male*	29 (71)	29 (71)	29 (78)	29 (78)	0.440
	Female	*Female*	12 (29)	12 (29)	8 (22)	8 (22)	
Race	*White*	*White*	29 (71)	29 (71)	22 (60)	22 (60)	0.246
	Black	*Black*	12 (29)	12 (29)	13 (35)	13 (35)	
	Asian	*Asian*	0 (0)	0 (0)	2 (5)	2 (5)	
Hypertention			29 (71)	29 (71)	31 (84)	31 (84)	0.172
CAD			15 (37)	15 (37)	21 (57)	21 (57)	0.074
Diabetes			14 (34)	14 (34)	13 (35)	13 (35)	0.927

N (%), mean±SD	*N (%), mean±SD*	*No AF (n=41)*	*No AF (n=41)*	*AF (n=37)*	*AF (n=37)*	*P-value*	*P-value*
Tobacco Use			5 (12)	5 (12)	1 (3)	1 (3)	0.116
Preop HCT (%)			33 ± 4	33 ± 4	34 ± 3	34 ± 3	0.430
Aspirin			32 (78)	32 (78)	22(60)	22(60)	0.076
Clopidogrel			10 (24)	10 (24)	7 (19)	7 (19)	0.559
Caprini Score			9 ± 2	9 ± 2	9 ± 2	9 ± 2	0.201
Fibrinolysis Phenotype	*Physiologic*	*Physiologic*	18(45)	18(45)	17(46)	17(46)	0.962
	Fibrinolysis - shutdown	*Fibrinolysis - shutdown*	13 (33)	13 (33)	12 (30)	12 (30)	
	Hyper-Fibrinolysis	*Hyper-Fibrinolysis*	9 (22)	9 (22)	9 (24)	9 (24)	
AF: Antifibrinolytic therapy; CAD: Coronary artery disease; HCT: hematocrit; SD: standard deviation	AF: Antifibrinolytic therapy; CAD: Coronary artery disease; HCT: hematocrit; SD: standard deviation	AF: Antifibrinolytic therapy; CAD: Coronary artery disease; HCT: hematocrit; SD: standard deviation	AF: Antifibrinolytic therapy; CAD: Coronary artery disease; HCT: hematocrit; SD: standard deviation	AF: Antifibrinolytic therapy; CAD: Coronary artery disease; HCT: hematocrit; SD: standard deviation	AF: Antifibrinolytic therapy; CAD: Coronary artery disease; HCT: hematocrit; SD: standard deviation	AF: Antifibrinolytic therapy; CAD: Coronary artery disease; HCT: hematocrit; SD: standard deviation	

Table 1

Table 2

Antifibrinolytic Therapy Outcomes	Antifibrinolytic Thera
N(%), median [IQR]	*No AF*
Hospital LOS (Days)	10 [8,17]
Chest Tube Days (Days)	3 [2,4]
Chest Tube Output (mL)	820 [485,1400]
EBL (mL)	775 [500,1050]
RBC Transfused (units)	2 [1,4]
All Cause Mortality	4 (10)
All Cause Morbidity	10 (25)
AF: Antifibrinolytic therapy; EBL: estimated blood loss; LOS: length of stay: RBC: red blood cells	AF: Antifibrinolytic t