OPTIMIZING ANTICOAGULATION THERAPY FOR ECMO PATIENTS USING ANTITHROMBIN III

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ABSTRACT

One of the most fundamental aspects of extracorporeal membrane oxygenation (ECMO) is maintaining proper anticoagulation management in order to prevent hemorrhagic or thrombotic events. Anticoagulation on ECMO is most commonly achieved with the use of unfractionated heparin to maintain a minimum anticoagulation level as monitored by activated clotting time (ACT). Heparin's main effect is exerted by binding to and potentiating antithrombin III. Many factors may contribute to a sub-therapeutic ATIII level that may decrease the effectiveness of heparin. A retrospective record review was performed on all adult ECMO patients at the University of Arizona Medical Center between 2008 and 2011, in order to determine optimal ATIII levels for maintaining proper anticoagulation. In addition, we investigated correlations between ATIII levels and hemorrhagic and/or thrombotic events. Variables measured include, ACTs, heparin dose, ATIII dose, ATIII levels, blood product use, and adverse events. Thirty-five patients received ATIII over the course of the ECMO run. Six patients did not receive ATIII and they were found to have used significantly more blood products than those who did receive ATIII. Also, heparin dose dropped significantly 24h after the first dose of ATIII. There is a significant positive correlation between the amount of ATIII given per day and the amount of packed red blood cells transfused per day. The results

suggest an ideal therapeutic range of ATIII dosing, where lack of or too much ATIII administration can lead to excessive bleeding.

BACKGROUND

ECMO

Extracorporeal membrane oxygenation (ECMO) is a form of mechanical circulatory support that is used in the management of life threatening pulmonary or cardiac failure. It is often utilized in emergent situations and only for temporary support. A requirement for extracorporeal membrane oxygenation is systemic anticoagulation. This happens to be a limitation as well due to bleeding complications. ECMO controls the gas exchange and perfusion, while stabilizing the patient physiologically and reducing the risk of iatrogenic injury. Gas exchange can be dependent on the thickness of the blood film, membrane material, fraction of inspired oxygen (FIO_2), and hemoglobin concentration[1]. Simultaneously, it allows time for diagnosis, treatment, and most importantly, recovery from injury or disease[2]. Circulation through the device occurs by draining right atrial blood from the venous circulation through a cannula to an artificial lung device and returning it to the patient through another cannula to the aorta (veno-arterial) or the right atrium (veno-venous). Veno-arterial cannulation may provide support for both the heart and lungs. Veno-venous oxygenation is used in series to the native lungs to assist in oxygenation for those in isolated respiratory failure.

The specific vessel cannulation for both modes of ECMO can vary depending on the needs of the patient. Veno-venous cannulation can be achieved multiple

ways through cannulation of the femoral vein and/or internal jugular vein. Veno-arterial cannulation is most commonly through cannulation of the femoral vein and femoral artery. For infants, with femoral vessels that are too small or difficult to reach, cannulation is most often via the internal jugular and carotid.

The overall purpose of veno-venous cannulation is to return oxygenated blood to the venous circulation, thereby increasing oxygen content and lowering CO_2 content in the right atrial blood. This blood is pumped through the functionally preserved cardiac system where the heart is solely responsible for systemic perfusion and blood flow. Patients remain both sedated and immobile while on this device. In addition, the lungs are still being ventilated on minimal settings despite their inability to oxygenate adequately in order to prevent additional damage.

Veno-arterial cannulation may provide full or partial cardiac support depending on the needs of the patient and the underlying function of the heart. Oxygen and carbon dioxide levels in the blood are a reflection of blood flow that is a combination of pumping from the heart as well as flow from the circuit. If the lungs are functioning poorly, then blood leaving the heart from the left ventricle will be similar to that entering the right atrium. The best location to determine optimal ECMO flow and measure cerebral perfusion is to take a blood gas from the right upper extremity. This is because the innominate is the last aortic arch vessel to

receive flow from the ECMO circuit when returned retrograde through the femoral artery.

Clinical syndromes indicated for ECMO include both cardiac and respiratory. ECMO is reserved for the most medically compromised patients that have exhausted all optimal care resources and present as a high mortality risk. Acute cardiac failure occurs when the heart cannot produce adequate cardiac output to supply the body with oxygenated blood. Acute respiratory failure occurs when the lungs can no longer efficiently oxygenate the blood and remove carbon dioxide.

Anticoagulation

A primary requirement for ECMO is systemic anticoagulation. The most common drug used to achieve this effect is unfractionated heparin. Heparin is one of the oldest anticoagulation drugs that is still in clinical use. It did not enter clinical trials, however, until 1935, for its use as a blood anticoagulant[3]. Today, it is commonly used for conditions such as acute coronary syndrome, atrial fibrillation, deep vein thrombosis, pulmonary embolism, cardiopulmonary bypass for heart surgery, as well as ECMO[4]. It continues to dominate anticoagulation therapy for ECMO because it is rapid acting, easily controllable, inexpensive and widely available. In addition, it is well tolerated by both adult and pediatric patients[5].

Heparin is naturally produced by basophils and mast cells. Commercially, it is most often derived from porcine or bovine sources. Commercial preparations typically include a wide range of molecular weights from 3,000 to 40,000 Daltons, with a mean molecular weight of 15,000 Daltons[6]. The structure of heparin is a heavily sulfated glycoaminoglycan polymer, making it strongly acidic and negatively charged. Heparin dosing is primarily dependent on its indication for use. Cardiopulmonary bypass requires a dose of 300-400 U/kg. ECMO requires between 20 and 70 u/kg/h. A unit of heparin is measured as a unit of activity. More specifically, activity is defined as the "amount of heparin that maintains the fluidity of 1mL of citrated sheep plasma for 1 hour after recalcification"[6]. This measurement technique is used to maintain consistency in dosing as different manufacturers vary the number of USP units per milligram of drug. Heparin exerts its main effect on the coagulation cascade. The plasma coagulation cascade is the process of fibrin clot formation in response to both intrinsic and extrinsic activation. Intrinsic activation results from contact of blood with foreign surfaces, whereas extrinsic activation results from injury of the vasculature. Both pathways converge to form the common pathway, beginning with the activated factor X, which converts prothrombin to thrombin. Thrombin converts fibrinogen into fibrin, resulting in the formation of a strong clot after fibrin cross-linking. In addition to activating fibrinogen, thrombin

also stimulates platelet activation, which results in further platelet aggregation and adherence to endogenous surfaces forming a strong platelet plug.

Alternatively, in order to prevent excessive clot formation and dissolve clots, the body has various negative feedback systems. Factors involved include, proteins C and S, antithrombin III, tissue factor inhibitor and tissue plasminogen activator. It is here that heparin exerts its main effects.

Heparin specifically provides its pharmacological effects by binding to and amplifying the enzymatic fuction of antithrombin III (ATIII) by more than 1,000 fold[6]. Antithrombin III primarily inhibits thrombin, as well activated factor X. It also inhibits factors IX, XII, and XI, to a lesser extent. The site on heparin that binds to ATIII is found on about 30% of heparin molecules. In the common pathway, factor Xa activated the conversion of prothrombin to thrombin which heparin blocks by binding to antithrombin III. Heparin does have minimal non-ATIII dependent anticoagulation effects. It can bind to and activate cofactor II, a natural thrombin inhibitor. Biologic activity varies between 30 minutes and 6 hours depending on systemic heparin concentrations[5]. Heparin is metabolized by the reticuloendothelial system in addition to the liver. Up to 50% can be excreted unchanged by the kidneys. Due to heparin's half-life, patients must be kept on a constant heparin infusion to maintain anticoagulation, with bolus infusions given as needed.

Some patients may exhibit heparin resistance, which tends to be those who have had prior heparin therapy or an ATIII deficiency. Small amounts of heparin may bind to plasma proteins such as vitronectin and fibronectin thereby decreasing its effectiveness and availability for ATIII[7]. ATIII levels may also be decreased in those that have been pretreated with heparin[6]. If this is the case, it has been shown that "purified ATIII even in small doses, significantly prolongs the ACT response to heparin"[8]. Heparin resistance is also often related to certain clinical conditions such as sepsis, liver disease, or any condition that exerts stress on the body that may deplete ATIII levels. Given that many of the critically compromised patients on ECMO are subject to prior or chronic heparin therapy and have conditions that induce stress on the body, this is clinically significant. If levels are low to begin with, prophylactic treatment may be indicated.

There is universal acceptance that ATIII levels fall upon initiation of ECMO, up to 50% [9], and also, that anticoagulation should be monitored using a combination of measurement techniques in order to understand the complete coagulation profile for each individual patient.

Complications Related to ECMO

Unfortunately, there are various complications related to ECMO. Most complications are due to the need for systemic anticoagulation. There is a fine

balance to be maintained between excessive anticoagulation resulting in bleeding, and under dosing resulting in excessive clot formation seen in the circuit tubing or oxygenator.

Bleeding or hemolysis can occur resulting in the need for replacement and transfusion of red blood cells. Bleeding can occur at the surgical sites from recent surgery or at the cannula insertion sites. Unfortunately, this is exacerbated by the use of heparin as a systemic anticoagulant. For that reason, if a patient is put on ECMO post-operatively, heparin is often withheld until bleeding is controlled.

Hemolysis is another negative side effect of ECMO blood replacement that may require red blood cell replacement. Fortunately, with further advances in technology such as low resistance gas exchange devices and second generation centrifugal pumps, hemolysis is not as common. Hemolysis occurs mainly from anything resulting in excessive negative pressures and turbulance[10]. Cavitation can occur when a fluid such as blood is exposed to an extreme negative pressure in excess of 650 mmHg. Centrifugal pumps operate at high rpms can cause in excess of 700mmHg negative pressure. This can occur when blood in the pump head is ejected, but nothing fills the void, therefore a vacuum is created resulting in cavitation and further hemolysis. Causes of this volume issue can be due to low blood volume, patient position, cannula size, cannula position, coughing and others[10]. This can be a common problem, especially in those post-operative patients

with excessive bleeding as measured in chest tube output. Volume replacement and maintaining safe flow parameters are the easiest solutions to avoiding hemolysis.

Other causes of hemolysis are related to shear stress, physical properties of the ECMO circuit, as well as sub-lethal damage to erythrocytes[11]. As proof of this hemolysis, the level of plasma free hemoglobin can increase by as much as 10 to 25 fold after just 24 hours of ECMO. Continuous renal replacement therapy, a common addition to the circuit for those patients in renal failure, is also known to cause hemolysis, therefore RBC transfusion due to excessive blood loss has a direct relationship with RBC hemolysis.

Various coagulopathy problems can occur with the use of ECMO as well. Due to the continuous contact of the patient's blood volume with the non-biologic surface of the circuit, there is activation of both contact and fibrinolytic systems. Also, within minutes of initiation of ECMO, there is consumption and dilution of all factors. Consumption of factors can result in with fewer factors available for coagulation resulting in bleeding. In a study by Arnold et al., it was found that there was both evidence of reduction in coagulation factors and activation of the coagulation cascade[12]. For this reason, factor replacement is a necessity.

Another complication related to ECMO is clot formation within the circuit. Clot formation is the most common mechanical complication resulting in potential thrombus[1]. This frequently at locations where there is high turbulence such as at

tubing connection points as well as in the membrane oxygenator. Severe consequences to clot formation include passing of clots into to systemic circulation or oxygenator failure.

Coagulation Management

The key to effective anticoagulation in these patients is the utilization of a variety of monitoring techniques. It is important to create a coagulation profile for each patient on a daily basis. This includes a combination of laboratory tests such as measurement of platelet count, antithrombin, aPTT, TEG, as well as hemoglobin requirements.

The easiest and most popular technique to use is the bedside measurement, termed activated clotting time (ACT). This measures the integrity of the intrinsic coagulation and common pathways using a whole blood sample. The acceptable range for ACT values is between 180-220 seconds for patients supported on ECMO. Despite its continued widespread use due to ease and instant results, ACT has a limited range of accuracy. Results may be affected by many factors related to patient characteristics, such as coagulopathy, immature coagulation system (such as in infants), platelet dysfunction, hypothermia, ATIII levels, age, and hemodilution from the circuit prime volume[5]. For this reason, it is important to consult other monitoring techniques as well.

Another common test for anticoagulation management is the thromboelastogram (TEG). The TEG is useful in that it accurately measures the viscoelastic properties of a blood sample in order to better understand a patient's whole clotting system as opposed to individual components. It describes clot formation and clot dissolution as part of fibrin breakdown, which is equally important. The ability to also characterize hypercoagulability is necessary in order to know if patients have the sufficient clotting factors available or if they need factor replacement.

Specifically related to the clotting cascade, we are also interested in measuring activated partial thromboplastin times (aPTT). This is the universal standard for monitoring heparin therapy, in addition to congenital and acquired factor deficiencies[13]. Measuring aPTT alone, however, is not the best indicator of heparin therapy, as aPTT can be prolonged for many reasons such as factor deficiencies, vitamin K deficiencies, as well as disseminated intravascular coagulation. It should be used in combination with the other techniques mentioned previously.

Despite improvements in the management of ECMO patients, complications remain high related to bleeding and thrombosis. These patients present a unique challenge with complicated disease states often involving pre-existing clotting disorders, that are exacerbated by heparin. Therefore, the best approach to reduce

incidence of adverse events is multidisciplinary among surgeons, physicians, perfusionists, nurses and ECMO specialists. To benefit the advancement of patient care, we present a unique study assessing anticoagulation parameters and outcomes related to the use of antithrombin III.

Previous Research

Currently, there is very little research supporting the topic of anticoagulation on ECMO specially related to ATIII. Previous studies have explored multiple coagulation parameters while patients are on ECMO. One particular study specifically looked at ATIII levels and tested two dosing mechanisms, comparing bolus versus continuous infusion. They found continuous infusion to show better overall outcomes by reducing activation of heparin more than bolus infusion[14]. They maintained ATIII levels at >100% and showed reduced surgical revision for bleeding within the first 48 hours. Other studies test for all coagulation factors at set time points and compare how they relate to patient outcomes[14,15]. The choice of using multiple coagulation tests in order to obtain a more accurate picture is that at times the ACT level alone can be limited due to issues such as consumptive coagulopathies, clotting factor deficiencies, platelet dysfunction, as well as fibrinolysis[15]. Another study measured antithrombin replacement during ECMO

and only hemorrhagic complications[16], finding that upon administration, there were no significant differences in bleeding and ATIII levels.

OBJECTIVES

This study will be the first to provide a detailed analysis of ATIII and how it relates to patient outcomes. It will enable us to more effectively manage ECMO patients and aid in the prevention of adverse events. Hemorrhage will be measured as packed red blood cell administration and thrombosis will be measured by circuit change outs or any other evidence of major clotting. At this time, it is uncertain at what minimum level patients should receive replacement prior to ECMO initiation. Secondarily, in the long term this project has the possibiility of helping reduce the costs of ECMO for these patients by preventing circuit change outs caused by clotting, educing the length of time spent on the assist device, as well as reduce expensive blood product transfusions.

It is important to monitor ATIII due to the hemodilution and activation of other factors upon initiation of ECMO. Currently, we measure ATIII levels throughout the ECMO run. The subsequent drop following initiation can be a potential hazard towards maintaining optimal anticoagulation. Low levels of ATIII may produce ACT levels below standard and the administration of more heparin without sufficient ATIII levels can lead to increased bleeding[17]. It is also important to take into consideration preexisting conditions that many patients recommended for ECMO have that may cause them to have reduced levels of ATIII initially.

PATIENTS AND METHODS

An institutional review board-approved retrospective chart review was performed on all adult ECMO patients supported at the University of Arizona Medical Center between the years of 2008 and 2011.

Indications for ECMO

ECMO is indicated for patients that suffer from severe acute cardiac and respiratory failure. Indications for those that suffer from respiratory failure in this specific population of patients include syndromes that result in the inability of the lungs to provide sufficient oxygenation, such as Acute Respiratory Distress Syndrome (ARDS), H1N1, sepsis, post lung transplantation, and others. Indications for cardiac failure include syndromes that result in the heart being unable to provide enough cardiac output or blood supply to the rest of the body, such as, failure to wean from cardiopulmonary bypass, post myocardial infarction, and cardiogenic shock. ECMO is used for those patients that have exhausted all other options for treatment and have an 80% mortality risk[2].

The ECMO circuit used at the University of Arizona Medical Center for all patients includes a Maquet Rotaflow centrifugal pump with the Quadrox heparin coated hollow fiber membrane oxygenator. Cannulation varied among patients and

included (i) intrathoracic, (ii) right internal jugular vein and common carotid artery, or (iii) femoral vein and artery.

Anticoagulation and Transfusion Protocols

Unfractionated heparin was used for anticoagulation purposes for all patients. Dosing was titrated at drip rates sufficient to maintain an activated clotting time between 160-200 seconds depending on bleeding issues. Packed red blood cells (pRBCs) were transfused to maintain a hematocrit of greater than 30%. Platelets and fresh frozen plasma were transfused as needed as well to maintain normal clotting factor levels.

ATIII levels were measured on all patients to maintain percentage activity between 80 and 120%. ATIII dosing to maintain normal levels was determined at the discretion of the physician in combination with manufacturer recommendations.

Data Collection and Analysis

Various demographics were collected from patient charts, such as age, gender, height, weight, and BSA. Indication for ECMO, length of time on ECMO, survival, and cannulation technique were also collected. Laboratory values included ACTs, heparin drip rates, ATIII levels, ATIII dosing, as well as blood product use.

Adverse events were recorded as bleeding, evidence of clots in the circuit, and cerebral vascular accidents (CVAs).

In order to determine the effect of ATIII on product use, packed red blood cells (pRBC), platelets, and fresh frozen plasma transfusions were measured. The amount of pRBCs transfused was used as a measure of bleeding requiring red blood cell replacement.

In order to determine the effect that ATIII had on heparin drip rates we measured heparin infusion at the time of the first dose of ATIII and subsequently 24 hours later. The first dose was used as to avoid potential confounding effects of multiple doses of ATIII.

RESULTS

Throughout the study period, 41 patients were supported on ECMO. One patient was excluded due to an ECMO duration of only three hours. The patients were divided into cardiac and respiratory due to the extreme differences in underlying pathology. The cardiac group (n=21) and respiratory group (n=20), had a significant difference in ages with a mean age of 57.7 ± 2.7 (mean ± SD) years, and a mean age of 39.4 ± 3.3 (Table 1) respectively. The cardiac group had a mean weight of 92 ± 4 kg, and the respiratory group had a mean weight of 84 ± 6 kg. The cardiac group had a statistically significant shorter length of stay at a mean of 7.4 days, while the respiratory group had a mean of 14.1 days. Survival differences were also statistically significant in that the cardiac group had a mean survival rate of 58%, and the respiratory group had a rate of 35%.

Indications for ECMO in these patients include both cardiac and respiratory failure disorders. Of the cardiac failure patients (n=21), indications include failure to wean, idiopathic cardiomyopathy, cardiogenic shock, post cardiac surgery (valve replacements, root replacements, CABG), post MI, post partum, etc. Of the respiratory failure patients, a majority of indications for ECMO include ARDS, respiratory failure, drug overdose, H1N1, sickle cell, pulmonary edema, pulmonary fibrosis, post lung transplant, etc.

When comparing the effect of ATIII on heparin drip rate at first dose and 24h later, the results show that there is a statistically significant ($p < .05$) decrease in the heparin drip rate 24 hours after ATIII was administered (Figure 1). The mean dose at heparin at ATIII administration was 803 units per hour, which decreased to an average of 594 units per hour after 24 hours. Six patients were not on heparin infusions at the time of the first dose of ATIII possibly due to uncontrolled bleeding post-operatively. One of the patients not on heparin infusion had a heparin allergy, so that patient was excluded as well. For those reasons, analysis was limited to 35 cases.

In comparing those patients who did receive ATIII replacement (n=35) to those that did not receive ATIII replacement (n=6), there was a significant difference for all blood products used between those that did not receive any ATIII and those that did receive ATIII (Figure 2-4). Those that did not receive ATIII were given a mean of 7.02 ± 1.25 units of pRBCs per day, 2.93 ± 0.37 units of platelets per day, and 4.61 ±1.36 units of FFP per day. This is compared with those who were not dosed with ATIII that were given 2.81 ± 0.30 units of pRBC per day, 0.77 ± 0.17 units of platelets per day, and 1.11 ± 0.21 units of FFP per day. The non-ATIII group used significantly more blood products on average per day compared with those who did receive ATIII.

Given that the results suggest ATIII is important, we wanted to determine how well our institution replacing it, in order to sustain therapeutic levels by comparing and measuring each group's ATIII levels post cannulation and the average ATIII level per day (Table 2). Post cannulation, the cardiac group had an average ATIII level of 47.7 ± 5.8%, whereas the respiratory group had an average ATIII level of 67.3 ± 8.2%. The average ATIII level per day was 86.5 ±1.4% for the cardiac group and 78.1 ±3.1% for the respiratory group. Subsequently, on average, the patients are being treated to the lower threshold of therapeutic level once replacement begins. The low levels post-cannulation are in support of the findings that factors are both consumed immediately and slightly hemodiluted.

The cardiac failure group had a significant correlation between the number of pRBCs transfused per day and the dose of ATIII given per day ($p<.05$) (Figure 5). There seemed to be a cluster of patients with less ATIII and less pRBCs possibly suggesting that there is an ideal amount of ATIII that should be given to avoid blood product use. On the same graph, there were a few patients with significantly more ATIII used which correlated with more pRBCs, possibly suggesting that too much ATIII, an anticoagulant, may result in more bleeding necessitating increased blood product use. The respiratory group, on the other hand, did not show any significant correlation (Figure 6) between the amount of blood products used per day and ATIII units given per day.

Adverse events were measured on a nominal scale as yes or no, indicating whether they were observed throughout the entire ECMO run. There was suggestive evidence of clotting in 33 (80%) patients. Clotting was visualized on the circuit itself as dark or white areas most often at the oxygenator or tubing connection sites. Despite the presence of clotting in many of the circuits, only 13 patients required one or more circuit changeouts throughout the ECMO run.

DISCUSSION

The results suggest that antithrombin is, in fact, an important component in the treatment of ECMO patients. Both high doses and lack of antithrombin III replacement are correlated with excessive blood product use. There appears to be a therapeutic range to dose ATIII to prevent bleeding. With this insightful information, we can continue advance and improve anticoagulation therapy in ECMO patients.

Other studies have measured the effect of preoperatively treating patients with ATIII for cardiopulmonary bypass during cardiac surgery. One study by Avidan, et al., found that treatment with antithrombin III was effective in restoring heparin effectiveness, in addition to promoting anticoagulation at therapeutic levels for cardiopulmonary bypass[18]. Few studies, however, have specifically looked at ATIII replacement in adult ECMO patients as it correlates with outcomes and blood product usage. It is recognized that ATIII will continue to be consumed in the presence of heparin, and there is both hemodilution and activation of clotting factors from the ECMO circuit. Based on these reasons and the evidence from previous studies, patients may truly benefit from the maintenance of normal ATIII activity levels.

As antithrombin is an anticoagulant, it is possible that it can contribute to increased bleeding in these patients. Our correlation results in the cardiac group (r^2

= .49) suggested the possibility that too much ATIII may lead to increased RBC replacement. Other studies have not found that bleeding or the need for pRBC transfusion increases significantly with ATIII administration[16]. Further research with more patients must be conducted to increase the significance of this data.

Our data shows that patients receiving no supplemental ATIII necessitated significantly more blood products. When trying to understand why this might be true, we looked at the individual patients. One possible explanation could be that patient's heparin dose continued to increase to maintain anticoagulation standards based on ACTs and the non-ATIII dependent anticoagulant effects of heparin resulted in bleeding. ECMO runs ranged between 2 and 9 days, therefore it was not a short length of stay that resulted in not receiving ATIII. One patient had a heparin allergy, which would explain why ATIII was not given to him. That patient was given argatroban, which is a direct thrombin inhibitor, therefore its use is not dependent on the presence of ATIII . Almost all patients were placed on ECMO after extensive heart or lung surgery, such as post lung transplant (two patients), mitral valve replacement, aortic arch and root replacement (two patients). One patient was seen post trauma with pulmonary edema.

Further analysis collecting d-dimer levels did show elevated levels above the threshold criteria of <0.5 μg/ml in 5 out of the 6 patients throughout the run. D-dimers are fibrin degradation products that arise from the breakdown of clots

degraded by fibrinolysis. Positive d-dimer results maybe be suggestive that the coagulation system has been activated, and a patient is in disseminated intravascular coagulation (DIC). This is also known as consumptive coagulopathy. It occurs when the body is rapidly and pathologically activating the coagulation mechanisms that result in small blood clots in the vessels of the body. The clots consume all of the clotting factors, which can lead to abnormal bleeding from locations such as surgical wounds, cannulation sites, etc. Excessive bleeding may explain why the patients did not receive antithrombin, a natural anticoagulant. It could be suggested that the traumatic surgery resulted in activation and further consumption of the clotting factors, leading to increased d-dimers as well. When comparing d-dimer levels of patients that did receive ATIII, they had positive levels as well. This is not surprising as other studies have found elevated d-dimer levels at all times during ECMO despite adequate anticoagulation[19].

We also investigated fibrinogen levels. Low levels of fibrinogen can indicate DIC when fibrinogen is consumed faster than synthesized. It was found that only 3 of the 6 patients had below threshold fibrinogen levels. Despite the fact that the presence of d-dimers and low fibrinogen levels suggest DIC, more research would have to be completed to correctly identify these patients as having this diagnosis that is difficult to identify in general.

As expected, we found a significant decrease in heparin drip rates. The reasoning behind this is that adding ATIII is known to restore heparin's effectiveness and to promote therapeutic anticoagulation[20]. This contrasts with a similar study that did not find any significant drop in heparin dose or measured ACT following ATIII administration[16]. Using less heparin to achieve the adequate anticoagulation level is beneficial in preventing the potential adverse effects of using too much heparin. One of the most dangerous complications with the use of heparin is intracranial brain hemorrhage[13].

When looking at the summary statistics between the cardiac and respiratory group, we noted several significant differences to be interpreted. To begin, the differences in age were statistically different. One explanation could be that the older patients are more likely to suffer from the acute heart failure issues that require them to be placed on ECMO. Also significant were differences between the lengths of ECMO runs for both groups. Respiratory patients were placed on ECMO for almost twice as long and survival was significantly lower. Both length of run and survival may be related to the underlying pathology of these patients. Perhaps respiratory patients have more irreversible diseases involving their lungs and other organ systems. It is also possible that the severity of their condition is discovered too late for ECMO to be of considerable benefit. The cardiac patients possibly suffer from issues that are more temporary and reversible.

The other variables measured did not show statistically significant differences. There was no significance measured between antithrombin replacement and ACTs, length of stay, circuit change outs, or the presence of clots in the circuit. ACTs can be affected by a number of variables which might explain the wide variability and lack of correlation. More patients would need to be studied in order to determine any significant results.

This study has various limitations. Being retrospective, it is not possible to control factors such as whether or not patients receive ATIII, timing and quantity of dose, and timing of ATIII activity level measurements. ATIII dose was subject to the attending physician, therefore timing and dose were not necessarily standardized or consistent. Due to the fact that not all patients were given ATIII on a daily basis, we had to standardize dosing by dividing the total amount of ATIII given by how many days the patients were on ECMO. Also, at times the physician recommended dose would be rounded up to a full vial to reduce waste of an expensive product. In future use of antithrombin III, it would be beneficial to standardize dosing based on weight of the patient (kg). Given these patients are very sick, other comorbidities may be confounding to the results. Obviously, we cannot control the unlimited number of potential differences between the patient's etiologies.

CONCLUSION

Summary

The management of anticoagulation and bleeding together is a complex issue. Without sufficient anticoagulation, there can be consumption of coagulation factors and platelets that can eventually lead to worsening of bleeding[16]. The present study suggests that ATIII replacement is necessary while patients are placed on an extra-corporeal membrane oxygenation device. We know that ATIII will consistently be utilized in the presence of heparin and also that there will be a drop in ATIII due to hemodilution and factor activation from the circuit. In addition, as the results suggest, blood product use increases significantly without ATIII administration. Also, the cardiac group data show that it is possible that excessive ATIII is associated with blood loss as well as measured by pRBC replacement. For this reason, we can conclude that there is an ideal therapeutic range for ATIII administration.

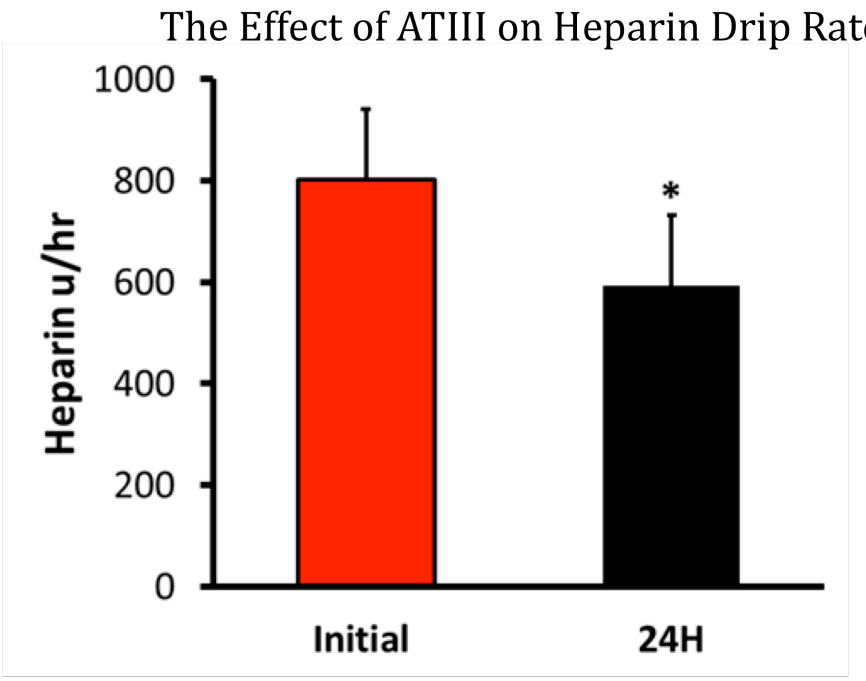
The benefits of this study are widespread. Most importantly, the ability to reduce bleeding would be beneficial. Reduction in the use of blood products via reduction in the amount of bleeding is advantageous to the patient by preventing the potential for transfusion reactions. Finally, reducing blood product use may be a financial incentive, despite the relatively high cost of antithrombin III.

Future Directions

There is great potential for future research to be performed in support of this data. It would be beneficial to require measurement of ATIII levels pre-cannulation to know what level patients have initially, in order to prevent excessive drops for reasons discussed previously, in patients that are dependent on heparin. This will benefit patients that have heparin resistance due to prior heparin therapy, and most importantly, those with decreased ATIII availability due to liver dysfunction as a result of sepsis or other disorders. In this way, we can also understand the average percentage drop in ATIII levels that can be expected from the initiation of ECMO. Also, establishing a protocol to standardize dosing would be beneficial to evaluate the effect of ATIII in a prospective manner. To date, no study has been performed to measure ATIII in ECMO patients, as it has been done successful in cardiopulmonary bypass patients. Eventually, we can extrapolate our findings to other patients such as those that are on total artificial heart and ventricular assist devices.

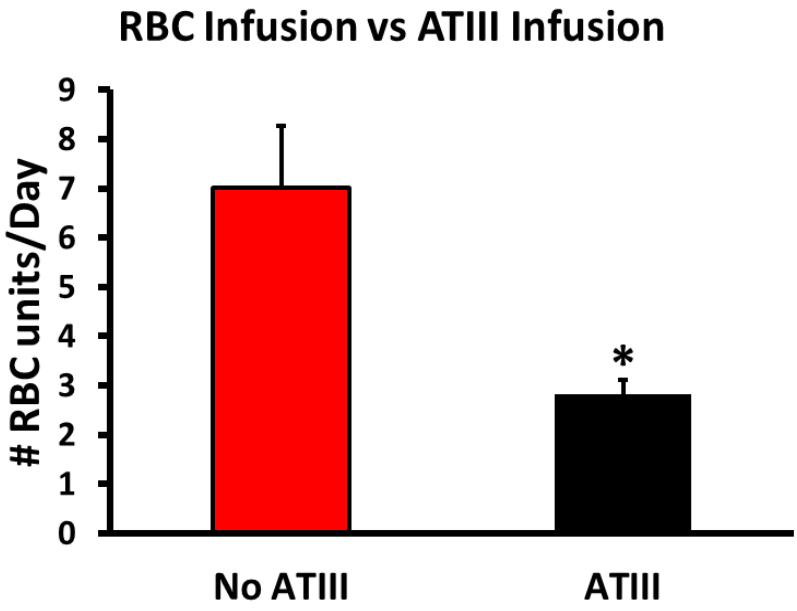
APPENDIX

Figure 1. Comparing heparin drip rate at first dose of ATIII and 24 hrs later.



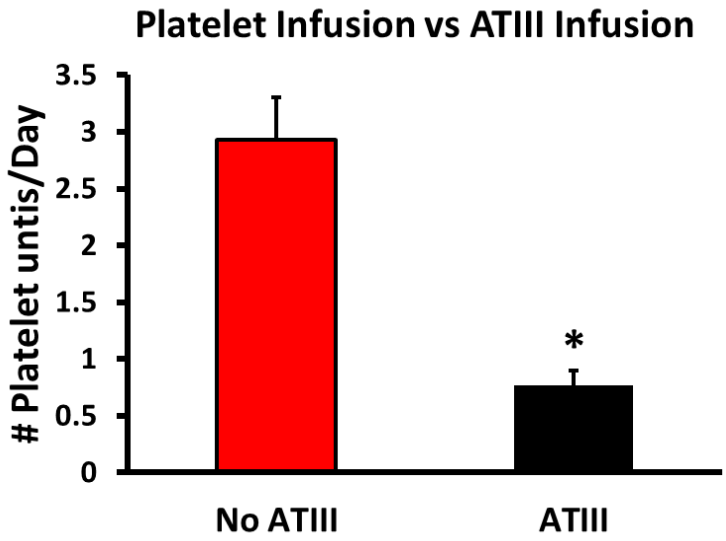
	Heparin at Dose	Heparin 24hr After
Mean	803	594.0703704
SE	138.203544	137.3237277
T-test		**0.032828587**

Figure 2. RBC Infusions measured at the units of RBCs given per day compared with ATII Replacement



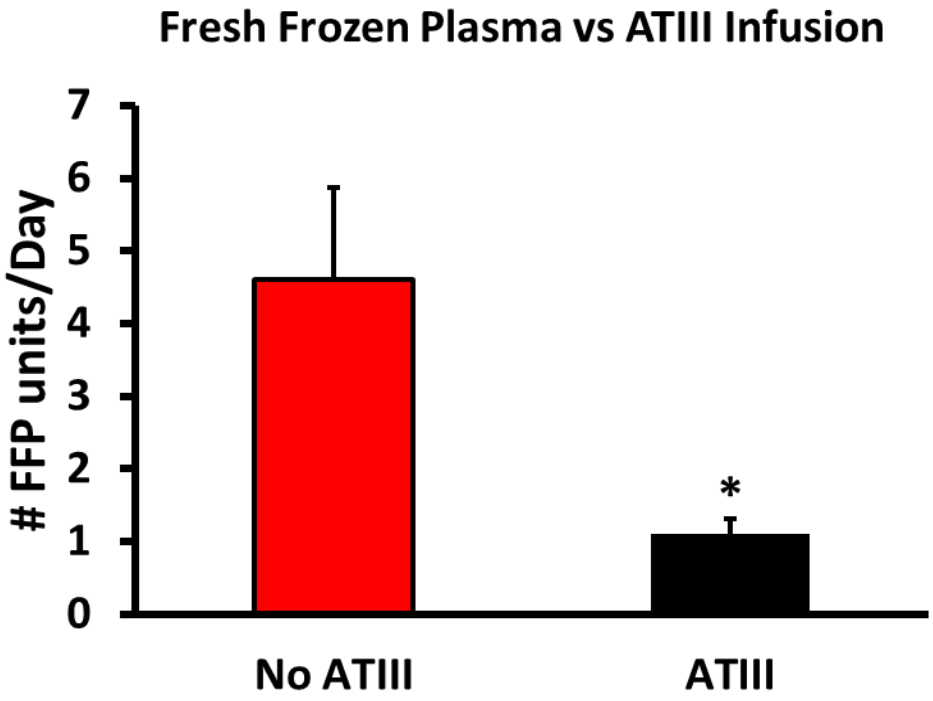
	RBC	
	NO ATIII	ATIII
MEAN	7.02	2.81
SEM	1.25	0.30
T-Test		2.20617E-05

Figure 3. Platelet Infusions measured at the units of Platelets given per day compared with ATII Replacement



	Platelets	
	NO ATIII	ATIII
MEAN	2.93	0.77
SEM	0.37	0.17
T-Test		3.18491E-05

Figure 4. FFP Infusions measured at the units of FFP given per day compared with ATII Replacement



	FFP	
	NO ATIII	ATIII
MEAN	**4.61**	**1.11**
SEM	**1.26**	**0.21**
T-Test		**1.11657E-05**

Figure 5.

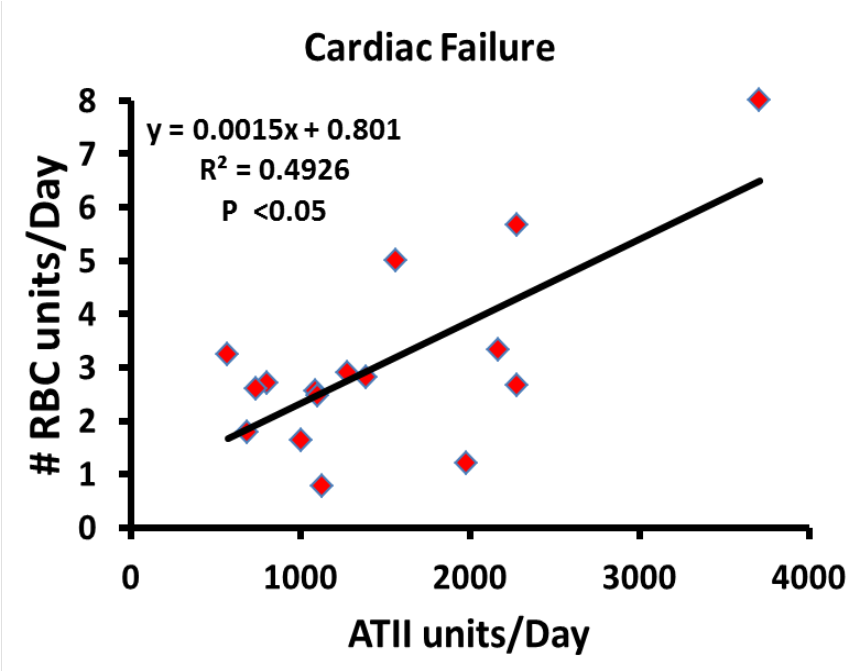

Cardiac Failure
y = 0.0015x + 0.801
R² = 0.4926
P <0.05
RBC units/Day
ATII units/Day
0
1
2
3
4
5
6
7
8
0
1000
2000
3000
4000

Figure 6.

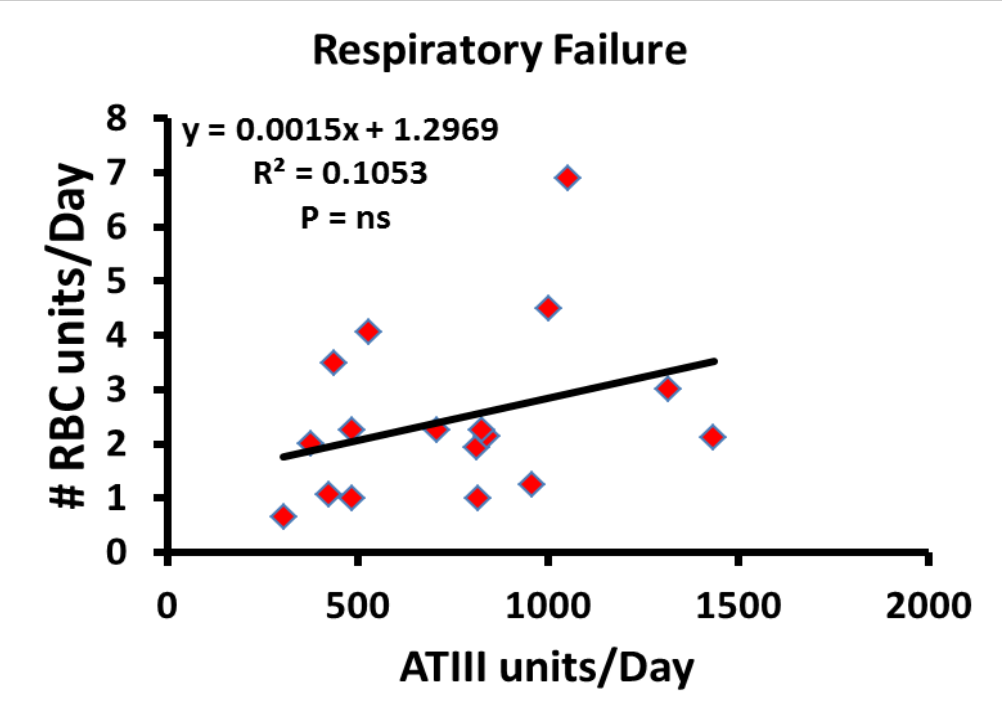

Respiratory Failure
y = 0.0015x + 1.2969
R² = 0.1053
P = ns
# RBC units/Day
0
1
2
3
4
5
6
7
8
0
500
1000
1500
2000
ATIII units/Day

Table 1. Summary statistics for cardiac and respiratory

Parameter	Units	Respiratory	Cardiac	P value
n		20	21	ns
Age	years	39.4 ± 3.3	57.7 ± 2.7	0.04
Weight	Kg	84 ± 6	92 ± 4	ns
BSA	M^2	1.9 ± 2.0	2.0 ± 0.1	ns
Gender	% males	50	68	ns
Length	days	14.1	7.4	0.0383
Survival	%	35	58	0.0002

Table 2.

ATIII Levels	Average ATIII Post Initiation (%)	Average ATIII Level/day (%)
Cardiac	47.7 ± 5.8	86.5 ± 1.4
Respiratory	67.3 ± 8.2	88.2 ± 5.5

REFERENCES

1. Allen, S., Holena, D., McCunn, M., et al. (2009). A review of the fundamental principles and evidence base in the use of extracorporeal membrane oxygenation (ECMO) in critically ill adult patients. *Journal of Intensive Care Medicine*, (26)1, 13-26.

2. Bartlett, R.H. & Gattinoni, L. (2010). Current status of extracorporeal life support (ECMO) for cardiopulmonary failure. *Minerva Anesthesiologica*, (76), 534-540.

3. Linhardt, R.J. Heparin: An important drug enters its seventh decade. *Chemistry & Industry*, (2), 45-50.

4. Chesterman, C.N., Chong, B.H. (1993).Uses of heparin. *British Medical Journal*, 306:871.

5. Oliver, W.C. (2009). Anticoagulation and Coagulation Management for ECMO. *Semin Cardiothoracic Vasc Anesth*, 13, 154-174.

6. Hensley, F.A., Martin, D.E., & Gravlee, G.P. (2008). Coagulation management during and after bypass. *A Practical Approach to Cardiac Anesthesia* (Fourth Ed., pp. 494). Philadelphia, PA: Lippincott Williams & Wilkins, a Wolters Kluwer Business.

7. Lefkovitz, J & Topol, EJ. (1994). Direct thrombin inhbitors in cardiovascular medicine. *Circulation*, 90, 1522-1536.

8. Levy, J.H., Montes, F., Szlam, F. & Hillyer, C.D. (2000). The In Vitro effects of antithrombin III on the activated coagulation time in patients on heparin therapy. *Anesthesia & Analgesia*, 90 (5), 1076-1079.

9. Hustead, V. & Kurth, M.H. (2006). Clinical Guideline: Antithrombin III. *ECMO Neonatal Clinical Management*. Minnesota Neonatal Physicians PA.

10. Toomasian, JM. & Bartlett, RH. (2011). Hemolysis and ECMO pumps in the 21st century. *Perfusion*, 26(1), 5-6.

11. Betrus, C., Remenapp, R., Charpie, J., et al. (2007). Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy. *Ann Thorac Cardiovasc Surg*, 13(6), 378-383.

12. Arnold PA, Jackson, S., Wallis, J., et al. (2001). Coagulation factor activity during neonatal extra-corporeal membrane oxygenation. *Intensive Care Med*, (27), 1395-1400.

13. Khaja, W.A., Bilen, O., Lukner, R.B., et al. (2010). Evaluation of Heparin Assay for Anticoagulation Management in Newborns undergoing ECMO. *American Journal of Clinical Pathology*, 134, 950-954.

14. Agati, S., Ciccarello, G., Salvo, D, et al. (2006). Use of a Novel Anticoagulation Strategy During ECMO in a Pediatric Population: Single Center Experience. ASAIO Journal, (52), 513-516.

15. Sievert, Alicia. Improvement in long-term ECMO by detailed monitoring of anticoagulation: a case report**.**

16. Neibler, R.A., Christenson, M., Berens, R., et al. (2011). Antithrombin Replacement During Extracorporeal Membrane Oxygenation. Artificial Organs, (35)11, 1024-1028.

17. Nankervis, C.A., Preston, T.J., Dysart, K.C., et al. (2007). Assessing Heparin Dosing in Neonates on Venoarterial Extracorporeal Membrane Oxygenation. ASAIO Journal, (53), 111-114**.**

18. Avidan, M.S., Levy, J.H. (2005). Recombinant human antithrombin III restores heparin responsiveness and decreses activation of coagulation in heparin-resistant patients during cardiopulmonary bypass. *The Journal of Thoracic and Cardiovascular Surgery*, (130), 107-113.

19. A.H., Willett, L.W., Fristoe, L., et al. (1995). Coagulation Monitoring during Extracorporeal Membrane Oxygenation: The Role of Thromboelastography. *The Journal of Extra-Corporeal Technology*, 27, 137-145.

19. Avidan, M.S., Levy, J.H., Scholz, J., et al. (2005). A Phase III, Double-blind, Placebo-controlled, Multicenter Study on the Efficacy of Recombinany Human Antithrombin in Heparin-resistant Patients Scheduled to Undergo Cardiac Surgery Neccesitating Cardiopulmonary Bypass. *Anesthesiology*, 102, 276-284.

20. Koster, A., Chew, D., Kuebler, W., et al. (2003). High antithrombin III levels attenuate hemostatis activation and leukocyte activation during cardiopulmonary bypass. *The Journal of Thoracic and Cardiovascular SurgeryI,* (126), 906-7.