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**Review Article**

# Flail chest with coagulopathy causes high mortality aggravated by acidosis and hypothermia

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## ABSTRACT

Flail chest is a condition where the ribs are broken in 2 or more places in successive ribs. The most common cause is blunt force trauma due to motorcycle accidents, falls or other conditions of bone abnormalities (congenital abnormalities, bone fragility) in young children or the elderly. This flail chest condition causes paradoxical movement of the chest when breathing. In line with the different breathing movements (moving inwards on inspiration and moving outward on expiration) this fracture compartment of the bone can injure the surrounding tissues which can cause complications such as pulmonary contusion with coagulopathy, inadequate ventilation which causes hypoxemia, and hypoventilation which causes acidosis due to reduced oxygenation of the tissues. Flail chest can also cause bleeding which ends in hypoperfusion causing hypothermia which will exacerbate coagulopathy. Flail chest is an important thing that needs to be assessed early after trauma so that no bad complications occur that lead to the triad of death (coagulopathy, acidosis, and hypothermia). Flail chest is an emergency condition frequently caused by blunt thoracic trauma. If it develops to pulmonary contusion it will lead to fatal condition implicates triad of death especially coagulopathy impaired by acidosis and hypothermia

**Keywords:** Flail chest, Hypothermia, Coagulopathy, Acidosis, Trauma, Mortality

## INTRODUCTION

Flail chest is a traumatic injury usually caused by a blunt trauma event of the thorax. It occurs when 3 or more ribs in sequence are broken in at least 2 places of the rib bone. These wounds result in a section of the chest wall moving apart from the remainder of the thoracic dome, which is known as a flail chest. The physiology of breathing can be significantly disturbed by a flailing chest. It is critical for people who are elderly or who have chronic lung illness to have this interruption in respiratory function. Significant physical damage to the chest wall is typically linked with a flail chest.[1]

Since there are segmental fracture on the rib bones, it can lead to distinct movement of the thoracic dome specifically on the fracture sites. Accordingly, while inspiration occurs, the motion should comprised contraction of diaphragm and inflation of respiratory muscle; but on the fracture sites will move inward. By expiration, the chest motion should be deflated yet on the fracture site will result in outward maneuver. These independent movement giving rise to the term 'paradoxical respiration'.[2] Pleural pressure, the size of the flail, and the contraction of the intercostal muscles during inspiration are the three elements that determine the intensity of this paradoxical motion and its physiological impact.[1]

There are three ways that a flail piece of the chest wall will harm breathing: inefficient ventilation, pulmonary contusion, and hypoventilation with atelectasis. higher dead space, lower intrathoracic pressure, and higher oxygen demand from wounded tissue all contribute to inefficient breathing. Nearly always, when the chest flails, there is pulmonary contusion in the nearby lung tissue. Edoema, haemorrhage, and even some necrosis result from pulmonary contusion. Gas exchange is hampered and compliance is decreased by pulmonary contusion. The pain of the injury leads to hypoventilation and atelectasis. Splinting due to pain reduces tidal volume and increases the risk of developing atelectasis.[1]

Up to 25% of blunt trauma fatalities are caused by thoracic injuries and its sequelae. The most frequent damage associated with blunt thoracic trauma, occurring in 30% to 75% of cases, is pulmonary contusion (PC). Explosion injuries can result in isolated PC, but most patients who have multiple wounds also have damage to the chest wall. On the other hand, considerable PC is frequently present in flail chest (FC), the most serious type of traumatic chest wall injury with death rates of 10% to 20%.[3] Flail chest complicates about 10% to 20% of patients with blunt chest trauma and is associated with a mortality rate ranging from 10% to 35%.[4] The recent study found that 19.9% of flail chest injury patients died. When combined with flail chest injury, sepsis, simultaneous head damage, and a greater ISS are independent risk factors for death.[5] In order to understand more about flail chest complication, this article aim to discuss the condition.

## FLAIL CHEST ETIOLOGY

Blunt thoracic trauma, including direct punches, falls from great heights, and automobile accidents, frequently results in flail chest. Typically, a flail chest is accompanied by other traumas such damage to extra-thoracic organs, shock, and blood loss.[6] The most frequent cause of flail chest is blunt thoracic trauma. Multiple sequence rib fractures are most occurs after motor vehicle accidents and falls, although it can also develop after intensive CPR or in patients with pathological rib fractures. In children, flail chest is rarely reported because the chest wall is more flexible; thereby when a child has a chest injury, it means a much greater extent of the injury. In scarce cases, flail chest can complicate and leads to rib surgery or appear in infants due to congenital malformations of the ribs.[7]

About 75% of serious traumas that result in flail chest are the consequence of motor vehicle crash. Another 15% is attributable to falls, especially in the elderly. Direct chest strikes and other traumatic events are more likely to result in two fractures on a single rib. Rollover and crush injuries are more likely to only break the ribs once, which lessens the likelihood of a flail chest. This disorder is predisposed in children with metabolic bone disease and osteogenesis imperfecta. The physiologic stiffening of the chest wall with advancing age, as well as the possibility of osteoporosis, predispose the elderly to flail chest. They also have a higher likelihood of having pre-existing lung illness, which puts them at greater risk for flail chest problems.[1] Due to the fragility of their bones, even low energy shocks in the elderly can produce flailing of the chest, but in children only 1% of major hits cause paradoxical chest motion since their ribs are more flexible.[8]

## FLAIL CHEST AND TRIAD OF DEATH

It has been demonstrated that the death triad-coagulopathy, hypothermia, and acidosis-is a reliable indicator of mortality in trauma patients. Triad of death can be seen when patients arrive at the emergency room, they have coagulopathy (international normalised ratio [INR] >1.5), hypothermia (temperature 35 °C evaluated by tympanic thermometers), and metabolic acidosis in whole blood (potential of hydrogen (PH) 7.2). It has been established that the death triad seen in trauma victims is an effective predictor of mortality. With the addition of all three elements of the death triad, the mortality of trauma patients at 24 h rose. The death triad correctly predicted 24 hours mortality in 96% of patients who had multiple traumas. The death triad accounted for 85% of mortality in patients with significant vascular injuries and abdominal gunshot wounds, with mortality rates as high as 40%. If the trauma patient displayed all three aspects of the death triad, the overall fatality rate may reach 47.8%.[9] Since flail chest is a considerable presentation of a fatal trauma, it is possible to found the death triad components on the clinical finding of the patients. Coagulopathy can be found in flail chest because underlying adverse condition such as pulmonary contusions that may be complicated by pneumothorax, hemothorax, or pleural effusion.[10]

Traumatic injury to a vessel's wall can reveal subendothelial collagen and activate tissue factors, which support the interaction between the cellular and humoral components of the hemostatic system and serve as a platform for circulating platelets to adhere to. Natural anticoagulants work as a counter-regulatory system to this pro-coagulant activity. By supplying endogenous anticoagulation and fibrinolysis, the combined effect of these two competing systems may cause the coagulatory response to be triggered at the site of endothelial injury while preventing uncontrolled microvascular thrombosis and tissue hypoperfusion. The process' components are intricately interwoven, with thrombin playing a crucial part because it can participate in both the coagulation and anticoagulation pathways as well as the inflammatory response.[11]

Hypothermia can develop after trauma due to heat loss, decreased heat generation, and fluid administration. At temperatures below 36 °C, clinically significant reductions in platelet function and coagulation factor activity begin to occur, and at temperatures below 33 °C,

these reductions become significantly worse. Several crucial coagulation phases are impacted by hypothermia, including the ones listed below: negatively impacts platelet function; decreases clotting factor enzyme activity; induces fibrinolysis to become active; the effects can be reversed by bringing the body temperature back to normal, which is a first-level objective that can be accomplished by using thermal blankets, other methods of physically warming the patient, or by giving them hot beverages (40 °C). Overall, the lethal triad's other two elements affect clotting at all stages.[11]

## DEFINITION OF COAGULOPATHY

A condition known as coagulopathy, often known as a bleeding disorder, affects the blood's capacity to coagulate (form clots). Coagulopathy is typically seen in the acute phase of trauma in patients with severe injuries. The coagulopathy known as trauma-induced coagulopathy is brought on by the trauma itself. Coagulation activation, hyperfibrinogenolysis, and consumption coagulopathy make up the pathophysiology of trauma-induced coagulopathy. The fibrinolytic phenotype of DIC is characterized by several pathophysiological processes. Coagulopathy is typically seen in the acute phase of trauma in patients with severe injuries, and it has a significant impact on the prognosis. There are several elements related to the trauma itself as well as specific interventions that contribute to this coagulopathy, which has been labelled by different names. The coagulopathy brought on by various trauma-related factors is referred to in this publication as "trauma-associated coagulopathy," whereas the coagulopathy brought on by the trauma itself is referred to as "trauma-induced coagulopathy".[12]

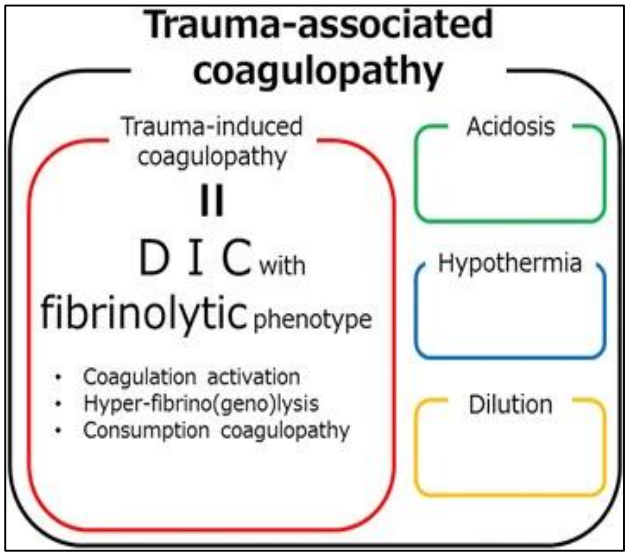


**Figure 1: Trauma-associated coagulopathy and trauma-induced coagulopathy. Trauma-associated coagulopathy is caused by multiple factors and includes trauma-induced coagulopathy, which is caused by trauma itself.**

Thrombin generation occurs in the systemic circulation due to the presence of procoagulants and impaired anti-coagulant activities. Antithrombin activity decreases, while thrombin generation increases in severe trauma. Soluble thrombomodulin and markers like D-dimer and FDP are elevated, indicating thrombin generation. Plasma fibrinogen level decreases earlier than other coagulation parameters. Patients with disseminated intravascular coagulation at an early phase of trauma show normal prothrombinase activity, increased systemic thrombin activity, and lower antithrombin levels. Soluble thrombomodulin is formed through proteolysis, while soluble fibrin and fibrinopeptide A reflect active thrombin. Histone and histone-complexed DNA fragments induce inflammation and coagulation activation.[12]

Prothrombotic or antithrombotic, fibrinolytic or antifibrinolytic processes must delicately coexist in order for physiological clot formation and disintegration to occur. Traumatic brain injury (TBI), shock, and other individual reactions to these insults combine to cause early and late phenotypes of trauma-induced coagulation (TIC). Additionally, the mechanisms behind various phenotypes can manifest themselves at various points following injury. As a result, TIC phenotypes come in a wide variety and evolve throughout time. Early TIC is often characterised by hypocoagulability, which causes bleeding; later TIC is characterised by a hypercoagulable state linked to venous thromboembolism and multiple organ failure. TIC is caused by a number of pathophysiological mechanisms, including the 'lethal trio' (coagulopathy, hypothermia, and acidosis), which intensifies endothelium, immune system, platelet, and clotting activation when tissue injury and shock are combined. Additionally, traumatic brain injury plays a unique function in TIC. Fibrinogen depletion, insufficient thrombin synthesis, compromised platelet function, and dysregulated fibrinolysis are all examples of hemostatic disorders.[13]

## COAGULOPATHY CAUSED BY FLAIL CHEST

Many acute inflammatory lung disorders, such as acute lung damage, are characterised by increased bronchoalveolar coagulation (extravascular fibrin deposition).[14] The term "pulmonary contusion" refers to the destruction of the lungs along with alveolar haemorrhage, which typically results from a blow to the chest without laceration. Pulmonary contusion should always be looked at in cases of severe blunt chest trauma, including flail chest as one of the background.[6]

When kinetic energy is transferred to the lung parenchyma, pulmonary contusion happens. As a result, lung tissue bleeds, becomes inflamed, and develops pulmonary edoema. The tissue of the lungs is severely altered by bleeding and edoema. Hypoxia, the most frequent result of pulmonary contusion, is one of these catastrophic changes. Within the first 24 hours,

parenchymal damage peaks. The production of local inflammatory chemicals also impairs immunological function, making the patient more vulnerable to infections. These mechanisms not only affect the wounded section of the lung but also other parts of the lung. The mechanism of trauma-induced pulmonary contusion still needs to be fully understood, and the pathophysiology of inflammation may differ from what is now understood.[6]

Both direct pulmonary injuries from forceful chest trauma and indirect ones from traumatic brain damage might result in respiratory failure. It should be kept in mind that the patient's respiratory discomfort in this case could be caused by brain damage. There could also be complicated diseases that cause both lung and brain damage. It's interesting to note that 29% of traumatic brain injuries are linked to pulmonary contusions, and that traumatic brain injuries are typically linked to thoracic injuries. In addition, trauma victims' hypercoagulability causes pulmonary embolism, which results in respiratory failure.[6]

A study by Brohi et al proposes that the pathology more closely resembles a consumptive coagulopathy compatible with the hemorrhagic DIC phenotype.[15] Another theory from Gando et al states that acute traumatic coagulopathy is begun by hypoperfusion and leads to systemic anticoagulation and excessive fibrinolysis via the activated protein C pathway.[16] There is a rise in sympathoadrenal activation with increasing trauma severity. This neurohumoral reaction both activates systemic anticoagulation mechanisms and causes local hemostasis, which may result in consumptive coagulopathy, which promotes coagulopathy. Whatever the mechanism, these individuals who present with early TIC (trauma induced coagulopathy) have a death risk that is up to four times higher.[17]

Experimental bacterial models of pulmonary coagulopathy are a major source of current knowledge. In these models, the tissue factor (TF); TF-FVIIa pathway appears to be the mechanism by which pulmonary coagulation is activated. This is supported by the finding that no enhanced markers of intrinsic pathway activity are present. A strong TF staining was also observed on alveolar epithelial cells, intraalveolar macrophages, and hyaline membranes in an immunohistochemistry examination of ARDS patients. Additionally, the TF-FVIIa pathway is inhibited, which attenuates the buildup of pulmonary fibrin.[14]

TF may be found on alveolar macrophages, pulmonary vascular adventitia, and pulmonary epithelium. Infiltrating and resident macrophages both persistently express TF. Normal lung conditions have low TF levels, while inflammatory lung diseases have levels that are more than ten times higher. Alveolar macrophages have a major role in TF-mediated pulmonary fibrin production. Endotoxin activates alveolar macrophages through NF-κβ. Increased levels of FVII and thrombin-antithrombin complexes (TATc) in bronchoalveolar lavage fluids (BALF) show that activation of alveolar macrophages causes TF expression to increase and the start of bronchoalveolar coagulation. Activated macrophages produce reactive oxygen species (ROS), cytokines, and chemokines in addition to TF expression. They can also express FVII, FXIII, and high affinity binding sites for FX/Xa and fibrinogen. An active coagulation cascade that produces extravascular fibrin can be formed and amplified by locally activated coagulation zymogens in conjunction with leakage of plasma proteins into the alveolar space brought on by microvascular damage.[14]

Urokinase plasminogen activator (uPA), whose levels rise in endotoxemia, is the most significant PA in the lung. Fibrinolytic activity first increases as a result of this. Plasminogen inhibitors quickly stop this rise in fibrinolytic activity. Plasminogen inhibitors 1 and 2 (PAI-1 and PAI-2) are both found in the pulmonary compartment. While alveolar macrophages largely express PAI-2, pulmonary epithelial cells and fibroblasts express PAI-1 and 2. Inflammation of the lungs induces the local synthesis of PAI-1 and PAI-2. Increased amounts of PAI-1 are released under inflammatory conditions by pulmonary epithelial cells, fibroblasts, and endothelial cells. Leakage of blood plasma into the lung also increases the amounts of PAI-1 and alpha-2-antiplasmin-1 and PAI-2 synthesis in response to inflammatory stimuli, a regulator function for the renin-angiotensin system has also been proposed. Angiotensin II (ANG II) can be produced locally in lung tissue, according to research (38). The synthesis of PAI-1 in endothelial and smooth muscle cells may be induced by ANG II.[14]

In practically all tissues, PAI-1 is recognised as the most significant inhibitor of fibrinolysis. The pulmonary compartment appears to be another area where PAI-2 has a significant impact. The fact that alveolar macrophages secrete relatively significant amounts of PAI-2 after being activated by endotoxin emphasises this. In this manner, following a brief stimulation by uPA, pulmonary fibrinolysis is decreased by a persistent rise in levels of both PAI-1 and 2.[14]

## EFFECTS OF HYPOTHERMIA ON COAGULATION

Due to the prevalence of accidental hypothermia (AH), hypothermia has a dubious place in the treatment of polytrauma patients including blunt chest trauma such as flail chest, penetrating abdominal trauma, and hemorrhagic shock. AH can be classified as mild (33-36°C), moderate (28-32.9°C), deep (11-27.9°C), profound (6-10.9°C), and ultraprofound (6°C) by its degree Celsius (°C). The forced volume control and exposure to chilly environments cause a drop in body core temperature. Following ATLS recommendations is essential to prevent the deadly trio of coagulopathy,

acidosis, and unintentional hypothermia, as these factors worsen patients' prognoses. After blunt chest and penetrating abdominal trauma, problems with significant mortalities associated with hemorrhagic shock develop in the clinical course.[18]

Temperatures below 34°C result in reversible thrombocytopenia and thrombocytopathy, which are coagulation diseases. Below 33°C, plasmatic coagulopathy with abnormal thrombin and fibrin function occurs. Coagulopathy is defined as a problem in the process of blood clot formation. Quantitatively, it was found that the PTT or aPTT value was 1.5x more than the normal value. In trauma, coagulopathy is a combination of blood loss, hemodilution, consumption of platelets, and clot formation factors, hypothermia and acidosis.[(19)] Hypothermia has a significant effect on coagulopathy. Coagulopathy contributes 4-5 times the risk of morbidity and mortality in severe trauma.[20] Trauma patients with low survival, 80% have a temperature of less than 34$^{O}$C at death. Patients with body temperature 36.1±0.7$^{O}$C, have 2.4 times the risk of blood loss during post-laparotomy compared to patients with a body temperature of 33.8±0.5$^{O}$C. The relationship of hypothermia to coagulopathy has long been described.[21]

It is important to know the coagulopathy in trauma patients by knowing the correct coagulation pathway. The goal of hemostasis is to produce a stable blood clot formed by fibrin and platelets. The process of hemostasis is divided into 3 phases, namely initiation, amplification and propagation. Clot initiation occurs when extravascular tissue factor, present after trauma, combines with factor VIIa. Factor VIIa is a coagulation factor that exists in an active form in the blood. This event activates factors V, IX and X and generates small amounts of thrombin. In the presence of platelets, thrombin will surround the factor by Willebrand and factor VIII, activating factors V and XI and causing platelet activation. This phase is called Amplification. Only once activated platelets are activated causing breakdown of thrombin resulting in insoluble fibrin in the propagation phase. Platelets play a major role in the cell-based theory of blood clot formation. This process requires metabolically active platelets for activation and aggregation. Without the surface platelets present at the site of injury, factor Xa and thrombin spread appropriately and are inactivated. The inactivation of these factors, coupled with the fibrinolysis mediated by proteins C and S, is more likely to lead to the placement of a blood clot at the site of trauma than to uncontrolled coagulation processes throughout the vascular system.[22]

Hypothermia interferes with the body's ability to form blood clots. When the temperature drops, the activity of the protease decreases, the activity of factor VII decreases as the temperature decreases, reducing up to 80% at 33$^{O}$C. But this effect is small compared to the effect of hypothermia on platelets. Platelet activation will decrease along with decreased interaction between vWF and collagen glycoprotein 1b and X (GP1b/X) loses its activity below 30$^{O}$C. As body temperature decreases, blood loss increases, mortality increases. Body temperature 34$^{O}$C significantly inhibits the physiological processes of platelets and decreases enzyme activity. Hypothermia triggers α-adrenergic stimulation with vasoconstriction, and exacerbates hypoperfusion of organs that are already hypotensive. This exacerbates the acidosis. Hypothermia induces morphological changes in platelet structure during activation, and induces coagulopathy by reducing the availability of platelet activator, thereby *in vitro*, thrombin inhibition, increased GMP-140 complex response, decreased GPIb-IX complex response, platelet aggregation, production Thromboxane B2, and platelet formation live. Every drop of 1$^{O}$C temperature, resulting in decreased production Thromboxane B2 and platelet aggregation. In platelets, the intracellular concentration of calcium, and the three catalyzing steps of arachidonic acid metabolism become Thromboxane A2 by lane cyclooxygenase closely related to temperature. Thus, hypothermia acts on platelet activation and adhesion by inhibiting the interaction between factors widebrand with the GP1b-IX-V complex. Systemic evaluation of temperature on coagulation enzyme activity showed: Factor Xa production was reduced by 13% at 33°C$^{O}$C compared to 37$^{O}$C, activity prothrombinase (FXa/Va) decreased in a certain pattern at 37$^{O}$C-33$^{O}$C, and thrombin production decreased by 25 percent at 33$^{O}$C. Under temperature 33$^{O}$C, a decrease in the ratio of enzymatic reactions inhibits the activity of coagulation factors. Thus, between temperatures of 37$^{O}$C-33$^{O}$C has defects in platelet aggregation and adhesion, and is under 33$^{O}$C there is inhibition of enzyme activity. Systemic hypothermia between temperatures of 31$^{O}$C-34$^{O}$C, increased microvascular thrombosis mediated by increased activation of GPIIb-IIIa receptors on platelets. Fibrinogen may bridge the occurrence of GPIIb-IIIa receptor activation. So the use of fibrinogen causes coagulopathy.[22-24]

The protein C pathway is one of the causes of coagulation-induced trauma, when trauma is associated with hypoperfusion. Hypoperfusion causes expression trombomodulin on the endothelial cell wall. During rupture thrombin combines with thrombomodulin and endothelial receptor protein C. This complex activates protein C, which plays a role in inhibiting factors V, VIII, and plasminogen factor inhibitor 1, causing hypercoagulable state and hyperfibrinolysis. However, some experts who disagree with the protein C pathway are of the view that coagulation in trauma patients is only a manifestation of coagulation Disseminated Intravascular Coagulation (DIC) with a fibrinolytic phenotype and decreased coagulation factors. They further stated that hypoperfusion causes excessive fibrinolysis but when bleeding is followed, reduced coagulation factors play a more important role. Fibrinogen levels, fibrin formation, and trauma-induced fibrinolysis have been major problems in studies of trauma-induced coagulopathy. The role of primary

fibrinolysis is important in trauma-induced coagulopathy and its onset is 1 hour post-traumatic. Fibrinolysis is associated with the incidence of multiple blood transfusions, coagulopathy, and death related to bleeding.[25]

The study by Fairchild et al stated that hypothermia prolongs the release of TNF-α via the NF-α pathway. According to Frank et al when excessive acute phase protein release due to inhibition of TNF-α clearance, which frequently occurs in patients with surgical procedural complications under hypothermic conditions, causes a threefold risk associated with heart disease. Other complications of hypothermia, such as wound infections, generalized sepsis, and coagulopathy, are also associated with complications of prolonged TNF-α release.[26]

## EFFECTS OF ACIDOSIS ON COAGULATION

Paradoxical movement of the chest caused by flail chest usually coexists with contusion resulting in shallow tidal volumes, alveolar collapse, arteriovenous shunting, and hypoxemia, which together with the pain cause respiratory insufficiency. While oxygen was administered, tidal volume values remained constant despite an increase in $PaO_2$ ($PO_2$ in alveoli), which was explained by a decrease in intrathoracic volume. As a result, it is incorrect to draw the conclusion that only flail chest is related to hypoxia. Hypoxia can be brought on by a number of things, but flail chest itself cannot. These things include ventilation/perfusion mismatch leading to contusion, haematoma or alveolar collapse, inadequate tissue oxygen delivery (due to pneumothorax). In addition to poor breathing and diminished consciousness, hypercarbia can also result in metabolic acidosis, which is a common finding that should not be disregarded.[2]

After trauma, patients frequently experience acidosis, which develops as a result of insufficient tissue oxygenation and the subsequent activation of anaerobic metabolism. Nearly all phases of clotting are jeopardised in an acidotic environment due to dysfunctional plasma proteins and the rapid breakdown of fibrinogen. When the pH falls below 7.4, we noticed reduced clotting factor activity, weakened thrombin generation, altered platelet shapes and structures, and decreased fibrinogen concentration; increased platelet-mediated neutrophil pro-inflammatory responses; increased fibrinogen degradation (caused by increased fibrinolysis and increased factor XIII levels) without effects on fibrinogen production; administration of bicarbonate to treat acidosis does not correlate with TIC reversal.[11]

Acidosis speeds up fibrinogen breakdown, which could result in a shortage of fibrinogen availability. Thrombin production was initially moderately reduced by acidosis of pH 7.1. However, acidosis significantly and continuously hindered the production of thrombin throughout the propagation phase, showing that acidosis severely hampered the activation of FV, FVIII, FIX, and FX as well as the creation of the FXase and prothrombinase complex. Since FVIIa is not a part of the propagation phase and acidosis causes severe suppression of thrombin formation during that phase, administering rFVIIa will not be able to reverse this inhibition. Therefore, administering rFVIIa along with pH adjustment may be a superior approach for treating individuals with acidotic coagulopathy. Acidosis on pH 6.9 also reported inhibited the platelet aggregation and decreased fibrinogen and platelet counts, even after pH neutralization the level are remained low.[21]

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