Effects of Activated Recombinant Factor VII (rFVIIa) on Coagulation Parameters in Hemorrhaged Acidotic and pH Corrected Swine.

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Introduction

Coagulopathy is a component of the lethal triad associated with the development of acidosis and hypothermia after traumatic injury. This coagulopathy associated with hemorrhage/trauma has been reported to be caused by a number of factors, one of which is acidosis. Metabolic acidosis occurs in severe hemorrhagic shock and trauma. Experimental acidosis that is induced by HCl infusion decreases thrombin generation and fibrinogen concentration, increases bleeding time and alters platelet function. Acidosis decreases clot strength and rFVIIa activity *in vitro*.

Although severe hemorrhage is associated with both hypo-coagulation and acidosis, particularly in the patients who eventually die, it is not know if correction of the acidosis in severe hemorrhage will correct or attenuate the coagulopathy.

rFVIIa has been used to treat uncontrolled bleeding refractory refractory to other means of hemorrhage control. It is reported that rFVIIa is ineffective in patients with acidosis. However, it is not clear whether correction of the acidosis will improve the response to rFVIIa.

Objective:

- To determine if acidosis causes hypo-coagulation seen after severe hemorrhagic shock similar to that seen in HCl infusion models of acidosis.
- To determine if acidosis affects rFVIIa activity in improving coagulation function.

Methods

• 40 kg swine were instrumented with cannulas in the femoral artery and vein, and in the right jugular and carotid vessels. The pig was intubated with an endotracheal tube and a surgical plane of anesthesia established and maintained using isoflurane inhalant anesthetic (1 – 3%), and ketamine 100-400µg/kg*min.

• Baseline pH was 7.41±0.01and ET pCO_2 was 45.3±1.9 mmHg (range from 36 to 52).

• Pigs were divided into 3 groups (n=8/group): 1) Control swine were catheterized but not hemorrhaged or made acidotic (Figure 1, black). 2) The acidosis group was made acidotic by controlled hemorrhage to lower and maintain MAP at 35mmHg by bleeding or reinfusion of shed blood. In addition, ventilation (tidal volume and/or rate) was also reduced until an arterial pH=7.1 was reached (Figure 1, red). 3) The acidosis corrected group was made acidotic as in group 2. The acidosis was then corrected (pH7.1 to 7.4) by iv infusion of 100ml/40kg of 8.4% Sodium Bicarbonate inj., and adjusting ventilation back to pre-hemorrhage levels (Figure 1,blue). All groups received equal volumes of fluid. Groups 1 and 2 were infused with saline, while group 3 received bicarbonate as mentioned.

•Arterial blood samples (30ml) were taken at baseline (pH 7.4), T1 (pH7.1) and T2 (pH corrected back to 7.4) as shown in Figures 1 and 2 for determination of coagulation function. rFVIIa was injected after T2 and blood sampled atT3 in all groups. Cardiovascular parameters were monitored via the carotid cannula. A representative animal is illustrated (Figure 2).

Figure 1

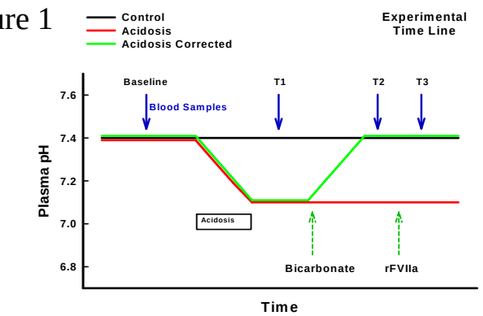


Figure 2

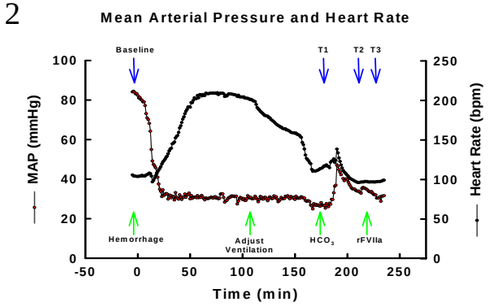


Figure 3

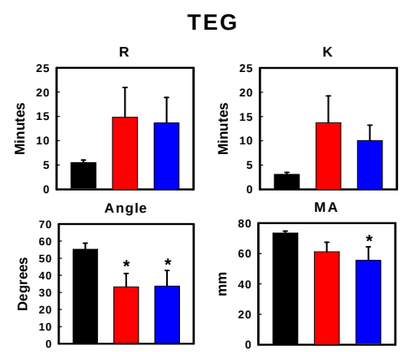
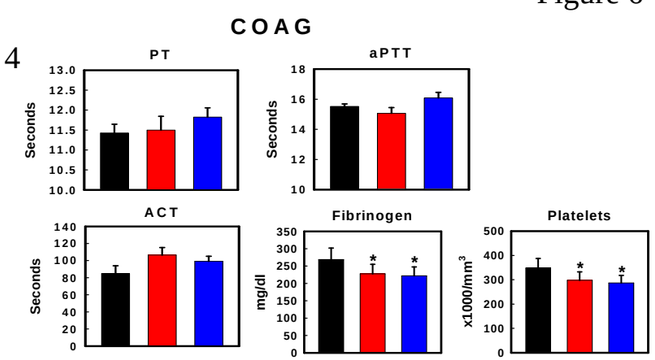


Figure 4



Legend for Figures 3, 4, 7

- pH 7.4 (baseline)
- pH 7.1
- pH 7.1 corrected to 7.4

Figure 5

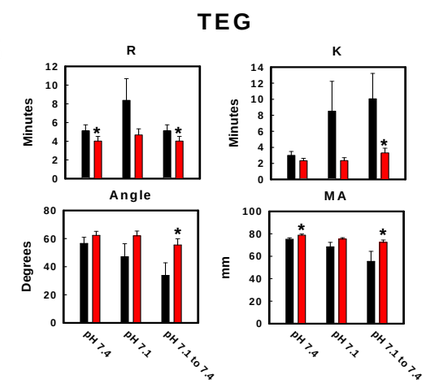
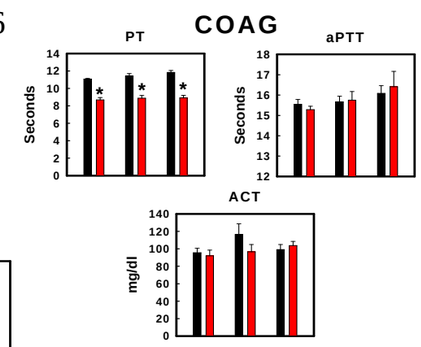


Figure 6



Results

1) Severe arterial acidosis (pH 7.1) was induced by a combination of a decrease in a) blood volume and b) respiration in anesthetized swine (Figures 1 and 2).
2) Acidosis led to a hypo-coagulation state as shown by Thrombelastography (TEG, Figure 3). However, classic coagulation tests PT, aPTT and ACT did not show significant changes (Figure 4).
3) Fibrinogen concentration and platelet number showed a slight but significant decrease after hemorrhage. This is presumably due to movement of extra-vascular fluid into the vascular space leading to a dilution of fibrinogen and platelets (Figure 4). Also, some loss could be due to consumption.
4) Correction of pH from 7.1 to 7.4 with bicarbonate infusion did not restore any TEG parameters to baseline (Figures 3 and 4).
5) Acidosis did not significantly affect rFVIIa function, based on PT. However, based on TEG, correction of acidosis with bicarbonate will improve rFVIIa action (Figs 5 and 6).

Conclusions

1) This metabolic/respiratory acidosis model is associated with hypo-coagulation.
2) The hypo-coagulation produced by this model was not corrected or attenuated after returning pH to 7.4 with Na Bicarbonate similar to what was observed with the HCl infusion model.
3) Acidosis correction should improve rFVIIa function.
4) Clinically, this type of coagulopathy is likely not corrected simply by normalizing arterial pH alone.

* P<0.05 as compared to baseline by 1-way ANOVA CRM followed by pairwise comparisons (Holm-Sidak method). Data expressed as Mean±SE. Before and after rFVIIa by t-Test.