Thrombin Generation in Response to Hemorrhage in Acidotic and pH Corrected Swine

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The use of Army medical and/or other Army records in the preparation of this material is acknowledged, but is not to be construed as implying official Department of the Army approval of the conclusions presented.

Objectives

To determine the effects of acidosis and pH correction on thrombin generation in swine.

Rationale:

•Approximately 25% of trauma patients with severe injuries are coagulopathic (INR≥1.5). These patients have a mortality rate four times higher than trauma patients without coagulopathy. This coagulopathy is manifested as an inability to form haemostatic clots, resulting in diffuse, persistent bleeding (1).

•Coagulopathy that is 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 decreased thrombin generation and fibrinogen concentration, increased bleeding time and altered platelet function.

•Although severe hemorrhage is associated with both hypo-coagulation and acidosis, it is not known if correction of the acidosis by bicarbonate will correct or attenuate the coagulopathy.

1) Brohi, Cohen and Davenport. Acute Coagulopathy of Trauma: mechanism, identification and effect. Curr Opin Crit Care 13:680, 2007.

Methods

•40kg 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 was established and maintained using isoflurane inhalant anesthetic (1 – 3%), and ketamine 100-400mg/kg/min.

•Three groups of swine (n=8/group) were used. Two groups (Acidosis and Corrected) were made acidotic by controlled hemorrhage to bring down and maintain MAP at 35mmHg, by bleeding or reinfusion of shed blood as needed. In addition, ventilation (tidal volume and/or rate) was also reduced until an arterial pH=7.1 was established (Figure 1).

• In the Acidosis Corrected group (Corrected, green, Fig1), the acidosis was corrected (pH7.1 to 7.4) by iv infusion of 100ml/40kg of 8.4% sodium bicarbonate, and by adjusting ventilation back to baseline levels. pH was not corrected in the acidotic group (Acidosis, red, Fig1) . The control group (Control, black, Fig1) was not hemorrhaged and pH was maintained at 7.4.

•Arterial blood samples were collected at baseline (pH 7.4), T1 (pH 7.1) and T2 (pH corrected back to 7.4), as shown in Figures 1 and 2, for determination of thrombin generation. Cardiovascular parameters were monitored via the carotid cannula. A representation of mean arterial pressure and heart rate is illustrated in Figure 2.

Thrombin Generation

•Thrombin generation was measured via the Fluorskan Ascent - Calibrated Automated Thrombinoscope (BioDis/Diagnostica Stago).

•Thrombin generation parameters measured include: endogenous thrombin potential (ETP), lag time, peak thrombin concentration, and time to peak (tt Peak).

•All results were obtained from thawed, citrated, platelet-poor plasma.

Figure 1

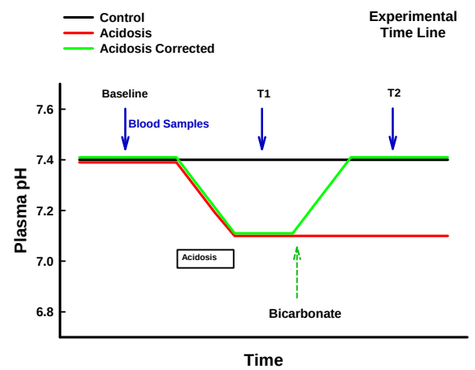


Figure 2

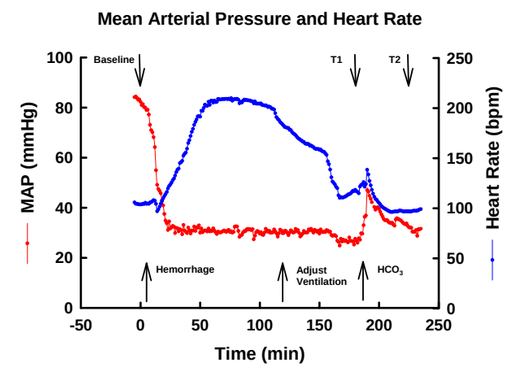


Figure 3

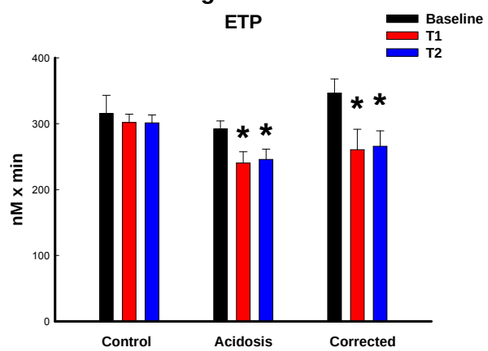


Figure 4

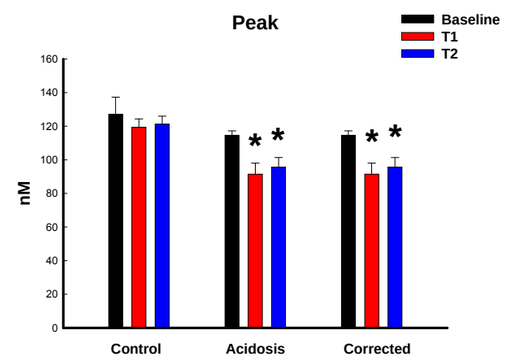


Figure 5

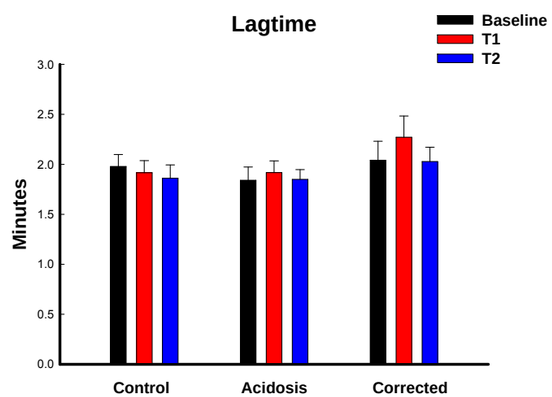


Figure 6

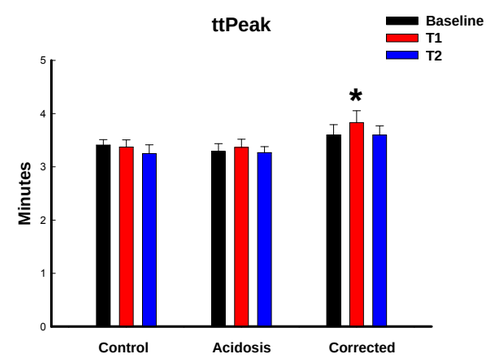
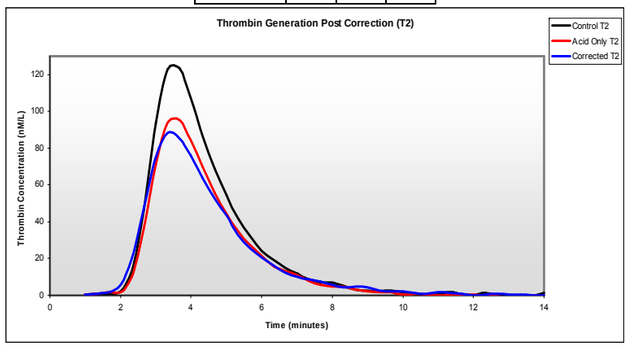


Figure 7

	Control	Acid Only	Corrected
Lagtime (min)	1.86	1.85	2.03
ETP (nM/L)	301.23	245.79	265.69
Peak (nM/L/min)	121.11	95.65	97.67
ttPeak (min)	3.25	3.27	3.60



Results

1) **Severe arterial acidosis (pH 7.1) was induced by a combination of a controlled hemorrhage and decreased ventilation in anesthetized swine (Figures 1 and 2).**
2) **Hemorrhagic/respiratory acidosis led to a 20% decrease in ETP and Peak thrombin concentration (Fig 3,4).**
3) **While the ETP and Peak parameters of thrombin generation were reduced by the acidosis (Fig 3,4), Lagtime and ttPeak remained relatively unchanged in all groups (Fig 5,6).**
4) **Correction of pH from 7.1 to 7.4 with bicarbonate infusion did not restore thrombin generation parameters to baseline (Figures 3-6).**
5) **A representative plot of thrombin generation parameters from each group is shown in Fig 7.**

Conclusions

1) **Decreases in ETP and Peak in both the Acidosis and Corrected groups could have been caused by a hemorrhage-induced decrease in clotting factors (Prothrombin and Factor X) or by acidotic pH, or both.**
2) **The irreversible decrease in ETP and Peak thrombin concentration suggest that low pH has a permanent effect on coagulation function and thrombin generation or that these parameters take longer to recover than the time frame of the study. It also suggests that pH may not be the sole contributor.**
3) **It is unclear at this point if the decreased thrombin generation parameters are due to the hemorrhage or the low pH. Further studies would be necessary to better understand the contributing factor, or factors.**

•P<0.05 as compared to baseline by 1-way ANOVA CRM followed by pairwise comparisons (Holm-Sidak method).

•Data expressed as Mean±SE.