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| **Abstract Title:** | **Low-flow Veno-venous Extracorporeal Life Support Does Not Increase The Coagulopathy Of Trauma After Smoke Inhalation And 40% TBSA Burn In Swine** |
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| **Objective:** | 1) Describe the challange of coagulopathy following smoke inhalation and burn injury.<br>2) Discuss coagulation monitoring strategies following smoke inhalation and burn injury.<br>1) 3) Discuss unique challenges for coagulation management in patients receiving ECLS following smoke inhalation and burn injury.. |
| **Abstract:** | **Background:** Coagulopathy following burn injury is a dynamic and complicated process that can result in both hemorrhagic and thrombotic complications. Thermal injury induces an early pro-inflammatory, hypercoaguable state that transitions to a delayed hypocoaguable state resulting from consumptive coagulopathy and fluid resuscitation. This coagulopathic response is an established risk factor for poor outcomes in burn patients; and assessment of coagulation throughout the course of treatment is essential to mitigate these risks.<br><br>Extracorporeal life support (ECLS) has been utilized in patients with severe respiratory failure following burns and smoke inhalation injury with successful outcomes; however, ECLS by itself also induces coagulation disturbances resulting from extensive exposure of blood to the foreign surfaces and shear stress from the device; as well as the mandated in critical care anticoagulant administration to prevent thrombosis. To date, comprehensive evaluation of coagulation disturbances in clinically relevant models of smoke inhalation and burns has been missing. The objective of this study was to assess coagulation status in swine from several different studies that received severe smoke inhalation injury (mean CoHB at end injury circa 80%) followed by a 40% TBSA deep flame burn, treated with 72 hours of post injury ICU care, airway toilet, burn resuscitation, mechanical ventilation (MV), and adjunct use of ECCO2R. Because low flow ECLS provides primarily CO2 removal and only minimal oxygenation this technique is often termed extracorporeal CO2 Removal or ECCO2R. We hypothesized that there is |

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| | no difference in coagulation status of subjects receiving ECCO2R following smoke inhalation and burn injury versus injured subjects receiving standard of care interventions nor healthy subjects receiving ECCO2R alone without injury.<br><br>**Methods:** Female Yorkshire swine (45-55kg) received smoke inhalation injury with 40% total body surface area burn. In the standard of care group (SOC; n=5) following injury subjects received MV support, vasopressors and fluid with 72-hour follow-up. In the treatment group (ECLS+Burn; n=10) subjects were placed on veno-venous (VV) ECCO2R using single-site jugular vein cannulation (19 Fr) with a pediatric device designed for extracorporeal CO2 removal (blood flow = 0.9-1.2 L/min; sweep gas = 3-10 L/min). We compared our findings to results from healthy swine receiving VV-ECLS for the same duration (ECLS Only group, n=5). In all groups, unfractionated heparin was administered to achieve an activated clotting time (ACT) of 150% of baseline value. We assessed standard plasma-based coagulation tests (prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, antithrombin III (AT3) activity, d-dimer and vWF concentration), as well as viscoelastic clotting test using thromboelastography (TEG), platelet aggregation and count, and ACT. Statistics were performed using SAS 9.4 (Cary, NC, USA). All tests were two-sided with an alpha = 0.05 for significance. Groups were tested independently using one-way mixed models with repeated measures and a Dunnett adjustment to test significant changes from baseline measurements. Between-group differences were examined using a two-way mixed model with repeated measures and a Tukey adjustment for multiple comparisons.<br><br>**Results:** In all 3 groups, PT and aPTT were elevated versus baseline at the start of ECLS through the end of study at 72 hours ($p<0.05$). Following injury AT3 was significantly reduced in the injured groups (SOC and ECLS+Burn) versus the uninjured controls (ECLS Only), which persisted through 48 hours ($p<0.001$). In the ECLS Only group, AT3 was reduced versus baseline from 24-72 hours ($p<0.05$). There was no difference in D-Dimer levels between groups or versus baseline. Beginning at 24 hours after injury, fibrinogen was significantly elevated within the SOC and ECLS+Burn Groups versus baseline; and both were elevated compared to the ECLS Only group at 24 and 72 hours ($p<0.05$). In all groups, fibrinogen was elevated compared to baseline from 24-72 hours ($p<0.05$); numerically, this effect was greatest in the injured groups (SOC and ECLS+Burn) and fibrinogen was significantly higher in the SOC animals versus ECLS Only at 24 and 72 hours. Platelet count was significantly reduced versus baseline in the SOC Group and ECLS Only Group at 48 hours ($p<0.05$); and was significantly lower in both groups compared to ECLS+Burn at this time ($p=0.04$). At 72 hours, platelet count |

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| | was higher in the ECLS+Burn group versus the SOC Group ($p<0.05$). Immediately after injury, at the start of ECLS, ADP and collagen stimulated platelet aggregation was suppressed in injured groups (SOC and ECLS+Burn) compared to the uninjured ECLS Only group; however, there was a trend towards elevated collagen-stimulated aggregation from 24-48 hours in all groups which was significant in the ECLS+Burn and ECLS Only Groups ($p<0.05$); but not in SOC. Elevated ADP-stimulated aggregation was observed from 24-72 hours in the ECLS+Burn Group and at 72 hours in the SOC Group ($p<0.01$); but no change was observed in the ECLS Only Group. At 72 hours, TEG clot formation time (K) was significantly lower ($p=0.001$) and amplification rate (alpha-angle) was significantly elevated ($p=0.002$) in the SOC group versus the ECLS+Burn group. TEG Clot Strength (MA) was initially reduced in both injured groups (SOC and ECLS+Burn) versus the ECLS only group at the start of ECLS ($p<0.05$); however, MA numerically increased in all group with time and was significantly greater than baseline at 72 hours. ACT was significantly elevated from 24-72 hours versus baseline in all groups ($p<0.001$) and was not different between groups.<br><br>**Conclusion:** In this clinically relevant swine model of severe SII and 40% TBS flame burn, low-flow VV-ECLS did not dramatically alter coagulation status vs. animals receiving standard of care alone signifying that ECCO2R is not a major contributor to post-burn coagulopathy. We did however observe marked differences in the injured groups versus healthy animals receiving ECLS support. The changes we observed in the injured animals treated with ECLS versus the SOC group – including preserved platelet count, reduced clot amplification and elevated clot formation time – do not suggest an elevated hemorrhagic or thrombotic risk with use of ECLS. This initial investigation poses intriguing questions and requires follow-on study to elucidate the pathophysiology of thermal injury-induced coagulopathy. Further investigation is important to inform clinical guidelines for use of ECLS following thermal injury because the injury itself, not use of ECLS, seems to be the deciding contributor to coagulopathy of trauma after smoke inhalation and burns. |