Anticoagulation with the Novel, Small-molecule Factor XIa (fXIa) Antagonist, EP-7041, Prevents Oxygenator Clotting but Conserves Hemostasis in a Canine Extracorporeal Circulation (ECMO) Model

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BACKGROUND / AIMS

Bleeding and thrombosis are the most common complications of veno-venous (V-V) ECMO support for patients with respiratory failure. ECMO requires anticoagulation to prevent clotting in the circuit, but heparin and other thrombin inhibitors significantly increase bleeding risk at therapeutic concentrations.

Inhibition of coagulation Factor XI/XIa is an appealing pathway for antithrombotic support of ECMO. Selective inhibition of the contact pathway of coagulation could improve bleeding risk, and because FXI is linked with the inflammatory and complement systems, it can also be viewed as a biologically plausible target for the prevention of pathologic thrombosis during ECMO.

EP-7041 is a parenteral, potent, and selective, small-molecule FXIa inhibitor with pharmacodynamic and pharmacokinetic characteristics that appear well-suited for use in a critical care environment. It is primarily excreted through the liver.

Aims: We aimed to show that intravenous administration of EP-7041 prevents clotting in the ECMO membrane oxygenator while causing less bleeding than heparin.

MATERIALS & METHODS

The canine model of V-V ECMO employs standard tubing, pumps, and oxygenator components (Medtronic) in large (>24kg) hounds. Animals were anesthetized and 14F cannulae were placed via cutdown in the jugular and femoral veins for venous drainage and return. Heparin and EP-7041 were dosed to target aPTT of 1.5× - 2× baseline (BL); diluent (normal saline) was administered to match active agent fluid volume as a negative (Vehicle) control. Study drug boluses and infusions were started 30 min prior to initiation of ECMO to allow anticoagulation to reach steady-state.

Low-flow (20 mL/kg/min) or Standard-flow (60 mL/kg/min) ECMO circulation was maintained for 2.5 hours or until pressure proximal to the oxygenator reached 350 mmHg due to clotting. Bleeding rates were determined by placing preweighed sponges on incision sites for 15 minutes at 30-minute intervals.

Treatment Group	Treatment Goal	Dose	N
Vehicle Control	"Normal" coagulation	Saline 1 mL/kg bolus + 5 mL/kg/hr infusion	3
Heparin Control	Steady-state aPTT = 1.5×-2.0× BL	25 IU/kg IV Bolus + 20-22 IU/kg/hr IV Infusion	12
EP-7041 Dose 1	Steady-state aPTT = 1.5×-2.0× BL	0.3 mg/kg IV Bolus + 0.6 mg/kg/hr IV Infusion	10
EP-7041 Dose 2	Steady-state aPTT = 2.0×-2.5× BL	1.0 mg/kg IV Bolus + 2.2 mg/kg/hr IV Infusion	9

- Solutions prepared to deliver similar total intravenous infusion volumes to all treatment groups (1 mL/kg bolus + 5 mL/kg/hr infusion)
- ECMO circuit and catheter flush solutions contained study drug at concentrations expected in plasma at steady-state

KEY FINDINGS

Figure 1a Pressure Proximal to Membrane Oxygenator During **Low-flow** ECMO

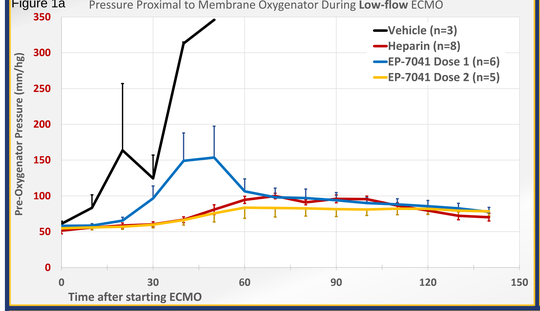
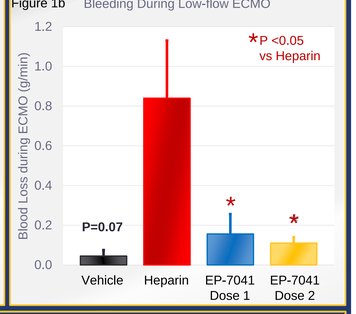


Figure 1b Bleeding During Low-flow ECMO



As expected, "low-flow" conditions near the MO's labeled lower limit of 500 mL/min accelerated thrombotic complications of ECMO. Pressure increased in all groups during ECMO. All Vehicle controls reached the system limit of 350 mmHg, requiring termination within 1 hour (Fig 1a). One Group 1 EP-7041 animal also occluded, but all other treated animals had only minor or transient pressure increases. Despite maintaining steady-state aPTT with heparin dosing near 1.5× BL, bleeding rates and total measured blood loss during ECMO were more than 5× greater with heparin treatment vs. EP-7041-treatment (Figs. 1b, 4, p <0.05).

Figure 2a Pressure Proximal to Membrane Oxygenator During **Standard-flow** ECMO

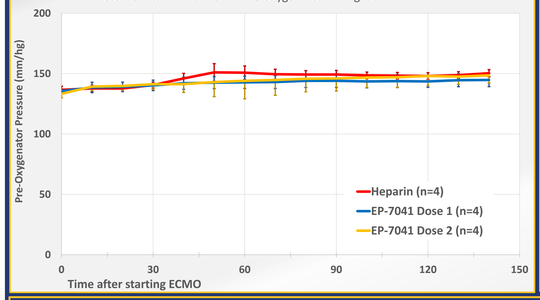
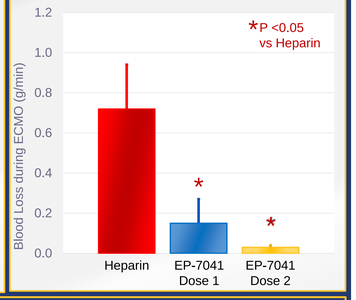


Figure 2b Bleeding During Standard-flow ECMO



With "standard flow," pressure was significantly higher at ECMO start, but only gradually increased during ECMO (Fig 2a). There were no differences in pressure between treatment groups under standard-flow conditions, but similarly to low-flow groups, heparin-treated animals consistently experienced significantly more bleeding (Fig 2b). There were no differences in study-drug concentrations or measured hematologic variables between low- and standard-flow groups.

RESULTS

The boluses and infusions of EP-7041 and heparin rapidly achieved target aPTTs (Fig 3). Despite maintenance of steady-state aPTT near 1.5× BL, the rate of hemorrhage increased over the course of the ECMO run in heparin-treated animals, but not in EP-7041-treated animals (Fig 4). Fibrinogen levels decreased in all groups while on ECMO. There were no significant changes in PT with either heparin or EP-7041 (Fig 5). The bolus dose of EP-7041 overshot steady-state, but plasma concentrations stabilized prior to ECMO initiation (Fig 6).

Figure 3 aPTT in Hounds Undergoing ECMO

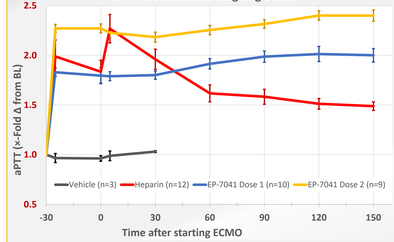


Figure 5 PT and Fibrinogen in Hounds Undergoing ECMO

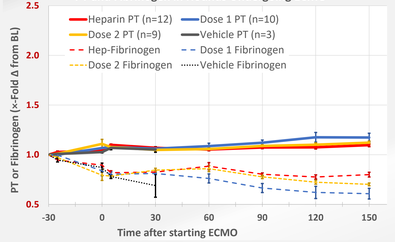


Figure 4 Timing of Bleeding in Hounds Undergoing ECMO

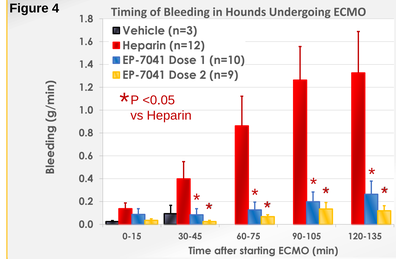
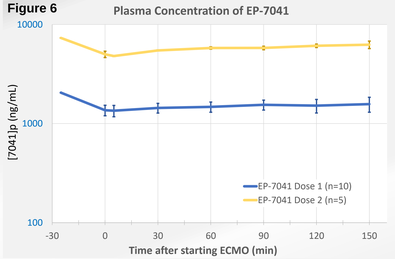


Figure 6 Plasma Concentration of EP-7041



SUMMARY/CONCLUSION

In this canine ECMO model, heparin dosed to an aPTT of 1.5× BL prevented occlusion of the oxygenator or circuit, but consistently caused cutaneous bleeding which increased as ECMO progressed.

EP-7041 prevented increases in oxygenator resistance as effectively as heparin but, unlike heparin, did not significantly impede hemostasis. Our findings support the key role of Factor XIa in driving thrombosis – but not hemostasis – during ECMO. As a Factor XIa antagonist EP-7041 is:

- **Potent and highly selective**
- **Short-acting**
- **Predictable PK/PD**

Further study of EP-7041 is warranted in ECMO, in other intravascular instrumentation, and in prevention and treatment of thrombosis in other settings.