**Purpose:** Acute limb compartment syndrome (CS), a devastating complication of musculoskeletal trauma, results in muscle necrosis and cell death. Fasciotomy, to decompress all affected compartments, remains the only gold standard treatment, but must be performed within a 6- to 8-hour surgical window. Recently, carbon monoxide (CO), liberated from the carbon monoxide releasing molecule-3 (CORM-3), has been shown to protect microvascular perfusion and reduce inflammation in a rat model of CS. The purpose of this study was to test the effect of CORM-3 in a preclinical setting, using a large animal model of CS (pig). The ultimate goal is the development of a rational pharmacologic adjunctive treatment for CS, capable of prolonging the surgical window, and reduce the morbidity and disability in patients.

**Methods:** Pigs were anesthetized with isoflurane, intubated, and had a femoral artery line put in for invasive cardiovascular monitoring/blood sampling. They underwent 6 hours of intracompartment pressure (ICP) elevation by infusing saline enriched with bovine serum albumin (0.4 g/L) into the anterior compartment of the right hind limb. CORM-3 (or its inactive counterpart, iCORM-3) was administered systemically (2 mg/kg, IV) at fasciotomy, and the muscle was allowed to reperfuse for 3 hours. Subsequently, tissue perfusion (orthogonal polarized spectral imaging), cellular injury (ethidium bromide [EB]/bisbenzimide [BB] staining ratio) and apoptosis (FLIVO/BB staining ratio) were assessed in the skeletal muscle of all pigs. In parallel, systemic polymorphonuclear leukocyte (PMN) activation (L-012 assay) was assessed at various time points during CS and reperfusion in all animals.

**Results:** Elevation of hind limb ICP for 6 hours resulted in significant microvascular perfusion deficits (44 ± 1% continuously perfused capillaries in CS vs 76 ± 4% in sham, P <0.001; 39 ± 3% nonperfused capillaries in CS vs 13 ± 2% in sham, P <0.001), increased tissue injury (EB/BB of 0.31 ± 0.07 in CS vs 0.17 ± 0.03 in sham, P <0.05), apoptosis (FLIVO/BB of 0.26 ± 0.06 in CS vs 0.13 ± 0.03 in sham, P <0.05), and activation of leukocytes in the systemic circulation (14.7 relative luminescence units / 106 PMNs in CS vs 1.0 ± 0.1 in baseline, P <0.001). Systemic application of CORM-3 (but not iCORM-3) at fasciotomy was able to increase the number of continuously perfused capillaries (68 ± 3%, P <0.001), decrease the number of nonperfused capillaries (25 ± 3%, P <0.05), diminish tissue injury (EB/BB of 0.13 ± 0.04, P <0.05), apoptosis (FLIVO/BB of 0.12 ± 0.03, P <0.05), and completely block the systemic leukocyte activation (3.9 ± 0.3 relative luminescence units / 106 PMNs, P <0.001).

**Conclusion:** Administration of CORM-3 at fasciotomy offered protection against CS-induced microvascular perfusion deficit, tissue injury, and systemic leukocyte activation. The data suggest the potential therapeutic application of CORM-3 to patients at risk of developing CS.