The Severity of Compartment Syndrome-Associated Microvascular Dysfunction May Be Diminished by the Neutralization of Proinflammatory Cytokines

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Background/Purpose: Compartment syndrome (CS), one of the most devastating consequences of musculoskeletal trauma, is defined as elevated pressure within a closed osseofascial compartment. The pathophysiology of CS includes elevation of intracompartmental pressure (ICP), resulting in damaged microcirculation, decreased oxygen delivery, tissue anoxia, and cell death. CS is a combined ischemic and inflammatory condition that induces the systemic inflammatory cascade. Within the first hour of reperfusion, a peak in the proinflammatory cytokine, tumor necrosis factor alpha (TNF-α) has been reported in complete ischemia-reperfusion literature. The purpose of our study was to examine the suspected systemic inflammatory cytokine/chemokine release in response to CS, and to evaluate the microvascular dysfunction, tissue injury, and inflammatory response following the neutralization of TNF-α.

Methods: 12 male Wistar rats were randomized into 3 groups: (1) sham (no CS), (2) CS (2-hour CS followed by Intra Vital Video Microscopy [IVVM]), and (3) TNF-α neutralizing (2-hour CS followed by TNF-α neutralizing antibody and IVVM). The 2-hour CS insult was followed by fasciotomy, and then 45 minutes of reperfusion. Serum levels of 24 different cytokines/chemokines were measured and obtained at 10-minute time intervals throughout the experiment, and analyzed using an xMap Luminex assay. IVVM was used to assess microvascular perfusion, inflammation in the postcapillary venules, and tissue injury.

Results: Of the 24 cytokines/chemokines sampled, 6 were significantly elevated from their baseline levels, and included the proinflammatory cytokines TNF-α, interleukin (IL)-1ß, GRO/KC (growth-related oncogene/keratinocyte chemoattractant), monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, and the anti-inflammatory cytokine IL-10. A CS insult resulted in a significant decrease in microvascular perfusion from 75.1% (standard error of the mean [SEM] 2.3) continuously perfused capillaries in the sham group, to 30.7% (SEM 3.6), and 35.7% (SEM 3.5) in the CS and TNF-α neutralizing groups, respectively, $P < 0.0001$. TNF-α neutralization did not alter the microvascular dysfunction seen in CS. CS-associated tissue injury was significantly decreased with TNF-α neutralization (33% [SEM 4.0]) in CS group versus 21% (SEM 4.0) in TNF-α neutralization group, $P < 0.05$). Additionally, TNF-α neutralization blocked leukocyte rolling and adherence (9.8 [SEM 3.2] leukocytes/30s/1000 μm2) and 14.1 (SEM 1.6) leukocytes/30s/1000 μm2, respectively, in the CS group versus 2.4 (SEM 1.0) leukocytes/30s/1000 μm2 and 0.9 (SEM 0.2) leukocytes/30s/1000 μm2, respectively in TNF-α neutralizing group, $P < 0.05$).

Conclusion: The results of our study have confirmed that CS induces a proinflammatory response. Neutralization of TNF-α led to a significant relative reduction of approximately

36% in tissue injury, while having no effect on the microvascular dysfunction associated with CS. TNF-α plays at least some role in the inflammatory response following a CS insult, and may represent a future therapeutic target in order to diminish the parenchymal injury associated with CS.

See pages 49 - 106 for financial disclosure information.