Mechanisms of Injury

Estrogen Effects after a Crush Muscle Injury and Acute Exposure to Hypobaric Hypoxia in Warfighters with Blast-related Muscle Injury

A research study sponsored by the Office of the Air Force Surgeon General (OAFSG), the Air Force Medical Support Agency, and conducted in collaboration with University of Nevada, Las Vegas and the 59th Medical Wing, Lackland Air Force Base (AFB), investigated the ability of estrogen and estrogen-like substances to counteract enhanced inflammatory or altered genetic responses induced by hypobaric hypoxia during en-route care. The purpose of this study was to better understand the potential role of hypoxia and the inflammatory responses to crush injury, particularly during en-route care, in which the aeromedical platform maintains a cabin pressure equivalent to an altitude of 8,000 ft. This environment lacks supplemental oxygen systems, which may worsen a patient's injuries via low oxygen content and an enhanced inflammatory response. A novel, non-invasive mouse model of LE muscle crush injury and a hypobaric hypoxia model for LE crush injury at high altitude were developed and validated. These models were used to determine the relationship between pro-inflammatory and anti-inflammatory proteins at altitude in ovarian-intact female (IF), ovariectomized-estradiol-treated (OE) and ovariectomized-placebo treated control (OC) mice. As assessed by histological analysis, IF mice with muscle crush only (i.e., no hypobaric hypoxia) had large clusters of regenerating fibers in the gastrocnemius muscle 96 hours after injury. For IF, OE, and OC mice with hypobaric hypoxic gastrocnemius muscle, muscle regeneration began but inflammatory cells were still present in high numbers 96 hours after injury. At 192 hours after injury, fewer inflammatory cells were present and regenerating fibers were distinct in the muscle of IF and OE mice, but not as much in the muscle of OC mice. Estradiol treatment did not significantly affect the post-injury inflammatory response, but may help promote early muscle regeneration. Cytokine interleukin-1 beta (IL1-β) and cytokine IL-6 in skeletal muscle may have an important role in facilitating and activating the inflammation and regeneration process early after a crush injury. These findings advance our understanding of the impact of hypoxia and inflammatory responses after crush injury and may promote the development of new therapies, such as the administration of estrogen en-route, that expedite recovery after a crush muscle injury and reduce hypoxic effects at altitude.