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Pathophysiology of Concurrent Trauma and Exsanguination

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Editorial

Trauma continues to remain the leading cause of morbidity and mortality in the developed countries [1]. Hemorrhage is the second most common cause of death after trauma, only outnumbered by traumatic brain injury [2]. Exsanguinating hemorrhage is the most common cause of mortality in the first hour of arrival to a trauma center and accounts for almost half of deaths in the first 24 h [3,4]. In addition, about 20-40% of trauma deaths that occur after hospital admission usually involve massive hemorrhage, in which death is potentially preventable [5]. Although the resuscitation protocols and management strategies for resuscitation of patients with exsanguinating hemorrhage have evolved in the past two decades, mortality among these patients remains high.

The type and site of injury are detrimental to the pathophysiology and to the outcome of traumatic exsanguination. While a penetrating injury rapidly provokes hypovolemia and its sequel, a blunt trauma and bleeding from extensive tissue damage triggers a strong inflammatory response. Trauma to the head or to the pelvis is associated with significant mortality and morbidity particularly when accompanied by progressive or uncompressible hemorrhage. The pathophysiology of traumatic exsanguination encompasses four major pillars: I) Profound depletions of cellular energy stores; II) Progressive end-organ vasoconstriction and hypo-perfusion; III) Exaggerated systemic inflammatory response (SIR); and IV) Obligatory fluid shifts and failure of early fluid mobilization. These four pillars are inter-dependent and interact in a vicious circle pattern to determine the outcome from a traumatic exsanguination.

Traumatic hemorrhage triggers a central neuroendocrine response that is characterized by an increased sympathetic drive and catecholamine surge. This compensatory mechanism aims to the redistribution of an already falling cardiac output away from large vascular beds like the splanchnic region, skin and skeletal muscle, to support central organs that are more vulnerable to ischemia and hypoxia. Although ischemia and hypoxia are not identical events at the biological and pathological level, both share a critical effect: a decreased supply of oxygen, resulting in a failure of cellular cytosolic energy (adenosine-5`-triphosphate, ATP) generation by oxidative phosphorylation with the following sequel: i) Profound depletions of cellular cytosolic energy stores [6,7]; ii) All energy-dependent processes, including active membrane transport, cell volume regulatory mechanisms and the endothelium-dependent control of vascular tone in the microcirculation are compromised; iii) Osmotic imbalances are caused by the failure to maintain normal ion gradients leading to paradoxical cellular edema [8-10], and similar abnormalities afflict membrane-bounded organelles including lysosomes and mitochondria; iv) Glycolysis is stimulated from the low energy charge (anaerobic), with the resultant accumulation of lactic acid, which decreases the pH of the ischemic tissue; and v) Both the plasma membrane and the organellar membranes become leaky because of osmotic stress and increased acidity. Lysosomal enzymes are released, and in their acidified environment, they attack cellular proteins, glycoproteins, glycolipids, phosphate esters, and other substrates to cause tissue injury.

Blood flow distributions among the body's various vascular circuits are typically altered in traumatic exsanguinations. This alteration occurs much in accordance with the exsanguination-induced changes in the local pressure head and the vascular resistance within the vascular circuit. By using direct or indirect methods of blood flow measurement techniques in different classes of traumatic exsanguinations, numerous studies have demonstrated decreased blood flow in the vascular circuits of different organs [11-16]. The decrease in organ blood flow during exsanguination constitutes a relative ischemia that is almost always associated with hypoxia as the blood flow delivery of O_2 decreases, and the O_2 extraction and utilization is also compromised by the inherent poor capillary filling [17,18]. In traumatic exsanguination, many factors impede capillary filling to drastically reduce the effective capillary surface area available for O_2 and nutrients exchange. Among these factors are vasomotion and the vascular tone, the vascular endothelium status, blood rheology and the pressure drop that directly modulate the pre-to-post capillary resistance ratio that determine capillary filling, and hence, tissue perfusion. The end-organ progressive vasoconstriction and hypo-perfusion elicited during exsanguination primes the vascular endothelium and the circulating white blood cells and platelets to trigger a systemic inflammatory response (SIR) [19]. SIR also originates from the damaged tissue that results from the traumatic injury. This controlled host-response is mediated by both pro-inflammatory as well as by anti-inflammatory cytokines, chemokines, lipid mediators, vasoactive peptides, and by enzymatic systems to orchestrate an acute response to tissue damage and a delayed tissue repair process [20,21].

Obligatory fluids shifts occur during traumatic exsanguination due to the cellular ionic disequilibrium, and to the perturbations of the physiologic imbalance of the Starling forces that govern the trans-capillary fluid exchange [9,10]. Several mechanisms contribute to the cellular swelling. Depletion of cellular energy stores during traumatic exsanguination impairs the energy-dependent Na^+-K^+-ATPase function to eventually leads to Na^+ accumulation and cellular swelling [22]. Cellular swelling is also favored by the accumulation of extracellular K^+ concentration, lactic academia and as seen in the brain by glutamate, which stimulates cationic receptors and subsequent accumulation of Na^+, depolarization and uptake of Cl^- [23-26]. Remarkable Na^+/H^+ exchanger-mediated endothelial cell swelling was observed in intestinal capillaries in hemorrhagic shock [8-10]. This is presumably due to cytosolic acidosis from the increased PCO_2 and the lactic acid build up from the anaerobic glycolysis, and from the effects of cytosolic acidification on the cell volume regulatory mechanisms

[27,28]. As reviewed elsewhere, the cell volume changes described herein markedly influence a wide variety of genes (for review see [29], particularly aldose reductase and the Na^+-coupled transport systems for proteins such as inositol, betaine, taurine and amino acids. These proteins serve cellular accumulation of osmolytes to restore cell volume constancy [29].

In summary, the pathophysiology of concurrent trauma and exsanguinations consists of complex interactions at the molecular, cellular, and tissue levels of dysfunctions created by a cytosolic energy failure and sustained by ischemic hypoxia. These dysfunctions interact with each other in a cause-effect relationship and a vicious circle pattern to finally result in death from cardio-circulatory arrest.

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