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Pathophysiology of Trauma – Multiple Organ Failure

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Summary: Background: Multiple organ failure (MOF) is not a disease, but the result of a series of events that in some cases may lead to the death of patients in the intensive care unit. Methods: This is a review of pathophysiologic alterations that may occur after trauma. In this respect emphasis will be placed on mechanisms and significance of trauma-related ischemia/reperfusion, activation of cellular/humoral systems, bacteria/endotoxin translocation, and related mediators that can cause or perpetuate the development of MOF. Results: In general, the body’s response to trauma or stress is mediated by mediators derived by activation of humoral cascades, such as complement and coagulation systems and/or by a variety of cells, such as the monocytes/macrophages. Such a response, manifested as inflammation, should be beneficial to the host. From a certain threshold level of activation/inactivation, however, there might be an imbalance of the mediator system that could harm the host by leading to the development of MOF. Although the pathogenesis of MOF is most likely multifaceted, the cell’s oxygen status, adherence of neutrophils to the endothelium with subsequent transmigration, gut barrier failure leading to the translocation of bacteria/endotoxin, and an initially hyperinflammatory state followed by delayed immunosuppression that predispose to infection have recently been considered as key events in this scenario. Conclusions: The precise mechanisms, however, of the development of MOF have not been clearly understood. The relative importance of the cascades/mediators and their interrelationships remains to be defined.

Pathophysiologie des traumatischen Multi-Organversagens

Zusammenfassung: Grundlagen: Multiples Organversagen (MOV) ist keine Krankheit, sondern das Ergebnis einer Reihe von Ereignissen, die in manchen Intensivfällen zum Tode führen können.


Ergebnisse: Normalerweise wird die körperliche Antwort auf Trauma oder Stress durch Mediatoren bestimmt, welche sich durch die Aktivierung der humoralen Kaskaden, etwa der Komplement- und Gerinnungssystem, bzw. aus verschiedenen Zellen, z. B. Monocyten und Makrophagen, entwickeln. Diese Antwort, in Form einer Entzündung, sollte für den Organismus von Vorteil sein. Ab einer gewissen Schwelle der Aktivierung/Deaktivierung kann es jedoch zu einem Ungleichgewicht des Mediatorsystems kommen und folglich zur Entstehung des MOV. Obwohl die Pathogenese des MOV höchstwahrscheinlich vielgestaltig ist, werden in letzter Zeit als Schlüssereignisse in diesem Szenario der Sauerstoffstatus der Zelle, die Anhaftung der Neutrophilen am Endothelium und ihre darauffolgende Transmigrat

Introduction

Although the literature on multiple organ failure (MOF) is characterized by different definitions, different criteria, and different observations, it is important to recognize that MOF is not a disease, but the result of a series of events that in some cases may lead to the death of patients in the intensive care unit (ICU). Early after major injury, hemorrhage, and resuscitation, patients develop a state of systemic hyperinflammation that, in collective terms, is defined as systemic inflammatory response syndrome (SIRS) (39, 90). While severe insult and severe SIRS can lead to early MOF ("one-hit model"), a less severe insult may "prime" the patients such that after an early second inflammatory insult SIRS is amplified, resulting in early MOF ("two-hit model") (4. 16, 49, 51). In spite of early management and control of the acute phase with advanced the ICU technology, MOF is a leading cause of late posttraumatic mortality in ICU patients. At a later stage, when SIRS is downregulated to limit an autogenous injury, delayed immunosuppression may develop, which is often associated with infection and late MOF (3, 90, 92).

In general, the body’s response to an initial insult, e.g. trauma or stress, is mediated by mediators derived by activation of humoral cascades, such as complement, kallikrein/kinin, and coagulation systems and/or by a variety of cells, such as monocytes/macrophages, and the release of cytokines, proteases, oxygen radicals, and nitric oxide (Fig. 1). Teleologically, such a me-

Fig. 1. Schematic depiction of the hypothetical mechanism of host response to trauma mediated by activation of the humoral and cellular systems. An imbalance of inflammatory response associated with translocation of bacteria/bacterial products may lead to the development of MOF.

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flammary mediators resulting in activation of leukocytes, macrophages, and endothelial cells (57, 96).

Cellular systems

Neutrophils: Neutrophils (PMNs) are believed to be the most active cellular participants in posttraumatic inflammation (95). After major trauma both hyper- or hypoactive PMNs may be implicated in the pathogenesis of MOF (22, 91, 123, 135). The stimulation, adhesion, and migration of polymorphonuclear cells (PMNs) are initial steps in the acute host response. These events are initiated by the expression and interaction of a number of adhesion molecules on both endothelial cells (ECs) and PMNs (2, 46, 86). PMN activation plays a crucial role in determining cytotoxicity, as do PMNs/ECs (see ECs below). The activity of PMNs may be augmented by a process termed "priming," which is defined as the amplification of a PMN response to a challenge after exposure to a different agonist (23, 98). The "priming" insult enhances oxygen radical formation in response to a subsequent stimulus but does not, by itself, activate the respiratory burst (60). From clinical data it appears that priming of PMNs is a universal early response to trauma (24, 125, 128).

Endothelial Cells: Initially the ECs were considered to be a passive barrier to the circulating cells, in particular to the neutrophils, which after injury, disruption, and/or breakdown of EC function can intrude into the extravascular space. Discoveries over the last decade, however, have revealed that ECs have additional functions, including the control of homeostasis, vascular tone, vascular permeability, and adhesion/transmigration of leukocytes, which may all be altered after trauma and injury.

The adherence of PMNs to the endothelium is an initial event in the inflammatory response. Chemotactic agents produced by ECs, such as PAF, IL-8, MCP-1, MIP-1α, placental growth factor, and complement products (C5a, C3a) and thromboxane A2, play an important role in this process, contributing both to the direction of leukocytes to the area of injury and to their activation (119). The importance of chemotactic agents is not limited to the initial recruitment of neutrophils. In the absence of chemotactic molecules the adherent neutrophils fail to migrate into the extravascular site of injury unless a chemotactic gradient is present (22). As the presence of adhesion molecules on the endothelium cannot be determined in vivo except by invasive biopsy techniques (99), the only available kinetic information concerning their activity is the serum level of the soluble forms. The soluble E-selectin levels, as a measure for the degree of endothelial activation, indicate a lower level of endothelial activation after trauma than following endotoxic shock, in which endothelial activation is held to occur (78). The lower sE-selectin level observed even in the presence of translocating endotoxin from the gut is probably due to the much lower endothelial levels in traumatic situations (78).

Monocytes/Macrophages (MO/MΦ): After migration into tissues or serous cavities the circulating monocytes (MO) initially released from the marrow may differentiate into various types of tissue macrophages (129). The responses of the MO/MΦ system to trauma are complex and site specific (67). Both MO and MΦ are capable of being activated/stimulated by a variety of chemical or physical stimuli, including nonoxidized/poorly opsonized particulate materials. Complement products, bacteria/chemical products, such as endotoxin (Lipopolysaccharide = LPS), and inflammatory mediators, which are directly generated by major trauma. After injury, MΦ phagocytize hematoma, bacteria, dead cells, and debris and take part in tissue repair. MΦ process bacteria to antigens, which are then presented to T cells, initiating specific immune responses. Thus, MO/MΦ can link the early nonspecific responses after trauma with later processes of specific immunity. In this respect, posttraumatic PMN sequestration in vital organs involves interleukin 8 (IL-8), the best studied chemotaxant, which is released by activated MΦ after trauma (68, 73).

After stimulation, MO/MΦ also produce a number of inflammatory mediators, which can act in autocrine or paracrine man-

### Hypoxia/reoxygenation

Hypoxia per se is thought to be a key factor in ischemic injury. Although ischemia associated with a reduced oxygen supply is a life-threatening event and reperfusion with oxygenated blood is essential to normoxic reoxygenation required to provide the substrate hypoxanthine and activate xanthine oxidase for oxygen radical formation by reoxygenation.

![Diagram](Fig. 2. Cellular changes during hypoxia required to provide the substrate hypoxanthine and activate xanthine oxidase for oxygen radical formation by reoxygenation.)