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Polytrauma and Organ Crosstalk

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Trauma is a leading cause of death and disability around the globe (World Health Organization, 2008). Its management is evolving rapidly and today offers previously unseen levels of care. Increasingly complex injuries are becoming salvageable, both in civilian and military settings, and throughout geographically and economically disparate areas. The severely injured, polytraumatised is centre-stage, both driving and benefiting from recent advances in trauma care. This article focuses on the polytraumatised patient, and the pathophysiology of the systemic implications and sequelae from these injuries.

Traditionally, multiple anatomical injuries were thought and considered as independent events and concepts. However, recent research points towards far more complicated and interacting systems, such that individual injuries can no longer be regarded in isolation (Gruen et al. 2012). Rather, the trauma stimulus manifests individual anatomical injuries, but triggers a whole body, inflammatory phenomenon, which may herald morbidity and mortality well beyond what simple summation of the individual injuries would suggest. Organ crosstalk is central in these events. Improved understanding of these events may assist clinical prediction of their severity and their diagnoses, as well as guide appropriate timing of intervention.

Definition of Polytrauma

The term polytrauma is used liberally among clinicians, and is also common in trauma literature. However, there remains little consensus on its precise definition (Butcher et al. 2009). Usually, the term is used to convey a degree of seriousness, and it is used where there are injuries affecting multiple anatomical regions, in combination with a physiological compromise. There are necessarily both anatomical and physiological aspects in the definition of polytrauma. While a loose definition is not a major issue among casual communication among clinicians, a more strict definition is essential for research, education, clinical resource allocation and the planning of trauma care (Butcher et al. 2009).

A practical and useful definition of polytrauma needs to be easy to apply, reproducible, and accurate. Furthermore, it needs to be measurable early in clinical care to be clinically relevant. In a recent review, our centre proposed a definition for polytrauma as two body regions with an anatomical injury score ≥3 in addition to a measurable systemic inflammatory response syndrome (SIRS) on at least one day during the first three days of admission (Butcher et al. 2009). The systemic inflammatory syndrome is proposed as a surrogate marker of such physiological derangements, and characterises the polytrauma patient (Butcher et al. 2013). However, as severe anatomical injury in two body regions is almost uniformly associated with SIRS, this anatomical injury pattern alone could be sufficient in defining polytrauma, and alleviate the need to calculate daily SIRS scores.

The physiological derangements encountered in polytrauma patients distinguish these patients beyond their anatomical injuries. Above certain anatomical injury thresholds, independent physiological derangement becomes evident (Butcher et al. 2013). The severity of the inflammatory syndrome that drives this pathophysiology varies, but all the patients experience inflammatory reactions and their consequences, beyond those that are attributable to the anatomical injury alone.

In summary, polytrauma is best described by severe, multiple region anatomical injury with associated physiological derangement. The anatomical injury to certain organs and the associated physiological compromise put uninjured organs at risk of organ dysfunction or failure. These three pillars—severe injury, physiological compromise, and remote or uninjured organ dysfunction—in the definition of polytrauma highlight the importance of organ crosstalk in the mechanism of post-injury organ failure.

The Inflammation of Trauma

Trauma stimulates an inflammatory response (Gruen et al. 2012). The precise triggers and methods of its activation, its subsequent pathological behaviour, and its complete clinical manifestations are complex and remain incompletely understood; these areas continue to be the subject of intense research. Improved pathophysiological understanding will hopefully translate into novel treatment strategies aimed at modulating these responses for the benefit of the patient (Namas et al. 2009).

It is clear that the initial trigger for inflammation arises due to the mechanical forces exerted on the body during the trauma event. Through tissue injury, and perhaps exacerbated by associated shock, cellular mechanisms trigger the release of a large number of inflammatory mediators to act on the immune system through both the innate and adaptive pathways (Gruen et al. 2012). These pathways and their associated systems normally exist for the purposes of tissue healing and restoration of physiological homeostasis after injury. However, in polytrauma patients, these systems may become overwhelmed and descend into a vicious cycle, leading to dysfunctional and maladaptive consequences. Positive feedback loops resulting in runaway reactions are seen in multiple pathways, such as with the alarmins released by the initial tissue injury, and also by the immune response activation (Namas et al. 2009).

Clinically, the inflammatory response may be first detected by observation of the four clinical parameters that define the SIRS (Butcher et al. 2013). If the inflammation is more severe, physiological measures of organ failure will manifest. Thus, there is a progression from SIRS to severe SIRS (defined as the presence of organ dysfunction), then to multiple organ dysfunction syndrome, and ultimately to multiple organ failure syndrome, and death. In this progression there is a gradual and accumulating loss of organ function. The inflammatory processes affect all the organs of the body, and are physically remote to the local inflammatory reactions in the organs exposed to the mechanical injury of the initial stimulus (White et al. 2011).

The magnitude of the inflammatory response to trauma is influenced by multiple factors. These include the demographic and genetic background of the patient, the severity of the shock associated with the trauma presentation, the extent of tissue injury, and the treatments received. Data are available to demonstrate different inflammatory responses according to patient age (Panda et al. 2009) and gender (Angele et al. 2000). The response may also be influenced by individual genetic variations. Similarly, the patient's pre-existing medical conditions and associated treatments will affect the situation. In terms of the treatments, these may be divided into those targeting the resuscitation in general, and those being trialled to modify the inflammatory response in the hope of improved outcome. In the former case, an excellent example where recently improved understanding has changed practice is the former use of large volumes of crystalloid during initial resuscitation.

The adverse impact that these infusions have on inflammation is now well observed, and as a result, large volume crystalloid infusions are no longer routine (Gruen et al. 2012). In the case of treatment for targeting inflammatory pathways, the differential effect of tranexamic acid, depending on the time of administration (CRASH-2 Collaborators, 2011),may potentially be the result of differences in the inflammatory processes in patients before and after three hours.

Crosstalk Between the Kidney and Other Organs

Acute kidney injury (AKI) in shocked patients was historically thought to be the result of reduced renal perfusion. However, in the hyperdynamic circulation associated with a SIRS, an increased total renal perfusion is actually observed (White et al. 2011). Instead of being a total organ perfusion issue, the AKI is manifested by local alterations in the renal microcirculation, and activation of renal cell apoptosis. This appears to be the result of signals originating from soluble and cellular inflammatory mediators from both local and distant sources (White et al. 2012).

The diagnosis of AKI in a septic patient is associated with an increase in morbidity and mortality beyond that predicted purely by the renal dysfunction (White et al. 2011). Indeed, renal replacement therapy would otherwise be able to ameliorate this problem. The worsened clinical outcome arises because AKI usually occurs hand in hand with other organ dysfunction (presumably the result of similar inflammatory processes in other organs), and because the AKI affects other organs. There is crosstalk between the kidney and these other target organs in both directions. The heart, lung, brain, liver and intestines have all been demonstrated to be intimately involved in these crosstalk signals (White et al. 2012).

To provide an example, the effect of AKI on the lung has been the focus of research for some time; it is well observed that patients with AKI often develop an acute lung injury (ALI) (White et al. 2012). The excess mortality associated with this, as well as the pathophysiology of the ALI, cannot be accounted for merely by the volume overload associated with the AKI. Changes in pulmonary vascular permeability as well as alterations in salt and water transportation through the air-pneumatocyte interface have been demonstrated secondary to AKI. Because of these alterations, there is decreased clearance of alveolar fluid and the lung becomes oedematous. Furthermore, pneumatocyte apoptosis is increased in ALI, and there is an organ-wide increase in local cytokine concentration. Then, in turn, the ALI releases further signals, and it is suggested that the acute kidney and lung injuries may form a self-propagating, vicious cycle (White et al. 2012).

As another example, the role of the intestine in patients with AKI is also the intense focus of research. Here, alterations in the microvascular milieu result in increased epithelial permeability, effecting changes in the interaction between the host and the pathogens in the intestinal lumen (White et al. 2011). Toxins may reach the lymphatic channels more easily, and reach the systemic circulation easily through lymphatic flow. Aldosterone is noted to upregulate a potassium channel regulator in the colon, and may explain the increased colonic potassium excretion that is seen in patients with AKI (White et al. 2011).

Conclusion

Modern polytrauma care draws on the recent developments in the understanding of the complex pathophysiology of inflammation, though the situation remains incompletely understood. The current definition of polytrauma acknowledges that there be presence of significant injuries in multiple anatomical areas, but also stresses the incidence of a systemic inflammatory response in these patients. This definition reflects the central role that inflammation plays in polytraumatised patients. The inflammatory phenomenon is a whole body process, with complex interactions between multiple organs. Integral to this inflammatory response is a well-coordinated system of communication, by neural and

endocrine means, involving tissues of all sizes, from individual cells to entire organs. It appears that where a certain threshold of initial injury is exceeded, the inflammatory pathways may become overwhelmed and dysfunctional, no longer facilitating the normal healing response and returning to physiological homeostasis for which they are designed.

These new understandings have led to a paradigm shift from the focus on individual anatomical injuries to an appreciation that the patient's pathophysiology is centre-stage. To minimise the impact of these inflammatory processes, that may become overwhelmed and detrimental to the patient's health, careful coordination of surgical procedures alongside the intensive medical therapies in resuscitation is required. As more understanding of these complex pathways is obtained, we hope novel therapeutic strategies will emerge to assist modulation of dysfunctional inflammation.

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