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Unusual relationship: Do organs talk to each other?

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Intact organ function is essential for survival and “positive outcomes” of burn patients [1]. Despite the need for intact organ function, a burn injury damages and affects the structure and function of almost every organ leading to an increased incidence of organ failure or even multi organ failure (MOF) [1, 2]. Various studies indicated that MOF occurs in 20% pediatric burn patients, 40–50% in adult burn patients, and up to 60% in elderly burn patients [2–4]. The organs that are most affected are the respiratory and cardiac system, but the organ with the highest mortality is the renal system. In general, MOF is correlated with large burn sizes, full thickness burns, the presence of inhalation injury, and sepsis. In terms of outcomes, patients with MOF have longer hospital stay, required more surgeries, had increased incidents of major infections, and increased mortality when compared to non-MOF patients. All studies have in common that both single organ failure as well as MOF are significant contributors to post-burn morbidity and mortality [2, 4].

In this issue of Critical Care Medicine, the study by Dr. Clemens and colleagues [5] from the Department of the US Army, Institute of Surgical Research, Fort Sam Houston, Texas, hypothesized that the kidney and lung are connected, and consequently acute kidney injury (AKI) will increase the risk of developing ARDS and that reciprocally ARDS will increase the risk of acute kidney injury. The authors included 830 adult burn patients, of which 400 patients (48%) were diagnosed with AKI. The authors found that patients who had AKI had a 73% increased risk of developing ARDS, after adjustment and controlling for age, gender, TBSA burn, and inhalation injury. ARDS was present in 299 or 36% of the patients, but more importantly, the authors found a strong signal that ARDS increases the risk of developing AKI. The authors therefore concluded that patients with AKI have a higher risk of developing ARDS and vice versa, patients with ARDS have a higher risk of developing AKI. The authors furthermore showed that there was a 24% overall mortality for patients with AKI or ARDS.

By looking at the results in more depth, it seems remarkable that patients with AKI and/or ARDS have such a high mortality, despite available treatment options. As aforementioned, AKI is not an uncommon occurrence in the early phases after burn, however it can be treated via hemofiltration or hemodialysis [6]. It is furthermore not uncommon after burn, that renal function returns and dialysis can be stopped. Similarly, ARDS can be treated via critical care protocols and treatment bundles [7]. Because there are available treatment options one would expect a lower mortality for AKI and ARDS. But the authors clearly showed that both, AKI and ARDS, are associated with a substantial mortality. It is difficult to speculate on the mechanisms based on the study by Dr. Clemens et al., but it seems likely that if a burn patient develops AKI the patient has a high risk to develop ARDS and vice versa. These results are suggestive that the impact of AKI is more profound than previously thought, and despite treatment options, it can lead to an increased ARDS, which can lead to an increased mortality. The concept of two organs being interconnected and resulting in both organs to fail, is not entirely new. Amongst others, a study using the hemorrhagic shock model by Perl and colleagues [8] showed that the lung and liver communicate and that either organ once affected can cause the other organ to fail. The authors of the current study did not look at liver failure, but taking the data from previously published studies, it seems evident that there is an axis between kidney, liver and lung, and heart, maybe even the central nervous system and that these organs communicate with each other.

If current treatments for AKI and ARDS don't affect the outcome, one of the few interventions that could result in an improved morbidity and mortality would be to prevent AKI and ARDS. Burn surgeons should undertake every effort to prevent the occurrence of renal failure as well as pulmonary failure with adequate therapeutic approaches. This then leads to the question how can AKI and/or ARDS be prevented? The answer to this question can in part be given: fluid resuscitation. Resuscitation of burn patients is central but has been controversially discussed and Greenhalgh et al showed that burn care providers use a variety of different resuscitation formulas or even resuscitation volumes [9, 10]. It seems evident that higher resuscitation volumes may save the kidneys, but higher resuscitation volumes lead to pulmonary, brain and other edema formations, which can lead to various complications, for example abdominal compartment syndrome. Therefore, too little resuscitation ruins the kidneys too much resuscitation ruins many other organs [11]. Once again, it comes down to the right amount of resuscitation, but as aforementioned the right amount of resuscitation is not entirely clear, led alone, amount and composition of the resuscitation formulas. Even the main indicator for adequate resuscitation, urinary output, has been flawed and controversially discussed. Novel approaches are needed to guide resuscitation better, e.g. the use of thermal dilution approaches with the PICCO system or the closed loop resuscitation. These approaches may represent better monitors/indicators for adequate resuscitation, which will lead to an improved maintenance of organ perfusion and subsequently organ function.

Lastly, if prevention fails and current treatment strategies are not effective, what novel treatments can be implemented to improve organ failure? In burns organ failure is in part due to hypermetabolic catabolic responses. Currently there are few anti-catabolic or anabolic agents in use that may improve organ function, for example insulin, oxandralone, or propranolol [12]. Unfortunately, there are only few studies looking at the effects of these

agents and the majority of these studies have enrolled only few patients that the answer is not entirely clear. While proteins and growth factors are limited in their ability, a novel therapeutic approach that is more experimental and far from a clinical introduction, but potentially much more effective is the use of cellular therapies. Stem cells have been used to improve survival after sepsis in animals [13], but stem cell therapy has not made its' clinical entrance. However, if autologous or allogenic stem cells can improve organ function by systemic administration, there would be a tremendous role for cell therapy in burn patients.

The study by Dr. Clemens is an important and fascinating study but there are some aspects that leave room for thoughts. The authors acknowledge that the development of ARDS was influenced by increasing fluid volumes to treat AKI, but they also indicated that under-resuscitation in an attempt to avoid fluid overload in the setting of decreased lung function resulted in AKI; realizing the conflicting connection between ARDS and AKI being opposing factors. Second, the authors can only show that AKI is a risk factor for ARDS, they cannot determine whether AKI is causing ARDS or ARDS causing AKI. But what the authors showed that there is an increased mortality and morbidity of patients who are suffering from AKI and ARDS, and that there is strong indication that these two organs communicate with each other and that if one fails, the other will most likely fail as well. Sadly, the authors did not determine liver failure or cardiac failure. It would have been interesting to see how these organs interact, communicate, and potentially lead to subsequent events of further organ failure and death of burn patients. Regardless, this important study is a first step in adult burn patients to understand and acknowledge and identify specific risk factors and alterations in large burn patients and novel avenues in terms of how to better treat our rising, which need to be answered in order to improve outcome of burn patients.

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