WHAT'S NEW IN SHOCK? FEBRUARY 2013

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It has been several years since I have had the privilege of providing an overview of the current issue's content in the "What's New in Shock, February 2013?" series. Like many I presume, I am guilty of relying too heavily on search engines and large public databases to scan literally thousands of journals for articles of interest. Although such an approach is clearly driven by specific interests and needs, it produces a rather boring investigator, one focused too closely on his/her own research interests. Being asked to write an overview of an issue of Shock is actually a pleasure because it gives me the opportunity to relax, explore new aspects of shock science, and delve into areas of interest to me that I have avoided because of lack of time. Taking this approach with the journal Shock is particularly rewarding, not only because of the quality of the work, but also its breadth. This is revealed no more clearly than in this issue where the reports range from outstanding reviews on clinically relevant topics such as traumatic coagulopathy and biomarkers for immunotherapies, to clinical investigations focused on improved management of patients with septic shock and the physiology of critical illness, to basic science investigations looking mechanistically at the signaling pathways that regulate host innate and adaptive immunity and novel therapeutic approaches for the treatment of shock.

I must admit that I am immediately drawn to the review articles especially when they overlap with my own interests. Like many I presume, my first examination is of the references, hoping to find one of our own articles cited (thanks to Dr. Rivers for citing two of our publications), and then cited correctly with our own view of the world. In this issue of Shock, Rivers and his colleagues at Henry Ford Hospital, UC-SD, and Mount Sinai School of Medicine provide a compelling argument that the future of immunotherapies for sepsis and shock relies on appropriate identification of patients who will benefit from specific immunotherapies (1). No argument there. The authors contend that current biomarkers for the severity of the inflammatory response occur before initiation of therapy (usually within the first 24 hours) and that therapeutic interventions are in discordance with the peak concentration of the biomarker in question. Although I have no argument with their conclusions, I would only add that biomarkers can have multiple purposes, including identification of patients who may or may not benefit from a given therapy, as well as identifying the response to the biological intervention. In the former, having a biomarker that is informative earlier than the appropriate use of the immunotherapy may actually be advantageous, whereas for the latter, the timing of the biomarker must be concordant with the administration of the therapeutic.

The second review by Pusateri and the Department of Defense Hemorrhage and Resuscitation Research and Development Steering Committee (2) covers a topic of great interest to me, but one that I am woefully ignorant: trauma-induced coagulopathy and the use of tranexamic acid as an antifibrinolytic agent. The review is particularly important because it is both an excellent summary of the literature and the recommendations of the Steering Committee. Importantly, it does not reflect the position of the federal government. Not only does the article do an excellent job summarizing the literature from both a military and civilian viewpoint, but also it identifies current gaps in our understanding of the linkage between coagulopathy, endothelial injury, and inflammation. Dr. Pusateri and the Steering Committee are appropriately conservative in their recommendations, but it is hard to come away with any conclusion other than this is an exciting area of research with great clinical potential for both the civilian and military populations. Furthermore, the article provides clear directions where research should go, and why such an approach is important for the treatment of the patient with traumatic shock and coagulopathy. This should become a highly cited publication.

Once I have made it through the reviews, my first attention is always to the clinical studies. As a basic scientist, I must admit that I am always curious about progress at the bedside. As someone who has worked in a surgery department their entire career, I can value the merits (and challenges) of good clinical and translational research, and I am rarely disappointed by the articles published in Shock. This issue is no exception. The first article in the Clinical Aspects section may seem esoteric, but in reality is a clinically relevant observational study. As the clinical leadership is fully aware, sepsis occurs in patients with many underlying comorbidities, cancer being a common one. Schnell and colleagues (3) from Paris have investigated 147 patients admitted to the intensive care unit with septic shock and evaluated vasopressor support in individuals recently treated for cancer, untreated cancer patients, and patients without cancer. Not surprisingly, the treated cancer patients were younger than patients without malignancy and had more frequently intra-abdominal sepsis. Interestingly, the need for vasopressor support, organ function, and mortality were not different among the three groups. Such findings are somewhat surprising, given that a significant proportion of the cancer patients receiving chemotherapy might be expected to be neutropenic at the time of sepsis, but the authors clearly show that the need for vasopressors was not dependent upon whether the patient was neutropenic. Although this is a single-site study by an
obviously qualified group, the studies suggest that with proper management, cancer patients finishing chemotherapy have rather similar vasopressor needs during septic shock and can be managed successfully by skilled intensivists.

Along the same lines, Burry and her colleagues (4) in Toronto examined corticosteroid insufficiency in patients with septic shock using an adrenocorticotropic hormone test and correlating those responses to outcome. In 219 consecutive patients, the authors found biochemical evidence of corticosteroid insufficiency in 71% of the patients. Using a retrospective analysis plan, the authors found no difference in survival between subjects given steroids versus those not given steroids in subjects who were defined as being nonresponders. However, in the subgroup that responded appropriately to adrenocorticotropic hormone stimulation, treatment with corticosteroids was associated with dramatic reductions in mortality from 45% to 8%. The results need to be interpreted cautiously because of the retrospective nature of the analysis and the lack of protocolized corticosteroid treatment. But the study is well powered and evocative in its findings. Clearly, additional research is required.

One of the major strengths of Shock as a journal is its broad examination of models of injury and their relevance to shock research. Much of what we have learned about the immunological changes that occur in shock have been recapitulated in other injury models, and we have grown to appreciate the commonality of both the innate and adaptive responses. This study by Edelman and colleagues (5) is a perfect example of how a surgical injury can teach us much about inflammatory responses and their similarities among a variety of disparate external stimuli. A perfect example of this is cardiopulmonary bypass for patients undergoing heart surgery, where interactions between blood and the oxygenation membrane are thought to explain the activation of blood leukocyte components. In this report, however, the authors examined neutrophil phenotype and ex vivo responses to N-formyl-Met-Leu-Phe (fMLF) or platelet activating factor (PAF) in 15 patients before and after cardiopulmonary bypass surgery without cardiopulmonary bypass. Not surprisingly to this reviewer, surgery in the absence of cardiopulmonary bypass had minimal effects on the basal expression of CD11b, CD18, or CD62L from blood neutrophils up to 5 days after surgery. However, the responsiveness of these cells in terms of CD11b and CBRM expression was markedly diminished in response to both fMLF and PAF after surgery. Conversely, the activation marker CD62L was increased in response to PAF after surgery. Such findings suggest that the operative procedure per se produces subtle but reproducible changes in the responsiveness of blood neutrophils.

Along the same lines, Lanspa and colleagues (6) examined dynamic parameters of volume resuscitation in patients being resuscitated for shock in nonventilated patients. The authors test in a pilot study a noninvasive method to evaluate the efficacy of volume expansion. Although the results are from a pilot study, they suggest that transhastatic echocardiography to measure vena cava collapsibility index, aortic velocity variation and stroke volume variation to assess adequacy of volume expansion can be used to predict the hemodynamic response to fluid challenge. Importantly, the thresholds in patients not on ventilator support were different than the thresholds for patients on mechanical ventilation.

When we move to the basic science aspects of this issue, I am constantly amazed and pleased by both the diversity and the strength of the work published in the journal. What we think we know about cell signaling systems has to be constantly revised. In that transition between human studies and more basic animal investigations, we find the study of White and colleagues (7), who have tested resuscitation formulas in an animal model of hemorrhagic shock and traumatic brain injury. Clearly, this is a study that has direct clinical applications. Using a swine model of hemorrhagic shock with or without traumatic brain injury, animals underwent limited resuscitation with a hemoglobin-based oxygen carrier (HBOC) versus crystalloid versus HBOC and nitroglycerin. Interestingly, the presence of traumatic brain injury made hemorrhagic shock easier to achieve (i.e., requiring less hemorrhage). More importantly, the findings argue for the complexity of resuscitation in the patient with traumatic brain injury. Surprisingly different to earlier studies using HBOC, the investigators noted significantly better survival with crystalloid than with the HBOC and nitroglycerin and marginally better outcomes than with HBOC alone. Although the findings are evocative and definitely require further examination, the authors are to be congratulated on their balanced assessment of the findings and conclusions, as well as the limitations. This is a controversial field, and the final answer is not yet in. However, the study will be well cited and is an important contribution to our better understanding this complex management.

Sawant and colleagues (8) from Texas A&M and Derive and colleagues (9) from INSERM examine cell signaling pathways in two different models of shock. Sawant et al. report unexpectedly that not only does the serum from rats undergoing hemorrhagic shock increase Fas and Fas ligand expression on lung endothelial cells, but a Fas inhibitor showed protection against increased permeability of these cells and decrease in tight junctions. These findings add to our appreciation of the complexity of Fas signaling and confirm that its actions during shock are not limited to cell death and apoptosis. Similarly, Derive et al. (9) using a pig model of septic shock infused a TREM-1–like derived peptide (LR12) and observed profound attenuations in the hemodynamic collapse and reduced norepinephrine requirements. Although TREM-1 pathways are thought to amplify the early cytokine storm to sepsis, the studies are powerful demonstration that these late mediator pathways can be appropriate targets for intervention.

Li and colleagues (10) from Shanghai also pursue the blockade of late mediators of sepsis, in this case, HMGB1. Using a selective α7 nicotinic acetylcholine receptor agonist, the authors demonstrate that they can suppress nuclear factor κB activation, cytokine expression, and HMGB1 expression in the liver following ischemia-reperfusion injury. The data are convincing, the model of 70% partial ischemia relevant, and the approach sound. The linkage to HMGB1 is associative, and as the other articles in this issue of the journal demonstrate, undoubtedly, the agonist is targeting multiple inflammatory properties. Whether the results can be explained entirely by HMGB1 or in combination with other mediators is still unresolved.
Along the same lines, Norris and his collaborators (11) from the University of North Carolina at Charlotte have examined the effects of a hydrogen sulfide donor in the perfused liver under conditions of vascular and oxygen delivery changes. The authors suggest that provision of hydrogen sulfide has differential effects on liver microcirculation, depending on the stimulus. With that said, however, their findings suggest that hydrogen sulfide production may contribute to the microcirculatory collapse that is seen in the progression of sepsis.

Marshall et al. (12) have continued their exploration of the metabolic consequences of burn injury and have examined hepatocyte apoptosis in mice using a JNK2 (C-jun N-terminal kinase 2) knockout mouse. The use of a JNK2 knockout mouse provides a powerful tool to distinguish upstream and downstream responses, and not surprisingly, endoplasmic reticulum (ER) stress was similar in both strains of mice. What was somewhat surprising was that the early inflammatory cytokine response was also unaffected, as were insulin signaling pathways and glucose tolerance. Hepatocyte apoptosis was markedly attenuated in the JNK2 knockout mice, and the recovery in liver injury was much more rapid. I am constantly amazed by the complexity of the mitogen-activated protein kinase pathway and wonder through what mechanisms JNK2 signaling is regulating the apoptotic response, clearly a fruitful area of investigation for the laboratory in the future.

One of the most common and troubling responses to severe injury, burns, and sepsis is a secondary acute lung injury. Unfortunately common, when it progresses to respiratory distress syndrome, it is frequently lethal. Even more unfortunate, little is known about the proteins and pathways that both induce and resolve acute lung injury. Using an in vitro model of rat type II alveolar cells, Howard et al. (13) demonstrate that induction of a stress response, in this case heat shock, prevents interleukin 1β-dependent inhibition of aENac expression and channel function. The inflammasome is clearly involved as heat shock also disrupts heat shock protein 90 binding to IRAK1. Taken together, the authors have demonstrated quite convincingly in their in vitro model system that stress responses, such as heat shock, protect the barrier function of the alveolar epithelium in acute lung injury in part by inhibiting interleukin 1-dependent pathways such as p38 mitogen-activated protein kinase, a very elegant study that needs to move into the in vivo realm.

Radaelli and colleagues (14) have assessed the baroreflex in rats administered endotoxin separate from the hemodynamic changes. Baroreflexes are a natural protective response aimed at maintaining adequate blood flow to vital organs. Using a dose of endotoxin that did not produce early blood pressure changes, the authors demonstrate that the baroreflex sensitivity was dramatically reduced within minutes of endotoxin administration, independent of blood pressure, a very dramatic finding and one that suggests that it might have diagnostic benefits. The Surviving Sepsis Campaign, for example, seeks to identify early sepsis and promote interventions that can reduce the progression to severe sepsis or septic shock. If similar responses are observed in humans, one can easily envisage an early baroreceptor test as part of the evaluation profile for early sepsis.

The final article in this issue should not be missed. Here Troitzsch and colleagues (15) have examined cyclosporine treatment on tissue oxygenation and cytochrome oxidase in skeletal muscle ischemia-reperfusion injury. They hypothesize that cyclosporine should suppress the mitochondrial permeability transition and reduce mitochondrial injury, mitophagy, and cell death. The authors clearly demonstrate that pretreatment with a single dose of cyclosporine sustained high-energy phosphate levels, improving mitochondrial viability. Although convincing that the drug reduced muscle injury, the potential mechanisms remain unelucidated. Further additional studies are required.

It has been a pleasure having the opportunity to review this month’s issue of Shock. I must admit that I have not had such a pleasurable weekend since the last time I was asked to provide such an overview. I am constantly amazed and pleased about how vibrant and dynamic the shock field remains. With government and industry funding near its nadir, it is reassuring to see such a continued high level of quality work coming from the shock community. In addition, it is great to see that the Shock journal maintains its international support with studies from all over the world. I feel comfortable that the journal continues in good health with the support of its readership.

REFERENCES

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