New Molecular Players in the Great Fluid Debate

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Anesthesiologists, it seems, will never agree on the optimal fluid resuscitation protocols for critically ill patients. The “Great Fluid Debate” is the anesthesiology equivalent of fashion in the art world—lots of opinions, with historical cyclic swings about what is “in.” Competing fluid resuscitation strategies will always be points for discussion and disagreement, unfortunately. Getting an answer about the best resuscitation strategies is understandably difficult because of heterogeneity in outbred humans, heterogeneity of complex clinical processes such as hemorrhage, and expense of clinical studies that require long-term follow-up data. Many clinical studies on massive hemorrhage focus on survival as the major end point of analysis after fluid resuscitation; rightly so, but survival is affected by many factors in resuscitation of critically ill patients, making it difficult to gain insight into fluid administration best practices.

In this issue of Anesthesia & Analgesia, Kozar et al. report their work comparing plasma versus lactated Ringer (LR) solution resuscitation in a rat hemorrhagic shock model. Resuscitation with plasma in clinical massive hemorrhage is controversial, and many trauma centers have withheld aggressive plasma resuscitation because of concerns about the risk of transmitting infection and risks of transfusion-associated lung injury. A trend toward increased early use of plasma for massive hemorrhage was prompted by recent observations in civilian and battlefield trauma settings that early use of plasma is associated with increased survival. For example, patients presenting to a Los Angeles County Hospital level I trauma center over a 6-year period were more likely to survive massive transfusion if the fresh frozen plasma/red blood cell ratio was 1:3. Five other studies with similar conclusions are cited in the Kozar et al. report (1–5). All of these influential studies are retrospective, with all the usual caveats inherent in retrospective work, and none of the studies can address mechanism of survival because of the nature of the data. The literature dealing with massive hemorrhage has been plagued by the lack of markers (laboratory data) that reliably guide prognosis or quantify the value of resuscitation maneuvers. In particular, static clotting times are difficult to interpret in the setting of massive hemorrhage and transfusion, and likely a matrix of laboratory studies and modeling will be necessary to guide therapy.

Enter potential new markers and monitors of hemorrhagic shock and resuscitation from hemorrhagic shock: the endothelial glycocalyx and syndecan-1. The endothelial glycocalyx is a complex barrier, enriched in proteoglycans of the syndecan and glypicans families as well as glycosaminoglycan attachments of heparan, dermatan and chondroitin sulfates, and hyaluronan. The endothelial glycocalyx regulates movement across blood vessel walls: glycocalyx damage or shedding results in protein extravasation from the circulation, contributing to end-organ edema, and also exposes the endothelium to pathologic white cell and platelet adhesion. Glycocalyx shedding is an important acute underlying pathologic factor in reperfusion injuries, systemic inflammatory response, trauma, sepsis, and chronically in vasculopathies, but no clinical trials directed at the glycocalyx have been performed. Syndecans are ubiquitous transmembrane proteoglycans that interact with the extracellular matrix, growth factors, and chemokines to regulate adhesion- and growth factor-mediated signaling pathways. Syndecans are emerging as integrators of the environments outside of the cell with signaling inside the cell.

In the Kozar et al. study, the hemorrhagic shock model imposed a mean arterial blood pressure (MAP) of 30 mm Hg for 90 minutes, then rats were resuscitated to MAP 80 mm Hg with either LR solution or plasma, and normal MAP was maintained for 2 hours. Venules from the small bowel mesentery were examined for glycocalyx morphology. Ninety minutes of shock resulted in clear loss (shedding) of the glycocalyx and decreased expression of syndecan-1 message, unchanged by resuscitation with LR solution, but significantly restored by plasma. Similarly in the lung, the normally abundant syndecan protein in the alveolar wall disintegrated as a function of shock, was unchanged by LR solution, but significantly restored by plasma resuscitation. Gross lung pathology was also improved by plasma. The rapidity of restoration of endothelial and pulmonary histologic appearance is remarkable, and sets the stage for examination of the effects of timing of plasma resuscitation on end-organ recovery.

This study certainly does not close the knowledge gap necessary to engender full confidence in early plasma resuscitation for hemorrhagic shock, but it does point to syndecan-1 and the glycocalyx as a whole as potential targets of therapies in shock patients. Similar to all good
pilot studies, it leads to more questions than it answers. A full battery of endothelial functional studies over a longer experimental timeframe, for example, could tell us more about the definitive therapeutic effects of plasma resuscitation. The most tantalizing prospect raised by this work is the potential for a real-time marker of shock and resuscitation. Will shed syndecan-1 and other glycocalyx fragments be useful for predicting outcome in hemorrhagic shock patients? The gut vasculature is particularly vulnerable to damage in the setting of shock, making it the logical experimental vascular bed for these pilot studies, but the degree of damage (and potentially recovery) may not be as exaggerated in other organs. For this reason, one of the next studies should include examination of accessible vascular beds that could be used for histologic monitoring. Is it possible that these studies could lead to a real-time, biopsy-based readout of hemorrhagic shock and its treatment? With more high-throughput studies, the authors may be able to identify a biomarker that reflects the important dynamics of glycocalyx damage and recovery. Considerably more animal and clinical work will be needed to address the usefulness of following the shedding and restoration of the glycocalyx as a marker of global physiologic status. But this clinically relevant study is an exciting launching pad for further work.

**DISCLOSURES**

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**REFERENCES**

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