Septic shock and anesthesia: Much ado about nothing?

It is a known fact that sepsis progressing to septic shock is a frequent condition with a high associated mortality.[1] As anesthesiologists we are often the so-called "first responders," in that many patients with early sepsis go straight from the emergency room to the operating room for a surgical procedure. From the operating room, the next destination for a postoperative septic patient is the Intensive Care Unit (ICU).

Does patient outcome depend solely on the entirety of care in the ICU? Is type of anesthesia affecting outcomes in sepsis? Are we as anesthesia providers not the "first-critical-link" in the chain of events that lead on to the complex conundrum that is septic shock and its mortality? Can we modify our anesthetic practices such that they would be the most important, early intervention in the surviving sepsis guidelines?

Pathology of sepsis is heterogeneous and multifactorial. Most commonly, mitochondrial dysfunction, aberration in the function of the immune system and endothelium, inability to deliver oxygen to tissues, excessive apoptosis, and uncontrolled release of the inflammatory mediators and reactive oxygen species are pointed as mechanisms. The current therapy of sepsis, as we all very well know, includes rapid identification of the offending pathogen (source control), pre-emptive and early implementation of antibiotics with rapid de-escalation, fluid resuscitation, pressor therapy if needed to support perfusion pressure, and minimizing the secondary organ failures.

If one looks at a standard anesthesia textbook, most of the literature on anesthesia and septic shock focuses on the use of ketamine as the "ideal" induction. However, management of septic shock in anesthesia goes way beyond that point.

Frequently, the first and most important question an anesthesiologist has to answer is the question of whether the proposed "emergent" procedure is indeed truly "emergent," considering the patient's tenuous status. Another question is 'whether it is feasible to transport the patient'? Numerous drips and supportive equipment often hamper efficient and safe transport and put the patient at risk of having some of the supportive devices accidentally removed. Finally, how should this patient be managed in the operating room?

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Now that the anesthesia provider has determined the patient to be truly "emergent" and has successfully transported him or her to the operating room, it is time to get started and induce anesthesia. Ketamine is a commonly mentioned drug for induction of anesthesia. It is the only anesthetic that increases contractility and systemic vascular resistance and directly counteracts the cardiovascular changes seen in septic shock assuming an intact sympathetic nervous system. The adrenal glands and part of the sympathetic system may be totally spent and famished of sympathetic hormones, in which case ketamine may not work to provide hemodynamic stability on induction. It has also been seen that the benefits of ketamine include attenuation of the inflammatory response, by limiting the secretion of the inflammatory cytokines *in vitro* and *in vivo*; animal studies suggest a benefit in sepsis.[2-6] Still, it remains to be seen if there is a clinical significance to this finding

Another frequently considered induction agent is etomidate. It was heralded as an ideal induction agent considering its very stable hemodynamic profile. Nevertheless, an increasing body of evidence points to the fact that etomidate can result in adrenal corticosteroid suppression, resulting in at least 48 h of impairment.[7,8,9] Several indirect studies suggested,[9] , that this adrenal suppression translates into less favorable outcome in the septic patient.[10,11] Putting this into perspective, and realizing how often we as anesthesiologists tend to reach out for a safe and hemodynamically stable drug with minimal evident side effects (e.g., etomidate), it is obvious that an effective communication with the ICU team should be accomplished. This communication should report that etomidate was used for induction, and that exogenous supplementation of steroids would be a strong consideration for this septic patient, both in the operating room and the ICU.

Propofol may augment hypotension in sepsis, and may result in a transient increase in pressor requirements. Interestingly, data shows that despite aggravating hypotension, propofol use did not adversely affect delivery of oxygen to the tissues.[12] Even more interestingly, there is a growing body of research suggesting that propofol can increase serum cytokine levels in sepsis.[13] This evidence has to be balanced against other studies showing some attenuation of sepsis due to the infusion of propofol.[14-16] Finally, it should not be forgotten that

propofol is prepared as an emulsion, which has the potential to harbor and nourish bacterial pathogens.[17]

Thiopental is probably a drug of the past as an induction medication. A bolus dose can frequently exaggerate hypotension, especially in under-resuscitated patients.[18] The immunomodulatory effects of thiopental are poorly defined. The production of antiinflammatory interleukin-10 can be increased in human leukocytes after exposing cells from healthy volunteers to thiopental.[16] Considering that attenuation of inflammation in septic shock is considered as one therapy, it is then surprising that pentobarbital can increase mortality in pseudomonas septicemia.[19]

Inhalation anesthesia is used with a potential benefit that it attenuates production of the inflammatory by-products, but the results are not uniform and depend on the stimulus used to excite leukocytes. This effect seems to translate into less lung injury, kidney damage, and liver failure in animal models of septic shock.[20-24] However, no clinical data are available for comparisons.

In addition to general anesthetics, several adjunct medications are used in providing anesthesia care for the septic patient. Opioids, sedatives, and muscle relaxation agents are frequently employed. One has to remember the very complex pharmacokinetics and pharmacodynamics of many of these drugs. Renal and liver failures are frequent in septic shock and the metabolism of these medications often depends on liver and renal homeostasis. Intuitively, a lower titrated dose should be employed, since cumulative effect may be more pronounced than expected from otherwise healthy individuals.[25]

Current recommendations seem to suggest avoidance of regional techniques in septic patients until the sepsis has been resolved.[26] Interestingly enough, there is a recent study showing a trend in improving the mortality and morbidity in the septic patient subjected to thoracic epidural anesthesia.[27]

Furthermore, it is important as an anesthesiologist to strategize intra-operative management with the goal of best preserving the patient's hemodynamic milieu. Preserving adequate perfusion pressure is an obvious goal, since it relates to oxygen delivery to the tissues. Since there are multiple reasons for tissue hypoxemia, avoidance of hypotension should minimize anaerobic metabolism. One has to remember that septic shock is characterized by low systemic resistance, and it is unclear what an adequate perfusion pressure is, or if there is a "magic-number" associated with better outcomes. Furthermore, the microcirculation is impaired in septic shock, adding to the uncertainty of whether cardiovascular support is adequate and optimal.

Septic shock patients frequently suffer from acute lung injury and require sophisticated modes of ventilation, which the operating room ventilator may not be capable of providing. This is a population where high inspiratory concentrations of oxygen and positive end-expiratory pressures (PEEP) are frequently employed. Removing PEEP even for brief periods of time (e.g., that might occur during transport or the intra-operative period) results in significant de-recruitment and worsening arterial hypoxia. Recruitment requires time, so even a short period of low PEEP may result in prolonged disturbances of oxygenation. Again, teamwork with the ICU team is the key word here, wherein the intensive care ventilator can be employed in the operating room. In that case, a change of anesthetic technique to total intravenous anesthesia (i.e., in the absence of vaporizers on the ICU ventilators) would be the way to go.

Moreover, while you ponder on your best fluid, and limit your choice to crystalloid versus albumin, also think about "goal-directed" resuscitation starting in the operating room itself. If one thinks this patient is sick enough to go to the ICU afterwards, help out your ICU team by choosing lines and hemodynamic monitoring to the same extent that the patient's continuum of care in the ICU would deserve. The tendency to think of "getting through surgery" with minimal monitoring, and leave advanced clinical assessment (e.g., transesophageal echocardiography) or an invasive line to the ICU team, is certainly less than what the septic patient on the table deserves.

We may have left most of our readers at this point wondering, "What were the learning objectives of this article?" The final question remains, "Does anesthesia have any overall effect on the mortality and morbidity of these septic surgical patients?" Several studies mentioned above suggest that different modes of anesthesia have immunomodulatory properties. In general, anesthesia seems to suppress immune system response in different models of sepsis and septic shock.[4-6,11,13-16,19,20,23,25] This seems to result in less end-organ damage.[21,22,28] Because sepsis is such a heterogeneous and complicated pathology, we have to be careful in extrapolating these results into the clinical setting. Numerous trials of immunomodulatory agents uniformly failed to show any benefit, and this may be true for different anesthetic agents as well.[29] The current state of knowledge should at least warrant larger studies relating anesthesia to mortality and morbidity in septic patients.

The bottom line is, we still do not know whether the use of one anesthetic agent versus the other makes a difference in outcomes in the septic patient whose first stop is the operating room. Nevertheless, we have to know that, as anesthesiologists, we are very much part of this "critical care" chain of events in the care of the septic surgical patient. We

have to act and think as intensivists and be accountable for the outcomes of our septic patients in the operating room. While there is no randomized trial designed to prove the anesthesiologist's role in a postoperative ICU patient's final outcome, there is an evidence to this 'lack of evidence" that warrants close attention!

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