

Resuscitation: When Less Is More

IN THIS issue of ANESTHESIOLOGY, Li *et al.*¹ report on a laboratory study of resuscitation from uncontrolled hemorrhagic shock in rats. For those who have not followed this topic in the trauma literature, the results might seem counterintuitive—even heretical. Resuscitate to a lower blood pressure? How could that possibly be better?

Although the physiologic reasons for this enigmatic effect are well understood—and become ever clearer year after year—the resolve to manage trauma patients at a lower-than-normal blood pressure is difficult to maintain in real-world practice.^{1–6} Residents in anesthesiology are quick to learn the “three-digit reflex,” the urge to maintain patient systolic blood pressure higher than 100 mmHg. One way to do this, of course, is *via* intravenous fluid. A fluid bolus works especially well in a hypovolemic patient, and fluid therapy is important to long-term recovery. However, as Li *et al.*¹ well illustrate, fluid administration can be actively harmful during early resuscitation—namely during the vulnerable period when the patient is still bleeding.

Vascular injury leads to hemorrhage—which leads to decreased cardiac filling, progressive vasoconstriction, and, when compensatory mechanisms are exhausted, hypotension. Intravenous fluid administration increases cardiac filling, which increases cardiac contractility through the Frank-Starling relationship, thus increasing blood pressure. When there are leaks in the circulation, however, increased blood pressure increases the amount of fluid lost and imperils the integrity of early extravascular clotting.² Furthermore, administration of asanguinous fluid dilutes erythrocyte mass and clotting factor concentration, both of which decrease the rate of clot formation. Bolus fluid therapy is likely to cause hypothermia. In addition, crystalloid and colloid fluids have been linked to changes in inflammatory response. Bolus fluid administration to an actively bleeding patient thus creates a vicious downward spiral of hypotension, fluid administration, restored blood pressure, increased bleeding, and recurrent hypotension that will prove fatal if not interrupted.

Clinical observation of this effect dates to the dawn of intravenous therapy itself. Cannon, in describing the use of intravenous fluids in casualties of the First World War, observed that “Injection of a fluid that will increase blood pressure has dangers in itself. ... If the pressure is raised before the surgeon is ready to check any bleeding that might take place, blood that is sorely needed may be lost.”³ The relationship between fluid therapy and increased bleeding has been periodically rediscovered by military physicians through the years, but it was not until the late 1980s that animal models of uncontrolled hemorrhagic shock were developed. Some of

the most important studies are cited by Li *et al.*¹ Another excellent summary of this field of study was presented by Shoemaker *et al.*⁴

Are rats really a good model for human hemorrhage? Normal mean arterial pressure is similar across most mammalian species at 70–100 mmHg. Clotting mechanisms are typically more robust in animals than in man, and prebleeding or aggressive hemodilution is often necessary in animal studies to achieve a coagulopathy consistent with human trauma victims. The fluid volumes administered to rat models in Li *et al.*¹ were reasonably consistent with what trauma patients might receive; 4.8–26.9 ml in a 250-g rat roughly equates to 1.5–8 l in an 80-kg human. The reduction in hematocrit to less than 10% in the extreme cases would be unusual in a trauma patient, but is not unprecedented, and we would not expect patients to survive any better than rats. In any case, the demonstrated laboratory benefits of deliberate hypotension during active hemorrhage have been augmented by the results of a pair of human trials conducted in the 1990s.^{5,6} In high-volume trauma centers today, deliberate hypotension is accepted as the standard of care.

What, then, is added by the work of Li *et al.*? The answer is in the granularity of the data and the intuitive way it is presented. The authors have used a well-accepted animal model to take a very fine look at outcomes based on a range of management strategies. Doing so, they have found that a mean arterial pressure of 50 mmHg during active hemorrhage produced the best results. Taking this finding as a starting point, they addressed the question of how long this deliberate hypoperfusion could be maintained. Again, their results are relatively clear: 90 min was tolerated but 120 min was not.

As with most studies in this complex area, some questions remain. Rats are not humans, as noted. In addition, the rats used were more uniform genetically than are trauma patients. The rats began the experiment in deep anesthesia, in a vasodilated state, whereas trauma patients typically present in pain and sympathetic crisis and are thus maximally vasoconstricted. The rats had a single source of tissue injury—a splenic laceration—whereas trauma patients likely have many and multiple injuries, each exerting its own effect on coagulation, inflammation, and the overall rate of hemorrhage. And, finally, no neurologic assessment performed to test whether survivors had suffered brain damage during hypotension. Although human survivors of hemorrhagic shock are usually neurologically intact, maintenance of cerebral perfusion must be a concern in any resuscitation study.

How then to move forward in this area of research? One

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idea would be to take the lethal “dose” of shock (depth of hypoperfusion integrated over the time it is sustained), shown by Li *et al.* to be just beyond 50 mmHg for 90 min, and examine it in relevant human examples, such as rural trauma or the evacuation of combat casualties. When is it a good idea to bring the blood pressure up? How high? How fast? Can we calculate an ideal resuscitation trajectory based on depth of shock and estimated time to hemostasis? Another idea would be to examine the role of anesthesia in outcomes from hemorrhagic shock. One might test the tantalizing prospect that administration of vasodilating agents might allow for improved perfusion even while preserving the benefits of controlled hypotension. In the laboratory, this model should serve as the basis for an equally precise examination of outcomes using various resuscitation fluids—or even for investigation of the shock-sparing effect of novel pharmacologic agents, such as oxygen therapeutics or sulfur dioxide gas.

In the details, however, we should not overlook the most important lesson of this research: the critical importance of resuscitation strategy in survival from life-threatening hemorrhage, and thus the critical role of the anesthesiologist.

Richard P. Dutton, M.D., M.B.A., Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, Maryland. rdutton@umaryland.edu

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