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Angiotensin-II: More Than Just Another Vasoconstrictor to Treat Septic Shock–Induced Hypotension?*

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Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation, and consequently vasopressors are needed to "maintain adequate blood pressure (1)." Norepinephrine is currently recommended as the first-choice vasopressor; epinephrine and vasopressin "can be added when an additional agent is needed" and/or "with the intent of either raising mean arterial pressure or decreasing norepinephrine dosage (1)." So far, despite the demonstration of beneficial effects in subgroup analyses, adding vasopressin to norepinephrine did not improve overall

survival in patients with septic shock (2), and a more recent pilot trial on the feasibility of using vasopressin as the initial vasopressor of choice was not powered to identify any effect on outcome (3). Given the potential deleterious side effects of high-dose norepinephrine (4), the search for an alternative is ongoing. One possible approach is using angiotensin-II, a physiological vasoconstrictor that has been used in small case series as a rescue therapy for septic shock that is unresponsive to norepinephrine (5, 6). At first glance, the experimental evidence does not easily support the use of angiotensin-II during circulatory shock: various studies in different species reported that angiotensin receptor antagonists (7–9), angiotensin-converting enzyme inhibitors (9, 10), or recombinant angiotensin-converting enzyme 2, which inactivates angiotensin-II (11), and its cleavage product angiotensin-(1–7) (12) protected against endotoxin- or ischemia/reperfusion-induced organ injury. It must be emphasized, however, that all these data originate from unresuscitated shock models in animals presenting with a hypodynamic circulatory state characterized by hypotension and depressed cardiac output. Under these conditions, any pure vasoconstrictor may aggravate organ injury due to a further reduction of tissue perfusion. This situation is, however, in sharp contrast to the hyperdynamic circulatory state of septic shock presenting with hypotension despite aggressive fluid resuscitation: short-term infusion (4–6 hr) in resuscitated, ovine sepsis induced by IV infusion of live *Escherichia coli*, infusing angiotensin-II (10–600 ng/kg/min) not only restored mean blood pressure without causing any deleterious effect on kidney-tissue bioenergetics as assessed by nuclear magnetic resonance spectroscopy of adenosine triphosphate and phosphor esters (13) but also improved urine output and glomerular filtration rate (as assessed by creatinine clearance) (14). Because renal macrocirculatory blood flow was also decreased, this increase in creatinine clearance was most likely due to an increased glomerular filtration pressure resulting from the preferential vasoconstrictor effect of angiotensin on the efferent arteriole (15). This observation may assume particular importance when considering the use of angiotensin during circulatory shock: increased urine concentrations of the angiotensin precursor angiotensinogen were identified as a predictor of acute kidney injury (AKI) after cardiac surgery (16). Nevertheless, the role of angiotensin-II during septic shock is far from being well understood: on the one hand, both *E. coli* and *Staphylococcus aureus* septicemia were associated with increased angiotensin-II blood concentrations while tissue angiotensin receptor expression was reduced, suggesting impaired angiotensin responsiveness (17). On the other hand, the increased angiotensin-II blood levels in patients with septic shock were directly related to microvascular dysfunction as assessed by near-infrared spectroscopy of postischemic thenar microvascular hemoglobin oxygen saturation (18).

In this issue of *Critical Care Medicine*, now report on comparing angiotensin-II with the standard treatment norepinephrine during long-term, resuscitated porcine fecal peritonitis-induced septic shock (19). The main result was that angiotensin-II was as efficient as norepinephrine in achieving the target blood pressure of 75–85 mm Hg, whereas variables of organ dysfunction did not show any significant intergroup difference. It should be noted, however, that the authors might have missed a beneficial effect of angiotensin-II due to insufficient severity of sepsis: clearly, the norepinephrine infusion rates were similar to those reported by other authors during porcine fecal peritonitis (20). However, at the end of the initial 12-hour observation period without resuscitation, blood lactate levels had increased from 0.8 to 1.5 and arterial base excess had decreased by 5.7 mmol/L, respectively, and the rise in plasma creatinine (from 1.1 to 1.6 mg/dL) was moderate. Furthermore, a significant increase in plasma creatinine before initiation of resuscitation was present only in the norepinephrine-treated control animals. Finally, lactic acidosis disappeared until the end of the experiment, and AKI according to the Risk, Injury, Failure, Loss, End-stage renal disease criteria was present only in one fourth of the animals, no matter the group assignment.

A third intervention arm in the study by Corrêa et al (19) was dedicated to the investigation of oral pretreatment with enalapril initiated 1 week before induction of peritonitis. In this group, even three times higher norepinephrine infusion rates did not allow achieving the target blood pressure. At the end of the experiment, these animals presented with creatinine blood levels twice as high as with norepinephrine and angiotensin-II treatment alone, finally resulting in the development of AKI in six of eight animals of this group. This finding is in good agreement with recent clinical data: Patients with septic shock and previous use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers had a twofold higher risk of AKI (21). Enalapril-pretreated animals also needed three times higher doses of fentanyl, whereas they required markedly less exogenous glucose supplementation to avoid hypoglycemia. This latter finding is particularly striking: gluconeogenesis is an energy-consuming process (22), and enalapril is well established to decrease the activity of complex I of the mitochondrial respiratory chain due to an increased content of uncoupling protein-2 (23). Consequently, enalapril can be expected to decrease rather than enhance the rate of gluconeogenesis (24). One can only speculate on this discrepancy, but the markedly higher noradrenaline infusion rates may have compensated any direct effect of enalapril on the endogenous glucose formation (22).

In summary, what do we learn from the study by Corrêa et al? The authors have to be commended for using a posttreatment design—resuscitation measures were started only after hyperdynamic sepsis had developed over 12 hours without intervention, which, furthermore, comprised administration of antibiotics and protocolized hemodynamic support. Thus, their model fulfills all criteria of a clinically relevant model. Furthermore, the authors' data are in good agreement with preliminary results of the ATHOS (Intravenous Angiotensin II for the Treatment of Severe Hypotension in High Output Shock) trial presented during the International Symposium on Intensive Care and Emergency Medicine (Brussels, March 18–21, 2014): angiotensin-II allowed marked reduction of the norepinephrine infusion rates needed to achieve target

hemodynamics in patients, although there were no apparent safety concerns. Hence, the present study adds important information to the search of the "ideal" vasopressor that could replace norepinephrine for the treatment of arterial hypotension associated with septic shock.

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