Early May Be Better: Early Low-Dose Norepinephrine in Septic Shock

In this issue of the *Journal*, Permpikul and colleagues (pp. 1097–1105) report on a phase 2 randomized controlled trial (RCT) of early low-dose norepinephrine (NE) in septic shock (1). Arguably the most important finding from studies of antibiotic timing (2, 3) and early goal-direct therapy (3, 4) is that early treatment of septic shock is beneficial. At first, the design may appear odd, but a close reading reveals a neat design that allows early testing of the intervention (early low-dose NE), allowing separation of the treatment groups without denying "standard" care and without forcing any patients to receive "late" NE.

The authors randomized patients to early low-dose NE ($n = 155$) or placebo infusion ($n = 155$) plus standard care, which included open-label vasopressors. NE study drug dose was weight-based infused via peripheral intravenous lines in many cases until a dose of 0.05 μg/kg/min was achieved (e.g., 3 μg/min in a 60-kg patient), plus open-label vasopressors and fluid resuscitation, and NE dose was unchanged for 24 hours. The primary outcome was control of shock defined by a composite of mean arterial pressure (MAP) greater than 65 mm Hg plus either urine output greater than 0.5 ml/kg/h or 10% decline in lactate from baseline, reasonable components of a composite, because each is associated with short-term mortality of septic shock (5, 6). Intervention patients had NE started sooner (93 vs. 192 min), indicating that the intervention (early NE) was indeed tested. The primary endpoint was achieved in significantly more of the intervention than control group (76.1% vs. 48.4%); each component of the composite was achieved significantly earlier in the intervention group (i.e., the composite was not driven by one major component). There was a nominally lower mortality in the intervention than control group (15.5% vs. 21.9%; $P = 0.15$). This phase 2 RCT was not powered for mortality, but it is satisfying to see these short-term mortality results. There was no difference in the fluids administered, but the net fluid balance was not reported. One might have expected that early NE would lower net fluid balance (7). Interestingly, the intervention group had significantly fewer patients with cardiogenic pulmonary edema (14.4% vs. 27.7%) or new-onset arrhythmias (11% vs. 20%). The authors conclude that early low-dose NE was associated with earlier shock control.

This RCT fits a growing body of evidence that vasopressors should probably be started earlier. It aligns with a recent artificial intelligence (AI) study in which the AI clinician recommended more patients with sepsis should have been given vasopressors (17% vs. 30%) (8). Although we should not change practice on the basis of the study by Permpikul and colleagues (1), this trial and other work suggests that we should not delay starting vasopressors. If there is delay inserting a central venous catheter, then one should consider peripheral low-dose dilute NE temporarily rather than delay

vasopressor(s). If clinicians delay starting vasopressor(s) because of a lack of critical care bed availability, then again, this RCT suggests they probably should not delay. Managing a patient on a general ward, without vasopressors, hoping that in time blood pressure will improve and thus not require critical care, may lead to worse outcomes for patients.

The investigators should be congratulated for conducting a high-quality trial, with an interesting design, incorporating a blinded placebo infusion in what is a challenging research area. The strengths of the study include computerized randomized controlled design, well-matched patients (although MAP was lower initially in the NE group), the composite primary endpoint, intention-to-treat primary analyses, and the method for organ dysfunction analyses (9). Remarkably, these investigators were able to identify, consent, and randomize patients within 1 hour of meeting inclusion criteria, which is fundamental in examining early treatment.

Limitations are that the effects of NE to increase MAP would have been apparent, and blinding was not 100% possible. Second, many (47%) trial patients not on dialysis or mechanical ventilation were transferred to medical wards for care, which may have increased the risks of protocol violations and adverse events.

The NE group achieved MAP and lactate clearance greater than 10% within 6 hours, and time to target urine output and lactate were lower. Thus, earlier NE may have improved general tissue and renal perfusion; the better urine output could be due to earlier MAP greater than 65 mm Hg and higher early renal perfusion pressure. However, this did not translate into less need for renal replacement therapy.

Early NE may be more effective than later NE because patients have less organ injury, and prevention of organ dysfunction is possible. Early NE may also allow lower doses of NE and so fewer adverse effects, and sustained elevation of NE down-regulates adrenergic receptors, which can further increase NE dose requirements (10) (Figure 1). Early low-dose NE could also beneficially modulate immunity in sepsis (11).

Although there are no clinical predictive biomarkers for response to NE, variants in the β_2-adrenergic receptor gene (12) associated with mortality of septic shock could be predictive biomarkers of response to NE.

What are the wider implications of the current RCT? The RCT by Permpikul and colleagues (1) is similar to prior RCTs of early vasopressin (13) versus NE, NE versus epinephrine (14), NE versus dopamine (15), and vasopressin versus NE in septic shock (16). These RCTs established that NE is superior to dopamine and equivalent to vasopressin and epinephrine. In VANISH (Vasopressin vs. Norepinephrine as Initial Therapy in Septic Shock) (13), early vasopressin was no different regarding mortality than standard care. There was no difference in overall mortality between vasopressin and NE in VASST (Vasopressin and Septic Shock Trial) (16), but vasopressin may have been more effective than NE in patients with less severe shock. A propensity-matched cohort study (17) showed that lower doses of vasopressin were associated with similar outcomes compared with
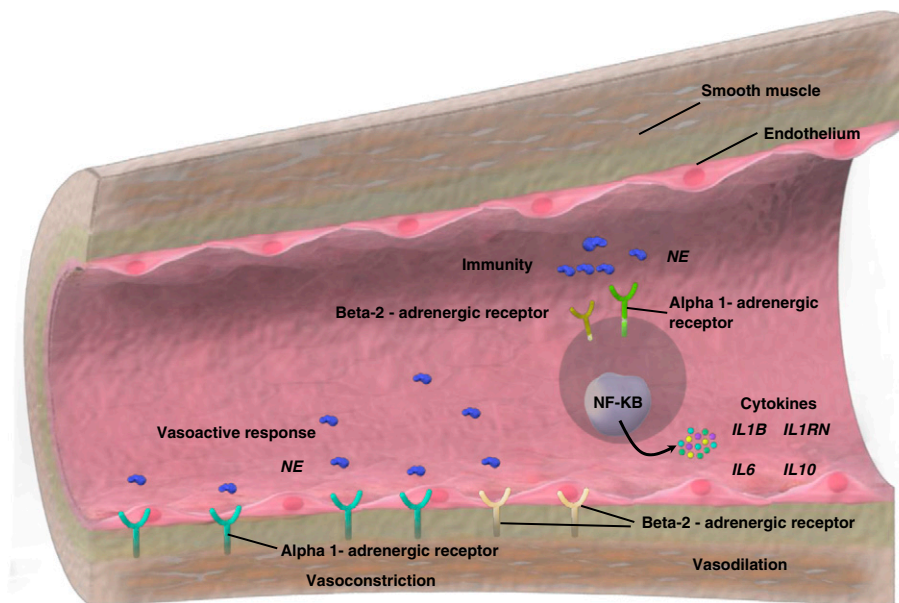
Figure 1. Norepinephrine (NE, blue) binds to α_1-adrenergic receptors of vascular smooth muscle to induce vasoconstriction and binds to α_1- and β_2-adrenergic receptors on leukocytes to differentially modulate immune response in sepsis. Exposure to NE also downregulates α_1- and β_2-receptor density, which could alter sensitivity to NE, thereby leading to increased infusion doses of NE and greater risk of adverse vascular and immune effects. NF = nuclear factor.

NE. An RCT of early vasopressin and NE versus NE monotherapy found that patients who received early vasopressin and NE achieved MAP of 65 mm Hg faster than those receiving NE monotherapy (18).

Thus, NE remains the primary vasopressor in septic shock, but the existing evidence underlines the importance of early appropriate treatment in sepsis. The current RCT suggests that early low-dose NE may be superior to current standard care. We now need a large multicenter phase 3 RCT of early low-dose NE powered for mortality and organ dysfunction. ■

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🔓 Sleep and Wakefulness Evaluation in Critically Ill Patients
One Step Forward

Over the last two decades, there has been a growing interest in sleep abnormalities of critically ill patients. Early studies using standard EEG criteria (1) have shown that these patients exhibit a reduction in REM and N3 stages of sleep and excessive sleep fragmentation, whereas the normal circadian rhythm is lost (2, 3). Thus, although the total sleep time may be normal, the quality of sleep is poor, and these patients could be considered as sleep deprived (4, 5). Sleep disturbances remain mostly undiagnosed, mainly owing to a lack of easily applicable diagnostic tools.

Recent studies have shown that in critically ill patients, the conventional EEG criteria for evaluation of sleep and wakefulness are difficult to apply (6, 7). In these patients, the K complexes and sleep spindles, used to identify N2 stage, are often absent (atypical sleep), whereas EEG during behaviorally confirmed wakefulness may be abnormal, characterized by an increase in slow-wave activity and a decrease in high-frequency activity (pathological wakefulness). These EEG patterns have been observed in 30–50% of critically ill patients and usually coexist (6, 8). It is important to realize that EEG during pathological wakefulness may be similar to non-REM sleep, and therefore the diagnosis necessitates behavioral criteria. It follows that sleep assessment offline is unable to distinguish pathological wakefulness from sleep.

Recently, Younes and colleagues described and validated a continuous index, the odds ratio product (ORP), for the evaluation of sleep depth in ambulatory patients, using EEG power spectrum analysis (9). The ORP is an index of sleep depth derived from the relationship of powers of different EEG frequencies in 3-second epochs, and it ranges between 0 (very deep sleep) and 2.5 (full wakefulness). An ORP value less than 1.0 predicts sleep, and an ORP value greater than 2.0 wakefulness with 95% accuracy, whereas the range between 1.0 and 2.0 represents unstable sleep. An ORP value greater than 2.2 predicts wakefulness with almost 100% accuracy (9).

In this issue of the *Journal*, Dres and colleagues (pp. 1106–1115) report, for the first time, ORP in mechanically ventilated critically ill patients during a 15-hour period preceding a spontaneous breathing trial (SBT) (10). The aim was to investigate if ORP and polysomnographic indices indicating atypical sleep and pathological wakefulness are associated with SBT outcome. Among 44 eligible patients, 37 had an acceptable quality of EEG recordings and were included in the study. ORP analysis was possible in 31 of them (84%). During the total recording period, the average ORP, the percentages of total recording time with ORP greater than 1.5, greater than 2.0, and greater than 2.2, and intraclass correlation coefficient between ORP in the right and left hemispheres (R/L ORP) were calculated. In the general population, the latter index averages 0.87 (0.76–0.95; 10th–90th percentile range) and is rarely less than 0.7 during the night (M. Younes, M.D., Ph.D., written communication, February 3, 2019), indicating that sleep depth changes in parallel in both hemispheres. Nineteen patients (51%) successfully passed the SBT, whereas 18 (49%) failed. Among the success group, 11 were extubated, and 8 were considered unready for extubation for various reasons. Pathological wakefulness or atypical sleep was highly prevalent, occurring in 14 (38%) and 17 (46%) patients, respectively, whereas conventional scoring of sleep was feasible only in 19 patients (51%). Neither atypical sleep/pathological wakefulness nor sleep architecture was associated with SBT outcome.

These results contrast with those of Thille and colleagues (8), who observed that in difficult-to-wean patients, atypical sleep was associated with longer weaning time. The difference is likely due to the patients studied because Thille and colleagues studied