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EDITORIAL COMMENT

Norepinephrine as a First-Line Inopressor in Cardiogenic Shock

Oversimplification or Best Practice?*

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All generalizations are false, including this one.
—Mark Twain (1)

An estimated 6% to 10% of patients with an ST-segment elevation myocardial infarction (MI) are complicated by cardiogenic shock (CS) (2). Before the revascularization era, the reported mortality rate ranged from 72% to 81% in patients with CS (3,4). Arguably, the single most important historical advancement was the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock?) trial, which established the life-saving role of routine early revascularization in patients with MI complicated by CS, changed clinical practice, and led to a decrease in CS mortality in population-based studies (2,5). In contemporary studies, however, temporal CS mortality has remained very high (30% to 34%) (2,6). In response, expert working groups have highlighted the need for further CS research, including defining the optimal vasoactive therapies (7). The study by Levy et al. (8) published in this issue of the *Journal* adds to our limited knowledge of the hemodynamic and biochemical responses to inopressors in this high-risk population.

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The only previous controlled study of epinephrine in CS randomized 30 patients with acute or chronic heart failure with dopamine-resistant CS to receive epinephrine alone or dobutamine and norepinephrine (9). The study, which was not powered for clinical outcomes, found no differences in cardiac index or mean arterial pressure (MAP), but the epinephrine arm had higher heart rates and lactate levels. In the present study (8), led by the same author, 57 patients with ischemic CS were randomized to receive epinephrine or norepinephrine. The study found no differences in the primary outcome of cardiac index or most secondary hemodynamic endpoints, including MAP, systemic vascular resistance index, cardiac power index, pulmonary arterial systolic pressure, wedge pressure, left ventricular ejection fraction, biomarkers, or the incidence of arrhythmias. Epinephrine, however, resulted in higher heart rates and lactate levels but a shorter duration of additional inotropic support.

This randomized study (8) builds on the previous research by evaluating epinephrine in the most common etiology of CS, and it advances our understanding of the temporal hemodynamic and biochemical changes attributable to epinephrine when used as a first-line agent in CS. It informs clinicians that both drugs, when titrated strictly to goal MAP, result in similar hemodynamic responses albeit with a few exceptions that may reflect their different pharmacodynamic properties. First, epinephrine has more potent beta$_1$-recepter activity and consequently increases chronotropic and inotropy more than norepinephrine. This activity may explain the lower incremental use of other inotropes and the excess chronotropy in the epinephrine arm. In clinical practice, these findings suggest that epinephrine could be theoretically advantageous in patients with bradycardia but deleterious in patients with ischemia, pre-treatment tachycardia, or at a high risk of

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arrhythmias. Second, epinephrine-associated excess lactic acidosis (also known as unexplained or type B lactic acidosis) has been well described in patients with septic shock and is potentially due to excessive α-adrenergic–mediated splanchnic vasoconstriction (9–11). The clinical implication of this finding is that epinephrine treatment may confound the interpretation of lactate clearance as a marker of restoration of systemic perfusion.

This small study (8) was not powered for clinical or safety outcomes, and thus interpretation of the 2 clinical endpoints requires caution. The study reported a higher risk of the composite of death or extracorporeal life support (ECLS) through 7 days. Importantly, this composite was not a pre-specified study endpoint, and the study did not have protocolized criteria for the initiation of ELCS. Hence, the ECLS endpoint is subject to patient selection bias. The lack of temporal treatment-related differences in Sequential Organ Failure Assessment scores, MAP, and biomarkers may support this postulate of nonrandom ECLS selection. The study was also terminated early by the data safety and monitoring board due to a higher incidence of refractory CS defined, in part, as major cardiac dysfunction, elevated lactate level, sustained hypotension, and acute organ dysfunction despite moderate doses of vasoactive therapies. It is important to note that this safety metric was defined 4 years after the start of the trial, and the interpretation of this composite endpoint is difficult for several reasons. The timing of the endpoint assessment is not provided, and there is no clear pathophysiological mechanism to explain why epinephrine is associated with refractory CS. In addition, the individual components of refractory CS composite endpoint between the treatment arms were not provided. Thus, it is possible that the composite safety endpoint may be driven solely by differences in type B lactic acidosis. Finally, ECLS-treated patients often require concurrent inopressor therapies. Thus, there is a potential that the safety outcome could also be confounded by the aforementioned ECLS initiation bias, but a definitive conclusion cannot be reached because the association between the provision of ECLS and refractory CS was not described. This finding emphasizes the need for a randomized controlled trial powered for efficacy and safety outcomes that mitigates the potential confounding of ECLS by defining standardized initiation criteria.

The selection of norepinephrine as an active comparator is appropriate and likely stems from the SOAP (Sepsis Occurrence in Acutely Ill Patients) II trial, which is the largest and most rigorously conducted trial of inopressor therapies in patients with any form of shock (12). In a subgroup of 280 patients with CS, norepinephrine was associated with a lower risk of 28-day mortality compared with dopamine. Despite the many strengths of SOAP II, its limitations include a lack of an operationalized definition of CS, unreported cardiovascular time and treatment variables related to revascularization, and grouping of shock pathophysiologies (obstructive, valvular, and post-cardiac surgery) that are not traditionally treated with dopamine within the CS subgroup. Moreover, the direct drug-to-drug comparison overlooks the growing recognition of the hemodynamic diversity of CS. The early hemodynamic description of post-MI CS included a low cardiac index and high systemic vascular resistance and high filling pressures (13). Although this cold and wet profile remains the most common hemodynamic phenotype of CS, secondary analyses from the SHOCK trial and contemporary registries have identified an expanded spectrum of hemodynamic phenotypes to include vasodilatory CS, euvolemic CS, normotensive CS, right ventricular CS, and biventricular CS (7). These phenotypes share a depressed cardiac index, but these studies have informed us that systemic vascular resistance, pulmonary capillary wedge pressure, and right ventricular function metrics (i.e., right atrial pressure/pulmonary capillary wedge pressure, right ventricular stroke work index, pulmonary artery pulsatility index) can vary (14–16). Importantly, no trial of vasoactive therapies in CS has evaluated treatment differences across various hemodynamic phenotypes of CS. Taken together, this perspective should not be misinterpreted as advocacy for any first-line vasoactive agent in CS; rather, it highlights the need to incorporate hemodynamic phenotypes of CS into future trial design and to evaluate the role of routine hemodynamic monitoring and tailoring in a CS population.

The limitations of existing trials of vasoactive therapies in the CS population discussed herein could be used to improve future study designs. First, the temporal increase in mechanical circulatory support and ECLS has the potential to create selection biases that can change hemodynamics and short-term mortality (17). Future trials of medical therapies in CS should seek to protocolize the initiation of these technologies. Second, these mechanical circulatory support technologies have the ability to prolong life in this acutely ill population without necessarily improving its quality. Thus, it is important that CS trials comprehensively examine metrics beyond