

**NOREPINEPHRINE IS NOT THE FIRST LINE PHARMACOLOGICAL
TREATMENT FOR CARIOGENIC SHOCK**

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The recently published AHA scientific statement entitled “Contemporary Management of Cardiogenic Shock” (CS) recommends the first line use of vasopressors in most situations.¹ This is debatable at different levels.

1. Epistemology. This approach is supported by a concept of CS mixing causes and consequences. This could be acceptable if the consequences were to exacerbate the causes, but such a vicious circle is not demonstrated. It leads to a shift from classic pathophysiological classification to phenotypic classification of CS. Therefore, the statement seems to support symptomatic treatment (norepinephrine when blood pressure fell) more than interventions on the understood mechanisms. However, the recent better understanding of CS consequences does not invalidate the mechanistic previous studies. Classically, CS was seen as an acute heart failure with a reduced cardiac output (CO) that no longer meets metabolic demands. The use of vasodilators in any stage of heart failure has reached a large consensus. The statement does not suggest any clear-cut break point supporting a completely opposite vasoactive strategy.

2. Pathophysiology. Basic physiology indicates that increasing afterload decreases the stroke volume and the ventricle efficiency, especially in the failing heart, with subsequent increase in the myocardial oxygen demand. This forward reduction in organ oxygen delivery is greatly variable among organs with preferential protection of the myocardium, brain, kidneys, and liver in relation with flow autoregulation. Even not fully clarified, the presence of a systemic inflammation following CS may influence this protection efficiency. In the absence of a more solid demonstration, the systematic use of vasopressors to restore adequate perfusion seems hazardous.² In other territories, CS triggers baroreflexes and immediate release of endogenous vasopressors. Additional vasoconstriction could lead to severe ischemia. Backward, the frequent elevation in the

venous pressure during CS may induce tissue congestion that additionally impairs perfusion. The global effect of vasopressors on venous stressed/unstressed volume and venous return is unpredictable, possibly inversely related to the volemia, and may increase capillary leak. Over time, the symptoms of any shock can be dominated by the inflammatory response. However, there is considerable inter-individual heterogeneity in the inflammatory and metabolic response,³ Moreover, when organ failure occurs, purely hemodynamic treatment is inefficient.⁴ These combined heterogeneities support the possibility of the limited efficiency of a monotone strategy.

3. Diagnosis. Instead of CO, blood pressure is known to be a poor indicator of tissue perfusion.² The systematic use of vasopressors may deteriorate the tissue perfusion despite correction of hypotension, which may induce confusion for clinicians.

4. Level of evidence. The use of norepinephrine as first line treatment of CS was suggested 65 years ago but has been rejected thereafter, favoring the use of selective inotropes.⁵ The statement does not provide clear evidence supporting the use of vasopressor alone but only indirect arguments taken from a post hoc analysis of the TRIUMPH study.

We believe that the CS treatment must be a compromise between the best possible tissue perfusion and the lowest myocardial energy cost. The individual specificities support the necessity of a personalized strategy, including adequately used vasopressors.

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Reply to Letter Regarding Article, "Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association"

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We thank Drs Squara and Payen for their interest in the AHA's scientific statement on cardiogenic shock (CS).¹ Their letter highlights the lack of consensus, variability in clinical practice, and overall paucity of research into first line vasoactive medical therapies.² We welcome the opportunity to clarify some of the opinions presented in their correspondence.

While we agree with the potential adverse hemodynamic effects of inopressors in some phenotypes of CS, we respectfully disagree with the assertions that utilization of "vasodilators at any stage of heart failure has reached consensus," and "norepinephrine as first line treatment of CS was suggested 65 years ago but has been rejected thereafter, favoring the use of selective inotropes." We are unaware of any randomized trials that have addressed the efficacy and safety of routine vasodilatory therapy as a first line agent in CS; though observational studies have reported that concurrent anti-hypertensive medications are associated with an increase in mortality.³

The statement describes the diverse hemodynamic phenotypes and multiple etiologies of CS, thus vasodilatory (or inotropic agents) as initial monotherapy may have potentially dangerous consequences. First, during the resuscitation phase, the etiology and phenotype may not be entirely clear and vasodilation in patients with unrecognized dynamic obstruction, valvular stenosis, obstructive, or vasodilatory CS may lead to further hemodynamic deterioration. Second, the response of stunned, infarcted, or fibrotic myocardium to inotropic agents is variable,⁴ thus inotropic monotherapy may predominantly lead to vasodilation and reduced perfusion. Finally, CS severity can range from normotensive CS to a pulseless state. This variability highlights the need for a common evidence-based CS severity nomenclature which may facilitate future trials of alternate vasoactive strategies in less severe CS subclasses. We have acknowledged that there may be subsets of patients who could be treated with inotropic monotherapy such as normotensive CS⁵ or a chronic cardiomyopathy with CS.

We believe that some of the authors' stated opinions may arise from a misinterpretation of the statement. First, the document carefully highlights the potential limitations of the major study advocating for norepinephrine as a routine first line agent in CS, and unequivocally states that in the opinion of the writing group "the optimal first-line vasoactive medication in CS remains unclear." The statement also identifies "optimal inotropic and vasopressor regimens across common causes and hemodynamic phenotypes of CS" as a future research priority.¹ Second, the statement does not support using blood pressure alone as a marker of tissue perfusion. The aforementioned heterogeneity of CS underscores our suggestion that clinicians should integrate clinical, hemodynamic, imaging, and biochemical markers to "assess the adequacy of end-organ and tissue perfusion in response to individualized targets." Finally, the authors' assertion that "the statement does not suggest any clear cut breaking point supporting a completely opposite strategy" does not reflect that Table 5 suggests the addition of an inotropic agent when the patient is stabilized.¹

We believe our scientific statement represents a scholarly evidence-based summary of contemporary best practices, but we do acknowledge a pressing need for more research in this area.

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