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Management of Refractory Vasodilatory Shock

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Refractory shock is a lethal manifestation of cardiovascular failure defined by an inadequate hemodynamic response to high doses of vasopressor medications. Approximately 7% of critically ill patients will develop refractory shock, with short-term mortality exceeding 50%. Refractory vasodilatory shock develops from uncontrolled vasodilation and vascular hyporesponsiveness to endogenous vasoconstrictors, causing failure of physiologic vasoregulatory mechanisms. Standard approaches to the initial management of shock include fluid resuscitation and initiation of norepinephrine. When these measures are inadequate to restore BP, vasopressin or epinephrine can be added. Few randomized studies exist to guide clinical management and hemodynamic stabilization in patients who do not respond to this standard approach. Adjunctive therapies, such as hydrocortisone, thiamine, and ascorbic acid, may increase BP in severe shock and should be considered when combination vasopressor therapy is needed. Novel vasopressor agents, such as synthetic human angiotensin II, can increase BP and reduce the need for high doses of catecholamine vasopressors in severe or refractory vasodilatory shock. Few effective rescue therapies exist for established refractory shock, which emphasizes the importance of aggressive intervention before refractory shock develops, including the earlier initiation of rational combination vasopressor therapy. The present review discusses the diagnosis and management of refractory shock to offer guidance for management of this important clinical problem and to provide a framework for future research.

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Circulatory shock is the most serious manifestation of cardiovascular failure encountered in critically ill patients and is characterized by hypotension and tissue hypoperfusion that can lead to inadequate cellular oxygen utilization and organ failure.[1] Management of shock involves correcting the triggering cause and restoring adequate organ perfusion by using fluid resuscitation and vasoactive medications, as necessary.[1] Circulatory shock develops in approximately 33% of critically ill patients worldwide.[2,3] Vasodilatory or distributive shock is the most common form of shock and will typically

ABBREVIATIONS: iNOS = inducible nitric oxide synthase; MAP = mean arterial pressure; NO = nitric oxide; NOS = nitric oxide synthase; RCT = randomized controlled trial

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require the use of vasopressor agents to restore adequate vascular tone.[1,4] Despite recent advances in therapy, the mortality of patients with shock remains as high as 30% to 50%, mainly due to multiorgan failure.[4-10]

The vasopressor dose required to maintain adequate mean arterial pressure (MAP) is one of the strongest predictors of short-term mortality in critically ill patients.[11-14] High doses of catecholamine vasopressors can produce a variety of adverse effects, contributing to morbidity and mortality.[15,16] The increased mortality in patients with higher vasopressor requirements reflects both a greater severity of underlying illness and potentially harmful effects of vasopressor drugs.[12,16,17] Adverse events are common during catecholamine therapy for shock, leading some authors to propose that high catecholamine doses are directly toxic to various tissues and organs. This theory may be supported by evidence suggesting a possible beneficial effect of β-blockade in patients with sepsis.[18] In addition, the use of higher vasopressor doses to achieve a higher MAP goal in patients with sepsis was associated with increased rates of cardiovascular adverse effects, although not with increased mortality.[19]

Refractory Shock Definition

There is no universal consensus definition of refractory shock. Proposed definitions include failure to achieve a BP goal despite vasopressor therapy, need for rescue vasopressor therapy, or need for high vasopressor doses.[20-23] Conventional methods of comparing total vasopressor dose among patients include conversion to norepinephrine equivalents (Table 1) or use of one of several previously published scores.[4-6,8,10,12,13,23-27] The recent Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) clinical trial used a norepinephrine-equivalent dose > 0.2 μg/kg/min to define refractory shock and reported worse outcomes in patients requiring ≥ 0.5 μg/kg/min of norepinephrine equivalents at baseline.[24,26] Norepinephrine-equivalent doses of 0.5 μg/kg/min or 1 μg/kg/min have been proposed as thresholds to define high-dose vasopressor therapy and refractory shock.[20-23] On the basis of these observations, a reasonable definition of refractory shock would be an inadequate response to high-dose vasopressor therapy (defined as ≥ 0.5 μg/kg/min norepinephrine-equivalent dose).[20] Observational studies suggest that, using this definition, 6% to 7% of critically ill patients may develop refractory shock.[21,28] Mortality rates in patients with refractory shock greatly depend on the definition used (e-Tables 1 and 2), with hospital mortality rates generally exceeding 50%.[21-24,28-31] There is no consistent relationship between norepinephrine-equivalent dose and short-term mortality in patients with refractory shock, implying that outcomes are poor once a refractory shock state develops independent of vasopressor dose.

TABLE 1] Converting Vasopressor Doses to Norepinephrine Equivalents[4-6,8,10,12,23,24,26,27]

Drug	Dose	Norepinephrine Equivalent
Epinephrine	0.1 μg/kg/min	0.1 μg/kg/min
Dopamine	15 μg/kg/min	0.1 μg/kg/min
Norepinephrine	0.1 μg/kg/min	0.1 μg/kg/min
Phenylephrine	1 μg /kg/min	0.1 μg/kg/min
Vasopressin	0.04 U/min	0.1 μg/kg/min

Pathophysiology of Refractory Shock

A central pathophysiologic feature of refractory shock is the impairment of vascular response to catecholamine stimulation (Fig 1).[20] Reduced catecholamine responsiveness and uncontrolled pathologic vasodilation (vasoplegia) can occur because of changes in receptor signaling, metabolic derangements, and depletion of endogenous vasoactive hormones. Inappropriate vasodilation typically occurs from the effects of inducible nitric oxide synthase (iNOS), which produces excessive amounts of vasodilatory nitric oxide (NO). NO increases vascular levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate to trigger vasodilation.[32,33] Activation of adenosine triphosphate-sensitive potassium channels in vascular smooth muscle cells prevents calcium entry required for vasoconstriction, representing a final common pathway linking metabolic derangements (tissue hypoxia and acidosis) and inflammation (including NO production) with vasoplegia.[20,32] Absolute or relative deficiencies of endogenous vasoactive hormones, such as cortisol, vasopressin, and angiotensin II, can develop in shock states, further decreasing vasopressor responsiveness.[34-36] Not all vascular beds are dilated in shock, and microcirculatory defects that create low- or no-flow zones are surrounded by areas of profound vasodilation and rapid flow, leading to inadequate tissue oxygen delivery.[37] The combination of pathologic vasodilation with vasoconstriction from vasopressor drugs produces heterogeneous effects on different