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Vasopressor Choice and Timing in Vasodilatory Shock

Patrick M. Wieruszewski[1] and Ashish K. Khanna[2,3*]

Abstract

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Introduction

Vasodilatory shock is the most common form of circulatory shock encountered in patients admitted to the intensive care unit (ICU) [1]. Sepsis is the predominant etiology, but other causes of vasodilatory shock include postoperative vasoplegia, anaphylaxis, spinal cord injury (i.e., neurogenic shock), systemic inflammatory response from acute pancreatitis, and direct vascular relaxation from general and neuraxial anesthetics. Vasodilatory shock is a medical emergency that requires prompt diagnosis and treatment. Regardless of etiology, vasodilatory shock is characterized by reduced systemic vascular resistance and arterial hypotension that warrants intravascular fluid resuscitation and pharmacological vasopressors to restore the vascular tone. Left untreated, perfusion pressures suffer, leading to inadequate cellular oxygen utilization, conversion to anaerobic metabolism, multiorgan failure, and death [2, 3]. For over a decade, norepinephrine has been recommended as the first-line vasopressor choice, with vague guidance on secondary agent selection and timing [4], leading to considerable heterogeneity in intensivist practice at the bedside [5]. Herein, we provide a contemporary review of factors that influence vaso-pressor selection and timing, challenging the classic treatment paradigms of vasodilatory shock.

A Balanced Vasopressor Approach

The classic approach to fluid-refractory vasodilatory shock treatment is to apply catecholamine vasopressors and titrate to achieve a specified mean arterial pressure (MAP). This stepwise approach traditionally involves initiation of norepinephrine, subsequent up-titration of dosage, often to toxic levels, waiting for a relative catechol amine-refractory state, and then moving on to the next vasopressor [4]. This strategy delays attainment of adequate perfusion pressures and ultimately leads to progressive multiorgan failure, and in turn, the chances of death rise with each progressive increase in the number of total organ failures [6]. Refractory vasodilatory shock is the end point of treatment failure and is clinically characterized by a lack of sustainable adequate MAP despite increasing doses of a single or multiple vasopressors [7]. This state is a molecular combination of a complex set of physiological alterations coming together, including but not limited to altered microcirculatory flow, membrane hyperpolarization, cellular relaxation, and vascular reactivity (Fig. 1).

This approach leaves intensivists with many uncertainties, including (1) at what point do you consider norepinephrine-treatment failure, (2) when do you apply a secondary vasopressor, and (3) which secondary vasopressor do you select? It is important to understand these

*Correspondence: akhanna@wakehealth.edu
[2] Department of Anesthesiology, Section on Critical Care Medicine, Wake Forest School of Medicine, Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC, USA
Full list of author information is available at the end of the article

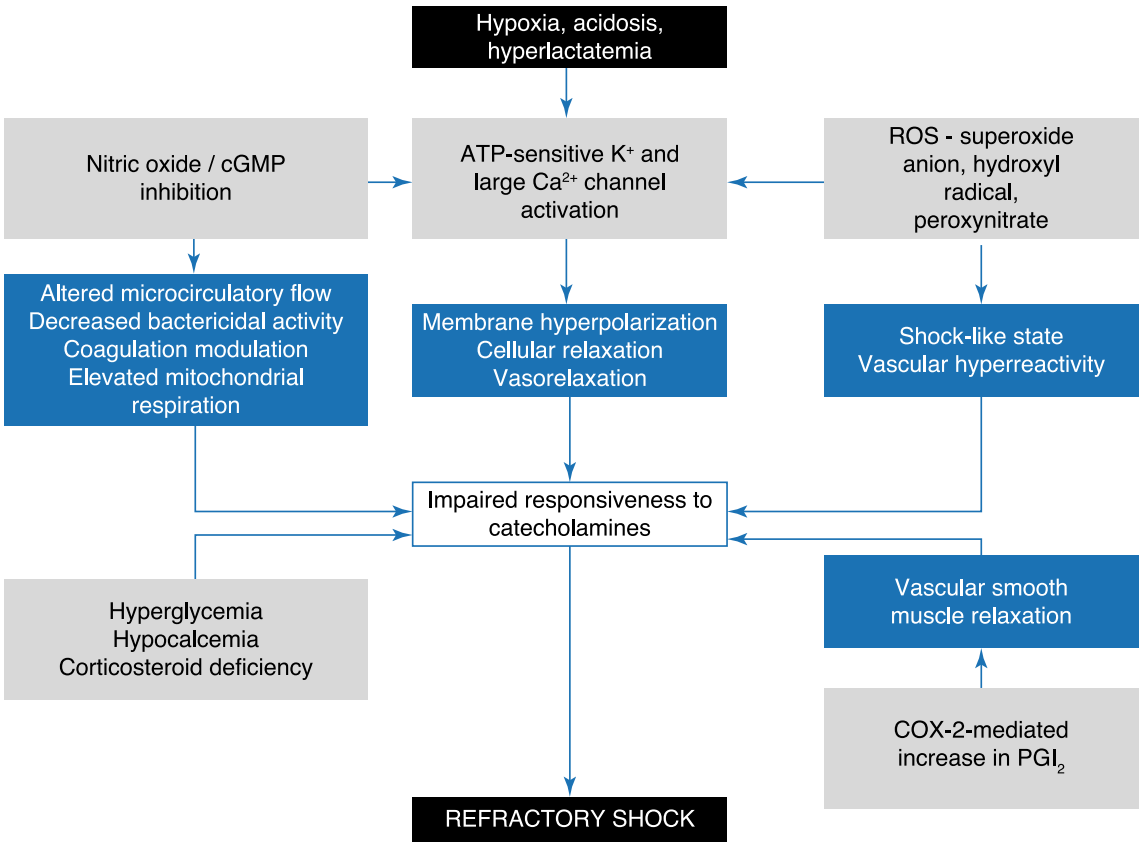

Fig. 1 Pathogenic mechanisms leading to refractory vasodilatory shock. *ATP* adenosine tri-phosphate, *cGMP* cyclic guanosine monophosphate, *COX-2* cyclooxygenase-2, *PGI2* prostaglandin I2, *ROS* reactive oxygen species. (From [8] with permission)

challenges and rationalize an early, multimodal balanced vasopressor strategy as an alternative to the classic step-wise approach. Normal blood pressure homeostasis and pathogenesis in shock, as well as the major determinants of shock outcomes including timing delays in perfusion, hyperlactate-mia, and catecholamine burden, particularly as it all relates to the pharmacology of vasopressors, is a critical discussion that deserves mention in this context.

Blood Pressure Homeostasis and Pathogenesis

Under normal physiological conditions, blood pressure and circulatory function are maintained in homeostasis by a complex counter regulatory interplay of the sympathetic nervous system, vasopressinergic system, and the renin-angiotensin system (Fig. 2).

When these systems are perturbed by an insult (e.g., sepsis), the homeostatic balance is disrupted. The most obvious objective finding is macrocirculatory dysfunction identified by directly measuring systemic blood pressure, although damage to tissues and the microvasculature regionally occurs in parallel and even preceding global evidence of hypotension [9].

In addition to direct insults from profound systemic inflammatory responses, the very systems responsible for homeostasis are impaired during shock. Although a stress-induced hyperdynamic state often accompanies septic shock, total heart rate variability is reduced suggesting impairment of the sympathetic system [10].

Similarly, in states of hypotension the posterior pituitary is expected to secrete endogenous vasopressin stores, although plasma vasopressin concentrations in vasodilatory septic hypotension have been shown to be inappropriately low (3.1 pg/ml) as compared to other hypotensive states also expected to experience this hormonal response, such as cardiogenic shock (22.7 pg/ml), $p < 0.001$ [11]. Finally, despite activation of the renin-angiotensin system in shock, various angiotensin receptors are downregulated, contributing to vascular hyporeactivity and also impaired endogenous catecholamine secretion [12, 13]. Despite this multifactorial and co-existent hormonal deficiency that is evident during the continuum of vasodilatory shock, the recommended approach remains a step-wise one where catecholamines are started with up-titration, often to toxic levels, and

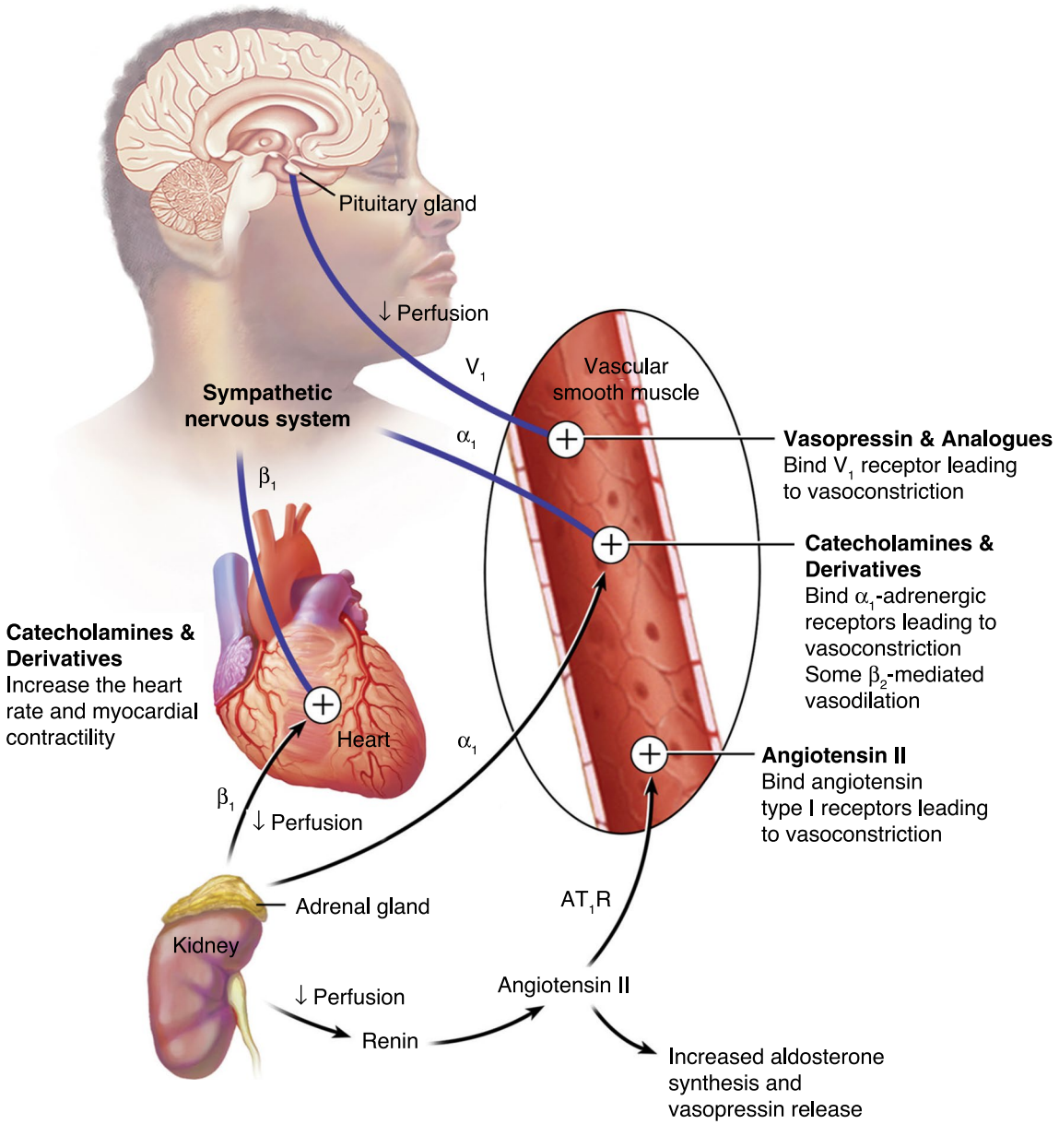

Fig. 2 Physiologic concert of the adrenergic, vasopressinergic, and renin-angiotensin systems in blood pressure homeostasis, and select mechanisms of pharmacologic vasopressors. *α1* alpha1-adrenergic receptor, *AT1R* angiotensin type 1 receptor, *β1* beta1-adrenergic receptor, *β2* beta2-adrenergic receptor, *V1* vasopressin 1 receptor. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

only then a potential introduction of a secondary agent [4].

Timing

Attainment of a satisfactory perfusion pressure to push arterial blood into capillaries and deliver oxygen to tissues is the ultimate goal of resuscitation in vasodilatory shock. Delays in restoring adequate perfusion are consistently associated with worse organ failures and an increased risk of death in vasodilatory shock [6, 14, 15]. Specifically, after adjustment for severity of illness, delay in vasopressor initiation was associated with an increase in in-hospital death (OR 1.02, 95% CI 1.01–1.03, $p < 0.001$), which was most profound when delays were in excess of 14.1 h

(OR 1.34, 95% CI 1.03–1.76, p = 0.048) [6]. Similar to the time-dependent mortality risk of delayed antimicrobials in sepsis, the risk of death has been shown to increase by 5.3% for every hour that vasopressor initiation is delayed [16]. In another cohort study, those who received vasopressors within 6 h of shock onset achieved goal MAPs twice as fast (1.5 vs. 3.0 h, p < 0.01), spent more time off vasopressors in the first 72 h of shock (34.5 vs. 13.1 h, p = 0.03), and were independently nearly 3 times as likely to survive at 30-days (mortality for vasopressors after 6 h; OR 2.9, 95%CI 1.3–7.0, p not reported) [15]. On the other hand, when vasopressor initiation is delayed beyond 4 h, the odds of worsening organ failure increase fourfold (OR 4.34, 95% CI 1.47–12.79, p = 0.008), when compared to those receiving vasopressors in < 4 h [14]. Indeed, a 2018 update to the Surviving Sepsis Campaign recommends including vasopressor initiation in the crucial 1-h bundle for fluid-resistant hypotension [17], although most recently in 2021, guidance regarding timing of vasopressor initiation is ambiguous [4].

Despite the evidentiary knowledge of worse outcomes with a delay in vasopres-sor initiation, there has been limited effort to drive protocolized practice in support of such a strategy. The CENSER study was an early pioneer of this concept in which norepinephrine initiation within 1 h of septic shock was evaluated in a prospective, double-blind, randomized setting [18]. Those that were randomized to early norepi-nephrine had greater likelihood (OR 3.4, 95% CI 2.09–5.53, p < 0.001) of shock reversal (MAP > 65 mmHg for 2 readings, urine output > 0.5 ml/kg/h for 2 h, and 10% reduction in lactate from baseline) at 6 h. There were no differences in hospital or 28-day mortality, although this phase II study was not powered for mortality. It is interesting, however, that early norepinephrine recipients were less likely to experience cardiogenic pulmonary edema (OR 0.70, 95% CI 0.56–0.87, p = 0.004) or arrhythmias (OR 0.74, 95% CI 0.56–0.94, p = 0.03).

While it is clear that earlier vasopressor initiation is better than later, timing of a secondary agent is less clear. However, recently, a large retrospective cohort study found that when vasopressin was added as a second-line agent to norepinephrine in septic shock, the risk of in-hospital mortality increased by an order of 12–18% with delay in initiation of vasopressin from shock onset (2.1–12.2 h) and increasing lactate concentration [19]. Perhaps these are all signals that more rapid attention to and an earlier opportunity for non-catecholamine vasopressors to act—while the physiological milieu is still favorable, or shock has not progressed to a point of irrevers-ibility—is key to improving outcomes in these patients.

Hyperlactatemia

In pathologic shock, arterial hypotension reduces oxygen delivery, leading to regional and global tissue hypoxia [20]. Consequently, oxygen utilization at the cellular level is impaired with inadequate mitochondrial oxidation. Concurrently, vaso-dilatory shock is often accompanied by a hyperdynamic state secondary to stress (e.g., sepsis) leading to aerobic glycolysis further contributing to excess lactate production [20]. The net result is a state of hyperlactatemia that is exacerbated by aci-demia impairing hepatic lactate clearance.

Hyperlactatemia has consistently been a hallmark of poor prognosis in vasodila-tory shock. In a cohort of severe sepsis and septic shock, initial lactate concentrations were higher (7.3 mmol/l) in those who died within 24 h of presentation compared to those alive after 24 h (3.3 mmol/l) [21]. In a multivariable analysis in this population, this initial lactate concentration (OR 1.19, 95% CI 1.05–1.35, p = 0.004) and organ failures as measured by the modified sequential organ failure assessment (mSOFA) score (OR 1.17, 95% CI 1.00–1.36, p = 0.046) were independent predictors of early death [21]. Similarly, outside of the immediate presentation period, lactate > 4 mmol/l has been independently associated with a threefold greater risk of 28-day death in septic shock (OR 3.0, 95% CI 2.1–4.1, p < 0.001), regardless of vasopressor use [22]. Even among patients with shock from sepsis requiring vasopressors, those experiencing at least one lactate concentration greater than 2.5 mmol/l at any time during their shock course, have nearly half the survival (57.1%) than those without hyperlactatemia (92.3%) at 100 days (p < 0.0001) [23]. Interestingly, even when the lactate concentration is within the generally considered 'normal limits', those with relative increases to the higher end of the normal range experience greater likelihood of death [24]. Taken altogether, hyperlactatemia in vasodilatory shock appears to epitomize a serious deficit in adequate organ perfusion. Indeed, the risk of multiorgan failure and death increases with increasing lactate concentration [25].

In addition to prognosis, lactate concentration may provide valuable insight into vasopressor selection and timing considerations, particularly when it comes to nonadrenergic vasopressors added to catecholamines. Although only less than half of patients receiving vasopressin experience a favorable hemodynamic response, response is twice as likely among those with lower lactate concentrations (OR 2.15, 95% CI 1.39–3.32, p < 0.001), which in turn, is associated with a greater likelihood of ICU survival [26]. Recently in a cohort study of patients with septic shock, when the addition of vasopressin to

Table 1 Norepinephrine dose and mortality

Study	Norepinephrine dose	Death type	Death rate (%)
Jenkins et al. 2009 [35]	> 100 μg/min	ICU	94
Brown et al. 2013 [32]	≥ 1 μg/kg/min	90-days	83
Dopp-Zemel et al. 2013 [34]	≥ 0.9 μg/kg/min	28-days	65
Martin et al. 2015 [29]	> 1 μg/kg/min	90-days	90
Auchet et al. 2017 [33]	> 1 μg/kg/min	28-days	60
		90-days	66
Brand et al. 2017 [36]	≥ 90 μg/min	Hospital	90

first-line norepinephrine was delayed, the odds of inhospital death increased with an increasing lactate concentration as much as 18% per mmol/l at 12.2 h from the shock onset (95% CI 1.07–1.32) [19]. Similarly, postmarketing experience with synthetic angiotensin II demonstrates a similar hemodynamic and survival response as it relates to lactate concentration. Despite a profound baseline severity illness amongst recipients of synthetic angiotensin II (baseline SOFA of 12 and APACHE II of 30), hemodynamic responders had a lower baseline lactate concentration (6.5 mmol/l) compared to non-responders (9.5 mmol/l), and in a multivariable model the likelihood of hemodynamic response was greater with lower lactate (OR 1.11 per mmol/l, 95% CI 1.05–1.17, $p < 0.001$) and 30-day mortality was lower with lower lactate (OR 0.94 per mmol/l, 95% CI 0.91–0.96, $p < 0.001$) [27].

Catecholamine Burden

The most obvious consequence to the classic stepwise vasopressor approach is overall catecholamine burden. With its potent vasoconstrictive effects at alphaadrenergic receptors throughout the vascular periphery, excess stimulation may be detrimental, with distal vessels remaining most susceptible leading to ischemic digits and splanchnic hypoxia and resulting in necrosis and serious morbidity [28, 29]. In addition to the desired vasoconstrictive effects of catecholamines, beta-receptor stimulation at the level of the myocardium (Fig. 2) has made these agents particularly intolerable. Arrhythmia is common and occurs in up to one-third of norepinephrine recipients in septic shock, and is associated with increased risk of death [30]. Duration and dosage of norepinephrine have shown value in predicting dysrhythmia, and the risk increases by 6% for every 5 μg/min increase in maximum norepinephrine dosage [30].

Cumulative dosage of norepinephrine exposure has been an easily identifiable objective measure for predicting prognosis in septic shock. Compared to an approximate 90-day mortality of 25% amongst > 3000 international patients with septic shock in the PRISM meta-analysis [31], those that required high-dose norepineph-rine had mortality rates ranging from 60% to in excess of 90% [29, 32–36] (Table 1).

In addition to prognosis, catecholamine dosage is an easy, bedside marker for deciding on vasopressor escalation. In the landmark VASST trial, patients who received vasopressin when the norepinephrine dosage was < 15 μg/min experienced lower 28-day (26.5% vs. 35.7%, $p = 0.05$) and 90-day (35.8% vs. 46.1%, $p = 0.04$) mortality [37]. Similarly, in a recent analysis of > 1500 septic shock patients, the risk of in-hospital mortality was increased by 20.7% for every 10 μg/min increase in norepinephrine dosage at the time of vasopressin addition as the second-line agent [19]. Most importantly, regardless of response rate and baseline severity of illness, risk of mortality is independently lower if there is a positive hemodynamic response to vasopressin (OR 0.51, 95% CI 0.35–0.76, $p = 0.001$) and angiotensin II (HR 0.50, 95% CI 0.35–0.71, $p < 0.001$) [26, 27]. All these data suggest that hemodynamic restoration and shock reversal is a crucial determinant in survival probability.

A Path Towards Personalization: Early Multimodal Vasopressor Therapy

To tailor vasopressor therapy in vasodilatory shock, phenotypic prognostication and pharmacologic response need to be characterized. There have been several emerging candidate biomarkers that have demonstrated association with vasopressor response and outcomes in septic shock (Table 2). Genetic variations in ARDβ2 encoding the β2-adrenergic receptor have been found to be associated with a higher norepinephrine requirement, greater renal, hematologic, hepatic, and neurologic dysfunction, and an increased 28-day mortality in septic shock [38]. Similarly, variants in AGTRAP, the angiotensin II receptor type 1 associated protein, have been associated with reduced MAP, lower vascular tone, and an increase in 28-day mortality [39]. Interestingly, defects in LNPEP (leucyl and cystinyl aminopeptidase), also known as vasopressinase, have been associated with increased clearance

Table 2 Potential biomarkers for vasopressor therapy

Biomarker	Pathologic variant/ threshold of harm	Vasopressor	Clinical association
Genetic polymorphisms			
ADRβ2	SNP rs1042717	Norepinephrine, epinephrine	↑organ dysfunction, ↑norepinephrine requirement, ↑septic shock mortality [38]
AGTRAP	SNP rs11121816	Angiotensin II	↓vascular tone, ↑septic shock ↑ortality [39]
LNPEP	SNP rs4869317	Vasopressin and analogues	↑vasopressin clearance, ↑septic shock mortality [40]
Circulating peptides			
Angiopoeitin-2	> 5807 pg/ml	Vasopressin and analogues	↑organ failure, ↑septic shock mortality [41]
Renin	> 40 pg/ml	Angiotensin II	↓hemodynamic response, ↑shock mortality [42, 43]
Vasopressin	Variable	Vasopressin	Mixed outcomes, variable hemodynamic response [44, 45]

ADRβ2 beta2-adrenergic receptor gene, *AGTRAP* angiotensin II receptor type 1 associated protein gene, *LNPEP* leucyl/cystinyl aminopeptidase gene

of plasma vasopressin and increased 28-day mortality [40]. Elevations of plasma angiopoietin-2 concentrations, an endothelial growth factor that promotes vascular leakage, have been associated with renal, hepatic, and coagulation dysfunction, as well as increased 7- and 28-day mortality [41]. While there is a so-called relative vasopressin deficiency in the early stages of septic shock [11], plasma vasopressin concentrations have not been shown to predict positive response to exogenous vasopressin administration, and outcome correlations are mixed [44, 45].

Although lactate has long been a prognosticator in critical illness and shock, serum renin is rapidly emerging as a potentially superior predictor of mortality in various shock states in the ICU. Two separate studies have shown that an absolute renin threshold concentration and a rate of rise of renin were both superior to lactate in associations with ICU and in-hospital mortality in critically ill patients [42, 46]. Importantly, renin appeared to be stable, and concentrations were not influenced appreciably by renal replacement therapy or drugs that alter the renin-angiotensin cascade (i.e., ACE inhibitors and angiotensin receptor blockers) [46]. Administration of exogenous angiotensin II has been shown to favorably benefit survival outcomes in those with high-renin shock [43, 47]. One of the biggest clinical barriers to the use of this biomarker in conjunction with or as an alternative to lactate is the lack of a true point-of-care assay that would allow targeted resuscitation at the bedside in response to concentrations in a timely manner [48, 49].

Our approach speaks to the use of early multimodal vasopressors, also termed 'broad-spectrum vasopressors' by others. This is analogous to the use of broad spectrum and early antimicrobials in suspected and confirmed sepsis. While there are not currently convincing data, as there are for the analogy with antimicrobials, there is certainly a physiological premise for the use of lower doses of multiple different classes of vasopressors as we initiate therapy in vasodilatory shock. This will need to be combined with the extensive use of biomarkers and de-escalation from multiple to a single agent could occur if one biomarker stands out as a clear signal of harm for a particular patient. For example, a patient with septic shock where vasopressin levels are disproportionately low compared with the increase in lactate and increase in angiotensin II (i.e., low renin), and where initial use of vasopressin has shown clinical benefit and laboratory correction of this anomaly could be slowly transitioned to a vasopressin-heavy approach after an initial broad-spectrum strategy that rapidly achieves perfusion targets. Similarly, an exquisite response to synthetic angiotensin II in the setting of high serum renin, would be an obvious rationale for continuing an angiotensin II predominant vasopressor approach. Indeed, the value of testing angiotensin II responsiveness has been proven in clinical studies and portends an excellent prognosis in appropriately chosen patients [50]. There will also be those with benign shock, where very low dose catecholamines may be all that is necessary and clearly not all patients will necessitate combination vaso-pressors. Finally, the use of non-vasoconstricting adjuncts (e.g., corticosteroids) targeted at the underlying pathology, as catecholamine-sparing strategies, should not be ignored to provide a balanced approach to the overall resuscitation of vaso-dilatory shock [7, 51].

Conclusion

The classic approach to vasodilatory shock management consists of a stepwise escalation of vasopressors which leads to prolonged states of hypoperfusion, hyper-lactatemia, excessive catecholamine exposure, and poor outcome. An early, balanced, multimodal vasopressor therapy strategy provides a physiologic-guided

approach to the complex, multifactorial pathogenesis of vasodilatory shock. Data are desperately needed in the development and deployment of biomarkers in the individualized approach to vasopressor therapy to improve shock outcomes.

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Author details
[1]Departments of Anesthesiology and Pharmacy, Mayo Clinic, Rochester, MN, USA. [2]Department of Anesthesiology, Section on Critical Care Medicine, Wake Forest School of Medicine, Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC, USA. [3]Outcomes Research Consortium, Cleveland, OH, USA.

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