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WHAT'S NEW IN INTENSIVE CARE

Ten tips to optimize vasopressors use in the critically ill patient with hypotension

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Hypotension is very common in critically ill patients and is associated with an increased morbidity and mortality. Hypotension, defined as low arterial blood pressure with proven of suspected organ hypoperfusion, often requires a differentiated catecholamine therapy, including vasopressors and inotropes. We here discuss ten tips to optimize vasopressor use in critically ill patients.

Set goals of mean or diastolic blood pressures

Mean arterial blood pressure (MAP) represents the entry pressure for perfusion pressure for most organs. The diastolic blood pressure is key for coronary perfusion pressure. Systolic blood pressure is greatly impacted by large blood vessels compliance and does not represent a key driver of perfusion pressure. In general, organ perfusion pressure (OPP) is influenced by the MAP and venous pressure (e.g. OPP = MAP-CVP). Defining targets of MAP aims to preventing organ hypoperfusion and ensuring oxygen delivery and avoid potentially unnecessary excessive exposure to vasopressors. Setting a target of diastolic blood pressure could also be indicated in patients with unstable coronary artery disease or chronic pulmonary hypertension at risk of low coronary perfusion pressure. While the indication of invasive blood pressure monitoring can be discussed on a case-by-case basis, overall, we consider that the need for vasopressors for more than a couple hours or need of high doses are indications.

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Individualize the arterial pressure targets goals

Results of the 65 trial [1] and the SEPSIPAM trial [2] suggest that a MAP of 65 mmHg is appropriate for most patients. Targeting higher blood pressure may be associated with increased risk of adverse events. Interpatient variability however exists regarding organ perfusion pressure. History of chronic hypertension is not per se an indication for higher MAP targets. While in the SEPSIPAM trial, patients with history of hypertension had lower incidence of severe acute kidney injury (AKI) in the higher target group, patients with history of hypertension in the 65 trial had lower 90 days mortality in the low pressure group (median MAP 65 mmHg, adjusted odds ratio, 0.67; 95% CI, 0.49–0.85). Increasing MAP with norepinephrine from 60 to 75 mmHg in patients with a distributive shock after cardiac surgery improved renal blood flow and glomerular filtration rate, while increasing further was associated with various responses [3]. These data suggest that it is legitimate to perform a 'higher MAP trial' in patients with persistent suspicion of hypoperfusion (e.g. progressing AKI, prolonged capillary refill time, altered mental status) using a vasopressor challenge in the absence of hypovolemia. Organ perfusion assessment is difficult and most often rely on functional surrogates (e.g. glomerular filtration rate, urine output). Bedside ultrasound can help assessing optimal perfusion pressure [4]. A known history of vascular disease (e.g. carotid stenosis) could also trigger such a trial in symptomatic patients. We recommend reassessing these targets on a regular basis (e.g. every 4–6 h), to avoid unnecessary exposure to higher doses of vasopressors.

Vasopressors induce an endogenous fluid recruitment and may limit positive fluid balance

Vasopressors increase blood pressure through the increase of systemic vascular resistance. Their vasoconstrictive effect on the venous system also contributes

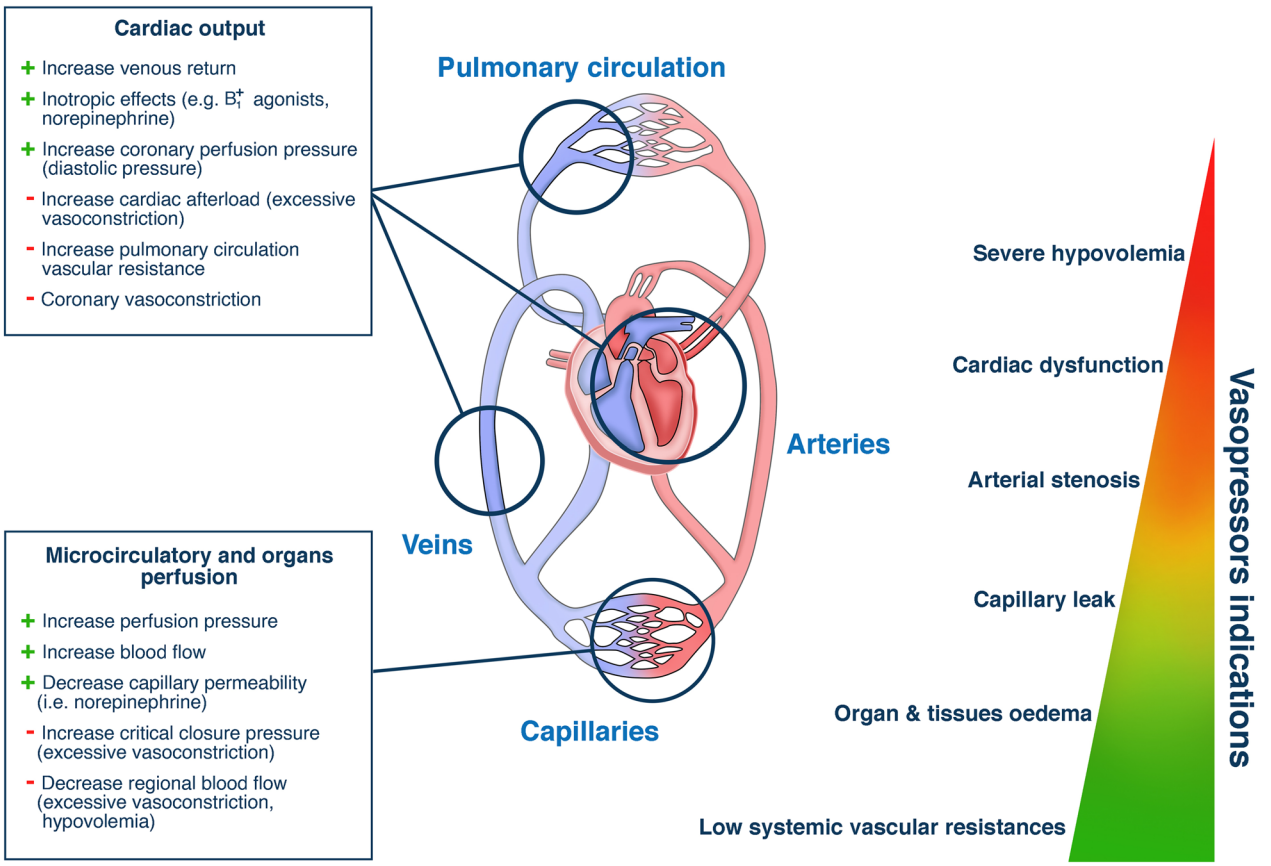

Fig. 1 Potential positive and negative hemodynamic effects of vasopressors in critically ill patients and factors to consider when using vasopressors in the critically ill

to increase the venous return (through increase of the "stressed volume" increasing systemic venous pressure) and subsequently increases cardiac output [5]. Administration of vasopressors can therefore simulate a fluid bolus through endogenous fluid recruitment. Furthermore, norepinephrine decreases inflammation induced capillary permeability [6]. Vasopressors use can limit the positive fluid balance (Fig. 1). While we recommend ruling out hypovolemia with a fluid challenge, we start vasopressor administration early (together with fluids) in patients with severe hypotension (e.g. MAP < 50–55 mmHg).

Reassess fluid status and cardiac output after initiation of vasopressors

The impact of pure vasopressors (i.e. vasopressin, which is a V1 receptor agonist) on cardiac function and cardiac output has long been a matter of concern. In a subgroup analysis of the Vasopressin and Septic Shock Trial, cardiac index was not different between low dose vasopressin (i.e. up to 0.03 unit/min) and norepinephrine (3.65 (standard deviation (SD) 1.52) vs 3.55 (SD 1.05) L/min/m^2 24 h after randomization), but with wide variability and at the expense of higher use if inotropes (74% vs 44%) [7]. Higher doses can cause excessive vasoconstriction, resulting in coronary, mesenteric, and digital ischemia. However, higher doses of vasopressors can alter cardiac output due to a reduced myocardial perfusion or an increased afterload [8, 9]. We recommend re-assessing cardiac function and cardiac output in hypotensive patients with vasopressors.

Consider agents with a different mechanism of action as a second line agent

Norepinephrine is recommended as the first line vasopressor for patients with sepsis or distributive shock [10]. Adding a second vasopressor agent with a different vasoconstrictive mechanism of action might limit the side effects of catecholamines. Low doses of vasopressin decrease the risk of atrial fibrillation [21% vs 29%, RR, 0.77 (95% CI 0.67–0.88)] [11], and may improve renal function in patients with vasodilatory shock. Angiotensin

II has been more recently available in some countries [12] with few data available on safety and impact on outcomes. Some patients show angiotensin II-deficiency due to a reduced angiotensin-converting enzyme (ACE) activity or an increased dipeptidyl peptidase 3 which inactivates angiotensin II [13]. Using angiotensin II in patients with a hyperreninemia, reflecting an angiotensin II deficiency, is associated with better outcomes. This biomarker is however not readily available. Septic AKI is associated with decreased angiotensin II-levels and/or expression of angiotensin1 receptors [14] and the use of angiotensin II in these patients was associated with a better outcome. These patients should be the primary target for angiotensin II use pending additional data. Safety data are lacking to recommend the use of non-selective nitric oxide inhibitors (i.e. methylene blue, hydroxocobalamin).

Consider adding hydrocortisone in patients on high doses of vasopressors

Evidence suggests that hydrocortisone with fludrocortisone decreases doses of vasopressors in patients with septic shock requiring high doses of vasopressors (e.g. norepinephrine equivalent ≥ 0.25 µg/kg/min) and who have multiple organ failures [10, 15]. Impact on outcome is unclear.

Vasopressin in patients with right ventricular failure

Due to the lack of V1-receptors in the pulmonary arteries, vasopressin does not increase pulmonary vascular resistance. Those data consider the physiology and arise from preclinical models with very limited clinical data beyond case reports [16]. On the other hand, norepinephrine was shown to slightly increase pulmonary vascular resistance and also improves right ventricle function through its inotropic effects. This may represent an advantage in patients with a reduced right ventricle function requiring vasopressors. To this end, among patients with systemic vasodilation and altered right ventricle function norepinephrine represents the first line agent but vasopressin with inotropes is an alternative.

There is no maximal dose of vasopressors

Not surprisingly, high doses of vasopressors have been associated with a higher risk of death given the higher severity of illness of these patients. Some institutions may set maximum doses of vasopressors. This may either self-limit the likelihood of recovery (e.g. withdrawing life support because the patients is considered too sick) or lead to tolerating a low blood pressure. Auchet et al. et al. reported 90 days survival of 40% in patients receiving vasopressor > 1 µg/kg/min underlining fair survival on very high doses of vasopressors [17].

Enteral tube feeding can be initiated while under vasopressors

Norepinephrine and low dose vasopressin have been shown to improve mesenteric perfusion and gut microcirculation. On the other hand, impaired gut microperfusion was reported with epinephrine. Enteral nutrition (EN) is safe among patients receiving less than 0.3 ɣ/kg/min of norepinephrine. At higher doses, risk of mesenteric ischemia increases with EN but remains very low. In the NUTRIREA 2 trial, patients with a high dose of vasopressors (norepinephrine at 0.44 [0.22–0.93] ɣ/kg/min) were randomized to receive early vs delayed EN. The early group showed higher incidence of mesenteric ischemia (2 vs 1%). The risk was significantly higher with the use of dobutamine and a higher Simplified Acute Physiology Score (SAPS) II (≥ 62) [18]. In this later population, EN should probably be delayed. Ultrasound (e.g. color Doppler resistive index) may be use to assess splanchnic perfusion [4].

Vasopressors can be safely administered through a peripheral catheter

Observational studies and randomized trials showed it is safe to administer vasopressors (i.e. norepinephrine) through a well-functioning peripheral catheter [19]. Therefore, obtainment of central venous access should not delay the initiation of vasopressors in the critically ill patients.

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Declarations

Conflicts of interest

ML declares no conflict of interest. AZ has received consulting and/or lecture fees from Astute Medical/BioMerieux, Fresenius, Paion, Guard Therapeutics, and Baxter, unrelated to the current study. AZ has received grant support from Astute Medical/BioMerieux, Fresenisu, and Baxter unrelated to the current study.

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