ICU
MANAGEMENT & PRACTICE

VOLUME 22
ISSUE 5

2022

Imaging the Critically Ill

Improving Haemodynamic Management of ICU Patients: Decatecholaminisation and Cardiac Stress Reduction

A summary of a symposium organised by AOP Health with presentations from Ricard Ferrer, Vall d'Hebron University Hospital, Barcelona, Spain; Bruno Levy, Centre Hospitalier Universitaire de Nancy, CHU Nancy · Réanimation Médicale Brabois, France; and Michael Fries, St. Vincenz Krankenhaus Limburg, Department of Anesthesiology, Germany.

Vasopressin in Catecholamine Refractory Septic Shock: Why, When and How?

Sepsis in critically ill patients should be considered a medical emergency. Septic shock is the most common cause of death in intensive care units (ICUs) with a mortality rate of 40 to 60% (Russell et al. 2008). Haemodynamic treatment in septic shock is typically guided by central venous pressure (CVP), mean arterial pressure (MAP) and central venous oxygen saturation ($ScvO_2$). In particular, MAP <60 mmHg is associated with high mortality (Varpula et al. 2005). As per the Surviving Sepsis Campaign Guidelines (SSC), timely and effective fluid resuscitation is essential to stabilise the patient. The guidelines recommend using a minimum of 30 ml/kg (ideal body weight) of IV crystalloids in initial fluid resuscitation (Evans et al. 2021). However, in recent years, this approach has been questioned as there is a lack of personalisation at the early phase of resuscitation.

The primary goals of fluid administration in septic patients is increasing intravascular volume, improving venous return and cardiac preload and increasing cardiac output. There is sufficient evidence to show a beneficial effect of combining fluids with vasopressors in the early phase of sepsis. Combining the two can increase mean systemic pressure and venous return and correct hypotension better. Also, a combined approach of fluids and vasopressors can limit fluid overload which is an independent factor of poor outcomes in patients with sepsis (Hamzaoui 2021). Early initiation of vasopressors in patients with septic shock has been shown to be associated with decreased short-term mortality, shorter time to achieve MAP and less volume of intravenous fluids within 6h (Yuting et al. 2020).

> "vasopressin is an effective alternative to catecholamine vasopressors"

Several studies have shown that in patients with septic shock, dopamine is associated with greater mortality and a higher risk of arrhythmic events compared to norepinephrine (De Backer et al. 2012). Norepinephrine is thus the vasopressor of choice. The SSC guidelines also recommend the use of norepinephrine as first-line vasopressor (Evans et al. 2021).

However, there are some patients with refractory septic shock who do not respond to norepinephrine. In these patients, a high dose of norepinephrine is associated with high mortality. In such cases, the SSC guidelines recommend vasopressin as second-line vasopressor to catecholamines. In clinical practice, vasopressin is added when norepinephrine dose is between 0.25-0.5 µg/kg/min. Activation of arginine-vasopressin is a hormonal response to vasodilation-related hypotension. It induces vasoconstriction through the activation of V1a receptors on the vascular smooth muscle cells. The activation of V1a receptors leads to platelet aggregation. Vasopressin also binds to V2 receptors leading to water re-absorption and V1b receptors stimulating insulin secretion. During septic shock, vasopressin plasma level is low. The more serious the infection, the lower is the vasopressin level. The vasoconstrictor properties of vasopressin are useful in the management of vasodilatory shock in patients with sepsis with low blood pressure and in decreasing norepinephrine infusion rate to facilitate decatecholaminisation (Demiselle et al. 2020). In the VASST trial, vasopressor and norepinephrine were administered to patients with septic shock who were resistant to fluids. Study findings showed no significant difference in 28-day mortality in the vasopressin and norepinephrine groups. There was also no significant difference in 90-day mortality, the rate of organ dysfunction, or the rate of serious adverse events between the two groups. Vasopressin infusion resulted in a rapid decrease in the total norepinephrine dose while maintaining MAP (Russell et al. 2008). Hence, vasopressin is an effective alternative to catecholamine vasopressors. The administration of vasopressin in addition to catecholamine vasopressors in patients with distributive shock has been found to be associated with a reduction in the risk of atrial fibrillation compared with catecholamines alone (McIntyre et al. 2018). The SSC review also shows that vasopressin with norepinephrine reduced mortality compared to norepinephrine

alone. As per the guidelines, in patients where the use of high dose of norepinephrine is not feasible, the addition of vasopressin is recommended instead of escalating the dose of norepinephrine and to start vasopressin when the dose of norepinephrine is in the range of 0.25-0.5 mg/kg/min (Evans et al. 2021). However, this recommendation may have some flaws. Some experts recommend that the pharmacologic response to norepinephrine should be characterised individually and should be based on a dose-response curve (Guerci et al. 2022).

Landiolol for Beta-Blockade in ICU: Why, When and How

Beta-blockers have multiple effects, including effects on the heart, increase in diastolic time, decrease in myocardial oxygen consumption and improvement in metabolic efficiency. Beta-blockers are also cardioprotective, antithrombotic and may also have anti-inflammatory effects. Landiolol, an ultra-short-acting beta-blocker, has a very short half-life of about 4 minutes and a quick onset of action (1 minute) compared to esmolol with a short half-life of 9 minutes. The duration of effect with landiolol is 15 minutes compared to 30 minutes for esmolol. Landiolol has a minimal effect on the duration of the action potential in cardiomyocytes and does not alter myocardial contractility. In addition, systolic blood pressure with landiolol remains unchanged compared to esmolol which results in a dose-dependent reduction. Hence landiolol has a minimum negative inotropic action. **Table 1** highlights the key differences between the leading beta-blockers used.

In the ICU, beta-blockers like landiolol can be used for multiple indications including atrial fibrillation, chronic cardiac failure, arrhythmia and electrical storm, VV and VA ECMO, aortic dissection without acute aortic insufficient and Tako-Tsubo and pheochromocytoma.

In a study in patients with sepsis-related tachyarrhythmia, landiolol resulted in achieving a heart rate of 60-94 bmp at 24 hours compared to the control group and significantly reduced the incidence of new-onset arrhythmia. Landiolol was also well-tolerated. However, it is recommended that when used, blood pressure and heart rate should be closely monitored due to the risk of hypotension in patients with sepsis and septic shock (Kakikhana et al. 2020).

Case reports of critically ill patients with tachyarrhythmias also demonstrate successful treatment with a continuous intravenous administration of landiolol. Landiolol resulted in an effective decrease of heart rate with minimal effects on blood pressure (Gangi et al. 2022).

Beta-blockers like landiolol can also help improve oxygenation in patients on veno-venous extracorporeal membrane oxygenation (VV-ECMO). In a study in hypoxaemic patients on VV-ECMO, the use of beta-blockers was associated with a moderate increase in oxygen saturation within 12 hours after start of treatment (Bunge et al. 2019). Another study demonstrated the efficacy and safety of ultrashort acting beta-blockers in refractory hypoxaemia during VV-ECMO in patients with COVID-19 pneumonia. Therefore, beta-blockers could potentially be used as an alternative to other rescue therapies (Emrani et al. 2022).

Product	Onset of effect	Elimination half-life	Duration of effect	Cardio- β1: β2 ratio	Effects
Rapibloc® (Landiolol)	1 min	4 min	15 min	255	HR ↓↓ BP →
Esmocard® (Esmolol)	2 min	9 min	30 min	33	HR ↓ BP ↓
Atenolol	5 min	6–7 h	12 h	4.7	HR ↓ BP ↓
Metoprolol	20 min	3–7 h	5–8 h	2.3	HR ↓ BP ↓

Table 1. Key differences between leading beta-blockers used. Adapted from AOP Health, 2022, *Rapibloc (Landiolol hydrochloride): Rapid Rate Control with Myocardial Protection, brochure.*

Septic Shock Management: Clinical Case With Vasopressin and Landiolol

The incidence of and risk factors for cardiac events during catecholamine vasopressor therapy is well-established. Findings from an observational study showed that adverse cardiac events occurred in 48.2% of surgical intensive care unit patients with cardiovascular failure. The extent and duration of catecholamine vasopressor treatment was also independently associated with adverse cardiac events (Schmittinger et al. 2012).

A case study from St. Vincenz Krankenhaus Limburg demonstrates the benefits of using vasopressin with landiolol. A 55-year-old male had a venous saphena bypass. The patient had a CABG surgery in 2018, history, persistent atrial fibrillation along with non-insulin-dependent diabetes mellitus, arterial hypertension and hyperlipoproteinemia. This patient has a rare reason for septic shock: necrotising fasciitis. The patient was taken to the OR for surgery. He was started on regular antibiotic treatment but suffered another massive septic shock in the ICU. The patient had high requirements for norepinephrine. Echocardiogram results showed that the patient's ejection fraction was reduced to 30%. Myocardial infarction was ruled out because he had no regional wall motion abnormalities, but he had severe cardiomyopathy. On top of norepinephrine and dobutamine, the patient was also treated with vasopressin, which started with a dose of 1IU/hour and was increased once blood pressure started to decrease. As heart rate also started to increase, landiolol was added, starting at a low dose and eventually increasing to 4µg/kg/min. Although the patient remained in atrial fibrillation all the time, the frequency was reduced to a more acceptable range of around 90 to 100. His systolic pressure rose to about 110mmHg, and the amount

of norepinephrine could be reduced. This shows how vasopressin can be used to increase blood pressure while reducing norepinephrine dose, while landiolol could be used for reducing heart rate, without negatively affecting blood pressure.

Conclusion

Septic shock should be handled as an emergency and it requires fast intervention. Hypotension should be resolved as quickly as possible while avoiding fluid overload and high norepinephrine dose. Vasopressin is recommended to be added at norepinephrine dose of 0.25-0.5µg/kg/min as per the SSC guidelines. This can help achieve target MAP while reducing norepinephrine doses and the adverse events related to it. It can also help reduce the risks of tachyarrhythmias and the need for RRT. The efficacy and safety of landiolol, an ultra-short-acting β-blocker, for treating sepsis-related tachyarrhythmias has been well-established in clinical studies. Landiolol has very high beta1-selectivity and effectively reduces heart rate with minimal negative effects on blood pressure and inotropy and is very well suited for the treatment of critically ill patients. ■

Disclaimer

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