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Cardiovascular Management in Sepsis: Improving Cardiac and Vascular Functions

Vasopressin and landiolol are critical therapies for ensuring the vascular and cardiac systems are as close to optimal conditions as possible during septic shock. Better cardiovascular management in septic shock can help improve septic shock management.

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer et al. 2016). Septic shock is defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality. The progression of sepsis is typically measured using the Sequential Organ Failure Assessment (SOFA) Score (Vincent et al. 1996) or a 3-parameter qSOFA version (Koch et al. 2020), with cardiovascular assessment as a key parameter of both scales. In patients with sepsis, the amount of time spent continuously below an MAP threshold of 65 mmHg is a strong predictor of mortality, with each additional 2-hour increment in the longest episode under threshold associated with a progressive increase in mortality rate (Vincent et al. 2018). Accordingly, the Surviving Sepsis Campaign Guidelines (SSCG) recommend intravascular fluid administration (using crystalloids) as the first step to counteract hypotension in septic patients (Evans et al. 2021).

Hypotension Refractory to Initial Fluid Resuscitation

When fluid administration alone is not sufficient to achieve target MAP, vasopressor administration should be initiated to resolve hypotension (Rhodes et al. 2017). Early administration of vasopressor (at less than six hours from initial hypotension) is critical to avoid prolonged hypotension and irreversible damage of vital organs due to low perfusion. The SSCG recommend norepinephrine as the first-line vasopressor for hypotension refractory to initial fluid resuscitation to maintain MAP ≥65 mm Hg (Evans et al. 2021). Septic shock patients are clinically identified by a requirement for vasopressor therapy to maintain a MAP of ≥65 mm Hg and serum lactate level >2 mmol/L (>18 mg/dL) in the absence of hypovolaemia (Singer et al. 2016). Norepinephrine, a catecholamine, activates the α1 and β1 adrenergic receptors and has a minimal effect on heart rate (Evans et al. 2021). Early vasopressor initiation has been reported to increase MAP, shorten the duration of hypotension and thereby improve vital organ perfusion and decrease serum lactate levels, resulting in better patient outcomes and decreased mortality rates (Bai et al. 2014; Colon Hidalgo et al. 2020).

Catecholamine Refractory Septic Shock

However, some patients become catecholamine refractory, suffering from impaired vascular responsiveness to catecholamines due to downregulation or decoupling of α1 adrenergic receptors. Persistent hypotension, despite norepinephrine administration, while the patient has adequate cardiac output and is non-responsive to fluids, is indicative of catecholamine refractory septic shock (Jentzer and Hollenberg 2021). The SSCG state that for adults with septic shock on norepinephrine with inadequate MAP levels, it is suggested to add vasopressin instead of escalating the dose of norepinephrine (Evans et al. 2021). Hence, the use of a second-line vasopressor with an alternative mode of action is recommended to increase vascular tone. It has been proposed that an early combination of moderate doses of multiple vasopressors with complementary mechanisms of action may avoid the toxicity associated with high doses of a single agent (Jentzer and Hollenberg 2021).

Vasopressin is a non-catecholamine endogenous peptide hormone which activates V1 receptors located on the vascular smooth muscles, resulting in increased vascular tone and increased arterial blood pressure. Vasopressin is usually started (at a dose of 0.01-0.03 IU/min) when the dose of norepinephrine is in the range of 0.25–0.5 μg/kg/min (Evans et al. 2021). The combined infusion of vasopressin and norepinephrine can increase MAP in catecholamine refractory (resistant) septic shock, where increasing MAP with norepinephrine alone is not possible (Dünser et al. 2003). Furthermore, by using vasopressin, the norepinephrine dosage can be reduced while maintaining MAP (Evans et al. 2021; Russell 2011). Adverse effects of norepinephrine/catecholamines include myocardial ischaemia and arrhythmia, hence by reducing the requirement for catecholamines, vasopressin decreases the stimulation of arrhythmogenic myocardial β1-receptors and associated myocardial oxygen demand (McIntyre et al. 2018). The positive outcomes from early administration of vasopressin in septic shock patients include a reduced noradrenaline requirement (Russell 2011), a lower risk of atrial fibrillation (McIntyre et al. 2018), less catecholamine-induced anti-inflammatory effects (Stolk et al. 2020), a reduction in the need for renal replacement therapy (Gordon et al. 2010; Russell et al. 2008) and less constriction of pulmonary arteries (Currigan et al. 2014). Moreover, there was a significantly higher probability of survival with vasopressin treatment (Russell et al. 2008) in less severe septic shock patients (norepinephrine doses <15 μg/min) and

when initiated at lower lactate levels (Sacha et al. 2018) or at higher arterial-pH (pH≥7.4) levels in patients with sepsis (Bauer et al. 2022) which collectively supports the early combination of vasopressin with norepinephrine during septic shock.

Compensatory Tachycardia

Tachycardia is very common in ICU patients and is associated with poor outcomes in septic shock (Leibovici et al. 2007; Parker et al. 1987). During sepsis, the sympathetic nervous system plays a key role in maintaining cardiac output and blood pressure, which is achieved through changes in heart rate (HR), contractility and vascular tone (Morelli et al. 2016). The baroreflex is a homeostatic mechanism that maintains MAP by adjusting sympathetic tone to antagonise MAP perturbations (Jentzer and Hollenberg 2021). The integrity of the baroreflex function is critical for the maintenance of haemodynamic homeostasis. Accordingly, in the early phases of sepsis, tachycardia becomes a crucial mechanism for compensating the decrease in stroke volume and indicates the efficacy of baroreflex activity (Morelli et al. 2016). Due to the compensatory origin of such tachycardia, adequate volume resuscitation often results in a concomitant decrease in HR. However, compensatory tachycardia may lead to arrhythmia (Boriani et al. 2019), particularly atrial fibrillation (AF). A clear association between sepsis and arrhythmias has been reported, with new-onset AF reported to be common in patients hospitalised with sepsis, compared to those without sepsis (5.9% vs 0.65%: OR 6.82, 95% CI 6.54–7.11) and has been related to an increased risk of in-hospital stroke (2.7-fold) and mortality (Walkey et al. 2011). After an arrhythmia is confirmed, patients with life-threatening haemodynamic instability (i.e. symptomatic hypotension and/or signs of hypoperfusion of vital organs) require immediate electrical cardioversion (ECV) or defibrillation (Dan et al. 2022). In the case of ECV failure or immediate relapse AF, an optimal next step is acute rate control with landiolol, which has been shown to be superior to standard rate-controlling therapy in septic patients who developed AF, with no significant complications related to hypotension or bradycardia (Dan et al. 2022; Okajima et al. 2015).

Non-Compensatory Tachycardia

Despite achieving haemodynamic stability, in many septic shock patients non-compensatory tachycardia may persist even after adequate fluid resuscitation and vasopressor therapy. In septic shock patients, non-compensatory tachycardia persists when the baroreflex response is impaired due to high levels of endogenous and exogenous catecholamines, leading to a hyper-adrenergic state, which is a sign of excessive sympathetic stimulation (Domizi et al. 2020; Dunser and Hasibeder 2009).

Landiolol ensures the safe reduction of heart rate during non-compensatory sinus tachycardia, reducing with it unnecessary sinus activation and cardiac stress

Patients who are tachycardic 24 hours after commencing norepinephrine infusion have a three-fold higher risk of death than those without tachycardia, which is likely due to an exhausted compensatory reflex mechanism (Domizi et al. 2020). Persistent tachycardia can detrimentally affect the heart by increasing myocardial oxygen demand, reducing diastolic filling, and inducing direct cardiotoxicity (Domizi et al. 2020). Hence, patients with non-compensatory tachycardia persisting at 24 hours after volume resuscitation and commencement of vasopressors represent a particularly severe subset of septic shock patients with very high mortality risk and with few available treatment options.

Landiolol for the Treatment of Non-Compensatory Sinus Tachycardia

Landiolol is a new ultra-short acting (T1/2=4 min), intravenous, super-selective β1 blocker for the treatment of supraventricular tachyarrhythmias such as AF, atrial flutter and non-compensatory sinus tachycardia (SmPC Rapibloc®). Landiolol is a β1-antagonist and, due to its pure S-enantiomer molecular structure (McKee et al. 2014), has minimal effects on blood pressure and inotropy (Shibata et al. 2012), in contrast to esmolol and metoprolol, which cause hypotension and have negative inotropic effects. Landiolol has excellent efficacy even at low doses (Krumpl et al. 2018), with a low volume distribution and low risk of toxicity (Abialbon 2019). Due to inactive metabolites and breakdown by plasma esterases, landiolol has a favourable safety profile for patients with renal and hepatic comorbidities (Yokoyama 2016), with no dose adjustment required for patients with renal dysfunction. Landiolol is metabolised mainly by pseudocholinesterases and carboxylesterases and not by CYP450, with two inactive metabolites (M1 and M2), which are excreted in the urine. Due to the highest cardioselectivity (β1/β2-selectivity = 255:1), landiolol has a minimal impact on respiratory function (Shibata et al. 2012) and β2-receptor-mediated coronary hyperaemia (Maman et al. 2017).

A randomised controlled study of landiolol versus conventional therapy (control group) investigated the efficacy and safety of landiolol for the treatment of sepsis-related tachyarrhythmias in 151 patients (Kakihana et al. 2020). In the study, non-compensatory tachycardia was defined as a heart rate of 100 bpm or more maintained for at least 10 min without a change in catecholamine dose. Furthermore, patients were only enrolled if the investigator confirmed the aforementioned symptoms and signs within 24h before randomisation. The mean dose of landiolol administered during the study period was 4.15 μg/kg per min with a mean cumulative dose per patient of 1526.20 mg (SD 2110.36) over a total infusion time of 94.5 h. In patients treated with landiolol, MAP was achieved, and a heart rate of 60–94 bpm was reported in most patients, with a significantly larger number of patients in the landiolol group achieving a heart rate of 60–94 bpm at 24 h compared to the conventional treatment

in the control group (55% [41 of 75] vs 33% [25 of 75]; p=0.0031), confirming that landiolol treatment was superior to conventional rate control therapy (Kakihana et al. 2020). Landiolol significantly reduced the incidence of new-onset arrhythmia in patients with sepsis-related tachyarrhythmias (Kakihana et al. 2020) compared with conventional treatment (9% [7 of 75] vs 25% [19 of 75]; p=0.015). Moreover, the efficacy and safety of landiolol were unaffected by patient characteristics, such as septic shock, LVEF≤50%, metabolic or respiratory acidosis or acute renal failure, supporting the use of landiolol in a wide range of patients who develop sepsis-related tachyarrhythmias, for whom the prognosis is otherwise poor (Matsuda et al. 2020). Furthermore, patients with respiratory infection receiving landiolol had lower mortality rates at 28 days (Matsuda et al. 2020) than the control group (hazard ratio 0.259; 95% CI 0.071 to 0.943). In a further study of 61 patients with severe sepsis, landiolol was shown to decrease heart rate in septic patients without causing negative effects on haemodynamics (Okajima et al. 2015).

Conclusion

Vasopressin and landiolol are critical therapies for ensuring that both the vascular and cardiac systems are as close to optimal conditions as possible during septic shock. Vasopressin ensures improvement of the vascular response in patients who are catecholamine refractory, with a significant body of evidence indicating that earlier addition of vasopressin leads to better patient outcomes. While landiolol ensures the safe reduction of heart rate during non-compensatory sinus tachycardia, reducing with it unnecessary sinus activation and cardiac stress, also reducing the risk of new-onset atrial fibrillation and improving patient survival. By improving cardiovascular management in septic shock, a further step can be taken in the overall improvement of septic shock management.

Disclaimer

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