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Patients and Families

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Cardiovascular Management in Septic Shock: Optimising Vascular and Cardiac Function

An overview of vasopressor management, current evidence on its use, when to initiate vasopressor therapy for best possible patient outcome and a discussion regarding the use of landiolol in septic patients with persistent tachycardia.

Optimising Vasopressin Initiation in Septic Shock

Patients with septic shock, and especially those with high vasopressor needs, are at risk for high mortality. The mortality rate of ICU patients with refractory septic shock is around 40 to 80% (Seymour et al. 2016; Annane et al. 2005; Angus et al. 2001; Vincent et al. 2006; Levy et al. 2003; Kaukonen et al. 2014). The difference in incidence of mortality is caused by the definition of refractory shock, as there is no universal definition for refractory shock in the literature.

There is also an ongoing debate about whether to start vasopressors earlier and then give additional fluids or opt for full fluid resuscitation and then start with vasopressors.

The first line vasopressor globally is norepinephrine. There is no universal definition of high-dose norepinephrine. Some doctors use 0.1 mcg/kg/min, while others say it should be 0.5 mcg/kg/min. In general, the threshold is around 0.25 mcg/kg/min in the Vasopressin Registry. In the Netherlands, this has been dropped down to 0.20 mcg/kg/min. However, a still ongoing study found that the average starting dose was 0.45 mcg/kg/min, suggesting that in the time between the decision to start a second vasopressor and the time it is actually started, the norepinephrine dose is already much higher, and the patients are already in severe septic shock.

Some studies have demonstrated that early initiation of norepinephrine is beneficial for patients with septic shock. In a meta-analysis published a few years ago, starting norepinephrine treatment early led to lower short-term mortality, faster achievement of the target mean arterial pressure, and

reduced intravenous fluid requirements within the first 6 hours. However, there was no significant difference in the length of stay in the intensive care unit between those who received early norepinephrine treatment and those who received it later (Li et al. 2020).

Considering vasopressin, the Surviving Sepsis Campaign shows mixed results as both an adjunctive treatment and as a first-line therapy. Vasopressin did not alter mortality when added to norepinephrine. A subset, however, demonstrated a survival benefit in patients with less severe septic shock. So, the concept of using a second vasopressor as a last resort should be reconsidered; instead, an early “multi-modal” vasopressor strategy should be considered. A reduced need for renal replacement therapy was noted with vasopressin compared with norepinephrine alone. A norepinephrine-sparing effect has been reported with vasopressin, leading to its recommendation as an adjunctive therapy (Evans et al. 2021).

Why not increase norepinephrine dosage? It is known that patients on high doses of norepinephrine have the highest mortality. That is not only due to the fact that they have the most severe septic shock. High-dose norepinephrine can have harmful effects itself. It can injure myocardial cells and can induce oxidative stress. There is also a negative effect on the immune system. Hence, restricted use of norepinephrine is recommended due to its multitude of adverse effects. In contrast, vasopressin does not have negative effects on the immune system (Stolk et al. 2020), and when combined, it can have a norepinephrine-sparing effect.

What about other effects? In a meta-analysis by McIntyre et al. (2020), combining vasopressin with catecholamine vasopressors reduced the risk of atrial fibrillation by 23%

compared to using catecholamines alone. Different studies found that vasopressin does not seem to constrict pulmonary arteries.

The VANISH trial compared the effects of early vasopressin compared to norepinephrine on kidney failure in patients with septic shock. Findings showed that there was a significantly lower need for renal replacement therapy in the vasopressin group than in the norepinephrine group by 55%. Patients in the vasopressin group demonstrated a lower trend of progression to renal failure or loss, more serum creatinine reduction compared with norepinephrine alone and a lower mortality rate (Gordon et al. 2016).

Regarding the timing of vasopressin, a recent study showed that the addition of vasopressin to norepinephrine within three hours of starting norepinephrine led to a significantly quicker resolution of shock, indicating the possibility of better clinical outcomes when vasopressin is added earlier in treatment (Brask et al. 2023).

Usage of Short-Acting Beta-Blockers in Septic Shock

There is a rationale for using beta-blockers in septic shock because beta-blockers have multiple useful effects. In the heart, they result in an increase in diastolic time, decrease myocardial oxygen consumption and improve metabolic efficiency. Beta-blockers are also cardioprotective and have an anti-thrombotic effect. They are also helpful in restoring downregulation of adrenergic receptors and have an anti-inflammatory effect.

When using beta-blockers, it is important to select those with very short half-lives because it's important in the Intensive Care Unit to use drugs that might disap-

pear after three or four minutes. These are mainly β_1 -selective blockers like esmolol or landiolol that have very short half-lives, are not influenced by renal and liver function and have a fast onset of action. Compared to esmolol, landiolol has a faster onset of action, faster elimination half-life and duration of effect. It can also be used at a dosage of 1-10 mcg/kg/min in patients with LVEF<40%. Furthermore, landiolol has a minimal effect on the duration of the action potential in cardiomyocytes. Systolic pressure of the left ventricle also remained unchanged with landiolol, while it was reduced dose-dependently with esmolol.

A study involving 54 hospitals examined the use of landiolol for treating sepsis-related tachyarrhythmias. They randomly assigned 151 sepsis patients with persistent tachyarrhythmia into two groups: one group received landiolol along with standard therapy, and the other received standard therapy alone (with some patients in the control group also receiving antiarrhythmics). The landiolol group had a 12% mortality rate, representing an 8% absolute reduction and a 40% relative reduction in the risk of death than in the control group. Landiolol was found to be effective and safe regardless of patient characteristics, such as septic shock, low LVEF, acidosis, and acute renal failure. Patients with respiratory infections receiving landiolol had a lower 28-day mortality rate than the control group. These results suggest that landiolol effectively controls heart rate and

reduces the risk of death in sepsis-related tachyarrhythmias (Matsuda et al. 2020).

Landiolol effectively controls heart rate and reduces the risk of death in sepsis-related tachyarrhythmias

Results from animal models show that beta-blockers improve cardiac function and vascular reactivity. They have a better metabolic profile associated with better lactate clearance. Beta-blockers decrease the pro-inflammatory state induced by sepsis, and mortality is improved. A randomised animal study by Kimmoun et al. (2015) showed that adding selective β_1 -blockade to the standard treatment for septic shock can improve the heart's pumping ability and the responsiveness of blood vessels to catecholamines. These benefits are mainly due to the anti-inflammatory properties of beta blockers.

A meta-analysis found that using ultra-short-acting β -blockers like esmolol and landiolol to treat sepsis patients with tachycardia despite initial treatment can significantly reduce 28-day mortality. This suggests a growing interest in using β -blockers like landiolol in patients with sepsis with persistent tachycardia (Hasegawa et al. 2022).

Conclusion

Early initiation of vasopressors in septic shock has been shown to have better patient outcomes in comparison to delayed initiation. The discussion and clinical evidence also highlight the benefits of landiolol in treating patients with cardiac dysfunction and sepsis patients with persistent tachycardia. Landiolol is a super-cardioselective beta blocker with a favourable safety profile for patients with renal and hepatic comorbidities.

Key Points

- A norepinephrine-sparing effect has been reported with vasopressin, leading to its recommendation as an adjunctive therapy. It often leads to a reduction of norepinephrine requirement, thus having a positive impact on the immune system and reducing the norepinephrine-induced side-effects.
- Higher vasopressin response rates and better patient outcomes are seen when the combination is started at lower norepinephrine doses, lower lactate levels and higher arterial-pH levels.
- β_1 -selective blockers like landiolol have very short half-lives, are not influenced by renal and liver function and have a faster onset of action.
- Landiolol was found to be effective and safe regardless of patient characteristics, such as septic shock, low LVEF, acidosis, and acute renal failure.
- Ultrashort-acting β -blockers like landiolol used to treat sepsis patients with tachycardia, despite initial treatment, can significantly reduce mortality.

Disclaimer

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References

- Angus DC, Linde-Zwirble WT, Lidicker J et al. (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* 29(7):1303-10.
- Annane D, Bellissant E, Cavaillon JM (2005) Septic shock. *Lancet.* 365(9453):63-78.
- Brask AL, Shemanski SM, Barnes TE, Holmes AK (2023) Timing of Vasopressin Addition to Norepinephrine and Efficacy Outcomes in Patients With Septic Shock. *Ann Pharmacother.* 57(5):521-526.
- Evans L, Rhodes A, Alhazzani W et al. (2021) Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Critical Care Medicine* 49(11):p e1063-e1143.
- Gordon AC, Mason AJ, Thirunavukkarasu N et al. (2016) Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *JAMA.* 316(5):509-18.
- Hasegawa D, Sato R, Prasitlumkum N et al. (2021) Effect of Ultrashort-Acting β -Blockers on Mortality in Patients With Sepsis With Persistent Tachycardia Despite Initial Resuscitation: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Chest.* 159(6):2289-2300.
- Kaukonen KM, Bailey M, Suzuki S et al. (2014) Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA.* 311(13):1308-16.
- Kimmoun A, Louis H, Al Kattani N et al. (2015) β_1 -Adrenergic Inhibition Improves Cardiac and Vascular Function in Experimental Septic Shock. *Crit Care Med.* 43(9):e332-40.
- Levy MM, Fink MP, Marshall JC et al. (2001) SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 31(4):1250-6.
- Li Y, Li H, Zhang D (2020) Timing of norepinephrine initiation in patients with septic shock: a systematic review and meta-analysis. *Crit Care.* 24(1):488.
- Matsuda N, Nishida O, Taniguchi T et al. (2020) Impact of patient characteristics on the efficacy and safety of landiolol in patients with sepsis-related tachyarrhythmia: Subanalysis of the J-Land 3S randomised controlled study. *EclinicalMedicine.* 28:100571.
- McIntyre WF, Um KJ, Alhazzani W et al. (2018) Association of Vasopressin Plus Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock: A Systematic Review and Meta-analysis. *JAMA.* 319(18):1889-1900.
- Seymour CW, Liu VX, Iwashyna TJ et al. (2016) Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 315(8):762-74.
- Stolk RF, van der Poll T, Angus DC et al. (2016) Norepinephrine Use in Sepsis. *Am J Respir Crit Care Med.* 194(5):550-8.
- Stolk RF, van der Pasch E, Naumann F et al. (2020) Norepinephrine Dysregulates the Immune Response and Compromises Host Defense during Sepsis. *Am J Respir Crit Care Med.* 202(6):830-842.
- Vincent JL, Sakr Y, Sprung CL et al. (2006) Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med.* 34(2):344-53.