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Tachycardia in Sepsis: Friend or Foe?

An overview of tachycardia in sepsis, the importance of rate control and the beneficial effects of beta-blockers.

Sepsis and Tachycardia – Aetiologic Factors

During sepsis, the sympathetic nervous system plays a key role in maintaining cardiac output and blood pressure. This is achieved through changes in heart rate, contractility, and vascular tone. The proper function of the baroreflex system is important for maintaining haemodynamic homeostasis. Tachycardia (increased heart rate) in the early phases of sepsis becomes a crucial mechanism for compensating the decrease in stroke volume (SV) and indicates the efficacy of baroreflex activity. Adequate volume resuscitation often decreases heart rate due to the compensatory origin of tachycardia (Morelli et al. 2016).

Tachycardia is very common in septic patients in the ICU. In septic shock, the baroreflex response is often impaired due to high levels of catecholamines, leading to a hyper-adrenergic state. This results in persistent tachycardia even after adequate fluid resuscitation in many septic shock patients, which is a sign of excessive sympathetic stimulation (Baygin and Kararmaz 2018).

Patients who were tachycardic 24 hours after starting norepinephrine infusion have a three-time higher risk of death than those without tachycardia. This may be due to an exhausted compensatory reflex mechanism. Persistent tachycardia can harm the heart by increasing oxygen demand, reducing diastolic filling, and causing direct cardiotoxicity (Domizi et al. 2020).

Studies report that the incidence of atrial fibrillation (AF) in septic patients is nearly 25.5%. This number increases to 31.6% for those in the ICU. Patients who have AF during sepsis have a higher five-year risk of hospitalisation for heart failure, ischaemic stroke and death compared to those without AF (Vélez-Gimón 2021). Heart failure (low left ventricular ejection fraction) and sepsis, independently, increase the risk of arrhythmias. AF is a common supraventricular arrhythmia in sepsis, accounting for up to 70% of cases. Rate control is the preferred treatment in ICU patients, as the majority will convert back to normal sinus rhythm once their acute illness has been resolved. A study of critically ill patients with AF showed that 81% returned to normal sinus rhythm via rate control alone (Jones et al. 2021).

> **“landiolol is a first-line treatment for patients with cardiac dysfunction with limited effect on blood pressure and inotropy”**

Limitations of Standard of Care

The conventional approach for the management of AF in septic patients with pre-existing heart failure may be the use of agents which are considered haemodynamically favourable (e.g., amiodarone and digoxin). However, current evidence suggests beta-blockers appear to be a better choice.

Sepsis causes overstimulation of adrenergic receptors, which contributes to cardiac dysfunction. Treatment with beta-blockers offers several benefits, such as attenuation of inflammatory cytokines, improvement of cardiac function, counteraction of metabolic dysregulation, prevention of negative consequences from sympathetic overstimulation and prevention of dobutamine-induced ventricular arrhythmias in decompensated heart failure with ejection fraction less than 35%. Given the benefits, it is suggested that chronic beta-blockers be continued in sepsis and heart failure (Jones et al. 2021).

The beneficial effects of beta-blockers in sepsis are due to the normalisation of the hypermetabolic state and the modulation of the immune system. The use of epinephrine and dobutamine in septic shock patients is linked to higher in-hospital mortality (Hasegawa et al. 2021). A study showed that beta-blockers reduced mortality compared to calcium channel blockers, digoxin, and amiodarone when used for intravenous intervention for 48 hours (Walkey et al. 2016).

Even among beta-blockers, there are certain limitations in critically ill patients with cardiac dysfunction. For example, esmolol has a negative inotropic effect and causes hypotension. Metoprolol has the same drawback, and combined with its late onset of action and an unpredictable effect, may not be the best choice.

Landiolol – A New Kind of β1-antagonist

Landiolol is a β1-antagonist with limited effects on blood pressure and heart pump function because of its pure S-enantiomer molecular structure. It has a favourable safety profile for patients with renal and hepatic comorbidities due to inactive metabolites and the breakdown by plasma esterases. Landiolol is metabolised mainly by pseudocholinesterases and carboxylesterases and not by CYP450. It has two inactive metabolites (M1 and M2) and does not require dose adjustment for patients with renal dysfunction. It is mainly excreted in urine and has excellent efficacy even at low doses, with a low volume distribution and lower risk of toxicity. Landiolol, due to the highest cardioselectivity (β1/β2-selectivity = 255:1) has a minimal impact on respiratory function and β2-receptor-mediated coronary hyperaemia.

A study was conducted across 54 hospitals to investigate the efficacy and safety of landiolol for the treatment of

sepsis-related tachyarrhythmias. A total of 151 patients with sepsis and persistent tachyarrhythmia were randomised into two groups, with 76 receiving landiolol and standard therapy (landiolol group) and 75 receiving only standard therapy (control group), where 33% of the control group received antiarrhythmics. In the study, the mortality rate in the landiolol group was 12%, resulting in an absolute reduction of 8% and a relative reduction of 40% in the risk of death. Additionally, 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 mortality rate at 28 days compared to the control group. The results suggest that landiolol effectively controls heart rate and reduces the risk of death (Matsuda et al. 2020; Kakikhana et al. 2020).

In another study of 61 patients with severe sepsis, landiolol was found to decrease heart rate in septic patients without causing negative effects on haemodynamics. The study found that landiolol administration resulted in a high rate of conversion to sinus rhythm, potentially due to its direct suppressive effect on sympathetic activity (Okajima et al. 2015).

Cost Effectiveness of Using Landiolol

There is sufficient evidence to establish that sepsis and septic shock are associated with cardiovascular problems, including tachyarrhythmia, myocardial injury, and changes in vascular endothelial function. Tachycardia and AF, if treated with less effective agents such as amiodarone, can increase the use of healthcare resources and costs (Krumpl and Walter 2022).

A study was conducted to analyse the cost-effectiveness of landiolol use instead of the standard of care treatment for tachyarrhythmias in septic patients in intensive care units. The authors also looked at the long-term health economic effects of sepsis and the elevated mortality rates after discharge for patients with new-onset AF during sepsis. Findings show that patients with sepsis-related tachyarrhythmia have higher mortality rates, complications, longer hospital stays, increased need for ventilation and higher costs, including hospitalisation and ICU costs. Using landiolol for the management of sepsis-related tachyarrhythmias resulted in an estimated lifetime cost of 58,100.71€ per patient and a gain of 4.02 quality-adjusted life-years (QALYs). The standard of care treatment resulted in 60,935.11€ per patient and 3.55 QALYs. Landiolol showed a cost savings of 2,834.40€ and a gain of 0.47 QALYs or 5.63 months in perfect health. The major source of cost reduction was found to be the reduced need for ICU care (Krumpl and Walter 2022).

Conclusion

The above discussion and clinical evidence highlight the benefits of rapid control of heart rate in patients with tachycardia and AF. Landiolol is a first-line treatment for patients with cardiac dysfunction with limited effect on blood pressure and inotropy. It has a favourable safety profile for patients with renal and hepatic comorbidities and is compatible with pulmonary disorder patients due to its super-cardioselectivity. ■

Key Points

- Tachycardia is common in sepsis patients in the ICU.
- Studies report that the incidence of atrial fibrillation in sepsis patients is nearly 25.5%.
- Rate control is the preferred treatment in ICU patients, as the majority will convert back to normal sinus rhythm once their acute illness has been resolved.
- Sepsis causes overstimulation of adrenergic receptors, which contributes to cardiac dysfunction. Treatment with beta-blockers offers several benefits.
- Landiolol, due to the highest cardioselectivity (β1/β2=255:1) has a minimal impact on respiratory function and β2-receptor-mediated coronary hyperaemia.
- Landiolol is a β1-antagonist with limited effects on blood pressure and heart pump function. Landiolol owns a well tolerated safety profile.

Disclaimer

Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

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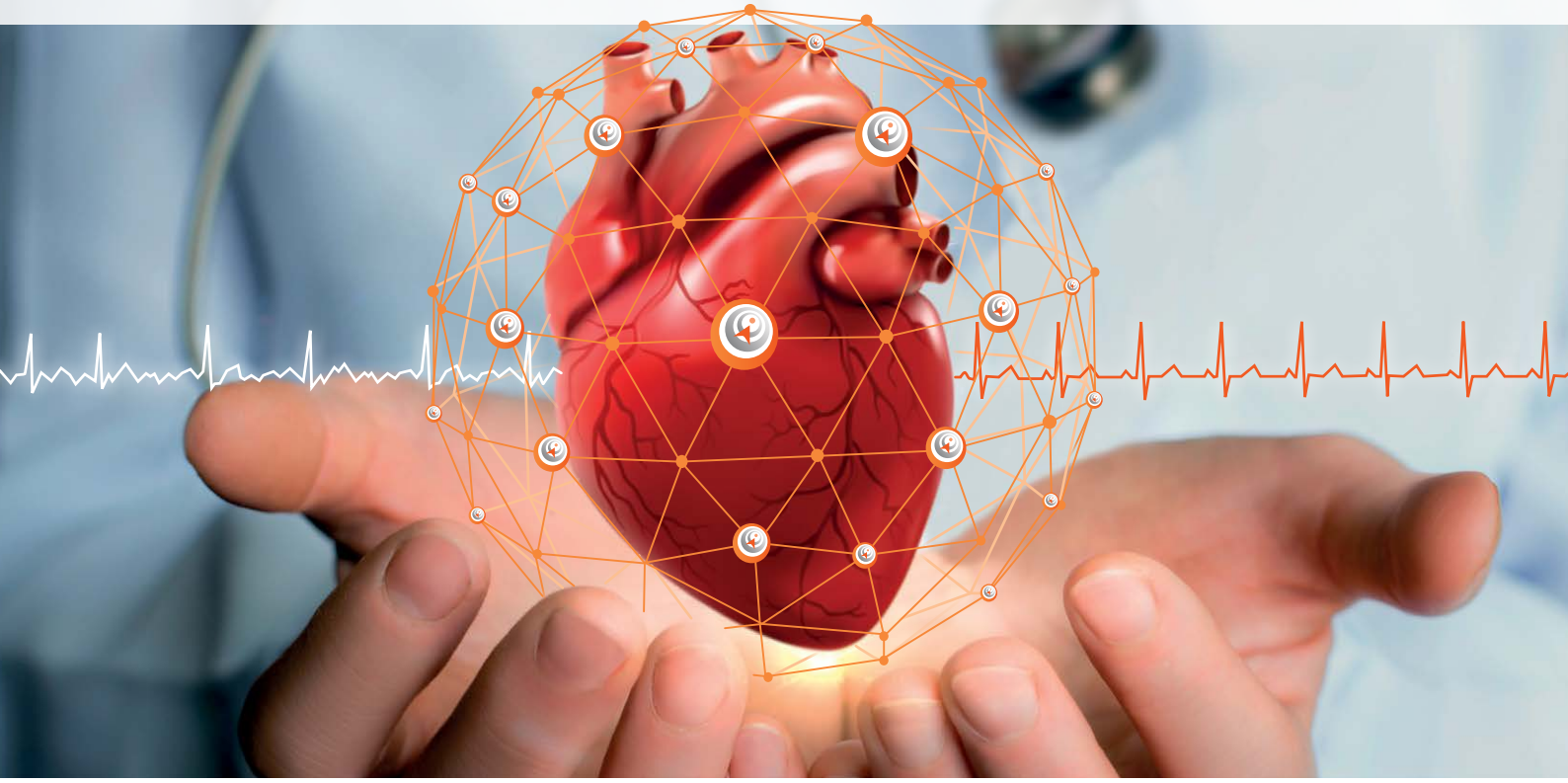
Landiolol hydrochloride

Rapid Rate Control with Myocardial Protection.[1]



Rapid control of ventricular rate in patients with SVTs and AF[1]

First-line for patients with cardiac dysfunction[2]

- **Limited effect** on blood pressure and inotropy[3]
- **Favourable safety profile for patients with renal and hepatic comorbidities** due to inactive metabolites and hydrolysis by plasma esterases[1,4]
- **Compatible with pulmonary disorder patients** due to highest cardioselectivity (β1/β2-selectivity = 255:1) among β1-blockers[5]
- **Limited rebound and tolerance effect** due to lack of pharmacochaperoning activity[6]

1 Summary of Rapibloc® Product Characteristics, current version. – **2** Hindriks G., et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journal (2020) 00, 1-126. – **3** Shibata et al. Direct Effects of Esmolol and Landiolol on Cardiac Function, Coronary Vasoactivity, and Ventricular Electrophysiology in Guinea-Pig Hearts. J Pharmacol Sci 118, 255 – 265 (2012). – **4** Yokoyama H. (2016) Stabilization in Off-Pump Coronary Artety Bypass. Springer Tokyo Heidelberg New York Dordrecht London © Springer Japan. – **5** European Heart Journal Supplements (2018) 20 (Supplement A), A1-A24. – **6** Nasrollahi-Shirazi S et al. Comparison of the b-adrenergic receptor antagonists landiolol and esmolol: receptor selectivity, partial agonism, and pharmacochaperoning actions. J Pharmacol Exp Ther 2016; 359:73–81

Rapibloc® 300 mg: Rapibloc® 300 mg powder for solution for infusion. **Composition:** A vial of 50 mL contains 300 mg landiolol hydrochloride which is equivalent to 280 mg landiolol. After reconstitution each mL contains 6 mg landiolol hydrochloride (6 mg/mL). Excipients with known effect: Mannitol E421, sodium hydroxide (for pH adjustment). **Therapeutic Indication:** Landiolol hydrochloride is indicated for supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable. Landiolol hydrochloride is also indicated for non-compensatory sinus tachycardia where, in the physician's judgment the rapid heart rate requires specific intervention. Landiolol is not intended for use in chronic settings. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, severe bradycardia (less than 50 beats per minute), sick sinus syndrome, severe atrioventricular (AV) nodal conductance disorders (without pacemaker): 2nd or 3rd degree AV block, cardiogenic shock, severe hypotension, decompensated heart failure when considered not related to the arrhythmia, pulmonary hypertension, non-treated phaeochromocytoma, acute asthmatic attack, severe, uncorrectable metabolic acidosis. For further information on warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy, lactation, effects on ability to drive and use machines, unsiderable effects, and habituation effects, please refer to the published SmPC
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