ICU

MANAGEMENT & PRACTICE

INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY

VOLUME 20 - ISSUE 2

The Night in the ICU

12

9 771377 756005

COVID-19 and the Potential Effects on the Cardiovascular System

COVID-19 affects the myocardium and myocarditis and cardiac injury is a common condition among hospitalised patients. Landiolol, a new ultra-short acting, intravenous most β1 selective blocker, can help reduce inflammation and provide therapeutic benefits.

Influenza, bacterial pneumonias, respiratory infections and viruses are well-established factors that cause cardiovascular disease (CVD) and are associated with high CVD risk (Madjid et al. 2020; Cowan et al. 2018). On the other hand, the underlying CVD disorder itself contributes to the increased incidence and severity of the infectious disease, thereby resulting in deteriorating the clinical outcome (Madjid et al. 2020).

COVID-19 and Cardiovascular Diseases: The Role of Inflammation

COVID-19 as a severe acute respiratory syndrome appears to affect myocardium and cause myocarditis. Cases of random autopsies have shown infiltration of myocardium by interstitial mononuclear inflammatory cells. Cases of severe myocarditis with reduced systolic function after COVID-19 have also been reported. Studies of cardiac biomarkers suggest a high prevalence of cardiac injury in hospital patients. Myocardial injury is most likely associated with infection related myocarditis and/or ischaemia and is an important predictor in COVID-19 patients (Madjid et al. 2020).

A report by Shi et al. (2020) demonstrates that cardiac injury is a common condition among hospitalised patients with COVID-19 and is associated with higher risk of in-hospital mortality. Of 416 patients, 10.6%, 5.3% and 4.1% had coronary heart disease, cerebrovascular disease and heart failure respectively. A total of 57 patients died, 42 of them had cardiac injury. The mortality rate increased in association with the magnitude of the reference value of hs-TNI (high-sensitivity troponin I).

Guo et al. (2020) reported results about related factors and outcomes in 187 patients hospitalised with COVID-19 (43 died, 144 discharged). In this study, 35% had underlying CVD (hypertension, coronary heart disease or cardiomyopathy) and 28% showed signs of acute myocardial damage (defined as increased troponin T [TnT)]). Mortality was significantly higher in subjects with high TnT compared to those with normal TnT levels (59.6% vs. 8.9%, respectively, $P < .001$). The investigators concluded that myocardial injury has a significant association with fatal outcomes in COVID-19 patients and is associated with impaired cardiac function and ventricular tachyarrhythmias. Inflammation may also be associated with myocardial injury.

Viral infections can cause acute coronary syndromes, arrhythmias and the development of heart failure. There are many mechanisms that cause the above, in particular the combination of important systemic inflammatory responses of the body plus localised vascular inflammation at the level of arterial plaque (Madjid et al. 2020).

COVID-19 Induces Arrhythmias

The abnormal systemic immune-inflammatory response of the body caused by the virus could further enhance the tendency to develop arrhythmias, including malignant ventricular arrhythmias (Lazzerini et al. 2020). IL-6 in particular:

- Participates in myocardial injury, leading to tachyarrhythmias.
- Remodels the ionic channels of cardiomyocytes (immediate prolongation of QTc).
- Inhibits CYP450 and specifically CYP3A4, resulting in an increase of the bioavailability of QT-prolonging medicines (indirect prolongation of QTc).
- Causes hyperstimulation of the sympathetic system, increasing electrical instability of the heart, which results in tachyarrhythmias.

In addition, prolongation of QTc was observed in patients with high levels of C-reactive protein (CRP) (Lazzerini et al. 2020).

Landiolol and Reduction of Inflammatory Cytokines

Landiolol is a new ultra-short acting, intravenous most β1 selective blocker for the treatment of supraventricular tachyarrhythmias such as atrial fibrillation (AF), atrial flutter (AFL), and non-compensatory sinus tachycardia. Landiolol is a new kind of β1-blocker, and is a pure S-enantiomer molecule with a distribution volume of 0.3 l/kg – 0.4 l/kg. In a 70kg man, the fluids contained in his body are 42 litres, hence the volume of distribution of landiolol ranges from 21-28 litres. This is very important because landiolol does not store in tissues,

thus avoiding possible toxicities.

On the contrary, the volume of distribution of amiodarone is enormous, and variable (about 5000 litres in a 70kg adult). There are also concerns regarding toxicity with amiodarone (Alpert et al. 2014). In a study, landiolol presented minimal effect on the refractory period during action potential of a cardiomyocyte compared to esmolol which dose-dependently shortens the refractory period. This is because landiolol does not affect the Ca ion currents, therefore myocardial contractility is not affected (Shibata et al. 2011). This is clinically important when using landiolol in patients with cardiac dysfunction as per the guidelines (ESC 2016). Also, landiolol has a T1/2 of 4 minutes. It has a rapid start of action of 1 minute, with a short action duration of 10 to 15 minutes. It has a steady state at 15 minutes in continuous infusion and 2–5 minutes when a loading dose is preceded. CYP-independent metabolism is direct from pseudocholinesterases and plasma carboxylesterases. Excretion is carried out by the kidneys with 75% of the drug excreted within 4 hours and 99% within 24 hours (Domanovits et al. 2018). The metabolites of landiolol are inactive and the dosage of the drug is not affected by renal function nor does it affect renal function (Nasrollahi-Shiraz et al. 2016).

Compared to esmolol, landiolol has shown very high cardioselectivity (b1/b2-selectivity=33:1 vs. 255:1) (Iguchi et al. 1992). This translates to eightfold higher cardioselectivity for landiolol compared to esmolol. Unlike esmolol, landiolol has a limited impact on blood pressure and is shown to reduce heart rate without undesired drop in blood pressure (Krumpl et al. 2017).

In another study, where inflammation was caused by the infusion of LPS (lipopolysaccharides-endotoxin), the use of landiolol slowed its progression as measured by TNF-a, IL-6 AND HMGB-1 (High Mobility Group Box 1=indicator of inflammation progression). Landiolol also reduced heart rate by controlling sympathetic stimulation, without causing hypotension. The researchers conclude that landiolol may offer therapeutic benefit to patients with sepsis through its ability to inhibit the inflammatory response (Hagiwara et al. 2009).

A clinical trial published in 2011 by Sezai et al. (PASCAL Trial), suggests that landiolol hydrochloride may be an anti-inflammatory drug. Postoperative levels of IL-6, IL-8, and hs-CRP (high sensitive CRP) were significantly lower in patients who were treated by landiolol, suggesting that the anti-inflammatory effect of this drug might have reduced AF. Another clinical trial (PLATON Trial) published in 2015 in heart failure patients undergoing heart surgery found that patients treated with landiolol had significantly lower level of the inflammatory marker hs-CRP than control (no landiolol treatment).

Horikoshi et al. (2017) reported that perioperative landiolol administration suppressed the incidence of new-onset of AF as well as sinus tachycardia, and the plasma IL-6 elevation in patients undergoing oesophageal cancer surgery.

It is known that norepinephrine (NE) contributes to increasing levels of IL-6. Li et al. (2015) reported that NE is capable of inducing IL-6 generation in macrophages via b-ADR-ROS-NF-kB signal pathway. Yang et al. (2014) also demonstrated that stress-related hormone NE induced IL-6 expression in GES-1 cells. The induction was via the ß-adrenergic receptor-cAMP-PKA pathway and mainly at the transcriptional level. Therefore, the administration of a beta-blocker supports the protection from the harmful effects of NE.

Landiolol's Cardioselectivity Favourable in Patients With COVID-19

In the heart where both β1 and β2 receptors are located, the binding of these receptors by catecholamines is associated with elevated heart rate (HR) and myocardial contractility, while in the arteries, veins and bronchi where only β2 receptors are located the binding of catecholamines causes dilation. This could be very useful for an athlete as he needs increased HR and contractility and greater dilation in the vessels to meet increased oxygen demands. However, for a patient with sepsis, it is important to reduce the HR in order to reduce oxygen consumption while maintaining contractility, as this can decrease stroke volume and reduce blood pressure. At the same time, it is necessary to maintain the binding of catecholamines to β2 receptors in coronary arteries and bronchi unaffected so that these tissues continue to be dilated and the patient continues to receive the maximum amount of oxygen, which would be affected by a beta blocker that has a β2 action (Sendon et al. 2004).

Landiolol is the first innovative drug for acute heart rate control for cardiovascular risk patients and offers a more advanced and improved treatment option.

Landiolol is marketed by AMOMED under the following brand names: Rapibloc®, Landiobloc®, Raploc®, and Runrapiq®. For more information regarding the product, please visit www.amomed.com. ■

References

Alpert JS et al. (2014) 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. JACC, 64(21).

Benussi S et al. (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal. doi:10.1093/eurheartj/ehw210

Cowan LT, Lutsey PL, Pankow JS, Matsushita K, Ishigami J, Lakshminarayan K (2018) Inpatient and outpatient infection as a trigger of cardiovascular disease: the ARIC study. J AmHeart Assoc, 7(22):e009683-e009683. doi:10.1161/JAHA.118.009683.

For full references, please email editorial@icu-management.org or visit https://iii.hm/13ut

Rapibloc®
Landiolol hydrochloride

_Rapid Rate Control.

No Compromise.

highest cardio-selectivity[3]
β1:β2
255:1

- **Ultra-rapid heart rate control**[2]
- **Limited effect** on blood pressure and inotropy[2–5]
- **Favourable safety profile**[3,5,6]
- **Precise controllability**[7]

Fast and precise management of acute atrial fibrillation.[3]
First-line also for patients with cardiac dysfunction.[1]

AMOMED

1 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016 Aug 27. pii: ehw2010. Available at: http:/eurheartj.oxfordjournals.org. **2** Krumpl G., et al.: Bolus application of landiolol and esmolol: comparison of the pharmacokinetic and pharmacodynamic profiles in a healthy caucasian group. Eur J Clin Pharmacol 2017; 73: 417-428. **3** Summary of Rapibloc® Product Characteristics, current version. **4** Tsuchiya H., et al.: Characteristic interactivity of landiolol, an ultra-short-acting highly selective β-1-blocker, with biomimetic membranes: comparisons with β-1-selective esmolol and non-selective propranolol and alprenolol. Front Pharmacol 2013 Dec 2; 4:150. **5** Syed Y. Y.: Landiolol: A Review in Tachyarrhythmias. Drugs 2018; 78:377–388. **6** Yamashita T., et al.: A prospective observational survey on landiolol in atrial fibrillation/ atrial flutter patients with chronic heart failure – AF-CHF landiolol survey. Journal of Cardiology 2019 Nov. Vol. 74, Issue 5: 418-425. **7** Plosker G.L.: Landiolol: a review of its use in intraoperative and postoperative tachyarrhythmias. Drugs 2013; 73:959-977.

LDL120_0620INT

Rapibloc® 300 mg: Rapibloc® 300 mg powder for solution for infusion. **Composition:** A vial of 50 mL contains 300 mg landiolol hydrochloride. After reconstitution each mL contains 6 mg landiolol hydrochloride (6 mg/mL). List of excipients: Mannitol E421, sodium hydroxide (for pH adjustment). Therapeutic Indication: Landiolol hydrochloride is indicated for supraventricular tachycardia and for rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, post-operative, 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, sick sinus syndrome, severe atrioven-tricular (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. **Undesirable effects:** Common: Hypotension, bradycardia. Uncommon: Pneumonia, hyponatraemia, cerebral ischemia, headache, cardiac arrest, sinus arrest, tachycardia, hypertension, pulmonary oedema, vomiting, nausea, liver disorder, ECG: ST segment depression, cardiac index abnormal, abnormal labo-ratory parameters: ALT/GPT, AST/GOT, blood bilirubin, white blood cell count, red blood cell count, haemoglobin haematocrit, platelet count, blood lactate dehydrogenase, blood urea, blood creatinine, blood creatinine phosphokinase, protein total, blood albumin, blood sodium, blood potassium, blood cholesterol, blood triglycerides, protein urine present. **Rare:** Mediastinitis, thrombocytopenia, platelet disorder, hyperglycaemia, cerebral infarction, cerebrovascular accident, seizure, myocardial infarction, ventricular tachycardia, atrial fibrillation, low cardiac output syndrome, atrioventricular block, bundle branch block right, supraventricular extrasystole, ventricular extrasystole, shock, hot flush, asthma, respiratory distress, respiratory disorder, bronchospasm, dyspnoea, hypoxia, abdominal discomfort, oral discharge, breath odour, hyperbilirubinemia, erythema, cold sweat, muscle spasms, renal failure, acute kidney injury, oliguria, pyrexia, chills, chest discomfort, administration site pain, blood pressure increased, electrocardiogram T wave inversion, electrocardiogram: prolonged QRS complex, heart rate decreased, pul-monary arterial pressure increased, PO2 decreased, neutrophil count abnormal, blood alkaline phosphatase abnormal, leukocyte alkaline phosphatase, free fatty acids abnormal, blood chloride abnormal, glucose urine. **Not known:** Application site pain, injection site reaction, sensation of pressure. **Prescription only/available only from pharmacy. Date of revision of the text:** September 2018. **Marketing authorization holder:** Amomed Pharma GmbH, Storchengasse 1, 1150 Wien, Austria