Landiolol for refractory tachyarrhythmias in the intensive care unit: case reports

Clemens Gangl¹, Konstantin A. Krychiuk¹, Robert Schoenbauer¹, and Walter S. Speid¹,²*

¹Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria; and ²Ludwig Boltzmann Institute for Cardiovascular Research, Vienna, Austria

KEYWORDS
Case report; Landiolol; Sepsis; Electrical storm

Tachyarrhythmias are common complications of critically ill patients treated on intensive care units. Landiolol is an ultra-short acting beta-blocker with a very high beta1-selectivity. Therefore, landiolol effectively reduces heart rate with only minimal negative effects on blood pressure and inotropy. This article describes two cases of successful treatment of supraventricular and ventricular tachycardias with landiolol in critically ill patients.

Introduction

Tachyarrhythmias are common complications of both surgical intensive care unit (ICU) patients after noncardiac¹ and cardiac² surgery and medical critically ill patients.³,⁴ Atrial fibrillation represents the most common arrhythmia affecting between 5.3% and 19.2% of all ICU patients.⁵ In particular, patients with sepsis are at increased risk to develop atrial fibrillation with rates of new onset atrial fibrillation between 23% to 40%.⁶ The incidence of ventricular tachycardias (VTs) has rapidly declined since the broad adoption of acute revascularization in patients with myocardial infarction and occurred in 2.2% of all ICU patients in a multicentre cohort study published in 2008.⁴ Importantly, it has been shown that critically ill patients with both supraventricular and ventricular arrhythmias have an increased mortality risk.⁴ Whereas rapid termination is the treatment goal for VTs, heart rate control has priority in critically ill patients with supra-VTs as it has been shown that sole rhythm control is of limited efficacy.⁷–⁹ Compared to other beta-blockers, landiolol is ultra-short acting with a high beta1-selectivity, translating to well controlable negative chronotropic effects with only marginal effects on blood pressure and myocardial contractility¹⁰ (Table 1).

In particular, landiolol could be used in vasopressor dependent patients without significant effects on blood pressure or dose of norepinephrine or vasopressin.¹³ The following two cases describe one patient with urosepsis that developed new onset tachycardic atrial fibrillation and one patient with electrical storm refractory to class III antiarrhythmic drugs.

Case 1—an immunosuppressed patient with urosepsis and new onset atrial fibrillation

The patient was a 62-year-old male with a complex medical history. He underwent double-lung transplantation because of stage 4 chronic obstructive pulmonary disease 8 years before and had been treated for urethelial carcinoma by transurethral resection of the bladder tumour 16 months before. He had stage 5 chronic kidney disease treated by intermittent haemodialysis. In addition, he had a history of bilateral pulmonary embolism 1 month after his bladder surgery treated with ultrasound-accelerated thrombolysis and suffered from a second pulmonary embolism with cardiac arrest and successful resuscitation 12 months later.
The patient who was under treatment with tacrolimus and phenprocoumon presented at the emergency department because of nausea and hypotension. On arrival, his blood pressure was 75/45 mmHg, and his heart rate was 120/min. His Glasgow Coma Scale score was normal with 15. Electrocardiogram (ECG) showed sinus tachycardia with a heart rate of 115/min. His body temperature was 38.2°C. Arterial blood gas testing revealed a metabolic acidosis (pH 7.09, base excess −17), and his serum lactate was 2.5 mmol/L. He had acute-on-chronic renal failure with serum creatinine of 13.9 mg/dL (his last creatinine assessment 4 weeks earlier was 2.6 mg/dL), blood urea nitrogen (BUN) was 148 mg/dL and serum potassium was 6.7 mmol/L. He was only minimally respiratory compromised requiring 4 L of nasal oxygen insufflation, and bedside echocardiography showed normal right and left ventricular (LV) function. Haemoglobin (14.2 g/dL) and platelet count (255 G/L) were normal, but his white blood cell count was increased with 27.2 G/L. C-reactive protein (CRP) was markedly elevated with 20.1 mg/dL. His urinalysis showed 2.6 mg/dL proteinuria, blood glucose (74 mg/dL) was normal, but his white blood cell count was increased with 148,000 cells/mm³. Urine testing strip was highly positive. Therefore, the patient was diagnosed with septic shock because of urosepsis. 30 mL/kg crystalloid solution was administered intravenously, and norepinephrine (0.12 µg/kg/min) was started. Potassium could be normalized by sodium bicarbonate and glucose/insulin infusion, and a therapy with intravenous ampicillin-sulbactam was initiated, and the patient was transferred to the medical ward for further therapy.

At admission, mean arterial blood pressure (MAP) was 74 mmHg, the heart rate was 95 beats/min and his oxygen saturation was 98%. His Sequential Organ Failure Assessment score was 10, and simplified acute physiology score (SAPS) III predicted an ICU mortality of 42%. After admission of a total amount of 3000 mL of crystalloids, norepinephrine could be reduced 0.06 µg/kg/min, lactate decreased to 0.8 mmol/L and the previously anuric patient started to produce 670 mL of urine within the next 12 h. At this time, the patient developed tachycardic atrial fibrillation with a rate between 120 and 140 beats/min (Figure 1A). To maintain a MAP > 65 mmHg, norepinephrine had to be increased to again. Continuous landiolol infusion was started with a rate of 2.5 µg/kg/min and was increased to 15 µg/kg/min in three steps without any effects on MAP. Five hours later, the patient converted to sinus rhythm (Figure 1B), and his MAP increased to 100 mmHg which led to a cessation of norepinephrine (see Figure 2 for detailed course).

Blood culture showed the growth of methicillin-resistant *Staphylococcus aureus*, and antibiotic therapy was switched to intravenous linezolid. The patient remained in sinus rhythm throughout his further stay at the ICU; however, some hours later, low-dose norepinephrine was started again. Finally, norepinephrine and landiolol were tapered within the next 48 h. The patient produced 2000 mL urine per day, and serum creatinine went down to 5.8 mg/dl. He was transferred to the medical ward for further therapy.

Case 2—a patient with nonischaemic cardiomyopathy and electrical storm resistant to amiodarone

We report on a 71-year-old male patient suffering from advanced nonischaemic cardiomyopathy with severely reduced LV function who was admitted to a local hospital by emergency medical services for recurrent VTs. The rhythm disorders were of sudden onset, and the patient’s implanted cardiac resynchronization therapy-defibrillator (CRT-D) responded by multiple therapy attempts.

Besides the cardiomyopathy, the patient suffers from chronic kidney disease stage 3b and has a history of transcatheter mitral valve repair (MitraClip) in 2016 as well as total atrioventricular node ablation due to highly symptomatic permanent atrial fibrillation following various ineffective prior treatment attempts. The patient underwent evaluation for heart transplantation in the past but refused active listing because of personal reasons. Furthermore, catheter ablation of premature ventricular complexes was performed approximately 2 weeks prior to the current event after which oral amiodarone therapy was initiated.

After admission to the local hospital, intravenous administration of amiodarone (in total 600 mg) was given as a first response. In addition, mild hypokalaemia of initially 3.5 mmol/L was substituted and the lower rate limit of the pacemaker was increased to 100 beats per minute. As no rhythmological stabilization could be achieved despite these measures, mild sedative therapy using midazolam was initiated, and the patient was

| Table 1 Pharmacokinetics of β-blockers.11,12 |
|---------------------------------------------|
|                                            |
| **Onset of action** | **Landiolol** | **Esmolol** | **Metoprolol** | **Bisoprolol** |
| Half-life          | 1 min         | 1-2 min     | 20 min         | 1-2 h          |
| Efficacy (β1:β2 affinity ratio) | 2.4-5 min     | 9 min       | 3.4 h          | 9-12 h         |
| Elimination        | 255           | 33          | 2.3            | 13.5           |
|                    | Pseudocholinesterase | Plasma esterases | Hepatic 95% | Hepatic 50%, renal 50% |
| Mode of administration | i.v.         | i.v.        | p.o./i.v.      | p.o.           |

i.v., intravenous; p.o., per os.
transferred to our tertiary centre in the later afternoon to undergo VT ablation scheduled for the next day.

On arrival at our ICU, the patient appeared conscious and alert (Glasgow Coma Scale score of 15). MAP was 72 mmHg, and the ECG showed a ventricularly inhibited (VVI)-paced rhythm of 100 beats per minute. Peripheral oxygen saturation was 99% under insufflation of 3 L of oxygen, with a slightly increased respiratory rate about 20/min. Arterial blood gas analysis revealed a mild respiratory alkalosis with hypocapnia (pH 7.5, pCO₂ 27.6 mmHg, pO₂ 120 mmHg). Lactate (1.4 mmol/L) and electrolytes (potassium 4.9 mmol/L, sodium 137 mmol/L, magnesium 1 mmol/L) were within their normal ranges at the time of admission. Blood laboratory examination revealed a mildly impaired renal function (creatinine 1.43 mg/dL, BUN 29.8 mg/dL) and showed no signs of infection (CRP 0.21 mg/dL).

Echocardiography showed a severely dilated LV (LV end-diastolic volume 290 mL, LV end-diastolic diameter 74.2 mm) with a highly reduced LV ejection fraction of ≈10% (Figure 3A, Movie 1A and B).

Interrogation of the CRT-D system revealed a total of 23 VT events in the prior 24 h. Unfortunately, most VT episodes were unresponsive to anti-tachycardic pacing and thus deteriorated to ventricular fibrillation, which were successfully terminated by internal defibrillation.

In addition to the continuous infusion of amiodarone (45 mg/h), the patient received an initial bolus of

---

**Figure 1** Electrocardiograms (25 mm/s) of the patient with septic shock caused by urosepsis. The patient developed tachycardic atrial fibrillation with a rate of up to 140/min (A). Five hours after the initiation of continuous landiolol infusion, the patient converted to sinus rhythm with a reduction of heart rate to 95/min (B).
400 mg magnesium chloride, and a continuous infusion of landiolol with a dose of 7 µg/kg/min was started, taking into account the severely reduced LV function. As a result, rhythmological stabilization with a reduction of VT events could be achieved, with only two more VT events (Figure 3B) occurring in the following 14 h until the ablation procedure (see Figure 4 for detailed course). Remarkably, MAP did not significantly decrease upon landiolol treatment.

On the next morning, the patient was intubated, and the ablation was performed under general anaesthesia. Continuous antiarrhythmic medication was paused, and the pacing rate was reduced to 70 b.p.m. After trans-septal puncture, LV access was guided by transesophageal echocardiography due to the history of MitraClip. Bipolar voltage mapping of the severely enlarged LV was performed. Based on that mapping information, extensive ablation was conducted. During the procedure, the patient’s condition worsened as he became increasingly haemodynamically compromised in the context of sustained VTs making repetitive external electrical cardioversions necessary. Subsequently, continuous intravenous norepinephrine infusion (0.2 µg/kg/min) was started, and volume substitution therapy was initiated. Blood gas analyses revealed a maximum lactate of 4.5 mmol/L at that time. As no further sustained VTs could be induced at that time, ablation procedure was discontinued due to the progressing haemodynamically unstable situation. After the procedure, landiolol remained paused, and amiodaron was switched to oral therapy.

After the patient was retransferred to the ICU, administration of low dose levosimendan (0.05 µg/kg/min for 24 h) was initiated in context of increasing oliguria and rising transaminases as signs of hypoxic hepatopathy. In the further course, lactate values were decreasing back to normal, and diuresis increased to 100 mL/h. As no further VTs occurred, sedation was weaned, and norepinephrine therapy could be stopped. The patient was extubated the following day. After an observational period of 24 h, a low-dose oral beta-blocker therapy (bisoprolol 1.25 mg once daily) was initiated, and the patient was transferred to a cardiac intermediate care ward for further therapy.

Discussion

In this report, we present two critically ill patients with tachyarhythmias who were successfully treated with a continuous intravenous administration of landiolol. Landiolol is a ultra-short acting beta-blocker with an elimination half-life of approximately 3–4 min. These characteristics render landiolol a substance that can be controlled easily if adverse effects like hypotension or bradycardia occur. Importantly, due to its high beta1-selectivity, only little effects on blood pressure and myocardial contractility occur.10

Sepsis, in particular septic shock, is associated with a strong activation of the sympathetic nervous system.14 Patients with septic shock require endogenous catecholamines to maintain adequate blood pressure which may induce the development of supraventricular tachyarrhythmias like atrial fibrillation and atrial flutter in these patients. The onset of such sepsis-induced atrial fibrillation has been associated with strongly increased mortality rates.15 Therefore, cardio-selective beta-blockers may be a logic treatment option to control heart rate in these patients, without affecting inotropy and blood pressure, a concept currently tested in clinical trials.16 Importantly, Morelli et al.17 have demonstrated that beta-blocker treatment is feasible and safe in patients with septic shock in sinus rhythm. A recent study retrospectively analyzed 61 septic patients that developed supraventricular tachyarrhythmias. Out of these, 39 patients were treated with landiolol.18 Similar to our case, landiolol treatment resulted in a significant decrease of heart rate with only minimal effects on blood pressure, while unfortunately no data on vasopressor treatment were reported. Interestingly, the study reported a conversion rate to sinus rhythm of 25.6% within 24 h compared to no conversion in patients without landiolol. The J-Land 35 open label randomized controlled trial randomized 151 septic patients suffering from tachyarrhythmia (HR >100/min) requiring catecholamine therapy to continuous landiolol infusion or conventional therapy.19 Patients randomized to landiolol achieved rate control more often, and therapy was well tolerated with few side effects. A recent systematic review and
A meta-analysis evaluating both esmolol and landiolol in the treatment of tachycardia in sepsis concluded that such therapy was associated with lower 28-day mortality and beneficial haemodynamics. The available (low quality) evidence thus supports this paradigm shift in critical care towards cautious beta-blockade treatment in sepsis and septic shock when complicated by tachyarrhythmias.

Besides amiodarone, beta-blocker treatment is recommended as first-line therapy in patients with electrical storm. However, due to the negative inotropic effects, intravenous beta-blocker treatment could result in further cardiac decompensation or development of cardiogenic shock in patients with severely depressed LV function. A prospective study examined the effect of landiolol in 42 patients with electrical storm. Three of these patients were catecholamine dependent, and the LV ejection fraction was 20-70%. Addition of landiolol to class III anti-arrhythmic drugs resulted in a rhythmological stabilization in 79% of patients without significant effects on blood pressure. The J-Land study randomized patients with LV dysfunction (LV ejection fraction 25-50%) and tachycardic atrial fibrillation or flutter to landiolol or digoxin. Cautious dosing of landiolol in the range of 1-10 µg/kg/min was associated with a low number of adverse events. Our patient showed a severely depressed LV function of ∼10%, and treatment
with landiolol was not associated with a significant decrease of blood pressure but resulted in a cessation of the electrical storm and was a feasible bridging therapy to ablation. The ultra-short half-life of landiolol offers additional safety in case of (perceived) negative inotropic effects as observed in our case highlighting a patient with end-stage heart failure.

In conclusion, we present two critically ill patients to demonstrate that a cardioselective, ultra-short acting beta-blocker is feasible in the treatment of haemodynamic unstable patients without adverse effects on blood pressure.

Conflict of interest: W.S.S. received speaker fees and consulting fees from AOP Orphan Pharmaceuticals AG. Other authors have no conflict of interest to declare.

Data availability

The individual patient data are available on request from the corresponding author, W.S.S.

References

1. Hollenberg SM, Dellinger RP. Noncardiac surgery: postoperative arrhythmias. Crit Care Med 2000;28:145-150.
2. Chung MK. Cardiac surgery: postoperative arrhythmias. Crit Care Med 2000;28:136-144.
3. Reinelt P, Karth GD, Geppert A, Heinz G. Incidence and type of cardiac arrhythmias in critically ill patients: a single center experience in a medical-cardiological ICU. Intensive Care Med 2001;27:1466-1473.
4. Annane D, Sebille V, Duboc D, Heuze J-Y, Sadoul N, Bouvier E, Bellissant E. Incidence and prognosis of sustained arrhythmias in critically ill patients. Am J Respir Crit Care Med 2008;178:20-25.
5. Heinz G. Atrial fibrillation in the intensive care unit. Intensive Care Med 2006;32:345-348.
6. Rehberg S, Joannidis M, Whitehouse T, Morelli A, Landiolol for managing atrial fibrillation in intensive care. Eur Heart J Suppl 2018;20:A15-A18.
7. Mayr A, Ritsch N, Knotzer H, Dünser M, Schobersberger W, Ulmer H, Mutz N, Hasibeder W. Effectiveness of direct-current cardioversion for treatment of supraventricular tachyarrhythmias, in particular atrial fibrillation, in surgical intensive care patients. Crit Care Med 2003;31:401-405.
Landiolol for refractory tachyarrhythmias

Lebbeau J-P, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL, Kirchhof P, Kühne M, Aboyans V, Ahlsson A, Balsam P, Bauersachs J, Benussi S, Brandes A, Braunischweig F, Camm AJ, Capodanno D, Casadei B, Conen D, Crijns HJGM, Delgado V, Dobrev D, Drexel H, Eckardt LF, Fitzsimons D, Folliguet T, Gale CP, Gorenek B, Haeseler KG, Heidbuchel H, Iung B, Katus HA, Kotecha D, Landmesser U, Leclercq C, Lewis BS, Mascherbauer J, Merino JL, Merkely B, Mont L, Mueller C, Nagy K, Oldgren J, Pavlović N, Pedretti RFE, Petersen S, Piccini JP, Popescu BA, Pürerfellner H, Richter DJ, Roffi M, Rubboli A, Scherr D, Schnabel RB, Simpson IA, Shlyakhto E, Sinner MF, Steffel J, Sousa-Uva M, Suwalski P, Svetlošak M, Touyz RM, Dagers H, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, Faucher L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau J-P, Lettino M, Lip GYH, Pinto FJ, Neil Thomas G, Valgimigli M, Van Gelder IC, Watkins CL, Delassi T, Sisakian HS, Scherr D, Chasnoits A, Paouw MD, Smaijić E, Shalagon T, Avraamides P, Kautzner J, Gerdse C, Alazz AA, Kampus P, Raatikainen P, Boveda S, Papiashvili G, Eckardt L, Vasilikos V, Csanádi Z, Arnar DO, Galvin J, Barsheshet A, Caldarola P, Rakiszewskaja A, Bytyçi I, Kerkmukova A, Kalejs O, Njejim M, Pudziukynas A, Groben L, Sammut MA, Grosu A, Boskovic A, Moustaghfir A, Groot Nd, Poposka L, Anfinsen O-G, Mitkowski PP, Cavaco DM, Siliste M, Mikhailov EN, Bertelli L, Kotaj H, Rataiainen P, Arribas F, Juhlin T, Sticherling C, Abid L, Atar I, Sychov O, Bates MGD, Zakirov NU. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation in noncardiac and cardiac surgery: a clinical update. Br J Anaesth 2021;127:373-498.

Johnston BW, Chean CS, Duarte R, Hill R, Blackwood B, McAuley DF, Br J Anaesth 2021.

11. Frishman WH. Beta-Adrenergic blockers: a 50-year historical perspective. Br J Anaesth 2021.

12. Oprea AD, Lombard FW, Kertai MD. Perioperative beta-adrenergic blockade in noncardiac and cardiac surgery: a clinical update. Br J Anaesth 2021;

13. Unger M, Morelli A, Singer M, Radermacher P, Rehberg S, Takahashi K, Yatabe T, Hishida O. Effect of ultrashort-acting beta-blockers on mortality in patients with sepsis with persistent tachycardia despite initial resuscitation: a systematic review and meta-analysis of randomized controlled trials. Chest 2021;159:2289-2300.

14. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggreve M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck K-H, Hernandez-Madrid A, Nikolau N, Norekvål TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2018;72:e91-e220.

15. Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bögelein D, Gauss A, Georgieff M, Stahl W. Incidence and prognostic significance of landiolol, an ultra-short-acting beta1-selective antagonist, for treatment of sepsis-related tachyarrhythmias in sepsis. World J Crit Care Med 2018;4:373-498.

16. Lalli R, Mistry D, Skillen E, Boota N, Regan S, Blond J, Gates S, Gordon AC, Lord J, McAuley DF, Perkins G, Singer M, Young D, Whitehouse T. Study into the reversal of septic shock with landiolol (beta-blocker): STRESS-L Study protocol for a randomised trial. BMJ Open 2021;11:e043194.

17. Morelli A, Ertmer C, Westphal M, Rebberg S, Kampmeier T, Ligges S, Orecchioni A, D’Egidio A, D’ippoliti F, Raffone C, Venditti M, Guaracino F, Girardi M, Trappepe L, Pietropaoli P, Mebazaa A, Singer M. Effect of heart rate control on esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 2013;310:1683-1691.

18. Okajima M, Takamura M, Taniguchi T. Landiolol, a ultra-short-acting beta1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis. World J Crit Care Med 2015;4:251-257.

19. Kakihana Y, Nishida O, Taniguchi T, Okajima M, Morimatsu H, Ogura H, Yamada Y, Nagano T, Morishima E, Matsuda N. Efficacy and safety of landiolol, an ultra-short-acting beta1-selective antagonist, for treatment of sepsis-related tachyarrhythmias (J-LAND 35): a multicentre, open-label, randomised controlled trial. Lancet Respir Med 2020;8:863-872.