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CASE REPORT

Effect of landiolol in patients with tachyarrhythmias and acute decompensated heart failure (ADHF): a case series

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Abstract

Tachycardia and rapid tachyarrhythmias are common in acute clinical settings and may hasten the deterioration of haemodynamics in patients with acute decompensated heart failure (ADHF), treated with inotropes. The concomitant use of a short-acting β1-selective beta-blocker, such as landiolol, could rapidly and safely restore an adequate heart rate without any negative inotropic effect. We present a case series of five patients with left ventricular dysfunction, admitted to our Intensive Cardiac Care Unit with ADHF deteriorated to cardiogenic shock, treated with a combination of landiolol and inotropes. Landiolol was effective in terms of rate control and haemodynamics optimization, enabling de-escalation of catecholamine dosing in all patients. The infusion was always well tolerated without hypotension. In conclusion, a continuous infusion of a low dose of landiolol (3–16 mcg/kg/min) to manage tachycardia and ventricular or supraventricular tachyarrhythmias in haemodynamically unstable patients may be considered.

Keywords Acute decompensated heart failure; Inotropes; Landiolol; Tachycardia; Tachyarrhythmias

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Introduction

Tachyarrhythmias, such as atrial fibrillation (AF), ventricular tachycardia (VT), and sinus tachycardia, occur commonly in patients admitted to the Intensive Cardiac Care Unit (ICCU). Specifically, tachycardia worsens cardiac performance in patients with acute decompensated heart failure (ADHF) and cardiogenic shock (CS) by decreasing diastolic filling and increasing the oxygen demand.[1,2]

Additionally, haemodynamically unstable patients frequently require inotropic support with catecholamines, which are known to induce adverse haemodynamic effects, such as excess sinus tachycardia, arrhythmias, increased oxygen demand, and afterload increase.[3]

Landiolol hydrochloride (Landiobloc, AMOMED Pharma, Italy) is an ultra-short-acting highly β1-selective adrenergic receptor blocker. It is similar to esmolol, but it has a greater chronotropic effect and a lesser negative inotropic effect.[4]

Given the results of the J-Land study, landiolol has become a milestone for rate control in AF and reduced cardiac function.[5] Recently, the safety and efficacy of landiolol have been investigated in patients with recurrent haemodynamically unstable VT, despite concerns about this indication.[6,7]

This report presents five cases of critically ill patients treated with a combination of inotropes and a low dose of landiolol (3–16 mcg/kg/min), admitted to our ICCU between November 2020 and May 2021.

We sought to document the safety and beneficial effect of landiolol on cardiac rhythm in patients with severe left ventricular (LV) dysfunction and ADHF deteriorating to CS.

Case report

The main baseline patient characteristics and information on catecholamines and landiolol treatment are listed in *Table 1*. Changes in vital, haemodynamic, and echocardiographic parameters and cardiac biomarkers after landiolol infusion are summarized in *Table 2*.

Case 1

A 55-year-old man affected by hypertrophic cardiomyopathy (CM) with ejection fraction (EF) of 45% was admitted to our ICCU with episodes of sustained VT and ventricular fibrillation (VF) with several appropriate implantable cardioverter-defibrillator (ICD) interventions. On arrival, arrhythmic storm

Table 1 Baseline patient characteristics

Case no.	1	2	3	4	5	Mean ±SD or *n*
Age, years	55	50	44	53	20	44.4 ± 14.3
Gender	M	M	M	M	F	M/F 4/1
Height, cm	180	180	180	175	155	174 ± 10.8
Weight, kg	120	130	74	60	50	86.8 ± 36.1
Duration HF	Chronic	Chronic	Chronic	Chronic	Chronic	
NYHA	III	III	III	III	II	NYHA III–IV 4 NYHA II 1
Clinical profile (Stevenson *et al*., classification)	Wet and warm	Wet and cold	Wet and cold	Wet and cold	Dry and cold	Dry and cold 1 Wet and cold 3 Wet and warm 1
HR, b.p.m.	70	130	140	135	120	119 ± 28.4
SBP, mmHg	90	100	130	70	88	95.6 ± 2.1
DBP, mmHg	60	60	70	45	50	57 ± 9.8
LVEF, %	15	19	15	15	25	17.8 ± 4.4
CVP, mmHg	20	17	25	1	5	13.6 ± 10.2
$ScVO_2$, %	60	41	43	66	72	56.4 ± 13.8
NT-proBNP, pg/mL	2465	20 000	1553	32 754	13 130	13 980.4 ± 13 004.3
Creatinine, mg/dL	1.3	3.3	0.8	1.57	1.1	1.6 ± 1
Type of arrhythmia	VT/VF	VT	Persistent AF	ST	Paroxysmal AF	
Oral therapy before admission						
Beta-blockers	+	+	+	+	+	
ACE-I/ARBs	+	+	+		+	
Diuretics	+	+	+	+	+	
Aldosterone blockers	+		+	+		
Amiodarone		+	+			
Inotropic therapy CAI	0	95	5	14	7	24.2 ± 40
Landiolol dose (mcg/kg/min)	10	3	9	16	6	8.8 ± 5
Duration of landiolol infusion, h	96	96	48	96	72	81.6 ± 21.5

ACE-I, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; CVP, central venous pressure; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; $ScVO_2$, central venous oxygen saturation; SD, standard deviation; ST, sinus tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.
CAI = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/min) + 10 × phosphodiesterase 3 inhibitor dose (μg/kg/min). High-dose catecholamine use was defined as use of CAI > 10.

Table 2 Response to intravenous treatment with landiolol

Case no.	1	2	3	4	5	Mean ± SD
HR, b.p.m.	60	85	90	99	66	80 ± 16.4
SBP, mmHg	110	100	120	110	100	108 ± 8.4
DBP, mmHg	60	60	70	60	50	60 ± 7
LVEF, %	25	21	35	18	25	24.8 ± 6.4
CVP, mmHg	10	5	9	1	1	5.2 ± 4.3
$ScVO_2$, %	74	54	77	65	61	66.2 ± 9.4
NT-proBNP, pg/mL	747	6746	1284	6401	7008	4437.2 ± 3136.7
Creatinine, mg/dL	1.2	1.6	0.7	1.26	1.0	1.2 ± 0.3
Inotropic therapy CAI	0	5	0	9	3	3.4 ± 3.8

CVP, central venous pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SBP, systolic blood pressure; $ScVO_2$, central venous oxygen saturation; SD, standard deviation.
CAI = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/min) + 10 × phosphodiesterase 3 inhibitor dose (μg/kg/min). High-dose catecholamine use was defined as use of CAI > 10.

was uncontrolled despite amiodarone infusion. Landiolol infusion was then initiated at 10 μg/kg/min, and it was rapidly effective in maintaining sinus rhythm (SR) without arrhythmic relapses. The prolonged arrhythmic storm had caused ADHF with a severe EF deterioration up to 15%. Non-invasive mechanical ventilation (NIMV) and concomitant infusion of furosemide and vasodilators were started. Landiolol was well tolerated without hypotension, and an improvement in tissue perfusion, pulmonary congestion, and EF was achieved. We also observed significantly decreased in central venous pressure (CVP), venous oxygen saturation (SvO_2), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels. Four days later, a transcatheter VT ablation was successfully performed and the patient was discharged on Day 10.

Case 2

A 50-year-old patient was admitted to the ICCU with CS and pulmonary oedema. He had a known history of heart failure, classed as 'New York Heart Association' (NYHA) III, due to ischaemic CM with biventricular dysfunction (LVEF $<$ 25%). Following our step-wise management algorithm of CS, we started vasoactive agents infusion (epinephrine and sodium nitroprusside) and NIMV.[8] Two hours later, we deployed a trans-femoral intra-aortic balloon pump (IABP) because haemodynamics did not improve.

Continuous veno-venous haemofiltration (CVVH) was initiated due to acute kidney injury. On Day 10, a levosimendan infusion improved haemodynamics and the IABP was successfully removed. Due to his comorbidities, especially severe obesity and advanced chronic kidney disease, the patient was not eligible for a heart transplant; LV assist device implantation was also excluded because of severe right ventricular dysfunction. Therefore, the ongoing pharmacological support was gradually reduced and switched to a low dose of milrinone for palliative purposes.

However, the patient experienced further haemodynamic deterioration, complicated by recurrent sustained VT with multiple ICD interventions, refractory to amiodarone infusion. A low dose infusion of landiolol (3 mcg/kg/min) was subsequently started and successfully suppressed VT episodes without changing the systolic blood pressure (SBP). The treatment (landiolol, milrinone, and epinephrine) was continued for 96 h and was well tolerated. During landiolol infusion, we saw a significant decrease in LV filling pressure and CVP. NT-proBNP and serum lactate (lac 1.3 mmol/L) also decreased, and hepatic and kidney function slowly returned to baseline. A mild improvement in LV contractility and stroke volume index (SVi) was noted and enabled epinephrine discontinuation. On Day 21, the patient was transferred to the Cardiology Ward with the discharge plan, supported by milrinone, of palliative care.

Case 3

A 44-year-old male patient self-presented to the emergency department (ED) with pulmonary oedema in chronic heart failure (NYHA III). He was affected by non-ischaemic dilated CM with LVEF $<$ 25% and persistent AF.

On admission to the ICU, the patient required epinephrine infusion to maintain a mean arterial pressure (MAP) $>$ 65 mmHg. The ventricular response of his AF was $>$140 b.p.m., and a landiolol infusion was started at 9 mcg/kg/min and continued for 48 h. Notably, 2 h after landiolol initiation, heart rate (HR) dropped to 90 b.p.m. without hypotension. During the following 24 h, the patient's clinical conditions improved (serum lactate persistently $<$2 mmol/L and SvO_2 $>$ 65%, CVP 9 mmHg), enabling progressive weaning from epinephrine. NT-proBNP notably also decreased without a remarkable rise in cardiac troponin.

On the day of discharge from the ICU, a transthoracic echocardiography showed improved cardiac contractility (LVEF 39%) with accompanying severe mitral regurgitation and electrocardiogram and continuous monitoring reported permanent AF with a better ventricular response rate.

Case 4

The patient was a 53-year-old man referred to our ICCU with acute pulmonary oedema and CS. He was on the waiting list for heart transplant because of a primitive dilated CM with LVEF 20%. Due to recurrent episodes of VT, he was on antiarrhythmic treatment with mexiletine and high-dose metoprolol. Clinical examination on admission revealed severely impaired haemodynamics and multiorgan failure. NIMV, intravenous infusion of epinephrine, milrinone, and furosemide were immediately started, whereas oral treatment with metoprolol was interrupted. Re-introduction of metoprolol during CS was contraindicated due to the acute haemodynamic instability, requiring sustained inotropic support. With this vasoactive support, the patient's clinical condition progressively improved over the next 48 h, but HR progressively increased up to 135 b.p.m., leading to several inappropriate ICD shocks on sinus tachycardia. A concomitant haemodynamic deterioration occurred, with significant hypotension (SBP 70 mmHg), low cardiac index (CI; 1.7 L/min/m^2), oliguria, and lactic acidosis. Therefore, intravenous continuous infusion of landiolol was initiated at 10 μg/kg/min in addition to epinephrine and milrinone. Two hours after the initiation of the landiolol infusion, HR was 110 b.p.m. and an improvement in haemodynamics was observed. During the next few days, as landiolol was titrated to 16 μg/kg/min, HR decreased to 80 b.p.m., while CI improved up to 3 L/min/m^2 and the epinephrine dosage was reduced. The landiolol infusion was

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continued for 96 h and a remarkable reduction in NT-proBNP and plasma creatinine was achieved. Because the patient was still dependent on inotropic support, he was then implanted with a paracorporeal LV assist device as a bridge to heart transplantation.

Case 5

A 20-year-old woman was referred to the ICCU with ADHF. Her cardiovascular history begun 2 years prior when she was diagnosed with non-obstructive hypertrophic CM and Wolff–Parkinson–White syndrome, as a pattern of Danon disease. The patient rapidly deteriorated; consequently, she was placed on the waiting list for heart transplant. On arrival, an atrial rhythm at HR of 100–130 b.p.m. with frequent episodes of atrioventricular nodal re-entrant tachycardia at 160 b.p.m. and concomitant hypotension (SBP 85 mmHg) were noted. Amiodarone infusion was ineffective and the patient rapidly deteriorated to a low cardiac output syndrome. Echocardiography showed biventricular hypertrophy with severe dysfunction and low estimated SVi (20 mL/m^2). Intravenous infusion of a medium-dose epinephrine and a low-dose landiolol (6 μg/kg/min) was started. Two hours after landiolol initiation, SR was restored. The concomitant infusion of landiolol and epinephrine was well tolerated without recurrence of prolonged episodes of supraventricular tachycardia and with an improvement in SVi to 30 mL/m^2. Laboratory tests also revealed lower NT-proBNP levels and a rise in SvO_2, associated with improved tissue perfusion. Consequently, a progressive reduction of the epinephrine dosage was possible. Five days after ICCU admission, the patient was dependent on inotropes, but still stable. Heart transplant was performed on Day 45.

Discussion

In this report, five patients with refractory tachyarrhythmias during ADHF and CS were successfully treated with a continuous infusion of landiolol.

Tachycardia significantly limits the cardiovascular capacity in severe LV dysfunction and heart failure by shortening the diastolic filling period and decreasing SVi. In addition, it increases intracellular cardiomyocyte Ca^{2+} handling, contributing to further LV dysfunction.[9]

Additionally, despite stabilizing haemodynamics, ventricular–arterial (V–A) decoupling may persist in patients with CS.[3,10] This decoupling is further exacerbated both by an increase in afterload through the administration of inotropes/vasoconstrictor agents and by tachycardia.[11]

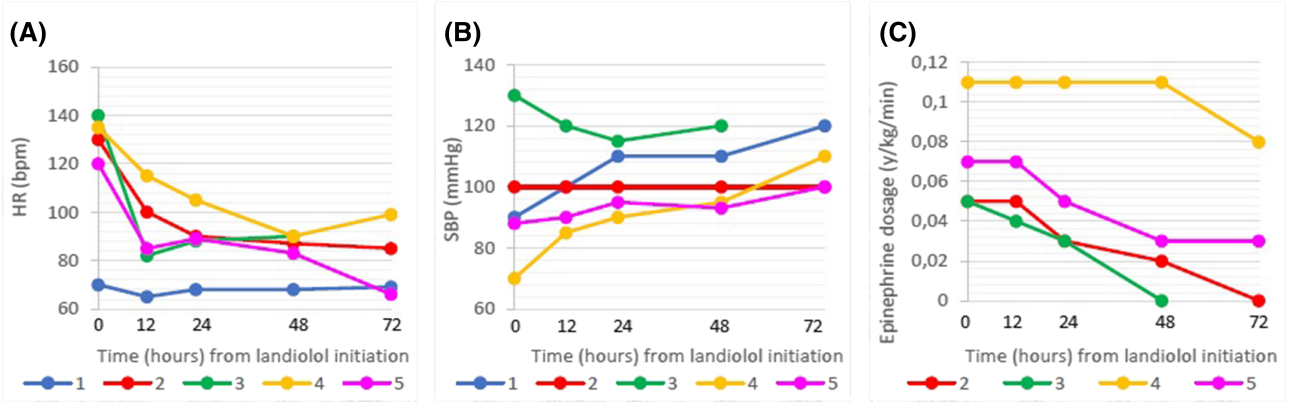
Given the side effects of adrenergic stimulation (tachyarrhythmias, increased cardiac oxygen consumption, and immune dysregulation), 'breaking' the adrenergic stressors with β-blocking could help to stabilize the cardiovascular function, although it may initially sound contradictory.

Bearing in mind that arterial elastance is related to HR and total peripheral resistances, β-blockade leads to both reduced afterload and prolonged duration of diastole (caused by HR reduction), which in turn allows increased LV filling, resulting in an increased stroke volume.

We believe that this physiological rationale is an indispensable prerequisite for the introduction of landiolol with optimized CS therapy.

The use of beta-blockers frequently results in rapid hypotension due to their negative inotropic activity. However, the highly β1 selectivity of landiolol allowed the maintenance of relative stable systolic and diastolic BP values, even in patients who received higher doses (9–16 μg/kg/min). Landiolol, compared with other beta-blockers, presents faster pharmacokinetics, higher potency, and cardioselectivity (β1/

Figure 1 Changes in heart rate (HR, Panel A), systolic blood pressure (SBP, Panel B), and dose of epinephrine (Panel C) during landiolol infusion in the patients studied.



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β2-selectivity 255:33) with less potent negative inotropic effect. These characteristics make it suitable to manage arrhythmias in critical patients without further deterioration of the cardiac function.

In our patients, landiolol infusion was effective in either restoring SR or reducing HR, as shown in *Figure 1A*. Interestingly, in three cases, approximately 120 min after landiolol infusion, tachyarrhythmias were converted to SR, emphasizing its potential role in this scenario. In all cases, the infusion was well tolerated and hypotension did not occur (*Figure 1B*). Conversely, HR reduction increased LV stroke volume, leading to a global haemodynamic improvement, which enabled a reduction in the infused catecholamine dose (*Figure 1C*).

In accordance with other recent studies, the combination therapy of landiolol and milrinone improved cardiac function and decreased HR for two of the patients studied.[12,13]

Conclusions

Based on our observations and current evidence, we suggest that the combination of inotropes/vasoconstrictor agents and a low dose of landiolol may be a new option to manage tachycardias and tachyarrhythmias in patients with CS, without any negative impact on cardiac function.[7,14] However, the positive haemodynamic effects (increase in SVi or LVEF) were still presumably driven mainly by inotrope support rather than landiolol administration.

Conflict of interest

None declared.

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