Addition of a β 1-Blocker to Milrinone Treatment Improves Cardiac Function in Patients with Acute Heart Failure and Rapid Atrial Fibrillation

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Keywords

Acute decompensated heart failure · β -Blocker · Milrinone · Atrial fibrillation · Tachycardia

Abstract

Background: Tachycardia worsens cardiac performance in acute decompensated heart failure (ADHF). We investigated whether heart rate (HR) optimization by landiolol, an ultra-short-acting β 1-selective blocker, in combination with milrinone improved cardiac function in patients with ADHF and rapid atrial fibrillation (AF). **Methods and Results:** We enrolled 9 ADHF patients (New York Heart Association classification IV; HR, 138 ± 18 bpm; left ventricular [LV] ejection fraction, $28 \pm 8\%$; cardiac index [CI], 2.1 ± 0.3 L/min⁻¹/m⁻²; pulmonary capillary wedge pressure [PCWP], 24 ± 3 mm Hg), whose HRs could not be reduced using standard treatments, including diuretics, vasodilators, and milrinone. Landiolol (1.5 – 6.0 μ g/kg⁻¹/min⁻¹, intravenous) was added to milrinone treatment to study its effect on hemodynamics. The addition of landiolol (1.5 μ g/kg⁻¹/min⁻¹) significantly reduced HR by 11% without changing systolic blood pressure (BP) and resulted in a significant decrease in PCWP and a significant in-

crease in stroke volume index (SVI), suggesting that HR reduction restores incomplete LV relaxation. Administration of more than 3.0 μ g/kg⁻¹/min⁻¹ of landiolol decreased BP, CI, and SVI. **Conclusion:** The addition of landiolol at doses of <3.0 μ g/kg/min to milrinone improved cardiac function in decompensated chronic heart failure with rapid atrial fibrillation by selectively reducing HR.

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Introduction

Tachycardia worsens cardiac performance in patients with acute decompensated heart failure (ADHF) and severe left ventricular (LV) dysfunction by decreasing diastolic filling and increasing myocardial oxygen demand [1]. Furthermore, tachycardia itself results in abnormalities in intracellular Ca²⁺ handling [2–4], LV dysfunction, and LV remodeling [5].

Landiolol (ONOACT[®]; Ono Pharmaceutical, Osaka, Japan) is an ultra-short-acting (elimination half-life 4 min) intravenous β 1-selective (β 1/ β 2 = 255) adrenergic receptor blocker that is similar to esmolol [6–8]. How-

ever, the important difference between the drugs is that landiolol has a greater chronotropic effect and a lesser inotropic effect than esmolol [6]. If a β 1-blocker can lower heart rate (HR) without suppressing cardiac function, the addition of a β 1-blocker would be beneficial for the treatment of ADHF with severe tachycardia. We previously reported that low-dose landiolol ($1.5 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$) in combination with milrinone safely decreased the HR in patients with severe ADHF and sinus tachycardia, thereby improving cardiac function, whereas high-dose landiolol (more than $3.0 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$) suppressed cardiac function [7]. In addition, we reported that $1.5 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$ of landiolol significantly decreased HR without lowering blood pressure (BP) in patients with rapid atrial fibrillation (AF) and heart failure (HF) [8]. These data suggested that HR control by low-dose landiolol is a new strategy for ADHF with tachycardia that is resistant to conventional HF treatments. We assessed whether HR optimization using landiolol in combination with milrinone improved LV function due to a rapid ventricular response to AF in ADHF patients.

Methods

We prospectively enrolled consecutive patients between March 2014 and December 2017. Patients were included if they were diagnosed with ADHF (New York Heart Association [NYHA] classification IV, depressed LV function [ejection fraction ≤ 0.35], HR ≥ 120 beats per minute [bpm], AF, and the absence of specific devices [intra-aortic balloon pump or percutaneous cardiopulmonary support system]) upon admission. Tachycardia (HR ≥ 120 bpm) must have been continuous for more than 4 h after standard treatment with diuretics, vasodilators, and milrinone. The enrolled patients underwent electrocardiographic and invasive hemodynamic monitoring with a Swan-Ganz catheter and an arterial catheter. Their baseline HR, BP, electrocardiographic findings, and cardiac hemodynamic variables were measured. The initial treatment included diuretics and vasodilators, followed by milrinone (0.25 – $0.5 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$). When hemodynamic parameters plateaued at ≥ 4 h after the initial treatment, landiolol (1.5 – $6.0 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$) was administered to study its effect on hemodynamic variables, and landiolol was dosed up in a step-wise manner every hour. The patients' hemodynamics were measured by a Swan-Ganz catheter. When there was a $>20\%$ decrease in systolic BP, when the systolic BP was <80 mm Hg, or when cardiac output was decreased twice in succession, further landiolol dosage increases were halted. The primary endpoint of this study was the change in hemodynamic variables (HR, BP, cardiac index [CI], stroke volume index [SVI], and pulmonary capillary wedge pressure [PCWP]) after landiolol administration. All echocardiography data were measured by an experienced echocardiographer who was blinded to the patients in the study. Landiolol was used in an off-label manner.

Statistical Analyses

Continuous variables are expressed as the mean $\pm$ standard deviation. The hemodynamic indices between 1.5 and $6.0 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$ of landiolol were compared with the index at $0 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$ using Dunnett's multiple comparison test. The Wilcoxon signed-rank test was used to compare hemodynamic changes between 0 and $1.5 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$ of landiolol. All analyses were performed using SAS (University Edition 3.6, SAS Institute Inc., Cary, NC, USA.). p values <0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 20 patients with ADHF (NYHA IV, clinical profile of "wet and cold," and rapid AF [HR ≥ 120 bpm]) who were admitted to Yamaguchi University Hospital were initially screened. Eleven out of these 20 patients fulfilled the key requirements of low LV ejection fraction (LVEF; $\leq 35\%$) and underwent Swan-Ganz catheter monitoring. Diuretics and/or vasodilators were initially administered to the 11 patients. In 2 of those patients, the HR gradually decreased to less than 120 bpm over 4 h. Therefore, these 2 patients were excluded from the analysis. In the remaining 9 patients, when the hemodynamic parameters plateaued at ≥ 4 h after treatment that included diuretics and/or vasodilators and milrinone, landiolol (1.5 – $6.0 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$) was administered to study its effect on hemodynamic variables.

The baseline characteristics before the intravenous administration of diuretics, vasodilators, and milrinone of the 9 patients are shown in Table 1. Five patients were diagnosed with nonischemic dilated cardiomyopathy (CM) and 4 were diagnosed with ischemic CM. The clinical severity of HF in all patients was NYHA IV and "wet and cold" according to the Nohria-Stevenson classification. Seven patients had chronic AF, while 2 had paroxysmal AF. Echocardiography data showed that the mean LV end-diastolic dimension and mean LVEF were 56 mm and 28%, respectively. Hemodynamic data revealed that the mean HR was 138.0 bpm, mean CI was $2.1 \text{ L}/\text{min}^{-1}/\text{m}^2$, mean PCWP was 23.5 mm Hg, and mean SVI was $15.0 \text{ mL}/\text{m}^2$. The oral medications, including ACE inhibitors, β -blockers, diuretics, and amiodarone, taken before admission are shown in Table 1.

Intravenous Administration of Diuretics, Vasodilators, and Milrinone prior to Landiolol Titration for the Treatment of ADHF

Table 2 shows the doses of diuretics, vasodilators, and milrinone used and the hemodynamic change prior to the

Table 1. Baseline characteristics of patients with ADHF and rapid AF

Case No.	1	2	3	4	5	6	7	8	9	Mean $\pm$ SD or <i>n</i>
Age, years	66	42	70	71	71	82	74	36	78	65.6 $\pm$ 15.8
Gender	F	M	F	M	M	M	F	M	F	5/4
<i>Diagnosis</i>										
Nonischemic CM	+	+	–	+	+	–	–	+	–	5
Ischemic CM	–	–	+	–	–	+	+	–	+	4
Duration of HF	Chronic	De novo	Chronic	Chronic	Chronic	Chronic	Chronic	De novo	Chronic	
NYHA functional class IV	+	+	+	+	+	+	+	+	+	10
Clinical profile (wet and cold)	+	+	+	+	+	+	+	+	+	10
HR, bpm	139	120	133	122	122	177	150	138	145	138.0 $\pm$ 17.9
SBP, mm Hg	132	91	114	136	120	89	73	116	136	116.9 $\pm$ 14.2
DBP, mm Hg	83	57	70	64	88	48	45	57	92	72.6 $\pm$ 20.9
Type of AF	Permanent	Permanent	Permanent	Permanent	Permanent	Permanent	Paroxysmal	Permanent	Paroxysmal	
<i>Blood examination</i>										
Serum creatinine, mg/mL	1.14	1.28	0.77	1.31	1.22	1.82	1.53	1.29	0.63	1.22 $\pm$ 0.36
eGFR, mL/min ^{–1} /1.73 m ^{–2}	37.3	50.7	56.4	42.5	45.9	28.4	26.2	52.5	68.1	45.8 $\pm$ 12.5
BNP, pg/mL	3,354	942	243	316	1,874	1,626	1,324	1,003	1,579	1,362 $\pm$ 935
<i>Echocardiography</i>										
LVDd, mm	63	61	46	54	55	68	53	65	40	56.1 $\pm$ 9.1
LVEF, %	20	30	35	35	20	25	35	15	35	27.8 $\pm$ 7.9
MR $\geq$ III	–	–	–	–	–	–	–	–	–	0
AR $\geq$ III	–	–	–	+	–	–	–	–	–	1
<i>Swan-Ganz data before intravenous administration of diuretics, vasodilators, and milrinone</i>										
mAP, mm Hg	97	67	106	72	100	63	53	85	113	84.1 $\pm$ 21.3
PCWP, mm Hg	28	28	22	19	21	24	23	22	25	23.6 $\pm$ 3.0
CI, L/min ^{–1} /m ^{–2}	2.06	1.95	2.10	1.84	1.30	2.56	2.0	2.60	2.0	2.05 $\pm$ 0.29
mPAP, mm Hg	33	33	29	28	28	33	27	30	37	30.1 $\pm$ 3.6
mRAP, mm Hg	20	14	10	9	10	11	9	10	16	12.1 $\pm$ 3.8
SVR, dyn/s/cm ^{–5}	1,920	1,222	2,286	1,484	3,789	946	1,354	2,069	2,676	1,972 $\pm$ 876
PAR, dyn/s/cm ^{–5}	123	115	167	209	295	164	123	180	331	200 $\pm$ 73
SVI, mL/m ²	14.7	16.3	15.8	13.6	15.4	14.7	13.3	17.3	13.8	15.0 $\pm$ 1.3
<i>Oral medication before admission</i>										
β -Blockers	+	–	+	+	+	+	+	–	+	7
ACE-I/ARBs	+	–	+	–	–	–	+	–	+	4
Diuretics	+	–	–	–	+	+	+	–	–	4
Aldosterone blockers	+	–	–	–	+	+	+	–	+	5
Nitrates	–	–	+	–	–	+	+	–	–	3
Digitalis	–	–	–	–	–	–	–	–	–	0
Amiodarone	–	–	–	–	–	–	+	–	+	2
Anticoagulants	+	–	+	+	+	+	–	+	+	7

CM, cardiomyopathy; NYHA, New York Heart Association; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LVDd, end-diastolic left ventricular diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; AR, aortic regurgitation; mAP, mean atrial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; SVR, systemic vascular resistance; PAR, pulmonary arterial resistance; SVI, stroke volume index.

administration of landiolol. As shown in Table 2 and Figure 1a, PCWP and right atrial pressure (RAP) significantly decreased and CI increased after the intravenous administration of these drugs as compared with those at baseline (change of PCWP -5.4 ± 4.2 mm Hg; change of RAP -4.4 ± 5.0 mm Hg, $p < 0.05$, respectively), whereas HR did not decrease (change of HR $+1.7 \pm 5.8$ bpm, $p = \text{ns}$).

Dose-Dependent Effect of Landiolol on Patient Hemodynamics

When compared with milrinone monotherapy with vasodilators and diuretics (at $0 \mu\text{g/kg}^{-1}/\text{min}^{-1}$ of landiolol), HR significantly decreased with landiolol treatment in a dose-dependent manner, and infusing landiolol did not decrease BPs at 1.5 and $3.0 \mu\text{g/kg}^{-1}/\text{min}^{-1}$ (Fig. 1a).

Table 2. Response to the initial intravenous treatment of ADHF prior to the addition of landiolol

Case No.	1	2	3	4	5	6	7	8	9	Mean $\pm$ SD or <i>n</i>
Furosemide, daily dosage, mg	60	60	40	30	20	50	100	60	80	55.6 $\pm$ 24.6
Vasodilators										
Nitroprusside, $\mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$	0.6	–	–	–	0.9	0.6	–	–	–	4
Nitroglycerin, $\mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$	–	–	–	0.3	–	–	–	–	–	1
Carperitide, $\mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$	–	–	0.025	–	–	–	–	0.025	0.025	3
Milrinone, $\mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$	0.2	0.25	0.2	0.25	0.45	0.15	0.36	0.15	0.25	0.25 $\pm$ 0.10
Change of RAP from baseline to prior to landiolol administration, mm Hg	–14	–7	0	–8	–1	0	0	–2	–8	–4.4 $\pm$ 5.0
Change of PCWP from baseline to prior to landiolol administration, mm Hg	–14	–8	–5	–5	–3	+1	–3	–4	–8	–5.4 $\pm$ 4.2
Change of CI from baseline to prior to landiolol administration, L/min/m ²	+0.86	+0.36	+0.15	–0.34	+0.48	+0.48	0.00	+0.5	+0.52	+0.33 $\pm$ 0.35
Change of HR from baseline to prior to landiolol administration, bpm	+1	0	–7	+13	+8	0	0	+2	–2	+1.7 $\pm$ 5.8

RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; HR, heart rate.

CI, SVI, and O₂ saturation of mixed venous blood peaked at 1.5, 3.0, and 1.5 $\mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$, respectively (Fig. 1a). Infusing more than 3.0 $\mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$ of landiolol decreased SVI, indicating the negative inotropism of landiolol. As summarized in Figure 1b, a dose of 1.5 $\mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$ of landiolol significantly decreased HR (140 $\pm$ 17 to 125 $\pm$ 16 bpm), which led to a decrease in PCWP (18 $\pm$ 3 to 15 $\pm$ 3 mm Hg), increases in CI (2.37 $\pm$ 0.31 to 2.61 $\pm$ 0.44 L/min/m²) and SVI (17 $\pm$ 3 to 21 $\pm$ 4 mL/beat/m²), and oxygen saturation of mixed venous blood (62 $\pm$ 7 to 68 $\pm$ 7%) without changing BPs, mean RAP, and systemic vascular resistance.

Discussion

The most important result was that the combination therapy of landiolol and milrinone improved cardiac function to a greater degree than milrinone monotherapy, including diuretics, vasodilators, and milrinone, in ADHF patients with refractory rapid AF. This is the first report showing that the addition of a landiolol to milrinone treatment rapidly restored hemodynamic variables following the optimization of HR by titration of landiolol in ADHF patients with rapid AF. There are several putative mechanisms by which the addition of a low-dose β -blocker to milrinone improves cardiac function. First, slowing the HR improves incomplete LV relaxation and decreases the myocardial oxygen demand [1]. All patients in the present study were ADHF patients with reduced LVEF, thereby indicating the “X” pressure (P)-volume (V) loop with decreased maximum elastance (E-max; Fig. 1c). Upon inducing tachycardia due to rapid AF, the “X” P-V loop shifts to the “Y” P-V loop, with the decreased SV and the elevated LV end-diastolic pressure (Fig. 1c). Tachycardia shortens the diastolic period, there-

by leading to impaired LV filling and decreasing SV [9]. In addition, tachycardia increases the diastolic Ca²⁺ concentration in the cytosol through diastolic Ca²⁺ leakage through the ryanodine receptor and decreased Ca²⁺ uptake due to Ca²⁺-ATPase on the sarcoplasmic reticulum, which leads to worsening of the impaired LV relaxation [2–5, 10]. This is because the diastolic P-V curve is shifted upward. The early phase of the diastolic P-V curve shows a particularly great shift [9]. This is a characteristic pattern of incomplete LV relaxation on the diastolic P-V curve. In the present study, landiolol slowed HR without inhibiting cardiac function, and HR optimization by landiolol in combination with milrinone restores “Y” to “X.” If landiolol slowed HR while inhibiting cardiac function, the LV end-diastolic pressure would be increased and SVI would be decreased.

Second, slowing the HR improves the contractile property on the force-frequency relationship curve in ADHF with rapid AF [11]. It has also been reported that the force-frequency relationship curve decreases at higher HRs in failing hearts, suggesting that there may be a detrimental effect on contractility at higher HRs [11]. Therefore, the addition of low-dose landiolol, which prevents myocardial damage, intracellular Ca²⁺ overload, and deterioration in hemodynamics due to tachycardia, may be a cardioprotective therapy in patients with ADHF.

Third, low-dose landiolol ameliorates intracellular Ca²⁺ handling abnormality in HF [4], irrespective of HR. Recently, we reported that: (i) landiolol inhibits Ca²⁺ leakage from failing RyR2 even at a low dose that did not suppress cardiomyocyte function, and (ii) milrinone treatment enhances Ca²⁺ leakage from failing RyR2, while adding low-dose landiolol to milrinone suppresses this milrinone-induced Ca²⁺ leakage, leading to greater improvement in cardiomyocyte function [4]. Additionally,

Fig. 1. Hemodynamic profiles of ADHF patients with reduced LVEF and rapid AF. **a** Changes in each hemodynamic parameter at the time of admission (baseline), pre-milrinone, post-milrinone (no landiolol), and during milrinone plus various doses of landiolol ($0-6 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$). All patients were first treated with milrinone, diuretics, and vasodilators, and then various doses of landiolol were added in a step-wise manner. **b** Changes of hemodynamic parameters between milrinone monotherapy and milrinone with $1.5 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$ of landiolol. Bars indicate the mean $\pm$ standard error. * $p < 0.01$. The Wilcoxon signed-rank test was used to compare hemodynamic changes between 0 and $1.5 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$ of landiolol. **c** Underlying mechanism for optimal reduction of HR and restoration of LV incomplete relaxation. The LV pressure-volume loop ("X") is shifted to "Y" when rapid AF is complicated in patients with heart failure and reduced E-max, who are treated with milrinone. "Y" is characterized by a decreased stroke volume and increased diastolic pressure, which is attributable to incomplete LV relaxation. HR optimization by landiolol in combination with milrinone restores "Y" to "X." Data are given as the mean $\pm$ standard error. * $p < 0.01$ versus milrinone therapy (at $0 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$ landiolol). Base, baseline; Pre-Mil, pre-milrinone; HR, heart rate; BPs, systolic arterial pressure; CI, cardiac index; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; mRAP, mean right atrial pressure; SVI, stroke volume index; SvO_2 , oxygen saturation of mixed venous blood; LV, left ventricle; E-max (maximum elastance), the slope of the end-systolic pressure-volume relation, representing an index of LV contractility; SV, stroke volume.

(Figure continued on next page.)

inotropes, such as milrinone or catecholamines, enhance diastolic Ca^{2+} leakage through RyR2, thereby resulting in lethal arrhythmias, such as ventricular tachycardia, due to delayed after depolarization [4, 12]. Therefore, low-dose landiolol in combination with milrinone may possess a significant advantage in preventing lethal arrhythmias in patients with acute HF.

ADHF patients with normal BP and CI should not easily be given inotropes. Inotropes do not improve the short- and long-term prognosis in ADHF, and can cause adverse effects such as lethal arrhythmia [13]. The 9 patients enrolled in the present study had a clinical profile of "cold and wet" according to the Nohria-Stevenson classification. In addition, as shown in Table 1, 7 patients

(case No. 1, 2, 3, 4, 5, 7, and 9) had Forrester subset IV baseline hemodynamics and 2 (case No. 6 and 8) had Forrester subset II that was equivalent to Forrester subset IV because of a very low SVI (14.7 mL/m² in case 6 and 17.3 mL/m² in case 8), even if their CI was more than 2.2 L/min/m². For peripheral circulatory failure, milrinone was co-administered, and landiolol titration was carried out because of the lack of decrease in HR. Taking advantage of this ultra-short-acting β 1-blocker, we clarified the beneficial effect of a low dose of landiolol, which has potent negative chronotropism but no negative inotropism, on hemodynamic changes (increased SVI and decreased PCWP).

Decongestion by diuretics is important for the treatment of ADHF with volume overload (high RAP), and successful decongestion generally improves hemodynamics (RAP, PCWP), and subsequently lowers the HR. However, in the present study, although diuretics, vasodilators, and then milrinone were added over more than 4 h, the HR did not decrease at all during these treatments. Although the duration of the initial treatment prior to landiolol administration might have been insufficient, RAP and PCWP prior to landiolol significantly decreased compared to the baseline (change of PCWP -5.4 ± 4.2 mm Hg; change of RAP -4.4 ± 5.0 mm Hg, respectively; Table 2). Based on these results, the very low stroke

volume due to severe LV dysfunction may explain why the HR did not decrease.

Regarding whether milrinone itself increased the HRs (adverse effect), there were no differences observed before and after administration (pre-milrinone 138.4 ± 17.9 bpm vs. post-milrinone [no landiolol] 140.1 ± 16.5 bpm, $p = \text{ns}$), as shown in Figure 1a. In addition, the doses of infused milrinone ($0.25 \pm 0.10 \mu\text{g}/\text{kg}^{-1}/\text{min}^{-1}$) were low in all cases. Based on these findings, we believe that the effect of milrinone on HR is not significant, while low output syndrome is central to the increased HR.

Finally, on the basis of evidence from trials [14], digitalis and amiodarone are recommended for acute HR reduction in ADHF patients with rapid AF, while intravenous β -blockers and non-dihydropyridine calcium-channel antagonists are not recommended because of their negative inotropic effect. However, low-dose landiolol, which has strong negative chronotropism but no negative inotropism, was shown to be useful and safe for HR control [4, 6–8, 15]. Therefore, in patients with severe ADHF and rapid AF ($\text{HR} \geq 120$ bpm), low-dose landiolol may be an alternative first-line therapy to intravenous digitalis and amiodarone, or an additional second-line therapy in ADHF patients with rapid AF refractory to intravenous digitalis or amiodarone administration. In addition, low-dose short-acting β -blockers may also be useful as a bridge to starting oral β -blockers in hemodynamically stable, hospitalized HF patients.

Limitations

There are several limitations to the present study. First, further clinical studies will help to conclusively demonstrate the effectiveness and safety of low-dose landiolol and the described treatment strategy since the patient population in the present study was small. In the present study, taking advantage of this ultra-short-acting β 1-blocker, we diligently and precisely examined the effect of a low dose of landiolol on hemodynamic changes by quick titration. Second, there are no parallel control data

of patients that received no therapy or active controls. Third, although we proposed that HR reduction by the addition of a low-dose landiolol to milrinone therapy has a critical role in improving LV relaxation impairment, as suggested by the shifts in the LV P-V loops in the present study, we could not calculate E-max. However, upon the addition of a low dose of landiolol to milrinone, SVI significantly increased and PCWP significantly decreased despite HR reduction. This mechanism might be attributable to the multiple effects of β -blockers (e.g., correction of intracellular Ca^{2+} handling abnormality, improvements in LV relaxation and myocardial O_2 consumption, as well as the force-frequency relationship of HR reduction).

Conclusions

The addition of landiolol at doses of $<3.0 \mu\text{g}/\text{kg}/\text{min}$ to milrinone improved cardiac function in ADHF with rapid AF by selectively reducing HR.

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Disclosure Statement

The authors declare no competing financial interests.

Statement of Ethics

The Institutional Review Board of Yamaguchi University Hospital approved this protocol (No. H19-87), and all patients provided written informed consent.

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