Low-Dose β -Blocker in Combination With Milrinone Safely Improves Cardiac Function and Eliminates Pulsus Alternans in Patients With Acute Decompensated Heart Failure

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Background: The purpose of this study was to determine whether a low-dose β -blocker, in combination with milrinone, improves cardiac function in acute decompensated heart failure (ADHF) with tachycardia.

Methods and Results: Twenty ADHF patients (New York Heart Association classification III, n=1, and IV, n=19; heart rate [HR], 107 ± 12 beats/min; left ventricular ejection fraction, $24 \pm 7\%$; cardiac index [CI], 2.2 ± 0.6 L $\cdot$ min $^{-1}$ $\cdot$ m $^{-2}$; pulmonary capillary wedge pressure [PCWP], 26 ± 8 mmHg) were enrolled in this study. The patients first underwent conventional therapy with milrinone, vasodilators and diuretics; landiolol (1.5 – 6.0 μ g $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$; i.v.), which is an ultra-short-acting β_1 -selective blocker, was then added to the treatment regimen to study its effect on hemodynamics. Low-dose landiolol (1.5 μ g $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$) significantly reduced HR by 11% without changing blood pressure (BP) and CI, whereas higher doses (≥ 3.0 μ g $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$) tended to decrease BP and CI while increasing PCWP and systemic vascular resistance. After treatment with landiolol (1.5 μ g $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$), hemodynamic parameters such as PCWP, stroke volume index, SvO $_2$, rate pressure product, filling time/RR, E/e', and Tei index were significantly improved.

Conclusions: A low-dose β -blocker in combination with milrinone improved cardiac function in ADHF patients with tachycardia; therefore, it may be considered as an adjunct therapy for use when standard therapy with milrinone is not effective at slowing HR. (*Circ J* 2012; **76**: 1646–1653)

Key Words: Acute decompensated heart failure; Betas-blocker; Inotropic agents; Tachycardia

The use of β -blockers in combination with inotropic agents to treat acute decompensated heart failure (ADHF) is controversial. Short-term studies using β -blockers to treat ADHF have not produced positive results. Low-dose β -blockers, however, which have modest negative chronotropic (but less negative inotropic) effects, are thought to improve cardiac function by decreasing myocardial oxygen demand and improving ventricular diastolic filling in patients with ADHF.¹

ing symptoms and improving endo-organ perfusion.^{2,3} In these circumstances, the most commonly used inotropes include the β -adrenergic agonists dopamine and dobutamine, and the phosphodiesterase inhibitor milrinone.^{2–5} Several studies have suggested that patients on chronic β -adrenergic blockade respond better to milrinone than to dobutamine, if they require inotropes.^{6–10} Furthermore, Gattis et al suggested that concomitant therapy with a β -blocker and milrinone did not worsen the outcomes of patients who were admitted for acute exacerbation of heart failure and who required inotrope therapy.^{8–13}

The reason that co-administration of milrinone is better than dobutamine for hemodynamic improvement may be due to their different modes of action. A β -blocker blunts the hemodynamic improvements induced by dobutamine by competi-

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Short-term inotropic therapy may be beneficial to those ADHF patients corresponding to Forrester subset IV, by reduc-

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Figure 1. Hemodynamic profiles of acute decompensated heart failure patients at the time of admission and during landiolol treatment. (A) Study protocol. (B) Change in each hemodynamic parameter at the time of admission and after various doses of landiolol (0–6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). All patients were first treated with milrinone, diuretics, and vasodilators. Data given as mean $\pm$ SE; (n), number of patients. BPs, systolic arterial pressure; CI, cardiac index; HR, heart rate; IABP, intra-aortic balloon pump; PAP, pulmonary arterial pressure; PAR, pulmonary arterial resistance; PCPS, percutaneous cardiopulmonary support system; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SVR, systemic vascular resistance; RPP, rate pressure product (HR $\times$ BPs); SVI, stroke volume index; SvO₂, oxygen saturation of mixed venous blood. #P<0.01 vs. admission; *P<0.01 vs. no landiolol.

Table. Baseline ADHF Patient Characteristics

Age (years)	56.2±17.8
Gender (M/F)	11/9
Diagnosis	
Non-ischemic CM	13 (65)
Ischemic CM	7 (35)
NYHA functional class	
Class III	1 (5)
Class IV	19 (95)
Heart rate (beats/min)	107.4±12.3
SBP (mmHg)	121.5±32.6
DBP (mmHg)	77.8±22.3
Sinus rhythm	20 (100)
Pulsus alternans	10 (50)
Blood examination	
Serum creatinine (mg/ml)	0.86±0.47
eGFR (ml·min ⁻¹ ·1.73 m ⁻²)	83.8±33.7
BNP (pg/ml)	831.3±679.4
Echocardiography	
LVDd (mm)	60.7±11.8
LVDs (mm)	51.7±12.3
LVEF (%)	23.8±7.2
MR ≥III	0 (0)
AR ≥III	0 (0)
Swan-Ganz data	
mAP (mmHg)	91.4±23.2
PCWP (mmHg)	26.3±8.2
CI (L·min ⁻¹ ·m ⁻²)	2.2±0.6
mPAP (mmHg)	37.9±11.1
mRAP (mmHg)	10.3±5.4
SVR (dyn·s·cm ⁻⁵)	1,842.8±780.3
PAR (dyn·s·cm ⁻⁵)	202.4±156.4
Concomitant therapy	
Furosemide	18 (90)
Spironolactone	1 (5)
Nitroglycerine	8 (40)
Nitroprusside	3 (15)
Carperitide	13 (65)
Nicorandil	2 (10)
Digoxin	0 (0)
Noradrenaline	0 (0)
Milrinone	20 (100)
Enalapril 2.5 mg/day	2 (10)
Carvedilol 3.125 mg/day	4 (20)

Data given as n (%) or mean±SD.

ADHF, acute decompensated heart failure; NYHA, New York Heart Association; PAR, pulmonary arterial resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; SVR, systemic vascular resistance.

tively binding to β -adrenergic receptors. In contrast, phosphodiesterase III inhibitors (ie, milrinone and enoximone), which are positive inotropic agents that increase the concentration of cyclic adenosine monophosphate in cardiac muscle, do not interfere with the effects of β -blockers during concomitant therapy.^{14–16}

Landirolol (ONOACT; Ono Pharmaceutical, Osaka, Japan) is

an ultra-short-acting i.v. β_1 -selective adrenergic receptor blocker, similar to esmolol. The important difference between the drugs is that landiolol has a greater chronotropic effect and a lesser inotropic effect than esmolol, as previously reported.^{17–19} Tachycardia worsens cardiac performance in ADHF patients with severe left ventricular (LV) dysfunction due to a decrease in diastolic filling and an increase in myocardial oxygen demand. Therefore, it is very important to decrease heart rate (HR) without inhibiting cardiac function. Here, we investigated whether landiolol, in combination with milrinone, safely improves cardiac function in ADHF patients with severe LV dysfunction and tachycardia.

Methods

This prospective study was conducted in the cardiac intensive care unit at Yamaguchi University Hospital (Ube, Japan) between 1 April 2009 and 30 June 2011. The inclusion criteria for patients included ADHF with both depressed LV function (ejection fraction ≤ 0.35) and HR >90 beats/min with sinus rhythm, not receiving i.v. inotropes, and the absence of specific devices (intra-aortic balloon pump or percutaneous cardiopulmonary support system) on admission. In addition, tachycardia (HR >90 beats/min) must have continued for ≥ 4 h after standard treatment with diuretics, vasodilators, and milrinone. The exclusion criteria were systolic blood pressure (BP) <80 mmHg, treatment with oral β -blockers (at a dose ≥ 5 mg of carvedilol or 2.5 mg of bisoprolol), acute coronary syndrome, severe valvular heart disease (ie, mitral regurgitation $\geq$ III and aortic regurgitation $\geq$ III), severe pulmonary disease, and severe renal disease. The institutional review board of Yamaguchi University Hospital approved this study, and all patients provided written, informed consent before participating in the study.

The 20 patients in the study underwent continuous electrocardiographic and invasive hemodynamic monitoring with a Swan-Ganz catheter and an arterial catheter. At the time of admission, their baseline HR, BP, electrocardiographic findings, and cardiac hemodynamic variables, including the filling time/RR ratio, the ratio of mitral inflow early diastolic velocity to peak early diastolic mitral annular velocity (E/e'), and Tei index were recorded. These variables were measured as the mean of 10 or 20 beats in the absence or presence of pulsus alternans, respectively. When the hemodynamic parameters plateaued, during continuous monitoring, ≥ 4 h after conventional therapy with milrinone (0.25 – $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), vasodilators, and diuretics, the hemodynamics were measured. Landiolol (1.5 – $6.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; i.v.) was then given to study its effect on the hemodynamic variables (Figure 1A). Landiolol is an ultra-short-acting (elimination $t_{1/2}$: 4 min) i.v. β -adrenergic receptor blocker that has a high β_1 -selectivity ($\beta_1/\beta_2=255$). Due to its ultra-short duration of activity,^{17–19} the acute hemodynamic changes were measurable immediately. In the ADHF patients, a safe and effective dosage of landiolol was established by increasing the dosage by $1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ every hour for 4 h (Figure 1A); HR, BP, and cardiac hemodynamic variables were recorded after each increase in dosage. When a $>20\%$ decrease in systolic BP, or systolic BP drop to below 80 mmHg, was induced, further landiolol dosage increases were halted. The primary endpoint of this study was the change in hemodynamic variables after landiolol was given. All echocardiography data were collected by an experienced echocardiographer who was blinded to the patients in the study.

Adverse Events and Clinical Outcome

Any adverse event that occurred during landiolol infusion, such as hypotension (defined as systolic arterial pressure <60 mmHg), angina, electrocardiographic evidence of ischemia, acute renal failure, dyspnea, or arrhythmia, was recorded. The clinical outcome for each patient was also recorded.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD or SE, and categorical variables are expressed as percentages. Comparisons between 2 groups were performed using Student's t-test. A chi-squared test was used to compare prevalence or frequencies. Wilcoxon's signed-rank test was used to analyze paired differences, and Wilcoxon's rank-sum test was used to evaluate the dose dependence of landiolol on hemodynamics in the clinical study. All analyses were performed using SPSS16.0J (SPSS Japan, Tokyo, Japan). $P<0.05$ was considered statistically significant.

Results

Patient Characteristics

The baseline characteristics of the 20 patients are listed in [Table](#). Thirteen patients were diagnosed with non-ischemic dilated cardiomyopathy and 7 were diagnosed with ischemic cardiomyopathy. In addition, the clinical severity of heart failure in all patients was $\geq$ New York Heart Association (NYHA) classification III (1 patient was class III; 19 patients were class IV). The mean LV end-diastolic dimension and mean LV ejection fraction were 61 mm and 24%, respectively. The mean HR was 107 beats/min, mean cardiac index (CI) was $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, and the mean pulmonary capillary wedge pressure (PCWP) was 26 mmHg.

Dose-Dependent Effect of Landiolol on Hemodynamics

As shown in [Figure 1B](#), the hemodynamics of ADHF patients

improved significantly after conventional treatment with milrinone, vasodilators, and diuretics (eg, CI 2.2 to $3.1 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$; PCWP, 26 to 16 mmHg), while the average HR and arterial pressures decreased with landiolol treatment in a dose-dependent manner. Notably, after infusing $1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ landiolol, the mean HR decreased by 11% ($P<0.001$ vs. baseline), without changes in BP and CI. At this dose of landiolol, PCWP was also significantly decreased. Infusing $\geq 3.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ landiolol, however, tended to decrease CI and systolic arterial pressure and increase systemic vascular resistance and pulmonary arterial resistance. In addition, because a $>20\%$ decrease in systolic BP occurred following infusion of $\geq 3.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ landiolol, the aforementioned hemodynamic parameters were not able to be measured in all cases. On the basis of these results, $1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ landiolol was defined as the low dose. As shown in [Figure 1B](#), low-dose landiolol increased the O_2 saturation of mixed venous blood (SvO_2) and stroke volume index significantly more than conventional therapy (milrinone, vasodilators, and diuretics). In addition, a low dose of landiolol significantly increased the filling times/RR and decreased the Tei indices and E/e' ratios ([Figure 2](#)), which suggested that a low-dose β -blocker in combination with milrinone improves both systolic and diastolic functions. The transmitral flow pattern was described as a summation pattern in all 20 cases before use of landiolol. Treatment with low-dose landiolol, however, resulted in the change of the transmitral flow pattern in some patients; it changed to a restrictive pattern in 2 cases and to an abnormal relaxation pattern in 1 case ([Figure 3A](#)). In 10 patients, pulsus alternans was observed before the addition of low-dose landiolol to the conventional therapy. Surprisingly, in all cases, low-dose landiolol eliminated the pulsus alternans ([Figure 3B](#)). A representative case is shown in [Figure 4](#).

Adverse Events and Clinical Outcome

In this clinical study, landiolol was well tolerated, without any adverse events. In all 20 patients, i.v. infusion of landiolol was

Figure 3. Effect of adding a low-dose β -blocker to milrinone treatment on transmitral flow patterns and pulsus alternans. (**A**) Doppler transmitral flow pattern and left ventricle (LV) outflow before and after the addition of low-dose landiolol in a representative case. A 71-year-old woman was admitted to hospital due to acute exacerbation of chronic heart failure. The transmitral flow pattern dramatically changed from a summation pattern to an abnormal relaxation pattern and the alteration of LV outflow, which represented pulsus alternans, disappeared upon adding low-dose landiolol to conventional therapy with vasodilators, diuretics, and milrinone. (**B**) Prevalence of pulsus alternans in the present 20 patients before and after the addition of low-dose landiolol.

replaced by oral β -blocker (carvedilol or bisoprolol) within 1 week (mean landiolol treatment duration was 5 ± 2 days). The usage of landiolol overlapped with that of the oral β -blocker for 2 days. The overall rate of survival was 100% for ≤ 30 days; 1 patient died of multi-organ failure on hospital day 40.

Discussion

The most important results from this clinical study are that (1) a low-dose β_1 -blocker, in combination with milrinone, rapidly improved the cardiac function of ADHF patients with tachycardia; and (2) low-dose landiolol eliminated pulsus alternans

Figure 4. Effect of low-dose landiolol on clinical status and hemodynamics in a representative case. A 26-year-old man was admitted to hospital due to acute exacerbation of chronic heart failure. On admission, the severity of heart failure was New York Heart Association class IV, and echocardiography (ECG) showed that the left ventricular end-diastolic dimension was 75 mm and the left ventricular ejection fraction was 25%. Despite conventional therapy with milrinone, carperitide, and diuretics, pulsus alternans, symptoms of heart failure (palpitation, dyspnea and cold sweating), sinus tachycardia (heart rate [HR], 125 beats/min) did not improve. Upon addition of $1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ landiolol to the conventional therapy, pulsus alternans disappeared and the cardiac index (CI) increased a little instead of a large decrease in HR. Surprisingly, symptoms of heart failure also diminished during infusion of low-dose landiolol between 1.5 and $3.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. As soon as the infusion stopped, however, increased HR and decreased CI resulted, leading to pulsus alternans and symptoms of heart failure, which were reproducibly eliminated by re-starting the infusion of low-dose landiolol.

Figure 5. Proposed treatment strategy with low-dose β -blocker in acute decompensated heart failure with tachycardia. CI, cardiac index; PCWP, pulmonary capillary wedge pressure.

in these patients. The putative mechanism by which the addition of a low-dose β -blocker to milrinone improves cardiac function is through slowing of the HR, which improves diastolic filling and decreases the myocardial oxygen demand.¹ The cardioprotective effect of the β -blocker is also thought to contribute to the improvement in hemodynamics. Severe LV dysfunction causes tachycardia as a result of intrinsic neurohormonal activation and, in turn, tachycardia worsens cardiac dysfunction. The severe LV dysfunction, tachycardia and neurohumoral activation, which induce necrosis, apoptosis, and abnormal intracellular Ca^{2+} handling through the elevation of oxidative stress in failing cardiomyocytes, led to cardiomyocyte loss and a deteriorating prognosis.^{20–24} 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.^{25,26} Therefore, the addition of low-dose β -blockers, which prevent myocardial damage, intracellular Ca^{2+} overload, and deterioration in hemodynamics due to tachycardia, may be a cardioprotective therapy in patients with ADHF.

This is the first report of the addition of a low-dose β -blocker, in combination with milrinone treatment, successfully eliminating pulsus alternans in ADHF patients (Figures 3B and 4). Because pulsus alternans, a sign of severe heart failure, is more likely to occur at higher HR,^{27,28} the reduction in HR by a low-dose β -blocker may be associated with elimination of pulsus alternans. Although the mechanism is still poorly understood, several studies have shown that pulsus alternans results from abnormal intracellular calcium cycling, involving the sarcoplasmic reticulum.^{29,30} Thus, the mechanism by which treatment with a low-dose β -blocker and milrinone eliminates pulsus alternans may involve the correction of intracellular Ca^{2+} handling during heart failure,^{31,32} in addition to the reduction in HR.

The subjects studied were ADHF patients with severe LV dysfunction and tachycardia, corresponding to NYHA subset 4, and whose HRs did not decrease (HR >90 beats/min) after ≥ 4 h of standard treatment with diuretics, vasodilators, and milrinone. Figure 1B shows that there was no difference between HR on admission and after conventional therapy with milrinone. The pathophysiology in these patients may be explained as follows: tachycardia was caused as a compensation for low output due to severe LV dysfunction. In turn, this continuous tachycardia worsened cardiac function. Thus, a vicious circle was formed from LV dysfunction and tachycardia. In these circumstances, therefore, an inotrope such as milrinone is needed and, if the HR does not decrease, low-dose landiolol is effective for the treatment of heart failure.

Finally, a treatment strategy for ADHF patients with severe LV dysfunction and tachycardia is presented in Figure 5. These patients, corresponding to Forrester subset IV, are recommended to first receive conventional treatment that includes diuretics, vasodilators, and milrinone. In cases in which heart failure is refractory to these conventional treatments (ie, a slowing of the HR is not observed), a low dose of landiolol should be considered as standard adjunct therapy.

Study Limitations

Further clinical studies are warranted to conclusively demonstrate the effectiveness and safety of low-dose β -blockers in the described treatment strategy because the number of patients in the present study was small. A landiolol-free control group may be needed in such studies in order to clarify whether the addition of low-dose landiolol to standard treatment with milrinone is responsible for the improved cardiac function.

Conclusions

The addition of a low-dose β -blocker to conventional milrinone therapy safely improves cardiac function in ADHF patients with tachycardia and completely eliminates pulsus alternans.

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