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ORIGINAL ARTICLE
Heart Failure

Urgent Control of Rapid Atrial Fibrillation by Landiolol in Patients With Acute Decompensated Heart Failure With Severely Reduced Ejection Fraction

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Background: We investigated the clinical usefulness of landiolol for rapid atrial fibrillation (AF) in patients with acute decompensated heart failure (ADHF) and identify the patients eligible for landiolol.

Methods and Results: A total of 101 ADHF patients with reduced ejection fraction (HFrEF) with rapid AF were enrolled. Immediately after admission, an initial dose of landiolol was given (1 μg/kg^{-1}/min^{-1}), and then the dose was increased to decrease heart rate (HR) to <110 beats/min and change HR (ΔHR) >20% in ≤24 h. Thirty-seven were monitored using right heart catheterization at 3 points (baseline, 1 μg/kg^{-1}/min^{-1}, and maximum dose). We checked the major adverse events (MAE) during initial hospitalization, which included cardiac death, HF prolongation (required i.v. treatment at 30 days), and worsening renal function. The average maximum dose of landiolol was 3.8±2.3 μg/kg^{-1}/min^{-1}. HR ($P<0.0001$) and pulmonary capillary wedge pressure ($P=0.0008$) decreased safely. MAE occurred in 39 patients. The patients with left ventricular (LV) end-diastolic volume index <84.0 mL/m^2 and mean blood pressure (mean BP) >97 mmHg had less frequent MAE ($P<0.0001$).

Conclusions: Landiolol was effective for safely controlling rapid AF in patients with HFrEF with ADHF, leading to hemodynamic improvement and avoidance of short-term MAE, especially in patients with relatively smaller LV and higher BP.

Key Words: Atrial fibrillation; Beta-blocker; Echocardiography; Heart failure; Prognosis

The number of people with atrial fibrillation (AF) has been increasing, and AF is associated with the deterioration of left ventricular (LV) systolic and diastolic function in patients with heart failure (HF).[1] The interaction between HF and AF is increased through the action of mechanisms such as the rate-dependent deterioration of cardiac function, fibrosis, and the activation of neurohumoral vasoconstrictors. AF can worsen cardiac symptoms in patients with HF, mainly due to the elevation of pulmonary capillary wedge pressure (PCWP). Conversely, worsening HF can promote a rapid ventricular response in AF,[2] further increasing the risk of HF.[3] Low-dose β-blockers, which have mild negative chronotropic effects and less negative inotropic effects, are thought to improve cardiac function by decreasing myocardial oxygen demand and improving ventricular diastolic filling in patients with acute decompensated HF (ADHF).[4]

Landiolol (Onoact; Ono Pharmaceutical, Osaka, Japan) is an ultra-short-acting β1-selective adrenergic receptor blocker, similar to esmolol. These 2 β-blocking drugs, however, have a key difference: landiolol has a greater chronotropic effect and a lesser inotropic effect than esmolol.[5–7] Tachycardia worsens cardiac performance in ADHF patients with LV dysfunction because of a decrease in diastolic filling and an increase in myocardial oxygen demand. The J-LAND study, which was a prospective randomized trial for ADHF (with rapid AF), showed that landiolol is more effective than digoxin in controlling rapid heart rate (HR) in AF patients with HF with reduced ejection fraction (HFrEF; LVEF 20–50%), and that it could be considered as a therapeutic option in clinical settings.[8]

In reference to critical patient condition and prognosis,

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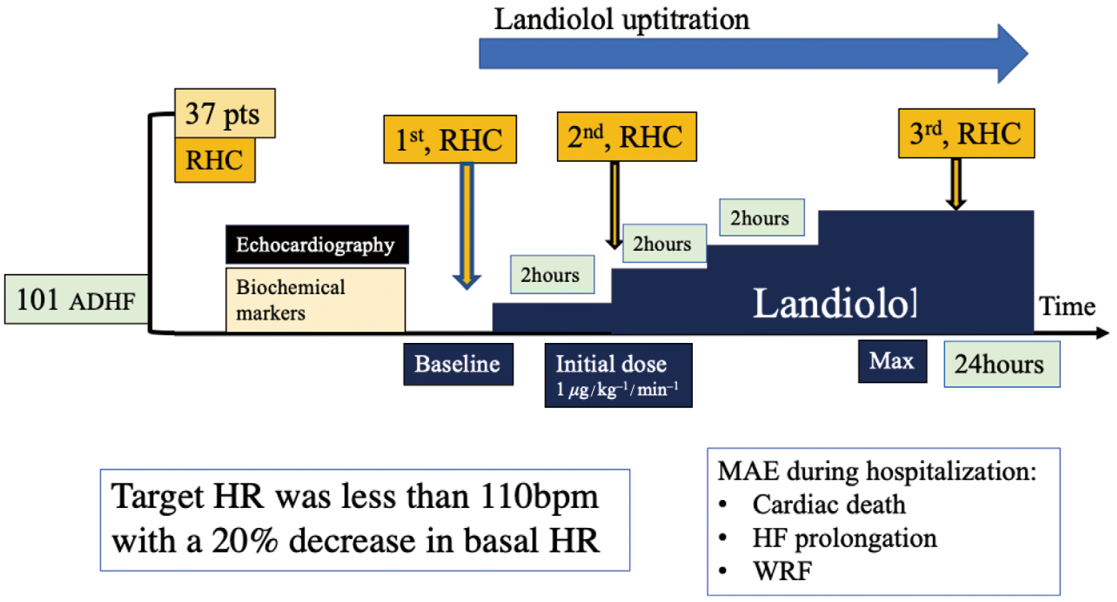


Figure 1. Study protocol. A total of 101 patients underwent landiolol treatment with continuous electrocardiographic monitoring. All 101 patients underwent echocardiographic evaluation and were checked and biochemical marker before starting treatment. The initial dose was 1 μg/kg^{-1}/min^{-1} titrated to a maximum dose of 10 μg/kg^{-1}/min^{-1} every 2 h according to the patient's condition. The target HR was 110 beats/min and 20% reduction in HR from the baseline. All the patients' HR and blood pressure (37 patients underwent RHC monitoring) were measured at baseline, initial dose, and maximum dose. ADHF, acute decompensated heart failure; HF, heart failure; HR, heart rate; MAE, major adverse events; RHC, right heart catheterization; WRF, worsening renal function.

however, rapid HR control remains controversial.[9,10] Beta-blockers have a negative inotropic effect and a risk of adverse effects in ADHF cases. PCWP usually enables physicians to evaluate the degree of congestion.[11] Therefore, we think that the examination of any change in PCWP after landiolol treatment is valuable, given that it can affect prognosis. The purpose of this study was therefore to identify the patients eligible for this treatment by simple methods through the assessment of prognosis. Furthermore, we examined the effect of the decrease in HR by landiolol treatment in HFrEF patients with ADHF.

Methods

This study was designed as a prospective, single-center study of the effectiveness of landiolol for controlling tachycardia in patients with AF and LV systolic dysfunction partly using right heart catheterization (RHC). The study was conducted at the Yokohama City University Medical Center in Japan between November 2013 and December 2017. The main inclusion criteria were as follows: male or female inpatients ≥20 years of age, New York Heart Association (NYHA) class IV, and AF with an LV ejection fraction (LVEF) <40% and HR >120 beats/min.

The main exclusion criteria were: necessity for electrical cardioversion; serious valve stenosis; implantable cardiac pacemaker and/or implantable defibrillator; necessity for mechanical ventilation; and cardiogenic shock (systolic blood pressure [BP] <90 mmHg). Atrial flutter was excluded from this study.[12] HR was calculated as an average through continuous monitoring for 60 s. Vital signs (BP, HR), blood test, electrocardiogram, chest radiograph, and echocardiogram were evaluated prior to the first landiolol treatment. A total of 101 patients were included in this study, and their biochemistry markers and echocardiography status were checked using vital signs. Of these, 37 patients were evaluated using RHC. Excepting emergency situations, anti-arrhythmic drugs, sympathomimetic drugs, defibrillator usage, and catheter ablation were prohibited until all observations were completed at 24 h after the start of landiolol treatment. Clinical scenario classification[13] and Nohria-Stevenson profiles[14] were used to estimate patient status. Informed consent was acquired from all patients before beginning landiolol treatment. The study protocol was approved by the Institutional Review Board of the Yokohama City University Medical Center, and the study was conducted in accordance with the Declaration of Helsinki (UMIN000020084).

Study Protocol

Figure 1 shows the study protocol. One hundred and one patients underwent landiolol treatment, to explore the role of landiolol to improve the short term prognosis. Of these, 37 patients were treated via RHC monitoring (RHC group) and 64 patients were treated without RHC monitoring (no-RHC group). RHC monitoring was performed based on the clinician's decision. At the time of admission, all the patients underwent echocardiography, and baseline HR, BP, and biochemistry markers were recorded. Non-invasive hemodynamic monitoring was performed prior to treatment with landiolol (baseline), at a dose of 1 μg/kg^{-1}/min^{-1} (initial dose); and following the maximum dosage (maximum dose). In the RHC group, invasive monitoring using RHC was also performed at baseline, at the initial dose, and at the maximum dose. Patients were continuously monitored on telemetry for up to 7 days following the initial landiolol

treatment. In patients receiving landiolol, continuous i.v. treatment was begun at the initial dose and titrated to the maximum dose of 10 μg/kg^{-1}/min^{-1} as determined by individual patient condition every 2 h. The target HR was <110 beats/min with a 20% decrease in basal HR, which is close to the current guidelines.[9] The initial dose level was maintained for 2 h to examine the effects of the minimum dose, after which point the dose level was titrated up to the maximum dose based on the patient's individual needs. These patients received a follow-up after 30 days of the hospitalization, and adverse events were examined. We showed the baseline indexes between the RHC group and non-RHC group.

Echocardiography

Baseline echocardiography was performed by experienced physicians (N.I., H.T.) using a commercially available ultrasound machine (Vivid q; GE Vingmed, Horten, Norway) and analyzed using EchoPAC PC. Measurements and recordings were obtained according to the American Society of Echocardiography recommendations.[15–17] Five consecutive cycles were calculated, and all values were averaged to obtain accurate values. The LV end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), and LVEF were obtained with the biplane modified Simpson method. Left atrial volume index was also calculated. The E (early diastolic) wave of transmitral flow was obtained. Early diastolic wave velocity (e') on tissue Doppler imaging at the mitral annulus was obtained, and then we calculated the ratio of mitral inflow early diastolic velocity to peak early diastolic mitral annular velocity (E/e'). The LV outflow tract (LVOT) velocity time integral (VTI) was calculated on pulse wave Doppler in the apical long axis view, which provides information regarding stroke volume (SV). Mitral regurgitation (MR) was graded by color Doppler as trivial, mild, moderate and severe. The diameter of the inferior vena cava (IVC) was measured.

Biochemistry Markers

Baseline blood test was used to assess cardiac function via brain natriuretic peptide level, as well as renal function via the estimated glomerular filtration rate (eGFR), which was calculated using creatinine level.

RHC

A total of 37 patients underwent RHC via the right internal jugular vein immediately following admission to the cardiac care unit and as part of the baseline, initial dose and maximum dose assessments of this study. Values were recorded for mean PCWP, mean right atrial pressure (RAP), systolic pulmonary artery pressure (PAP), mean PAP, and diastolic PAP. An estimate of cardiac output (CO) was created from the mean of 5 thermodilution curves after the rapid injection of 10 mL cool saline. Mixed venous oxygen saturation (SvO_2) was measured on blood gas analysis of PAP. BP was measured simultaneously with the RHC. The following formulas were used to calculate the standard hemodynamic parameters derived from the aforementioned measurements: cardiac index (CI)=CO/body surface area; systemic vascular resistance index (SVRI)=(mean BP−mean RAP)×80CI. When the dose of landiolol was added, cardiac power output (CPO), measured in watts, was calculated as mean BP×CO/451, where the mean BP=[(systolic BP−diastolic BP)/3]+diastolic BP. RHC implantation was started after confirming the patient's safety. We calculated the absolute change (Δ) of HR, BP, PCWP, and SV between baseline data and 24 h after landiolol.

Safety Assessments/Side-Effects of Landiolol

Patients were assessed for adverse reactions to landiolol treatment, including atrioventricular block, bronchospasm, asystole, bradycardia with cardiac symptoms requiring a pacemaker,[18] or HR <50 beats/min, severe hypotension (systolic BP <80 mmHg), and worsening symptoms of HF.

Adverse Events

During hospitalization, each patient was examined for major adverse events (MAE), including cardiac death and prolonged HF requiring hospitalization at 30 days. Furthermore, worsening renal function (WRF) was an important endpoint,[17] defined as change in serum creatinine ≥0.3 mg/mL during the first 5 days.[19] For patients experiencing more than 1 acute event, only the first event was considered in the analysis of MAE.

Statistical Analysis

Data are expressed as mean±SD or percentage of patients or median (IQR) according to distribution. Student's t-test and chi-squared test or Wilcoxon-Mann-Whitney U-test were used to compare the means and percentages, respectively, between the 2 groups. The changes (pretreatment, 1 μg/kg^{-1}/min^{-1}, and maximum dose) in HR/BP and the parameters of RHC after starting landiolol were compared using analysis of variance (ANOVA). The following covariance structures were considered: unstructured, compound symmetrical, first-order autoregressive, and Toeplitz. The patients were divided into 2 groups according to RHC status. Based on the cut-off value of median values, we analyzed the indexes to administer landiolol by the presence of MAE or not, and analyzed to detect the proportion for the groups divided by mean BP and LVEDVI using the Fisher's exact test. Potential independent predictors were identified on logistic regression analysis. All univariate predictors were then entered into a backward elimination, multiple logistic regression analysis, with entry and retention set at a significance level of $P<0.05$. Parameters with 2-sided $P<0.05$ were considered statistically significant. All analyses were performed using JMP Pro version 12.0 (SAS Institute, Cary, NC, USA).

Results

Patient Disposition and Baseline Characteristics

Table 1 lists the patient characteristics of all 101 patients, and according to RHC status. The average maximum dose of landiolol was 3.8±2.3 μg/kg^{-1}/min^{-1}.

Of the 101 patients, 95 (94%) achieved target HR in ≤24 h. In the RHC group, 34 patients (92%) achieved target HR, and 61 patients (95%) achieved target HR in the no-RHC group in ≤24 h.

Safety

No serious side-effects including bradycardia and severe hypotension were observed throughout the landiolol treatment.

MAE

Of the 101 patients, 3 patients (3%) died of HF during the initial hospitalization. HF prolongation and WRF occurred

Table 1. Baseline Patient Characteristics

	Total (n=101)	RHC (n=37)	No RHC (n=64)	P-value (RHC vs. No RHC)
Age (years)	73 (63–81)	67 (59–79)	75 (64–82)	0.14
Male	63 (62)	22 (61)	41 (63)	0.85
BSA (m^2)	1.62 (1.5–1.84)	1.63 (1.5–1.84)	1.63 (1.5–1.84)	0.66
Systolic BP (mmHg)	125 (114–144)	123 (116–147)	126 (113–144)	0.84
Diastolic BP (mmHg)	83 (67–98)	82 (63–97)	82 (69–101)	0.56
Mean BP (mmHg)	97 (82–115)	96 (81–113)	97 (82–115)	0.79
HR (beats/min)	140 (133–156)	142 (131–150)	140 (133–156)	0.59
Echocardiography				
LVEDVI (mL/m^2)	86 (66–107)	90 (68–107)	84 (63–100)	0.58
LVESVI (mL/m^2)	66 (50–82)	68 (50–82)	62 (48–80)	0.23
LVEF (%)	22 (18–32)	22 (16–28)	23 (18–28)	0.91
E-TMF (cm/s)	102 (85–121)	100 (83.5–120)	109 (85–131)	0.17
E/e'	23.3 (16.0–31.7)	23.5 (16.3–30.7)	23.4 (15.0–32.7)	0.97
LAVI (mL/m^2)	45 (35–52)	47 (37–62)	43 (34–49)	0.05
MR>moderate	35 (35)	11 (29)	24 (37)	0.27
IVC (mm)	22 (19–24)	22 (19–25)	22 (19–24)	0.79
LVOT-VTI (cm)	10.6 (8.0–13.1)	9.4 (7.6–12.3)	10.9 (8.2–13.9)	0.21
Clinical scenario				0.06
1	59 (58)	19 (52)	40 (61)	
2	31 (31)	9 (25)	22 (34)	
3	6 (6)	4 (11)	2 (3)	
4	5 (5)	4 (11)	1 (1)	
5	0 (0)	0 (0)	0 (0)	
Nohria-Stevenson				0.13
Warm and Wet	82 (81)	26 (75)	56 (86)	
Cold and Dry	1 (1)	1 (2)	0 (0)	
Cold and Wet	18 (17)	9 (25)	9 (14)	
Hypertension	69 (68)	28 (76)	41 (64)	0.22
Diabetes mellitus	34 (33)	14 (38)	20 (31)	0.49
Disease				0.94
Ischemic	20 (20)	7 (19)	13 (20)	
Non-ischemic	81 (80)	29 (81)	52 (80)	
βeta-blocker on admission	34 (20)	14 (38)	20 (31)	0.49
Inotropic agents	29 (29)	14 (38)	15 (24)	0.06
PDEIII inhibitor	27 (26)	13 (35)	14 (23)	0.06
Maximum landiolol dose ($\mu g/kg^{-1}/min^{-1}$)	3.8±2.3	3.9±2.4	3.7±2.2	0.72
No. patients with max dose ($\mu g/kg^{-1}/min^{-1}$)				0.50
1	10 (10)	2 (5)	8 (13)	
2	24 (24)	10 (27)	14 (22)	
3	24 (24)	11 (29)	13 (20)	
4	12 (12)	2 (5)	10 (15)	
5	16 (16)	7 (19)	9 (14)	
≥6	15 (15)	5 (15)	10 (15)	
Biochemistry markers				
BNP (pg/mL)	721 (447–1,312)	767 (4,457–124)	650 (453–1,342)	0.22
Creatinine (mg/dL)	0.91 (0.76–12.6)	1.04 (0.77–1.33)	0.89 (0.74–1.2)	0.24
eGFR ($mL/min/1.73\,m^2$)	55.6 (40.6–67.7)	52.4 (34.1–61.7)	59.4 (43.4–70.7)	0.16

Data given as median (IQR), n (%) or average±SD. BNP, brain natriuretic peptide; BP, blood pressure; BSA, body surface area; E, early diastolic wave velocity; e', early diastolic wave velocity on tissue Doppler imaging; eGFR, estimated glomerular filtration rate; HR, heart rate; IVC, inferior vena cava; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVOT, left ventricular outflow tract; MR, mitral regurgitation; PDEIII, phosphodiesterase III; RHC, right heart catheterization; TMF, transmitral flow; VTI, velocity time integral.

Table 2. Patient Characteristics vs. MAE Status

	MAE (+) n=39	MAE (–) n=62	P-value†
Age (years)	76 (63–82)	70 (60–79)	0.13
Male	26 (67)	37 (60)	0.48
Clinical scenario			0.05
1	19 (44)	42 (67)	
2	12 (36)	17 (28)	
3	4 (10)	2 (3)	
4	4 (10)	1 (2)	
Nohria-Stevenson			0.2
Warm and Wet	29 (82)	53 (85)	
Cold and Wet	10 (26)	8 (13)	
Cold and Dry	0 (0)	1 (2)	
SBP (mmHg)	121 (109–127)	132 (120–154)	0.0001
DBP (mmHg)	70 (58–84)	89 (79–108)	0.0001
mBP (mmHg)	86 (78–98)	103 (92–121)	<0.0001
HR (beats/min)			
Baseline	140 (132–150)	142 (132–158)	0.27
Initial	110 (97–133)	111 (102–125)	0.78
Maximum	98 (87–107)	95 (88–101)	0.24
Max dose of landiolol	3 (2–4)	3 (2–5)	0.53
LVEDVI (mL/m^2)	95.6 (76.6–109.9)	82 (58.2–106.7)	0.04
LVESVI (mL/m^2)	70.1 (56.7–82.4)	62.1 (45.6–79.8)	0.17
LVEF (%)	25 (17–28)	22 (16–29)	0.19
LAVI (mL/m^2)	44.4 (32.4–57.1)	44.1 (35.1–49.1)	0.77
MR>mild	20 (32)	14 (36)	0.7
IVC (mm)	22 (19–25)	22 (19–25)	0.9
BNP (pg/dL)	732 (477–1,445)	703 (402–1,221)	0.39
eGFR (mL/min/1.73 m^2)	47.4 (28.9–61.8)	60.6 (47.4–71.0)	0.005

Data given as median (IQR) or n (%). †ANOVA. DBP, diastolic BP; MAE, major adverse events; mBP, mean BP; SBP, systolic blood pressure. Other abbreviations as in Table 1.

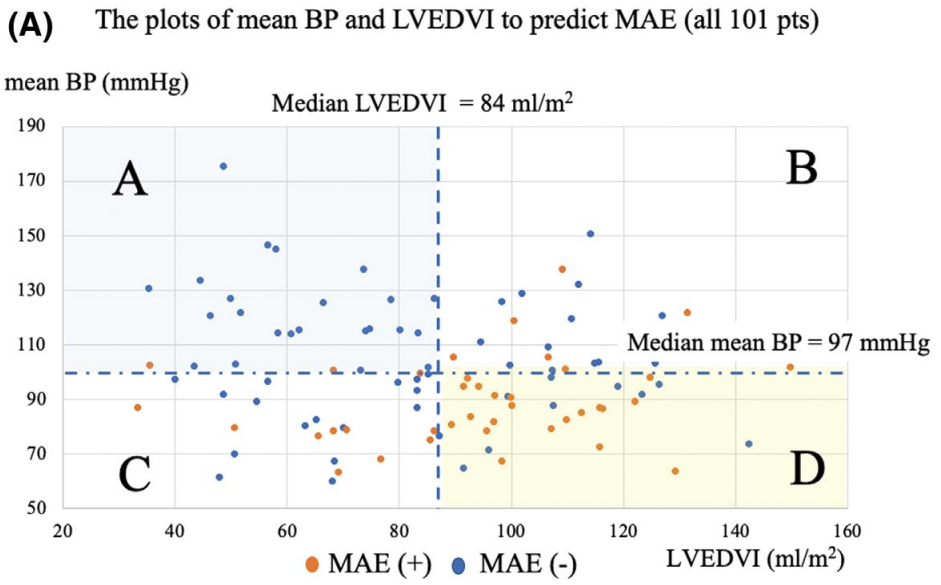
in 14 patients and 24 patients, respectively. For patients with more than 1 acute event, only the first event was considered in the analysis of primary endpoint, therefore in total 39 MAE occurred. **Table 2** lists the characteristics according to MAE status. There were significant differences between the 2 groups, in BP, LVEDVI and eGFR. Next, we sought to determine the predictor for MAE, then we divided the patients by median values into 4 groups (**Figure 2**): group A, LVEDVI <84.0 mL/m^2 and mean BP >97 mmHg; group B, LVEDVI ≥84.0 mL/m^2 and mean BP >97 mmHg; group C, LVEDVI <84.0 mL/m^2 and mean BP ≤97 mmHg; and group D, LVEDVI ≥84.0 mL/m^2 and mean BP ≤97 mmHg. Significant differences in the frequency of MAE were seen between the 4 groups (P=0.0001, Fisher exact test; **Figure 2B**). Group D had significantly higher frequency of MAE. Conversely, the patients in Group A were frequently free from MAE. **Table 3** lists the univariate and multivariate logistic regression analysis for MAE. On univariate analysis age, mean BP and LVEDVI were the significant predictors, and on multivariate analysis both mean BP and LVEDVI were the independent predictors.

Change of Hemodynamic Condition and RHC Data

The changes in average values of HR, BP, and RHC data during the administration of landiolol (baseline, initial dose, and maximum dose) in the RHC group are shown in **Table 4**. As previously reported, landiolol significantly decreased HR over the course of treatment. PCWP also decreased, as did the systolic, diastolic, and mean PA. SV and SV index (SI) increased. CO, SvO_2, RAP, SVR, and SVRI did not change substantially. The median HR reduction (ΔHR) was 40.4 beats/min (IQR, 32.5–55.1 beats/min), and the median ΔPCWP reduction was 5.0 mmHg (IQR, 2.0–10.5 mmHg). PCWP was decreased by the titration of landiolol. **Figure 3** shows the multipoint PCWP and HR plots and the relationship between the changes in HR and PCWP. According to **Table 4**, **Figure 3**, the changes in HR and PCWP corresponded with the increase in landiolol titration.

Discussion

This is the first study to demonstrate the clinical usefulness of landiolol treatment measured on RHC monitoring and according to short-term prognosis in order to identify patients eligible for landiolol treatment. Landiolol was shown to be safe and effective in rapidly decreasing HR in ADHF patients with HFrEF complicated by rapid AF in acute settings. The patients with relatively smaller LV and higher mean BP (LVEDVI <84.0 mL/m^2 and mean BP >97 mmHg) had fewer adverse events. Furthermore, on RHC monitoring the changes in HR and PCWP corresponded with the increase in landiolol titration.



(B) The patients numbers of 4 categories

Category	MAE(+)	MAE(-)	Total
A	2 (5)	23 (37)	25
B	9 (23)	18 (29)	27
C	8 (21)	12 (19)	20
D	20 (51)	9 (15)	29
Total	39	62	101

Figure 2. (**A**) Prediction of major adverse events (MAE) according to median mean blood pressure (BP; 97 mmHg) and median left ventricular end-diastolic volume index (LVEDVI; 84.0 mL/m^2) in 101 patients. Group A, LVEDVI <84.0 mL/m^2 and mean BP >97 mmHg; group B, LVEDVI ≥84.0 mL/m^2 and mean BP >97 mmHg; group C, LVEDVI <84.0 mL/m^2 and mean BP ≤97 mmHg; and group D, LVEDVI ≥84.0 mL/m^2 and mean BP ≤97 mmHg. Blue plots, patients without MAE (n=62); red plots, patients with MAE (n=39). (**B**) This figure shows the number of each of the four categories in (**A**). Fisher's exact test shows that each category had significant relationships with the presence of MAE (Fisher's exact test, P<0.0001).

Table 3. Logistic Regression Analysis to Predict MAE

	Univariate			Multivariate		
	OR	95% confidence interval	P-value	OR	95% confidence interval	P-value
Age	1.023	0.988–1.059	0.194	1.024	0.98–1.072	0.287
Gender	1.35	0.589–3.175	0.478			
Mean BP	0.954	0.927–0.976	<0.0001	0.957	0.929–0.981	0.0003
LVEDVI	1.016	1.001–1.034	0.039	1.022	1.001.043	0.033
Log BNP	1.284	0.343–4.954	0.71			

OR, odds ratio. Other abbreviations as in Tables 1,2.

Urgent HR Control by Low-Dose Landiolol in ADHF

The optimal target HR in the treatment of AF in patients with LV dysfunction has not yet been established.[20] The European Society of Cardiology (ESC) guidelines recommend a target HR of 110 beats/min.[21] In the present study landiolol provided safe and effective control of HR in rapid AF, even in patients with ADHF. The mechanism of effectiveness and safety of landiolol treatment in the present study may be explained as follows. Given that landiolol is an ultra-short-acting β1-blocker and has a minimum negative inotropic effect, the CO and CPO did not decrease substantially (**Table 4**). Low-dose landiolol treatment itself

Table 4. Change in Hemodynamic Parameters

	Landiolol			P-value†
	Baseline	Initial dose (1 μg/kg⁻¹/min⁻¹)	Maximum dose	
Systolic BP (mmHg)	127±21	120±17	116±17	0.06
Diastolic BP (mmHg)	83±23	73±15	71±15	0.04
Mean BP (mmHg)	96±22	88±15	86±15	0.05
HR (beats/min)	143±17	113±22	97±19	<0.0001
CVP (mmHg)	13.2±6.7	11.9±6.0	10.1±4.5	0.21
Systolic PA (mmHg)	41.5±10.1	38.3±9.8	35.1±8.7	0.03
Diastolic PA (mmHg)	24.5±7.4	22.2±6.8	19.2±5.2	0.004
Mean PA (mmHg)	31.1±8.2	28.2±7.6	25.0±5.3	0.004
PCWP (mmHg)	23.6±7.8	21.1±7.5	17.3±6.3	0.0008
CO (L/min)	3.1±1.2	3.2±1.2	3.2±1.0	0.89
CI (L/min/m²)	1.8±0.6	1.9±0.6	1.9±0.6	0.84
CPO (W)	0.70±0.34	0.64±0.27	0.60±0.21	0.41
CPI (W/m²)	0.41±0.19	0.37±0.15	0.35±0.12	0.4
SvO_2 (mmHg)	58.9±8.5	60.4±9.3	60.9±9.6	0.79
SV (mL/beat)	25.5±13.6	30.3±12.4	32.4±11.6	0.02
SI (mL/beat/m²)	14.9±7.2	17.3±6.8	19.5±7.7	0.01
SVR (dyne-s/cm⁵)	2,188±665	2,178±665	2,033±700	0.26
SVRI (dyne-s/cm⁵/m²)	3,538±1,009	3,532±1,009	3,387±1,068	0.13

Data given as average±SD. †ANOVA. BP, blood pressure; CI, cardiac index; CO, cardiac output; CPI, CPO index; CPO, cardiac power; CVP, central venous pressure; HR, heart rate; PA, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SI, stroke volume index; SV, stroke volume; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index.

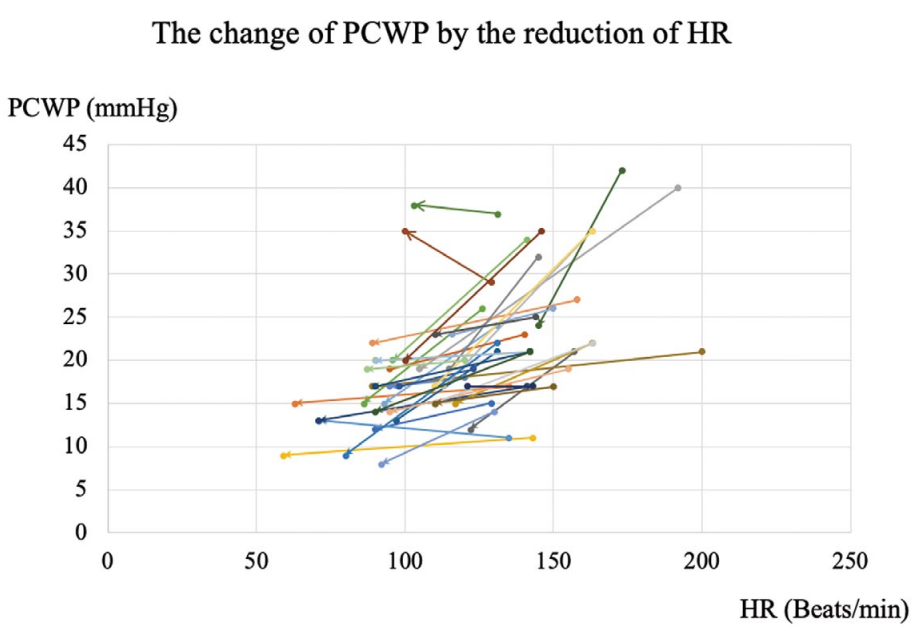


Figure 3. Change in pulmonary capillary wedge pressure (PCWP) according to reduction in heart rate (HR) due to landiolol treatment (arrows). Of 37 patients, 34 had decreased PCWP ≤24 h after landiolol treatment.

has been shown to be beneficial in terms of HR reduction;[22] we think that the reduction of HR broke the vicious cycle of ADHF; and sometimes impaired LV function recovers after HR control.[23] Furthermore, the larger HR decrease achieved with a β-blocker led to good prognoses in previous patients with ADHF.[24] Given the effectiveness of low-dose landiolol, we can treat critical and severe cases rapidly without adverse effects.

Optimal Target HR for Rapid AF in ADHF

The ESC recommendation for HF indicates that a resting ventricular rate in the range of 60–100 beats/min may be better.[9] GWTG-HF shows that a higher admission HR is independently associated with worse outcomes in patients admitted for HF, irrespective of sinus rhythm and AF.[25] Also, a HR decrease to <110 beats/min may decrease mortality.[25] Six of the present patients did not achieve the target HR (HR <110 beats/min and ΔHR >20%). However, there was a significant relationship between baseline HR and ΔHR ($r=0.63$, $P<0.0001$). Given that symptoms depend on ΔPCWP, focus should be shifted to HR reduction to stabilize the hemodynamic status in such severe cases.

Role of Echocardiography in Landiolol Patient Selection

This study has effectively demonstrated the hemodynamic effect of landiolol through RHC. Although 2-D echocardiography has become a useful daily tool even in AF cases,[26] the Doppler assessment of LV diastolic function is limited by the variability in cycle length, the absence of organized atrial activity, and the frequent occurrence of left atrial enlargement regardless of filling pressure.[16] In the present study, good responders had a relatively smaller LV and a higher mean BP (**Table 2**).

We think that there are some reasons for this. The LV volume in groups A and C (mean LVEDVI=64 mL/m^2; IQR, 50–76 mL/m^2) was not as small as that in normal subjects;[27] thus, we think that the vicious cycle of rapid AF may play an important role in the ADHF in such patients. In contrast, rapid AF plays a compensatory role in the patients with extremely large LV, especially with low BP. Therefore, we should administer landiolol for the patients in Group D more carefully. In the present study, according to the RHC data, the SV in group D did not improve, which seemed to be different from the other 3 groups (ΔSV in group D vs. in the other 3 groups: 0.7±7.5 vs. 7.8±9.8, $P=0.05$). This suggests that eligible patients can be selected using echocardiography and simple vital signs.[28] LV size was also reported to be an important prognosticator.[29] These median values were similar to the values calculated on receiver operating characteristics curves (**Supplementary Figure**). We think that administering landiolol in patients with a collapsed volume status should be avoided. Although HR control is essential in patients with rapid AF, it does not constitute the entire treatment regimen for ADHF patients. Therefore, HR reduction and PCWP reduction may be affected by the other drugs, too.

Novelty of This Study

Despite the impressive results of the J-LAND study,[8] we conducted this study for several reasons. First, although the J-Land study showed that treatment with landiolol is effective in rapidly decreasing HR, the hemodynamic effects induced by this reduction are unknown. Second, because it is unclear whether the effectiveness improves prognosis, we wanted to resolve this issue. Third, although patients in the J-LAND study had reduced EF, their EF were still >25%. In our daily practice, many patients have severely reduced EF and they are usually difficult cases. Finally, we believe it is important to be able to determine which patients are eligible for landiolol treatment.

Clinical Implications

This study proposed the strategy of landiolol treatment for ADHF. A large number of the patients could be good candidates for landiolol treatment, because landiolol is now available in many countries.[30] Landiolol is able to replace amiodarone or digoxin in such situations because of rapid hemodynamic improvements. According to the present results, we can select the patients who should be treated with landiolol based on simple echocardiographic and BP measurements. Patients with relatively smaller LV volume with higher BP are the most eligible patients for landiolol treatment, but we emphasize that landiolol is also effective for other ADHF patients with rapid AF.

Study Limitations

First, we could not conduct a randomized controlled trial comparing patients without landiolol treatment; therefore, we could not describe the true effectiveness of landiolol in comparison with control subjects who were treated without landiolol. Landiolol apparently has a stronger chronotropic effect compared with digoxin,[8] but we have successfully demonstrated the favorable hemodynamic effects of rapid HR control of rapid AF by landiolol treatment. Second, this was a single-center study, and the number of the patients was not large, but they had HFrEF, and hence the results provided valuable information. Third, RHC was undergone only when the patient's vital status and physical conditions were available. Fourth, measuring LV size and function using echocardiography in patients with AF is still challenging even with many cardiac cycles, and therefore our study has some uncertainty. Finally, other treatments also might affect PCWP reduction. Despite having some limitations, it is a very useful discovery that simple measurements of LV size and BP enable identification of the patients eligible for landiolol treatment.

Conclusions

Landiolol is a useful and safe i.v. drug for patients with rapid AF and LV systolic dysfunction. Landiolol was effective for urgent HR control without serious side-effects. A relatively smaller LV volume and higher baseline mean BP suggested greater hemodynamic improvements and better short-term prognosis after landiolol treatment. Therefore, simple measurements of echocardiographic indexes and vital signs provide important information when considering landiolol treatment in patients with ADHF and severe LV systolic dysfunction. In most cases, landiolol treatment achieved hemodynamic improvement (PCWP reduction) rapidly and safely. Further studies are needed to confirm the clinical usefulness of landiolol in an emergency.

Declarations

Ethics approval and consent to participate: Ethics committee of Yokohama City University Medical Center.

Consent for Publication

Not applicable.

Availability of Data and material

Not applicable.

Author Contributions

All authors read and approved the final manuscript.

Disclosure

M. Kosuge is a member of *Circulation Reports*' Editorial Team. The other authors declare no conflicts of interest.

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Supplementary Files

Please find supplementary file(s);
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