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Original Article

Practical applicability of landiolol, an ultra-short-acting β1-selective blocker, for rapid atrial and ventricular tachyarrhythmias with left ventricular dysfunction

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ABSTRACT

Background: Landiolol effectively controls rapid heart rate in atrial fibrillation or flutter (AF/AFL) patients with left ventricular (LV) dysfunction. However, predicting landiolol Responders and Non-Responders and patients who will experience adverse effects remains a challenge. The aim of this study was to clarify the potential applicability of landiolol for rapid AF/AFL and refractory ventricular tachyarrhythmias (VTs) in patients with heart failure.

Methods: A total of 39 patients with AF/AFL with ventricular response ≥120 bpm and 12 VTs were retrospectively enrolled. Landiolol Responders for rapid AF/AFL were defined as patients whose ventricular response was suppressed to less than 110 bpm or decreased by ≥20% from the initial heart rate after administration of landiolol. Responders for VTs were defined as patients with no recurrent VTs during the 24 h after the initiation of landiolol.

Results: For AF/AFL, 29 patients (74%) were Responders. In nine patients (31%), AF was spontaneously terminated after starting landiolol. Eight Non-Responders (80%) needed to have AF terminated by cardioversion. Left ventricular ejection fraction (LVEF) at baseline was significantly associated with landiolol efficacy. For VTs, seven patients (58%) were Responders, and smaller LV diastolic and systolic diameters were associated with landiolol efficacy. Hypotension after landiolol treatment occurred in 5 of 51 patients, and lower LV systolic function was associated with the development of adverse events.

Conclusions: Landiolol is effective in patients with heart failure not only due to rapid AF/AFL but also due to VTs. However, preserved LVEF is important for efficacy and safety in landiolol treatment.

1. Introduction

Rapid ventricular contractions caused by various tachycardias, such as atrial fibrillation (AF), atrial flutter (AFL), atrial tachycardia (AT), ventricular tachycardia, or even frequent ventricular ectopic beats, can induce left ventricular (LV) systolic dysfunction in clinical settings [1,2]. Tachypacing is one of the most useful methods to induce LV dysfunction in an animal model of heart failure (HF) [3] as a consequence of the extracellular (Ca^{2+} overload) and cellular modification of various ion channels and transporters [4,5], and beta-adrenergic receptors [3,6,7]. Beta-blockers have both negative chronotropic action and a pleiotropic effect on cardioprotection, leading to the recovery of impaired LV function in various structural and rhythm disorders, including idiopathic cardiomyopathy [8] and ventricular tachycardia [9]. The antiarrhythmic effects of β-blockers are well-known, although their negative inotropic and even proarrhythmic action in some cases with advanced HF [10] may be non-negligible.

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Landiolol is an ultra-short-acting, β1-superselective, titration intravenous β-adrenergic blocker that is rapidly metabolized to inactive forms, and has relatively smaller negative inotropic effects on the cardiac output [11]. Landiolol is more effective for controlling rapid heart rate than digoxin in AF/AFL patients with LV dysfunction [12] and is also applicable for rhythm maintenance after catheter ablation [13]. A low-dose β1-blocker, landiolol, in combination with milrinone, improves intracellular Ca^{2+} handling in failing cardiomyocytes [14]. However, there are only a few clinical practice reports that examine how we can predict landiolol Responders and Non-Responders and patients who will experience adverse effects [15,16], especially in a study population including patients with much lower LVEF ($<25\%$). The aim of this study was to clarify the potential applicability of landiolol for rapid AF and refractory ventricular tachyarrhythmias (VTs) in patients with HF.

2. Methods

2.1. Patients and data collection

From May 2013 to May 2014, a total of 39 patients with rapid AF (72 ± 11 years old, 51% male, average heart rate 152 ± 19 bpm) and 12 patients with refractory VTs (59 ± 15 years old, 75% male, mean cycle length of 415 ± 105 ms) who were treated with landiolol at the National Cerebral and Cardiovascular Center and Shiga University of Medical Sciences were retrospectively surveyed.

Rapid atrial tachyarrhythmia was diagnosed if a patient had AF, AFL, or AT with ventricular response ≥ 120 bpm. AF subtypes were classified as paroxysmal (PAF), persistent AF (Per-AF), or long-standing Per-AF according to the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines [17].

Refractory VTs were defined as repetitive VTs, including sustained (≥ 30 s) or incessant nonsustained (<30 s) ventricular tachycardia (ventricular rate ≥ 100 bpm) or ventricular fibrillation (VF), if one or more class III antiarrhythmic drugs were administered. Electrical storm was defined if repetitive sustained ventricular tachycardia occurred three times or more in 24 h [18,19]. In patients with implanted defibrillators (implantable cardioverter defibrillators [ICDs] or cardiac resynchronization therapy with defibrillation capability [CRT-Ds]), a discharge of appropriate shock therapy was applied for sustained VTs even if this had terminated within the duration mentioned above. The incidence of VTs was calculated for 24 h before and after administration of landiolol with reference to preceding research using parenteral antiarrhythmic agents for refractory VTs [20]. Concomitant drugs other than landiolol were unrestricted. This study was approved by the ethics committee of the National Cerebral and Cardiovascular Center (M26-126).

2.2. Echocardiographic and electrophysiological indices

Echocardiography was performed to evaluate LV systolic function by calculating dimensions and left ventricular ejection fraction (LVEF). In patients with rapid AF, LVEF was evaluated during both an acute episode with a rapid heart rate and during stable status after the heart rate was controlled, because LVEF may decrease when rapid AF persists. In patients with VTs, LVEF was measured after they were stabilized. Serum B-type natriuretic peptide (BNP) level was measured before and after administration of landiolol. QT (QTc) interval at baseline was measured and calculated by Bazett's formula if an electrocardiogram (ECG) could be obtained before tachyarrhythmias.

2.3. Landiolol initiation and titration

For patients with rapid AF/AFL, landiolol was administered intravenously at the lowest recommended dosage of 1 μg/min/kg, which is specified as the minimal dosage for patients with LV dysfunction [12].

For patients with VTs, oral or intravenous class III antiarrhythmic drugs were administered first. However, if these had no or incomplete effect, the addition of landiolol was initiated using the same titration method as that for rapid AF. If landiolol was tolerated, the dosage could be titrated upward stepwise with careful monitoring by 1 μg/min/kg up to 10 μg/min/kg, until a positive or adverse effect appeared.

2.4. Efficacy and safety of landiolol

Landiolol Responders for rapid AF were defined as patients in whom the ventricular response was suppressed to less than 110 bpm or decreased by $\geq 20\%$ from the initial heart rate after administration of landiolol [12]. The time to achieve the reduction to the target heart rate was also examined. If the target heart rate reduction could not be achieved within 3 h after landiolol administration, patients were classified as Non-Responders.

On the other hand, Responders for VTs were defined as patients with no recurrent VTs for 24 h after landiolol initiation as commonly used [20–22]. Non-Responders were defined as patients in whom more than one episode of VTs was observed during the 24 h after landiolol initiation.

Adverse effects were defined as follows: (1) blood pressure reduction to less than 80 mmHg, (2) heart rate drop to less than 50 bpm, or (3) other hemodynamic deterioration, including hypoxia due to congestion. When adverse events were observed, landiolol was discontinued, even if favorable antiarrhythmic effects were seen.

2.5. Statistics

Numerical data are reported as either mean $\pm$ standard deviation (SD), standard error (SE), or median and interquartile range, as appropriate. To compare numerical data between two groups, an unpaired *t*-test or Mann–Whitney *U* test was used. The chi-square test was used to compare the prevalence of characteristics between two groups. A two-tailed probability (p) value less than 0.05 was accepted as significant. A software package (JMP 9.0; SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

3. Results

3.1. Rapid atrial arrhythmias

3.1.1. Baseline characteristics

The baseline characteristics of 39 patients with rapid AF are shown in Table 1. In these patients, 34 had AF, one had combined AF and AFL, and 4 had AT. The baseline heart rate was higher in patients with AT (176 ± 29 bpm) than in patients with AF (149 ± 16 bpm) ($p=0.006$) and patients with AFL with AF (145 bpm). Twelve patients (31%) had ischemic heart disease (IHD). Other etiologies of HF were valvular heart disease (6 patients), hypertensive heart disease (3), constrictive pericarditis (1), cardiac amyloidosis (1), idiopathic dilated cardiomyopathy (1), hypertrophic cardiomyopathy (1), cardiac tamponade (1), congenital heart disease (1), and thyrotoxic crisis (1). The remaining 11 patients were considered to have tachycardia-induced HF without preexisting structural heart disease. Thirty-four patients (87%) presented with severe heart failure (New York Heart

Table 1
Baseline clinical characteristics comparing landiolol Responders (RSP) and Non-Responders (Non-RSP) with rapid AF/AFL/AT.

	Total ($n=39$)	RSP ($n=29$)	Non-RSP ($n=10$)	p Value
Age, yr	72 ± 11	73 ± 10	69 ± 15	0.33
Male, *n* (%)	20 (51)	15 (52)	5 (50)	0.93
NYHA III/IV, *n* (%)	34 (87)	25 (86)	9 (90)	0.76
IHD, *n* (%)	12 (31)	10 (34)	2 (20)	0.39
PAF/Per-AF	21/18	16/13	5/5	0.78
Heart rate, bpm	152 ± 19	152 ± 19	153 ± 20	0.83
Blood pressure, mmHg	116 ± 20	117 ± 20	113 ± 23	0.60
BNP, pg/ml[a]	421 (151–864)	387 (134–663)	820 (321–1699)	0.23
LVEF, %	34 ± 16	37 ± 16	25 ± 12	0.049
LVDD, mm	49 ± 10	49 ± 11	47 ± 6	0.57
LVDS, mm	37 ± 11	36 ± 11	39 ± 9	0.63
eGFR, ml/min/1.73 m^2	45 ± 22	42 ± 23	56 ± 15	0.06
Digoxin, *n* (%)	13 (33)	8 (28)	5 (50)	0.20
β-Blocker, *n* (%)	17 (44)	14 (48)	3 (30)	0.31
Amiodarone, *n* (%)	3 (8)	2 (7)	1 (10)	0.76
ACEI/ARB, *n* (%)	11 (28)	9 (23)	2 (5)	0.50
Aldosterone antagonists	7 (18)	5 (13)	2 (5)	0.84
Inotrope infusion, *n* (%)	13 (33)	8 (28)	5 (50)	0.20
Vasodilators, *n* (%)	14 (36)	9 (23)	5 (13)	0.28
Intubation, *n* (%)	12 (31)	7 (24)	5 (50)	0.14
Maximum dose, μg/kg/min	4.8 ± 3.3	4.5 ± 3.0	5.5 ± 4.2	0.40
After treatment				
Heart rate, bpm	88 ± 29	79 ± 19	114 ± 38	0.0005
Blood pressure, mmHg	103 ± 20	104 ± 19	103 ± 24	0.90
BNP, pg/ml[a]	292 (135–650)	291 (126–683)	394 (206–627)	0.70
LVEF, %	43 ± 16	44 ± 15	39 ± 19	0.43
LVDD, mm	49 ± 8	49 ± 8	49 ± 6	0.91
LVDS, mm	37 ± 9	36 ± 10	39 ± 9	0.58
Cardioversion, *n* (%)		–	8 (80)	NA
Adverse event, *n* (%)	3 (8)	2 (7)	1 (10)	0.76
Sinus rhythm, *n* (%)	21 (54)	16 (55)	5 (50)	0.93
β-Blocker, *n* (%)	29 (74)	22 (76)	7 (70)	0.72
Digoxin, *n* (%)	4 (10)	2 (7)	2 (20)	0.28
Infusion duration, days[a]	3 (1-7)	3 (1-8)	2 (1-4)	0.08
Survival, *n* (%)	31 (79)	24 (83)	7 (70)	0.40

NYHA, New York Heart Association functional class; IHD, ischemic heart disease; PAF, paroxysmal atrial fibrillation; per-AF, persistent atrial fibrillation; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension; LVDS, left ventricular end-systolic diameter; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

[a] Variables were represented as median (interquartile range).

Association [NYHA] functional class III or IV) symptoms. Twelve patients (31%) required mechanical ventilation because of severe hypoxia due to congestive heart failure. One-third of patients had been treated with inotrope infusion (dopamine alone in 2, dobutamine alone in 1, noradrenaline alone in 1, a combination of dopamine plus dobutamine in 6, dopamine plus noradrenaline in 1, and dobutamine plus noradrenaline in 2. The use of these inotrope infusions was not statistically different between the landiolol Responders and Non-Responders (Table 1). Vasodilators were used in combination with landiolol in 14 patients (carperitide in 8, nitrate in 4, nicorandil in 1, and nicardipine in 1). Before landiolol treatment, intravenous digoxin was attempted in 13 patients (33%) at a uniform dosage of 0.25 mg; however, the heart rate was only reduced from 158 ± 18 to 148 ± 21 bpm ($p=0.20$). Oral β-blockers were prescribed in 17 patients (44%) at baseline (bisoprolol in 11 [2.78 mg per day on average] and carvedilol in 6 [6.04 mg per day on average]). Previous oral β-blocker usage was independent of the effect of landiolol.

3.1.2. Responders vs. Non-Responders

Of 39 patients with rapid AF/AFL/AT, 29 (74%) were Responders and 10 (26%) were Non-Responders. In Responders, the heart rate was reduced by 36.8% from baseline (152 ± 19 to 96 ± 17 bpm, $p<0.0001$) for 2.2 ± 1.8 h (Fig. 1, middle). In contrast, in Non-Responders, the heart rate was unchanged during landiolol administration (153 ± 20 to 137 ± 22, $p=0.11$) for 1.9 ± 0.7 h (Fig. 1, right). Furthermore, in 9 (31%) of the 29 Responders, AF was

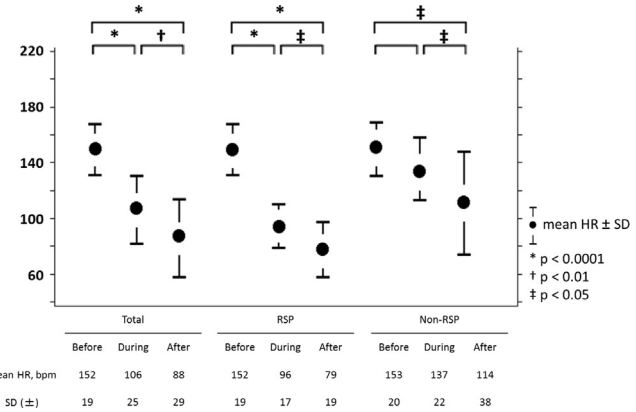

Fig. 1. Heart rate change with landiolol for rapid atrial arrhythmias. Each data set represents heart rate before, during, and after treatment with landiolol. In Responders (RSP), heart rate was significantly reduced by 36.8% from baseline (152 ± 19 to 96 ± 17 bpm, $p<0.0001$) with landiolol for 2.2 ± 1.8 h. In contrast, in Non-Responders (Non-RSP), heart rate was unchanged with landiolol (153 ± 20 to 137 ± 22, $p=0.11$) for 1.9 ± 0.7 h.

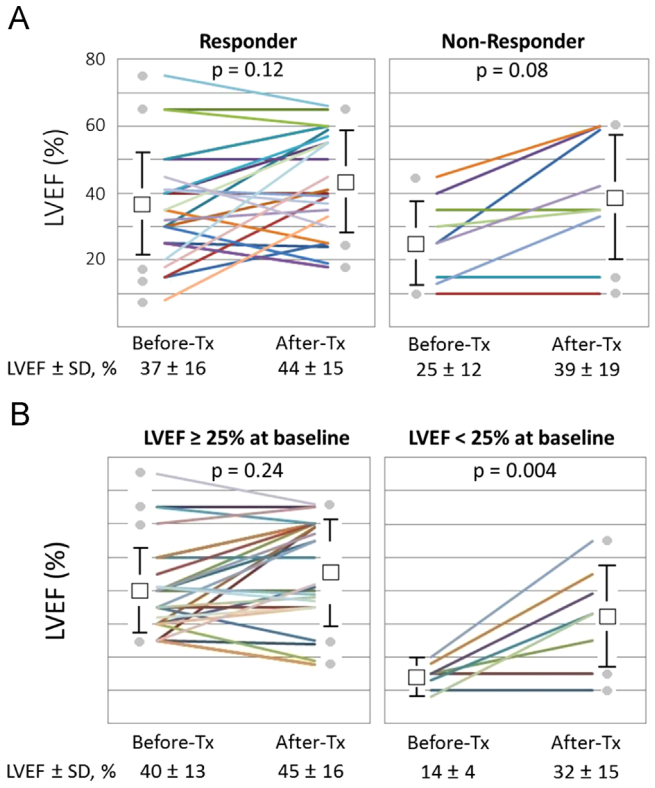

Fig. 2. Change in LVEF with landiolol in Responders vs. Non-Responders (A), and in LVEF $<25\%$ vs. $\geq 25\%$ (B). (A) In Responders, average LVEF was not changed after landiolol therapy (left panel), whereas in Non-Responders, LVEF after treatment tended to be increased (right panel). (B) LVEF was significantly increased in patients with much lower LVEF ($<25\%$) at baseline (left panel), whereas there was no change in those with relatively higher LVEF ($\geq 25\%$) (right panel).

spontaneously terminated without mechanical defibrillation or an additional antiarrhythmic drug after landiolol administration. In contrast, 8 of the 10 Non-Responders underwent cardioversion using an external defibrillator. In 6 of these patients, AF was successfully terminated as sinus rhythm, and 5 maintained sinus rhythm. Landiolol was continued for a median of 3 and 2 days in Responders and Non-Responders, respectively. On final observation, sinus rhythm was maintained in 21 patients (16 Responders, 5 Non-Responders), independent of the effect of landiolol.

Table 1 compares clinical characteristics between Responders ($n=29$: 25 AF, 1 AF+AFL, and 3 AT) and Non-Responders ($n=10$: 9 AF and 1 AT). Of several hemodynamic indices, only LVEF at baseline was significantly lower in Non-Responders compared with Responders. The initial heart rate, NYHA functional class, and LV dimensions were similar between both groups. BNP value before treatment was also not significantly different between Responders and Non-Responders. Furthermore, a change in BNP level was not associated with the effect of landiolol (BNP decreased by 119 ± 117 [SE] pg/ml in Responders, and 345 ± 220 [SE] pg/ml in Non-Responders, $p=0.39$), suggesting that landiolol did not worsen HF. In terms of hemodynamic changes, both LVEF and BNP level after treatment were comparable between Responders and Non-Responders (LVEF: $44 \pm 15\%$ vs. $39 \pm 19\%$, $p=0.43$; BNP: 292 [IQR: 126–683] vs. 394 [IQR: 206–627], $p=0.70$) (Table 1; after treatment). To exclude the beneficial effect of AF termination, we separately analyzed the change of LVEF in patients with or without AF termination during treatment. There was no significant improvement in LVEF in Responders and Non-Responders (Fig. 2A), independent of rhythm status after treatment. Among Non-Responders, there was a tendency toward a small but insufficient increase in LVEF in patients with sinus rhythm after treatment (Supplemental figure, right).

Table 2
Clinical characteristics comparing patients with rapid AF and LVEF $\geq 25\%$ and $<25\%$.

	LVEF $\geq 25\%$ $N=28$	LVEF $<25\%$ $N=9$	p Value
Age, yr	71 ± 10	73 ± 17	0.67
Male, n (%)	416 (57)	4 (44)	0.51
NYHA III/IV, n (%)	23 (82)	9 (100)	0.17
IHD, n (%)	10 (36)	2 (22)	0.45
PAF/Per-AF	16/12	4/5	0.51
Heart rate, bpm	152 ± 20	156 ± 13	0.63
Blood pressure, mmHg	117 ± 22	116 ± 18	0.85
BNP, pg/ml[a]	359 (266-747)	558 (496-996)	0.14
LVEF, %	40 ± 13	14 ± 4	$<.0001$
LVDD, mm	48 ± 11	50 ± 7	0.60
LVDS, mm	34 ± 11	44 ± 6	0.04
eGFR, ml/min/1.73 m^2	47.7 ± 21.8	42.2 ± 21.4	0.52
Digoxin, n (%)	8 (29)	4 (44)	0.38
β-Blocker, n (%)	13 (46)	4 (44)	0.92
Amiodarone, n (%)	3 (11)	0	
Inotrope infusion, n (%)	8 (29)	3 (33)	0.79
Intubation, n (%)	7 (25)	3 (33)	0.62
Maximum dose, μg/kg/min	4.4 ± 2.8	6.3 ± 4.6	0.14
Responder, n (%)	22 (79)	5 (56)	0.07
After treatment			
Adverse effect, n (%)	1 (4)	2 (22)	0.10
LVEF, %	45 ± 16	32 ± 15	0.049
Sinus rhythm, n (%)	16 (57)	4 (44)	0.64
BNP, pg/ml[a]	264 (121–634)	463 (178–1138)	0.70
β-Blocker, n (%)	22 (79)	5 (56)	0.18
Survival, n (%)	24 (86)	5 (56)	0.06

Abbreviations as in Table 1.

[a] Variables were represented as median (interquartile range).

3.1.3. *Landiolol for patients with LVEF < 25%*

Lower LVEF was the only predictor of Non-Responders to landiolol therapy. Thus far, we have compared the effects of landiolol between patients with LVEF $\geq 25\%$ ($n=28$) and $<25\%$ ($n=9$) at baseline (Table 2), except for 2 patients lacking LVEF data during an acute episode. No statistical significance was found between the two groups for underlying etiology, initial heart rate, premedication, maximum dose, and efficacy of landiolol. Patients with LVEF $>25\%$ usually maintained sinus rhythm until the end of landiolol therapy, whereas average LVEF did not change (from $40 \pm 13\%$ to $45 \pm 16\%$, $p=0.24$) (Fig. 2B, left). In contrast, LVEF was significantly improved in patients with LVEF $<25\%$ (from $14 \pm 4\%$ to $32 \pm 15\%$, $p=0.004$) since most underwent cardioversion that terminated AF as sinus rhythm (Fig. 2B, right).

3.1.4. *Rate control therapy after landiolol*

Oral β-blockers were prescribed at discharge in 29 patients (74%) (bisoprolol in 24 [3.37 mg per day on average], metoprolol in 1 [20 mg per day], and carvedilol in 4 [5.42 mg per day on average]). Of 29 Responders, 7 did not receive oral β-blocker therapy at final observation because of in-hospital death in 2, severe chronic obstructive pulmonary disease in 1, symptomatic bradycardia in 2, hospital transfer with parenteral treatment in 1, and low cardiac output due to mitral regurgitation while awaiting cardiac surgery in 1. Although landiolol was ineffective, oral β-blockers could be used in all the Non-Responders who were discharged alive (bisoprolol in 6 [2.40 mg per day on average], carvedilol in 1 [5 mg per day]); the remaining 3 patients died in-hospital.

3.2. *Ventricular tachyarrhythmias*

3.2.1. *Baseline characteristics*

The baseline characteristics of 12 patients with landiolol treatment for VTs (6 with electrical storm, 4 with sustained VT, and 2 with

Table 3
Baseline clinical characteristics comparing landiolol Responders (RSP) and Non-Responders (Non-RSP) with lethal VTs.

	Total ($n=12$)	RSP ($n=7$)	Non-RSP ($n=5$)	p Value
Age, yr	59 ± 15	59 ± 18	60 ± 12	0.86
Male, *n* (%)	9 (75)	5 (71)	4 (80)	0.74
LVEF, %	26 ± 17	32 ± 19	18 ± 10	0.17
LVDD, mm	62 ± 13	55 ± 9	71 ± 13	0.02
LVDS, mm	52 ± 15	44 ± 11	64 ± 13	0.02
eGFR, ml/min/1.73 m^2	48 ± 21	45 ± 21	53 ± 24	0.53
β-Blocker, *n* (%)	10 (83)	6 (86)	4 (80)	0.79
Amiodarone[a], *n* (%)	10 (83)	7 (100)	3 (60)	0.07
Inotrope infusion, *n* (%)	1 (8)	1 (14)	0 (0)	0.38
VT subclass, *n*				
Electrical storm	6	4	2	
Sustained VT	4	2	2	NA
Incessant NSVT	2	1	1	
VT CL, ms	415 ± 105	382 ± 73	460 ± 134	0.22
VT QRS, ms	186 ± 40	170 ± 36	213 ± 35	0.09
VT morphology, *n*				
LBBB	1	0	1	
RBBB	10	7	3	NA
Unclassified	1	0	1	
VT QRS axis: inferior/superior	6/6	3/4	3/2	0.56
Blood pressure before treatment, mmHg	92 ± 16	95 ± 15	86 ± 18	0.40
Initial QTc, ms	504 ± 92	518 ± 112	484 ± 59	0.56
ICD/CRT-D, *n* (%)	10 (83)	5 (71)	5 (100)	0.19
Landiolol max dose, μg/kg/min	4.2 ± 1.6 (SE)	5.2 ± 2.6 (SE)	2.7 ± 1.78 (SE)	0.47
BNP before treatment, pg/ml[b]	612 (116–971)	624 (335–1273)	462 (73–845)	0.35
BNP after treatment, pg/ml	166 (137–540)	251 (72–511)	166 (162–1327)	0.36
Adverse event, *n* (%)	2 (17)	1 (14)	1 (20)	0.79

NSVT, non-sustained ventricular tachycardia; CL, cycle length; LBBB, left bundle branch block; RBBB, right bundle branch block; CRT-D, cardiac resynchronization therapy with defibrillation capability; ICD, implantable cardioverter defibrillator; SE, standard error, other abbreviations as in Tables 1 and 2.

[a] Oral and/or parenteral prescription.
[b] Variables were represented as median (interquartile range).

Table 4
Characteristics of patients with adverse effects (AE).

	#1	#2	#3	#4	#5
Adverse effect			Hypotension		
Arrhythmia	VTs	PAF	Chronic AF	VTs	Chronic AF
Age, yr	66	92	80	74	70
Sex	F	F	M	M	M
LVEF before treatment, %	–	10	15	–	32
LVEF before treatment, %	15	10	25	20	35
RSP/Non-RSP	Non-RSP	Non-RSP	RSP	RSP	RSP
Initial heart rate, bpm	110	170	147	200	140
Underlying heart disease	Sarcoidosis	TIC	CP	NICM	VHD

RSP, Responder; TIC, tachycardia-induced cardiomyopathy; CP, constrictive pericarditis; NICM, non-ischemic cardiomyopathy; VHD, valvular heart disease, other abbreviations as in Tables 1–3.

Table 5
Comparison between patients with and without adverse effects (AE).

	AE (+) $N=5$	AE (−) $N=46$	p Value
VTs/AF, *n*	2/3	10/36	0.36
Age, yr	76 ± 10	68 ± 13	0.18
Blood pressure[a], mmHg	102 ± 10	112 ± 23	0.38
LVEF[b], %	18 ± 8	33 ± 17	0.06
LVDD[b], mm	64 ± 12	51 ± 12	0.03
LVDS[b], mm	55 ± 12	40 ± 14	0.046
BNP, pg/ml[c]	1568 (294–2482)	455 (268–794)	0.15
β-Blocker, *n* (%)	1 (20)	26 (57)	0.12
Amiodarone, *n* (%)	2 (40)	11 (24)	0.43
Inotrope infusion, *n* (%)	2 (40)	12 (26)	0.51
Landiolol max dose, μg/kg/min	3.6 ± 1.8	4.7 ± 4.1	0.56

Abbreviations as in Tables 1–4.

[a] Variables during acute situation.
[b] Variables during stable state.
[c] Variables represented as median (interquartile range).

incessant nonsustained VT) are shown in Table 3. All patients had nonischemic etiologies. Ten of 12 patients received ICDs (6 CRT-D, 4 ICD) and 2 wore external LV assist devices before the events. Hemodynamic collapse during VTs occurred in two patients and one required a temporary cardiopulmonary assist device. Oral β-blockers were prescribed in 10 patients. Oral class III antiarrhythmic agents were prescribed in 9 patients (amiodarone in 4, sotalol in 2, amiodarone combined with sotalol in 3). Parenteral class III antiarrhythmic agents were administered before landiolol in 7. Five patients were not administered parenteral class III antiarrhythmics because all had received one or two oral maintenance class III antiarrhythmics and 4 presented with a prolonged QTc duration.

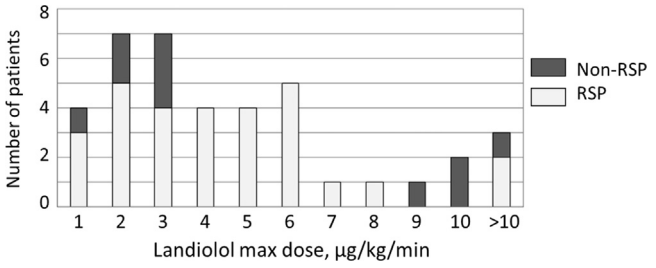

Fig. 3. Maximum dose and efficacy of landiolol for rapid atrial arrhythmias. Number of patients administered the maximum dose of landiolol who achieved the endpoint; based on both heart rate <110 bpm or $\geq 20\%$ decrease in the heart rate from baseline within 3 h after initiation.

3.2.2. Responders vs. Non-Responders

Of 12 patients with refractory VTs, 7 had no recurrent VTs during continuous landiolol infusion. A comparison between Responders and Non-Responders for VTs is shown in Table 3. Both LV end-diastolic (LVDD) and end-systolic dimension (LVDS) were significantly larger in the Non-Responder group compared with the Responder group. BNP level was markedly high in both groups before landiolol infusion. LVEF was comparable, while LV dimension was significantly enlarged in Non-Responders. Antiarrhythmic pretreatment, especially amiodarone (oral or parenteral), was prone to this response.

Electrophysiological study and catheter ablation were performed in 4 patients (2 Responders and 2 Non-Responders). Non-reentrant VTs corresponding to clinical VTs were induced in 2 of 2 Responders, whereas reentrant VTs were provoked in 2 of 2 Non-Responders. Catheter ablation eliminated clinical VTs in 3 of these 4 patients.

3.3. Adverse effects of landiolol (AF and VTs)

Adverse effects, all involving hypotension, were observed in 5 patients as detailed in Table 4 (10% of all patients: 3 in the AF group, 2 in the VT group, 3 in Responders). However, landiolol was discontinued in all five patients immediately after adverse effects developed.

We also compared patients with (AE [+]) or without adverse effects (AE [−]). Table 5 shows that the incidence of adverse effects was associated with impaired LV function, rather than with the dose of landiolol.

4. Discussion

A reduction in rapid ventricular response is one of the most effective therapeutic strategies in patients with tachycardia-related HF. This retrospective multicenter survey revealed that landiolol, an ultra-short-acting β1-selective blocker, was effective in more than half of patients with HF not only in association with rapid AF/AFL, but also refractory VTs, which had already been treated with other antiarrhythmic agents, mainly amiodarone. Much lower LVEF and larger LV diastolic or systolic diameters were possible predictors for the efficacy and safety of landiolol treatment.

4.1. Practical use of landiolol for rapid AF

In acute decompensated HF, the rapid ventricular response is both the cause and consequence of hemodynamic deterioration [23]. Of several negative chronotropic agents, only digoxin and β-blockers are theoretically of practical use in HF patients with reduced LVEF [24]. Recently, the J-Land study [12] demonstrated that landiolol was more effective for controlling the rapid heart rate than digoxin in AF/AFL patients with LV dysfunction. In comparison with the J-Land study, landiolol in this clinical survey was used in patients with more unfavorable situations, such as a higher ventricular rate in atrial arrhythmias, a higher prevalence of mechanical ventilation, more severe renal dysfunction, and a higher prescribed dose of oral β-blockers at baseline. Despite these unfavorable clinical situations, landiolol could reduce the heart rate within 2.2 ± 1.8 h after starting an infusion in Responders. Furthermore, the maximum dose of landiolol varied from 1 to 10 μg/kg/min and was independent of the efficacy (Fig. 3); this is consistent with the previous study [12]. With regard to specific dosage and efficacy among the10 Non-Responders in the AF/AFL/AT study, 1 required immediate cardioversion because of decreasing blood pressure at 3 μg/kg/min, and 4 continued on landiolol up to 9 μg/kg/min. Among the remaining 5, mandatory cardioversion was performed in 3; 2 of these were performed after 190 and 195 min at 3.2 μg/kg/min and 2 μg/kg/min, respectively, and were considered Non-Responders; 1 underwent attempted cardioversion after 20 h of landiolol at 2 μg/kg/min. We do not completely exclude the possibility of "potential responders", but none of the Non-Responders received cardioversion before adequate titration of landiolol. Furthermore, in the J-Land study, landiolol dosage and efficacy were not directly correlated. These findings suggest that the 10 patients were actually Non-Responders. Thus, in clinical practice, landiolol has higher potency for reducing rapid heart rate in patients with much more severe LV dysfunction; however, prediction of the efficacy or adverse effects remains unresolved.

4.2. Responders vs. Non-Responders to landiolol for rapid AF

In this study, most of the baseline clinical parameters between Responders and Non-Responders were similar. However, of several hemodynamic indices, only LVEF might be associated with the response to landiolol. On the basis of the force-frequency relationship, rapid ventricular response can facilitate cardiotonic action in both a single cardiomyocyte and in the non-failing heart; however, tachypacing promotes an opposite action, thus decreasing the hemodynamic state in the failing heart [23]. It is difficult to estimate the force-frequency relationship in individuals with HF, and even more challenging to determine the optimal heart rate for the patients. This study suggested that landiolol may not be appropriate for HF patients with extremely low LVEF. However, landiolol is an ultra-short-acting β1-selective blocker, and can be stopped and quickly washed-out if it is ineffective or induces AE.

In the J-Land study [12], landiolol was shown to rapidly reduce the heart rate compared with digoxin. There were no significant differences between the two groups in terms of the change in clinical parameters at final observation. Furthermore, the rapid decrease in the heart rate was not associated with symptomatic relief in those patients. In this study, heart rate reduction was more immediate in Responders compared with Non-Responders; however, there was no significant difference in the hemodynamic parameters, including systolic blood pressure, LVEF, BNP level, and LV dimensions after treatment. Thus, as shown in Table 1, landiolol treatment does not always affect the prognosis of patients.

4.3. Practical use of landiolol for lethal VTs

A previous study suggested that the efficacy of landiolol for electrical storm due to the acute coronary syndrome depends on the patient's general condition, such as a lower Acute Physiology and Chronic Health (APACHE) II score [25]. On the other hand, patients in this study had nonischemic cardiomyopathy, no apparent progressive organ failure, and were under treatment with strong antiarrhythmic therapy including prior device implantation. A class III antiarrhythmic agent, amiodarone, suppresses reentrant VTs by multiple mechanisms, but mainly by prolongation of ventricular refractory periods. In this study, amiodarone was administrated in all landiolol Responders, and 60% (3 of 5) of the Non-Responders ($p = 0.07$). Landiolol, a selective β1-adrenergic receptor inhibitor, may suppress VTs due to triggered activities rather than reentrant mechanisms. Thus, landiolol can be useful for some patients with recurrent unstable VT or VF storm, even after class III antiarrhythmics have been administered.

To assess efficacy, we used 24-hour observation for controlling VTs in accordance with previous studies [20–22,25]. The mechanisms of sustained VT and electrical storm, incessant NSVT, and VF are sometimes different, but the available prior research strongly indicated that 24 h without VT/VF events should be enough to evaluate at least the short-term efficacy of treatment for lethal ventricular arrhythmias.

4.4. Study limitations

There are some important limitations. First, this study was retrospective and nonrandomized, and employed a small sample size at two cardiovascular hospitals. In addition, the follow-up period was short. Further study is required to investigate the efficacy and safety of landiolol in the long term. Second, we performed this study to evaluate the efficacy and safety of landiolol in patients with atrial or ventricular tachyarrhythmias. As such, we did not compare landiolol with digoxin or a control (only conventional therapy).

5. Conclusion

Landiolol is a new therapeutic option for (1) rapid AF in patients with decompensated HF and reduced LVEF, and has minimal adverse effects; and (2) refractory VTs in patients with nonischemic cardiomyopathy who have been receiving class III antiarrhythmic pretreatment. Further clinical evidence is needed to clarify the efficacy of landiolol in combination with other antiarrhythmic or heart rate control drugs.

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Conflict of interest

Takeshi Aiba has received consulting fees from Ono pharmaceutical. Yasuyuki Tsujita has received lecture fees from Ono Pharmaceutical. The other authors declare that there is no conflict of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.joa.2015.09.002.

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