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Original Article

Prevention of immediate recurrence of atrial fibrillation with low-dose landiolol after radiofrequency catheter ablation

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ABSTRACT

Background: Immediate recurrence of atrial fibrillation (AF) after radiofrequency (RF) catheter ablation is commonly observed within 3 d after the procedure. The mechanism and pharmacological management of immediate AF recurrence remain unclear.
Methods: A total of 50 consecutive patients with paroxysmal AF were randomized to receive either low-dose landiolol (landiolol group) or a placebo (placebo group). In the landiolol group, intravenous landiolol (0.5 μg kg^{-1} min^{-1}) was administered for 3 d after AF ablation.
Results: No serious adverse event associated with RF catheter ablation or landiolol administration was observed. The prevalence of immediate AF recurrence ($\leq$3 d after RF catheter ablation) was significantly lower in the landiolol group than in the placebo group (16% *vs.* 48%, $p=0.015$). Although the postprocedural change in heart rate was significantly lower in the landiolol group compared to that in the placebo group, the changes in blood pressure and body temperature were not different between the two groups. Multiple logistic regression analysis revealed that landiolol treatment was the only independent predictor of immediate AF recurrence after ablation (odds ratio: 0.180; 95% confidence interval: 0.044–0.729; $p=0.016$).
Conclusions: Prophylactic administration of low-dose landiolol after AF ablation may be effective and safe for preventing immediate AF recurrence within 3 d after AF ablation.

1. Introduction

Radiofrequency (RF) catheter ablation is becoming an effective therapy for drug-resistant atrial fibrillation (AF) [1]. However, the rate of AF recurrence after successful RF catheter ablation remains relatively high [2], and recurrences are common within 3 d after the procedure [3,4]. Immediate AF recurrence interferes with postprocedural management, prolongs hospital stays, and increases healthcare costs. However, immediate pharmacological management after AF ablation is often difficult because of a lack of drugs with both good efficacy and dose adjustability. Therefore, a new treatment strategy is needed for preventing immediate AF recurrence after ablation.

Although there is considerable evidence for a mechanistic link between cardiac sympathetic nervous dysfunction and the development of AF [5,6], it is not clear whether sympathetic nerve activity is related to immediate AF recurrence after catheter ablation. As left atrial (LA) ganglionated plexi is present in the vicinity of the pulmonary vein (PV), RF energy applications around the PV affect sympathetic nervous activation [7] and may be associated with immediate AF recurrence after catheter ablation. Several recent studies have described the efficacy of landiolol hydrochloride, an ultra-short-acting beta adrenoceptor antagonist, for the prevention of AF after open-heart surgery [8–11]. It has mainly been used to treat AF after cardiovascular surgery. Because of its extremely short half-life (4 min) and high β1 selectivity, landiolol may also be useful for controlling AF after RF catheter ablation without major side effects. At low doses, landiolol exerts a clinically relevant negative chronotropic effect without negative inotropic effects [11–14]. Accordingly, the purpose of the present study was to investigate the prophylactic effect of continuous low-dose landiolol administration against immediate AF recurrence after catheter ablation.

2. Methods

2.1. Patients

This study included 50 consecutive patients with symptomatic, drug-resistant, non-valvular paroxysmal AF who underwent RF

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Table 1
Baseline patient characteristics.

	All patients ($n=50$)	Placebo group ($n=25$)	Landiolol group ($n=25$)	p-Value
Age, years	58 ± 9	59 ± 10	57 ± 8	0.193
Male gender, *n* (%)	39 (78)	21 (84)	18 (72)	0.306
Systolic blood pressure, mmHg	118 ± 14	119 ± 12	117 ± 16	0.593
Diastolic blood pressure, mmHg	72 ± 10	72 ± 9	72 ± 11	0.855
Heart rate, bpm	64 ± 9	62 ± 11	66 ± 8	0.148
Duration of AF history, months (IQR)	38 (19–88)	35 (10–69)	39 (23–101)	0.218
$CHADS_2$ score, 0/1/2	25/21/4	16/8/1	9/13/3	0.126
Structural heart disease	8 (16)	3 (12)	5 (20)	0.700
Hypertension, *n* (%)	22 (44)	11 (44)	11 (44)	1.000
Diabetes mellitus, *n* (%)	4 (8)	1 (4)	3 (12)	0.602
TIA/stroke, *n* (%)	0 (0)	0 (0)	0 (0)	–
Dyslipidemia, *n* (%)	22 (44)	13 (52)	9 (36)	0.255
Medications				
ACE inhibitors or ARBs, *n* (%)	14 (28)	6 (24)	8 (32)	0.529
Oral β-blocker, *n* (%)	22 (44)	10 (40)	12 (48)	0.569
Statin, *n* (%)	10 (20)	4 (16)	6 (24)	0.724
Ineffective AADs				
Number of ineffective AADs (IQR)	3 (1–3)	2 (1–3)	3 (2–3)	0.337
Class I, *n* (%)	45 (90)	24 (96)	21 (84)	0.346
Amiodarone, *n*, (%)	8 (16)	1 (4)	7 (28)	0.054
Bepridil, *n* (%)	13 (26)	6 (24)	7 (28)	0.747
Laboratory data				
eGFR, mL/min · 1.73 cm^2	78 ± 16	80 ± 14	77 ± 17	0.492
hsCRP, mg/dL (IQR)	0.041 (0.027–0.077)	0.034 (0.024–0.055)	0.056 (0.029–0.090)	0.140
BNP, pg/mL (IQR)	34 (15–50)	25 (14–48)	37 (22–66)	0.048
Echocardiographic parameters				
LA diameter, mm	39 ± 6	39 ± 6	39 ± 6	1.000
LV end-diastolic dimension, mm	50 ± 5	49 ± 4	50 ± 5	0.749
LV ejection fraction, %	64 ± 7	64 ± 6	64 ± 9	0.969
RF catheter ablation				
Fluoroscopy time, min	87 ± 28	80 ± 21	96 ± 32	0.054
Procedure time, min	233 ± 48	241 ± 50	224 ± 46	0.221
CTI blockline, *n* (%)	14 (28)	8 (32)	6 (24)	0.529
CFAE ablation, *n* (%)	13 (26)	8 (32)	5 (20)	0.333

Data are presented as mean ± standard deviation. AAD, antiarrhythmic drug; ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; $CHADS_2$, congestive heart failure; hypertension; age ≥ 75; diabetes mellitus; prior stroke, transient ischemic attack, or thromboembolism; CFAE, complex fractionated atrial electrogram; CTI, cavotricuspid isthmus; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LA, left atrium; LV, left ventricle; RF, radiofrequency; TIA, transient ischemic attack.

catheter ablation at Yamagata University Hospital (Table 1). All patients had symptomatic, paroxysmal AF, which was defined as AF episodes that spontaneously terminated and lasted for > 30 s and < 7 d during treatment with antiarrhythmic drugs (AADs). All AADs were discontinued five half-lives before AF ablation with the exception of amiodarone, which was discontinued at least 6 weeks before the RF procedure. Patients who were treated with oral β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and/or statins at study enrollment continued to take these drugs with no change in dose until the end of AF ablation. Ethical approval was obtained from the institutional review committee (approval date, February 15, 2010; approval number, 148), and all patients gave their informed, written consent before participation.

2.2. Study protocol

This study was designed as a prospective, randomized, single blind study. All patients were equally randomized for treatment with landiolol (landiolol group) or a placebo (placebo group) on the first day of their hospitalization. In the landiolol group, 1 mg/mL of landiolol hydrochloride (Onoact, Ono Pharmaceutical Co., Osaka, Japan) in a 0.9% sodium chloride solution was administrated intravenously (0.5 μg kg^{-1} min^{-1}) for 3 d immediately after catheter ablation [15]. A placebo solution (0.9% sodium chloride) was intravenously administered to patients in the placebo group. All patients remained hospitalized under continuous rhythm monitoring from admission to discharge. Immediate AF recurrence was defined as AF or atrial tachycardia (AT) lasting > 5 min [10]. The primary end points of the study were the proportion of patients who were free of recurrent AF/AT in the 3 d immediately after catheter ablation and any serious complications caused by catheter ablation or landiolol treatment.

2.3. RF catheter ablation

Extensive PV isolation was performed with 3-dimensional mapping (CARTO®, Biosense Webster Inc., USA). After transseptal catheterization, a 7-Fr 10-polar ring catheter (Lasso, Biosense Webster, Inc., Diamond Bar, CA, USA) and a 7-Fr quadripolar ablation catheter with a 3.5-mm distal electrode and deflectable tip (ThermoCool, Biosense Webster) were positioned in the LA. Intravenous heparin was given to maintain an activated clotting time of 300–350 s during the entire procedure. After selective PV angiography, a single Lasso catheter was then positioned inside the PV within 5 mm of the ostium to map PV potentials. RF energy was delivered using the temperature control mode with a target temperature of 42 °C and a maximum power output of 25–35 W. The endpoint of extensive PV isolation was the creation of an extensive ipsilateral bidirectional conduction block, which was confirmed from the atrium to the PV and *vice versa*. In addition, the bidirectional conduction block was reconfirmed at least 60 min after successful PV isolation [6]. After PV isolation, if AF was sustained or induced with coronary sinus (CS) burst pacing at a