Journal of the American Heart Association

ORIGINAL RESEARCH

Preprocedural Troponin T Levels Predict the Improvement in the Left Ventricular Ejection Fraction After Catheter Ablation of Atrial Fibrillation/Flutter

Daisetsu Aoyama, MD; Shinsuke Miyazaki, MD, FHRS; Kanae Hasegawa, MD; Kenichi Kaseno, MD; Eri Ishikawa, MD; Moe Mukai, MD; Minoru Nodera, MD; Kosuke Miyahara, MD; Akira Matsui, MD; Yuichiro Shiomi, MD; Naoto Tama, MD; Hiroyuki Ikeda, MD; Yoshitomo Fukuoka, MD; Tetsuji Morishita, MD; Kentaro Ishida, MD; Hiroyasu Uzui, MD; Hiroshi Tada, MD, FHRS

BACKGROUND: Left ventricular (LV) systolic dysfunction is reversible in some patients once the arrhythmia is controlled. However, identifying this arrhythmia-induced cardiomyopathy among patients with LV systolic dysfunction is challenging. We explored the factors predicting the reversibility of the LV ejection fraction (LVEF) after catheter ablation of atrial fibrillation and/or atrial flutter in patients with LV systolic dysfunction.

METHODS AND RESULTS: Forty patients with a reduced LVEF (LVEF <50%; 66.2±10.7 years; 32 men) who underwent atrial fibrillation/atrial flutter ablation were included. Transthoracic echocardiography was performed before and during the early (<4 days) and late phases (>3 months) after the ablation. Responders were defined as having a normalized LVEF (≥50%) during the late phase after the ablation. The LVEF improved from 39.8±8.8 to 50.9±10.9% at 1.2±0.6 days after the procedure, and to 56.2±12.2% at 9.6±8.0 months after the procedure (both for $P<0.001$). Thirty (75.0%) patients were responders. The preprocedural echocardiographic parameters were comparable between the responders and nonresponders. In the multivariate analysis, the preprocedural high-sensitivity troponin T was the only independent predictor of the recovery of the LV dysfunction during the late phase after ablation (odds ratio, 1.17; 95% CI, 1.06–1.33; $P=0.001$), and a level of ≤12 pg/mL predicted recovery of the LV dysfunction with a high accuracy (sensitivity, 90.0%; specificity, 76.7%; positive predictive value, 56.3%; and negative predictive value, 95.8%).

CONCLUSIONS: Preprocedural high-sensitivity troponin T levels might be a simple and useful parameter for predicting the reversibility of the LV systolic dysfunction after atrial fibrillation/atrial flutter ablation in patients with a reduced LVEF.

Key Words: arrhythmia-induced cardiomyopathy ■ atrial fibrillation ■ catheter ablation ■ left ventricular dysfunction ■ troponin T

It has been widely accepted that left ventricular (LV) systolic dysfunction is reversible in a part of the patients once the arrhythmia is controlled, which is called arrhythmia-induced cardiomyopathy.[1] The LV ejection fraction (LVEF) is a well-known powerful factor for predicting the clinical outcome in patients with a reduced LVEF, and an improved or recovered LVEF by medical therapy contributes to a lower mortality and less frequent hospitalizations.[2] Catheter ablation of atrial fibrillation (AF) is gaining a significant role in heart failure treatment of patients with concomitant AF and atrial flutter (AFL), as confirmed by the guidelines,[3,4] and the superiority over antiarrhythmic drug therapy with respect to the mortality, hospitalizations, exercise capacity, and quality of life, has been reported in randomized control trials and meta-analyses.[3,5–7] However, in patients with

Correspondence to: Shinsuke Miyazaki, MD, FHRS, Department of Cardiovascular Medicine, Faculty of Medical Sciences, University of Fukui, 23-3 Matsuokashimoaizuki, Eiheiji-cho, Yoshida-gun, Fukui 910-1193, Japan. E-mail: mshinsuke@k3.dion.ne.jp

For Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The preprocedural high-sensitivity troponin T level was the only independent predictor of the recovery of the left ventricular (LV) systolic dysfunction during the late phase after the ablation, and a level of ≤12 pg/mL predicted the recovery of the LV dysfunction with a high accuracy.
- The preprocedural echocardiographic parameters could not differentiate between the responders and nonresponders.
- The preprocedural high-sensitivity troponin T levels did not correlate with any preprocedural echocardiographic parameters, but did with the ΔLV ejection fraction and ΔLV end-diastolic diameter.

What Are the Clinical Implications?

- The preprocedural high-sensitivity troponin T level could be an indicator for predicting the reversibility of the LV systolic dysfunction, which might aid in discriminating between arrhythmia-induced cardiomyopathy and dilated cardiomyopathy.

Nonstandard Acronyms and Abbreviations

ACEI	angiotensin-converting-enzyme inhibitor
AF	atrial fibrillation
AFL	atrial flutter
AIC	arrhythmia-induced cardiomyopathy
ARB	angiotensin 2 receptor blocker
BNP	brain natriuretic peptide
CFAEs	continuous fractionated atrial electrograms
DCM	dilated cardiomyopathy
hs-TnT	high-sensitive troponin T
LAD	left atrial diameter
LV	left ventricular
LVEF	left ventricular ejection fraction
LVDd	left ventricular end-diastolic diameter
LVDs	left ventricular end-systolic diameter
OR	odds ratio

AF and a reduced LVEF, there have been no absolute parameters that can distinguish arrhythmia-induced cardiomyopathy from dilated cardiomyopathy before the procedure. A few studies found that a smaller LV chamber size and less advanced ventricular fibrosis, which were evaluated by gadolinium-enhanced cardiac magnetic resonance imaging, predicted the improvement in the LV systolic function after AF ablation; however, a quantitative analysis is often challenging, and a simpler predictor is required in clinical practice.[8–10] The purpose of the present study was to explore the simple parameters predicting the reversibility of LV systolic dysfunction after catheter ablation of AF/AFL in patients with a reduced LVEF and concomitant AF/AFL.

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. This was a single-center, retrospective cohort analysis. Among 891 consecutive patients who underwent catheter ablation of AF/AFL in our hospital between January 2014 and December 2018, 40 with a reduced LVEF (<50%) before the catheter ablation in whom echocardiographic follow-up data were available at >3 months after the procedure, and a repeat procedure was not performed within 3 months of the blanking period. Two patients with implanted cardiac resynchronization therapy devices and those with renal failure on hemodialysis were excluded in advance. Finally, a total of 40 patients (AF/AFL/AF+AFL=30/6/4) were included in this study. The study complied with the Declaration of Helsinki. All patients gave their written informed consent. The study protocol was approved by the hospital's institutional review board. The data that support the findings of this study are available from the first author upon reasonable request.

Medical Treatment and Evaluation of the LV Function

All patients with AF/AFL and heart failure were on optimal tolerated medical therapy, which included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, diuretics, and digoxin when appropriate according to the guidelines.[11]

Transthoracic echocardiography was performed before, within 4 days (early phase), and at >3 months after the procedure (late phase) in all patients. A reduced LVEF was defined as an LVEF <50%, including heart failure with a reduced LVEF and midrange LVEF according to the latest guidelines.[11] A recovery of the LV dysfunction was defined as a normalization of the LVEF (≥50%) during the late phase after the ablation. The LVEF was measured by the Simpson method or M-mode using transthoracic echocardiography by independent technicians unaware of this study.

The serum high-sensitivity troponin T (hs-TnT) levels were analyzed using a highly sensitive quantitative

electrochemiluminescence immunoassay (Elecsys 2010; Roche Diagnostics, Mannheim, Germany). The lower limit of detection of the high-sensitivity assay was 3 pg/mL. The value of the hs-TnT levels at the 99th percentile in healthy populations is reported to be 14 pg/mL.[12] The plasma level of the high-sensitivity C-reactive protein and brain natriuretic peptide were also measured.

Catheter Ablation and Follow-Up

The procedure was performed under moderate sedation obtained with dexmedetomidine. A bolus of 5000 U of heparin was administered immediately following the venous access, and heparinized saline was additionally infused to maintain the activated clotting times at 300 to 350 seconds. A single transseptal puncture was performed using a radiofrequency needle (Baylis Medical., Montreal, Quebec, Canada). Pulmonary vein isolation was performed with either a 28-mm second-generation cryoballoon (Arctic Front Advance, Medtronic, Minneapolis, MN) or contact force-sensing irrigated-tip radiofrequency catheter (SmartTouch Surround Flow, Biosense Webster, Diamond Bar, CA) guided by a 3-dimensional mapping system (CARTO3, Biosense Webster). Bidirectional conduction block was created at the cavo-tricuspid isthmus, and additional substrate modification was performed according to the operators' preference.

After the procedure, we continued in-hospital electrocardiographic monitoring for 3 to 5 days. Regular follow-up by outpatient clinic visits was performed at 1 and

Table 1. Patient Clinical Characteristics

	Nonresponders (n=10)	Responders (n=30)	*P* Value
Age, y	69.8±10.9	65.0±10.6	0.23
Male sex, n (%)	8 (80.0)	24 (80.0)	1.00
Height, cm	164.1±12.8	166.9±9.4	0.46
Weight, kg	66.7±26.5	68.4±10.4	0.77
Body mass index, kg/m^2	24.1±5.9	24.5±3.1	0.76
Coronary artery disease, n (%)	2 (20.0)	6 (20.0)	1.0
Hypertension, n (%)	7 (70.0)	12 (40.0)	0.10
Diabetes mellitus, n (%)	5 (50.0)	9 (30.0)	0.25
Ablation methods			0.36
Radiofrequency ablation, n (%)	9 (90.0)	23 (76.7)	
Cryoballoon, n (%)	1 (9.0)	7 (23.3)	
Details of ablation procedures			
Pulmonary vein isolation, n (%)	10 (90.0)	25 (83.3)	0.61
Cavo-tricuspid isthmus, n (%)	10 (90.0)	26 (86.7)	0.78
Superior vena cava isolation, n (%)	1 (9.0)	0 (0)	0.08
Mitral isthmus line ablation, n (%)	4 (40.0)	12 (40.0)	1.0
Roof line ablation, n (%)	5 (50.0)	10 (33.3)	0.35
Bottom line ablation, n (%)	0 (0)	1 (3.3)	0.56
CFAEs ablation, n (%)	3 (30.0)	3 (10.0)	0.13
Nonpulmonary vein foci, n (%)	1 (9.0)	2 (6.7)	0.73
Physiological function test			
Heart rate, bpm	81.1±25.4	94.3±24.9	0.16
LV ejection fraction, %	37.7±11.1	40.5±8.0	0.38
LV end-diastolic diameter, mm	54.7±6.6	51.1±5.0	0.08
LV end-systolic diameter, mm	43.7±8.3	40.3±4.4	0.10
Left atrial diameter, mm	45.4±5.4	42.2±4.3	0.08
Laboratory test			
Brain natriuretic peptide, pg/mL	260.2±193.0	132.4±107.0	0.01
C-reactive protein, mg/dL	1.10±3.08	0.24±0.37	0.13
High-sensitivity troponin T, pg/mL	21.2±10.1	9.4±6.2	0.00008
Creatinine, mg/dL	1.15±0.26	0.99±0.22	0.07

Values are reported as the mean±standard deviation or number of patients (%) unless otherwise noted. CFAEs indicates continuous fractionated atrial electrograms; and LV, left ventricular.

3 months after the procedure. Subsequent follow-up visits consisted of a clinical interview, 12-lead ECG, and/or 24-hour Holter ECG recordings every 3 months. Recurrence was defined if an atrial arrhythmia lasting longer than 30 seconds was documented after a 3-month blanking period following the latest guidelines.[4]

Statistical Analysis

Continuous data are expressed as means±SD for normally distributed variables or the median [25th, 75th percentiles] for nonnormally distributed variables, and were compared using a Student *t* test or Mann–Whitney *U* test, respectively. Categorical variables were compared using the chi-square test. A paired t test was used when the subject was measured repeatedly. Statistical analysis of the echocardiographic parameters was initially analyzed using a repeated measures ANOVA. When group differences were found, a 1-way ANOVA with a Tukey-Kramer paired comparison method was used. A Pearson's correlation coefficient was used to determine the relationship between the hs-TnT levels and other variables. A multivariate stepwise logistic regression model was built to identify the independent preprocedure clinical parameters with an LVEF improvement, associated with an entry criterion of $P<0.1$ of the model in the univariate analysis. To evaluate the predictive value of the hs-TnT levels for the discrimination of the responders from the nonresponders, a receiver operating characteristic analysis was used, the area under the curve was calculated, and the possible cutoff points were selected. A *P* value of $P<0.05$ was considered statistically significant.

RESULTS

Catheter Ablation, Patient Characteristics, and Measurements Parameters

Catheter ablation was performed in all patients, and no procedural complications were observed except for transient gastric hypomotility in 2 patients. The LVEF increased at 1.2±0.6 days after the ablation (early phase: 39.8±8.8 to 50.9±10.9 [%]; $P<0.0001$). Furthermore, the LVEF during the early phase after the ablation further increased at 9.7±8.1 months after the ablation (late phase: 50.9±10.9 to 56.2±12.2 [%]; $P=0.001$). Sinus rhythm was maintained until the late phase of the follow-up period in all patients. On the basis of the results of the LVEFs during the late phase after the ablation, the patients were divided into 2 groups: patients whose LVEF was normalized (≥50%; n=30 [75%]; responders) and those with an LVEF <50% (n=10 [25%]; nonresponders).

The patient characteristics are shown in Table 1. No significant difference was found in the ablation methods or baseline (preprocedural) echocardiographic parameters between the responders and nonresponders. However, the baseline brain natriuretic peptide levels ($P=0.01$) and hs-TnT ($P=0.00008$) were lower in the responders than in the nonresponders.

The medications received before and after the ablation are shown in Table 2. The responders received diuretics less frequently than the nonresponders both before ($P=0.03$) and after ($P=0.001$) the ablation (Table 2). Five (41.7%) responders who had received diuretics before the ablation could stop taking them

Table 2. Medications Before and After the Ablation Procedure

	Nonresponders (n=10)	Responders (n=30)	*P* Value
Preprocedure			
Diuretics, n (%)	8 (80.0)	12 (40.0)	0.03
ACEI or ARB, n (%)	5 (45.5)	9 (30.0)	0.25
β-Blocker, n (%)	8 (72.7)	23 (76.7)	0.70
Aldosterone antagonist, n (%)	4 (36.4)	4 (13.3)	0.20
Antiarrhythmic drug, n (%)	7 (63.6)	16 (53.3)	0.71
Type I, n (%)	1 (9.1%)	10 (33.3)	
Type III, n (%)	6 (54.5)	6 (20.0)	
Postprocedure			
Diuretics, n (%)	8 (80.0)	7 (23.3)	0.001
ACEI or ARB, n (%)	4 (36.3)	14 (46.7)	0.71
β-Blocker, n (%)	7 (63.6)	20 (66.7)	0.70
Aldosterone antagonist, n (%)	4 (36.4)	5 (16.7)	0.16
Antiarrhythmic drug, n (%)	6 (54.5)	11 (16.7)	0.46
Type I, n (%)	1 (9.1)	4 (13.3)	0.76
Type III, n (%)	5 (45.5)	8 (26.7)	0.43

Values are reported as the number of patients (%) unless otherwise noted. ACEI indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin 2 receptor blocker.

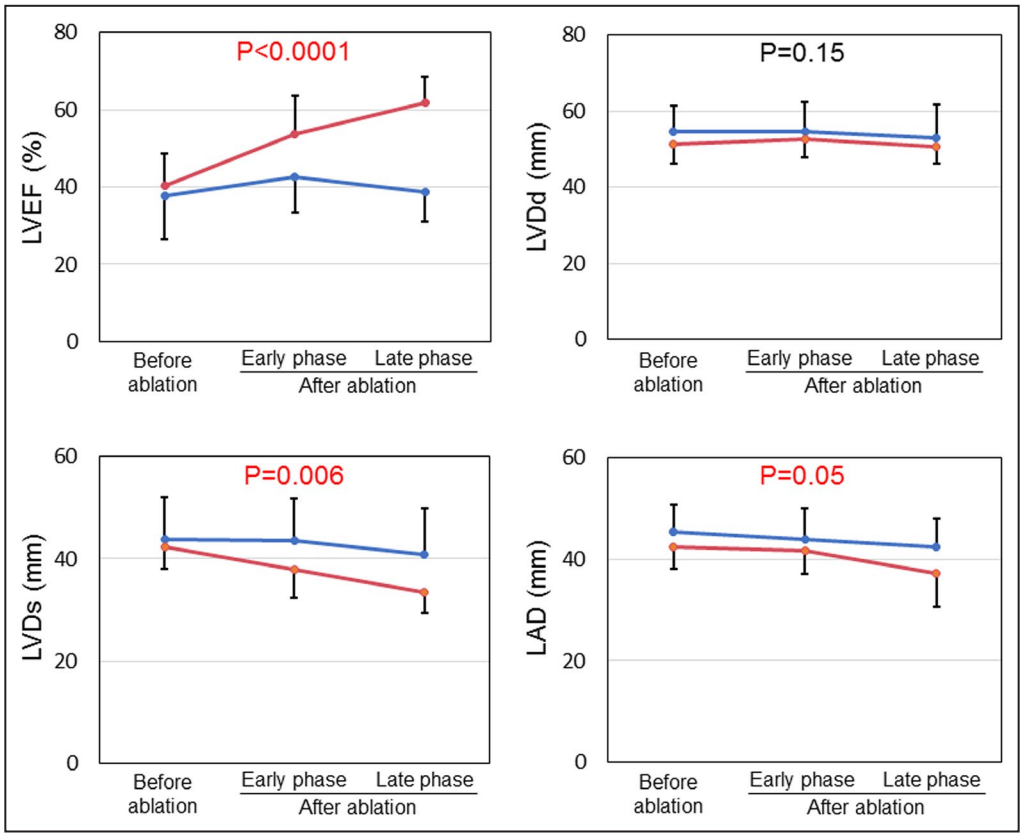

Figure 1. The serial changes in the left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), and left atrial diameter (LAD) before and after the ablation.
The red and blue lines indicate the responders and nonresponders, respectively.

after the ablation. However, in 8 (80.0%) nonresponders receiving diuretics before the ablation, none could discontinue the administration of the diuretics after the ablation.

Changes in the Echocardiographic Parameters After the Ablation

The time-course pattern during the follow-up period of the LV end-systolic diameter (LVDs; *P*=0.006) and left atrial diameter (LAD; *P*=0.05) as well as LVEF (*P*<0.0001) differed between the responders and nonresponders (Figure 1). Before and at early and late phases after the ablation, the LVDs as well as LVEF was smaller in the responders than in the nonresponders (all for *P*<0.05).

Predictors of an LVEF Improvement

A multivariable logistic regression analysis with a stepwise selection revealed that the preprocedural hs-TnT level was the only independent predictor of the LVEF improvement (LVEF ≥50%) during the late phase after the ablation (odds ratio, 1.17; 95% CI,

Table 3. Predictors of an LVEF Improvement in the Multivariate Stepwise Logistic Regression Analysis

	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Diuretics, n	6.00	1.24–44.56	0.02			
LVDd, mm	1.16	0.99–1.31	0.08	1.10	0.97–1.33	0.11
LAD, mm	1.18	0.99–1.46	0.06			
BNP, pg/mL	1.01	1.00–1.01	0.02			
hs-TnT, pg/mL	1.16	1.06–1.31	0.0007	1.17	1.06–1.33	0.001

Values are reported as the CI and odds ratio. BNP indicates brain natriuretic peptide; hsTnT, high-sensitivity troponin T; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter.

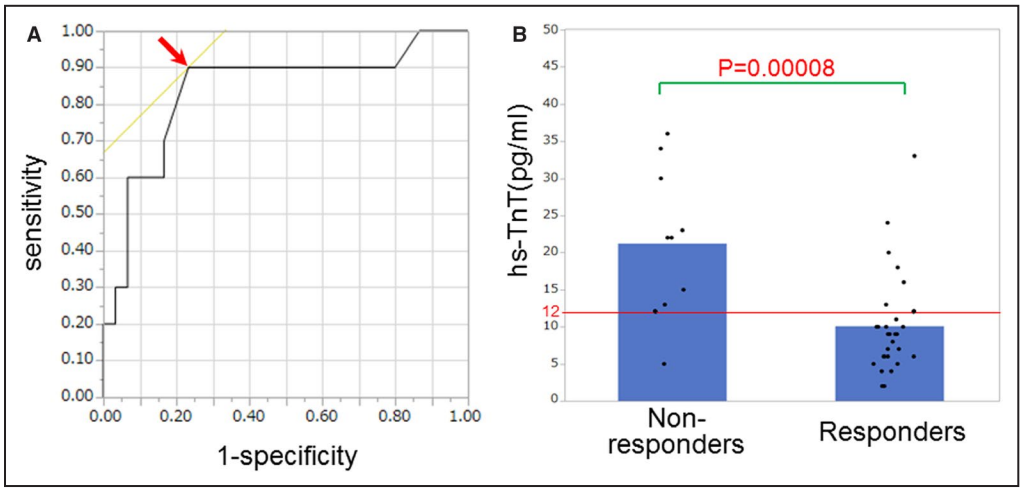

Figure 2. Receiver operating characteristic curve for the serum level of high-sensitivity troponin T (hs-TnT) to predict a recovery of the left ventricular dysfunction and the serum levels of the hs-TnT in the responders and non-responders.

A. Receiver operating characteristic curve showing the accuracy of the serum level of hs-TnT for predicting a recovery of the left ventricular dysfunction (ejection fraction ≥50%) after the ablation. The red arrow indicates the best cutoff value of the hs-TnT level predicting a significant LVEF increase after the procedure. **B.** The blue bars indicate the average hs-TnT level in the non-responders and responders. Each black dot indicates the hs-TnT value in each patient. The red line is the best cutoff value of the hs-TnT level (≤12 pg/ml) to predict a recovery of the left ventricular dysfunction during the late phase after the procedure.

1.06–1.33; *P*=0.001; Table 3). By a receiver operator characteristic analysis, an hs-TnT level of 12 pg/mL was the threshold value for a recovery of the LVEF with a 90.0% sensitivity, 76.7% specificity, 56.3% positive predictive value, and 95.8% negative predictive value (area under the curve, 0.83; *P*=0.004; Figure 2A). The baseline hs-TnT levels in the nonresponders were greater than those in the responders (*P*<0.0001; Figure 2B). An LVEF improvement was achieved in 92.3% of the patients with a preprocedural hs-TnT level of ≤12 pg/mL.

The magnitude of the LVEF improvement during the late phase after the ablation from the baseline (ΔLVEF) was significantly greater in the patients with an hs-TnT value of ≤12 pg/mL (20.8±9.7%) than in those without (hs-TnT >12 pg/mL; 8.1±10.4%; *P*=0.0007). The patients with a low hs-TnT level (≤12 pg/mL) were older (*P*=0.04) and received diuretics (*P*=0.008) less frequently than those without (Table 4). However, the preprocedural echocardiographic parameters were comparable between the patients with an hs-TnT value of ≤12 pg/mL and those without.

Relationship Between the Preprocedural hs-TnT Level and Echocardiographic Parameters

The preprocedural hs-TnT level was not correlated with the preprocedural LVEF (*r*=−0.097; *P*=0.55), left ventricular end-diastolic diameter (*r*=0.11; *P*=0.49), or LVDs (*r*=0.16; *P*=0.32). A weak positive correlation was found in the preprocedural hs-TnT level and preprocedural LAD (*r*=0.37; *P*=0.02).

The preprocedural hs-TnT level was not correlated with the changes in the left ventricular end-diastolic diameter (*r*=0.068; *P*=0.68) or LAD (*r*=0.12; *P*=0.47) from the baseline to the late phase after the ablation (Figure 3). However, it significantly correlated with from the changes in the LVEF (ΔLVEF; *r*=−0.47; *P*=0.002) and LVDs (ΔLVDs; *r*=0.37; *P*=0.02) from baseline to the late phase after the ablation (Figure 3).

Long-Term Outcome After the Ablation

During a mean follow-up of 20.3±14.1 months, a total of 8 (20%) patients including 5 (50%) nonresponders and 3 (10%) responders (*P*=0.01), experienced recurrent AF. None of the responders were hospitalized due to heart failure. However, 2 nonresponders experienced hospitalizations attributable to heart failure. Both patients had recurrent AF, and the preprocedural hs-TnT levels exceeded the cutoff value of 12 pg/mL (30 and 36 pg/mL). No patients had any thromboembolic events or death during a long-term follow-up period.

DISCUSSION

Major Findings

The results of this study that included AF/AFL patients with LV systolic dysfunction undergoing catheter ablation demonstrated the following: (1) After the ablation

Table 4. Clinical Parameters in Patients With Low (≤12 pg/mL) and High (>12 pg/mL) Levels of the hs-TnT

	Low TnT Group (n=26)	High TnT Group (n=14)	*P* Value
Age, y	63.7±10.8	70.9±9.8	0.04
Male sex, n (%)	21 (80.8)	12 (85.7)	0.87
Height, cm	167.6±9.3	163.6±11.8	0.25
Weight, kg	68.9±10.8	66.3±22.3	0.62
Body mass index, kg/m^2	24.5±3.1	24.3±5.2	0.90
Coronary artery disease, n (%)	4 (15.4)	4 (28.6)	0.32
Hypertension, n (%)	10 (38.5)	9 (64.3)	0.12
Diabetes mellitus, n (%)	7 (26.9)	7 (50.0)	0.14
Medications			
Diuretics, n (%)	9 (34.6)	11 (78.6)	0.008
ACEI or ARB, n (%)	8 (30.8)	6 (42.9)	0.44
β-Blocker, n (%)	21 (80.8)	9 (64.3)	0.25
Aldosterone antagonist, n (%)	3 (11.5)	4 (28.6)	0.18
Antiarrhythmic drug, n (%)	16 (61.5)	6 (42.9)	0.26
Type I, n (%)	10 (38.5)	1 (7.1)	
Type III, n (%)	6 (23.1)	5 (35.7)	
Ablation methods			0.14
Radiofrequency ablation, n (%)	19 (73.1)	13 (92.9)	
Cryoballoon, n (%)	7 (26.9)	1 (7.1)	
Physiological function test			
Heart rate, bpm	92.4±24.1	88.4±28.3	0.55
LV ejection fraction, %	39.6±8.3	40.2±10.0	0.93
LV end-diastolic diameter, mm	51.8±4.9	52.5±6.7	0.96
LV end-systolic diameter, mm	40.8±4.9	41.8±7.2	0.99
Left atrial diameter, mm	42.3±4.4	44.5±5.3	0.48
Laboratory test			
Brain natriuretic peptide, pg/mL	131.9±113.3	224.6±173.3	0.14
C-reactive protein, mg/dL	0.25±0.37	0.83±2.61	0.32
Creatinine, mg/dL	0.98±0.19	1.12±0.30	0.15

Values are reported as the mean±standard deviation or number of patients (%) unless otherwise noted. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; hs-TnT, high-sensitivity troponin T; and LV, left ventricular.

and restoration of sinus rhythm, the LVEF progressively improved, and it normalized during the late phase after the ablation in 75% of the patients (responders); (2) the preprocedural echocardiographic parameters could not tell the difference between the responders and nonresponders; (3) the preprocedural hs-TnT level was the only independent predictor of the recovery of the LV systolic dysfunction during the late phase after the ablation, and its level of ≤12 pg/mL predicted the recovery of the LV dysfunction with a high accuracy; and (4) the preprocedural hs-TnT levels did not correlate with any preprocedural echocardiographic parameters but did with the ΔLVEF and ΔLVDs. These findings indicated that the preprocedural hs-TnT level is a simple and reliable predictor of the reversibility of the LV systolic dysfunction after catheter ablation of AF/AFL.

Cardiac Troponins

Cardiac troponins are sensitive markers of cardiac injury and have been widely used for the diagnosis of acute coronary syndrome. However, recent evidence using the developed assay with an improved sensitivity suggest that cardiac troponins can be elevated in chronic disease states, including stable coronary arterial disease, heart failure,[13] and AF/AFL, and apparently healthy subjects.[14] However, the origin behind an elevated cardiac troponin level is still under debate, and the pathophysiology behind the serum troponin T may be distinct from that seen during myocardial infarctions. It may be attributable to mechanisms such as an oxygen demand/mismatch and myocardial ischemia, volume and pressure overloads, changes in the microvascular blood flow, atrial calcium overload, oxidative stress, or alterations in the tissue structure.[15] The results are consistent in patients with dilated cardiomyopathy: persistently increasing troponin T concentrations were associated with ongoing deterioration of the cardiac function and adverse outcomes in patients with dilated cardiomyopathy,[16] and the patients with elevated hs-TnT values (>14 pg/mL) had significantly more frequent cardiac events than did those with normal values.[17] These data suggested that troponin T was a quantitative marker that could indicate the presence of injury and the extent of damage to myocardial cells, and that an elevated troponin T level indicated persistent subclinical myocyte degeneration.

In patients with heart failure and/or AF/AFL, elevated troponin levels are also associated with more severe disease and a worse outcome.[16,18,19] In the present study, the preprocedural echocardiographic parameters were comparable between the responders and nonresponders, but the hs-TnT level was lower in the responders than nonresponders. Furthermore, the preprocedural hs-TnT level was the only independent predictor of the recovery of the LV function after the ablation. The magnitude of reverse remodeling of the LVDs and LAD following the ablation was greater in the responders than in the nonresponders, and the preprocedural hs-TnT levels correlated with the ΔLVEF and ΔLVDs. These data suggested that a preprocedural hs-TnT level, not a

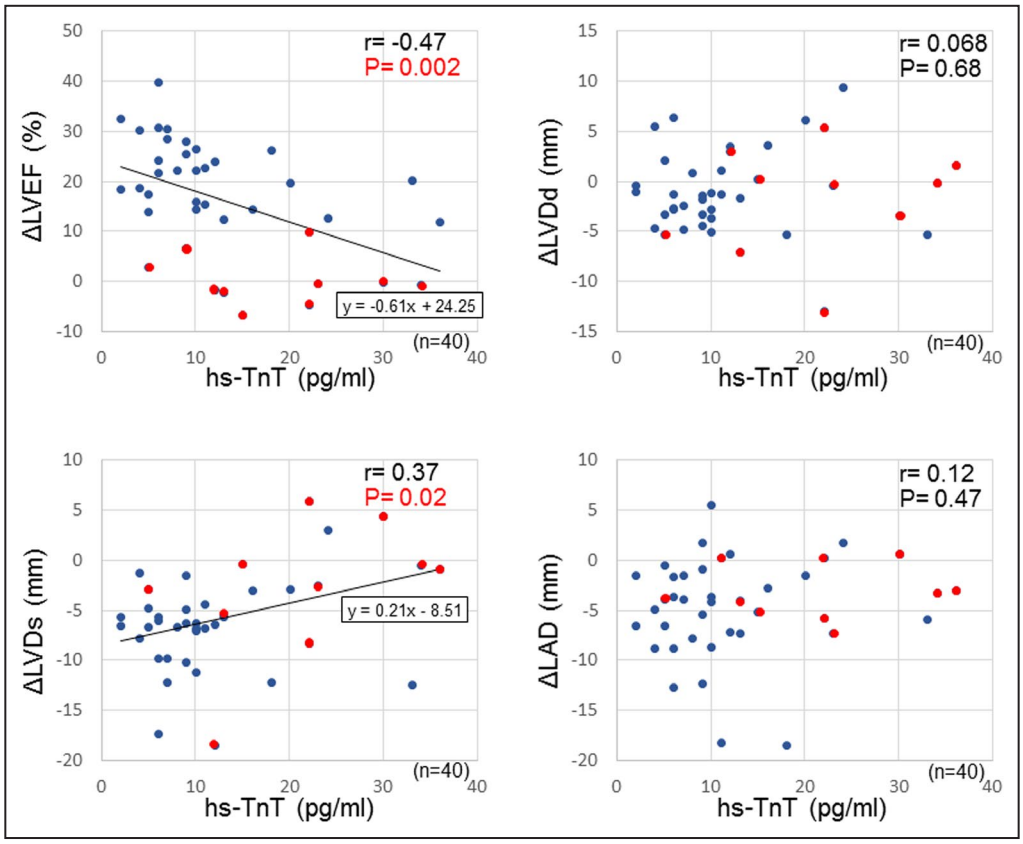

Figure 3. Correlations between the serum high-sensitivity troponin T (hs-TnT) level and changes in the echocardiographic parameters from baseline to the late phase after the ablation.
The red and blue circles indicate the responders and non-responders, respectively. LAD indicates left atrial diameter; LVDd(s), left ventricular end-diastolic (end-systolic) diameter; and LVEF, left ventricular ejection fraction.

preprocedural echocardiographic parameter, was a sensitive and useful predictor of reverse structural remodeling including the recovery of the LV dysfunction in AF/AFL patients with LV systolic dysfunction following the ablation. It is well known that reverse structural remodeling more likely occurs in patients who have a relatively healthy myocardium with less fibrosis.[10] In this study, the responders might have had a healthier myocardium with less fibrosis than the nonresponders, and the preprocedural hs-TnT levels could detect latent myocardial damage.[19]

Reverse Structural Remodeling and Cardiac Troponins

The present study showed that the LVEF significantly improved by 16.4% during the late phase after catheter ablation of AF/AFL. This was in line with the 8% to 18% improvement in the LVEF after AF ablation in patients with systolic dysfunction in the prior studies,[10,20] suggesting that the baseline patient characteristics and medical therapy in the present study were similar to the other studies.

With the restoration and maintenance of sinus rhythm, some AF patients with LV systolic dysfunction have an sufficient improvement in the cardiac dysfunction and reverse structural remodeling, but others do not.[21,22] For predicting AF recurrences after the ablation, several parameters, including the LA size and AF type and duration, have been reported. However, few studies have focused on AF/AFL patients with LV systolic dysfunction or attempted to clarify the predictors of reverse structural remodeling after ablation. Further, no studies have examined the relationship between the hs-TnT levels and reverse structural remodeling in those patients. In the present study, we demonstrated for the first time that the preprocedure hs-TnT level could predict reverse remodeling including the recovery of the LV dysfunction after AF/AFL ablation. The preprocedural echocardiographic parameters were not useful for predicting the reverse remodeling.

In the present study, the LVEF and LVDs progressively improved after the ablation, but the reduction in the LAD became apparent >3 months after the ablation in the responders. Previous studies also reported

the same findings, indicating the time discrepancy of the reverse remodeling between the atrium and ventricle.[23,24] We think that an interruption in the vicious circle between AF and heart failure and restoration of regular cardiac cycles might make a relatively faster reverse remodeling of the ventricle possible in patients with LV systolic dysfunction. However, it might take a longer time to reverse structural remodeling of the atria in those patients.

Clinical Implications

In clinical practice, predicting the reversibility of LV systolic dysfunction after treatment of AF/AFL is often challenging before the procedure. Our study clarified that the preprocedural hs-TnT level could be an indicator predicting the reversibility of the LV systolic dysfunction, which might aid in discriminating between arrhythmia-induced cardiomyopathy and dilated cardiomyopathy. Moreover, it is a preprocedural predictor, and might be independent of the preprocedural echocardiographic parameters. The measurement of the hs-TnT level is easy and available in the vast majority of hospitals. The general availability of cardiac troponin measurements for routine care in most hospitals worldwide makes cardiac troponin a very attractive candidate for use to identify patients with arrhythmia-induced cardiomyopathy (responders) among the patients with a reduced LVEF.

Limitations

This study had some limitations. First, this was a single-center retrospective study, and the sample size was relatively small. This may alter the power of the statistical analysis, and several confounding parameters could potentially interact with the results. The results need to be consolidated in a prospective study. Second, the hs-TnT level after the ablation was not measured, and its utility was unclear. However, the magnitude of the myocardial injury, including the hs-TnT levels, differ with the different energy sources of AF ablation,[25] and the assessment of the postprocedural hs-TnT levels might be difficult in the era of radiofrequency and balloon ablation. Third, gadolinium-enhanced cardiac magnetic resonance imaging was not performed in this study because of the high cost and lack of reimbursement for AF patients in Japan.

CONCLUSIONS

The LV systolic function significantly improved after catheter ablation of AF/AFL in patients with LV systolic dysfunction and concomitant AF/AFL. The preprocedural serum hs-TnT level might be a simple and useful preprocedural parameter predicting the reversibility of LV systolic function.

ARTICLE INFORMATION

Received October 29, 2019; accepted February 11, 2020.

Affiliations

From the Department of Cardiovascular Medicine, Faculty of Medical Sciences, University of Fukui, Japan.

Acknowledgments

We thank John Martin for his help in the preparation of the manuscript.

Disclosures

None.

REFERENCES

1. Huizar JF, Ellenbogen KA, Tan AY, Kaszala K. Arrhythmia-induced cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:2328–2344.
2. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, Burkman G, Siwamogsatham S, Patel A, Li S, Papadimitriou L, Butler J. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. *JAMA Cardiol*. 2016;1:510–518.
3. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC Multicenter Randomized Trial. *Circulation*. 2016;133:1637–1644.
4. Calkins H, Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *J Arrhythm*. 2017;33:369–409.
5. Ichijo S, Miyazaki S, Kusa S, Nakamura H, Hachiya H, Kajiyama T, Iesaka Y. Impact of catheter ablation of atrial fibrillation on long-term clinical outcomes in patients with heart failure. *J Cardiol*. 2018;72:240–246.
6. Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. *Eur Heart J*. 2016;37:2478–2487.
7. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol*. 2013;61:1894–1903.
8. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018;378:417–427.
9. Campos B, Jauregui ME, Park KM, Mountantonakis SE, Gerstenfeld EP, Haqqani H, Garcia FC, Hutchinson MD, Callans DJ, Dixit S, et al. New unipolar electrogram criteria to identify irreversibility of nonischemic left ventricular cardiomyopathy. *J Am Coll Cardiol*. 2012;60:2194–2204.
10. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. *J Am Coll Cardiol*. 2017;70:1949–1961.
11. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200.
12. Everett BM, Cook NR, Magnone MC, Bobadilla M, Kim E, Rifai N, Ridker PM, Pradhan AD. Sensitive cardiac troponin T assay and the risk of incident cardiovascular disease in women with and without diabetes mellitus: the Women's Health Study. *Circulation*. 2011;123:2811–2818.
13. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol*. 2010;56:1071–1078.
14. Park KC, Gaze DC, Collinson PO, Marber MS. Cardiac troponins: from myocardial infarction to chronic disease. *Cardiovasc Res*. 2017;113:1708–1718.

15. Eggers KM, Lind L, Ahlstrom H, Bjerner T, Ebeling Barbier C, Larsson A, Venge P, Lindahl B. Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. *Eur Heart J*. 2008;29:2252–2258.
16. Sato Y, Yamada T, Taniguchi R, Nagai K, Makiyama T, Okada H, Kataoka K, Ito H, Matsumori A, Sasayama S, et al. Persistently increased serum concentrations of cardiac troponin T in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. *Circulation*. 2001;103:369–374.
17. Baba Y, Kubo T, Yamanaka S, Hirota T, Tanioka K, Yamasaki N, Sugiura T, Kitaoka H. Clinical significance of high-sensitivity cardiac troponin T in patients with dilated cardiomyopathy. *Int Heart J*. 2015;56:309–313.
18. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. *Circulation*. 2003;108:833–838.
19. Tamura S, Doi A, Matsuo M, Katayama H, Yoshiyama T, Tatsumi H, Izumiya Y, Yoshiyama M. Prognostic value of high-sensitive troponin T for predicting cardiovascular events after atrial fibrillation ablation. *J Cardiovasc Electrophysiol*. 2019;30:1475–1482.
20. Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E, Bergamasco L, Boffano C, Valentini MC, Cesarani F, et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol*. 2013;62:1990–1997.
21. Machino-Ohtsuka T, Seo Y, Ishizu T, Yanaka S, Nakajima H, Atsumi A, Yamamoto M, Kawamura R, Koshino Y, Machino T, et al. Significant improvement of left atrial and left atrial appendage function after catheter ablation for persistent atrial fibrillation. *Circ J*. 2013;77:1695–1704.
22. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol*. 2014;7:31–38.
23. Kagawa Y, Fujii E, Fujita S, Ito M. Association between left atrial reverse remodeling and maintenance of sinus rhythm after catheter ablation of persistent atrial fibrillation. *Heart Vessels*. 2020;35:239–245.
24. Lo LW, Chen SA. Cardiac remodeling after atrial fibrillation ablation. *J Atr Fibrillation*. 2013;6:877.
25. Casella M, Dello Russo A, Russo E, Al-Mohani G, Santangeli P, Riva S, Fassini G, Moltrasio M, Innocenti E, Colombo D, et al. Biomarkers of myocardial injury with different energy sources for atrial fibrillation catheter ablation. *Cardiol J*. 2014;21:516–523.