Rate Versus Rhythm Control in Tachycardia-Induced Cardiomyopathy Patients with Persistent Atrial Flutter

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Summary

Tachycardia-induced cardiomyopathy (TIC) is a potentially reversible cardiomyopathy caused by tachyarrhythmia. For atrial flutter (AFL)-induced TIC, a rhythm control strategy, such as catheter ablation, has been recommended. However, the efficacy of rate control has remained unclear due to the difficulty of achieving control using arrhythmic medications.

We prospectively assessed 47 symptomatic heart failure (HF) patients with left ventricular ejection fraction (LVEF) < 50% and suspected persistent AFL-induced TIC. Patients were divided into the rhythm control strategy (n = 22; treatment with catheter ablation or electrical cardioversion) and rate control strategy (n = 25; treatment with bisoprolol) groups. The latter was further divided into the strict rate control strategy (average heart rate < 80 bpm) and lenient rate control strategy (average heart rate < 110 bpm) subgroups. The primary outcome was left ventricular (LV) function recovery, which was defined as an increase in LVEF ≥ 20% or to a value of ≥ 55% after 6 months.

In the rhythm control strategy group, more patients achieved LV function recovery after 6 months (95.2% versus 60.9%, P = 0.010). The cumulative incidence of worsening HF events was significantly higher in the rate control strategy group than in the rhythm control strategy group (hazard ratio, 4.66; 95% confidence interval, 1.01-21.57). The subgroup study revealed the advantage of the strict rate control strategy for achieving LV function recovery (83.3% versus 36.4%, P = 0.036).

The rate control strategy was significantly inferior to the rhythm control strategy for the LV function recovery in TIC patients with persistent AFL. Our findings suggest that the strict rate control strategy should be aimed if the rhythm control strategy cannot be performed.

Key words: Tachyarrhythmia, Heart failure, Left ventricular dysfunction

Tachycardia-induced cardiomyopathy (TIC) is a potentially reversible left ventricular (LV) dysfunction caused by tachyarrhythmia.1) The early recognition of TIC and treatment of the culprit arrhythmia using pharmacological therapy or catheter ablation before the progression of cardiac remodeling result in LV function recovery.2) In TIC cases induced by atrial flutter (AFL), invasive rhythm control strategies, such as catheter ablation, electrical cardioversion, or His bundle ablation with pacemaker implantation, are reportedly effective.3,4) In contrast, the efficacy of the rate control strategy for AFL-induced TIC has never been elucidated due to the difficulty of achieving pharmacological rhythm or rate control in AFL. However, not all patients with AFL-induced TIC are candidates for rhythm control therapy; thus, a rate control strategy using β-blockers is sometimes required.

This prospective study aimed to establish whether a rate control strategy using a β-blocker is as effective as an invasive rhythm control strategy for achieving LV function recovery in patients with AFL-induced TIC.

Methods

Study population: This study included symptomatic heart failure (HF) patients with LV ejection fraction (LVEF) < 50% suggestive of rapid AFL-induced TIC. Consecutive HF patients who were hospitalized at Fujieda Municipal General Hospital (Japan) and documented persistent AFL were screened for eligibility. All participants provided written informed consent before enrollment. We divided the patients into the rhythm control strategy group (treated with catheter ablation or electrical cardioversion) and the rate control strategy group (treated with bisoprolol) according to the patients’ decisions based on their informed consent. In the rate control strategy group, the targeted average heart rate ranged from 50 to 109 bpm.

The exclusion criteria were as follows: all-cause in-hospital death, age < 20 years, New York Heart Associa-
tion (NYHA) class I, LVEF $\geq 50\%$, brain natriuretic peptide (BNP) level $< 100 \, \text{pg/mL}$, AFL rate at admission $< 100 \, \text{bpm}$, inadequate heart rate control (average heart rate of $< 50 \, \text{bpm}$ or $\geq 110 \, \text{bpm}$), estimated glomerular filtration rate (eGFR) $< 30 \, \text{mL/minute/1.73 m}^2$ or hemodialysis, malnutrition, active malignant tumor, active inflammatory disease, active bronchial asthma or allergy to contrast media, pregnancy, refusal to provide informed consent, ischemic, or other cardiomyopathy, significant valvular heart disease, history of atrial fibrillation or AFL, medication for arrhythmia, myocardial infarction, cardiac surgery, and pacemaker implantation. Myocardial ischemia was detected using coronary angiography. Patients with coronary artery stenosis $\geq 90\%$ on angiography were excluded for having ischemic cardiomyopathy. Patients with extracellular volume fraction (ECV) $> 26\%$ calculated on cardiac magnetic resonance (CMR) were excluded for having other cardiomyopathy.  

The study protocol was in accordance with the 1975 Declaration of Helsinki and approved by the ethics committee of Fujieda Municipal General Hospital.

**Baseline evaluation and data collection:** At admission, all patients underwent blood examinations and electrocardiography. The common-type AFL was defined as inverted P’ waves (sawsmooth pattern) in leads II, III, and aVF and upright P’ waves in lead V1. The baseline AFL heart rate was determined by recording electrocardiography for 3 minutes. Serum hemoglobin, eGFR, and BNP levels were measured. Moreover, the BNP level was measured routinely at 6 months. Average heart rates were evaluated using Holter electrocardiography immediately after the therapeutic intervention. At admission and at three and six months after the start of treatment, ultrasonic echocardiography was performed by two cardiologists who were blinded to the patients’ backgrounds using Aplio 400™ (Canon Medical Systems Corporation, Tochigi, Japan). LVEF was measured using the modified Simpson method. All CMR tests were conducted using a 3.0-Tesla Ingenia™ scanner (Philips, Eindhoven, Netherlands) with a 32-element cardiac receiver coil. T1 maps were generated before and 15 minutes after injection with gadolinium contrast (Gadovist™ 0.1 mmol/kg) using a modified Look-Locker inversion recovery sequence during end-expiration breath-holding. This was performed to produce 11 raw images with increasing inversion times (TI, 100-5000 ms) in a LV short-axis view (TR/TE, 2.20/1.02 ms; flip angle, 20°). Blood samples were collected for hematocrit determination within 24 hours prior to the scan. All maps were analyzed using ZioStation2™ ver.2.9 2-2 (Ziosoft, Tokyo, Japan). Myocardial T1 values were determined by drawing regions of interest in each segment of the LV slice according to the American Heart Association 16-segment model. ECV was calculated using the following formula: ECV = (1 – hematocrit) $\times$ (1/T1 value myocardium post – 1/T1 value myocardium pre) / (1/T1 value blood post – 1/T1 value blood pre). 

**Outcomes:** Patients were prospectively followed up, and their outcomes after 6 months were compared. The primary outcome was LV function recovery, which was defined as an increase in LVEF $\geq 20\%$ or to a value of $\geq 55\%$ at 6 months (Table I). Secondary outcomes were the cumulative incidence of worsening HF events: HF re-hospitalization or urgent HF visit (definitions are presented in Table I), NYHA class, serum BNP level, LV end-diastolic dimension (LVEDd), and ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity ($E'/e'$) at six months. 

**Subgroup study:** Referring to the Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison Between Lenient and Strict Rate Control II (RACE II) study, the
rate control strategy group was further divided into the strict rate control strategy (average heart rate, 50-79 bpm) and lenient rate control strategy (average heart rate, 80-109 bpm) subgroups; these two groups were compared upon LV function recovery at 6 months. Furthermore, LV function recovery was also compared between the rhythm and strict rate control strategy groups.

Statistical analysis: We included data obtained from all patients in the analysis of baseline characteristics, primary outcome, and secondary outcomes according to the intention-to-treat principle. Patient baseline characteristics were summarized as means and standard deviation (SD). Student’s t-test was used to compare the differences between the two groups of normally distributed variables. The categorical variables were compared using Fisher’s exact test. Time-to-event data was evaluated using the Kaplan-Meier estimate. The predictive values of the variables were assessed using the univariate or stepwise multivariate Cox proportional hazards analysis. The baseline variables with P values < 0.10 in the univariate analysis were included in the multivariable models. In the univariate and multivariate Cox proportional hazards analyses, 1-SD increases in the values of the continuous variables were examined. All statistical tests were two-tailed, and P values < 0.05 were considered significant. IBM® SPSS® Statistics version 19.0 (SPSS, Chicago, IL, USA) was used for statistical analyses.

Results

Patients: A total of 77 HF patients with persistent AFL were hospitalized between April 1, 2017 and June 1, 2019 and screened for eligibility. The flow diagram of the recruitment of this cohort is presented in Figure 1. A total of 47 patients were enrolled and divided into the rhythm (n = 22) and rate (n = 25) control strategy groups. The baseline characteristics of the two groups are presented in Table II. The rate control strategy group consisted of more elderly and female patients than the rhythm control strategy group. No significant differences were observed in baseline heart rate, NYHA class, LVEF, LVDd, E/e’, serum hemoglobin, eGFR, and BNP levels.

Arrhythmias: At admission, all participants were diagnosed with common-type AFL with a ventricular response /c033 100 bpm. As most patients were unaware of their arrhythmia, the duration of AFL from onset to diagnosis was usually unknown. In the rhythm control strategy group, 16 of 22 (72.7%) patients underwent radio frequency catheter ablation to control the arrhythmias, whereas the others were treated with electrical cardioversion. After treatment, the average heart rate was 71.7 ± 12.6 bpm. The duration of AFL from diagnosis to restoration of sinus rhythm was 4.9 ± 6.4 weeks. Moreover, 18 (81.8%) patients remained in sinus rhythm and were free from arrhythmias after 6 months. In contrast, as a result of the rate control strategy, sinus rhythm was restored in only 6 of 25 (24.0%) patients. Another nine patients (36.0%) of the rate control strategy group remained in AFL, whereas the others were converted to atrial fibrillation. After treatment, the average heart rate was 87.1 ± 15.2 bpm.

The arrhythmic medications prescribed at discharge are presented in Table II. For patients with LV dysfunction, bisoprolol is one of the few available agents used to control the AFL heart rate by slowing down atrioventricular nodal conduction and prolonging refractoriness. It was
Table II. Baseline Characteristics

| Backgrounds                                      | Rhythm control strategy group | Rate control strategy group | P-value  |
|--------------------------------------------------|-------------------------------|-----------------------------|----------|
| **Age [years]***                                 | 71.2 ± 8.8                    | 79.7 ± 6.8                  | 0.001*** |
| **Male gender [%] ***                            | 17 (77.3)                     | 8 (32.0)                    | 0.001*** |
| **Body mass index [kg/m²]**                      | 21.7 ± 2.9                    | 21.5 ± 4.3                  | 0.881    |
| **NYHA class**                                   | 3.1 ± 0.8                     | 3.1 ± 0.8                   | 0.962    |
| **Systolic blood pressure [mmHg]**               | 129.6 ± 13.4                  | 126.5 ± 21.9                | 0.561    |
| **AFL heart rate [bpm]**                         | 137.3 ± 14.8                  | 135.8 ± 17.1                | 0.742    |
| **Hypertension**                                 | 9 (40.9)                      | 14 (56.0)                   | 0.312    |
| **Type 2 diabetes mellitus**                     | 9 (40.9)                      | 7 (28.0)                    | 0.362    |
| **Hemoglobin [g/dL]**                            | 14.0 ± 2.1                    | 13.6 ± 1.6                  | 0.463    |
| **eGFR [mL/minute/1.73 m²]**                     | 59.4 ± 15.9                   | 58.5 ± 19.2                 | 0.861    |
| **BNP [pg/mL]**                                  | 649.4 ± 308.3                 | 538.4 ± 410.0               | 0.305    |
| **LAD [mm]**                                     | 44.7 ± 8.5                    | 43.6 ± 6.0                  | 0.611    |
| **LVEDd [mm]**                                   | 51.1 ± 7.1                    | 48.0 ± 6.5                  | 0.136    |
| **LVEF [%]**                                     | 30.8 ± 11.0                   | 34.7 ± 10.1                 | 0.213    |
| **E/e’**                                         | 13.7 ± 5.8                    | 14.3 ± 5.4                  | 0.586    |
| **Medication at discharge**                      |                               |                             |          |
| **Bisoprolol [%]**                               | 21 (95.5)                     | 25 (100)                    | 0.329    |
| **Digoxin [%]**                                  | 0 (0.0)                       | 1 (4.0)                     | 0.354    |
| **Amiodarone [%]**                               | 6 (27.3)                      | 0 (0)                       | 0.011*** |
| **ACEi/ARB [%]**                                 | 17 (77.3)                     | 19 (76.0)                   | 0.920    |
| **MRA [%]**                                      | 8 (36.4)                      | 9 (36.0)                    | 0.990    |
| **Loop diuretics [%]**                           | 20 (90.9)                     | 25 (100)                    | 0.162    |
| **Tolvaptan [%]**                                | 1 (4.5)                       | 1 (4.0)                     | 0.925    |
| **SGLT2i [%]**                                   | 6 (27.3)                      | 3 (12.0)                    | 0.202    |

Plus–minus values are means ± standard deviations. All statistical tests were two-tailed, and P < 0.05 was considered significant (*). AFL indicates atrial flutter; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LAD, left atrial dimension; LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; E/e’, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Figure 2. Primary outcome. A: Left ventricular (LV) function recovery, defined as an increase in LV ejection fraction (LVEF) ≥ 20% or to a value of ≥ 55%. B: The percentage of patients with an LVEF ≥ 55% at 6 months alone.

used in all the patients in the rate control strategy group. In the rhythm control strategy group, amiodarone was used in six patients treated with electrical cardioversion. None of the patients experienced the adverse effects of their arrhythmic medications. Primary outcome: More patients achieved LV function recovery after 3 and 6 months in the rhythm control strategy group (3 months: 72.7% versus 26.1%, P = 0.007; 6 months: 95.2% versus 60.9%, P = 0.010; Figure 2A) than in the rate control strategy group. After 6 months, the percentages of patients with LVEF normalization (LVEF ≥ 55%) were significantly higher in the rhythm control strategy group than in the rate control strategy group (76.2% versus 34.8%, P = 0.008; Figure 2B). In the rate control strategy group, 4 of 9 patients who remained in AFL during 6 months exhibited LV function recovery, of whom
Secondary outcomes: The cumulative incidence of worsening HF events was significantly higher in the rate control strategy group than in the rhythm control strategy group (log-rank: \( P = 0.03 \); hazard ratio [HR], 4.66; 95% confidence interval [CI], 1.01-21.57; Figure 3). To determine the predictors of worsening HF events, established HF parameters and TIC-related variables were evaluated using the Cox proportional hazard analysis. The univariate Cox proportional hazard analysis revealed that age (HR, 1.12; 95% CI, 1.04-1.21), NYHA class (HR, 1.83; 95% CI, 1.04-3.21), treated average heart rate (HR, 1.97; 95% CI, 1.09-3.56), sinus rhythm restoration (HR, 0.09; 95% CI, 0.01-0.68), and LV function recovery within 3 months (HR, 0.10; 95% CI, 0.01-0.77) were independent predictors of worsening HF events (Table III). In the stepwise multivariate Cox proportional hazard analysis, NYHA class (HR, 4.93; 95% CI, 1.98-12.29) and LV function recovery within 3 months (HR, 0.05; 95% CI, 0.004-0.70) remained as significant predictors of worsening HF events (Table III). The NYHA class improved to 1.3 ± 0.6 in the rhythm control strategy group and 1.5 ± 0.6 in the rate control strategy group (\( P = 0.238 \)). At 6 months, the rhythm control strategy group exhibited a significantly lower mean BNP level than the rate control strategy group (184.4 ± 175.2 pg/mL versus 394.2 ± 282.4 pg/mL, respectively, \( P = 0.005 \); Figure 4A). No significant intergroup differences were observed in LVDd or E/e’ at 6 months (47.1 ± 6.3 mm versus 46.4 ± 5.6 mm, \( P = 0.668; 13.0 ± 6.1 \) versus 14.7 ± 8.9, \( P = 0.448 \), respectively; Figure 4B, C).
Figure 4. Secondary outcomes and subgroup study. A: The effects of the rhythm and rate control strategies on the brain natriuretic peptide (BNP) level. B: Left ventricular (LV) end-diastolic dimension (Dd). C: Ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e’). D: The percentages of LV function recovery in the rhythm control strategy group and strict and lenient rate control strategy subgroups.

Subgroup study: We divided the rate control strategy group into the strict rate control strategy (n = 12) and lenient rate control strategy (n = 12) subgroups according to the results of the Holter electrocardiography assessment. The percentages of patients whose LV function recovered after 6 months were significantly higher in the strict rate control strategy subgroup than in the lenient rate control strategy subgroup (3 months: 41.7% versus 9.1%, \( P = 0.155 \); 6 months: 83.3% versus 36.4%, \( P = 0.036 \), respectively; Figure 4D). However, no significant differences were observed between the rhythm control and strict rate control strategy groups in terms of LV function recovery after 6 months (95.2% versus 83.3%, \( P = 0.602 \)).

Discussion

Recovery of LV function: This study revealed that the rhythm control strategy is significantly superior to the rate control strategy in terms of LV function recovery in TIC patients with persistent AFL. In the rhythm control strategy group, 76.2% of the patients achieved LVEF normalization after 6 months. This result is consistent with those of previous reports on the treatment effects of catheter ablation for TIC due to AFL or atrial fibrillation. However, the proportion of LVEF normalization in the rate control strategy group was significantly smaller than that in previous studies. The advantage of the rhythm control strategy in LV function recovery among TIC patients with persistent AFL was suggested.

Another primary finding of this study is that the strict rate control strategy using bisoprolol is as effective as an invasive rhythm control strategy for LV function recovery in TIC patients with persistent AFL. For the strict rate control strategy subgroup, treatment with bisoprolol achieved LV function recovery at a high rate. In addition, the following results suggested that the rate control strategy is not completely invalid: (1) more than half of the patients in the rate control strategy group achieved LV function recovery and (2) LVDd reductions were similarly observed in both the rate and rhythm control strategy groups. Sairaku et al. reported that rate control during atrial fibrillation without sinus conversion may result in an incomplete cure of TIC, suggesting an advantage of the rhythm control strategy. However, several studies controversially reported high efficacy of the rate control strategy for TIC due to atrial fibrillation. In other words, the rhythm control strategy is the ultimate rate control strategy. As the high ventricular response rate is the most integral factor in the TIC etiology, the most important factor that should be considered for its treatment may not be the way of arrhythmic control itself but the achievement of strict heart rate reduction. Thus, our study findings indicated that for the treatment of AFL-induced TIC, the rate control strategy should be employed if rhythm control therapy cannot be performed. In those cases, the targeted heart rate should be strict whenever possible.

Re-hospitalization or urgent visit for HF: The worsening HF event rate was higher in the rate control strategy group than in the rhythm control strategy group. Re-hospitalization or urgent visit for HF occurred predomi-
nantly within 100 days. Univariate and multivariate Cox proportional hazard analyses revealed that LV function recovery within 3 months is an independent predictor of worsening HF events. At 3 months following the therapeutic intervention, 72.7% of the patients in the rhythm control strategy group and 26.1% of those in the rate control strategy group achieved LV function recovery. The rhythm control strategy improved LV function sooner than the rate control strategy. This difference affected the result.

Additionally, univariate Cox proportional hazard analysis revealed that sinus rhythm restoration was also an independent predictor of worsening HF events in this study. Although the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study suggested equivalent outcomes of the pharmacological rhythm control strategy and rate control strategy for HF with atrial fibrillation, investigators emphasized the potential benefit of maintaining the sinus rhythm if it was achieved without the adverse effects of arrhythmic medications. Then, several studies evaluated HF patients with atrial fibrillation and demonstrated the efficacy of maintaining the sinus rhythm with catheter ablation for HF treatment. Furthermore, based on the results of meta-analysis, β-blocker therapy led to the improvement of HF prognosis in patients with sinus rhythm, but not in patients with atrial fibrillation. Thus, evidence of the efficacy of the β-blocker for HF without sinus rhythm is lacking. These results indicate the important contribution of atrial systole and atrioventricular synchrony to the total cardiac output. Unsurprisingly, in this study, the percentage of patients with sinus rhythm restoration was higher in the rhythm control strategy group than in the rate control strategy group. Thus, more patients in the rate control strategy group than in the rhythm control strategy group had AFL with weak atrial systole or atrial fibrillation without atrial systole and atrioventricular synchrony. The significant reduction of the serum BNP level after 6 months in the rhythm control strategy group indicated a reduction in atrial wall stress. Differences between patients with and without sinus rhythm could also influence the left atrial performance and results.

For HF patients with TIC, the restoration and maintenance of both atrial and ventricular function recovery. To prevent the worsening of HF events in TIC patients with AFL, the rhythm control strategy should be employed whenever possible.

**Study limitations:** This study has several limitations. First, it was a small non-randomized cohort study conducted at a single center. Thus, several biases were possible; in particular, the older mean age of the rate control strategy group could have negatively affected various outcomes. Although the time-to-event data should be evaluated using the age-adjusted Kaplan-Meier estimates and the Cox proportional hazards models, this was impossible due to the limited number of cases. Second, only 3 of the 77 patients who were screened for eligibility underwent myocardial biopsy; thus, we performed coronary angiography and CMR to increase the diagnostic accuracy of TIC. However, the possibility that patients with other cardiomyopathy were still included cannot be denied. Furthermore, cases of other arrhythmias such as atrial tachycardia might have been included because a cardiac electrophysiological study was not conducted in all participants. Third, we performed only a short-term assessment of LV function. If the follow-up period had been longer, there might have been more patients in the rate control strategy group in whom LV function had been restored.

**Conclusion**

The rate control strategy is significantly inferior to the rhythm control strategy for LV function recovery in TIC patients with persistent AFL. The rhythm control strategy should be the first choice of treatment for AFL-induced TIC. For cases not indicated for the rhythm control strategy, the strict rate control strategy should be aimed.

**Disclosure**

**Conflicts of interest:** The authors declare no conflicts of interest.

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