When should antiarrhythmic drugs concomitant with catheter ablation for persistent atrial fibrillation be discontinued? –The importance of left atrial reverse remodeling–

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February 15, 2025

Abstract

Introduction: Antiarrhythmic drugs are often administered after catheter ablation (CA) in patients with atrial fibrillation (AF); however, it is unclear for how long it should be continued. **Methods:** We administered hybrid therapy consisting of CA and bepridil to 130 patients with persistent AF and left atrial (LA) enlargement (volume index >48 ml/m ^{2}). After a 2-month of hybrid therapy, bepridil discontinuation was attempted. All patients underwent echocardiography 6 months after CA. We investigated the relationship between the duration of bepridil administration and the recurrence of AF after bepridil discontinuation. **Results:** After excluding patients who were unable to maintain sinus rhythm during bepridil administration (n=18), and those who disagreed to bepridil discontinuation (n=17), 95 patients were divided into the short-term continuation (bepridil discontinued for <6 months [median 3.0 months] after CA [n=63]), and long-term continuation (bepridil discontinued for >6 months [median 11.4 months] after CA [n=32]) groups. During the mean follow-up period of 28±15 months, the groups showed a similar incidence of recurrent AF after bepridil discontinuation. In the long-term continuation group, 13 patients had recurrence, with 8 (62%) cases occurring within 4 months after discontinuation. A multivariate Cox regression analysis revealed that left atrial (LA) reverse remodeling (>15% decrease in LA volume index at 6 months) was an independent predictor of recurrent AF after CA (p<0.01). **Conclusions:** Long-term bepridil administration after CA did not affect the recurrence of AF after discontinuation. The assessment of LA reverse remodeling may be useful for decision-making regarding the discontinuation of antiarrhythmic drugs after CA.

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data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

funding statement: The authors did not receive support from any organization for the submitted work.

conflict of interest disclosure: The authors declare no conflicts of interest in association with the present study.

ethics approval statement: The study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Niigata University Medical and Dental Hospital (Approval No. 2024-0149).

patient consent statement: We applied Opt-out method to obtain consent on this study by using the poster approved by the Institutional Review Board.

permission to reproduce material from other sources: We did not use any reproduced materials.

clinical trial registration: This study is not a clinical trial.

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Abstract

Introduction: Antiarrhythmic drugs are often administered after catheter ablation (CA) in patients with persistent atrial fibrillation (AF); however, it is unclear for how long it should be continued.

Methods: We administered hybrid therapy consisting of CA and bepridil to 130 patients with persistent AF and left atrial (LA) enlargement (volume index >48 ml/m^2). After a 2-month of hybrid therapy, bepridil discontinuation was attempted. All patients underwent echocardiography 6 months after CA. We investigated the relationship between the duration of bepridil administration and the recurrence of AF after bepridil discontinuation.

Results: After excluding patients who were unable to maintain sinus rhythm during bepridil administration (n=18), and those who disagreed to bepridil discontinuation (n=17), 95 patients were divided into the short-term continuation (bepridil discontinued for <6 months [median 3.0 months] after CA [n=63]), and long-term continuation (bepridil discontinued for >6 months [median 11.4 months] after CA [n=32]) groups. During the mean follow-up period of 28±15 months, the groups showed a similar incidence of recurrent AF after bepridil discontinuation. In the long-term continuation group, 13 patients had recurrence, with 8 (62%) cases occurring within 4 months after discontinuation. A multivariate Cox regression analysis revealed that left atrial (LA) reverse remodeling (>15% decrease in LA volume index at 6 months) was an independent predictor of recurrent AF after CA (p<0.01).

Conclusions: Long-term bepridil administration after CA did not affect the recurrence of AF after discontinuation. The assessment of LA reverse remodeling may be useful for decision-making regarding the discontinuation of antiarrhythmic drugs after CA.

Key words: bepridil, atrial fibrillation, catheter ablation, reverse remodeling

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia observed in clinical practice. It can occur even in the absence of heart disease and is associated with a significant burden on patients and healthcare. Recently, it has been suggested that rhythm control therapy, including antiarrhythmic drugs (AADs) and catheter ablation (CA), may prevent not only subjective symptoms such as palpitations and shortness of breath but also AF-related death, heart failure, and stroke in high-risk patients.[1] However, in patients with an enlarged left atrium (LA), the sinus rhythm maintenance rate is reported to be only 40–60%.[2,3] A large number of patients are treated with AADs in combination with CA for refractory AF.[4] Bepridil is effective in terminating long-lasting persistent AF,[5] and is recommended as the standard AAD for rhythm control in persistent AF in the guidelines for AF.[6] However, it is unclear how long bepridil in combination with CA should be continued and the benefits of long-term administration remain to be determined. Prolonged use of bepridil sometimes causes remarkable QT prolongation and life-threatening arrhythmias, including torsades de pointes, particularly in the elderly.[7]

In some cases of AF, the LA size decreases after rhythm control, which is considered to indicate LA reverse remodeling.[8] In addition, previous experimental studies have suggested that bepridil has a reverse electrical remodeling effect.[9,10] LA reverse remodeling could lead to favorable outcomes in the late phase.[11,12] In this study, we investigated the differences in post-ablation outcomes depending on the duration of the concomitant use of bepridil, and the impact of LA reverse remodeling on maintenance of sinus rhythm after hybrid therapy **consisting of CA and bepridil.**

Methods

Study population

We enrolled 130 consecutive patients who received CA and bepridil for persistent AF with severe LA enlargement for the first time at Niigata University Medical and Dental Hospital and Niigata Medical Center between 2017 and 2021. All patients were hospitalized for AF. Persistent AF was defined as continuous AF lasting for more than 7 days. We considered an LA volume index >48 ml/m^2(as measured by echocardiography) to indicate severe LA enlargement.[13]

To observe the outcomes following the discontinuation of bepridil, cases in which bepridil discontinuation was not attempted as well as those in which AF was noted before bepridil discontinuation were excluded. Patients with any history of cardiomyopathy, moderate-to-severe valvular heart disease, or renal insufficiency (serum creatinine level [?]1.5 mg/dl) were also excluded. None of the patients reported any history of hospitalization associated with heart failure. This study was approved by the Institutional Research Board of the Niigata

University Medical and Dental Hospital. Niigata, Japan, and was conducted in accordance with the Declaration of Helsinki.

Echocardiography

Two-dimensional (2D) echocardiography was performed within 1 month before CA and at 6 months of follow-up. Comprehensive transthoracic echocardiography was performed using commercially available equipment (Vivid 7 or Vivid E95; GE Vingmed Ultrasound AS; Horten, Norway). LV end-diastolic and LA diameters were measured using 2D echocardiography according to the recommended criteria.[14] LV ejection fraction (LVEF) was calculated from 2D recordings using the modified biplane Simpson's method. The LA volume was assessed using the modified biplane area-length method and indexed to the body surface area. Doppler flow and tissue Doppler imaging measurements were performed to assess conventional diastolic parameters. During AF rhythm before CA, the peak early (E) diastolic velocity was assessed from the mitral inflow velocity pattern. Mitral annular motion velocity was recorded from the septal corner of the mitral annulus in the apical 4-chamber view using pulsed tissue Doppler. The peak early diastolic velocity (e') of the annulus was measured, and the ratio of the peak early diastolic transmitral flow velocity to the annular velocity (E/e') was calculated. The average of 5 consecutive Doppler signals was used for all measurements.

Ablation procedure

All patients provided their written informed consent before the ablation procedures. All patients received effective anticoagulation therapy with a direct oral anticoagulant for >1 month. Catheterization of the LA was performed using a 1-puncture 2-sheath technique. Unfractionated heparin was administered intravenously to maintain an activated clotting time of 300–350 s after the transseptal puncture. Thereafter, a 3.5-mm irrigated ablation catheter with contact force monitoring (ThermoCool Biosense Webster; Biosense Webster, Inc., Diamond Bar, CA, USA) and Pentaray Catheter (Biosense Webster, Inc.) were introduced through the sheaths. Bilateral circumferential PV isolation was performed using a 3D mapping system (CARTO3; Biosense Webster, Inc.). The radiofrequency current was delivered point-by-point for 30–35 s with a power of up to 35 W, a target temperature of <43degC, and an irrigation rate of 30 ml/min. The power of the radiofrequency current was limited to 25 W on the posterior wall close to the esophagus. The endpoint of PV isolation was bidirectional conduction block of the PVs identified by a multipolar catheter. If AF continued after this procedure, internal electrical cardioversion was performed. Αδδιτιοναλ αβλατιον, συςη ας τηατ οφ τηε ΛΑ λινεαρ λεσιον (ΛΑ ροοφ λινε ανδ μιτραλ ιστημυς λινε) ανδ ρεγιονς ωιτη ςομπλεξ φραςτιοναтεδ ελεςτρογραμς, ωας περφορμεδ ιφ τηε ΑΦ ςουλδ νοτ βε ελεςτριςαλλψ ςαρδιοερτεδ αφτερ Π″ ισολατιον. Αφτερ ρεστορατιον οφ σινυς ρηψτημ, α ςαοτριςυσπιδ ιστημυς λινε ωας ςρεατεδ ωιτη τηε ενδποιντ οφ βιδιρεςτιοναλ ςονδυςτιον βλοςκ ιν αλλ πατιεντς. Ιφ τηερε ωερε νον-Π″ φοςι υνδερ ισοπροτερενολ ινφυσιον (5–10 μγ/μιν), ωε αβλατεδ τηεμ.

Bepridil administration and discontinuation

Bepridil was administered to all patients at an initial dose of 100 mg/day within 1 month before CA and continued for at least 2 months after CA. The maximum dose of bepridil was 200 mg/day. If the QTc interval exceeded 500 ms, bepridil was either discontinued or the dosage was reduced. All patients were recommended to discontinue bepridil 2 to 3 months after CA. However, continuation was allowed upon the patient's request, and subsequent discontinuation was determined based on mutual agreement between the attending physician and the patient.

Follow-up

Follow-up was performed every 1–2 months at the outpatient clinic. Patient history and

12-lead electrocardiograms were recorded at every visit. If patients experienced symptoms suggestive of arrhythmia between scheduled visits, they were instructed to visit the emergency department. Electrocardiography was performed to identify the cause of their symptoms. Recurrence of AF was defined as documentation of AF lasting more than 30 s and confirmed by ECGs. The first 3 months after CA were defined as the blanking periods for recurrent AF.[15] If AF was identified during the blanking period, cardioversion was performed and sinus rhythm restoration was confirmed.

Definition of LA reverse remodeling

To study the determinants of reverse remodeling of the LA after rhythm control therapy, all patients underwent echocardiography 6 months after CA. To ensure the same duration of sinus rhythm, patients undergoing cardioversion for AF during the blanking period underwent echocardiography 6 months after the last cardioversion. The study population was divided into 2 groups according to the extent of the decrease in LA volume index. LA reverse remodeling was defined as a [?]15% reduction in LA volume index at 6 months after CA.[16]

Data analyses

Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Data are expressed as the mean±standard deviation (SD) or number (percentage). Differences in parameters between responders and non-responders were analyzed using Student's *t*-test for continuous variables and Fisher's exact test for categorical variables. The Mann-Whitney U test was used for continuous variables that were highly skewed. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. The association between potential predictors of the recurrence of AF after bepridil discontinuation was assessed by a univariate Cox regression analysis. The following variables were selected for the univariate analysis: age, sex, body mass index, AF history, presence of hypertension, diabetes mellitus, CHADS2 score, duration of bepridil use, LA volume index, LA reverse remodeling, and the recurrence of AF during the blanking period. Predictive factors with P values of <0.05 in a univariate analysis were entered into the multivariate Cox regression analysis. Two-sided P values of <0.05 were considered statistically significant.

Results

Patient characteristics at baseline

Of the 130 patients with persistent AF and severe LA enlargement who received CA and bepridil, 18 were unable to maintain sinus rhythm for more than 1 month during bepridil administration, and 17 did not agree to discontinue treatment. The remaining 95 patients were divided into the short-term continuation group (bepridil discontinued for <6 months [median 3.0 months] after CA [n=63]) and long-term continuation group (bepridil discontinued for >6 months [median 11.4 months] after CA [n=32]). Of the long-term continuation group, 5 patients discontinued bepridil due to QT prolongation, and the remaining 27 patients discontinued bepridil when the attending physician recommended discontinuation and the patient agreed. PV isolation was successfully performed in all 95 patients.**Nine patients (4 in the short-term** continuation **group and 5 in the long-term** continuation **group) underwent cardioversion for AF during the blanking period.**

The comparison of baseline characteristics between the short- and long-term continuation groups **is summarized in Table 1. Patients in the long-term** continuation **group were older than those in the short-term** continuation **group (mean age, 63±9 vs. 67±8 years; P=0.043). There were no marked differences in the other clinical characteristics.**

Clinical outcomes

The follow-up periods after CA in the short-term and long-term continuation groups were 27 ± 15 months

and 29 ± 15 months, respectively, while the follow-up periods after bepridil discontinuation in the same groups were 24 ± 14 months and 17 ± 15 months, respectively. A Kaplan-Meier analysis of recurrent AF with the date of ablation procedure (A) and the date of bepridil discontinuation (B) as the starting points is shown in Figure 1. The frequency of recurrent AF was similar between the 2 groups. In the long-term continuation group, 13 patients had recurrence, with 8 (62%) cases occurring within 4 months after bepridil discontinuation (Figure 1B).

Change in LA volume index after CA

The changes in the LA volume index before and 6 months after CA or t**he last cardioversion** in both groups are shown in Figure 2. Only 2 patients in the short-term continuation group were in AF rhythm at follow-up. The others were in sinus rhythm. In comparison to baseline, the LA volume index was significantly decreased at follow up in both groups (both $p<0.01$). There were no significant differences in the LA volume index between the two groups at the follow-up. Based on the cutoff value ([**?**] 15% reduction in LA volume index), the percentage of patients who achieved LA reverse remodeling was comparable between patients in the short-term continuation group (46/63, 73%) and long-term continuation group (19/32, 59%) ($p=0.24$).

Predictors of the recurrence of AF

Univariate and multivariate analyses were performed to identify the predictors of the recurrence of AF after CA. The results of the Cox regression analysis are presented in Table 2. In the multivariate analysis, LA reverse remodeling (hazard ratio, 0.19; 95% confidence interval, 0.08–0.46; $p<0.01$) and early recurrence during the blanking period (hazard ratio, 3.03; 95% confidence interval 1.12–8.12; $p=0.027$) were independently associated with the recurrence of AF after CA.

The Kaplan-Meier analysis showed that patients who achieved LA reverse remodeling had significantly fewer recurrences of AF after CA than those who did not (Figure 3).

Discussion

The present study showed that (1) among **patients treated with CA plus bepridil for persistent AF with severe LA enlargement,** the duration of bepridil use did not affect the rate of recurrent AF after CA, and (2) the presence of LA reverse remodeling at 6 months of follow-up was an independent predictor of the recurrence of AF after CA.

Concomitant use of AADs after CA

Some reports have demonstrated the benefit of the concomitant use of AADs after CA. A previous randomized controlled trial in patients with paroxysmal AF showed that the continued use of AADs beyond the blanking period after CA significantly reduced the incidence of recurrent AF.[17] A retrospective cohort study reported that the concomitant use of bepridil was particularly useful for suppressing AF after CA.[18] However, data on the duration of AADs combined with CA for AF are still limited. In the EAST-AF and AMIO-CAT trials, the use of AADs limited to the blanking period after CA did not reduce the overall rate of recurrent AF during long-term follow-up.[19,20] To our knowledge, this is the first report comparing the effects of the short-term and long-term use of bepridil after CA for persistent AF. In our cohort, the duration of bepridil administration did not affect the outcome after bepridil discontinuation. Notably, most cases of recurrent AF in the long-term continuation group occurred within a few months of bepridil discontinuation, suggesting that bepridil significantly contributed to the maintenance of sinus rhythm, but did not have a carryover effect after discontinuation in these patients.

LA reverse remodeling as a predictor of the maintenance of sinus rhythm after bepridil discontinuation

AF causes shortening of the refractory period and conduction delay (electrical remodeling) in the atrial myocardium due to downregulation of L-type Ca2+ channels, which leads to contractile and structural remodeling of the atria.[21,22] This remodeling has been demonstrated to facilitate the initiation and maintenance of AF and to cause LA enlargement.[8,21,23] Like some of our cohort, active restoration of sinus rhythm could induce anatomic and/or functional reverse remodeling of the cardiac chambers.[24,25]

Bepridil has been reported to have a reverse electrical remodeling effect, as well as an antiarrhythmic effect, by blocking multiple ion channels.[6] In a canine model, bepridil suppressed effective atrial refractory period shortening, inducibility, and duration of AF.[9,10] Bepridil has also been reported to improve calcium handling in the atrial muscle and to promote recovery from mechanical remodeling.[26] The combined use of bepridil after CA may more potently promote LA reverse remodeling and may be effective in patients with persistent AF fibrillation and LA enlargement.[18] Conversely, patients without LA reverse remodeling at follow-up after hybrid therapy may have irreversible structural remodeling and may be more likely to experience a recurrence of AF after bepridil discontinuation. For such patients, it may be better to continue bepridil to maintain sinus rhythm, focusing on its antiarrhythmic effects rather than reverse remodeling effect. The assessment of LA reverse remodeling may be useful for predicting the recurrence of AF after bepridil discontinuation.

Limitations

The present study was associated with several limitations. First, this was a non-randomized, retrospective study. Second, the small number of patients with AF may have influenced the interpretation of the results. Third, asymptomatic AF episodes may have been missed after CA. Fourth, there are no uniform standards for introducing bepridil. Finally, the duration of bepridil use was left to the discretion of the individual physicians in outpatient clinics. Thus, a prospective, randomized controlled study is needed to confirm these findings.

Conclusion

Our analysis demonstrated that long-term bepridil administration after CA in patients with persistent AF with an enlarged left atrium did not significantly reduce the rate of recurrent AF after the discontinuation of bepridil. The evaluation of LA reverse remodeling at 6 months after CA by echocardiography may be useful for predicting outcomes after the discontinuation of antiarrhythmic drugs.

Acknowledgments: The authors are grateful to Brian Quinn for editing the English text of this paper**.** We did not obtain any funding for this study.

Conflicts of interest Statement: The authors declare no conflicts of interest in association with the present study.

Declarations:

- **Approval of the research protocol:** All protocols in the present study were approved by the **Institutional Research Board of the Niigata University Medical and Dental Hospital (2024-0149)** .
- **Informed Consent:** N/A
- **Registry and the Registration No. of the study/trial:** N/A
- **Animal Studies:** N/A

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Figure 1.

Kaplan–Meier analysis of freedom from atrial fibrillation recurrence. (A) Starting point was defined as the date of ablation procedure. (B) Starting point was defined as the date of bepridil discontinuation.

Figure 2.

Changes in left atrial volume index before and after catheter ablation in the short-term continuation group and long-term continuation group. Box plots show the median, interquartile range, and range of the results. LA, left atrial; CA, catheter ablation

Figure 3.

Kaplan–Meier analysis of freedom from atrial fibrillation recurrence according to with or without left atrial reverse remodeling. (A) Starting point was defined as the date of ablation procedure. (B) Starting point was defined as the date of bepridil discontinuation. LA, left atrial

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