



ORIGINAL RESEARCH

Baroreflex Sensitivity in Patients With Atrial Fibrillation

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BACKGROUND: It has been reported that atrial fibrillation (AF) may contribute to impairment of baroreflex sensitivity (BRS). However, the difference of BRS between patients with persistent AF (PeAF) and those with paroxysmal AF (PAF) is unknown. We tested the hypothesis that patients with PeAF have a more impaired BRS compared with those with PAF.

METHODS AND RESULTS: From October 2015 onwards, a total of 67 patients (14 women [20.9%]; mean age 65.2±10.1 years) with PAF (n=46, 68.7%) and PeAF (n=21, 31.3%), who underwent catheter ablation, were prospectively enrolled. The baseline BRS was evaluated during sinus rhythm. The baseline BRS in patients with PeAF was significantly lower than those with PAF (2.97 [0.52–6.62] ms/mm Hg versus 4.70 [2.36–8.37] ms/mm Hg, $P=0.047$). The BRS was significantly depressed after catheter ablation in all the patients (4.66 [1.80–7.37] ms/mm Hg versus 0.55 [–0.15 to 1.22] ms/mm Hg, $P<0.001$). However, the depression of BRS because of catheter ablation appeared attenuated in patients with PeAF when compared with those with PAF. The number of patients who did not show depression of BRS was significantly greater, that is, patients with PeAF (3/12, 25%) than those with PAF (0/46, 0%, $P<0.01$).

CONCLUSIONS: Our findings demonstrated that the baseline BRS was more depressed in patients with PeAF compared with PAF. Catheter ablation depressed BRS irrespective of the type of AF, with a greater effect in patients with PAF than PeAF.

Key Words: atrial fibrillation ■ baroreflex sensitivity ■ pulmonary vein antrum isolation ■ radiofrequency catheter ablation

The evaluation of baroreflex sensitivity (BRS), obtained by measuring changes in heart rate in response to changes in blood pressure induced by vasoactive drugs such as phenylephrine, is one of the most useful tools for assaying autonomic function, particularly parasympathetic nerve function, of the cardiovascular system.¹ Therefore, evaluation of the BRS provides valuable information in patients with cardiovascular diseases, especially for risk stratification.^{2,3}

The association of atrial fibrillation (AF) with the autonomic nervous system is complex. It has been reported that AF could induce the impairment of cardiovascular autonomic function,^{4,5} while cardiac

autonomic dysfunction could play an important role in the genesis of AF.⁶ A recent study demonstrated that the BRS in patients with persistent AF (PeAF) was significantly decreased compared with healthy subjects, and restoring sinus rhythm improved the BRS in that population.⁷ On the other hand, radiofrequency catheter ablation (CA) for AF is known to depress cardiovascular vagal function. In fact, we recently demonstrated that BRS is drastically affected by CA in patients with paroxysmal AF.⁸

In general, PeAF, as compared with paroxysmal atrial fibrillation (PAF), is considered to be the progressed form of AF. However, it remains unclear

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Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018019>

For Sources of Funding and Disclosures, see page 8.

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CLINICAL PERSPECTIVE

What Is New?

- This study measured the baroreflex sensitivity, one of the parameters for cardiac autonomic function, in patients with paroxysmal and persistent atrial fibrillation (AF) before and after catheter ablation, and demonstrated that baroreflex sensitivity was more impaired in patients with persistent AF compared with paroxysmal AF.
- Catheter ablation for AF depressed the baroreflex sensitivity, irrespective of the type of AF, with a greater effect in patients with paroxysmal AF than persistent AF.

What Are the Clinical Implications?

- Depressed baroreflex sensitivity, also known as intrinsic parasympathetic nervous dysfunction, may contribute to the high recurrence rate after catheter ablation in patients with persistent AF.

Nonstandard Abbreviations and Acronyms

BRS	baroreflex sensitivity
CA	catheter ablation
PAF	paroxysmal atrial fibrillation
PeAF	persistent atrial fibrillation
PV	pulmonary vein
PVAI	pulmonary vein antrum isolation
UMIN	University Hospital Medical Information Network

whether the BRS in patients with AF would be different depending upon on the type, that is, paroxysmal or persistent. Therefore, we prospectively evaluated the baseline BRS in patients with PAF and PeAF undergoing radiofrequency CA. We also evaluated whether the suppressive effects of CA on BRS were different depending on the type of AF, that is, PeAF and PAF.

METHODS

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

Patient Selection

This study has prospectively enrolled 67 patients with PAF (n=46) and PeAF (n=21), who underwent radiofrequency CA for AF at our institutes between

October 2015 and February 2020. Their mean age was 65.2±10.1 years old. The study group comprised 14 women and 53 men. Patients with prior AF ablation, cardiovascular implantable electronic devices, those who presented an inability to measure BRS during sinus rhythm because of frequent premature beats, and those with changes in cardiac medications during enrollment were excluded from this study. PAF and PeAF were defined according to the 2017 HRS/EHRA/ECAS/APHS/SOLAECE expert consensus statement.⁹ Briefly, PAF is defined as an episode of AF that terminates spontaneously or with intervention in <7 days, and PeAF is defined as episodes that are sustained for >7 days and are not self-terminating. Transthoracic and transesophageal echocardiograms were performed before the ablation to evaluate the left ventricular function and left atrial diameter and to exclude the presence of thrombi using the Vivid 7 ultrasound system (GE Vingmed, Horten, Norway). In patients with PAF, all antiarrhythmic drugs were discontinued for at least 5 half-lives before the measurement of the baseline BRS. On the other hand, amiodarone was prescribed to 9 patients with PeAF for the restoration of sinus rhythm after cardioversion, and was continued until the measurement of baseline BRS. The study protocol was approved by the Ethics Committee of Oita University Hospital (Approval number: 1330). Written informed consent was obtained from each patient. The study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. This study is registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000041278) as “Prognostic value of baroreflex sensitivity in patients with atrial and ventricular arrhythmia.” All of the procedures were conducted in accordance with institutional guidelines.

Blood Sampling

Fresh peripheral blood samples were collected for the measurement of brain natriuretic peptide, glucose, hemoglobin A1c, serum urea nitrogen, creatinine, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and blood cell count from the patients in fasting state in the first 24 hours after admission.

BRS Measurements

For BRS assessment, all subjects were studied while lying supine in a quiet room between 11 AM and 1 PM. In the PAF group (n=46), BRS was measured during sinus rhythm. In the PeAF group (n=21), BRS was measured immediately after the restoration of sinus rhythm by cardioversion. Arterial blood pressure was recorded noninvasively by using tonometry

(Jentow-7700; Nihon Colin, Hiroshima, Japan). Arterial blood pressure and the ECG were monitored simultaneously. Data were stored in a pulse code modulation data recorder (RD-200T; TEAC, Tokyo, Japan). After an interval of 30 minutes to allow the stabilization of vital signs, the patient was asked to breathe at 15 breaths per minute (measured using a metro-nome). BRS was assessed using the phenylephrine method, as we previously reported.³ Phenylephrine (2–3 µg/kg) was injected intravenously over 15 seconds to increase systolic blood pressure by 15 to 40 mm Hg.¹⁰ The BRS was calculated as the slope of the linear regression line and related changes in SBP to changes in the RR interval. As previously described, regression lines with >20 data points and a correlation coefficient (*r*) >0.9 have been used for analyses.¹⁰

Pulmonary Vein Antrum Isolation by Catheter Ablation

Contact force-guided pulmonary vein antrum isolation (PVAI) was performed by 2 operators. Circumferential PVAI was done in the integrated 3D image using an open-irrigated ThermoCool SmartTouch catheter (Biosense Webster, Diamond Bar, CA) in all patients. The ablation catheter was advanced into the left atrium via the long sheath. Radiofrequency energy was delivered at 30 W in the anterior aspect of the circumferential PVAI line and 25 W in the posterior aspect using a Stockert 70 generator system (Biosense Webster) radiofrequency generator. The operator attempted to keep the contact force between 10 and 20 g during the PVAI. While radiofrequency energy was being delivered, the catheter tip was dragged by about 2 mm every 5 to 15 seconds. The end point of PVAI was the elimination of all pulmonary vein (PV) potentials recorded by a circular catheter (Lasso, Biosense Webster) placed at the ostium of the PV and the PV-to-left atrium block during pacing from 10 pairs of the circular catheter at 10 V output with 1-ms pulse width. Isoproterenol (4 µg) was injected intravenously in an attempt to induce AF from the non-PV foci. When a non-PV focus was identified, focal ablation was performed at the foci, except for one in the superior vena cava where segmental isolation was performed. Superior vena cava isolation was performed if the length of the superior vena cava sleeve was regarded as longer than 30 mm.¹¹ Cavotricuspid isthmus linear ablation was also performed if an atrial flutter was documented before ablation or induced during the ablation procedure.

Follow-Up

Follow-up was carried out at 1, 3, 6, and 12 months after CA using a 12-lead ECG and 24-hour Holter monitoring at each visit. Any atrial tachyarrhythmia lasting 1 minute or

more was considered as a recurrence. In addition to the palpitation, patients were asked to check whether their pulse was regular or not in their free time. If a recurrence was suspected, additional 24-hour Holter monitoring was performed. The discontinuation of anti-arrhythmic drugs was recommended at the 3-month follow-up.

Immunohistochemistry Using Human Left Atrium Appendage Specimen

Human left atrium appendage specimens from 10 patients with AF (5 paroxysmal, and 5 persistent) who underwent left atrium appendage excision during cardiovascular surgery from January 2015 to April 2020 were fixed in 4% paraformaldehyde, embedded in paraffin, and cut into 5-µm sections that were labeled with primary antibodies against choline acetyltransferase (Abcam, Cambridge, UK), and the appropriate biotin-conjugated secondary antibody (ABC reagent; Vector Laboratories, Burlingame, CA, or DAKO EnVision+ System, Peroxidase; DakoCytomation, Glostrup, Denmark). Images were acquired and digitized on a BZ-9000 Biolevo epifluorescence microscope with an attached digital camera (Keyence).

Statistical Analysis

Data of baseline clinical characteristics are presented as mean with SD or frequency with percentage as appropriate. For continuous variables, normality of the distribution was tested using the Shapiro-Wilk test. BRS values are presented as median with interquartile range (IQR) because of its skewed distribution. For continuous variables, an unpaired *t* test was used to test a difference between the PAF group and PeAF group. For categorical variables, χ^2 test and Fisher exact test were used. For BRS analysis, Wilcoxon rank sum test and Wilcoxon signed-rank test were used. To assess the relationship between systolic blood pressure and R-R interval, the linear regression analysis was performed.

A value of *P*<0.05 was considered significant. All computations were performed using the SPSS statistical software version 26.0 (Cary, NC) running on Windows 10 (Microsoft, Redmond, WA).

RESULTS

Patient Characteristics and the Baseline BRS of Patients With PAF and PeAF

Baseline characteristics of the enrolled patients with PAF and PeAF are presented in Table 1. The percentage of women in the PeAF group was significantly smaller than that in the PAF group (*P*=0.028). Left atrial diameter and the level of brain natriuretic peptide in patients with PeAF was significantly greater than those with PAF (*P*<0.001). Nine patients with PeAF took

Table 1. Baseline Clinical Characteristics of Patients with PAF or PeAF Enrolled in This Study

	PAF	PeAF	P Value
	(n=46)	(n=21)	
Age, y	64.9±11.0	66.9±7.9	0.445
Female, n (%)	13 (28.3)	1 (4.8)	0.028
CHADS2 score	1.02±1.01	1.33±1.35	0.301
Hypertension, n (%)	22 (47.8)	12 (57.1)	0.539
DM, n (%)	7 (15.2)	7 (33.3)	0.103
Echocardiographic findings			
LAD, mm	38.9±5.5	43.6±3.8	<0.001
Ejection fraction (%)	66.2±6.9	63.0±8.6	0.116
E/e'	10.2±3.4	10.8±2.9	0.474
Medication			
ACEI or ARB, n (%)	13 (28.3)	9 (42.9)	0.269
β-blocker, n (%)	15 (32.6)	7 (33.3)	1.000
Statin, n (%)	19 (41.3)	9 (42.9)	0.962
Amiodarone, n (%)	0 (0)	9 (42.9)	<0.001
CCR, mL/min	83.4±29.6	81.6±23.9	0.806
BNP, pg/mL	27.5±36.7	100.0±63.0	<0.001
HbA1c (%)	5.78±0.45	5.95±0.43	0.166
LDL-C, mg/dL	109.0±25.5	98.8±29.5	0.154
HDL-C, mg/dL	53.3±14.5	56.7±20.1	0.438
BMI, kg/m ²	26.5±6.2	25.1±2.9	0.331
WBC	5516±1264	5582±1225	0.845
Neutrophil (%)	56.9±7.7	60.7±8.3	0.074
Monocyte (%)	5.8±1.4	6.0±1.5	0.460
Hb, g/dL	13.9±1.5	15.1±1.6	0.003
Platelets (×10 ⁴ /μL)	21.7±5.8	20.6±4.6	0.445

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; CCR, creatinine clearance; DM, diabetes mellitus; Hb, hemoglobin; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LAD, left atrial diameter; LDL-C, low-density lipoprotein cholesterol; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; and WBC, white blood cell.

Data are shown as mean±SD for continuous variables and frequency, (%) for categorical variables. Means were compared using unpaired *t* test. Frequency was compared using χ^2 test.

amiodarone as an anti-arrhythmic drug, while no patient with PAF took amiodarone.

The baseline value of BRS in patients with PeAF was significantly lower than in those with PAF (2.97 [0.52–6.62] ms/mm Hg versus 4.70 [2.36–8.37] ms/mm Hg, median [IQR], $P=0.047$, Figure 1). The representative images describing the differences of BRS between the patients with PAF and those with PeAF are shown in Figure 2. In a patient with PAF, the RR interval was obviously prolonged in proportion to the rise in blood pressure after administration of phenylephrine (left, Figure 2). On the other hand,

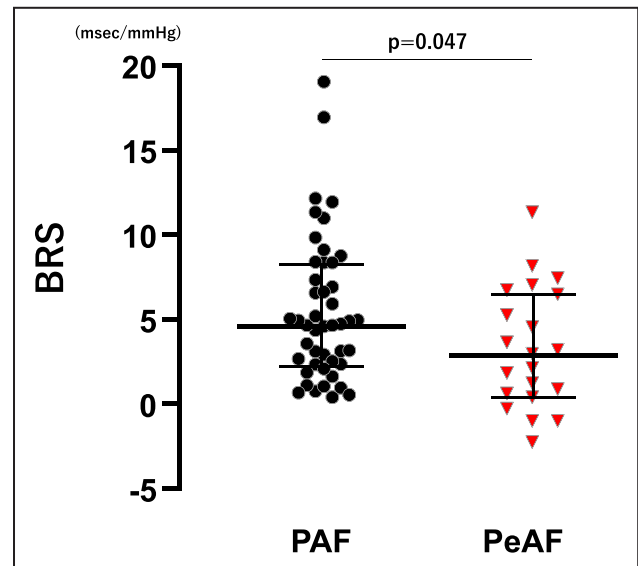


Figure 1. Baseline BRS in patients with PeAF was significantly smaller than that in patients with PAF (2.97 [0.52–6.62] ms/mm Hg vs 4.70 [2.36–8.37] ms/mm Hg, median [IQR], $P=0.047$).

BRS indicates baroreflex sensitivity; IQR, interquartile range; PAF, paroxysmal atrial fibrillation; and PeAF, persistent atrial fibrillation.

the prolongation of the RR interval was obviously impaired in spite of the increase of SBP in a patient with PeAF (right, Figure 2). Consistent with these findings, immunohistochemistry staining revealed that choline acetyltransferase, which is an enzyme responsible for biosynthesis of the neurotransmitter acetylcholine, was obviously reduced in the patient with PeAF compared with PAF (Figure S1).

Periprocedural Alteration of BRS in Patients with PAF and PeAF

Periprocedural measurements of BRS (preablation and postablation) were performed in 58 patients. BRS was significantly depressed in all of the patients irrespective of the type of AF (4.66 [1.80–7.37] ms/mm Hg versus 0.55 [–0.15 to 1.22] ms/mm Hg, median [IQR], $P<0.001$, $n=58$, Figure 3A). Particularly in patients with PAF, the BRS was invariably depressed after CA (4.70 [2.36–8.37] ms/mm Hg versus 0.62 [–0.14 to 1.59] ms/mm Hg, median [IQR], $P<0.001$, $n=46$, Figure 3B). In patients with PeAF, the degree of depression in BRS by CA was not so prominent (2.71 [–0.81 to 6.97] ms/mm Hg versus 0.06 [–0.30 to 0.87] ms/mm Hg, median [IQR], $P=0.027$, $n=12$, Figure 3C). As shown in Figure 3C, 3 patients with PeAF did not show depression in BRS after CA. Thus, the number of patients who did not show depression in BRS was significantly greater among the PeAF group (3/12, 25%) than the PAF group ($P<0.01$, χ^2 and Fisher exact test, Table 2). In addition, the

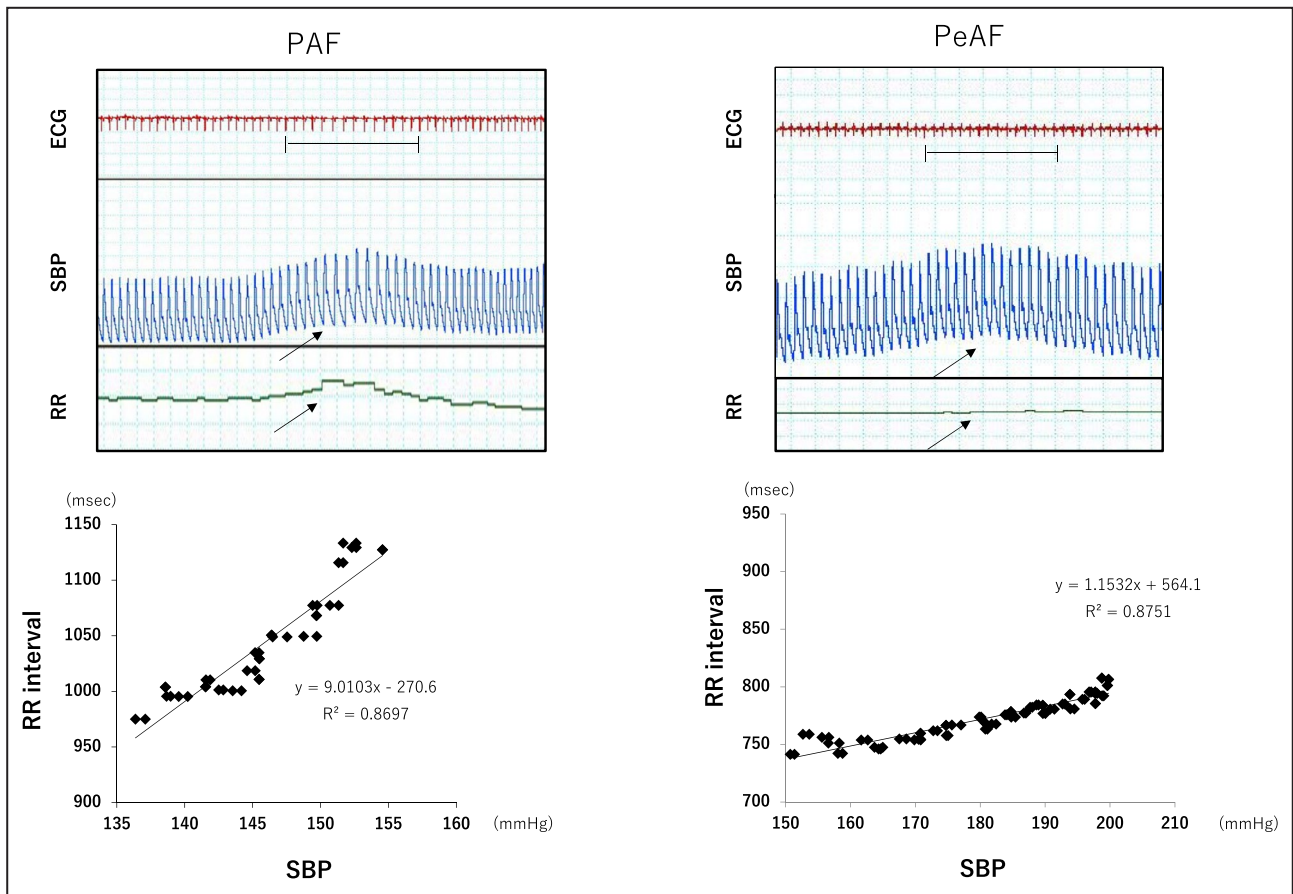


Figure 2. Representative images and graphs describing the BRS measurements in patients with PAF and PeAF; the BRS measurement of a patient with PAF is on the left (BRS=9.0103), and that of a patient with PeAF is on the right (BRS=1.1532). Arrows in the graphs indicate that RR interval was substantially prolonged in proportion to the increase of SBP in the patient with PAF, on the other hand, the prolongation was attenuated even though SBP was increased in the patient with PeAF. BRS indicates baroreflex sensitivity; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; and SBP, systolic blood pressure.

correlation of BRS depression after ablation with clinical outcome of catheter ablation in each group was evaluated. The difference in BRS before and after ablation (Δ BRS) in patients without recurrence was significantly greater compared with that in patients with recurrence only in the PAF group (4.21 [2.5–8.19] ms/mm Hg versus 1.97 [0.46–2.88] ms/mm Hg, median [IQR], Figure 4A, $P=0.011$). On the other hand, in the PeAF group, there was no difference in Δ BRS between the patients with recurrence and those without (3.82 [1.21–6.28] ms/mm Hg versus -0.07 [-1.59 to 5.66] ms/mm Hg, median [IQR], Figure 4B, $P=0.325$). These findings indicated that the prognostic ability of Δ BRS to predict AF recurrence is promising in patients with PAF.

Effect of an Anti-Arrhythmic Drug, Amiodarone, on BRS

When patients with PeAF were divided into those with amiodarone administration ($n=9$) and those without ($n=12$), the baseline values of BRS among the

amiodarone (+) group tended to be greater than those among the amiodarone (–) group (5.25 [1.51–7.25] ms/mm Hg versus 1.53 [-0.81 to 3.55] ms/mm Hg, median [IQR], $P=0.082$, Figure 5).

DISCUSSION

The important findings from this study are as follows: (1) The baseline value of BRS in patients with PeAF was significantly lower than that in patients with PAF; (2) BRS was significantly and dramatically

Table 2. Contingency Table Analysis Using Fisher Exact Test

	Depression of BRS	Nondepression of BRS	Total
PeAF	9	3	12
PAF	46	0	46
Total	55	3	58

Fisher exact test $P=0.0075$. BRS indicates baroreflex sensitivity; PAF, paroxysmal atrial fibrillation; and PeAF, persistent atrial fibrillation.

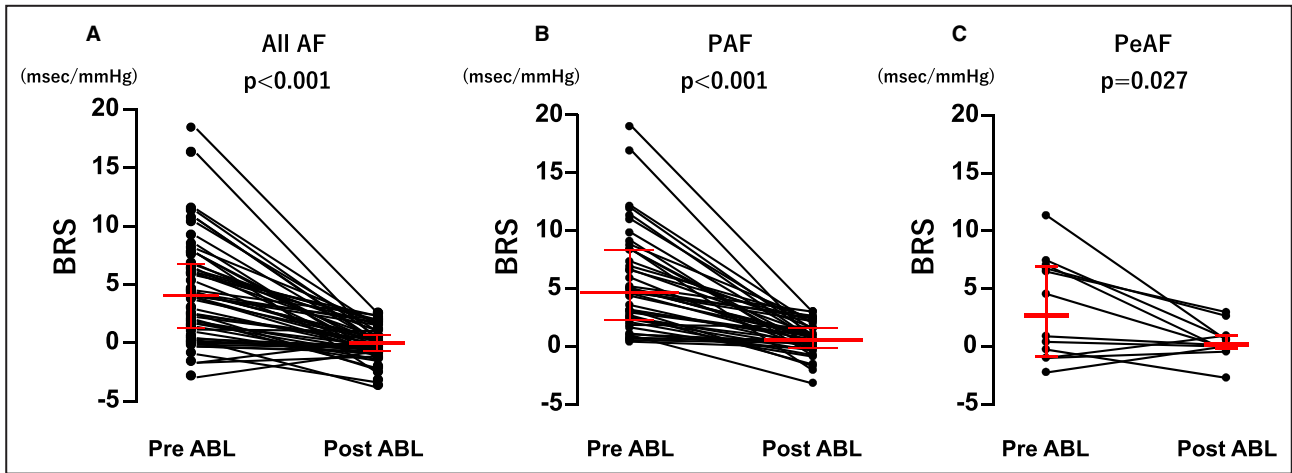


Figure 3. BRS was significantly depressed in all of the patients with AF (4.66 [1.80–7.37] ms/mm Hg vs 0.55 [–0.15 to 1.22] ms/mm Hg, median [IQR], $P < 0.001$, $n = 58$).

(A), mainly because of more massive depression in patients with PAF (4.70 [2.36–8.37] ms/mm Hg vs 0.62 [–0.14 to 1.59] ms/mm Hg, median [IQR], $P < 0.001$, $n = 46$) (B) as compared with the patients with PeAF (2.71 [–0.81 to 6.97] ms/mm Hg vs 0.06 [–0.30 to 0.87] ms/mm Hg, median [IQR], $P = 0.027$, $n = 12$) (C). ABL indicates ablation; AF, atrial fibrillation; BRS, baroreflex sensitivity; IQR, interquartile range; PAF, paroxysmal atrial fibrillation; and PeAF, persistent atrial fibrillation. Red lines indicate median with IQR.

depressed after CA irrespective the type of AF; (3) The decrease in BRS because of CA appeared more prominent in patients with PAF as compared with the patients with PeAF; and (4) Amiodarone did not significantly affect the baseline BRS value, but it tended to improve the BRS.

Depressed BRS has clinical significance.¹² In the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study, the significance of BRS was clinically demonstrated, that is, depressed BRS using the phenylephrine method was an independent predictor of cardiac mortality in patients with previous

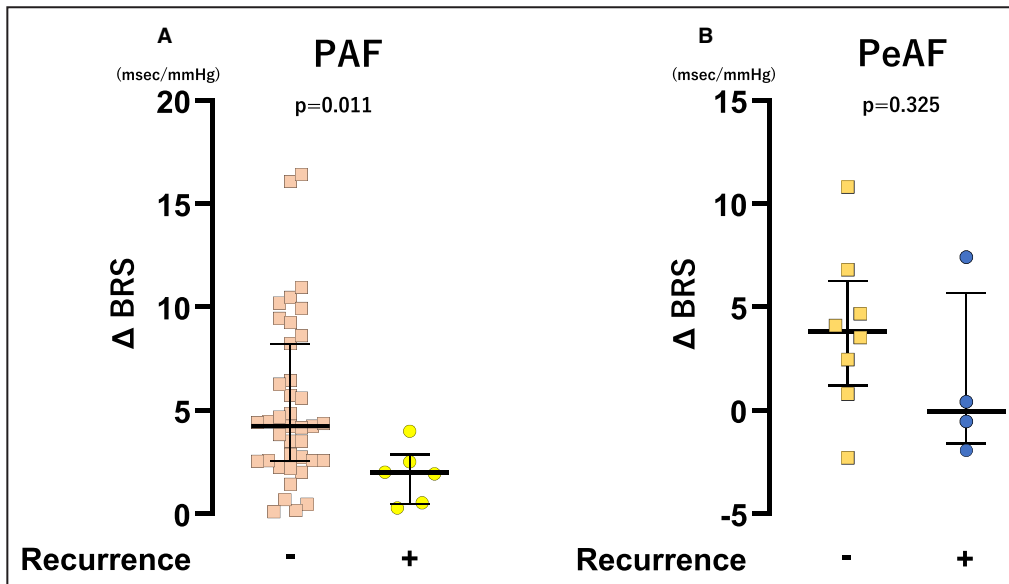


Figure 4. The difference of BRS before and after ablation in patients without recurrence was significantly greater than those in patients with recurrence in the PAF group (4.21 [2.5–8.19] ms/mm Hg vs 1.97 [0.46–2.88] ms/mm Hg, median [IQR], $P = 0.011$).

(A), whereas there was no significant difference between the patients with recurrence and those without in the PeAF group (3.82 [1.21–6.28] ms/mm Hg vs –0.07 [–1.59 to 5.66] ms/mm Hg, median [IQR], $P = 0.325$) (B). BRS indicates baroreflex sensitivity; IQR, interquartile range; PAF, paroxysmal atrial fibrillation; and PeAF, persistent atrial fibrillation.

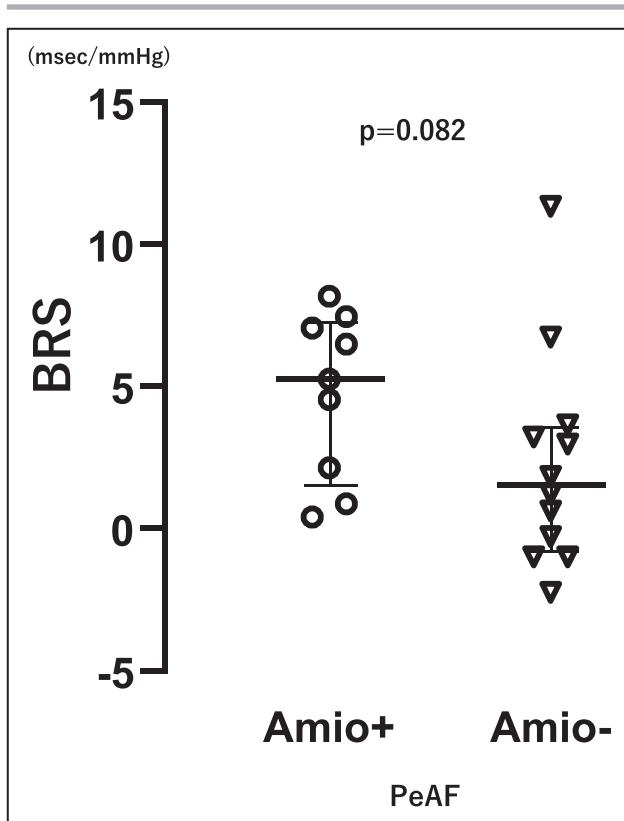


Figure 5. There is no significant difference in the value of BRS between the patients who took amiodarone and those who did not (5.25 [1.51–7.25] ms/mm Hg vs 1.53 [–0.81 to –3.55] ms/mm Hg, median [IQR], $P=0.082$).

Amio indicates amiodarone; BRS, baroreflex sensitivity; and IQR, interquartile range.

myocardial infarction, independent of the left ventricular ejection fraction.²

The mechanism in which AF impairs the baseline BRS is unclear. It is widely known that AF is associated with atrial dilatation in association with its inflammation and fibrosis,^{13–16} which may lead to downregulation of the cardiopulmonary baroreceptors. From this viewpoint, it has been reported that structural abnormalities, including cardiac fibrosis, were more progressive in patients with PeAF than in those with PAF.¹⁷ The cardiac fibrosis itself and/or proinflammatory processes that cause cardiac fibrosis might contribute to the reasons for the prominent depression of baseline BRS observed in patients with PeAF. In addition, patients with AF have enhanced endothelial dysfunction, leading to the impaired vascular function,^{18,19} which theoretically could alter the input to the arterial baroreceptors and, thus, adversely modulate baroreflex function.

As with other parameters for cardiac autonomic function, BRS, which is reported to be one of the parameters of cardiovascular parasympathetic activity,³ was also affected by CA irrespective of the type of AF

in this study. In this regard, we have recently demonstrated that in patients with PAF, the smaller difference in BRS before and after ablation (Δ BRS) was associated with the high recurrence rate of AF after CA.⁸ Together with our current observations that the decrease in BRS by CA was not prominent in patients with PeAF as compared with PAF, it can be conceived that the impairment of intrinsic parasympathetic nervous function may contribute to the high recurrence of AF after CA in patients with PeAF. Consistently, a recent study demonstrated that anatomic ganglionated plexus modification was not adequate in case of persistent AF.²⁰

Unexpectedly, the baseline value of BRS in patients treated with amiodarone tended to be greater than in those without, because it is well known that amiodarone reduces the sinus rate, which could result in underestimation of the BRS. Our findings appeared to be consistent with the recent report that demonstrated that amiodarone could have the potential to improve cardiac autonomic function.²¹ The comparison of patients with and without amiodarone is limited in number and may not represent the entire population.

LIMITATIONS

There are 5 limitations in the present study. First, the number of patients is small. Hence, these significances might be because of low sample size. Second, we did not re-evaluate the BRS measurement in each patient during the follow-up period. Third, cardioversion could affect BRS in patients with PeAF. BRS could be underestimated just after cardioversion because of the insufficient recovery of sinus node activity. However, most of the patients (18 patients) with PeAF had recurrence of AF within 1 week after cardioversion. Hence, we could not evaluate the time course of BRS recovery in these patients. Fourth, the test for evaluation of BRS, requiring intravenous administration of a vasopressor agent, could reduce more widespread use of this technique, which carries inherent limitation. Lastly, less invasive techniques to assess autonomic function could be used, such as heart rate turbulence²² or deceleration capacity²³ in this study.

CONCLUSIONS

Our findings demonstrated that the baseline value of BRS was more deteriorated in patients with PeAF as compared with those with PAF. The finding also suggested that CA for AF depressed the BRS, irrespective of the type of AF, and that the depressive effects were attenuated in patients with PeAF as compared with those with PAF.

ARTICLE INFORMATION

Received June 11, 2020; accepted October 19, 2020.

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Sources of Funding

None.

Disclosures

None.

Supplementary Material

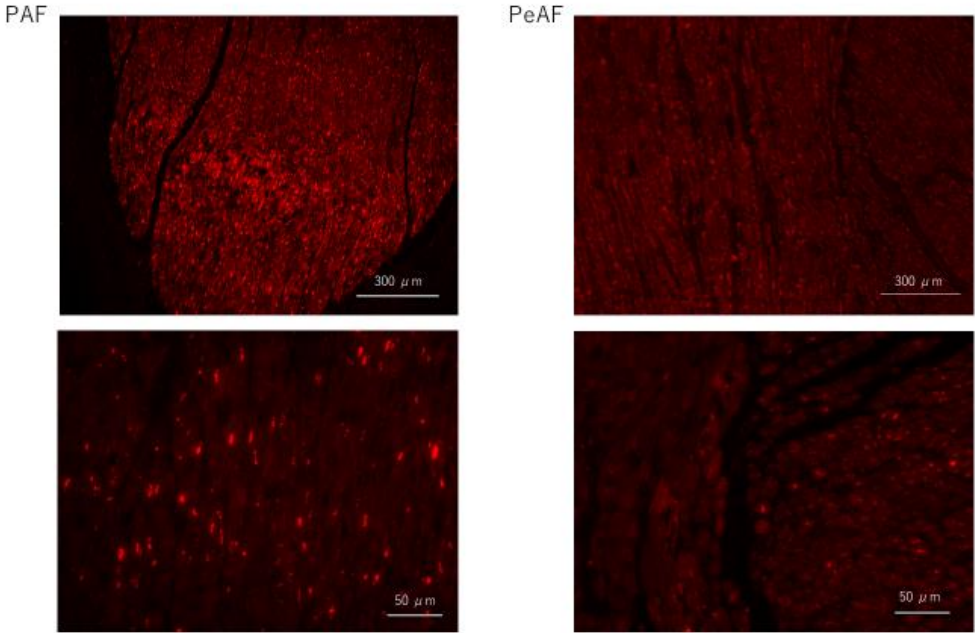
Figure S1

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Supplemental Material

Figure S1. Immunohistochemistry staining showed that the expression levels of choline acetyltransferase was obviously attenuated in the patient with PeAF compared to PAF.



PeAF – persistent atrial fibrillation; PAF – paroxysmal atrial fibrillation