

Baroreceptor Reflex Sensitivity in Patients with Atrial Fibrillation

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Abstract

Purpose: Persistent atrial fibrillation decreases baroreflex sensitivity (BRS), which is considered an indicator of cardiac autonomy. Furthermore, atrial fibrillation ablation has also been found to reduce the BRS. The baseline BRS of patients with paroxysmal atrial fibrillation (PAF) and persistent atrial fibrillation (PeAF) was compared and the BRS-modifying effect of ablation was investigated. *Methods:* The BRS was measured before and after the procedure and the presence or absence of atrial fibrillation recurrence was assessed. *Results:* Pre-operative BRS was significantly lower in patients with PeAF compared with those with PAF. The BRS was significantly reduced postoperatively in all patients, with a particularly large reduction in PAF patients. The BRS decreased to a lesser extent with ablation in patients with recurrent PAF. *Conclusions:* Baseline BRS was lower in patients with PeAF. Atrial fibrillation ablation reduced BRS in both PAF and PeAF patients but had a stronger reduction effect in PAF patients.

Keywords

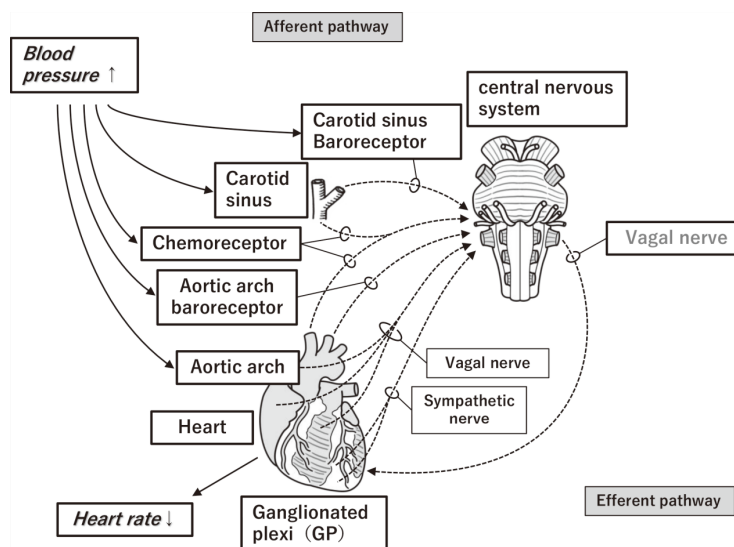
Atrial fibrillation
Baroreflex sensitivity
Pulmonary vein antrum isolation
Radiofrequency catheter ablation

1. Introduction

An overview of the baroreceptor reflex in humans via the autonomic nervous system is shown in **Figure 1**^[1]. When arterial pressure rises, baroreceptors in the carotid sinus and aortic arch detect and transmit the signal afferently to the medulla oblongata. The vagal nerve is then activated centripetally and reflexively and transmits

the signal to the autonomic ganglia of the heart, resulting in a decrease in the automaticity of the sinus node and heart rate. The sharpness of this response is quantitatively assessed by baroreflex sensitivity (BRS). Measurement of BRS using phenylephrine is a useful tool for assessing cardiac autonomic nervous system activity (especially parasympathetic

Figure 1. Baroreceptor reflexes via the human autonomic nervous system



function) and is used to assess risk in patients with various cardiovascular diseases such as acute myocardial infarction [2-4]. The relationship between atrial fibrillation and the cardiac autonomic nervous system is very complex, with atrial fibrillation causing cardiac autonomic dysfunction [5,6], whereas cardiac autonomic dysfunction being implicated in the origin of atrial fibrillation [7]. It has been reported that BRS in patients with persistent atrial fibrillation (PeAF) can be improved by maintenance of sinus rhythm [8], while atrial fibrillation ablation with extended pulmonary vein isolation has also been reported to reduce BRS in patients with paroxysmal atrial fibrillation (PAF) [9]. However, the BRS reduction in the latter case is likely to be seen as an autonomic modulatory effect of the ablation (also known as heart rate variability [HRV] modification).

In general, PeAF patients are expected to have more advanced cardiac autonomic neuropathy and lower cardiac autonomic modifying effects of ablation compared to PAF patients. To date, there have been no reports examining differences in BRS between PAF and PeAF patients, nor have differences in the BRS modifying effect of AF ablation on PAF and PeAF patients been identified. We hypothesized that PeAF patients would have a lower baseline BRS than PAF patients, as well as the BRS modifying effect of AF

ablation would be stronger in PAF patients than in PeAF patients.

2. Methods

A prospective, observational study enrolled 67 atrial fibrillation patients (46 in the PAF group and 21 in the PeAF group) who underwent atrial fibrillation ablation by extended pulmonary vein isolation at our hospital after October 2015. Baseline BRS was measured using tonometry with the phenylephrine method in sinus rhythm 2 days before ablation; in the PeAF group, BRS was measured in sinus rhythm after electrical cardioversion. Postoperative BRS measurements were performed on the second day after ablation. Patients were visited at 1, 3, 6, and 12 months after the procedure, and 12-lead and Holter electrocardiograms (ECGs) were performed to assess for recurrence of AF. A total of 45 patients in the PAF group and 12 patients in the PeAF group attended all the follow-ups. Furthermore, choline acetyltransferase (ChAT, highly expressed in the parasympathetic nervous system) fluorescence immunostaining was performed on the left atrial myocardium of 10 patients with atrial fibrillation (5 in the PAF group and 5 in the PeAF group) who had undergone open heart surgery in our cardiovascular surgery unit after January 2015 and who had undergone left ventriculectomy. Local parasympathetic

dysfunction was assessed.

3. Results

3.1. Patient background

The clinical background of the 67 patients with AF (46 with PAF and 21 with PeAF) is shown in **Table 1**^[10]. The mean age was 65.2 ± 10.1 years, 14 (21%) were women, with a lower proportion of women in the PeAF group than in the PAF group ($P = 0.028$) and a larger left atrial diameter and higher amount of brain natriuretic peptide. Nine of 21 patients in the PeAF group were also taking the anti-arrhythmic drug, amiodarone.

3.2. BRS

A representative example of BRS measurements in patients with PAF and PeAF is presented in **Figure 2**^[10]. In patients with PAF, there was a high degree of ECG RR interval prolongation in response to the increase in systolic blood pressure after phenylephrine administration, whereas in PeAF patients the RR interval was only mildly prolonged in response to the systolic blood pressure increase. A comparison of BRS before AF ablation and at baseline is shown in **Figure 3**^[10]. Baseline BRS was significantly lower in PeAF patients than in PAF patients ($2.97 [0.52-6.62]$ vs. $4.70 [2.36-8.37]$ ms/mm, $P = 0.047$).

Table 1. Clinical background of each patient group

	PAF (n = 46)	PeAF (n = 21)	P value
Age (years)	64.9 ± 11.0	66.9 ± 7.9	0.445
Female, n (%)	13 (28.3)	1 (4.8)	0.028
CHADS ₂ score	1.02 ± 1.01	1.33 ± 1.35	0.301
HT, 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/é	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 (0.0)	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	5,516 ± 1,264	5,582 ± 1,225	0.845
NEUT (%)	56.9 ± 7.7	60.7 ± 8.3	0.074
MONO (%)	5.8 ± 1.4	6.0 ± 1.5	0.460
Hb (g/dL)	13.9 ± 1.5	15.1 ± 1.6	0.003
PLT ($\times 10^4/\mu\text{L}$)	21.7 ± 5.8	20.6 ± 4.6	0.445

HT: hypertension; DM: diabetes mellitus; LAD: left atrial diameter; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CCR: creatinine clearance; BNP: brain natriuretic peptide; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; BMI: body mass index; WBC: white blood cell; NEUT: neutrophil; MONO: monocyte; Hb: hemoglobin.

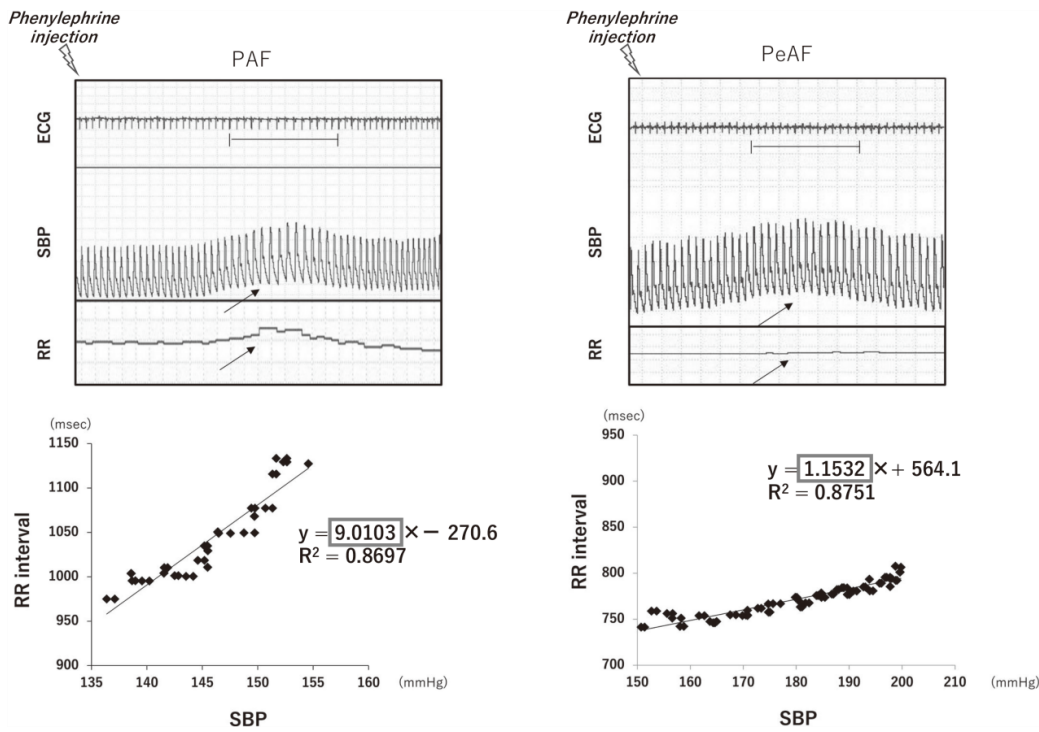


Figure 2. BRS measurements in patients with PAF and PeAF. The BRS of the PAF patients (left) is 9.0103 and the BRS of the PeAF patients (right) is 1.1532. PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; SBP: systolic blood pressure; BRS: baroreflex sensitivity.

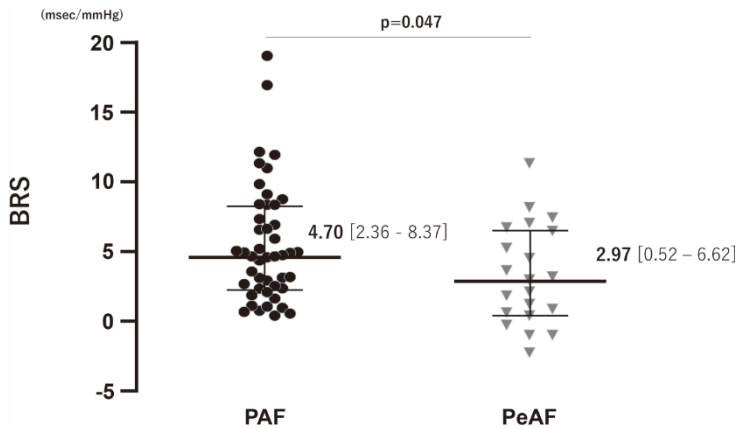


Figure 3. Baseline BRS. See **Figure 2** for abbreviations.

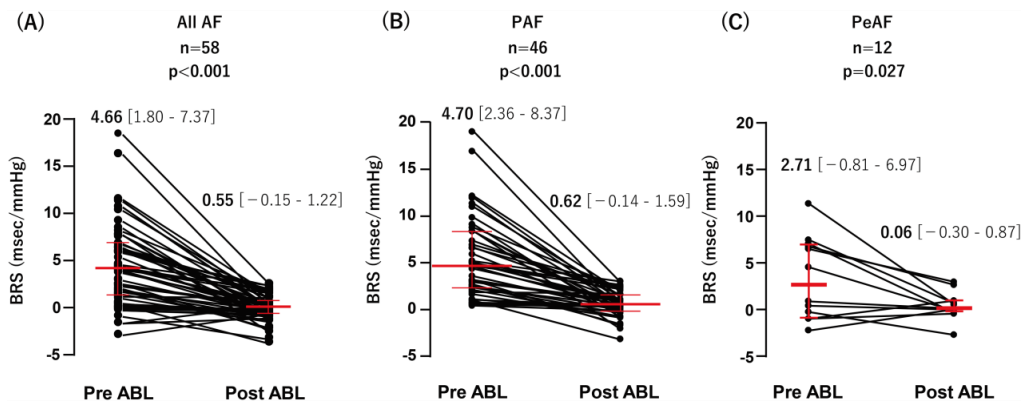


Figure 4. BRS comparison before and after ablation. (A) all patients; (B) PAF group; (C) PeAF group; ABL: ablation; see **Figure 2** for other abbreviations.

Pre- and post-ablation BRS measurements were performed in 58 patients; the BRS decreased significantly after ablation in all patients (4.66 [1.80–7.37] to 0.55 [-0.15–1.22], $P < 0.001$, **Figure 4A**), where both PAF group (4.70 [2.36–8.37] to 0.62 [-0.14–1.59], $P < 0.001$, **Figure 4B**) and PeAF group (2.71 [-0.81–6.97] to 0.06 [-0.30–0.87], $P = 0.027$, **Figure 4C**) showed a significant decrease of BRS^[10]. In particular, all 46 patients in the PAF group showed a reduction in BRS after ablation. However, BRS decreased only in 9 out of 12 patients in the PeAF group. The Fisher test indicated the BRS modifying effect was stronger in the PAF group than in the PeAF group ($P = 0.0075$).

The presence or absence of AF recurrence one year after ablation and the degree of BRS reduction before and after ablation were then examined separately in the PAF and PeAF groups: in the PAF group, the degree of BRS reduction before and after ablation was greater in recurrence-free patients (4.21 [2.5–8.19] vs. 1.97 [0.46–2.88], $P = 0.011$). However, in the PeAF group, the presence or absence of recurrent AF was not associated with the degree of BRS reduction (3.82 [1.21–6.28] vs. -0.07 [-1.59–5.66], $P = 0.325$, **Figure 5**)^[10]. These results suggest that in the PAF group, the degree of postoperative BR's decline is a useful predictor of postoperative recurrence.

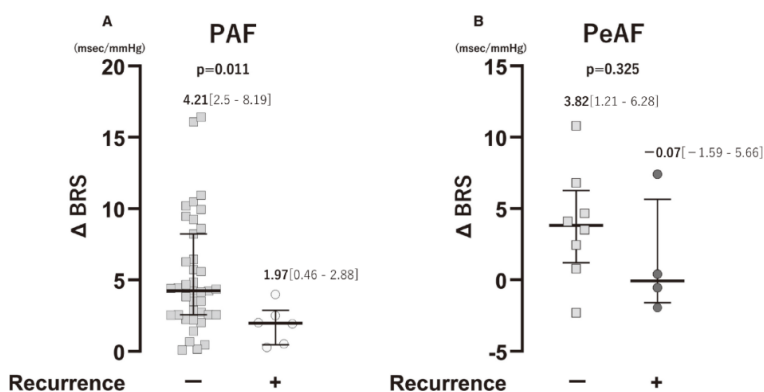


Figure 5. Degree of BRS reduction in the PAF and PeAF groups according to the presence or absence of recurrence after ablation. See **Figure 2** for abbreviations.

The effect of amiodarone on BRS was examined in the amiodarone-using (9 patients) and non-using (12 patients) groups, although only in the PeAF group patients were taking amiodarone and a trend towards higher BRS was observed in the amiodarone-using group (5.25 [1.51–7.25] vs 1.53 [-0.81–3.55], $P = 0.082$, **Figure 6**)^[10].

3.3. Histological study

The results of fluorescent immunostaining for choline acetyltransferase in left auricular sections are shown in **Figure 7**^[10]. Choline acetyltransferase is considered an indicator of parasympathetic function, and its expression was significantly lower in PeAF patients, histologically demonstrating that local parasympathetic function in the myocardium was impaired.

4. Consideration

The results of the present study are summarized below:

- (1) Baseline BRS was significantly lower in the PeAF group as compared to the PAF group.
- (2) BRS was significantly reduced after ablation regardless of AF type.
- (3) The BRS-modifying effect of ablation was stronger in the PAF group than in the PeAF group.

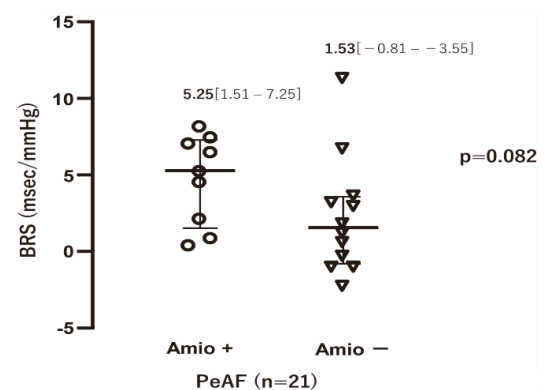


Figure 6. Amiodarone and BRS in the PeAF patient group. There was a trend towards higher BRS in the amiodarone group. Amio: amiodarone, see **Figure 2** for other abbreviations.

Figure 7. Fluorescence immunostaining images. Choline acetyltransferase expression was lower in PeAF patients (right) as compared to PAF patients (left).

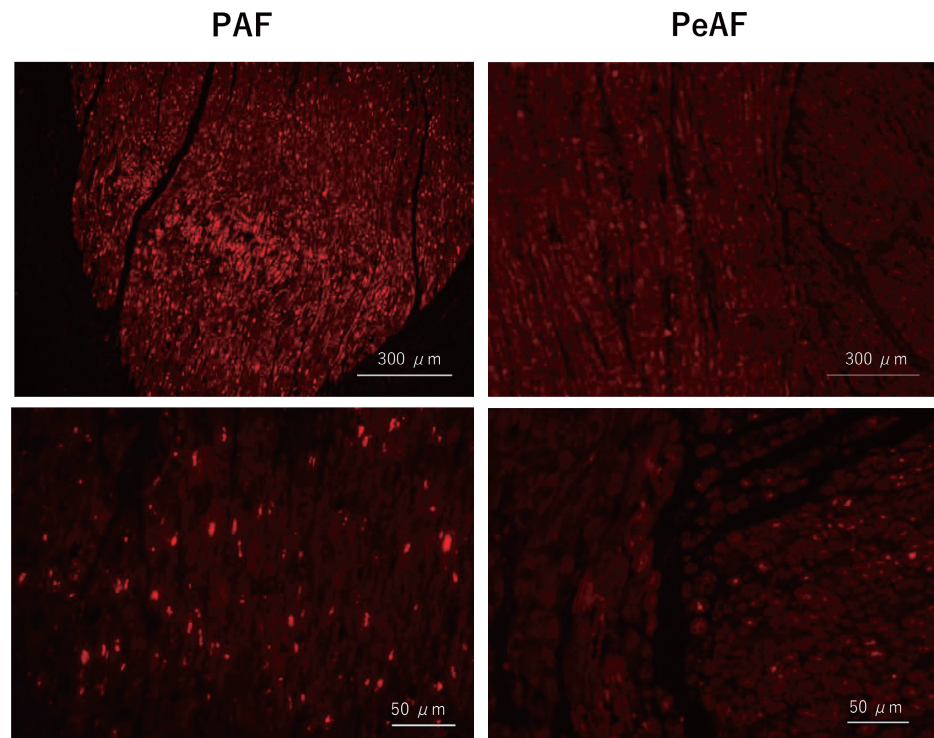
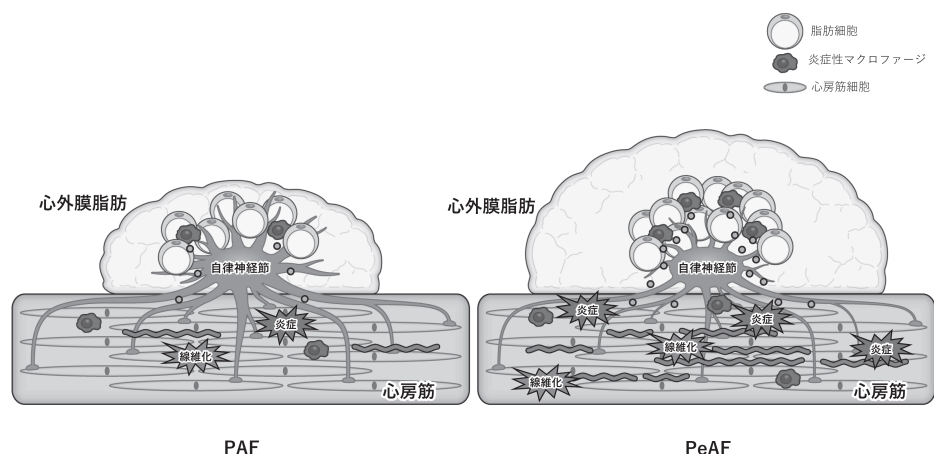


Figure 8. Atrial fibrillation and epicardial fat with autonomic ganglion. Compared to patients with paroxysmal atrial fibrillation, patients with persistent atrial fibrillation may have increased epicardial fat volume and worsened quality. Epicardial fat, both in quality and quantity, may impair myocardium and autonomic ganglion cells, which may result in decreased BRS.



- (4) In the PAF group, the degree of BRS reduction before and after ablation was greater in recurrence-free patients.
- (5) Amiodarone had no significant effect on BRS, but there was a tendency for BRS to improve.

It is generally known that persistent atrial fibrillation causes atrial remodeling due to inflammation and fibrosis^[11-14], but studies investigating AF and endothelial function using FMD and End-PAT have reported that persistent AF also causes progressive vascular endothelial dysfunction^[15,16].

When paroxysmal symptoms progress to persistent AF, vascular dysfunction also progresses simultaneously, i.e. vascular function in the carotid sinus and aortic arch is similarly impaired, and the baroreceptors in these areas are reduced or their baroreceptor sensitivity is decreased, which is thought to have resulted in a lower BRS in patients with persistent AF. In recent years, several reports have investigated the relationship between atrial fibrillation and epicardial fat. It has been reported that the quantity and quality of epicardial fat increase with persistent AF^[17,18], which may impair

the myocardium and autonomic ganglion cells in the epicardial fat, resulting in a reduced BRS (**Figure 8**). In the present study, BRS tends to be higher in patients taking amiodarone. Amiodarone has been reported to have beta-blocking properties and may improve cardiac autonomic function^[19], which is consistent with our results.

5. Conclusion

Baseline BRS was lower in patients with PeAF compared with those with PAF. Atrial fibrillation ablation modifies BRS, whether paroxysmal or persistent, but was shown to have a stronger effect in patients with PAF. Evaluation of BRS before and after atrial fibrillation ablation could be used to predict treatment efficacy and postoperative recurrence.

Disclosure statement

The authors declare no conflict of interest.

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