Decreased anxiety after catheter ablation for paroxysmal atrial fibrillation is associated with augmented parasympathetic reactivity to stress

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BACKGROUND Psychological improvement after catheter ablation for atrial fibrillation (AF) has been reported, but its mechanism is unclear.

OBJECTIVE This study aimed to clarify the relationship between cardiac autonomic modification and psychological changes after catheter ablation for paroxysmal AF (PAF).

METHODS Thirty-five consecutive patients (60.5 ± 11.9 years; male, n = 24) with PAF treated by catheter ablation were enrolled. Autonomic activity and reactivity to stress and psychological status were measured before (baseline) and at 1 and 3 months after ablation. We assessed autonomic activity and reactivity to stress by measuring heart rate variability (HRV) at rest (Rest), and during (Task) and after (After) the execution of a task and assessed relationships between HRV parameters and psychological changes using the State-Trait Anxiety Inventory (STAI) and Self-Rating Depression Scale (SDS).

RESULTS The STAI state and trait scores significantly decreased at 3 months compared with baseline, whereas SDS scores essentially remained unchanged. The high-frequency (HF) response index (Task/Rest) and HF recovery index (After/Rest) were significantly higher than baseline at 3 months (0.40 [0.29–0.90] vs 1.30 [0.64–2.18], P = .007 for HF response index; 1.13 [0.92–2.19] vs 1.87 [1.19–2.97], P = .049 for HF recovery index). Reductions in STAI scores positively correlated with increments in the HF recovery index in the entire cohort as well as in 5 patients with recurrent AF.

CONCLUSIONS Some augmentation of parasympathetic reactivity to stress correlated with reduced anxiety, implying that cardiac autonomic modification plays roles in psychological improvement after catheter ablation for AF.

KEYWORDS Anxiety; Catheter ablation; Parasympathetic activity; Paroxysmal atrial fibrillation; Reactivity

Introduction

Atrial fibrillation (AF) imposes a significant psychosocial burden, including anxiety and depression, that can impair quality of life (QOL).[1–3] Several studies have shown that catheter ablation for AF not only abolishes arrhythmia but improves psychological status.[2,4] Freedom from symptoms of AF is an important factor for psychological improvement. However, even patients with recurrent AF after catheter ablation notably experience such improvement. Wokhlu and colleagues[2] described equivocal improvements in the psychological status of 38 and 281 patients with and without recurrent AF, respectively, after catheter ablation. In contrast, the psychological status of patients who achieved freedom from AF using antiarrhythmic drugs does not change.[5,6]

For example, Yu and colleagues[5] found no changes in the psychological status of 102 patients who were treated with antiarrhythmic drugs, even though 48 (47%) of them maintained sinus rhythm. These findings suggest that factors other than AF rhythm control are associated with psychological improvement after AF ablation.

Pulmonary vein (PV) isolation (PVI) is a cornerstone of AF ablation, and extensive circumferential PVI (ECPVI) is a widely adapted method of ablation. The ganglionated plexi of cardiac autonomic nerves are located mainly along the epicardial aspects of the PV antrum. Therefore, ECPVI apparently withdraws cardiac vagal tone by damaging ganglionated plexi along the PV antrum.[7,8] This modification of autonomic function might underlie the psychological changes after ablation. Autonomic status is commonly associated with psychological distress such as anxiety and depression.[9,10] Stimulation of the vagus nerve is effective against depression, implying interaction between efferent parasympathetic tone and psychological status.[11] This study aimed to determine associations between autonomic modification

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KEY FINDINGS

- This is the first report to demonstrate a link between cardiac autonomic modification and psychological changes after catheter ablation for paroxysmal atrial fibrillation.

- Our results suggested that augmented parasympathetic reactivity to stress by radiofrequency ablation might contribute to psychological improvement after catheter ablation for atrial fibrillation.

- Autonomic function was assessed by not only heart rate variability at rest but also its response to stress using a random number generation task.

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and psychological changes after AF ablation in patients with paroxysmal AF (PAF). Psychological status is affected by personal surroundings that likely differ more over time. Furthermore, whether cardiac autonomic modification is maintained beyond 3 months after ablation is controversial.[7,12] We selected a short-term follow-up of 3 months, in which no significant life events occurred, to focus on interactions between changes in these 2 factors.

Autonomic modification was assessed by measuring heart rate variability (HRV), namely beat-to-beat variations in heart rate, which are commonly used to evaluate autonomic function.[13] Variations in the high-frequency (HF) range revealed by power spectrum analysis are associated with respiration-dependent parasympathetic activity.[14] Anxious and depressed individuals have low HF and also have HF less reactive to stress.[15,16] Assessing autonomic reactivity to stress provides information with which to evaluate anxiety and depression. We therefore measured HRV while participants were at rest, while they were under stress performing a random number generation task, and during rest after the task to determine autonomic activity and reactivity to stress.[17]

We also measured skin conductance (SC), reflecting the amount of secreted sweat, which is regulated solely by sympathetic nerves. We recorded SC at the palm side of the fingers, which reflects sweat secreted in response to arousal and stress.[9,18,19] Sweat secretion then served as a systemic sympathetic parameter in this study, while low-frequency (LF) component / HF component ratio by power spectrum analysis is associated with cardiac sympathetic activity.[13,14] We placed more importance on the values of SC rather than those of LF/HF ratio, because we focused on feedback from the cardiac center induced by changes in cardiac autonomic function after ablation.

Methods
Study population
The present study enrolled 35 consecutive patients with PAF who were referred for initial catheter ablation from September 2015 to August 2016 in our institution. All patients agreed to participate in this study, and none of

them had undergone prior left atrial ablation. The study was approved by the local institutional review board, and all included patients provided written informed consent to participate in this study. This study complied with the guidelines set forth in the Declaration of Helsinki.

Study design
Clinical details of all patients were obtained after enrollment. The severity of AF-related symptoms was assessed using the Canadian Cardiovascular Society Severity in Atrial Fibrillation (CCS-SAF) scale.[20] The frequencies of AF episodes were determined from the findings of patient interviews, 12-lead electrocardiography (ECG), 24-hour Holter ECG, or events recorded using an HCG-9-recorder 1 (Omron, Kyoto, Japan). Psychological status and HRV values were determined at 18 hours before (baseline), and at 1 (1M) and 3 months (3M) after ablation. One physician followed up all study participants.

Psychological status assessment
The psychological status of patients was assessed using the self-reporting State-Trait Anxiety Inventory (STAI)[21] and Self-Rating Depression Scale (SDS) questionnaires.[22] The state and trait scores on the STAI reflect anxiety at the time of measurement and in daily life during the previous 2 weeks, respectively. The SDS reflects depressiveness. The total scores on both scales range from 20 to 80, with higher scores indicating more anxiety and depressiveness.

Heart rate variability assessment
Conventional ECG proceeded with a gain of 10,000 and a time constant of 0.1 seconds, and signals were stored on a computer for off-line analysis using Autonomic Mental Assessment System (GM3, Tokyo, Japan). We created R-R interval trends using R peaks, and fluctuations were analyzed by MemCalc using the maximum entropy method (GMS, Tokyo, Japan). Unlike HRV analysis using fast Fourier transform, MemCalc is capable of estimating the power spectrum density from short time series data.[23] We used maximum entropy method for power spectrum analysis because it has been applied to trend data with a minimum duration of 30 seconds and it is useful for incorporating measurements of multiple behavioral states. Based on R-R interval data, HF and LF components of the spectrum were measured every 2 seconds by integrating the power from 0.15 to 0.4 Hz and that from 0.04 to 0.15 Hz, respectively, for the preceding 30-second periods. R-R intervals were also converted to heart rates every 2 seconds. Patients with large R-R interval irregularities due to premature beats ($\geq$5 beats/min [bpm]) or AF at the time of examination were excluded from the analysis.

Skin conductance measurement
SC was measured at a constant 0.5 V and a sampling rate of 600 Hz using a Model 2701 Bioderm meter (UFI, Morro Bay, CA). Ag-AgCl electrodes of 8 mm in diameter were attached to the palm side of the middle phalanges of the first and

second fingers of the right hand. Fluctuations in SC are generated by the spontaneous and simultaneous activation of many sweat glands in response to arousal or stressful events, and they reflect psychological changes.[18,19] Those with an amplitude >0.05 micro-Siemens (μS) were counted, and the number of fluctuations per minute was evaluated as the parameter reflecting sympathetic activity.[9]

Random number generation task

The random number generation task was imposed on the patients as a source of stress. This task is simple, less affected by education, and suitable for assessing individuals with various social backgrounds.[17] The task requires that the patients focus on orally generating a random series of 100 digits using the numbers 0–9 at a rate of 1 Hz, as though they were repeatedly casting a die. The rate was indicated by a metronome.

Both HRV and SC were recorded at rest before (baseline), during, and after the task at rest. After an acclimation period of at least 5 minutes, the patients relaxed as much as possible in a chair for approximately 60 seconds (Rest) before engaging in the random number generation task for 100 seconds (Task). The patients then relaxed for another 60 seconds during ECG recording (After). The HF Task/Rest ratio was calculated by dividing the HF value during the task by the HF value during rest, and was defined as the HF response index. The HF After/Rest ratio was similarly defined as the HF recovery index. The HF After/Task ratio was also calculated similarly. The LF/HF response and recovery indexes were defined in the same way.

Catheter ablation

All antiarrhythmic drugs were discontinued for at least 5 half-lives, and all patients were anticoagulated for ≥2 months before the procedure. The session proceeded under conscious sedation with dexmedetomidine. Surface ECG and intracardiac electrograms were continuously monitored and stored on a Lab System Pro digital recording system (Bard Electrophysiology, Lowell, MA). A 6F 20-pole 2-site (right atrium and coronary sinus) BeeAT mapping catheter (Japan Lifeline, Tokyo, Japan) was inserted through the right jugular vein. Two Lasso decapolar circular catheters (Biosense Webster Inc, Diamond Bar, CA) were then introduced into the left atrium via transseptal puncture.

All patients underwent ECPVI with guidance from a CARTO 3-dimensional mapping system (Biosense Webster) using a double Lasso technique. A radiofrequency (RF) current was delivered via a ThermoCool catheter (Biosense Webster) with a power maximum of 35 W. The endpoint was a bidirectional conduction block between the left atrium and the PV. Thereafter, isoproterenol was continuously infused and adenosine triphosphate was rapidly injected to elicit non-PV ectopies. If superior vena cava ectopies initiated the AF, the superior vena cava was isolated. Nonthoracic vein ectopies initiating AF were targeted with the endpoint of being unable to provoke ectopy by creating a cluster lesion. Patients with a clinical history of typical right atrial flutter or induced typical flutter during ablation underwent cavotricuspid isthmus ablation.

Table 1   Baseline patient characteristics (N = 35)

Age (years)	60.5 ± 11.9
Male, n (%)	24 (69)
Body mass index (kg/m²)	23.1 (21.1–24.4)
AF history (months)	36 (6–72)
AF family history, n (%)	3 (9)
SSS, n (%)	4 (11)
CAD, n (%)	2 (6)
Hypertension, n (%)	16 (46)
Diabetes, n (%)	3 (9)
Stroke, n (%)	2 (6)
Structural heart disease, n (%)	4 (11)
Vagal AF, n (%)	7 (20)
CCS-SAF scale	2.2 ± 0.7
Laboratory data	
CRP level (mg/dL)	0.047 (0.031–0.125)
NT-ProBNP level (pg/mL)	415 (248–500)
Echocardiographic findings	
LVDd (mm)	48 (43–51)
LVEF (%)	69 (62–70)
LAD (mm)	38 (35–44)
Medications	
ACEI or ARB, n (%)	10 (29)
β-blocker, n (%)	12 (34)
Statin, n (%)	7 (20)
Ablation pattern	
EAPVI, n (%)	35 (100)
CTI block, n (%)	6 (17)
SVCI, n (%)	5 (14)
Trigger ablation in RA, n (%)	1 (3)
Trigger ablation in LA, n (%)	1 (3)

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCS-SAF = Canadian Cardiovascular Society Severity of Atrial Fibrillation; CRP = C-reactive protein; CTI = cavotricuspid isthmus; EAPVI = extensive antral pulmonary vein isolation; LA = left atrium; LAD = left atrial diameter; LVDd = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction; NT-ProBNP = N-terminal pro-brain natriuretic peptide; RA = right atrium; SSS = sick sinus syndrome; SVCI = superior vena cava isolation.

Statistical analysis

Continuous variables are expressed as means ± standard deviation or medians (interquartile range [IQR]), and categorical variables are expressed as numbers (n) with percentages (%). Differences between before and after ablation (Pre vs 1M and Pre vs 3M) were tested using paired Student *t* test. Correlations were analyzed using the Pearson correlation test. The alpha coefficients of STAI scores were calculated to evaluate internal consistency. Statistical significance was considered at $P < .05$. Data were statistically analyzed using GraphPad Prism 5 (GraphPad, La Jolla, CA) or SPSS version 24 (SPSS, Inc, Chicago, IL).

Results
Patients and ablation

Table 1 summarizes the baseline characteristics of the 35 included patients (male, n = 24; mean age, 60.5 ± 11.9 years). The AF event frequencies per 3 months before ablation were 1
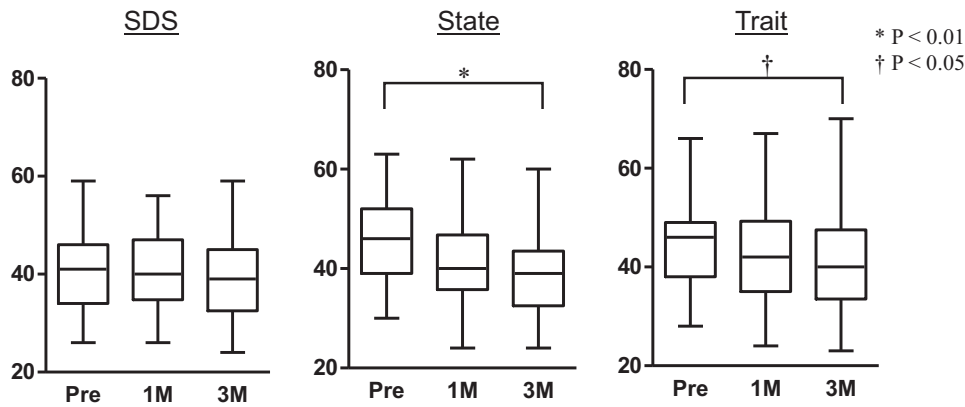
Figure 1   Changes in psychological status scores by time intervals before (Pre) and 1 (1M) and 3 months (3M) after ablation. SDS = self-rating depression scale.

in 10 patients (29%), 2 in 10 patients (29%), 3 in 9 patients (26%), 4 in 2 patients (6%), and ≥5 in 4 patients (11%).

The mean duration of the ablation procedure was 215 ± 32 minutes and the success rate of ECPVI was 100%. At discharge, all patients were in sinus rhythm and no patients developed severe complications, such as cardiac tamponade or thromboembolic events. Five (14%) patients experienced AF recurrence during a follow-up period of 3 months.

Psychological status
The SDS scores at 1 and 3 months after ablation did not significantly change compared with those before ablation. The STAI state and trait scores decreased at 1M after (median 40 [IQR 35.8–46.8] and 42 [35–49.3], respectively), and significantly decreased at 3M after (39 [32.5–43.5], $P < .001$ and 40 [33.5–47.5], $P = .025$), compared with before (46 [39–52] and 46 [38–49]) ablation (Figure 1). The alpha coefficients of STAI state and trait scores were 0.59 and 0.64, respectively, before ablation, 0.55 and 0.53 at 1M, and 0.56 and 0.50 at 3M. Standard errors of the STAI state and trait scores were 1.5 and 1.5, respectively, before ablation, 1.7 and 1.8 at 1M, and 1.5 and 2.0 at 3M after ablation.

Heart rate variability
Ten patients were excluded from the analysis of HRV before and 1M after ablation, and 7 were excluded at 3M after ablation owing to large R-R interval irregularities. The heart rate at rest significantly increased at 1M (75.3 [68.9–92.7] bpm, $P < .01$) and 3M (78.1 [68.1–84.1] bpm, $P = .01$), compared with before ablation (67.9 [60.9–75.7] bpm). Figure 2A shows HF profiles before ablation (Pre) and at 1M and 3M under the conditions of Rest, Task, and After. Before ablation (Figure 2A, Pre), HF decreased during task execution and returned to baseline during rest after the task (After).

The V-shape profile of HF in response to the task was obscure at 3M (Figure 2A, 3M) and the HF components during and at rest after the task were higher at 3M than before ablation. The HF response (HF Task/Rest ratio) and HF recovery (HF After/Rest ratio) indexes significantly increased (0.40 [0.29–0.90] vs 1.30 [0.64–2.18], $P = .007$ and 1.13 [0.92–2.19] vs 1.87 [1.19–2.97], $P = .049$, respectively) at 3M (Figure 2B). The median HF After/Task ratio was 2.4 [1.1–5.1] at Pre, 2.3 [0.9–4.1] at 1M, and 1.5 [0.6–3.5] at 3M. There was no significant difference in the HF After/Task ratio between Pre and 1M or between Pre and 3M.

Median HF scores during initial rest (Figure 2B, rest) and at task at 1M and 3M after ablation tended to be lower than those before ablation, but the difference did not reach statistical significance (HF at rest: 121.3 [25.1–566.9] ms² at Pre, 14.7 [5.6–86.9] ms² at 1M, 18.4 [10.4–44.6] ms² at 3M; HF at task: 67.3 [24.8-158.9] ms² at Pre, 12.3 [5.5-35.1] ms² at 1M, 19.5 [8.2–126.5] ms² at 3M). HF scores after the task at 1M (25.3 [13.4-156.2] ms²) was significantly lower ($P = .039$) than that at Pre (223.6 [47.6–770.8] ms²), while there was no significant difference between that at 3M (45.8 [17.5–178.9] ms²) and Pre.

The profiles of LF/HF ratio were shown in Supplemental Figure 1A. There were considerable individual differences in the response of LF/HF ratio to the task both before and after ablation. There were no significant differences in median LF/HF ratio at rest, LF/HF response index, or LF/HF recovery index between before and after ablation (Supplemental Figure 1B).

Changes in skin conductance
Figure 2C shows individual SC profiles at rest and during and after the task. Fluctuations in SC increased during the task. This inverse V-shape response was evident before and at 1M and 3M after ablation. However, the mean SC fluctuation at rest significantly increased at 1M and 3M, compared with before ablation (2.9 ± 3.0/min and 2.9 ± 3.2/min vs 1.5 ± 2.2/min; $P = .049$ for 1M vs Pre and $P = .031$ for 3M vs Pre; Figure 2D). Meanwhile, mean values during and after the task at 1M and 3M were equivocal compared with those before ablation (Figure 2D). Changes in SC at rest and in STAI scores were not significantly associated.
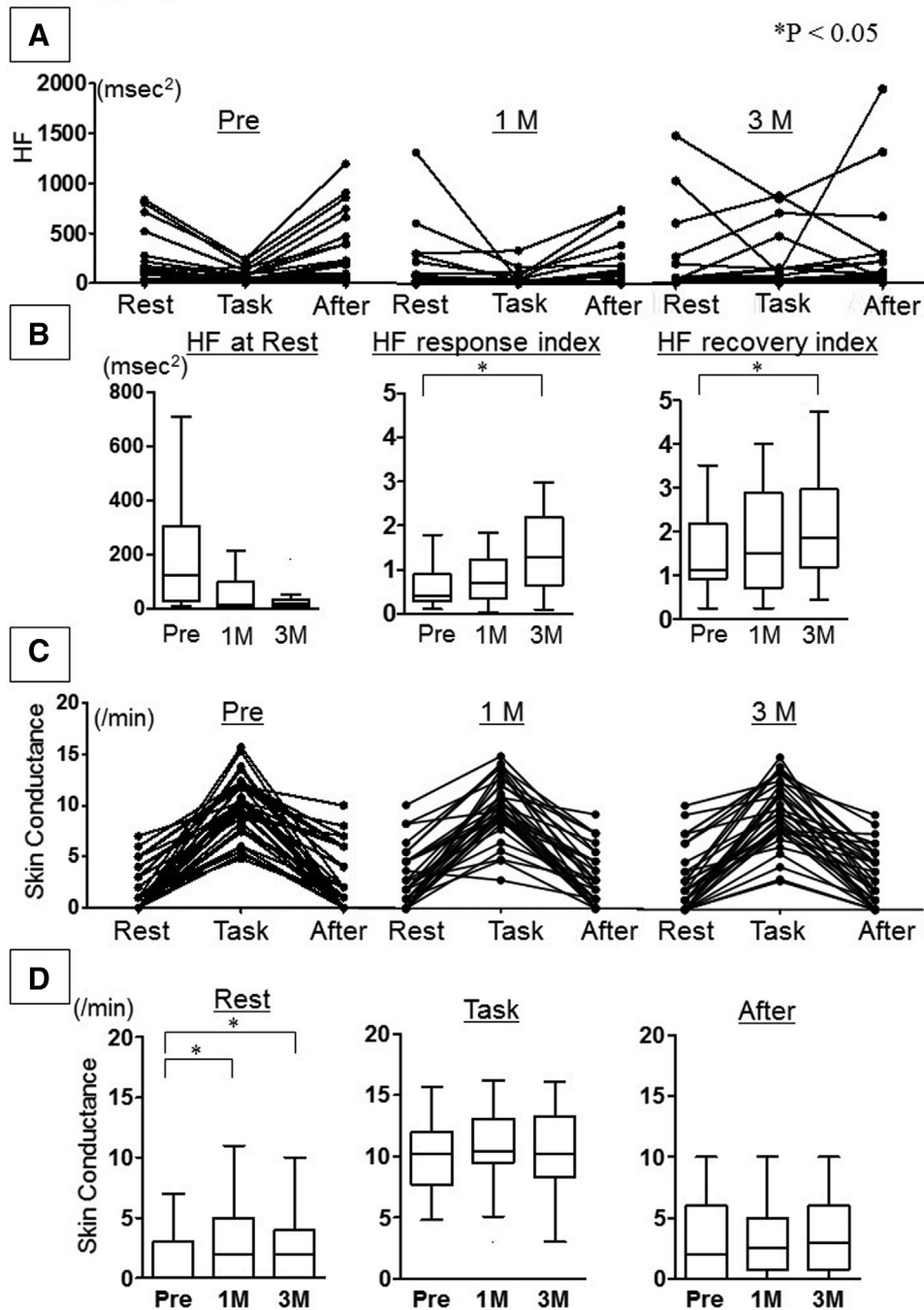
Figure 2   High-frequency (HF) component (**A, B**) and skin conductance (SC) (**C, D**) during initial rest (Rest), task execution (Task), and rest after the task (After), before (Pre), and at 1 (1M) and 3 (3M) months after ablation. **A, C:** Individual data under 3 conditions. **B:** Box plots of HF values at Rest, HF response index, and HF recovery index. **D:** Box plots of SC at Rest, Task, and After.

Association between psychological status and heart rate variability

Figures 3 and 4 show the increment in HF at rest ([HF at rest at 1M or 3M after ablation] / [HF at rest before ablation]), the increment in HF response index ([HF response index at 1M or 3M] / [HF response index before ablation]), and the increment in HF recovery index ([HF recovery index at 1M or 3M] / [HF recovery index before ablation]) plotted as functions of re-

ductions in STAI scores. The increment in HF at rest and HF response index at 1M and 3M did not significantly correlate with reductions in STAI scores. In contrast, reductions in STAI scores significantly correlated with increments in the HF recovery index at 1M and 3M after ablation (STAI states at 1M and 3M: R = 0.59, P = .006, n = 20 and R = 0.48, P = .03, n = 21, respectively; STAI traits at 1M and 3M: R = 0.68, P = .001, n = 20 and R = 0.80, P < .001, n = 21,

1 month to baseline ratio   3 month to baseline ratio

HF at rest

HF response index
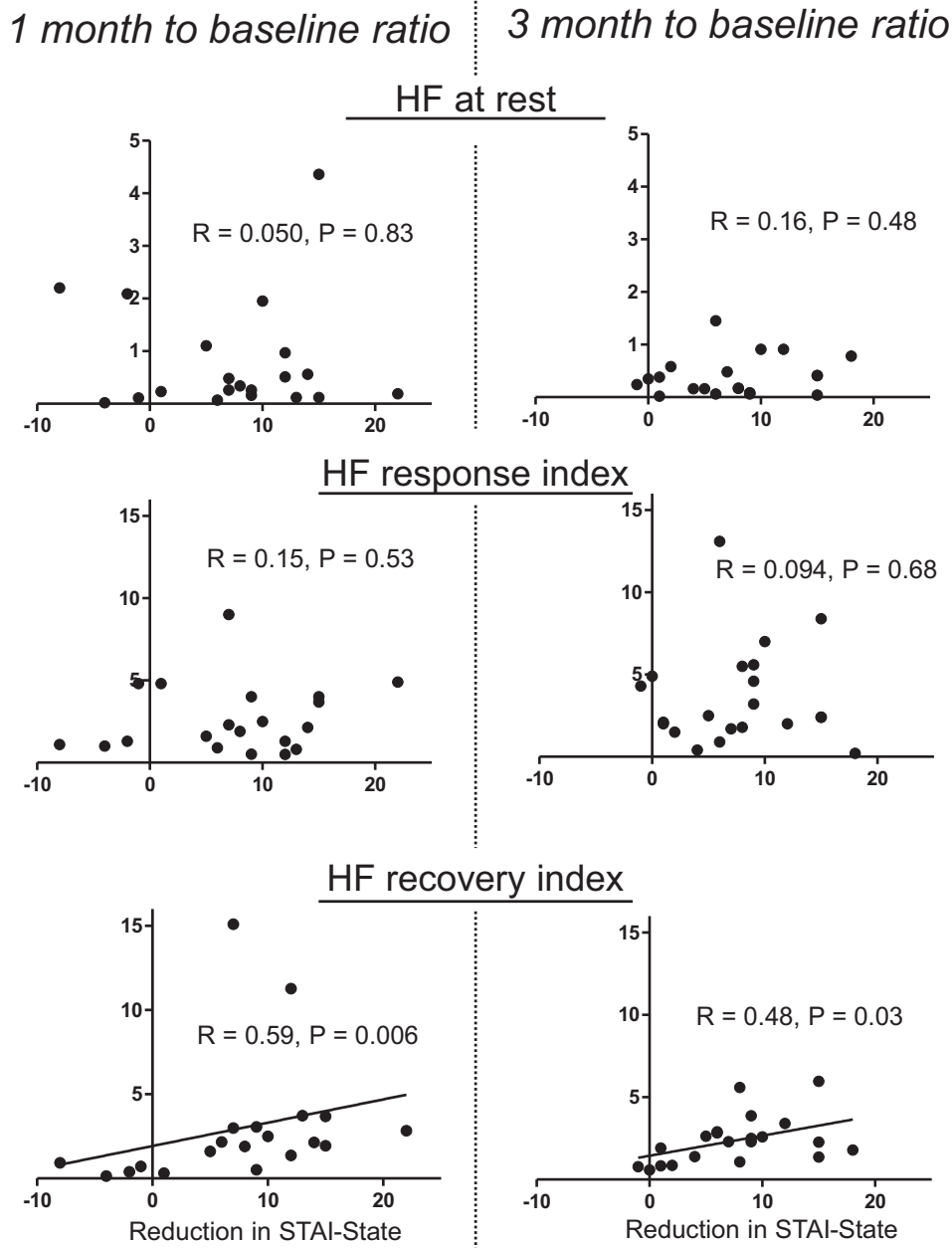
HF recovery index

Figure 3   Relationship between reductions in State-Trait Anxiety Inventory (STAI) state scores and changes in high-frequency (HF) component at rest, HF response index, and HF recovery index at 1 and 3 months after ablation. Reductions in STAI state scores and increments (ratio of values at 1 or 3 months after vs that before ablation) in HF at rest or HF response index did not significantly correlate. Reductions in STAI state scores and increments in HF recovery index significantly correlated.

respectively). There were no significant correlations between the decrease in STAI scores and the frequency of AF episodes during 3 months before ablation (Supplemental Figure 2).

Patients with recurrent atrial fibrillation

AF recurred in 5 patients during the 3 months post ablation. The STAI state scores significantly decreased at 1M (38.0 [30.5–39.0], $P < .026$) and 3M (37.0 [31.5–40.0], $P < .015$), compared with before (44.0 [39.5–46.5]) ablation in these 5 patients. The STAI trait score decreased at 1M (40.0 [35.5–41.5], $P = 0.10$) and 3M (39.0

[31.5–41.5], $P = .11$), compared with before (44.0 [40.0–46.5]) ablation, although the differences did not reach statistical significance. Table 2 summarizes details of these 5 patients. Figure 5 summarizes changes in STAI scores and the relationship between reductions in STAI scores and changes in the HF recovery index in these patients. One patient was excluded from the HRV analysis owing to a large R-R interval irregularity at the time of examination. Reductions in STAI scores positively correlated with increases in the HF recovery index in these patients and in the entire cohort.
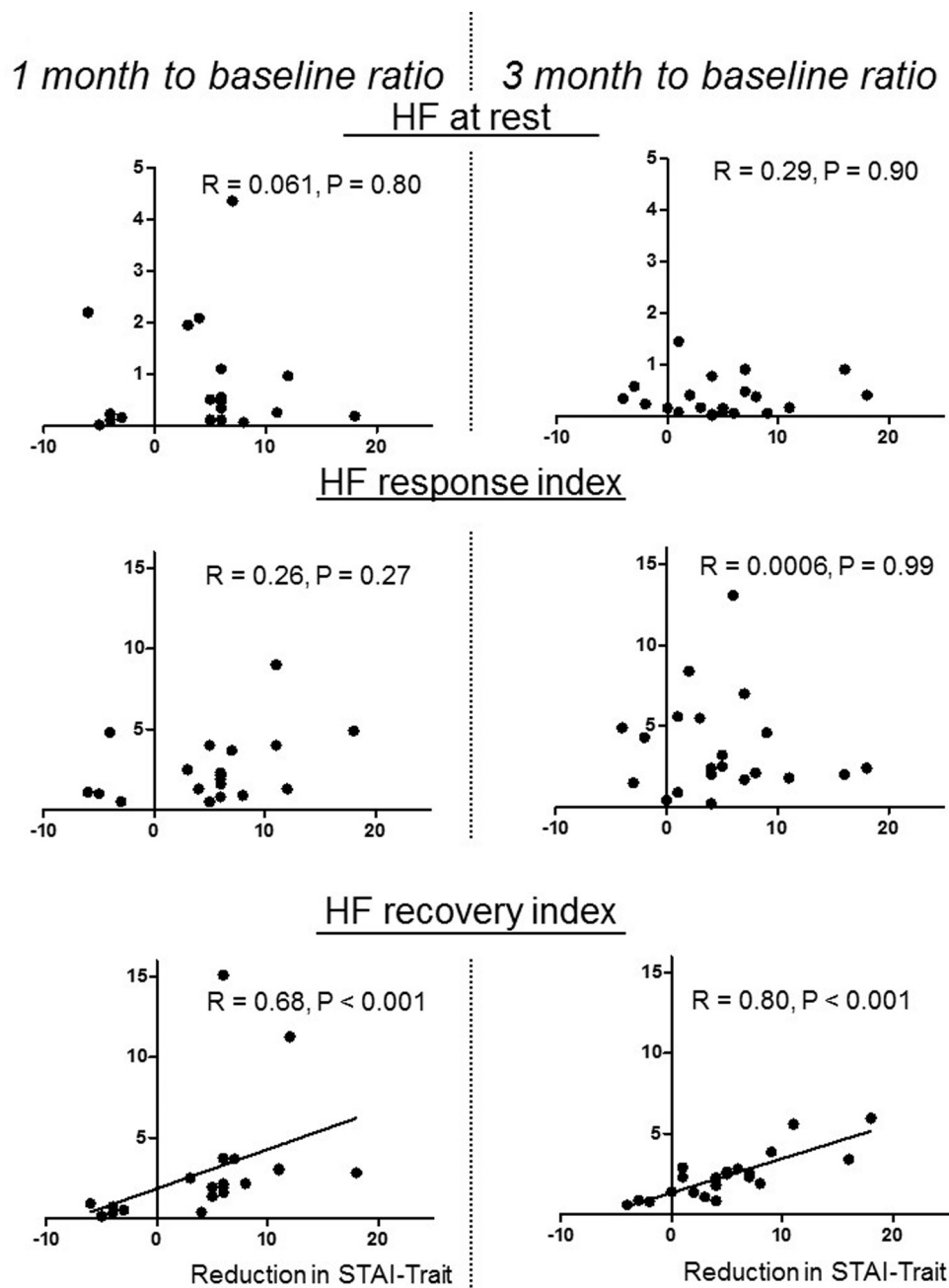
Figure 4   Relationships between reductions in State-Trait Anxiety Inventory (STAI) trait scores and changes in high-frequency (HF) component at rest, HF response index, and HF recovery index at 1 and 3 months after ablation. Reductions in STAI trait scores and increments (ratio of value at 1 or 3 months after vs that before ablation) of HF at rest or HF response index did not significantly correlate. In contrast, reductions in STAI trait scores and increments in HF recovery index significantly correlated.

Discussion

To the best of our knowledge, this is the first report of an association between cardiac autonomic modification and psychological changes after catheter ablation for PAF. The key findings were as follows. Parasympathetic reactivity to stress and parasympathetic activity at rest became modified after AF ablation. The change in HF at rest after ablation did not reach statistical significance, probably owing to large inter-subject variation within the small sample. Reduced STAI scores significantly correlated with the increment in HF

recovery index, indicating that augmented parasympathetic reactivity to stress might contribute to psychological improvement after AF ablation.

Circumferential PVI with RF energy withdraws both cardiac vagal and sympathetic tone documented by HRV.[8] The cardiac center, located in the medulla oblongata, controls cardiac autonomic tone.[11] Considering a feedback mechanism, cardiac autonomic tone withdrawal might increase efferent autonomic tone from the cardiac center. In fact, SC at rest increased after ablation, implying an increase in efferent

Table 2 Details of the patients with recurrent atrial fibrillation

Patient no.	Age (years)	Sex	AF frequency per 3 months before ablation	AF frequency per 3 months after ablation	ΔState at 1 month after ablation	ΔState at 3 month after ablation	ΔTrait at 1 month after ablation	ΔTrait at 3 months after ablation
1	49	M	2	4	15	12	7	16
2	62	M	3	3	8	7	6	9
3	61	M	2	3	6	5	8	5
4	73	F	1	1	1	2	-4	-3
5	59	F	2	3	9	10	6	5

AF = atrial fibrillation; ΔState = reduction in State-Trait Anxiety Inventory state score; ΔTrait = reduction in State-Trait Anxiety Inventory trait score.

sympathetic tone via a positive feedback system. On the other hand, SC during the task was comparable between before and after ablation. The random number generation task might increase sympathetic tone to the maximum level, and SC might not further increase even under positive feedback from the cardiac center. Systemic parasympathetic tone is presumed to be increased like sympathetic tone, although a method to measure it does not exist. Therefore, we interpreted the results of parasympathetic activity based on feedback after damage to the cardiac autonomic system.

Parasympathetic tone documented by HRV is reportedly associated with psychological status.[15,16] Here, we found that the HF component reacted to stress. The HF response and HF recovery indices increased after catheter ablation. Increased efferent parasympathetic tone from the cardiac center (positive feedback) might have affected HF during the task and at rest after the task. On the other hand, there was no significant difference in the HF After/Task ratio between before and after ablation, suggesting that the positive feedback from the cardiac center seemed to work equivocally between during and after the task.

Under normal conditions, the HF component is reduced during tasks and returns to the baseline value thereafter.[15,16] Such inhibition of parasympathetic activity by task stress disappeared after ablation, and parasympathetic augmentation was indicated. These changes in HF values and reactivity are consistent with those found in depressed patients.[16] The cardiac center is presumed to work as feedback to restore the depression-like response to normal. The degree of the increment in the HF recovery index correlated with the reduction in STAI scores, suggesting that increased efferent parasympathetic tone functions as a positive feedback system that might contribute to psychological improvement (Figure 6). The increase in HF response index reflects autonomic dysregulation related to bad mental status when caused by psychiatry illness, whereas that induced by interventions by catheter ablation might lead to good mental status because a positive regulatory feedback from the cardiac center is expected to restore the depression-like response to normal.

In contrast, reducing anxiety by eliminating AF through ablation might lead to changes in HRV parameters but, if so, not only rebound reactivity of HF but HF at rest, HF during tasks, and sympathetic SC will all be affected as well. The correlations between reduced STAI scores and increased HF recovery index imply that the augmentation of cardiac parasympathetic reactivity to stress after AF ablation in the central autonomic system may generate psychological changes. These notions are supported by the findings that the decrease in STAI scores and positively correlated with the increment in the HF recovery index even in patients with recurrent AF during follow-up (Figure 5) and anxiety was substantially reduced in some patients with recurrent AF, even when the AF frequency increased or did not change. In addition, there were no significant correlations between decrease in STAI scores and the frequency of AF episodes before ablation, indicating a small contribution of AF rhythm control by ablation to the improvement in mental status.
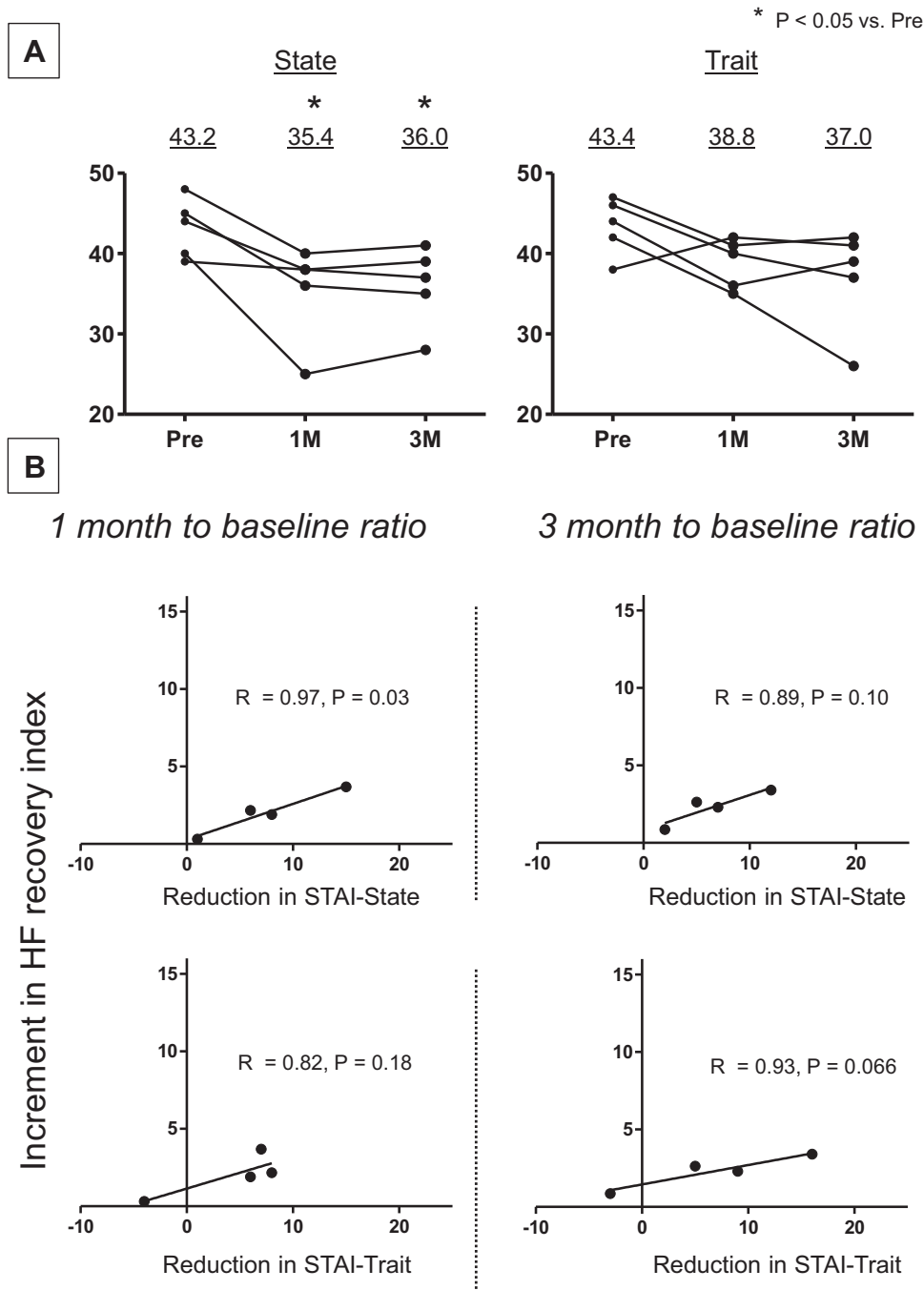
Figure 5   Individual changes in State-Trait Anxiety Inventory (STAI) scores (**A**) and relationship between reductions in STAI scores and changes in high-frequency (HF) component recovery index (**B**) in patients with recurrent atrial fibrillation (AF) after ablation. **A:** Individual STAI state and trait scores before (Pre) and at 1 (1M) and 3 (3M) months after ablation are connected by lines. Mean values of each score are described above the chart. **B:** Positive correlations between reductions in STAI scores and increments in HF recovery index were indicated in patients with recurrent atrial fibrillation as well as the whole cohort.

In contrast to HF scores, changes in SC did not correlate with reductions in STAI scores. In general, parasympathetic tone is associated with anxiety and depression,[24] whereas sympathetic tone is associated with anger, fear, and vigor.[25] The present finding that changes in HF reactivity correlated with changes in anxiety but changes in SC reactivity did not is likely associated with the nature of parasympathetic and sympathetic nerves.

Several studies have examined relationships between cardiac vagal tone modification and AF ablation outcomes.[26] Yoshida and colleagues[27] found significantly lower scores for the HF component after segmental PVI in patients without AF recurrence. One important cause of AF recurrence is PV reconnection. However, a clinical study found that PV reconnections did not significantly differ between patients with and without AF recurrence, suggesting that a mechanism of AF
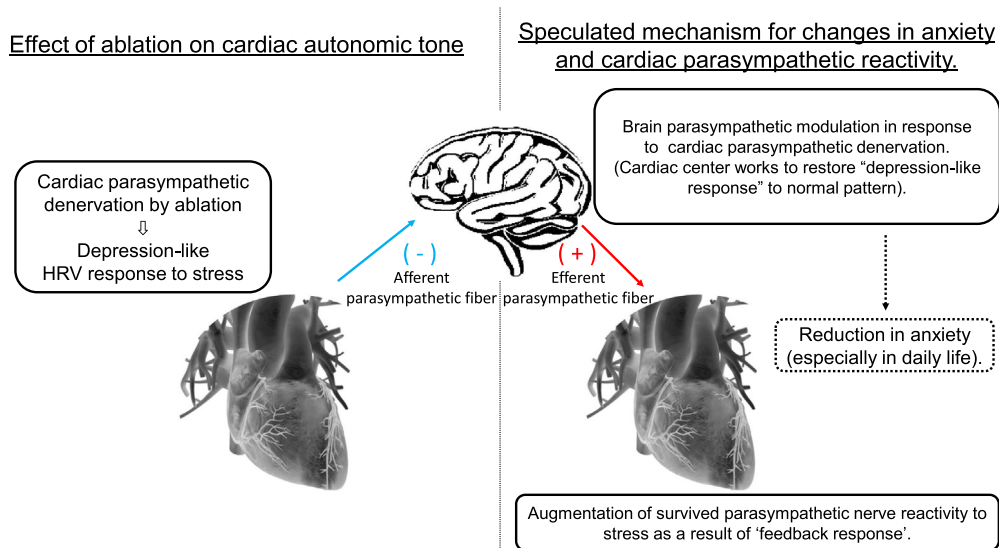
Figure 6   Estimated mechanism for anxiety reduction via feedback response to cardiac parasympathetic denervation. HRV = heart rate variability.

recurrence other than PV reconnections is involved.[28] Cardiac vagal denervation might prevent shortening of the atrial action potential duration and a decrease in the wavelength of the atrial reentrant circuit, leading to reduced AF recurrence after ablation. On the other hand, the relationship between psychological status and AF has been investigated in detail. Deftereos and colleagues[1] reported that improved physical and psychological health-related quality-of-life scores are related to a reduction in AF recurrence. Increases in inflammatory markers including interleukin-6 and C-reactive protein might be one mechanism of anxiety-related AF recurrence.[4] Besides electrophysiological changes, psychological improvement might also function in reducing the likelihood of AF recurrence via vagal denervation. Autonomic modification and psychological changes interact in a complex manner after AF ablation. Creating rigid lesions along the PV antrum by delivering a sufficient amount of RF energy is important for AF ablation from the viewpoints of durable PV isolation and cardiac vagal activity modifications that might improve psychological status.

Study limitations
First, this study assessed a small cohort of patients. Nonetheless, the correlations between reductions in STAI scores and increments in the HF recovery index were significant.

Second, the possibility that placebo effects could influence our findings, particularly psychological status, could not be ruled out. However, several investigators have found that psychological status improves after catheter ablation for AF. Third, our follow-up period was relatively short, and longer follow-up periods might result in different outcomes. However, we focused on changes over a short period to clarify the interaction between autonomic modification and changes in psychological status. Fourth, although there was a correlation between some augmentation of parasympathetic reactivity to stress and reduction in anxiety after

ablation, further study is needed to elucidate the cause-effect relationship. Fifth, SC reflects systemic sympathetic activity indirectly via the activity of peripheral sweat glands. Therefore, SC may not represent the sympathetic activity in other organs, especially the response from the cardiac center. However, the reverse V-shape profile of the SC in response to the task implies that SC reflected systemic sympathetic activity to a certain extent. Sixth, the increase in HF response and recovery index might be attributable to the decrease in HF at rest, which was the denominator of these indexes. However, this would not be probable, because the absolute values in HF at task and HF at rest after the task, which were the numerators of the indexes, were also affected by catheter ablation. Finally, differences between before and after ablation were not tested by repeated-measures analysis of variance, resulting in the lack of assessment on the changes over the course of time. In this study, multiple paired t tests (Pre vs 1M and Pre vs 3M) were applied because we focused on changes caused by ablation from the baseline (Pre).

Conclusion
The present findings suggested interactions between cardiac autonomic modifications and changes in psychological status. Augmentation of parasympathetic reactivity to stress correlated with reduced anxiety, implying that cardiac autonomic modification plays roles in psychological improvement after catheter ablation for AF. Creating rigid lesions along the PV antrum during AF ablation is important from the perspectives of both durable PVI and cardiac vagal activity modification that might improve psychological status.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2020.05.008.

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Disclosures

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