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Vagal response during pulmonary vein isolation: Re-recognized its characteristics and implications in lone paroxysmal atrial fibrillation

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ABSTRACT

Background: The role of autonomic innervation around the pulmonary vein (PV) antrum in the genesis of atrial fibrillation (AF) has been demonstrated but the characteristics of radiofrequency induced vagal response (VR) in the PV antrum and its clinical impact on pulmonary vein isolation (PVI) for paroxysmal AF need to be further elucidated.

Method: Of 995 consecutive patients with symptomatic paroxysmal AF undergoing PVI at a single center over a 2-year period, 516 met exclusion criteria and the remaining 479 patients, 156 positive VR (PVR) and 323 negative VR (NVR), underwent 12-month follow-up. The primary endpoint was freedom from AF or other sustained atrial tachycardia (AT), verified by monthly visits and electrocardiographic monitoring. The frequency-domain analysis was performed to evaluate the autonomic activity before and after the procedure.

Results: VR was most commonly elicited during PVI at the LSPV roof (65.4%) and anterior RSPV (44.9%, with a >5 s sinus pause in 37/70 [52.8%] cases). Compared with the NVR group, ablation was associated with reduced AF recurrence at 12 months in the PVR (hazard ratio: 0.53, 95% confidence interval: 0.22–0.89). Furthermore, the PVR group showed a significantly abbreviated AF cycle length at the left PV, and significantly lower HF and LF parameters with stable LF/HF ratio during follow-up.

Conclusion: Complete elimination of vagal response, most commonly elicited by radiofrequency application around the roof of LSPV and anterior RSPV, appeared associated with reduced 12-month recurrence of AF and with marked heart rate variability changes consistent with autonomic nervous withdrawal.

1. Introduction

The autonomic nervous system facilitates genesis and maintenance of atrial fibrillation (AF) [1–2] and atrial denervation effectively reduces AF inducibility [3–4]. The autonomic nerve density is usually highest in the left atria (LA) within 5 mm from the PV-LA junction [5]. It has been shown that triggered firing in pulmonary vein (PV) with combined parasympathetic and sympathetic nerve stimulation and autonomic tone is also important in maintaining AF [6]. Both studies indicate the critical role of PV innervation region in the pathophysiology of AF.

Pappone et al. made an interesting observation in which vagal response (VR) was induced by radiofrequency ablation [7]. However, several deficiencies certainly existed: 1) the features and distributions of VR around PV antrum have not been clarified in detail; 2) ablation success rate appears to be unrealistic due to the standard of post-ablation follow-up was not as stringent as today; 3) it is hard to make valid lesion to nerve bundles by application of non-irrigated catheter since the epicardium was predominantly innervated by autonomic nerves. Therefore, the purpose of this study is to study paroxysmal atrial fibrillation (PAF) patients referred for catheter ablation to demonstrate the characteristics of VR around PV antrum and determine if elimination of the VR using irrigated-tip catheters truly confers a better ablation success based on the standard follow-up recommended by the expert consensus of HRS/EHRA (Calkins, 2007, 2012).

2. Methods

2.1. Patients

Of 995 consecutive patients with paroxysmal AF who underwent pulmonary vein isolation (PVI) at the Shanghai Chest Hospital from January 2013 to December 2014, 479 were prospectively enrolled based on the following exclusion criteria: valvular heart disease, cardiomyopathy, sick sinus syndrome, diabetes mellitus, stroke, renal failure, thyroid dysfunction, left ventricular ejection fraction <45%, left atrial diameter >45 mm and history of ablation procedures to treat atrial tachyarrhythmias. Anti-arrhythmic agents were discontinued for at least 5 half-lives before the study or for 5 months in the case of amiodarone. All patients provided written informed consent for the electrophysiological study and ablation. This study was approved by our institutional review board.

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2.2. Electrophysiological study and ablation procedure

All study patients underwent PVI only. Details of the ablation procedure were described in our previous studies [8–9]. Briefly, catheter ablation was performed with the guidance of an electro-anatomical mapping system (CARTO, Biosense Webster, CA, USA). Radiofrequency power output was up to 40 W, at 43 °C, with 20–30 s duration for each lesion and saline infusion rate of 20–25 mL/min.

A positive vagal response was defined as a >20% decrease in heart rate (HR) during sinus rhythm or AV conduction block during AF. Ablation was stopped upon occurrence of sinus bradycardia (<40 bpm), asystole, or serious AV block. The immediate ablation endpoint in these sites was lack of a vagal response during repeat ablation. If the vagal response was not eliminated by one 30 s RF application, additional 20 s radiofrequency (RF) applications were delivered. The average AF cycle length was defined by measuring 10 s of AF that was randomly selected.

In AF induction, burst protocol (4–5 Hz, 10 mA, 2 s) was used after procedure; if induction failed, isoproterenol (ISP, 2 μg/min) was administered intravenously to improve inducibility before burst pacing.

2.3. Study outcomes

The primary study outcome with respect to ablation efficacy was freedom from AF or other sustained (duration >30 s) atrial tachyarrhythmia from months 3 to 12 post-ablation after a single procedure. Secondary study outcomes included location of RF-induced VR, fluoroscopy time, procedural time, and rate of procedure-related adverse events, including death, myocardial infarction, cardiac tamponade, and stroke.

2.4. Heart rate variability

The mean heart rate and heart rate variability (HRV) were analyzed using 24 h ambulatory monitoring before the procedure and at the first week, 3, 6 and 12 months after ablation. The autonomic modulation was assessed by frequency-domain HRV analysis with commercially available software (MemCalc/CHIRAM, GMS, Tokyo, Japan).The frequency-domain analysis was performed by a fast Fourier transform of the NN intervals. The low frequency (LF; range: 0.04–0.15 Hz), high frequency (HF; range: 0.15–0.40 Hz), and LF/HF ratio were calculated by frequency-domain analysis. During the analysis, only normal beats were measured, and all AF, extrasystolic beats, and artifacts were eliminated.

2.5. Follow-up

According to the occurrence of vagal response during ablation, all patients were divided in two groups: positive vagal response (PVR) and negative vagal response (NVR). After the ablation procedure, patients in two groups were hospitalized for at least 3 days and cardiac rhythm was continuously monitored during the first 48 h. Outpatient visits and 24-h Holter monitoring were scheduled at 3, 6, and 12 months and every 6 months thereafter. A successful outcome during the follow-up period was defined as the lack of AF or other sustained atrial arrhythmia recorded by ECGs or ambulatory electrocardiography and subjective symptomatic improvement after a 3-month blanking period. We defined the blanking period as the immediate period post-ablation during which recurrence of transient atrial arrhythmias was not considered as RF catheter ablation failure. Follow-up was discontinued for patients who underwent repeat procedures for any tachycardias.

2.6. Statistical analysis

Continuous and discrete variables are expressed as mean ± standard deviation and percentages and compared using independent samples t-test and x^2 test, respectively. LF and HF powers were logarithmically transformed to normalize the distribution. And the normality of the continuous variables was examined. Kaplan–Meier survival analysis with the log-rank test was used to compare recurrence-free survival between the two groups. All covariates with a $P < 0.05$ by means of univariate Cox regression were entered into a multivariate Cox regression model. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported. All tests of significance were 2-sided. A probability value of <0.05 was considered significant. Analyses were performed using SPSS version 18.0.

3. Results

3.1. Patient characteristics

During the 2-year enrollment period, a total of 995 symptomatic paroxysmal AF patients undergoing PVI were screened and 479 patients were enrolled in this study based on the exclusion criteria mentioned in the "Methods" section. All patients had frequent episodes of symptomatic and asymptomatic AF that lasted for mean 5.3 and 4.5 in positive vagal response (PVR) and negative vagal response (NVR) group, respectively. Left atrial size were 37.8 ± 5.1 mm and 38.5 ± 6.2 mm ($P > 0.05$) in PVR and NVR group, respectively (Table 1). Population characteristics are shown in Table 1.

3.2. Ablation characteristics and PV innervation

PVI procedure was performed in PVR and NVR group with no significant difference in mean procedural (69.9 ± 23.4 min vs 64.1 ± 20.2 min, $P = 0.05$) and radiofrequency (48.5 ± 11.6 min vs 42.8 ± 10.4 min, $P > 0.05$), respectively. A total of 99 patients had spontaneous AF during the procedure, 38 (24.4%) in PVR group and 61 (18.9%) in NVR group. Spontaneous AF was terminated by PVI in 31 (19.9%) PVR patients and 52 (16.1%) NVR patients. Pacing induced atrial tachyarrhythmia after procedure was observed in 92 patients (24 PVR; 68 NVR), with similar tachyarrhythmia (AF or AFL/AT) type distribution. In terms of AF triggers, AF wave cycle length (CL) was significantly shorter in left than right PV, and PVR vs NVR patients showed relatively faster electrical activity in left PV (Table 2).

A vagal response was elicited by RF application in 156 (32.6%) of the 479 enrolled patients, most commonly at the cranial junction between the roof of left superior PV (LSPV) and LA (65.4%) (Fig. 1 and Table 3). The sites at the anterior junction between the right superior PV (RSPV) and LA usually caused prolonged bradycardia (44.9%) with a >5 s sinus pause associated with syncope in 37 of 70 (52.8%) patients (Fig. 2). An additional site in the posteroinferior junction between the

Table 1
Baseline characteristics.

	Positive VR (n = 156)	Negative VR (n = 323)	P value
Age, y	65.1 ± 11.7	64.3 ± 12.1	0.49
Male, n(%)	97(62.2)	185(57.3)	0.67
Hypertension, n(%)	45(28.8)	87(26.9)	0.47
Coronary heart disease, n(%)	22(14.1)	36(11.1)	0.35
AF duration, y	5.3 ± 4.8	4.5 ± 5.5	0.12
Echocardiographic parameters			
LAD, mm	37.8 ± 5.1	38.5 ± 6.2	0.22
LVEDD, mm	45.3 ± 4.7	44.4 ± 3.1	0.06
RAD, mm	35.7 ± 3.4	34.9 ± 3.5	0.22
LVEF, %	57.2 ± 5.2	58.4 ± 7.5	0.07
AADs administration before procedure			
Class I AADs	33 (21.1)	51 (15.8)	0.15
Amiodarone	21 (13.5)	49 (15.2)	0.62
Beta-blocker	40 (25.6)	107 (33.1)	0.09

LAD, left atrium diameter; LVEDD, left ventricular end diastolic diameter; RAD, right atrium diameter; LVEF, left ventricular ejection fraction; AADs, anti-arrhythmia drugs.