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Differences in endothelial dysfunction induced by paroxysmal and persistent atrial fibrillation: Insights from restoration of sinus rhythm by catheter ablation☆

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ABSTRACT

Background: Atrial fibrillation (AF) is associated with endothelial dysfunction. Studies have shown the incidence of cardiovascular events to be greater in patients with persistent AF (PeAF) than paroxysmal AF (PAF).
Objective: The aim of this study was to investigate whether endothelial dysfunction and the impact of catheter ablation on the endothelial function differs between PAF and PeAF.
Methods: We prospectively measured the endothelial function by reactive hyperemia peripheral arterial tonometry (RH-PAT) in 103 PAF, 75 PeAF, and 51 control patients at baseline, with follow-up in the AF patients at 6 and 12 months after the catheter ablation.
Results: The log-transformed RH-PAT index (ln RHI) was the highest in the control group, followed by the PAF and PeAF (0.67 ± 0.23, 0.57 ± 0.29, and 0.45 ± 0.3, respectively, $p < 0.001$) groups. PeAF was determined to be an independent factor of endothelial dysfunction (ln RHI <0.55) even after adjustment for the conventional cardiovascular risk factors. For 12 months after the catheter ablation, 102 (99%) PAF and 72 (96%) PeAF patients maintained sinus rhythm. On average, the ln RHI in the PAF group did not change during the follow-up, but it significantly increased in the PeAF group to a level comparable to that of the PAF patients 6 months after the catheter ablation (0.53 ± 0.28, $p = 0.034$), and maintained the same level at 12 months after the catheter ablation.
Conclusions: The persistent form of AF may independently contribute to endothelial dysfunction. In addition, by catheter ablation, the maintenance of sinus rhythm may protect against exacerbations of endothelial dysfunction.

1. Introduction

Atrial fibrillation (AF) is not only associated with an increased incidence of embolic strokes and systemic emboli, but also with an increased risk of heart failure and other cardiovascular events [1–3]. Patients with AF frequently have comorbid hypertension, diabetes mellitus, and dyslipidemia, and these diseases are known to contribute to endothelial dysfunction [4–6]. In addition, several studies have demonstrated that a beat-to-beat variation in the blood flow, which occurs in patients with AF, adversely affects the endothelial function [7,8]. Subsequently, restoration of sinus rhythm with either cardioversion or catheter ablation has been reported to improve the endothelial function in patients with persistent AF (PeAF) [9,10]. It remains unclear whether the degree of endothelial dysfunction is affected by the type of AF. A recent meta-analysis demonstrated that non-paroxysmal AF is associated with a higher risk of thromboembolisms and all-cause mortality than paroxysmal AF (PAF) [11]. These findings may be explained by the degree of endothelial dysfunction for each type of AF. The aim of this study was to investigate whether the endothelial function is worse in patients with PeAF versus patients with PAF using reactive hyperemia peripheral arterial tomography (RH-PAT), a well established parameter of the endothelial function approved by the Food and Drug Administration. In addition, we investigated whether the restoration of the endothelial function after catheter ablation differed in patients with PAF as compared to those with PeAF using RH-PAT.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

2.1. Study population

A total of 201 AF patients referred to our hospital for catheter ablation were enrolled in this study from May 2013 to February 2015. The patients were divided into two groups based on diagnoses of either PAF or PeAF, which were made according to the HRS definitions [12]. Patients who did not complete the study were excluded. Patients with permanent AF, concurrent dialysis, a previous catheter ablation, or a lack of maintenance of sinus rhythm during the follow-up were also excluded from this study. Patients with prior atherosclerotic disease, including coronary artery disease, peripheral artery disease, or aortic aneurysms, were included, and defined as "vascular disease." The final study population consisted of 102 patients with PeAF and 72 with PAF. For a control group, 51 age-matched patients who underwent catheter ablation for either paroxysmal supraventricular tachycardia (PSVT) or premature ventricular complexes (PVCs) during the same period were included (Fig. 1). Of 35 PSVT patients, 16 with atrioventricular nodal reentrant tachycardia (AVNRT), 9 with atrioventricular reentrant tachycardia (AVRT), and 10 with focal atrial tachycardia (AT) were included. In the control group, 12 (23.5%) patients, including 8 with AVRT and 4 with PVCs, required a left-heart-system approach. Written informed consent regarding the data acquisition was obtained from all participants. This study conformed to the 1975 Declaration of Helsinki, as reflected by the approval from the Institutional Review Board of our hospital.

2.2. Study protocol

All patients underwent RH-PAT with an EndoPAT2000 (Itamar Medical, Caesarea, Israel) on the day of admission. RH-PAT is a noninvasive, automatic, reproducible, and quantitative test that measures the digital hyperemic response. The ability of digital RH-PAT to evaluate the endothelial function has been previously verified [13]. After measuring the baseline blood volume changes, a blood pressure cuff placed on the patient's arm was inflated above the systolic pressure and subsequently deflated after 5 min. This procedure induced reactive hyperemia in a specific arm. The RH-PAT index (RHI) was used to reflect the extent of reactive hyperemia, and was calculated as the ratio of the average amplitude of the RH-PAT signal for 1 min starting after cuff deflation (control arm, A; occluded arm, C) divided by the average amplitude of the RH-PAT signal for 2.5 min before cuff inflation (baseline) (control arm, B; occluded arm, D). Thus, RHI = (C/D)/(A/B) × (baseline correction). The log-transformed RHI (ln RHI) was then calculated to provide a normal distribution. The precision of the RHI during AF has also been demonstrated [14]. However, we compared the RHI during AF with that during sinus rhythm 3 h after electrical cardioversion in the same consecutive 30 PeAF patients to validate the accuracy of the RH-PAT measurement during AF once again. The cut-off value of the ln RHI was 0.55, equal to an RHI of 1.73, and was defined by the median value of this study; this cut-off value was used to diagnose endothelial dysfunction. We repeated the RH-PAT measurements at 6 and 12 months after the catheter ablation.

2.3. Catheter ablation procedure

Catheter ablation was performed in the following manner. After a double transseptal puncture, heparin was injected to maintain the activated clotting time between 300 and 350 s. Next, three-dimensional geometry of the left atrium (LA) and pulmonary veins (PVs) was determined via a CARTO system, and all PVs were mapped with a decapolar circular catheter (Lasso; Biosense Webster, Diamond Bar, CA, USA). An open irrigation 3.5-mm-tip deflectable catheter (Thermocool; Biosense Webster) was used for mapping and ablation. Radiofrequency energy was delivered at a maximum power output of 35 W, flow rate of 17 or 30 mL/min, and maximum temperature of 45 °C. Initially, a wide circumferential PV isolation was performed. An electrical isolation of the superior vena cava or posterior wall of the LA was included as needed. No complex fractionated atrial electrogram ablation or linear ablation of the mitral isthmus was performed. The procedural endpoints were defined as follows. No documented ATP-induced dormant conduction between the PVs and LA; no recurrence of AF after sinus rhythm conversion under an isoproterenol infusion (1 or 2 μg); and no induction of sustained AF. All patients with AF received oral anticoagulant therapy for at least 4 weeks prior to the catheter ablation, and were continued on medication for at least 12 months.

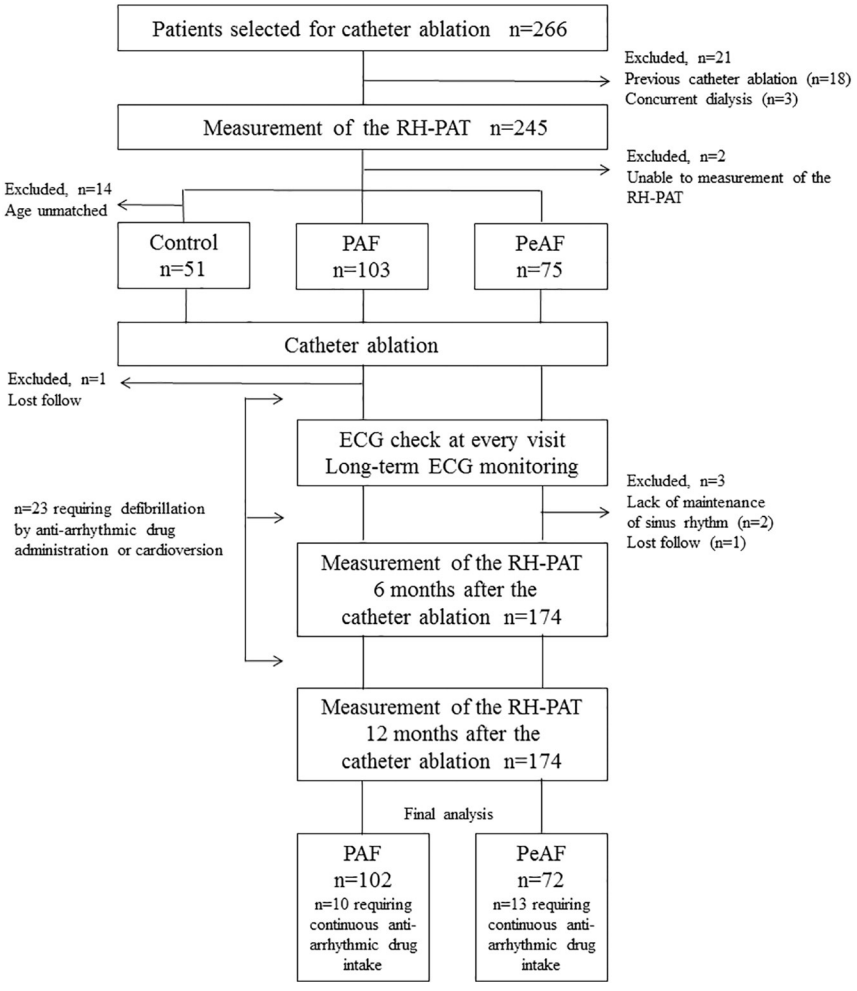

Fig. 1. Flow chart of the study participants. A total of 201 AF patients referred to our hospital for catheter ablation were enrolled from May 2013 to February 2015. Finally 102 PAF and 72 PeAF patients were evaluated in this study. Fifty-one age matched PSVT or PVC patients were used as a control. AF indicates atrial fibrillation; RH-PAT, log-transformed reactive hyperemia peripheral arterial tonometry; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; ECG, electrocardiogram.

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