Successful catheter ablation decreases platelet activation and improves endothelial function in patients with atrial fibrillation

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BACKGROUND Nonvalvular atrial fibrillation (AF) confers a five-fold increased risk of stroke. Whether catheter ablation (CA) subsequently decreases prothrombotic risk is unknown.

OBJECTIVE The purpose of this study was to assess the long-term effects of CA for AF on prothrombotic risk.

METHODS Fifty-seven patients undergoing CA for AF were prospectively studied. Platelet activation (CD62P [platelet P-selectin] and PAC-1 [glycoprotein IIb/IIIa] expression) and endothelial function (asymmetric dimethylarginine [ADMA] levels) were measured at baseline and 6-months postablation.

RESULTS Thirty-seven (65%) patients remained in sinus rhythm (SR group) and 20 (35%) sustained AF recurrence (AF recurrence group) at 6-months. Patients with AF-recurrence were older, had a higher proportion of hypertension and long-standing persistent AF. There were no significant differences in CD62P ($P = .3$), PAC-1 ($P = .1$) and ADMA ($P = .7$) levels at baseline between the two groups. In the SR group, markers of platelet activation decreased significantly at 6-month follow-up compared to baseline; log CD62P % 0.79 $\pm$ 0.28 vs 1.03 $\pm$ 0.27 ($P < .05$) and log PAC-1 % 0.22 $\pm$ 0.58 vs 0.89 $\pm$ 0.31 ($P < .01$). This was not significant in the AF-recurrence group ($P = .8$, log CD62P; $P = .1$, log PAC-1). For endothelial function, ADMA levels decreased significantly at 6-months compared to baseline in the SR group (log ADMA μM/L 0.15 $\pm$ 0.02 vs 0.17 $\pm$ 0.04; $P < .05$), but did not alter significantly in the AF-recurrence group ($P = .4$, log ADMA).

CONCLUSION Catheter ablation and successful maintenance of SR leads to a decrease in platelet activation and improvement in endothelial function in patients with AF. These findings suggest that AF is an important determinant of the prothrombotic state and that this may be reduced by successful catheter ablation.

KEYWORDS Atrial fibrillation; Catheter ablation; Thrombotic risk; Stroke prevention; Endothelial dysfunction; Platelet activation

ABBREVIATIONS **ADMA** = asymmetric dimethylarginine; **AF** = atrial fibrillation; **CHA_2DS_2-VASc score** = *c*ongestive heart failure, *h*ypertension, *a*ge $\geq$75 (doubled), *d*iabetes, *s*troke (doubled), *v*ascular disease, *a*ge 65–74, *s*ex category (female); **ECG** = electrocardiography; **LA** = left atrial; **SR** = sinus rhythm

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Introduction

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder encountered in clinical practice and confers a 5-fold increased risk of stroke.[1] Patients with AF are known to exhibit a prothrombotic state with evidence of increased platelet activation and endothelial dysfunction.[2–5] Abnormal platelet activation and endothelial dysfunction play intrinsic roles in thrombus formation and are known to contribute to the risk of stroke in AF by virtue of Virchow's triad.[6]

Whether increased platelet activation and endothelial dysfunction are a cause or a consequence of AF is unknown. Cardiovascular comorbidities associated with AF in themselves can result in platelet activation and endothelial dysfunction.[7] Several studies in patients with AF successfully cardioverted to sinus rhythm (SR) have shown a subsequent decrease in platelet activation and endothelial dysfunction.[8–10] These findings imply that AF itself may be a

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cause of the abnormal platelet and endothelial function. However, data on the response of these indices after catheter ablation are limited.

We hypothesized that successful reversion of AF and maintenance of SR by catheter ablation would lead to a decrease in platelet activation and endothelial dysfunction, by measuring platelet expression of P-selectin (CD62P) and glycoprotein IIb/IIIa (PAC-1) as markers of platelet activation and asymmetric dimethylarginine (ADMA) as a marker of endothelial dysfunction.

Methods

Study population

Fifty-seven consecutive patients undergoing elective catheter ablation for paroxysmal, persistent, or long-standing persistent AF were prospectively recruited. Patients were excluded from the study if they had an acute cause of AF (eg, infection, alcohol excess, pulmonary emboli), valvular or congenital heart disease, renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 m^2), chronic liver disease, chronic infection or inflammatory condition, left ventricular dysfunction, acute cardiovascular or cerebrovascular events (eg, myocardial infarction, acute coronary syndrome, stroke) within the last 3 months, had intracardiac thrombus on transesophageal evaluation, or were taking antiplatelet medications. All patients underwent baseline transthoracic echocardiography, and transesophageal echocardiography was performed within 2 days before the procedure to exclude left atrial (LA) thrombus. All patients provided written informed consent to the study protocol, which was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, Australia.

All antiarrhythmic drugs were stopped 5 half-lives before the procedure. All patients underwent anticoagulation with warfarin to maintain an international normalized ratio between 2 and 3 for ≥ 6 weeks before the procedure. Warfarin was stopped 7 days before the procedure and substituted with enoxaparin at a dose of 1 mg/kg twice per day until ≥ 12 hours before the procedure.

Paroxysmal AF was defined according to the expert consensus statement as recurrent AF that terminates spontaneously within 7 days.[11] Persistent AF was defined as AF that is sustained for >7 days or that lasts <7 days but necessitates pharmacologic or electrical cardioversion.[11] Long-standing persistent AF was defined as continuous AF of >1-year duration.[11]

Catheter ablation procedure

Electrophysiologic study and ablation were performed with sedation using midazolam and fentanyl. The technique used for mapping and ablation of AF in our laboratory has been previously described.[12,13] In brief, the LA was accessed using a single transseptal puncture, after which repeated bolus unfractionated heparin was used to maintain the activated clotting time between 300 to 350 seconds. The following catheters were used for the procedure: (1) 10-pole catheter (Daig Electrophysiology, Minnetonka, Minnesota) positioned within the coronary sinus; (2) 10-pole circumferential catheter (Lasso, Biosense Webster, Diamond Bar, California) to map the pulmonary veins; and (3) 3.5-mm-tip externally irrigated ablation catheter (Thermocool, Biosense Webster) for ablation. All patients underwent circumferential pulmonary vein isolation. Additional substrate modification using either linear ablation (roofline and/or mitral isthmus) and/or ablation of complex fractionated atrial electrograms was undertaken in patients with long episodes of AF (>48 hours), evidence of structural heart disease, or large LA (largest dimension >57 mm). Cavo-tricuspid isthmus ablation with an end-point of bidirectional isthmus block was performed only in patients with a history of typical flutter or if mapping confirmed typical flutter during the procedure. Ablation of the pulmonary veins was performed using a delivered power of 25 to 30 W with irrigation rates of 17 to 30 mL/min. Linear ablation was performed with a delivered power of 30 to 35 W with irrigation rates of 17 to 60 mL/min.

Postablation follow-up

All patients were prospectively followed up at 6 weeks, 3 months, and 6 months after a single procedure by physician review. All patients remained on the same medications at baseline and throughout the study period. Seven-day Holter monitoring was performed on all patients at 6 weeks, 3 months, and 6 months prior to follow-up. Electrocardiography (ECG) was also performed at each follow-up, and patients were instructed to present for ECG analysis if any symptoms occurred. AF recurrence during this 6-month follow-up period was noted with a blanking period for the first 3 months used. Arrhythmia recurrence was defined as any episode lasting >30 seconds and confirmed by ECG or Holter monitoring.

Blood sampling and analysis

Peripheral blood samples were obtained at baseline at the start of the procedure, before any ablation, before administration of medications such as heparin, and at 6 months postprocedure during outpatient follow-up. Laboratory personnel who conducted the platelet and endothelial function testing were blinded to patient characteristics.

Whole blood flow cytometry

Blood was collected using a slow withdrawal technique, with the first 10 mL discarded, and immediately transferred into citrated tubes. Flow cytometry was performed within 24 hours. Surface expression of the platelet activation receptors CD62P (P-selectin) and PAC-1 (glycoprotein IIb/IIIa activity) were determined by flow cytometry using specific monoclonal antibodies. Citrated whole blood was diluted 1:9 in tris-buffered saline (10 mM tris, 0.15 M sodium chloride) before 5 μL antibody per 500 μL tris-buffered blood was added. After incubation, the sample was fixed by adding 400 μL of CellFix solution (BD Biosciences, San Jose, California). The presence of platelet-expressing ligands