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Effect of Atrial Fibrillation on Atrial Thrombogenesis in Humans: Impact of Rate and Rhythm

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Objectives We sought to assess the effect of atrial fibrillation (AF) on atrial thrombogenesis in humans by determining the impact of rate and rhythm.

Background Although AF is known to increase the risk of thromboembolic stroke from the left atrium (LA), the exact mechanisms remain poorly understood.

Methods We studied 55 patients with AF who underwent catheter ablation while in sinus rhythm; 20 patients were induced into AF, 20 patients were atrial paced at 150 beats/min, and 15 were control patients. Blood samples were taken from the LA, right atrium, and femoral vein at baseline and at 15 min in all 3 groups. Platelet activation (P-selectin) was measured by flow cytometry. Thrombin generation (thrombin-antithrombin [TAT] complex), endothelial dysfunction (asymmetric dimethylarginine [ADMA]), and platelet-derived inflammation (soluble CD40 ligand [sCD40L]) were measured using enzyme-linked immunosorbent assay.

Results Platelet activation increased significantly in both the AF ($p < 0.001$) and pacing ($p < 0.05$) groups, but decreased in control patients ($p < 0.001$). Thrombin generation increased specifically in the LA compared with the periphery in both the AF ($p < 0.01$) and pacing ($p < 0.01$) groups, but decreased in control patients ($p < 0.001$). With AF, ADMA ($p < 0.01$) and sCD40L ($p < 0.001$) levels increased significantly at all sites, but were unchanged with pacing (ADMA, $p = 0.5$; sCD40L, $p = 0.8$) or in control patients (ADMA, $p = 0.6$; sCD40L, $p = 0.9$).

Conclusions Rapid atrial rates and AF in humans both result in increased platelet activation and thrombin generation. Prothrombotic activation occurs to a greater extent in the human LA compared with systemic circulation. AF additionally induces endothelial dysfunction and inflammation. These findings suggest that although rapid atrial rates increase the thrombogenic risk, AF may further potentiate this risk. (J Am Coll Cardiol 2013;61:852–60)

Atrial fibrillation (AF) confers a 5-fold increased risk of stroke in the absence of valvular heart disease (1). Although epidemiological studies have linked various clinical and echocardiographic risk factors to stroke, the exact mechanism of increased risk of stroke in AF remains poorly understood. Although the heightened risk of stroke after

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cardioversion has been attributed to atrial mechanical dysfunction, it has been increasingly recognized that AF may in itself exhibit a prothrombotic state (2). There have been suggestions that atrial flutter, a more organized rhythm, may also be associated with an increased risk of stroke (3). However, the mechanisms by which rapid atrial rates and/or rhythm contribute to left atrial (LA) thrombogenesis have not been well studied.

Several studies have found baseline regional differences in platelet activation and hypercoagulability in the LA compared with systemic circulation in patients with valvular and nonvalvular AF (4,5), suggesting local contributing factors. Animal studies have demonstrated increased platelet activation and endothelial dysfunction with acute AF (6,7). However, the acute effect of AF on thrombogenesis in the human LA has never been studied before.

We hypothesized that acute-onset AF results in increased prothrombotic risk (by platelet activation, thrombin generation, endothelial dysfunction, and inflammation) within the human atria. Furthermore, we aimed to distinguish whether this effect was rate or rhythm related.

Abbreviations and Acronyms

ADMA = asymmetric dimethylarginine
AF = atrial fibrillation
CV = coefficient of variation
FV = femoral vein
LA = left atrium
RA = right atrium
sCD40L = soluble CD40 ligand
SR = sinus rhythm
TAT = thrombin-antithrombin-complex

Methods

Study population. The study comprised 55 patients with a history of AF and 15 patients with left-sided accessory pathways as a reference group who underwent catheter ablation. Consecutive patients with paroxysmal or persistent AF who were in sinus rhythm (SR) ≥48 h before the procedure (by continuous monitoring) were included. Exclusion criteria were history of valvular heart disease, left ventricular dysfunction, previous myocardial infarction, unstable angina, surgical or ablation procedure within the preceding 3 months, congenital heart disease, chronic inflammatory condition, chronic infection, chronic renal failure, chronic liver disease, and patients on antiplatelet agents.

All patients underwent baseline transthoracic echocardiography and transesophageal echocardiography within 2 days of the procedure (8). All antiarrhythmic medications were ceased 5 half-lives before the procedure. All patients underwent anticoagulation with warfarin to maintain their 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 a day until ≥12 h before the procedure.

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.

Electrophysiology study and ablation. Electrophysiological study and ablation were performed with sedation using midazolam and fentanyl. The technique used for mapping and ablation of AF in our laboratory was previously described (9). In brief, the following catheters were utilized 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) a 3.5-mm-tip externally irrigated ablation catheter (Thermocool, Biosense-Webster) for ablation. All patients underwent circumferential ablation of the pulmonary veins with the endpoint of electrical 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 h), evidence of structural heart disease, or with a large LA (largest dimension > 57 mm).

Study protocol. For the clinical procedure, a conventional single transeptal puncture was performed using an SLO sheath (St. Jude Medical, St. Paul, Minnesota) and a BRK-1 needle (Daig Corporation). The ablation catheter was advanced through the same puncture into the LA. Following transeptal puncture, and 5 min after intravenous administration of unfractionated heparin (bolus of 100 IU/kg), blood samples were simultaneously collected from the peripheral femoral venous (FV) sheath (systemic sample), right atrial (RA) sheath, and LA sheath. Samples from the RA and LA were collected with care using a slow withdrawal technique, with the sheath positioned in the midchamber. Patients were then randomized either into the AF group, pacing group, or to serve as control patients.

Of the 55 patients with a history of AF who presented in SR, AF was induced by burst atrial pacing in 20 patients, commencing at a cycle length of 250 ms and ramping down to loss of 1:1 capture. This process was repeated up to 3 times from 3 sites, as required. Another 20 patients underwent atrial pacing at 150 beats/min. The rate of atrial pacing was limited to prevent induction of AF. To control for the effects of the transeptal puncture and procedure duration, 15 patients served as a control group, who neither underwent AF induction nor pacing. After 15 min of AF, atrial pacing, or in control patients, blood sampling was repeated from the LA, RA, and FV. No ablation was performed before the completion of the study protocol.

In addition to the control group of AF patients, to evaluate the effect of transeptal puncture on prothrombotic markers, 15 non-AF patients with left-sided accessory pathways who underwent an electrophysiological study and transeptal puncture during this period were also recruited as a reference group. Blood samples were obtained from the LA, RA, and FV following transeptal puncture at baseline. With the same exclusion criteria, consecutive patients with