Left atrial remodeling in patients with atrial septal defects

Kurt C. Roberts-Thomson, MBBS, PhD,*† Bobby John, MD, PhD,* Stephen G. Worthley, MBBS, PhD,* Anthony G. Brooks, PhD,* Martin K. Stiles, MBChB, PhD,* Dennis H. Lau, MBBS,* Pawel Kuklik, PhD,* Nicholas J. Shipp, PhD,* Jonathan M. Kalman, MBBS, PhD,† Prashanthan Sanders, MBBS, PhD*

*From the *Cardiovascular Research Centre, Department of Cardiology, Royal Adelaide Hospital, and the Disciplines of Medicine and Physiology, University of Adelaide, Adelaide, Australia; and the †Department of Cardiology, Royal Melbourne Hospital, and the Department of Medicine, University of Melbourne, Melbourne, Australia.*

BACKGROUND Information regarding left atrial (LA) substrate in conditions predisposing to atrial fibrillation (AF) is limited.

OBJECTIVE This study sought to characterize the left atrial remodeling that results from chronic atrial stretch caused by atrial septal defect (ASD).

METHODS Eleven patients with hemodynamically significant ASDs and 12 control subjects were studied. The following were evaluated using multipolar catheters: effective refractory period (ERP) at 7 sites, P-wave duration (PWD), conduction time, and inducibility of AF. LA electroanatomic maps were created to determine atrial activation, and regional conduction and voltage abnormalities.

RESULTS Patients with ASDs showed significant LA enlargement ($P < 0.001$), unchanged or prolonged atrial ERPs, increase in LA conduction times ($P = 0.03$), prolonged PWD ($P < 0.001$), regional conduction slowing ($P < 0.001$), greater number of double potentials or fractionated electrograms ($P < 0.0001$), reduced atrial voltage ($P < 0.001$), and more frequent electrical scar ($P = 0.005$) compared with control subjects. In addition, patients with ASDs showed a greater propensity for sustained AF with single extrastimuli (4 of 11 vs. 0 of 12, $P = 0.04$).

CONCLUSION ASDs are associated with chronic left atrial stretch, which results in remodeling characterized by LA enlargement, loss of myocardium, and electrical scar that results in widespread conduction abnormalities but with no change or an increase in ERP. These abnormalities were associated with a greater propensity for sustained AF.

KEYWORDS Atrial septal defects; Stretch; Electrical remodeling; Left atrium

(Heart Rhythm 2009;6:1000–1006)

Introduction

In patients with atrial septal defects (ASD), it is well recognized that the prevalence of atrial arrhythmias increases with age.[1,2] The mechanisms responsible for the development of atrial arrhythmias in these patients have not been well characterized. Although it is recognized that an ASD results in chronic right volume overload with resultant right atrial stretch and right atrial remodeling, its effects on the left atrium (LA) are not well known.[3] This is of particular importance because it is generally accepted that in most patients, atrial fibrillation (AF) is in large part a LA condition.[4–6] There is a paucity of information on the LA substrate for arrhythmia in any condition predisposed to AF. This clinical study was designed to characterize the presence and nature of LA remodeling in patients with a hemodynamically significant ASD.

Methods

Study population

The study comprised 11 patients with hemodynamically significant ASDs undergoing percutaneous septal defect closure. Selection criteria for ASD closure were as follows: (1) symptoms attributable to the ASD, and (2) significant left-to-right shunt (pulmonary:systemic flow ratio [Qp:Qs] of >1.5:1). Patients were excluded from the study if they had other conditions that could result in atrial remodeling: prior myocardial infarction, heart failure, valvular heart disease, or atrial arrhythmias. Twelve patients having radiofrequency ablation for atrioventricular reentrant tachycardia caused by left-sided accessory pathway without evidence of

This study was supported in part by a Grant-in-Aid (G 08A 3646) from the National Heart Foundation of Australia and New Zealand. Dr. Roberts-Thomson is the recipient of a Postgraduate Research Scholarship from the National Health and Medical Research Council of Australia. Dr. John is supported by the Biosense-Webster Electrophysiology Scholarship, University of Adelaide. Dr. Brooks is supported by a Postdoctoral Fellowship from the National Heart Foundation of Australia. Dr. Stiles is supported by the National Heart Foundation of New Zealand and the Dawes Scholarship, Royal Adelaide Hospital. Dr. Lau is supported by the Earl Bakken Electrophysiology Scholarship, University of Adelaide, a Kidney Health Australia Biomedical Research Scholarship, and a Postgraduate Research Scholarship from the National Health and Medical Research Council of Australia. Dr. Sanders is supported by the National Heart Foundation of Australia. Dr.Sanders has served on the advisory board of and has received lecture fees and research funding from St Jude Medical, Medtronic, Bard Electrophysiology, and Biosense-Webster. Presented in part at the 28th Annual Scientific Sessions of the Heart Rhythm Society, Denver, Colorado, May 2007, and published in abstract form (Heart Rhythm 2007;4:S347). **Address reprint requests and correspondence:** Dr. Prashanthan Sanders, Cardiovascular Research Centre, Department of Cardiology, Level 5, McEwin Building, Royal Adelaide Hospital, Adelaide, SA 5000, Australia. E-mail address: prash.sanders@adelaide.edu.au. (Received February 15, 2008; accepted March 25, 2009.)

  doi:10.1016/j.hrthm.2009.03.050

structural heart disease or history of atrial arrhythmia served as the control population. All medications were ceased ≥5 half lives before the study. No patient received amiodarone in the 6 months before the study. All patients gave written informed consent for the study protocol, which was approved by the Clinical Research and Ethics Committee of the Royal Adelaide Hospital, Adelaide, Australia.

Transthoracic echocardiography

Maximal preatrial-systolic atrial volume (V) was determined as previously described.[3] In brief, the atrial diameter is measured in 2 views (apical 4-chamber and parasternal long axis; D_1 and D_2) and the length is measured in the apical 4-chamber view (L). The volume is then determined by the equation of a prolate ellipsoid: $V\ (ml) = \pi D_1 D_2 L/6$. Because the parasternal long axis measurements of the right atrium could not be made, the equation was modified to $V\ (ml) = \pi D_1 D_1 L/6$ for the right atrium.

Electrophysiological study

Electrophysiological study was performed in the post-absorptive state with sedation with midazolam. Multipolar catheters were positioned as follows: (1) a 10-pole catheter with 2-5-2 mm interelectrode spacing (Daig Electrophysiology, Minnetonka, MN) in the coronary sinus (CS) with the proximal bipole positioned at the CS ostium as determined in the best septal left anterior oblique view, and (2) a 10-pole catheter with 2-5-2-mm interelectrode spacing (Biosense-Webster, Diamond Bar, CA) was inserted into the LA via the ASD or transseptal puncture. This catheter was stabilized with the use of a long sheath (Preface, Biosense-Webster or SLO, Daig Electrophysiology) and sequentially positioned as follows: (1) LA-roof, (2) inferior-LA, (3) mid-posterior-LA, and (4) LA-appendage (Figure 1).

Surface electrocardiogram (ECG) and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system for off-line analysis (Bard Electrophysiology, Lowell, MA). Intracardiac electrograms were filtered from 30 to 500 Hz, and measured with computer-assisted calipers at a sweep speed of 200 mm/s.

Effective refractory period

Atrial effective refractory periods (ERPs) were evaluated at twice diastolic threshold at cycle lengths (CLs) of 600 and 450 ms using an 8-beat drive followed by an extrastimulus (S_2), starting with an S_2 coupling interval of 150 ms increasing in 10-ms increments. The ERP was defined as the

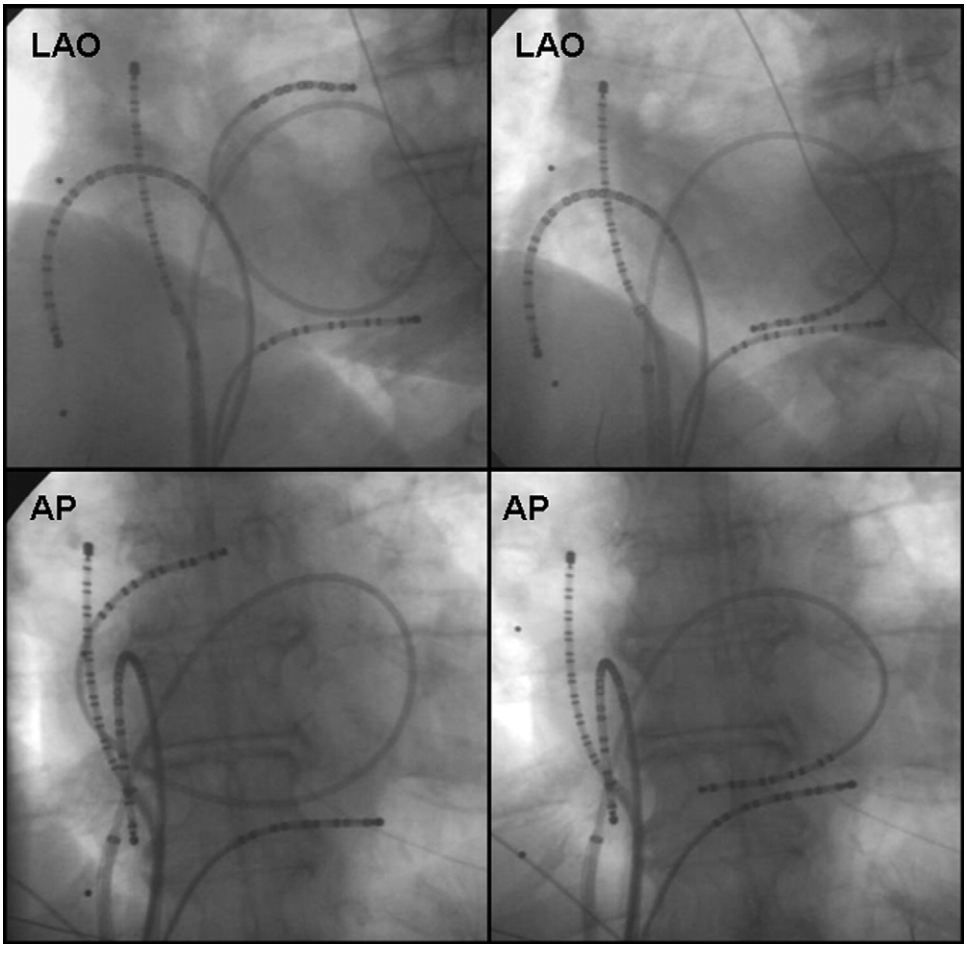

Figure 1 Fluoroscopic images of the catheter positions in the left anterior oblique (LAO) and the anteroposterior (AP) views. Note in the left panels the LA catheter is placed along the roof and then is withdrawn to the inferior LA (right panels).