Effect of Chronic Right Atrial Stretch on Atrial Electrical Remodeling in Patients With an Atrial Septal Defect

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Background—Adults with an atrial septal defect (ASD) frequently develop late atrial arrhythmias. We sought to characterize the pattern and persistence of atrial electrical remodeling caused by chronic right atrial (RA) stretch in this group.

Methods and Results—Thirteen ASD patients without atrial arrhythmia (42±10 years old; RA volume, 65±16 mL) and 17 normal control subjects (44±11 years old; RA volume, 38±8 mL) had electrophysiological study to measure (1) atrial effective refractory period (AERP) from the low lateral/high lateral/high septal RA and distal coronary sinus (CS), (2) dispersion of AERP, (3) lateral-RA and CS conduction time during constant pacing, (4) conduction delay across the crista terminalis measuring the number of crista catheter bipoles (0–10) recording discrete double potentials during pacing, (5) corrected sinus node recovery time, and (6) P-wave duration. After ASD closure (8.3±5.6 months), follow-up echo studies (n=12) and electrophysiological study (n=4) were performed. The low-lateral AERP, P-wave duration, sinus node recovery time, and extent of conduction delay across the crista terminalis were significantly greater in ASD patients. No differences were found for other measured electrophysiological study parameters. At follow-up, there was incomplete resolution of RA volume (47±12 mL; P<0.01 versus before surgery), a trend toward shortening of the AERP at the lateral RA and an increase at the distal CS and high septal RA, but persisting extensive, widely split crista double potentials.

Conclusions—Chronic RA stretch because of ASD causes electrical remodeling with modest increases in RA ERP, conduction delay at the crista terminalis, and sinus node dysfunction. Conduction delay at the crista terminalis persists beyond ASD closure and may contribute to the long-term atrial arrhythmia substrate in this condition. (Circulation. 2003;107:1775-1782.)

Key Words: remodeling ■ fibrillation ■ defects

The natural history of adults with an atrial septal defect (ASD) and chronic right atrial (RA) volume overload is characterized by an increased risk for the development of atrial arrhythmias that appears to be minimally altered by ASD closure. Although surgical lines of block may form the substrate for “scar-related” atrial macroreentry after surgical ASD repair, there is limited information concerning the impact of chronic RA stretch and volume overload on atrial electrophysiology in ASD patients.

Animal studies of chronic atrial enlargement have demonstrated an increased vulnerability to atrial arrhythmias, and atrial electrical remodeling (ER) has been described in response to chronic atrial stretch. Although initial studies of atrial ER focused on tachycardia-induced changes in atrial refractoriness for the promotion of atrial fibrillation (AF), more recent studies concerning chronic atrial stretch and ER have emphasized the contribution of heterogeneous disturbances in atrial conduction.

In patients with atrial arrhythmias, abnormalities in conduction may be regionally distributed to key anatomic areas. The crista terminalis (CT) is recognized as an important anatomic structure in atrial arrhythmogenesis, and anisotropic conduction delay and block along this structure have been shown to play a key role in the development of typical atrial flutter, atypical forms of flutter such as lower loop reentry, and indeed in AF. A number of clinical studies have also demonstrated that patients with atrial arrhythmias have anatomically determined functional conduction block along this structure.

The aim of the present study was to characterize the pattern of atrial ER caused by chronic RA stretch in adults with an ASD and to determine whether ER reverses after ASD...
closure. We hypothesized that chronic RA stretch would lead to regional disturbances in atrial conduction, and in particular, conduction across the CT was rigorously evaluated. To clearly characterize the type of ER seen in ASD patients with chronic RA volume overload and atrial enlargement without the confounding or supervening effects of subsequent atrial arrhythmias, patients with a history of such arrhythmias were excluded from the study.

Methods
Patient Population and Selection
All patients provided written informed consent to participate in the research study, and the study protocol was approved by the ethics committee of the Royal Melbourne Hospital.

The ASD group (n = 13; 6 men; mean age, 41.6 ± 10.3 years; range, 21 to 63 years) was enrolled from those patients referred to our institution with a known ASD for diagnostic right and left heart catheterization. Selection criteria for ASD closure were any of the following: (1) symptoms attributable to the ASD, (2) previous paradoxical embolism, (3) significant left to right shunt (pulmonary/systemic flow ratio [Qp/Qs] of >1.5:1), or (4) evidence of significant right ventricular enlargement. Exclusion criteria were a previous history of atrial arrhythmia, coronary artery disease, left ventricular dysfunction, or significant comorbidity. The control group (controls; n = 17; 9 men; mean age, 43.6 ± 11.0 years; range, 26 to 59 years; P = NS versus ASD group) was enrolled from those patients referred to our institution for diagnostic electrophysiological study and either documented or suspected paroxysmal supraventricular tachycardia. Exclusion criteria were suspected or known atrial arrhythmia, evidence of structural heart disease, and amiodarone therapy in the preceding 6 months. At electrophysiological study, 13 of 17 had inducible supraventricular tachycardia and underwent successful radiofrequency ablation (atrioventricular nodal reentrant tachycardia, n = 10; atrioventricular reentrant tachycardia, n = 3). Four of 17 had no inducible supraventricular tachycardia.

Transcatheter Echocardiography
Maximal preatrial–systolic atrial volume (V) was determined by use of the equation for a prolate ellipsoid: V (ml) = πD1D2L/6, where D1 and D2 are the minor axis (width) as measured in 2 views (apical 4-chamber and parasternal long-axis) and L is the major axis (length) of the atrium as measured in the apical 4-chamber view. In the latter view, width was measured in the midcavity and length from the posterior atrium to the level of the mitral or tricuspid annulus. For RA volume measurements, a parasternal long-axis determination of posterior atrium to the level of the mitral or tricuspid annulus was performed. ARA width could not be made, and hence, the equation was modified to V (ml) = πD1D2L/6.

Electrophysiological Study
Patients were studied in the fasting state under either benzodiazepine/opioid sedation or general anesthesia. All antiarrhythmic agents were stopped at least 5 drug half-lives before the procedure. Before the electrophysiology research protocol was begun, autonomic blockade was administered by slow infusion with intravenous atropine (0.04 mg/kg) and propranolol (0.2 mg/kg).

The following electrophysiology catheters were inserted from the right femoral vein: (1) A 6F decapolar catheter (2-mm interelectrode and 5-mm interbipole distance: “2-5-2-mm spacing”) positioned in the coronary sinus (CS) such that the proximal bipole was at the level of the CS ostium. (2) Another 6F decapolar catheter with the same electrode spacing positioned in the RA parallel to the tricuspid annulus such that bipole 1/2 was in the low lateral RA (LLRA) and bipole 9/10 was at the high lateral RA (HLRA). This catheter was subsequently moved to a high septal RA (HSRA) position. (3) A 7F 20-pole with 1-mm interelectrode and 3-mm interbipole distance introduced via a long vascular sheath and positioned along the long axis of the CT with bipole 1/2 cranial and bipole 19/20 caudal. Bipole 3/4 was positioned at the junction of the superior vena cava and RA. In a subset of patients, the catheter position was confirmed by intracardiac echocardiography.

The following electrophysiology parameters were measured.

1. Atrial effective refractory period (AERP) measured from the distal CS, LLRA, HLRA, and HSRA at 3 basic drive cycle lengths (CLs) of 600, 500, and 400 ms. Pacing was performed using a pulse width of 2 ms and a current output of twice the local diastolic threshold. If the latter was >2.0 mA, the catheter was repositioned and the threshold repeated. AERP was performed using an 8-beat drive train and a single extrastimulus incremented by 5 ms from a starting point of 170 ms. Each AERP was repeated 3 times, and the mean was taken. At each CL, the dispersion of refractoriness was measured by subtracting the minimum from the maximum AERP across the 4 sites.

2. Conduction time measured at the lateral RA and CS after 30 seconds of constant pacing at a CL of 600, 500, and 400 ms. Pacing was performed from the distal bipole1.2 of the respective decapolar catheter. Conduction time was measured from the pacing artifact to the onset of the first initial sharp deflection recorded by the proximal bipole9.10 of the same catheter.

3. P-wave duration in lead II from a standard ECG.

4. Sinus node function. The sinus node recovery time and heart rate–corrected sinus node recovery time were measured after 30 seconds of constant atrial pacing at a CL of 600 and 500 ms. Each episode was repeated 3 times, and the mean was taken.

5. Transverse conduction properties of the CT. To evaluate the transverse conduction properties of the CT, we used intracardiac echo–guided mapping of double potentials (DPs) along that structure as described in previous studies.9,12,13 The conduction properties of the CT were evaluated both during constant atrial pacing and with the delivery of a single extrastimulus 5 to 10 ms above the AERP. Pacing was performed at 3 CLs (600/500/400 ms) from 4 sites (distal CS/LLRA/HLRA/HSRA). Two specific measurements were made: (1) the number of bipoles on the crista catheter recording discrete DPs (0 to 10 bipoles). DPs were defined as discrete electrograms separated by an isoelectric phase; and (2) the maximal conduction delay between the onset of the first and second split components of the DPs (the maximum DP conduction delay).

6. AF inducibility. The inducibility of short-lived AF (>2 seconds) and of sustained AF (>10 minutes) during AERP testing were recorded. Further measurement of EP parameters were deferred until 15 minutes after AF termination.

Electrophysiology studies were performed with an EP Med electrophysiology system. Electrogram signals were filtered between 30 and 250 Hz. All measurements were made offline using on-screen calipers at 400 mm/s display speed.

Follow-Up Cohort of Patients
Twelve patients underwent ASD closure either by direct surgical closure (n = 3), surgical closure using a bovine pericardial patch (n = 1), or transcatheter Amplatzer device closure (n = 8). One patient refused surgery. At 12.4 ± 7.3 months after closure, all patients had echocardiographic follow-up to assess for resolution of right heart enlargement. Each patient was also asked to return for a repeat electrophysiological study 3 to 12 months after ASD closure.

Statistics
Data are presented as mean ± SD. Comparisons between groups were performed with either Student’s paired or unpaired t test, the Wilcoxon rank-sum test, or the Mann-Whitney U test for data that were not normally distributed, or χ2 analysis. A probability value of P < 0.05 was considered statistically significant.

Results
Baseline Evaluation
Transcatheter Echocardiography
Atrial dimensions and volumes are presented in Table 1. All ASD patients had evidence of right ventricular enlargement (mean end-diastolic diameter, 3.8 ± 0.2 cm; normal, < 3.2
The atrial volumes in control patients were within the normal range. In the ASD group, there was significant RA and mild left atrial (LA) enlargement. The difference in atrial volumes between ASD and control patients was highly significant \( (P<0.01\) for both RA and LA volumes).

### Right Heart Catheterization in ASD Patients

The following mean values were obtained at baseline: Qp:Qs, 5.6:2.2 mm Hg (normal, 1 to 5 mm Hg); right ventricular and pulmonary artery peak-systolic/end-diastolic pressures were at the upper limit of the normal range (right ventricular, 29.3±6.7/7.0±3.1 mm Hg; pulmonary artery, 24.6±5.1/8.3±2.8 mm Hg). The mean pulmonary capillary wedge pressure was normal (7.8±2.0 mm Hg).

### Electrophysiological Study

#### Atrial Effective Refractory Period

Baseline AERP data are presented in Table 2. Although the AERP was longer in ASD patients than controls at each of the 4 sites and 3 CLs tested, this difference reached statistical significance only for the LLRA (all CLs) and HSRA at a 600-ms CL. There was no significant difference in the dispersion of refractoriness between the ASD and control groups at any CL tested (600-ms CL, 48±27 versus 53±16 ms, \( P=NS\); 500 ms CL, 45±21 versus 54±17, \( P=NS\); 400 ms CL, 43±24 versus 42±14, \( P=NS\)). A normal pattern of rate adaptation of the AERP was observed in both groups at all sites.

#### P-Wave Duration

P-wave duration was significantly lengthened in the ASD group compared with controls: 119±7 versus 102±6 ms, \( P<0.001\).

#### Conduction Time

There was no significant difference between ASD and control groups for the lateral RA conduction time when measured at any CL (600 ms, 39±5 versus 38±6 ms, \( P=NS\); 500 ms, 40±7 versus 39±6 ms, \( P=NS\); 400 ms, 40±6 versus 39±6 ms, \( P=NS\)). The CS conduction time was shorter than that at the lateral RA, but there were no differences between the

### Table 1. Echocardiographic RA and LA Dimensions and Volumes in Control and ASD Patients (Before and After ASD Closure)

<table>
<thead>
<tr>
<th></th>
<th>Control (n=17)</th>
<th>Before ASD (n=13)</th>
<th>( P, ) Before ASD vs Control</th>
<th>Before ASD Closure (n=12)</th>
<th>After ASD Closure (n=4)</th>
<th>( P, ) Before vs After ASD Closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA length, cm</td>
<td>4.5±0.5</td>
<td>5.8±0.4</td>
<td>&lt;0.01</td>
<td>5.1±0.5</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>RA width, cm</td>
<td>4.0±0.3</td>
<td>4.6±0.5</td>
<td>&lt;0.01</td>
<td>4.1±0.5</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>LA length, cm</td>
<td>4.6±0.5</td>
<td>5.8±0.7</td>
<td>&lt;0.01</td>
<td>5.3±0.5</td>
<td>NS</td>
<td>0.01</td>
</tr>
<tr>
<td>Apical LA width, cm</td>
<td>4.1±0.2</td>
<td>4.5±0.4</td>
<td>&lt;0.01</td>
<td>4.0±0.3</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Parasternal LA width, cm</td>
<td>3.3±0.6</td>
<td>3.9±0.5</td>
<td>0.01</td>
<td>3.8±0.6</td>
<td>NS</td>
<td>0.03</td>
</tr>
<tr>
<td>RAV, mL</td>
<td>37.8±8.2</td>
<td>64.8±15.6</td>
<td>&lt;0.01</td>
<td>46.6±11.5</td>
<td>&lt;0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>LAV, mL</td>
<td>33.1±7.9</td>
<td>53.5±11.7</td>
<td>&lt;0.01</td>
<td>42.5±10.1</td>
<td>0.07</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Apical indicates apical 4-chamber view; Parasternal, parasternal long-axis view; RAV, RA volume; and LAV, LA volume.

*At a mean follow-up of 12.4±7.3 months.

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### Table 2. AERP by Pacing Site and Drive CL Before and After ASD Closure

<table>
<thead>
<tr>
<th>AERP (ms) Site and CL</th>
<th>Control (n=17)</th>
<th>ASD (n=13)</th>
<th>( P, ) Control vs ASD Before ASD Closure (n=4)</th>
<th>After ASD Closure</th>
<th>( P, )* Before vs After ASD Closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCS 600</td>
<td>256±31</td>
<td>255±37</td>
<td>NS</td>
<td>258±17</td>
<td>NS</td>
</tr>
<tr>
<td>DCS 500</td>
<td>255±27</td>
<td>240±29</td>
<td>NS</td>
<td>240±18</td>
<td>NS</td>
</tr>
<tr>
<td>DCS 400</td>
<td>235±19</td>
<td>221±26</td>
<td>NS</td>
<td>225±16</td>
<td>NS</td>
</tr>
<tr>
<td>LLRA 600</td>
<td>220±22</td>
<td>247±24</td>
<td>0.01</td>
<td>227±12</td>
<td>NS</td>
</tr>
<tr>
<td>LLRA 500</td>
<td>214±21</td>
<td>241±20</td>
<td>0.003</td>
<td>223±12</td>
<td>NS</td>
</tr>
<tr>
<td>LLRA 400</td>
<td>206±17</td>
<td>229±29</td>
<td>0.02</td>
<td>218±14</td>
<td>NS</td>
</tr>
<tr>
<td>HLRA 600</td>
<td>224±25</td>
<td>239±22</td>
<td>0.09</td>
<td>215±20</td>
<td>NS</td>
</tr>
<tr>
<td>HLRA 500</td>
<td>216±23</td>
<td>230±17</td>
<td>0.06</td>
<td>213±18</td>
<td>NS</td>
</tr>
<tr>
<td>HLRA 400</td>
<td>207±22</td>
<td>222±19</td>
<td>0.11</td>
<td>203±11</td>
<td>0.03</td>
</tr>
<tr>
<td>HSRA 600</td>
<td>257±22</td>
<td>274±29</td>
<td>0.04</td>
<td>291±14</td>
<td>NS</td>
</tr>
<tr>
<td>HSRA 500</td>
<td>251±19</td>
<td>262±27</td>
<td>0.09</td>
<td>271±12</td>
<td>NS</td>
</tr>
<tr>
<td>HSRA 400</td>
<td>229±17</td>
<td>239±19</td>
<td>0.25</td>
<td>251±12</td>
<td>0.04</td>
</tr>
</tbody>
</table>

DCS indicates distal CS.

*Comparison between before and after ASD closure AERP values in this subgroup.
ASD and control groups (600 ms, 34±5 versus 33±5 ms, P=NS; 500 ms, 33±4 versus 32±6 ms, P=NS; 400 ms, 34±5 versus 33±5 ms, P=NS).

**Sinus Node Function**
The heart rate–corrected sinus node recovery time was significantly longer in the ASD patients at both a CL of 600 ms (396±146 versus 229±64 ms, P<0.01) and 500 ms (372±110 versus 262±56 ms, P=0.01).

**Transcristal Conduction**
At no site or CL was either the number of DPs or the maximum DP split component conduction delay greater in control than ASD patients. During constant pacing, the number of DPs was consistently greater in the ASD group than the control group (Figures 1a, 2a, and 3a); however, this achieved statistical significance only at the HSRA at a CL of 600 ms (ASD versus control group, 5.2±3.4 versus 1.9±1.5 bipoles). The maximum conduction delay between DP split components was significantly greater in ASD patients than controls at 2 of 4 sites at each CL (Figures 1c, 2c, and 3c).

During AERP testing, with delivery of a tightly coupled extrastimulus, the differences between control and ASD patients for both the number of DPs (Figures 1b, 2b, and 3b) and maximum DP split components (Figures 1d, 2d, and 3d and Figure 4) was exaggerated and became statistically significant at most sites and CLs.

**AF Inducibility**
AF (duration ≥2 seconds) was induced in 6 of 13 ASD and 3 of 17 control patients (P=0.09). AF was sustained and
lasted >10 minutes in 4 of 13 ASD and 2 of 17 control patients (P=0.20). One patient from each group required DC cardioversion to terminate AF; otherwise, termination was spontaneous.

Follow-Up Evaluation
ASD closure was uncomplicated in all patients. None of the 4 patients undergoing surgical closure had postoperative AF or atrial flutter.

Follow-Up Echocardiography
The results of repeat echocardiography (n=12) at a mean follow-up of 12.4±7.3 months are presented in Table 1. There was incomplete normalization of RA and LA volumes, and the mean RA volume remained significantly greater than in control patients (P=0.04).

Follow-Up Electrophysiology Study
Only 4 of 12 patients (mean age, 41±3 years) agreed to repeat electrophysiological study (8.3±5.6 months) after ASD closure. These patients did not differ in baseline electrophysiology, procedural outcome, or postclosure atrial size from those who elected not to return.

Evaluation of transcristal conduction at follow-up did not demonstrate any significant change from baseline. Extensive widely split DPs were still observed during pacing from each site, suggesting that no recovery of conduction had occurred even late after ASD closure (Figure 5). Table 3 presents the data for transcristal conduction during pacing at a representative CL of 600 ms with delivery of a single tightly coupled extrastimulus (S1S2) and with shortening of drive CL. Conduction time remained unchanged, as recorded at both the CS and lateral RA. No statistically significant change in heart rate–corrected sinus node recovery time was recorded at either the 600 ms CL (before, 329±127 ms versus after, 308±40) or 500 ms CL (before, 373±121 ms versus after, 289±47 ms). There was a nonsignificant reduction in the mean P-wave duration (121±9 to 116±9 ms, P=NS), which remained significantly greater than that of the control group (102±6 ms, P=0.01).

Figure 3. Figures 1–3 are formatted similarly to demonstrate extent of transcristal conduction delay for both ASD patients (solid columns) and controls (open columns) at a pacing CL of 600 ms (Figure 1), 500 ms (Figure 2), and 400 ms (Figure 3). In each figure, A and B present number of DPs (bipoles 0 to 10) recorded during constant pacing (A) and with delivery of a tightly coupled extrastimulus (B) from each pacing site (DCS indicates distal CS). C and D present maximal conduction delay between DP split components (Max. DP Conduction Delay; ms) recorded during constant pacing (C) and with delivery of a tightly coupled extrastimulus (D). Number of recorded DPs and Max. DP conduction delay were greater in ASD patients. This difference was exaggerated with delivery of a tightly coupled extrastimulus (S1S2) and with shortening of drive CL.

Figure 4. Baseline transcristal conduction in ASD patient during pacing from HLRA at 600-ms CL with introduction of an S2 at a coupling interval of 270 ms. There are extensive DPs (splits; 10/10) recorded on crista catheter (Cl 1-2 to 19-20) with maximal DP conduction delay of 60 ms recorded on Cl 1-2 and Cl 9-10 (arrows). Also shown are ECG recordings (leads I, II, aVL) and HLRA and distal/proximal CS (CS d/CS p) electrograms.
AF was inducible in 2 of 4 returning subjects, 1 of whom required a DC cardioversion for sustained AF.

**Discussion**

This study evaluated atrial electrophysiology in patients with an ASD and significant RA enlargement but without previous atrial arrhythmia. As such, this group provides a model for assessing the impact of chronic atrial stretch on ER, without arrhythmia-induced ER as a confounding factor. Compared with age-matched controls, subjects with an ASD demonstrated the following electrophysiological findings.

1. A trend toward an increase in AERP. Although this was statistically significant at 2 sites only, this result demonstrates that the type of ER associated with chronic atrial stretch caused by an ASD is different from that observed as a result of atrial arrhythmias, in which a consistent fall in ERP has been described.6

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**Figure 5.** A, Left and right anterior oblique (LAO/RAO) views of catheter position at follow-up study 12 months after ASD device closure. Decapolar catheters are positioned in CS and lateral RA. A duodecapolar catheter is located in posterior RA against CT (Crista). B, Recordings obtained at follow-up after ASD closure demonstrating persisting functional block across CT during pacing from LLRA at a 600 ms CL with introduction of an S2 at a coupling interval of 235 ms. There are extensive DPs (splits; 10/10) recorded on crista catheter (Ct 1-2 to 19-20), with maximal DP conduction delay of 70 ms recorded on Ct 13-14 (arrows). Also shown are ECG recordings (leads I, II, V6), distal and proximal CS (CS d/CS p), and HLRA and LLRA electrograms.

**TABLE 3.** Transcristal Conduction Before and After ASD Closure (n=4) During Pacing at a CL of 600 ms With Delivery of a Tightly Coupled Single Extrastimulus

<table>
<thead>
<tr>
<th>Pacing Site</th>
<th>Before ASD Closure</th>
<th>After ASD Closure</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCS pacing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of DPs</td>
<td>5.3±3.4</td>
<td>4.5±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum DP</td>
<td>56.0±30.6</td>
<td>59.3±33.0</td>
<td>NS</td>
</tr>
<tr>
<td>LRLA pacing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of DPs</td>
<td>6.5±2.1</td>
<td>7.8±2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum DP</td>
<td>68.0±25.5</td>
<td>66.3±19.7</td>
<td>NS</td>
</tr>
<tr>
<td>HRLA pacing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of DPs</td>
<td>5.0±4.2</td>
<td>7.8±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum DP</td>
<td>49.5±13.4</td>
<td>60.5±19.8</td>
<td>NS</td>
</tr>
<tr>
<td>HSRA pacing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of DPs</td>
<td>6.5±4.9</td>
<td>6.3±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum DP</td>
<td>54.0±15.6</td>
<td>35.7±9.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

DCS indicates distal coronary sinus.
2. Anatomically determined conduction delay at the CT, as evidenced by the extent of DPs and the magnitude of conduction delay between DP split components recorded along the CT. In experimental and clinical studies of macroreentry and atrial arrhythmia, DP or double-spike electrograms have been validated as representing conduction delay or block across a functional or fixed barrier.8,9,12–15

3. No difference in conduction along the CS or in the RA free wall.

4. Evidence of impaired sinus node function.

Importantly, after ASD closure, there was incomplete normalization of atrial size, as previously reported in a younger population.16 Furthermore, in a subgroup at late follow-up electrophysiological evaluation (8.3±5.6 months), there was persistent significant conduction delay at the CT, with extensive DPs still being recorded along this structure both during constant pacing and with the delivery of a tightly coupled extrastimulus.

**Electrical Remodeling Resulting From AtrialEnlargement and Atrial Stretch**

The concept of ER in response to atrial arrhythmias was elegantly described by Wijffels et al.6 and the findings have been strikingly consistent. Fall in ERP and loss of rate adaptation have been widely observed in response to even brief periods of AF. The fall in ERP produces a decrease in atrial wavelength and is at the center of the seminal observation that “AF begets AF.”

In contrast, studies of ER associated with atrial stretch and atrial enlargement have yielded divergent results. Clinical studies and studies in animals and isolated preparations of the effects of acute stretch have shown inconsistent findings, with some showing a decrease in AERP, while others observed no change or even an increase in AERP.3,17 Although the initial focus in atrial ER was on the role of the AERP, more recently, Allessie et al.18 suggested that a “second factor” may be more important in the formation of atrial arrhythmia substrate during chronic remodeling. In a number of recent studies, this second factor has been identified as the development of intra-atrial conduction disturbances associated with interstitial fibrosis and structural change.3,19

In the present study, although ASD patients showed a trend toward an increase in AERP, which might be expected to reduce the likelihood of late atrial arrhythmias, the most striking finding was the presence of persistent anatomically determined functional conduction delay at the CT.

**Regional Conduction Abnormalities and the Role of the CT in Atrial Arrhythmogenesis**

It has long been recognized that patients with atrial arrhythmias have evidence of abnormal conduction slowing in response to atrial premature depolarizations.20 Papageorgiou et al.21 demonstrated that these abnormalities in atrial conduction may be regionally distributed to key anatomic areas, such as the posterior region of the triangle of Koch, in which anisotropic conduction delay may be important in the genesis of AF. This group also demonstrated slowing of conduction between the HLRA and the triangle of Koch and postulated conduction slowing across the CT as a potential mechanism.

The CT is an anatomic region demonstrating marked anisotropy of conduction because of directional differences in gap junction distribution.21 The role of anisotropy and functional conduction delay at the CT in a range of atrial arrhythmias has been extensively detailed.9,10,11 The present study identifies significant conduction delay at the CT in ASD patients and provides preliminary data to suggest that this might persist beyond ASD closure. Although the role of these conduction abnormalities at the CT in the development of late arrhythmias was not studied, it has previously been shown that the CT plays an important role in the development of typical atrial flutter.6,8,9 in atypical forms of flutter such as lower loop reentry,10 and in AF.11 Pacing studies have demonstrated that conduction delay across the CT in patients with a history of atrial flutter is functional, manifesting predominantly at short pacing CLs and with extrastimulus testing, as was also observed in this study.12,13 Furthermore, experimental and clinical studies have suggested that changes in the extent of functional block at the CT are important in the transition between typical atrial flutter, rapid atypical atrial flutter, and AF.10,22

**Mechanism of Arrhythmias Late After ASD Closure**

Although the precise pathogenesis of late arrhythmias in ASD patients is unclear, important contributing factors might include atrial enlargement and the presence of an atriotomy scar. It has been elegantly demonstrated that the anatomic position of the atriotomy scar will determine whether reentry occurs around the scar itself (anteroatriotomy) or will involve the anterior free wall and septum (posteroatriotomy close to the CT).2 Furthermore, functional extension of the anatomic line of block will also be of importance in determining the arrhythmia mechanism. In an era in which the majority of ASDs are closed percutaneously, it is interesting to speculate that in the future, we might see a decrease in the incidence of late atrial arrhythmias. Although this study did not address the question of arrhythmia mechanism, the demonstration of persistent functional block along the CT suggests a potential mechanism for late atrial arrhythmias even in the absence of an atriotomy scar.

The present study suggests that shortening of AERP, which has been observed in some situations of atrial stretch,17 does not occur in patients with an ASD and therefore may not be an important factor in the development of late atrial arrhythmias.

This study is consistent with previous work demonstrating SN dysfunction before ASD closure,23 and it raises the possibility that it may be caused by chronic RA stretch. The concept of SN remodeling was first described by Elvan et al.24 in the context of chronic atrial arrhythmias and more recently has also been observed in patients with atrial dilatation caused by 3 months of asynchronous pacing.5 Although the relationship between SN dysfunction and AF has not been completely elucidated, sinus bradycardia may be important in the initiation of AF.

**Limitations**

To evaluate the effects of chronic atrial stretch resulting from an ASD on atrial remodeling without the confounding effects
of atrial arrhythmias, such patients were necessarily excluded from the study. It is uncertain whether the observed abnormalities are of similar importance in patients who do develop atrial arrhythmias. Furthermore, whether the observed conduction abnormalities are a result of development of structural change could not be addressed in this study. In view of the limitation in number of sites sampled in a clinical electrophysiology laboratory protocol, the role of dispersion of refractoriness could not be evaluated in detail. In particular, heterogeneity between RA and LA electrophysiology because of unequal degrees of stretch may be an important arrhythmogenic factor in the ASD group and deserves further evaluation. Conduction time was measured from a catheter with a fixed distance between measurement sites and assumes a constant conduction path. Differences in the conduction path between patients would potentially confound these data. Finally, although the appearance of DPs may have varying explanations, there is substantial literature to suggest that DPs recorded at the CT reflect conduction delay or block.8,9,12–15

Conclusions
Chronic RA stretch resulting from ASD causes ER with anatomically determined conduction delay at the CT, a trend toward an increase in RA ERP, and impaired SN function. Conduction delay at the CT persists beyond ASD closure. We speculate that impaired conduction at the CT may contribute to the long-term atrial arrhythmia substrate in this condition.

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Effect of Chronic Right Atrial Stretch on Atrial Electrical Remodeling in Patients With an Atrial Septal Defect
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