Electrical Remodeling of the Atria in Congestive Heart Failure

Electrophysiological and Electroanatomic Mapping in Humans

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Background—Atrial fibrillation (AF) frequently complicates congestive heart failure (CHF). However, the electrophysiological substrate for AF in humans with CHF remains unknown. We evaluated the electrophysiological and electroanatomic characteristics of the atria in patients with CHF.

Methods and Results—Twenty-one patients (aged 53.7±13.6 years) with symptomatic CHF (left ventricular ejection fraction 25.5±6.0%) and 21 age-matched controls were studied. The following were evaluated: effective refractory periods (ERPs) from the high and low lateral right atrium (LRA), high septal right atrium, and distal coronary sinus (CS); conduction time along the CS and LRA; corrected sinus node recovery times; P-wave duration; and conduction at the crista terminalis. In a subset, electroanatomic mapping was performed to determine atrial activation, regional conduction velocity, double potentials, fractionated electrograms, regional voltage, and areas of electrical silence. Patients with CHF demonstrated an increase in atrial ERP with no change in the heterogeneity of refractoriness, an increase of atrial conduction time along the LRA and the CS, prolongation of the P-wave duration and corrected sinus node recovery times, and greater number and duration of double potentials along the crista terminalis. Electroanatomic mapping demonstrated regional conduction slowing with a greater number of electrograms with fractionation or double potentials, associated with areas of low voltage and electrical silence (scar). Patients with CHF demonstrated an increased propensity for AF with single extrastimuli, and induced AF was more often sustained.

Conclusions—Atrial remodeling due to CHF is characterized by structural changes, abnormalities of conduction, sinus node dysfunction, and increased refractoriness. These abnormalities may be responsible in part for the increased propensity for AF in CHF. (Circulation. 2003;108:1461-1469.)

Key Words: arrhythmia ■ atrium ■ electrophysiology ■ heart failure ■ remodeling

Congestive heart failure (CHF) is a major public health problem in the western world. In the United States alone, approximately 5 million patients have CHF and nearly 500,000 patients are diagnosed for the first time each year. Of these, 30% to 40% will develop atrial fibrillation (AF) during the course of the disease.1 When AF develops, it is associated with increased morbidity and mortality.2,3

Despite the clinical implications of AF in CHF, the reasons for its high prevalence are poorly understood. Although atrial enlargement no doubt plays a role, the atrial electrophysiological characteristics that predispose to AF in patients with CHF have not been determined. Studies of atrial electrical remodeling that occurs as a result of AF have provided some insights into the changes in atrial electrophysiology that maintain AF4,5 but do not explain the nature of the underlying substrate that leads to AF in CHF.

Animal studies of atrial electrical remodeling in CHF have demonstrated discrete regions of slow conduction associated with the development of interstitial fibrosis but without apparent change in atrial effective refractory periods (ERPs).6 Whether similar abnormalities also develop in humans is unknown. The present study was designed to determine the electrophysiological and electroanatomic properties of the atria in patients with CHF.

Methods

Study Population

The study consisted of 21 patients with symptomatic CHF. Patients were excluded if they had recent myocardial infarction (≤3 months),
ongoing cardiac ischemia, infiltrative cardiomyopathy, primary valvular heart disease, or atrial arrhythmias. A further 21 age-matched patients having radiofrequency ablation for AV node reentry tachycardia or AV reentry tachycardia without evidence of structural heart disease were also studied. Antiarrhythmic drugs, including calcium blockers, were ceased ≥5 half-lives before the study. No patient received amiodarone in the preceding 6 months. All patients gave written informed consent to the study, which was approved by the Clinical Research and Ethics Committee of the Royal Melbourne Hospital.

**CHF Definition**
CHF was defined by a left ventricular ejection fraction of ≤35% associated with symptoms (New York Heart Association class II or greater). All patients with CHF were evaluated with transthoracic echocardiography, gated blood pool scan, coronary angiography, and cardiac pressure measurement. Left ventricular ejection fraction was defined by gated blood pool scan.

**Electrophysiological Study**
Electrophysiological study was performed in the postabsorptive state with sedation utilizing midazolam and with autonomic blockade. Multipolar catheters were positioned as follows: (1) 10-pole catheter with 2.5-2.5-mm interelectrode spacing in the coronary sinus (CS) with the proximal electrode pair positioned at the ostium of the CS; (2) 20-pole catheter with 2-5-2-mm interelectrode spacing placed along the lateral right atrium (LRA), with the first 10 electrodes in a linear arrangement along the LRA border; (3) 8-pole catheter with 2.5-2.5-2.5-mm interelectrode spacing along the high septal right atrium (SRA); and (4) 20-pole “crista” catheter with 1-3-1-mm interelectrode spacing positioned along the crista terminalis (CT) with the aid of a long sheath to assist with its placement in close apposition to the CT, and standardized such that the second bipole lay at the junction of the superior vena cava with the right atrium (RA) as determined by intracardiac echocardiography. The intracardiac echocardiography imaging system consisted of a 9-MHz rotating ultrasound transducer mounted at the tip of a 9F catheter.

Surface ECG and bipolar endocardial electrograms were monitored continuously and stored on a computer-based digital amplifier/recorder system with optical disk storage for offline analysis. Intracardiac electrograms were filtered from 30 to 500 Hz and measured with computer-assisted calipers at a sweep speed of 400 mm/s.

**Effective Refractory Period**
Atrial ERP was evaluated at twice diastolic threshold at cycle lengths (CLs) of 600, 500, and 400 ms with an 8-beat drive followed by an extrastimulus (S₂), starting with an S₁ coupling interval of 150 ms and increasing in 5 ms increments. ERP was defined as the longest coupling interval that failed to propagate to the atrium. ERP was measured from the distal CS, low LRA, high LRA, and high SRA. At each site, the ERP was measured 3 times during each CL. If maximum and minimum measurements differed by >10 ms, 2 more measurements were taken, and the total was averaged. Heterogeneity of atrial ERP was determined by the coefficient of variation of ERP at each CL, by expressing the SD as a percentage of the mean ERP (SD/mean × 100%).

**Atrial Conduction**
Local conduction time was assessed along the CS by pacing the distal bipole (1-2) of the CS catheter and measuring activation time to the proximal bipole (9-10) and along the LRA by pacing the distal bipole (1-2) of the LRA catheter and measuring activation time to bipole 9-10. Conduction was measured at CLs of 600, 500, and 400 ms after stable capture for at least 10 seconds. Conduction time was determined 10 times at each CL and averaged. P-wave duration (PWD) in sinus rhythm, measured on lead II of the surface ECG and averaged over 10 beats, was analyzed as a surrogate marker of interatrial conduction time.

**Anatomically Determined Conduction Delay**
At the CT, we investigated the presence of anatomically determined conduction delay, during a drive of 600 ms, and the earliest extrastimulus that conducted to the atrium from the low LRA, high LRA, and high SRA. Conduction delay at the CT was analyzed on each recording bipole of the crista catheter and defined as the presence of discrete double potentials (DPs) separated by an isoelectric interval. Both the number of bipoles that demonstrated discrete DPs and the maximum interpotential duration were evaluated. To explore the functional properties of conduction across the CT, decremental extrastimuli were delivered at the high LRA at a CL of 600 ms until ERP was reached (10-ms decrements from an S₁ of 350 ms).

**Sinus Node Function**
The corrected sinus node recovery time (CSNRT) was assessed at CLs of 600, 500, and 400 ms after a 30-second pacing train. The CSNRT was repeated 3 times at each CL and averaged.

**Inducibility of Atrial Fibrillation**
The inducibility of AF by single extrastimulus was noted during ERP determination. AF was defined as irregular atrial activity that lasted greater than 30 seconds. AF lasting ≥5 minutes was considered persistent. When this occurred, no further data were acquired.

**Electroanatomic Mapping**
In a subset of 8 patients in each group, RA electroanatomic maps were created during distal CS pacing using the CARTO mapping system. The system records the 12-lead ECG and bipolar electrograms from the mapping and reference catheters filtered at 30 to 400 Hz. Endocardial contact during point acquisition was facilitated by fluoroscopy, the catheter icon on the CARTO system, and intracardiac echocardiography. Points were acquired if the stability criteria in space (≤6 mm) and local activation time (LAT; ≤5 ms) were met. High-density mapping was performed along the CT, SRA, and areas of low voltage. Editing of points was performed offline. LAT was manually annotated to the beginning of the first rapid deflection from the isoelectric line on bipolar electrograms. Points not conforming to the 12-lead ECG P-wave morphology or <75% of the maximum voltage of the preceding electrogram were excluded. For the purposes of the electroanatomic map, the following definitions were used: (1) fractionated signals—complex activity of long duration (>50 ms); (2) DPs—potentials separated by an isoelectric interval, with LAT on DP annotated at the largest potential; (3) electrically silent areas (scar)—absence of recordable activity or a bipolar voltage amplitude ≤0.05 mV; and (4) low-voltage areas—contiguous areas of bipolar voltage ≤0.5 mV.

**Atrial Voltage Analysis**
RA bipolar voltage amplitude was determined regionally at the high and low SRA, the high and low LRA, and the high and low posterior RA. At each of these regions, an average of 10 points was determined. An index of heterogeneity of bipolar voltage amplitude was obtained by calculating the coefficient of variation of voltage of all points. The contribution to the surface area of voltage was determined with offline software. The software system determines the voltage contribution to the surface area of each point using the distance to the nearest neighboring point, presenting the probability density graph of surface area to bipolar voltage.

**Regional Conduction Velocity Analysis**
The CARTO system determines the conduction velocity between 2 points by expressing the linear distance between the points as a function of the difference in LAT. To determine regional conduction velocity, isochronal maps (5-ms intervals) of the atria were created. Conduction velocity was determined at the high and low SRA, the high and low LRA, and the high and low posterior RA by an average of the conduction velocity between 5 pairs of points through areas of least isochronal crowding.
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CHF (n = 21)</th>
<th>Controls (n = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.7 ± 13.6</td>
<td>52.8 ± 11.1</td>
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</tr>
<tr>
<td>Idiopathic cardiomyopathy, n</td>
<td>11</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n</td>
<td>10</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>25.5 ± 6.0</td>
<td>67.6 ± 6.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>45.9 ± 7.3</td>
<td>33.6 ± 4.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>65.2 ± 7.9</td>
<td>47.6 ± 4.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>56.0 ± 8.0</td>
<td>29.5 ± 3.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV fractional shortening, %</td>
<td>16.0 ± 4.5</td>
<td>37.4 ± 6.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RA pressure, mm Hg</td>
<td>9.1 ± 3.3</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Pulmonary wedge pressure, mm Hg</td>
<td>16.0 ± 5.8</td>
<td>...</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>21.3 ± 7.1</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.7 ± 0.6</td>
<td>1.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; LA, left atrial; LV, left ventricular; and NYHA, New York Heart Association.

Statistical Analysis
All variables are reported as mean ± SD. Sequential data measurements were analyzed by repeated-measures ANOVA followed by the Newman-Keuls test. Comparison between groups was performed with either Student’s t test or Wilcoxon rank-sum test. Proportions were compared with the Fisher exact test. Statistical significance was established at P < 0.05.

Results

Patient Characteristics
Patients had CHF due to either idiopathic dilated cardiomyopathy (n = 11) or chronic ischemic cardiomyopathy (n = 10); these patients did not differ significantly in baseline characteristics (Table 1). The mean left ventricular ejection fraction was 25.2 ± 6.0%, which was associated with a New York Heart Association class of 2.7 ± 0.6. The control group was matched with regard to age. Patients with CHF had a significantly larger left atrial diameter (P < 0.0001).

Atrial Refractoriness
At all sites and at all CLs evaluated, there was a greater ERP in patients with CHF than in controls (Figure 1). This reached statistical significance at the high LRA at 400 ms (P < 0.05); low LRA at 600 ms (P < 0.01), 500 ms (P < 0.01), and 400 ms (P < 0.01); high SRA at 600 ms (P < 0.01) and 500 ms (P < 0.01); and distal CS at 600 ms (P < 0.01). There was no significant difference in the heterogeneity or rate adaptation of ERP.

Atrial Conduction
In the LRA, there was marked prolongation in the conduction time in patients with CHF compared with controls (P < 0.0001) at 600 ms (49.9 ± 10.6 versus 36.4 ± 5.4 ms; P < 0.01), 500 ms (50.3 ± 10.5 versus 35.4 ± 5.1 ms; P < 0.01), and 400 ms (50.2 ± 8.7 versus 36.6 ± 6.6 ms; P < 0.01). There was a trend to prolonged conduction time along the CS in patients with CHF compared with controls at 600 ms (18.1 ± 5.8 versus 16.0 ± 5.8 ms), 500 ms (16.0 ± 5.8 versus 15.5 ± 6.0 ms), and 400 ms (15.5 ± 6.0 versus 15.5 ± 6.0 ms).

Anatomically Determined Conduction Delay
There was evidence of significant conduction delay along the CT in patients with CHF, with a greater number of DPs and greater maximum interpotential distance than in controls (Table 2). These differences were present both during the drive and on the most tightly coupled extrastimulus (P < 0.0001; Figure 2A). When the degree of conduction delay on the tightly coupled S2 was compared with the

TABLE 2. Transverse CT Conduction

<table>
<thead>
<tr>
<th></th>
<th>S1</th>
<th>S2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>CHF</td>
</tr>
<tr>
<td>No. of DPs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low LRA</td>
<td>1.2 ± 1.2</td>
<td>7.0 ± 2.6*</td>
</tr>
<tr>
<td>High LRA</td>
<td>2.2 ± 1.4</td>
<td>7.3 ± 2.8*</td>
</tr>
<tr>
<td>High SRA</td>
<td>2.3 ± 1.9</td>
<td>8.8 ± 1.6*</td>
</tr>
<tr>
<td>Maximum interpotential duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low LRA</td>
<td>18.6 ± 15.5</td>
<td>56.8 ± 12.7*</td>
</tr>
<tr>
<td>High LRA</td>
<td>24.9 ± 16.0</td>
<td>58.9 ± 12.9*</td>
</tr>
<tr>
<td>High SRA</td>
<td>21.3 ± 18.1</td>
<td>61.3 ± 20.7*</td>
</tr>
</tbody>
</table>

S1 refers to the drive (600 ms), and S2 refers to first captured atrial extrastimulus using an incremental technique.

*p < 0.01.
Conduction delay on the basic drive, there was a significantly greater increase in interpotential distance from all sites and a trend toward a greater number of bipoles with DP. These observations suggest that the delay at the CT was functional. The number of DPs and magnitude of the interpotential distance were similar for all pacing sites.

The nature of the functional delay across the CT was explored in more detail with decremented extrastimuli from the high LRA at a CL of 600 ms. With progressively earlier extrastimuli, there was a stepwise increase in conduction delay across the CT as evidenced both by an increase in the number of bipoles with DPs \((P=0.001; \text{Figure 2B})\) and the maximal interpotential distance \((P=0.0001; \text{Figure 2C})\) in patients with CHF.

**Sinus Node Function**

CSNRT was significantly prolonged in patients with CHF compared with controls \((P<0.0001)\) at 600 ms \((350.2\pm87.5 \text{ ms} \text{ versus } 240.3\pm77.3 \text{ ms}; P<0.01)\), 500 ms \((408.1\pm101.1 \text{ ms} \text{ versus } 262.1\pm78.2 \text{ ms}; P<0.01)\), and 400 ms \((445.3\pm189.7 \text{ ms} \text{ versus } 270.9\pm84.5 \text{ ms}; P<0.01)\).

**Inducibility of AF**

Patients with CHF developed AF more frequently than controls with single extrastimuli \((8 \text{ of } 20 \text{ patients with CHF versus } 3 \text{ of } 19 \text{ controls}; P=0.16)\). AF terminated spontaneously in all control patients in \(127.0\pm145.7 \text{ seconds}\). Persistent AF \((>5 \text{ minutes})\) occurred in 6 of 20 patients with CHF and 0 of 19 controls \((P=0.02)\).

**Electroanatomic Mapping**

A mean of \(231.3\pm57.5 \text{ points/patient}\) were analyzed, with no significant difference in the number of points analyzed in each group.

**Bipolar Voltage Mapping**

The mean RA bipolar voltage amplitude was significantly reduced in patients with CHF \((1.4\pm0.4 \text{ mV})\) compared with controls \((1.9\pm0.2 \text{ mV}; P=0.01)\). Six of 8 patients with CHF and none of the controls demonstrated large areas of low voltage and patchy electrical silence \((P=0.007; \text{Figure 3})\), 2 with ischemic and 4 with idiopathic CHF. Atrial scar was observed predominantly in the low posterior RA but also in the LRA and formed \(5.1\pm8.5\%\) of points in the CHF group. The probability density plot of voltage to surface area demonstrates the peak density of surface area in patients with CHF in a lower voltage range than in control patients (Figure 4A).

Regional bipolar voltage was lower at each of the RA locations evaluated in patients with CHF (Figure 4B) and reached significance at all low atrial sites \((P<0.01)\). There was greater heterogeneity of the voltage in patients with CHF than in controls \((84.4\pm13.0\% \text{ versus } 58.5\pm5.5\%; P=0.0005)\). The extent of low-voltage regions was similar in patients with ischemic and idiopathic CHF.

**Activation Mapping**

During distal CS pacing, earliest activation of the RA in control patients occurred uniformly over a wide area of the septum, consistent with breakthroughs superiorly at Bachmann’s bundle, inferiorly at the CS ostium, and, in some, the region of the fossa ovalis (Figure 5). Thus, latest activation in controls was in the LRA. However, in the CHF patients, earliest activation occurred at the CS ostium, with relatively late activation in the superior region near Bachmann’s bundle. The difference in activation time between the CS ostium and high SRA (Bachmann’s bundle) was significantly greater in CHF patients than in controls \((98.5\pm16.6 \text{ ms} \text{ versus } 46.2\pm8.0 \text{ ms}; P=0.0001)\), consistent with delayed conduction over...
Bachmann’s bundle or within the left atrium. The total RA activation time in patients with CHF was significantly prolonged compared with controls (125.3±14.9 versus 103.3±12.1 ms; P=0.006).

Patients with CHF demonstrated a greater percentage of points with DPs and fractionated signals than controls (Figure 6A): 18.9±4.7% versus 3.2±1.9% (P=0.0005) and 27.1±7.9% versus 9.0±2.7% (P=0.0005), respectively. These were found throughout the RA, with dense distribution along the posterior RA and SRA. Regional atrial conduction velocity was slower in all regions evaluated in patients with CHF (Figure 6B), being significant along the high SRA (P<0.01) and low SRA (P<0.01) and at the high LRA (P<0.05).

**Discussion**

This study presents new information regarding the electrophysiological and electroanatomic remodeling of the atria in patients with CHF. First, structural and anatomic abnormalities were observed. Not only were the atria significantly enlarged, but there was also evidence of loss of functioning atrial myocardium, with regions of low-voltage amplitude and spontaneous scarring.

Second, together with and possibly as a result of structural changes, there was evidence of significantly impaired atrial conduction observed throughout the RA by both conventional and electroanatomic mapping techniques. There was also anatomically determined functional conduction delay at the CT and indirect evidence of conduction slowing across the left atrium and Bachmann’s bundle.

Third, in contrast to the type of atrial remodeling seen in response to rapid atrial rates, we did not observe a fall in atrial ERP in patients with CHF. Indeed, in these patients, there was an increase in ERP at all sites compared with the controls. There was no change in dispersion or rate adaptation of ERP.

Fourth, patients with CHF, in the absence of prior atrial arrhythmia, demonstrated significant prolongation of the CSNRT compared with controls, which suggests the presence of some impairment of sinus node function.

Finally, CHF patients demonstrated increased inducibility and duration of AF, which may be a consequence of the demonstrated electrophysiological abnormalities.
Thus, the present study suggests that the substrate for AF in patients with CHF may be due to structural abnormalities and conduction delay rather than changes in refractoriness as occurs in remodeling due to rapid atrial rates.

**Atrial Electrical Remodeling**

Wijffels et al. described the concept of atrial electrical remodeling in a landmark study in conscious goats. In that study, atrial arrhythmias produced a fall in ERP and a decrease in atrial wavelength, providing the seminal observation that "AF begets AF." A recent animal study has provided some insights into the atrial electrophysiological consequences of CHF, demonstrating atrial remodeling of a "different sort." In dogs with pacing-induced CHF, Li et al. found that although there was no change in ERP at longer CLs, there was an increase in ERP at shorter CLs. These dogs did not demonstrate a change in conduction velocity but did show a significant increase in heterogeneity of conduction due to discrete regions of slow conduction associated with interstitial fibrosis. Presumably as a result of these structural changes and despite the absence of a fall in wavelength, there was a highly significant increase in AF duration.

Clinical studies have suggested the importance of atrial conduction abnormalities in patients with atrial arrhythmias. However, to the best of our knowledge, there are no prior studies of the effects of CHF on atrial electrophysiology in humans. Studies in humans of the effects of chronic atrial stretch are also limited. Although these studies in patients with atrial enlargement due to loss of AV synchrony or atrial septal defect have tended to demonstrate an increase in ERP with or without abnormalities in conduction, the underlying pathophysiology in CHF is unique and may not be comparable.

Unlike the "AF begets AF" model, in which a decrease in ERP is critical to the development of sustained AF, this does not appear to be the case in CHF. The present study found no difference or even an increase in ERP despite the fact that the overall milieu appears to be favorable to the development of AF. In the present study other critical factors promoting AF development included atrial enlargement, conduction slowing, anatomically determined conduction delay, and, importantly, structural abnormalities.

**Atrial Structural Remodeling**

Pathology studies of the atria in CHF have demonstrated that structural abnormalities are present with interstitial fibrosis, cellular hypertrophy, and degeneration. Atrial fibrosis has been demonstrated in the atria of patients with CHF due to prior myocardial infarction and from those with idiopathic CHF. Indeed, atrial arrhythmias themselves may result in structural changes.

In the present study, patients with CHF, atrial enlargement, and no prior arrhythmias demonstrated extensive structural abnormalities, evidenced by low atrial voltage, areas of electrical silence (scarring), and widespread regions of fractionated signals and DPs. These latter findings have been demonstrated to represent inhomogeneous and slowed conduction and conduction delay or block, respectively, all important preconditions for reentry.

In addition to the presence of widespread abnormalities of conduction, significant functional conduction delay at the anatomic region of the CT was observed. This conduction delay was present when pacing from a variety of different sites. Although the role of these conduction abnormalities at the CT in the development of atrial arrhythmias was not studied, it has been shown that the CT plays an important role in the development of typical atrial flutter and atypical forms of flutter, such as lower-loop reentry, and in AF. Pacing studies have demonstrated that conduction delay across the CT in patients with a history of atrial flutter is functional, manifesting predominantly at short CLs and with extrastimulus, as in the present study. Experimental and clinical studies suggest 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.
Several studies have reported the presence of areas of low voltage and spontaneous scarring in patients with atrial arrhythmias. Indeed, these areas have been shown to be critical to the arrhythmia mechanism, with the scar acting as a central barrier around which reentry may occur and with low-voltage areas forming regions of slow conduction critical to the circuit.

Several plausible mechanisms may explain the observed changes within the atrium in patients with CHF. Although the primary etiological factors (ischemia or inflammation) may be implicated in the development of atrial fibrosis, it is noteworthy that structural changes occurred in both the ischemic and idiopathic CHF groups. A recent animal model of atrial ischemia has demonstrated regions of atrial necrosis at sites of significant conduction delay.

Other factors that might be involved in the development of atrial fibrosis include chronic atrial stretch and various neurohormonal abnormalities associated with CHF. Atrial stretch alters cellular gene expression, in part via stretch-activated channels, and results in initiation of cellular hypertrophy, alterations in ionic transmembrane currents and action potential duration, and switching on of angiotensin II synthesis. Neurohormonal activation of the renin, angiotensin, and aldosterone systems occurs in CHF, and these substances are potent stimuli for fibrosis. Indeed, Li et al demonstrated an attenuation of the structural abnormalities within the atrium due to experimental CHF with the use of ACE inhibitors.

Sinus Node Remodeling
Sinus node remodeling has been observed due to rapid atrial rates and in the setting of chronic atrial stretch. The present study demonstrates that CHF may also be associated with impairment of sinus node function. Sinus node dysfunc-
tion has been implicated in the development of bradycardia-dependent AF and is therefore a potential factor in the development of AF in patients with CHF.

**Study Limitations**

Whether the electrophysiological abnormalities observed in patients with CHF in the present study are responsible for the increased incidence of clinical AF seen in patients with CHF remains speculative, because patients with prior AF were necessarily excluded from the study. Importantly, the development of clinical AF is complex and depends not only on substrate, but also on other factors such as triggers and initiators that were not addressed by the present study.

In this clinical study in the electrophysiology laboratory, detailed evaluation could only be performed in the RA. Although we did evaluate ERP and conduction in the CS, this may not reflect the findings in the left atrium. Nevertheless, mechanistically, the possible causes of our findings would be expected to affect both atria.

**Conclusions**

The present study demonstrates that patients with CHF and no prior atrial arrhythmias have significant atrial remodeling characterized by anatomic and structural changes, including atrial enlargement, regions of low voltage, and scarring; abnormalities of conduction, including widespread conduction slowing and anatomically determined conduction delay and block; increased refractoriness; and sinus node dysfunction. These abnormalities were associated with an increased inducibility and sustainability of AF and may be responsible in part for the increased incidence of atrial arrhythmias in patients with CHF.

**Acknowledgments**

This work was funded by a grant-in-aid from the National Health and Medical Research Council of Australia. Dr Sanders is the recipient of a Medical Postgraduate Research Scholarship from the National Health and Medical Research Council of Australia. Dr Morton is the recipient of a Postgraduate Medical Research Scholarship from the National Heart Foundation of Australia. The authors would like to thank Russell C. Creek, BApplSc, MSc, for assistance with software analysis.

**References**

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_Circulation_. published online September 2, 2003;
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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