Remodeling of Sinus Node Function in Patients With Congestive Heart Failure
Reduction in Sinus Node Reserve

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Background—Experimental and clinical studies have demonstrated diffuse atrial remodeling in congestive heart failure (CHF). We hypothesized that patients with CHF would demonstrate derangement of sinus node function.

Methods and Results—Eighteen patients with symptomatic CHF (left ventricular ejection fraction, 26±5%) and 18 age-matched control subjects were studied. Under autonomic blockade, the following were evaluated: intrinsic sinus cycle length, corrected sinus node recovery time (CSNRT), sinoatrial conduction time, number and duration of fractionated electograms or double potentials along the crista terminalis, and location of the earliest sinus activity. Electroanatomic mapping was performed to evaluate the location and nature of the sinus node complex, to characterize sinoatrial propagation, and to evaluate conduction abnormalities and voltage amplitude along the crista terminalis. Patients with CHF demonstrated the following findings compared with age-matched control subjects: prolongation of the intrinsic sinus cycle length (P<0.005), prolongation of CSNRT (P<0.0001), caudal localization of sinus activity both during sinus rhythm (P=0.03) and after pacing (P=0.002), prolongation of sinoatrial conduction time (P=0.02), greater number (P<0.0001) and duration (P<0.0001) of fractionated electrogams or double potentials along the crista terminalis, loss of voltage amplitude along the crista terminalis (P=0.02), and abnormal and circuitous propagation of the sinus impulse.

Conclusions—This study demonstrates that patients with CHF have significant sinus node remodeling characterized by anatomic and structural changes along the crista terminalis with a reduction in functional sinus node reserve. This finding may have implications for the development of clinical bradycardia in CHF and for the use of negatively chronotropic agents and pacing in this condition. (Circulation. 2004;110:897-903.)

Key Words: atrium ■ electrophysiology ■ heart failure ■ sinoatrial node ■ remodeling
defined by a left ventricular ejection fraction of ≤35% associated with symptoms (NYHA class ≥2 for ≥6 months). A further 18 age-matched patients having radiofrequency ablation for AV tachycardia or AV nodal tachycardia, without evidence of structural heart disease or history of atrial fibrillation (AF), also were studied. Demographic details of these patients are presented in the Table.

Antiarrhythmic drugs, including β-blockers and calcium blockers, were stopped ≥5 half-lives before the study. No patient received amiodarone in the 6 months before the study. All patients gave written informed consent to the study, which was approved by the Clinical Research and Ethics Committee of the Royal Melbourne Hospital.

Electrophysiological Study
Electrophysiological study was performed in patients in the postabsorptive state with sedation using midazolam and with autonomic blockade as previously described.8 Details of catheter positioning have been previously described.9 In brief, these included a decapolar catheter in the coronary sinus with bipolar 9,10 at the coronary sinus ostium, a 20-pole deflectable catheter along the crista terminalis with bipolar 3,4 at the superior vena cava (SVC)–right atrial (RA) junction, and an 8-pole catheter at the high septal RA. Catheter positioning was confirmed by intracardiac echocardiography.

Surface ECG and bipolar endocardial electrograms were continuously monitored 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.

Intrinsic Sinus Cycle Length
The intrinsic sinus cycle length was determined and averaged over 10 consecutive cycles after autonomic blockade.

Sinus Node Recovery Time
The corrected sinus node recovery time (CSNRT) was determined at a cycle length (CL) of 600, 500, and 400 ms after a 30-second pacing train from the high septal RA and determined as the duration from the stimulus artifact to the earliest activity along the crista terminalis corrected for the baseline sinus cycle length. The CSNRT was repeated 3 times at each CL and averaged.

Sinus Pacemaker Location
The site of the sinus pacemaker complex along the crista terminalis was defined by the bipole demonstrating the earliest activity during sinus rhythm and for the first sinus beat after a 30-second pacing train at a CL of 600, 500, and 400 ms.

Sinoatrial Conduction
Sinoatrial conduction time (SACT) was determined by introducing a brief 8-beat atrial pacing train using the modified method of Narula et al10 and according to the following formula: SACT= (return cycle – basic CL)/2.

The presence of discrete double potentials (DP) separated by an isoelectric interval or complex fractionated activity of ≥50 ms duration along the crista terminalis (sinus node complex) was analyzed on each recording bipolar of the crista catheter. Both the number of bipoles demonstrating conduction abnormalities and the maximum electrogram duration were evaluated.

Electroanatomic Mapping
In 8 patients in each group, RA electroanatomic maps were created with a 4-mm-tip catheter. The electroanatomic mapping system has been described in detail previously.11 In brief, the 3D geometry of the chamber is reconstructed in real time with electrophysiological information, which is color coded and superimposed on the anatomic map. During point acquisition, endocardial contact 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 in local activation time (≤5 ms) were met. High-density mapping was performed along the crista terminalis. Editing of points was performed offline. Local activation time was manually annotated to the beginning of the first rapid deflection from the isoelectric line on bipolar electrograms. Points were excluded if they did not conform to the 12-lead ECG P-wave morphology or if they were <75% of the maximum voltage of the preceding electrogram.

Sinus Pacemaker Complex and Sinus Impulse Propagation
For the purposes of evaluating the number of early sites of activation in the sinus node complex, we defined multicentric sites of origin as those separated by ≥10 mm with an activation time difference of ≤5 ms. The number of such sites was calculated during stable sinus rhythm in each patient.

Atrial propagation from the sinus node was qualitatively assessed and described with anatomically correct nomenclature. The following definitions were used to determine the presence of abnormal conduction at the crista terminalis during sinus rhythm: fractionated electrogram, complex activity of long duration (>50 ms); and DP, potentials separated by an isoelectric interval, with the local activation time on DP annotated at the largest potential. These are expressed as a percentage of the total number of points.

Voltage Analysis Along the Crista Terminalis
The bipolar voltage amplitude was determined at the high, mid, and low crista terminais by averaging the voltage amplitude of 5 points at each of these regions along this structure. For the purposes of evaluating bipolar voltage, the following definitions were used12: electrically silent areas (scar), absence of recordable activity or a bipolar voltage amplitude ≤0.05 mV; and low-voltage areas, contiguous areas ≤0.5 mV on bipolar voltage maps.

Statistical Analysis
All variables are reported as mean±SD. Sequential data measurements were analyzed by repeated-measures ANOVA, followed by Scheffé’s test for post hoc analyses. Comparison between groups was performed with either an unpaired Student’s t test or the Wilcoxon rank-sum test. Statistical significance was established at P<0.05.

Results
Patient Characteristics
Patients had CHF caused by either idiopathic dilated cardiomyopathy (n=9) or chronic ischemic cardiomyopathy (n=9) with LVEF of 26±5%, NYHA symptom class of 2.7±0.6, RA pressure of 10±3 mm Hg, pulmonary wedge pressure of 17±5 mm Hg, and a left ventricular end-diastolic pressure of 23±6 mm Hg (Table). The control group was age matched.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>CHF (n=18)</th>
<th>Control Subjects (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±14</td>
<td>53±12</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26±5</td>
<td>68±6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>46±7</td>
<td>33±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>66±8</td>
<td>48±4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>57±7</td>
<td>30±4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV fractional shortening, %</td>
<td>16±4</td>
<td>37±5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; LA, left atrial.
Intrinsic Sinus Cycle Length
Patients with CHF demonstrated significantly longer intrinsic sinus cycle lengths compared with age-matched control subjects: 876±158 ms (range, 700 to 1242 ms) versus 733±108 ms (range, 570 to 931 ms; \( P=0.005 \)).

Sinus Node Recovery Time
The CSNRT was significantly prolonged at each CL evaluated in patients with CHF compared with age-matched control subjects (\( P<0.0001 \); Figure 1): at a CL of 600 ms, 363±84 ms versus 237±81 ms (\( P<0.01 \)); at a CL of 500 ms, 422±96 ms versus 256±80 ms (\( P<0.01 \)); and at a CL of 400 ms, 426±112 ms versus 277±87 ms (\( P<0.01 \)).

Sinus Pacemaker Location
During sinus rhythm, the earliest site of activation along the crista terminalis was located significantly more caudally along this structure in patients with CHF compared with age-matched control subjects. Earliest activity originated 18.3±6.7 mm caudal to the SVC-RA junction in CHF patients versus 12.4±3.0 mm in control subjects.

In addition, using the definition of multicentric pacemaker origin described above, sinus pacemaker activity was observed to arise from 2.5±0.7 sites separated by 11.3±1.2 mm in patients with CHF compared with 4.0±1.4 sites separated by 33.0±12.8 mm in age-matched control subjects (Figure 3).

Sinus Pacemaker Complex and Sinus Impulse Propagation
From the SVC-RA junction, the site of earliest sinus pacemaker activity was located more caudally in patients with CHF compared with age-matched control subjects. Earliest activity originated 18.3±6.7 mm caudal to the SVC-RA junction in CHF patients versus 12.4±3.0 mm in control subjects.

In half the patients with CHF, the sinus impulse was observed to exit preferentially anteroinferior to the crista terminalis. Sinus impulse propagation was then observed to encounter areas of marked conduction delay and conduction block, particularly at the crista terminalis, resulting in circu-"tous activation and therefore delayed activation on the septal side (Figures 4 and 5). In the other half of the patients with CHF, activation spread radially away from the crista terminalis toward both the septum and lateral wall. Uniform radial propagation away from early sites of crista terminalis activity occurred in all control patients.

In addition, patients with CHF demonstrated a greater percentage of points along the crista terminalis with DP or fractionated electrograms compared with age-matched control patients (25.3±8.5% versus 11.1±1.9%).

Bipolar Voltage Along the Crista Terminalis
The bipolar voltage amplitude in the superior region of the crista terminalis was reduced in patients with CHF compared with age-matched controls: 1.0±0.6 versus 1.7±0.5 mV (\( P=0.03 \)) at the high crista terminalis. However, there was no significant difference in mean bipolar voltage amplitude at lower crista terminalis sites: 1.3±0.4 versus 1.4±0.3 mV at the mid and 1.1±1 versus 1.6±0.5 mV at the low crista terminalis.

In addition, 3 of the 8 patients with CHF and 0 control subjects had regions of electrical silence (scar) along the crista terminalis (Figure 6).

Electroanatomic Mapping
A mean of 153±27 points per patient were acquired within the RA for analysis.
Discussion
This study presents new information demonstrating sinus node remodeling in patients with CHF with a reduction in sinus node reserve in this condition. CHF results in structural change with evidence of loss of voltage amplitude in the superior region of the crista terminalis, possibly representing loss of functioning atrial myocardium. An important finding is that patients with CHF demonstrated an anatomically more localized sinus node complex with significant prolongation of the intrinsic sinus CL and CSNRT. In addition, there is evidence of impaired sinoatrial conduction with prolongation of the SACT and abnormal and circuitous propagation of sinus activity around the crista terminalis.

Sinus Node Physiology
The physiological sinus pacemaker complex extends over a large area from the SVC-RA junction virtually to the inferior vena cava–RA junction along the long axis of the crista terminalis.13,14 Elegant mapping studies by Boineau and associates13,14 have observed that early activation in sinus rhythm could occur simultaneously from >1 site in this complex and that sympathetic activation leads to dominance of faster cranial foci and vagal activation to slower more caudal foci. The widely distributed nature of this complex implies that development of significant sinus node dysfunction would require widespread atrial pathology rather than a more localized process. Indeed, this has recently been dem-

Figure 3. Activation mapping to demonstrate the sinus node complex in a patient with CHF and an age-matched control subject. Both atria are oriented so that the crista terminalis is en face. Note the localized region of early sinus activation (red) in the patient with CHF and points demonstrating DP (blue dots) and fractionated electrograms (FS; brown dots) along this structure. IVC indicates inferior vena cava; SVC, superior vena cava.

Figure 4. Normal sinus propagation in control patient from sinus origin at crista terminalis. Atria are oriented so that crista terminalis is en face. Note radial spread of activation. Blue dots indicate points with DP.
onstrated in patients presenting for pacemaker implantation with advanced sinus node dysfunction.\textsuperscript{15}

**Sinus Node Remodeling**

Elvan et al\textsuperscript{16} were the first to recognize the occurrence of sinus node remodeling in a chronic pacing-induced model of AF in dogs. In this model, there was prolongation of the CSNRT and a decrease in the maximal and intrinsic heart rates. A prolonged CSNRT has also been observed in humans after the cardioversion of chronic AF.\textsuperscript{17,18} Hadian et al\textsuperscript{19} have recently demonstrated sinus node remodeling even after brief durations (10 to 15 minutes) of rapid atrial pacing. Sparks et al\textsuperscript{20} demonstrated the recovery of sinus node function (reverse remodeling) after the termination of chronic atrial flutter, suggesting that atrial flutter also results in sinus node remodeling. In addition, reverse remodeling of sinus node function has been documented after the ablation of AF, suggesting that this process is reversible.\textsuperscript{21}

Recent studies in patients with significant atrial septal defects\textsuperscript{9} or asynchronous ventricular pacing,\textsuperscript{22} conditions known to be associated with the development of atrial arrhythmias, have also observed sinus node remodeling with prolongation of the CSNRT. In the present study in patients with CHF and no prior atrial arrhythmias, we observed not only evidence of sinus node dysfunction but also structural change along the crista terminalis that resulted in abnormal conduction at this structure.
Structural Remodeling of the Atria

The presence of atrial structural abnormalities is now being increasingly recognized in a range of conditions affecting the atrium. There is evidence from both animal and human studies that AF can lead to altered patterns of connexins, changes in myocyte cellular substructure, interstitial fibrosis, and apoptotic atrial myocyte death. In addition, recent studies directed toward evaluating the role of the substrate predisposing to AF have demonstrated similar abnormalities.

Verheule et al studied the effects of chronic mitral regurgitation in a canine model using percutaneous transmural avulsion of the mitral valve. With chronic remodeling, these animals showed areas of increased interstitial fibrosis and chronic inflammation. It was suggested that regional fibrosis potentially might be associated with preferential regional abnormalities in conduction to account for the increased propensity for AF in this model.

In dogs with 5 weeks of pacing-induced CHF, Li et al found a significant increase in heterogeneity of conduction caused by discrete regions of slow conduction associated with interstitial fibrosis. Similar changes have recently been observed in patients with CHF. These patients with no prior evidence of atrial arrhythmia demonstrated widespread structural change associated with conduction abnormalities and a propensity for AF. The mechanism of sinus node remodeling is not addressed by the present study, but it is interesting to speculate that both chronic stretch and neurohormonal activation may have played a role.

Interestingly, a recent study in patients with sinus node disease demonstrated evidence of loss of atrial myocardium along the crista terminalis and areas of electrical silence (scar) associated with a loss of the normal multicentric sinus pacemaker complex and circuitous propagation of the sinus impulse.

Clinical Implications

The present study demonstrates that patients with CHF will have electrophysiological evidence of impaired sinus node function even in the absence of clinical features of the “sick sinus syndrome.” This condition may be further aggravated by the frequent use of a cocktail of negatively chronotropic drugs, including β-blockers, digoxin, and antiarrhythmics such as amiodarone. In the presence of these agents, clinical sinus node dysfunction is indeed common and may reflect an underlying reduction in sinus node reserve observed in the present study.

It has long been recognized that AF and sinus node disease frequently coexist in the “tachycardia-bradycardia syndrome,” but it is unclear which of the 2 abnormalities is primary. Evidence exists to implicate AF in the development of sinus node dysfunction, but evidence also exists to suggest that the reverse may be true. The present study raises a third possibility, which is that the primary underlying pathophysiology, in this case CHF, leads to remodeling, which produces an environment that is conducive to AF and results in sinus node dysfunction.

Study Limitations

In this clinical study in highly symptomatic CHF patients, we elected to continue treatments directed at CHF (diuretics, ACE inhibitors, angiotensin II receptor blockers). An effect of these agents on sinus node function, although unlikely, cannot be excluded.

Conclusions

This study demonstrates that patients with CHF and no prior atrial arrhythmias have significant sinus node remodeling characterized by (1) anatomic and structural changes along the crista terminalis, (2) prolonged sinus node recovery and sinoatrial conduction, and (3) caudal localization of the sinus node complex with circuitous propagation of the sinus impulse. This reduction in sinus node reserve may have implications for the development of clinical bradycardia in CHF and for the use of negatively chronotropic agents and pacing in this condition.

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References


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