Atrial Ionic Remodeling Induced by Atrial Tachycardia in the Presence of Congestive Heart Failure

Tae-Joon Cha, MD; Joachim R. Ehrlich, MD; Liming Zhang, MSc; Stanley Nattel, MD

Background—Atrial fibrillation (AF) and congestive heart failure (CHF) produce discrete forms of atrial ionic remodeling. The in vivo effects of atrial tachycardia (AT) remodeling are altered by CHF. This study evaluated underlying mechanisms at the level of ionic remodeling.

Methods and Results—We studied 4 groups of dogs: (1) unpaced controls (CTLs); (2) CHF caused by 2-week ventricular tachypacing (VTP, 240 bpm); (3) AT (400 bpm x7 days); and (4) CHF+AT (2-week VTP with AT for the last 7 days). CHF and CHF+AT groups equally increased left atrial pressure. AF duration was increased in all paced groups. Effective refractory period (ERP) was decreased by 42% in AT versus CTL but only 24% in AT+CHF versus CHF. CHF reduced L-type Ca$^{2+}$ ($I_{NCX}$), transient-outward ($I_{to}$), and the slow delayed-rectifier ($I_{k}$) currents while increasing the Na$^+$$-$$Ca^{2+}$ exchanger ($I_{NCX}$) and not affecting the inward-rectifier ($I_{k1}$) current. AT reduced $I_{k}$ and leaving $I_{k}$ unaltered. The addition of AT to CHF failed to alter $I_{to}$, $I_{k}$, or $I_{NCX}$ beyond the effect of CHF alone, decreased $I_{k}$ slightly compared with CHF alone, but had smaller effects on $I_{CA}$ and $I_{K1}$ compared with AT alone. Thus, CHF+AT, as would occur in a CHF patient who develops AF, produced an ionic remodeling pattern different from that of CHF or AT alone and from what would have been predicted from additive effects of CHF and AT.

Conclusions—The presence of CHF alters AT-induced ionic remodeling. Thus, the ionic remodeling caused by cardiac arrhythmias in the presence of cardiac pathology is not necessarily predictable from the effects of either alone, with important potential implications for understanding the pathophysiology of arrhythmias in the diseased heart.

Key Words: heart failure • ion channels • atrium • fibrillation

Atrial tachycardia (AT)-induced electrical remodeling plays a key role in the pathophysiology of atrial fibrillation (AF). Alterations in ion-channel function (“ionic remodeling”), including decreased transient-outward ($I_{to}$) and L-type Ca$^{2+}$ ($I_{NCX}$) currents and an increased inward-rectifier ($I_{k1}$) current, contribute to AT-induced electrical remodeling and the self-perpetuating nature of AF. Congestive heart failure (CHF) is an important cause of AF and also causes ionic remodeling. Like AT, CHF also decreases $I_{to}$; however, CHF-induced remodeling differs from AT remodeling in that CHF reduces $I_{CA}$ to a lesser extent, decreases the slow delayed-rectifier ($I_{k}$), and increases the Na$^+$$-$$Ca^{2+}$ exchanger ($I_{NCX}$). Consequently, instead of decreasing action potential duration, CHF leaves atrial action potential duration unchanged or increased. Whereas AT-induced ionic remodeling promotes atrial reentry by decreasing the wavelength in a spatially heterogeneous fashion, CHF-induced ionic remodeling increases the wavelength and may contribute to AF promotion by inducing afterdepolarization-related ectopic activity due to enhanced $I_{NCX}$.

When AF occurs in a patient with CHF, AT remodeling develops on the background of an atrial substrate conditioned by preexisting CHF. The effective refractory period (ERP) changes caused by AT in the presence of CHF are less than those in its absence. These observations suggest that AT-induced ionic remodeling in the context of CHF may be different from AT-induced changes in the undiseased heart; however, there are no studies in the literature comparing AT-induced ionic remodeling in subjects with CHF with AT remodeling in normal hearts. We undertook the present studies to compare ionic changes produced by AT and CHF alone with those caused by AT in the presence of CHF.

Methods

The animal model was prepared as previously described in detail. All animal care procedures followed Canadian Council on Animal Care guidelines and were approved by the Animal Research Ethics Committee of the Montreal Heart Institute. A total of 100 adult mongrel dogs (19 to 39 kg) were divided into control (CTL; n=27), CHF-only (n=20), AT-only (n=25), and CHF+AT (n=28) groups. Some control animals (n=3) were sham controls like CHF dogs but without pacemaker activation. Results were the same for sham and acute controls; therefore, all were grouped for analysis. Right ventricular (RV) and right atrial (RA) unipolar pacing leads were connected to pacemakers implanted in the neck, and pacing begun 24 hours later. In CHF-only dogs, the ventricular pacemaker was programmed to capture at 240 bpm for 2 weeks. In AT-only dogs, atrioventricular block was created by radiofrequency ablation, the
TABLE 1. Hemodynamics at Open-Chest Study

<table>
<thead>
<tr>
<th></th>
<th>CTL (n=14)</th>
<th>CHF (n=14)</th>
<th>CHF+AT (n=10)</th>
<th>AT (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP</strong></td>
<td>139±7</td>
<td>118±6</td>
<td>114±7</td>
<td>137±6</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td>78±5</td>
<td>69±4</td>
<td>69±6</td>
<td>78±4</td>
</tr>
<tr>
<td><strong>LVSP</strong></td>
<td>127±7</td>
<td>110±6</td>
<td>107±5</td>
<td>123±6</td>
</tr>
<tr>
<td><strong>LVEDP</strong></td>
<td>2.7±0.4</td>
<td>13.6±1.5†</td>
<td>13.2±2.5†</td>
<td>3.3±0.4</td>
</tr>
<tr>
<td><strong>LAP</strong></td>
<td>2.1±0.3</td>
<td>12.1±1.3†</td>
<td>12.2±2.5†</td>
<td>2.1±0.2</td>
</tr>
<tr>
<td><strong>RAP</strong></td>
<td>1.7±0.2</td>
<td>4.9±0.7†</td>
<td>4.0±0.6*</td>
<td>1.7±0.2</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; and LAP and RAP, LA and RA mean pressure (all mm Hg). All other abbreviations are as defined in text.

*P<0.05, †P<0.01 vs CTL.

RV was paced at 80 bpm, and the RA was paced at 400 bpm for 1 week. CHF+AT dogs were RV-paced like CHF-only dogs, but RA tachypacing (400 bpm) was added for 1 week after 1 week of ventricular tachypacing alone.

On study days, dogs were anesthetized (morphine 2 mg/kg SC; α-chloralose 120 mg/kg IV load, 29.25 mg · kg⁻¹ · h⁻¹) and mechanically-ventilated. ERPs were measured at the left atrial (LA) appendage with 15 basic (S₁) stimuli, followed by premature (S₂) stimuli with 5-ms decrements (ERP = longest S₁-S₂ failing to capture; all stimuli twice-threshold current, 2 ms). AF (defined as an irregular atrial rhythm >400 bpm) was induced by burst pacing (10 Hz, 2 ms, 4× threshold-current pulses). Mean AF duration was determined in each dog on the basis of 10 inductions for AF sustained: cardioversion was not performed, and electrophysiological assessment was terminated. Hemodynamic data were obtained with fluid-filled catheters and disposable transducers. After in vivo assessment, hearts were excised and atrial cells were isolated from the LA free wall by circumflex-artery perfusion.

Cellular Electrophysiology

Currents were recorded with whole-cell patch-clamp (36±0.5°C). Borosilicate-glass electrodes had tip resistances of 1.5 to 3.0 MΩ. Compensated series resistance and capacitive time constants averaged 3.1±0.9 MΩ and 263±5 ms, respectively. Cell capacitance averaged 87±2 pF (CTL), 112±6 pF (CHF), 113±4 pF (CHF+AT), and 80±3 pF (AT; n=100/group, P<0.01 for CHF and CHF+AT versus CTL and AT). To control for cell-size variability, currents are expressed as densities (pA/pF). Junction potentials averaged 9.7±0.7 mV and were not compensated. The amplitudes of time-dependent currents (eg, Iᵥ, Iᵣ, and Iₛᵥᵥᵥᵥ) were measured from peak to steady-state values after current decay.

Solutions

The solution for cell-storage contained (in mmol/L) KCl 20, KH₂PO₄ 10, dextrose 10, mannitol 40, l-glutamic acid 70, β-hydroxybutyric acid 10, taurine 20, EGTA 10, and 0.1% bovine serum albumin (pH 7.3, KOH). Tyrode’s solution contained (in mmol/L) NaCl 136, KCl 5.4, MgCl₂ 1, CaCl₂ 1, NaH₂PO₄ 0.33, HEPES 5, and dextrose 10 (pH 7.35, NaOH). For delayed-rectifier current recording, nifedipine (5 μmol/L), 4-aminopyridine (2 mmol/L), and atropine (200 mmol/L) were added to suppress Iᵥ, Iᵣ, and 4-aminopyridine–dependent, muscarinic K⁺ currents, respectively. Dofetilide (1 μmol/L) was added for Iᵣ recording. For Iᵣ, Iₛᵥᵥᵥᵥ recording, nifedipine was replaced by CdCl₂ (200 μmol/L). Iᵣ was studied in the presence of 10 mmol/L tetraethylammonium to inhibit the ultrarapid delayed-rectifier current. Na⁺ current contamination was avoided by using a holding potential of −50 mV or substituting equimolar Tris-HCl for NaCl. The internal solution for K⁺-current recording contained (in mmol/L)

![Figure 1](image1.png)

Figure 1. Mean±SEM values for AF duration (A) and ERP (B). Abbreviations are as defined in text.
Results

Hemodynamic Indices
All dogs in CHF and CHF+AT groups showed pulmonary congestion and pericardial effusion during open-chest study. Ventricular and arterial systolic pressures were reduced in CHF dogs, and LV end-diastolic, LA, and RA pressures were significantly increased (Table 1). AT dogs were hemodynamically indistinguishable from CTLs.

In Vivo Electrophysiology
AF duration was significantly prolonged in CHF, AT, and CHF+AT groups (Figure 1A). CHF increased atrial ERP at all basic cycle lengths (BCLs) (Figure 1B). AT decreased atrial ERP at all BCLs and suppressed ERP rate adaptation. AT in the presence of CHF decreased ERP by ~24% versus CHF alone. In animals without CHF, AT decreased ERP ~42% from CTL.

Ionic Remodeling

In Figure 3, I\(_{\text{K1}}\) recordings during 4-second depolarizing test pulses followed by 2-second repolarizations to \(-30\) mV from CTL (A), CHF (B), CHF+AT (C), and AT (D) cells. I\(_{\text{K1}}\) density of tail (E) and step (F) current (n=15, 12, 12, and 13 cells in CTL, CHF, CHF+AT, and AT respectively). Abbreviations are as defined in text.

Statistics
Nonlinear curve fitting was performed with Clampfit in pCLAMP6. Group data are presented as mean±SEM. Statistical comparisons were by multway ANOVA with F tests for interaction, and t tests with Bonferroni correction were used to compare differences between individual group means. Because of the large number of comparisons possible, we show in the figures only the statistical significance of overall group differences from CTL. A 2-tailed \(P<0.05\) indicated statistical significance.

Potassium aspartate 110, KCl 20, MgATP 5, LiGTP 0.1, HEPES 10, sodium phosphocreatine 5, and EGTA 5.0 (pH 7.3, CsOH).

The external solution for \(I_{\text{Na}}\) recording contained (in mmol/L) NaCl 140, CaCl\(_2\) 2, MgCl\(_2\) 1, dextrose 10, HEPES 10, sodium phosphocreatine 5, and EGTA 5.0 (pH 7.3, CsOH).

I\(_{\text{K1}}\) recordings during 4-second depolarizing test pulses followed by 2-second repolarizations to \(-30\) mV from CTL (A), CHF (B), CHF+AT (C), and AT (D) cells. I\(_{\text{K1}}\) density of tail (E) and step (F) current (n=15, 12, 12, and 13 cells in CTL, CHF, CHF+AT, and AT respectively). Abbreviations are as defined in text.

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Ionic Remodeling

I\(_{\text{K1}}\) Typical I\(_{\text{K1}}\) was recorded from CTL cells (Figure 2A). Currents were reduced in CHF (Figure 2B), AT (Figure 2C), and CHF+AT (Figure 2D) cells. Mean I\(_{\text{K1}}\) density was significantly and similarly reduced in all 3 groups (Figure 2E). I\(_{\text{K1}}\) activation voltage dependence was assessed from data obtained as shown in Figure 2A through 2E, based on the relation I\(_{\text{K1}}\)=I\(_{\text{max}}\)(V-V\(_{\text{r}}\))(G\(_{\text{v}}\)/G\(_{\text{max}}\)), where I\(_{\text{K1}}\), G\(_{\text{v}}\), and G\(_{\text{max}}\) are maximum current and conductance, respectively, at voltage V; V\(_{\text{r}}\), and G\(_{\text{max}}\) are maximum current and conductance, respectively; and V\(_{\text{r}}\) is the reversal potential (Figure 2F). V\(_{\text{r}}\), as evaluated by tail currents after 2.2-ms depolarizations to +50 mV, averaged +71.5±1.4 mV, +70.6±3.0 mV, +70.2±2.8, and +69.5±1.2 mV (without junction-potential correction) in CTL, CHF, CHF+AT, and AT groups, respectively (6 cells per group, P=NS). Activation V\(_{\text{1/2}}\) based on Boltzmann fits to data in each experiment averaged 10.8±2.7 mV (CTL), 10.3±2.0 mV (CHF), 9.9±1.3 mV (CHF+AT), and 10.3±0.9 mV (AT; 10 cells per group, P=NS). Inactivation voltage dependence was studied with 1000-ms prepulses from -70 mV, followed by 200-ms test pulses to +50 mV. Boltzmann fitting provided inactivation V\(_{\text{1/2}}\) averaging -29.3±1.5 mV (CTL), -29.7±2.5 mV (CHF), -30.2±1.5 mV (CHF+AT), and -29.3±0.4 mV (AT; P=NS). I\(_{\text{K1}}\) decay time constants showed no differences among groups (Figure 2G). Time to peak current, an index of activation speed, was...
not changed by CHF, CHF+AT, or AT. A paired-pulse protocol with identical 150-ms depolarizations (P1, P2) from −70 to +50 mV with varying P1-P2 intervals was used to analyze recovery kinetics. Current during P2 normalized to current during P1 was a monoexponential function of P1-P2 interval (Figure 2H). Recovery time constants averaged 31.1±2.4 ms (CTL), 33.0±2.7 ms (CHF), 30.3±0.9 ms (CHF+AT), and 29.7±1.2 ms (AT; n=7 cells per group, P=NS).

**I** _K_s_ Typical **I** _K_s_ recordings are shown in Figure 3A through 3D. CHF cells and CHF+AT cells had reduced tail (Figure 3E) and step (Figure 3F) current densities compared with CTL or AT. Voltage dependence of **I** _K_s_ activation (tail-current analysis) was not altered by CHF, CHF+AT, or AT (V_{1/2} 23.1±1.7, 20.1±1.0, 20.7±1.9, and 23.4±1.3 mV, respectively, n=12 cells per group). **I** _K_s_ activation kinetics at +40 mV were biexponential, with slow-phase time constants averaging 2224±340, 2232±278, 1980±211, and 1979±332 ms in CTL, CHF, CHF+AT, and AT groups, respectively (P=NS, n=10 cells per group). Fast-phase time constants averaged 248±25, 243±27, 241±20, and 221±20 ms in CTL, CHF, CHF+AT, and AT dogs, respectively (P=NS, n=10 cells per group).

**I** _K_ _I_ Representative 1 mmol/L Ba^{2+}–sensitive **I** _K_ _I_ recordings are illustrated in Figure 4A through 4D. **I** _K_ _I_ density was similar in CTL and CHF, but **I** _K_ _I_ density was increased in AT dogs (Figure 4E). In the presence of CHF (CHF+AT), AT increased **I** _K_ _I_ less than with AT alone (P=NS versus CTL).

**I** _Ca_ **I** _Ca_ recordings are illustrated in Figure 5A through 5D. **I** _Ca_ density decreased significantly with all interventions (Figure 5E), but the decrease in CHF was less than in AT, with CHF+AT having intermediate values. The voltage dependencies of **I** _Ca_ activation and inactivation were unaffected by CHF, CHF+AT, or AT (Figure 5F). _V_ _r_ determined by extrapolation of the ascending I-V curve to the voltage axis was similar in CTL, CHF, CHF+AT, and AT dogs (62.5±1.0, 62.1±1.6, 63.5±1.4, and 61.0±0.8 mV, respecti-
Disease-related ionic remodeling is an important contributor to a variety of cardiac arrhythmias. However, cardiac arrhythmias themselves cause ionic remodeling, which then superimposes on underlying disease-related remodeling. We were unable to identify studies in the literature of the ionic effects of such a combined remodeling paradigm. Therefore, we examined the ionic remodeling induced by AT alone, by CHF alone and by AT+CHF, as would occur when a patient with CHF develops AF. Our results indicate that AT effects on ion-current density are altered in the presence of CHF, producing a different ionic-current profile for the combination than anticipated based on additive ionic-remodeling effects of AT and CHF alone.

**Combined Remodeling Paradigms**

AF frequently occurs in the presence of preexisting heart disease, so combined remodeling paradigms involving AF-induced changes superimposed on disease-related ionic remodeling are common. Shinagawa et al showed that AT-induced ERP alterations in the presence of CHF are smaller than in normal hearts. The present study suggests that smaller AT-induced electrophysiological effects in CHF compared with normal hearts are due to reduced ionic remodeling along with changes expected from simple additive effects: predicted fractional current relative to CTL in CHF+AT = measured fractional mean current in presence of AT only (I_AT/I_CTL) x measured fractional mean current in the presence of CHF only (I_CHF/I_CTL). These predicted changes are compared with measured fractional mean currents in CHF+AT (I_AT+I_CHF/I_CTL), where I_AT and I_CHF are currents in the presence of CHF+AT and CTL, respectively, all expressed as percentage changes from CTL. Probability values for the CHF-AT interaction are shown in the last column.

The CHF+AT profile differs from CHF only by an increase in I_Ks not seen with CHF alone, along with a larger decrease in I_Ca than with CHF only. The CHF+AT profile differs from that of AT only on the basis of a decrease in I_Ca not seen with AT only, smaller changes in I_Ca and I_Ks, and a larger change in I_NCX than with AT only. CHF+AT differs from expectations on the basis of purely additive effects by virtue of smaller than expected changes in all currents except for I_Ks.

### Discussion

**Interactions Between CHF and AT Effects**

AT-induced percentage decreases in mean current densities from CTL are indicated in Table 2. Also shown are percentage changes produced by AT in the presence of CHF, as obtained by comparing the value in CHF+AT with the value in AT only. If there were no interaction, the percentage change caused by AT should be the same for control and CHF backgrounds. In fact, the effects of AT are different from this expectation: effects in the presence of CHF are generally smaller, and in some cases (eg, for I_Ca and I_NCX), no perceptible effect is observed.

The ionic-remodeling patterns produced by AT only, CHF only, and CHF+AT relative to CTL are shown in Table 3, along with changes expected from simple additive effects: predicted fractional current relative to CTL in CHF+AT = measured fractional mean current in presence of AT only (I_AT/I_CTL) x measured fractional mean current in the presence of CHF only (I_CHF/I_CTL). These predicted changes are compared with measured fractional mean currents in CHF+AT (I_AT+I_CHF/I_CTL), where I_AT and I_CHF are currents in the presence of CHF+AT and CTL, respectively, all expressed as percentage changes from CTL. Probability values for the CHF-AT interaction are shown in the last column.

#### Table 2. AT-Induced Changes in Undiseased (AT vs CTL) and CHF (CHF+AT vs CHF-Only) Hearts

<table>
<thead>
<tr>
<th></th>
<th>AT vs CTL</th>
<th>CHF+AT vs CHF Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>I_Ca at +40 mV</td>
<td>↓ 49%</td>
<td>↓ 3%</td>
</tr>
<tr>
<td>I_Ca tail (pulse to +50 mV)</td>
<td>↑ 0.4%</td>
<td>↓ 5%</td>
</tr>
<tr>
<td>I_Ca at -120 mV</td>
<td>↑ 72%</td>
<td>↑ 39%</td>
</tr>
<tr>
<td>I_Ca at +10 mV</td>
<td>↓ 61%</td>
<td>↓ 25%</td>
</tr>
<tr>
<td>I_Ks at -120 mV</td>
<td>↑ 64%</td>
<td>↓ 3%</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in text.

**Figure 6.** Recordings of I_NCX in CTL (A), CHF (B), CHF+AT (C), and AT (D) cells. E. Mean±SEM. I_NCX density in CTL, CHF, CHF+AT, and AT cells (n=17, 11, 12, and 10, respectively). Abbreviations are as defined in text.
It would be interesting to understand the mechanisms by which CHF alters AT-induced remodeling. If the same signal transduction systems were used by both CHF and AT and were near-maximally engaged by either, the response to simultaneous stimulation would be limited. Little is known about the signal transduction involved in ion-channel remodeling. A recent study suggests that a cAMP-binding response element is involved in \( I_{\text{Ks}} \) downregulation associated with cardiac memory.\(^{14} \) The interaction between CHF and AT-induced remodeling appears to depend on the CHF state, rather than the AF substrate per se, based on observations during recovery from CHF. After full hemodynamic recovery from experimental CHF, the AF substrate and associated interstitial fibrosis remain,\(^{15} \) but CHF-induced ionic remodeling disappears\(^{16} \) and AT-induced ERP changes become indistinguishable from those in the normal heart.\(^{15} \)

**Relation to Previous Studies and Potential Significance**

The ionic remodeling we observed in response to AT only and to CHF only is compatible with previous reports. As in previous studies,\(^{2-5} \) we found \( I_{\text{Kr}} \) to be reduced and \( I_{\text{Cl}} \) to be unaltered by AT. We also noted increased \( I_{\text{Kt}} \), as have previous investigators,\(^{3,4,6} \) but unlike our previous detailed analysis of AT-induced ionic remodeling.\(^{2} \) This discrepancy may be partly due to rejection in the latter study of cells with depolarized resting potentials,\(^{2} \) but not affected by either CHF or AT alone (eg, \( I_{\text{CIC-Kr}} \), the canine ultrarapid delayed-rectifier \( I_{\text{fast-Kr}} \), or T-type \( \text{Ca}^{2+} \) current) could be affected by the combination of CHF+AT. We examined cells from only 1 atrial location (the LA free wall). Because of regional heterogeneity in atrial ionic electrophysiology\(^{19,20} \) and in the interactions between AT and CHF,\(^{9} \) our findings are not necessarily applicable to all atrial regions.

We induced remodeling with regular, rapid, atrial tachypacing, which does not reproduce the irregularity of atrial rhythm in AF. Although AT is believed to be the principle stimulus to AF-induced remodeling,\(^{1} \) direct extrapolation to AF-induced ionic remodeling should be cautious. We used specific voltage protocols and a variety of pharmacological agents to isolate currents of interest. These approaches are required for the analysis of individual currents in native cardiomyocytes and are standard in such investigations but do have the potential to affect the currents studied. Although currents should have been affected similarly for all experimental groups, this limitation must be considered in evaluating our results.

We did not assess directly the mechanisms underlying changes in ion-channel function. Although there is evidence for transcriptional downregulation as a mechanism for AT-induced decreases in ion-current density in animal models\(^{21} \) and in humans,\(^{3,22} \) Schotten et al\(^{23} \) did not find \( I_{\text{Ca}} \)-protein to be reduced in atrial samples from AF patients. Therefore, other mechanisms at the regulatory level, such as enhanced phosphatase activity (Christ et al, unpublished observations) and alterations in \( \text{Ca}^{2+} \)-calmodulin kinase II,\(^{24} \) may also be involved. Further work on mechanisms underlying AT- and CHF-induced ion-channel dysfunction would be of great interest.

We studied the CHF-AT interaction by superimposing AT on CHF. It would be interesting to reverse the order of experimentation and assess ionic remodeling that occurs when AT is applied first, followed by CHF.

**Conclusions**

We found that AT-induced ionic remodeling is altered in the presence of CHF. Therefore, ion-channel function changes caused by an intervention in the normal heart cannot necessarily be directly extrapolated to the diseased heart, with potentially important implications for understanding arrhythmia mechanisms and therapy.

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References
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