Failing atrial myocardium: energetic deficits accompany structural remodeling and electrical instability

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Cha, Yong-Mei, Petras P. Dzeja, Win K. Shen, Arshad Jahangir, Chari Y. T. Hart, Andre Terzic, and Margaret M. Redfield. Failing atrial myocardium: energetic deficits accompany structural remodeling and electrical instability. Am J Physiol Heart Circ Physiol 284: H1313–H1320, 2003; 10.1152/ajpheart.00337.2002.—The failing ventricular myocardium is characterized by reduction of high-energy phosphates and reduced activity of the phototransfer enzymes creatine kinase (CK) and adenylate kinase (AK), which are responsible for transfer of high-energy phosphoryls from sites of production to sites of utilization, thereby compromising excitation-contraction coupling. In humans with chronic atrial fibrillation (AF), impairment of atrial myofibrillar energetics linked to oxidative modification of myofibrillar CK has been observed. Nevertheless, the bioenergetic status of the failing atrial myocardium and its potential contribution to atrial electrical instability in CHF have not been determined. Dogs with (n = 6) and without (n = 6) rapid pacing-induced CHF underwent echocardiography (conscious) and electrophysiological (under anesthesia) studies. CHF dogs had more pronounced mitral regurgitation, higher atrial pressure, larger atrial area, and increased atrial fibrosis. An enhanced propensity to sustain AF was observed in CHF, despite significant increases in atrial effective refractory period and wavelength. Profound deficits in atrial bioenergetics were present with reduced activities of the phototransfer enzymes CK and AK, depletion of high-energy phosphates (ATP and creatine phosphate), and reduction of cellular energetic potential (ATP-to-ADP and creatine phosphate-to-Cr ratios). AF duration correlated with left atrial area (r = 0.73, P = 0.01) and inversely with atrial ATP concentration (r = -0.75, P = 0.005), CK activity (r = -0.57, P = 0.054), and AK activity (r = -0.64, P = 0.02). Atrial levels of malondialdehyde, a marker of oxidative stress, were significantly increased in CHF. Myocardial bioenergetic deficits are a conserved feature of dysfunctional atrial and ventricular myocardium in CHF and may constitute a component of the substrate for AF in CHF.

Although the fundamental mechanisms that promote development of sustained AF in CHF have not been fully defined (29a), previous studies have indicated structural, electrophysiological, and ionic remodeling of the failing atrial myocardium (11, 26, 27, 30).

The failing ventricular myocardium is characterized by progressive reduction of high-energy phosphates (38) and reduced activity of the phototransfer enzymes creatine kinase (CK) and adenylate kinase (AK), which are responsible for transfer of high-energy phosphoryls and their metabolites from sites of production to sites of utilization (17, 20). These phototransfer systems function to maintain intracellular energetic homeostasis and serve as metabolic signal transducers, coupling the energetic status of the cell to ion channel function and membrane excitability (8, 19, 34, 51). Disruption in phototransfer reactions has been associated with cardiac electrical instability (8). Indeed, in the ventricle, induction of fibrillation has been associated with myocardial energetic disturbances and altered behavior of nucleotide-regulated ion channels (21, 24, 25, 34).

In the atrial myocardium of humans with chronic AF unassociated with CHF (29), discrete impairment of myofibrillar and mitochondrial energetics has been observed (45). Specifically, decreased atrial CK activity was attributed to the tyrosine nitrosylation of the myofibrillar CK isoform as a result of increased generation of reactive oxygen and nitrogen species (29). Furthermore, AF may aggravate changes in ATP and creatine phosphate (CrP) levels in atrial tissue (4). Although these data suggest that a cellular energetic deficit may be linked to AF, the bioenergetic status of the failing atrial myocardium and its potential contribution to atrial electrical instability in CHF have not been determined.

Here the relationship between electrical stability and bioenergetic status of the atrial myocardium, in conjunction with structural and electrophysiological correlates, was determined in the absence and presence of experimental CHF produced by rapid ventricular pacing.

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MATERIALS AND METHODS

Male dogs with (CHF, n = 6) and without (control, n = 6) rapid ventricular pacing-induced CHF underwent echocardiography, hemodynamic assessment, electrophysiological study with induction of AF, and atrial biopsy. In harvested tissue, atrial histological and bioenergetic parameters were determined. All experimental procedures were designed in accordance with National Institutes of Health guidelines and were approved by the Mayo Institutional Animal Care and Use Committee.

Model of CHF. Experimental CHF was produced by progressive rapid right ventricular pacing as previously established (49). Under thiopental sodium (20 mg/kg) and isoflurane (0.5–2.5%) anesthesia, a right ventricular epicardial pacing lead and generator (Legacy 8161 and 8165, Medtronic) were placed. After 2 wk, ventricular pacing was begun at 180 beats/min for 14 days, and pacing was continued at 200, 220, and 240 beats/min for 1 wk at each rate for a total of 5 wk of pacing.

Echocardiographic analysis. Before hemodynamic and electrophysiological study, echocardiography was performed in sinus rhythm in the conscious state. Left ventricular cavity dimension and ejection fraction (EF) were measured by two-dimensional guided M-mode. Left atrial (LA) area and EF and the mitral regurgitant jet area were measured from two-dimensional and color flow imaging. Images were digitally acquired and analyzed off-line (system 5, GE, Horten, Norway).

Hemodynamic study. To obtain hemodynamic data, the pacemaker was turned off, dogs were anesthetized with pentobarbital sodium (25 mg/kg in control group and 12.5 mg/kg in CHF groups supplemented with 50-mg boluses titrated to the anesthetic effect), intubated, and ventilated. Anesthetized animals were instrumented with pulmonary and femoral artery catheters.

Electrophysiological analysis. After collection of the hemodynamic data, a sternotomy was performed, and four contact bipolar epicardial electrodes were sutured on the appendage and free wall of each atrium. Surface electrocardiogram and epicardial electrograms were recorded (AR-6 Simultrace recorder, Electronics for Medicine, Milwaukee, WI). The atrial effective refractory period (ERP) was measured separately from the four sites using a decremental extra-stimuli method. Four pacing cycle lengths (350, 300, 250, and 200 ms) were applied to each location to determine the restitution curves for atrial refractoriness. Conduction velocity was calculated from the conduction time and distance between epicardial electrodes. Wavelength was calculated as the product of ERP and conduction velocity. Conduction velocity and wavelength were measured at a cycle length of 300 ms. After determination of ERP and conduction velocity, a biopsy was obtained from both atrial appendages and flash frozen in liquid nitrogen.

Induction of AF. After biopsy, the AF induction protocol was performed. This included programmed stimulation with one and then two extra stimuli followed by burst atrial pacing from the right and left atrial appendages. Atrial extra stimuli were applied with 10-ms decrements after eight beats of atrial pacing at two times the pacing threshold. After the longest S1S2 loss of capture (ERP), programmed stimulation with two extra stimuli began with S1/S2 + 40 ms/S3 + 40 ms. Burst pacing (10-s train) was conducted from 300 beats/min to the atrial refractory period with 20 beat/min increments. The mode of induction and duration of induced AF were recorded. The ease of induction was graded 3 if a single extra stimulus induced AF, 2 if two extra stimuli induced AF, and 1 if burst pacing was required to induce AF. Cardioversion was performed if AF was sustained (AF duration ≥30 min). An epicardial 10–J shock was used to terminate AF and was also administered to dogs without sustained AF to control for any effects of cardioversion on atrial bioenergetics. At 15 min after restoration of sinus rhythm, a second atrial biopsy was obtained from both atrial free walls and flash frozen in liquid nitrogen. Additional atrial samples were preserved in 10% neutral buffered formalin for study of atrial histology.

Histology. Masson’s trichrome-stained atrial tissue was analyzed by the Image-pro software system (Huntley, IL). The entire tissue sample (3–8×100 power fields) from each slide was analyzed. The percent fibrosis in each field was calculated and averaged. Pericardial and endocardial connective tissues were excluded.

Bioenergetic parameters. Tissue samples were pulverized in liquid nitrogen and extracted in a solution containing 0.6 M HClO₄ and 1 mM EDTA as described previously (15). Proteins were pelleted by centrifugation, and protein content was determined with a DC protein assay kit (Bio-Rad). Proteins were pelleted by centrifugation, and protein content was determined with a DC protein assay kit (Bio-Rad). Extracts were neutralized with 2 M KHCO₃. ATP, ADP, and CrP levels were measured using coupled enzyme assays with fluorometric detection (17). GTP and GDP concentrations were determined by high-performance liquid chromatography (36). The activities of CK and AK were measured by spectrophotometry as previously described (17, 20, 36). Measurements were made in samples from the free wall and appendage from the right and left atra. Total tissue creatine (Cr) was measured using a colorimetric procedure after mild acid hydrolysis of CrP (13). Free Cr value was obtained by subtracting CrP from the total Cr content. The level of malondialdehyde (MDA), a marker of lipid peroxidation and oxidative stress, was measured in HClO₄ extracts from atrial tissues using the lipid peroxidation assay kit (Calbiochem).

Statistical analysis. Comparisons of parameters between groups were performed with Student’s t-test if data were normally distributed and on logarithmically transformed values if data were not normally distributed. Correlations between continuous factors were calculated using Pearson’s correlation coefficient. The ERP was analyzed using repeated measures for the analysis of rate adaptation. P < 0.05 was considered significant.

RESULTS

Atrial structure and function in the normal and failing heart. Incremental ventricular pacing resulted in a marked deterioration in cardiac contractile function with reduction in the left ventricular EF (66 ± 3% in control vs. 31 ± 4% in CHF, P = 0.0001). Although ventricular dysfunction is well characterized in pacing-induced CHF (49), less is known of atrial functional and structural changes. EF in the LA was significantly decreased in the CHF group (Table 1). Reduced atrial contractile performance was associated with atrial dilation (Fig. 1A), development of mitral regurgitation, and increased atrial pressures in the CHF group (Table 1). Atrial pressure/volume overload, dilation, and contractile dysfunction were associated with atrial fibrosis (Fig. 1B), which presented as diffuse increases in interstitial fibrosis with areas of focal fibrosis (Fig. 1, C and D).
Atrial electrical activity in normal and failing hearts. In the control and CHF groups, the ERP shortened proportionally to the decremental pacing cycle length (P < 0.01 for both groups; Fig. 2A), a phenomenon recognized as rate-dependent adaptation. However, in failing hearts, the average atrial ERP was longer at all pacing cycle lengths (Fig. 2A). Although the averaged atrial conduction velocity was similar in the two groups (Fig. 2B), the averaged atrial wavelength was longer in the CHF group (Fig. 2C). With AF induction, none of the control dogs developed sustained AF. However, three of the six CHF dogs had sustained AF or atrial flutter, one had AF for 18 min, and one died of pulmonary edema after 12 min of atrial flutter. The mean AF duration was increased in the CHF group (1,115 ± 316 and 44 ± 13 s in CHF and control, respectively, P < 0.05; Fig. 2D). The AF cycle length was prolonged in CHF dogs (129 ± 5 and 115 ± 4 ms in CHF and control, respectively P < 0.05). Mode of AF induction as assessed by the induction score was comparable in the two groups (2.17 ± 0.31 and 1.83 ± 0.40 in control and CHF, respectively, P = 0.52).

Atrial bioenergetics and oxidative stress in normal and failing hearts. The failing ventricular myocardium is in a state of apparent energy deficit (18), yet the energetics of the atrial myocardium in CHF have not been determined. Here, the atrial myocardium of CHF dogs displayed a profound bioenergetic deficit characterized by reduced phosphotransfer capacity coupled with nucleotide imbalance (Table 2). Specifically, the activity of AK was reduced by 23%, along with a concomitant similar reduction in CK activity. Inasmuch as AK and CK catalyze transfer of the majority of high-energy phosphoryls in the myocardium (20), their cumulative deficit could disrupt atrial energetic homeostasis. Indeed, there was a marked reduction in atrial ATP and CrP levels within the failing atrium and a decrease in the CrP-to-ATP ratio, an index of the cellular energetic potential. The inability of the failing atria to maintain the adenine nucleotide and high-energy phosphoryl pools was further evidenced by the significant reduction in the ATP-to-ADP and CrP-to-Cr ratios in total atria, as well as a reduction in the GTP-to-GDP ratio in the atrial free wall (Table 2). The balance between these high-energy phosphoryls and their metabolites controls adenine- and guanine nucleotide-sensitive cellular components, including ion channels (14, 34, 47). Thus the atrial myocardium of failing hearts displays a mismatch between energy transduction, transfer, and consumption processes, reducing the tolerance of atrial tissue to hemodynamic and metabolic demand. We also observed a reduction in total Cr concentrations in atrial tissue, a finding previously described in failing ventricular myocardium (38). Heart failure is associated with oxidative stress and increased production of reactive oxygen species, which have the ability to inhibit ATP-generating and transfer processes (16, 29), aggravating myocardial energetic deficit. Oxidative stress in atrial tissue, however, is poorly characterized. Here, the level of MDA, a marker of lipid peroxidation and cellular oxidative stress, was increased by 50% in failing atrial tissue (18.3 ± 1.3 and

Table 1. Atrial structure and function in control and CHF dogs

<table>
<thead>
<tr>
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<th>Control</th>
<th>CHF</th>
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<tbody>
<tr>
<td>LA EF, %</td>
<td>32 ± 2</td>
<td>21 ± 2*</td>
</tr>
<tr>
<td>MR area/LA area</td>
<td>0</td>
<td>0.20 ± 0.03*</td>
</tr>
<tr>
<td>PA wedge pressure, mmHg</td>
<td>4.2 ± 1.5</td>
<td>20.4 ± 4.5*</td>
</tr>
<tr>
<td>RA pressure, mmHg</td>
<td>0.8 ± 0.02</td>
<td>5.3 ± 1.6*</td>
</tr>
</tbody>
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Values are means ± SE. LA, left atrial; EF, ejection fraction; MR, mitral regurgitation; PA, pulmonary artery; RA, right atrial; CHF, congestive heart failure. *P < 0.05 vs. control.
12.2 ± 3.0 nmol/mg protein in CHF and control, respectively, *P = 0.03.

Relationship between atrial structural and bioenergetic status and the propensity for sustained AF. Atrial enlargement has been previously considered a critical risk factor for sustained AF (53). Indeed, we found a close correlation between the duration of induced AF and LA area (Fig. 3A), but not with the extent of atrial fibrosis (r = 0.14, *P = 0.56). The energetic status of the cell, through phosphotransfer reactions, is tightly coupled with ion channel function and membrane excitability (8, 14, 34, 51). We provide the first evidence that the duration of induced AF correlates with atrial bioenergetic parameters, namely, ATP levels (Fig. 3B), as well as the respective activities of the phosphotransfer enzymes CK (Fig. 3C) and AK (Fig. 3D). This suggests a potential role for the cellular energetic homeostasis in maintaining the electrical stability of atrial muscle.

Table 2. Atrial bioenergetic function in control and CHF dogs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CHF</th>
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<tbody>
<tr>
<td>CK, μmol·min⁻¹·mg protein⁻¹</td>
<td>5.25 ± 0.52</td>
<td>4.02 ± 0.39‡</td>
</tr>
<tr>
<td>AK, μmol·min⁻¹·mg protein⁻¹</td>
<td>0.28 ± 0.02</td>
<td>0.22 ± 0.01*</td>
</tr>
<tr>
<td>ATP, nmol/mg protein</td>
<td>25.6 ± 1.01</td>
<td>11.9 ± 3.24*</td>
</tr>
<tr>
<td>ADP, nmol/mg protein</td>
<td>3.65 ± 0.31</td>
<td>4.40 ± 0.51</td>
</tr>
<tr>
<td>ATP/ADP</td>
<td>4.85 ± 0.31</td>
<td>2.67 ± 0.19*</td>
</tr>
<tr>
<td>CrP, nmol/mg protein</td>
<td>31.3 ± 2.50</td>
<td>10.2 ± 3.91*</td>
</tr>
<tr>
<td>Total Cr, nmol/mg protein</td>
<td>57.84 ± 5.06</td>
<td>34.57 ± 9.86†</td>
</tr>
<tr>
<td>CrP/CrFree</td>
<td>1.11 ± 0.10</td>
<td>0.38 ± 0.06*</td>
</tr>
<tr>
<td>CrP/ATP</td>
<td>1.22 ± 0.09</td>
<td>0.78 ± 0.11*</td>
</tr>
<tr>
<td>GDP, nmol/mg protein</td>
<td>0.70 ± 0.06</td>
<td>0.82 ± 0.08</td>
</tr>
<tr>
<td>GDP, nmol/mg protein</td>
<td>0.12 ± 0.01</td>
<td>0.33 ± 0.06*</td>
</tr>
<tr>
<td>GDP/GDP</td>
<td>5.89 ± 0.55</td>
<td>2.69 ± 0.26*</td>
</tr>
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Values are means ± SE from total atrial muscle, except for GTP and GDP, which were measured in biopsies from atrial free wall. CK, creatine kinase; AK, adenylate kinase; Cr, creatine; CrP, creatine phosphate. *P < 0.05; †P < 0.06; ‡P < 0.09 vs. control.

DISCUSSION

Although the characteristics of the ventricular myocardium in CHF are well documented, little is known regarding alterations in the failing atrial tissue that may contribute to electrical instability. Here, experimental CHF was associated with atrial pressure/volume overload, dilation, fibrosis, and contractile dysfunction. Furthermore, the failing atrial myocardium displayed an enhanced propensity to sustain induced AF, despite increases in atrial ERP and wavelength, electrophysiological properties that are not inherently proarrhythmic. Associated with these changes in atrial structure and contractile and electrical function were profound deficits in atrial bioenergetics with reduced activities of phosphotransfer enzymes, depletion of high-energy phosphoryls, and reduction in the cellular energetic potential. Although others have established that atrial dilation predisposes to sustained AF (35, 53), we provide evidence that the propensity for sustained AF correlates tightly with the cellular energetic state. These observations suggest that perturbations in energetic homeostasis may alter the electrical stability of the atrial myocardium in CHF.

Studies in humans with lone AF and in animal models of spontaneous AF produced by rapid atrial pacing with normal ventricular rates have demonstrated that AF itself induces electrophysiological changes, specifically shortening of the ERP and wavelength, which perpetuates AF (26, 53). The rapid ventricular pacing model is increasingly used to investigate the electrophysiological properties of the failing ventricular and atrial myocardium (23, 26). An enhanced propensity to sustained AF after induction of AF by extra stimuli or burst pacing has been described in this model and is believed to be a marker for the propensity to AF in CHF (26). Thus rapid ventricular pacing-induced CHF provides a model of the substrate...
for AF in CHF uncomplicated by the effects of AF itself on atrial electrophysiological properties (26–28).

In contrast to chronic AF models where atrial refractoriness and wavelength are decreased, experimental CHF is associated with increases in atrial ERP (26, 35, 53) and wavelength. In experimental CHF, localized areas of conduction dispersion within the atria were also demonstrated. Whether this dispersion was due to heterogeneous atrial stretch (53), fibrosis (26), or other factors is unclear. In the present study, the structural and electrophysiological remodeling in CHF was similar to that described previously (26). Atrial refractoriness and wavelength were prolonged, rate-dependent refractoriness was maintained, and conduction velocity was unchanged. Furthermore, the AF cycle length was increased in CHF, a finding consistent with ERP prolongation. Moreover, the observed increases in fibrosis and marked atrial dilation may predispose to electrical heterogeneity. In our study, the severity of atrial dilatation, but not fibrosis, correlated with the duration of induced AF. This finding is consistent with a study of animals allowed to recover from pacing-induced CHF, where the gradual normalization of atrial dimensions was associated with gradual improvement in atrial and ventricular systolic function and gradual reduction in induced AF duration, despite persistence of atrial fibrosis (39).

Vigorous atrial contractile and electrical activity depends on an integrated energetic system that ensures the optimal supply of high-energy phosphoryls (18). Here, failing atria were characterized by reduced activities of CK and AK. These two enzymes facilitate ATP delivery and promote removal of ADP, P_i, and H^+ from cellular ATPases (20), thus leaving the failing atrium in a state of deficient phosphotransfer capacity. Consequently, the failing atrium was unable to sustain ATP and CrP levels, depleting the intracellular high-energy phosphoryl pool. These alterations precipitated reduction in the ATP-to-ADP and CrP-to-Cr ratios, which normally provide the driving force for the functional and structural integrity of a cardiomyocyte (42, 43). Discrete defects in myofibrillar and mitochondrial energetics develop in the atrial myocardium in humans with chronic AF unassociated with CHF, suggesting a potential link between bioenergetic derangements and electrical perturbations (29, 45). Moreover, the GTP-to-GDP ratio was altered in the failing atrial wall, which could result in defective regulation of guanine nucleotide-gated ion channels, such as the acetylcholine-sensitive potassium channel (I_{KAC}) implicated in the genesis of atrial fibrillation (29, 45).

Energetic deficits in the failing ventricular myocardium include decreased phosphotransfer enzyme activity and adenine nucleotide pool size (17, 20, 38, 50). The mechanisms responsible for depletion of ATP in failing ventricular myocardium are incompletely defined but may involve depletion of Cr (also seen in atrial myocardium in the present study) in a compensatory role to maintain the phosphotransfer potential and the ATP-to-ADP ratio (38). Bioenergetic dysfunction in chronic AF was recently linked to the increased generation of nitric oxide and oxygen-derived reactive species (29). Indeed, we found increased atrial levels of MDA, a sensitive marker of oxidative stress that is
increased in the plasma of patients with CHF (10). This is significant, inasmuch as oxidative stress can damage various components responsible for cellular energetic and mitochondrial homeostasis, including phosphotransfer enzymes and ion channels, ultimately disrupting myocyte structure and function (9, 29).

The tight relationship between myocardial energetic dynamics and cardiac electrical activity is further supported by studies that have recently identified molecular mechanisms responsible for coupling ion channel regulation and cellular metabolism (1, 8, 29, 33). Although the pathogenesis of fibrillation in cardiac muscle is complex and multifactorial, ventricular fibrillation could be predicted from changes in intracellular CrP content and ionic alterations, indicating a causative relation between energetic and electrical abnormalities (21, 32). It was demonstrated that metabolic energy-driven oscillations in potassium currents produce cyclical changes in the cardiac action potential and contribute to the genesis of arrhythmias (34), whereas disruption of bioenergetic pathways or ion channels with metabolic-sensing properties predisposes the myocardium to electrical instability (2, 52). Furthermore, a more recent study indicates that the expression levels of the mitochondrial cytochrome oxidase B subunit III and the ATP synthase subunit 6 play a critical role in the development of ventricular fibrillation (40). Indeed, in the present study, CK activity, AK activity, and ATP concentration were tightly correlated with AF duration, supporting the notion that impairment in atrial energetics may contribute to the substrate for AF in CHF. Accumulation of defects at various steps in atrial energetic signaling may compromise the ability to adequately restore electrical stability in the face of induced AF.

Potential limitations of this study include the fact that the energetic status of the atrial myocardium was assessed by measuring metabolite concentrations in tissue extracts, rather than by in vivo techniques using $^{31}$P NMR spectroscopy. Although a good correlation was found between metabolite levels measured by $^{31}$P NMR in situ and by high-performance liquid chromatography or biochemical assays in tissue extracts, some differences do exist (22, 31, 32, 44). This could be due to sample preparation and the existence of metabolite pools bound to or segregated in intracellular components invisible to $^{31}$P NMR (3, 6, 7). Measured ADP and GDP levels in tissue extracts do not reflect free nucleotide concentrations in the cellular environment (48). Changes in ATP-to-free ADP or GTP-to-free GDP ratio are expected to be more pronounced than changes in total ATP-to-ADP and GTP-to-GDP ratios and could be different in separate cellular compartments (37).

In summary, CHF is a complex syndrome characterized by numerous structural, functional, and biochemical perturbations. The association of AF with CHF is common but not invariably and, perhaps, unlikely to be explained by a single morphological, electrophysiological, or biochemical parameter. In the present study, we report profound bioenergetic derangements in the atrial myocardium of failing hearts and show that these bioenergetic parameters correlate with the duration of induced AF. These findings suggest that myocardial bioenergetic deficits are a conserved feature of dysfunctional atrial and ventricular myocardium in CHF and may constitute an additional component of the substrate for AF in CHF.

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