Promotion of Atrial Fibrillation by Heart Failure in Dogs
Atrial Remodeling of a Different Sort

Danshi Li, MD, PhD; Samir Fareh, MD; Tack Ki Leung, MD; Stanley Nattel, MD

Background—Studies of atrial fibrillation (AF) due to atrial tachycardia have provided insights into the remodeling mechanisms by which “AF begets AF” but have not elucidated the substrate that initially supports AF before remodeling occurs. We studied the effects of congestive heart failure (CHF), an entity strongly associated with clinical AF, on atrial electrophysiology in the dog and compared the results with those in dogs subjected to rapid atrial pacing (RAP; 400 bpm) with a controlled ventricular rate (AV block plus ventricular pacemaker at 80 bpm).

Methods and Results—CHF induced by 5 weeks of rapid ventricular pacing (220 to 240 bpm) increased the duration of AF induced by burst pacing (from 8±4 seconds in control dogs to 535±82 seconds; P<0.01), similar to the effect of 1 week of RAP (713±300 seconds). In contrast to RAP, CHF did not alter atrial refractory period, refractoriness heterogeneity, or conduction velocity at a cycle length of 360 ms; however, CHF dogs had a substantial increase in the heterogeneity of conduction during atrial pacing (heterogeneity index in CHF dogs, 2.76±0.16 versus 1.46±0.10 for control and 1.51±0.06 for RAP dogs; P<0.01) owing to discrete regions of slow conduction. Histological examination revealed extensive interstitial fibrosis (connective tissue occupying 12.8±1.9% of the cross-sectional area) in CHF dogs compared with control (0.8±0.3%) and RAP (0.9±0.2%) dogs.

Conclusions—Experimental CHF strongly promotes the induction of sustained AF by causing interstitial fibrosis that interferes with local conduction. The substrates of AF in CHF are very different from those of atrial tachycardia–related AF, with important potential implications for understanding, treating, and preventing AF related to CHF. (Circulation. 1999;100:87-95.)

Key Words: arrhythmia ■ antiarrhythmia agents ■ conduction ■ remodeling ■ heart failure ■ electrocardiology

Our understanding of atrial fibrillation (AF) has been advanced by studies showing that rapid atrial activation, whether by AF itself or by rapid atrial pacing (RAP), causes AF-promoting electrical alterations, including decreased atrial effective refractory period (ERP), slowed atrial conduction, and increased electrophysiological heterogeneity. These results provide insight into how AF alters atrial electrophysiology to promote its own maintenance but do not account for the substrate supporting the AF that induces remodeling. Congestive heart failure (CHF) is a particularly common clinical cause of AF. Very little is known about the mechanisms by which CHF promotes AF. Preliminary studies suggest that experimental CHF promotes AF without reducing refractoriness, leaving the underlying mechanisms unclear. The present study was designed to assess the changes in atrial electrical function and structure caused by experimental CHF, determine whether these changes are part of an atrial substrate that supports AF, and compare the atrial remodeling caused by CHF with that resulting from rapid atrial activation.

Methods

Animal Preparation
Thirty-six mongrel dogs (weight, 22 to 30 kg) were studied in 3 groups, as follows: (1) There were 8 dogs in the control group. Three of the control dogs were instrumented and monitored like CHF dogs but without pacemaker activation. The results in these sham dogs were the same as in 5 acute control animals; therefore, the results of all 8 control dogs were grouped together for analysis purposes. We have previously shown that atrial pacemaker implantation without activation does not alter atrial electrophysiology for periods of ≤6 weeks. (2) The CHF group comprised 18 dogs, each with a ventricular pacemaker (model 8084, Medtronic) implanted in a subcutaneous pocket in the neck under pentobarbital anesthesia (30 mg/kg IV) and attached to a pacing lead in the right ventricular (RV) apex. The pacemaker was programmed to capture the RV at 240 bpm for 3 weeks, followed by 2 weeks at 220 bpm. CHF was established by clinical signs (lethargy, dyspnea, and edema) and confirmed by hemodynamic measurements. (3) Finally, the RAP group consisted of 10 dogs. Right atrial (RA) pacing at 400 bpm was performed for 1 week as previously described except that the ventricular response was controlled to prevent ventricular dysfunction due to a rapid response to AF. Radiofrequency ablation of the AV node was performed, and a programmable ventricular VVIP pacemaker was implanted to pace the RV at 80 bpm. All tachycardia pacemakers...
Figure 1. Schematic of electrode arrays. Bipolar electrode sites are indicated by dots. Arrows indicate series of electrodes used for CV measurement in each zone. Dashed lines delineate regions where dispersion in ERP and regional variability in AFCL were assessed. AVR indicates atrioventricular ring; SVC, superior vena cava; IVC, inferior vena cava; and PV, pulmonary vein.

were kept on standby for 24 hours after implantation before the initiation of RAP or ventricular pacing.

On study days, dogs were reanesthetized with morphine (2 mg/kg SC) and α-chloralose (120 mg/kg IV, followed by 29.25 mg · kg⁻¹ · h⁻¹) and ventilated to maintain physiological arterial blood gases. Body temperature was maintained at 37°C, and the left femoral

Group Characteristics and Hemodynamic Findings

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>RAP</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before pacing</td>
<td>26±0.9</td>
<td>27±0.4</td>
<td>27±0.5</td>
</tr>
<tr>
<td>After pacing</td>
<td>27±0.5</td>
<td>26±0.7</td>
<td></td>
</tr>
<tr>
<td>Heart weight, g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>109±7</td>
<td>116±5</td>
<td>131±5‡</td>
</tr>
<tr>
<td>RV</td>
<td>39±4</td>
<td>41±1</td>
<td>43±3</td>
</tr>
<tr>
<td>RV/LV/BW, g/kg</td>
<td>4.2±0.2</td>
<td>4.2±0.1</td>
<td>5.0±0.2‡</td>
</tr>
<tr>
<td>SR, bpm</td>
<td>138±5</td>
<td>140±1</td>
<td>138±4</td>
</tr>
<tr>
<td>Atrial rate during pacing, bpm</td>
<td>400</td>
<td>139±5</td>
<td></td>
</tr>
</tbody>
</table>

Pressures, mm Hg

| BPs                     | 118±5   | 125±5| 96±3§ |
| BPs                     | 77±2    | 70±6 | 56±3‡ |
| LVSP                    | 124±5   | 120±5| 98±4‡ |
| LVEDP                   | 2±0.8   | 2±0.6| 19±1.3§ |
| LAP                     | 6±0.3   | 6±0.3| 20±1.5§ |
| RAP                     | 3±0.3   | 3±0.4| 12±1.0§ |

LV/BW indicates ratio of left ventricular to body weight; RV/BW, ratio of right ventricular to body weight; SR, sinus rate; BPs, systolic arterial pressure; BPD, diastolic arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LAP, mean LA pressure; and RAP, mean RA pressure.

*P<0.05; †P<0.01 vs control; ‡P<0.05; §P<0.01 vs atrial pacing.

Figure 2. A, Activation during RAA pacing with BCL of 150 ms (lines are 10-ms isochrones). B, Example of phase-difference calculation at 1 site. Activation time differences from a site to its neighbors were calculated and divided by interelectrode distance. C, Maximum normalized phase differences between each site and its neighbors were plotted as a phase map. D, From phase-difference histograms, median (P<0.05), conduction inhomogeneity (P<0.05), and heterogeneity index (P<0.05/P<0.05) were calculated.
artery and both femoral veins were cannulated for pressure monitoring and drug administration. A median sternotomy was performed, and bipolar, Teflon-coated, stainless steel electrodes were hooked into the right and left atrial appendages for recording and stimulation. A programmable stimulator was used to deliver 2-ms pulses at twice-threshold current. In CHF and RAP dogs, the surface ECG was recorded before surgery to confirm 1:1 pacing, and atrial electrograms were recorded in CHF dogs to check the atrial rate during ventricular pacing. The implanted pacemaker was then deactivated. Five silicon sheets containing 240 bipolar electrodes were attached, and stimulation and recording were performed as previously described (Figure 1).6

Electrophysiological Study
ERPs were measured at the left atrial (LA) appendage (LAA) and the RA appendage (RAA) with a train of 15 basic (S1) stimuli followed by a premature (S2) stimulus and a 1-second pause, with the ERP defined as the longest S1S2 interval that failed to produce a propa-
Histology
At the end of experiments, the atria were isolated and immersed in 10% neutral buffered formalin for ≥24 hours. Tissue samples were obtained from BB, the appendages, the PW and IW of the LA, and the crista terminalis and free wall (FW) of the RA. From each of 6 tissue zones, longitudinal and transverse sections were obtained, cut at 5-μm intervals and stained with Masson trichrome. Microscopic images were qualitatively analyzed by an experienced cardiac pathologist (T.-K.L.) and then subjected to quantitative analysis.

Microscopic images were scanned into a Power personal computer with Scion Image software. Image files were analyzed with SigmaScan 4.0 (Jandel Scientific). Connective tissue was differentiated on the basis of its color and was expressed as a percentage of the reference tissue area. There was <5% variability for repeated measures of the same sample. Blood vessels and perivascular interstitial cells were excluded from the connective tissue quantification.

Data Analysis
The distance of each of 3 to 4 consecutive sites in the direction of longitudinal propagation was plotted against activation time, and CV was determined from the slope of the best-fit regression line, with a clear linear relation (r>0.99) required for analysis. The local wavelength was calculated as the product of local CV and local ERP.

To evaluate spatial conduction inhomogeneities, phase maps were constructed based on previously reported methods. Figure 2A shows activation during RAA pacing at a BCL of 150 ms in a control dog. For each electrode, the phase differences (activation time difference between the central electrode and each of the surrounding sites) were determined (Figure 2B) and divided by interelectrode distances. The largest value at each site was then used to create a phase map as shown in Figure 2C, with values also displayed as a histogram (Figure 2D). The P<0.05, expressing the range between the 5th and 95th percentiles of the phase-difference distribution, was used to express absolute heterogeneity. The variation coefficient (P<0.05/P<0.05) was used as a heterogeneity index to express heterogeneity independently of CV, as previously described.

We calculated AF cycle length (AFCL) at each epicardial recording site by counting the number of activations over a 5-second recording. We assessed regional variability in AFCL by calculating the SD of the mean AFCL in each of the 8 zones in which ERP was measured directly, ie, RAA, RA-PW, RA-IW, RA-BB, LAA, LA-PW, LA-IW, and LA-BB (Figure 1).

Statistical Analysis
Statistical comparisons of multiple group means were obtained by variance analysis (ANOVA). A t test with Bonferroni correction was used to evaluate the significance of differences between individual mean values. χ² tests were used for contingency comparisons. All results were expressed as mean±SEM, and P<0.05 was considered statistically significant.

Results
Changes in Hemodynamic Indexes
Overall group characteristics and hemodynamic data are provided in the Table. LV weight and ventricular diastolic and atrial pressures increased in CHF dogs, whereas arterial and ventricular systolic pressures decreased. RAP dogs showed no significant hemodynamic alterations. The atrial rate during ventricular pacing at 220 bpm in CHF dogs was not different from the spontaneous unpaced sinus rate, excluding significant retrograde conduction.

General Electrophysiological Variables and Properties of AF
Both RAP and CHF dogs had significantly increased AF duration (Figure 3A). AF was sustained in 10 of 18 CHF dogs. The spontaneous cycle length between trains averaged 432±10 ms (control), 438±6 ms (RAP), and 430±8 ms (CHF), which was not significantly different among groups. The mean of 3 ERP values at each basic cycle length (BCL) was used for data analysis. On rare occasions when the 3 ERP values differed by >10 ms, 1 or 2 additional ERP measurements were obtained, and the mean of all determinations was taken to represent ERP. To determine ERP dispersion, ERPs were measured at a BCL of 300 ms at 8 stimulation sites (Figure 1): RAA, RA posterior wall (RA-PW), RA inferior wall (RA-IW), RA Bachmann’s bundle (RA-BB), LAA, LA-PW, LA-IW, and LA-BB. ERP and conduction velocity (CV) measurements were obtained after 2 minutes at each BCL.

AF induction was attempted with up to 3 consecutive extrastimuli at a BCL of 360 ms and then atrial burst pacing (10 Hz for 1 to 10 seconds). AF was considered sustained if it required electrical cardioversion for termination (cardioversion was never performed before the end of experiments was continued.

Figure 6. Regional distribution of atrial ERP, CV, and wavelength (WL) in control (CTL), RAP, and CHF dogs (BCL=300 ms).

*P<0.05, **P<0.01 vs CTL, #P<0.05, ###P<0.01 vs CHF
and 3 of 10 RAP dogs versus none of the control dogs. RAP decreased ERP, wavelength, and AFCL (Figure 3B and 3C) and increased the regional dispersion in ERP and AFCL (Figure 3D and 3E). CHF did not affect any of these variables. Figure 4 shows typical ECG and pressure and atrial electrogram recordings during sustained AF from an RAP and a CHF dog. Atrial electrograms were more organized and AFCL was longer in CHF dogs. AF was induced by burst pacing in all 18 CHF dogs and by single premature atrial beats in 4 (22%). AF was induced by single extrastimuli in all RAP dogs. Extrastimuli failed to induce AF in any control animals. AFCL averaged 103±4 ms in control dogs, 106±4 ms in CHF dogs (P=NS), and 83±4 ms in RAP dogs (P<0.05 versus control, P<0.01 versus CHF).

**Figure 7.** Effects of CHF on heterogeneity of conduction. Isochronal (10 ms) activation maps (A), phase maps (4-ms isochrones; B), and phase-delay histograms (C) at BCL of 360 ms are shown for 1 control (CTL), 1 RAP, and 1 CHF dog.

Cycle-Length Dependence and Regional Variability in Atrial Electrophysiological Properties

Rate-dependent ERP adaptation was obvious in control dogs, slightly reduced in CHF dogs, and strongly attenuated in RAP dogs (Figure 5A). ERP was significantly reduced at all BCLs in RAP dogs, whereas it was unchanged at longer BCLs and increased at short BCLs in CHF dogs. CV remained unaltered in both CHF and RAP dogs (Figure 5B). Wavelength was not altered by CHF but was shortened at all BCLs in RAP dogs (Figure 5C).

Figure 6 displays regional values of atrial ERP (A), CV (B), and wavelength (C). CHF slightly increased ERP at some LA sites and did not affect overall regional ERP variability. RAP shortened ERP considerably in some regions without affecting it in others, increasing regional ERP variability. Neither CHF nor RAP significantly altered CV in any region. Wavelength was not substantially altered by CHF but was significantly decreased, particularly in RA-FW, LA-FW, and RA-IW, in RAP dogs. Overall, RAP dogs displayed a variety of alterations (decreased ERP and wavelength and increased ERP heterogeneity) that promote multiple wavelet reentry, whereas CHF dogs did not. To gain insights into the potential substrate for AF in CHF dogs, we investigated further the finer properties of conduction.

**Local Conduction Abnormalities**

Figure 7 shows isochronal activation maps (A), phase maps (B), and phase-time histograms (C) during 1:1 pacing at the RAA with BCLs of 360 ms from representative control, RAP, and CHF dogs. In the control and RAP dogs, conduction was homogeneous, phase maps showed a narrow range of values (<2 ms/mm), and phase-time histograms were narrow. In the CHF dog, local regions of conduction slowing were apparent, producing zones of marked phase delay on the phase map and a broad phase-time histogram.

Figure 8 provides mean data for the phase-delay analysis in 18 CHF, 10 RAP, and 8 control dogs. Neither CHF nor RAP
significantly changed the median phase time (P50), consistent with the lack of change in overall CV. The absolute range of phase delays (P5–95) and the heterogeneity index (P5–95/P50) increased at all BCLs in CHF dogs. P95 increased significantly in heart failure dogs (eg, 3.07 ± 0.18 versus 1.74 ± 0.14 ms/mm at BCL of 360 ms; P < 0.01), whereas P5 remained unchanged. Thus, the increases in heterogeneity indexes were due to the appearance of large regional phase delays in heart failure dogs, reflecting localized regions of slow conduction.

Histology
Histological studies were performed to identify the potential pathological substrate underlying conduction abnormalities and AF in CHF dogs. Representative histological sections from each group are shown in Figure 9. Both control (Figure 9A) and RAP (Figure 9B) atria appeared grossly normal under light microscopy. In CHF dogs (Figure C), there was extensive interstitial fibrosis accompanied by cell loss, degenerative changes, and hypertrophy. Bundles of myofibers were packed less tightly than in control animals and were separated by thick layers of fibrous tissue. There was also an increase in connective tissue between individual cells. The connective tissue was composed of increased numbers of fibroblasts, large amounts of collagen, ground substance, and occasionally fat cells. Hypertrophy was frequently present, and cell size varied considerably within specimens. Degenerating cells were characterized by a focal to extensive disruption of sarcomeres and loss of myofibrils. Cell-to-cell junctions appeared intact. Histological changes were similar in both atria but were more extensive in the LA.

A quantitative analysis of fibrosis is shown in Figure 10. The percentage of fibrosis was significantly greater in all atrial regions in CHF dogs (Figure 10A), and fibrosis was greatly increased overall (Figure 10B). There were no discernible differences between control and RAP atria.

Discussion
In the present study, we explored the effects of CHF on the atrial substrate for AF and found that consistent with clinical experience, CHF promotes the maintenance of AF. In contrast to chronic atrial tachycardia, which promotes AF maintenance by reducing the wavelength for reentry and increasing the regional disparity of refractoriness, heart failure does not alter these variables in a fashion that would be expected to favor AF. Rather, the key changes in atrial electrophysiology caused by heart failure appear to involve alterations in local atrial conduction properties caused by interstitial fibrosis.

Substrate for AF in Experimental Models
In the present study, RAP dogs with a controlled ventricular response showed reduced atrial ERP, reduced ERP rate adaptation, reduced wavelength, and increased ERP heterogeneity, consistent with previous observations of atrial tachycardia–induced remodeling.1–6 The principal factor that induces remodeling during AF appears to be atrial tachycardia,11 possibly causing Ca2+ overload.5 Like remodeling caused by atrial tachycardia, vagal stimulation decreases ERP and increases the dispersion of atrial refractoriness.12 The electrophysiological changes associated with RAP and vagal stimulation promote multiple wavelet reentry, which is suggested by activation mapping during AF.4,12 The substrate of CHF-related AF in the present study was quite different: ERP was not reduced, and ERP heterogeneity was not increased. Rather, local conduction abnormalities and fibrosis were prominent in CHF dogs and absent in control and RAP animals. The ultrastructural changes that we observed were qualitatively similar to those noted by Boyden et al in studies of atria from dogs with mitral insufficiency,13 and from cats with cardiomyopathy,14 both of which develop spontaneous AF. Fibrosis may impair atrial conduction at a local level and permit the induction of microreentry.15

Atrial Electrophysiological Alterations Induced by CHF and Potential Relationship to AF Maintenance
There has been extensive investigation of the electrophysiological abnormalities caused by CHF at the ventricular level.16,17 Much less information is available about the effects of CHF on atrial electrophysiology, despite the clinical importance of CHF as a cause of AF. Boyden et al13 reported that action potential duration was not altered in the RA of cats.
Figure 9. Transverse sections of LA (Masson trichrome stain) from a representative control dog (A), an RAP dog (B), and a CHF dog (C). Magnification: left, ×500; right, ×1250.
Localized conduction abnormalities have been related to fibrotic tissue infiltration in atrial tissue preparations, in ventricular tissue from patients with idiopathic dilated cardiomyopathy, and in animal models of myocardial infarction. Localized atrial conduction abnormalities have been suggested to provide the basis for unidirectional conduction slowing or block and the initiation and maintenance of atrial reentrant arrhythmias. Given the extensive nature of the atrial histological abnormalities and associated local conduc-

tion disturbances caused by CHF, it is plausible that these stabilized reentry and thereby promoted AF. This idea is consistent with preliminary mapping studies pointing to macroreentry and fibrillatory conduction as the mechanism of CHF-related AF, although additional work, particularly involving endocardial mapping, is needed to define the mechanism more fully.

Clinical Relevance and Potential Significance

Although studies of atrial remodeling caused by tachycardia have provided valuable insights into how AF promotes its own maintenance, they do not explain the occurrence of the AF that causes remodeling. CHF is one of the most common clinical causes of AF. In addition, many other conditions predisposing to AF, including rheumatic valve disease and the aging process, are associated with atrial ultrastructural abnormalities (particularly fibrous tissue infiltration) like those observed in the present study. Our observations are therefore relevant to understanding how heart failure, and possibly a variety of other common causes of AF, creates a substrate for the arrhythmia. Furthermore, our findings are significant in demonstrating that the electrophysiological changes produced by tachycardia-induced remodeling are not essential for the initiation of sustained AF.

Drug therapy to prevent AF has traditionally targeted atrial electrophysiological properties to promote sinus rhythm maintenance. Collateral changes in ventricular electrophysiology have produced undesirable consequences, particularly ventricular proarrhythmia and potential increases in mortality. If, however, structural changes of the type we observed play an important role in AF promotion, drug therapy could potentially be directed against structural remodeling. For example, the renin-angiotensin system is believed to be important in ventricular remodeling, including fibrotic changes, caused by CHF. There is evidence that ACE inhibitors can reduce the prevalence of AF in patients with CHF. Additional studies of the biochemical mechanisms underlying atrial structural remodeling may lead to novel therapeutic approaches to AF prevention that target substrate development rather than the final electrical consequences.

Potential Limitations

We studied CHF with the use of a well-established (but quite specific) animal model. The histological changes we observed are similar to those noted previously in animal and clinical studies of subjects with atrial volume and/or pressure overload. Nevertheless, it would be incorrect to assume that our results can be directly extrapolated to AF substrates in clinical heart failure or necessarily to AF in other animal models. The chronic atrial stretch caused by CHF in our dogs could have contributed to electrophysiological changes.

Sustained AF was readily induced by burst pacing in a majority of dogs with CHF; however, premature extrastimuli induced AF relatively infrequently. This observation is likely due to the lack of ERP abbreviation in dogs with heart failure: short ERPs appear to be an important determinant of vulnerability to AF induction by premature complexes. Clinical studies have shown that AF induction with single premature extrastimuli is uncommon, whereas prolonged atrial
tachyarrhythmias can be induced by burst pacing in ≈80% of patients with a history of atrial arrhythmias. The limited ability of single premature beats to induce AF may be a protective mechanism that limits the occurrence of AF in patients with CHF. AF might be initiated by a brief run of atrial tachycardia due to another mechanism or by a premature beat in the face of a transient neurohormonal or autonomic alteration that abbreviates atrial refractoriness. Once AF occurs, electrical remodeling would likely follow as a result of sustained atrial tachycardia. Thus, AF in association with heart failure might begin with the pathophysiology demonstrated in the present study, but subsequent atrial remodeling could change the electrophysiological substrate, with multiple circuit reentry eventually supervening. The potentially dynamic nature of the substrate for AF may need to be considered in treating the arrhythmia.

Conclusions
Our study provides the first detailed insights into the functional and structural changes underlying the ability to sustain AF in an animal model of CHF. These results are important in pointing toward potentially different electrical and structural substrates of AF in different settings and the need for considering such differences to understand the mechanisms and potential treatment of the arrhythmia.

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