Consequences of Atrial Tachycardia-Induced Remodeling Depend on the Preexisting Atrial Substrate

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Background—All animal studies of atrial tachycardia (AT) remodeling to date have been performed in normal hearts, but clinical atrial fibrillation (AF) often occurs in the setting of heart disease. This study evaluated the effects of a pathological AF substrate on AT-induced remodeling.

Methods and Results—Fourteen control dogs, 12 AT-only dogs (400 bpm for 1 week), 14 congestive heart failure (CHF) dogs (CHF only, ventricular tachypacing, 220 to 240 bpm for 5 weeks), and 13 CHF+AT dogs (ventricular tachypacing–induced CHF, 1 week of AT superimposed on the last week of ventricular tachypacing) were studied for evaluation of AT effects in normal hearts (AT-only versus control dogs) and CHF hearts (CHF+AT versus CHF-only dogs). In normal hearts, AT strongly decreased the effective refractory period (ERP) and abolished ERP rate adaptation, whereas conduction velocity was unaltered. In CHF dogs, AT reduced ERP to a significantly lesser extent, did not alter ERP rate adaptation, and reduced conduction velocity. AT alone increased atrial vulnerability to extrastimuli and prolonged AF. In the presence of CHF, AT had no clear effect on atrial vulnerability but increased the prevalence of prolonged AF.

Conclusions—The electrophysiological effects of AT are different in hearts with a CHF-induced pathological substrate for AF than in normal hearts. These findings have potentially important implications for understanding how AF occurring in diseased hearts begets AF. (Circulation. 2002;105:251-257.)

Key Words: heart failure • remodeling • arrhythmia

Atrial fibrillation (AF) alters atrial electrophysiology to promote its own maintenance. AF-induced remodeling is due to the rapid atrial rate, and atrial tachycardia (AT) produces similar remodeling, reducing the atrial effective refractory period (ERP), reducing the wavelength, promoting multiple-circuit reentry, and decreasing the chance of spontaneous AF termination.

Clinical studies of AF support the relevance of experimental studies of AT-induced remodeling, but changes have been more variable and sometimes smaller than in animal models. All previous experimental work on AT remodeling has been performed in normal animals. Clinical AF commonly occurs in the presence of atrial pathology, and AT could have different electrophysiological effects in pathological compared with normal atria.

Congestive heart failure (CHF) creates atrial structural remodeling that promotes AF maintenance. A substantial proportion (15% to 30%) of CHF patients develop AF. Furthermore, atrial pathological changes caused by experimental CHF resemble those in other clinical conditions, such as valve disease and senescence, associated with AF. The present study tested the hypothesis that the electrophysiological effects of AT in the presence of a CHF-induced pathological AF substrate are different from those in normal hearts.

Animal Preparation

Fifty-three mongrel dogs (weight 19 to 39 kg) were studied. Control dogs (n=14) included 3 dogs instrumented and followed up like CHF dogs but without pacemaker activation, as well as 11 acute controls. Results were the same for sham-implanted and acute controls; therefore, all were grouped for analysis. All chronic dogs were instrumented transvenously with right ventricular (RV) and right atrial (RA) unipolar pacing leads under ketamine (5.3 mg/kg IV), diazepam (0.25 mg/kg IV), and halothane (1% to 2%) anesthesia. The leads were connected to ventricular and atrial pacemakers (Medtronic) implanted in the neck. Pacing began 24 hours after pacemaker implantation. In CHF-only dogs (n=14), the ventricular pacemaker was programmed at 240 bpm for 3 weeks, followed by 220 bpm for 2 weeks, whereas the atrial pacemaker was not activated. CHF was established by clinical signs (lethargy, dyspnea, or edema) and confirmed by hemodynamic measurements. In AT-only dogs (n=12), AV block was created by radiofrequency catheter ablation, the RV pacemaker was programmed to 80 bpm, and the RA was stimulated at 400 bpm for 1 week. CHF+AT dogs (n=13) were subjected to RV pacing as were CHF-only dogs, but RA pacing at 400 bpm was performed along with ventricular tachypacing for 1 week after 4 weeks of ventricular tachypacing alone. Atrial thresholds and outputs averaged 0.8±0.1 and 3.3±0.1 V, respectively, in AT dogs and 0.9±0.1 and 3.4±0.1 V in CHF+AT dogs (P=NS).

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), maintained at 37°C, and ventilated mechanically. A median sternotomy was performed. A programmable stimulator (DCI) delivered 2-ms twice-
threshold current pulses. Silicon plaques containing 240 bipolar electrodes (3.1 to 4.0 mm interelectrode distance) were sewn onto the atrial epicardial surfaces, and stimulation and recording were performed as described previously.12

Electrophysiological Study

ERP was measured with 15 basic (S1) stimuli at basic cycle lengths (BCLs) of 150, 200, 250, 300, and 360 ms at 8 stimulation sites: RA appendage, RA posterior wall, RA inferior wall, RA Bachmann’s bundle; left atrial (LA) appendage, LA posterior wall, LA inferior wall, and LA Bachmann’s bundle. AF was induced by single extrastimuli and then burst pacing (10 Hz, 4 times threshold, 2-ms stimuli for 1 to 10 seconds). To estimate mean AF duration (DAF) in each dog, AF was induced 10 times for AF ≤20 minutes and 5 times for 20 to 30 minutes of AF. AF >10 minutes on 2 separate occasions was defined as prolonged AF. AF >30 minutes was cardioverted with a synchronized DC shock. After 2 cardioversions, no further AF inductions were performed.

Histology

Atria were immersed in 10% neutral-buffered formalin. Tissue samples obtained from Bachmann’s bundle, 4 LA regions, and 2 RA regions were stained with Masson trichrome. Microscopic images were scanned with Scion-Image software, and image files were analyzed with Sigmascan 4.0 (Jandel Scientific).12 Images were analyzed without knowledge of group assignment.

Data Analysis

Conduction velocity (CV) was determined from the regression of distance on activation time at 4 electrode sites in the direction of rapid propagation,4 with \( r \geq 0.99 \) required. To obtain an index of local conduction slowing, phase maps were constructed.16 For each electrode on each array, the activation time differences to neighboring points were normalized to interelectrode distance. The largest local phase differences at each site were used to define phase delay. The phase delays at all sites were used to create a phase map and to obtain a phase-delay histogram. The median (P50) of the phase-delay histogram reflects average conduction speed, and the P95 (95th percentile) reflects regions of slowest local conduction. The variation coefficient (P5–95/P50) is a heterogeneity index expressing inhomogeneity in conduction.12

Statistical comparisons were by ANOVA, with an interaction analysis to evaluate the significance of the presence or absence of CHF as a determinant of AT effects. Because of the large number of individual comparisons possible (between control, AT-only, CHF-only, and CHF+AT dogs at each BCL in each region), the primary statistical comparisons were limited to the roles of CHF, AT, and the interaction as revealed by ANOVA. Average results are given as mean ± SEM, and a 2-tailed \( P < 0.05 \) was considered statistically significant.

Results

Ventricular diastolic and atrial pressures increased significantly in CHF-only dogs and CHF+AT dogs but were unchanged in AT-only dogs compared with control (Table). There were no significant hemodynamic differences between CHF-only dogs and CHF+AT dogs. The atrial rate during ventricular pacing at 220 bpm in CHF-only dogs (158±12 bpm) was not significantly different from their spontaneous unpaced sinus rate (150±12 bpm), reflecting a lack of retrograde ventriculoatrial conduction.

Changes in Properties of AF

DAF increased relative to control (29±11 seconds) in CHF-only dogs (416±185 seconds, \( P < 0.05 \)), AT-only dogs (638±248 seconds, \( P < 0.05 \)), and CHF+AT dogs (679±193 seconds, \( P < 0.01 \) versus control; \( P = \text{NS} \) among paced groups). Prolonged AF occurred in 0 of 14 control dogs, 2 (14%) of 14 CHF-only dogs (\( P = \text{NS} \)), 4 (33%) of 12 AT dogs (\( P < 0.05 \) versus control), and 8 (62%) of 13 CHF+AT dogs (\( P < 0.01 \) versus control, \( P < 0.05 \) versus CHF-only dogs). A single premature extrastimulus was able to induce AF in 4.2% of sites in control dogs, 55.7% (\( P < 0.0001 \)) in AT-only dogs, 6.3% (\( P = \text{NS} \) versus control) in CHF-only dogs, and 16.2% (\( P = \text{NS} \) versus control) in CHF+AT dogs.

Figure 1 shows ECG, blood pressure, and atrial electrogram recordings during sustained AF in a CHF-only dog, an AT-only dog, and a CHF+AT dog. The atrial electrogram patterns were more organized and regular in CHF-only dogs.
than in AT-only dogs. CHF+AT dogs had more disorganized and irregular electrograms than CHF-only dogs but less so than AT-only dogs. AF cycle length averaged 108±3 ms in control, 121±4 ms in CHF-only dogs (P<0.05 versus control), 94±3 ms in AT-only dogs (P<0.05 versus control), and 106±3 ms in CHF+AT dogs (P=NS versus control).

**Electrophysiological Remodeling**

Figure 2 shows ERP values at various BCLs in 8 atrial regions. AT-only dogs had ERP changes typical of AT-induced remodeling: decreased ERP and loss of ERP rate adaptation. The effects of AT were regionally heterogeneous, being smaller in some regions than in others. CHF-only dogs had increased ERP. In the presence of CHF, AT reduced ERP (CHF+AT versus CHF-only dogs), but generally to a lesser extent than in normal dogs (AT-only versus control dogs). Over all regions, ANOVA revealed both CHF and AT to be highly significant determinants of ERP (P<0.0001). In addition, there was a highly significant interaction between CHF and AT (P<0.0001), which indicates that the effect of AT was determined by the presence or absence of CHF.

To analyze the interaction further, we evaluated separately the impact of CHF in various regions on the ERP shortening of AT effect, as well as on its effect to reduce ERP rate adaptation. Figure 3 shows the AT-induced ERP reduction at a BCL of 300 ms in various atrial regions. The probability values shown are the statistical significance of the CHF-AT interaction in determining ERP (i.e., the significance of CHF as a determinant of the ERP-reducing effect of AT) over all cycle lengths in the region shown. In normal dogs, AT reduced ERP by 25 to 52 ms in various regions (open bars). In CHF dogs, the AT reduction averaged 15 to 22 ms (filled bars). Significant interactions between CHF and AT were noted in the 5 regions with AT-induced ERP reductions in normal dogs averaging >40 ms. In the 3 regions with smaller changes in AT-only dogs, the interactions were not statistically significant. These data indicate that CHF attenuates the magnitude of the ERP-reducing effect of AT in a regionally determined way.

Figure 4 shows rate adaptation of ERP (the percentage reduction in ERP over the cycle length range from 360 to 150 ms) in all atrial regions in each group. ERP rate adaptation varied from 13% to 25% in control dogs (Figure 4A). In AT-only dogs (Figure 4B), ERP rate adaptation was virtually abolished in all regions (P<0.001 versus control). In contrast, ERP rate adaptation was well preserved in both CHF-only dogs (17% to 28%; Figure 4C) and CHF+AT dogs (Figure 4D; 19% to 28%, P=NS versus CHF-only or control dogs). There was a highly significant interaction between CHF and AT in governing changes in ERP rate adaptation (P<0.001).

An analysis of changes in CV is shown in Figure 5. As in previous studies, CV was not significantly altered in AT-only or CHF-only dogs. However, CHF+AT dogs tended to have smaller CVs, and the interaction between CHF and AT was a highly significant determinant of CV over all BCLs and regions (P<0.001). When results at each BCL were examined, there were significant interactions between CHF
and AT in determining CV at BCLs of 250 (P=0.002), 300 (P=0.005), and 360 (P=0.003) ms.

Whereas global CV is not affected by CHF only, the analysis of local conduction by phase-delay histograms reveals significant disturbances in local conduction. Figure 6 provides mean data for the phase-delay histogram analysis of conduction heterogeneity in each group. In control dogs, which were characterized by rapid and homogeneous conduction, the median phase time (P50), maximum phase delay (P95), and heterogeneity index (P5/P95/P50) were small. AT-only dogs had values indistinguishable from control. CHF significantly increased P95 and P5/P95/P50 (P<0.001). Although values for CHF+AT dogs tended to be larger than those for CHF-only dogs, the overall interaction was not statistically significant (P=0.07 for each). When analyzed at each BCL, only a borderline-significant interaction (P=0.05) was attained for P5–P95/P95 at a BCL of 150 ms; for other BCLs and for P95, there were no significant interactions.

**Histology**

Interstitial fibrosis appears to be important in the AF-promoting properties of CHF. We therefore analyzed interstitial fibrous tissue content quantitatively from 7 atrial regions in each dog. CHF substantially increased fibrous tissue content (Figure 7), with LA regions and Bachmann’s bundle being particularly affected, whereas AT did not. Overall mean fibrous tissue content was 2.6±0.3% in control dogs, 3.3±0.3% in AT-only dogs, 11.9±0.6% in CHF-only dogs.
dogs, and 12.6±0.7% in CHF+AT dogs. CHF significantly increased fibrous tissue content (P<0.0001), but there was no significant interaction between CHF and AT.

Discussion

In the present study, we compared the electrophysiological effects of atrial tachycardia in the presence of CHF with effects in normal hearts. We found that the effects of AT-induced electrical remodeling were appreciably affected by the presence of a CHF-induced AF substrate. In the presence of CHF, AT had substantially smaller effects on atrial ERP, no longer eliminated ERP rate adaptation, and slowed intra-atrial conduction.

Relationship to Previous Observations Regarding Atrial Tachycardia–Induced Remodeling

The effects of AT in normal hearts have been reported in numerous previous experimental studies. All studies showed strong ERP reduction and loss of rate adaptation. Changes in CV with long-term (several-week) atrial pacing have been variable, with some studies suggesting a decrease in CV and others no change; however, no studies have shown that AT slows conduction significantly in normal hearts over a 1-week period.

No previous experimental studies have addressed the effects of AT in the presence of preexisting cardiac pathology. The present work shows that the electrophysiological changes caused by AT in the presence of CHF differ from those in normal hearts. Clinical studies of AF-induced electrical remodeling have produced more variable results than experimental studies in normal hearts, with ERP alterations and ERP rate maladaptation varying much more widely than in experimental studies. Our results suggest that these discrepancies may be due to the effects of cardiac pathology on AT-induced remodeling. The extent and nature of cardiac disease associated with AF varies in different clinical populations, with this variation potentially being reflected in different results of AF-induced remodeling in different studies. AT-induced remodeling effects have been shown to be spatially heterogeneous after 24 hours. The present study shows that AT remodeling is also spatially heterogeneous after 7-day AT and demonstrates that the interaction with the CHF substrate is spatially determined (Figures 2 and 3). These findings may account for clinical observations of regionally variable effects of AF-related remodeling.
In a previous study, we found that CHF increased ERPs at short BCLs and left them unaltered at long BCLs, whereas in the present study, CHF increased ERP over the entire range of BCLs. CHF affects a variety of currents in atrial myocytes, modestly decreasing both L-type Ca\(^{2+}\) currents (\(I_{\text{Ca,L}}\), which tends to reduce action potential duration [APD]) and transient outward and delayed-rectifier K\(^{-}\)-currents (which tends to increase APD) and increasing the Na\(^{+}\),Ca\(^{2+}\)-exchange current (which tends to increase APD). The net result of these offsetting effects is a tendency for APD to increase, which may be variably manifest depending on the rate dependence of various currents and subtle differences in the relative magnitude of CHF effects on each.

**Potential Underlying Mechanisms**

Decreases in \(I_{\text{Ca,L}}\) contribute importantly to AT-induced changes in atrial ERP and ERP rate adaptation. Decreases in \(I_{\text{Na}}\) may contribute to CV changes after 6-week AT in the dog. Changes in connexins may also occur but are less clear. AT also affects cellular Ca\(^{2+}\) handling, with potentially important effects on action potential dynamics. Both AT and CHF reduce \(I_{\text{Ca,L}}\), and thus AT may decrease APD less in the presence of CHF because \(I_{\text{Ca,L}}\) is already decreased by CHF itself. However, this explanation would not account for maintained ERP rate adaptation in CHF+AT dogs, nor for the CV slowing observed only in CHF+AT dogs. The interactions between CHF and AT do not appear to be due to AT-induced worsening of CHF, because hemodynamic abnormalities were indistinguishable in CHF-only versus CHF+AT groups (Table). Further work is needed to define the differences in ionic remodeling caused by AT in the presence of CHF versus its absence, as well as the underlying basis.

**Potential Significance**

The concept of AT-induced electrophysiological remodeling was an important advance in our understanding of AF and has provided many important insights into the pathophysiology of the arrhythmia. The present study suggests that care is required in the extrapolation of observations regarding AT-induced remodeling in normal hearts to the alterations that might occur in the presence of heart disease. Further work will be needed to evaluate the effects of AT in other experimental models of heart disease, to evaluate whether the underlying cardiac substrate determines the effects of remodeling in humans, and to analyze underlying signal transduction mechanisms.

Previous work suggested that AT-induced remodeling promotes AF in large measure by reducing ERP, promoting multiple circuit reentry by virtue of a decreased wavelength. The present study shows that in the presence of a CHF-induced substrate, the ERP changes caused by AT are less prominent, changes in conduction may play a role, and AF promotion is relatively less pronounced compared with changes in normal hearts. ERP rate adaptation was unaffected by 1 week of AT in the presence of CHF, in marked contrast to the rapid loss of ERP rate adaptation caused by AT in the normal heart. AT-induced loss of ERP rate adaptation results in very short ERP values at slower rates and greatly enhances vulnerability to AF induction by premature atrial extrasystoles. The lack of ERP rate adaptation changes in CHF+AT dogs resulted in very limited enhancement of atrial vulnerability. This observation may provide insight into the potential sources of variability in early AF recurrence after cardioversion in clinical populations.

**Potential Limitations**

We studied a specific model of CHF produced by sustained ventricular tachycardia and used a tightly controlled experimental design with specific durations of atrial and ventricular tachypacing in each experimental group. Our experimental design allowed us to compare the effects of AT in the absence of ventricular tachypacing with those in the presence of CHF induced by ventricular tachypacing. It remains to be determined how longer- and shorter-duration AT affects atrial electrophysiology in the presence of the CHF substrate. Another issue that will need to be addressed is whether and how other pathological atrial substrates affect tachycardia-induced remodeling. The atrial tissue pathology in our canine model resembles the pathology in clinical cases of mitral valve disease, senescence, and dilated cardiomyopathy. AT (such as AF) arising in the context of these conditions may thus cause remodeling with features like the ones we observed in the setting of CHF; however, this possibility remains to be evaluated.

The production of AV block was needed in AT-only dogs to prevent a component of ventricular cardiomyopathy due to a rapid ventricular response to AT. There was no effective ventriculoatrial conduction during ventricular tachypacing in CHF dogs, so differences in AV nodal conduction are unlikely to have influenced the results.

ERP was increased by CHF. If this had resulted in slower atrial rates, remodeling would have been altered. To ensure continuous 1:1 atrial capture during AT, we paced the atria at >3 times threshold and recorded ECGs to ensure 1:1 capture at least 3 times over the 7-day AT period. At no time was 1:1 capture lost in any dog. Rates could also have been different during spontaneous AF. Of the dogs in the study, 0 of 14 control dogs, 0 of 14 CHF-only dogs, 2 of 13 CHF+AT dogs, and 2 of 13 AT dogs spontaneously developed AF during the AT period. The results were not significantly altered when only dogs without AF were considered.

In CHF dogs, AT increased the prevalence of prolonged AF but did not significantly alter vulnerability to single extrastimuli or mean DAF. The lack of significant change in vulnerability is attributable to the attenuated ERP-abbreviating effect of AT at long BCLs in CHF dogs. The nonsignificant increases in mean DAF may also be due to the modest ERP reductions caused by AT, as well as to large interanimal variability in DAF. These results underscore the fact that various indices of AF promotion are affected differentially by specific components of the AF substrate.

**Conclusions**

AT-induced remodeling can produce quantitatively different atrial electrophysiological changes in the setting of AF-promoting atrial pathology compared with tachycardia-induced
remodeling in normal hearts. These findings have potentially important implications for understanding how AF promotes itself in the presence of cardiac pathologies that lead to AF.

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