Contrasting Efficacy of Dofetilide in Differing Experimental Models of Atrial Fibrillation

Danshi Li, MD, PhD; Agnes Bénardeau, PhD; Stanley Nattel, MD

Background—Rapid atrial pacing (RAP) and congestive heart failure (CHF) produce different experimental substrates for atrial fibrillation (AF). We tested the hypothesis that AF maintained by different substrates responds differently to antiarrhythmic-drug therapy.

Methods and Results—The class III antiarrhythmic agent dofetilide was given intravenously at doses of 10 (D10) and 80 (D80) μg/kg to dogs with AF induced either (1) after 7 days of RAP at 400 bpm or (2) in the presence of CHF induced by rapid ventricular pacing. Dofetilide terminated AF in all CHF dogs, but D10 failed to terminate AF in any RAP dog, and D80 terminated AF in only 1 of 5 RAP dogs (20%) (P<0.01 for efficacy in CHF versus RAP dogs). Dofetilide was highly effective in preventing AF induction by atrial burst pacing in dogs with CHF but was totally ineffective in dogs with RAP. Dofetilide increased atrial effective refractory period and AF cycle length to a greater extent in CHF dogs. Epicardial mapping with 248 bipolar electrodes showed that CHF-related AF was often due to macroreentry, with dofetilide terminating AF by causing block in reentry circuits. RAP-related AF was due to multiple–wave front reentry, with dofetilide slowing reentry and decreasing the number of simultaneous waves, but not sufficiently to stop AF.

Conclusions—The mechanism underlying AF importantly influences dofetilide efficacy. The dependence of drug efficacy in AF on the underlying mechanism has potentially significant implications for antiarrhythmic drug use and development and may explain the well-known therapeutic resistance of longer-duration AF. (Circulation. 2000;102:104-112.)

Key Words: arrhythmia • dofetilide • ventricles • remodeling

Both atrial tachycardia and congestive heart failure (CHF) produce experimental substrates for persistent atrial fibrillation (AF), but the underlying mechanisms appear to be different. Rapid atrial activation, whether by AF1,2 or by rapid atrial pacing (RAP),3–5 decreases atrial effective refractory period (ERP),1–5 slows atrial conduction,3–4 and increases electrophysiological heterogeneity.5,6,7 These changes promote AF occurrence and maintenance by favoring multiple–circuit reentry.5 In contrast, experimental CHF does not shorten atrial ERP or increase heterogeneity but causes interstitial fibrosis that interferes with local conduction and thus favors AF maintenance.8 In preliminary studies, we observed that dofetilide, a selective blocker of the rapid delayed–rectifier current (I_Kr),9 seemed more effective in CHF-related AF than previously observed in a vagotonic AF model.10 We therefore postulated that AF with different mechanisms responds differently to antiarrhythmic drugs. To evaluate this hypothesis, we compared the effects of dofetilide on AF in RAP and CHF models.

Methods

Animal Preparation
Twenty-five mongrel dogs (22 to 32 kg) were studied in 2 groups: (1) CHF group (n=15): CHF was produced by right ventricular pacing as previously described.8 The presence of CHF was confirmed by clinical signs (lethargy, ascites, dyspnea, pulmonary congestion) associated with appropriate hemodynamic abnormalities. (2) RAP group (n=10): Atrial pacing (400 bpm) was performed for 1 week as previously described, with radiofrequency AV-nodal ablation and a ventricular pacemaker (80 bpm) used to control the ventricular response.5,8 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 a femoral 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 atrial appendages for recording and stimulation. A programmable stimulator was used to deliver 2-ms twice–threshold pulses. In CHF dogs, atrial electrograms were recorded to confirm that atrial rate was not affected by ventricular pacing. The implanted pacemaker was then deactivated.

Electrophysiological and Pharmacological Study
Five silicon sheets containing 248 bipolar electrodes were sutured onto the atrial surfaces (Figure 1). A decapolar catheter electrode was positioned against the septum under fluoroscopic guidance to record 5 bipolar electrograms (interpole distance 2.5 mm, interelectrode distance 10 mm). Stimulation and recording were then performed, and atrial activation was mapped as previously described.6,8

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Results

Overall group characteristics and hemodynamic data are provided in the Table. There were no significant differences between CHF and RAP dogs in body weight, sinus rate, arterial pressure, or percentage of dogs with persistent AF. Dofetilide did not affect sinus rate and reduced arterial pressure slightly, with the change being statistically significant only after the higher dose in RAP dogs. CHF dogs had higher RA (111.1±0.6 mm Hg) and LA (19.0±0.8 mm Hg) pressure than RAP dogs (3.4±0.5 and 6.2±0.4 mm Hg, respectively, P<0.0001 for each).

Drug Effects on AF

AF from the 2 models responded differently to dofetilide (Figure 2). In the RAP group, D10 failed to terminate AF in any of the 3 dogs with persistent AF and failed to prevent AF induction in any dog (Figure 2A). Mean AF duration in RAP dogs was unaffected by D10 (Figure 2B). D80 terminated persistent AF in only 1 of 5 RAP dogs, with termination occurring 5 minutes after the end of the loading dose (Figure 2C). AF could be induced in the presence of D80 in all RAP dogs, including the dog with persistent AF that had converted 5 minutes after the end of the loading dose. D80 reduced mean AF duration slightly but not significantly (Figure 2D).

In contrast to RAP, dofetilide had striking effects on AF in CHF dogs. D10 terminated persistent AF within 3 minutes (mean 55±26 seconds, range 0 to 180 seconds) of the end of the infusion in all 5 dogs with persistent AF (Figure 2A). D10 prevented AF reinduction in 4 of 5 converted animals and in all 3 with nonpersistent AF. In the 1 dog with inducible AF after D10-induced conversion, induced AF was very short-lasting (duration 3 to 15 seconds). D10 dramatically reduced mean AF duration, from 436±124 to 0.4±0.6 seconds (P<0.01, Figure 2B). D80 terminated AF within 30 seconds of the end of drug infusion in all 4 CHF dogs with persistent AF that received it (Figure 2C). Short-lasting AF (0 to 5 minutes at each BCL).

AF induction was then attempted by atrial burst pacing (10 Hz for 1 to 10 seconds). AF >20 minutes requiring electrical cardioversion was considered persistent. To estimate mean AF duration, AF was induced 10 times for AF duration <10 minutes and 5 times for AF between 10 and 20 minutes. If persistent AF was induced twice under a given condition, no further AF inductions were performed. A 30-minute rest period was allowed after electrical cardioversion before the experiment was continued.

In initial studies, we used a single loading dose of dofetilide of 80 μg/kg over a period of 10 minutes, as in previous work. After we had studied 11 dogs (7 CHF and 4 RAP), we noted categorically different efficacies in the 2 models and decided to evaluate the effects of a lower dose as well. Therefore, in the remaining 14 dogs (8 CHF, 6 RAP), we studied the effects of an initial dose of 10 μg/kg over 5 minutes, and then of a subsequent dose of 70 μg/kg (over 10 minutes), which achieved a total load of 80 μg/kg. These doses are consistent with previous studies showing maximal effects at 100 μg/kg in dogs. We have previously shown that dofetilide effects are stable for >1 hour after loading doses in dogs. The 10-μg/kg dose will be designated D10 and the 80-μg/kg dose (whether achieved by a single dose or by cumulative dosing) D80.

In dogs with persistent AF, baseline measurements were obtained, AF was induced, and then dofetilide was administered. If D10 failed to convert AF within 15 minutes after the end of the loading dose, the next dose (70 μg/kg) was given. If AF persisted after D80, electrical cardioversion was applied, and electrophysiological measurements were repeated. In dogs with nonpersistent AF (duration <20 minutes), dofetilide was given during sinus rhythm, and effects on electrophysiological variables, AF inducibility, and AF duration were determined after each dose. Solutions of dofetilide (kindly supplied by Pfizer Pharmaceuticals) were prepared fresh for each experiment and protected from light.

Data Analysis

CV was determined from the regression line between electrode distance and activation time as previously described. The wavelength was calculated as the product of local CV and ERP. AF cycle length (AFCL) was determined by counting activation cycles over 2 seconds at each of 82 epicardial recording sites (half each from the RA and LA).

Multiple group means were compared by ANOVA, followed by t tests with Bonferroni’s correction. Fisher exact tests were used for contingency comparisons. Results are expressed as mean±SEM, and a 2-tailed P<0.05 was considered statistically significant.

**Table:** Group Characteristics and Hemodynamic Findings

<table>
<thead>
<tr>
<th>Group Characteristics and Hemodynamic Findings</th>
<th>CHF (n=15)</th>
<th>RAP (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>Before pacing 28.4±0.8 30.8±1.1</td>
<td>27.9±0.8 30.5±1.2</td>
</tr>
<tr>
<td>Sinus rate, bpm</td>
<td>Before drug 136±5 138±15</td>
<td>129±10</td>
</tr>
<tr>
<td></td>
<td>D10 135±5</td>
<td>129±7</td>
</tr>
<tr>
<td></td>
<td>D80 129±6</td>
<td>129±7</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>Before drug 77±3 85±4</td>
<td>74±5 71±5*</td>
</tr>
<tr>
<td></td>
<td>D10 74±5</td>
<td>80±7</td>
</tr>
<tr>
<td></td>
<td>D80 74±4</td>
<td>71±5*</td>
</tr>
<tr>
<td>Both D10 and D80 administration, n</td>
<td>8 6</td>
<td>7 4</td>
</tr>
<tr>
<td>Persistent AF, n, %</td>
<td>5, 63</td>
<td>3, 50</td>
</tr>
<tr>
<td>Only D80 administration, n</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Persistent AF, n, %</td>
<td>4, 57</td>
<td>2, 50</td>
</tr>
<tr>
<td>Persistent AF/total, n, %</td>
<td>9/15, 60</td>
<td>5/10, 50</td>
</tr>
</tbody>
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*P<0.05.
seconds) could be induced after AF termination in only 1 of these. In all the other dogs with persistent or nonpersistent AF, the arrhythmia could not be induced in the presence of D80 (Figure 2D).

Potential Mechanisms of Differential Efficacy

Figure 3 illustrates arterial pressure, ECG, and atrial electrogram recordings from CHF and RAP dogs with persistent AF. Recordings at the top were obtained 5 minutes before D80 administration, and recordings at the bottom were obtained immediately after drug infusion. Before the drug, AF showed a coarser pattern with a relatively long AFCL (114 ± 3 ms) in CHF compared with RAP dogs (AFCL 95 ± 8 ms, P < 0.01 versus CHF). Before conversion, D80 prolonged AFCL in CHF dogs (to a mean of 159 ± 10 ms 4 seconds before conversion, P < 0.05), with particularly long cycles immediately before conversion. In RAP dogs, D80 also prolonged AFCL (to 135 ± 14 ms, P < 0.01), and AF became more organized. AFCL was also prolonged by D10, from 114 ± 5 to 148 ± 6 ms (P < 0.01) in CHF dogs and from 92 ± 6 to 116 ± 14 ms (P < 0.01) in RAP dogs.

Dofetilide produced concentration-dependent increases in atrial ERP and wavelength at a BCL of 350 ms (Figure 4). Changes in ERP were larger in CHF than in RAP dogs and were greater in the LA than RA. Whereas both D10 and D80 significantly increased ERP in both the RA and LA of CHF dogs, the drug significantly increased ERP in RAP dogs only in the LA at the higher dose. Baseline ERPs were significantly greater in CHF dogs (P < 0.001 versus RAP), and the percentage ERP increases caused by D80 were not significantly different for CHF versus RAP. Dofetilide did not significantly alter CV (Figure 4B) and caused dose-dependent wavelength increases (Figure 4C) that paralleled ERP changes.

Figure 5 shows the BCL dependency of ERP in the RA and LA before and after dofetilide. Under control conditions, the ERP was shorter and showed less ERP adaptation in RAP dogs than in CHF dogs. The differences between groups were more marked in the LA than the RA. Dofetilide increased ERP significantly and to a greater extent in CHF dogs, producing particularly small and statistically nonsignificant effects on RA ERP in RAP dogs.

Figure 2. Efficacy of dofetilide in terminating AF, preventing induction, and reducing mean AF duration. *P < 0.05, **P < 0.01 vs CHF (left) or predrug (right).

Figure 3. Blood pressure, ECG, and electrogram recordings during AF before and after dofetilide in 1 CHF and 1 RAP dog. For CHF dog, recording at time of AF termination is shown.
Drug Effects on Epicardial Activation During and at the End of AF

Activation mapping was performed at the time of dofetilide-induced AF termination in 8 CHF dogs with persistent AF that received dofetilide during the arrhythmia. In all dogs, there was evidence for prominent and consistent macroreentrant circuits that appeared to be central to AF maintenance, with drug-induced block in the reentry circuit occurring immediately before termination. In 4 dogs, block led directly to termination. One example is shown in Figure 6. Figure 6A shows selected atrial electrograms (labeled a to j) from the low RA and the septum. Figure 6, B to E, shows consecutive isochronal activation maps at the time of dofetilide-induced AF termination. For the first of these cycles (Figure 6B), the earliest activation is in the lower RA free wall (site a). Activation proceeds in a clockwise direction around a zone of functional block (note low-amplitude double potentials at d and e). The next cycle (Figure 6C) again begins with activation near site a, with clockwise propagation in the RA free wall around a zone of functional block, this time failing to activate site f. Reactivation at a initiates the next cycle (Figure 6D). Activation in the RA free wall proceeds similarly to previous cycles but blocks in the lower RA near the atrioventricular ring (sites failing to activate are shown by x’s in the Figure). Site f is activated late, possibly from the septum. Subsequent reactivation at site a initiates the next cycle (Figure 6E), with site e activated at nearly the same time. Most atrial sites show failure of activation, with failure of propagation leading to arrhythmia termination.

In the other 4 cases, block in a macroreentrant circuit also appeared to be involved in termination, but the basis of the last cycles was less clear, appearing to involve alternative reentry circuits and/or ectopic foci. Figure 7 shows 1 example. Electrograms from a region in the RA free wall during the last 5 cycles of AF are shown in 7A, with corresponding activation maps shown in Figure 7, B through F. In the first cycle (Figure 7B), there appears to be clockwise reentry around a line of functional block in the RA (from a to i), with another zone of functional block in the LA free wall. Activation again proceeds from a to i in Figure 7C, with a zone of functional block and possible reentry once again also seen in the LA. This time, however, site a fails to be reactivated from the region around site i. Reentry terminates in the RA, and activation in D is initiated in the LA, with sites a through i activated more or less simultaneously via a broad wave front. LA activation proceeds around a line of functional block, and the cycle in E begins in the lateral LA with a delay relative to preceding cycles and shows much less functional block (presumably because of greater time for recovery of excitability). There is a further delay to the cycle in Figure 7F, which originates in periseptal areas and activates the atria rapidly. The events leading to arrhythmia termination in Figure 7 are less clear than those in Figure 6, but block in the RA free-wall circuit appears to have played an important role.

In contrast to activation during CHF-associated AF, RAP-related AF appeared to involve multiple, unstable areas of reactivation, with dofetilide reducing the number of wave
Figure 6. Activation maps during dofetilide-induced AF termination in a CHF dog. A, Selected atrial electrograms during last 5 cycles of AF (positions correspond to locations shown on maps in B through E). B through E, Consecutive isochronal (20-ms) activation maps during last 5 cycles (corresponding to mapping windows shown in A) of AF. Solid lines represent arcs of block; dashed arrows, propagation that initiates activity in next cycle; LAA, LA appendage; RAA, RA appendage; and AVR, atrioventricular ring. For discussion, see text.
Figure 7. Dofetilide-induced AF termination in another CHF dog. Overall format and abbreviations as in Figure 6.
Before Dofetilide

After Dofetilide

Figure 8. Activation maps during AF in a RAP dog. A through C, Three consecutive cycles 5 minutes before (top) and after (bottom) administration of D80. Abbreviations as in Figure 6.

In the present study, we evaluated the effects of dofetilide in 2 experimental models of AF and found marked differences in response. The great efficacy of dofetilide in dogs with AF maintained in a substrate established by CHF contrasted with its inefficacy in suppressing AF induced in dogs subjected to RAP. These differences in efficacy were associated with differences in electrophysiological changes and in effects on activation during AF, which give insights into the mechanisms underlying the disparate efficacy of dofetilide in the 2 models.

Mechanisms of Effects Observed and Relationship to Previous Findings in Experimental Models of AF

$\beta$-selective blocking drugs have been found to have limited efficacy in terminating AF in a vagotonic dog model, in which AF appears to be maintained by multiple-circuit reentry. Wijffels et al recently described the effects of several antiarrhythmic drugs on AF in goats with AF-induced remodeling. AF terminated after the administration of hydroquinidine, cibenzoline, flecainide, and $d$-sotalol; however, persistent AF could be induced shortly thereafter in virtually all animals. $d$-Sotalol did not produce any obvious atrial ERP prolongation, and the mechanisms of AF termination after $d$-sotalol administration were not clear. Like Wijffels et
al, we found that a class III drug did not prevent AF induction in animals with tachycardia-induced atrial remodeling. Unlike them, we found dofetilide to be ineffective in terminating RAP-related AF. This difference may be due to differences in the model (AF-induced remodeling in chronic goats versus rapid-pacing–induced remodeling in anesthetized dogs) or in drugs used (d-sotalol versus dofetilide). Unlike dofetilide, which has little effect on ionic currents other than $I_{Kr}$, higher doses of sotalol can depress other currents, including inward-rectifier and Na$^+$ currents.\textsuperscript{15} We were unable to identify other published studies of antiarrhythmic-drug action in experimental AF in RAP or CHF models.

Dofetilide produced much larger ERP increases in CHF dogs than in RAP dogs (Figure 4), potentially contributing to the greater efficacy of the drug in CHF-related AF. The larger effect of dofetilide on repolarization in CHF dogs may be partly due to the downregulation of $I_{Kr}$ in CHF dogs,\textsuperscript{16} which is not seen with RAP.\textsuperscript{17} Atrial $I_{Kr}$ downregulation by CHF may increase the dependence of repolarization on $I_{Kr}$, resulting in greater prolongation with $I_{Kr}$ blockade. Another potentially important factor may be the underlying arrhythmia mechanism. CHF-related AF appears to be maintained by macroreentry involving a small number of stable reentry mechanisms. To the best of our knowledge, our study is the first to show consistently high conversion rates for dofetilide of CHF-related AF in the present study may be relevant to understanding the greater resistance of AF to dofetilide-induced termination.

Different patterns of atrial activation have been observed during high-density activation mapping in patients with AF.\textsuperscript{25} More complex, type III patterns are consistent with a multiple reentering wavelet mechanism, and more discrete type I patterns may suggest a single macroreentrant circuit with a variable response giving rise to the ECG appearance and irregular ventricular response of AF.\textsuperscript{25} These patterns may correspond to “fine” and “coarse” clinical AF and parallel the features of AF in our RAP and CHF dogs, respectively. If so, our observations raise the possibility that different clinical forms of AF may differ in their sensitivity to class III drugs like dofetilide. It is interesting in this regard that dofetilide was recently found to be highly effective in promoting AF termination and preventing AF in patients with CHF and left ventricular dysfunction.\textsuperscript{26}

Clinical studies consistently indicate that longer-duration AF is more resistant to termination by dofetilide.\textsuperscript{18,27} In addition to CHF, a variety of other clinical entities associated with AF, including mitral valve disease and senescence, produce atrial histopathology similar to that caused by experimental CHF.\textsuperscript{28,29} It is possible that the initial substrate for AF in such cases resembles that produced by experimental CHF and may be particularly susceptible to termination by dofetilide. If AF persists in such patients, however, tachycardia-induced remodeling would occur, producing a pathophysiological mechanism more similar to that of RAP dogs and inducing resistance to dofetilide. Our results may therefore be relevant to understanding the greater resistance of longer-standing AF to dofetilide-induced termination.

Conclusions

The efficacy of dofetilide is quite different in dogs with AF related to tachycardia-induced remodeling compared with dogs with CHF-related AF. These observations suggest that the efficacy of an antiarrhythmic drug in AF may be determined by the underlying reentrant substrate. These findings may be relevant to understanding the response to class III antiarrhythmic drugs in different patient populations with AF and to the long-recognized resistance of longer-standing AF to antiarrhythmic drug therapy.

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Potential Significance and Clinical Relevance

Experimental studies of AF were greatly limited by a dearth of clinically relevant animal models before groundbreaking studies of AF in atrial tachycardia–induced remodeling.\textsuperscript{1–3} More recently, experimental CHF has also been shown to produce a substrate that favors AF maintenance via mechanisms distinct from those of tachycardia-induced remodeling.\textsuperscript{8} In the present study, we found dofetilide to be ineffective in dogs with RAP-related AF and, in contrast, to be quite effective in dogs with AF related to CHF-induced atrial remodeling. Electrophysiological measurements and epicardial mapping suggest that the differential efficacy of dofetilide in the 2 models is related to differences in the degree of ERP prolongation and to the different arrhythmia mechanisms. To the best of our knowledge, our study is the first to provide evidence that antiarrhythmic drugs may have very different effects on experimental AF, depending on the underlying mechanism.

References


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