Widening of the Excitable Gap During Pharmacological Cardioversion of Atrial Fibrillation in the Goat
Effects of Cibenzoline, Hydroquinidine, Flecainide, and d-Sotalol

Maurits C.E.F. Wijffels, MD, PhD; Rick Dorland, BSc; Frans Mast, PhD; Maurits A. Allessie, MD, PhD

Background—Previous studies suggest that the antifibrillatory action of class I and III drugs is due to prolongation of the atrial wavelength. The aim of the present study was to directly evaluate the electrophysiological action of antifibrillatory drugs in a goat model of chronic atrial fibrillation (AF).

Methods and Results—Six goats were instrumented with multiple atrial electrodes, and sustained AF was induced by electrical remodeling. During sustained AF, the effects of intravenous infusion of cibenzoline, hydroquinidine, flecainide, and d-sotalol on AF cycle length (AFCL), refractory period (RP AF), conduction velocity (CV AF), pathlength (PL AF), wavelength (WL AF), temporal (AFCL - RP AF), and spatial (PL AF - WL AF) excitable gap were studied. The RP AF was measured by determining the earliest moment at which single stimuli could capture the fibrillating atria. CV AF was measured during regional entrainment of AF. Contrary to our expectation, cardioversion of AF could not be attributed to prolongation of WL AF. Hydroquinidine and d-sotalol did not affect WL AF significantly, whereas cibenzoline and flecainide even shortened WL AF by 18% and 36%, respectively. PL AF was increased by hydroquinidine and d-sotalol by 30%, whereas cibenzoline and flecainide did not prolong PL AF. The only parameter that correlated consistently with cardioversion of AF was a widening of the temporal excitable gap (cibenzoline 176%, hydroquinidine 105%, flecainide 86%, d-sotalol 88%).

Conclusions—Pharmacological cardioversion of AF cannot be explained by prolongation of WL AF. An alternative explanation for the antifibrillatory effect of class I and III drugs may be a widening of the temporal excitable gap.

(Circulation. 2000;102:260-267.)

Key Words: fibrillation ■ drugs ■ conduction ■ waves

Mapping studies have shown that during atrial fibrillation (AF), multiple wavelets are propagating through the atria.1-4 Class I and III drugs are effective in cardioverting AF.5,6 Some studies have suggested that this antifibrillatory action is based on a prolongation of the atrial wavelength.7-10 When the wavelength during AF gets longer, the average number of multiple wavelets decreases, and the statistical chance that AF will terminate increases. In our goat model of chronic AF, a marked shortening of the atrial refractory period occurred during the first days of AF (AF-induced electrical remodeling).11 The resulting shortening of atrial wavelength and increase in the number of fibrillation waves are thought to play an important role in the development of sustained AF in this model.11 In a recent study, we compared the antifibrillatory efficacy of several class I and class III drugs in the goat.12 Surprisingly, although all drugs were highly effective in cardioverting AF, the atrial wavelength measured immediately after cardioversion was not prolonged. Accordingly, the vulnerability of the atria after cardioversion was still very high, and AF could easily be reinduced by single premature stimuli. This discrepancy between the high efficacy of these drugs in cardioverting AF and their inefficacy in preventing recurrences cannot be easily understood on the basis of our present knowledge of the action of these drugs.

In the present study, we used a new technique to measure the atrial refractory period during AF. In this way, the effects of class I and III drugs on the atrial refractory period, wavelength, and excitable gap could be directly evaluated during AF. Contrary to our expectation, the action of antifibrillatory drugs could not be attributed to a prolongation of the atrial wavelength. Instead, pharmacological cardioversion of AF was consistently associated with a progressive widening of the temporal excitable gap during AF.

Methods
Six female goats (weight 55±7 kg) were used for this study. During general anesthesia and open-chest surgery,11,12 83 electrodes were sutured onto the surface of both atria (23 on Bachmann’s bundle, 30 on the right atrium, and 30 on the left atrium). The interelectrode
distance on Bachmann’s bundle was 4 to 10 mm and on the atrial free wall, 4 to 5 mm (Figure 1). Four electrodes were sutured onto the left ventricle. Three subcutaneous silver plates were used as indifferent electrode and to record a precordial ECG. After recovery from surgery, the goats were connected to an external fibrillation pacemaker to induce sustained AF. Pharmacological cardioversion was performed after AF had become sustained (lasting >24 hours). During cardioversion, all electrograms were recorded simultaneously (gain 200 to 400, bandwidth 1 to 500 Hz, sampling rate 1 kHz). The AF cycle length (AFCL) was measured by an automatic algorithm detecting the moments of local activation during 300 consecutive AFCL intervals. Refractory period (RP AF) and conduction velocity (CV AF) were measured every 5 to 10 minutes during AF. From these values, the average pathlength of the multiple wavelets can be calculated (PL AF = AFCL × CV AF). Also, the wavelength during AF (WL AF = RP AF × CV AF), the temporal excitability gap (difference between AFCL and atrial refractoriness during AF), and the spatial excitability gap (difference between pathlength and wavelength) can be estimated.

It was shown previously that the existence of a small excitability gap during AF permits regional entrainment of the atria. The RP AF was determined by single stimuli applied after every 50 to 100 fibrillation cycles through a pair of electrodes on the free wall of the right or left atria. Stimulus strength was 4 times entrainment threshold; duration was 2 ms. The stimuli were synchronized to the fibrillation electrogram recorded from the pacing electrodes. Starting well within the refractory period, the coupling interval was incremented in steps of 1 to 2 ms. Each stimulus was repeated 10 times; the shortest coupling interval that captured the atrium ≥2 of 10 times was taken as the RP AF. Local capture of the atria by single stimuli was determined at a neighboring electrode 4 mm from the pacing site. Failure of capture was characterized by (1) a long delay between stimulus artifact and next activation, (2) a normal AFCL, and (3) a clear R wave in the electrogram after the stimulus. Criteria for capture were (1) a short latency between stimulus and response, (2) a short AFCL, (3) a specific electrogram configuration (broad negative waveform, low amplitude, absence of R wave), and (4) a compensatory long AFCL after the captured response or acceleration of AF (Figure 2). Capture was verified by activation maps. With mapping used as the gold standard, the sensitivity, specificity, and positive and negative predictive values of the electrogram criteria were high (91%±6%, 96%±2%, 94%±3%, and 94%±5%, respectively).

Conduction velocity was measured during stable entrainment of AF of the free right or left atrial wall (stimulus strength 4 times threshold) with an interval equal to the median AFCL. The activation maps during entrainment were triangulated, and in each triangle, the local conduction velocity was calculated from the local vector (Figure 3). The average median conduction velocity of 5 consecutive entrained beats was taken as the CV AF. The window of entrainment was determined by gradually shortening or lengthening the pacing interval in steps of 1 to 2 ms until entrainment was lost. The difference between the longest and shortest intervals by which entrainment could be maintained was defined as the window of stable entrainment. The window of unstable entrainment (defined as capture by 5 consecutive stimuli) was determined in a similar fashion.

During control, the AFCL, RP AF, and CV AF were measured ≥6 times. Then drug infusion was started, and AFCL, RP AF, and CV AF were measured every 5 to 10 minutes. Cibenzoline and flecainide were infused at a speed of 0.1 mg · kg⁻¹ · min⁻¹; hydroquinidine and d-sotalol at 0.2 mg · kg⁻¹ · min⁻¹. Infusion was terminated when sinus rhythm was restored or adverse drug effects occurred (QRS prolongation of >70% or ventricular proarrhythmia). The different drugs were applied in an arbitrary but nonrandom order. Sufficient time was allowed between experiments for complete washout of the drugs. Conversion to atrial flutter was not observed in the present series, and in all cases, during pharmacological cardioversion, atrial cycle length, atrial electrogram morphology, and ventricular rate remained irregular. Data are given as mean±SD. For statistical analysis, a paired Student’s t test was used. A value of P<0.05 was considered statistically significant.

**Results**

**Cibenzoline**

In Figure 4, an example is given of the measurement of the RP AF during infusion of cibenzoline. Cibenzoline caused a clear dose-dependent prolongation of the median AFCL from 98 to 169 ms. During control, a stimulus with a coupling...
interval of 76 ms captured the atrium. Cibenzoline clearly prolonged the \( \text{RP}_{\text{AF}} \), the shortest coupling interval now capturing the atrium being 100 ms. The captured response showed a negative low-amplitude waveform, whereas the AFCL during capture was shorter than expected and was followed by a long AFCL. In Figure 5, the electrophysiological effects of cibenzoline during pharmacological cardioversion are plotted. AF was cardioverted after 43 minutes of infusion, when the median AFCL had been prolonged from 96 to 198 ms. Because the \( \text{RP}_{\text{AF}} \) was prolonged only from 74 to 115 ms, the temporal excitable gap (excitable period, \( \text{EP}_{\text{AF}} \)) widened from 22 to 83 ms. As expected, \( \text{CV}_{\text{AF}} \) progressively decreased from 63 to 39 cm/s. Because the prolongation of \( \text{RP}_{\text{AF}} \) was counterbalanced by a slowing in \( \text{CV}_{\text{AF}} \), the \( \text{WL}_{\text{AF}} \) did not change significantly (4.6 versus 4.4 cm). However, because the AFCL prolonged more than the \( \text{CV}_{\text{AF}} \) decreased, the estimated pathlength of the fibrillation waves increased from 6.1 to 7.6 cm. Thus, the spatial excitable gap (\( \text{PL}_{\text{AF}} = \text{WL}_{\text{AF}} \)) also prolonged from 1.5 to 3.2 cm. In Table 1, the effects of cibenzoline are given for all goats. At the highest concentration, cibenzoline increased AFCL by 79%, \( \text{RP}_{\text{AF}} \) by 37%, and \( \text{EP}_{\text{AF}} \) by 191% (all \( P < 0.01 \)). The windows of stable and unstable entrainment widened from 12±4 to 37±6 ms and from 31±5 to 63±4 ms, respectively (both \( P < 0.001 \)). \( \text{CV}_{\text{AF}} \) decreased by 42% (\( P < 0.01 \)). Although the
changes in PL_{AF} and WL_{AF} were not statistically significant, the EG_{AF} increased by 70% (P<0.05).

**Hydroquinidine**

In Figure 6, the effects of hydroquinidine are given. Before drug infusion, the median AFCL was 99 ms and RP_{AF}, 72 ms. Hydroquinidine progressively increased AFCL until AF cardioverted at a cycle length of 148 ms. Because the RP_{AF} remained as short as 87 ms, the EP_{AF} increased from 27 to 61 ms. CV_{AF} decreased only slightly, from 87 to 76 cm/s. Therefore, the PL_{AF} increased from 8.7 to 11.2 cm, whereas the WL_{AF} of 6.2 cm was not affected. In all 5 goats (Table 1), the prolongation of AFCL from 96±17 to 148±11 ms (57%; P<0.001) was associated with an increase in RP_{AF} from 67±15 to only 79±15 ms (16%; P<0.05). The EP_{AF} thus widened from 29±10 to 69±16 ms (157%; P<0.01). The window of entrainment increased from 12±11 to 34±15 ms (stable capture; P<0.001) and from 32±7 to 70±12 ms (unstable capture; P<0.001). The wavelength was not changed (4.8±1.8 versus 4.9±1.7 cm).

**Flecainide**

In Figure 7 and Table 1, the effects of flecainide on AF are given. Flecainide prolonged AFCL by 48%, whereas RP_{AF} did not change significantly. Thus, the excitable period increased from 23±5 to 63±9 ms (189%; P<0.01). The windows of stable and unstable entrainment increased from 9±5 to 30±13 ms and from 27±8 to 55±13 ms, respectively (P<0.05). Because RP_{AF} did not change and CV_{AF} was depressed by 44%, flecainide shortened the atrial wavelength during AF by 41% (P<0.05).

**d-Sotalol**

In Figure 8 and Table 1, the effects of d-sotalol are given. Compared with the class I drugs, d-sotalol prolonged AFCL less markedly (24%; P<0.001). As expected, CV_{AF} was not affected by d-sotalol. In addition, RP_{AF} was not prolonged (71±18 versus 70±20 ms), and WL_{AF} was unaltered (4.5±1.9 versus 4.8±1.9 cm; P=0.17). The EP_{AF} prolonged from 23±3 to 47±11 ms (102%; P<0.01), and the stable and unstable windows of entrainment widened from 7±10 to

<table>
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<th>TABLE 1. Effects of 4 Drugs for All Goats</th>
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<td><strong>Cibenzoline max</strong></td>
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<td><strong>Hydroquinidine control</strong></td>
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<td><strong>Hydroquinidine25%</strong></td>
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<td><strong>Flecainide max</strong></td>
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<td><strong>d-Sotalol control</strong></td>
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<tr>
<td><strong>d-Sotalol20%</strong></td>
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<td><strong>d-Sotalol max</strong></td>
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Numbers represent mean±SD. Values were obtained during control, at AFCL prolongation of 20% or 25%, and at maximal AFCL prolongation.

\*P<0.05; †P<0.01; ‡P<0.001.
20±14 ms ($P<0.05$) and from 27±9 to 54±6 ms, respectively ($P<0.01$). The estimated $PL_{AF}$ prolonged from 5.9±2.3 to 7.9±2.5 cm (39%; $P<0.01$), whereas the $EG_{AF}$ widened from 1.4±0.5 to 3.1±0.9 cm (126%; $P<0.01$).

Electrophysiological Determinants of Pharmacological Cardioversion

The electrophysiological effects of cibenzoline, hydroquinidine, flecainide, and $d$-sotalol just before cardioversion are listed in Table 2. Both hydroquinidine and $d$-sotalol successfully restored sinus rhythm in all 5 goats. Cibenzoline and flecainide were less effective and restored sinus rhythm in 80% and 40%, respectively. Of the different class I drugs, cibenzoline increased $AFCL$ more (69%) than hydroquinidine (37%) and flecainide (30%), whereas the class III drug $d$-sotalol increased $AFCL$ by only 21%. In all cases, the prolongation in $AFCL$ outweighed the increase in $RPAF$. As a result, the excitable period before cardioversion was markedly prolonged by all drugs. Class IC drugs (cibenzoline and flecainide) depressed $CV_{AF}$ most. In contrast, cardioversion of $AF$ by $d$-sotalol occurred without any significant slowing of conduction. The $WL_{AF}$ was not altered by hydroquinidine and $d$-sotalol. Restoration of sinus rhythm by cibenzoline and flecainide was associated with a shortening of $WL_{AF}$ of 18% and 36%, respectively. The $PL_{AF}$ was either shortened or lengthened during the last minutes before cardioversion of $AF$. Because of its marked depression of $CV_{AF}$, flecainide shortened the average pathlength of the fibrillation waves by 22%, whereas cardioversion by hydroquinidine and $d$-sotalol was associated with an increase in path length of 30%. Cibenzoline had no effect on $PL_{AF}$. The spatial excitable gap before cardioversion was prolonged by 3 of the 4 drugs (67% to 102%). In contrast, cardioversion of $AF$ by flecainide was not associated with widening of the $EG_{AF}$.
Widening of the Temporal Excitable Gap During AF
Measurement of the RP\textsubscript{AF} by single premature stimuli revealed that all 4 drugs widened the EP\textsubscript{AF}. Figure 9 shows that this is not an artifact and may have functional implications. The unipolar atrial electrogram during AF was recorded after 40 minutes of hydroquinidine infusion. As a result, the AFCL was prolonged from 70 to 135 ms. Despite this slowing in fibrillation rate, the characteristics of AF were still preserved, and variations in electrogram morphology and cycle length were associated with a totally irregular ventricular rhythm. In the middle of the tracing, a single early stimulus of 48 ms was delivered, which resulted in a sudden marked acceleration of AF. The interval plot below the tracing shows that the AFCL shortened from 135 to <70 ms. Acceleration of AF was also observed during administration of the other drugs, confirming that the drug-induced slowing of AF was associated with a widening of the functional excitability period.

In Figure 10, the effects of all drugs are compared qualitatively. The prolongation of AFCL was most pronounced for cibenzoline and hydroquinidine, less for flecainide, and relatively small for d-sotalol. In either case could the prolongation in AFCL be satisfactorily explained by an increase in the RP\textsubscript{AF}. In some experiments, prolongation of AFCL and cardioversion of AF were even associated with a shortening of the refractory period. As a result, all drugs widened the EP\textsubscript{AF}. Cibenzoline and flecainide (class IC) slowed CV\textsubscript{AF} markedly, whereas hydroquinidine depressed conduction only slightly. The slight increase in CV\textsubscript{AF} by d-sotalol can be explained by a slowing in atrial rate and the associated improved recovery of excitability.

Discussion
Antifibrillatory Drugs Do Not Prolong the Wavelength During AF
In chronically instrumented dogs, it was found that the atrial wavelength played a crucial role for the induction of atrial arrhythmias.\textsuperscript{7} Kirchhof et al\textsuperscript{5} explained the antifibrillatory action of ORG7797 by a wavelength prolongation at high pacing rates. In a canine model of vagally mediated AF, Wang et al\textsuperscript{9,10} found that the degree of AFCL prolongation by various drugs was similar to the increase in atrial refractory period during rapid pacing. Because mapping of AF showed a reduction in the number of wavelets, they concluded that the antifibrillatory action was based on prolongation of the atrial wavelength.\textsuperscript{9,10} Our data are in clear contrast to these results. In a previous study, we reported that after pharmacological cardioversion, the atrial wavelength was short (7 to 9 cm) and AF was readily induced by a single premature stimulus.\textsuperscript{12}

Measurements of the refractory period during AF now directly demonstrated that cardioversion by class I and III drugs cannot be attributed to prolongation of the wavelength. Although theoretically, prolongation of the atrial wavelength can certainly lead to termination of AF, actually the antifibrillatory action was based on another mechanism. Because it is unknown whether the present findings are species-dependent or due to electrical remodeling, it would be worthwhile to measure the excitable gap during pharmacological cardioversion of human AF.

Antifibrillatory Drugs Prolong the Excitable Period During AF
During AF, functional and anatomic reentry occurs,\textsuperscript{2–4} leaving a short temporal excitable gap between the fibrillation waves.\textsuperscript{13} Below, we propose a number of mechanisms by which the EP may be prolonged by class I drugs. In an anatomic circuit, the EP is the difference between the conduction time around the anatomic obstacle and the refractory period. Drugs that slow conduction thus widen the EP by prolonging the revolution time. During functional reentry, the impulse is circulating around a line of functional conduction block, often making a sharp U-turn at the pivot points.\textsuperscript{14} At these sites, because of the high wavefront curvature, a current-to-load mismatch exists that leads to conduction delay at the pivot point. In a canine model of atrial flutter, Ortiz et al\textsuperscript{15} showed that moricizine increased the flutter cycle length by 23% to 44%, whereas the refractory period was only slightly prolonged (<7%). Termination of flutter was not due to wavelength prolongation but rather to preferential conduction slowing at the pivot point.\textsuperscript{15} The observed widening of the excitable period during AF by class I drugs thus may be due to aggravation of the wavefront-curvature effect of the turning fibrillation waves. During AF, random reentry\textsuperscript{16} also occurs when a wavelet reenters an area previously activated by another wavelet. In this case, the excitable period is determined by the time the cells have to wait until they are excited by another wavelet. Drugs that decrease the number of wavelets will widen the EP\textsubscript{AF} because with a lower number of wavelets available, the average waiting time for reexcitation will become longer. If the size of functional circuits increases, anatomic obstacles may become incorporated in the circuit. Such a shift from functional to anatomic reentrant pathways may be an additional reason for widening of the EP\textsubscript{AF} by antifibrillatory drugs.
Is Widening of the Excitable Gap Antifibrillatory? Although cibenzoline, hydroquinidine, flecainide, and \(d\)-sotalol all were effective in cardioverting chronic AF, they exerted different effects on \(R_{PAF}\), \(CV_{AF}\), \(PL_{AF}\), and \(WL_{AF}\). The only action these 4 drugs had in common was a widening of the temporal excitability gap during AF. Although of course this does not prove anything, it raises the question of whether the antifibrillatory drug action is caused by a widening of the excitability gap. According to Moe’s multiple-wavelet hypothesis, the stability of AF is determined by the average number of wavelets. Mapping studies have indicated that during AF, the stability of AF is determined by the average number of wavelets. The exact mechanism of wavelet formation must be high. The exact mechanism of wavelet generation during AF is still poorly understood. Foci of abnormal automaticity, multiple offsprings of a mother wave or a rotor, and bifurcation of wandering wavelets may all be the source of new fibrillation waves. The widening of the \(EP_{AF}\) by drugs will lower the chance that fibrillation waves encounter areas of partially refractory tissue. As a result, slowing of conduction and fragmentation of wavelets will occur less frequently. Because widening of the excitatory gap will also promote fusion of fibrillation waves, the balance between generation and extinction is expected to change toward a lower number of fibrillation waves.

In summary, we propose the following hypothesis for termination of AF by class I drugs: (1) The lowering of the availability of rapid sodium channels causes preferential depression of conduction of wavelets with a high curvature. Because the life span of fibrillation waves is rather short, the rate of generation of wavelets varies considerably as a result of the balance between fusion and fragmentation of wavelets. (2) This results in preferential conduction delay at the pivot points of turning wavelets. (3) The delay at the pivot points causes an increase in the average AF cycle length and a widening of the temporal excitatory gap. (4) Because of a better recovery of excitability, the balance between fusion and fragmentation of wavelets will change in favor of fusion. (5) The resulting reduction in the average number of fibrillation waves increases the statistical chance of termination of AF.

### Limitations

An important limitation of the present study is that apart from the presence of electrical remodeling, the atria were normal. Although clinically, electrical atrial remodeling may also play a role, in humans the arrhythmia is often associated with atrial abnormalities due to dilatation, ischemia, or old age. The number of animals used in this study was rather small. However, because the drug effects were quite large and consistent, most of the observed changes were statistically significant. We cannot exclude the possibility that other parameters will also show significant changes if studied in a larger series of animals. The mechanisms underlying the observed widening of the excitatory gap during AF were not directly evaluated. Therefore, although we consider preferential slowing at pivot points an attractive explanation, other mechanisms, such as slowing of conduction in anatomic circuits, prolongation of the “waiting time” of random reentry, and even depression of automatic foci, cannot be excluded. The antifibrillatory mechanism of \(d\)-sotalol remains obscure, because during AF in remodeled atria, \(d\)-sotalol exerted no class III effect. Whether the observed increase in excitability gap was due to blockade of sodium channels by high concentrations of \(d\)-sotalol remains unknown. Finally, drug effects on \(CV_{AF}\) were studied during entrainment of AF. Although this method has the advantage that beat-to-beat changes in direction and fragmentation of the fibrillation waves do not occur, it may underestimate the actual effects of class I drugs on conduction during AF when the safety factor of the fibrillation waves is lowered by fragmentation.

### Table 2. Effects of 4 Drugs Just Before Cardioversion

<table>
<thead>
<tr>
<th>Drug</th>
<th>AFCL, ms</th>
<th>(R_{PAF}), ms</th>
<th>(EP_{AF}), ms</th>
<th>(CV_{AF}), cm/s</th>
<th>(PL_{AF}), cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cibenzoline</td>
<td>80</td>
<td>98 ± 2</td>
<td>165 ± 8</td>
<td>72 ± 7</td>
<td>97 ± 17</td>
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<tr>
<td>Hydroquinidine</td>
<td>100</td>
<td>96 ± 16</td>
<td>130 ± 17</td>
<td>67 ± 15</td>
<td>74 ± 19</td>
</tr>
<tr>
<td>Flecainide</td>
<td>40</td>
<td>96 ± 8</td>
<td>125 ± 2</td>
<td>68 ± 10</td>
<td>71 ± 17</td>
</tr>
<tr>
<td>(d)-Sotalol</td>
<td>100</td>
<td>94 ± 17</td>
<td>114 ± 20</td>
<td>71 ± 18</td>
<td>70 ± 20</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>80</td>
<td>96 ± 1</td>
<td>134 ± 19</td>
<td>70 ± 2</td>
<td>78 ± 11</td>
</tr>
</tbody>
</table>

CAF indicates chronic AF. Numbers represent mean ± SD of the mean and the mean percentage change in the given parameters.

\*\(P<0.05\); †\(P<0.01\); NS, not significant, control vs values before sinus rhythm.
This study was supported by the Netherlands Organization for Scientific Research.

References

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_Circulation_. 2000;102:260-267  
doi: 10.1161/01.CIR.102.2.260

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Copyright © 2000 American Heart Association, Inc. All rights reserved.  
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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