Consequences of atrial electrical remodeling for the anti-arrhythmic action of class IC and class III drugs

M. Duytschaever¹, Y. Blaauw¹, M. Allessie*

Department of Physiology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, Netherlands

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Abstract

Objective: Atrial fibrillation (AF) induces electrical and ionic remodeling of the atria. We investigated whether AF-induced remodeling alters the electrophysiological and anti-fibrillatory effects of class I (flecainide) and class III (d-sotalol, ibutilide) anti-arrhythmic drugs.

Methods: In 9 goats, the effects of flecainide (6 mg/kg) and d-sotalol (6 mg/kg) on atrial electrophysiology were measured both before and after 48 h of electrically induced AF. During a 1-h infusion period the atrial effective refractory period (AERP) and conduction velocity (CV) were measured both during slow and rapid pacing (interval 400 and 200 ms). In 8 other goats, the rate-dependent effects of ibutilide (0.12 mg/kg) on AERP were determined.

Results: The effects of flecainide on atrial conduction and refractoriness were not altered after 48 h of AF. At a dose of 6 mg/kg flecainide reduced the CV200 by 19 ± 5% in normal atria and by 21 ± 9% after 48 h of AF (p = 0.20). The AERP200 was prolonged by 10 ± 6% and 8 ± 7%, respectively (p = 0.40). In contrast, the effect of d-sotalol on atrial refractoriness was markedly diminished. During control d-sotalol prolonged the AERP400 by 17 ± 6% compared to only 6 ± 5% after 2 days of AF (p < 0.01). Also ibutilide lost much of its class III effect on the AERP by electrical remodeling (from 15 to 5%; p < 0.05). The loss of class III action was less pronounced at rapid heart rates.

Conclusions: AF-induced atrial electrical remodeling in the goat did not modulate the action of flecainide on atrial conduction and refractoriness. In contrast, the class III effects of d-sotalol and ibutilide on the atria were strongly reduced after 2 days of AF. The prolongation of QT-duration was not affected.

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Keywords: Antiarrhythmia agents; Atrium; Electrophysiology; Fibrillation; Remodeling

1. Introduction

Experimental and clinical studies have established that atrial fibrillation (AF) induces a shortening of atrial refractoriness (electrical remodeling) [1,2]. This AF-induced shortening of the atrial action potential has been shown to be due to downregulation of a number of ionic currents (ionic remodeling). The L-type Ca²⁺ (I_{Ca,L}), the transient outward current (I_{to}) and the ultrarapid delayed rectifier current (I_{Kur}) become reduced after prolonged rapid atrial pacing or AF [3–5]. Whereas Lai et al. showed a reduced expression of HERG in humans with longstanding AF, [6] others found no changes in HERG or I_{Kr}-current density [3,7].

It remains unclear whether AF also induces depression of intra-atrial conduction and/or downregulation of I_{Na} current. In a canine model, rapid atrial pacing was associated with a slowing of intra-atrial conduction and reduction of the rapid Na⁺-current (I_{Na}) [8]. In contrast, in patients with chronic AF, densities and biophysical properties of I_{Na} were found to be unaltered [9]. Similarly, in the goat conduction velocity remained unaltered, suggesting no major changes in sodium current [2].

If the relative contribution of different ionic currents to the atrial action potential changes by electrical remodeling, also the sensitivity for certain specific ion-channel blockers may be altered. This may explain why some antiarrhyth-
mic agents lose their efficacy to cardiovert AF with time [10–12].

In the present study we evaluated the changes in electrophysiological effects of class IC and class III drugs in the goat model of ‘lone’ AF. The effects of intravenous infusion of flecainide, D-sotalol and ibutilide on atrial refractoriness and conduction were measured both before and after 48 h of atrial fibrillation.

2. Methods

2.1. The goat model of atrial fibrillation

Seventeen goats (46 ± 14 kg) were used for this study. The experiments were carried out according to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and approved by the Animal Investigation Committee of the University of Maastricht. Anesthesia was induced by administration of Nesdonal (15 mg/kg) and maintained by ventilation with halothane (1–2%) and a mixture of O₂ and N₂O. A thoracotomy was made to expose the heart and a teflon-felt plaque containing 30 electrodes (3 × 2.5 cm, inter-electrode distance 4 mm) was sutured on the free wall of each atrium. A 10-cm long plaque with three rows of electrodes (54 electrodes; inter-electrode distance 5 mm) was implanted on Bachmann’s bundle (BB) from the tip of the right to the tip of the left atrial appendage. A small plaque with 3 electrodes was sutured on the left ventricle. Three silver plates were left under the skin of the thorax to record a precordial ECG and to serve as indifferent electrode. The leads were tunneled subcutaneously to the neck and exteriorized by four 30-pole connectors. Postoperatively the animals received buprenorfine for 2–4 days. Experiments were performed during 30-min of saline infusion. During this baseline period the refractory period of the right (n = 6 goats) or left atrium (n = 3 goats) and the conduction velocity along Bachmann’s bundle were measured every 10 min during regular pacing with an interval of 400 and 200 ms. Then flecainide or D-sotalol were administered at a constant infusion rate of 0.1 mg/kg/min and the electrophysiological measurements were repeated every 10 min. After 1 h of drug infusion the inducibility of AF was re-evaluated by applying single early premature stimuli at the RA (n = 6) or LA (n = 3). The electrophysiological action of ibutilide was studied in a separate series of 8 goats. Ibutilide was infused at a rate of 0.002 mg/kg/min for 1 h. To evaluate both the rate- and site-dependent action of ibutilide, the refractory period was measured at pacing intervals of 400, 350, 300, 250, 225 and 200 ms both at the RA and LA.

The chosen drug dosages were based on previous experiments in the goat [14]. At the dosages used the drugs were well tolerated and the electrophysiological effects were comparable to the effects of clinically used dosages. Clinically, flecainide (2 mg/kg) prolongs the QRS duration by 18% [15] whereas D-sotalol (1.5 mg/kg) and ibutilide (2 mg/30 min) prolong the QT-time by respectively 15% and 22% [16,17]. In our experiments flecainide widened the QRS complex by 15–18% and D-sotalol and ibutilide prolonged the QT-time by respectively 19–23% and 9–11%. Thus, although in the goat the dosages were higher than used clinically, the biological effects of flecainide, D-sotalol and ibutilide were comparable.
2.4. Statistical analysis

For the flecainide and D-sotalol experiments data of the right \((n=6)\) and left atria \((n=3)\) were pooled. The effects of ibutilide on RA and LA are given separately. Data are given as mean ± SD. Differences between groups were determined by the paired Student’s t-test. Serial measurements were analyzed by ANOVA with repeated measures. A p-value of <0.05 was considered as statistically significant.

3. Results

3.1. Flecainide

The effects of flecainide on atrial conduction before and after 48 h of AF are shown in Fig. 1. In the example in the left panel, flecainide lowered the conduction velocity along Bachmann’s bundle during rapid pacing (interval 200 ms) from 121 to 95 cm/s in non-remodeled atria (−21%) and from 133 to 105 cm/s in remodeled atria (−21%). In the right panel the effects of flecainide on atrial conduction (S1–S1: 200 ms) are plotted for all goats \((n=9)\). Before and after electrical remodeling conduction velocity along Bachmann’s bundle was similar \((124\pm12\text{ versus }125\pm14\text{ cm/s}; p=0.79)\). At a dosage of 6 mg/kg, flecainide depressed atrial conduction in normal atria by 21 ± 9% \((p=0.20)\). Also at lower pacing rates the effect of flecainide on atrial conduction and refractoriness was not affected by electrical remodeling (Table 1). During rapid pacing flecainide increased the AERP by 8–10% \((p=0.4)\) and during slow pacing by 4–7% \((p=0.53)\). Also the prolongation of the QRS complex by flecainide was not affected by 2 days of AF \((15\text{ vs. }18%; p=0.72)\) (Table 1).

3.2. D-Sotalol

The class III effects of D-sotalol before and after electrical remodeling are shown in Fig. 2. In non-remodeled atria D-sotalol \((6\text{ mg/kg})\) clearly prolonged the atrial refractory period. In the given example the AERP\(_{400}\) at the RA prolonged from 156 to 186 ms (+30 ms). As expected, after 48 h of AF atrial refractoriness was abbreviated and the AERP\(_{400}\) had shortened to 74 ms. Single premature stimuli now induced paroxysms of AF. Administration of the same dosage of D-sotalol \((6\text{ mg/kg})\) prolonged the AERP\(_{400}\) of the RA by only 4 ms (from 74 to 78 ms) and induction of AF was not prevented. In the right part of Fig. 2, the effects of D-sotalol on the AERP\(_{400}\) are plotted for all 9 goats. At a dosage of 6 mg/kg, D-sotalol prolonged the AERP\(_{400}\) in normal atria by 17 ± 6% and by 6 ± 5% after 2 days of AF \((p<0.01)\). As shown in Table 1, this loss of class III effect was less at higher pacing rates. During pacing at a cycle length of 200 ms D-sotalol still prolonged the refractory period in remodeled atria by 13 ± 5% compared to 17 ± 5% during control \((p=0.10)\).

![Fig. 1. Effects of flecainide on conduction velocity along Bachmann’s bundle during rapid atrial pacing from the left atrial free wall (S1–S1: 200 ms). Left: Electrograms recorded along Bachmann’s bundle. Both before (normal atria) and after 48 h of remodeling, flecainide (6 mg/kg) significantly depressed atrial conduction velocity. Right: Equal effects of flecainide on atrial conduction during a 1 h infusion (0.1 mg/kg/min) in 9 goats before (open circles) and after remodeling (closed circles). LAA=left atrial appendage, BBleft =left part of Bachmann’s bundle, BBmid =middle part of Bachmann’s bundle, BBright =right part of Bachmann’s bundle, RAA=right atrial appendage. NS=non-significant.](image-url)
3.3. Ibutilide

In a separate series of 8 goats the site-dependent class III effect of ibutilide was studied before and after 2 days of AF. Whereas in normal atria ibutilide (0.12 mg/kg) prolonged the AERP400 of the right and left atrium respectively from 161 ± 17 and 156 ± 17 ms to 186 ± 25 (15 ± 8%) and 180 ± 24 ms (16 ± 9%), in remodeled atria the class III effect was reduced to 4 ± 7 and 6 ± 8% (p<0.05). In Fig. 3 and Table 1, the average effects on the right and left atrial refractoriness period are given. The rate-dependence was evaluated by measuring the effects on atrial refractoriness at different cycle lengths between 400 and 200 ms. In non-remodeled atria a normal physiological rate adaptation was present and the AERP shortened from 158 ± 16 to 145 ± 15 ms. Ibutilide (0.12 mg/kg) prolonged the atrial refractory period less at faster than at slower pacing rates (24 ± 12 vs. 16 ± 5 ms at 400 and 200 ms interval), resulting in a slight increase in the slope of the normal rate-adaptation curve. In electrically remodeled atria the physiological rate adaptation was lost and became slightly inverted (right part Fig. 3). Note that at low pacing rates the AERP was now shorter (93 ± 17 ms) than during rapid pacing (114 ± 15 ms). In remodeled atria the class III effect of ibutilide was reduced at all pacing rates. However, since this loss was more marked at slower rates, 2 days of AF converted the normal reverse rate-dependence of ibutilide into a moderate rate-dependent action. At a cycle length of 400 ms the AERP was prolonged by 4 ± 6 ms compared to 12 ± 9 ms during pacing with a cycle length of 200 ms (p<0.05).

### Fig. 2. Effects of d-sotalol on atrial refractoriness in normal and remodeled atria (S1–S2; 400 ms). Left: In normal atria d-sotalol (6 mg/kg) prolonged the AERP from 156 to 186 (+30 ms), whereas after 48 h of AF the AERP lengthened only by 4 ms (from 74 to 78 ms). Induction of AF was not prevented by the high dosage of d-sotalol. Right: The average effects of d-sotalol on the AERP400 in normal and remodeled atria (n=9). *p<0.01; Δ% normal versus remodeled.

### Table 1

Effects of flecainide (6 mg/kg), d-sotalol (6 mg/kg) and ibutilide (0.12 mg/kg) in normal and remodeled Atria

<table>
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<tr>
<th></th>
<th>QRSD or AERP400</th>
<th>AERP200</th>
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<th>CV200</th>
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<td>QT (ms)</td>
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<td>144 ± 9</td>
<td>138 ± 6</td>
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<tr>
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<tr>
<td>Δ%</td>
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<td>+4 ± 9%</td>
<td>+10 ± 6%</td>
<td>−10 ± 8%</td>
</tr>
<tr>
<td>Remodeled</td>
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<td>83 ± 16</td>
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<td>+8 ± 7%</td>
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<tr>
<td><strong>D-Sotalol</strong></td>
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<td></td>
</tr>
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<td>229 ± 18</td>
<td>146 ± 13</td>
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<tr>
<td>D-Sotalol</td>
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<td>171 ± 19</td>
<td>165 ± 8</td>
<td>125 ± 16</td>
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<tr>
<td>Δ%</td>
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<td>+17 ± 6%</td>
<td>+17 ± 5%</td>
<td>−2 ± 4%</td>
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<tr>
<td>Remodeled</td>
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<td>81 ± 14</td>
<td>87 ± 17</td>
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<tr>
<td>Δ%</td>
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<td>+6 ± 5%**</td>
<td>+13 ± 5%</td>
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<tr>
<td><strong>Ibutilide</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
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<td>158 ± 16</td>
<td>145 ± 15</td>
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<tr>
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<td>+15 ± 7%</td>
<td>+12 ± 4%</td>
<td>−1 ± 3%</td>
</tr>
<tr>
<td>Remodeled</td>
<td>213 ± 17</td>
<td>93 ± 17</td>
<td>114 ± 15</td>
<td>127 ± 17</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>233 ± 26</td>
<td>98 ± 19</td>
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<tr>
<td>Δ%</td>
<td>+9 ± 6%</td>
<td>+5 ± 7%*</td>
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<td>+0 ± 4%</td>
</tr>
</tbody>
</table>

Δ% normal versus remodeled, QRSD: duration of the QRS-complex.

* p<0.05.

** p<0.01.

The prolongation of the QT time by D-sotalol was the same before and after 48 h of atrial fibrillation (23% vs. 19%; p=0.20).
3.4. Effects of flecainide, d-sotalol and ibutilide on inducibility and duration of AF

In Fig. 4 the effects of flecainide, d-sotalol, and ibutilide on the inducibility of AF are given. After 48 h of atrial electrical remodeling, flecainide, d-sotalol and ibutilide prolonged the AERP by only 5–7%. Compared to normal atria, the class III effect of d-sotalol and ibutilide was significantly decreased (Table 1). In non-remodeled atria premature stimuli induced atrial fibrillation in 33% of the animals. Due to the shortening of atrial refractoriness, in remodeled atria single premature stimuli induced AF in 100% of the cases. Even at high dosages none of the drugs could prevent the induction of AF (still 100%). Admin-
istration of flecainide, D-sotalol, or ibutilide also did not shorten the median duration of AF paroxysms. With and without drugs, paroxysms of AF lasted, respectively, 4 (range 1–44) and 7 s (2–52) (flecainide), 4 (1–59) and 3 s (1–62) (D-sotalol) and 4 (2–500) and 3 s (1–8) (ibutilide); all p = ns).

4. Discussion

4.1. Main findings

In the present study we evaluated the effects of 2 days of AF-induced electrical remodeling on the electrophysiological action of one class IC (flecainide) and two class III agents (D-sotalol and ibutilide). The effect of flecainide on atrial conduction and refractoriness was not changed by electrical remodeling. In contrast, the class III effect of D-sotalol and ibutilide were strongly reduced. All three drugs failed to prevent induction of atrial fibrillation in electrically remodeled atria by single premature beats.

Importantly, the effects on the QRS-complex and QT-duration were similar before and after atrial remodeling, suggesting that the biological availability of the drugs were not different. The effective dosages in our experiments were comparable to the clinically used dosages since the prolongation of the QRS-complex and QT-interval was similar to the changes observed clinically [15–17].

4.2. Consequences of electrical remodeling for the action of class IC drugs

Class IC anti-arrhythmic agents are often used for termination of atrial fibrillation. However, various clinical studies have shown that the anti-fibrillatory efficacy of class IC drugs declines when AF persists for a longer period of time [10,11]. Crijns et al. showed that flecainide cardioverted AF in 74% of patients if given less than 24 h after the start of the arrhythmia. In contrast, when AF had persisted for longer than 24 h, flecainide did not terminate AF in any of the patients [11].

The failure of flecainide to cardiovert AF of >24 h can be explained either because electrical remodeling makes the fibrillatory process more resistant to class I drugs [18], or because it diminishes the class I action of the drug itself. The latter possibility could be excluded in the present study by showing that 48 h of AF did not alter the electrophysiological action of flecainide on atrial conduction and refractoriness. This supports the concept that failure of class IC drugs to cardiovert AF must be due to a higher resistance of AF, rather than to a lower sensitivity of remodelled atrial myocardium to sodium channel blockers.

Our finding that the effect of flecainide on atrial conduction was unaltered in remodeled atria is in agreement with other studies. Sato et al. showed that slowing of conduction by the class IC agent pilscainide was not affected by 14 days of rapid atrial pacing in the dog [19]. Wijffels et al. observed that flecainide still markedly depressed atrial conduction in goats after more than 4 weeks of persistent AF [20]. Like in our previous studies we observed only a moderate but consistent rate dependent prolongation of the AERP by flecainide [14,20]. In the present study we observed that this prolongation was not affected by electrical remodeling. This moderate prolongation is different from studies by Wang et al. who found that propafenone caused a marked and use-dependent prolongation of refractoriness in canine atria [21]. In human atria, Le Grand et al. showed that flecainide only increased the action potential duration and effective refractory period if the transmembrane potentials had a long plateau preceded by a notch [22].

It still remains to be determined whether the preserved electrophysiological effects of flecainide on atrial conduction means that the \( I_{Na} \) current is unaltered in remodelled atria. Whereas conduction velocity and \( I_{Na} \) current density were found to be reduced in remodelled canine atria [8,23], in the goat intra-atrial conduction was not altered after several weeks of AF [2], and also in patients with chronic AF the density of \( I_{Na} \) current was not changed [9].

4.3. Consequences of electrical remodeling for the action of class III drugs

Although class III agents are often used to prevent or terminate atrial fibrillation [24], several observations suggest that they become less effective in the setting of electrical remodeling. Tieleman et al. showed that class III antiarrhythmic drugs could not prevent early recurrences of AF after successful electrical cardioversion [25]. Similarly, in the SAFIRE-D study the probability to maintain sinus rhythm for at least 7 days after electrical cardioversion was not different in patients treated with dofetilide or placebo. Only after a follow up of 1 year of dofetilide turned out to be slightly superior to placebo in preventing AF recurrences [26]. The efficacy of class III drugs to terminate AF clearly declines when AF is present for a longer period of time. Whereas ibutilide terminated AF of recent-onset in approximately 70% of patients, this success rate dropped to 30% in cases of long-lasting AF [10,12].

In the present study we tested the hypothesis that AF-induced electrical remodeling reduces the electrophysiological effects of class III drugs. We found that the prolongation of atrial refractoriness was significantly reduced after 2 days of atrial fibrillation. This loss of class III action was the same in the right and the left atrium. Neither D-sotalol or ibutilide could prevent re-induction of AF by single premature beats in remodelled atria (inducibility 100%). These findings imply that class III drugs cannot be expected to prevent early recurrences of AF in remodelled atria. It has been shown that most relapses occur during the first days after cardioversion of AF when the atrial refractory period is still short [25]. It may take several days before the atria are...
recovered from electrical remodeling and the normal electrophysiological action of $I_{Kr}$-blockers is restored.

Our findings are in agreement with other studies. Li et al. showed that the ability of dofetilide to prolong atrial refractoriness and to cardiovert AF was lower in dogs subjected to prolonged rapid atrial pacing compared to dogs with congestive heart failure and normal AERPs [27]. Also in humans there are indications that the action of class III drugs is affected by electrical remodeling. Tse et al. reported a reduced effect of Dl-sotalol on atrial refractoriness in patients with previous episodes of atrial fibrillation [28]. Opposite results were reported by Shiroshita-Takeshita et al. who observed a preserved effect of the $I_{Kr}$-blocker E4031 and the $I_{Kr}/I_{Ks}$-blocker azimilide in dogs subjected to 14 days of rapid atrial pacing [29]. However, in the latter study the degree of electrical remodeling was quite moderate and the AERP$_{400}$ was only shortened by 27 ms after 14 days of rapid pacing.

The mechanisms responsible for the reduced effect of class III drugs in electrically remodeled atria remain speculative. Both Dl-sotalol and ibutilide prolong the action potential mainly by blocking the rapid component of the delayed rectifier $K^+$-current ($I_{Kr}$-blockade) [30]. Still only limited information is available regarding the effects of AF on $I_{Kr}$. Whereas Lai et al. showed a reduced expression of HERG in humans with longstanding AF [6], others found no changes in HERG or $I_{Kr}$-current density [3,7]. Theoretically a reduced HERG expression (or $I_{Kr}$ current density) would lead to a greater efficacy of $I_{Kr}$-blockade. The reduced availability of $I_{Kr}$-channels reduces the repolarization reserve and will render the atria more vulnerable to blockade of repolarizing currents. The fact that we observed a lower rather than a higher efficacy of $I_{Kr}$-blockers in remodeled atria raises some doubts about the significance of the reported changes in HERG expression. An alternative explanation for the reduced class III effect of $I_{Kr}$ blocking agents might simply be that the contribution of this current to atrial repolarization is reduced. When the action potential is shortened by a reduction of the plateau phase due to down-regulation of the $I_{Ca,L}$, the membrane will be repolarized by earlier activated potassium currents like $I_{Ko}$, $I_{KAcch}$ and $I_{Kur}$. Because $I_{Kr}$ is activated later during the action potential, the actual contribution of this current may diminish. Under these conditions, blockade of $I_{Kr}$-channels obviously will exert less effect. This latter explanation, proposed by the group of Nattel, is based on a mathematical model of the human atrial action potential in which inhibition of the $I_{Kr}$-current produced less prolongation of the action potential when the cells were ‘electrically remodeled’ [31]. These investigators stated that: ‘because $I_{Kr}$ is activated relatively late during the action potential, the inhibition does not disturb the delicate balance of currents during phase 1 repolarization or during the initial phase of the action potential plateau’. These computer simulations were recently supported by experimental evidence from the goat showing that the reduced efficacy of $I_{Kr}$ blockers could be immediately and completely restored by restoration of the plateau phase of the remodeled atrial action potentials [32].

5. Limitations

An important limitation of the present study is that no in-vitro studies were performed. For this reason, the cellular mechanisms underlying the loss of class III effect of $I_{Kr}$-blockers remain speculative. Obviously, additional studies will be required to determine the ionic basis of the changed action of class III drugs in electrically remodeled atria.

Although we did not verify plasma concentrations, the effects of flecainide, Dl-sotalol and ibutilide on QRS-and QT-duration were the same before and after electrical remodeling. It therefore seems highly unlikely that the reduced class III action was the result of a lower effective dosage. All drugs were infused at a single constant rate during 1 h. Steady state dose-dependent effects were not measured. On the other hand, since the effective dosage during a 1 h infusion period gradually increases, we can exclude that our observations are limited to a single or narrow range of dosages.

Extrapolation of experimental results to the human situation should always be done with great caution. Marked differences exist in the distribution of cardiac ionic currents between species. In humans the duration of the action potential is longer than in goats and also the degree of AF-induced electrical remodeling is less [1]. It is therefore quite possible that in humans the reduced class III effect of $I_{Kr}$-blockers is less marked than in goats. In addition, electrophysiological measurements were only performed at the free wall of the right and left atrium. We cannot exclude that in other parts of the atria (especially with longer action potential duration between the right and left atrium of the dog [33], Differences in species and experimental conditions may explain these discrepancies.

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References


