AVE0118, Blocker of the Transient Outward Current ($I_{to}$) and Ultrarapid Delayed Rectifier Current ($I_{Kur}$), Fully Restores Atrial Contractility After Cardioversion of Atrial Fibrillation in the Goat

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Background—The loss of atrial contractile function after cardioversion of atrial fibrillation (AF) contributes to the thromboembolic risk associated with AF. The newly developed blocker of the transient outward current ($I_{to}$) and ultrarapid delayed rectifier current ($I_{Kur}$) AVE0118 prolongs atrial action potential duration and might therefore enhance atrial contractility. We compared the ability of AVE0118 to restore atrial contraction after cardioversion of AF with the efficacy of conventional positive inotropic compounds in the goat model of AF.

Methods and Results—Eighteen goats were chronically instrumented with epicardial electrodes, a pressure transducer in the right atrium, and piezoelectric crystals to measure right atrial diameter. Atrial contractility and refractoriness and QT duration were measured before and after 1 week (3 to 8 days) of AF induced by repetitive burst pacing. The measurements were repeated after administration of digoxin (0.02 mg/kg), dobutamine (5 μg·kg$^{-1}$·min$^{-1}$), the Ca$^{2+}$ sensitizer EMD57033 (1 mg · kg$^{-1}$ · min$^{-1}$), the L-type Ca$^{2+}$ channel agonist BayY5959 (0.1 mg · kg$^{-1}$ · min$^{-1}$), and AVE0118 (0.01 to 0.2 mg · kg$^{-1}$ · min$^{-1}$). The effect of AVE0118 on the configuration of atrial monophasic action potentials was determined for comparison. After 1 week of AF, atrial contractility during sinus rhythm or slow atrial pacing was reduced to $\frac{1}{10}$. Digoxin and dobutamine failed to increase atrial contractility. EMD57033 restored 41% and BayY5959 restored 48% of atrial contractility at baseline. BayY5959 significantly prolonged QT duration by 24.7%. AVE0118 enhanced atrial contraction to 156% of the baseline value. The positive inotropic effect was accompanied by a pronounced prolongation of atrial action potential duration and refractoriness, whereas QT duration remained unchanged.

Conclusions—Conventional positive inotropic drugs showed limited effect on atrial contractility after cardioversion of AF or produced QT prolongation. In contrast, the $I_{to}/I_{Kur}$ blocker AVE0118 fully restored atrial contraction without proarrhythmic effects on the ventricle. (Circulation. 2006;114:1234-1242.)

Key Words: electrophysiology ■ fibrillation ■ inotropic agents ■ ion channels ■ stroke

Morbidity and mortality of patients with atrial fibrillation (AF) are to a large extent attributable to thromboembolic complications of the arrhythmia. AF reduces atrial blood flow velocity,1 produces structural remodeling of the atrial endocardium,2 and causes a prothrombotic or hypercoagulable state of blood platelets.3 Together, these factors are responsible for the high prevalence of left atrial thrombi in patients with AF. Every year, depending on the underlying structural heart disease, between 1% and 8% of all patients with AF experience stroke.4–6 Thus, restoration of sinus rhythm (SR) is still the primary goal in the treatment of AF.

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In the 1960s, it was reported that cardioversion of AF temporarily increases the risk of thromboembolism.7 Initially, it was thought that restoration of organized and vigorous atrial contractions may dislodge fresh thrombi that had been formed during AF,8 but it became clear that these events often are caused by new thrombus formation obviously favored by the low blood flow velocity in the left atrial appendage after cardioversion of AF.9

The development of a therapy for AF-induced atrial contractile dysfunction with positive inotropic drugs has been hampered by the limited efficacy and low safety of these compounds. In some studies, isoprenaline10 and dobutamine11 showed only very limited effect on atrial contraction in patients after cardioversion of AF. In another study, dobutamine and intravenous administration of Ca$^{2+}$ nearly restored atrial contraction, but these drugs, given for days to weeks,
may cause arrhythmias and ventricular cardiomyopathy, obviously limiting their use in the clinical setting of AF.12 Blockade of the transient outward current (Ito) and the ultrarapid delayed rectifier current (Iur) prolongs action potential duration exclusively in the atria13,14 and might thereby enhance atrial contractility without adverse effects on the ventricle.

The goal of the present study was to evaluate the efficacy of the Ito/Iur blocker AVE0118 in restoring atrial contraction after cardioversion of AF and to compare it with the effect of conventional positive inotropic drugs in chronically instrumented awake goats.

## Methods

### Animal Model

In 18 goats (weight, 41 to 69 kg), a left intercostal thoracotomy was performed according to the institutional guidelines and was approved by the local ethics committee.

The study was performed according to the institutional guidelines (model 1675P, Boston Scientific Instruments) and stored on hard disk for offline analysis. To correct for rundown during recording (~30 minutes), the amplitudes of the monophasic action potentials (model 1675P, Boston Scientific Instruments) and stored on hard disk for offline analysis. To correct for rundown during recording (~30-80 minutes), the amplitudes of the monophasic action potentials were normalized.

### Statistical Analysis

Data are expressed as mean±SEM. Differences in means between baseline, after 1 week of AF, and after treatment with an inotropic compound (in case of AVE0118 at different dose levels) were calculated with a repeated-measures 1-way ANOVA. To determine the significance of differences between 2 means (eg, baseline versus 1 week of AF or before and after treatment after 1 week of AF), Tukey posttests were performed. A value of P<0.05 was considered statistically significant.
The positive inotropic effect of digoxin was tested in 5 goats during atrial pacing at 400 ms. Thirty minutes after spontaneous cardioversion, AWI was 1.1±0.4 mm · mm Hg. Digoxin 0.02 mg/kg was infused within 1 hour, and AF was reinduced to prevent reverse remodeling. Three hours after the start of infusion, the RR interval had increased from 368±25 to 524±37 ms. Atrial contractility was again assessed 30 minutes after spontaneous cardioversion. AWI was 1.4±0.5 mm · mm Hg, which was not significantly different from the AWI before digoxin.

In 6 goats, the positive inotropic effect of dobutamine (5 μg · kg⁻¹ · min⁻¹) was studied. In these goats, the spontaneous SR cycle length after cardioversion was 479±21 ms and shortened to 335±18 ms during administration of dobutamine. Because of the positive chronotropic effect of dobutamine, quantification of atrial contractility was performed during atrial pacing at a cycle length of 300 ms. After 1 week of AF, AWI had declined by ∼85% from 20.3±1.9 mm · mm Hg at baseline to 3.1±0.5 mm · mm Hg. AWI measured in the presence of dobutamine was not significantly different from AWI before administration of the drug (4.0±0.7 mm · mm Hg). During administration of dobutamine, right atrial diameter declined by 15.8% from 27.4±2.4 to 23.1±1.9 mm (P<0.05). In 4 goats, we readjusted the right atrial diameter to 28.0±2.2 mm by rapid infusion of 1 L saline within 10 minutes while continuing dobutamine infusion. Under these conditions, AWI was 7.3±1.4 mm · mm Hg, which was 36% of atrial contractility measured at baseline.

The Ca²⁺ sensitizer EMD57033 (1 mg · kg⁻¹ · min⁻¹) partly restored atrial contractility. AWI (400-ms cycle length) increased from 1.2±0.3 to 5.3±1.5 mm · mm Hg (n=6 goats; P<0.05), which is 41% of atrial contractility at baseline. There were no significant changes in right atrial AERP (47±9 ms before versus 48±11 ms after infusion of EMD57033; P=NS) or QT duration (249±5 ms before versus 262±6 ms after infusion of EMD57033; P=NS).

The L-type Ca²⁺ channel agonist BayY5959 (0.1 mg · kg⁻¹ · min⁻¹) restored 48% of the atrial contractility at baseline (0.8±0.2 to 6.8±0.9 mm · mm Hg; n=7 goats; P<0.05). AERP increased from 91±7 to 122±11 ms (P<0.05) and QT duration from 247±5 to 308±7 ms (24.7%; P<0.05).

**TABLE 1. Characteristics of Animals Receiving Positive Inotropic Compound**

<table>
<thead>
<tr>
<th>Goats, n</th>
<th>Weight, kg</th>
<th>Time of AF, d</th>
<th>AWI, mm · mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin 5</td>
<td>44.2±2.8</td>
<td>5.00±0.71</td>
<td>1.06±0.44</td>
</tr>
<tr>
<td>Dobutamine 6</td>
<td>49.6±3.1</td>
<td>4.83±0.40</td>
<td>0.77±0.41</td>
</tr>
<tr>
<td>EMD57033 6</td>
<td>47.5±2.9</td>
<td>5.17±0.60</td>
<td>1.17±0.34</td>
</tr>
<tr>
<td>BayY5959 7</td>
<td>47.9±3.4</td>
<td>5.00±0.72</td>
<td>0.83±0.24</td>
</tr>
<tr>
<td>AVE0118 9</td>
<td>48.7±3.0</td>
<td>5.00±0.41</td>
<td>0.25±0.36</td>
</tr>
</tbody>
</table>

No significant differences were found in weight, number of days the animals were in AF before they received the compound (time of AF), or AWI (measured during atrial pacing at a cycle length of 400 ms) before administration of the compound.
and right atrial ERP was shortened to 95±10 ms. On infusion of AVE0118, there was a pronounced and dose-dependent increase in the amplitude of the right atrial pressure recording (Figure 4). The increase of the pressure recording amplitude was related mainly to an enhancement of the a-wave. Figure 5 (top left) shows the simultaneous recording of right atrial pressure and diameter during atrial pacing at 400 ms. Both the a-wave and shortening of the atria during atrial systole (atrial systolic shortening) were enhanced after infusion of AVE0118. As a result, the PV loop reopened, indicating restoration of active atrial contractility (Figure 5, top right). Figure 5 (bottom left) shows the average AWI measured in 9 goats during infusion of AVE0118. The effect of AVE0118 was dose dependent and occurred within 5 to 10 minutes of infusion. At dose level 4 (0.1 mg · kg⁻¹ · min⁻¹), AWI was not significantly different from contractility at baseline. The highest dosage used (0.2 mg · kg⁻¹ · min⁻¹) increased AWI even to supranormal levels (156%; P<0.05 versus baseline).

The strong effect of AVE0118 on AWI was due to both an increase in pressure amplitude of the a-wave and enhanced shortening of the atria. At the highest dosage, the pressure amplitude in the right atrium increased from 20% to 248% of the amplitude at baseline and the maximal shortening velocity was normalized, with comparable effects of AVE0118 in...
right and left atria (Table 2). The positive inotropic effect of AVE0118 was present at all atrial pacing rates. As previously described, the normal positive rate adaptation of atrial contractility was lost after 1 week of AF.17 During administration of 0.2 mg · kg⁻¹ · min⁻¹ AVE0118, the positive rate adaptation was fully restored (Figure 5, bottom right; n=6 goats).

AVE0118 dose dependently prolonged the AERP in right and left atria (Figure 6 and Table 2). At the highest dosage, AERP tended to be longer than at baseline. In contrast, changes in QT duration were small, not reaching significance at any dosage of AVE0118. Infusion of the vehicle did not enhance atrial contractility (0.6 ± 0.3 versus 0.7 ± 0.2 mm · mm Hg; n=3; P=NS), nor did it change atrial refractoriness (87 ± 12 versus 91 ± 14 ms; n=3; P=NS).

**TABLE 2. Dose-Dependent Effects of AVE0118**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1-wk AF</th>
<th>0.01</th>
<th>0.02</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
</tr>
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<tbody>
<tr>
<td>AWI, mm · mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RA</td>
<td>12.4±1.9</td>
<td>0.7±0.6*</td>
<td>3.6±1.4*</td>
<td>8.2±1.3*</td>
<td>12.5±1.8</td>
<td>15.2±2.1</td>
<td>19.5±1.9*</td>
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<tr>
<td>ΔP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>2.2±0.5</td>
<td>0.2±0.1*</td>
<td>0.4±0.1*</td>
<td>1.5±0.4</td>
<td>2.8±0.6</td>
<td>4.5±0.6</td>
<td>5.2±0.8*</td>
</tr>
<tr>
<td>ΔD/dtmax, mm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>76±8</td>
<td>36±7*</td>
<td>42±5*</td>
<td>52±6*</td>
<td>64±4</td>
<td>62±6</td>
<td>62±5</td>
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<tr>
<td>LA</td>
<td>128±22</td>
<td>43±7*</td>
<td>68±9*</td>
<td>96±4*</td>
<td>83±15</td>
<td>100±19</td>
<td>107±22</td>
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<td>AERP, ms</td>
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<tr>
<td>RA</td>
<td>146±8</td>
<td>95±10*</td>
<td>110±7*</td>
<td>123±10</td>
<td>145±16</td>
<td>165±17</td>
<td>176±17</td>
</tr>
<tr>
<td>LA</td>
<td>150±6</td>
<td>105±5*</td>
<td>126±8</td>
<td>155±11</td>
<td>154±9</td>
<td>167±8</td>
<td>174±7</td>
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<tr>
<td>QT, ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LV</td>
<td>256±5</td>
<td>236±5</td>
<td>235±8</td>
<td>236±8</td>
<td>241±5</td>
<td>246±6</td>
<td>251±7</td>
</tr>
</tbody>
</table>

Dose-dependent effect of AVE0118 on AWI, the pressure amplitude of the a-wave (ΔP), maximal shortening velocity (ΔD/dtmax), and AERP in the right atrium (RA) and left atrium (LA) in 9 goats recorded during right atrial pacing at a cycle length of 400 ms. QT durations (QT) were determined from a left ventricular (LV) electrogram.

*P<0.05 vs baseline.
To compare the changes in atrial contractility during AVE0118 infusion with alterations of the action potential configuration, we recorded right atrial monophasic action potentials during infusion of AVE0118 (4 goats) and left atrial PV loops (3 goats) after cardioversion of AF (0.1 mg · kg$^{-1}$ · min$^{-1}$, right atrial pacing at 400-ms cycle length).

Figure 7 (top) shows PV loops and action potentials recorded in 1 goat. At baseline, the PV loop was closed, indicating loss of atrial contractility. The action potential was triangular and as short as 97 ms (APD$_{90}$). Within minutes after the start of infusion, the PV loop opened, and the action potential became progressively longer. After 5 minutes of infusion, APD$_{90}$ was 149 ms. Restoration of atrial contractility and prolongation of the action potential followed the same time course and reached steady state within 5 to 10 minutes after the start of infusion (Figure 7, bottom). In all 4 goats (bottom right), the relative prolongation of the action potential was more pronounced at 30% than at 90% repolarization. APD$_{30}$ increased by 209% from 111 ± 33 to 34 ± 16 ms, whereas APD$_{90}$ increased by only 56% from 111 ± 33 to 173 ± 28 ms.

**Discussion**

The present study demonstrates that the $I_{r}/I_{Kur}$ blocker AVE0118 fully restores atrial contractility after cardioversion in the goat model of AF. The positive inotropic effect of AVE0118 was stronger than that of conventional inotropic agents and did not result in undesirable proarrhythmic side effects on the ventricle.

**AF-Induced Loss of Atrial Contraction**

In the goat model of AF, atrial contractility is nearly completely abolished after a couple days of AF. The area enclosed by the atrial part of the PV loop and the pressure wave during atrial contraction were reduced to 10% of the baseline value. Both right and left maximal shortening velocity declined to $\approx 40\%$ of control, indicating severe reduction in atrial contractility in both atria comparable to the reduction in transmitial blood flow velocity in patients.$^1$ It is important to note that the loss of atrial contraction in this model is not due to short-term metabolic adaptation, which can be induced by minutes to hours of AF. As previously demonstrated, up to several hours of AF results in a relatively mild and transient contractile dysfunction with fast-onset and -offset kinetics.$^{17}$ In contrast, 1 week of AF results in complete loss of atrial contraction, which takes a couple days to recover, more resembling delayed recovery of atrial contraction after cardioversion of AF in patients. Thus, the mechanisms underlying AF-induced loss of atrial contraction depend strongly on the duration of AF, suggesting also that the efficacy of positive inotropic drugs to restore atrial contraction might change during the course of AF.

**Rationale of Positive Inotropic Treatment of Atrial Contractile Dysfunction**

Development of atrial thrombi in patients with AF is a complex process that involves all 3 aspects of the classic Virchow triad. Numerous studies support the hypothesis that loss of atrial contractile function causing stasis of blood near the atrial wall is one of the important mechanisms of atrial thrombus formation.$^{18–20}$ Recently, it has been found that AF...
produces a hypercoagulable state associated with platelet activation and an increase in thrombogenesis and fibrin turnover. Finally, endocardial fibroelastosis and downregulation of endocardial nitric oxide synthase activity might also favor the development of atrial thrombi in AF patients.

Despite the multifactorial pathogenesis of atrial thrombi in patients with AF, there is strong evidence that low atrial and low atrial appendage blood flow velocities are commonly associated with the development of spontaneous echo contrast, which in turn correlates with the occurrence of thromboembolic events. In conclusion, enhancing blood flow velocity in the atria can be expected to lower the chance of spontaneous echo contrast and thrombus formation.

Recent studies have demonstrated that in general atrial contractility and blood flow velocity can be significantly enhanced by direct positive inotropic stimulation in patients undergoing cardioversion of atrial flutter or AF. At least in some patients, these interventions prevented the development of spontaneous echo contrast. However, the pharmacological compounds used in these studies (dobutamine, isoproterenol, intravenous Ca2+) are of questionable benefit in the clinical setting of AF because of their potential proarrhythmic effect. The present study shows that I_{Kur} blockade by AVE0118—provided that its efficiency can be proved in humans—might be a realistic therapeutic approach to increase atrial contractility without the cost of proarrhythmic side effects.

For several reasons, restoring atrial contractility after cardioversion of AF by I_{Kur} blockade appears to be more promising than the use of the other positive inotropic compounds tested. Digoxin and dobutamine failed to increase atrial contractility after cardioversion of AF. In the case of dobutamine, the lack of effect obviously was related, at least in part, to a decline in the preload of the atria at the onset of the atrial contraction. Even after readjustment of the preload, dobutamine increased atrial contractility to not more than 36% of contractility at baseline. This limited efficacy might be due to increased dephosphorylation of protein kinase A targets resulting from increased phosphatase activity, as recently suggested. The positive inotropic effects of the Ca2+ sensitizer EMD57033 and the L-type Ca2+ channel agonist BayY5959 were limited at dosages expected to produce potentially harmful side effects. EMD57033 was reported to cause impairment of diastolic function already at low dosages and might provoke ventricular arrhythmias by increasing ventricular wall stress. BayY5959 caused a prolongation of the QT duration by 24.7%. In contrast, AVE0118 could be given at dosages that completely restored atrial contractility. At the highest dosage, atrial contractions were even stronger than at baseline. Changes in QT duration were small and not significant, whereas AERP became progressively longer, emphasizing the atrial specificity of the effect of the compound on repolarization. Finally, we recently demonstrated that AVE0118 also has strong antiarrhythmic potential. Using the same animal model, Blauw et al showed that AVE0118 not only prolongs AERP but also decreases the fibrillatory rate during AF, often results in cardioversion, and decreases the inducibility of the arrhythmia. Thus, in the goat model of AF, I_{Kur} blockade by AVE0118 combines effective positive inotropic stimulation with strong antiarrhythmic activity, making it a potentially interesting new therapeutic principle for AF management.

**Mechanisms of Positive Inotropic Action of AVE0118**

Although the present study was not designed to unravel the exact cellular mechanisms of action of AVE0118, our data shed some light on the mode of positive inotropic action of this compound. In agreement with our previous report, AVE0118 caused a pronounced prolongation of atrial refractoriness and duration of monophasic action potentials in goats with electrically remodeled atria. In the monophasic action potential recordings of the present study, the effect on APD30 was more pronounced than the effect on APD90, indicating that AVE0118 primarily prolongs early repolarization, indicating an increase in the “plateau potential” of the atrial action potential. The latter parameter was recently introduced by Wettwer et al, who demonstrated that in human atrial trabeculae of patients with AF, AVE0118 increased the plateau potential, defined as the average potential in a time window of 20 to 80 ms after the action potential upstroke, from −15 to 5 mV. Mathematical modeling predicted that a similar increase in the plateau potential would increase the L-type Ca2+ inward peak current (I_{CaL}) by 85%, which might well explain a strong increase in active force generation.

Besides I_{to} and I_{Kur}, the G protein–gated K+ current I_{Kach} was reported to be blocked by AVE0118. Because I_{Kach} has been shown to be constitutively active in atria of dogs undergoing rapid atrial pacing and in atria of patients with AF, blocking this current might be particularly effective in prolonging the action potential in electrically remodeled atria. It is uncertain, however, how far this prolongation would contribute to the positive inotropic effect of AVE0118 because blocking I_{Kach} is expected to affect primarily final repolarization, which plays a limited role in determining excitation–contraction coupling in atrial myocytes.

**Study Limitations**

In goats, the atrial action potential is shorter and the degree of shortening resulting from AF is more pronounced than in humans. Therefore, in these 2 species, the relative contribution of I_{to} and I_{Kur} to repolarization and the effect of blockade of these currents on the shape of the action potential might differ, with obvious consequences for the positive inotropic effect of the drug. On the other hand, the recent study of Wettwer et al demonstrated a strong prolongation of the atrial action potential and an increase in the plateau potential in the presence of AVE0118 in human atrial trabeculae isolated from patients with chronic AF.

Another reason why the data of this study should be interpreted with caution is that the mechanisms underlying AF-induced atrial contractile dysfunction might be dependent on the duration of AF. Although in the goat model of AF the atrial contractile dysfunction produced by several days of AF is probably a consequence of a reduced amplitude of I_{CaL} in humans with prolonged AF, other mechanisms such mild myolysis, altered energetics of the myofibrils, impaired systolic release of Ca2+ from the sarcoplasmic reticulum.
with increased leak of \( \text{Ca}^{2+} \) during diastole,\(^{34,35} \) and upregulation of the \( \text{Na}^-/\text{Ca}^{2+} \) exchanger probably contribute to the loss of atrial contractility.\(^{36} \)

Finally, downregulation of \( I_o \) and the sustained outward \( K^+ \) current \( (I_{\text{Kout}}) \), of which \( I_{\text{Kur}} \) is a major component, has been reported in patients with persistent AF.\(^{37} \) Reducing \( I_o \) and \( I_{\text{Kur}} \) potentially, but not necessarily, results in a decrease in the relative contribution of these currents to repolarization, which would diminish the positive inotropic effect of AVE0118 in such patients. Although we could recently report a pronounced increase in active force development in atrial muscle bundles of patients with chronic AF in the presence of AVE0118,\(^{38} \) it remains to be determined whether \( I_o/I_{\text{Kur}} \) blockade effectively and safely restores atrial contraction in patients after cardioversion of AF.

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**Disclosures**

AVE0118 was a gift from Sanofi Aventis, France, to Dr Schotten.

The authors report no other conflicts.

**References**


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CLINICAL PERSPECTIVE
The loss of atrial contractile function after cardioversion of atrial fibrillation (AF) contributes to the thromboembolic risk associated with AF. The development of a therapy for AF-induced atrial contractile dysfunction with positive inotropic drugs has been hampered by limited efficacy and low safety of these compounds. The newly developed blocker of the transient outward current (Ito) and the ultrarapid delayed rectifier current (IKur) AVE0118 prolongs atrial action potential duration and might therefore enhance atrial contractility. In chronically instrumented goats, AVE0118 fully restored atrial contractility after cardioversion of AF. The positive inotropic effect of AVE0118 was stronger than that of conventional inotropic agents and did not result in undesirable proarrhythmic side effects on the ventricle. Provided that its efficiency can be demonstrated in humans, Ito/IKur blockade might be a realistic therapeutic approach to reduce the incidence of thromboembolic events by enhancing atrial contractility.
AVE0118, Blocker of the Transient Outward Current ($I_{to}$) and Ultrarapid Delayed Rectifier Current ($I_{Kur}$), Fully Restores Atrial Contractility After Cardioversion of Atrial Fibrillation in the Goat

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