Atrial effects of the novel K⁺-channel-blocker AVE0118 in anesthetized pigs

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Abstract

Objectives: AVE0118 is a novel blocker of the K⁺ channels Kv1.5 and Kv4.3 which are the molecular basis for the human cardiac ultrarapid delayed rectifier potassium current (I_Kur) and the transient outward current (I_to). The objective of this study was to investigate the effect of AVE0118 on atrial refractoriness (ERP), left atrial vulnerability (LAV) and on left atrial monophasic action potentials (MAP) in pentobarbital anesthetized pigs in comparison to the selective I_Kr blocker dofetilide in order to assess the therapeutic potential of the novel K⁺ channel blocker for atrial fibrillation.

Methods: Atrial ERP was determined with the S1–S2-stimulus method in the free walls of left and right atrium at 240, 300 and 400 ms basic cycle length (BCL). The inducibility of mostly nonsustained atrial tachyarrhythmias by the premature S2 extrastimulus, which is very high in the left pig atrium and referred to as LAV, was evaluated before and after drugs. Left atrial epicardial MAP was recorded to study the influence of the potassium channel blockers on the time course of repolarization. Left ventricular epicardial MAP, ERP and QT interval were measured to investigate a possible effect of AVE0118 on ventricular repolarization.

Results: ERPs determined at 240, 300 and 400 ms BCL were significantly shorter in the left vs. right atrium (99±3, 133±6, 142±7 ms vs. 113±3 ms; p<0.001; n=21). AVE0118 administered i.v. dose-dependently prolonged the atrial ERP independent from rate and inhibited LAV (100% at 0.5 and 1 mg/kg) while having no effect at all on the corrected QT (QTc) interval. At 1 mg/kg (n=5) AVE0118 prolonged left vs. right atrial ERP by 49.6±4.1 ms vs. 37.7±9.7 ms (mean±SEM of changes at 240, 300, and 400 ms BCL), respectively, corresponding to a relative increase of 53.2±6.2% vs. 27.6±6.8% (p<0.05 for percent increase of left vs. right atrial ERP). In a separate group of pigs (n=5) AVE0118 had no effect on left ventricular ERP at 333, 400 and 500 ms BCL and no effect on MAP duration and QT at 600 ms BCL. After 1 mg/kg of AVE0118 the atrial MAP was significantly prolonged already at 10% repolarization (P<0.05; n=7) reaching the maximum at 40% repolarization. In contrast to AVE0118 the effect of dofetilide (10 μg/kg) on atrial MAP started to become significant only at 60% repolarization (n=6) with a maximum increase at 90%. Dofetilide, which prolonged the QTc interval by 16.9% (P<0.001), had a significantly stronger effect on right (34.7±7 ms) vs. left atrial ERP (23.5±7 ms) at 300 ms BCL, respectively, but did not significantly inhibit LAV (14%; n=6).

Conclusion: The novel K⁺ channel blocker AVE0118 prolonged atrial ERP and showed strong atrial antiarrhythmic efficacy with no apparent effect on ventricular repolarization in pigs in vivo.

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Keywords: Atrial fibrillation; Effective refractory period; Kv1.5; Kv4.3; Potassium channel blocker; Dofetilide; Atrial vulnerability; QT-prolongation; Pigs

1. Introduction

Treatment of atrial fibrillation/flutter with available potassium channel blockers (class III antiarrhythmic agents which mainly block the delayed rectifier current, I_Kr) is associated with ventricular proarrhythmia. Prolongation of ventricular repolarization leads to early afterdepolarizations from which torsades de pointes arrhythmias can evolve [1]. Therefore, blockade of a cardiac current of exclusive relevance in the atria is highly desirable as it is expected to be devoid of ventricular proarrhythmic effects. The ultrarapid delayed rectifier potassium current (I_Kur) seems an ideal atrial antiarrhythmic target since it is found to contribute to...
action potential repolarization in the atrium but not the ventricle [2,3]. The molecular correlate of the human cardiac ultrarapid delayed rectifier potassium current seems to be the potassium channel Kv1.5 [2,4–6]. The aim of this project was to find potent inhibitors of the Kv1.5 channel for the development of drugs against atrial fibrillation. AVE0118 has been identified and characterized as a potent Kv1.5 blocker/I_{Kur} blocker. Apart from I_{Kur} blockade the compound has relevant inhibitory effects on Kv4.3/I_{to} and I_{KACH}, but, most important, it is devoid of an inhibitory effect on I_{Kr} and I_{K1} at presumed therapeutic concentrations [7]. Since, in contrast to I_{Kur}, Kv4.3/I_{to} is also present in the ventricles and also inhibited by AVE0118 the question of an effect of the novel blocker on ventricular repolarization was of particular importance.

In this study we investigated the effect of AVE0118 in vivo on pig heart electrophysiology. Apart from the question of an atrial selective effect of AVE01118, comparison of its atrial effects to those of the most potent and selective I_{Kr} blocker dofetilide was of particular interest. In the atria we studied the effect of the compounds on left and right atrial ERP, MAP and on LAV, which we have previously introduced as a new atrial arrhythmia model [8,9]. The pig left atrium, which has significantly shorter ERP than the right atrium, is highly vulnerable to premature S2-stimuli (mostly brief, self-limiting runs of flutter or fibrillation). This is in contrast to the right atrium, where such susceptibility for tachyarrhythmias hardly exists. To judge the effect of AVE0118 on ventricular repolarization we determined ventricular ERP, MAP and QT intervall.

2. Material and methods

The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-13, revised 1996). Male castrated pigs (25–32 kg) of the German Landrace were anaesthetized with pentobarbital as described previously [9]. After left thoracotomy the lung was retracted, the pericardium incised and the heart suspended in a pericardial cradle. Bipolar body surface ECG was recorded using subcutaneous needle electrodes in the classical lead II or lead III arrangement. The contact pressure proved to be of critical importance. Therefore, a particular effort had to be made to obtain atrial MAP of sufficient quality for a detailed analysis of the influence of the potassium channel blockers on the different phases of repolarization. Drugs were administered only if a regular baseline and amplitude of the MAPs could be maintained for at least 10 min. The positioning procedure was repeated if changes of the shape of the MAP occurred during the 10-min interval. Small negative deflections or notches seen just before the upstroke of the MAP were accepted. After 10 min of stable MAP shape vehicle or drug was given i.v. The negative chronotropic effects of dofetilide made it necessary to keep the heart rate at a constant level by pacing the right atrium from a region nearby the sinus node. The heart rate was kept 10 beats above its initial rate by stimulation at twice-diastolic threshold. Left atrial MAP duration was evaluated from 10% to 90% repolarization (MAPD10 to MAPD90; at a 10% step) at different times after drug injection. To provide the highest quality of data, MAP analysis and ERP measurements were made in separate groups of pigs, and we limited the MAP investigation to the left atrium with its controlled epicardial access.

2.2. Left atrial vulnerability (LAV)

During the ERP-measurement procedure the S2-extrastimulus, which followed the 10 conditioning S1 stimuli during the ERP-measurement procedure, frequently triggered runs of atrial tachycardia in the left, but not in the right atrium. Whether or not a run of S2-triggered atrial tachyarrhythmia (at least four extra beats) occurred during the ERP-measurement procedure at a given BCL was noted. The occurrences of triggered tachyarrhythmias were summed up for the three BCLs tested over three time points during a 30-min period before or after drug application and served as a measure of atrial vulnerability. Thus, the maximum occurrence of induced atrial tachyarrhythmia was nine (3 BCL × 3 time points) corresponding to an arrhythmia incidence of 100%.

2.3. MAP recording in the left atrial free wall for the analysis of the influence of the potassium channel blockers on the time course of repolarization

MAP electrode and position of the electrode were the same as used for atrial ERP measurements (see above). The MAP pacing catheter was covered by a sponge and fixed epicardially in the middle of the left atrial free wall in an approximately perpendicular position by a holding device [10]. The contact pressure proved to be of critical importance. Therefore, a particular effort had to be made to obtain atrial MAP of sufficient quality for a detailed analysis of the influence of the potassium channel blockers on the different phases of repolarization. Drugs were administered only if a regular baseline and amplitude of the MAPs could be maintained for at least 10 min. The positioning procedure was repeated if changes of the shape of the MAP occurred during the 10-min interval. Small negative deflections or notches seen just before the upstroke of the MAP were accepted. After 10 min of stable MAP shape vehicle or drug was given i.v. The negative chronotropic effects of dofetilide made it necessary to keep the heart rate at a constant level by pacing the right atrium from a region nearby the sinus node. The heart rate was kept 10 beats above its initial rate by stimulation at twice-diastolic threshold. Left atrial MAP duration was evaluated from 10% to 90% repolarization (MAPD10 to MAPD90; at a 10% step) at different times after drug injection. To provide the highest quality of data, MAP analysis and ERP measurements were made in separate groups of pigs, and we limited the MAP investigation to the left atrium with its controlled epicardial access.
2.4. Effect of drugs on ventricular repolarization

In a separate group of five pigs, the effect of AVE0118 on left ventricular repolarization was investigated. The MAP pacing catheter was positioned on the epicardium of the left ventricle (as otherwise described for the left atrium) for the MAP evaluation and ERP measurements. MAP duration at 90% repolarization and QT were measured at 600 ms BCL (with left atrial pacing). Left ventricular effective refractory periods for AVE0118 were determined as described above for the left atrium. In order to avoid hemodynamic instability in the anesthetized pigs BCLs used for ventricular stimulation (333, 400 and 500 ms) were lower than in the atria.

2.5. Drugs

AVE0118 and dofetilide were synthesized in the Department of Medicinal Chemistry of Aventis Pharma Deutschland. AVE0118 was dissolved in 0.5 ml DMSO, 2.5 ml of polyethylene glycol (PEG) 400 (Riedel-de Haen, Seelze, Germany) was added, and the solution was administered i.v. over 5 min. Vehicle as a control was injected at least 30 min before the drug. Doses between 0.1 and 1 mg/kg were administered. Due to limitations in solubility higher doses than 1 mg/kg were not given. Dofetilide was given at the clinically used dose for acute cardioversion (10 μg/kg), with saline as a vehicle over an i.v. infusion period of 5 min.

2.6. Statistical analysis

Data were presented as means ± SEM. The longest ERP at each pacing rate after drug administration was taken and expressed as absolute or percent increase from vehicle control. Interatrial dispersion of the ERP was calculated as the difference between the left and right atrial ERP. One- or two-way ANOVA for repeated measures followed by Student's t-test was used for the calculation of statistically significant differences between left and right atrial ERP prolongations at the three basic cycle lengths, the inhibition of LAV, MAP duration and the difference between right and left atrial ERP (dispersion of the ERP). A value of \( p < 0.05 \) was accepted as significant.

3. Results

3.1. Basal atrial ERPs

ERPs determined at 400, 300 and 240 ms BCL were clearly shorter in the left vs. right atrium (113 ± 3, 106 ± 4 and 99 ± 3 ms vs. 149 ± 5, 142 ± 4 and 133 ± 4 ms, respectively; \( p < 0.001; n = 21 \)) as previously reported [9]. Original registrations in Fig. 1 show this difference with longer right atrial MAPs.

3.2. Effect of drugs on atrial ERPs

Vehicle had no effect on atrial refractoriness. AVE0118 caused a dose-dependent rise in atrial ERPs in both atria. Baseline ERP and ERP after 0.3 (\( n = 3 \)), 0.5 (\( n = 5 \)) and 1 mg/kg (\( n = 5 \)) for the three BCLs of the left atrium are shown in Fig. 2. Table 1 shows the absolute values before Fig. 2. Effect of AVE0118 on left atrial ERP in anesthetized pigs at 240, 300 and 400 ms BCL. Differences are significant for all values. Open symbols show baseline values, closed symbols values after AVE0118, 0.3 (circles, \( n = 3 \)), 0.5 (squares, \( n = 5 \)), 1 mg/kg (triangles, \( n = 5 \))
and after different doses of AVE0118. Between 240 and 400 ms BCL there is a similar increase in the ERP with no evidence for a rate-dependent effect. For better comparison of the effects on the left and right atrium, the mean increase in milliseconds of the three BCLs at doses of 0.1 to 1 mg/kg i.v. was calculated and shown in Fig. 3. Although there was only a trend for stronger left compared to right absolute ERP prolongations at 0.5 and 1 mg/kg the relative increases (in percent of baseline ERP) in the left atrial ERP were significantly stronger (*p < 0.05) because the baseline left atrial ERP was much shorter. Dofetilide, 10 μg/kg (*n = 6), like other *I*<sub>Kr</sub> blockers [8], had a significantly stronger effect (*P < 0.05) on right than on left atrial ERP (Fig. 4). A trend for a negative rate-dependent effect can be seen in the right atrium.

Since dofetilide had a stronger effect on the right atrium, which already had a much longer ERP at baseline compared with the left atrium as shown above, the difference between left and right atrial ERP increased significantly (*p < 0.05), while after AVE0118 this difference tended to decrease (Table 2).

### Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>0.5 mg/kg</th>
<th>1.0 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVE0118</td>
<td>45 ± 4</td>
<td>49 ± 5</td>
</tr>
<tr>
<td>AVE0118</td>
<td>40 ± 9</td>
<td>49 ± 4</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>33 ± 4</td>
<td>34 ± 9</td>
</tr>
</tbody>
</table>

Values in the table show the interatrial ERP difference before and after drugs at three different BCLs. Dofetilide significantly increased the interatrial ERP difference.

*p < 0.05 for change after drug.
3.3. Left atrial vulnerability

As previously reported [8,9] in pigs the extrastimulus S2 following the regular 10 S1 conditioning stimuli during the S1–S2–ERP measurement procedure frequently elicits mostly nonsustained and brief runs of atrial fibrillation/flutter as shown in an original registration (Fig. 5). Fig. 6 shows the dose-dependent inhibition of these arrhythmias by AVE0118 in comparison to dofetilide, 10 μg/kg. At 0.5 and 1 mg/kg AVE0118 abolished the arrhythmias. The incidence of S2-induced left atrial tachyarrhythmias was 94 ± 6%, 85 ± 10%, 60 ± 19%

Fig. 5. Typical example of the left atrial arrhythmias that are elicited by a premature beat (S2) during the S1–S2–ERP measurement procedure (LAV). Upper panel: S2 after 10 conditioning S1 stimuli (black line) induces a run of nonsustained tachycardia (dashed line). Lower panel shows the absence of S2-induced arrhythmias after AVE0118, 0.5 mg/kg i.v.

Fig. 6. Inhibition of LAV in pigs at different doses of AVE0118 in comparison with dofetilide. Columns show % inhibition of LAV. *p < 0.05; n = 3 for 0.1 and 0.3 mg/kg and n = 5 for 0.5 and 1 mg/kg AVE0118; n = 6 for dofetilide.
and 85 ± 10% before AVE0118 and 33 ± 32%, 11 ± 11%, 0 ± 0% and 0 ± 0% at 0.1, 0.3, 0.5 and 1.0 mg/kg, respectively. The selective \( I_{Kr} \) blocker dofetilide did not significantly inhibit the incidence of atrial tachyarrhythmias induced by the S2-extrastimulus (64 ± 15% before vs. 56 ± 14% after drug corresponding to 14% inhibition; \( n = 6 \)).

### 3.4. Effect of drugs on left atrial monophasic action potential (MAP)

AVE0118 (1 mg/kg; \( n = 7 \)) and dofetilide (10 \( \mu \)g/kg; \( n = 6 \)) both prolonged the left atrial MAP. Typical original registrations for AVE0118 and dofetilide are shown in Fig. 7. Fig. 8 shows the MAP prolongation at different degrees of repolarization 6 min after drug injection where the maximum effect was reached. AVE0118 started to prolong the MAP already at 10% of repolarization and its effect was already maximal at 40% repolarization. At 80% and 90% repolarization the prolongation induced by AVE0118 tended to decrease again (Figs. 7 and 8). In contrast, after dofetilide the first significant prolongation was observed at 60% repolarization and the prolongation reached its maximum at 90% of repolarization.

![Fig. 7. Typical original registrations of left atrial MAPs before and after administration of AVE0118 (superimposed), 1 mg/kg (upper panel) and dofetilide, 10 \( \mu \)g/kg (lower panel). Shorter MAPs in each panel are baseline MAPs.](image)

![Fig. 8. Increase in MAP duration in milliseconds by AVE0118, 1 mg/kg (\( n = 7 \)) and dofetilide 10 \( \mu \)g/kg (\( n = 6 \)) at different degrees of repolarization. AVE0118 (close squares); dofetilide (open circles). Means ± SEM. *\( p < 0.05 \) for the first value that reached statistical significance.](image)

### 3.5. Effect of drugs on ventricular repolarization

AVE0118 did not prolong the QT or QTc interval indicating that it is devoid of a meaningful effect on ventricular repolarization. In the pigs, in which atrial ERP measurements were performed, QTc was 426 ± 15 ms before and 423 ± 12 ms after 1 mg/kg AVE0118 10 min after injection. Dofetilide, 10 \( \mu \)g/kg, showed the expected prolongation of the QTc-interval (16.9% increase; from 456 ± 15 ms to 533 ± 12 ms; \( p < 0.001 \)) as previously reported by us [8,9].

In the separate group of pigs, in which the effect on ventricular ERP and MAP duration and QT was studied (\( n = 5 \)), repolarization was not changed by the vehicle or AVE0118, 1 mg/kg. MAPD90 and QT at 600 ms BCL were 305 ± 11 and 352 ± 12 ms before and 311 ± 11 and 352 ± 9 ms after vehicle, respectively. MAPD90 and QT at 600 ms BCL were 300 ± 12 and 348 ± 15 before and 303 ± 13 and 355 ± 17 ms after 1 mg/kg AVE0118, respectively. At the three BCLs tested, 333, 400 and 500 ms, the left ventricular epicardial ERPs were 219 ± 12, 235 ± 14 and 254 ± 14 ms before and 221 ± 12, 237 ± 11 and 251 ± 11 ms after AVE0118, respectively. Vehicle had no effect on ERP. During the measurements with AVE0118 and vehicle, local capture (MAP potential on the left ventricular epicardium) was always followed by a left ventricular contraction as judged by the left ventricular pressure curve and the QRS complex.

### 4. Discussion

Our results in anesthetized pigs show that AVE0118 is a potent and atrium selective antiarrhythmic compound with no apparent effect on ventricular repolarization. It prolongs atrial refractoriness dose-dependently and abolishes the
mostly nonsustained runs of atrial fibrillation/flutter induced by a premature extrastimulus (S2), defined as LAV. The high atrial antiarrhythmic efficacy occurs in the absence of a noticeable effect on ventricular repolarization as indicated by measurement of the QT-interval, left ventricular MAP duration at 90% repolarization and left ventricular ERP. The data are in agreement with in vitro data [7]. In different in vitro tests AVE0118 inhibited \( I_{so} \), \( I_{kur} \) and \( I_{K(Ca)} \), to a relevant extent but not \( I_{kr} \) or \( I_{K1} \). Since AVE0118 did not prolong ventricular repolarization at strong atrial ERP prolongation it is expected to be devoid of the typical ventricular proarrhythmic effects of \( I_{kr} \)-blockers (early after-depolarizations leading to torsades de pointes arrhythmias). The selective \( I_{kr} \) blocker dofetilide (10 µg/kg) prolonged the QTc interval to a similar extent as (right) atrial ERP. It is of scientific interest to note that \( I_{so} \) blockade by AVE0118 obviously does not prolong ventricular repolarization in pigs.

Previously we have compared \( I_{kr} \) blockers with two other novel \( I_{kur} \) blockers and we have already shown superior atrial actions of the latter with no effect on the QT-interval [8]. The advantage of AVE0118 over those previously published \( I_{kur} \) blockers is that AVE0118 is suited for clinical development and meanwhile in phase I clinical studies.

The MAP technique delivers potentials of sufficient quality for an evaluation of the time course of repolarization (not for voltage) in the ventricles, but atrial MAPs were of lower quality most likely because the critical pressure for depolarizing the area underneath the electrode tip is more difficult to maintain in the thin atrial wall with the low atrial pressure. The contact pressure proved to be of critical importance, and we finally were able to record high-quality atrial MAPs. It could be shown that both dofetilide and AVE0118 prolonged the left atrial MAP, but AVE0118 acted durably. The slow inactivation of the \( I_{kr} \) because its major contribution to repolarization in a premature action potential is linked to the question why AVE0118 is so effective whereas \( I_{kr} \) blockade is less effective against this type of arrhythmia. The altered repolarization as a consequence of a shortened diastolic interval is referred to as restitution. It reflects the time-dependent kinetics of the membrane currents [12]. As pointed out premature excitation (via the S2 stimulus) frequently induces left atrial tachyarrhythmias in the pig. Whether a tachyarrhythmia follows the S2-induced action potential may not depend on the duration and refractoriness of the S1-induced action potential with its relatively large preceding diastolic interval, but on the duration of the S2 induced action potential, which has a very brief preceding diastolic interval. Attempts to determine the refractoriness of the S2-induced action potential via a further S3 stimulus failed because of the strong arrhythmogenic effect of the procedure. The slow inactivation of the \( I_{kur} \) [6] may play an important role. It can be assumed that in a premature excitation the \( I_{kur} \) is increased because of its slow inactivation. This may lead to early repolarization and, consequently, to reentrant arrhythmias. Blockade of \( I_{kur} \) would then prevent early repolarization explaining the high efficacy against atrial vulnerability. In addition, an accelerated repolarization of a premature action potential would diminish the contribution of the \( I_{kr} \), because its major contribution to repolarization is later in the action potential. This is reflected in the late effect of the selective \( I_{kr} \) blocker dofetilide on atrial MAP in the pig (Figs. 6 and 7) and might explain the weak efficacy of \( I_{kr} \) blockade. Taken together, the contribution of \( I_{kur} \) to repolarization in a premature action potential may increase at the expense of the contribution of \( I_{kr} \). High efficacy of \( I_{kur} \) blockade and low efficacy of \( I_{kr} \) blockade against the arrhythmogenic effect of a premature beat seem to be linked.

The interatrial differences demonstrated in our pigs—shorter left atrial ERPs and action potentials, stronger left atrial ERP prolongation by \( I_{so}/I_{kur} \) blockade, existence of a high LAV (and its absence in the right atrium) and its nearly
exclusive inhibition by \( I_{to} / I_{Kur} \) blockers—point to interatrial differences in the expression or function of the atrial ion channels. A unifying explanation could be a higher \( I_{Kur} \) and/or \( I_{to} \) vs. \( I_{Kr} \) ratio in the pig left atrium. Heterogeneity of restitution kinetics as a consequence of a stronger left atrial \( I_{Kur} \) with its slow inactivation may strongly alter the spatial pattern of repolarization during premature stimulation. This would further increase the preexisting baseline interatrial ERP differences (as measured at 240, 300 and 400 ms BCL), and thereby explain the high extent of S2-induced left atrial arrhythmias.

Expression of Kv1.5 mRNA and protein are only one part of the complex machinery that finally results in in vivo function and spatial distribution of \( I_{Kur} \) \( \beta \)-subunit composition and autonomic regulation are additional factors [2,3], and it is unclear at present why there is ventricular expression of Kv1.5 without function (no measurable ventricular \( I_{Kur} \) [13]. On that background a molecular approach to answer the question of interatrial differences in \( I_{Kur} \) would have been beyond the scope of this study.

An alternative explanation for interatrial differences in ion channels is a shorter left atrial calcium current. It would also lead to shorter left atrial action potentials and to stronger left atrial action potential prolongation by \( I_{Kur} \) blockade (according to a mathematical model of the human atrial action potential for the calculation of the prolongation conferred by \( I_{Kur} \) blockade in case of a reduced calcium current Ref. [11]).

The concept of left atrial arrhythmias induced by a premature stimulus (S2) seems to be of particular relevance since in human atrial fibrillation the left atrium receiving ectopic activity mainly from the pulmonary veins is thought to play an important role in the initiation of this tachyarrhythmia [14,15]. Therefore it is important to find out how the left atrium responds to premature stimulation and whether a drug is able to inhibit its vulnerability. Although our LAV model tests whether an artificial premature beat is able to elicit mostly nonsustained atrial fibrillation/flutter, it is easy to imagine that frequent ectopic beats could cause a nearly sustained atrial tachyarrhythmia that would give rise to nonsustained atrial fibrillation/flutter [16,17]. This would result in a further shortening of the action potential mainly through downregulation of the calcium current and induce persistent atrial fibrillation. Apart from downregulation of the calcium current, changes in \( K^- \) channels have also been found in chronic atrial fibrillation as a consequence of electrical remodeling ([18] for review). \( I_{to} \) seems to be diminished [17]; transcription of Kv4.3 decreased [19]. Concerning Kv1.5 mRNA, protein, or \( I_{Kur} \) conflicting results were published; decreases [20,21] or no changes [19,22] were reported. A possible limitation of this study with AVE0118 is that ERP was measured in anesthetized pigs in sinus rhythm (in the non-remodeled state). Assuming only decreases in \( I_{to} \) and \( I_{Kur} \) in chronic atrial fibrillation (not other ion currents) one could expect that blockade of these channels would less effectively translate into ERP prolongation in chronic atrial fibrillation compared to sinus rhythm. However, the overall relevance of the respective ion conductances in the remodeled state still depends on their fractional contribution to the whole cell conductance. Taking this into account \( I_{to} \) and \( I_{Kur} \) blockade in the remodeled atrium could be even more effective on ERP [11]. In fact, this could be observed in the remodeled atrium of chronically fibrillating goats [23]. AVE0118 showed an even stronger effect on the atrial ERP compared with sinus rhythm. The preserved or even stronger effect of AVE0118 in atrial fibrillation is in clear contrast to \( I_{Kr} \) blockers, which, in the remodeled state, lose most of the ERP-prolonging effect they have in sinus rhythm [23].

5. Conclusion

In pigs AVE0118 prolonged the atrial ERP and showed strong atrial antiarrhythmic efficacy with no apparent effect on ventricular repolarization. Apart from the lack of effect on ventricular repolarization, the atrial efficacy profile of AVE0118 is remarkably different from that of \( I_{Kr} \) blockade. Based on these properties AVE0118 is a promising new type of atrial selective antiarrhythmic drug.

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