Electrophysiological and haemodynamic effects of vernakalant and flecainide in dyssynchronous canine hearts

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Aims

About one-third of patients with mild dyssynchronous heart failure suffer from atrial fibrillation (AF). Drugs that convert AF to sinus rhythm may further slowdown ventricular conduction. We aimed to investigate the electrophysiological and haemodynamic effects of vernakalant and flecainide in a canine model of chronic left bundle branch block (LBBB).

Methods and results

Left bundle branch block was induced in 12 canines. Four months later, vernakalant or flecainide was administered using a regime, designed to achieve clinically used plasma concentrations of the drugs, n = 6 for each drug. Epicardial electrical contact mapping showed that both drugs uniformly prolonged myocardial conduction time. Vernakalant increased QRS width significantly less than flecainide (17 ± 13 vs. 34 ± 15%, respectively). Nevertheless, both drugs equally decreased LVdP/dtmax by ≏15%, LVdP/dtmin by ≏10%, and left ventricular systolic blood pressure by ≏5% (P = n.s. between drugs).

Conclusions

Vernakalant prolongs ventricular conduction less than flecainide, but both drugs had a similar, moderate negative effect on ventricular contractility and relaxation. Part of these reductions seems to be related to the increase in dyssynchrony.

Keywords

Vernakalant • Flecainide • Dyssynchrony • Epicardial electrical activation mapping • Canine • Atrial fibrillation • Left bundle branch block

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and affects 1—2% of the general population.1—4 The prevalence is probably closer to 2%, since AF can remain ‘silent’ for a long time and many of these patients will never present to a hospital.5 Moreover, the prevalence of AF increases significantly with worsening heart failure (HF).4 Atrial fibrillation is a serious independent risk factor for cardiovascular complications or death.5

Several drugs are capable of converting recent-onset AF into sinus rhythm. Flecainide is one of the most successful drugs used for pharmacological conversion of AF and can be used to prevent episodes of paroxysmal AF after direct current cardioversion.6,7 It is a Class Ic drug and primarily acts through blockade of the sodium channel, thus slowing down myocardial conduction.8

In search of a more atrial-specific drug, vernakalant was developed. The electrophysiological characteristics and mechanism of action of vernakalant have been recently reviewed.9 Vernakalant blocks the potassium currents IKur, IK(ACh), IKr, and IK1 and the sodium channel INa,b but it has little effect on IK1 and IKr.10 Vernakalant increases the atrial effective refractory period in a dose-dependent manner through blockage of the potassium channels. Furthermore, the inhibition of the sodium current was shown to be rate- and voltage-dependent, accordingly Vernakalant may slow down conduction more in fast fibrillating atria than in the slower beating ventricles.11—13

Current European Union (EU) guidelines contraindicate the use of flecainide and vernakalant in patients with New York Heart Association (NYHA) Classes III and IV because of increased risks of arrhythmia and hypotension.14,15 Further evidence is scarce since these patients are often excluded in clinical trials. However, the guidelines...
What’s new?

- Recently, vernakalant has been introduced as a novel drug for pharmacological cardioversion of atrial fibrillation (AF). Current European Union (EU) guidelines contraindicate the use of flecainide and vernakalant in patients with New York Heart Association (NYHA) Classes III and IV. However, the guidelines do recommend pharmacological conversion of AF in patients with recent-onset AF and no or minimal structural heart disease. Interestingly, the guidelines do not mention the presence of ventricular conduction abnormalities, such as left bundle branch block, as a potential contraindication for the use of these drugs.
- To our knowledge, we are the first to describe the electrophysiological and haemodynamic effects of vernakalant and flecainide in hearts with mild structural heart disease and dyssynchrony.
- This study shows lesser conduction slowing by vernakalant when compared with flecainide, but a similar impairment of haemodynamic function by both drugs.

Methods

Animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive for the Protection of Vertebate Animals used for Experimental and Other Scientific Purposes (86/609/EU). The protocol was approved by the Experimental Animal Committee of Maastricht University.

Experimental models

The experiments were performed on 12 adult mongrel dogs of either sex, weighing 21.7 ± 4.4 kg. After induction with pentothal, anaesthesia was maintained by continuous infusion of midazolam (0.25 mg/kg/h) and sufentanil (3 μg/kg/h). During a sterile closed-chest procedure, LBBB was induced by radiofrequency ablation as described in detail previously. Final experiments were performed 16~18 weeks after onset of LBBB. At that time, the animals were induced using the same anaesthesia as used for the first procedure.

Infusion protocol

Dogs were arbitrarily assigned to receive vernakalant (n = 6) (Meda Pharma B.V.) or flecainide (n = 6) (Medtronic). Both drugs were administered in a two-stage regime. The first stage of vernakalant consisted of a slow IV infusion of 5.7 mg/kg in 15 min, followed by an interval of 15 min before the second infusion. The second infusion contained 2.3 mg/kg and was given in the same way over a 15 min period. The aim of the split infusion regimen was to achieve a high, clinical used, plasma concentration. To verify whether the concentration levels of vernakalant were within the designated range, plasma was collected. Plasma samples were analysed for concentration of vernakalant at Cardiome Pharma Corp. Similarly, flecainide was administered in two stages. In the first stage, 1.5 mg/kg of flecainide was administered intravenously over a 10 min period. The second infusion of 2.5 mg/kg was given after a 15 min interval. Based on earlier canine experiments, this dosage was expected to reach a plasma concentration of 5.0 μg/mL, which has comparable effects in canines as the highest clinically used plasma concentrations in patients.

To take haemodynamic alterations due to changes in heart rate into account, the entire experiment was performed with atrial pacing ~10% above the intrinsic rhythm present at baseline. This heart rate was kept constant throughout the protocol. Haemodynamic status was continuously monitored throughout the protocol. Electrical activation maps were recorded once every minute during infusions and after infusion.

Data from historical controls (n = 5) were used to take changes over time into account. These data were derived from previous experiments testing different ways of ventricular pacing, interspersed with control, no ventricular pacing, intervals.

Data analysis

Depolarization times were calculated for each individual epicardial electrode as the difference between earliest activation (earliest onset of Q-wave in all electrograms) and time of steepest deflection in the individual electrogram (−dV/dt). Based upon those depolarization times, the total activation time (AT) was defined as maximal depolarization time difference. Electrocardiographic parameters were derived from the limb leads of the surface electrocardiogram. While QRS width and total AT reflect overall electrical dyssynchrony, they do not express the spatial progression of the electrical wave front. For that purpose, AT vectors were calculated. For each electrode, a sub-vector was calculated using the depolarization time as amplitude and anatomical location, with the LV centre as reference, for direction. The sub-vectors were summed to construct a mean epicardial mapping vector. Dyssynchrony can then be expressed by the contact mapping vector amplitude (VA-CM), while the main direction of conduction was expressed by the contact mapping vector direction (VD-CM). The contact mapping vector direction (VD-CM) was measured as angle from the reference to the RV free wall (0°), anterior LV (90°), and LV free wall (180°) with the aid of custom MATLAB software (MathWorks). Left ventricular conduction velocity (CV) was determined by pacing an antero-lateral electrode in the
epicardial electrode array at ~50% above the threshold and calculating the time between the pace artefact and the time of depolarization from four electrodes, two on both sides of the paced electrode. These times were divided by the known distances between paced and recording electrodes (1 and 2 cm, since the interelectrode distance from the array is 1 cm). The average value of these four measurements was taken as CV.

Mechanical interventricular dyssynchrony (MIVD) was assessed from the time difference of the upslope of LV and RV pressures.25 LV dP/dtmax, the maximal first derivative of LV pressure, is a common index of contractility.

**Statistical analysis**

Data are presented as mean ± standard deviation. Statistical analysis was performed using Statistical Package for Social Sciences for Windows version 20.0 (SPSS Inc.). During infusion, electrical activation maps and haemodynamic status were sampled every minute. Baseline electrical and haemodynamic data were obtained just prior to infusion. Final data were obtained within the first 2 min after the respective drug was entirely prepared. All electrical and haemodynamic variables are essentially constant over the 45 min duration of the protocol, except for a small but significant increase in heart rate (Table 1).

Plasma levels of vernakalant reached values of 3.7 ± 0.8 µg/mL at the end of the infusion protocol.

Data from the historical control animals indicated that in the animal preparation used, all electrical and haemodynamic variables are essentially constant over the 45 min duration of the protocol, except for a small but significant increase in heart rate (Table 1).

Results

Eleven of the 12 canines completed the protocol allowing evaluation of the haemodynamic and electrophysiological effect at baseline and after each of the two different doses. One dog in the flecainide group died during the second stage of infusion due to cardiogenic shock. Data during the first stage of infusion from this dog are included in Figure 3.

**Electrophysiological effects**

The electrical maps in the left panels of Figure 1 show a typical LBBB type electrical activation pattern, which starts in the RV and then progresses around the LV wall towards the basal LV-free lateral wall. The right panels show activation maps after administration of flecainide and vernakalant. While the sequence of activation remains similar, as can be deduced from the regular distribution of isochrones lines, the crowding of the isochrone lines and the increase in the number of colours indicate that both drugs slow down ventricular conduction. This was objectified by a tendency of a decrease in conduction velocity by vernakalant and a significant decrease in conduction velocity by flecainide (Table 1).

Both drugs significantly increased the duration of depolarization (QRS width) and the duration of atrial/atrioventricular conduction (PQ time), but no significant effect on repolarization time (QTc interval) was observed (Table 1). Flecainide increased QRS width and total AT significantly more than vernakalant. On average, QRS width increased by 13 ± 5 vs. 34 ± 15% for vernakalant and flecainide, respectively. Along with QRS width, total AT was prolonged by a similar extent (12 ± 6 vs. 32 ± 5%, respectively) (Table 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Haemodynamic and electrical activation data at baseline and after infusion of vernakalant and flecainide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Vernakalant</td>
</tr>
</tbody>
</table>
| Heart rate (b.p.m.) | 136 ± 11 | 144 ± 15* | 147 ± 3* | 147 ± 3* | 144 ± 8* | 150 ± 4*** | 94 ± 11 | 126 ± 19±*
| QRS width (ms) | 97 ± 12 | 96 ± 15 | 92 ± 11 | 103 ± 10±# | 96 ± 3#
| PQ time (ms) | 141 ± 35 | 137 ± 32 | 126 ± 27 | 141 ± 27 | 148 ± 35 | 163 ± 53* | 358 ± 29 | 394 ± 25
| QTc (ms) | 355 ± 17 | 353 ± 19 | 350 ± 10 | 361 ± 9 | 87 ± 11 | 117 ± 20# |
| Total AT (ms) | 80 ± 16 | 82 ± 17 | 90 ± 10## | 96 ± 3### | 11 ± 10 | 117 ± 20# |
| Conduction velocity (m/s) | N/A | N/A | 0.85 ± 0.10 | 0.79 ± 0.12 | 0.83 ± 0.28 | 0.63 ± 0.12## |
| VA-CM (degrees) | 178 ± 8 | 179 ± 10 | 190 ± 19 | 191 ± 18 | 197 ± 14 | 196 ± 16 |
| VA-CM (ms) | 59 ± 1 | 57 ± 2 | 63 ± 10 | 69 ± 10 | 57 ± 5 | 78 ± 11## |
| MIVD (ms) | 38 ± 13 | 37 ± 13 | 18 ± 11# | 22 ± 3 | 30 ± 9# | 37 ± 15## |
| LV systolic pressure (mmHg) | 78 ± 16 | 79 ± 12 | 86 ± 15 | 82 ± 16 | 77 ± 6## | 72 ± 6### |
| LV diastolic pressure (mmHg) | 3 ± 3 | 4 ± 3 | 8 ± 1 | 9 ± 2## | 13 ± 5 | 14 ± 4 |
| LVDp/dtmax (mmHg/s) | 1187 ± 212 | 1214 ± 142 | 1160 ± 300 | 1125 ± 281### | 1215 ± 285 | 978 ± 231### |
| LVDp/dtmin (mmHg/s) | −1199 ± 320 | −1277 ± 303 | −1944 ± 404 | −1236 ± 433### | −1333 ± 454 | −1134 ± 272### |
| Tau (ms) | 41 ± 5 | 39 ± 4 | 35 ± 15 | 37 ± 16 | 39 ± 9 | 41 ± 6 |
| RV systolic pressure (mmHg) | 23 ± 12 | 26 ± 13 | 48 ± 14## | 43 ± 11 | 36 ± 8 | 33 ± 7 |
| RV diastolic pressure (mmHg) | 8 ± 5 | 8 ± 4 | 11 ± 5 | 12 ± 8 | 7 ± 8 | 9 ± 8 |

*P < 0.05 compared with own baseline.
**P < 0.05 flecainide compared with vernakalant at the time interval.
*P < 0.05 compared with control at the same time interval. Mean values and SD are presented.
conduction, was ~1252

Data are expressed as percentage of baseline.

Baseline values haemodynamic parameters, relative to their own

Figure 1 Activation maps derived from the two epicardial electrode arrays, around the base and mid level of the heart, with a total of 102 electrodes and the apical electrode array of 4 electrodes, plotted on a three-dimensional (3D) model of the LV and RV epicardium as previously reported. Both drugs show an increase in after drug infusion by crowding of isochrone lines and blue colours. Dotted lines resemble the level of the septum.

Figure 2

Table 2 Changes in electrophysiological and haemodynamic parameters, relative to their own baseline values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vernakalant</th>
<th>Flecainide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>100 ± 3</td>
<td>104 ± 6</td>
</tr>
<tr>
<td>QRS width</td>
<td>113 ± 5*</td>
<td>134 ± 15*</td>
</tr>
<tr>
<td>PQ time</td>
<td>113 ± 13*</td>
<td>117 ± 15*</td>
</tr>
<tr>
<td>QTc</td>
<td>103 ± 2</td>
<td>106 ± 6</td>
</tr>
<tr>
<td>Total AT</td>
<td>112 ± 6*</td>
<td>132 ± 5*</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>90 ± 4</td>
<td>81 ± 10*</td>
</tr>
<tr>
<td>VD-CM</td>
<td>99 ± 1</td>
<td>99 ± 3</td>
</tr>
<tr>
<td>VA-CM</td>
<td>113 ± 5</td>
<td>130 ± 2*</td>
</tr>
<tr>
<td>MIVD</td>
<td>118 ± 16</td>
<td>122 ± 25*</td>
</tr>
<tr>
<td>LV systolic pressure</td>
<td>95 ± 6</td>
<td>94 ± 5*</td>
</tr>
<tr>
<td>LV diastolic pressure</td>
<td>102 ± 16*</td>
<td>110 ± 19</td>
</tr>
<tr>
<td>LVDp/dtmax</td>
<td>83 ± 4*</td>
<td>85 ± 9*</td>
</tr>
<tr>
<td>LVDp/dtmin</td>
<td>89 ± 12*</td>
<td>90 ± 13*</td>
</tr>
<tr>
<td>RV systolic pressure</td>
<td>94 ± 9*</td>
<td>94 ± 10</td>
</tr>
<tr>
<td>RV diastolic pressure</td>
<td>112 ± 37</td>
<td>113 ± 48</td>
</tr>
<tr>
<td>Tau</td>
<td>111 ± 6</td>
<td>111 ± 27</td>
</tr>
</tbody>
</table>

Data are expressed as percentage of baseline.

*P < 0.05 compared with own baseline.

Flecainide compared with vernakalant at the same dosage level.

The VD-CM, a marker for the main direction of ventricular conduction, was ~200°, reflecting a direction of conduction predominantly from the RV to the LV-free wall (Table 1, Figure 2). The contact mapping vector direction practically did not change during the protocol, indicating a stable main direction of conduction for both drugs. The contact mapping vector amplitude, the amplitude of the conduction vector, tended to increase after infusion with vernakalant and increased significantly after flecainide, indicating an increase in unidirectional electrical dyssynchrony by flecainide.

Haemodynamic effects

Baseline MIVD values were significantly lower in the vernakalant group compared with the other two groups, despite equality in all other related variables. Flecainide increased MIVD significantly, while the increase by vernakalant did not reach the level of significance (Table 1). At the end of the infusion protocol, LV systolic pressure was mildly (~5%) reduced by both drugs, but this decrease was only significant for flecainide.

LVDp/dtmax decreased significantly after vernakalant by 17 ± 4% which is similar to the 15 ± 9% decrease of LVDp/dtmax by flecainide (Table 2). The difference in relative decrease of LVDp/dtmax between the two drugs was not statistically significant. Both drugs also reduced LVDp/dtmax, an index of LV isovolumic relaxation. The drugs did not cause a significant change in tau, the time constant of decay of LV pressure in early diastole. Effects of both drugs on RV pressure were small (Table 1). To evaluate the relation between QRS widening and change in LVDp/dtmax during administration of the two drugs, a time course of these variables during the infusion protocol was reconstructed and is depicted in Figure 3. Flecainide caused a steady increase in QRS width, in parallel with a decrease in contractility during the first and second stage of infusion. This resulted in a significant correlation between QRS duration and LVDp/dtmax (r = 0.66 ± 0.22; P < 0.01 and 0.65 ± 0.23; P < 0.01 for the first and second dose, respectively). A similarly high correlation coefficient was found during the first infusion stage of vernakalant (r = 0.79 ± 0.20; P < 0.01). However, during the second stage of vernakalant infusion, contractility decreased without an increase in QRS width, resulting in a lack of correlation between these parameters (r = 0.25 ± 0.22; P = 0.57). The mean slope of the QRS duration–LVDp/dtmax relation was ~10⁻⁵ mmHg/s² for both vernakalant and flecainide.

Discussion

In the established model of chronic canine LBBD, with moderately depressed cardiac function, vernakalant and flecainide slow down ventricular conduction in a uniform manner, but vernakalant does so significantly less than flecainide. Both drugs equally reduced LV contractility, relaxation, and systolic blood pressure. Therefore, haemodynamic side effects appear to be comparable for both drugs.

Electrophysiological effects

In the canine model of proximal LBBD, the impulse conduction in the LV is entirely dependent on slow cell-to-cell conduction within the ‘working myocardium,’ rather than the rapid Purkinje system. Hence, the present data indicate that both drugs delay the slow cell-to-cell conduction, albeit this delay is more pronounced for flecainide than for vernakalant. The slower conduction results in a greater electrical dys synchrony, as indicated by increased VA-CM and QRS width. In combination with an unchanged VD-CM of
200°, this indicates a greater spatial imbalance between LV and RV activation. The lack of change in the main direction of conduction after the drugs certifies that the increased dysynchrony is a result of uniform slowing down of cell-to-cell conduction within both ventricles and is not a result of change in the direction of the activation wavefront. In line with these observations is the increase in MIVD, increasing significantly after flecainide and missing the 0.05 level of significance for vernakalant.

The relatively large effect of flecainide on ventricular conduction is well established, notwithstanding that most data have been derived from hearts with a normal conduction system. The increases in QRS width ranging from 11 up to 27% found in these studies are similar to the increase we observed in our dyssynchronous hearts of 34 ± 15%.

The increase in QRS width by vernakalant in the present study appears to be comparable with the observations in human hearts by Dorian et al., who reported an increase in QRS width of 11 ± 11% (15 ms) during RV pacing, which creates a similar conduction pattern as LBBB. These investigators also noted a trend towards a similar relative increase in QRS width during atrial pacing, when ventricular impulse conduction uses the rapid Purkinje system instead of the slow cell-to-cell conduction. An ~10% increase in QRS width was also found in a Phase II trial of vernakalant in patients without HF or conduction disturbances and in rat hearts.

The reduction in myocardial conduction velocity by vernakalant can be caused by a partial or less potent blockage of the fast sodium channel. The cardiac sodium channel is responsible for the fast upstroke of the cardiac action potential (Phase 0) initiating cellular depolarization and propagation of the action potential. As shown by Fedida et al., the blockade of the sodium channel is, among others, rate-dependent. The electrophysiological effects in the present study may be somewhat pronounced, due to the relatively high heart rate (150 b.p.m.), a result of the design to keep the heart rate constant although this heart rate is equal to the shortest cycle length (400 ms) used by Dorian et al. In addition, it is not uncommon that the ventricular rate exceeds 150 b.p.m. in a patient with untreated AF.

Flecainide has a 10-fold more potent $I_{Na}$ blocking capacity than vernakalant. Vernakalant is difficult to fit into the Vaughn–Williams classification since it is atrial selective. Furthermore, its capacity to both block early activated potassium channels as well as sodium channels makes it possible to group vernakalant in both Classes I and III. The disparity in effects on CV, QRS width, and total AT between vernakalant and flecainide in the present study reflects these known differences in binding kinetics and relative potency on sodium channel activity.

Blockage of ventricular potassium channels by vernakalant could theoretically prolong QTc, but this was not observed. The lack of significant increase in repolarization time caused by vernakalant can potentially be attributed to concomitant blockage of sodium currents. The minor effects of vernakalant and flecainide on QTc are comparable with findings in previous studies and appears to be in line with the

![Figure 2](image_url)

**Figure 2.** Left panel: example of a 3D representation of cardiac activation, the ring of dots representing the location of the electrodes from which the short-axis maps in the other panels are derived. The short-axis views depict the ATs (colours) in a vernakalant and flecainide experiment and the size and amplitude of the activation vector (arrow). The VA-CM values below the figures refer to the mean values and standard deviation (SD) of the groups of animals.
absence of ventricular arrhythmias in earlier studies and in the present study.

Haemodynamic effects

An important and interesting finding, in this model with at most mild cardiac dysfunction, is the relation between dyssynchrony (QRS width) and contractility (LVdP/dtmax). This implies that the negative inotropic effect of these drugs is related to their decrease in conduction velocity. This is especially strong during the first stage of infusion of the drugs. This relationship fits with the known adverse effect of any dyssynchrony on cardiac pump function, such as LBBB and RV pacing. However, the QRS width—LVdP/dt_max relation may also be secondary to reduced calcium loading as a consequence of the drug-induced sodium channel blockade. The latter idea seems supported by the disappearance of this correlation during the second stage of infusion of vernakalant.

The increase in dyssynchrony seems to affect not only LV systolic function but also relaxation, as reflected by an increase in LVdP/dt_min. These data indicate that special attention seems warranted in patients with AF in NYHA Class I or II and a conduction disorder, since myocardial conduction may be even slower than in our animal model.

Vernakalant and flecainide both caused a mild reduction in blood pressure. The hypotensive effect of flecainide is also known from previous studies, and could be related to the decrease in LVdP/dt_max. Flecainide is known to induce hypotension in almost a quarter of the patients. The present study suggests that special attention may be warranted for patients with a wide QRS complex in this regard.

The mild hypotension induced by vernakalant was, in our model, preceded by a brief hypertensive phase (data not shown). Such increase in LV systolic pressure has been observed earlier in a human study where a slight increase in blood pressure of 3 mmHg was found at a plasma concentration of 3 μg/ml, the plasma level also reached in our study. Correspondingly, vernakalant increased the mean arterial pressure in conscious Beagle dogs by as much as 10%, although this increase did not reach the level of significance. Such rise in blood pressure may partly be due to peripheral vasoconstriction that was observed in an in vivo rat hind limb model. Furthermore, it appears that this vasoconstrictive effect fades out at higher plasma concentrations, as was also shown by others. The present study indicates that also a reduction in contractility may contribute to the transition from slightly elevated to slightly reduced LV systolic pressure.

Comments on the experimental model

In the animal model used in the present study, LV function is reduced by 20–30% when compared with normal canine hearts under the

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**Figure 3** Time course of QRS width (grey)/LVdP/dt_max (black) during infusion of vernakalant (top) and flecainide (bottom). Mean values and SD are presented. X-axis represents the time in minutes.
same conditions, but no overt HF is present, based on relatively low end-diastolic pressures. Cardiac dysfunction and conduction may therefore approach those of patients with NYHA Class I and a wide QRS complex. This is a specific subset of patients in which both drugs are not contraindicated, but these patients potentially are more susceptible to the negative effects described above. Besides the specific subset of patients, this model sets a baseline dys-synchrony condition, concealing the effect on the Purkinje system.

We specifically paced at a fixed atrial rate to ascertain that the observed haemodynamic and electrical changes were not influenced by changes in heart rate. The constant heart rate during the protocol also resulted in low variability between doses and protocols, so any electrical or haemodynamic changes cannot be attributed to differences in heart rate.

It is also important to consider that these data have been acquired in anaesthetized animals. It is not known as to whether midazolam/sufentanil anaesthesia modulates the effects reported here or whether the effects are reproducible in awake animals. On the other hand, many factors not present in isolated cell or isolated muscle models can be taken into account in the canine LBBB model. In that regard, it is interesting that a recent study in isolated trabeculae from explanted human hearts did not find a negative inotropic effect of vernakalant. An important difference between isolated papillary muscle preparations and our in vivo model is that the muscles are field stimulated and, therefore, are not dependent on cell-to-cell conduction. Therefore, the slower impulse conduction, as reported here for vernakalant in the present study, would not influence conduction in the isolated muscle preparation. In addition, isolated preparations are not connected to the peripheral circulation and to feedback systems in the body, such as the autonomic nervous system. In contrast, the current in vivo model gives a closer approximation of the clinical situation, especially for patients with LBBB. Clearly, the results of the present in vivo animal study warrant confirmation in patients to properly judge their clinical relevance.

Conduction velocity was calculated using the pace electrode as reference for time of activation. However, that approach creates two uncertainties. First, there is an unknown delay between the stimulus and actual depolarization of cells underneath the pace electrode. Secondly, the size of the first activated area depends upon the pulse strength. While these factors influence the absolute value of CV, their effect is systematic, so that a change in CV by a drug still is reliably observed.

Conclusions
From the current data, we conclude that flecainide and vernakalant cause a uniform slowing down of ventricular impulse conduction, as reflected by increases in QRS width and epicardial AT and unchanged vector direction, but that this effect is significantly smaller for vernakalant. Both drugs similarly reduce contractility, which should be taken into account when using these drugs for treatment of AF in patients with mild HF and a conduction disorder.

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Conflict of interest: None declared.


References
Real-time assessment of bidirectional block during pulmonary vein cryoablation

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Real-time assessment of the occurrence of bidirectional block during balloon cryoablation is not routinely performed.

We paced continuously inside the pulmonary vein (PV) at high amplitude (12 mA/1.0 ms) with the Achieve® catheter (lasso 7–8). These tracings illustrate the left superior PV before and during the beginning of balloon cryoablation. The left atrium (LA) was constantly captured (change in P-wave morphology—†) at a rate slightly faster than the spontaneous sinus rhythm (preserved exit conduction). Observe that the first intracardiac electrograms clearly shows a sharp PV potential (e.g. lasso 2–3 and 7–8) in spontaneous sinus rhythm (preserved entrance conduction). An ectopic beat is shown (‡) (also demonstrating preserved exit conduction because originated within the PV), followed by loss of LA capture (Δ—exit block). Immediate stopping of pacing after loss of LA capture allowed the demonstration of the entrance block (loss of PV potentials within the Achieve®). The bidirectional block was confirmed by the presence of a dissociated PV potential (black arrow) and an atrial fibrillation spontaneously induced inside this very active vein (dotted arrow) without conduction to the LA (Figure).

Real-time assessment of exit block may be of interest, as an alternative to entrance block evaluation, when PV potentials are not very clear or when the presence of far-field from the LA appendage impairs the analysis of the potentials.


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