Pulmonary vein reentry—Properties and size matter: Insights from a computational analysis

Elizabeth M. Cherry, PhD,*† Joachim R. Ehrlich, MD,‡ Stanley Nattel, MD,§ Flavio H. Fenton, PhD*‖

From the *Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, New York, †Department of Physics and Astronomy, Hofstra University, Hempstead, New York, ‡Division of Cardiology, Section of Electrophysiology, J. W. Goethe-Universität, Frankfurt, Germany, §Research Center, Montreal Heart Institute and Université de Montréal, Montreal, Ontario, Canada, ‖The Heart Institute, Beth Israel Medical Center, New York, New York.

BACKGROUND Pulmonary vein (PV) ablation plays an important role in atrial fibrillation (AF) therapy but suffers from a limited mechanistic understanding of PV arrhythmogenicity. Rapid focal activation has been suggested, but some evidence points to underlying reentry.

OBJECTIVE This study was performed to evaluate how the electrophysiological properties of PVs may make them a site for reentry and to analyze specifically the roles of PV dimensions and coupling properties.

METHODS A computer model designed to efficiently reproduce electrophysiological behaviors was fit to action potentials from canine left atria (LA) and PVs. To assess structural and functional arrhythmogenic determinants, an idealized PV of varying length and circumference was attached to LA tissue, and 5 seconds of activity after extrastimulation were simulated.

RESULTS PV reentrant activity depended critically on vein size and coupling properties. With cumulative removal of transverse and longitudinal connections, sustained (n = 23) or nonsustained (n = 93) reentries could be observed (687 simulations) for veins 1–3 cm long and 1–2 cm in circumference. The prevalence of sustained reentry increased with PV length (8% for 1 cm vs. 22% and 31% for 2 and 3 cm, respectively; P < .05 for each). The PV circumference did not affect the incidence of sustained reentry (25%, 17%, and 21% for 1-, 1.5-, and 2-cm circumferences; P = NS), but the number of reentrant events increased from 12/201 simulations for PVs with a 1-cm circumference to 48/232 and 56/254 events for PVs with 1.5- and 2-cm circumferences, respectively (P < .05). Sustained reentry cycle lengths were approximately 200–250 ms (16/23), except for the longest PVs.

CONCLUSION Reentry occurs readily in PVs with realistic properties in the context of specific connection heterogeneities. Reentry properties and incidence depend on PV anisotropy and dimensions but could certainly contribute significantly to PV arrhythmogenesis.

KEYWORDS Catheter ablation; Arrhythmia mechanism; Ion channels; Remodeling; Atrial fibrillation; Therapy; Mathematical models; Ion currents; Reentry

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Introduction

Unraveling the role of pulmonary veins (PVs) in atrial fibrillation (AF) remains an important goal for experimental and clinical research. Since the first note on the importance of AF initiation and maintenance,1 a large number of studies (at both the basic and clinical science levels) have been devoted to deciphering the mechanisms of PV arrhythmogenicity. Despite this effort, a precise mechanistic understanding has yet to evolve.

In line with initial clinical observations of rapid focal activity within the PVs, one experimental study found triggered arrhythmia due to delayed and early after-depolarizations along with increased pacemaker current in native PVs, which became exaggerated under conditions of tachycardia remodeling.2 Other work observed triggered activity only under specific conditions such as calcium overload or neurohumoral stimulation.3,4 Other studies were unable to demonstrate any focal arrhythmias.5–8 PV cardiomyocytes express a specific profile of ionic currents leading to shorter action potential (AP) duration (APD) in comparison with left atrial (LA) tissue.6 Impulse propagation within PVs is highly anisotropic owing to fiber arrangement (abrupt direction shifts and circumferential orientations) with reduced connexin (Cx) expression.5,9 These observations suggested that PVs may have a substrate that is suitable for reentry and point to a possible reentrant mechanism of PV arrhythmogenesis.
genicity. PV reentry is enhanced with neurohumoral stimulation with acetylcholine or isoproterenol. Clinical observations of PV reentry have been made in small patient series. Based on the AP and coupling properties of PV cardiomyocytes, we hypothesized that PVs may serve as a site for reentry, which may depend critically on PV size and coupling properties. To probe this possibility, we created a mathematical model that accurately reproduces the known AP properties of PV and LA cardiomyocytes and then performed in silico analysis to determine whether these properties would allow for preferential PV reentry. To vary coupling over a range of clinically relevant inhomogeneous fiber arrangement conditions, we removed longitudinal or transverse intercellular connections according to a randomization scheme.

Methods
Model generation and validation
Using previously reported data, we created a computationally efficient model of canine LA and PV myocyte APs (Figure 1). This formulation differs from more complex ionic models in that instead of reproducing as many individual currents as possible, it is designed to account for the sum of all the currents represented in three main categories: fast inward, slow inward, and slow outward currents. We have previously shown that these currents retain enough structure of the currents involved in cardiac excitation to reproduce AP morphologies accurately under a wide range of physiologically relevant conditions. Model parameters can be fitted to replicate properties and dynamics of more complex ionic models as well as of experimental data, such as APD and conduction velocity restitution curves, thresholds for excitation, upstroke velocities, and diastolic intervals.

The differential equations for the model voltage \( u \) and gates \( v \), \( w \), and \( s \) are as follows:

\[
\frac{du}{dt} = -(I_{fi} + I_{si} + I_{so}),
\]

\[
\frac{dv}{dt} = \frac{(1 - H(u - u_c))(1 - v) - H(u - u_c)v}{\tau_v} - \frac{H(u - u_c)v}{\tau_v},
\]

\[
\frac{dw}{dt} = \frac{(1 - H(u - u_c))(1 - w) - H(u - u_c)w}{\tau_w} - \frac{H(u - u_c)w}{\tau_w},
\]

\[
\frac{ds}{dt} = r_s(0.5(1 + \tanh((u - u_{c,s})k)) - s),
\]

where

\[
\tau_v = \tau_{v1} H(u - u_c) + \tau_{v2}(1 - H(u - u_c)),
\]

\[
\tau_w = \tau_{w1} H(u - u_c) + \tau_{w2}(1 - H(u - u_c)),
\]

\[
r_s = r_{s1} H(u - u_c) + r_{s2}(1 - H(u - u_c)).
\]

The transmembrane currents were computed using the following equations:

\[
I_{fi} = \frac{-v H(u - u_c) (u - u_c) (u_m - u)}{\tau_d},
\]

\[
I_{si} = \frac{-w s H}{\tau_{si}},
\]

Figure 1  Generated model APs for LA and PV cardiomyocytes were in good agreement with the experimental data on which they were based. (A, B) The PV exhibited stronger rate dependence, and the model captures correct AP morphologies for CLs of both (A) 2000 ms (experimental, gray; model, black solid) and (B) 500 ms (experimental, gray; model, black dashed). (C) In contrast, the LA exhibited minimal rate dependence and is shown at a CL of 1000 ms (experimental, gray; model, black solid). Characteristically, the LA AP had more negative resting membrane potential (−88 vs. −65 mV), larger AP amplitude (118 vs. 99 mV), and less triangular morphology than the PV AP. (D) Rate adaptation of APD_{50} for the LA (solid) and PV (dashed) models compared with experimental results (filled circles). In all cases, the model voltage in millivolts is given by rescaling the normalized variable \( u \) as 118u−88.
$I_{so} = \frac{(u - u_{iso})(1 - \text{H}(u - u_{iso}))}{\tau_{so}} + \text{H}(u - u_{iso})\tau_a + 0.5(a_{so} - \tau_a)(1 + \tanh((u - b_{so})/c_{so}))$,

where

$$\tau_{so} = \begin{cases} 1.3\tau_0 & \text{if } u \geq 0.35 \\ (5.25 - 12.8571u)\tau_0 & \text{if } 0.35 > u \geq 0.28 \\ 2.2\tau_0 & \text{if } u < 0.28 \end{cases}$$

for the PV model and $\tau_{so} = \tau_0$ for the LA model. Throughout, the Heaviside function $\text{H}(x)$ had the value of 1 if $x > 0$ and 0 otherwise. The values of all parameters are given in Table 1. Initial conditions were $u = 0$, $v = 1$, $w = 1$ and $s = 0$.

The model successfully reproduces representative AP morphologies for the PV and LA experimental data at different cycle lengths (CLs), as shown in Figures 1A–C. In accordance with experimental findings, rate dependence is evident, the Heaviside function $\text{H}(x)$ had the value of 1 if $x > 0$ and 0 otherwise. The values of all parameters are given in Table 1. Initial conditions were $u = 0$, $v = 1$, $w = 1$ and $s = 0$.

The model successfully reproduces representative AP morphologies for the PV and LA experimental data at different cycle lengths (CLs), as shown in Figures 1A–C. In accordance with experimental findings, rate dependence is more pronounced for the PV model than for the LA model (Figure 1D).

### Creation of three-dimensional PV geometry

To analyze PV-LA interactions, we created a simplified geometry of a single PV attached to a piece of LA (Figure 2). The model is quasi-three-dimensional, with the vein attaching orthogonally to the plane of the LA. The PV itself was topologically a cylinder, as there were no edges, and its length and circumference were varied to investigate the effects of PV dimensions on the induction and maintenance of reentry. The vein representations that were used correspond to the portion of the PVs containing cardiomyocytes, that is, myocardial sleeves. For simplicity, the LA sheet was a square with the same length as the PV (1, 2, or 3 cm). To reproduce periodicity in the atria, periodic boundary conditions were used along one direction of the LA, while zero-flux boundary conditions were used for the other. The LA was paced at a CL of 700 ms to simulate normal sinus rhythm. All simulations lasted 5 seconds. In total, 1067 simulations were performed.

### Simulation of anisotropic conduction

The LA-PV tissue structure was integrated numerically following the standard cable equation formulation, using the explicit Euler method with a time step of 0.075 ms and a spatial resolution of 0.0125 cm. The diffusion coefficient was set to 0.00025 cm$^2$/s for the longitudinal cell direction. The transverse diffusion coefficient was set to 10% of the longitudinal diffusion value (in accordance with the normal 10:1 atrial anisotropy ratio) except in the reduced anisotropy case, in which it was set to 20%.

### Randomization procedure

To introduce heterogeneity within the PV, specified fractions of the cell-to-cell connections both longitudinally along the length of the vein and transversely around its circumference were removed, mimicking properties seen histologically. Simulated cells were arranged in a grid. Each of the connections to neighboring cells had a discrete probability of being removed, leaving the cell and its neighbor in that direction disconnected. For convenience, the fractions of connections removed were always multiples of 5. The specific locations of disconnections affected propagation patterns within the vein, so results depended to some extent on the specific randomization used. Therefore, simulations were repeated using different randomizations to characterize this effect.

### Data analysis

Reentry was classified as nonsustained (<2 seconds) or sustained (≥2 seconds). Statistical comparison between groups was performed using Fisher’s exact test and Student’s t-test as appropriate.

### Results

Because of the slow and heterogeneous nature of PV propagation, discontinuous conduction could give rise to a reentrant circuit that could activate the LA. Figures 2 and 3 and the accompanying interactive movies (see online Supplement) depict two examples of rapid PV activity caused by circus movement reentry within the PV and driving the LA. In Figure 2, a premature atrial activation induced a PV reentrant wave that repetitively activated the LA. Heterogeneous refractoriness in the vein after the sinus beat blocked

### Table 1  Parameter values for LA and PV models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_c^e$</td>
<td>3.33</td>
</tr>
<tr>
<td>$\tau_c^{rl}$</td>
<td>19.2</td>
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<tr>
<td>$\tau_c^{gl}$</td>
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<tr>
<td>$\tau_w$</td>
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<td>$\tau_{\theta1}$</td>
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<tr>
<td>$\tau_{\theta2}$</td>
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<tr>
<td>$\tau_d$</td>
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<tr>
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<tr>
<td>$\tau_0$</td>
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<td>$\tau_a$</td>
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<tr>
<td>$u_c$</td>
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<tr>
<td>$u_v$</td>
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<td>$u_w$</td>
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<td>$u_0$</td>
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<tr>
<td>$u_m$</td>
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<tr>
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<tr>
<td>$u_{\theta2}$</td>
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<td>$r_{a1}$</td>
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<td>$r_{a2}$</td>
<td>1.2</td>
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<td>$a_{so}$</td>
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<tr>
<td>$b_{so}$</td>
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</tr>
<tr>
<td>$c_{so}$</td>
<td>0.02, 0.07</td>
</tr>
</tbody>
</table>

Values that differ for LA and PV are given as LA value, PV value.
the premature beat from propagating within the vein in most locations, but propagation occurred in one area. This small wave initiated a figure-of-8 reentrant circuit along the vein (indicated by the arrows) that repetitively activated the LA at a CL of 250 ms. In Figure 3, a single reentrant beat was initiated without a premature beat. In this case, the heterogeneous conduction of the sinus beat allowed reentry to occur. Two areas largely disconnected from their neighbors closer to the LA were activated by a neighboring area between them, but the large current required to do so caused the area to repolarize more quickly and contributed to block distal to that site. As the wave continued to propagate, it was able to propagate retrogradely toward the LA through the repolarized region and activate the LA.

**Nonsustained and sustained PV reentry**

In some cases, reentry was nonsustained (<2 seconds) and activated the LA once or a small number of times. In other cases, reentries were sustained (≥2 seconds) and recurrently activated the LA. Figure 4 illustrates different types of nonsustained and sustained activity that occurred within the PV-activating LA tissue, with premature and simulated sinus beat timings indicated by dotted vertical lines. If a large number of connections remained, activation from the LA propagated along the entire length of the vein. If too few connections remained, activation from the LA was blocked completely and did not propagate along the vein at all. For fractions of connections between these two cases, reentries could develop within
the vein and reactivate the LA sporadically or repetitively (n = 116 of 687 simulations using the nine possible combinations of vein lengths of 1, 2, and 3 cm and circumferences of 1, 1.5, and 2 cm). While the premature beat usually was necessary to induce reentry, this was not always the case, as shown in Figure 3 and in Figure 4A, where reentrant activation occurred before the early beat. However, such reentries (n = 16 of 116) were never sustained and activated the LA at most twice (n = 1 of 16) before self-terminating. With the premature beat present (n = 100 of 116), the LA could be reactivated one (n = 58; Figure 4B) or more (n = 19; Figure 4C) times during a nonsustained reentry (n = 77). For sustained reentries (n = 23), sinus activity in some cases was masked entirely by the driving PV reentry, which prevented all subsequent sinus beats from capturing the LA.

Figure 3 The mechanism of PV activation of the LA due to heterogeneous venous conduction without the necessity of a premature beat. To allow simultaneous viewing of the entire vein surface, the PV was unwrapped as indicated on the left. The sinus beat propagated heterogeneously along the vein. Because of disconnections, some portions of the vein were not activated as the wave propagated away from the LA but instead were activated as the wave turned and reentered down the length of the vein toward the LA, along the direction of the arrows. The reentrant wave then activated the LA. Vein length is 1 cm, and circumference is 2 cm, with 30% longitudinal and 65% transverse disconnections.

Figure 4 Types of nonsustained (<2 seconds, A–C) and sustained (≥2 seconds, D–F) activation of the LA due to heterogeneous conduction leading to reentry within the PV. Both regularly occurring sinus beats and the single premature beat at 285 ms are indicated by vertical dotted lines. Five seconds of activity are shown. Vertical bars to the left of the trace indicate the percentages of transverse and longitudinal disconnections; lower and upper horizontal bars represent 0 and 100% disconnection, respectively. (A) In 17% of all nonsustained activity shown in Figure 6 (16 of 93 cases), reentry occurred within the PV and activated the LA before the premature stimulus, which was blocked. Conversely, reentry occurred after the premature stimulus in 77 of 93 cases. (B) In 78% of all nonsustained activity shown in Figure 6 (73 of 93 cases), a premature stimulus initiated reentry that produced a single activation in the LA. (C) In 22% of all nonsustained activity shown in Figure 6 (20 of 93 cases), multiple activations in the LA were elicited. (D) The recurrent activation of the LA was completely independent of subsequent sinus beats for 17% of all sustained activity shown in Figure 6. (E, F) For the remaining sustained activity shown in Figure 6, the recurrent LA activation interacted regularly with simulated sinus beats (E, 4%) or intermittently (F, 78%). Vein length was 3 cm in panel A, 1 cm in panel E, and 2 cm in all other panels. Vein circumference was 1 cm in panel C and 1.5 cm in all other panels. For panels A–F, respectively, longitudinal disconnection percentages were 45%, 45%, 20%, 80%, 55%, and 35%; and transverse disconnection percentages were 55%, 45%, 75%, 15%, 40%, and 60%.
(n = 4 of 23; Figure 4D). In other cases, the sinus beats interacted with the PV reentry. In rare cases, interactions with sinus beats were necessary to sustain the reentry (n = 1 of 23), which manifest as bigeminy (Figure 4E). Often, sinus activity complicated the LA activation sequence by propagation from PV reentries and by some sinus beats (n = 18 of 23; Figure 4F).

**Role of anisotropic conduction**

To assess the coupling conditions associated with sustained reentry, we plotted activity type as a function of longitudinal and transverse disconnection percentages for a given vein length and circumference. Figure 5 indicates activity for combinations of longitudinal and transverse disconnections for a vein of length 2 cm and circumference 1.5 cm with normal (high) and reduced (low) anisotropy. A total of 84 and 72 combinations were tested for this vein size for high and low anisotropy (Figure 5), respectively. When high anisotropy was used, the longitudinal and transverse disconnection percentages that gave rise to nonsustained or sustained reentry occurred along a diagonally oriented band where the sum of the longitudinal and transverse disconnection percentages was between 90 and 105, with four sustained and 14 nonsustained events. Thus, for highly anisotropic tissue, it is primarily the total percentage of connections that matters for reentry induction, rather than the percentage of longitudinal or transverse disconnections alone. Among nonsustained events, eight activated the LA only a single time before terminating (including one that occurred before the premature stimulus), five activated the LA twice, and one activated the LA three times. The effect of low anisotropy was also tested for the same size vein (Figure 5B). Under these conditions, reentry was much more difficult to induce: only one nonsustained reentrant event occurred.

**Influence of PV geometry**

Similar plots for different PV lengths (1, 2, and 3 cm) and different circumferences (1, 1.5, and 2 cm) using normal (high) anisotropy are shown in Figure 6. Reentry again occurred along the diagonally oriented band with the sum of the longitudinal and transverse disconnection percentages totaling between 85 and 105. When the absolute numbers of longitudinal and transverse disconnection combinations resulting in reentry and the relative frequency of nonsustained versus sustained reentry were grouped according to vein length or vein circumference, several trends appeared (Figure 7). The absolute number of reentrant events did not vary much with PV length, but the percentage of reentries that were sustained increased with length (Figure 7A), from 8% for a length of 1 cm to 22% and 31% for lengths of 2 and 3 cm, respectively (P < .05 each). When the circumference was increased, the percentage of reentries that were sustained remained roughly constant (25%, 17%, and 21%, P = NS), but the absolute number of reentrant events increased from 12 events for a circumference of 1 cm to 48 and 56 events for circumferences of 1.5 and 2 cm, respectively (P < .05; Figure 7B). The CLs of sustained reentries did not vary much with either vein length (230.7 ± 6.4, 230.6 ± 13.3, and 287 ± 79.8 ms for lengths of 1, 2, and 3 cm, respectively).
cm; $P = \text{NS}$) or vein circumference ($261.3 \pm 63.3$, $251 \pm 44.8$, and $266.0 \pm 77.8$ ms for circumferences of 1, 1.5, and 2 cm; $P = \text{NS}$) and fell primarily between 200 and 250 ms ($n = 16$ of 23). However, the longest vein length of 3 cm also was capable of supporting slower reentries with CLs between 250 and 333 ms ($n = 7$ of 23; Figure 7C).

**Influence of randomization scheme**

Because the propagation pattern depended on the specific locations of disconnections, the series of random numbers generated to specify disconnection locations affected the values of disconnection percentages that resulted in reentry. Figure 8 presents results obtained using four additional
randomization sets for a vein length of 2 cm and circumference of 1.5 cm. When compared with each other and with the high-anisotropy case in Figure 5, which depicts the same size vein using a fifth randomization scheme, the average number of reentrant events was 15.6 ± 4.0, and the average percentage of sustained events was 20.9% ± 12.0%. The number of cases in which reentry developed without the need for the premature beat also varied with the randomization scheme between 0 and 4, with an average of 1.4 ± 2.8 and representing 8.5% ± 1.0% of the reentries. Differences in the specific disconnection values leading to reentry also occurred. However, the average CLs of non-sinus-dependent sustained reentries for the four randomization schemes that produced sustained reentry remained constant (230, 224, 232, and 241 ms; \( P = \text{NS} \)), and overall trends for the relationship between uncoupling and reentrant activity were qualitatively the same.

**Discussion**

AF is a highly prevalent arrhythmia with substantial impact on morbidity, mortality, and health care costs. PV-focused interventional therapy is having a significant impact on AF burden. In the present study, we examined the role of PV properties and geometry in the generation of reentrant PV activation using a computer model.

**PV reentry as a potential mechanism for AF induction and sustenance**

Previous clinical observations have highlighted the importance of focal PV activity in initiating AF. The small size of PVs would seem to make PV reentrant activity unlikely; however, previous work indicated a possibility of inducing sustained reentrant tachycardia (with CLs between 114 and 280 ms) within 2.6% of isolated PVs after ablation, and Belhassen et al\(^1\) reported a single case of AF initiated by local reentry within the right superior PV. Most observations of PV reentry in the present study showed tachycardia CLs between 200 and 250 ms, compatible with those observed clinically. Another study in 56 patients showed that PV tachycardia with a CL shorter than that of the LA was present in >80% of superior PVs before ablation and that the inducibility of sustained AF decreased after PV isolation. The investigators accordingly concluded that PV tachycardia may contribute to AF maintenance.\(^16\) Kumagai and coworkers\(^12\) used a 64-pole basket catheter to map human PVs during electrophysiologic study. Focal discharges from the distal PV often initiated reentry at the LA-PV border. Anisotropy in impulse conduction within the vein was important for reentry, in line with the importance of anisotropy in our study. Such behavior of PVs is supported by experimental work demonstrating regional heterogeneity in Cx distribution. Cx40 was predominantly located at the lateral sides of atrial myocytes, and a reduced amount was found in PV tissue, compatible with locally increased anisotropy.\(^17,9\)

Experimental studies of basic PV electrophysiology have identified electrical and structural characteristics distinct from the LA. A detailed characterization of PV features found less negative resting membrane potential owing to reduced \( I_{K1} \). Combined with increased delayed rectifier potassium currents and decreased inward calcium currents (consequently shorter AP duration), this suggested a potential substrate for reentry in PVs.\(^6\) PV cardiomyocytes exhibited increased constitutively active Kir3-current leading to enhanced PV repolarization with relevance for tachyarrhythmias. These findings are in line with PVs being a preferred site for reentry.\(^18,19\) Optical mapping demonstrated both focal activity and reentry in PVs.\(^10\) Sustained PV reentry was only inducible after adrenergic stimulation, hinting at the importance of neurohumoral factors. Recent work by Po and coworkers\(^8\) using a combined approach of optical mapping and microelectrode recording confirmed that PVs may provide a favorable substrate for reentry formation. Sustained PV tachycardias required the presence of acetylcholine and were very rapid (mean CL 93 ± 15 ms) and were accompanied by classical electrophysiological criteria for reentry, which was confirmed by optical mapping.

In contrast, other studies observed only nonreentrant focal PV activity after remodeling induced by rapid atrial pacing.\(^20\) Similarly, Honjo et al\(^2\) found ectopic PV activity in remodeled states with interventions leading to intracellular calcium overload like ryanodine or beta-adrenergic stimulation.
Role of PV size for AF initiation and reentry generation

Our results suggest that PV circumference and length may be important determinants of PV reentry. Our three-dimensional PV was modeled with canine PV sizes rather than with human sizes since the model was based on canine data. A broad range of human PV sizes has been reported, and the circumferences we tested are toward the smaller end. Verheule et al reported canine PV myocardial sleeve lengths of 0.4–2.0 cm, similar to the lengths used here. In clinical studies, arrhythmogenic PVs have larger diameters than nonarrhythmogenic PVs, and there is evidence that conditions associated with paroxysmal AF (e.g., arterial hypertension) increase PV diameter, potentially creating conditions for persistent reentry. Similarly, increased atrial pressure leads to faster activation and organization of waves emanating from the PV regions in a sheep model.

Potential limitations

The randomization has an influence on which specific combinations of connection removals lead to reentry. The sheer number of simulations required prevented us from testing randomization for more than one vein length/circumference combination. The results presented in this manuscript already combine the outcomes of more than 1000 individual simulations. Although the specific numbers of reentrant events and the specific longitudinal and transverse disconnection percentages producing reentry were not identical with different randomizations, we observed the same mechanism giving rise to reentry independent of the randomization used.

This study was performed entirely in silico and did not include in vivo confirmation, for example, by optical mapping. It would be very interesting to induce PV reentry in intact cardiac preparations, perform optical mapping, and relate the tissue coupling/reentry relationship to model predictions. However, such experiments are beyond our present technical expertise. The complex PV anatomy poses significant obstacles to detailed optical mapping, and it is not presently possible to map electrical coupling of an in situ tissue at the microscopic level that would be necessary. Because of these practical limitations, our study was designed to determine whether reported PV AP and coupling properties are sufficient to permit PV reentry and, if so, to define the properties of...
such reentry in terms of CL, sustainability, and dependence on PV anatomy and coupling. We were able to show that the known features of the PVs allow reentry to be initiated and maintained within them and that there are specific determinants in terms of PV dimensions and coupling. Some of the predictions of our model are amenable to assessment with present technologies in clinical electrophysiology laboratories, and we hope that experimental methods will advance sufficiently to permit detailed testing within in situ systems.

**Conclusion**

The present study suggests that PV reentry in PVs can occur with realistic PV properties. PV reentry is dependent on heterogeneous and anisotropic conduction and occurs more frequently in wider veins, while it is more often sustained in longer veins. This work helps to improve our understanding of the potential mechanisms and determinants of PV arrhythmogenic activity.

**Supplementary data**

Please see online version of this article to view accompanying videos.

**References**


