Distinguishing Properties of Cells From the Myocardial Sleeves of the Pulmonary Veins

A Comparison of Normal and Abnormal Pacemakers

Sandra A. Jones, PhD; Mitsuru Yamamoto, MD; James O. Tellez, PhD; Rudi Billeter, PhD; Mark R. Boyett, PhD; Haruo Honjo, MD; Matthew K. Lancaster, PhD

Background—A common source of arrhythmogenic spontaneous activity instigating atrial fibrillation is the myocardial tissue, or sleeves, at the base of the pulmonary veins. This study compared the properties of cells from the myocardial sleeves of the pulmonary veins (PVm) with cells from the normal cardiac pacemaker (the sinoatrial node) and regions of the atria. Our objective was to identify key features of these cells that predispose them to becoming the focus of cardiac arrhythmias.

Methods and Results—Single cells were isolated from samples of rabbit PVm, central and peripheral sinoatrial node, crista terminalis, and left and right atria. Detailed morphology of cells was assessed and intracellular calcium concentrations measured with the use of Fluo-3. Cells from the PVm were smaller than atrial cells and showed large elevations in diastolic calcium during activation at physiological rates, a feature the PVm cells shared with cells from the sinoatrial node. Unstimulated spontaneous activity was observed in a minority of cells from the PVm, but numerous cells from this region showed spontaneous activity for a brief period immediately subsequent to stimulation at physiological rates. This was not observed in atrial cells. Assessment of calcium removal pathways showed sarcolemmal calcium extrusion in cells from the PVm to have a high reliance on “slow” extrusion pathways to maintain intracellular calcium homeostasis because of a low expression of sodium–calcium exchanger.

Conclusions—We conclude that cells from the PVm share some features with cells from the sinoatrial node but also have distinctly unique features that predispose them to the development of spontaneous activity. (Circ Arrhythmia Electrophysiol. 2008;1:39-48.)

Key Words: arrhythmia ■ pacemakers ■ pulmonary vein ■ sinoatrial node ■ intracellular calcium ■ atria

The sinoatrial (SA) node is the normal site of initiation of the cardiac action potential. Cells isolated from this area of tissue show spontaneous depolarization as the result of the activation of various ionic fluxes, many of which are strongly modulated by intracellular calcium. Regulation of intracellular calcium, however, is not uniform when cellular properties are compared across the nodal structure, and this variance in regulation correlates with differences in spontaneous activity.1

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Intracellular calcium regulation is critical not only for the modulation and generation of the cardiac action potential at its normal origin. Disruption of calcium regulation also can lead to the initiation of ectopic and potentially arrhythmogenic activity. Clinically, the most important origin of supraventricular ectopic activity is the proximal tunica-media of the pulmonary veins.2 Commonly referred to as the myocardial sleeves of the pulmonary vein (PVm), where the left atrial tissue surrounds the insertions of the pulmonary veins, it is well established that this site is a common focus for the formation of atrial fibrillation. Bursts of spontaneous activity arising in the PVm tissue can initiate such arrhythmias, and encircling ablation of this region has proved in many cases an effective treatment of sustained atrial fibrillation, even in patients resistant to pharmacological interventions.3

Simple maneuvers known to produce increases in diastolic calcium in cardiac tissue promote spontaneous activity from the PVm region.4 Increasing the cardiac beating rate and applying cardiac glycosides are common physiological and clinical manipulations that increase intracellular calcium in cardiac tissue, improving contractile function but also increasing the risk of an event liable to promote atrial fibrillation. These findings implicate a

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From the Faculty of Biological Sciences, University of Leeds, Leeds, UK (M.K.L.); Biomedical Sciences, University of Hull, Kingston-Upon-Hull, UK (S.A.J.); Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan (M.Y., H.H.); School of Medicine, University of Manchester, Manchester, UK (J.O.T., M.R.B.); and the School of Biomedical Sciences, University of Nottingham, Nottingham, UK (R.B.).
Correspondence to Dr Matthew K. Lancaster, Institute of Membrane and Systems Biology, Faculty of Biological Sciences, University of Leeds, Leeds LS2 9JT, United Kingdom. E-mail m.k.lancaster@leeds.ac.uk
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role for intracellular calcium in driving the transition of PVm cells from bystanders in cardiac electrical activity to ectopic pacemakers. Because intracellular calcium is a potent regulator of spontaneous activity in the normal cardiac pacemaker, the SA node, does the unwanted pacemaker arising in the PVm share properties with the normal pacemaker of the heart?

Our investigation sought to assess the properties of single cells isolated from the PVm region to elucidate mechanisms underlying the propensity of cells from this region to develop dangerous spontaneous activity. The result is a comparative evaluation of the characteristics of the cells of the normal cardiac pacemaker (the SA node) and the most common ectopic source of atrial fibrillation (the PVm), together with the encircling tissue with which they interact (the atrial muscle).

Methods

Punch-biopsy samples of 1.5 mm² were taken from sites centered on the leading site of activation within the SA node (determined with activation-mapping techniques)—the periphery of the SA node and crista terminalis. Additional samples were taken from the left and right atrial muscle and PVm. All samples were from New Zealand White rabbits (n=8), and procedures were performed in accordance with the United Kingdom Animals (Scientific Procedures) Act 1986.

Single myocytes were generated by enzymatic digestion of the samples as described previously. Cells were continuously perfused by HEPES-buffered (pH 7.4) Tyrode’s solution containing 2 mmol/L Ca²⁺ at 35°C and were allowed to beat spontaneously or electrically paced by field stimulation electrodes. Measurements of intracellular Ca²⁺ were made as described previously. The rise and decay times are given from and to the half-amplitude point and the peak of the transient. As a measure of calcium transient duration, the time difference between a transient reaching half the peak systolic value and decaying halfway back to the diastolic level was used, a parameter termed “the full width at half maximum.”

Measurements of cell size and volume were performed as described previously. Briefly, cells were loaded with calcium by using the acetoxymethyl ester form of the dye (5 μmol/L, 30 minutes). By confocal microscopy (LSM 510, Zeiss, Germany) a “Z-stack” series of images was taken of each cell. From these images, 2-dimensional projections were created and the length and width at 50% of the length obtained. Three-dimensional images were constructed from the image series with Bitplane Imaris Measurement Pro (Bitplane AG, Zürich, Switzerland).

From 7 hearts, total RNA was isolated and quantitative PCR performed to assess the abundance of transcripts encoding the sarcoplasmic reticulum calcium ATPase (SERCA), ryanodine receptor (RYR), and sodium–calcium exchanger (NCX), as described previously.

Values are shown as mean±SEM. Statistical analysis of the data was performed by 1-way analysis of variance with post-hoc tests that used Holm-Sidák comparisons. Statistical differences were considered significant if P<0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Comparative Cell Morphology

Example images of cells isolated from the left atrium, right atrium, crista terminalis, PVm, and peripheral and central regions of the SA node are shown in Figure 1. Cells from the atria, crista terminalis, and PVm were rectangular in projection and cylindrical in shape. In contrast, cells isolated from the SA node showed greater heterogeneity in structure, being normally fusiform, although in some cases having multiple projections. Others, however, were cylindrical. Cells with multiple projections were found only in tissue from the center of the SA node and accounted for 7 of 30 central SA node cells analyzed.

Summary dimensional data of the cell types are shown in Figure 2. The longest cells isolated were from the crista terminalis (Figure 2A). Left and right atrial cells, together with those from the PVm and periphery of the SA node, showed no differences in length, but all were significantly longer than cells from the center of the SA node. The only differences identified in cell width were between the atrial cells and cells isolated from the PVm, center of the SA node, or periphery of the SA node, which were all significantly narrower than atrial cells (Figure 2B).

Cells from the atria, PVm, and SA node are considered to possess very few t-tubules, which make a limited contribution to membrane capacitance. With this assumption, and that of a membrane capacitance of 1 μF/cm², it is possible to make a theoretical calculation of the capacitance of the cells by using the surface area of the 3-dimensional cell images (Figure 2C). The results are in broad agreement with published literature in which capacitance has been measured with electrophysiological methods. Cells ranged in calculated...
capacitance from 40±3 pF in small cells of the central SA node to 125±6 pF in left atrial myocytes (n=15). The central cells of the SA node possessed a lower calculated capacitance than all other cell types (Figure 2C). Cells from the PVm region had a smaller calculated capacitance than left and right atrial cells but were not significantly different from cells of the crista terminalis.

Cell volumes were calculated from the rendered 3-dimensional images (Figure 2D). Cells from the central SA node had the smallest volume of all cell types studied. Atrial cells and cells from the crista terminalis were not significantly different from one another. Cells from the PVm were smaller than atrial cells but not significantly different in volume from cells from the periphery of the SA node or crista terminalis. The ratio of surface area to volume showed no significant differences apart from those between central SA node cells and cells from the crista terminalis or left atrium (Figure 2E).

To summarize, the constituent cells of the normal pacemaker of the heart are the smallest cardiac cells, with the lowest volume and capacitance, which is particularly evident in the central region of the SA node. Cells from the left or right atrium are morphologically indistinguishable, but those of the crista terminalis show subtle structural differences, being longer in length. Cells from the PVm are narrower, with a smaller volume and surface area than atrial cells, which gives them structural similarity to cells from the periphery of the SA node.
Intracellular Calcium Transients

Example calibrated recordings of intracellular calcium transients in spontaneously active single cells from the center and periphery of the SA node and electrically stimulated cells from the left atrium, right atrium, and PVm are shown in Figure 3. The SA nodal cells showed spontaneous activity at a frequency of \(2.9 \pm 0.3\) Hz. No spontaneously active cells were observed among cells from the atria or crista terminalis. Two percent of cells from the PVm showed spontaneous activity; however, such cells were not used for this part of the study. For appropriate comparison, electrical field stimulation at a frequency of 3 Hz was used to pace nonspontaneous cell types.

The initial activation of the atrial and pulmonary vein cells after a 2-minute rest period shows a staircase effect that is particularly evident in cells from the left atrium and pulmonary vein. Diastolic and systolic calcium rapidly equilibrate to a steady state in cells from the crista terminalis and atria (within \(10 \pm 3\) beats), but establishment of such a steady state takes longer in cells from the PVm, where 18 \(\pm 5\) stimuli are required.

Resting diastolic calcium did not differ significantly between nonspontaneously active cells (\(P=0.76\)). During steady-state activity at 3 Hz, cells from the periphery of the SA node had significantly higher diastolic calcium than cells from either atrium or the crista terminalis (\(P<0.001\); diastolic calcium of \(395 \pm 35\) nmol/L in SA node cells versus \(186 \pm 32\) nmol/L in left atrial cells). Cells from the PVm also had significantly higher diastolic calcium during steady-state activity at 3 Hz than did cells from the left atrial muscle. Diastolic calcium concentration in cells from the PVm was not significantly different from that observed in cells from the center or periphery of the SA node (diastolic calcium of \(309 \pm 42\) nmol/L in PVm cells versus \(288 \pm 39\) nmol/L in central SA node cells).

During steady-state activity, peak systolic calcium was significantly lower in central SA node cells (mean peak systolic calcium of \(528 \pm 85\) nmol/L) than in all other cell types.
types ($P=0.002$). Peak systolic calcium did not differ between the other cell types, which had an overall mean systolic calcium of $762\pm 51$ nmol/L. The rise time of the calcium transient did not differ significantly between any of the cells studied (Figure 4A), and the half-decay time of the transients was significantly slower in PVm cells only when compared with cells from the periphery of the SA node (Figure 4B). There was also no significant difference in the duration of the calcium transient between any of the cell types (Figure 4C).

What was surprising, however, was the slow decay to resting diastolic calcium after cessation of stimulation in PVm cells (Figure 5A). This decay was significantly slower in these cells than in cells from the atria or crista terminalis ($P=0.02$) (Figure 4E).

Intracellular calcium responses to stimulation showed considerable variability in PVm cells, which is highlighted by examples shown in Figure 5. Intracellular calcium during and on cessation of a brief period of electrical field stimulation at 1 Hz is shown in the left-hand trace of Figure 5B. A slow decay of calcium to resting diastolic levels is observed. This decay is complicated in this example by low-level oscillations of intracellular calcium during the decay phase. At these stimulation frequencies, such oscillations were observed in 3 of 18 PVm cells and were not found in any of the atrial cells studied. The incidence of calcium oscillations on ceasing stimulation increased in frequency and magnitude when cells were stimulated at 3 Hz (right-hand trace of Figure 5B); 7 of 18 PVm cells stimulated at this frequency showed spontaneous activity, with full calcium transients being produced immediately after cessation of the burst of stimulation. Such periods of spontaneous activity lasted $7\pm 3$ seconds, with a frequency of spontaneous activity at $1\pm 0.5$ Hz for the first
second, decaying to $0.6 \pm 0.3$ Hz by 5 seconds after stimulation. This accompanied a slow decline in diastolic calcium, with which the spontaneous oscillation frequency correlated significantly.

An example of a spontaneously active cell isolated from the PVn is shown in Figure 5C. Two percent of PVn cells showed spontaneous activity. When evident, spontaneous activity occurred at $0.7 \pm 0.3$ Hz, and, despite showing irregularities in periodicity, this activity was maintained for the duration of observation in a manner comparable to a cell from the SA node.

Effects of 2 μmol/L Ryanodine
Ryanodine depletes the sarcoplasmic reticulum (SR) of cardiac cells of their calcium store and can modify spontaneous activity of SA node pacemaker cells.1 In PVn preparations, it has been shown that ryanodine can promote ectopic pacemaker activity,2 a curious finding if we consider ectopic pacemaker activity to result from intracellular calcium overload. We sought to determine the effect in single cells from the PVn region.

Figure 6 shows intracellular calcium transients and the decay of calcium on ceasing stimulation in example cells from the left atrium (A) and base of the pulmonary veins (B) under control conditions and in the presence of 2 μmol/L ryanodine. Ryanodine reduced the amplitude of the calcium transient and slowed its decay in all cells apart from those from the center of the SA node (Figure 4D). The slowing of the transient was greatest in cells from the PVn. In this population of cells, the transient duration was increased to $164 \pm 7\%$ of its control value by ryanodine, compared with an average prolongation to $139 \pm 5\%$ in atrial cells.

Ryanodine was observed to produce a significant change in steady-state diastolic calcium during stimulation at 3 Hz only in cells from the PVn region, in which ryanodine reduced diastolic calcium to a level not significantly different from that found in cells from the atria and crista terminalis (diastolic calcium in ryanodine of $170 \pm 42$ nmol/L in cells from the PVn versus $156 \pm 19$ nmol/L in cells from the left atrium). The decay of calcium after cessation of stimulation was slowed by ryanodine in all nonspontaneous cells; however, the effect was greatest in cells from the PVn ($P<0.01$). Ryanodine slowed the decay of calcium to diastolic steady state by an average of $244 \pm 67\%$ in PVn cells, compared with an average slowing of $84 \pm 19\%$ in atrial cells (Figure 4F).

Assessment of Sarcolemmal and SR Calcium Fluxes
Rapid application of 10 mmol/L caffeine during stimulation at 3 Hz, or spontaneous activation in the case of SA node cells, was used to analyze the contribution of the SR to the
recorded calcium signals. The amplitude of the caffeine-evoked calcium transient, a measure of steady-state SR calcium content, was smaller in central SA node cells than in all other cell types studied apart from those from the PVm region (Figure 7A). Cells from the PVm region had a caffeine-evoked response smaller than that observed in cells from both atria and the crista terminalis. All other comparisons showed no significant differences.

The rate constant for the decay of the caffeine transient was slower in cells from the PVm than in cells from the left atrium (Figure 7B). The decay of the caffeine transient was also significantly faster in cells from either atrium than in cells from the center of the SA node. All other comparisons showed no significant differences.

Using the 2 rate constants, it is possible to estimate the amount of calcium removed at the sarcolemma by the nickel-sensitive NCX and other “slow” pathways of calcium extrusion. Comparisons showed cells from the PVm to have significantly higher efflux on these “slow” routes of extrusion than cells from all other areas studied (P<0.001) (Figure 7D). This implies that a larger proportion of calcium is removed
from these cells on exposure to caffeine by routes such as the sarcoplasmic reticulum ATPase rather than the NCX.

To further assess the basis for the differences in calcium regulation, a comparison was made of the expression of mRNA encoding the sarcoplasmic reticulum ATPase (SERCA2a), the sarcoplasmic reticulum calcium release channel (RYR2), and the sodium–calcium exchange (NCX1) between tissue from the PVm region, the center and periphery of the SA node, and the right atrium. Tissue from the PVm region proved to have significantly lower expression of mRNA encoding RYR2 than tissue from the right atrium (Figure 8A), a feature also shared by tissue from the center and periphery of the SA node. However, no significant differences in the expression of SERCA2a mRNA were found between any of the regions studied (Figure 8B).

An examination of mRNA encoding NCX1 showed the PVm region to have significantly lower amounts of NCX1 mRNA than those present in right atrial muscle or periphery of the SA node (Figure 8C). No significant difference in NCX1 mRNA expression was observed between tissue from the PVm region and center of the SA node.

In summary, cells from the PVm region showed subtle morphological distinctions from atrial cells, higher increases in diastolic calcium during steady-state stimulation at physiological frequencies, and a slower decay in diastolic calcium on ceasing stimulation. This slow decay appears to be due to a lower amount of NCX expression and activity. A smaller SR store of calcium than that present in the surrounding atrial tissue was also observed. Application of ryanodine significantly reduced the calcium transient and diastolic calcium in PVm cells; however, it also further slowed the decay of diastolic calcium on cessation of stimulation. The observed calcium regulation characteristics are associated with the observed potential for, and incidence of, spontaneous activity in cells from the PVm region and demonstrate many parallels to characteristics of cells from the SA node, while also proving to be a distinct cellular phenotype. The heterogeneity of responses, including a subpopulation of cells with spontaneous activity, offers further insight into a heterogeneous tissue with high potential for erratic electrical activity.

**Discussion**

Considerable heterogeneity of cellular properties exists within the SA node, a heterogeneity that seems important for the functioning of the normal cardiac pacemaker.11 Here we have noted significant structural differences across the SA node and also made comparisons between the cells of the SA node and other areas regulating the electrical activity of the atria and initiation of the heart beat. The center of the SA node contains small, diverse cells with small calcium transients and a small internal calcium store during steady-state function. Progressing from this point, the cardiac action potential propagates through the cells of the peripheral SA node, which, while displaying spontaneous activity, also show some structural similarities to the cells of the atria, although being narrower in width and smaller in volume. At the crista terminalis, the cardiac action potential accelerates away to rapidly spread to the rest of the heart. The crista terminalis is one of the key pathways linking the SA node and atrioventricular node of the heart. The long cells found in this region are well suited to rapidly conducting the action potential between these nodes, although in other respects they
appear the same as atrial cells. The cells of the 2 atria proved to have no significant differences when compared in terms of the properties studied, but they provide the mechanical function leading from the electrical activity arising in the specialist tissues embedded within them.

**Distinguishing Features of PVm Cells**

Cells from the PVm tissue were narrower and smaller than atrial cells, giving them structural similarities to cells from the periphery of the SA node. Further features distinguishing cells of the PVm region from the left atrial tissue were the changes in intracellular calcium observed during simple maneuvers.

During rest, cytosolic calcium did not significantly differ between normally quiescent cell types, including cells from the PVm. However, during steady-state stimulation at 3 Hz, diastolic calcium rose to a higher level in PVm cells than in cells from the atria or crista terminalis, a level not significantly different from that observed in the spontaneously active cells of the SA node. This high diastolic calcium has previously been shown to be important for moderating and instigating spontaneous activation in the SA node.

A further significant distinguishing feature was observed when the decay of intracellular calcium on ceasing stimulation was compared. The decay was protracted in cells from the PVm compared with those from the atria or crista terminalis. This slow decay to resting cytoplasmic levels increased further in the presence of ryanodine, an effect that apparently is associated with enhanced probability and occurrence of spontaneous rhythm generation in the PVm region.

As a contrast to the present work, a recent study failed to identify differences in intracellular calcium regulation between cells from the canine PVm region and atrial muscle. However, a further study, also in canine heart, reported that spontaneous activity from the PVm region is associated with voltage-independent calcium release. How do we reconcile these differences? The study by Chou et al. noted finding “node-like” cells, as previously identified by others in the rat pulmonary vein. These cells, mainly located in the endocardium of the PVm area, were postulated to contribute to spontaneous activity in this region. Reconciling these studies with our data, we show that significant cellular heterogeneity exists within this region of the heart. Cells from the PVm region display properties in many cases comparable to those of the peripheral SA node, particularly in terms of calcium regulation, some structural features, and, in 2% of cases, spontaneous activity. What remains to be answered is whether it is specifically this subset of cells from this region that are the cause of the unwanted activity and whether these are the spontaneous cells identified by other studies. As such, we remain uncertain whether differences between our data and the data of Coutu et al. represent a species difference or an example of heterogeneity of cell populations confounding the achievement of a simple conclusion. Such heterogeneity of observation has previously presented problems for inter-

The spontaneous activity observed, however, showed considerable heterogeneity and irregularity, in contrast to cells from the SA node. Presumably, this might reflect a lack of the plethora of controlling currents that combine to regulate the activity of SA node tissue. The finding of such heterogeneous responses and activity in the PVm cell population indicates that, as is the case within the SA node, the PVm region is heterogeneous in composition. As such, the arrangement and combination of the cells in the PVm region is an important future consideration for understanding why this region is a potent source for ectopic activity. Parallels to the SA node structure continue because it has also been shown that cells from the PVm have a reduced expression of connexin 43 relative to the surrounding atria. In the SA node, a similar profile of gap-junction expression is important to prevent suppression of the spontaneous activity of the node and operates in conjunction with the heterogeneity of the SA node structure to permit pacemaker function. A similar functional arrangement may play a role at the base of the pulmonary veins and contribute to the formation of a viable ectopic pacemaker. That this region is not normally spontaneous shows that the identified spontaneously active cells must, however, normally be suppressed, either by virtue of electrotonic interactions with surrounding tissue or by the fact that their slow intrinsic rate means they are normally overdrive suppressed. Further studies of the expression of connexin 43 with connexins 45 and 40, the latter known to be prevalent in the pulmonary myocardium, along with high-resolution conduction studies and appropriate modeling, will help answer the question of how the ectopic pacemaker forms and operates. It remains unclear whether the few spontaneously active cells identified can be responsible for forming an ectopic pacemaker and whether such cells are grouped or part of a more distributed architecture within the PVm region.

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pretting the pacemaker activity of the SA node. For now, the evidence suggests that structural, electrical, and calcium-regulatory factors combine to make the PVm region such a prevalent source for ectopic and arrhythmogenic activity.

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**Disclosures**
None.

**References**

**CLINICAL PERSPECTIVE**

Normally, the cardiac action potential originates at the center of the sinoatrial node, from whence it radiates through the periphery of the node to the right atrium, left atrium, and crista terminalis, which conducts the action potential to the atrioventricular node. In atrial arrhythmias, this process is disrupted because of ectopic pacemaker activity or disruption of the normal conduction pathway. A commonly identified focus for such atrial arrhythmias is ectopic pacemaker activity from the base of the pulmonary veins. Indeed, encircling ablations of this area have proved effective in treating atrial arrhythmias. A detailed comparison of cells from across the atria, sinoatrial node, and myocardial tissue at the base of the pulmonary veins revealed distinctive differences in cellular morphology and regulation of intracellular calcium. A limited number of cells from the base of the pulmonary veins show spontaneous activity when isolated, although at a lower frequency than pacemaker cells from the sinoatrial node. Other cells from this region showed large increases in diastolic cytoplasmic calcium concentrations when stimulated at elevated frequencies. The increased calcium concentrations were associated with subsequent bursts of spontaneous activity when stimulation was halted. The implication is that physiological and medical interventions that elevate diastolic calcium will predispose to arrhythmogenic activity from the myocardial tissue at the base of the pulmonary veins. However, cells from this region show a distinctive profile of expression of transporters that buffer intracellular calcium, which indicates that directed interventions may prove able to suppress arrhythmogenic activity in this disruptive area of the heart.
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