Turbulent electrical activity at sharp-edged inexcitable obstacles in a model for human cardiac tissue

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Submitted 8 August 2013; accepted in final form 26 July 2014

Majumder R, Pandit R, Panfilov AV. Turbulent electrical activity at sharp-edged inexcitable obstacles in a model for human cardiac tissue. Am J Physiol Heart Circ Physiol 307: H1024–H1035, 2014. First published August 8, 2014; doi:10.1152/ajpheart.00593.2013.—Wave propagation around various geometric expansions, structures, and obstacles in cardiac tissue may result in the formation of unidirectional block of wave propagation and the onset of reentrant arrhythmias in the heart. Therefore, we investigated the conditions under which reentrant spiral waves can be generated by high-frequency stimulation at sharp-edged obstacles in the ten Tusscher-Noble-Noble-Panfilov (TNNP) ionic model for human cardiac tissue. We show that, in a large range of parameters that account for the conductance of major inward and outward ionic currents of the model [fast inward Na+ current (I_{Na}), L-type slow inward Ca2+ current (I_{CaL}), slow delayed-rectifier current (I_{Ks}), rapid delayed-rectifier current (I_{Kr}), inward rectifier K+ current (I_{K1})], the critical period necessary for spiral formation is close to the period of a spiral wave rotating in the same tissue. We also show that there is a minimal size of the obstacle for which formation of spirals is possible; this size is ~2.5 cm and decreases with a decrease in the excitability of cardiac tissue. We show that other factors, such as the obstacle thickness and direction of wave propagation in relation to the obstacle, are of secondary importance and affect the conditions for spiral wave initiation only slightly. We also perform studies for obstacle shapes derived from experimental measurements of infarction scars and show that the formation of spiral waves there is facilitated by tissue remodeling around it. Overall, we demonstrate that the formation of reentrant sources around inexcitable obstacles is a potential mechanism for the onset of cardiac arrhythmias in the presence of a fast heart rate.

From the point of view of the genesis of cardiac arrhythmias, the most important effect of conduction inhomogeneities is the development of functional blocks in the path of a propagating wave and the subsequent formation of reentrant sources of arrhythmias, i.e., spiral waves. In most cases, such propagation blocks result from source-sink mismatch, i.e., the condition that arises when the local current generated by the wave front has to be spread to a large area because of tissue geometry and the wave cannot sufficiently excite the tissue in front of it. This situation has been studied by Rohr et al. (56), who have shown that, at the point of abrupt expansion of cardiac tissue, wave propagation can be slowed down or blocked. Similar effects in two-dimensional (2D) geometry, for the interaction of the wave front of a plane wave stimulus with a narrow isthmus, have been investigated both experimentally and numerically by Cabo et al. (9). In an experimental preparation of sheep ventricular epicardial tissue, they created isthmuses, both parallel and perpendicular to the fiber orientation, and observed that the planar wave front of the electrical stimulus is diffraction at the isthmus to an elliptical front, with curvature similar to that produced by point stimulation. The curvature of the front varies as a function of distance from the isthmus. The velocity of the wave front is also affected. Their studies reveal that changes in curvature may lead to slow conduction or propagation block. However, in the situations studied by Cabo et al. (9) and Rohr et al. (56) wave breaks lead to the total blockage of wave propagation; they do not result in the formation of reentrant sources of arrhythmias.

Situations in which the conduction heterogeneities may result in the formation of new arrhythmia sources were studied in a 2D active medium, described by the simplified Fitz-Hugh-Nagumo equations, by Panfilov and Pertsov (47). They showed that when an electrical wave bends around an inexcitable strip, the wave detaches from the boundary with the formation of a tip; this tip eventually evolves into a rotating spiral wave. This effect was then studied theoretically and experimentally by Cabo et al. (10) in sheep epicardial tissue, by using voltage-sensitive dyes and video imaging techniques, under the influence of high-frequency stimulations or with partial blockage of the Na+ channels of the myocyte cell membrane. Such destabilization led to the formation of self-sustained vortices of electrical activity in the heart, in a manner similar to vortex shedding in hydrodynamic flows past obstacles (73).

Sometimes the location of an inexcitable obstacle (e.g., an infarction scar) is intramural, with a preserved endocardial/epicardial rim (5, 17); in such situations, during normal sinus activation or during ectopic activation occurring at some dis-
tance away from a scar, this scar faces the incoming waves directly. In such a case, wave breaks and vortices can also be formed under the conditions of high-frequency stimulation, which has been shown in generic models of excitable media (48, 50, 65) and in experiments with the Belousov-Zhabotinsky (BZ) reaction (1).

The aim of this paper was to study a possible process of spiral wave formation at inexcitable heterogeneity in the ionically realistic ten Tusscher-Noble-Noble-Panfilov (TNNP) model for human ventricular cells (67). We show that, under the influence of high-frequency stimulation, a train of plane waves impinging on an inexcitable obstacle can result in the formation of spiral waves. Furthermore, in the cardiac model that we study, the critical frequency at which such formation can take place is related to the frequency of rotation of a spiral wave in such tissue. We illustrate how the process of spiral wave formation depends on the size of the obstacle, its shape, and the excitability of the medium. We also discuss the importance of this mechanism for the onset of cardiac arrhythmias.

METHODS

In a continuum model, electrical wave propagation in cardiac tissue can be described with the monodomain formulation (31), which in two dimensions (2D) is

\[
\frac{\partial V}{\partial t} = \text{div}(D \text{grad} V) - \frac{I_{\text{ion}}}{C_m}
\]

where \(V\) is the transmembrane potential, \(C_m\) is the membrane capacitance per unit area, \(\text{div}\) and \(\text{grad}\) indicate the divergence and the gradient operators, and \(D\) is a symmetrical 2 \(\times\) 2 matrix responsible for the anisotropy of cardiac tissue. For human cardiomyocytes, we have described the total ionic current \(I_{\text{ion}}\) by using the TNNP model (67). It is expressed as a sum of the following ionic currents:

\[
\begin{align*}
I_{\text{ion}} &= I_1 + I_2, \\
I_1 &= I_{Na} + I_{Ca} + I_0 + I_{Ks} + I_{Kd} + I_{K1}, \\
I_2 &= I_{NaCa} + I_{NaK} + I_{pCa} + I_{pK} + I_{bNa} + I_{bCa}.
\end{align*}
\]

\(I_{Na}\) is the fast inward \(Na^+\) current, \(I_{Ca}\) the \(L\)-type slow inward \(Ca^{2+}\) current, \(I_0\) the transient outward current, \(I_{Ks}\) the slow delayed-recovery current, \(I_{Kd}\) the rapid delayed-recovery current, \(I_{K1}\) the inward rectifier \(K^+\) current, \(I_{NaCa}\) the \(Na^+\)/\(Ca^{2+}\) exchanger current, \(I_{NaK}\) the \(Na^+\)-\(K^+\) pump current, \(I_{pCa}\) the plateau \(Ca^{2+}\) current, \(I_{pK}\) the plateau \(K^+\) currents, \(I_{bNa}\) the background \(Na^+\) current, and \(I_{bCa}\) the background \(Ca^{2+}\) current.

Time \(t\) is measured in milliseconds, voltage \(V\) in millivolts, conductances (\(G_{\chi}\)) in nanoSiemens per picofarad, intracellular and extracellular ionic concentrations (\(X_{\chi}\), \(X_{\chi0}\)) in millimoles per liter, and current densities (\(I_{\chi}\)) in microamperes per unit area in square centimeters, as used in second-generation models (see, e.g., Refs. 7, 35, 36, 67). For a detailed list of the parameters of this model and the equations that govern the spatiotemporal behaviors of the transmembrane potential and currents see, e.g., References 61 and 67.

The diffusion constant \(D\) is a tensor, whose elements are \(D_{11} = 0.00154 \text{ cm}^2/\text{ms}, D_{22} = \frac{D_{11}}{4},\) and \(D_{12} = D_{21} = 0\). We assume that the \(x\)-axis is directed along the direction of the cardiac muscle fiber, whereas the \(y\)-axis is directed transverse to the fiber. \(C_m\) measures the membrane capacitance per unit area (\(\mu\text{F/cm}^2\)).

To solve Eq. 1 for the temporal evolution of the transmembrane potential \(V\), we use the forward-Euler method, with a time step \(\delta t = 0.02\) ms; we compute the spatial part of Eq. 1 by using a centered, second-order finite-difference scheme. The diffusion constant is different along the longitudinal and transverse directions (\(D_{11} = 4D_{22}\)), so, to ensure dynamical stability of our numerical scheme, we use different spatial step sizes for the longitudinal \((x)\) and transverse \((y)\) directions. We use \(\delta x = 0.04\) cm and \(\delta y = 0.02\) cm, such that \(\frac{D_{11}}{\delta x^2} = \frac{D_{22}}{\delta y^2}\). To model the inexcitable obstacle, we set \(D = 0\) at the location of the obstacle and apply zero-flux Neumann boundary conditions at its edges.

For our studies with the 2D TNNP model, we use a large tissue containing \(512 \times 512\) grid points to reduce boundary effects. Thus the size of the tissue is \(20.48\) cm \(\times\) \(10.24\) cm. We pace the medium periodically by applying an external, high-frequency stimulation along the left boundary of the tissue (\(x = 1\)). We choose the amplitude of the applied voltage stimulus to be roughly three times the threshold value, i.e., \(150\) pA/pF. We start periodical pacing at a high frequency, which results, however, in a 1:1 response at the stimulation site. This frequency, which is different for different values of the ionic conductances studied in this article, ranges from 2.5 Hz to 4.0 Hz. At a given frequency, we keep pacing until the spatial wavelengths of the plane waves in the wave train stabilize, i.e., the difference between two successive wavelengths is \(<5\%\).

We then increment the frequency by 0.01 Hz and repeat the pacing procedure. We continue incrementing the frequency until a further increment leads to the disappearance of a pulse at the stimulation site. If we need to obtain waves with frequencies close to the maximal frequency, we repeat simulations from the last 1:1 point, with a smaller value of the increment (half of the previous value) up to 0.001 Hz. We then stop the external stimulation and allow the system to evolve.

For the configuration shown in Fig. 9, we use a tissue containing \(624 \times 1,248\) grid points, with \(\delta x = 0.04\) cm, \(\delta y = 0.02\) cm, and \(\delta t = 0.02\) ms. The physical size of the tissue used is \(24.96\) cm \(\times\) \(24.96\) cm.

To generate a spiral, we use the S1-S2 protocol, with the S1 stimulus applied at the left boundary (\(x = 1\)) of the tissue and the S2 stimulus applied, for 2 ms at \(t = 440\) ms after the application of the first stimulus, when the wave back of the S1 wave crosses one-fourth of the extent of the tissue in the \(x\)-direction. The S2 stimulus, with amplitude \(150\) pA/pF, is applied over the region \(y \leq 312\). The core of the spiral wave forms at the point of intersection of the S2 stimulus and the wave back of the S1 wave.

In most of our studies, we use rectangular, conduction-type obstacles of different sizes; in addition, we also study two representative cases of \(r\)-shaped obstacles. Such obstacles are constructed from rectangles of different dimensions. Figure 1 shows schematic diagrams of the different kinds of obstacles that we use in our studies; Fig. 1B shows the \(r\)-shaped obstacle, Fig. 1C shows a laterally inverted \(r\)-shaped obstacle, and Fig. 1D shows the distribution of obstacles in a large tissue, which we use in our simulations, along with the positions and sizes of each of the obstacles in units of grid points.

For simulations involving many obstacles (Fig. 9, B and C) and the simulation shown in Fig. 10D, we surround each inexcitable obstacle by a localized heterogeneity with conductance \(G_x\). To do this, we use a phase-field-type formulation (see, e.g., Ref. 23); we define a parameter \(\varphi\) whose values are, initially, \(\varphi = 0\) inside the obstacles and \(\varphi = 1\) outside. Then we evolve \(\varphi\) spatiotemporally for a short time by using the following relaxation-type equations:

\[
\begin{align*}
\frac{\partial \varphi}{\partial t} &= \zeta^2 \nabla \varphi - \frac{\partial G}{\partial \varphi}; \\
G(\varphi) &= -\frac{(2\varphi - 1)^2}{4} + \frac{(2\varphi - 1)^4}{8}.
\end{align*}
\]

This causes the sharp boundary between the \(\varphi = 1\) and \(\varphi = 0\) regions to smoothen out. We then use this distribution of \(\varphi\) for the next part of the calculation. The parameter \(\zeta\) controls the spatial range over which the heterogeneity exists. We choose \(\zeta = 0.025\). Next, to
introduce the ionic heterogeneity around the obstacles, we relate the ionic conductance \( G_X \) for ion \( X \) to \( \varphi \) as follows:

\[
G_X = fG_X^{\text{normal}} + \phi G_X^{\text{normal}}(1 - f) \quad \text{for } \phi \neq 0, G_X^{\text{normal}} \quad \text{otherwise}
\]  

Here, \( G_X^{\text{normal}} \) is the normal value of \( G_X \) from the original parameter set of the TNNP model. In Fig. 9B, we use \( f = \frac{1}{3} \). To check the validity of our results in more realistic conditions (Figs. 9C and 10D), we modify the properties of cardiac tissue around each obstacle, as prescribed by Arevalo et al. (4), to mimic gray zone (GZ) cells; specifically, we reduce the peak Na\(^+\) current to 38\% of its normal value (\( f = 0.38 \)), the peak L-type Ca\(^{2+}\) current to 31\% of its normal value (\( f = 0.31 \)), and the peak K\(^+\) currents \( I_{K1} \) and \( I_{Ks} \) to 30\% and 20\% of their respective normal values, i.e., \( f = 0.30 \) and 0.20, respectively.

In the case studied in Fig. 9A, no localized heterogeneity is assumed around the obstacles; thus the value of \( G_X \) remains constant over the whole tissue; in the case studied in Fig. 9B, all conductances except \( G_{Kr} \) remain spatiotemporally constant; \( G_{Kr} \) obeys relation shown in Eqs. 4 and 5 with \( f = \frac{1}{3} \). This is similar to the work of Campbell et al. (12), who also introduce a gradient in \( I_{Kr} \) to induce a heterogeneity around the obstacles.

Finally, to model realistic scar tissue, we apply the following protocol: We use GIMP 2.6 (a Linux-based open-source imaging software package) to read the image from Fig. 2B of Reference 57. We then desaturate its color code and create two object groups. In the first group, which represents the scar, we include all the different heterogeneities shown in the figure; in the second group, which represents the cardiomyocytes, we include everything outside the scar from Fig. 2B of Reference 57. We then use the thresholding tool of GIMP 2.6 to coarse-grain the resulting image, in order to remove noise and filter out a well-defined boundary for the scar. This is important because in numerical simulations the treatment of boundaries often becomes a crucial determinant of the results of the study.

The original image was obtained from a slice of a rat heart; a human heart is substantially larger than a rat heart, so we have rescaled this image as follows. We have taken mirror images of the scar along the x-axis and the y-axis (to make it symmetrical and thus circumvent boundary effects arising from asymmetry of the scar) and have scaled it up 50 times; the total area of the rescaled scar we use is \( \sim 17 \text{ cm}^2 \), which is close to that reported in a human heart (19.3 \( \pm \) 13.4 \( \text{cm}^2 \)) (17). Finally, we have used MATLAB 7.5 to read the resulting image and convert it into a binary input file that stores the configuration of the scar.

RESULTS

When a plane wave, generated from a line stimulus that is applied along the left edge of the tissue, impinges on an obstacle, it splits at the front and develops a gap between the upper and lower portions of the wave. We find that, at pacing periods \( T_{\text{pacing}} \) higher than a critical value \( T_{\text{critical}} \), this gap shrinks and disappears as the wave front of the interacting wave leaves the right edge of the obstacle. Figure 2 illustrates the process described above for a rectangular obstacle of size \( 0.8 \text{ cm} \times 3.6 \text{ cm} \) when paced with a period \( T_{\text{pacing}} > T_{\text{critical}} \). The incident plane wave stimulus hits the obstacle (Fig. 2, A and D) and splits into two parts (Fig. 2, B and E), which go around the obstacle and rejoin (Fig. 2, C and F); no spiral formation takes place in this case.

However, when the period of pacing becomes equal to the critical period (i.e., \( T_{\text{pacing}} = T_{\text{critical}} \)), we find that the wave cannot follow the boundary of the obstacle, as the wave front and wave back of the wave leave the right edge of the obstacle. The split waves thus produced then curl about their respective broken tips, and spiral formation takes place within the tissue. Figure 3 illustrates the process described above with reference to a rectangular obstacle of size \( 0.8 \text{ cm} \times 3.6 \text{ cm} \) when paced with a period that is equal to the critical pacing period. The incident plane wave of electrical activation hits the obstacle (as shown in Fig. 3, A and D) and wave breaks appear; they detach from the obstacle, and the gap between the breaks increases (Fig. 3, B and E); finally, these wave breaks give rise to two fully developed spiral waves (Fig. 3, C and F).

Previous studies of chemical waves interacting with inexcitable obstacles (1, 48) have shown that \( T_{\text{critical}} \) is close to the period of spiral waves rotating in the same medium. Therefore, in order to study the dependence of \( T_{\text{critical}} \) on parameters of the model, as well as on the time period \( T_{\text{spiral}} \) of a spiral wave in the absence of obstacles, we explored the variations of both \( T_{\text{critical}} \) and \( T_{\text{spiral}} \) for the same parameter values. In our study we varied the values of the conductances \( G_{Na}, G_{Ca}, G_{K1}, G_{Kr}, \) and \( G_{Kr} \), which control the main inward ionic currents, \( I_{Na} \) and \( I_{Ca} \), and the main outward ionic currents, \( I_{K1}, I_{Kr} \), and \( I_{Kr} \), respectively. These currents are major determinants of action potential shape and are targets of antiarrhythmic drugs of class I (Na\(^+\) channel blockers), class III (K\(^{+}\) channel blockers), and class IV (Ca\(^{2+}\) channel blockers) (75). These currents are also changed during various cardiac pathologies, e.g., long and short QT syndromes (30, 41, 52). Figure 4, A–E, illustrate the dependence of \( T_{\text{critical}} \) and \( T_{\text{spiral}} \) on the values of \( G_{Na}, G_{Ca}, G_{K1}, G_{Kr}, \) and \( G_{Kr} \), respectively, expressed as percentages of their original values. We observe that, in a wide range of
parameters, \( T_{\text{spiral}} \) is close to \( T_{\text{critical}} \), and only for few values of the parameters do we see significant differences between \( T_{\text{spiral}} \) and \( T_{\text{critical}} \) (see Fig. 4).

For spiral formation, another important parameter is the height of the obstacle \( h \). For \( T_{\text{pacing}} = T_{\text{critical}} \), spiral formation takes place only when \( h \) is above a critical value. If the obstacle does not meet this critical size requirement, then, no matter what the pacing period, spiral formation does not occur; instead, we observe a situation similar to that illustrated in Fig. 2. To study the role of \( h \) in the formation of spirals, we perform studies similar to those of Fig. 3 for progressively decreasing obstacle sizes [decreasing \( h \), with width (\( d \)) held fixed at 0.8 cm], until we find a minimum \( h \) below which spiral waves do not form. We record this value of \( h \) as \( h_{\text{critical}} \) and repeat the entire procedure for other values of \( G_{Na} \), \( G_{Ca} \), \( G_{K1} \), \( G_{Kr} \), and \( G_{Ks} \); Fig. 5, A–E, respectively, illustrate our results. We observe that \( h_{\text{critical}} \) is around a few centimeters. In addition, we see that the critical \( h \) is substantially affected by the parameters of the model. When we decrease \( G_{Na} \), the obstacle size decreases more than twofold. A decrease of \( G_{Ca} \) results in a fivefold decrease in the value of \( h_{\text{critical}} \). The trend is just the opposite for conductances \( G_{K1} \), \( G_{Kr} \), and \( G_{Ks} \). We note that as \( G_{K1} \) increases the critical obstacle size reduces to half of its value, whereas an increase in \( G_{Ks} \) leads to a fivefold reduction in the obstacle size; the variation with \( G_{Ks} \) follows the same trend as that for \( G_{K1} \).

Another characteristic spatial constant of the system is the spatial distance between the successive waves in the wave train, which we refer to as the spatial wavelength (\( \lambda \)). Note that this spatial wavelength is a product of the velocity and the period (cycle length) and it differs from the wavelength widely used in physiological literature, which is the product of the.

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1 Supplemental Material for this article is available online at the Journal website.
The wavelength changes when we change the conductivities of the ionic currents; therefore, we study whether the change in $h_{\text{critical}}$ can be explained just by the change in $\lambda$. In Fig. 6, we plot the dimensionless size of the obstacle given by $h_{\text{critical}}/\lambda$ vs. different ionic conductances (cf. Fig. 5 for $h_{\text{critical}}$). We observe that $h_{\text{critical}}$ and $T_{\text{critical}}$ for most parameter values are close to each other. The only exceptions to this statement are the cases of $G_{Na} = 5\%$, where $T_{\text{critical}}$ is significantly shorter than $T_{\text{spiral}}$ ($P < 10^{-10}$, $T_{\text{spiral}} = 436.74 \pm 3.23$ ms). Also, $T_{\text{spiral}}$ is significantly shorter than $T_{\text{critical}}$ for 25% $G_{K1}$ ($P = 0.01$; $T_{\text{spiral}} = 324 \pm 5$ ms, $T_{\text{critical}} = 350 \pm 2$ ms), for $G_{Ks} = 25\%$ ($P = 0.02$; $T_{\text{spiral}} = 290 \pm 1.1$ ms, $T_{\text{critical}} = 300 \pm 2.1$ ms), and for $G_{Kr} = 5\%$ ($P = 0.04$; $T_{\text{spiral}} = 237 \pm 1.1$ ms, $T_{\text{critical}} = 249 \pm 2.5$ ms).

Next, we study how the geometry of the obstacle affects $T_{\text{critical}}$. We obtain $T_{\text{critical}}$ for different values of $G_{Na}$ and $G_{Ca}$ from plots similar to those in Fig. 4. In these studies, we set $h = 3.6$ cm (the critical $h$ for $G_{Na} = 100\%$ and $G_{Ca} = 100\%$) and vary $d$ (see Fig. 1A). We find that, for a rectangular obstacle, if $h$ meets the critical requirement then $T_{\text{critical}}$ is independent of the value of $d$. This is illustrated in Fig. 7 (dashed line). However, $T_{\text{critical}}$ is influenced slightly by the shape of the obstacle for nonrectangular obstacles. To demon-
strate this influence, we conduct studies on obstacles of two representative shapes. In one case we use an r-shaped obstacle (see Fig. 1B), and in the other case we use a laterally inverted r-shaped obstacle (see Fig. 1C).

In both of these cases, we use $h_1 = 3.6$ cm, $h_2 = d_2 = 0.8$ cm, and $d_2 = d$. The dependence of $T_{\text{critical}}$ on $d$ for an r-shaped obstacle is shown in Fig. 7 (dash-dot line); the dependence of $T_{\text{critical}}$ on $d$ for a laterally inverted r-shaped obstacle is also shown in Fig. 7 (solid line with circles). We observe that $T_{\text{critical}}$ increases very slightly with an increase in $d$ in the case of the r-shaped obstacle; by contrast, $T_{\text{critical}}$ decreases very slightly with an increase in $d$ in the case of the laterally inverted r-shaped obstacle.

In addition to its dependence on the shape and size of the obstacle, $T_{\text{critical}}$ depends on factors such as the angle of incidence of the external stimulation on the boundary of the obstacle. To verify this, we position the obstacle at the center of the tissue, as shown in the schematic diagram of Fig. 8A. The position of the obstacle is marked by a filled rectangle; we then pace the medium from a square region of area $0.8$ cm $\times$ $0.8$ cm, which is shown in Fig. 8A by an open square. We then shift the geometric center of the pacing site along the perimeter of an ellipse, and, for each location of the pacing site, we measure $T_{\text{critical}}$. We measure the angle $\theta$ with respect to the horizontal. The size of the obstacle used for these studies is $0.8$ cm $\times$ $3.6$ cm. Figure 8B shows the angular dependence of $T_{\text{critical}}$ for the original values of the parameters $G_{Na}$ and $G_{Ca}$. We observe that $T_{\text{critical}}$ at $\theta = 0^\circ$ agrees with our findings for pacing by a line stimulus. As $\theta$ increases, $T_{\text{critical}}$ decreases slightly. At large values of $\theta$ (>60$^\circ$), spiral formation is no longer observed, because the pacing site is then close to the short edge of the obstacle, the length of which is less than the critical size of the obstacle required for the formation of spirals.

From our results we can conclude that formation of breaks at obstacles is not very likely to be a primary mechanism of spiral wave formation in cardiac tissue from the normal sinus rhythm. This is because such break formation requires that the frequency of the upcoming waves is faster than that of a spiral wave, and thus the heart rate should already be as fast as that during cardiac arrhythmia (3–4 Hz). However, it can be a potential secondary mechanism for spiral wave formation if the arrhythmia has appeared by a different mechanism, although, even in that case, the frequency of the arrhythmia should be faster than that of rotating spiral waves. This means that in a homogeneous cardiac tissue a rotating spiral wave cannot produce a secondary reentrant source, as the frequency of the spiral wave must be lower than the critical frequency necessary for break formation. It is reasonable to assume that properties

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**Fig. 5.** Dependence of $h_{\text{critical}}$ on the conductances of the major ionic currents in the model. **A–E** show the dependence of $h_{\text{critical}}$ on $G_{Na}$, $G_{Ca}$, $G_{K1}$, $G_{Kr}$, and $G_{Ks}$, respectively, expressed as % of their original values. We observe that $h_{\text{critical}}$ is of the order of a few centimeters for $d = 0.8$ cm.
of tissue around obstacles can differ from those in the rest of the cardiac tissue. In such cases, we can observe the formation of secondary spiral waves via the mechanism we have elucidated above. To check this in direct numerical simulations, we study spiral wave dynamics in a large, homogeneous, anisotropic tissue, in the presence of many obstacles of varying lengths, which are located at different angles with respect to the core of the parent spiral wave. The results of this study are illustrated in Fig. 9. In Fig. 9A, we use the original parameter values of the TNNP model throughout the tissue. We find that the presence of multiple obstacles does not affect spiral wave dynamics significantly, except for a local influence around each obstacle; this influence is confined in space and does not spread as the system evolves. Such wave patterns, reminiscent of the excitation during ventricular tachycardia (VT), are characterized by a single stable reentrant source (25). In Fig. 9B, we illustrate a state of ventricular fibrillation (VF), characterized by multiple wavelet reentrant patterns (25, 40), brought on by the presence of a heterogeneity in $G_{Kr}$ localized in the region surrounding each obstacle. This is in consonance with the work of Campbell et al. (12).

We have also performed simulations in which the local heterogeneity, around the obstacles, is based on the measured properties of cardiac tissue around an infarction scar region. In particular, we use a GZ-type heterogeneity (see METHODS). The results for this simulation are illustrated in Fig. 9C. We see secondary spiral formation around the obstacles; Fig. 9A shows a state that is the analog of VT, whereas Fig. 9, B and C, show analogs of VF.

Finally, we conduct three representative simulation studies of high-frequency pacing and spiral wave dynamics in the presence of experimentally obtained and designed infarct tissue. In these studies, we simulate a sheet of myocardial cells containing a patch of inexcitable obstacles; the shape of this patch is obtained from Reference 57. By using the GIMP 2.6 imaging software package, we read the image from Fig. 2B of Reference 57 (for details, see METHODS). Because the original image was captured from a slice of a rat heart and the size of the human heart is substantially bigger than that of the rat heart, we had to rescale the image 50 times; this resulted in a total area of the scar of $\sim 17 \text{ cm}^2$, which is close to that reported in the human heart ($19.3 \pm 13.4 \text{ cm}^2$) (17).

We apply the pacing protocols that we have used to obtain Figs. 2 and 9; we then study wave propagation around such realistic obstacles under periodical forcing and also in the presence of a preexisting spiral wave (in both homogeneous and heterogeneous cases). The results of these calculations are illustrated in Fig. 10. We find that periodic forcing causes the formation of secondary spirals (Fig. 10A) and the critical period for spiral formation in this case is 254 ms, which is slightly shorter than the critical period of
spiral formation around a rectangular obstacle, for original parameters of the TNNP model (260 ms). This may be in part because of the angular dependence of $T_{critical}$ (see Fig. 8) and in part because of differences in the interaction of waves with a boundary of complex shape. Spiral wave formation here takes place at sharp, distinct regions in the obstacle, where the curvature changes abruptly. We obtain four secondary spirals (see Fig. 10A), which, after the cessation of the forcing, evolve in time into fully developed, self-sustained spiral waves (Fig. 10B and Supplemental Video S5).

Furthermore, to study the effect of such an obstacle on preexisting spiral waves of electrical activation in the medium, we use a spiral wave as the initial condition and place the obstacle at the center of the tissue. The primary spiral wave is produced by an S1-S2 cross-field protocol, such that its core is located away from the center of the tissue. We find that, as the system is allowed to evolve, the primary spiral wave remains detached from the obstacle; secondary spiral formation does not take place (Fig. 10C); however, if we introduce a GZ-type ionic heterogeneity around the obstacle, then the tip of the primary spiral wave forms secondary spiral waves. This result is illustrated in Fig. 10D (and its spatiotemporal evolution is demonstrated in Supplemental Video S6).

**DISCUSSION**

In this report we show that high-frequency simulation can result in the formation of spiral waves around inexcitable obstacles. We carried out studies in the TNNP ionic model for human ventricular tissue and show that, in a large range of parameters, the critical time period of pacing necessary for spiral formation is related to the period of a spiral wave rotating in the same tissue. We also show that there is a minimal size of the obstacle for which the formation of spirals is possible, and this size is fairly large: In normal conditions it is $\sim 3 \text{ cm}$ and it decreases with a decrease of the excitability of cardiac tissue, and at low tissue excitabilities it can be as low as $0.7 \text{ cm}$. These sizes are comparable to typical scar sizes reported in clinical studies (17). We also show that other factors, such as the obstacle shape and the direction of stimulation in relation to the obstacle, are of secondary importance and affect the conditions for spiral wave initiation only slightly.

**Effects of major ionic currents.** In the present study we have changed the conductances $G_{Na}$, $G_{Ca}$, $G_{K1}$, $G_{Kr}$, and $G_{Ko}$ that control the main inward and outward ionic currents. For inward currents we have considered blocks up to 5% of the normal value, and for the outward currents we have considered blocks up to 20%, as well as gains up to 200% of the original value. The blocking of these currents mimics the action of various antiarrhythmic drugs. In many cases, a drug can affect multiple currents. For example, it has been reported that one of the most widely used antiarrhythmic preparations, namely, amiodarone, blocks the inward $Na^+$ and $Ca^{2+}$ channels as well as the outward $K^+$ channels (24, 27, 33, 43, 53, 74, 78, 80, 82, 84); its effects on a single cardiomyocyte include a slight elevation in the normal resting membrane potential of healthy and ischemic cells and prolongation of the APD, although in some cases it can lead to APD shortening as well, and it leads to a reduction of the action potential amplitude. Amiodarone is also found to decrease the conduction velocity and the wavelength of signals in healthy cardiac tissue, whereas in ischemic tissue the same drug leads to an increase of the wavelength. Cardiac arrhythmias can also occur as a result of adverse side effects of noncardiological drugs, e.g., cisapride (13, 19, 76, 80), which works mainly by inhibiting $I_{Kr}$. In a cardiomyocyte, cisapride
GZ-type heterogeneity at the infarction scar boundary (image recorded at 4.78 s after the formation of the primary spiral wave). In A, around each obstacle we decrease \(G_{Kr}\) smoothly from its original value to up to 1⁄3 of the original value, at the boundaries of the obstacles. This regional slowing down of the electrical activation of the medium facilitates the formation of secondary spirals in B, such secondary spirals are completely absent in A. In C, we further modify properties of cardiac tissue around the obstacles, to mimic changes around an infarction scar (see METHODS for details). All 3 images are recorded at \(t = 5\) s after the formation of the primary spiral wave. The spatiotemporal evolution of transmembrane potential \(V\) in cases A–C is shown in Supplemental Videos S2–S4, respectively.

does not affect the resting membrane potential or the action potential amplitude significantly but prolongs the APD in both healthy and ischemic cases; furthermore, it does not affect the signal conduction velocity but increases the wavelength in cardiac tissue. Therefore, to study the effects of drugs on the mechanisms studied in this report one needs not only to analyze the change caused by the individual ion channels but also to study specific combinations reproducing specific drug effects. Such research can be done in the future with modeling approaches as in Reference 80.

Similar questions arise in various forms of genetic diseases, such as in the Brugada syndrome, in which there is a 50% \(I_{Na}\) loss of function localized in the right ventricular outflow tract; this is considered severe (8, 79). However, in addition to the change in \(I_{Na}\) the Brugada syndrome is also associated with several other changes, e.g., an increase in the fibrosis of cardiac tissue (15). Therefore, it is interesting to study the combination of changes in ionic currents with other factors (e.g., fibrosis); such issues can also be addressed by using modeling approaches (45, 69).

Critical pacing period and critical obstacle size. We have shown that the critical obstacle height \(h_{critical}\) and pacing rate \(T_{critical}\) depend on the conductances of inward \((G_{Na}, G_{Ca})\) and outward \((G_{K1}, G_{Kr}, G_{Ks})\) currents. The critical pacing rate is determined in a wide range of parameters by the period of a spiral wave rotating in the same tissue. Such dependence can be qualitatively explained in the following way: When a plane wave, from a train of pulses paced at the critical pacing period, impinges upon an obstacle, it breaks at the edges of the obstacle that are parallel to the direction of propagation of the incident waves. After breaking at the obstacle, the wave forms two free ends. Under normal conditions of tissue excitability, these free ends grow toward each other and rejoin to form an intact wave; spiral formation does not take place. However, the velocity of motion of the broken wave’s free ends, toward each other, decreases with a decrease in the excitability of the medium (49, 65).Tissue excitability is known to decrease in the presence of high-frequency pacing of the medium (48, 65). Furthermore, rotating spiral waves can be considered to exhibit periodic (e.g., circular) motion of a wave break. Thus the period of a spiral wave can be considered as the pacing period, at which the free ends of the broken wave cease to move toward each other, thus enabling the formation of spiral waves. This explains why \(T_{critical}\) is comparable to the time period of rotation of the spiral wave. A more accurate estimate of \(T_{critical}\) for low-dimensional models (i.e., models with fewer variables than the present model) can be obtained by using the analytical methods developed in Reference 65. It would be interesting to develop a more quantitative description of the observed pro-
cesses. Interesting results in that direction can potentially be derived from the study of Starobin et al. (65), who have studied the formation of vortices around single and multiple L-shaped obstacles in generic models of excitable media and have derived analytical estimates for wave front-obstacle separation and vortex formation by using singular perturbation theory. They have shown that any decrease in tissue excitability favors vortex formation; also, the formation of secondary vortices takes place in the presence of multiple obstacles. It would be interesting to study whether their approach can explain the large difference between the spiral and critical pacing period at low excitability (as shown in Fig. 4A) and the differences for points where \( T_{\text{critical}} > T_{\text{spiral}} \) or \( T_{\text{critical}} < T_{\text{spiral}} \) shown in Fig. 4A.

Our results show that a decrease of the inward currents or an increase of the outward currents decreases the critical obstacle size and also the APD. Both these factors decrease the APD and some \( (G_{\text{Na}}, G_{\text{Ca}}, G_{\text{K}}) \) velocity of the wave. As the formation of two counterrotating spiral waves requires two action potentials to enter the gap separating the free ends of the waves, we can assume that a smaller spatial break separation is necessary at the obstacle for a shorter spatial APD. This can explain the observed decrease of the critical obstacle size shown in Fig. 5.

Critical period and refractoriness. We relate the critical period for spiral wave formation via pacing to the period of the spiral wave rotating in the same tissue. However, the period of spiral wave rotation, by itself, is determined by the refractory properties of cardiac tissue and an excitable gap, which is again determined by the curvature (source-sink mismatch) effects (14, 46, 51). In highly excitable tissue, the refractoriness is expected to be the main determinant of the spiral wave period (46). This may explain the findings of References 10 and 50, where the refractory period has been shown to be a potential determinant of the critical pacing frequency for spiral wave formation. The value of the refractory period, however, depends on the frequency of excitation of cardiac cells and other experimental conditions, such as the threshold of stimulation, stimulation protocol, etc. (6, 86). It would be interesting to perform a detailed study of the relation between the spiral wave period and the refractory period of cardiac tissue in various conditions and possibly relate the results observed in our study to other measurable characteristics of cardiac tissue.

Dependence on shapes, geometries, and types of obstacles. In this article, we study the formation of spiral waves, with high-frequency stimulation, around an excitable obstacle with no-flux conditions at its boundaries. However, similar processes can also occur in the presence of intrinsic heterogeneities in cardiac tissue. Xu and Guevara (83) studied the effects of high-frequency stimulation, in a heterogeneous medium with heterogeneity induced by regional myocardial ischemia, by using the modified Luo-Rudy ionic (LRI) model for cardiac tissue. They observed that at a high pacing frequency the wave front separates increasingly from the boundary of heterogeneity, which eventually results in the formation of a spiral wave; the core of this spiral lies outside the heterogeneity. It would be interesting to study a similar process in the TNNP model and relate the frequency of onset of spiral waves in that situation with the frequency of spiral waves rotating in the same tissue.

Our results are similar to the vortex shedding results in Reference 10. As in Reference 10, we show that high-frequency pacing and low excitability favor the formation of spiral waves at sharp edges. The main mechanism of spiral wave formation is the detachment of the wave from the obstacle boundary.

Although Cabo et al. (10) show that the main mechanism for the formation of spiral waves is the detachment of the wave from the obstacle boundary, in our simulations we find different patterns of interaction between the wave and the inexcitable obstacle. In particular, we must account for both the upcoming wave and the wave following the boundary of the medium. Furthermore, we extend this line of research by providing a generic estimate of the critical pacing period \( T_{\text{critical}} \) necessary for spiral wave formation, and we relate it to the period of a spiral wave. We estimate the critical size \( h_{\text{critical}} \) of the obstacle necessary for spiral formation at different levels of tissue excitabilities and account for its dependence on \( G_{\text{Na}}, G_{\text{Ca}}, G_{\text{K}}, G_{\text{Kr}}, \) and \( G_{\text{Ks}} \).

The relation of the critical period of stimulation \( T_{\text{critical}} \) and the period of spiral wave rotation has not been studied so far in direct experiments in cardiac tissue. However, Cabo et al. (10) found that spiral formation at an inexcitable barrier in sheep epicardial tissue occurred only if the interval between stimuli did not exceed >10% of the refractory period of the tissue. A similar condition has also been proposed theoretically by Pertsov et al. (50). As in cardiac tissue, the spiral wave period is close to the refractory period; the finding by Cabo et al. indicates that, indeed, the spiral wave period can be a good estimate for \( T_{\text{critical}} \).

We show in Figs. 9 and 10 that, in the presence of heterogeneity, a rotating spiral wave can induce a fibrillatory excitation pattern about an obstacle. This is similar to the mechanism of mother rotor fibrillation studied in References 12 and 58. It would be interesting to study the dynamics of the observed fibrillatory patterns obtained by this mechanism for a long time interval and characterize them in terms of regularity and their power spectra. However, if obstacles are associated with tissue remodeling, as, e.g., around an infarction scar, the formation of secondary spiral waves around the obstacles becomes possible and may potentially result in the onset of ventricular fibrillation by the mother rotor mechanism (58). We defer a detailed study of this issue to future work.

We have performed simulations for large-sized tissues in order to separate the effects of 1) the interaction of waves with the inexcitable obstacle and 2) boundary effects. Because wave interactions with an obstacle or scar are local, all our results regarding the formation of wave breaks and their initial dynamics should be unchanged for tissues whose size is smaller than those we consider. The formation of sustained spiral waves from wave breaks requires some space, so such spiral formation might well depend on the size of the tissues. We propose to study these issues in detail in future research in which we plan to extend our work here by using anatomically accurate ventricular models and boundaries, three-dimensional tissue slabs with muscle fiber orientation.

Limitations. The principal limitations of our study are the following: We do not use a detailed representation of the anisotropy of cardiac tissue; in many important situations wave propagation is three dimensional, and thus it would be interesting to study similar processes in three dimensions, especially in an anatomically realistic heart with various shapes of realistic scars; we do not study in detail the effects of possible tissue remodeling around the obstacles, except in one simulation (Fig. 10); our study can also benefit from using a bidomain description for the cardiac tissue, especially if we study defibrillation of the observed patterns.
Acknowledgments

R. Majumder thanks Soling Zimik for his help during the revision of the manuscript.

grants

We thank the Department of Science and Technology (DST), India, the University Grants Commission (UGC), India, the Council for Scientific and Industrial Research (CSIR), India, and the Robert Bosch Centre for Cyber Physical Systems (IISc) for support and the Supercomputer Education and Research Centre (SERC, IISc) for computational resources. The research of A. V. Panfilov is supported by the Research-Foundation Flanders (FWO Vlaanderen).

disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).

author contributions

Author contributions: R.M. performed experiments; R.M. and A.V.P. analyzed data; R.M. and A.V.P. interpreted results of experiments; R.M. prepared figures; R.M. and A.V.P. drafted manuscript; R.M., R.P., and A.V.P. edited and revised manuscript; R.M., R.P., and A.V.P. approved final version of manuscript; A.V. conception and design of research.

references


