Small size ionic heterogeneities in the human heart can attract rotors

Arne Defauw,1 Nele Vandersickel,1 Peter Dawyndt,2 and Alexander V. Panfilov1,3

1Department of Physics and Astronomy, Ghent University, Ghent, Belgium; 2Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium; and 3Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia

Submitted 16 June 2014; accepted in final form 5 September 2014

Defauw A, Vandersickel N, Dawyndt P, Panfilov AV. Small size ionic heterogeneities in the human heart can attract rotors. Am J Physiol Heart Circ Physiol 307: H1456–H1468, 2014. First published September 12, 2014; doi:10.1152/ajpheart.00410.2014.—Rotors occurring in the heart underlie the mechanisms of cardiac arrhythmias. Answering the question whether or not the location of rotors is related to local properties of cardiac tissue has important practical applications. This is because ablation of rotors has been shown to be an effective way to fight cardiac arrhythmias. In this study, we investigate, in silico, the dynamics of rotors in two-dimensional and in an anatomical model of human ventricles using a Ten Tusscher-Noble-Noble-Panfilov (TNNP) model for ventricular cells. We study the effect of small size ionic heterogeneities, similar to those measured experimentally. It is shown that such heterogeneities cannot only anchor, but can also attract, rotors rotating at a substantial distance from the heterogeneity. This attraction distance depends on the extent of the heterogeneities and can be as large as 5–6 cm in realistic conditions. We conclude that small size ionic heterogeneities can be preferred localization points for rotors and discuss their possible mechanism and value for applications.

Sudden cardiac death is the largest cause of mortality in the industrialized world, accounting for more than 400,000 deaths per year in the United States alone (8). In most of the cases, it occurs as a result of cardiac arrhythmias. Therefore, it is important to study the mechanism of initiation of cardiac arrhythmias, to study the factors affecting arrhythmia initiation and dynamics, and to find new ways to manage them. These phenomena are studied using a wide variety of methods, including experimental and clinical research as well as computer modeling.

One of the most important mechanisms of arrhythmias are reentrant sources of excitation, which may form spiral waves also called rotors. Rotors were first predicted in modeling studies (29) and then discovered experimentally (1, 4). Recently, they have attracted a lot of attention, as clinical studies by the group of Narayan et al. (17, 18) showed that identification and ablation of these rotors can result in termination or slowing of atrial fibrillation. Similar research is being done in the ventricles (10). Thus factors that determine the formation of rotors and the possible position of rotors in the heart are of great practical interest. Therefore, it is of paramount importance to know whether the final position of the rotor is affected by specific local properties (substrate) of cardiac tissue.

From a general point of view, prevalence of a rotor at a specific position can be the result of the formation of a rotor at a given place, or it can be due to some process that brings the rotor from one location to another and stabilizes it there. It is well known that a rotor can be locally stabilized due to anchoring to an inexcitable obstacle (4, 25, 26, 35), i.e., process when a rotor attaches to the boundary of such an obstacle. Later, it was shown that rotors can anchor to other types of heterogeneities: ionic heterogeneities (30, 31), blood vessels (40), pectinate (42), and papillary muscles (13). Also in Refs. 3, 43, it was shown that rotors can be anchored to regions of prolonged action potential duration (APD; created through regional cooling) in the rabbit heart. Due to subsequent collision with the boundaries, a rotor could also be eliminated (43).

In this article, we investigate in silico the possibility for anchoring of a rotor at ionic heterogeneities of realistic size and shape, similar to those measured in the ventricles of the human heart (7). We show that such small size ionic heterogeneities with prolonged APD can anchor a rotor locally. Moreover, we find that these heterogeneities can also attract rotors from a substantial distance (up to 5–6 cm), while inexcitable obstacles do not show this property. We confirm this result both in simple geometries and in an anatomical model of the human ventricles. In addition, we discuss the mechanism of this attraction and its potential usage for removing rotors from the heart.

MATERIALS AND METHODS

Model. In this article, we consider a monodomain description of cardiac tissue (12) that has the following form:

\[
C_m \frac{\partial V_m}{\partial t} = \left( \frac{\partial}{\partial x_i} D_{ij} \frac{\partial V_m}{\partial x_j} \right) - I_{ion},
\]

where \( D_{ij} \) is a diffusion matrix accounting for anisotropy of cardiac tissue; \( i, j = 1 \ldots n, \) where \( n = 1 \) in 1 dimension (D), 2 in 2D, \( C_m \) is membrane capacitance; \( V_m \) is transmembrane voltage; \( t \) is time; and \( I_{ion} \) is the sum of the ionic transmembrane currents describing the excitable behavior of the individual ventricular cells. To represent the human ventricular electrophysiological properties, we used the ionic TP06 model (37, 39). This model provides a detailed description of voltage, ionic currents, and intracellular ion concentrations for human ventricular cells. A complete list of all equations can be found in Refs. 37, 39. We used the default parameter settings from Ref. 39 for epicardial cells. All parameter changes made to obtain tissue heterogeneity are enlisted in the text.

Numerical methods. The diffusion tensor is given by

\[
D_{ij} = (D_L - D_T) \tau_{ij} \delta_i \delta_j + D_T \delta_{ij},
\]

with \( \delta_{ij} \) the Kronecker delta and \( \tau_i \) a normalized vector oriented along the fibers.

For 2D computations, the fibers are directed along the x-axis \( \tau = (1,0) \), \( D_L = 0.128 \text{ mm}^2/\text{ms} \), and \( D_T = D_L/4 \).

For 3D whole heart simulations, we used an anatomical model of the human ventricles. For a more detailed description, we refer to Ref.

Address for reprint requests and other correspondence: A. V. Panfilov Dept. of Physics and Astronomy, Ghent Univ., Krijgslaan 281, S9, 9000 Ghent, Belgium (e-mail: alexander.panfilov@ugent.be).
36. This model takes anisotropy into account by reconstructing the fiber direction field described in Ref. 11. We assume that the diffusion coefficient across the fibers $D_T$ is four times less than the diffusion coefficient along the fibers $D_L$, which is set to 0.154 mm$^2$/ms.

To solve the differential equations, we used a finite difference approach. For 2D simulations, we used a rectangular mesh of about half a million points and for 3D simulations one million points. To approximate the diffusion term, we used a stencil of 5 grid points for 2D and 17 points for 3D. We used an explicit first order Euler method to solve the discretized system, which for 2D tissue is:

$$\frac{\tilde{V}_{ij} - V_{ij}}{\Delta t} = \frac{1}{\Delta x^2} \sum_{s=1}^{5} w_{ij}^{s} V_{i+s,j} + w_{ij}^{r} V_{i,j+s} - I_{\text{os}}(V_{ij}, \ldots),$$

(3)

where the time step is $\Delta t = 0.02$ ms, $\Delta x$ is the space step, and $w_{ij}^{s}$ are the weights corresponding to the diffusion tensor at location $i, j$. The space step is 0.2 mm for 2D simulations and 0.5 mm for 3D simulations. To integrate the Hodgkin-Huxley-type equations for the gating variables of the various time-dependent currents ($m, h, f$ and $s$ for $I_{Na}$; $r$ and $s$ for $I_{Ko}$; $x_1$ and $x_2$ for $I_{Ks}$; $x_3$ for $I_{Ks}$; $d, f_1, f_2$, and $f_{can}$ for $I_{CaL}$), the Rush and Larsen scheme (28) was used.

**Heterogeneity.** To study heterogeneity, we changed the parameters $G_{Ks}$ and $G_{Kr}$ from their default values 0.3923 and 0.153 nS/pF for epicardial cells in Ref. 39. For example, to raise the APD by 10 ms in half a million points and for 3D simulations one million points. To approximate the diffusion term, we used a stencil of 5 grid points for 2D and 17 points for 3D. We used an explicit first order Euler method to solve the discretized system, which for 2D tissue is:

$$\frac{\tilde{V}_{ij} - V_{ij}}{\Delta t} = \frac{1}{\Delta x^2} \sum_{s=1}^{5} w_{ij}^{s} V_{i+s,j} + w_{ij}^{r} V_{i,j+s} - I_{\text{os}}(V_{ij}, \ldots),$$

where the time step is $\Delta t = 0.02$ ms, $\Delta x$ is the space step, and $w_{ij}^{s}$ are the weights corresponding to the diffusion tensor at location $i, j$. The space step is 0.2 mm for 2D simulations and 0.5 mm for 3D simulations. To integrate the Hodgkin-Huxley-type equations for the gating variables of the various time-dependent currents ($m, h, f$ and $s$ for $I_{Na}$; $r$ and $s$ for $I_{Ko}$; $x_1$ and $x_2$ for $I_{Ks}$; $x_3$ for $I_{Ks}$; $d, f_1, f_2$, and $f_{can}$ for $I_{CaL}$), the Rush and Larsen scheme (28) was used.

**Heterogeneity.** To study heterogeneity, we changed the parameters $G_{Ks}$ and $G_{Kr}$ from their default values 0.3923 and 0.153 nS/pF for epicardial cells in Ref. 39. For example, to raise the APD by 10 ms in single cell, it is necessary to decrease $G_{Kr}$ by 0.073 nS/pF and $G_{Ks}$ by 0.048 nS/pF. The APD is measured at 80% repolarization level.

For our 2D simulations, we used four tissue configurations as shown in Fig. 1. Figure 1A is the same heterogeneity as modeled in the baseline model of Ref. 5. It is qualitatively similar to heterogeneity of the human ventricular tissue measured in Ref. 7. In particular, the maximal and minimal values of APD are approximately the same and the size at 50% heterogeneity [for APD = (minimal APD + maximal APD)/2] in both cases is $\sim 1 \times 0.6$ cm. This APD distribution is the distribution at tissue level when paced at a frequency of 500 ms, which matches the APD distribution of the experimental preparations in Ref. 7 when paced at the same frequency. Note that sizes for heterogeneities presented in Ref. 7 are the sizes of regions isolated from the neighbors by a local APD gradient of 15 ms/mm. This algorithm results in much smaller heterogeneity sizes by choosing the regions that are much closer to the maximal APD values. In our research we estimate the size at 50% heterogeneity, because this, in our view, describes the heterogeneity better than a maximal APD region. The exact underlying reason of the APD difference in Ref. 7 was not studied. However, as for the case of other APD heterogeneities between cardiac cells studied experimentally in Refs. 32, 33, it can be achieved by changing the $I_{Ks}$ and $I_{Kr}$ conductances. In our case we did it by setting $G_{Ks} = 0.1532$ nS/pF and $G_{Kr} = 0.3923$ nS/pF outside the heterogeneity and $G_{Ks} = 0.0948$ nS/pF and $G_{Kr} = 0.0$ nS/pF inside the heterogeneity. These values were initially estimated using an approach we developed earlier (6). In Fig. 1, B–D, we take the same values for $G_{Ks}$ and $G_{Kr}$ outside the heterogeneity as in Fig. 1A, but different values for $G_{Ks}$ and $G_{Kr}$ inside the heterogeneity. This results in heterogeneities with different maximal APD value. Due to electrotonic effects, the size at 50% heterogeneity remains the same. The latter probably reflects the fact that in that parameter range, electrotonic coupling is linear with respect to the amplitude of the heterogeneity.

In Fig. 2, A–D, we present the action potential (AP) both in the center of the heterogeneities (APc) shown in, respectively, Fig. 1A, but different values for $G_{Ks}$ and $G_{Kr}$ inside the heterogeneity. We see that in our case prolongation of APD inside the heterogeneity is caused by...
the prolongation of phase 2 of the AP that occurs as a result of the decrease of $GK_s$ and $GK_r$.

To set up heterogeneity in the whole heart, we used the following method. We first took an intersection of the ventricles, parallel to the z-axis (see section 1, demonstrated in Fig. 9, B and C). Next, we set up a region, with the shape of an ellipse in this plane. We labeled the points inside this ellipse with the number $H_0 = H(0) = 10$ and then let it diffuse for 300 steps in the isotropic version of our whole heart model, using $\frac{\partial H}{\partial t} = \nabla^2 H$ with $\Delta a = 0.00008$, and $\Delta x = 0.5$ mm. As a final step, all points for which $H(x) > 0.05$, we defined as being part of the heterogeneity. Unless stated otherwise, we use, in all the whole heart models that contain a heterogeneity, the same initial ellipse as a starting configuration for our diffusion-based algorithm, with a major axis of 6.5 mm and a minor axis of 2.5 mm, but each time located at a different position in section 1 (see Fig. 9).

RESULTS

Ionic heterogeneities as attractors of rotors in 2D cardiac tissue. As an initial step, we generate a heterogeneity that has size and value similar to that reported in experimental work by Glukhov et al. (7). We study its effect on a rotor, which is originally located at some distance from the heterogeneity (for more details, we refer to MATERIALS AND METHODS and to Fig. 1A). Figure 3 shows typical dynamics of a rotor in a 2D medium with such a heterogeneity. In particular, we initiate a rotor rotating in the center of the medium and position the ionic heterogeneity at a distance of 4.1 cm from the center (the distance along the x-axis to the center is the same as the distance along the y-axis). We then simulate for 10 s and investigate the influence of the ionic heterogeneity on rotor dynamics (see Supplemental Movie S1; Supplemental Material for this article is available online at the Journal website). At first, the effect of the heterogeneity on the spiral wave rotation is small. We see that the spiral rotates at its initial position. At the heterogeneity, we see the formation of two breaks that cannot penetrate into the heterogeneity and we get a classical Wenckebach 1:2 block (see Fig. 3, from 0 to 1 s). However, for the next rotation, the gap between the wavebreaks at the heterogeneity has become large enough, and we observe formation of a figure-of-eight reentry pattern (time = 1.36 s). The waves generated by it propagate through the heterogeneity and interact with the wave generated during the following rotation of the original spiral (time = 1.4 s). As a result of this interaction, the figure-of-eight reentry disappears. However, it reappears at the next rotations with the wavebreaks at a larger distance (time = 5.3 s) and new reentry patterns now affect spiral wave rotation in a larger region (time = 5.41 s). This effect spreads and newly formed reentrant patterns approach the center of the spiral (time = 5.46 s, time = 6.85 s, and time = 6.94 s). Their interaction with a rotor tip eventually moves the core of the spiral to another location closer to the heterogeneity (time = 7 s, time = 7.18 s, and time = 7.24 s). This process is repeated again (time = 7.3 s, time = 7.42 s, time = 7.49 s, time = 7.57 s, and time = 7.79 s) and again (time = 8.34, time = 8.41 s, and time = 8.45 s), and after this complex interaction, the rotors tip touches the heterogeneity and eventually anchors at it (time = 8.62 s).

We performed analogous simulations as described in Fig. 3, where we vary the location of the heterogeneity. We always start from a rotor located at the center of the medium and investigate if the rotor will anchor around the heterogeneity after 10 s. The results are shown in Fig. 4A. Here, position (0,0) is located at the center of the medium. We then move the heterogeneity along the x-axis (i.e., along the fibers), along the y-axis and along the first bisector. The dots in Fig. 4A show the location of the heterogeneity for a certain tissue configuration. Black dots indicate an anchored rotor after 10 s, while no anchoring occurred after 10 s for the white dots. We find...
that if we move the heterogeneity along the fibers, it can attract spirals rotating within 6 cm or less, while perpendicular to the fibers this distance decreases to ~4 cm. Along the first bisector it is ~5 cm. In all cases the process leading to the attraction and anchoring of the rotor at the heterogeneity is similar to that of Fig. 3 (or Supplemental Movie S1). We refer to Supplemental Movies S2 and S3 where we show the process of attraction of a rotor when the rotor is initially at a distance of 5.3 cm along the fibers and 3.7 cm across the fibers, respectively, from the heterogeneity. In both cases we see that at first wavebreaks are generated at the heterogeneity. After a few rotations, the distance between these newly formed wavebreaks increases and we observe the formation of a reentry pattern at the heterogeneity which start to affect spiral wave rotation. In the same way as in Fig. 3, a complex interaction between newly generated rotors and the tip of the original rotor, shifts the rotor to a position closer to the heterogeneity. This process is repeated, until the spiral eventually anchors at the heterogene-

Fig. 3. Ionic heterogeneity attracts a rotor. The ionic heterogeneity is taken from Fig. 1A and is located at a distance of 4.1 cm from the center of the tissue. The white line shows the size of the heterogeneity. Initially, the rotor rotates at the center of the tissue (time = 0 s). At time = 8.62 s, the rotor anchors to the heterogeneity. A–D: intermediate wave patterns. More explanation can be found in the text. The total size of the medium is 15 × 15 cm.
ity. The process of attraction is thus not a continuous process in which the spiral slowly drifts towards the heterogeneity, but a stepwise process with a random component in which the spiral is shifted due to a complex interaction with newly generated rotors, after which we normally observe a phase during which the spiral stabilizes for a few rotations. After that, the process of interaction between the spiral and newly generated rotors is repeated until the spiral is anchored to the heterogeneity.

Next, we study the influence of the degree of heterogeneity on the attraction and anchoring of a rotor. We performed simulations similar to those of Fig. 3, while changing the APD distribution. This is done according to Fig. 1, A–D, with a ΔAPD of 72.5 ms (A), 62.2 ms (B), 38.5 ms (C), and 18.2 ms (D). Simulations were performed in a tissue with a total size of 15 × 15 cm and a duration of 10 s.

We find that the distance for which the heterogeneity attracts the spiral wave decreases if the degree of heterogeneity is decreased. Indeed, the distance along the fibers, for which it is possible to attract rotors, decreases from 6 to 4.5, 3, and 1.2 cm, respectively (see Fig. 4, A–D). In all cases the mechanism of attraction is similar to that described above. Note, that in Fig. 4, B and C, there are few points with no anchoring inside the anchoring zone: in Fig. 4B for a distance of 2.9 cm and 3.7 cm, and in Fig. 4C for a distance of 2.9 cm. If, however, we increase the simulation time, the rotors anchor at these points as well (the extra time needed to achieve anchoring at these points is 0.24, 2.4, and 3.6 s, correspondently).

To characterize a metric for the propensity for anchoring, we have also studied the time it takes for a rotor to anchor around a heterogeneity vs. the initial distance and positioning of the rotor, and extent of the heterogeneity (Fig. 5). In Fig. 5A the
rotor is positioned at a certain distance from the heterogeneity along the fibers, in Fig. 5B perpendicular to the fibers, and in Fig. 5C diagonal to the fibers. We present results for the three largest heterogeneities shown in Fig. 1 (ΔAPD = 72.5 ms in black, ΔAPD = 62.2 ms in red, and ΔAPD = 38.5 ms in green). We see that for most of the cases, if the initial distance of the rotor to the heterogeneity is smaller, it takes less time for the rotor to anchor to the heterogeneity. The figure also reflects a random component of the process.

We also checked if our results are valid if we change the size of the heterogeneity, while keeping the ionic properties inside and outside the heterogeneity the same. For that we used the heterogeneity as shown in Fig. 1A (G_Ks = 0.0948 nS/pF and G_Ks = 0.0 nS/pF) and performed the same simulations as in Fig. 4 but now for a heterogeneity with a size that is 50% less and, respectively, 50% more than the original size. We refer to Fig. 6. We find that both heterogeneities are able to attract rotors from a substantial distance. As expected, the region of attraction of the heterogeneity with a decreased size is smaller than that for an increased size.

In conclusion, we find that the ionic heterogeneities attract rotors from a substantial distance and that this distance is substantially affected by the degree of heterogeneity. We also find that if the heterogeneity is located at a larger distance from the rotor, it takes longer for the rotor to anchor to the heterogeneity.

Both experimental (4, 26) and modeling studies (31) showed that rotors can anchor to inexcitable obstacles. Therefore, we compared our results on anchoring of rotors at ionic heterogeneities with the anchoring at inexcitable obstacles. We generate an inexcitable obstacle with the same size as the ionic heterogeneities shown in Fig. 1 and perform the same simulation as in Fig. 3. The results are shown in Fig. 7 and the Supplemental Movie S4: we find that the effect of the obstacle on spiral wave dynamics is very small. The rotor remains rotating stationary at the center of the tissue, and we do not see any wavebreak formation or other important effects.

Next, we perform a similar series of simulations, where we start from a rotor rotating in the center of the tissue and position an obstacle at similar locations as we did for ionic heterogeneities (as in Fig. 4). We investigate whether the obstacle can attract and anchor rotors. From Fig. 8, we see that the inexcitable obstacle can only anchor rotors if it is located very close to it: along the fibers, the maximal distance for which it is possible to attract rotors is ~2 cm, while perpendicular to the fiber direction it is ~0.5 cm. We performed the same simulations (not shown) for an inexcitable obstacle with a size that is two times larger than the size of the obstacle used in Fig. 7 and obtained the same result: anchoring and no anchoring, respectively, occurred for the same locations of this obstacle as for the original obstacle shown in Fig. 8.

Comparing Fig. 8 with Fig. 4, we find that ionic heterogeneities, having an APD difference that is large enough (in our case ~30 ms), can attract rotors rotating within larger distances than an inexcitable obstacle of the same size: ionic heterogeneities based on experimentally measured values can attract and anchor rotors rotating within 5–6 cm (see Fig. 4A), while for an inexcitable obstacle of the same size this distance is only ~1–2 cm.

Fig. 7. Inexcitable obstacle does not attract the rotor. The inexcitable obstacle is located at a distance of 4.1 cm from the center of the tissue. The white line shows the size of the obstacle. The effect of the obstacle on spiral wave dynamics is very small. The total size of the medium is 15 × 15 cm. In the text, we further elaborate on this result.
Ionic heterogeneities as attractors of rotors in an anatomical model of the heart. We performed similar simulations in an anatomical model of human ventricles. We initiated a rotor in the left ventricle, containing an ionic heterogeneity as in Fig. 9. We refer to MATERIALS AND METHODS for more details on the heterogeneity. The size, maximal, and minimal APD are again comparable to heterogeneities measured in ventricular tissue in Ref. 7 (see sections shown in Fig. 9, C and D).

In Fig. 10, we show the evolution of a rotor and the corresponding filament, both in a homogeneous anatomical model (left) and in the heterogeneous model of Fig. 9 (right). In both cases, we initiated a rotor at the same location, and followed its rotation for 10 s. In the homogeneous model, we see that the rotor remains rotating stationary at the place where it is initiated. In contrast, the rotor anchors around the heterogeneity in the heterogeneous model and continues to rotate around it for the rest of the simulation (we also refer to the Supplemental Movie S5). We see a slight shift of the filament if we compare the initial and final location (see Fig. 10, G vs. H) (as the heterogeneity is located close to the initial location of the rotor, the shift is rather small in this case).

Now, we move this heterogeneity to different locations, while keeping its size and magnitude constant, in the free wall of the left ventricle and investigate if the heterogeneity attracts the rotor from larger distances. In all cases the rotor has the same initial location as in Fig. 10.

Firstly, in Fig. 11, we show the results for two simulations with a heterogeneity located close to the apex. In both simulations, we see that the rotor is attracted and eventually anchored to the heterogeneity (see also Supplemental Movies S6 and S7 for the results illustrated in the top and bottom, respectively). The dynamics of this attraction is similar to these in 2D cardiac tissue: at first, spiral wave rotation is not affected by the heterogeneity and we just observe wavebreaks at the heterogeneity; later, the effect of the heterogeneity on the waves spreads, and the gap between the wavebreaks increases; then, the wavebreaks start to affect spiral wave rotation, and due to complex interaction, its tip moves towards the location of the heterogeneity, where it eventually anchors.
Secondly, in Fig. 12, we show the results for two similar simulations as in Fig. 11 but now with a heterogeneity located close to the base of the ventricles. At the top, we see the same results as before: after some rotations, the rotor is anchored to the heterogeneity (we refer to Supplemental Movie S8). However, in case of Fig. 12, bottom, after \( \frac{11011}{5} \) s the rotor disappears.

We illustrate this process of removal of a rotor further in Fig. 13 and in Supplementary Movie S9. In Fig. 13, we see that, similar to previous simulations, the rotor is first attracted to the heterogeneity (from 0 to 4.46 s), and then, for one rotation (approximately from 4.54 to 4.82 s), the rotor is anchored to the heterogeneity. However, subsequently, the tip of the rotor disappears at the top border of the left ventricle (\( \frac{11011}{4.82} \) s) and spiral wave rotation ends.

Thus we observe that if the heterogeneity is located close to the boundary of the ventricle, it cannot only attract and anchor a rotor, but it can also eliminate it.

In the next series of simulations, we checked if our results also hold for heterogeneities of different sizes. For this, we changed the size of the ellipse used as a starting configuration for our diffusion based algorithm described in MATERIALS AND METHODS. In particular we decreased (see Fig. 14) and increased (see Fig. 15), respectively, the size of this ellipse by 50%. The ionic properties inside and outside the heterogeneity were the same as previously. When positioned at the same location as the heterogeneity shown in Fig. 9, we obtained a maximal value of APD of 342 and 368 ms, respectively, if we decrease and increase, respectively, the size of the heterogeneity. Minimal APD is unchanged and is 286 ms.

We have tried the same initial locations of both the rotor and the heterogeneities used in Figs. 9, 11, and 12 and obtained the following results for smaller and larger heterogeneities. For the heterogeneity with decreased size at the location as in Fig. 9, we again observed attraction and anchoring of the rotor (results not shown). When we moved this heterogeneity to the apex, as in Fig. 11, we did not observe anchoring of the rotor around the heterogeneity after 10 s. However, after we shifted the heterogeneity \( \sim 9 \) mm closer to the initial position of the rotor (see Fig. 14A), we again find that the heterogeneity can anchor and attract the rotor after 10 s (see Fig. 14D). For heterogeneity locations close to the base, as in Fig. 12, we found that the heterogeneity attracted and anchored the rotor (see Fig. 14E). Also, if we move the heterogeneity even closer to the base (see Fig. 14C), we observed that the rotor, as in Fig. 12, was removed. However, to remove the rotor in that case we needed a simulation time of 12.8 s, i.e., longer than the 5.03 s needed for that in Fig. 12.

For larger sized heterogeneities, for all locations shown in Figs. 9, 11, and 12, we observed attraction and anchoring of the rotor, similar as for the heterogeneity of original size. The only difference was that for the location closest to base (see Fig. 15C), the removal of the rotor occurred after 13.4 s, compared with 5.03 s in Fig. 12.

From these simulations, we can conclude that our results on attraction, anchoring, and removal of rotors also hold for heterogeneities of decreased and increased size. As in 2D, we observed that the region of attraction becomes smaller if the size of the heterogeneity is decreased.

**DISCUSSION**

In this article, we study the effect of small size ionic heterogeneities on spiral wave rotation. These heterogeneities have a size and magnitude similar to these measured by Glukhov (7).

We show that in 2D, these type of heterogeneities can attract and eventually anchor a rotor rotating within 6 cm along the fibers, 4 cm across the fibers, and \( \sim 5 \) cm at 45°. In the whole heart, if the degree of heterogeneity was large enough, it was always anchored (or eventually removed). Thus the basin of
attraction of these ionic heterogeneities is very substantial compared with the typical size of the human heart, the height of which is \( \sim 10 \) cm. We showed that this attraction over large distances is a property of ionic heterogeneities alone, i.e., it does not hold for non-conducting heterogeneities.

In our anatomical model of the ventricles, we demonstrate that if the heterogeneity is located close to the base, it cannot only attract and anchor a rotor but can also remove it. This is an interesting result, as it suggests that some types of heterogeneities have antiarrhythmic effect. In Ref. 43, such regions of prolonged APD were already created in an experimental setup through regional cooling, and they were indeed shown to be able to remove a rotor from the heart. It would be interesting to study this antiarrhythmic effect when the heterogeneity is created in the same way as studied here, for example, by changing the local expression of genes responsible for the conductance of the \( I_{\text{KS}} \) and \( I_{\text{KR}} \) currents. Of course, this is a very controversial statement and it takes into account only one effect of heterogeneity: on attraction and anchoring of rotors. It does not consider its role in the formation of new rotors, for example.

The mechanism of attraction of rotors to heterogeneities can be attributed to a generic behavior of rotors in heterogeneous tissue. In Refs. 24, 27, 38, it was shown that rotors tend to drift to the regions of longer period of rotation. A longer period of rotation of a rotor is normally associated with a longer APD (23, 38). Thus it is very natural to expect that in our simulations the rotors are to be attracted by the heterogeneity, as in our case the heterogeneity has a longer APD compared with the rest of the tissue.

Studies of the effect of heterogeneities on 2D wave propagation in various models of cardiac tissue were also performed in a series of publications (30, 31). In particular, in Ref. 31, they studied dynamics of rotors in a low dimensional (Panfilov) model (20) and the ionic Luo-Rudy I model (14) of cardiac tissue in presence of squared ionic heterogeneities and inexcitable obstacles of \( 4 \times 4 \) cm, placed at various locations in cardiac tissue. The observed dynamics include spiral turbulence, a rotating spiral, and the quiescent state. They showed that the fractal-like boundary separates the basins of attraction of these regimes. One of the regimes observed was anchoring of rotors at the heterogeneity. In the follow up study (30), they compared the dynamics of waves around squared inexcitable obstacles and ionic heterogeneities of \( 3 \times 3 \) cm in four models of cardiac tissue (2, 14, 20, 37). In all models they report various regimes of interaction of rotors with the obstacles. These regimes depend, in a complex way, on the obstacle location. In some situations they also observed anchoring of rotors. These articles give an excellent overview of possibilities that can occur in systems which contain an ionic hetero-
geneity or an inexcitable obstacle. It would be interesting to study which of these regimes can be realized with heterogeneities and obstacles of size and shape derived from direct experimental measurements.

Anchoring around 3D inexcitable obstacles was also studied in Refs. 16, 34, 41. A study of the interaction of a rotor with a heterogeneity with a shorter APD in an anatomical model of the rabbit and pig heart was performed in Ref. 15. It was shown that in that case, a rotor rotating close to the heterogeneity can anchor around it and that parts of this wave can enter the region in which this inhomogeneity is present. This is an interesting observation that shows that even heterogeneities with a shorter APD than the surrounding tissue can serve as anchoring sites for rotors (see also Refs. 16, 30).

In this article, we studied the possibility of anchoring of an existing rotor to a heterogeneity. In our previous study (5), we found that similar ionic heterogeneities can be proarhythmic and that rotors can be formed at such heterogeneities under high frequency external pacing. Note, that the final state in Ref. 5 was also a rotor rotating around the heterogeneity. In view of the results of this article, we can explain it as a consequence of attraction of the initiated rotor to the heterogeneity.

In our whole heart simulations, heterogeneity was located at different positions with respect to the endocardial and epicardial surface (compare for instance Fig. 11A with Fig. 11D). In all of these cases, we found that the rotor was anchored to the heterogeneity. Therefore, transmural location of the heterogeneity does not seem to affect the possibility of attraction of a rotor.

In our 2D simulations, we considered parallel fibers and did not study the effect of more complex cases of fiber orientation on anchoring and attraction of a rotor by a heterogeneity. As anisotropy of cardiac tissue affects spiral wave dynamics, other types of fiber orientation could lead to more complex regions of attraction than these shown in Fig. 4.

We have studied the behavior of a single stable rotor in the presence of a single heterogeneity. It would be interesting to extend this study to the case when several heterogeneities are present in the heart or to other regimes of spiral wave dynamics: for example, to spiral breakup (21, 22), when multiple interacting rotors coexist in cardiac tissue.

In this article, we considered only a stepwise change in $G_{Kr}$ and $G_{Ks}$ in single cell to model heterogeneities at tissue level. Although the change in APD values is stepwise at single cell level, it is gradual at tissue level, due to electrotonic effects. In our case the space constant for such changes is $\sim 3-5$ mm (we refer to Ref. 6 for a detailed discussion). Therefore, we expect that if instead of stepwise changes, more gradual changes at the
single cell level would be used, it should not change the
conclusion of our article, provided these variations are less than the space constant for electrotonic coupling.

A limitation of this study is that it is based on heterogeneities in the subendocardial zone of the left ventricle, measured on the surface of a wedge, and the data do not provide depth information. This means that we do not have information on the 3D structure of the heterogeneity, which we nonetheless modeled in an anatomical model of the ventricles. It can also be that the amount of heterogeneity reported in Ref. 7 is overestimated if used for the whole heart, due to possible additional electrotonic load in situ. In addition, as the heterogeneity has some 3D structure, we do not know if the cut surfaces shown in Ref. 7 are really cut surfaces through the center of the heterogeneity. If this is not the case, the real heterogeneities can have a larger spatial scale. Thus although we extended the research for heterogeneities of various size and at various locations, this study should be considered as a starting point and more detailed investigations of the role of heterogeneity of various type, shape, and origin on rotor dynamics in the heart are therefore needed.

Another limitation is that this study was conducted in only one model of the human ventricles. It would be interesting to test if the results obtained here could be confirmed in other human cell models (9, 19).

Overall, we can conclude that ionic heterogeneities of small size can be preferred regions of localization of rotors. This means that ablation of these heterogeneities can be beneficial as it may reduce chances of stabilization of rotors at the heterogeneity. Alternatively, artificial creation of such heterogeneities close to the boundary of the heart, e.g., in a basal region, may attract the rotors to the boundaries and result in their elimination. Of course, this is a very controversial idea, which requires much more in silico and experimental verification.

ACKNOWLEDGMENTS
The computational resources (STEVIN Supercomputer Infrastructure) and services used in this work were kindly provided by Ghent University, Flemish Supercomputer Center (VSC), Hercules Foundation, and Flemish Government-Department EWI.

GRANTS
A. Defauw, P. Dawyndt, and A.V. Panfilov acknowledge the support of Ghent University (Multidisciplinary Research Partnership–Bioinformatics: From Nucleotides to Networks). N. Vandersickel is supported by the Research-Foundation Flanders (FWO Vlaanderen).

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

Fig. 15. Attraction, anchoring, and removal of a rotor by an ionic heterogeneity of increased size in an anatomical model of the ventricles (see text for details). The ionic properties inside and outside the heterogeneity are the same as in Fig. 9, resulting in a minimal APD = 286 ms and a maximal APD = 368 ms. When positioned at the same location as the heterogeneity shown in Fig. 9, the size at 50% heterogeneity is 0.85 × 1.55 cm for section 1 and 1.55 × 0.85 cm for section 2. The color maps in A–C show the APD distribution in ms in section 1. In D and E, we show the corresponding position of the wavefront after 10 s and in F after 13.4 s.
AUTHOR CONTRIBUTIONS

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

REFERENCES