Far field pacing supersedes anti-tachycardia pacing in a generic model of excitable media

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\textbf{Abstract.} Removing anchored spirals from obstacles is an important step in terminating cardiac arrhythmia. Conventional anti-tachycardia pacing (ATP) has this ability, but only under very restrictive conditions. In a generic model of excitable media, we demonstrate that for unpinning spiral waves from obstacles this profound limitation of ATP can be overcome by far field pacing (FFP). More specifically, an argument is presented for why FFP includes and thus can only extend the capabilities of ATP in the configurations considered. By numerical simulations, we show that in the model there exists a parameter region in which unpinning is possible by FFP but not by ATP. The relevance of this result regarding clinical applications is discussed.

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1. Introduction

Excitable media can exhibit spatiotemporal activation patterns like plane waves, spiral waves and turbulent chaotic dynamics. In cardiac tissue, spiral waves and turbulent dynamics (which is also composed of unstable spiral waves) are called arrhythmia, leading to possibly life threatening diminished organ efficiency. Being able to control spiral wave dynamics therefore is a key requirement of any method for terminating arrhythmia. A standard method of controlling chaos in the heart is defibrillation, which ends any activity in the tissue by exciting the whole medium at once through a high energy electric current. However such large amounts of energy may also lead to cardiac lesions and scars, implying a higher probability for future arrhythmias.

1.1. Anti-tachycardia pacing (ATP)

One way of terminating arrhythmia in a more gentle way (regarding the required energy) is known as ATP. This method uses a train of pacing waves emitted locally from one electrode, with a frequency higher than the frequency of the irregular activity. It exploits a generic effect in excitable media: a pacing wave train traveling in the direction of a spiral vortex can approach this vortex if the pacing frequency is higher than the frequency of the spiral. If the medium is homogeneous the approaching wave fronts will, after having reached the phase singularity, induce a drift and thus terminate the spiral in a finite medium [1]. ATP has a relatively high success rate of about 60–90% in clinical applications [2], but there are generic topological arrangements which lead to failure of ATP and thus may explain some of the unsuccessful 10–40%.

Cardiac tissue is naturally heterogeneous. Besides small variations in the local properties (refractory time, excitability, etc) it also contains obstacles (blood vessels and scars) which are characterized by abrupt conductance changes. Spirals can pin to such obstacles. Already in 1946 Wiener and Rosenblueth concluded that a spiral which is pinned to an obstacle cannot be removed from it by external pacing [3] (figure 1(a)). Any wave approaching the obstacle will split into two counter-rotating waves at the obstacle, only one of which will annihilate with the original spiral. One of the new spirals is left over, which leads to an overall unchanged topological situation. This argumentation assumes that the spiral is directly attached to the obstacle. Such a spiral cannot be terminated by ATP from a remote electrode regardless of the pacing frequency.
Figure 1. Standard ATP. Filled circle: obstacle; arrows: direction of wave propagation. (a) Unsuccessful unpinning by ATP. ATP waves are emerging from the pacing site P, indicated in the first frame. After interaction of the waves the situation \( t = 37 \) has not changed compared to \( t = 34 \). (b) Successful unpinning by ATP. The path of the spiral tip is indicated by a thin white line. At \( t = 51 \) the spiral has been unpinned. A detailed study of this ATP unpinning mechanism is performed in [4].

Free spirals in the medium can have a finite core, defined here as the area which the spiral tip path encloses and which is not excited by the spiral. If the free spiral core size is larger than a given obstacle, the spiral can be anchored at this obstacle without touching it. In this case, there is a minimum pacing frequency—which is higher than the frequency required to induce drift for a free the spiral—for ATP to be successful in unpinning the spiral (investigated in detail in [4]). Thus, unpinning a spiral wave from an obstacle by ATP in this situation is not impossible (figure 1(b)). Obviously, a necessary condition for this mechanism to work is a spiral core size larger than the size of the obstacle.

1.2. Far field pacing (FFP)

The second method of terminating arrhythmia presented here is FFP. It exploits the fact that an electric field applied to a whole piece of tissue leads to depolarizations and hyperpolarizations (so-called Weidmann zones) at the boundaries of conductivity changes. If the depolarization is supra-threshold, the heterogeneity can act as a virtual electrode [5]–[9]. This effect stems from the redistribution of intra- and extracellular currents in the presence of an obstacle. In a simple monodomain model, such an obstacle—meaning a domain of zero conductivity—is implemented by an additional no-flux boundary condition, more specifically [10]

\[
\mathbf{n} \cdot \nabla (e + \mathbf{E} \cdot \mathbf{x}) = 0,
\]  

(1)

where \( e \) is the membrane potential relative to the resting potential, \( \mathbf{E} \) is the applied electric field, \( \mathbf{n} \) is the normal vector to the boundary of the obstacle, and \( \mathbf{x} \) is a point on the boundary. Via (1), the effect of an electric field can be studied numerically. It has already been shown numerically and experimentally that virtual electrodes can be used to unpin waves from obstacles [10]–[13]. One of the mechanisms is nucleating a wave in the refractory tail of the pinned spiral (figure 2). This mechanism of unpinning will be subject to scrutiny in this paper. Other mechanisms of unpinning by FFP are not taken into account.
Figure 2. Successful unpinning by FFP. At $t = 20$ (just after the pulse) the new wave $N$ has been nucleated. At $t = 21$, end F has disconnected from the obstacle, end E forms a pinned wave and collides with the original spiral ($t = 22$). The result ($t = 40$) is a free spiral, formed by the free end F. The new spiral core is indicated by a circular white line.

What can be seen immediately is that for free spirals not pinned to an obstacle, the success or failure of FFP is completely analogue to ATP. In this case, FFP just provides a new way of stimulating the medium without the need for a physical electrode to be implanted. The situation is different for pinned spirals: here FFP provides the possibility of applying a localized electrical stimulus directly at the spiral core. Placing such a stimulus at the right instant in time in the refractory tail of a spiral wave has been shown to be one way to circumvent the difficulties with applying conventional ATP to pinned spirals [14, 15]. As explained above, conventional ATP unpinning (from a distance) can only be successful for free spiral core sizes larger than the size of the obstacle, at which the spiral wave is anchored. FFP does not have such obvious limitations but other possibilities of failure such as pacing wave detachment and repinning have been indicated [10, 13] although a clear connection to properties of the medium is difficult to grasp. A numerical study investigating the limitations of FFP and comparing it to the performance of ATP in a model of an excitable medium has not yet been carried out.

In their experimental realization both ATP and FFP will consist of a sequence of stimuli delivered to the medium. In our analysis, we will restrict ourselves to a single pulse, in order to keep wave patterns simple and thus be able to perform a structured analysis. In reality, the stimuli following the first pulse will (depending on pacing frequency) influence the result, e.g. by inducing further drift of the spiral or by causing repinning. Nevertheless our analysis, as a first approximation, yields important results comparing these two fundamentally different methods of stimulating an excitable medium.

1.3. Model

For our numerical analysis, we use the reaction–diffusion equations

$$\frac{\partial u}{\partial t} = \varepsilon^{-1}u(1-u) \left( u - \frac{v+b}{a} \right) + \nabla^2 u, \quad \frac{\partial v}{\partial t} = u - v \quad (2)$$

with parameters $a$, $b$ and $\varepsilon$, known as the Barkley model [16]. The parameter $\varepsilon$ determines the timescale of the fast variable $u$ (corresponding to the membrane potential) and will be fixed to 0.02 throughout this paper. The slow variable $v$ corresponds to a recovery process. The strength of the transmembrane currents and thus the excitability of the medium is controlled by the parameters $a$ and $b$ (see figure 3). Larger $a$ increases the action potential duration, whereas larger $b/a$ increases the excitation threshold.

All numerical simulations have been carried out on a $240 \times 240$ grid with $\Delta x = 1/6$ and no-flux boundary conditions, using a simple Euler time step with $\Delta t = 1/400$ and a nine-point

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Figure 3. Parameter space of the Barkley model \cite{17, 18}. In the S region (gray), the medium exhibits excitable dynamics and supports spiral waves. In the shrinking waves (SW) region (black) broken plane waves do not form spirals but shrink (called subexcitable in \cite{18}). The right and top white regions represent non-excitable dynamics: bistability and no waves, respectively. Successful unpinning by ATP as in figure 1(b) for an obstacle with radius $R = 3$ is only possible in the region A inside S. In the large rest of the S region, the configuration is as in figure 1(a), i.e. ATP fails to unpin spirals from obstacles of size $R = 3$.

Laplacian for the diffusion operator. For imposing the boundary condition (1) at the obstacle, the first spatial derivatives have been approximated to second order by centered finite differences.

2. Simulations

For the S region in the parameter space, where the medium supports spirals (see figure 3), simulations of free spirals have been carried out in order to determine free spiral core size with steps ($\Delta a, \Delta b$) = (0.05, 0.005) in the parameter plane. For circular cores, this procedure is straightforward. In the case of meandering (which is only possible in the lower left part of S), an upper boundary for the relevant core diameter was found by taking the maximum distance between an arbitrary starting point of the phase singularity and its position during the two following (high frequency wave) rotations.\footnote{Of course, this is only a valid measure if we consider the higher frequency motion of the compound rotation \cite{16, 19} to be the relevant one for our investigation: the critical situation is a spiral meandering around an obstacle with a low frequency while performing smaller amplitude higher frequency rotations (if they were not of smaller amplitude, they would be a suitable upper boundary anyway). When we apply ATP to this spiral, there will be a point in time when the ATP wave fronts have reached the tip and could potentially induce a drift. As the interaction takes place on a timescale comparable to the high frequency rotations, the situation is only negligibly different to a free spiral rotating rigidly with this high frequency and the corresponding core radius at the place where the meandering spiral was met. Thus this spiral should not be regarded anchored unless there is an obstacle in the core corresponding to the high frequency rotations. An upper boundary for this radius is measured by our method.}

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The region of parameters where the measured free spiral core radius is larger than $R = 3$ is shown in figure 3. The transition from the S to the SW region is characterized by an increasing spiral core size which eventually diverges at the boundary. The solid line borders (from below) the region in which the necessary condition for ATP unpinning core size > obstacle size for an obstacle size $R = 3$ is fulfilled. Thus in the region A between the dashed line and the SW region, ATP could potentially be successful in unpinning a spiral from an obstacle of radius $R = 3$, depending on ATP frequency, initial conditions (whether the spiral is attached to the obstacle), location of ATP stimulations and maybe other factors. In the rest of the S region, however, unpinning by ATP from a distance is definitely not possible, because a necessary condition for the mechanism is not fulfilled.

For the FFP simulations a spiral wave attached to an obstacle of size $R = 3$ was produced. This is done by starting a plane wave from the boundary of the medium. Upon reaching the obstacle at the center of the medium, this plane wave splits in two spirals attached to the obstacle. One of them is terminated by resetting the half plane containing it to $u = 0$, the other then rotated as a pinned spiral for at least one period before doing any measurements (to account for transients). For the unpinning trials, the electrical field strength was fixed to 7 (unit $u$ amplitude/unit length) with a pulse duration of 0.1 time units. This roughly corresponds to the effect of a pulse of 0.8 V cm$^{-1}$ with a pulse duration of 10 ms in experiments.

For FFP with fixed amplitude and pulse duration, the time at which the pulse is delivered is the critical factor determining whether FFP will be successful in unpinning a spiral wave from an obstacle or not. A pinned spiral exhibits exactly periodic dynamics (at least in the Barkley model and in this isolated, idealized situation). Let us therefore restrict the following considerations to one period of rotation, starting at the point in time when the spiral passes the side of the obstacle, which will be depolarized by the far field. The typical situation for a broad range of model parameters $a$ and $b$ is this: a pulse which is delivered too early, before a critical time $t_{\text{min}}$, cannot initiate a wave at all, because the area depolarized by the electric field is still too refractory (i.e. the time interval between the last excitation by the pinned spiral and the far field pulse is too short). On the other hand, if the pulse is delivered after a critical time $t_{\text{max}}$, the initiated wave will produce two spirals rotating in opposite directions, because the time since the last excitation by the pinned spiral is too long and thus the boundary of the obstacle is not refractory enough in order to prevent the new wave from propagating along it behind the original spiral (compare the successful case in figure 2). The original spiral and the newly created spiral of opposite direction of rotation annihilate, leaving one pinned spiral with the same direction of rotation as the original pinned spiral.

However, these are not the only mechanisms of FFP failure [10, 13]. One mechanism which proved very important during the analysis is repinning: As described above, during successful unpinning by FFP, one end of the newly created wave detaches from the obstacle because of refractoriness and forms a spiral, which is free at this instant. However, due to a possibly nonzero core size and further interaction between the free end and the refractory tail of the original spiral under time evolution, the path of the free end may take it back to the boundary of the obstacle where it repins.

3. Results

The simulations for determining the unpinning window $t_{\text{max}} - t_{\text{min}}$ were started at a parameter combination $(a, b)$ near the subexcitable boundary of the S domain (see figure 3). For these
Figure 4. Parameter dependence of unpinning window width. Left: for $a = 0.8$, the width of the unpinning window is plotted against the model parameter $b$. The solid and dashed lines represent the size of the unpinning window, normalized by the spiral rotation period $T$, for two different obstacle radii. Error bars are not shown, as (due to the algorithm) accuracy is constantly $\pm 1/96 T$. For $b = 0.06$ this means that the unpinning window is smaller than $T/96$. Right: the same data, but plotted against the spiral rotation period $T$, normalized by the maximum rotation period $T_{\text{max}}$ at $b = 0.14$.

parameters the period of the spiral was determined in a simulation without FFP. Then FFP simulations were carried out with 96 different pulse times, distributed equally over one rotation period. The unpinning window was taken as the width of the largest continuous interval of successful pulse times—successful meaning that the spiral could be detached from the obstacle and did not reattach within at least one rotation. Then $b$ was decremented by $\Delta b = 0.005$ and the same procedure was carried out for the new parameters $(a, b - \Delta b)$. This procedure was repeated until $(a, b_{\text{min}})$, for which none of the pulse times produced successful unpinning. From the results of this algorithm the unpinning window could be determined to an accuracy of $\pm T/96$, where $T$ is the spiral period. The results of a series of simulations for $a = 0.8$ can be seen in figure 4.

The algorithm described above has been carried out for all values of $a$ in the range from 0.4 to 1.2 with a step size of $\Delta a = 0.1$ each producing data like figure 4. The parameter values at which the unpinning window vanishes were used to determine the area in the parameter diagram where unpinning can definitely be achieved by FFP (figure 5). As the parameter scan (see above) stopped at the zero unpinning window line, a region below the dashed line could exist in which FFP is also successful. But even this lower estimate of the success of FFP clearly covers a larger region in the parameter diagram than the equivalent upper estimate for ATP (figure 3). The difference becomes even more pronounced if we increase the obstacle size from 3 to 4.5: in the case of ATP, the necessary condition core size > obstacle size is fulfilled in an even smaller region close to the SW boundary (compared to figure 3). Simulations for this obstacle size using FFP show that the region of success for this method stays nearly constant. In figure 4, the unpinning window width is also plotted for $R = 4.5$. The value of $b$ at which it vanishes is identical to that of $R = 3$. The only difference is a generally larger unpinning window.

It should be emphasized that despite the arbitrary choice of obstacle radius for the simulations, the fact that FFP is more effective than ATP in unpinning spirals is a general feature of this model, not depending on obstacle size: as mentioned above, FFP capabilities must include those of ATP, because in cases where ATP can be successful (i.e. for spirals anchored to but not touching an obstacle), FFP is acting as a virtual electrode only and therefore is entirely equivalent to ATP. The results shown here now prove that the capabilities of FFP are strictly
Figure 5. Performance of FFP. The area B, bounded by a dashed line, marks the parameter combinations for which the unpinning window is certainly nonzero. In this region, unpinning by FFP is successful, if the pulse is given at the right time. The vertical white dotted line corresponds to the parameter values shown in figure 4. The horizontal black dotted line indicates the value of $b$ at which the unpinning window vanishes for this choice of $a$ (compare figure 4).

larger than those of ATP in a mathematical sense, as there exists a large class of configurations, for which FFP is successful but ATP is not.

Interestingly, repinning seems to play an important role in the disappearance of the unpinning window: e.g. for $a = 0.9$ and low values of $b$ (just above the value of $b$ at which the unpinning window vanishes), pulse times below $t_{\text{min}}$ and above $t_{\text{max}}$ are both able to initiate a new wave with one end detached from the obstacle. This is a qualitative difference to the general case of higher values of $b$ described above, where before $t_{\text{min}}$ no wave at all can be initiated, but after $t_{\text{max}}$ two pinned spirals are produced. Nevertheless unpinning for these pulse times is not successful, because the free end reattaches to the obstacle in less than one rotation. Most notably we know that for low values of $b$, the spiral core size is negligible. Thus this kind of repinning cannot be explained by spiral core size that is too large compared to the distance from the obstacle to the free end. In fact, the mechanism must be based on the interaction between the free end and the refractory tail of the pinned spiral.

4. Conclusion

We have shown that in a generic model of excitable media FFP can overcome the inability of traditional ATP to unpin spirals from obstacles larger than the free spiral core size. Although the Barkley model is only a qualitative model this gives rise to the conjecture that arrhythmia termination based on FFP could yield higher success rates in clinics than state-of-the-art ATP. In order to obtain a realistic idea of the experimental consequences, the effect of multiple stimuli should be included in further work on this topic. Furthermore, the physical mechanism of the vanishing unpinning window has still to be understood in order to estimate the relevance of this limitation for real cardiac tissue and other biological excitable media.
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