Dynamic mechanism for conduction block in heart tissue

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Abstract. Previous work has shown that dynamic heterogeneity and conduction block can occur in homogeneous heart fibres during prolonged pacing at rapid rates. Here we investigated the mechanism for conduction block following the delivery of one to four premature stimuli using a coupled maps computer model of a one-dimensional canine heart fibre. The coupled maps model allowed us to identify the roles that velocity ($V$) restitution, action potential duration ($D$) restitution and cardiac memory ($M$) played in the development of spatial heterogeneity and conduction block. We found that the likelihood of conduction block could be reduced by three methods. (1) By altering the $V$ restitution function so that conduction slowed at very short rest intervals ($I$). (2) By altering the $D$ restitution function to reduce the sensitivity of $D$ to changes in $I$. (3) By increasing the contribution of cardiac memory ($M$). Although the results of this study need to be confirmed experimentally, they suggest several potential interventions that may reduce the probability of arrhythmia induction.

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1. Introduction

Catastrophic heart rhythm disorders are among the leading causes of death in the United States. The most dangerous of these arrhythmias is ventricular fibrillation, a disturbance in which disordered wave propagation causes a fatal disruption of the synchronous contraction of the ventricle. Although the exact mechanism for fibrillation is still being debated, one theory proposes that fibrillation is a state of spatiotemporal chaos consisting of the perpetual nucleation and disintegration of spiral waves [4, 26], in association with a period doubling bifurcation of local electrical properties [13, 14, 16, 18]. Nucleation of the initiating spiral wave pair is caused by local conduction block (wave break) secondary to spatial heterogeneity of refractoriness in the ventricle [2, 4, 22, 25, 26]. Until recently, spatial heterogeneity was thought to result solely from regional variations of intrinsic cellular electrical properties [22, 27] or from stimulation at more than one spatial location [20, 24, 25]. However, it is now appreciated that purely dynamical heterogeneity can be sufficient to cause conduction block during single-site stimulation in both homogeneous one-dimensional models of canine heart tissue and in rapidly paced canine Purkinje fibres [8, 12]. A similar mechanism has been shown to precipitate conduction block and spiral break-up in models of homogeneous two-dimensional tissue [9].

The period doubling bifurcation implicated in the transition to conduction block is manifest as alternans, a beat-to-beat long–short alternation in the duration of the cardiac action potential [13, 14, 16, 18, 24]. Previous investigators have hypothesized that alternans can be accounted for by a simple uni-dimensional return map called the action potential duration restitution function [5, 6, 15, 17]. This hypothesis assumes the duration $D$ of an action potential depends only on its preceding rest interval $I$ through some function $f(I)$ that is measured experimentally. If the $D$ restitution function has a slope $\geq 1$, then a period doubling bifurcation occurs for some value of the stimulus period $T$, where $T = D + I$. The velocity $V$ at which an action potential propagates can also be described by a restitution function, where $V = c(I)$.

It has been shown previously that the combination of a steeply sloped $D$ restitution function and a monotonically increasing $V$ restitution function is sufficient to produce dynamical conduction block during sustained pacing at a short cycle length [11, 12]. This observation may provide a generic mechanism for wave break and the onset of ventricular tachycardia and
fibrillation. However, it is unlikely that the conditions used to demonstrate this phenomenon experimentally apply to the clinical situation, where the induction of ventricular tachyarrhythmias is typically associated with the interruption of normal cardiac rhythm by only a few premature beats. A single premature beat is sufficient to cause spatial heterogeneity in the form of discordant alternans [24], but the conditions required for the development of conduction block in this setting have not been investigated.

To address this issue, in the present study we determined whether dynamic heterogeneity and conduction block occur in a computer model of canine heart fibres in which pacing at a slow rate is interrupted by one to four premature stimuli. This protocol simulates the interruption of sinus rhythm by one to four premature ventricular complexes (PVCs), a situation that can lead to the onset of ventricular fibrillation clinically. Furthermore, we determined whether such conduction block can be accounted for by the same dynamical mechanism that underlies the development of conduction block during rapid pacing. A coupled maps model of heart tissue was used for the study, which allowed us to identify the roles that $V$ and $D$ restitution play in the development of dynamic heterogeneity. We also considered the additional contribution of cardiac memory ($M$) to the development of dynamical heterogeneity and conduction block.

2. Methods

We studied the mechanism for conduction block following the delivery of multiple premature stimuli using a one-dimensional computer model of a canine heart fibre. The length of the fibre was 4 cm, which is similar to the length of fibres used for previous experimental studies [12]. The fibre was stimulated at one end at a cycle length near normal canine sinus rhythm ($S_1 = 500$ ms). After ten beats at $S_1$, four premature stimuli were delivered ($S_2$, $S_3$, $S_4$ and $S_5$) at the same site. The coupling intervals between these premature intervals were varied and the conduction of the resultant action potentials was observed (figure 1). For each combination of premature stimuli, one of three possible outcomes occurred:

1. the stimulus elicited an action potential that propagated down the entire fibre;
2. the stimulus did not produce an action potential (type I block);
3. the stimulus elicited an action potential that blocked before reaching the end of the fibre (type II block).

The first two cases would not be conducive to the development of wave break and initiation of re-entry, in that conduction of the premature response either does not occur at all or occurs equally well everywhere along the fibre. The third case, however, could lead to wave break and spiral wave initiation if it occurred in two- and three-dimensional tissue, provided the block was local. The development of local block would be facilitated in intact myocardium by twist anisotropy and intrinsic heterogeneity.

To assess the vulnerability of the simulated tissue to type II block, the $S_2$–$S_3$–$S_4$–$S_5$ combinations were applied in the following way: the $S_1$–$S_2$ interval was varied from the minimum value that conducted ($S_1$–$S_{2\text{min}}$) to $S_1$–$S_{2\text{min}} + 20$ ms. For each $S_1$–$S_2$ interval, the $S_2$–$S_3$ interval and the $S_3$–$S_4$ interval were varied in combination from the minimum value that conducted up to a value of 250 ms for each interval. Finally, for each $S_2$–$S_3$–$S_4$ combination that conducted, the $S_4$–$S_5$ interval was varied from the minimum that generated an action potential at the site of stimulation to the minimum value that conducted down the entire fibre. If no
Figure 1. (a) Schematic representation of the relationships between stimulus period \((T)\), action potential duration \((D)\), diastolic interval \((I)\) and memory \((M)\).

(b) Example of the stimulation protocol. The model fibre was paced for ten beats at a constant S1–S1 interval, after which a series of premature stimuli (S2–S5) was delivered. R indicates the refractory period of a cardiac cell, during which the delivery of a stimulus does not produce a propagated response.

S2–S3–S4–S5 combination was found that produced conduction block for more than a 20 ms window in either the S2–S3 interval or the S3–S4 interval, the search was halted for that interval. All intervals were varied in steps of 1 ms.

2.1. Coupled maps model

The study was conducted using a coupled maps model of a one-dimensional cardiac fibre that has been described in detail elsewhere [10, 12]. Briefly, the model is based on the equation

\[
I_{n+1}(x_i) = T_{n+1}(x_i) - D_{n+1}(x_i). \tag{1}
\]

\(T_{n+1}(x_i)\) was the time interval between activations of site \(x_i\). It was determined by including the time delays caused by the propagation from the pacing site to site \(x_i\), which yielded

\[
T_{n+1}(x_i) = \tau + \sum_{j=0}^{i-1} \frac{\Delta x}{V_{n+1}(x_j)} - \sum_{j=0}^{i-1} \Delta x \frac{\Delta x}{V_{n}(x_j)}. \tag{2}
\]

\(\tau\) was the time interval between activations applied to the pacing site and \(\Delta x = 0.1\) was the length of a single cell (time units in milliseconds and space units in millimetres). The conduction
velocity \( V_n(x_i) \) depended only on \( I \) through the velocity recovery function \( V_n = c(I_n) \) given by \( c(I) = V_{\text{max}}(1 - \exp(-(I + \beta)/\delta)) \). \( V_{\text{max}} = 0.72, \delta = 14, \) and \( \beta \) varied to adjust the value of \( V \) at \( I = I_{\text{min}} \). \( D \) was determined locally based on a memory model mapping [10] given by

\[
M_{n+1} = g(M_n, I_n, D_n) = e^{-I_n/\tau_m}[1 + (M_n - 1)e^{-D_n/\tau_m}]
\]

\[
D_{n+1} = f(M_{n+1}, I_n) = (1 - \alpha M_{n+1})(A + \frac{B}{1 + e^{-(I_n-C)/\tau_D}}).
\]

\( \tau_m \) was the time constant of accumulation and dissipation of memory (both constants were chosen to be the same). \( A = 88, B = 122, C = 40 \) and \( \tau_m = 180 \) [10]. \( \alpha \) and \( \tau_D \) were varied in this study. \( \alpha \) (which varied between zero and unity) determined the influence of memory on \( D \), and \( \tau_D \) was used to adjust the dependence of the \( D \) recovery function on \( I \). We note that, for memory models, the dependence of \( D \) on \( I \) (as well as the occurrence of a period doubling bifurcation) is not related to the steady-state restitution slope in a simple manner [10].

Coupling between sites was included by using the diffusion terms from Echebarria and Karma [8]. These terms modelled the electrotonic current that flowed out of (into) a cell and into (out of) its neighbour if the action potential of the first cell was longer (shorter) than that of its neighbour. Including diffusion then yielded

\[
D_{n+1} = f(M_{n+1}, I_n) + \xi^2 \nabla^2 D_{n+1} - w \nabla D_{n+1},
\]

with \( \xi = 1.0 \) and \( w = 0.35 \). Discretizing the derivatives produced a tri-diagonal linear system of equations that could then be solved easily. The defining equation for the model was therefore

\[
M_{n+1} = g(M_n, I_n, D_n)
\]

\[
D_{n+1} = f(M_{n+1}, I_n) + \xi^2 \nabla^2 D_{n+1} - w \nabla D_{n+1}
\]

\[
I_{n+1}(x_i) = \tau + \sum_{j=0}^{i-1} \frac{\Delta x}{c(I_{n+1}(x_j))} - \sum_{j=0}^{i-1} \frac{\Delta x}{c(I_n(x_j))} - D_{n+1}(x_i).
\]

Finally, conduction block was modelled by setting \( f = 0 \) for \( I < I_{\text{min}} = 2 \).

3. Results

3.1. Characteristics of conduction block in the wild type model

Figure 2 shows a typical example of type II conduction block in the baseline model (hereafter called the wild type model). Despite the homogeneous state that existed at the end of the S1 stimuli, dynamical heterogeneity developed following delivery of S2, secondary to \( V \) restitution (see below). Heterogeneity was manifest as a short-to-long gradient in \( I \), which was magnified by subsequent premature stimuli until the action potential generated by the S5 stimulus encountered a region where \( I < I_{\text{min}} \) and conduction failed.

Figure 3 shows a histogram of type II conduction block at various S2 and S3 intervals generated from the wild type model. Note the presence of a large peak centred at an S2 very close to the minimum value for conduction and at an S3 approximately 50 ms longer than the minimum value for conduction. Surrounding the peak is a flat plateau region of five to ten blocks per bin that extends throughout the entire (S2, S3) region that was explored numerically. An overwhelming majority of these instances of block occurred after the S5 stimulus. However, six examples of ‘early block’ were found after an S4 stimulus, and one was found after an S3
Figure 2. Example of type II conduction block in the coupled maps model. Each panel shows $I$ as a function of cell number for the last $S1 = 500$ ms beat (left panel) and for beats $S2 = 207$ ms, $S3 = 146$ ms, $S4 = 148$ ms and $S5 = 106$ ms. Note the difference in scale for each beat. Conduction block, corresponding to $I < I_{\text{min}}$, occurs near cell 100 on the $S5$ beat and is denoted by two horizontal black lines.

Since conduction block occurs when $I < I_{\text{min}}$, changes in $I_{\text{min}}$ will produce significant changes in the incidence of conduction block. Because $I_{\text{min}}$ is a component of the functions that control $V$ restitution, $D$ restitution and $M$, changes in $I_{\text{min}}$ influence all three dynamic variables. In this study, we held $I_{\text{min}}$ fixed and individually studied the roles that $V$ restitution, $D$ restitution and $M$ played in determining the risk of type II block, as assessed by the $S2$–$S3$–$S4$–$S5$ protocol.

3.2. Contribution of $V$ restitution to conduction block

$V$ restitution played two important roles in the development of conduction block. First, as mentioned above, $V$ restitution was the source of the initial heterogeneity after delivery of the stimulus. The latter explain the presence of the plateau in the histogram; the plateau is made up of ‘degenerate’ counts in which long $S2$ or $S3$ intervals that maintained the initial $S1$ homogeneity were followed by early block intervals leading to block at $S5$. 

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Figure 3. Histogram of the incidence of type II conduction block in the wild type model. $\alpha = 0.2$, $\tau_D = 28$ and $\beta = 17.408$. The height at each point in (S2, S3) space corresponds to the number of blocks found at beat S3, S4 or S5 for a given (S2, S3) pair. S2\text{\textsubscript{min}} and S3\text{\textsubscript{min}} are as defined in the methods section. Total counts = 67 205.

S2 stimulus. The S2 stimulus was delivered just after the refractory period of the last S1 beat so that $I$ at the site of stimulation was short (see figure 1). The short $I$ produced slow $V$, which increased $I$ for cells distal to the stimulus site. This initial dispersion in $I$ following S2 was magnified by steep $D$ restitution at each subsequent beat, ultimately leading to conduction block several beats later.

Second, the value of the $V$ restitution curve at $I_{\text{min}}$ was an important parameter in determining the likelihood of conduction block, as illustrated by figure 4. Panel (a) shows $V$ restitution curves with four different values for the $V(I_{\text{min}})$ (90, 75, 50, and 25% of $V_{\text{max}}$). $V(I_{\text{min}})$ in the wild type model was 75% of $V_{\text{max}}$. Panel (b) shows a histogram for $V(I_{\text{min}}) = 50\%$ of $V_{\text{max}}$ and panel (c) shows the histogram for $V(I_{\text{min}}) = 90\%$ of $V_{\text{max}}$. For $V(I_{\text{min}}) = 90\%$ of $V_{\text{max}}$, the model had roughly 30\% more instances of conduction block than in the wild type model, whereas the model with the lower cut-off values produced dramatically fewer instances of conduction block. In fact, the model with $V(I_{\text{min}}) = 25\%$ of $V_{\text{max}}$ produced no cases of type II block. This result did not depend on the steepness of the $V$ restitution curve. For example, no cases of type II block were found for a model with $\beta = -1.4$ and $\delta = 2.0$, which also had $V(I_{\text{min}}) = 25\%$ of $V_{\text{max}}$, but had a much steeper slope. The lack of type II block when $V(I_{\text{min}}) = 25\%$ of $V_{\text{max}}$ can be understood by noting that if the $V$ restitution curve approaches zero at $I_{\text{min}}$, then a propagating wave that approaches a region with a very small $I$ can slow down to allow $I$ to increase just in front of it, permitting continued conduction.

3.3. Contribution of $D$ restitution to conduction block

As mentioned above, $D$ restitution contributed to conduction block by magnifying heterogeneity in $I$. If the $D$ restitution function had weak dependence on $I$, any initial dispersion of $I$ due to $V$
Figure 4. The role of $V$ restitution in type II block. (a) $V$ restitution for four cases: $\beta = 17.408$ (black; wild type), $\beta = 7.704$ (red; $V(I_{\text{min}}) = 50\%$ of $V_{\text{max}}$), $\beta = 2.028$ (green; $V(I_{\text{min}}) = 25\%$ of $V_{\text{max}}$) and $\beta = 30.236$ (blue; $V(I_{\text{min}}) = 90\%$ of $V_{\text{max}}$). (b) Histogram for $V(I_{\text{min}}) = 50\%$ of $V_{\text{max}}$. Total counts = 8879 (cf 67205 for wild type). (c) Histogram for $V(I_{\text{min}}) = 90\%$ of $V_{\text{max}}$. Total counts = 86032. There were no counts for $V(I_{\text{min}}) = 25\%$ of $V_{\text{max}}$. 

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Figure 5. The role of $D$ restitution in type II block. (a) Steady-state $D$ restitution for four cases: $\tau_D = 28$ (black; wild type; max. slope = 1.09), $\tau_D = 32$ (red; max. slope = 0.97), $\tau_D = 40$ (green; max. slope = 0.82) and $\tau_D = 20$ (blue; max. slope = 1.45). (b) Histogram for $\tau_D = 32$. Total counts = 39 688. (c) Histogram for $\tau_D = 40$. Total counts = 21 185. (d) Histogram for $\tau_D = 20$. Total counts = 364 301.

Restitution would be lessened on subsequent stimulations. Figure 5 shows the effect of altering $D$ restitution slope by increasing and decreasing the parameter $\tau_D$. Panel (a) shows steady state restitution curves for four different values of $\tau_D$. The wild type model was $\tau_D = 28$. As shown in panels (b) and (c), increasing $\tau_D$ led to a significantly smaller peak in the histogram, as well as fewer total instances of conduction block. Conversely, decreasing $\tau_D$, which led to a steeper steady state restitution slope, had significantly more counts (panel (d)). However, it is important to note that even for the $\tau_D = 40$ model, which had a maximum steady state slope of 0.82, instances of type II block were found.

3.4. Contribution of $M$ to conduction block

Because increasing $M$ in the coupled maps model has been shown to eliminate steady state alternans, it was hypothesized that increasing $M$ also would lead to fewer instances of type II block. Figure 6 illustrates the effect of changing $M$ on the likelihood of conduction block in the
model by increasing and decreasing the parameter $\alpha$. Panel (a) shows steady-state restitution for four different values of $\alpha$. The wild type model was $\alpha = 0.2$. In panel (b) $\alpha = 0.58$, which eliminated alternans but maintained a slope $\geq 1$. In fact, the steady state restitution slope was 1.62, even larger than in the wild type model. In panel (c) $\alpha = 0.8$ and the maximum steady state restitution slope was 2.65. Both panels (b) and (c) show smaller peaks and fewer total counts than the wild type model. In panel (d) $M$ was decreased ($\alpha = 0.1$) and the maximum steady state slope is 1.09. The decreased memory model shows more instances of conduction block than the wild type model. This result did not depend on the magnitude of $D$. For example, shifting the curve from panel (c) by adding 70 ms to the function $f(M_{n+1}, I_n)$ did not produce more instances of type II block (in fact slightly fewer (39 229) were found). Similarly, shifting the curve from panel (d) down by subtracting 70 ms from $f(M_{n+1}, I_n)$ produced roughly the same number of blocks (94 151) as in panel (d). Two other observations can be made. First, increasing $M$ did not seem to be as effective as increasing $\tau_D$ in reducing the likelihood of block. Second, the steady-state $D$ restitution function is not predictive of the likelihood of block.

### 3.5. Contribution of electrotonic interactions to conduction block

Electrotonic effects have been shown to prevent alternans in some models [7]. Therefore, changes in electrotonic current may be expected to have an effect on the incidence of conduction block. The coupled maps model allowed for the complete removal of electrotonic interactions by eliminating the diffusion terms in equation (4). As shown in figure 2, the potential for conduction block was present when the previous beat generated a short-to-long pattern in $I$. This pattern led to a short-to-long pattern in the following $D$. In the wild type model, both the first and second derivative diffusion terms tended to decrease the long $D$ and increase the short $D$, reducing the amount of heterogeneity and thereby reducing the likelihood of type II block. Accordingly, elimination of the diffusion terms was expected to increase the incidence of type II block and this expectation was confirmed; total counts of type II block were 88 603 (histogram not shown).

### 4. Discussion

In this study type II conduction block following the delivery of multiple premature stimuli was caused by the same sequence of events that caused conduction block during sustained rapid pacing in our previous study [12]. Stimulation at a short $I$ produced a gradient of increasing $I$ (and, consequently, of $D$ and $V$) along the fibre. The succeeding stimulus, if delivered at an appropriate interval, encountered a progressively decreasing $I$ as it propagated down the fibre (i.e., the new wavefront encountered the waveback of the previous excitation). Thus, a short–long sequence of $D$ at the site of stimulation was associated with the development of a long–short sequence of $D$ at the opposite end of the fibre, similar to the pattern established during stable discordant alternans [19, 20, 24]. When the gradient in $I$ along the fibre was sufficiently steep in the ascending direction, the subsequent action potential encountered an $I < I_{\text{min}}$ and conduction block occurred.

Previous studies have shown that the location of the block can be predicted, given the spatial profile of $D$ for the preceding beat [22]. If this information is not known, however, then developing a quantitative theory for the type II block observed in this study becomes difficult, not only because the model consists of complicated nonlinear difference equations in both space and time, but also because the phenomenon of interest is a transient. Therefore, the usual
Figure 6. The role of $M$ in type II block. (a) Steady-state $D$ restitution for four cases: $\alpha = 0.2$ (black; wild type; max. slope = 1.09), $\alpha = 0.58$ (red; max. slope = 1.62), $\alpha = 0.8$ (green; max. slope = 2.65) and $\alpha = 0.1$ (blue; max. slope = 1.09). (b) Histogram for $\alpha = 0.58$. Total counts = 48 387. (c) Histogram for $\alpha = 0.8$. Total counts = 43 715. (d) Histogram for $\alpha = 0.1$. Total counts = 87 433.

tools of nonlinear dynamics, such as finding steady-state solutions and analysing their stability, do not apply. Still, inspection of the defining equations produces a qualitative understanding of the results presented in this study. The mechanism for conduction block relies on three determinants. First, a non-constant $V$ restitution function produces spatial heterogeneity in $I$. Next, this heterogeneity is amplified (or at least it does not decay rapidly) due to sensitive dependence of $D$ on $I$. Finally, the $V$ restitution function does not drop sufficiently close to zero at very short $I$, causing the wave to collide with the refractory period of the preceding excitation.

Preventing the first aspect of type II block could only be done by forcing the $V$ restitution curve to be constant. Even in that case, type II block could still occur if there were intrinsic heterogeneity in the fibre. Therefore, we explored how the likelihood of type II block could be diminished by two different methods. The first method was to alter the $V$ restitution function so that conduction slowed at very short $I$, thus preventing encroachment on the refractory period. It is important to note that this method is only viable if the decrease in conduction velocity occurs at

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short $I$. Decreasing maximum conduction velocity is in fact pro-arrhythmic, because it decreases the wavelength [9]. Although selective slowing of conduction at short rest intervals may create a greater dispersion of refractoriness after a premature beat, the benefits of this intervention seem to outweigh the risks, at least under the conditions of this study. Whether a similar strategy will suppress conduction block in 2D or 3D tissue with realistic intrinsic heterogeneity remains to be determined.

The second method for reducing the likelihood of type II block was to reduce the sensitivity of $D$ on $I$. If the system is uni-dimensional, this is done by decreasing the $D$ restitution slope. The lower the slope of the $D$ restitution relation, the lower the likelihood of spatial dispersion of repolarization secondary to dispersion of $I$. However, the model used in this study did not have a simple relationship between the slope of the steady-state $D$ restitution function and the likelihood of block. Instead, the important quantity is the sensitivity of $D$ to the preceding $I$, given by

$$
\gamma = \frac{df}{dI} = \frac{\partial f}{\partial M} \frac{\partial M}{\partial I}.
$$

(6)

The quantity $\gamma$ is the amplification factor relating the dispersion in $D$ to the dispersion in the preceding $I$. If $\gamma$ is small, then any initial dispersion in $I$ will decay quickly. If $\gamma$ is large, the dispersion of $I$ can persist or even be amplified. It can be shown that at short cycle lengths the first term dominates, giving

$$
\gamma \approx \frac{\partial f}{\partial I} = (1 - \alpha M^*) \frac{B}{\tau_D} \frac{e^{-(I^*-C)/\tau_D}}{1 + e^{-(I^*-C)/\tau_D}}.
$$

(7)

$M^*$ and $I^*$ are the steady state values at a given cycle length. This equation is of limited quantitative use since the system never reaches steady state (and the cycle length is continuously changing). Still, it suggests that the likelihood of block can be reduced by either increasing $\tau_D$ or by increasing $\alpha$. The simulation results support this qualitative argument. This result highlights the fact that the dynamics during premature stimulation cannot be predicted from the steady-state $D$ restitution function. In fact, the more relevant experimental measure would be the $S_1$–$S_2$ $D$ restitution function at very short $S_2$. The slope of this curve at short $I$ would directly measure the dispersion of $D$ after a very short $S_1$–$S_2$ interval had produced some initial dispersion in $I$. However, relating the $S_1$–$S_2$ curve to any quantitative prediction about type II block is not straightforward.

Programmed electrical stimulation has been used extensively in the past to induce ventricular arrhythmias in patients thought to be at risk for the development of ventricular fibrillation [1]. However, the stimulation protocol used in the clinical studies differs significantly from that used here, in that arrhythmia induction was attempted using tightly coupled premature stimuli, which produced block similar to the type I block described in our study. Once the patient’s arrhythmia had been induced using multiple premature stimuli, the test was repeated after administration of an antiarrhythmic drug. In many cases a drug could be found that would suppress the patient’s inducible arrhythmia. Yet the results of large scale clinical trials eventually revealed that patients sent home on such medications were as or more likely to die suddenly than patients who did not receive such treatment [3, 23]. Clearly, the induction of arrhythmias using this particular stimulation protocol was not predictive of the development of ventricular fibrillation.

The failure of the standard method of programmed stimulation to accurately assess vulnerability to ventricular fibrillation may relate to the fact that this method was designed...
primarily to induce conduction block and re-entry by perturbing intrinsic heterogeneity. The potential contribution of dynamic heterogeneity to the development of conduction block would not be assessed adequately using such a protocol. In addition, interventions that were intended to prevent the induction of arrhythmias using the standard protocol, such as slowing of conduction or prolongation of refractoriness, might be effective in that regard, secondary to a reduction in intrinsic heterogeneity, but might not reduce dynamic heterogeneity. Consequently, the beneficial effects of such interventions on arrhythmias induced by the standard stimulation protocol might not correspond to a reduction in the incidence of ventricular fibrillation, if induction of the latter is influenced importantly by dynamic heterogeneity.

Dynamically induced heterogeneity and conduction block is one of many potential mechanisms for spiral break-up in cardiac tissue (see for example [9]). Because wave propagation in the heart is extremely complex and influenced by many factors, it is unlikely that only one mechanism is responsible for induction and maintenance of all cardiac arrhythmias. Nevertheless, the results of this study suggest several potential interventions that may reduce the probability of arrhythmia induction, including flattening the $D$ restitution slope, decreasing $V$ at short $I$ and increasing $M$. There is experimental support for the idea that flattening $D$ restitution suppresses ventricular fibrillation [21], but altering $V$ and $M$ with the objective of preventing ventricular fibrillation has not been attempted. Tests of these options may not be likely in the near future, however, given that drugs that increase the recovery of sodium channels at depolarized potentials are not, to our knowledge, currently available, and alteration of $M$ may not be possible until the ionic basis for this phenomenon has been established. Nevertheless, judicious alterations of $D$, $V$ and $M$ may hold future promise for new and more effective therapies for ventricular fibrillation.

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