A SIMPLIFIED METHOD OF EVALUATION OF THE SAFETY FACTOR OF CONDUCTION IN CARDIAC TISSUE

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Abstract: Fatal arrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF) usually occur as a result of a cardiac failure in the propagation of the excitation, so that many studies have undertaken the evaluation of the safety of conduction against failure. Several authors have defined the safety factor (SF) as an indicator for this phenomenon, although computational problems arise. We propose a simplified method (SF_m) of evaluating the SF based on the one proposed by Shaw and Rudy. This simplification consists on setting the integration interval (II) at the period comprised between the instant when the membrane potential derivative (dV/dt) reaches 1% of its maximum ($t_{1\%}$) and the moment when the membrane potential is maximum (t_{Vmax}). The validity of SF_m has been tested. It is almost insensitive to small changes in the II, it is sensitive to factors implicated in the propagation process and drops below unity just when failure of propagation occurs. This method facilitates its application in 2D and 3D tissues.

Introduction

Ventricular tachycardia (VT) and ventricular fibrillation (VF) are known to be potentially mortal arrhythmias intimately related to re-entrant electrical activity [1]. It is also well-known that the generation of these re-entries needs the blockage of electrical propagation [1]. Traditionally, some properties of electrical propagation, mainly its velocity, were used as indicators of the boundaries of successful maintenance of the wavefront [2]. However, these parameters have been turned out to be inefficient under certain conditions [2].

In the last years, a quantitative parameter called SF, which is based on the source-sink relationship that governs the propagation, has been formulated by different groups, such as Delgado et al. [3], Leon et al. [4] and Shaw & Rudy [2]. It is the formulation proposed by the last group the one that has turned out to be the most accurate one as its SF decreases with membrane inexcitability and drops below the unity before propagation failure occurs [2].

Despite the accuracy of Shaw & Rudy SF formulation, its implementation is not easily extendible for 2D and 3D tissues [5].

In this paper, we present a new and simplified method of evaluation of the safety factor for conduction based on the formulation of the SF proposed by of Shaw and Rudy.

Materials and Methods

A modified version of the 2000 Luo-Rudy model [Faber] was used in order to simulate cardiac action potentials. In this work, 160-cell 1D strands were considered under different conditions.

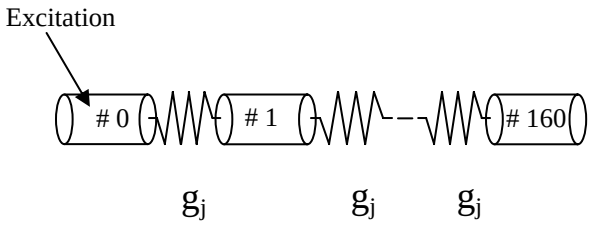

Figure 1: Representation of the cardiac tissue and the location of the stimulus, being g_j the intercellular conductivity.

To account for a wide range of situations where propagation takes place, not only active properties of the membrane have been considered but also passive characteristics. On the one hand, the former group of properties has been modified by reducing the membrane excitability, it is, extracellular potassium concentration ($[K^+]_o$) has been increased from its value under normal conditions, 4.5 mM, to 13.5 mM. On the other hand, intercellular conductivity (g_j) has been reduced to 0.05, being the normal value 2.5 µS, in order to include different passive conditions. Thus, four cases of study are generated from the combination of these values.

The stimulus protocol consists on a train of 10 driven rectangular pulses of 2 ms in duration and twice the diastolic threshold current in amplitude at a basic length of 500 ms. The excitatory current was applied in the first fibre cell.

Prior to the selection of the new integration interval (II), the influence of the II on the SF was analysed by means of two functions: SF_{ti} and SF_{tf}. The first one evaluates the SF depending on the lower limit of integration (t_i), being the upper limit of integration (t_f) the moment when the membrane potential is maximum (t_{Vmax}), while the second function varies t_f, fixing t_i at

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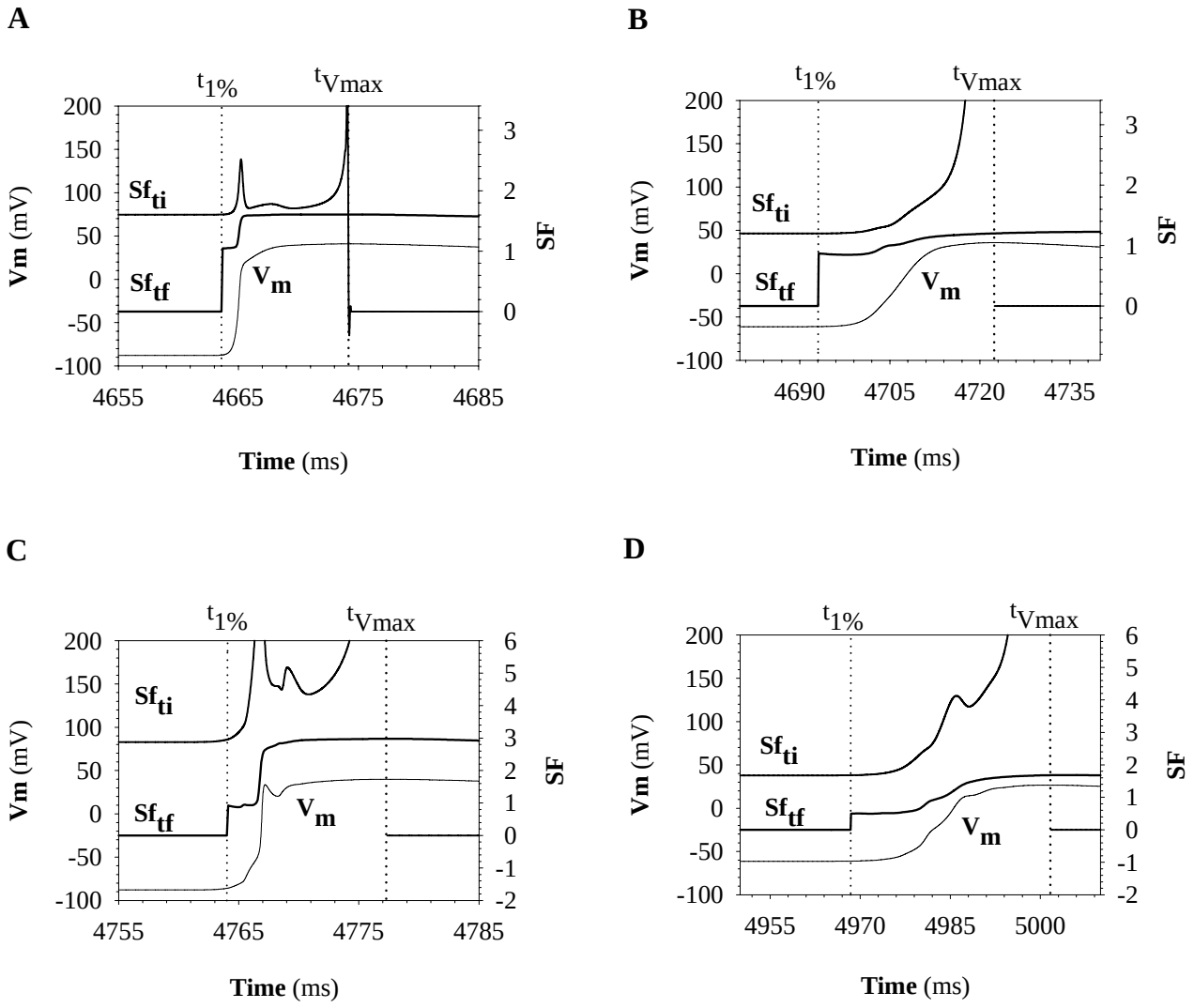

Figure 2. Sensitivity study of the SF to the II. SF_{ti}, SF_{tf} and V_m are represented by thin lines $t_{1\%}$ and t_{Vmax} by dotted lines. Each panel belongs to each case of study: A) normoxia ($[K^+]_o$ = 4.5 mM, gj = 2.5μs), B) decreased membrane excitability ($[K^+]_o$ = 13.5 mM, gj = 2.5μs), C) high uncoupling ($[K^+]_o$ = 4.5 mM, gj = 0.005μs) and D) High uncoupling and decreased membrane excitability ($[K^+]_o$ = 13.5 mM, gj = 0.005μs). For all cases, SF_{ti} is almost constant before $t_{1\%}$ and SF_{tf} suffers insignificant changes around t_{Vmax}.

instant when the membrane potential derivative (dV/dt) reaches 1% of its maximum ($t_{1\%}$). The details of the Shaw & Rudy SF definition are available in [2].

Results

In first place, the sensitivity of the SF to t_i has been analyzed. For this purpose, we have obtained the curve defined by SF_{ti} in all four cases previously described. Figure 2 reveals that the SF_{ti} acquires an almost constant value if t_i is prior to the beginning of the depolarization phase, while the SF_{ti} changes abruptedly if the chosen t_i belongs to this phase. The criteria we have applied to define the beginning of the depolarization phase is based on the evolution of the dv/dt, because dv/dt is a very easily obtainable parameter. Specifically, $t_{1\%}$ seems to be a good instant to fix t_i, as for all studied cases SF_{ti} has reached its stable value at that instant. Therefore, the sensitivity of the SF to t_i is negligible before $t_{1\%}$.

In second place, the study of sensitivity of SF to t_f, has been carried out similarly to the previous study. In

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this case, the evolution of SF_{tf} has been analysed along development of the action potential (AP). For all four cases, the curve generated by SF_{tf} suffers very small deviations around t_{Vmax} (Fig. 2), so the sensitivity of the SF to t_f is negligible around t_{Vmax}.

As the sensitivity study reveals that outside the depolarization phase, defined from $t_{1\%}$ to t_{Vmax}, small variations in the II produce negligible changes in the SF, it seems reasonable to fix the II at the period comprised from $t_{1\%}$ to t_{Vmax}. Therefore, the SF_m is now defined as the sum of two integrals, one of the capacitive current (I_c) and other of the axial current that leaves the cell (I_{out}), divided by the integral of the axial current that penetrates he cell membrane (I_{in}):

$$SF_m = \frac{\int_A I_c \cdot dt + \int_A I_{out} \cdot dt}{\int_A I_{in} \cdot dt}$$

$$A|\ t \in [t_{1\%}, t_{Vmáx}] \qquad (1)$$

The II for all these three integrals is the period is the interval defined by $t_{1\%}$ and t_{Vmax}.

The three main advantages generated by considering this new II, are the following: a) the liberation of the formulation from the evolution of the membrane charge (Q_m), which is the integral of I_m (ionic membrane current), b) the unification of the criteria of obtaining the II and c) the simplification of this criteria.

The first advantage suppresses I_m and its integral from the implementation of the SF_m, the second one, dilucidates the independence of the calculus of SF_m from the situation of the cell respect the possible inhomogeneities [5] and the third one is due to the fact that it is easier the detection of $t_{1\%}$ and t_{Vmax} than the instants when Q_m becomes positive, firstly, and negative, later, or the rapid phase of this parameter.

This SF_m has been tested in several situations, specifically, during propagation failure and in fibres with different active and passive properties.

On one hand, for all cases of study, SF_m drops below unity whenever propagation failure occurs. An example of block caused by inhomogeneous coupling is shown in Figure 3. This figure depicts the SF_m along the proximities of the propagation failure and the correspondent AP of several cells. It seems clear that the $SF_m > 1$ while the impulse propagates successfully, which takes place where the fibre is highly uncoupled (g_j = 0.07 µS), and the SF_m drops below unity when block occurs, where the fibre is normally coupled (g_j = 2.5 µS). These results are consistent with those published by Wang and Rudy [5].

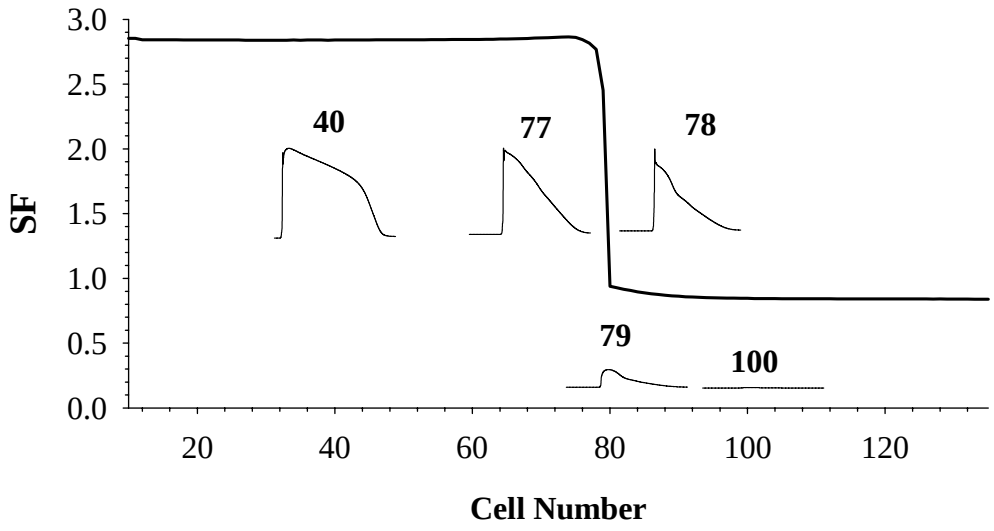

Figure 3. Representation of the SF_m (thick line) along a fibre with a block of the electrical propagation. In this example the filure is caused by inhomogeneous coupling, being the gj 0.07 µS from cell 0 to 79 and changing to 2.5 µS from cell 80 to 160. $SF_m > 1$ while gj = 0.07 µS and it drops below the unity when block occurs (gj = 2.5 µS). APs of the numbered cells are also included (thin line) to show where the propagation failure occurs and the correlation between the SF_m and the AP of a certain cell.

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On the other hand, the SF_m for cases with different properties related to electrical propagation has been obtained. As shown in Table 1, SF_m reaches the value of 1.6 at normoxia. Regarding active properties in the impulse propagation, this SF declines to 1.2 when $[K^+]_o$ is 13.5 mM This result is easily foreseeable as for that $[K^+]_o$ it is well known that the membrane excitability is highly reduced. As for passive properties the SF_m augments at strong cell uncoupling conditions (SF_m=2.95, gj=0.005μs). These results are in accordance with other simulation studies [2]. Consequently, SF_m is also sensitive to factors implicated in the propagation process.

Table 1. Dependence of the SF_m from the properties related to the electrical propagation. The passive properties are represented by the intercellular coupling (g_j) while the active ones by $[K^+]_o$.

		$[K^+]_o$ (mmol/L)	
		4.5	13.5
g_j (μS)	2.5	1.60	1.20
	0.05	2.95	1.83

Discussion and Conclusions

This work intends to simplify the formulation of the SF with the aim of extend in the future the definition of this parameter to 2D and 3D tissues. The advantages of this method have been commented and the validity of this method has been proved.

A simplified method of evaluating the SF has been proposed. This method, which is based on the definition of the SF formulated by Shaw & Rudy, fixes the II to the period comprised between $t_{1\%}$ and t_{Vmax}. In practice, this modification results in smaller computational magnitude resources.

The validity of SF_m has also been proved, as it is almost insensitive to small changes in the II, it is sensitive to factors implicated in the propagation process, such as intercellular coupling and membrane excitability, and drops below unity just when failure of propagation occurs.

All in all, this new method facilitates the study of the SF 2D and 3D tissues.

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