Safety Factor in Simulated 2D Cardiac Tissue. Influence of Altered Membrane Excitability

L Romero, B Trenor, JM Ferrero (Jr), J Saiz,
G Moltó, JM Alonso

Universidad Politécnica de Valencia, Valencia, Spain

Abstract

The safety factor (SF) is an indicator of the safeness of electrical conduction in the myocardium. In the present work, the estimation of the SF based on the formulation proposed by Shaw and Rudy (1997) has been extended to 2D (SF-2D) and evaluated. Furthermore, the effect of the increment of extracellular potassium concentration ([K+]o) on the SF-2D of a convex wavefront has also been studied and compared with the results published by our group for 1D strands (SF-1D).

Our results revealel that a) the SF-2D is sensitive to variations of membrane excitability and its value drops below unity whenever failure of conduction occurs, b) the SF-2D shows a biphasic behavior with $[K^+]_o$, which is consistent with the supernormal conduction phenomenon, and c) compared with the SF-1D, the SF-2D for a convex wavefront is less sensitive to $[K^+]_o$ and reaches smaller values.

1. Introduction

It is well known that failure in the propagation of the electrical excitation is an important factor causing breakout of fatal cardiac arrhythmias [1]. For this reason, much attention has been paid to the evaluation of the safety of conduction [2-5]. Different quantitative indicators have been considered for this purpose, such as conduction velocity and amplitude of the action potential (AP). However, the most straightforward indicator that guarantees the success of propagation is the safety factor (SF) of conduction, whose definition is related to the source-sink relationship [1].

Among all the formulations for the SF available in the literature [2, 3, 4], the one proposed by Shaw & Rudy [4] has provoked a special interest as it takes into account the main parameters involved in the phenomenon of propagation. Furthermore, it is the unique formulation that drops below unity just before propagation failure occurs and decreases when membrane excitability is reduced [4].

Our aim is to extend to 2D (SF-2D) the SF proposed by Shaw & Rudy simplifying of the estimation of the integration interval, as our group proposed and evaluate it [6]. Furthermore, the effect on the SF-2D of a convex wavefront in a tissue of altered membrane excitability has also been studied and compared with the results published by our group for 1D strands (SF-1D) [7].

2. Methods

The electrical activity of each cell was reproduced using a modified version of the 2000 Luo-Rudy dynamic action potential model (LRd00) [8] with the calcium dynamics of LRd95 [9].

In this paper, two sets of 2D myocardial tissues have been simulated: on the one hand, an homogeneous 1 x 1 cm ventricular tissue with altered membrane excitability and, on the other hand, inhomogeneous 2.5 x 2.5 cm tissues.

As regards the first set of myocardial tissues, in order to modify the membrane excitability, the extracellular potassium concentration ($[K^+]_o$) was elevated from 4.5 mmol/L (normal conditions) up to 14.5 mmol/L. A pulse of 2 ms in duration and twice diastolic threshold current in amplitude was applied to the lower left corner of the tissue so that a convex wavefront was generated.

For the second group of simulations, sharp and linear inhomogeneities where considered in a 2.5 x 2.5 cm tissues. As shown in figure 1, the inhomogeneities where created varying the electrophysiological parameters that suffer the most important changes during acute ischemia up to values experimentally registered. Specifically, the values assumed by these parameters ranged from those registered in healthy cardiac tissue $[K^+]_o$ was 4.5 mmol/L, intracellular ATP concentration ($[ATP]_i$) and intracellular APD concentration ($[APD]_i$) were set to 6.8 mol/l and 15 µmol/l respectively, and sodium and calcium channels were unaltered), up to 13.5 mmol/l of $[K^+]_o$ [10, 11], 4.6 mmol/l and 99 µmol/l for $[ATP]_i$ and $[APD]_i$ respectively [10] and a reduction of 40% of sodium and calcium channels [12, 13].

Regarding the layout of these tissues, they where composed by three altered 1 x 1 cm squares (A, B, C) and the remaining normal tissue (D), as schematized in Figure

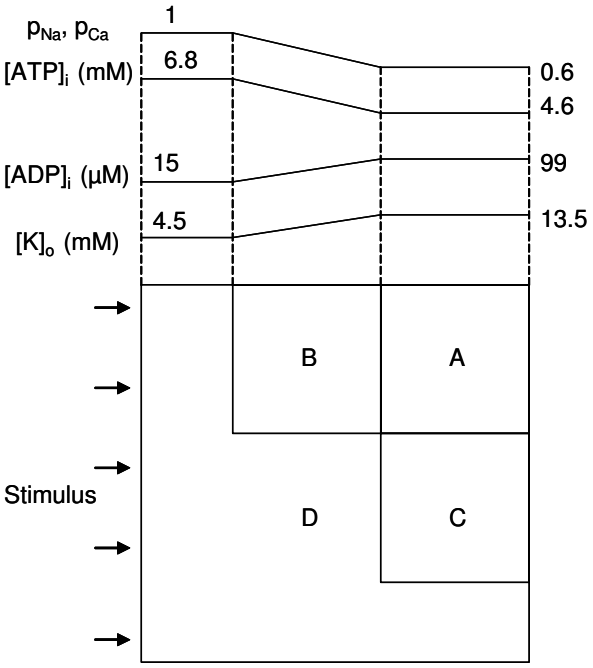

Figure 1. Two-dimensional 2.5 x 2.5 cm sheet composed by four different areas A, B, C and D. Each square is 1 x 1 cm. The lineal transient from the normal zone (D), to the globally ischemic zone (A), through the squares C and D is represented at the top of the figure.

1. The first of them, A, reproduced identical ischemic conditions in each of its cells, and the remaining two squares varied its properties linearly and continuously from the healthy tissue to the ischemic area. The globally ischemic square (A) was placed on one corner of the tissue and the other two squares patches (B, C) where placed at the left and lower edges of it.

The calculus of the SF-2D is based on the formulation of Shaw and Rudy [4] and includes the estimation of the integration interval published by our group [6].

3. Results

Figure 2 summarizes the influence of the membrane excitability not only in the SF-2D of a convex wavefront but also in the SF-1D of a fiber. The SF-2D shows a biphasic behavior with increased hyperkalemia. Initially, the SF-2D value registered in normal conditions (1.3) increases for small increments of $[K^+]_o$ up to 1.4 at 8.5 mmol/L and then the SF-2D begins to decrease, reaching a value of 1.1 at 14.6 mmol/L. This result was consistent with the supernormal conduction phenomenon [4, 14]. Compared to SF-1D, the SF-2D curve was flatter and reached lower values, but both curves approached as $[K^+]_o$ increases (for $[K^+]_o$= 4.5 mmol/L SF-1D = 1.63, for 8.5 mmol/L SF-1D = 1.70 and for 14.5 mmol/L SF-1D = 1.14). These lower values of SF-2D for a convex wavefront seem reasonable since upstream cells had to provide current to a higher number of downstream cells [1]. Therefore, the extension of the safety factor to 2D seems to be sensitive to membrane excitation and to account for the curvature of the wavefront.

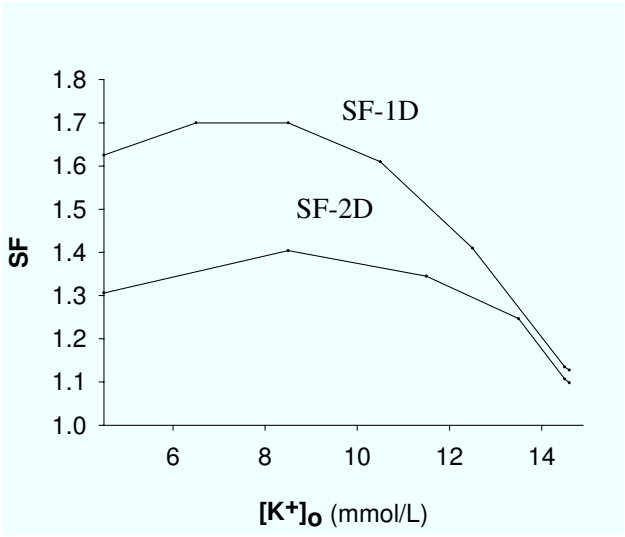

Figure 2. Effect of hyperkalemia (altered membrane excitability) in the safety factor of conduction of an impulse in a homogeneous fiber (SF-1D) and of a convex wavefront in a homogeneous 2D tissue (SF-2D).

Once the influence of the membrane excitability in the SF-2D of a convex wave propagating in a homogeneous tissue was analyzed, we tested the validity of the extension of the SF to 2D inhomogeneous tissues.

Figure 3 describes the failure of a longitudinal propagation wave provoked by the alteration of the membrane excitability in an inhomogeneous cardiac tissue. In this figure, and the value of the SF-2D correspondent to every cell is represented by the selected contour lines, a transversal and longitudinal cut are also included and the AP of several cells are depicted.

As can be seen in Figure 3A, the impulse started to propagate with a uniform SF-2D of 1.64 on the left edge of the tissue since electrophysiological parameters are identical in these cells and the wavefront reached longitudinally every cell. This result was in close agreement with other studies of 1D virtual tissues [5]. However, the SF-2D started to increase at 0.5 cm from the left edge of the tissue and 1.5 cm from the lower edge, where the tissue started to be inhomogeneous, as shown in Fig. 3B. This local variation of the SF proximal to the inhomogeneity is consistent with other simulation studies [5].

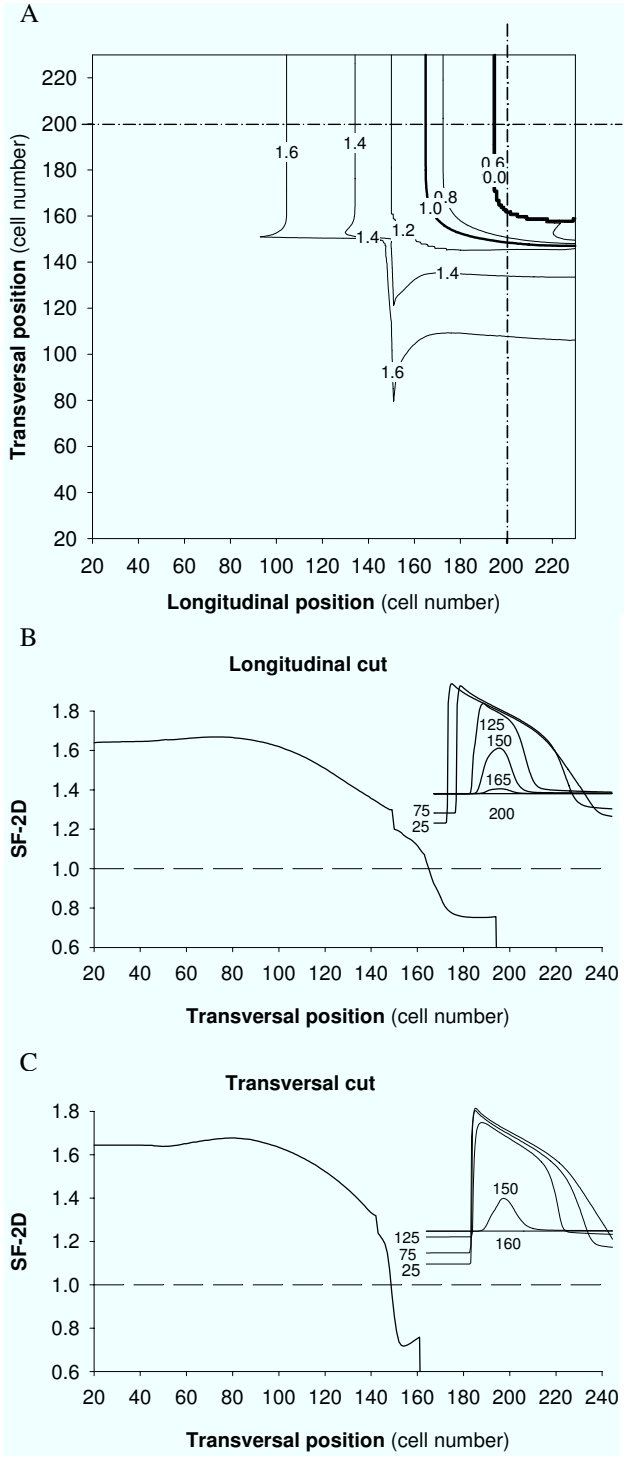

Figure 3. Failure in the propagation of a longitudinal impulse in an inhomogeneous 2D tissue. Representation of the SF-2D by the selected contour lines (A), a longitudinal view at 2 cm from the bottom edge (B) and a transversal cut at 2 cm from the right (C). Insets in panels B and C show the AP developed by the cell corresponding to the number written nearby. Dotted and dashed lines in A indicate the position of the transversal and longitudinal cuts, and dashed lines in B and C indicate the value of unity in SF-2D

Figure 3B displays the evolution of the SF-2D of the wavefront at 2 cm from the bottom edge of the tissue showing that the SF-2D suffered small increments up to 1.67 at cell 75 and then started to decrease more sharply dropping below unity at cell 165. This biphasic behavior reproduces the phenomenon of supernormal conduction, though very slightly because, concomitant with hyperkalemia, acidosis and hypoxia were simulated. Similarly, Figure 3C shows the variation of the SF-2D along the transversal cut at 0.5 cm of the right edge of the tissue. In this case, the SF-2D inside the homogeneous ischemic square decreased more sharply than longitudinally, which may be due to the fact that the wavefront was more convex, so fewer quantity of depolarizing current was available for each cell.

Finally, regarding the AP representations, it seems clear that the SF-2D was smaller than unity when propagation blocks.

In conclusion, our results revealed that the extension of the SF to 2D proposed in this paper was sensitive to variations of membrane excitability and fluctuated as soon as the wavefront reached an inhomogeneity and its value dropped below unity whenever failure of conduction occurred.

4. Discussion and conclusions

Many authors evaluated the SF under different conditions, but the interest of this work lies on the extension and evaluation of the SF to 2D tissues based on the formulation of Shaw and Rudy.

In this paper, the SF-2D has been tested under different conditions. In conclusion, a) an extension of the SF to 2D has been successfully formulated, b) The SF-2D shows a biphasic behavior with $[K^+]_o$ and c) compared to the SF-1D, the SF-2D for a convex wavefront is less sensitive to $[K^+]_o$ and reaches smaller values.

Acknowledgements

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Address for correspondence

Lucía Romero Pérez
Universidad Politécnica de Valencia
Camino de Vera s/n
46071 Valencia
Spain
E-mail: lurope@doctor.upv.es