A Sensitivity Study of the Safety Factor for Conduction in the Myocardium

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

Center for Reseach and Innovation in Bioengineering, 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, we have studied the sensitivity of the SF defined by Shaw and Rudy to the integration interval (II) using computer simulations, and then defined and evaluated a new and simplified method to calculate SF (SF_m).

Our results reveal that the sensitivity of the SF to the II is negligible outside the depolarization phase, delimited by the instant when membrane potential derivative (dV/dt) reaches 1% of its maximum ($t_{1\%}$) and the instant when membrane potential is maximum (t_{Vmax}), so we have computed the SF considering this II. Our SF_m shows a desirable behaviour as a) it drops below unity when propagation failure occurs and b) the SF_m registered during normoxia decreases when membrane excitability is reduced, and increases when high cell uncoupling is forced. This computational simplification could facilitate the use of the SF in heterogeneous 2D and 3D tissues.

1. Introduction

As cardiac failure in the propagation of excitation is usually one of the factors which cause fatal arrhythmias breakout [1], many studies have undertaken the evaluation of the safety of conduction against failure [2-5]. There are some indicators traditionally related to conduction success, such as propagation velocity, amplitude of the action potential (AP) or maximum upstroke velocity, but they are not able to guarantee the success of AP propagation [4].

Recently, a quantitative parameter called safety factor (SF) of propagation, which is related to the source-sink relationship, has been defined [1]. Several authors, such as Delgado et al. [2], Leon et al. [3] and Shaw & Rudy [4], have proposed different formulations for this indicator. The formulation of Shaw & Rudy is computed from the main parameters involved in the phenomenon of propagation, and it is the one that has reached the best results as it drops below unity just before propagation failure and it decreases when membrane excitability is reduced [4]. However, its computational magnitude makes this formulation difficult for 2D and 3D tissues [4].

Our aim is to simplify the calculus of this parameter in order to be applied to 2D and 3D tissues. For this purpose, we have studied the sensibility of the SF proposed by Shaw and Rudy to the integration interval and we have tested and proposed a modified integration interval.

2. Methods

Cardiac action potentials of a 160-cell 1D strand were obtained by means a modified version of the 2000 Luo-Rudy model [6].

To reduce membrane excitability in this strand, extracellular potassium concentration ($[K^+]_o$) was elevated in different simulations from 4.5 mM (normal) to 13.5 mM, while intercellular conductivity (g_j) was reduced from 2.5 µS (normal) to 0.05 µS.

A train of 10 driven rectangular pulses of 2 ms in duration and twice diastolic threshold current in amplitude was applied in one edge of the fiber. The SF was calculated for the tenth AP propagation.

The sensitivity study of the SF to the II was carried out by analyzing, firstly, the influence of the lower integration limit (t_i) and, secondly, the influence of the upper one (t_f). The details of the definition of the SF can be found in [4] and [5]. In order to evaluate the SF depending on the II, two functions (SF_{ti} and SF_{tf}) based on the SF formulation of Shaw & Rudy have been defined. The value of SF_{ti} for a certain instant is obtained by fixing the beginning of the II (t_i) to that instant and the end of the interval (t_f) to the moment when the membrane potential is maximum (t_{Vmax}). Similarly, the value of SF_{tf} for a selected instant is obtained by fixing t_i to the instant when membrane potential derivative (dV/dt) reaches 1% of its maximum ($t_{1\%}$) and t_f to the instant of study.

3. Results

In this study of the sensitivity of the SF to the II, the influence of passive and active properties of the cell has been taken into account. Thus, propagation along four different fibers has been considered resulting from combining normal and low (g_j = 0.05 μS) cell coupling with normal and reduced ($[K^+]_o$=13.5 mM) excitability. We first have studied the sensitivity to t_i and then to t_f.

To start with the sensitivity to t_i, the behavior of SF_{ti} has been analyzed. For all cases, SF_{ti} is almost constant before the beginning of the depolarization phase, while it changes sharply as depolarization advances (Figure 1). In order to distinguish both parts, membrane potential derivative time course has also been represented in Figure 1. After analyzing the results, we conclude that, when t_i is prior to the instant when membrane potential derivative (dV/dt) reaches 1% of its maximum ($t_{1\%}$) the sensitivity of the SF to t_i is negligible.

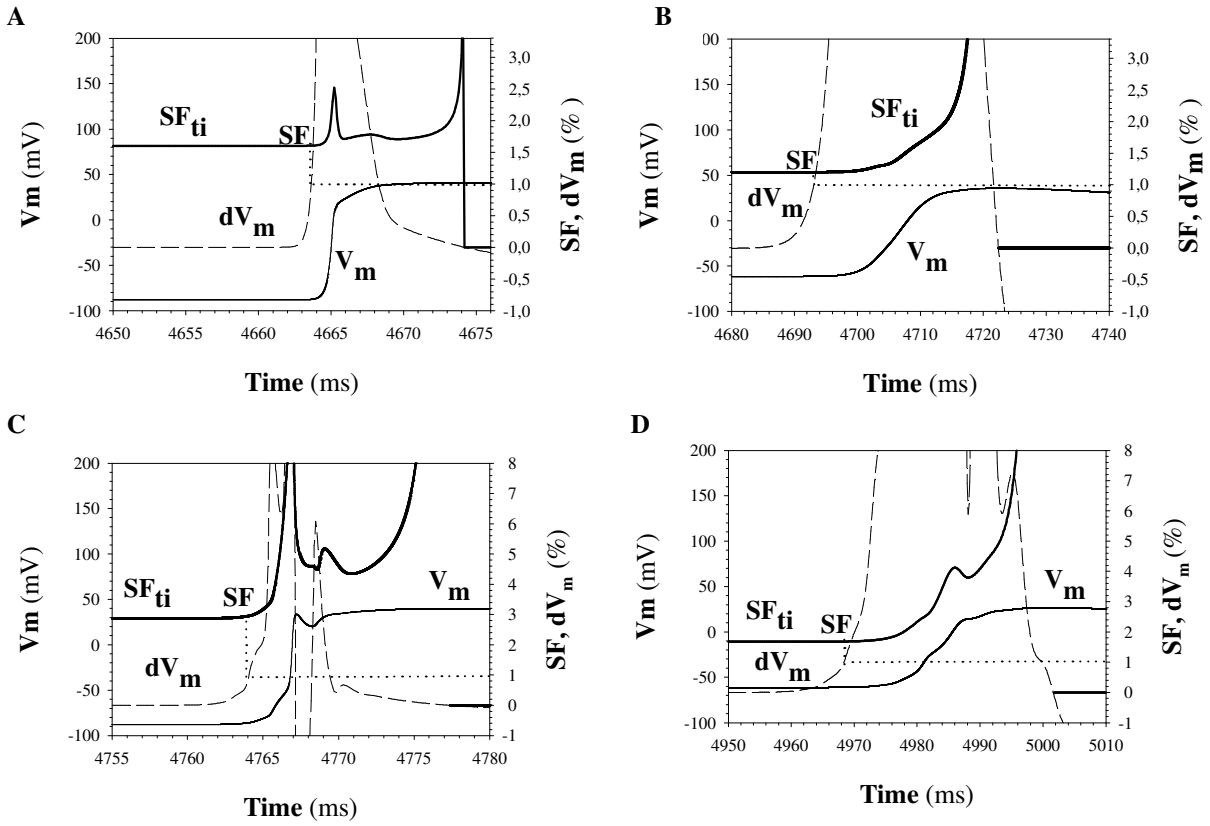

Figure 1. Dependence of SF_m from t_i. Four cases: A) normoxia, B) decreased membrane excitability, C) high uncoupling and D) high uncoupling and decreased membrane excitability. Representation of the SF_{ti} (thick line), membrane potential time curse (thin line) and dV/dt expressed in percentage of its maximum value (slashed line). $t_{1\%}$ is represented by dotted lines.

Regarding sensitivity to *tf*, SF_{tf} is represented by a very flat curve around t_{Vmax} (instant when membrane potential is maximum). Small variations (5ms) of t_f around t_{Vmax} generate minor deviations in the SF (<3%).

Once it seems clear that the sensitivity of the formulation of SF proposed by Shaw and Rudy to the II is negligible before $t_{1\%}$ and after t_{Vmax}, we have chosen these limits to the II. Thus, we formulate the SF_m as the

addition of the integral of the capacitive current (I_c) and the integral of the axial current that leaves the cell (I_{out}), divided by the integral of the axial current that enters the cell membrane. The II for all these integrals is the period comprised between $t_{1\%}$ and t_{Vmax}.

$$SF_m = \frac{\int_A I_c \cdot dt + \int_A I_{out} \cdot dt}{\int_A I_{in} \cdot dt} \quad A \mid t \in [t_{1\%}, t_{V\text{máx}}]$$

We have then studied the behaviour of SF_m during propagation failure and under other different tissue conditions.

Figure 2 depicts a propagation failure forced by uncoupling in a fibre of reduced excitability (40% of conductance maximum of sodium rapid current, g_{Na}). In this figure, AP of several cells and SF_m along the fibre are represented, showing that a) SF_m in those cells where propagation success is constant and higher than unity and b) it drops below unity when AP propagation blocks. These results are in accordance with those published by Wang & Rudy [5].

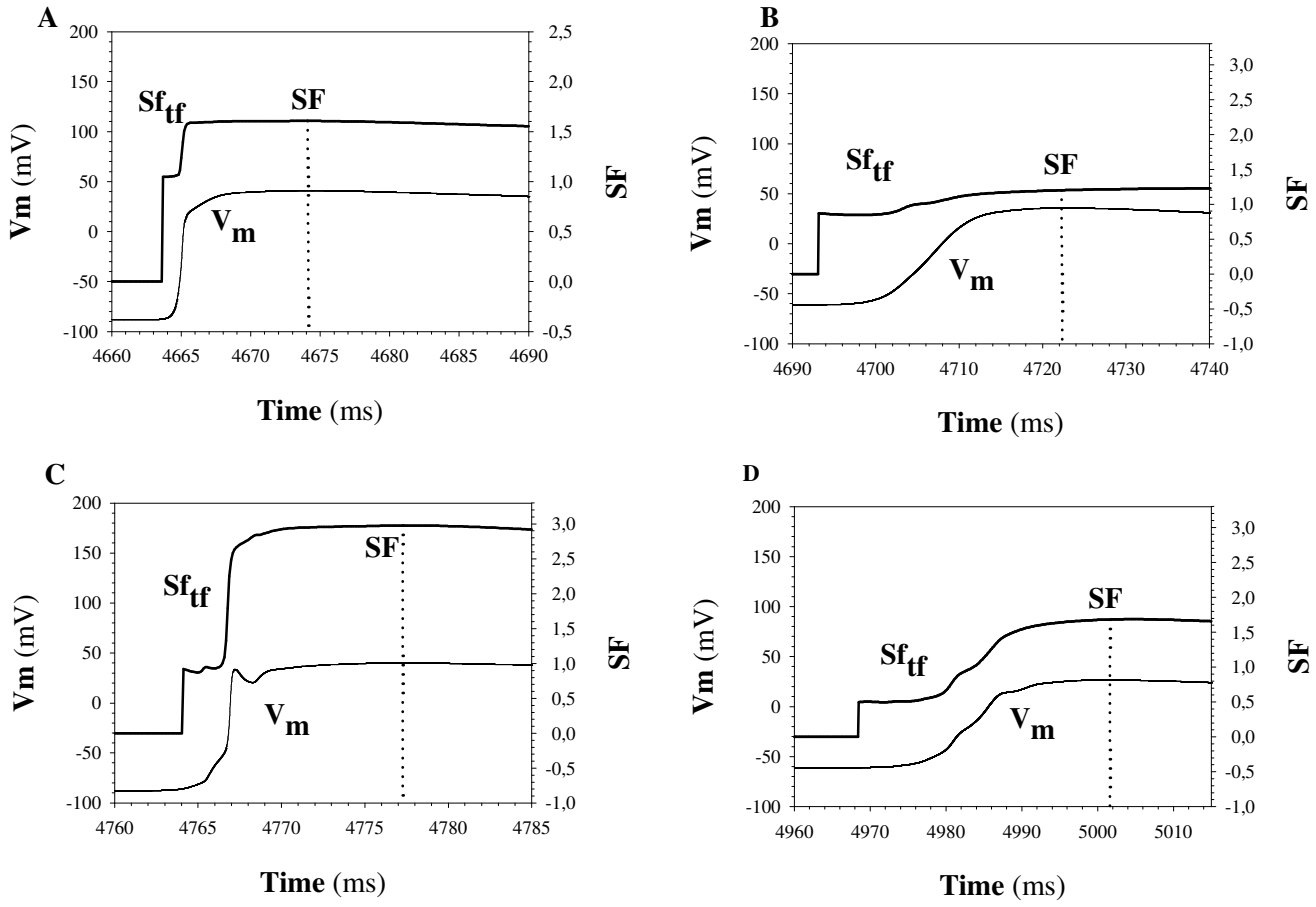

Figure 2. Dependence of SF_m from t_f. Four cases: A) normoxia, B) decreased membrane excitability, C) high uncoupling and d) high uncoupling and decreased membrane excitability. Representation of the SF_{tf} (thick line) and membrane potential time curse (thin line). t_{Vmax} is represented by dotted lines.

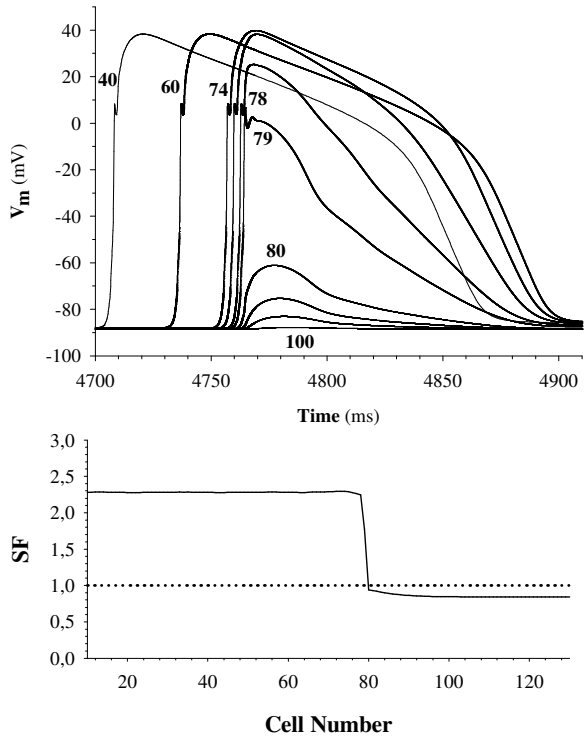

Figure 3. Example of failure in the electrical propagation. A) Representation of AP from different cells (number indication) and B) SF_m distribution along the fiber.

SF_m has been calculated for the four cases previously described. On the one hand, we have seen that the value of SF_m registered in normal conditions, 1.6, decreases to 1.2 when membrane excitability is reduced ($[K^+]_o$=13.5 mM). This reduction of the SF_m with restrained membrane excitability is easily predictable as membrane excitability integrates the active mechanisms of AP propagation. This result is also in close agreement with those obtained by Shaw and Rudy. On the other hand, the normal SF_m value increases to 2.95 when high cell uncoupling is forced (g_j = 0.05 μS). This result is in accordance with those studies of the mechanisms of very slow conduction as well as with the results of Shaw and Rudy. Therefore, we conclude that SF_m is sensitive not only to the active factors but also the passive ones that influence the propagation phenomenon.

4. Conclusions

In conclusion, the sensitivity of the formulation of SF to the II is negligible prior to $t_{1\%}$ and arround t_{Vmax}, and so this interval is valid to compute the SF.

The SF_m (with its II now defined by $t_{1\%}$ and t_{Vmax}) has been tested under different tissue conditions, showing a desirable behaviour as it drops below unity when propagation failure occurs, and the value of SF_m depends of those factors that influence the AP propagation.

This computational simplification could facilitate the use of the SF in heterogeneous 2D and 3D tissues.

Acknowledgements

This work was partially supported by (1) the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica del Ministerio de Educación y Ciencia of Spain (TIC 2001-2686 and TIC 2004-03602) and (2) the Programa Incentivo a la Investigación de la Universidad Politecnica de Valencia (CAMAV Project 20020418).

References

[1] Kleber AG, Rudy Y. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. Physiol Rev 2004; 84(2):431-488.

[2] Delgado C, Steinhaus B, Delmar M, Chialvo DR, Jalife J. Directional differences in excitability and margin of safety for propagation in sheep ventricular epicardial muscle. Circ Res 1990; 67(1):97-110.

[3] Leon LJ, Roberge FA. Directional characteristics of action potential propagation in cardiac muscle. A model study. Circ Res 1991; 69(2):378-395

[4] Shaw RM, Rudy Y. Ionic mechanisms of propagation in cardiac tissue. Roles of the sodium and L-type calcium currents during reduced excitability and decreased gap junction coupling. Circ Res 1997; 81(5):727-741.

[5] Wang Y, Rudy Y. Action potential propagation in inhomogeneous cardiac tissue: safety factor considerations and ionic mechanism. Am J Physiol Heart Circ Physiol 2000; 278(4):H1019-H1029.

[6] MG. Faber, Y Rudy, "Action potential and contractitility changes in $[Na^+]_i$ overloaded cardiac myocytes: a simulation study", Biophys. J., 2000; 78:2392-2404.

Address for correspondence

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