Effects of Acute Ischemia and Its Components on the Safety Factor of Conduction: A Simulation Study

L Romero, JM Ferrero, B Trenor, J Saiz

Center for Reseach and Innovation in Bioengineering, Universidad Politécnica de Valencia, Valencia, Spain

Abstract

In this work, we have studied the changes that acute myocardial ischaemia exerts in our formulation of the safety factor of conduction (SF_m) which consists on a modification of the SF proposed by Shaw and Rudy. Specifically, the effect of each component of ischemia (hyperkalemia, hypoxia and acidosis) was studied separately, and also the evolution of the SF_m after the onset of ischemia was obtained.

The results show that a) the three components of ischemia tend to reduce SF_m (except mild hyperkalemia), with strong hyperkalemia being the most important one and with hypoxia playing a mayor role only at high extracellular K concentration ($[K^+]_o$), and b) the SF_m decreases continuously as ischemia progresses.

1. Introduction

As many potentially mortal cardiac arrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF), are normally caused by a failure in the cardiac impulse [1], much attention has been paid to the evaluation of safeness of the propagation of the electrical impulse [2]. Recently, a quantitative parameter, called safety factor (SF), has been used for this purpose [2].

It is well known that acute myocardial ischemia facilitates the appearance of VT and VF [1]. Indeed, the electrophysiological changes that occur during acute ischemia profoundly affect the action potential (AP) conduction characteristics. Among these changes, it is worthy to mention the reduction of the membrane excitability [3], and decrease of the depolarization velocity [4] and the prolongation of the refractory period.

As VT and VF normally take place in acute ischemia, we have simulated the three main components of ischemia separately to analyse the changes that each of them provokes on our formulation of the SF (SF_m), and we have also reproduced the situation at 0, 5 and 10 minutes after the onset of ischemia to study the evolution of this parameter.

2. Methods

The electrical activity of an homogeneous 160-cell strand has been simulated using a modified version of the 2000 Luo-Rudy action potential model [5].

Acute ischaemia has been mimicked by means of its three components, hyperkalemia, hypoxia and acidosis. The simulations were defined in a way that tries to reproduce the evolution of ischemia. The parameters affected by the components of ischemia were assigned the values registered experimentally (Table 1). Firstly, hypoxia was taken into account by partially activating the ATP-sensitive K^+ current ($I_{K(ATP)}$), which was formulated as Ferrero Jr. et al. [4] and intracellular values of ATP and ADP ($[ATP]_i$ and $[ADP]_i$) were comprised in the range 6.8-4.6 mmol/L and 15-199 μmol/L respectively [6,7]. Secondly, hyperkalemia was considered by elevating extracellular K^+ concentration ($[K^+]_o$), specifically, $[K^+]_o$ was set to a value in the range 5.4-12.5 mmol/L [7,8]. Finally, acidosis was accounted by means of a multiplicative factor (f_{pH}) that reduces up to a 25 % the fast inward Na^+ current (I_{Na}) and the Ca^{2+} current through the L-type channels ($I_{Ca(L)}$) [9,10].

	Normoxia Onset of ischemia	5 min after the onset of ischemia	10 min after the onset of ischemia
$[K^+]_o$	4.5 mM	12 mM	12 mM
pH	7.4	6.9	6.4
f_{ATP}	0 %	0.25 %	0.25 %

Table 1. Significant parameters affected by acute ischemia and its corresponding values for the selected instants after the occlusion of the coronary artery.

Different tissue conditions were simulated: one subgroup of simulations considered each component of ischaemia separately, while other subgroup mimicked conditions after 0, 5, and 10 minutes of myocardial

ischemia.

The fiber was stimulated by a train of 10 driven rectangular pulses of a basic cycle length of 500 ms, 2 ms in duration and twice diastolic threshold current in amplitude. This current was applied in one edge of the fiber and the SF_m was calculated for the last AP.

3. Results

The influence in the SF_m of each component of ischemia separately is shown in Figure 1. Firstly, the results show that hyperkalemia produces a biphasic behaviour in the SF_m (Figure 1.A). Small increments in $[K^+]_o$ slightly augment the normal SF_m value (1.606), reaching a maximum of 1.666 at 7.5 mM, but below that $[K^+]_o$ SF_m begins to decrease, reaching a value of 1.122 at 14.6 mM. This biphasic behaviour is in accordance with other experimental [11] and theoretical [12] studies. Secondly, as depicted in Figure 1.B, acidosis tends to decrease the SF_m, as the more reduced the membrane excitability, the fewer the value of registered SF_m. Indeed, 1.276 is the value of SF_m when I_{Na} and $I_{Ca(L)}$ are reduced by 20% (f_{pH} = 20%). The reduction of the SF_m with increasing inexcitability is foreseeable, as propagation of the impulse becomes more difficult as inexcitability of a tissue augments. Thirdly, as reflected in Figure 1.3, it seems clear that hypoxia by itself produces a very slight decrement on the SF_m so it can be considered that hypoxia has a negligible influence on the SF_m. So, we conclude that the three components of ischemia by themselves decrement the SF_m, except mild hyperkalemia.

The appearance of failure in the electrical conduction when combining the components of ischemia has also been analysed. On one hand, we have combined a realistic level of acidosis during ischemia (I_{Na} and $I_{Ca(L)}$ reduced to 75%) with hyperkalemia, and we have found that propagation failure (SF_m<1) occurs at $[K^+]_o$=13.55mM. On the other hand, when moderate hypoxia (f_{ATP}=0.5%) was also added to acidosis (75% I_{Na} and $I_{Ca(L)}$ reduction) SF_m drops below unity at $[K^+]_o$=12 mM. Therefore, hypoxia plays a major role at high $[K^+]_o$, despite having a negligible effect for moderated $[K^+]_o$.

All in all, it seems clear that the three components of ischemia tend to reduce SF_m (except mild hyperkalemia), with strong hyperkalemia being the most important one and with hypoxia playing a mayor role only at high $[K^+]_o$.

Finally, regarding the evolution of SF_m during ischemic episodes, this parameter reaches a value of 1.393 five minutes after the onset of ischemia, becoming 1.263 after 10 minutes. So the SF_m decreases continuously as ischemia progresses.

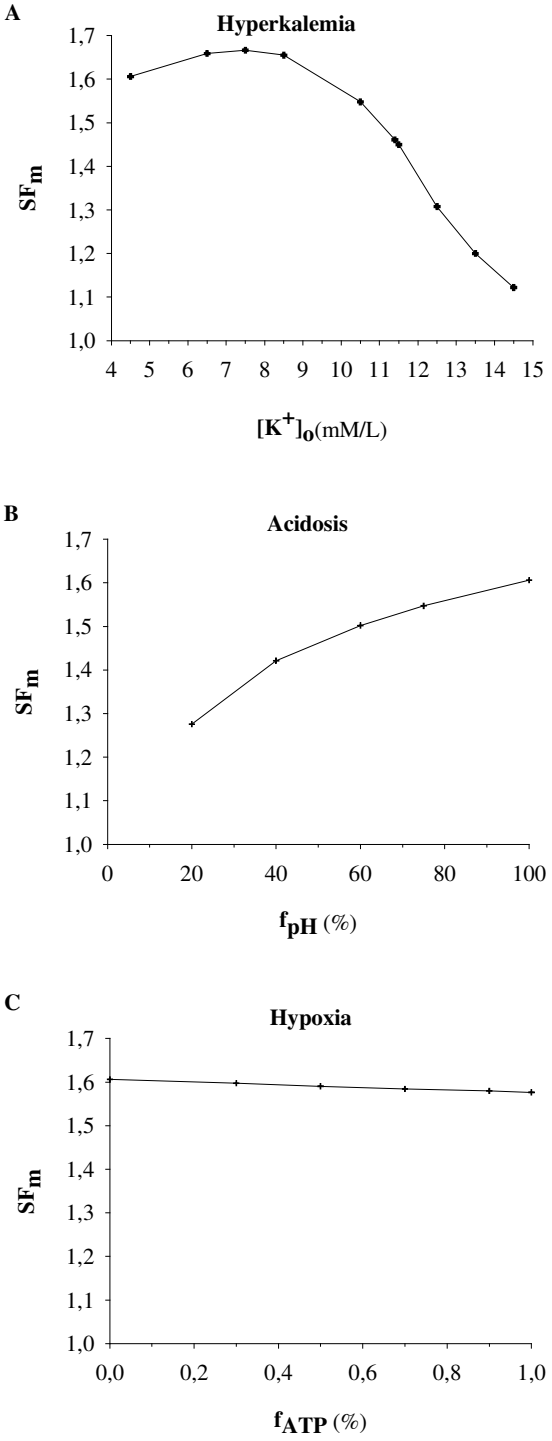

Figure 1. Effect of each component of ischemia on the SF_m separately. A) Hyperkalemia, B) Acidosis (f_{pH} is the factor that reduces I_{Na} and $I_{Ca(L)}$ and it depends on the pH) and C) Hypoxia (f_{ATP} is the fraction of activated K(ATP) channels, this parameter is determined by $[ATP]_i$ and $[ADP]_i$)

4. Conclusions

Some papers have considered the study of the SF under different conditions, but the interest of this work lies on the fact that the effect of the main components of acute ischemia on the SF_m has been considered.

This study tries to throw a light on the effects of acute ischemia on the SF_m by analysing not only the contribution of each component of ischemia to both SF_m and appearance of the conduction failure, but also the evolution of this indicator after the onset of ischemia.

Our results show that a) the three components of ischemia tend to reduce SF_m (except mild hyperkalemia), with strong hyperkalemia being the most important one and with hypoxia playing a mayor role only at high $[K^+]_o$, and b) the SF_m decreases continuously as ischemia progresses.

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] Wit A, Janse MJ. The ventricular arrhythmias of ischemia and infarction. Electrophysiological mechanisms. Mount Kisco, NY: Futura Publishing Company, 1993.

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

[3] Janse MJ, Kleber AG. Electrophysiological changes and ventricular arrhythmias in the early phase of regional myocardial ischemia. Circ Res 1981; 49(5):1069-1081.

[4] Cole WC, McPherson CD, Sontag D. ATP-regulated K+ channels protect the myocardium against ischemia/reperfusion damage. Circ Res 1991; 69(3):571-581.

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

[6] Ferrero (Jr) JM, Saiz J, Ferrero JM, Thakor NV. Simulaion of action potentials from metabolically empaired cardiac myocytes. Role of ATP-sensitive K^+current. Circ. Res. 1996;79:208-211.

[7] Weiss JN, Venkatesh N, Lamp ST. ATP-sensitive K^+ channels and cellular K^+ loss in hypoxic and ichaemic mammalian ventricle. J. Physiol. (Lond.) 1992;447:649-673.

[8] Coronel R. Heterogeneity in extracellular potassium concentration during early myocardial ischaemia and reperfusion: implications for arrhythmogenesis. Cardiovasc. Res. 1994;28(6):770-777.

[9] Yatani A, Brown AM, Akaike N. Effect of extracellular pH on sodium current in isolated, single rat ventricular cells. J. Membr. Biol. 1984;78(2):163-168.

[10] Irisawa H, Sato R. Intra- and extracellular actions of proton on the calcium current of isolated guinea pig ventricular cells. Circ. Res. 1986;59(3):348-355.

[11] Kagiyama Y, Hill JL, Gettes LS. Interaction of acidosis and increased extracellular potassium on action potential characteristics and conduction in guinea pig ventricular muscle. Circ Res 1982; 51(5):614-623.

[12] Shaw RM, Rudy Y. Electrophysiologic effects of acute myocardial ischemia. A mechanistic investigation of action potential conduction and conduction failure. Circ Res 1997; 80(1):124-138.

Address for correspondence

Name 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