A SIMULATION STUDY OF THE SAFETY FACTOR OF PROPAGATION IN METABOLIC INHIBITION

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Abstract: As potentially mortal arrhythmias usually occur as a result of a cardiac failure in the propagation of the excitation under ischemic and metabolically impaired conditions, we have studied the effects of acute ischemia in the safety factor of conduction proposed by our group (SF_m), which is a modification of the safety factor defined by Shaw and Rudy. For this purpose, the three main components of acute ischemia have been taken into account: hyperkalemia, hypoxia and acidosis. Firstly, hyperkalemia was simulated by increasing extracellular K concentration ($[K^+]_o$), secondly hypoxia was reproduced by partially activating K(ATP) current, and finally, acidosis was considered by restraining the availability of Na and Ca channels. In this work two types of simulations were carried out, on the one hand, just one component of ischemia was mimicked, and on the other hand several minutes after the onset of ischemia were reproduced. Our results show that a) ischemia tends to reduce the SF_m except moderated hyperkalemia, being this component the most significative and hypoxia just influying at high $[K+]_o$ and b) SF_m decreases as ischemia progresses except for the first two minutes.

Introduction

It is well known that most potentially mortal arrhythmias, as ventricular tachycardia (VT) and ventricular fibrillation (VF) usually occur as a result of a failure in the propagation of the cardiac impulse [1]. It is also widely believed that these arrhythmias are likely to take place during episodes of acute cardiac ischemia [1] because of the electrophysiological changes that acute ischemia involves. These changes provoke significant deviations on the action potential (AP), such as a decrease of the membrane excitability [2], a slowness of depolarization velocity [3] and a prolongation of the refractory period.

Due to the importance of the study of the safeness of the electrical impulse, many quantitative parameters are used with the aim of characterising the electrical conduction. However, it seems that the safety factor of conduction (SF) is the most suitable for the evaluation of this phenomenon [4]. So that, several studies have undertaken the study of propagation failure under different conditions using this parameter [4].

As VT and VF usually appear under ischemic and metabolically impaired conditions [1], we have studied the effects of acute ischemia in the safety factor (SF_m) of conduction defined by our group based on the safety factor defined by Shaw and Rudy. Specifically, we have analysed the changes produced on the SF_m by each component of ischemia separately, the apperance of failure in the conduction when combining some of these components and also the evolution of SF_m during ischemic episodes.

Materials and Methods

Cardiac action potentials of homogeneous 160-cell strands were simulated by means of a modified version of the 2000 Luo-Rudy model [5]. Excitation was applied in cell number 0 and both edges of the fiber were sealed.

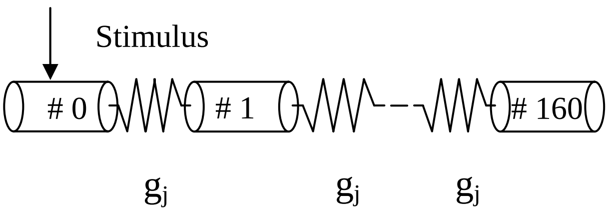

Figure 1: Diagram of the simulated tissue and the stimulus applied with g_j being the intercellular conductance

The three main components of acute ischemia have been taken into account (hyperkalemia, hypoxia and acidosis) by adequating the evolution of those elecrophysiologial parameters affected by them to those values experimentally observed (Figure 1). In first place, hyperkalemia was simulated by increasing extracellular K concentration ($[K^+]_o$), in the range 5.4-12.5 mmol/L [6,7]. In second place, hypoxia was reproduced by partially activating K(ATP) current ($I_{K(ATP)}$). For this purpose, we have taken the formulation of $I_{K(ATP)}$ implemented by Ferrero Jr. et al. [6] and intracellular values of ATP and ADP ([ATP]i and [ADP]i) were comprised in the range of 6.8-4.6 mmol/L and 15-199 µmol/L respectively [7,8]. In last place, acidosis was considered by restraining the

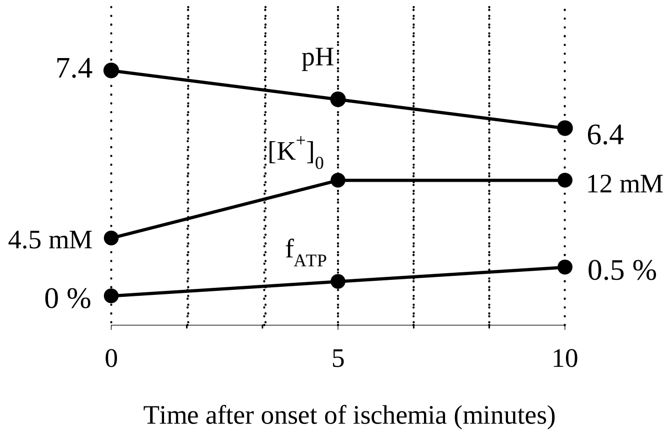

Figure 2: Evolution of the electrophysiological parameters affected by acute ischemia (solid lines). The seven instants simulated are indicated by dotted lines and the parameters for 0, 5 and 10 minutes after the onset of ischemia are highlighted y gross points.

Table 1: Effect of hyperkalemia and acidosis on the SF_m. Hyperkalemia provokes a biphasic behaviour on the SF_m as it increases its value for $[K^+]_o$ smaller than 7.5 mM while it shows a opposited effect for higher $[K^+]_o$. Acidosis tends to reduce the SF_m

Hyperkalemia		**Acidosis**	
$[K^+]_o$	**SF**	$\%g_{Na}$,$\%g_{Ca}$	**SF**
4.5	1.606	100	1.606
6.5	1.659	75	1.547
7.5	1.666	60	1.502
8.5	1.655	40	1.421
10.5	1.548	20	1.276
12.5	1.307	17.5	1.241
13.5	1.200	15	1.185
14.5	1.120	14	0.856

availability of Na and Ca channels down to a 75 % [9,10].
In this work, two different types of simulations were carried out. Each simulation of the first set just considered a certain level of severity of one of the components of ischemia, although in some occasions the combination of these components was also accounted. The second set of simulations tried to reproduce different instants after the onset of ischemia. Indeed, seven equidistant instants were considered for the study of the 10 first minutes. The correspondent stages of ischemia at these instants are indicated at Figure 2 by dotted lines.

Excitatory current consisted on a train of 10 driven rectangular pulses of 2 ms in duration and twice diastolic threshold current in amplitude, with a a basic cycle length of 500 ms. The SF_m was calculated for the last AP.

Results

Regarding the effect of hyperkalemia in the SF_m, this parameter shows a biphasic behavior as schematized in Table 1. This table reveals that the SF_m registered at normoxia (1.606) suffers small increments while the $[K^+]_o$ in the fiber is less than 7.5 mM, concentracion at which the SF_m reaches its maximum (1.666). Once $[K^+]_o$ goes above 7.5 mM, the SF_m starts to decresase rapidly and continuously reaching 1.12 at 14.5 mM. This biphasic tendency is consistent not only with other theoretical studies [4,11] but also with other experimental results [12].

As for acidosis, this component of ischemia tends to reduce the SF_m throughout the range of severity analysed, achieving the value of 1.185 when Na and Ca currents (I_{Na} and I_{Ca}) are reduced by 15 % (Table 1). It is well known that acidosis provokes the reduction of I_{Na} and I_{Ca} excitability, being both currents crucial for the propagation of the cardiac impulse. So the decrement of the SF_m with acidosis was expected. The effect of acidosis at high $[K^+]_o$ has been also studied. For this purpose, mild acidosis (reduction of I_{Na} and $I_{Ca(L)}$ maximum conductances to 75%) has been combined with hyperkalemia. Under these conditions, the failure of the cardiac impulse, which is indicated by a SF_m that is not able to reach unity, takes place whenever the $[K^+]_o$ is equal or greater than 13.55 mM, which is consistent with other studies [11]. At this range of $[K^+]_o$ the SF_m is grater than unity when just hyperkalemia is considered, so acidosis also tends to reduce the SF_m when joined to hyperkalemia. Therefore, acidosis decrements the SF_m at any $[K^+]_o$ registered during ischemia.

The study of the effect of hypoxia by itself on the SF_m reveals that its influence is almost negligible. For example, this indicator acquires the value of 1.612 during strong hypoxia (the fraction of activated K(ATP) channels (f_{ATP}) is 1%) which is quite similar to 1.666, the SF_m registered at normoxia. However, its influence is much more significant when it is combined with the other ischemic components. Indeed, electrical propagation at $[K^+]_o$=12 mM during mild hypoxia (f_{ATP}=0.5%) and acidosis (75% Na and Ca reduction) turns out to be impossible, which is also in accordance with other simulation works [11], while without hypoxia the failure does not occur up to $[K^+]_o$=13.55 mM as previously commented. Therefore, the effect of hypoxia is just significant at high $[K^+]_o$.

As for the evolution of the SF_m after the onset of ischemia, Figure 3 depicts the results obtained after applying the condicions resumed at Figure 2. The curve depicted by the SF_m starts elevating its value up to 1.666 during the first two minutes, then it changes its tencency and decreases significatively until the fifth minute when it takes the value of 1.393. After the first five minutes, the SF_m continues decreasing much more slowly. It could be said that during 5th-8th minute this parameter remains almost constant, and that after this period it decreases up to 1.263 at the 10th minute after the onset of ischemia. Regarding the morphology of the evolution of the SF_m during the first 5 minutes, it seems to be determined by the influence of hyperkalemia although the effect of acidosis and hypoxia starts to be appreciated as $[K^+]_o$ increases. From the 5th minute to the 8th minute after the onset of ischemia the SF_m does not exerts significant differences as the $[K^+]_o$ has been stabilized though at the 8th minute the SF_m continues decreasing more vividly due to the high level of acidosis and hypoxia. All in all, the SF_m decreases as ischemia progresses except for the first two minutes.

Discussion and Conclusions

This paper has intended to study the behaviour of the SF_m proposed by our group and based on the SF defined by Shaw and Rudy during ischemia. Thus, the effect on the SF_m of each component of ischemia has been considered separately and also the occurrence of propagation failure in different situations has been studied. Moreover the evolution of the SF_m during ischemic episodes has been studied.

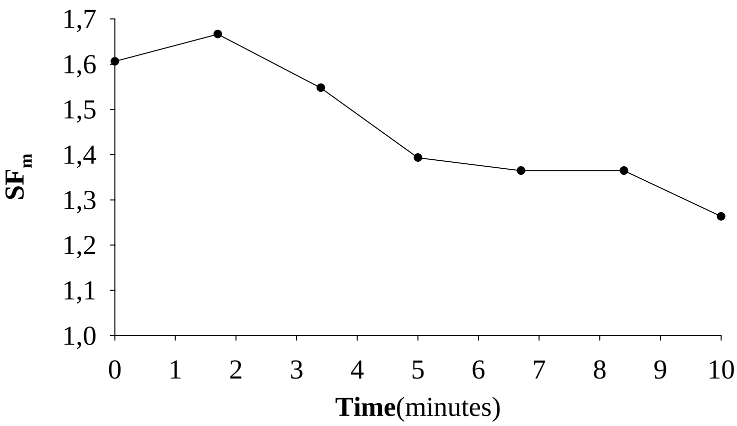

Figure 3: Time course of the SF_m during acute ischemia. SF_m starts elevating its value up to 1.666 during the first two minutes, then it decreases significatively until the fifth minute when it takes the value of 1.393 and after this moment the SF_m continues decreasing much more slowly, being almost constant during 5th-8th minute

Other studies have undertaken the issue of the SF under several tissue conditions, but in this paper we have pursued the study of the SF_m focussed on each part of ischemia.

All in all, our results reveal that on the one hand, the components of ischemia tend to reduce the SF_m except moderated hyperkalemia, being this component the most significant and with hypoxia just influying at high $[K^+]_o$, and on the other hand, the SF_m decreases as ischemia progresses except for the first two minutes.

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