Effects of Physical Exercise and Glibenclamide on Local Activation Waves during Ventricular Fibrillation

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Abstract

This study is aimed at characterizing cardiac mapping recordings during Ventricular Fibrillation (VF) according to the fragmentation level and occurrence ratio of its Local Activation Waves (LAWs), in order to analyse the effects of physical exercise in the electrical activity of VF, compared to the effects of Glibenclamide drug.

Three groups of rabbits were used. G1: control (sedentary rabbits), G2: trained (rabbits under a running program) and G3: drugged (sedentary rabbits treated with Glibenclamide). VF was induced during each experiment, and two recordings were acquired: maintained perfusion and ischemic damage.

LAWs were detected using the maximal derivative and were classified according to its fragmentation. The complexity level was measured with the Fractionated LAW Ratio (FLR). Finally, the activation rate was quantified using the LAWs Occurrence Rate (LOR).

The temporal evolution of FLR showed that, with maintained perfusion or ischemic damage, the trained group has the lowest values, and no differences were found between drugged and control groups. Regarding LOR, the results depend on the perfusion conditions. When perfusion is maintained, drugged group has the lowest values ($p<0.05$). On the contrary, when there is ischemic damage, drugged group has the highest LOR values ($p<0.05$). No significant differences were found between LOR of control and trained groups.

Obtained results show that physical exercise and Glibenclamide modify LAWs properties. Physical exercise reduces its fragmentation, decreasing the complexity of LAWs. In contrast, Glibenclamide modifies the activation interval, related to speed of fibrillation.

1. Introduction

During cardiac atrial and ventricular fibrillation different morphology and complexity waves appear. Simple activation waves appear in case of a single deflection produced by a front wave, and multiple and fragmented waves are identified in case of several front waves at the same time or a complex activation mechanism is present [1]. In case of atrial fibrillation (AF) these waves are known as Complex Fractionated Atrial Electrogram (CFAE) and they are used for a guide in ablation techniques for AF treatment [2]. Areas showing CFAE and high activation frequency are usually identified as critical for the AF continuity [3,4].

This work analyses the role of chronic physical exercise and their associated modifications affecting the existence of multiple LAWs during ventricular fibrillation [5,6]. Especially under myocardic ischemia situations, the regional dispersion of the refractory period has an important role in the VF continuity [7]. For this reason, the study was developed in both perfusion and ischemia situations. Isolated rabbit heart was used for the experiments in order to eliminate the possible contributions of other influences as the autonomic nervous system.

Furthermore, the aim is to know if intrinsic changes in fibrillation produced by chronic physical exercise are related to changes in K^{+}_{ATP} channels. Different experiments are using a drug for blocking K^{+}_{ATP} channels called Glibenclamide which is proven to reduce heterogeneity generated by ischemia and thus having a defibrillatory effect [7,8]. Thus, results show a comparison between physically trained subjects and those corresponding to sedentary subjects being administered Glibenclamide.

Section 2 shows the used methodology for data acquisition and signal processing. Results are shown in the next section and finally, conclusions will be drawn.

2. Methods

2.1. Data

Recordings were obtained at the cardiac electrophysiology laboratories in University of Valencia using a 256 channel commercial mapping system

(MAPTECH). The acquisition was done using a matrix electrode consisting on 240 leads located in the left ventricle of isolated rabbit heart perfused by a Langendorff system [9]. Interlead distance was 1 mm.

Three groups were analysed: control (G1: no training, N=20), trained (G2, N=11) and drug administered (G3, N=15). Physically trained group was formed by rabbits under controlled exercise in a treadmill. Drug administered group subjects were not physically trained and the used drug was Glibenclamide. In all cases, VF was induced by increasing pacing frequencies with a maximum recording time of 300 seconds at a 1 kHz sampling frequency.

Two consecutive recordings were made for each of the subjects. This procedure makes a first recording under Langendorff controlled perfusion for 300 seconds and, right after this, a second recording with a ligation in the circumflex coronary artery. This ligation will produce an ischemia in a region inside the cardiac mapping recording and thus, 300 seconds are recorded under this situation. In some cases, fibrillation was spontaneously finished and thus, all results were analysed for the record duration of the shortest VF period.

2.2. Detection and classification of Local Activation Waves - LAWs

When a LAW reaches a unipolar electrode, it generates a negative deflection related to the potential increase of the intracellular action potential in the excited cell [10]. This work is using the maximal negative derivative to detect LAWs. The developed algorithm includes the following stages:

- Derivative signal assessment. Maximum value normalization.
- Thresholding technique for noise removal.
- Maximal negative derivative detection.
- Classification. A refractory period is defined (RP) according to the minimum separation between consecutive LAWs. The RP value was experimentally obtained according to the used heart type and was fixed to 40 ms. The classification criteria are:
  - Simple wave: with derivative maximum values between RP and 3.5RP.
  - Multiple wave: with derivative maximum values lower than RP. The number of maximums provides the wave multiplicity.

Figure 1 shows an example of the detection-classification algorithm behaviour. LAWs detections correspond to those maximum negative derivative points. In this case, all of them are single except three multiple waves detected (marked with discontinuous line), two of them being double (t=0.35s and t=0.65s), and the third being triple (t=0.42s).

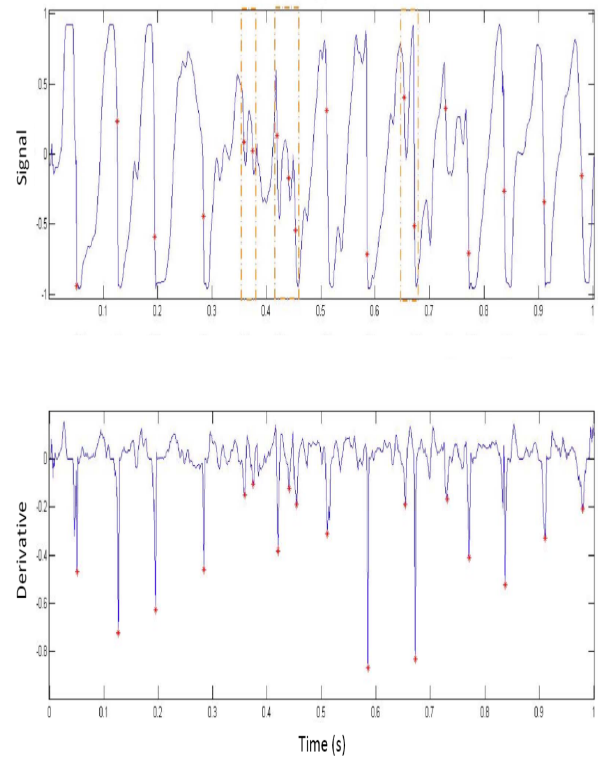

Figure 1. LAWs detection example. Red dots are the maximal negative derivative points in the signal (top) and its derivative (bottom). Discontinuous red lines show multiple waves.

2.3. Parameter calculation

The detection and classification stages generate the activation marks from which two parameters were calculated. The first parameter is the percentage of multiple waves compared with the total detected waves in all mapped channels, FLR (Fractionated LAW Ratio). This parameter is related to the activation process complexity (higher values are for higher complexity). The second parameter is related to the VF activation frequency, called LAW Occurrence Rate (LOR), showing the average value of periods between successive activations for all mapped channels. In both cases, the statistical significance analysis was done using the permutations test [11].

3. Results

Figure 2 shows the results obtained for FLR parameter in each of the three data groups. It can be observed that both in perfusion and ischemia, the physically trained group G2 shows lower FLR values, which is related with higher homogeneity in activation and thus, a more stable response to arrhythmias. Groups G1 and G3 (control and drugged) result in similar FLR values, with a constant increase related to the ischemia duration.

In case of the activation rhythm given by the LOR parameter, it can be observed a different behaviour in case of perfusion and ischemia for all data groups. During perfusion, the activation frequency decreases in time (higher period). In this case, the drugged group G3 shows important lower values for LOR. On the other hand G1 and G2 groups show similar values.

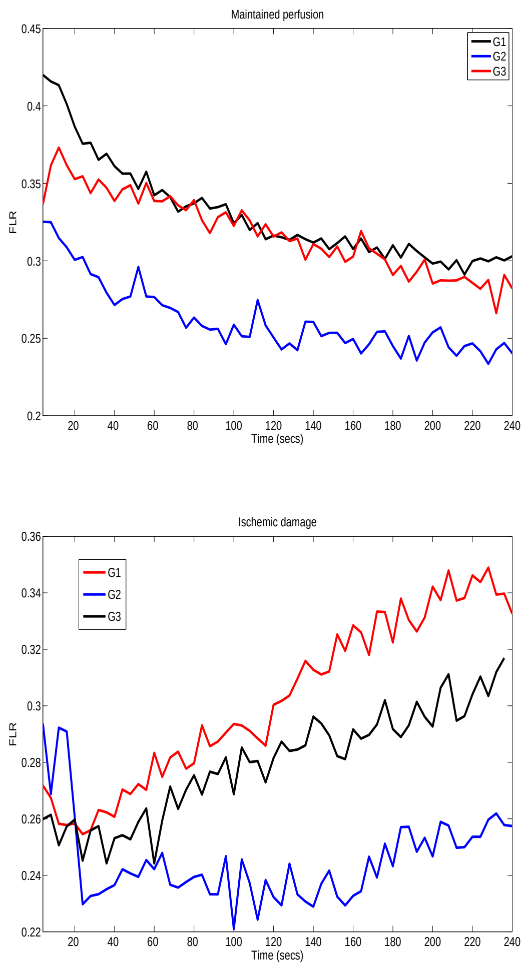

Figure 2. Temporal variation of FLR parameter under perfusion (top) and ischemia (bottom). G1: control group; G2: trained group; G3: drugged group

Under ischemia conditions, all three groups show initial low values which are increased after the first minute of arrhythmia. From this time point, LOR values decrease for the three groups though the drugged group shows higher LOR values. This result is related with a lower ventricular activation frequency during ischemia for G3, proving that this drug involves an anti-arrhythmic effect.

4. Conclusions

This work studied the effect of modifications in spatial regularity of VF induced by the chronic physical exercise on the LAWs existence and the activation frequency. All of these are key factors in the arrhythmia duration. In order to test if those modifications are related to changes in K^{+}_{ATP} channels, results of trained subjects are compared with a control group of sedentary subjects and another group where subject were administered Glibenclamide. In addition, the study was made under perfusion and ischemia conditions.

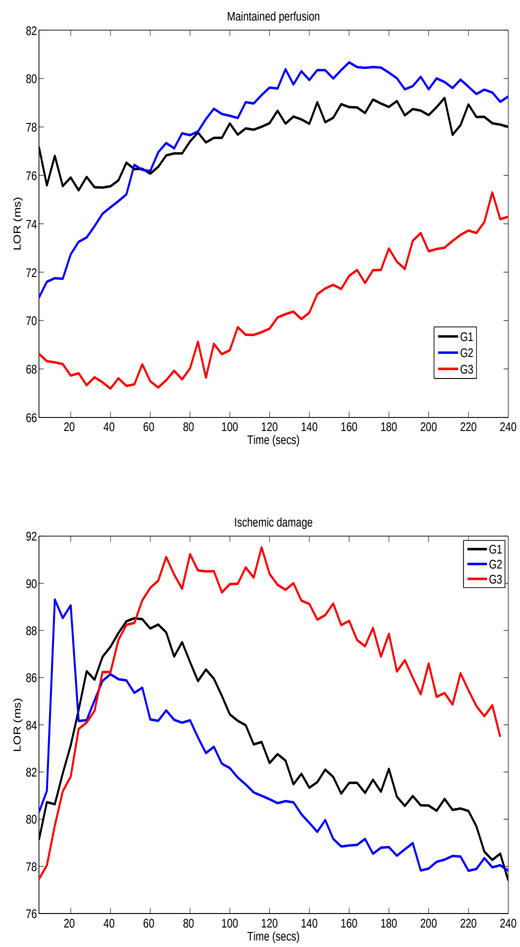

Figure 3. Mean value of activation periods in LAWs (LOR) under perfusion and ischemia. G1: control group; G2: trained group; G3: drugged group.

Concerning the existence of multiple LAWs, the trained group shows lower values tan control and drugged groups both under perfusion and ischemia. Furthermore, while control and drugged groups increase the number of multiple LAWs in time, this value is stable for the trained group.

In case of the ventricular activation frequency, it shows a higher frequency in the drugged group during perfusion, being similar in case of control and trained groups. However, in the first minute of arrhythmia under ischemic conditions, the frequency decreases and is followed by a progressive increase in the activation frequency. Despite all groups show a similar behaviour, the drugged group shows lower activation frequencies than the other groups.

Obtained result show that physical exercise has a regulatory effect in LAW fractioning, both under perfusion and ischemia. Glibenclamide administration also has an anti-arrhythmic effect, maintaining a low activation frequency during ischemia.

In addition, results are not coincident for the trained and drugged groups, suggesting that modifications induced by the physical exercise are not exclusively related with the blocking mechanisms of K^{+}_{ATP} channels.

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