QT Dispersion Induced by Local Temperature Variations

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Abstract

Abnormally long and short QT intervals (QTi) have been shown to be associated with an increased risk for life-threatening ventricular arrhythmias and sudden cardiac death. Because of its electrophysiological effects temperature can influence this parameter. Therefore hypothermia or/and hyperthermia can be used for modulate QTi in studies with experimental models. In this work, a novel electrode-device to perform epicardial mapping and simultaneous thermal modifications is presented. In ten preparations of isolated rabbit hearts (Langendorff-perfused) changes in QTi was analyzed in two different left ventricular areas. One area was thermally modified, while the other remained in basal conditions, the QTi were measured in both areas. During hypothermia the differences between them increased mainly due to the prolongation of the QTi in altered area. Hyperthermia had the opposite effect.

1. Introduction

The electrophysiological myocardial properties play a decisive role in generating and sustaining cardiac arrhythmias. The myocardial activation during the ventricular fibrillation is related to electrophysiological parameters recorded during the normal conduction [1], and these parameters are modulated by temperature [2].

However, there are very few studies [3] in which the effects of localized temperature variations over these electrophysiological parameters are analyzed. The aim of this study is to examine the influence of local hypothermia and hyperthermia on the QTi, an electrophysiological parameter representative of the ventricular myocardial conduction [4-6].

The study has been carried out on an experimental model using isolated and perfused rabbit hearts, according to the Langendorff technique. Using a device developed for this purpose, temperature has been changed in a limited area of the ventricle, and its electrical activity has been recorded. Simultaneously, in another area of the ventricle temperature remains in basal conditions (37 °C), and the electrical activity is registered by using a conventional electrode. The modified area has been subjected to different steps of hypothermia and hyperthermia. Epicardial signals have been analyzed by measuring QTi in both areas. The heterogeneity induced by the local hypothermia and hyperthermia has been quantified.

2. Methods

2.1. Developed device

The device has been designed to allow the controlled induction of local thermal changes in the epicardium of the isolated heart, whereas the electrical activity in the affected area is mapped. The cooling/warming system is based on previous developments [7-9].

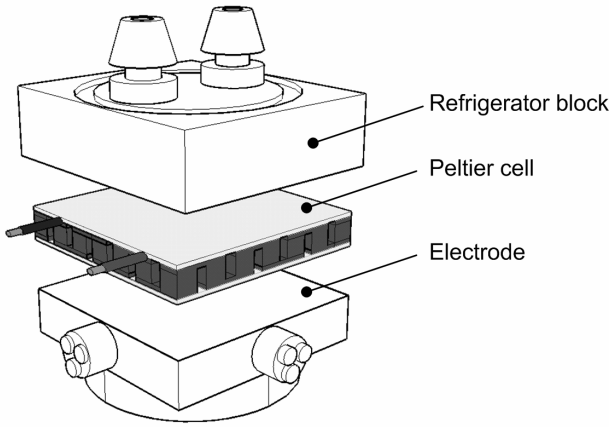

Figure 1. Schematic view of cooling/warming device, consisting on three parts. From top to bottom: liquid cooling block, Peltier cell and recording electrode.

As shown in Figure 1, the device has a modular design. The system consists of three parts in stratified disposition. The central part is a flat shaped Peltier cell. Because of thermoelectric properties of the

semiconductor materials, heat is pumped from one face of the cell to the other, proportionally to the electric current injected. One side is cooled and the other one is heated, being the process reversible by the inversion of the current direction. A cooper-made refrigerator block contains a coolant liquid circulating through a centrifugal pump. This provides the evacuation of the heat produced in the heat face of the cell. A resin-made piece (improved thermal conduction epoxy) houses 128 unipolar electrodes arranged in a matrix. The distance between the electrodes is 1mm. The system also includes a K thermocouple to measure the local temperature. The surface in contact with the epicardium has been shaped in order to fit the epicadial surface. This improves the contact between surfaces. Figure 2 represents this piece, highlighting the face in contact with the epicardium.

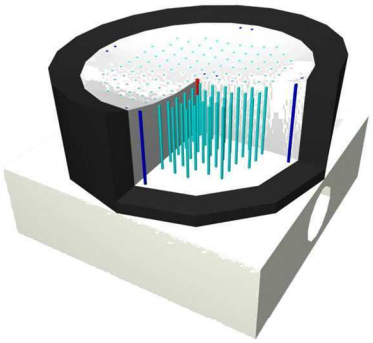

Figure 2. Resin-made body of the device. Curved shape to fit the epicardial contact surface, and electrode wires.

2.2. Experimental preparation and instrumentation

All experiments complied with the "European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes" (Strasbourg, 18.III.1986). Ten preparations of isolated rabbit hearts has been used for this study (race New Zealand, weight 2.47±0.25 kg).

After anesthesia with ketamine and heparinization, the hearts (8.83±1.62 g) were removed and immersed in cold Tyrode solution (4 ºC). After isolation, the aorta was connected to a Langendorff system for perfusion of Tyrode solution at constant pressure (60 mmHg, 37±0.5 ºC). The composition of the perfusion fluid was (mM) 130 NaCl, 24.2 $NaHCO_3$, 4.7 KCl, 2.2 $CaCl_2$, 1.2 NaH_2PO_4, 0.6 $MgCl_2$, and 12 glucose. Oxygenation was carried out with a mixture of 95% O_2 and 5% CO_2.

Figure 3 shows the placement of recording electrodes in the ventricular epicardium. This is a left side view of the preparation. The developed device (Em) is placed on the anterior wall of the left ventricle (LVAW), containing 128 unipolar electrodes, and a K thermocouple to record the temperature of the modified area (Tm). In the posterior wall of the left ventricle (LVPW), is placed a conventional electrode (En), with 105 register points (also arranged in a matrix and 1mm spaced too). The temperature of the non-modified area (Tn) is also recorded through a K thermocouple.

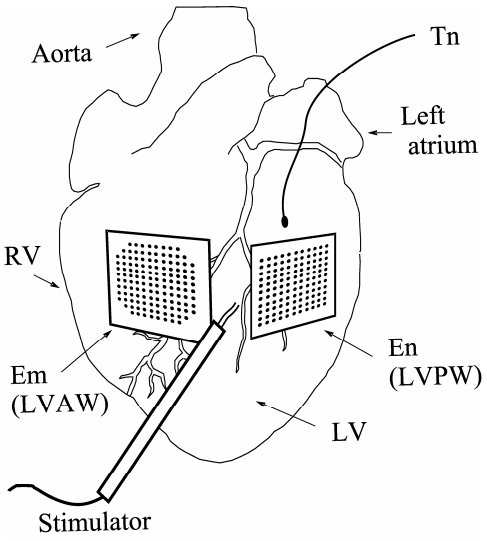

Figure 3. Placement of the electrodes. Electrode for thermal modifications (Em) and conventional electrode (En). Thermocouple of the non-modified area (Tn). The Thermocouple of the modified area is integrated in Em.

The reference electrode consisted of a 4x6 mm silver plaque located over the cannulated aorta. An electrical stimulating electrode was placed between Em and En to perform a global electrophysiological analysis. Nevertheless, parameters analyzed in this study correspond to signals obtained without external pacing. The cardiac mapping system MAPTECH was used to acquire the electrical activity of the epicardium. The electrograms were amplified with a gain of 50-300, broadband (1-400 Hz) filtered, multiplexed and recorded. The sampling rate for each channel was 1 kHz. Temperatures (Tm and Tn) were measured with miniaturized thermocouples and registered with a digital thermometer Fluke® 54.

2.3. Protocol

The protocol described below has been applied to all experiments. The temperature of the modified area has been modified and stabilized in stages, acting on the Em (Peltier cell). Figure 4 shows the sequence of temperature steps.

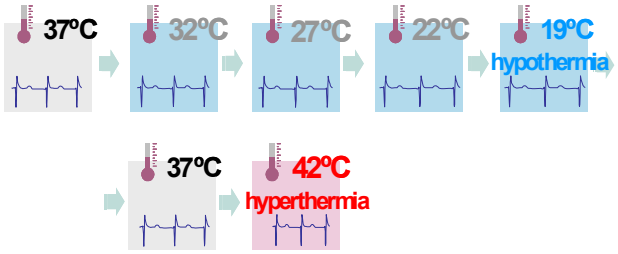

Figure 4. Temperature sequence. At each step, the electrograms of modified and non-modified area were recorded and analyzed.

Various degrees of hypothermia were achieved reducing the temperature from 37 ºC, in 5 °C steps, by regulating the electric current of the thermoelectric cooler. After reaching the lowest step (19 ºC), the temperature was incremented directly to 42 ºC (by inverting polarity at the terminals of the Peltier cell) thus reaching hyperthermia.

The ventricular signals of the modified (Em) and non-modified area (En) have been recorded during basal sinus rhythm at each step in temperature. Temperatures Tm and Tn were also measured at each step.

Pacemap (the specific software of the acquisition system MAPTECH) was used to perform semi-automatic marking on signals and manual determination of Q and T instants. QTi was obtained following two procedures (see Figure 5):

- QTp interval: from the onset of activation to the peak of the T wave.

- QTf interval: from the onset of activation to the end of the T wave (considering this instant when the slope of the wave changes or intersects with the isoelectric line).

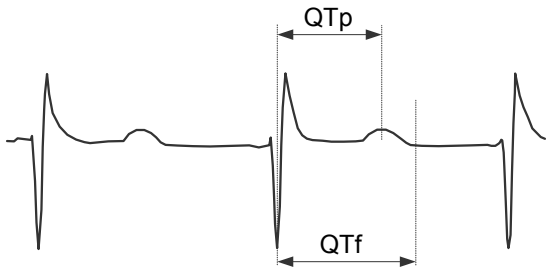

Figure 5. Measures of QTp and QTf taken on an electrogram.

In this way QTf and QTp has been obtained for Em (modified area) and for En (non-modified area) as the average of a group of five adjacent channels located in the centre of each array.

3. Results

The results for QTf in the modified (QTfm) and non-modified area (QTfn) at each step of temperature are showed in Table 1. It has also been obtained dQTf as difference of QTf inter-areas to provide an indicator of the degree of heterogeneity of QTf induced by the local temperature changes.

The repeated-measures ANOVA procedure was used to perform comparisons. Differences were considered statistically significant at $p<0.05$.

The changes of temperature clearly modified the values of QTfm and dQTf (Table 1). The slight variations observed in QTfn were not significant ($p> 0.4$).

Figure 6 shows the evolution of QTf with temperature for each area (standard deviation is represented). It shows clearly the progressive increase in QTfm, during the induced hypothermia. During hyperthermia, the effect is the opposite one. The difference between QTfm and QTfn disappears after hypothermia suppression, showing the reversibility of its effect.

Table 1. QTf mean and standard deviation (SD), in milliseconds, at different temperatures in modified area (QTfm) and non-modified area (QTfn), and difference between areas (dQTf = QTfm - QTfn). *$p<0.001$.

Tm [ºC]	37	32	27	22	19	37	42
QTfm*	149	174	188	198	226	149	142
SD	11	25	36	45	37	18	18
QTfn	146	148	154	158	171	154	153
SD	13	15	20	25	29	24	20
dQTf*	3	26	34	40	55	-5	-11
SD	8	13	25	27	13	8	7

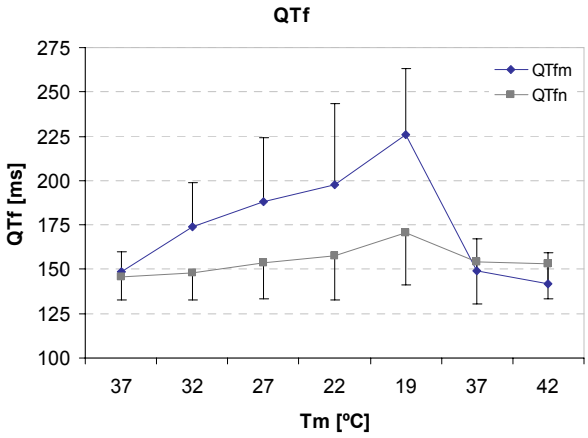

Figure 6. QTf values and standard deviation (SD) at different temperatures in modified area (QTfm) and non-modified area (QTfn).

In an analogous way results and their representation for QTp are displayed (Table 2 and Figure 7).

Table 2. QTp mean and standard deviation (SD), in milliseconds, at different temperatures in modified area (QTpm) and non-modified area (QTpn), and the difference between areas (dQTp = QTpm - QTpn). *p<0.001.

Tm [ºC]	37	32	27	22	19	37	42
QTpm*	133	145	152	162	183	132	121
SD	11	18	21	37	34	18	15
QTpn	132	133	136	140	150	137	138
SD	14	18	19	23	28	22	20
dQTp*	1	12	16	22	33	-5	-16
SD	6	4	9	17	10	7	10

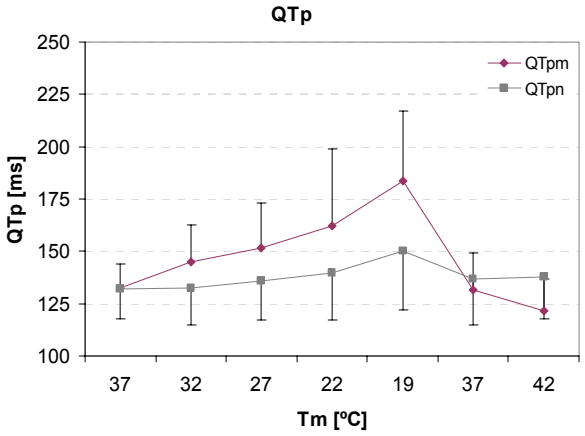

Figure 7. QTp values and standard deviation (SD) at different temperatures in modified area (QTpm) and non-modified area (QTpn).

The QTp variation is consistent with the changes in QTf. The changes of temperature clearly modified the values of QTpm and dQTp (Table 2). The slight variations observed in QTpn were not significant (p> 0.7). The results obtained for QTf and QTp are qualitatively similar. Due to the morphology of the signals and electrical noise, the peak of the T wave is determined with better precision than its end. That can explain the lower SD in QTp at lower temperatures.

4. Conclusions

Localized hypothermia induces heterogeneity in the QT by prolongation of this interval in the modified area. The magnitude of this change depends on the degree of thermal variation achieved.

In the same way, the local hyperthermia increases the dispersion in the QT by reduction of the interval in the modified area.

Acknowledgements

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