Effect of 2, 3 Butanedione Monoxime(BDM) on Ventricular Fibrillation

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Abstract

Optical mapping is commonly used to study ventricular fibrillation (VF). Electro-contractile uncouplers like 2,3 Butanedione Monoxime (BDM) are used in these studies to stop the mechanical activity, under the assumption that they do not have an effect on the electrical activity. Our objective is to test this assumption.

Male guinea pigs were used in this study. The Animals were anaesthetized and median sternotomy and pericardiectomy were performed to expose the heart. An Intracardiac injection of BDM was administered and VF was induced. Epicardial unipolar recordings were made for 4s using an electrode array along with a video recording of the heart. The procedure was repeated for saline and control. Quantitative analysis of the data was performed using autocorrelation analysis.

BDM significantly decreases the mechanical activity of the heart and increased the level of temporal organization during VF.

1. Introduction

Ventricular fibrillation is a leading cause of sudden cardiac death that claims about 250, 000 lives in United States. Present knowledge about the mechanisms for initiation, development and termination of VF is limited. One important tool used for studying VF is the use of cardiac mapping systems. Most studies have used an electro-contractile uncoupler (BDM) to stop the mechanical activity of the heart during the recording, thus, minimizing the interference by mechanical activity. The assumption in these studies to use the drug is that the drug itself has no effect on the electrical characteristics of VF.

Our experiment specifically questions the validity of the above assumption.

2. Methods

Fifty retired male breeder guinea pigs weighing more than 800 g were used in this study. The animals were anaesthetized using IV propofol. Respiration was maintained via a tracheotomy tube and ventilator. Blood pressure was monitored via a femoral artery catheter and the electrocardiogram (Lead I) was also continuously monitored. Median sternotomy and pericardiectomy were done to expose the heart. VF was induced by 60Hz AC stimulation and 4s of data was recorded using a (14×14) Ag/AgCl electrode plaque. The animal was then defibrillated with a biphasic rectangular waveform, 7/2 ms duration. The great vessels were clamped and an intracardiac injection of saline was administered, which rapidly replaced the extracellular fluid. The clamp was removed and VF was induced and 4s of data was recorded. The animal was defibrillated as before and the process was repeated with BDM (0, 10, 20, 40, 100, 150, 200, 250 mM/l). The whole process from clamping to defibrillation was video recorded. Doses of BDM >100 mM/l were categorized as high does or doses that effectively reduced contractility and doses < 100 mM/l were categorized as low doses.

Quantitative analysis was done using the autocorrelation analysis with interval ratio (IR) as a measure of the degree of organization. IR was defined as the ratio of the time delays between the first and second repeats of the signal. In case of periodic signals, where the signal repeats itself in multiples of its period, the IR will be two. For aperiodic signals, the IR can take any value.

3. Results

An example of the autocorrelation analysis is shown in figure 1. The proportions of animals having IR in the range of 1.95-2.05 to the total number of animals in that group was: control=12/44, saline=7/44, low drug dose=6/26, high drug dose=12/14. There was a significant difference between high drug dose and all the other groups ($p<0.001$) (figure 2).

Analysis of the video recordings and drop in femoral arterial blood pressure showed that high doses of BDM had a significant effect in lowering cardiac contractility ($p<0.01$) when compared with low doses and saline.

4. Discussion

Prior studies show that BDM suppressed both intracellular Ca^{2+} release flux and intra-membranous

charge movements [1]. Adams et al reported that BDM caused a decrease of sarcoplasmic reticulum calcium content and potentiated the systolic calcium transient by stimulating Ca^{2+} induced Ca^{2+} release [2]. However, in spite of these cellular effects, BDM was used in optical mapping studies under the assumption that it does not have any effect on the electrical activity of the heart.

This study shows that BDM increases the organization of VF with doses that are comparable to those used in traditional mapping studies. Our results agree with isolated tissue studies, where they used transmembrane recordings of canine endocardial tissues to show that BDM exposure caused VF to progressively regularize into a periodic rhythm [3].

We conclude that BDM may be unsuitable for use as an electro-contractile uncoupler for optical mapping studies of VF as it not only reduces the mechanical activity of the heart, but also affects the electrical activity.

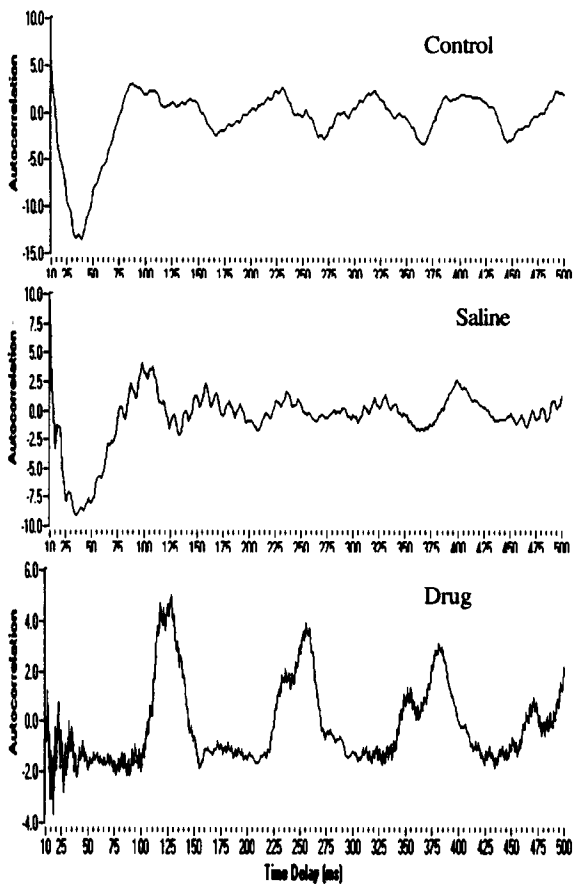

Figure1. Autocorrelation graphs for control, saline and drug (250mM)

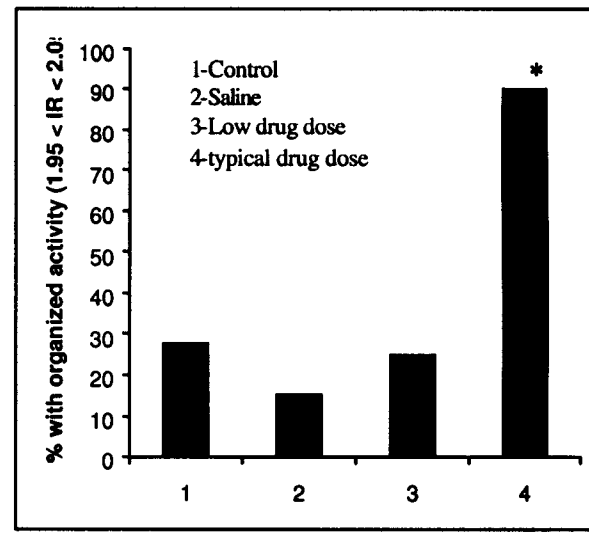

Figure2: Effect of BDM on the interval ratios for autocorrelation (* = $p < 0.001$).

References

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