Melatonin Prevented Early Activation Slowing and Ventricular Fibrillation in a Porcine Model of Acute Myocardial Ischemia

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Background

Frequent development of ventricular fibrillation (VF) as a complication of acute myocardial ischemia warrants search for cardioprotective agents with antiarrhythmic properties. Melatonin has been shown to decrease the frequency and / or duration of ventricular tachyarrhythmias, but the mechanism of its antiarrhythmic action remains largely unclear.

Using a porcine myocardial ischemia model, we aimed to study the effect of melatonin on myocardial electrophysiological parameters (activation delay, duration and dispersion of repolarization) and electrocardiographic indices (duration of QRS, Tpeak-Tend and QT intervals) and their relationship with the incidence of VF during progression of ischemia.

Methods

❑ 40 minutes LAD occlusion in anesthetized pigs (n=25)

✓**Melatonin group**: I.v. injection of melatonin (4 mg/kg) at the 1st minute of ischemia (n=12)

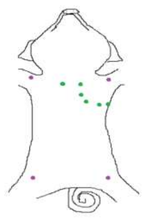
✓**Control group**: I.v. injection of saline at the 1st minute of ischemia (n=13)

❑ Recordings were done at baseline and at 1, 2.5, 5, 10, 15, 20, 25, 30, 35, 40 min of coronary occlusion

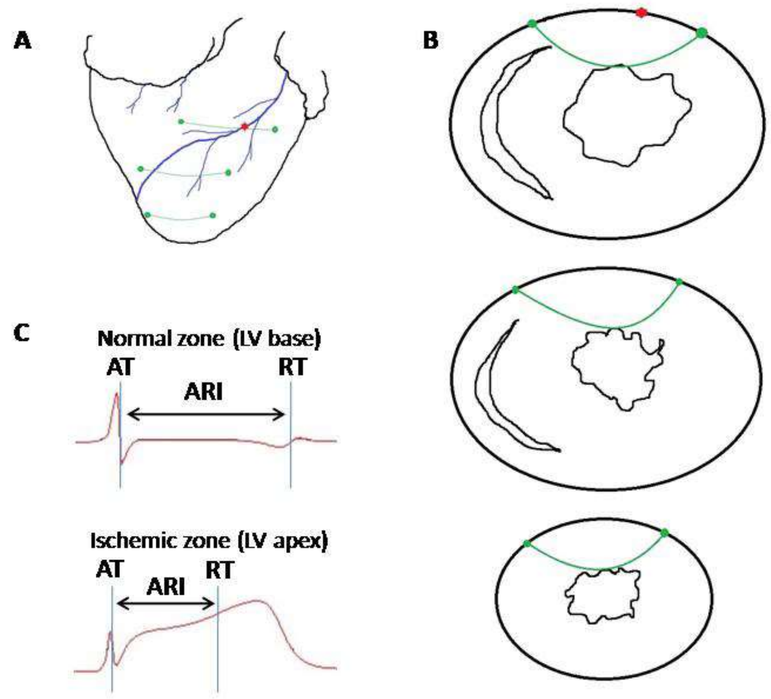
✓**Myocardial electrophysiological parameters**:
-Activation time (AT)
-Repolarization time (RT)
-Activation-repolarization intervals (ARI)

Three flexible plunge transmural electrodes (16 lead terminals each)

✓**ECG parameters** :
-QRS duration
-Tpeak-Tend



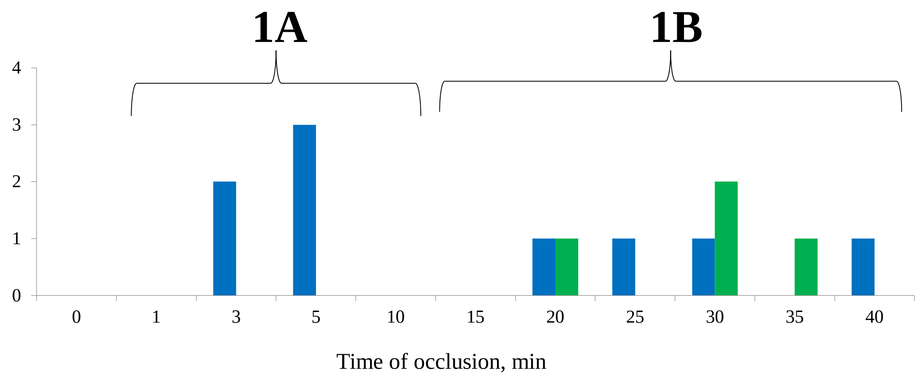
Continuous recording in 12 standard leads



Electrophysiological recordings from the pig heart. Panels A and B show schematic presentation of the distribution of flexible plunge electrodes (green) in respect to superficial anatomical landmarks (panel A) and ventricular cross-cuts (panel B). Green filled circles indicate entry and exit points of electrode filaments. A red asterisk indicates the place of LAD ligation. Panel C shows representative electrograms with activation time (AT), end of repolarization time (RT) and activation-repolarization interval (ARI) markers. See significant ARI shortening in the electrogram from the ischemic zone (LV apex). From: Tsvetkova et al., Front Physiol, 2020, https://doi.org/10.3390/ijms22010328

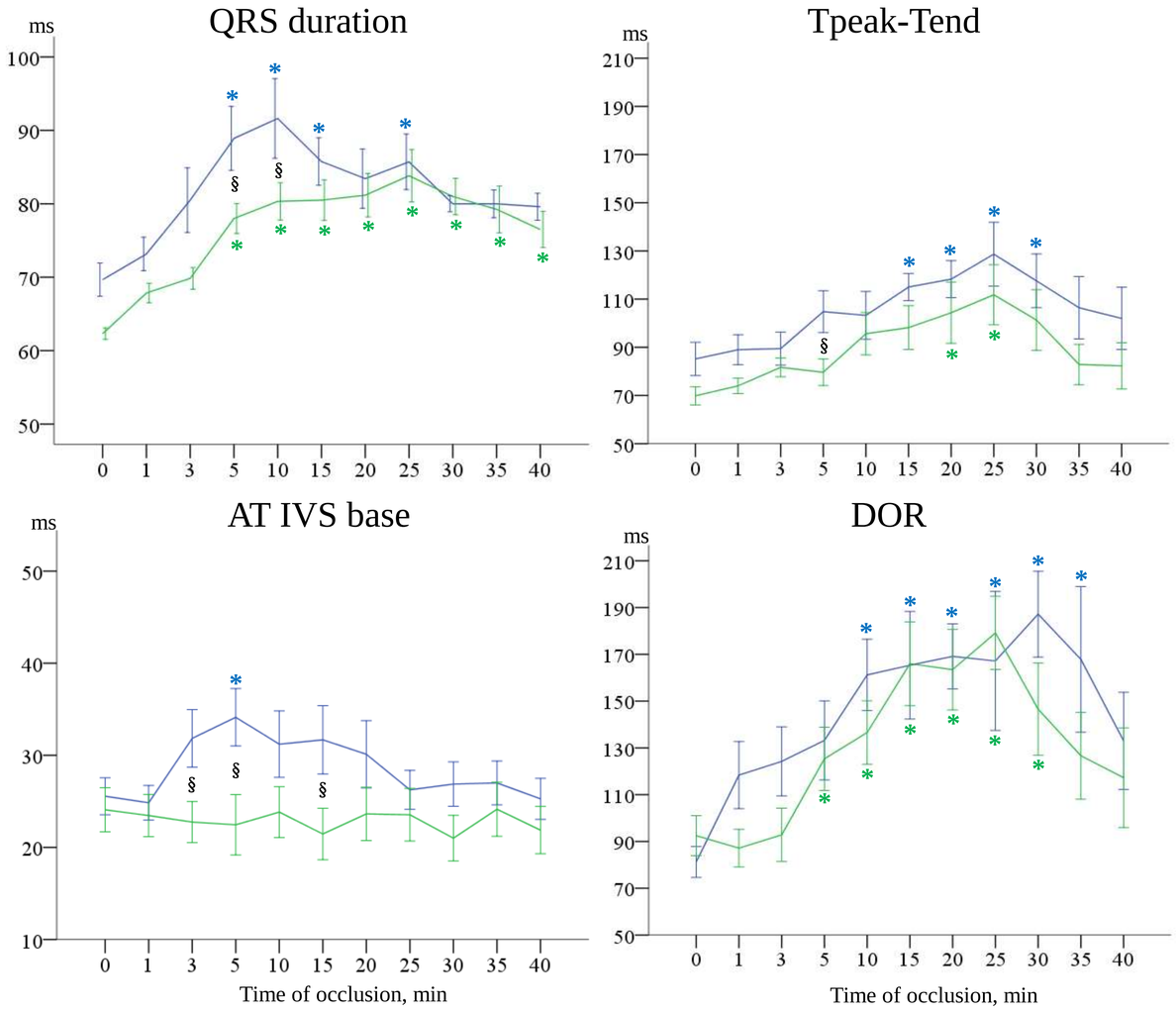
Results

During acute myocardial ischemia, a total of 13 animals experienced VF (control – blue, melatonin – green). VF episodes clustered in early (1–5 min, five cases) and delayed (17–40 min, eight cases) phases, which are referred to as 1A and 1B phase, respectively:



The myocardial electrophysiological and ECG parameters were shown to predict VF in logistic regression analysis:

	Predictors	OR (95% CI) and *p* Early VF	OR (95% CI) and *p* Delayed VF
Myocardial	AT delay	1.049 (1.018 – 1.080); p=0.002	1.071 (1.023 – 1.121); p=0.003
	DOR	1.015 (1.005 – 1.026); p=0.003	1.020 (1.005 – 1.036); p=0.010
ECG	QRS	1.040 (1.002 – 1.080); p=0.038	NS
	Tpeak-Tend	NS	1.025 (1.003 – 1.048); p=0.027



Ischemia induced changes of myocardial (AT in the interventricular septum (IVS) base and DOR) and ECG (QRS and Tpeak-Tend) parameters in the control (blue) and melatonin-treated (green) animals. * - p<0.05 for ischemia-related changes; § - p<0.05 between the control and melatonin groups.

Melatonin treatment blunted the early AT delay in the IVS and QRS duration and prevented 1A phase VF. DOR and Tpeak-Tend predicting 1B phase VFs were not modified by melatonin, and 1B phase VFs were not prevented by melatonin.

Conclusion

Melatonin attenuated ischemia-related increases in the duration of myocardial activation and thereby prevented early but not delayed VF development.