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# Effects of echinochrome on ventricular repolarization in acute ischemia☆,☆☆

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**Abstract**

**Background:** Myocardial ischemic electrophysiological alterations are associated with the generation of reactive oxygen species. However, electrophysiological effects of antioxidants are unclear. Our objective was to determine the effects of the antioxidant echinochrome on ventricular repolarization in a feline model of 30-min ischemia.

**Methods and results:** Activation–recovery intervals were measured from 64 ventricular electrograms recorded before and during the LAD ligation in untreated animals (controls, n = 5) and animals given echinochrome (1 mg/kg, n = 5 and 2 mg/kg, n = 7). In controls, ischemia resulted in the increase of repolarization dispersion, QTc and Tpeak–Tend intervals and precordial T wave amplitude dispersion. Echinochrome attenuated the ischemic increase of repolarization dispersion. The increased dose of echinochrome abolished the ischemic ECG repolarization changes but did not modify the incidence of ventricular arrhythmias.

**Conclusion:** Echinochrome modified ischemic alterations of repolarization dispersion that were associated with the changes of the body surface T wave amplitude dispersion and Tpeak–Tend interval.



*Keywords:* Ischemia; Repolarization; Antioxidant; Animal model

## Introduction

Acute cardiac ischemia causes electrophysiological alterations that may lead to fatal arrhythmias. Among these alterations is the increase in the content of reactive oxygen species (ROS), which produce a wide spectrum of proarrhythmic effects [1]. Antioxidants may reduce the susceptibility to cardiac arrhythmias by the prevention of oxidative stress [2]. A pigment of sea urchins echinochrome A (2,3,5,7,8-pentahydroxy-6-ethyl-1,4-naphthoquinone), an antioxidant agent characterized by iron chelation and free-radical scavenging abilities [3], has been reported to render cardioprotective effects in ischemia/reperfusion models [4], but its electrophysiological effects, that may underlie a potential antiarrhythmic action, are not well understood.

The assessment of cardiac repolarization on the basis of ECG analysis during acute coronary syndrome is of clinical importance as to the prognosis of arrhythmias and evaluation of antiarrhythmic therapies. Specifically, the ECG indices of ventricular repolarization including the QT interval, T wave and Tpeak–Tend durations, the T wave voltage and morphology could reflect the vulnerability of the ventricles to the life-threatening reentrant arrhythmias. The total dispersion of repolarization, which is associated with both the arrhythmic susceptibility and the generation of the T wave, is determined by several so-called ventricular repolarization gradients with the contribution of transepicardial (i.e., apicobasal, interventricular and anteroposterior) gradients being superior to that of the transmural gradient [5–9].

The action potential duration predominantly shortens in the ischemic conditions thereby modifying dispersion of repolarization [10]. We hypothesized that echinochrome as an antioxidant agent could influence the ventricular repolarization-associated

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manifestations of myocardial ischemia. The objective of the present study was to measure the effects of echinochrome on repolarization durations and dispersion and to test if these effects were associated with the changes of the body surface ECG parameters in an open-chest feline model of 30-min ischemia.

## Material and methods

The study was carried out in accordance with the Guide for the Care and Use of Laboratory Animals, 8th Edition published by the National Academies Press (US) 2011, and the experimental protocol was approved by the local institutional ethical committee. The experiments were performed in a total of 17 adult mongrel cats of both sexes, weighing 2.5 to 4.5 kg. Animals were anesthetized with zoletil (ZOLETIL® 100, Virbac S.A., Carros, France; 15 mg/kg, i.m.) and xylazine (XYLA, Interchemie, Castenray, Holland; 1 mg/kg, i.m.). Then, the animals were intubated and artificially ventilated. Catheters (internal diameter 1 mm) were inserted into the femoral vein for the administration of drugs and saline. Stainless steel needle electrodes were inserted subcutaneously to record ECGs in the standard bipolar limb leads and six modified precordial leads (J1–J6). Taking into account the further midsternal access to the heart, these leads were shifted from the usual level upwards to the jugular notch (J1–J3) and downwards to the inferior costal margin (J4–J6). The positions of J2 and J5 were in the midline, J1 and J6 in the right anterior axillary line, and J3 and J4 in the left anterior axillary line (Fig. 1). A shortening of action potentials in the apical part of the heart ventricles due to occlusion of the left descending coronary artery was expected to result in an increase of the apicobasal difference in action potential durations and these changes were expected to be documented by the recording of ECGs in the modified precordial leads system with the leads J1–J3 reflecting potentials of the ventricular base and the leads J4–J6 reflecting potentials of the ventricular apex.

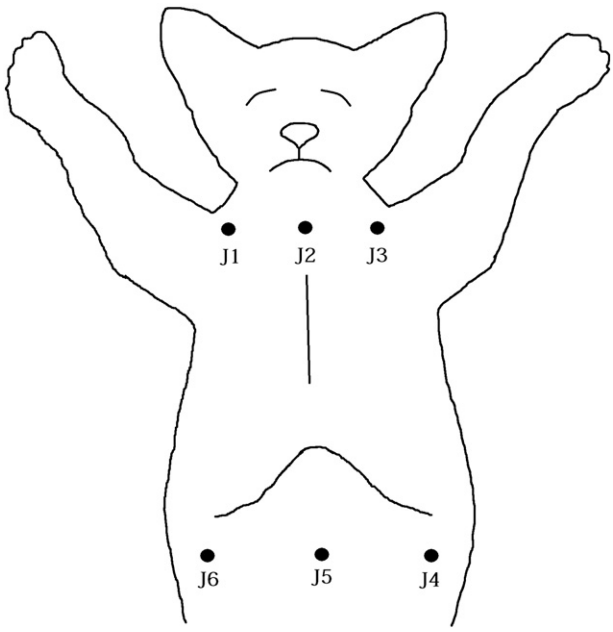


Fig. 1. Schematic presentation of the distribution of precordial leads.

The heart was exposed through a midsternal approach and was suspended in a pericardial cradle. In order to induce coronary occlusion, a polycaproamide ligature (No. 3-0) was placed around the left anterior descending coronary artery (LAD). During the experiment, the core temperature was monitored and maintained constant at 35–37 °C. Warm (37 °C) saline was applied intermittently to the heart to moisten the epicardium and prevent surface cooling. A 64-electrode epicardial sock was placed on the heart ventricles to record unipolar electrograms. The signals were isolated, amplified, multiplexed, and recorded by a custom-designed 144-channel computerized mapping system with a bandwidth of 0.05–1000 Hz at a sampling rate of 4000 Hz. The data were obtained at baseline and 5, 15, and 30 min of coronary occlusion with the incision being sutured before the recordings.

The ischemic area and the leads enclosed within this area were determined by two methods. The elevation of the ST segment on the recorded epicardial electrograms served as the evidence of acute ischemia. After the experiment the 1.5 ml of 0,5% Evans blue dye (Reanal, Hungary) was injected via the carotid artery catheter. The leads in the noncontrasted zone coincided with the leads, where the elevation of the ST segment was observed during coronary occlusion. The perfused regions were designated as a nonischemic zone (Supplementary 1).

The animals were divided into three groups. Two groups were given echinochrome in the doses of 1 mg/kg and 2 mg/kg (n = 5 and n = 7 respectively) being administered as a 0.2% solution in a 0.1% sodium bicarbonate solution 5 min before coronary occlusion. Five cats served as the controls and underwent LAD ligation, but did not receive antioxidant treatment. Instead, an equivalent volume of saline was infused to the control animals before coronary occlusion.

The analysis of the recorded epicardial electrograms included the measurement of activation–recovery intervals (ARIs), which were used for the evaluation of local repolarization duration. Each ARI was defined as the interval between the activation time and the end of the repolarization time, determined as dV/dt min during the QRS complex and dV/dt max during the ST-T complex respectively [11]. The dV/dt max moment was determined automatically, inspected by the observer, and corrected manually if necessary. The dispersion of repolarization was calculated as the difference between the longest ARI in the nonischemic area and the shortest ARI in the ischemic zone.

The QRS, QT and Tpeak–Tend intervals were measured in the limb lead II ECG and the QT interval was corrected to heart rate by the formula $QTc = QT - 0{,}175*(RR-300)$ [12]. The T wave amplitudes were measured in the modified precordial leads. Two averaged values were calculated for the "basal" (J1–J3) and "apical" (J4–J6) leads, respectively, and the difference between these values ("apical" minus "basal") was defined as the longitudinal T wave amplitude dispersion.