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Effects of central sympathetic activation on repolarization-dispersion during short-term myocardial ischemia in anesthetized rats

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ABSTRACT

Aims: Sympathetic activation during myocardial ischemia enhances arrhythmogenesis, but the underlying pathophysiologic mechanisms remain unclear. We investigated the central sympathetic effects on ventricular repolarization during the early-period post-coronary artery occlusion.
Main methods: We studied 12 Wistar rats (254 ± 2 g) for 30 min following left coronary artery ligation, with (n = 6) or without (n = 6) pretreatment with the central sympatholytic agent clonidine. Mapping of left and right ventricular epicardial electrograms was performed with a 32-electrode array. As an index of sympathetic activation, heart rate variability in the frequency domain was calculated. Heart rate and repolarization duration were measured with a custom-made recording and analysis software, followed by calculation of *intra*- and *inter*-ventricular dispersion of repolarization.
Key findings: Heart rate and heart rate variability indicated lower sympathetic activation in clonidine-treated rats during ischemia. Repolarization duration in the left ventricle prolonged after clonidine at baseline, independently of heart rate, but no differences were present 30 min post-ligation. Dispersion of repolarization in the right ventricle remained stable during ischemia, whereas it increased in the left ventricle, equally in both groups. A similar trend was observed for *inter*-ventricular dispersion, without differences between groups.
Significance: In addition to *intra*-ventricular repolarization-dispersion, anterior-wall myocardial ischemia may also increase *inter*-ventricular repolarization-dispersion. Progressive central sympathetic activation occurs during myocardial ischemia, but it does not affect *intra*- or *inter*-ventricular dispersion of ventricular repolarization during the early phase. Further research is warranted on the potential effects during subsequent time-periods.
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1. Introduction

Ventricular tachyarrhythmias, triggered by acute coronary occlusion, often lead to sudden cardiac death, and constitute a major health-related problem worldwide [17]. Based on its impact on society, in-depth understanding of the pathophysiology of ischemia-induced ventricular tachyarrhythmias has been at the center of ample research efforts, aiming at lowering mortality rates of acute coronary syndromes.

Sympathetic activation during myocardial ischemia has been long recognized as an important contributor to arrhythmogenesis [37], but the underlying mechanisms remain under investigation. Of the ensuing multifaceted electrophysiologic effects, catecholamine-induced dispersion of ventricular repolarization has been extensively explored; as part of this mechanism, spatial differences in repolarization in the ischemic-myocardium can form functional substrates for reentrant circuits [17].

Under normal conditions, repolarization-dispersion is also present between right (RV) and left (LV) ventricular sites, secondary to differences in repolarizing potassium currents [10]. Such heterogeneity is enhanced in long-QT animal-models [42] and patients [11], and plays a critical role in arrhythmogenesis. However, the magnitude and the temporal pattern of *inter*-ventricular repolarization-dispersion, evoked by myocardial ischemia, have not been thoroughly investigated. This mechanism, particularly relevant in ischemic areas located adjacent to the RV, may be exaggerated by sympathetic activity, which exerts opposite effects on normal and ischemic myocardium [31].

Ischemia-induced sympathetic activation entails complex responses that involve the entire sympatho-adrenal axis [18]; in the heart, immediate norepinephrine release occurs from intrinsic sympathetic nerve-terminals *via* exocytosis, followed by reverse-mode action of the norepinephrine transporter [37]. This mechanism occurs independently of autonomic innervation, evidenced by its demonstration *ex vivo*, in

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isolated, beating preparations [33]. However, in the *in vivo* setting, central autonomic inputs play additional pathophysiologic role; they consist of efferent discharges from the brain stem, in response to locally-produced metabolites that stimulate afferent myocardial nerve fibers. Autonomic disturbances during myocardial ischemia produce global electrophysiologic alterations in the LV and RV, and may contribute to arrhythmogenesis; this long-standing hypothesis [44] is supported by animal [47] and clinical [38] studies, demonstrating the precedence of ventricular tachyarrhythmias by enhanced sympathetic activity.

Despite the accumulated knowledge, the effects of central sympathetic inputs on *intra-* and *inter*-ventricular repolarization-dispersion remain unclear. To further address these issues, we investigated the effects of regional myocardial ischemia on ventricular repolarization in the LV and the RV in rats *in vivo*, a model with intact neural axis. We focused on the early period of ischemia, given the clinical importance of this time-frame, as it corresponds to the critical pre-hospital phase of acute coronary syndromes.

We performed spatial repolarization mapping in the ischemic-LV- and neighboring RV-myocardium with a multi-electrode array; temporal changes were assessed by measurements prior to, and 5 and 30 min after the onset of ischemia. To dissect the effects of central sympathetic activation on these changes, we employed a 'subtraction model', produced by pharmacological inhibition of sympathetic preganglionic neurons by clonidine.

2. Materials and methods

2.1. Animal study-population and ethics

The study-population consisted of 12 male Wistar-rats, 14–15 weeks of age, weighing 240–270 g. The animals were housed in plexiglas-cages in groups of two, with free access to standard pellet-diet and water. The laboratory conditions were kept optimal, in terms of temperature (20–22 °C), humidity (~70%) and light/dark cycles (12/12 h), according to European legislation (*European Union directive for the protection of animals used for scientific purposes* 609/1986, revised in 2010/63/EU). The study protocol adheres to the principles of the Declaration of Helsinki, and was approved by the institutional ethics committee and by the regulatory state authorities.

2.2. Clonidine-administration

The effects of central sympathetic activation were examined after administration of the centrally-acting sympatholytic agent clonidine in six animals, whereas the remaining six received saline and served as controls; this model of clonidine pre-treatment is widely used in *in vivo* animal-studies of ventricular arrhythmogenesis [35]. After an initial peripheral α1-stimulation, the central effects of clonidine prevail, resulting in inhibition of sympathetic preganglionic neurons; this action reduces sympathetic drive after various stimuli. As before [46], clonidine was given intraperitoneally (0.5 mg/kg), one hour prior to the experiments; this dosing regimen was shown to effectively decrease indices of baseline sympathetic activity and (mainly) to blunt its responses post-coronary ligation [20].

2.3. Induction of myocardial ischemia

After tracheal intubation, the rats were mechanically ventilated (rodent-apparatus model 7025, Ugo Basile, Comerio, Italy) and anesthesia was maintained with a mixture of oxygen and 2.5% sevoflurane. As in previous experiments [19], ischemia was induced by ligation at the middle segment of the left coronary artery, guided by the anatomic landmarks provided by the pulmonary cone, the left atrium and the apex; following these guides ensures comparable ischemic-areas [2]. Visual inspection of a pale, akinetic area, and prominent ST-segment elevation in a 6-lead electrocardiogram (QRS-Card digital PC-ECG, Pulse Biomedical Inc., *PBI*, Norristown PA, USA) validated successful procedures.

2.4. Multi-electrode array mapping

Unipolar ventricular electrograms were recorded from 32 electrodes, in reference to Wilson's central terminal, according to previously described setup [23]. Compared to bipolar recordings, unipolar electrograms display improved morphology that permits easier identification of repolarization, especially in the rat-model. The electrodes were selected from a commercially available multi-electrode array (FlexMEA72, Multi Channel Systems, MCS, GmbH, Reutlingen, Germany); it consists of titanium nitrate electrodes, with golden contact-pads and track-material (providing an impedance of 50 kΩ), mounted on polyimide-foil. The electrode arrangement configured a 4 × 8 array with a 1.25 × 1.50 mm inter-electrode distance, resulting in total dimensions of 4.375 × 6.000 mm. The array was connected *via* an adaptor (ADPT-FM-72, MCS) to two noise-rejecting, shielded input/output connector-blocks (SCB-68A, 782536-01, National Instruments, NI, Austin, Texas, USA) and finally to a data acquisition system (NI PCI-6289, M-Series DAQ, NI) *via* two shielded cables (SHC68-68-EPM, NI).

The multi-electrode array was placed on the anterior LV- or the adjacent RV-epicardium in a consistent manner, guided by the aforementioned anatomical landmarks (Fig. 1A). Unipolar electrograms were recorded with a custom-designed software-program, at a sampling frequency of **5** kHz; electrical noise was eliminated by application of a 50/60 Hz band-pass filter, and motion artifacts were eliminated by inverse Chebyshev, elliptic and wavelet filters.

The LabView-based software provides measurements aided by automated point-recognition (Fig. 1B), based on previous definitions [26]. The accuracy of such measurements is enhanced, by validating all intervals on the same electrograms displayed in reverse polarity, a feature particularly useful with respect to repolarization duration. For purposes of the present study, the interval between two maximal positive deflections was measured, and heart rate (HR) was derived as a mean of 10 successive sinus beats. In addition, repolarization time (RT), describing the duration of ventricular repolarization, was defined as the interval from the end of depolarization to the end of repolarization (Fig. 1C).

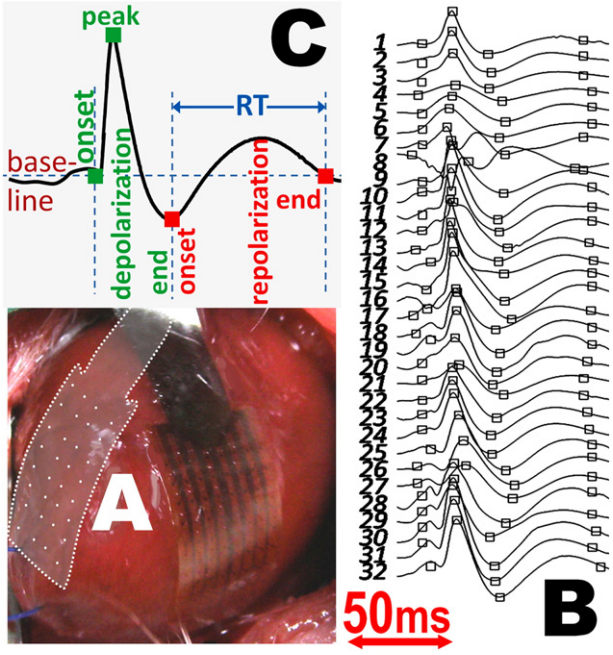

Fig. 1. Title: Electrogram recording and analysis. Legend: Examples of ventricular recording sites (A), automated point recognition in the electrograms (B), and measurement (C) of repolarization time (RT).

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