The selective late sodium current inhibitor eleclazine attenuates ventricular fibrillation spectral characteristics modifications produced by acute myocardial stretch.

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Background/Introduction
Pathophysiological processes as cardiac overload or dyssynchronous contraction produces mechanical stretch that is an arrhythmogenic factor. Stretch can induce an increase in Na\textsuperscript{+} influx into myocytes related to an activation of the Na\textsuperscript{+}/H\textsuperscript{+} and reverse mode of the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchangers, increasing intracellular Ca\textsuperscript{2+} and giving rise to detrimental electrophysiological changes. Eleclazine, a selective inhibitor of INaL, could prevent these effects taking in account that this current is associated to the intracellular Ca\textsuperscript{2+} increase due to stretch.

Purpose
The aim of this study was to investigate, by the ventricular fibrillation (VF) spectral analysis, whether eleclazine prevents some arrhythmogenic electrophysiological effects due to acute ventricular local stretch.

Methods
In twelve Langendorff-perfused rabbit hearts VF recordings were obtained using epicardial multiple electrodes on the left ventricle free wall under control conditions and during perfusion of different concentrations of eleclazine (0.35, 0.7 and 1.4 µM). VF was induced by pacing at increasing frequencies, without interrupting coronary perfusion. After the induction of VF, stretch was produced by an "ad hoc" device introduced to the left ventricle and maintained for three minutes. Dominant frequency (DF) of VF and spectral concentration (SpC) were determined using spectral techniques. A two-factor ANOVA test was used and significance was reached when p<0.05.

Results
Myocardial stretch significantly increased DF with respect to pre-stretch values in control conditions (12.9 ± 3.4 vs. 16.7 ± 4.6 Hz) and also during the eleclazine perfusion at the concentrations 0.35 µM (12.6 ± 3.7 vs. 15.0 ± 3.6 Hz) and 0.7 µM (11.9 ± 2.1 vs. 14.0 ± 2.6 Hz), but not at 1.4 µM (11.8 ± 4.8 vs. 12.1± 3.0 Hz, ns). The magnitude of the stretch-induced increment in DF under 1.4 µM eleclazine was significantly lower than in control conditions (control: 32.3 %, 1.4 µM: 10.5 %). The significant stretch-induced decrease in SpC in control conditions (31.2 ± 10.8 vs. 22.4 ± 4.7 %) was also observed under 0.35 µM eleclazine effects (30.1 ± 8.8 vs. 23.2 ± 6.0 %), whereas the highest concentrations of drug prevented this reduction (0.7 µM: 28.1 ± 6.9 vs. 24.6 ± 5.2 %, ns; 1.4 µM: 33.5 ± 10.9 vs. 40.1 ± 16.2 %, ns). Moreover, during stretch, arrhythmia regularity and organization, evaluated by SpC, was greater under 1.4 µM eleclazine than in control conditions (control: 22.4 ± 4.7 %; 1.4 µM: 40.1 ± 16.2 %).
Conclusion
The accelerating and disorganizing effects on ventricular activation during the arrhythmia, promoted by acute myocardial stretch, are reduced by the selective late sodium current inhibitor eleclazine.