Abstract

Cardiac electrophysiology allows the study of the electrical activity in specific regions of the heart and, therefore, the analysis of the modifications of its characteristics in regions subjected to changes such as acute myocardial stretch. Myocardial stretch modifies the electrophysiological properties of cardiomyocytes, causing cardiac arrhythmias in different pathological situations. The mechanical effects of stretching induce related calcium changes, and there are several mechanisms that have been implicated, including an increase in the influx of Na^+ and the sequential activation of the Na^+/H^+ and Na^+/Ca^{2+} (reverse mode) exchangers, related to autocrine/paracrine events.

This doctoral thesis has as its main objective the study of the possible involvement of these mechanisms in the electrophysiological responses to stretch by analyzing the pharmacological modifications of these responses.

The changes in the characteristics of myocardial activation during ventricular fibrillation (VF) and myocardial electrophysiological properties induced by acute myocardial stretch have been studied in 44 isolated rabbit hearts perfused on a Langendorff system using epicardial multiple electrodes and electrical mapping techniques under control conditions (n=9) and during the perfusion of the angiotensin II type-1 receptor antagonist losartan 1μM (n=8), the endothelin-A receptor blocker BQ-123 0.1μM (n=9), the Na^+/H^+ exchanger inhibitor 5-(N-ethyl-N-isopropyl)-amiloride (EIPA) 1 μM (n=9) and the late Na^+ current blocker ranolazine 5 μM (n=9).

Spectral techniques and techniques for myocardial activation detection have been used for analysis in the frequency and in the time domain of fibrillatory signal, studying parameters related to the frequency, the organization (or regularity) and the complexity of myocardial activation during VF and ventricular refractoriness and conduction velocity.

The results show the pharmacological modifications of the electrophysiological effects of stretching. EIPA and ranolazine attenuated the increase in the VF dominant frequency produced by stretch. During stretch, myocardial activation during VF was more complex in the control series than with EIPA or ranolazine, evaluated by the percentages of activation map types, while the organization of activation, assessed by means of spectral concentration, was greater under EIPA and ranolazine. Losartan and BQ-123 did not modify the electrophysiological responses to myocardial stretch.

In conclusion, the inhibition of the late inward Na^+ current by ranolazine and the inhibition of the Na^+/H^+ exchanger by EIPA attenuate the electrophysiological effects responsible for the acceleration of the activation and the increase of the complexity of myocardial activation during VF produced by acute local stretching. In contrast, the angiotensin II receptor blocker losartan and the endothelin receptor blocker BQ-123 do not modify these effects.

In summary, the mechanisms involved in the electrophysiological responses to acute local stretch are counteracted by inactivation of late Na^+ current and Na^+/H^+ exchanger, whereas the release of angiotensin II and endothelin do not seem to be involved in the chain of events related to the electrophysiological effects of stretch.