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Abstract Preview

Frontiers in Cardiovascular Biomedicine 2022

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Title : Endothelin-1 amplifies ventricular repolarization heterogeneities in chronic myocardial infarction pigs

Topic : 41.2.4 - Ion Channels, Electrophysiology

Option : Young Investigator Award (YIA)

Funding Acknowledgements : PID2019-105674RB-I00 - Type of funding sources: Public grant(s) – National budget only - Ministerio de Ciencia e Innovación (Spain) Diputación General de Aragón - I agree that this information can be anonymised and then used for statistical purposes only

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Introduction: Endothelin-1 (ET-1) is a vasoconstrictor peptide secreted by endothelial cells and cardiac myocytes and fibroblasts. It is involved in oxidative stress, apoptosis regulation and ventricular remodeling processes associated with heart failure and ischemic cardiomyopathy, including myocardial hypertrophy, fibrosis and impaired conduction. ET-1 has been shown to influence cardiac electrophysiology by modulation of calcium and potassium currents and to contribute to arrhythmogenesis and sudden cardiac death.

Purpose: We aim to characterize the functional role of ET-1 in the electrophysiology of healed myocardial infarction (MI) by analysis of porcine ventricular slices as a highly representative model of ventricular tissue with preserved cellular cross-talks and architecture.

Methods: Domestic pigs (60–80 kg, n = 3) were infarcted by temporal occlusion of the left anterior descending coronary artery. 8-12 weeks after infarct induction, animals were cardioplegically arrested under deep anesthesia and sacrificed. All animal procedures conformed to the guidelines from Directive 2010/63/EU and were approved by local authorities.
350 µm-thick ventricular slices were produced from transmural tissue blocks of healed MI ventricles. Tissue blocks were taken from remote, adjacent and border zones of the infarct area. Slices were optically mapped within 8 hours after tissue collection to record transmembrane potential and intracellular calcium. Action Potential Duration (APD) and Calcium Transient Duration (CaTD) were measured at 80% repolarization for 0.5, 1 and 2 Hz pacing frequencies in the presence and absence of 100 nM ET-1.
The notation n/N is used to denote n tissue slices from N pigs.

Results: ET-1 prolonged the APD at all frequencies in remote zones, with mean prolongation percentages of 30.5%, 32%, 26.2% at 0.5, 1 and 2 Hz, respectively, n/N=7/3. However, only minor effects were observed in adjacent (mean APD prolongation of 3.3%, 4.9% and 10.7%, n/N=5/3) and border zones (7%, 4% and 3.6%, n/N=5/3).
ET-1 caused an increase in CaTD at 1 Hz in the three zones, with no significant regional differences in the amount of CaTD increase: mean prolongation of 14.1% (n/N=7/3) in the remote zone, 12.4 % (n/N=5/3) in the adjacent zone and 20.9% (n/N=4/3) in the border zone.

Conclusions: In chronic MI pigs, ET-1 induces strong APD and moderate CaTD prolongation of remote normal myocardium at low (0.5 Hz) to high (2 Hz) frequencies. The ET-1-induced effects on the AP of normal tissue, but not on CaT, are disrupted in the border zones of the infarct area and in its proximity. Our results point to ET-1 acting to enhance ventricular repolarization dispersion in chronic MI pigs, which might contribute to increased arrhythmia vulnerability.