Chronic myocardial infarction attenuates transmural heterogeneities and alters the response to endothelin and β-adrenergic stimulation in porcine ventricles

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Increased susceptibility to ventricular arrhythmias is well documented after myocardial infarction (MI), and there is consistent evidence supporting differences in transmural and apicobasal repolarization gradients as substrates for ventricular tachycardia and arrhythmogenesis.

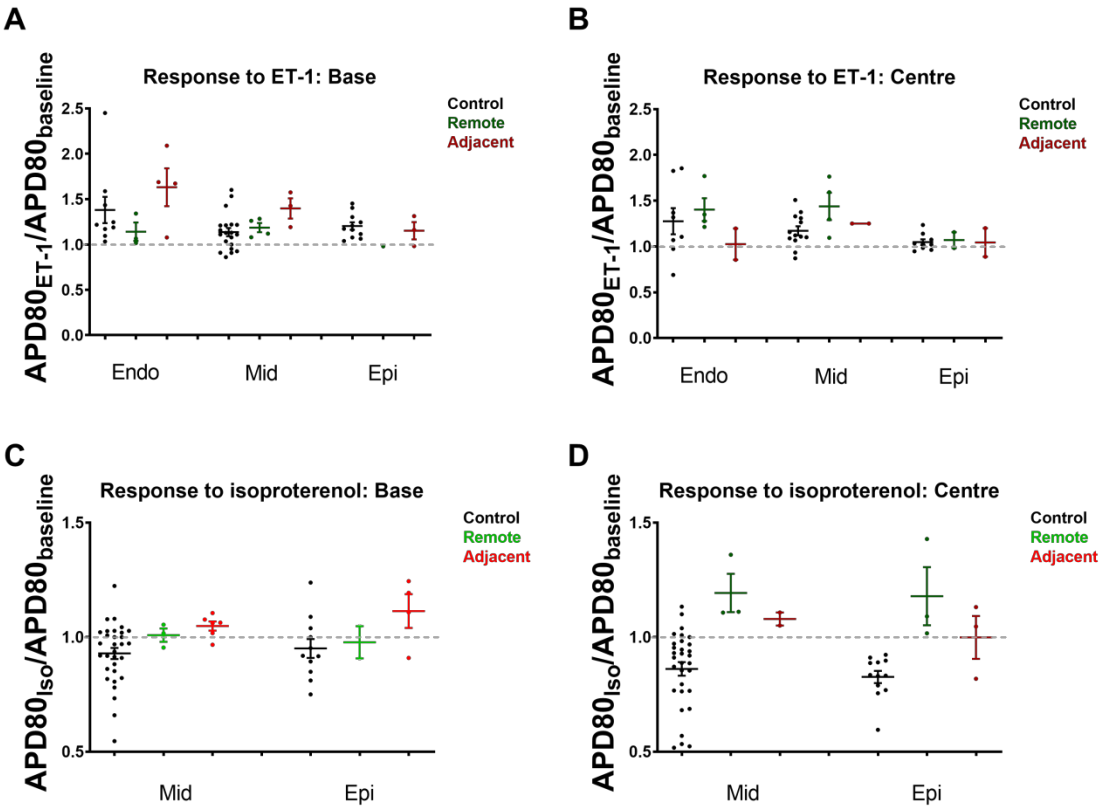
Nonetheless, there is limited direct evidence on how post infarct dynamics may differentially affect transmural regions in the heterogeneous peri-infarct zone. Information on how different cell types contribute to an arrhythmogenic electrophysiological profile is also scarce.

Aim: to assess the effects of chronic MI on centre-to-base transmural repolarization gradients, at baseline, and in response to adrenergic stimulation (isoproterenol) and endothelial factors (endothelin-1, ET-1).

Methods: Domestic pigs (n=5) were infarcted by temporal occlusion of the left circumflex (LCx) coronary artery. 7-12 weeks after infarct induction, animals were cardioplegically arrested under deep anaesthesia and sacrificed. Healthy pigs (n=11) were used as controls. All animal procedures conformed to the guidelines from Directive 2010/63/EU and were approved by local authorities. Ventricular slices were produced form transmural tissue blocks obtained from remote and adjacent zones of the infarct area at the base and in the centre of the ventricular wall. Same areas of the ventricle from healthy pigs were taken as controls. Slices from the endocardium, mid-myocardium and epicardium were optically mapped to record transmembrane potential. Action Potential Duration (APD) was measured at 80% repolarization at 1Hz pacing frequency at baseline conditions and after the addition of ET-1 100nM or isoproterenol 100nM.

Results: Transmural heterogeneities in APD80 at basal conditions were attenuated in the infarcted tissue: endocardial and epicardial tissue presented a prolongation of the APD80 in the base of the infarcted hearts, especially in the adjacent to the infarct areas, while the mid-myocardial tissue presented a slight decrease. In the centre, APD80 was decreased at all layers of the transmural wall, but this effect was more pronounced in the adjacent to the infarct areas in the mid-myocardium. ET-1 produced a prolongation of 38, 13 and 20% (endocardium, mid-myocardium and epicardium, respectively) of the APD80 in the base and of 28, 17 and 5% in the centre, this response was enhanced in the base in the areas adjacent to the infarct (63, 40 and 15) and maintained in the remote areas (14, 18 and -3%). In the centre, the response to ET-1 was slightly diminished in the adjacent areas (3, 25 and 5%). Isoproterenol shortened APD80 by 8 and 5% (mid-myocardium, epicardium) in the base and by 14 and 17% in the centre of healthy ventricles. There was no response, however, in the base of the infarcted hearts (remote +1 and -3% and adjacent +5 and +11%), and the response in the centre was inverted (remote +19% and +18% and adjacent +8 and +0%).

Conclusions: chronic MI by occlusion of LCx in pigs led to attenuation of transmural heterogeneities, heterogeneous response to adrenergic stimulation and increased sensibility to ET-1. All these factors may indicate an increased susceptibility to ventricular arrhythmias. Future studies of the mechanisms underlying the here described transmural heterogeneous remodelling in MI would lead to improved antiarrhythmic therapies.



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