171 NANO-STRUCTURAL AND MOLECULAR REMODELLING EXTENDS TO THE REMOTE REGION IN THE POST MYOCARDIAL INFARCTED PORCINE HEART Â€ " A BASIS FOR HEART FAILURE DEVELOPMENT?

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Introduction A common consequence of coronary artery disease is myocardial infarction (MI). Following an MI a sequence of pathological events occur with necrosis and acute inflammation leading to the formation of a stable fibrous scar. However, although many patients now survive an MI many also go on to develop heart failure (HF), with cellular remodelling implicated as a precipitating factor. However, the nano-architectural changes and associated molecular remodelling remains poorly understood. Mitochondria occupying between 30–40% of the cardiomyocyte volume, play a central role in cardiac energetics, with evidence to indicate dysfunction in the post-MI heart.[1] Here we have combined 3-D electron microscopy with biochemical and quantitative mass spectrometry methods, to investigate morphological changes to mitochondria within both the peri-infarct and remote regions. We have interrogated structural changes in the context of protein, molecular, level remodelling.

Methods and results We have employed a translationally relevant porcine model of MI, presenting mild to moderate left ventricular dysfunction (n = 3, control and MI).[2] Animals were studied 1 month post-MI when the scar region has stabilised. Tissue was sampled from the peri-infarct and remote regions and a corresponding region from the control hearts, fixed and prepared for serial block face scanning electron microscopy as previously described.[3] Tissue was also lysed and analysed by quantitative mass spectrometry and western blotting. 3-D reconstruction of the mitochondria within both the peri-infarct region and remote area determined that they were smaller in terms of volume (no. of mitochondria = 389, $P < 0.01$; no. of mitochondria =262 $P < 0.05$ respectively) compared to control. There was also a change to the distribution of the subsarcolemmal and inter-fibrillar mitochondria in both regions post-MI. Quantitative mass spectrometry identified between 1400–2000 proteins within each tissue sample with alterations (both up and down regulation) of proteins associated with Î² oxidation and OXPHOS.

Conclusion These data reveal that mitochondrial structural rearrangements are accompanied by expression level changes to proteins regulating cardiac energetics. Importantly, the data also indicate that while morphological remodelling is more acute within the peri-infarct region the remote areas of the infarcted heart are also undergoing cellular maladaptations. Currently, there are no treatments that specifically target cellular structural remodelling post-MI. Here we show that mitochondrial remodelling is a feature of the post-MI heart; targeting these changes at the structural and molecular level may represent a novel treatment strategy for improved outcomes.

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172 A SLOW-RELEASING SYNTHETIC PROSTACYCLIN AGONIST Â€ŒONO 1301-SRÂ€ COMBINED WITH OMENTAL FLAP INCREASES MYOCARDIAL BLOOD FLOW AND REDUCES MICROVASCULAR RESISTANCE, ASSOCIATED WITH FUNCTIONAL RECOVERY, IN A PORCINE CHRONIC MYOCARDIAL INFARCTION MODEL

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Introduction Coronary microvascular dysfunction (MVD) has been shown to be the major cause of persistent myocardial ischaemia and progressive left ventricular (LV) remodelling in the chronic myocardial infarction (MI) heart. ONO-1301SR is a slow-releasing synthetic prostacyclin agonist, being developed to induce angiogenesis by upregulating a variety of proangiogenic cytokines in the targeted region. In addition, pedicle omental flap covering over the LV surface reportedly yields proangiogenic effects on chronic MI heart. We herein hypothesised pedicle omental flap covering, combined with ONO-1301SR placement. over the LV surface may be effective on the MVD and related functional deterioration in a chronic MI heart. To test this hypothesis, clinically latest imaging studies were applied in a porcine chronic MI model.

Methods A mini-pig chronic MI model was generated by placing an ameroid constrictor around the left anterior descending artery for 4 weeks. The mini-pigs were then randomly assigned into the following 4 groups; sham group, omental flap alone (OM group), ONO-1301SR alone (ONO group), ONO-1301SR plus omental flap (ONO+OM group, n = 6 each).

Results At 4 weeks after the treatment, ^{13}N-ammonia PET study showed that the ONO+OM group, but not the other groups, displayed a significantly increase in myocardial blood flow (189 ± 89% increase, $P < 0.05$) and coronary flow reserve (179 ± 121% increase, $P < 0.05$) under the stress compared to those under the rest. This trend was predominated in the left circumflex territory. In addition, coronary angiogram and pressure-temperature sensor wire study showed that the ONO+OM and the ONO groups, but not the OM group, showed a significantly greater number of collateral arteries and smaller indexed of microvascular resistance, in particular, in the left circumflex territory, compared to the sham group. Moreover, echocardiographical EF was significantly greater in the ONO+OM group (50 ± 7%) and the ONO group (48 ± 3%), compared to the OM group (41 ± 3%) and the sham group (38 ± 5%) at 4 weeks. Furthermore, histological density of CD31-positive capillaries and CD31SMA-double positive arterioles were significantly greater in the ONO+OM group than the sham group or the OM group, in association with a significantly smaller myocyte size and interstitial fibrous area in the ONO+OM and the ONO group compared to those in the other groups. However, expression of proangiogenic cytokines, such as *vascular*