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INTEGRATED PROTEOMIC AND METABOLOMIC ANALYSIS REVEALS NADH-MEDIATED TCA ENERGY METABOLISM DISORDER IN CHRONIC PROGRESSIVE HEART FAILURE

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Objectives Although great progress has been made in heart failure (HF), it is still the major cause of mortality and morbidity worldwide. Typically, research associated with heart failure has focused on heart failure induced by acute myocardial infarction. However, most clinical HF is gradually generated by chronic progressive heart Failure (CHF). A proper model is needed to reveal its identification, quantification, and characterisation, understand the mechanism of heart failure (HF). The initial goal of the present study is to build up a chronic progressive Heart Failure model, characterise the time course and the pattern of regional myocardial contractile function during the development of progressive coronary artery stenosis, since most prior studies on this topic have only collected infrequent measurements. The second goal is to determine the underlying molecular mechanism for CHF.

Methods Here we place ameriod constrictor on the left anterior descending coronary artery (LAD) of the mini-swine. It has a tendency to slowly absorb fluid and swell, thus slowly obstructing the vessel inside the constrictor lumen, which is more in line with changes in clinical development of CHF. Dynamic detection of electrocardiogram, echocardiography and coronary angiography are applied to diagnosis the chronic progressive Heart Failure model. Then two-dimensional gel electrophoresis (2-DE)-based proteomics and nuclear magnetic resonance (NMR) and Gas chromatography coupled with mass spectrometry (GC-MS) based metabolomics are applied to investigate its characterisation of the ischaemia tissue, and bioinformatic analysis including Gene Ontology (GO) and KEGG pathway analysis is used to understand the mechanism of chronic progressive heart failure.

Results Based on dynamic detection of electrocardiogram, echocardiography and coronary angiography, the model shows a steady cardiac function from 8 weeks to 12 week, which EF value is about 50%, can be diagnosed as Chronic progressive Heart Failure. What is more, the model shows specific and interesting pathological changes, which ischaemia region only involve bellowing the mitral lesions. Then two-dimensional gel electrophoresis (2-DE)-based proteomics and nuclear magnetic resonance (NMR) and Gas chromatography coupled with mass spectrometry (GC-MS) based metabolomics are applied to investigate its characterisation of the ischaemia tissue, and bioinformatic analysis including Gene Ontology (GO) and KEGG pathway analysis is used to understand the mechanism of chronic progressive heart failure. We find that mitochondrial respiratory chain mediated by NADH is the critical pathway; it leads to down-regulation of important rate-limiting enzyme of citric acid cycle- malate dehydrogenase, which causes insufficient energy supply to the cardiac contractility and relaxation. And what more, we find that the CHF model is not dealt with any lipid intervention, even no high fat diet, the results of proteomics and metabolomics show that visible changes of ApolipoproteinA-I, LDL and VLDL in plasma are seen, myocardial ischaemia can lead to the disorder of lipid metabolism in plasma conversely through glycerolipid metabolism.

Conclusions In present study, we describe a stable and easily reproducible technique to induce CHF model by Ameriod constrictor placing on the LAD. The model closely resembles the CHF in human with respect to structural and functional characteristics which is consistent with the progress of chronic progressive heart failure. NADH-mediated TCA and energy metabolism disorders are the key pathophysiological mechanisms for CHF. Myocardial ischaemia can lead to the disorder of lipid metabolism in turn. Overall, these results provide potential biomarkers for monitoring the therapeutic intervention of CHF and offer important new knowledge for gaining insights into the molecular mechanisms of CHF.