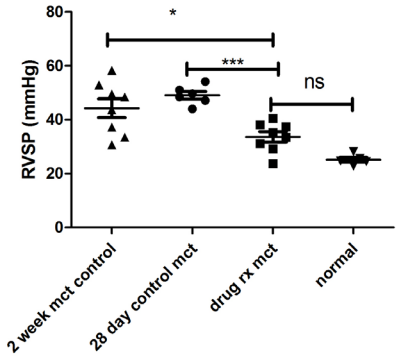
in a prevention strategy, or after 14 days in a treatment strategy. Both prevention and treatment methods were further employed in a second monocrotaline animal model. Haemodynamic measurements (right ventricular systolic pressure RVSP, right ventricular hypertrophy RVH) were performed, and lungs were removed for immunohistochemistry (IHC) and biochemical analysis. Multiplex ELISA was used to analyse cytokine profile in rat serum. Primary PAF were isolated and siRNA techniques employed to knockdown p38MAPKα. IHC for p38 MAPKα was performed on human tissue from patients with idiopathic pulmonary arterial hypertension.

Results siRNA to p38MAPKα inhibited the hypoxic induced proliferation of PAFs. Increased levels of total p38 MAPK activity and increased expression of the alpha isoform was found in the lungs of both chronic hypoxic and MCT animals compared to normal. Using the p38 MAPK inhibitor in the chronic hypoxic and monocrotaline *in vivo* prevention study resulted in lower RVSP and RVH in the drug treated animals ($p<0.005$). In the reversal study of both animal models the inhibitor reversed established pulmonary hypertension as determined by RVSP and RVH ($p<0.001$). Both serum and whole lung levels of IL-6 were lower in the drug treated animals compared to normal. Increased expression of p38 MAPK was observed in lungs from IPAH patients compared to control.

Conclusions Our study suggests p38 MAPK alpha is important in pulmonary hypertension. Inhibition of this pathway can prevent the development of PH and perhaps more clinically relevant, can reverse established disease *in vivo*. Reduction in IL-6 may be a mechanism underlying this process.



Inhibition of p38 MAPKα reverses pulmonary hypertension in monocrotaline animal model

Abstract S36 Figure 1

S37 CAN THE LUNG REVERSE REMODEL? GENE THERAPY FOR CARDIAC FAILURE ALTERS PULMONARY GENE EXPRESSION

doi:10.1136/thoraxjnl-2012-202678.043

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Introduction Irreversible alveolar capillary membrane (ACM) remodelling accompanies chronic heart failure (CHF), contributing to dyspnoea, the predominant symptom that limits quality of life in CHF. Gene therapy is aimed at improving myocardial function in CHF. Restoration of Sarco-endoplasmic reticulum calcium ATPase (SERCA2a) gene expression in animal models of CHF restores haemodynamic parameters towards normal.

The lungs are the direct upstream target of raised left atrial pressure and hence pulmonary venous hypertension. We hypothesised that mechanical strain at the pulmonary micro vasculature associated with PVH up-regulates mediators leading to pulmonary inflammation and ACM remodelling. We have previously shown that gene expression of monocyte chemoattractant protein (MCP)-1, interleukin(IL)-6, endothelin (ET)-1, endothelin receptors (ETR) A and B, and endothelial converting enzyme (ECE) are altered in the lungs of Sprague-Dawley rats at 16 weeks after left coronary artery ligation. We now sought to determine the effect of SERCA2a gene therapy on gene expression of these mediators in the lung.

Methods Gene expression of components of the ET-1 pathway, MCP-1 and IL-6 were investigated in whole lungs of rats at 16 weeks after LCA, at 16 weeks post LCA with tail vein injection of adeno-associated viral (AAV) gene transfer of SERCA2a at 12 weeks post LCA, or sham procedure(n=5 in each group). Lungs were snap frozen in liquid nitrogen, RNA extracted using a modified Trizol and RN easy protocol and gene expression determined in reverse transcribed cDNA by qPCR.

Results Expression of ET-1, ETAR, MCP-1 and IL-6 genes were elevated in heart failure animals and reduced to or towards normal in SERCA2a treated animals. In heart failure animals there was a trend towards reduced ETRB expression which was significantly improved by SERCA2a gene therapy (figure 1). ECE gene expression was not altered by LCA or gene therapy.

Conclusion SERCA2a gene therapy directed at the myocardium in heart failure also affects gene expression in the lungs of CHF animals. This may provide therapeutic benefit to the lungs in addition, reducing inflammation and stimuli associated with structural and vascular remodelling.

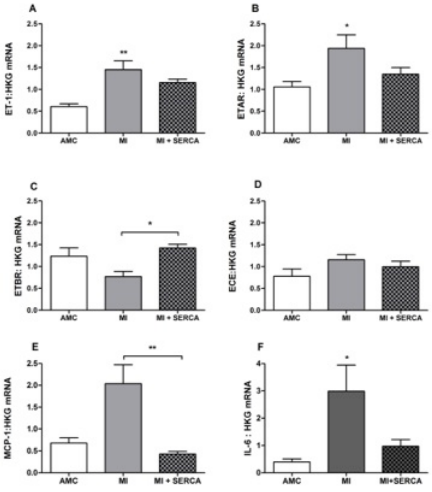

Figure 1 Effect of treatment with SERCA gene therapy on endothelin-1 (ET-1), endothelin receptor (ETR) a & B, endothelin converting enzyme (ECE), Monocyte chemoattractant protein (MCP)-1 and Interleukin (IL)-6 mRNA expression in chronic heart failure in the rat.

Abstract S37 Figure 1

S38 TGF-BETA1 NEGATIVELY REGULATES BMP4 SIGNALLING IN HUMAN PULMONARY ARTERY SMOOTH MUSCLE CELLS VIA A SMAD3-DEPENDENT MECHANISM

doi:10.1136/thoraxjnl-2012-202678.044

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Introduction BMP4 signals via the Smad pathway to induce the expression of the ID dominant-negative basic helix-loop-helix transcription factors (ID1–4) that regulate cell differentiation. We have shown that ID induction is blunted in human pulmonary artery smooth muscle cells (HPASMCs) from pulmonary arterial hypertension (PAH) patients with mutations in the bone morphogenetic type-II receptor (BMPR-II). TGFβ1 is implicated in the pathogenesis of PAH. We therefore examined whether TGFβ1 and BMP4 signalling directly interact in HPASMCs.