

**Introduction** Supplemental oxygen has long been used as a therapeutic agent in the management of ischaemic chest pain, but without a sound scientific basis. We proposed to investigate the effect of high-flow oxygen on coronary physiology, invasively and non-invasively, in those with severe coronary artery disease (CAD).

**Methods** 30 volunteers and 30 patients with severe CAD were allocated to receive high-flow air and oxygen in a random blinded order. They underwent cardiovascular magnetic resonance (CMR) T2\* blood-oxygen level dependent (BOLD) and dynamic contrast-enhanced perfusion imaging. Myocardial blood flow (MBF), perfusion reserve (MPR), first-pass extraction fraction (E), blood volume fraction ( $v_b$ ) and capillary permeability-surface area product (PS) were quantified using bookend T<sub>1</sub> based non-linearity correction and distributed parameter model constrained deconvolution.

Invasive coronary physiology measurements were performed in severe CAD patients (Fractional Flow Reserve <0.75), also randomised to high-flow air and oxygen, using a pressure wire (Radi, St Jude Medical, Uppsala, Sweden). The mean transit time of a room temperature 3–4 ml bolus of saline was recorded at rest and hyperaemic (adenosine) stress for both inspired gases. Resistance Index (RI), Resistance Reserve Index (RRI), Index of Microvascular Resistance (IMR) and Coronary Flow Reserve (CFR) were derived.

**Results** In volunteers the change in BOLD Air-T2\* was  $6.1 \pm 7.5$  ms vs. O<sub>2</sub>-T2\*  $7.8 \pm 8.1$ , P = 0.575. Rest Air-MBF was  $0.88 \pm 0.40$  ml/min/g vs. O<sub>2</sub>-MBF  $0.95 \pm 0.45$ , P = 0.168 and hyperaemic Air-MBF  $3.46 \pm 1.67$  vs. O<sub>2</sub>-MBF  $3.35 \pm 2.05$ , P = 0.821.

In patients, ischaemic region change in BOLD Air-T2\* was  $1.1 \pm 6.6$  ms vs. O<sub>2</sub>-T2\*  $2.7 \pm 8.2$ ms, P = 0.583 compared to Air-T2\*  $11.2 \pm 8.7$  vs. O<sub>2</sub>-T2\*  $2.9 \pm 2.5$ , P = 0.004 in remote myocardium. Remote Air-MBF was  $0.81 \pm 0.19$  vs. O<sub>2</sub>-MBF  $0.76 \pm 0.15$ , P = 0.087 and hyperaemic Air-MBF  $1.31 \pm 0.047$  vs. O<sub>2</sub>-MBF  $1.50 \pm 0.53$ , P = 0.249; whilst ischaemic region Air-MBF was  $0.83 \pm 0.20$  vs. O<sub>2</sub>-MBF  $0.85 \pm 0.28$ , P = 0.725 and hyperaemic Air-MBF  $1.26 \pm 0.055$  vs. O<sub>2</sub>-MBF  $1.35 \pm 0.59$ , P = 0.407. Rest ischaemic Air-E was  $0.69 \pm 0.14$  vs. O<sub>2</sub>-E  $0.66 \pm 0.17$ , P = 0.408 and remote Air-E was  $0.73 \pm 0.13$  vs. O<sub>2</sub>-E  $0.64 \pm 0.15$ , P = 0.044. Ischaemic region Air-PS was  $0.67 \pm 0.38$  ml/min/g vs. O<sub>2</sub>-PS  $0.58 \pm 0.32$ , P = 0.227; whilst remote region Air-PS was  $0.72 \pm 0.38$  vs. O<sub>2</sub>-PS  $0.53 \pm 0.32$ , P = 0.024.

Invasively there was an increase in rest transit time  $0.69 \pm 0.35$  vs.  $0.97 \pm 0.50$ , P = 0.001, resistance index  $51.0 \pm 26.6$  vs.  $75.0 \pm 38.0$ , P < 0.001, coronary flow reserve  $2.21 \pm 1.30$  vs.  $2.90 \pm 1.51$ , P = 0.019 and resistance reserve index  $2.62 \pm 1.37$  vs.  $3.54 \pm 1.74$ , P = 0.006 in the air vs oxygen groups respectively.

**Conclusion** Supplemental high-flow oxygen (and hence hyperoxaemia) results in increased microvascular resistance in patients with severe CAD, demonstrated during invasive coronary physiology studies. We have also shown with novel CMR techniques that, in patients with severe CAD, whilst there is no difference in absolute myocardial blood flow, high-flow supplemental oxygen results

in a reduction in first-pass extraction fraction and capillary permeability-surface area product. This results in a reduction in myocardial oxygenation in the remote, non-ischaemic, myocardium. Supplemental high-flow oxygen should therefore be avoided in patients who are not hypoxic.

## E MICRORNA-140-5P AND SMURF1 REGULATE PULMONARY ARTERIAL HYPERTENSION

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10.1136/heartjnl-2016-309890.224

**Background** Clinical therapies for the treatment of pulmonary arterial hypertension (PAH) target vasoconstriction. However, the proliferative pulmonary vascular remodelling that drives disease persists contributing to significant patient morbidity and mortality. MicroRNA (miR) are short non-coding RNA that mediate post-transcriptional regulation of mRNA targets. We hypothesise that dysregulation of miR leads to de-repression of cellular targets central to disease pathogenesis.

**Objective** To identify dysregulated circulating miR in patients with PAH, determine their phenotypic effect using *in vitro* and *in vivo* models and identify key mechanistic regulators that may represent novel therapeutic targets.

**Methods and results** Expression of miR-140-5p was reduced in whole blood samples from patients with PAH. Reduced expression of miR-140-5p at the time of diagnosis identified patients with adverse clinical characteristics. Transfection with miR-140-5p inhibitor resulted in increased proliferation PSMC and de-repression of key targets. Nebulised delivery of miR-140-5p mimic attenuated progression of established PAH in the SuHx rat model. Network and pathway analysis identified SMAD Specific E3 Ubiquitin Protein Ligase 1 (SMURF1) as a key miR-140-5p target. Whole blood mRNA and pulmonary vascular immunoreactivity of SMURF1 was increased in patients with PAH implicating SMURF1 in the pathology of human disease. Direct regulation of SMURF1 by miR-140-5p was demonstrated in-vitro by 3'UTR luciferase activity. Both miR-140-5p mimic and SMURF1 siRNA increased BMP response element activity identifying SMURF1 as a key negative regulator of BMP signalling in PSMC. Genetic ablation of SMURF1 in C57BL6 mice conferred allele dependent protection from SuHx induced PAH.

**Conclusions** These studies suggest that miR-140 and SMURF1 are key regulators of BMP signalling and disease pathology in PAH and highlight SMURF1 as a potential novel therapeutic target.