Sca1+ cells mapped to the proliferation-associated path and positioned prior to cells expressing cell cycle markers in pseudotime, supporting the hypothesis that Sca1+ cells represent a primed stage.

As VSMCs expand clonally in vitro as in vivo, we conducted functional analysis of SCA1+ VSMCs using an in vitro model of clonal proliferation. While proliferation was not restricted to SCA1+ cells, attachment and clonal expansion of SCA1+ cells was increased and temporally advanced compared to SCA1- VSMCs. As genes differentially expressed along the proliferation associated path were also associated with the GO terms of cytoskeletal regulation and migration, we explored functional differences of SCA1+ VSMCs via imaging flow cytometry of F-actin and ROCK1. SCA1+ VSMCs from healthy vessels had a marked reduction in both proteins, suggestive of a less contractile and more migratory phenotype, in line with the hypothesis that these cells are primed.

These findings cannot be directly translated to human disease as a human SCA1 orthologue is unknown. Therefore, we conducted scRNA-seq of the healthy human aorta, with the aim of identifying an equivalent population. Single-cell profiling of the human aorta also revealed a gradient of VSMC phenotypes, and trajectory analysis indicated remarkably similar gene expression changes to those that occur in the mouse injury model.

Our findings elucidate mechanisms underlying selective VSMC activation by characterizing the associated transcriptional signature and suggest that phenotypic switching is advanced in VSMCs that are 'primed' in a cell-intrinsic manner. Analysis of human scRNA-seq data indicates that this primed population is relevant in disease, and that functional testing of identified candidate drivers can enable targeted treatments of VSMC dysregulation in atherosclerosis.

Conflict of Interest none

Young investigators award

A C-REL DRIVES ATHEROSCLEROSIS AT SITES OF DISTURBED BLOOD FLOW

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Atherosclerosis is an inflammatory disease that develops preferentially at bends and branches of the vasculature exposed to disturbed flow and low shear stress (LSS). These mechanical conditions modify endothelial cell (EC) physiology by regulating proliferation, inflammation and other fundamental processes. Shear stress alters multiple transcriptional programs, including those regulated by the NF-κB family of transcription factors. Although some members of the NF-κB pathway are known to respond to shear, the influence of this haemodynamic force on the c-Rel NF-κB subunit and its role in atherogenesis are still unknown.

The expression and function of c-Rel was studied using human umbilical vein EC (HUVEC) and human coronary artery EC (HCAEC) exposed to LSS or high shear stress (HSS) using *in vitro* flow systems. Western blotting revealed that LSS strongly induced c-Rel expression in HUVEC and HCAEC. Gene silencing coupled to transcriptome profiling demonstrated that c-Rel promotes pathogenic EC processes (inflammation, proliferation) via induction of p38 MAP kinase and non-canonical p100/p52 NF-κB signalling.

Consistently, immunofluorescent *en face* staining of murine aortas revealed a striking enrichment of c-Rel at LSS regions compared to HSS regions. Genetic deletion of c-Rel, either specifically in EC or in the whole body, rescued EC function, reduced arterial inflammation and decreased atherosclerotic lesion area in hypercholesterolemic AAV-PCSK9-treated mice, indicating that c-Rel promotes atherosclerosis by inducing EC pathological changes.

Our data demonstrate that c-Rel promotes EC pathophysiological changes at LSS regions and is a driver of atherosclerosis via activation of MAPK and non-canonical NF-κB pathways. These data identify c-Rel as a novel therapeutic target to reduce atherosclerosis.

B SAFETY AND OUTCOMES OF A HIGH INTENSITY EXERCISE PROGRAMME IN YOUNG PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY: THE SAFE-HCM STUDY

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Background Moderate intensity exercise training in older patients with hypertrophic cardiomyopathy (HCM) can improve functional capacity, without significant harm. However, younger patients are attracted to high intensity training (HIT) regimes.

Purpose To assess the feasibility, safety and outcomes of an individually tailored, HIT programme in young patients with HCM, and whether observed benefits are sustained at 6 months.

Methods Eighty patients with HCM (45.7y±8.6) underwent baseline clinical and psychological assessment. Individuals were randomised to a 12-week HIT programme (n=40) or usual care (n=40). Baseline evaluation was repeated at 12 weeks (T12). Feasibility, safety, health and psychological benefits were assessed. At 12-weeks individuals were encouraged to continue with the frequency and intensity of physical activity (PA) achieved at the end of the cardiac rehabilitation programme. Participants in the exercise arm were invited to follow-up at 6 months (T6m).

Results The majority (83%) of participants completed the 12-week study. Reasons for refusal included travel, work and family commitments. Resource requirements were similar to other programmes. All individuals felt supported, more confident to exercise, and found educational materials clear and informative. At T12 there was no significant difference between groups in the composite arrhythmia safety outcome (p=0.99). There was no significant difference between groups in episodes of non-sustained ventricular tachycardia (NSVT) (p=0.573) or ectopic burden (p=0.729). The indices of exercise capacity were significantly improved in the exercise compared to the control group; peak VO2 (+3.7 ml/kg/min [CI 1.1,6.3], p=0.006), VO2/kg at anaerobic threshold (VO2/

kgAT) (+2.44 ml/kg/min [CI 0.6,4.2], p=0.009), time to AT (+115s [CI 54.3,175.9], p<0.001) and exercise time (max ET) (+108s [CI 33.7,182.2], p=0.005). The exercise group also demonstrated greater reduction in systolic BP (-7.3 mmHg [CI -11.7,-2.8], p=0.002), BMI (-0.8 kg/m^2 [CI-1.1,-0.4], p<0.001), anxiety (-2.6 [CI-3.6,-1.6], p≤0.001) and depression (-1.1 [CI -2.0,-0.2], p=0.015) scores. At T6m patient reported exercise adherence was comparable to baseline PA, in 33/34 of the exercise group attending for follow up. Most exercise gains dissipated with the exception of time to AT (p=0.002), max ET (p=0.003), VO2/kgAT (p=0.04) and anxiety score (p<0.001). There were no sustained episodes of atrial or ventricular arrhythmias. The incidence of NSVT did not differ between time points (p=0.09).

Conclusion A 12-week HIT programme in young patients with HCM offers considerable gains in fitness and psychological outcomes, with no increase in arrhythmic burden. Further research is still required to assess the long-term safety of high intensity exercise in the HCM population. At T6m exercise levels as well as most physiological adaptations and health benefits returned to baseline, as seen in other studies when formal participation in an exercise programme comes to an end. This highlights the importance of the implementation of strategies to encourage ongoing engagement in PA. Potential solutions include identification of barriers to exercise, as well as adoption of novel tele-rehabilitation approaches.

C IMPAIRED MYOCARDIAL ENERGETICS AS THE BASIS FOR EXERCISE-INDUCED PULMONARY CONGESTION IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Background Abnormal cardiac mitochondrial function and energetics are implicated in the pathogenesis of heart failure with preserved ejection fraction (HFpEF). Transient pulmonary congestion during exercise is emerging as an important determinant of reduced exercise capacity and symptoms in HFpEF. We sought to determine if an abnormal cardiac energetic state underpins this process.

Methods We recruited 42 patients across the spectrum of diastolic dysfunction and HFpEF (healthy controls n=10, type 2 diabetes (T2DM) n=9, HFpEF n=14, and severe diastolic dysfunction due to cardiac amyloidosis n=9). Cardiac energetics were measured using phosphorus spectroscopy to define the myocardial phosphocreatine to adenosine triphosphate ratio (PCr/ATP). Cardiac function was assessed by cardiovascular magnetic resonance (CMR) cine imaging and echocardiography, and pulmonary congestion using MR proton density mapping. Studies were performed at rest and during submaximal exercise using an MRI-ergometer.

Results Paralleling the stepwise decline in diastolic function across the groups (E/e' ratio p<0.001) was an increase in NT-pro BNP (p<0.001) and a reduction in PCr/ATP (control 2.00 [1.86, 2.15], T2DM 1.71 [1.61, 1.91], HFpEF 1.66 [1.44, 1.89], cardiac amyloidosis 1.30 [1.16, 1.53], p<0.001). During 20W exercise, reduced left ventricular (LV) diastolic filling rate (r=0.41, p=0.008), left atrial (LA) dilatation (r=-0.35, p=0.03), reduced right ventricular (RV) contractile reserve (RV ejection fraction change r=0.46, p=0.003), reduced right ventricular-pulmonary arterial (RV-PA) coupling (r=0.36, p=0.02) and right atrial dilatation (r=-0.68, p<0.001) were all linked to this reduction in PCr/ATP. Along with these changes, proton-density mapping revealed transient pulmonary congestion in patients with HFpEF (+4.4% [0.5, 6.4]) and cardiac amyloidosis (+6.4% [3.3, 10]), which was not seen in healthy controls (0.25% [-1.8, 3.1]) or T2DM without HFpEF (0.8% [-1.7, 1.9]). Importantly, the development of exercise-induced pulmonary congestion was associated with reduced PCr/ATP (r=-0.36, p=0.02).

Conclusions A gradient of myocardial energetic deficit exists across the spectrum of HFpEF. This energetic deficit is related to markedly abnormal exercise responses in all four cardiac chambers, which leads to detectable pulmonary congestion. The findings support an energetic basis for transient exercise-induced pulmonary congestion in HFpEF.

D RADIOTRANSCRIPTOMIC ANALYSIS OF PERIVASCULAR ADIPOSE TISSUE QUANTIFIES VASCULAR INFLAMMATION IN COVID-19 FROM ROUTINE CT ANGIOGRAMS: *STRATIFICATION OF "NEW UK VARIANT" INFECTION AND PREDICTION OF IN-HOSPITAL OUTCOMES*

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Background Evidence suggests that adverse outcomes in COVID-19 may be driven by a cytokine-induced vascular inflammatory response, caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).

Aim We aimed to develop a non-invasive method for quantifying cytokine-driven vascular inflammation in patients with acute COVID-19 infection that could allow risk stratification.

Methods We developed a platform for rapid development of novel imaging biomarkers of vascular inflammation, by applying quantitative radiotranscriptomics to images from standard Computed Tomography Angiography (CTA). We used this platform to train a radiotranscriptomic signature (C19-RS) from the perivascular space around the aorta and the internal mammary artery, visualized in routine chest CTAs, to best describe cytokine-driven vascular inflammation, defined using transcriptomic profiles from RNA sequencing data from human arterial biopsies. This signature was tested externally in 435 clinically indicated CT pulmonary angiograms (CTPAs) from patients with or without COVID-19 from 3 different geographical regions.