

Abstracts

Cardiac magnetic resonance imaging (MRI), vessel perfusion, vascular casting, immunohistology and qPCR were used to evaluate cardiovascular changes after endoglin knockdown.

Results Loss of endoglin leads to a massively enlarged heart and cardiomyocyte hypertrophy. These changes occur within 5 weeks of endoglin depletion. Cardiac output initially increases, but then the ejection fraction starts to fall, progressing to high output heart failure (HOHF) associated with increased cardiac expression of brain natriuretic peptide, atrial natriuretic peptide and alpha-skeletal actin. As HOHF may result from arteriovenous malformations (AVMs) or from anaemia, we first tested for these phenotypes in Eng-iKO^e mice. However, we did not detect any AVMs in major organs or found evidence of anaemia to account for the rapid increase in cardiac output. On the other hand, we did observe defects in regulation of vascular tone that are currently under investigation.

Conclusion These data describe a novel phenotype and highlight the importance of endothelial endoglin in the maintenance of cardiac structure and function.

Introduction Current intervention criteria for the thoracic aorta concentrate on size. However, the complexity of aortic disease is not fully exposed by aortic dimensions alone, and morbidity or mortality can occur before intervention thresholds are reached. Computational fluid dynamics (CFD) is a non-invasive approach to quantify haemodynamics in assessment of aneurysms and rupture risk.

Wall shear stress (WSS) measuring viscous shearing forces on the endothelium, and oscillatory shear index (OSI) measuring disturbed flow, are a pathophysiological stimulus to gene expression, extracellular-matrix remodelling, and aortic wall thinning.

We aimed to evaluate the efficacy of a new patient-specific approach to CFD of the thoracic aorta, and its functional and haemodynamic indices in assessment of aortic pathology.

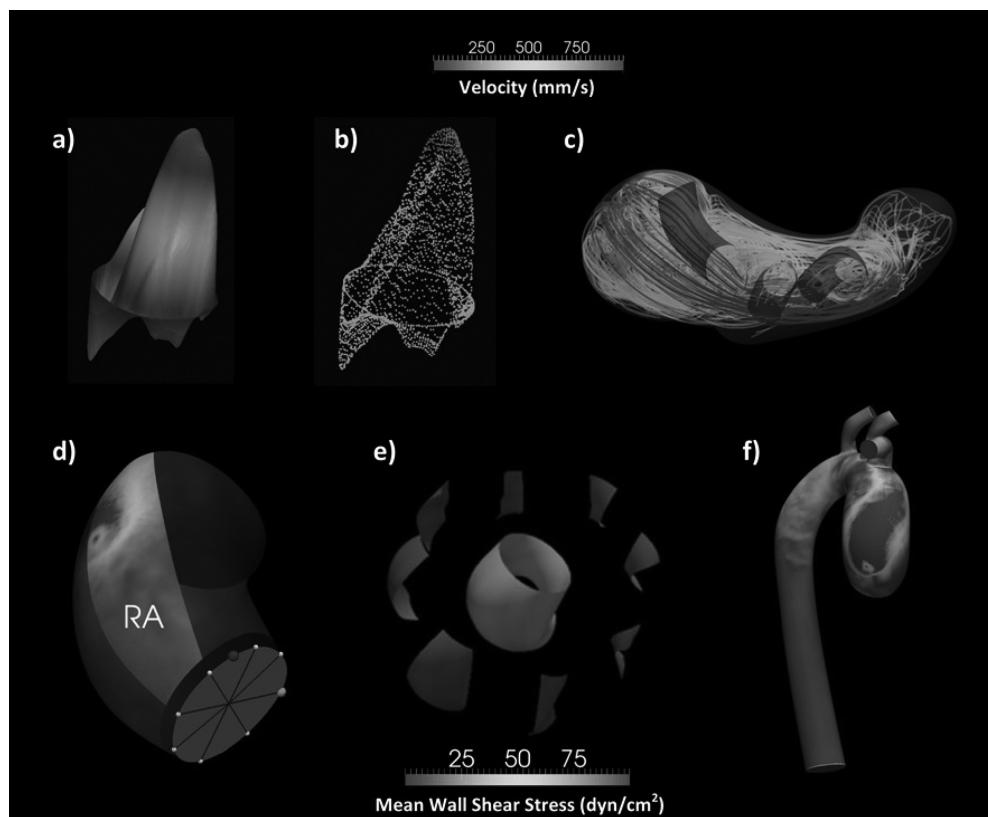
Methods 45 subjects were divided into 5 groups: Volunteers, AR-TAV, AS-TAV, AS-BAV(RL), AS-BAV(RN), where AR=aortic regurgitation, AS=aortic stenosis, TAV=tricuspid aortic valve, BAV=bicuspid aortic valve, RL=right-left cusp fusion, RN=right-non cusp fusion. Subjects underwent magnetic resonance angiography, with phase-contrast MRI at the sino-tubular junction to define patient-specific inflow velocity profiles. Three-dimensional aorta models were constructed from MRA data and discretized to form a finite element mesh. The 3D velocity profile from PC-MRI was mapped onto the inflow mesh, allowing prescription of patient-specific inflow boundary conditions. Blood pressure, cardiac output, and cross-sectional area of each vessel were processed to assign outflow boundary conditions to arch vessels and descending aorta.

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COMPUTATIONAL FLUID DYNAMICS – A PATIENT-SPECIFIC ASSESSMENT OF THE THORACIC AORTA

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Abstract 183 Figure 1 a) Patient-specific inflow velocity profile above the aortic valve; b) red dots depict top 15% of maximal velocity; c) velocity streamlines showing high velocity jet spiralling around the arch; d) and e) division of the ascending aorta into 8 anatomical sectors for sub-analysis; f) wall shear stress map showing high levels of shear stress in the greater curvature

Results CFD enabled measurement of WSS throughout the thoracic aorta. WSS was significantly elevated in aortic stenosis, highest in AS-BAV(RN) (mean WSS=37.1 ± 4.0 dyn/cm², compared to 19.9 ± 1.9 dyn/cm² for AS-BAV(RL), 25.7 ± 1.2 dyn/cm² in AS-TAV, 12.3 ± 3.4 dyn/cm² in AR-TAV, and 9.9 ± 5.4 dyn/cm² in healthy volunteers, p < 0.05). Aortic stenosis patients displayed asymmetrical WSS distributions, the greater curvature experiencing the highest WSS. OSI was lower in bicuspid right-non fusion (p < 0.05).

Eccentricity of flow was higher in bicuspid patients (Flow_{asymmetry}= 84.1 ± 5.4%, compared to 28.1 ± 21.5 for tricuspid, p < 0.05). Helicity of flow was assessed by the Helical Flow Index (HFI), which was higher in bicuspid right-left fusion (HFI_{systole}= 0.39 ± 0.04, compared to 0.28 ± 0.03 for all others, p < 0.05).

Conclusions BAV displays eccentric flow with high helicity. Presence of AS, particularly in BAV-RN led to higher WSS and lower OSI in the greater curvature of the ascending aorta. Patient-specific CFD provides non-invasive functional assessment of the thoracic aorta, and enables development of a personalized approach to diagnosis and management of aortic disease beyond traditional guidelines.

184 CARDIOPROTECTIVE ROLE OF HEXARELIN IN A MOUSE MODEL OF MYOCARDIAL INFARCTION

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This study aimed to determine whether Hexarelin (HEX), a synthetic growth hormone secretagogue, preserves cardiac function and attenuates remodelling in mouse models of myocardial infarction.

Myocardial ischemia was induced by ligation of the left descending coronary artery in C57BL/6J mice followed by HEX (n = 16) or vehicle (VEH) (n = 16) administration at 0.3 mg/kg/day for 21 days. Treated and Sham mice were subjected to magnetic resonance imaging using a T₁-weighted late gadolinium enhancement sequence (LGE) at 9.4 Tesla (T) to measure left ventricular (LV) function, mass and infarct size at 24hrs and 21 days. HEX mice demonstrated a significant improvement (P < 0.05) in ejection fraction (EF) compared with VEH at 24 h (42% vs 34% respectively) and at 21 days (49% vs 36%).

A significant decrease in LV mass, interstitial collagen and collagen concentration was demonstrated after 21 days within the HEX group. This was accompanied by a decrease in TGF- β 1 and α -SMA and increase in MMP-13 in the HEX group. Furthermore, heart rate variability analysis demonstrated that HEX treatment shifted the balance of autonomic nervous activity towards a parasympathetic predominance, evidenced by a smaller low/high-frequency power ratio and increased normalised high frequency power. This was combined with a significant decrease in Troponin-I, IL1- β and TNF- α levels with HEX treatment compared with VEH treatment after 24 h.

These results demonstrate that GHS may preserve ventricular function and favourably remodel the process of fibrotic healing in mouse models of myocardial infarction; this may be through anti-inflammatory mechanisms.

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GLYCOPROTEOMICS REVEALS DECORIN PEPTIDES WITH ANTI-MYOSTATIN ACTIVITY IN HUMAN ATRIAL FIBRILLATION

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Background Myocardial fibrosis is a feature of many cardiac diseases. We used proteomics to profile glycoproteins in the human cardiac extracellular matrix (ECM).

Methods and Results Atrial specimens were analysed by mass spectrometry after extraction of ECM proteins and enrichment for glycoproteins or glycopeptides. Out of all ECM proteins identified, the small leucine-rich proteoglycan decorin was found to be the most fragmented. Within its protein core, eighteen different cleavage sites were identified. In contrast, no cleavage was observed for biglycan, the most closely related proteoglycan. Decorin processing differed between human ventricles and atria and was altered in disease. The C-terminus of decorin, important for the interaction with connective tissue growth factor, was predominantly detected in ventricles compared to atria. In contrast, atrial appendages from patients in persistent atrial fibrillation had higher levels of full-length decorin but also harboured a cleavage site that was not found in atrial appendages from patients in sinus rhythm. This cleavage site preceded the N-terminal domain of decorin that controls muscle growth by altering the binding capacity for myostatin. Myostatin expression was decreased in atrial appendages of patients with persistent atrial fibrillation and hearts of decorin null mice. A synthetic peptide corresponding to this decorin region dose-dependently inhibited the response to myostatin in cardiac myocytes and in perfused mouse hearts.

Conclusion This proteomics study is the first to analyse the human cardiac ECM. Novel processed forms of decorin protein core, uncovered in human atrial appendages can regulate the local bioavailability of anti-hypertrophic and pro-fibrotic growth factors.

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PLATELETS AS KEY REGULATORS OF FIBRIN-CLOT ARCHITECTURE AS ASSESSED BY FRACTAL ANALYSIS OF VISCOELASTIC PROPERTIES; EFFECTS OF STANDARD ANTI-PLATELET THERAPIES

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Introduction Platelets are critical drivers of thrombus formation with high on-treatment platelet reactivity despite dual