ischaemia protects the heart against progression to heart failure. Whether inhibition of miR-34a protects the female heart is unknown. In the present study, we examined the effect of silencing miR-34a in males and females in a mouse model of dilated cardiomyopathy (DCM).

Methods: Non-transgenic and DCM male and female mice (n=4-8/group) were administered with a locked nucleic acid-modified oligonucleotide (LNA-control or LNA-antimiR-34a) at 6-7 weeks of age when the model displayed cardiac dysfunction. Cardiac function was assessed by echocardiography before and six weeks after treatment. Molecular/histological analyses were performed on heart tissue.

Results: Untreated male and female DCM mice displayed cardiac enlargement, lung congestion and increased expression of cardiac stress genes. LNA-antimiR-34a provided more protection in female DCM mice than male DCM mice. Disease prevention in LNA-antimiR-34a treated DCM female mice was characterised by attenuated heart enlargement and lung congestion, lower expression of cardiac stress genes (B-type natriuretic peptide, β-myosin heavy chain, collagen gene expression), and better cardiac function (15% higher fractional shortening vs. untreated, n=6-7/group, $p<0.05$). Sex- and treatment-dependent regulation of miRNAs was identified in the diseased heart, and may explain the differential response of males and females.

Conclusion: These studies highlight the importance of examining the effect of miRNA-based drugs in cardiac disease settings in males and females.

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Disease Insight Using Papillary Muscles: A Cardiovascular Magnetic Resonance Study

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Hypertrophy of left ventricular papillary muscles (LVPM) can occur, particularly in Fabry disease (FD), and could aid in differentiating the aetiology of left ventricular hypertrophy (LVH).

Aim: To characterise LVPM mass across a range of heart diseases with LVH; to gain further insight into the mechanisms of LVPM hypertrophy in FD using T1 mapping.

Methods: 478 cases were retrospectively recruited: 125 FD, 85 hypertrophic cardiomyopathy (HCM), 67 amyloid, 82 aortic stenosis (AS), 40 hypertension, 79 controls. LVPM contribution to LVM was measured using CMR manual contouring methods. T1 values (septal and LVPM) were quantified using ShMOLLI maps in FD and controls.

Results: In LVH+ve cohorts: LVPM contribution to LVM was significantly increased in FD and HCM, compared to all other groups (FD 13±3%, HCM 10±3%, amyloid 8±2%, AS 7±3%, hypertension 7±2%, controls 7±1%; $p<0.001$). In LVH-ve cohorts: only FD had significantly increased LVPM (11±3%; $p<0.001$). In FD there was concordant septal and LVPM T1. LVH+ve FD: when septal T1 was low, LVPM T1 was low in 90%. LVH-ve FD: when septal T1 was normal, LVPM T1 was normal in 70% (indicating no detectable storage), and when septal T1 was low, 75% had low LVPM T1 (indicating storage). LVPM hypertrophy was similar in low and normal septal T1 subgroups (11±3% vs 10±3%, $p=0.08$).

Conclusion: Disproportionate hypertrophy of LVPMs in LVH+ve hearts is seen in FD and HCM. This phenomenon also occurs in LVH-ve FD. Low T1 is not always present in FD LVPM hypertrophy, implying additional mechanisms activating hypertrophy signalling pathways.

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Disparate Functional Responses to β-adrenergic and Ischaemic Challenge in Male and Female Hypertrophic Cardiomyocytes

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Cardiac hypertrophy is the most potent cardiovascular risk factor after age, with relative mortality risk greater in women. The cognate issue of whether ischaemia coincident with hypertrophic co-morbidity has differing gender aetiology/outcome has not been addressed. We used a novel polygenic model of hypertrophy to examine male/female cellular stress responses in normal and hypertrophic cardiomyocytes. A range of cardiomyocyte morphologic and electro-mechanical functional studies were performed using microfluorimetric techniques. Hypertrophic females exhibited pronounced cardiac/cardiomyocyte enlargement, equivalent to males. Under basal conditions, a lower twitch amplitude in female myocytes was prominent in normal but not hypertrophic myocytes. The cardiomyocyte Ca^{2+} responses to β-adrenergic challenge differed in hypertrophic male/female cardiomyocytes (amplitude Ca^{2+} %basal; male hypertrophy 202±12% vs female hypertrophy 150±14%, n=9-11 cells from 4-5 hearts/group, $p<0.05$), with the accentuated response in males abrogated in females – even while contractile responses were similar. In simulated ischaemia, a marked and selective elevation of end-ischaemia Ca^{2+} in normal female myocytes was completely suppressed in hypertrophic female myocytes – even though all groups demonstrated similar shifts in myocyte contractile performance. After 30mins

simulated reperfusion, the Ca^{2+} desensitisation characterising the male response was distinctively absent in female cardiomyocytes (Ca^{2+} at 50% relaxation, F360/380; male control 1.96±0.12, female control 1.96±0.17, male hypertrophy 4.14±1.43, female hypertrophy 1.74±0.16, n=5-8 cells from 4-6 hearts/group, $p<0.05$ sex-strain interaction). Our data demonstrate that cardiac hypertrophy produces dramatically different stress-induced patho-phenotypes in female and male–origin cardiomyocytes. These findings have implications for sex-specific refinement of reperfusion therapeutic interventions.

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Dynamic Left Ventricular Outflow Tract Obstruction with Intracardiac Pressure Tracings - A Case Study

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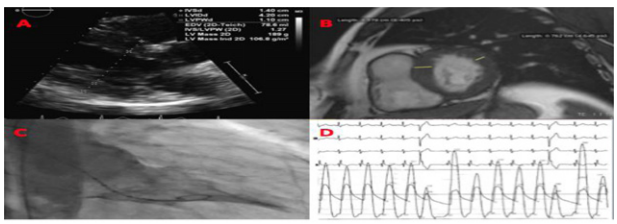
Mr VZ is a 69 year old male who presents with recurrent syncopal episodes. He sustained a facial fracture from one of those episodes and he also described some chest pain on exertion. His background includes hypertension, COPD and GORD. An echocardiogram done revealed asymmetrical septal hypertrophy with systolic anterior motion of the mitral valve. An MRI confirmed this with a septal measurement of 14 mm and an RV biopsy performed revealed myocyte hypertrophy. A left heart study revealed a significant gradient across the left ventricular outflow tract with no gradient across the aortic valve. He also underwent an electrophysiology study, which was negative for inducible VT but revealed a marked drop in systolic blood pressure with rapid atrial and ventricular pacing. A dual chamber PPM was implanted and his beta-blocker dose uptitrated. Conclusion: Dynamic LVOT obstruction can be worsened by decreased preload and tachycardia,and can cause syncope.



A and B: Transthoracic echocardiogram and MRI demonstrating asymmetrical septal hypertrophy. **C:** Left ventriculogram with apical obliteration of LV. **D:** Intracardiac pressure tracing demonstrating LVOT gradient and Brockenbrough phenomenon

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Follistatin-like 3 Is Associated with Increased Left Ventricular Mass in an Ageing Population

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Background: The physiologic changes of human cardiac ageing include left ventricular hypertrophy (LVH), cardiac fibrosis that can subsequently lead to the development of systolic, diastolic heart failure, and atrial fibrillation. To date, it remains completely unknown which biochemical factor(s) that modulate ageing-associated changes in cardiovascular physiology. Follistatin-like 3 (FSTL-3) binds to activin A, and has been shown to contribute to cardiac remodelling, and hypertrophy. In a normal ageing population, we sought to examine whether circulating FSTL-3 level is a predictor of increased left ventricular mass.

Methods and Results: In 67 patients, age (68±6 yrs), without existing cardiovascular disease or previous antihypertensive therapy were studied. Left ventricular (LV) volumes and mass indexed to height (2.7) (LVMI) were calculated from transthoracic echocardiography. Despite the absence of clinically-defined LVH, there was a significant relationship between high FSTL-3 levels and LV mass ($R=0.5$, $p<0.001$, Figure 1). High FSTL-3 levels is also associated with age ($R=0.3$, $p<0.05$), BMI ($R=0.4$, $p<0.01$), and increased C-reactive protein (CRP) ($R=0.3$, $p<0.05$), while systolic BP (SBP) was not a significant predictor of increased FSTL-3 ($R=0.2$, $p=0.1$). On backward multiple linear regression indexed for age, gender, BMI, renal function, CRP, and SBP; increased LV mass remained a predictor of increased FSTL-3 levels ($\beta=0.3$, $p=0.007$).

Conclusions: In this ageing normotensive population free of established cardiovascular disease, FSTL-3 appears to play a role in modulating early ageing-associated LVH development prior to any significant functional changes.

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Follistatin-like 3 Predicts Aortic Root Enlargement in Patients with Bicuspid Aortic Valve

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Background: Bicuspid aortic valve (BAV) is the most common congenital heart defect, affecting up to 2% of the population. One of the major consequences of BAV is the development of progressive dilatation of the aortic root and