Mechanoregulation of Cardiovascular Physiology in Marfan Syndrome

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Abstract

Marfan Syndrome (MFS) is a common systemic connective tissue disorder caused by mutations that alter the architecture or decrease the formation of the extracellular matrix (ECM) protein fibrillin-1, a component of microfibrils and elastic fibers. Mutations in Fbn1 impair the structural integrity and cell-ECM interaction leading to maladaptive tissue remodeling. MFS patients present with multiple cardiovascular (CV) diseases including thoracic aortic aneurysm (TAA) with dissection (TAAD) and dilated cardiomyopathy (DCM) (Fig 1). We have previously described a primary DCM phenotype in a progressively severe mouse model of MFS. Despite appropriate surgical intervention, patients with MFS may suffer perioperative and postoperative heart failure suggestive of a sub-clinical phenotype at baseline. To date, there is no adequate mouse model that replicates the post-operative cardiac physiology in patients with MFS that have undergone an ascending aortic repair. We propose to model the post-operative surgical physiology with use of a transverse aortic constriction (TAC) (Fig 2) in a subclinical mouse model of MFS to better replicate the acute increase in left ventricular afterload and reduced ascending aortic compliance

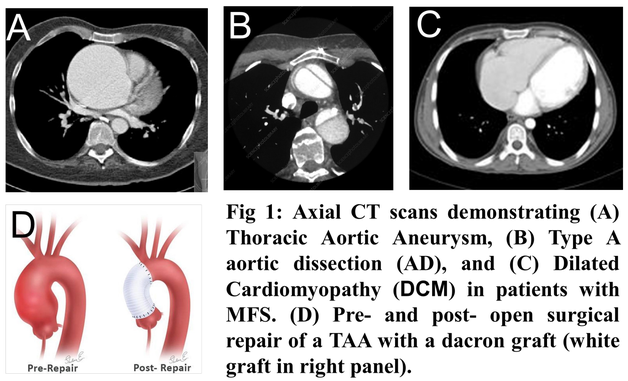
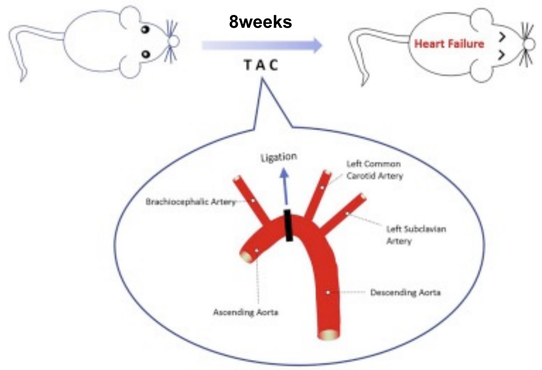


Fig 1: Axial CT scans demonstrating (A) Thoracic Aortic Aneurysm, (B) Type A aortic dissection (AD), and (C) Dilated Cardiomyopathy (DCM) in patients with MFS. (D) Pre- and post- open surgical repair of a TAA with a dacron graft (white graft in right panel).

Transverse aortic constriction (TAC) model

Fig 2 (below): Transverse aortic constriction or sham surgery was performed on 8-week-old WT and Fbn1$^{+/-}$ male and female mice. Aortic constriction was achieved using a 27 guage needle as a guide for 70% aortic arch stenosis. Following recovery, mice underwent transthoracic echo at 4- and 8-weeks post-operation.



Baseline Cardiac Function in Subclinical Model of Marfan Syndrome

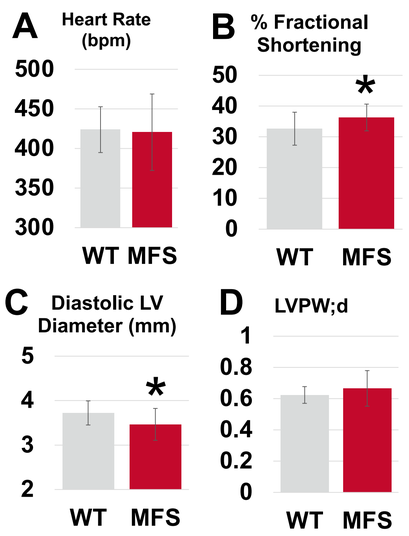


Fig 3 (Left): Transthoracic echocardiographic (TTE) evaluation of left ventricular function in 2-month-old wild type (WT; n = 16; 8 males) and Fbn1$^{+/-}$ mice (MFS; n = 14; 6 males). Data displayed as average +/- StDev. Asterix (*) marks p-value < 0.05 by two-tailed T-test. Heart rate and left ventricular posterior wall in diastole (LVPW;d) were not statistically different between groups. MFS mice demonstrated increased percent fractional shortening as well as ejection fraction (data not shown) and reduced left ventricular diameter in diastole.

Postoperative TAC

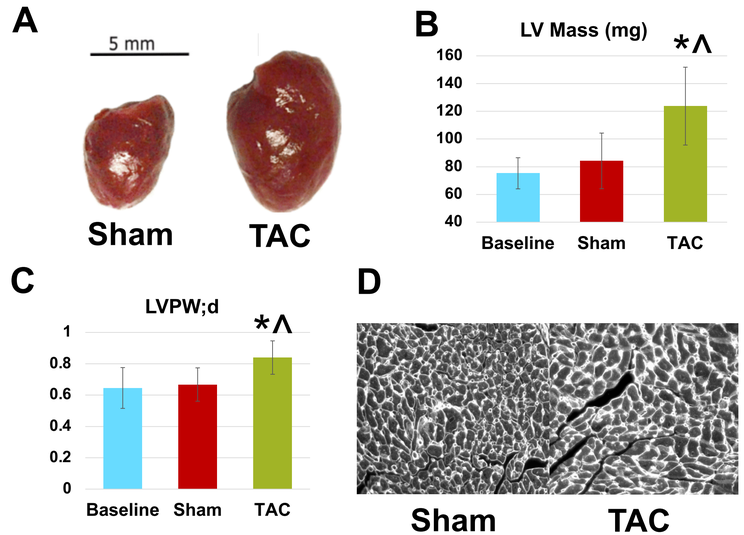


Fig 4 (above): MFS mice underwent sham (sternotomy) or TAC and were evaluated at 8 weeks post-procedure. (A) TAC mice demonstrated increased heart size and left ventricular weight (B). Data displayed as average +/- StDev. (C) Left ventricular posterior wall was also thicker in TAC but not sham mice. (D) Cross-sectional imaging of myocardial response to TAC. * marks p-value < 0.05 by two-tailed T-test vs, sham, ^ marks p-value < 0.05 vs. baseline, n = 5 per TAC and sham.

Conclusion and future direction

- Baseline Fbn1$^{+/-}$ mice demonstrate a subclinical hyperdynamic cardiac physiology compared to WT littermates which may be a precursor to the dilated cardiomyopathy seen in the more severe MFS models.
- Mini-thoracotomy with transverse aortic constriction (TAC) in 2-month-old mice is a viable surgical mechanism to increase left ventricular afterload within 8 weeks post procedure.
- Post-op TAC mice demonstrate increased heart mass and left ventricular posterior wall thickness.
- Ongoing studies are necessary to better understand the long-term consequences of acute increases in LV afterload

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