

## Determining the Threshold for Protective Effects of Aerobic Exercise on Aortic Structure in a Mouse Model of Marfan Syndrome Associated Aortic Aneurysm

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**Abstract :** Aortic aneurysm is the leading cause of death in Marfan syndrome (MFS), a connective tissue disorder caused by mutations in fibrillin-1 gene (FBN1). MFS aneurysm is characterized by weakening of the aortic wall due to elastin fibers fragmentation and disorganization. The above-average height and distinct physical features make young adults with MFS desirable candidates for competitive sports; but little is known about the exercise limit at which they will be at risk for aortic rupture. On the other hand, aerobic cardiovascular exercise has been shown to have protective effects on the heart and aorta. We have previously reported that mild aerobic exercise can delay the formation of aortic aneurysm in a mouse model of MFS. In this study, we aimed to investigate the effects of various levels of exercise intensity on the progression of aortic aneurysm in the mouse model. Starting at 4 weeks of age, we subjected control and MFS mice to different levels of exercise intensity (8m/min, 10m/min, 15m/min, and 20m/min, corresponding to 55%, 65%, 75%, and 85% of VO<sub>2</sub> max, respectively) on a treadmill for 30 minutes per day, five days a week for the duration of the study. At 24 weeks of age, aortic tissue were isolated and subjected to structural and functional studies using histology and wire myography in order to evaluate the effects of different exercise routines on elastin fragmentation and organization and aortic wall elasticity/stiffness. Our data shows that exercise training at the intensity levels between 55%-75% significantly reduces elastin fragmentation and disorganization, with less recovery observed in 85% MFS group. The reversibility of elasticity was also significantly restored in MFS mice subjected to 55%-75% intensity; however, the recovery was less pronounced in MFS mice subjected to 85% intensity. Furthermore, our data shows that smooth muscle cells (SMCs) contractility in response to vasoconstrictor agent phenylephrine (100nM) is significantly reduced in MFS aorta ( $54.84 \pm 1.63$  mN/mm<sup>2</sup>) as compared to control ( $95.85 \pm 3.04$  mN/mm<sup>2</sup>). At 55% of intensity, exercise did not rescue SMCs contraction ( $63.45 \pm 1.70$  mN/mm<sup>2</sup>), while at higher intensity levels, SMCs contraction in response to phenylephrine was restored to levels similar to control aorta [65% ( $81.88 \pm 4.57$  mN/mm<sup>2</sup>), 75% ( $86.22 \pm 3.84$  mN/mm<sup>2</sup>), and 85% ( $83.91 \pm 5.42$  mN/mm<sup>2</sup>)]. This study provides the first time evidence that high intensity exercise (e.g. 85%) may not provide the most beneficial effects on aortic function (vasoconstriction) and structure (elastin fragmentation, aortic wall elasticity) during the progression of aortic aneurysm in MFS mice. On the other hand, based on our observations, medium intensity exercise (e.g. 65%) seems to provide the utmost protective effects on aortic structure and function in MFS mice. These findings provide new insights into the potential capacity, in which MFS patients could participate in various aerobic exercise routines, especially in young adults affected by cardiovascular complications particularly aortic aneurysm. This work was funded by Midwestern University Research Fund.

**Keywords :** aerobic exercise, aortic aneurysm, aortic wall elasticity, elastin fragmentation, Marfan syndrome

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