Marfan syndrome (MFS) is an autosomal dominant disorder caused by mutations in the gene \(FBN1\) encoding fibrillin-1, the major component of extracellular matrix (ECM) microfibrils. In the pathogenesis of MFS, matrix metalloproteases and over activity of TGF-\(\beta\) are directly involved. The syndrome carries an increased risk of aneurysm and dissection of the ascending aorta, and alterations in eyes, skeleton and lungs. Although lung mechanics in MFS could be affected by changes in elastic and tensile strength of connective tissue, there are no data available on the effects of this monogenetic disease in lung mechanics. The aim of this work is to assess whether lung scaffold stiffness and \textit{in vivo} lung elastance is affected in a Marfan mouse model. Twelve 9 month-old C57BL/6 mice (6 healthy controls and 6 Marfan mice heterozygous for an \(Fbn1\) allele encoding a cysteine substitution, \(Fbn1(C1039G/)\)) were used. Control and Marfan mice were intraperitoneally anesthetized (urethane, 1.5 g/kg), paralyzed (pancuronium bromide, 0.1 mg/kg) and subjected to volume-control mechanical ventilation (100 breaths/min, 0.30 ml tidal volume). Subsequently, the chest wall was opened and a positive end-expiratory pressure of 2 cmH\(_2\)O was applied. The signals of tracheal pressure and flow during mechanical ventilation were recorded at the entrance of the tracheal cannula and lung elastance was determined by conventional linear regression. The animals were euthanized by exsanguination, the left lung lobule was excised and decellularized with a conventional protocol based on freezing/thawing cycles and sodium dodecyl sulfate detergent. Acellular lung slices (12 micron thick) were obtained in order to measure nanomechanics (Young’s modulus) of different regions of the lung scaffold (alveolar septum, tunica adventitia and tunica intima) with atomic force microscopy using pyramidal cantilevers (nominal spring constant 0.03 N/m) at an operating indentation of 500 nm. Marfan mice exhibited an \textit{in vivo} lung elastance that was 42\% lower than controls (21.7±2.7 and 37.1±2.5 cmH\(_2\)O/ml, respectively; mean±SEM; \(p<0.05\)). Remarkably, no significant differences were found in the local stiffness of the acellular lung between Marfan mice and controls: 36.4±3.7 vs 38.4±10.0 kPa, 63.2±17.5 vs 48.2±6.8 kPa and 125.2±10.2 vs 119.8±23.7 kPa in the alveolar septum and the lung vessels tunicae adventitia and intima, respectively. In conclusion, these data suggest that the higher \textit{in vivo} compliance observed in Marfan lungs are not caused by a softening of the acellular lung scaffold, as demonstrated by AFM measurements of the local nanomechanical properties of the extracellular matrix of the lung. These changes could be attributed to alterations in the 3-D structure of the lung.

References:


Figures:

Figure 1: Effective elastance ($E$) computed from control (white) and Marfan mice (gray) during in vivo conventional mechanical ventilation. Mean ± SE. Asterisk indicates $p<0.05$.

Figure 2: Local stiffness at different acellular lung parenchyma of control (white) and Marfan mice (gray). Mean ± SE. There are no significant differences.