Aortic microcalcification is associated with aortopathy in Marfan Syndrome; potential marker for imaging.

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Introduction

Marfan syndrome (MFS) is a genetic connective tissue disorder (FBN1 gene), in which aortic rupture is the major cause of death. MFS patients with an aortic diameter below the advised limit for prophylactic surgery (<5cm) may unexpectedly experience an aortic dissection or rupture, despite yearly monitoring. Hence, there is a clear need for improved prognostic markers to predict such aortic events. We hypothesize that elastin fragments play a causal role in aortic calcification in MFS and that microcalcification serves as a novel marker for aortic disease severity. To address this hypothesis, we analyzed MFS patient and mouse aortas.

Elastin peptides involved in aortic calcification

Elastin degradation and calcification

Enhanced Alkaline Phosphatase (ALP) in cultured smooth muscle cells

Figure 2. Vascular calcification is controlled by balancing extracellular levels of the mineral ions calcium and inorganic phosphate (Pi) versus mineralization inhibitors and inorganic pyrophosphate (PiP). Alkaline phosphatase (ALP) decreases extracellular PiP levels and thereby enhances vascular calcification. Elastin peptides (E= VGVAPG) enhance ALP mRNA (A) and activity (C) in cultured human umbilical cord artery SMC as compared to incubation with control scrambled peptides (S= VVGPQA). Basal ALP is already enhanced in murine Marfan (MFS) aortic smooth muscle cell (FblbS1/1000 mice) cultures (B, D) as compared to wild type (WT) littermate aortic SMC cultures. The increase in ALP is probably mediated via the elastin receptor complex, which can be blocked by incubation with lactose or blockade of the ERK1/2 signalling cascade. Indeed, simultaneous treatment with lactose (L), or the MEK1/2 inhibitor (MEKI), attenuates the effect of elastin peptides on ALP activity (C) and in the MFS aortic SMC (D).

\*p<0.05, **p<0.01, ***p<0.001.

Affiliations

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Conclusion

We have shown that elastin fragments promote SMC microcalcification, which is enhanced in Marfan SMC, and in particular in the dilated ascending aorta in Marfan mice and patients, where most of the elastin fragmentation was observed. We propose that elastin fragment-mediated microcalcification may contribute to aortic disease in Marfan and that it may serve as a novel imaging marker to detect aortic damage.