Familial thoracic aortic aneurysms and dissections
- studies on genotype and phenotype

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvaret i sal B, Unod T, 9tr, Norrlands Universitetssjukhus fredagen den 19 maj, kl. 09:00.
Avhandlingen kommer att försvaras på svenska.

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Abstract

Background: Thoracic aortic aneurysms and dissections (TAAD) have a genetic component with an estimated 20-25% of the patients having a positive family history. An aneurysm often precedes a dissection. Acute aortic dissections are associated with high mortality and morbidity, even when operated on. Complications due to prophylactic surgery are considerably fewer. Therefore, patients at risk for dissection should be identified, followed-up and evaluated for prophylactic intervention.

Aims: 1. To establish reference values for ascending (AoA) and descending aortic (AoD) diameters measured by computed tomography. 2. To study the effectiveness of phenotypic cascade screening in families with an inherited form of thoracic aortic aneurysms and dissections (FTAAD) and to address questions that arise when screening for a genetic disorder is applied. 3. To study the agreement of aortic diameters obtained by TTE and MRI and to study aortic stiffness in individuals from families with FTAAD. 4. To perform exome sequencing in order to identify pathogenic sequence variants causing FTAAD, to characterize the phenotype, and to compare thoracic aortic diameter and stiffness in mutation carriers and non-carriers.

Results: Paper I: The diameter of the thoracic aorta increased by 0.17 mm (0.12 – 0.20 mm) per year. The mean sex-related difference in diameter was 1.99 mm (1.28 – 2.60 mm) with men having larger aortas than women. The mean difference in aortic diameter per unit BMI was 0.27 mm (0.14 – 0.44 mm). Upper normal limits for the AoA can be calculated by the formula D (mm)=31+0.16*age and for the AoD by D (mm)=21+0.16*age.

Paper II: Of 106 individuals from families with FTAAD but without known thoracic aortic disease, 19 individuals (18%) were identified to have a dilated AoA. The expected number of individuals in this group with an autosomal dominant disease would have been 40 (p<0.0001). In first-degree relatives younger than 40, we found only one individual with a dilated aorta although the expected number of individuals with disease causing mutation would have been 10.

Paper III: Of 116 individuals investigated, 21 were identified with thoracic aortic dilatation and 95 individuals with normal thoracic aortic diameter. Aortic stiffness increased with age and diameter. The individuals with aortic dilatation were older than those without (49 vs. 37 years, p=0.001) and showed lower aortic elastic properties. The diameters measured by TTE and MRI correlated strongly (r²=0.93). The mean difference in diameters between the two methods was 0.72 mm (95% CI 0.41-1.02) with TTE giving larger diameters than MRI.

Paper IV: From exome sequencing and segregation analysis, a 2-bp deletion in the MYLK gene (c.3272_3273del) was identified to cause FTAAD. The age and the aortic diameter at dissection or rupture varied in the family members. We did not find any differences in aortic diameter, aortic stiffness, or pulse wave velocity between carriers and non-carriers.

Conclusions: Thoracic aortic diameter increases with age, and sex and body size are also associated with the diameter. In FTAAD, screening identifies family members with a previously unknown aortic dilatation. However, a normal aortic diameter does not exclude an individual from being a carrier of FTAAD. TTE can be used in follow-up for the ascending aorta. Individuals identified to have a dilated thoracic aorta have increased aortic stiffness compared to individuals with normal thoracic aortic diameter. The MYLK mutation (c.3272_3273del) causes thoracic aortic dissections with variable clinical expression. No differences in aortic stiffness were identified between MYLK mutation carriers and non-carriers.

Keywords: Thoracic aorta, familial aortic aneurysm, familial aortic dissection, genetics, aortic stiffness