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Screening for Familial Thoracic Aortic Aneurysms with Aortic Imaging Does Not Detect All Potential Carriers of the Disease

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Abstract

Background: **About 20% of patients with thoracic aortic aneurysm or dissection (TAAD) have a first-degree relative with a similar disease. The familial form (FTAAD) of the disease is inherited in an autosomal-dominant pattern. Current guidelines for thoracic aortic disease recommend screening of first-degree relatives of TAAD patients. In known familial disease, screening of both first- and second-degree relatives is recommended. However, the outcomes of such a screening program are unknown.**

Methods: **We screened all first- and second-degree relatives in seven families with known FTAAD with echocardiography. No underlying gene defect had been detected in these families.**

Results: **Of 119 persons investigated, 13 had known thoracic aortic disease. In the remaining 106 cases, we diagnosed 19 additional individuals with a dilated ascending thoracic aorta; for an autosomal-dominant disease, the expected number of individuals in this group would have been 40 ($p<0.0001$). Further, only one of the 20 first-degree relatives younger than 40 years had a dilated aorta, although the expected number of individuals with a disease-causing mutation would have been 10.**

Conclusions: **In most families with TAAD, a diagnosis still relies on measuring the diameter of the thoracic aorta. We show that a substantial number of previously unknown cases of aortic dilatation can be identified by screening family members. It is, however, not possible to consider anyone free of the condition, even if the aortic diameter is normal, especially at a younger age.**

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Key Words

Aorta • Aortic aneurysm • Aortic dissection

Introduction

Acute dissection of the thoracic aorta is a serious condition associated with a high risk of complications in different organ systems and an in-hospital mortality rate that averages 20-25% [1-3]. Thoracic aortic aneurysms are usually asymptomatic until acute dissection or aortic rupture occurs; therefore, they often remain undetected until an acute and catastrophic complication arises.

Thoracic aortic aneurysms and dissections (TAAD) can be divided into sporadic and inherited forms. An estimated 20% of patients with TAAD have a family history of the disease, indicating a significant genetic component [4]. The inherited forms might be either syndromic or nonsyndromic, with the most common syndromic forms occurring with Marfan syndrome, (MS; *FBN1* gene), vascular Ehlers-Danlos syndrome (vEDS; *COL3A1* gene), and Loeys–Dietz syndrome

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(LDS; *TGFBR1, TGFBR2, TGFB2*, and *SMAD3* genes) [5]. The inheritance shows an autosomal-dominant pattern in most syndromic and nonsyndromic familial forms.

The clinical heterogeneity of familial TAAD (FTAAD) suggests that multiple genes are involved, and several have been identified, including ACTA2, MYH11, MYLK, and the PRKG1 genes [5, 6]. Even though several genes are associated with FTAAD, only about 20% of TAAD families have mutations in these genes [4]. Mutation carriers in the genes for LDS do not always develop the syndromic form of the disease but may present with a milder phenotype or an isolated TAAD. The penetrance is depressed and the expression varies in gene mutations associated with FTAAD.

The risk of rupture increases with an increasing diameter of the thoracic aorta. An ascending aortic diameter of greater than 55 mm indicates a high risk for dissection, and prophylactic intervention is recommended at this stage. Studies additionally suggest that dissections occur at a younger age and a smaller diameter in the inherited forms compared with the sporadic forms [4]. The risk of aortic dissection is also determined by the specific underlying gene defect, and the gene defect influences the localization of an aneurysm. Aneurysms in MS are mainly localized to the aortic root, whereas aneurysms in LDS and vEDS can arise all over the arterial tree, including the aortic root or the ascending aorta (AoA). Aneurysms in sporadic forms are often found in the AoA.

In the 2010 multi-specialty Guidelines for Diagnosis and Management of Patients with Thoracic Aortic Disease, aortic imaging is recommended for first-degree relatives of patients with an aortic aneurysm or a dissection [7]. In familial forms, defined as more than one family member having an aortic aneurysm or dissection, aortic imaging is recommended for both first- and second-degree relatives if none of the known disease-causing genes are identified. If the genetic cause is known, aortic imaging is performed only in the carriers of the mutant gene.

We investigated how many new cases with a dilated aorta that could be identified by screening families with an inherited form of TAAD. In addition, we address questions that arise when a screening program for a genetic disorder is applied.

Methods

Study Population

The study population consisted of the first seven families referred to the Centre for Cardiovascular Genetics, Umeå University Hospital, with FTAAD in whom the genetic cause was unknown. Each family had a history of at least two verified TAADs, and 11 individuals from these families had died from aortic dissection. All first- and second-degree family members older than 18 years without TAAD were offered participation in the study. The families consisted of 135 family members of whom 13 living individuals had had an aortic dissection, an elective repair of a dilated thoracic aorta, or a known dilatation, and thus were not included in the screening (Figure 1). Sixteen individuals did not participate in the study. Seven of them, mainly adolescents, declined participation. Eight individuals living in other cities did not have the opportunity to participate. One individual was not offered participation because of concomitant serious disease.

The remaining 106 family members formed the study population and were screened for thoracic aortic aneurysms. No exclusion criterion other than age was applied. A total of 56 individuals were first-degree relatives, and 50 individuals were second-degree relatives.

The individuals were judged to have arterial hypertension or coronary artery disease if they had medical therapy for these diagnoses.

The regional ethical review board at Umeå University approved the study. Signed informed consent was obtained from the participants after both oral and written information was provided.

Molecular Genetic Analysis

DNA was extracted from peripheral blood lymphocytes using a standard salting-out method and sent to an accredited laboratory. No disease-causing gene mutations had been identified in the families. In families 1–3, the genes *ACTA2, COL3A1, COL5A1, COL5A2, EFEMP2, FBN1, FBN2, GATA5, MYH11, MYLK, NOTCH1, SLCA10, SMAD3, TGFB2, TGFBR1,* and *TGBFR2* were analyzed. In families 4–7, the genes *FBN1, COL3A1, TGFBR1, TGBR2, ACTA2, and SMAD3* have so far been analyzed.

Measurements

Clinical Measurements. Height and weight were measured using a calibrated stadiometer and scale. Body surface area (BSA) was calculated according to the formula by DuBois and DuBois [8].

Transthoracic Echocardiographic Examination. All patients underwent transthoracic echocardiographic examination with a Vivid 7 (GE Medical Systems, Horten, Norway) echocardiography machine equipped with a 2D transthoracic transducer. The aortic diameter was measured from the parasternal long-axis view at the sinuses of Valsalva (SoV) and at the widest level of the AoA; thus, AoA measurements were not made at exactly the same level in all patients.

All measurements were made in end-diastole, considering the inner-edge-to-inner-edge distance from the parasternal

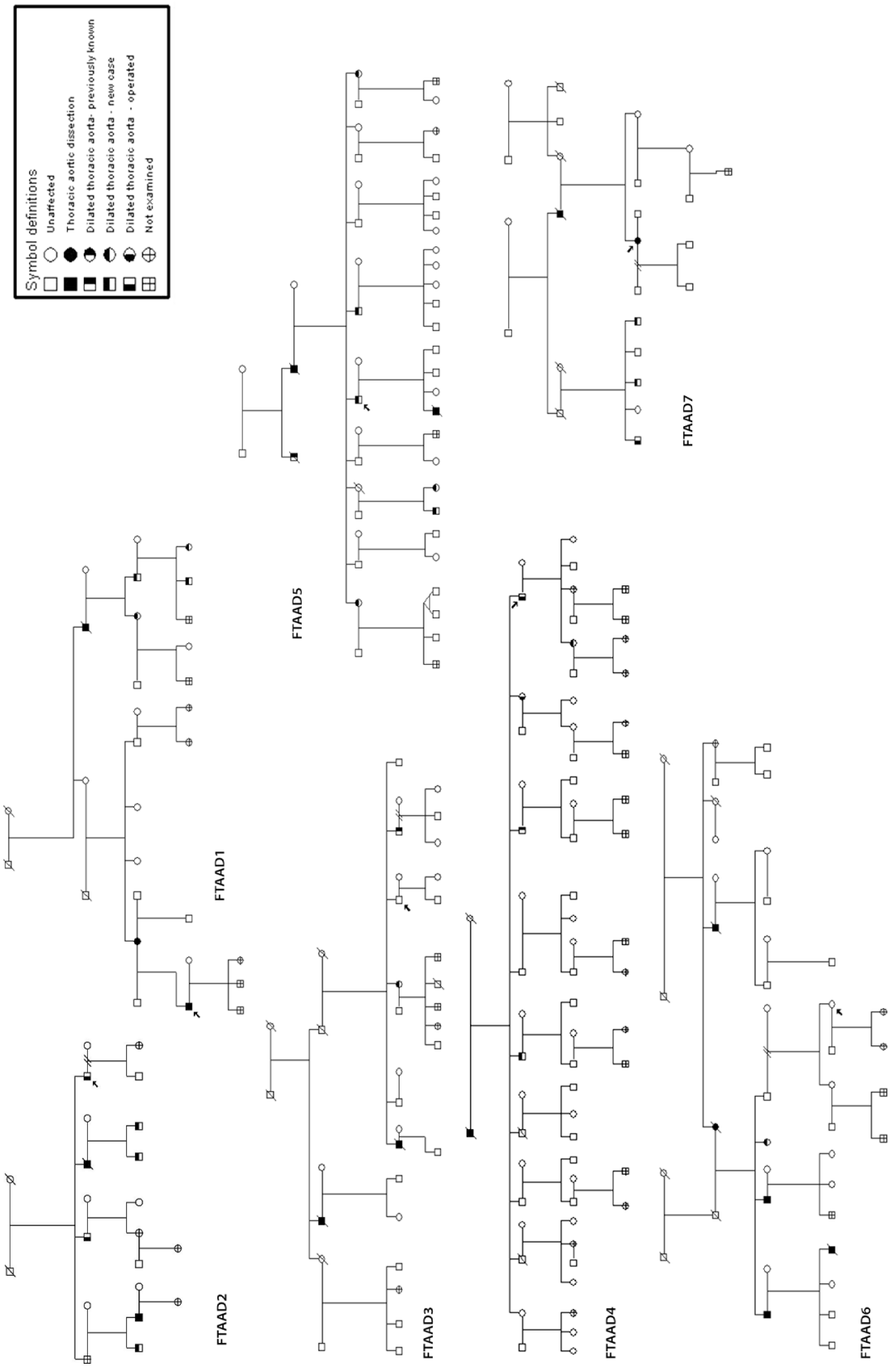

Figure 1. The pedigrees of the families.

long-axis view. Measurements were made in M-mode after verifying correct position and alignment in the 2D image (Figure 2).

All examinations were performed by one of two sonographers. The studies were then reviewed and analyzed offline by one investigator with an international accreditation in echocardiography. The average of three measurements in different cardiac cycles was calculated.

As a reference for the echocardiographic measurements, data published by Mirea et al. were used [9]. That study has defined normal aortic diameters based on 500 individuals with normal echocardiographic findings, and the measurements were performed by inner edge convention in diastole in both SoV and AoA, as in our measurements. The diameters were indexed to age, sex, and body surface area (BSA). The upper normal limit was set to the mean + 2SD.

Magnetic Resonance (MR). All individuals underwent Magnetic Resonance Imaging. The diameter measured by MR was used if the ascending aorta was not visualized clearly enough with echocardiography. Imaging was performed on a 3.0 Tesla MR system (Achieva, Philips, Best, The Netherlands) with the patient in the supine position. All imaging was cardiac gated with a three-lead vector ECG and acquired during expiratory breath hold. Localizer sequences were followed by transaxial T1- and T2-weighted "black blood" sequences over the heart and the great vessels. The internal diameters of the ascending and descending aorta were measured at the level of the pulmonary bifurcation by a single reader without knowledge of the diameters obtained with echocardiography.

As reference values for the MR measurements in the ascending and descending aorta, data published by Davies et al. were used [10].

Statistical Analysis

All data were analyzed using a commercially available software package (SPSS 22, IBM, Armonk, NY, USA). Summary statistics were compared by Chi^2 tests for categorical variables. P values less than 0.05 were considered statistically significant.

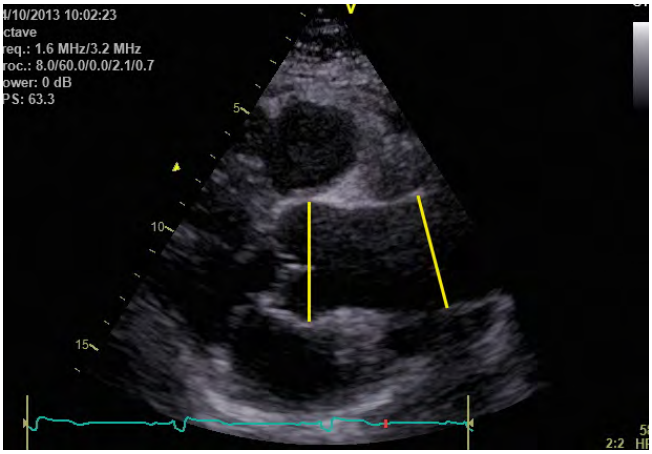

Figure 2. The echocardiographic measurements at the sinuses of Valsalva and at the widest part of the ascending aorta.

Table 1. Summary of the phenotype of individuals in the Families.

Summary of Findings / Family	1	2	3	4	5	6	7	TOT
Previously known – dead due to dissection	1	1	2	1	2	3	1	11
Previously known – dissection, alive	2	1				2	1	6
Previously known – prophylactic operation		2		2			1	5
Previously known – aorta dilated			1	1				2
New cases	4	3	1	2	6	1	2	19
Normal aortic dimension	5	2	15	23	24	13	5	87

Phenotypes of 11 deceased, 13 living patients, and 106 participants, for a total number of 130. The individuals in the families that did not participate in study (n=16) were excluded.

Results

The median age of acute dissection among the family members who had experienced one was 48 years. In those who survived the dissection, the median age was 46 years (n=6, range 38–49 years) and 64 years (n=11, range 15–75 years) in those who died from it. The two youngest persons, 15 and 23 years, were in the group that died because of the dissection. In these two cases, the thoracic aortas were not dilated at autopsy. Although the youngest persons were in this group, overall, those who died from their dissection were older than those who survived the dissection (59 vs. 46 years). The diameter at the time of dissection varied between 44–55 mm in family members in which aortic imaging had been done and the examination could be reviewed.

Eleven individuals had been operated with a graft in the AoA, five of them prophylactically because of an aneurysm and six of them acutely because of an aortic dissection type A (Table 1). Two individuals had a known dilatation of the AoA and are currently included in a periodic follow-up program.

A total of 106 individuals without known disease were investigated. The demographic data for the population are shown in Table 2. Nineteen individ-

Table 2. Demographic data of the first- and second-degree relatives.

Characteristics	Total	Men	Women
Number of individuals, (%)	106	59 (56)	47 (44)
Age 18y-29y, n	28	13	15
Age 30y-39y, n	29	17	12
Age 40y-49y, n	24	11	13
Age 50y-59y, n	13	10	3
Age 60y-69y, n	11	8	3
Age 70y+ , n	2	1	1
Age, y (range)	40 (18–73)	42	38
Weight, kg (range)	78 (49–121)	87 (64–121)	67 (49–95)
Height, cm (range)	175 (157–198)	181 (168–198)	168 (157–182)
Current smoker, n (%)	11 (10.4)	6 (10)	5 (11)
Arterial hypertension, n (%)	19 (18)	11 (19)	7 (15)
Coronary artery disease, n (%)	2 (1.7)	2 (3)	0 (0)
Other arterial disease, n (%)	0 (0)	-	-

uals (18%) met the criteria for dilated thoracic AoA related to age and BSA. Fifteen of them were first-degree relatives and four were second-degree relatives (Table 3). In an autosomal dominant disease, the expected number of individuals in this group with the disease-causing mutation would have been 40 ($p<0.0001$). Further, only one of the 20 first-degree relatives younger than 40 years had a dilated aorta, although the expected number of individuals with disease causing mutation would have been 10.

Six individuals were dilated only in the aortic root at the level of the Sinuses of Valsalva (SoV), nine individuals were dilated only in the AoA, and four individuals were dilated at both levels. One of the participants dilated at both levels had a previously undiagnosed bicuspid aortic valve with an asymptomatic mild to moderate aortic regurgitation. No other participants in the study population had bicuspid aortic valves.

In these 19 individuals the diameter at the level of SoV varied between 35 to 50 mm (18.4–23.6 mm/m^2); at the AoA, the diameter varied from 30 to 46 mm (18.7–22.8 mm/m^2) (Table 4).

Table 3. Number of new and expected cases.

Age, y	1 st-degree relative, n	Dilated aorta, n	2nd-degree relative, n	Dilated aorta, n	Dilated aorta, total n
18–30	10	0	18	1	1
30–39	10	1	19	3	4
40–49	13	6	11	0	6
50–59	11	5	1	0	5
60–69	10	3	1	0	3
70+	2	0	0	0	0
Total (expected)	56	15 (28)	50	4 (12.5)	19 (40.5)

The majority of individuals with dilatation of the aorta were found among first-degree relatives. The number of new cases (19) was significantly lower than would be expected for dominant inheritance (40).

Approximately 50% of the family members (57 of 106) were younger than 40 years, but only five of them had a dilated AoA. The diameters in these individuals were quite modest; in one, it was 30 mm. Three individuals were dilated at the SoV to a diameter of 35–37 mm, and one participant was dilated at both levels.

No dilatation was diagnosed in the descending aorta at the level of the pulmonary artery bifurcation. The diameter in the descending aorta varied between 14–24 mm in women and 17–29 mm in men.

Of the 24 individuals with previous aortic involvement, 20 (83%) were men, and 4 (17%) were women. Of the 19 new cases, 11 (58%) were men, and 8 (42%) were women. In three participants, the AoA was poorly visualized with echocardiography; accordingly, they were investigated with MR imaging only.

Discussion

The international consensus guidelines recommend screening by aortic imaging for all first-degree relatives of patients with sporadic TAAD and all first- and second-degree relatives in families with TAAD in which the genetic cause is not known. The result of this guideline is that many individuals will be screened. In our study, we have followed the guide-

Table 4. Aortic dimensions for individuals with a dilated aorta on screening.

Case	Age (years)	Sex (M/F)	BSA (M^2)	SoV/BSA (mm/m^2)	AoA/BSA (mm/m^2)	SoVdiam (mm)	AoA-diam (mm)
1	48	F	1.75	**20.8**	**20.5**	**36**	**36**
2	26	F	1.55	18.3	**19.5**	28	30
3	59	M	1.98	**21.4**	18.2	**42**	36
4	31	M	2.00	**18.5**	**19.3**	**37**	**39**
5	43	M	2.24	17.1	**18.7**	38	**42**
6	47	M	2.13	18.8	**20.5**	40	**44**
7	55	M	2.00	18.8	**20.0**	38	**40**
8	60	F	1.87	**21.3**	**22.8**	40	**43**
9	65	M	1.93	**21.3**	18.8	41	36
10	35	F	1.64	**21.7**	16.3	36	27
11	58	M	2.05	19.5	**19.8**	40	**40**
12	56	M	1.99	16.9	**19.9**	34	**40**
13	39	M	2.03	**18.4**	14.1	**37**	29
14	65	F	1.72	20.4	**22.7**	35	**39**
15	37	F	1.75	**19.9**	17.1	**35**	30
16	48	F	1.79	15.9	**21.4**	29	**38**
17	47	F	1.66	17.8	**20.5**	30	**34**
18	55	M	2.12	**23.6**	**20.4**	**50**	**43**
19	49	M	2.09	**22.0**	16.5	**46**	34

The diameter and indexed values at two levels, SoV and AoA, are shown. The pathological values are in bold.
BSA, body surface area; SoV, sinuses of Valsalva; AoA, ascending aorta; M, male; F, female.

lines and performed screening of all first- and second-degree relatives in seven families with FTAAD. In these families, 14 individuals had previously had a dissection and six of them were still alive. Five individuals had undergone surgical repair of an aneurysm, and two were in a surveillance program because of an aneurysm. Therefore, the concern in relatives is substantial, and family members want to know if they are at risk for aortic dissection.

In these families, of 106 individuals, we identified 19 persons (18%) with a dilated SoV and/or AoA. However, we would have expected many more to be carriers of a disease-causing gene mutation. In an autosomal-dominant disease, the risk for first-degree relatives of inheriting the pathogenic sequence variant is 50%, and for second-degree relatives, it is 25%. In our families, 56 individuals were first-degree relatives, and 50 were second-degree relatives (Table 3). Thus, 40 individuals (28 first-degree and 12 second-degree relatives) on average would be expected to be carriers of a disease-causing, dominant allele. However, not all mutation carriers will experience an aortic dissection because of reduced penetrance and variable expressivity of the disease.

In particular, very few carriers with aortic disease below the age of 40 years could be detected with this method. A single screening with echocardiography is feasible for identifying patients with dilated aortas who should enter a follow-up program or be offered surgery. However, a single screening is definitely not enough for excluding individuals from risk or from being carriers of FTAAD-related alleles, in particular young individuals. Thus, screening in patients with an inherited disease highlights several clinical problems and ethical questions.

One of these questions involves defining when the thoracic aorta is dilated. Several studies have addressed reference values of normal aortic diameters with different imaging modalities [9, 11-14]. The method of measuring aortic diameter varies from study to study (external vs. internal diameter, leading edge-to-leading-edge vs. inner edge-to-inner-edge convention, systole vs. diastole). Some studies only measured the aortic root or AoA, whereas others have measured the thoracic aorta at different levels. All of the studies point out the importance of taking age, sex, and body size into account when judging whether the aorta is dilated. It is important to consider which imaging modality was used and how the measurements were taken.

We measured the internal diameter in diastole with echocardiography so that the values could be compared with those from other imaging modalities (computed tomography, MRI) in which the internal diameter was measured. Transthoracic echocardiography has several advantages (rapid, bedside, accurate, cost-effective) and permits adequate assessment of several aortic segments. However, in some individuals, the proximal thoracic aorta cannot be visualized and another imaging modality must be used.

All aneurysms in the current work were located in the aortic root or AoA. The diameters in the aortic root

varied from 35 mm to 50 mm and in the AoA from 30 mm to 44 mm. Individuals with a small body size tend to have relatively small aortic diameters, which can be seen in Table 4. The upper normal limits used in clinical practice today are likely higher than those presented in the latest studies. Most often, one common upper normal limit is used for men and women, and the values are not always related to age and body size. The upshot is a substantial risk of not identifying all dilated aortas. At the same time, it is justifiable to ask if some diagnoses are false positives in patients who are not carriers of a disease-related allele. In such cases, these patients may be exposed to unnecessary clinical controls and anxiety.

Another question that requires attention is the kind of information family members should receive. Before a cascade screening of individuals with a genetic disorder is started, they must receive information about the advantages and the limitations. If the disease-causing mutation is not known, the diagnosis relies on measuring the thoracic aortic diameter. In some cases, a clearly pathologically dilated thoracic aorta can be found; however, the majority of individuals will have a normal aortic diameter. As the calculation of individuals at risk for being carriers shows, we do not identify them all by measuring aortic size, at least not at younger ages. Therefore, it is not possible to conclude that individuals with a normal aortic diameter at a young age do not need to be followed. A control program is probably needed even for those with normal diameter. However, such a program would result in a large number of examinations, higher health care costs, and increased anxiety for individuals, some of whom would not be at risk for aortic dissection.

A third question related to the screening guidelines is how to organize families for screening, especially if they are spread over a large geographic area. The controls might be difficult to manage, and there is a risk that family members will have different surveillance in different health care units. Knowledge about inherited thoracic aortic dissections is still limited in the health care system in general, and the disease might be confused with abdominal aneurysms. Special units with a focus on inherited cardiovascular diseases might organize the controls in a systematic way.

Future Perspectives

With a known disease-causing mutation in the family, it is possible to offer genetic counselling and predictive testing to first-degree relatives. Mutation carriers will be offered prevention and surveillance, and noncarriers will benefit from certain knowledge of not being at risk. However, at this time only about 20% of families with FTAAD will gain from genetic testing. Whole-exome sequencing will hopefully increase the rate and efficiency of novel gene identification and allow us to understand the pathophysiology involved in the genetics of aortic aneurysms and dissections.

We will also study mechanical properties of the thoracic aorta, such as compliance, in order to identify other potential markers for progression of the disease than diameter.

Conclusion

In this study, we have shown that screening for aortic aneurysms is encouraged in families with thoracic aortic disease and that family members with a dilated aorta can be identified. Still, screening carries many limitations and a normal aortic diameter is definitely not sufficient for excluding a person from being at risk for aortic disease, in particular in young individuals.

Acknowledgments

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Conflict of Interest

The authors have no conflict of interest relevant to this publication.

Comment on this Article or Ask a Question

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