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ORIGINAL ARTICLE

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Aortic wall thickness in patients with ascending aortic aneurysm versus acute aortic dissection

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Abstract

OBJECTIVES: Recent studies have shown that aortic diameter alone is an insufficient parameter to identify patients at risk for aortic dissection. The aim of this study was to determine the value of the ratio of aortic diameter to medial wall thickness as a new marker of risk.

METHODS: We obtained data from 181 patients with an ascending aortic aneurysm ($n = 94$) or an acute type A aortic dissection ($n = 87$), surgically treated at our institution (1996–2012). Measurements of the maximum aortic diameter and the medial wall thickness were conducted by retrospective review of preoperative imaging studies and histological specimens, respectively.

RESULTS: Nearly 60% of the dissection patients had aortic diameters smaller than 50 mm. There was a significant negative linear correlation between medial wall thickness and aortic diameter ($P = 0.01$) in the dissection group only. Among patients with aortic diameters above 50 mm, dissection patients had significantly thinner aortic media ($P = 0.04$). Among patients with a mildly dilated aorta (>45 mm), the aortic diameter to medial wall thickness ratio was significantly higher in the dissection group ($P = 0.04$).

CONCLUSIONS: Among patients with a dilatation of the ascending aorta of more than 45 and 49 mm, patients experiencing aortic dissection have a significantly higher aortic diameter to wall thickness ratio and a thinner aortic media, respectively. In the subset of patients with mild aortic dilatation, wall thickness might in the future serve as an additional parameter to help identify those patients who would benefit from prophylactic aortic surgery.

Keywords: Aortic aneurysm • Aorta • Aortic dissection • Wall thickness

INTRODUCTION

Acute type A aortic dissection is a relatively rare but catastrophic cardiovascular condition. In fact, the in-hospital mortality still averages between 10 and 35%. Elective aortic root surgery is feasible with a low mortality rate, reported ∼0.5–1.5% for young, otherwise healthy individuals [1]. The mainstay of prevention of aortic dissection has been prophylactic aortic root surgery in patients with a dilated ascending aorta. Aortic dilatation is considered to be an important marker of increased risk for aortic dissection and surgical repair is recommended when the maximum aortic diameter exceeds 55 mm. Coexisting conditions such as severe aortic valve disease, a bicuspid aortic valve, rapid growth of the ascending aorta (>5 mm in 1 year), a hereditary history of dissection or connective tissue disease, Marfan syndrome, for example, suggest intervention even at smaller aortic diameters [1–5].

Data from the International Registry of Acute Aortic Dissection showed that aortic diameter is an imperfect predictor of acute type A aortic dissection. At the time of presentation with acute type A aortic dissection, 62% of the patients have a maximum aortic diameter of <55 mm, and over 20% even have a maximum diameter of <45 mm [6]. The observation that this condition occurs in patients with only mildly dilated or even normal aortas led us to search for an additional marker of risk to assist in the timing of elective aortic root surgery in patients at risk of aortic dissection.

The wall stress (σ_θ) created by the internal pressure on a vessel can be estimated by using the Young–Laplace equation, where P is the internal pressure, D is the inside diameter of the vessel and t is the wall thickness:

$$\sigma_\theta = \frac{PD}{2t}$$

Aortic diameter and systemic hypertension have classically been considered as the principal determinants of wall stress. It has recently been reported that the aortic medial wall is significantly thinner in Marfan syndrome patients with acute aortic dissection compared with those undergoing elective aortic root surgery for indications other than dissection [7]. These observations have led us to suggest that wall thinning might also be an important contributing factor that increases wall stress. Therefore, we retrospectively examined our database of patients who underwent aortic root replacement at our institution, either for acute type A dissection or for other indications (elective surgery).

It was the goal of this study to assess the possible value of medial wall thickness and the relation of aortic diameter to medial wall thickness as markers of risk for aortic dissection.

MATERIALS AND METHODS

Patient population

Data were obtained from hospital records of 433 patients who had undergone aortic root repair at our centre (University Hospital Leuven, Belgium) between 1996 and 2012. The Ethical Committee of the hospital granted approval for this data collection and the need for individual patient consent was waived. Patients were identified by a search of the surgical database for all cases of acute dissection involving the ascending aorta and all cases of prophylactic aortic root surgery. Patients without preoperative imaging or without an aortic specimen available for histology were excluded. Two subgroups of patients were identified: an ascending aortic aneurysm group (with or without associated valve disease), $n = 99$, and an acute type A aortic dissection group, $n = 116$. Patients with poor quality histological specimens that precluded quantitative analysis were excluded. This resulted in 181 patients being included in the final analysis, 94 in the aneurysm group and 87 in the dissection group.

Information regarding demographics, anthropometric data and medical history was collected from an institutional computerized database, and body surface area was calculated using the Dubois and Dubois formula [8].

Aortic diameter

Data were collected by a retrospective review of a computerized imaging database, consisting of computed tomography and/or magnetic resonance imaging, performed preoperatively. Maximum aortic diameters were measured on cross-sectional tomograms perpendicular to the long axis of the ascending aorta.

Histopathological studies

The aortic specimens were stained with haematoxylin and eosin and microscopically evaluated by a pathologist. For each patient, the results of these histological studies were available in a computerized database, from which they were retrieved. These studies were retrospectively analysed for the presence and degree of four histological features: cystic medial necrosis, elastic fragmentation, inflammation and atherosclerotic features.

These stained histological specimens were available in an institutional database from which they were retrieved to allow for digitalization of the specimens. Digital image processing software (AxioVision, Carl Zeiss Meditec AG, Jena, Germany) was utilized by two independent observers to each conduct a minimum of three manual measurements of the medial wall thickness. Using these measurements, the average medial wall thickness of each aortic specimen was determined (Fig. 1).

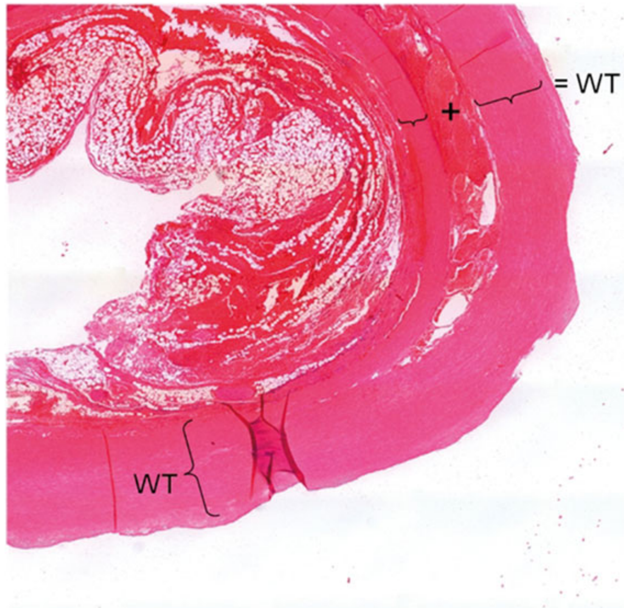

Figure 1: Measuring medial wall thickness (WT) on a digitalized histological specimen. The medial wall thickness of the true lumen is added to the medial wall thickness of the false lumen to determine the predissection medial wall thickness.

Data analysis

Basic data analysis was performed with the use of Statistica (Dell, Inc., Round Rock, TX, USA) and Microsoft Office Excel software (Microsoft Corp., Redmond, Washington, DC, USA). Summary statistics that compare the two groups are presented as frequencies and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. The variables were compared using the unpaired Student's *t*-test. Linear regression analysis was used to detect a correlation between aortic wall thickness and aortic diameter.

RESULTS

Table 1 reports the demographic and clinical characteristics of the patient population. Our study included 181 individuals; of these patients, 51.93% were operated on because of aortic aneurysm and 48.07% because of dissection of the ascending aorta. The average patient age was 60.0 ± 14.0 years and 70.7% were male. More than 50% of patients had a history of systemic hypertension and nearly 60% of patients had a history of smoking. One patient was affected by Turner syndrome and 2 patients were affected by Marfan syndrome. There was no statistically significant difference between subjects with aortic dissection and those without, except for an increased prevalence of aortic valve disease and bicuspid aortic valve morphology in the aneurysm group.

The results of the histopathology studies are summarized in Table 2. Patients with aortic dissection had a higher prevalence of inflammation ($P = 0.007$) when compared with patients with an aneurysm, but all other variables examined were of similar prevalence.

The mean ascending aortic diameter was 51.5 ± 8.24 mm in the aneurysm group with a range from 29.9 to 86.3 mm. Among all patients in the dissection group, the mean ascending aortic

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Table 1: Demographic and clinical history

	All	Aneurysm	Dissection	*P*-value
No. (%)	181	94 (51.93)	87 (48.07)	
Demographics–anthropometrics				
Age, years (SD)	60.0 (14.0)	62.0 (12.6)	57.8 (15.1)	0.05
Male, *n* (%)	128 (70.7)	68 (72.3)	60 (69.0)	0.62
Body surface area, m^2 (SD)	1.92 (0.24)	1.91 (0.25)	1.94 (0.23)	0.49
History				
Hypertension, *n* (%)	102 (56.4)	49 (52.1)	53 (60.9)	0.24
Diabetes mellitus, *n* (%)	10 (5.5)	6 (6.4)	4 (4.6)	0.60
Smoking, *n* (%)	107 (59.1)	52 (55.3)	55 (63.2)	0.28
Connective tissue disorder, *n* (%)	3 (1.7)	1 (1.1)	2 (2.3)	0.53
Aortic valve disease, *n* (%)	147 (81.2)	89 (94.7)	58 (66.7)	<0.001
Bicuspid aortic valve, *n* (%)	39 (21.5)	31 (33.0)	8 (9.2)	<0.001

Table 2: Histological characteristics

	All	Aneurysm	Dissection	*P*-value
Cystic medial necrosis, *n* (%)	32 (17.7)	20 (21.3)	12 (13.8)	0.19
Elastic fragmentation, *n* (%)	6 (3.3)	2 (2.1)	4 (4.6)	0.36
Inflammation, *n* (%)	16 (8.8)	3 (3.2)	13 (14.9)	<0.01
Atherosclerotic features, *n* (%)	58 (32.0)	34 (36.2)	24 (27.6)	0.22

diameter was 50.5 ± 11.2 mm (29.9–83.0 mm). Nearly 60% of the dissection patients had diameters <50 mm, compared with 40% of patients in the aneurysm group (Fig. 2). Between the two groups, there was no statistically significant difference with regard to aortic size. A small percentage of patients in the aneurysm group underwent elective surgery unrelated to aortic dilatation; however, because of the poor quality of the ascending aortic tissue as assessed intraoperatively, they underwent aortic root repair. The average aortic medial wall thickness was 1528 ± 0291 µm (range: 919–2329 µm) in aneurysm patients and 1504 ± 312 µm (range: 647–2312 µm) in the dissection group. There was no significant difference between the two groups.

In patients with dissection, regression analysis revealed a significant (*P* = 0.02) inverse association (*r* = −0.265) between the medial wall thickness and the aortic diameter. In contrast, the relation between medial wall thickness and aortic diameter in the aneurysm group was not nearly so strong (*r* = −0.001), with a wide variance of medial wall thickness and aortic diameter measurements around the regression line (Fig. 3).

Comparing patients with a moderately dilated aorta (cut-off at 49 mm), the medial wall thickness in the dissection group (*n* = 40) was significantly lower than that of the aneurysm group (*n* = 64) [1412 ± 254 µm (range: 897–1896 µm) versus 1525 ± 302 µm (range: 999–2329 µm)] (*P* = 0.049) (Fig. 4).

Figure 5 demonstrates the aortic diameter to medial wall thickness ratio, compared between the two groups for all patients with an aortic diameter of more than 45 mm. The diameter to medial wall thickness ratio was significantly higher in the dissection group (*n* = 54), mean = 0.040 ± 0.012 (range: 0.020–0.082), compared with the aneurysm group (*n* = 78), mean = 0.036 ± 0.008 (range: 0.021–0.069) (*P* = 0.049).

DISCUSSION

Acute type A aortic dissection is a relatively rare cause of cardiovascular death with a suggested incidence of 2.9–3.5 cases per 100 000 people per year as documented by population-based studies [9–12]. Despite sophisticated imaging modalities and advanced cardiac surgical techniques, ∼20% of patients die before treatment can be initiated, 25% die during their hospital admission following urgent aortic root repair and a further 20% die within 10 years of discharge [9, 13–15].

The only effective prophylactic treatment for aortic dissection, aside from treatment of systemic hypertension, remains an elective aortic root replacement in patients with established clinical risk factors. Elective aortic root surgery is quite safe in the current era, resulting in an operative mortality of less than 2% in high-volume centres [16, 17]. Current guidelines for prophylactic aortic root repair are founded on the knowledge of experienced clinicians and on data from clinical series. Taking into account these guidelines, surgery to prevent dissection of the dilated ascending aorta should be suggested when the ascending aortic diameter reaches 55 mm in patients without coexistent risk factors and 45 mm in patients with connective tissue disease or a bicuspid aortic valve [1–5].

For this study, we examined the aortic size after dissection had occurred. This methodology could potentially lead to an overestimation of the aortic diameter in the dissection patients as there is increasing evidence in the literature that the ascending aortic diameter increases as a result of aortic dissection [18]. However, there are also reports stating that the aortic diameter is minimally affected by the formation of aortic dissection [19]. Our results agree with recent studies that showed that, at the time of

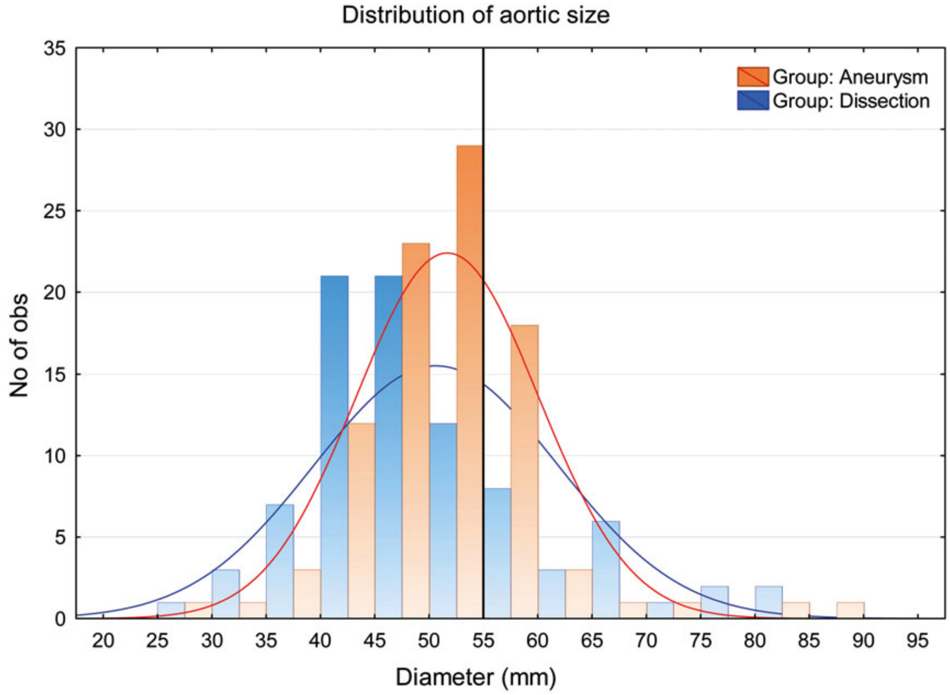

Figure 2: Distribution of the aortic size by the number of observed cases (No of obs) at the time of presentation. A black line depicting the traditional cut-off for elective aortic root replacement.

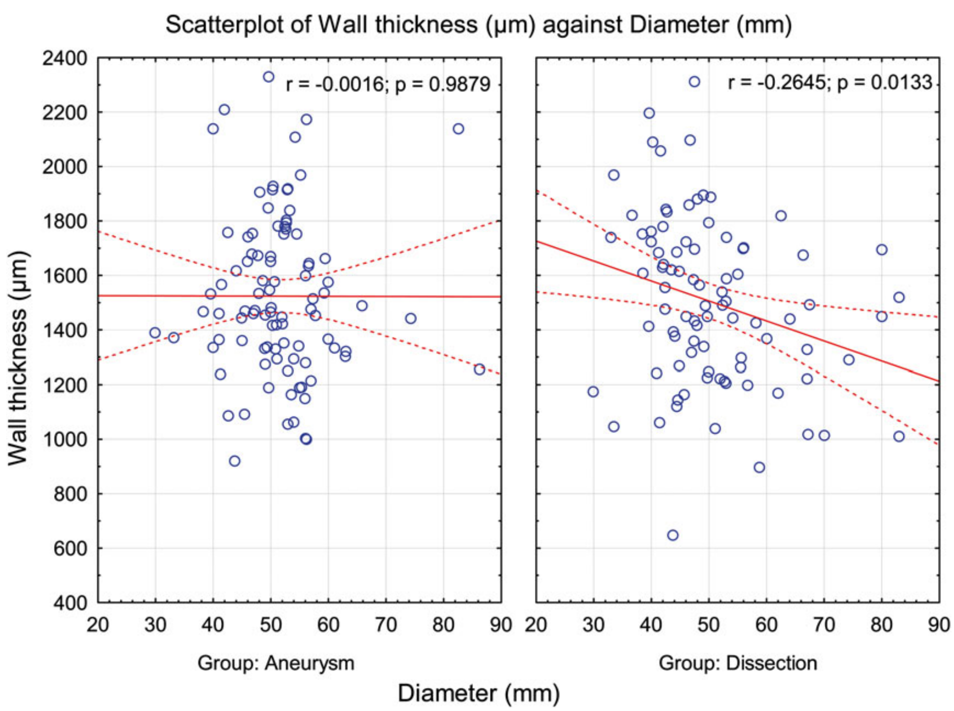

Figure 3: Regression model demonstrating the medial wall thickness in elective aortic root replacement (left) and acute aortic dissection (right) incorporating the aortic diameter. The medial wall thickness was inversely associated with the aortic diameter in patients with an acute aortic dissection.

presentation, the majority of the dissection patients do not have manifest dilated aortae: more than 60% of the aortic dissection patients in our study presented with a diameter of <55 mm and 30% presented even with a diameter of <45 mm [2, 6, 20]. These patients would not qualify for prophylactic aortic root replacement according to the currently established indications and, therefore, aortic dissection would not have been prevented even if they had undergone aortic imaging prior to their presentation with an aortic dissection. In the future, we will be faced with the challenge of establishing a follow-up strategy for an increasing number of patients with an incidental finding of mild aortic dilatation because of the widespread application of high-quality

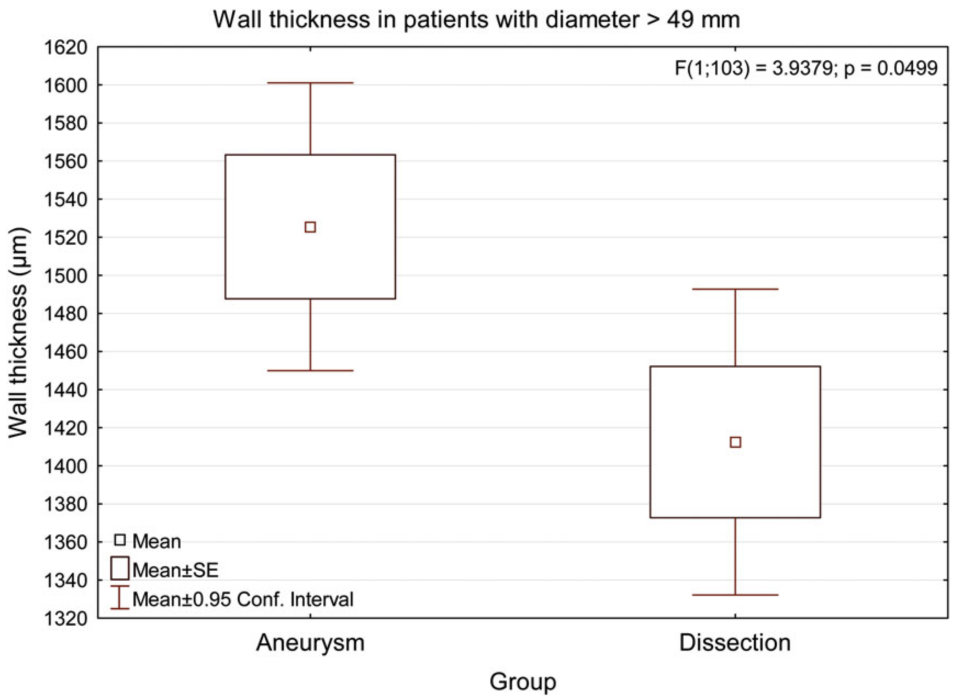

Figure 4: Comparison of the aortic medial wall thickness for the aneurysm group (left) and the dissection group (right) for patients with a moderately dilated aorta of >49 mm. The bar graph depicts the mean and standard error (SE) and 95% confidence interval of the mean. Note the significantly lower wall thickness for acute dissection patients.

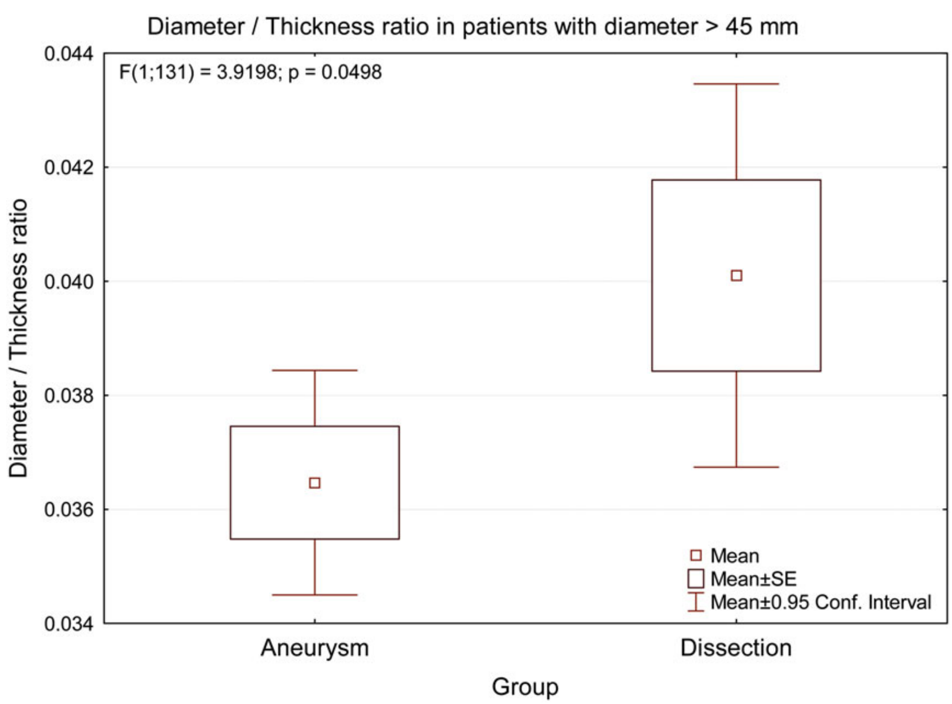

Figure 5: Comparison of the aortic diameter to the medial wall thickness ratio between the aneurysm group (left) and the dissection group (right) for patients with a mildly dilated aorta of >45 mm. Note the significantly higher aortic diameter to medial wall thickness ratio for acute dissection patients.

echocardiography, high-resolution computed tomography and magnetic resonance imaging. Hence, there is a need for a new clinical index that helps delineate the subjects at higher risk of dissection even at mildly dilated aortic diameters.

To identify additional parameters that affect the risk of dissection, Shiran *et al.* attempted to analyse the aortic wall pathology and the medial wall thickness of 69 patients with connective tissue disorders. They concluded that the medial wall thickness was significantly thinner in connective tissue disorder patients with aortic dissection compared with those undergoing prophylactic aortic root surgery [7]. We therefore suggest that wall thinning might play an important role in the pathogenesis of acute aortic dissection in all patients with smaller aortic diameters.

In contrast to the data presented by Shiran *et al*., our study did not show a significant thinner medial wall in aortic dissection patients. However, the structural weakening of the aortic wall in patients with a connective tissue disorder might have amplified the effect of wall thinning in the patients involved in that study.

What we did find was that patients with an aortic dissection revealed a significant inverse association between medial wall thickness and aortic diameter, while in the aneurysm group there was no relation.

When we specifically looked at those patients with a moderately dilated aorta of more than 49 mm, we see a clearly thinner wall in dissection patients, compared with the patients with an aortic aneurysm. Although it could be suggested that this thinning of the medial wall was a result of the increase in absolute aortic diameter, the absence of this relation in aneurysm patients argues that this is not the case. This delineates the importance of wall thinning as an additional, independent marker for structural weakness of the aortic wall. This finding remains a hypothesis. Other authors have found more thickened aortic walls with poor cohesion, specifically in patients with aortic regurgitation, but possibly other pathophysiological processes are involved here [21].

Furthermore, there is a significant higher diameter to medial wall thickness ratio, and therefore higher wall stress in the dissection patients, when we look at those patients with at least a mildly dilated aorta (cut-off at 45 mm). This new marker could play a crucial part in the development of an effective algorithm that can identify patients with mildly dilated aortae, between 45 and 55 mm, who would benefit from prophylactic aortic root replacement, especially since current ultrasensitive imaging techniques, such as ECG-gated computed tomography, intravascular ultrasound and high-resolution magnetic resonance imaging, are improving in the capability of measuring the aortic wall thickness [22, 23]. Additionally, there is increasing interest in the study of dynamic mechanical factors, like aortic root motion and twisting forces on the aortic wall, that initiate dissection, and the development of complex mathematical models capable of accurately computing the wall tension throughout the aneurysm [24, 25].

Our study has several strengths and limitations. The study is retrospective and has not captured all patients with a diagnosis of acute type A aortic dissection evaluated at our centre during the study time because only patients with an aortic specimen available were included, which could have introduced selection bias. Our comparison between the two groups might be influenced by the reported heterogeneity in the subgroups introduced by the higher prevalence of aortic valve disease and of bicuspid aortic valve morphology found in the aneurysm group. The analysis is limited to the type of preoperative imaging available because we elected to partially base our analysis on mixed-imaging data. Preoperative imaging not perfectly orthogonal to the long axis of the aorta might produce small errors. Another source of bias might occur as a result of fragmented specimens not perfectly perpendicular to the aortic longitudinal axis. As the aortic diameter might be bigger after dissection than immediately before dissection, this could have led to an overestimation of the aortic diameter in the dissection group in our study. Among its strengths, this study is unique in its presentation of information on the medial thickness from a large series of acute type A aortic dissections and adds to the current clinical need for additional markers of risk for aortic dissection.

Aortic diameter as such has been proved to be an insufficiently specific marker of risk for aortic dissection, and the majority of acute aortic dissections is currently not being prevented by the surgical guidelines. Our data have suggested that in the specific cohort of patients with moderate dilatation of the ascending aorta, patients experiencing aortic dissection have a significantly thinner aortic media. In patients with an ascending aortic diameter of more than 45 mm, the aortic diameter to medial wall thickness ratio was significantly higher. This might serve as an additional prognostic factor for patients in this specific subgroup of patients. As currently our findings only relate to those with an aortic diameter above 49 mm (57% of our patient group), more research will be necessary to verify the full clinical meaning of our results. But in the future, the data from this study could have potentially important clinical implications and assist in the formation of effective prevention strategies for aortic dissection in the setting of mildly dilated aortic diameters.

Conflict of interest: none declared.

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EDITORIAL COMMENT

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Too thin a beam of light in thick fog

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Keywords: Aortic aneurysm • Aorta • Aortic dissection • Wall thickness

Van Puyvelde *et al*. presented a histological investigation of aortic medial thickness in patients undergoing aortic surgery, reporting the evidence of thinner aortic media in dissection patients compared with aneurysm patients, but only in the subgroup with an aortic diameter exceeding 49 mm [1]. As current guidelines recommend to consider a lower threshold for surgical indication (50 mm instead of 55 mm) in patient subsets with adjunctive risk factors for dissection [2], the evidence that among patients with aortic diameter >49 mm those with dissection have a thinner aortic media seems to argue that aortic wall thickness might be among those factors to consider. However, the light that this study sheds on the issue of the unpredictability of aortic dissection may actually be weaker than it may seem, and the above argument fails to be persuasive, after taking into account some considerations that we will present below.

Firstly, the statistical strength of the analysis was poor: the mean medial thickness was 1528 μm in aortic aneurysm patients versus 1504 μm in aortic dissection patients (P = NS), and only excluding those with a diameter <49 mm, the result of such comparison barely reached statistical significance (1412 vs 1525 μm, $P = 0.0499$). From the scatterplots illustrating the paper, one can appreciate that the difference is made fundamentally by those patients having a diameter in the 50- to 60-mm range. However, nearly 60% of dissection patients had a diameter ≤49 mm [1]; thus, the relatively rare dissections occurring on an overly dilated aorta drove the result, which therefore does not apply to the majority of dissections. It is now well known that, in most cases, aortic dissection occurs at a diameter smaller than the threshold defining an aneurysm [3, 4]; therefore, the critical part of the aortopathy patient population is represented by the patients with normal or mildly dilated diameter, on whom research should focus on to identify new risk predictors. Thus, the authors introduced the ratio of the diameter to medial thickness, which was found to be significantly higher in dissection patients with a diameter >45 mm (actually barely significant again, with $P = 0.0498$). Frankly this looks like a mere statistical trick: the real 'meat' of the analysis was the weak ($r = -0.26$) though significant negative correlation between diameter and thickness found only in dissection patients, not in aneurysm patients. As a consequence, dividing diameter by thickness artificially amplifies the difference between the two groups.

Secondly, the authors failed to perform further analysis that could have provided some more elements for the interpretation of their finding: for example, although they performed histological grading of 'cystic medial necrosis', elastin fragmentation,