Limited role of aortic size in the genesis of acute type A aortic dissection

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Abstract

Objective: Increased dimension of the aortic root and proximal aorta is considered a significant risk factor for catastrophic events that involve the ascending aorta. The objective of this study was to determine the possible correlation between pre-dissection aortic diameter and the occurrence of Stanford type A aortic dissection. **Methods:** Samples of dissected ascending aortas were obtained from 220 patients at the time of their operation. Two groups were identified: patients with connective tissue disorders (Group 1, $n = 94$) and those without (Group 2, $n = 126$). Measurements of the true (intimal) lumen were conducted and extrapolated as reliable approximation of pre-dissection aortic diameter. The possible association of intimal diameter with anthropometric and demographic data was analyzed. **Results:** Median aortic diameter was, respectively, 41.8 and 41.3 mm for patients with and without connective tissue disorders (41.4 mm for the entire cohort). Data analysis indicated that 57% of patients had aortic diameter above 40 mm, while patients with frank aneurysm accounted only for 10%; this proportion was higher in Group 1 compared to Group 2 (17.2% vs 4.7%). Poor or no correlation was demonstrated between aortic size and any of the anthropometric or demographic variables essayed. Significant subgroup differences were found among patients with a history of cigarette smoking, hypertension, diabetes, chronic renal insufficiency, and bicuspid aortic valve. **Conclusion:** Although aortic diameter remains a strong indication for preventive surgery in patients with inherited connective tissue disorders, acute aortic dissection occurs rarely in the setting of true ascending aortic aneurysms, and despite normal or near-normal aortic size in more than one-third of subjects. Dissection superimposing on small aortic diameters can be regarded as an expression of substantial functional tissue susceptibility to aortic catastrophic events.
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1. Introduction

Aortic diameter has classically been considered a risk factor for the development of acute aortic dissection. Recent studies have emphasized the importance of aortic diameter as principal determinant of wall stress, and postulated the necessity of aortic dilatation for the genesis of dissection [1,2]. In current clinical practice, the use of maximal aortic diameter as a marker of increased risk for catastrophic aortic events that include dissection appears therefore justified [3,4]. Maximal aortic size is an expression of both biomechanical tissue resistance and conformational stress, and can be considered as an indirect measure of both.

Nevertheless, the importance and role of aortic diameter in the genesis of aortic dissection in particular await further clarification.

The rapid separation within the *media* that follows the development of an intimal tear leads to a rapid, acute increase of aortic diameter, and to a significant weakening of the arterial wall (hence the term "dissecting aneurysm", first coined by Laennec in 1819). Despite the large diameters that can result from the acute dissecting process, the true lumen, defined by the intimal flap, retains a size that closely approximates the original (pre-event) aortic diameter.

We speculated that the size of the true lumen is minimally affected by the process of dissection/acute aortic dilatation, and allows for a retrospective measurement of the pre-dissection aortic diameter.

According to this assumption, and with the objective of clarifying the role of aortic size in the development of acute

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aortic dissection, we herein present the results of our ex vivo measurements.

2. Material and methods

2.1. Patient population

Between 1994 and 2005, 220 aortic specimens were collected from two centers (University of Caen, France and University of Siena, Italy) following protocol review and approval by the respective Institutional Review Boards. The specimens were retrieved from patients who had undergone urgent aortic repair for acute type A aortic dissection.

The 64 females and 156 males that composed our study population ranged in age between 26 and 87 years (median: 61 years).

None of the patients included in this cohort exhibited pathological features of chronic dissection; furthermore, patients considered to have a true intramural hematoma of the aorta and those with "incomplete dissecting aneurysm" (as previously defined by Schlatmann and Becker [5]) were excluded from the study. Patients suffering from intra-operative dissection and those presenting with acute aortic dissection after previous cardiac surgical procedures were excluded as well.

Two subgroups of patients were identified: a dystrophy group (Group 1) including patients with clinical *stigmata* of Marfan and Ehlers—Danlos syndrome [6,7], familiar aortic dissection, or bisuspid aortic valve [8] and (Group 2) those without signs or suspicion of connective-tissue disorders. In Group 1, 15 had clinical evidence of Marfan syndrome and 6 of Ehlers—Danlos syndrome.

Demographic and anthropometric data regarding surgical patients were retrieved from institutional computerized databases; these included gender, age, weight, height, and body surface area (BSA). Other relevant information, such as cardiovascular risk factors or familial history of dissection, was obtained from clinical files or by interview with the patients or their referring physicians.

2.2. Aortic measurements

The operative technique for the treatment of type A acute aortic dissection is similar in the two institutions by whom the material presented was collected. An "open technique" is employed to perform the distal anastomosis. The diseased ascending aorta is transected at both the distal and proximal anastomotic sites and removed. The majority of aortic specimens were retrieved in an almost intact state, as a cylinder. We could therefore identify the site of the primary tear and retrieve adequate size rings or aortic tissue for measurement.

Measurements of the inner aortic layer were recorded (Fig. 1); the *intima* was gently separated from the outer layer in order to avoid any fracture of the specimen. These measurements were performed on aortic rings (or strips), in a plane orthogonal to the longitudinal aortic axis; for this purpose a Hegar dilator of adequate size was utilized to reconstitute the approximate aortic shape before section. The ring (or strip) of maximal diameter was selected for
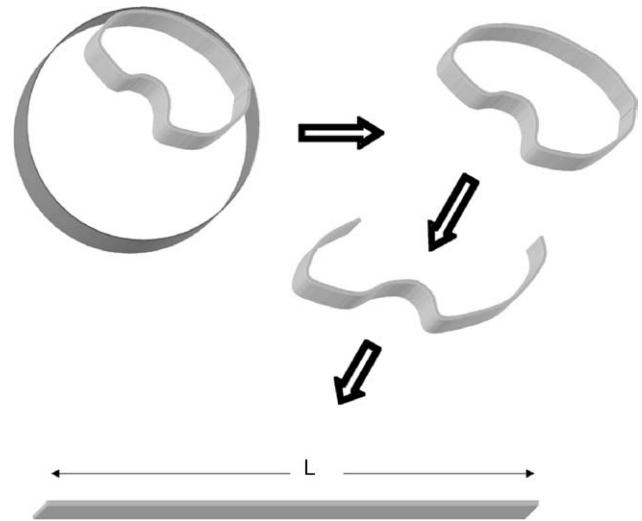

Fig. 1. The illustration depicts the inner layer measurement technique. The length "L" represents the perimeter of intimal layer.

measurement. Preparation and sizing of the fresh surgical specimens was performed in the operating room.

A digital caliper (China Yong Feng Corp., Ltd., Qing Dao, China) was utilized to determine the perimeter (length) of the aortic specimen; the mean of three successive measurements was taken as the result for the particular specimen.

Given the obvious absence of perfusion pressure and the possible consequential shrinking of the arterial wall in smaller diameter aortas (partly due to muscle cell decay) we corrected the measured size for the circumferential extension ratio (λ_θ); this corresponds to the amount that the vessel that must be stretched in order for it to return it to the in vivo length [9].

Therefore, the pre-dissection aortic diameter was obtained by the formula:

$$\text{Diameter} = \lambda_\theta \left(\frac{\text{perimeter of the specimen}}{\pi} \right)$$

We assumed a conventional value of the coefficient $\lambda_\theta = 1.2$ for all patients [10].

The theoretical aortic diameter was calculated according to allometric equations for ascending aorta [11]. The derived variable, resulting from the difference between theoretical and observed diameters, was used for analysis; this indexed variable has the advantage to be independent from age and anthropometric variability.

2.3. Histopathology studies

For each patient the results of histologic studies were available in a computerized database from which they were retrieved for analysis.

In both institutions, since the early 1980s, aortic speci-mens from patients with acute aortic dissection are routinely examined by the pathologist and microscopically evaluated according to the five criteria introduced in 1977 by Schlatmann and Beker [1,12]: (1) fibrosis, (2) medionecrosis, (3) cystic medial necrosis (mucoid material accumulation),

(4) changes in smooth muscle cells orientation, and (5) elastic fragmentation; moreover, (6) inflammation and (7) athero-sclerotic features were also sought and graded according to the criteria of Klima et al. [13]; an aortic wall score, sum of the grades of these seven histologic features, was calculated [14]. The grades (1—3) were determined on the basis of the worst area observed in each specimen.

2.4. Statistical analysis

Given the non-normal distribution of observed variables continuous data were expressed using the median, range, and 25th—75th percentile. Accordingly, the statistical analysis was carried out by using non-parametric tests; the Spearman and Kendall rank indexes, sign test (or test on the medians), Fisher exact test on counts, Mann—Whitney rank sum test, and non-parametric association analysis were used where appropriate.

Separate analyses were conducted with regard to the entire patients' population and on the two subgroups of patients with (Group 1) or without (Group 2) aortic tissue dystrophy.

For statistical analysis we used computation routines and graphics procedures implemented in Mathematica 4.0 (Wolfram research Inc., Champaign, IL).

3. Results

3.1. Aortic size and relationship with demographical—anthropometric characteristics

Table 1 summarizes the demographic, clinical, and anthropometric characteristics of the patient population; measurements of aortic diameter for overall population and for each subgroup are also listed: there was no statistically significant difference (with regard to aortic size) between subjects with aortic tissue dystrophy (Group 1) and those without ($p = 0.48$, using Mann—Whitney rank sum test). Also the analysis of the differences from theoretical diameter was not significant ($p = 0.24$). Measured aortic diameter distributions (summarized by means of histograms and box-and-whiskers plots) are shown in Fig. 2. From the graphical representation it appears that, in each subgroup and in the overall patient population, the measured size has high dispersion around the median (with evident asymmetrical right tails) representing the few patients with extremely enlarged aortas.

The median difference between theoretical and measured aortic diameters was near to 0 (median: 2.88 mm; 25th—75th percentile: 0.78—7.8 mm; range: −16.8 to 48.2 mm) (Fig. 3); however, this difference was statistically significant (test on the medians, two-sided $p < 0.0001$). Also for each of the two groups the differences were statistically different from 0. In Group 1, the median difference was 2.86 mm (25th—75th percentile: 0.70—12.9 mm; range: −10.8 to 48.2 mm; two-sided $p < 0.0001$) and in Group 2 the median difference was 2.91 mm (25th—75th percentile: 0.83—5.95 mm; range: −16.8 to 38.7 mm; two-sided $p < 0.0001$); however, the values of the differences were not significantly different between the two groups (two-sided $p = 0.24$ using the Mann—Whitney rank sum test) (Fig. 3).

We observed no correlation between theoretical and measured aortic diameter ($r^2 = 0.027$), which reflects the scarce association between aortic diameter and anthropometric factors used to calculate theoretical size, these include gender, age, height, and weight.

Table 2 illustrates the differences from theoretical aortic diameters according to the clinical characteristics of patients.

Female gender or presence of Marfan or Ehlers—Danlos syndrome and diabetes were not associated to significant differences in aortic size compared to patients without these factors.

Table 1
Patient characteristics

|	Group 1 (N = 94)	Group 2 (N = 126)	All (N = 220)	P value[*]
Female	27 (28.7%)	37 (29.4%)	64 (29.1%)	0.99
Hypertension	75 (79.8%)	126 (100%)	201 (91.4%)	<0.001
Cigarette smoking	21 (22.3%)	41 (32.5%)	62 (28.2%)	0.12
Diabetes	31 (33.0%)	56 (44.4%)	87 (39.5%)	0.09
Cocaine use	0	2 (1.6%)	2 (0.9%)	0.50
COPD	23 (24.5%)	41 (32.5%)	64 (29.1%)	0.23
Chronic renal insufficiency	12 (12.8%)	11 (8.7%)	23 (10.5%)	0.37
Age (year), median (range)	52 (26—74)	64 (38—87)	61 (26—87)	<0.0001
25th—75th percentile	43—59	52—76	47—73	
Weight (kg), median (range)	70 (40—104)	75 (41—108)	72 (40—108)	0.26
25th -75th percentile	63—82	65—84	65—83	
Height (cm), median (range)	164 (140—189)	164 (143—188)	164 (140—189)	0.74
25th—75th percentile	156—178	155—173	156—174	
BSA (m^2), median (range)	1.79 (1.39—2.10)	1.81 (1.30—2.15)	1.80 (1.30—2.15)	0.35
25th—75th percentile	1.63—1.93	1.69—1.94	1.66—1.94	
Aortic diameter (mm), median (range)	41.8 (23.6—85.3)	41.3 (23.6—80.6)	41.4 (23.6—85.3)	0.48
25th—75th percentile	37.4—50.6	38.6—45.5	38.1—46.4	
Difference from theoretical aortic diameter (mm), median (range)	2.8 (−10.8 to 48.2)	2.9 (−16.8 to 38.7)	2.8 (−16.8 to 48.2)	0.24
25th—75th percentile	0.7—12.9	0.8—5.9	0.7—7.8	
Aortic score (patients), median (range)	14.5 (8—19)	14 (9—18)	14 (8—19)	0.55
25th—75th percentile	13—15	13—16	13—16	

[*] Group 1 versus Group 2.
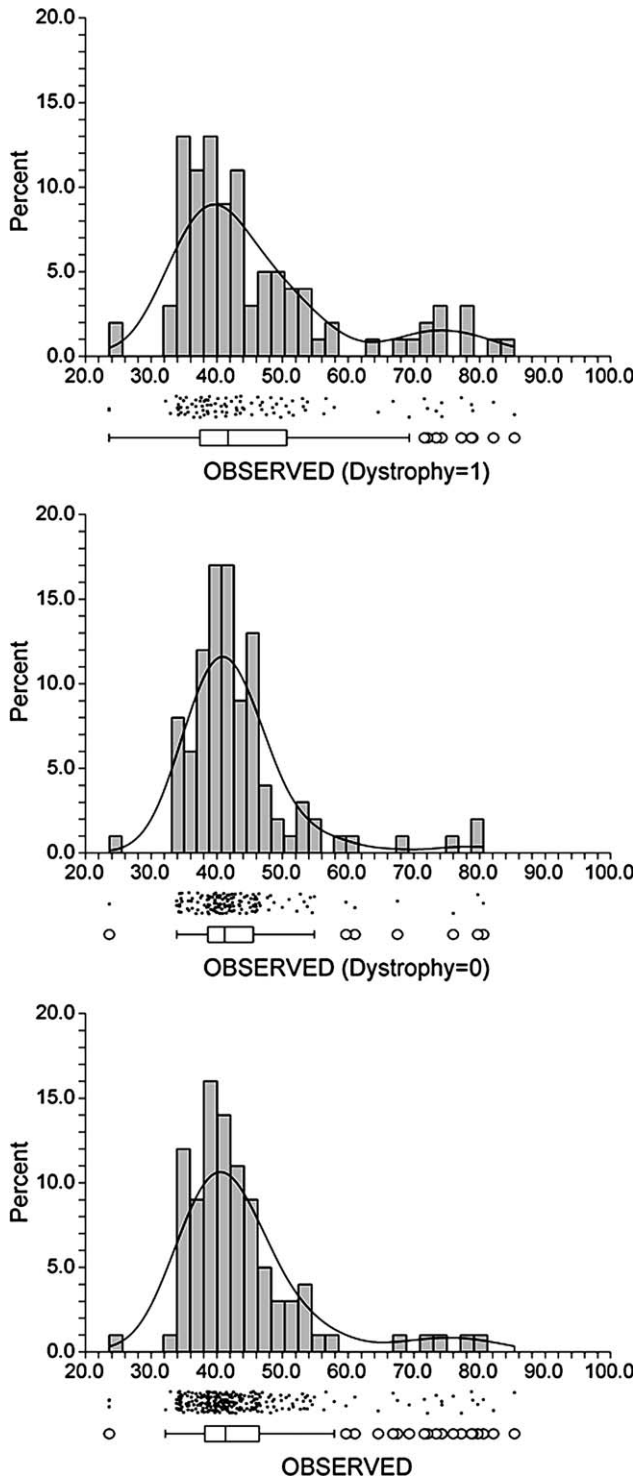
Fig. 2. Analysis of the distributions of aortic diameters in the entire population and in each subgroup: distributions are illustrated using box and whiskers plots and density histograms.

Fig. 3. Analysis of the distributions of the differences from theoretical aortic diameter.

In patients with bicuspid valve dissection occurred at relatively larger aortic sizes whilst patients with history of familiar dissection, hypertension, cigarette smoking, COPD, and chronic renal insufficiency dissection occurred at aortic diameters significantly less discordant from the theoretical size.

Hypertension was ubiquitous in Group 2, whereas it was present in only 79% of Group 1 patients ($p < 0.001$). Group 1
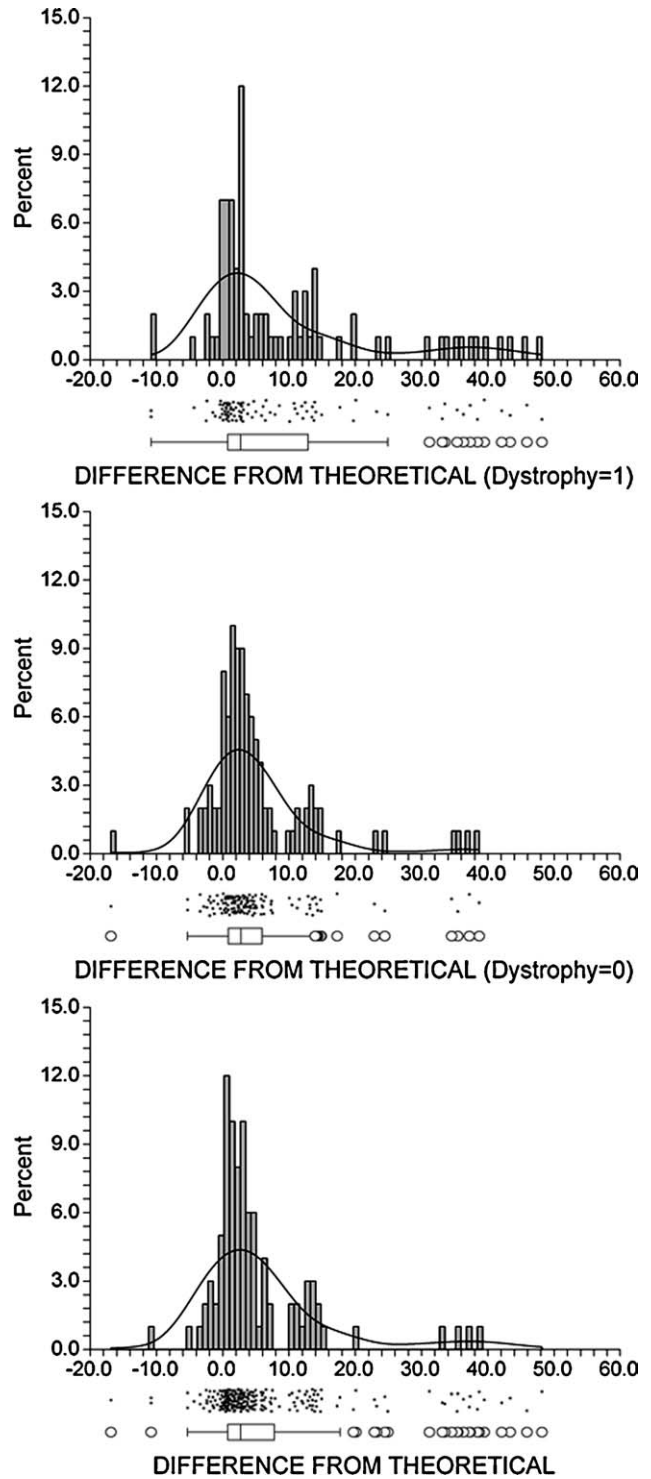
patients with hypertension experienced dissection at relatively smaller aortic sizes, when compared to those without hypertension (42.4 mm vs 51.4 mm; $p = 0.0024$).

Between the 36 patients with familiar dissection and the other subjects without this characteristic a significant difference, with regard to the aortic size, was observed (38.3 mm vs 43.7 mm; $p = 0.011$); also, cigarette smoking

Table 2
Differences from theoretical aortic diameters according to the clinical characteristics of patients (all: n = 220)

	With factor	Without factor	p
Female	3.0 (1.5—12.7)	2.8 (0.7—7.0)	0.22
Bicuspid aortic valve	3.4 (0.9 -13.2)	2.6 (0.6—5.9)	0.03
Familiar dissection	1.1 (0.0—2.3)	5.1 (0.8—21.4)	0.001
Hypertension	2.7 (0.7—6.3)	11.2 (2.8—23.3)	<0.0001
Cigarette smoking	1.7 (0.4—4.9)	3.2 (1.1—11.2)	0.01
Diabetes	3.3 (1.6—7.3)	2.5 (0.4—10.6)	0.13
COPD	2.0 (0.4—5.7)	3.2 (0.9—10.8)	0.02
Chronic renal insufficiency	2.8 (0.7—6.3)	4.2 (1.4—34.5)	0.01
Marfan and Ehlers—Danlos syndrome	2.3 (0.5—21.6)	2.9 (0.8—7.3)	0.3

Median aortic size and 25th—75th percentiles are expressed in millimeters.

(36.2 mm vs 43.3 mm; $p = 0.009$), chronic renal insufficiency (40.1 mm vs 46.73 mm; $p = 0.017$), and COPD (38.4 mm vs 43.3 mm; $p = 0.03$) were associated with significantly smaller diameters.

3.2. Do patients with acute dissection have a larger aorta?

The empirical distribution functions of both observed aortic diameter and difference from theoretical aortic diameter indicate that 42.7% (70% CI: 39.9—46.4%) of patients had an aortic diameter equal or less than 40 mm and that 77.2% (70% CI: 73.9—80.2%) had a difference from theoretical diameter within 10 mm (Fig. 4).

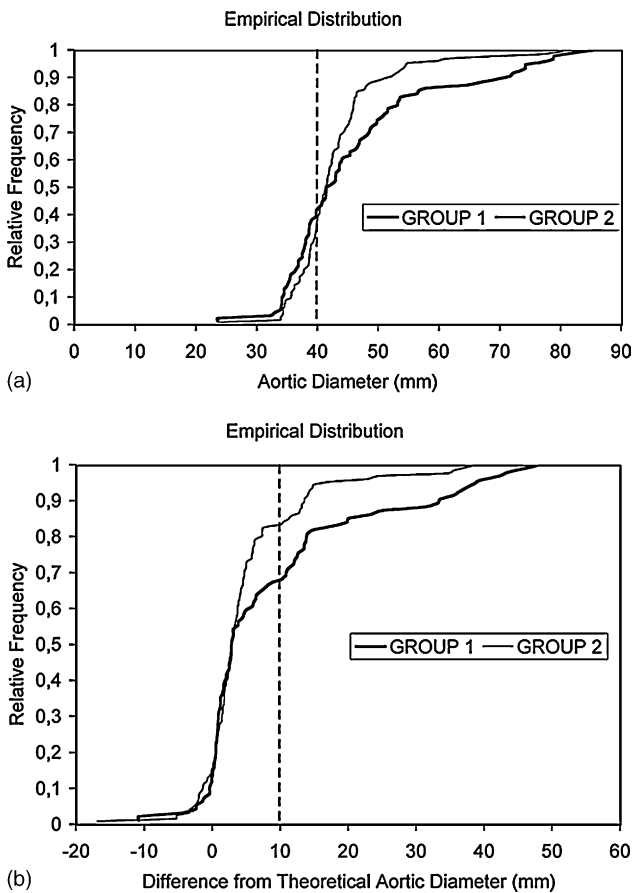Fig. 4. Diagrams illustrate the empirical distribution functions of aortic diameter (a) and of the differences from theoretical aortic diameter (b).

Similar proportions of Groups 1 and 2 patients had an aortic diameter equal or less than 40 mm (57.5%; 70% CI: 51.5—63.1% vs 57.4%; 70% CI: 52.1—62.0%; $p = 0.97$); nevertheless, the number of patients with a difference from theoretical diameter within 10 mm was significantly ($p = 0.002$) higher in Group 2 (84.1%; 70% CI: 80.5—87.5%) than in Group 1 (68.0%; 70% CI: 62.3—73.3%) (Fig. 4).

According to the standard definition, an arterial aneurysm is a permanent dilation of an artery having at least a 50% increase in diameter compared to the expected normal diameter of the artery in question [15]. Using theoretical aortic diameter we found that only 22 of the 220 patients in this study (10%; 70% CI: 7.8—12.5%) had indeed an ascending aortic aneurysm (Table 3).

4. Limitations of the study

The major limitation of the study involves the measurement of non-perfused vessels, taken in absence of a distension pressure that might mostly alter the evaluation of smaller diameters [16]. We therefore decided to correct the estimated true lumen diameter by introducing in the formula a coefficient (the circumferential extension ratio λ_θ), which corresponds to the amount that the vessel must be stretched to return to the in vivo diameter. As we did not measure the λ_θ, we assumed an approximate mean value for human thoracic aorta according to Learoyd and Taylor [10].

The aorta has a complex shape and its transverse section is not a perfect circle; this conversion into a more elementary geometrical conformation may again result in a bias of estimates. Other sources of bias might result from fragmented specimens, from aortic rings or strips not perfectly orthogonal to the aortic longitudinal axis, or from specimens that might not represent the largest aortic diameter. The large sample of the study tends to counterbalance the importance of these errors (indeterminate errors).

Table 3
Proportions of patients on the basis of the standard definition of ascending aorta aneurysm

	Aneurysm
All patients	22/220 (10%)
Group 1	16/94 (17.2%)
Group 2	6/126 (4.7%)

5. Discussion

As previously mentioned, dilatation of the thoracic aorta is classically considered to be a risk factor for the development of acute dissection [17]. Fundamental work from the University of Carolina group [1,2] demonstrated, using mathematical models, the "theoretical necessity" of a dilatation phase of the ascending aorta in order to produce an intimal tear followed by the acute dissection process. These authors theorized that dissection occurs not only in dilated but in dilating aortas as well; nevertheless, in more a recent study, they also advocate other biomechanical factors (such as aortic root motion), that could play a major role in the initiation of the dissection process [18].

The problem of aortic size has been particularly studied in patients with congenital connective tissue abnormalities, and in particular with Marfan syndrome. In this population, the size of the aorta is a critical issue with regard of prophylactic surgery and optimal timing of aortic root replacement; nevertheless, the decision to replace the aortic root in an asymptomatic patient on the basis of the size of the root alone is still controversial [19,20]. Data from Gott et al. [19] indicates in fact an indistinct relationship between aortic size and the risk of dissection in patients with Marfan syndrome. Almost half the adult patients with aortic dissection in the Johns Hopkins series had an aortic diameter of 6.5 cm or less; moreover, comparison of the data for the group of patients with an aortic-root diameter of 6.1–7.0 cm (approximately 20% of whom had dissections) with the data for the group of patients with an aortic-root diameter of 4.1–5.0 cm (of which 30% had dissections) showed no statistically significant difference in the incidence of dissection.

Although with less emphasis on preventive surgery, the same concern about the risk of dissection in function of the size of the aorta exists in the general population [3,21]. The Yale group has provided an analysis of the natural history of aortic aneurysms, showing that larger aneurysms had a greater risk of dissection and rupture [22]. From a clinical point of view, the goal of balancing the risk of the untreated natural history of the lesion with that of surgical treatment is achieved in these reports [3,22]; nevertheless, from a pathological point of view, they do not differentiate the risk of rupture from that of dissection given a specific aortic diameter. Even though an aortic size of 6.0 cm or greater was associated with nearly a fourfold increase in the incidence of rupture, no statistically significant association was observed between an enlarged aorta and the occurrence of dissection involving the ascending aorta.

Few studies deal with ascending aortic diameters of patients experiencing subsequent acute dissection and the difficulty in retrieving large number of patients is obvious. Prenger et al. [23], for example, postulated that a dilated ascending aorta at the time of valve replacement predicted subsequent dissection: all 10 subjects who experienced dissection in their series had an aortic diameter of 50 mm or more. The largest study that matches the size the aorta with the risk of subsequent aortic events, analyzes a population of 24 patients who experienced dissection [3].

To assess this important issue in a larger number of patients, we therefore have adopted the indirect method of study presented herein. The methodological advantage was in the possibility to detect, within a sample population of acute type A aortic dissection, the distribution of aortic diameter and estimate the prevalence of size abnormalities with reasonable accuracy. Starting from these premises, we found that most subjects had increased aortic diameters; nonetheless, the number of patients with true aortic aneurysm was small (Table 3). We found that acute aortic dissection superimposing on a true aortic aneurysm was not frequent, accounting for only 1/10 of all events. This proportion, as expected, is higher in patients with inherited connective tissue disorders, with relevant consequences in terms of prevention and prophylactic surgical treatment. As it appears from the Table 1, Group 1 patients have slightly smaller aortic diameters, however, they tend to develop an aneurysm before dissection more frequently than Group 2.

Actually the smaller proportion of Group 1 patients with an aortic diameter above 40 mm is compatible with data that underscore the tendency to experience dissection at comparatively smaller diameters among patients with Marfan syndrome [20,24]. In our study, this may also reflect the older age of the patients in Group 2.

With regard to the histological analysis, our study substantially confirms the non-specificity of histological findings in the media observed in cases of aortic dissection and additionally demonstrates that aortic size is unrelated to gross structural modifications [12].

The analysis of aortic diameters in particular subgroups of our patient cohort helped in delineating subjects that might be at higher risk of dissection even at smaller aortic diameters. Actually the characteristic to experience an acute dissection at small aortic size can be regarded as an expression of substantial functional tissue susceptibility.

It has been demonstrated that certain risk factors negatively influence elastic properties of tissues and aortic stiffness; among these: cigarette smoking, renal insufficiency, hypertension, and renal failure [25]. Our data confirm that most of these factors are also associated in our study group to relatively smaller aortic diameters: this should prompt a strict follow-up and risk factor modification in subjects at risk. Cigarette smoking cessation and control of hypertension assume a particular prophylactic significance, especially in patients with family history of dissection, suspected connective tissue disease, Marfan syndrome or bicommissural aortic valves. In addition, to afford protection from catastrophic events, perhaps surgical correction in these subjects (at very high risk and unpredictable evolution) should be performed early, in presence of a slightly dilated (40–45 mm) aorta.

However, beyond any pessimistic perception, an effective prevention, in the settings of small aortic diameters, should probably rely on clinical indexes and tests that are still to be developed.

6. Conclusion

Acute aortic dissection is often superimposed on a dilated aorta, although approximately one-third of subjects experience dissection despite a normal or minimally enlarged aorta and only one-tenth of patients will have a pre-existing true ascending aortic aneurysm.

Although aortic diameter remains an important issue for preventive surgery in patients with inherited connective tissue disorders and bicommissural aortic valves, it should be kept in mind that these patients will often experience dissection at smaller aortic diameters. Dissection superimposing on small aortic diameters can be regarded as an expression of substantial functional tissue susceptibility.

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