Aortic Size Distribution in the General Population: Explaining the Size Paradox in Aortic Dissection

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Abstract

Background: Current guidelines recommend a diameter of 5–5.5 cm as the threshold for surgery on the ascending aorta. However, a study from the International Registry of Acute Aortic Dissection showed that nearly 60% occurred at <5.5 cm (the ‘aortic size paradox’) – leading to a debate whether the size threshold should be lowered. However, the study showing dissection at small size had no knowledge of the population at risk. Herein, we aim to calculate the relative risk of aortic dissection at sizes <5.5 cm by analyzing both the number of occurring dissections (numerator) and the population at risk at each aortic size (denominator).

Methods: Using a publicly available database of 3,573 multiethnic subjects (46% male, mean age 60.7 years) from the general population, we plotted a distribution curve of ascending aortic size (by magnetic resonance imaging). The relative risk of aortic dissection was calculated by dividing the proportion of dissections occurring at each size (numerator) by the proportion of aortas of that same size in the general population (denominator).

Results: The mean ascending aortic diameter of the reference population was 3.2 cm (±0.4 cm). The largest diameter was 4.9 cm in women and 5.0 cm in men. The proportion of subjects with an aorta <3.5 cm was 79.2%, that of subjects with 3.5–3.9 cm was 18.0%, that of subjects with 4.0–4.4 cm was 2.6%, and that of subjects with ≥4.5 cm was 0.22%. The relative risk of dissection in those categories was found to be 0.055, 2.5, 4.9, and 346.8, respectively. Patients with an aorta ≥4.5 cm were 6,305 times more likely to suffer aortic dissection than those with an aorta <3.5 cm.

Conclusions: The normal aorta is deceptively small, most commonly <3.5 cm. The aortic size paradox is a byproduct of the very large number of patients in small size ranges. This study fully supports current recommendations for surgical intervention at 5–5.5 cm.

Key Words
Aorta · Aortic dissection · Imaging · Size · Diameter
Introduction

Acute aortic dissection (AAD) is a catastrophic and highly fatal disease. It is estimated that 3–4 dissections occur yearly per 100,000 people in the US [1, 2]. AAD is a devastating disease, with an in-hospital mortality rate reaching nearly 30% [3]. Despite advanced diagnostic techniques, AAD remains an underrecognized condition, as its presentation can mimic many other acute chest and abdominal syndromes. In addition, the aneurysmal disease that underlies AAD is indolent and usually asymptomatic, and many individuals at risk remain undiagnosed [4]. Until now, the only prevention resides in identifying aortas that are at risk for dissection by virtue of aneurysmal dilation and pursuing prophylactic surgical replacement. Although hypertension and specific genetic syndromes predispose to aortic aneurysm and dissection [5–7], it is difficult to predict aortic dissection with accuracy. Current recommendations are based on expert opinion and retrospective data and suggest that the ascending aorta should be replaced at 5.5 cm for the general population [7]. However, a study by the International Registry of Acute Aortic Dissections (IRAD) has shown that aortas can dissect at smaller sizes, as reported by Pape et al. [3] – the ‘aortic size paradox’.

In that IRAD study, Pape et al. [3] examined the distribution of the sizes of aortas that had already dissected. They found that, of 591 type A dissections, 59% occurred at sizes less than the current guideline of 5.5 cm; furthermore, 40% occurred at <5.0 cm. Debate ensued about whether the current surgical threshold should be decreased. We hypothesized an explanation for the aortic size paradox based on a suspicion that normal aortic size would distribute normally, so that huge numbers of patients would be at risk for potential dissection as one moved leftward from the right ‘tail’ of the bell curve, toward smaller sizes (fig. 1). A very large number of patients in small size ranges would render the relative risk of dissection at small sizes small [8].

Relative risk of aortic dissection = \[
\frac{\text{Dissections observed}}{\text{Population at risk}}
\]

This study is meant to explore the validity of this hypothesis that the aortic size paradox originates in the vast number of patients under the bell curve in the smaller aortic sizes.

What exactly constitutes a ‘normal aorta size’ is still under discussion, especially as it has been observed that age, height, body habitus, gender and even ethnicity seem to affect aortic size. Accepted studies underlying classic echocardiographic guidelines are limited by small sample sizes and homogeneity of cohort studies [9]. More recent studies based on CT scan data have set out to establish distribution curves [10, 11]; however, these are also limited by homogeneity in cohort character and original study indication (prejudicing observed aortic size).

This lack of robust data on aortic size in the ‘normal’ population represents a clinically important knowledge gap, particularly in light of the findings by Pape et al. [3]. Yet, while the majority of dissections may occur at aortic diameters below the surgical threshold, it is also true that the vast majority of aortas within the population are considerably smaller than this threshold – representing an enormous pool of individuals potentially at risk for aortic dissection. That is, if the numerator is the number of patients with realized aortic dissection, the appropriate denominator would be the number of patients at risk in the corresponding size category in the general population. Thus, the true statistical risk of aortic dissection at small aortic diameters may well be negligible given the anticipated enormous patient pool in the small aortic size range. A population study of ‘normal’ aortic size could, therefore, serve to inform the calculation of numerator over denominator for aortic dissection.

To determine the hypothetical risk of aortic dissection at subsurgical diameters, we sought to define the distribution of aortic diameters within the general population. To do this, we analyzed magnetic resonance imaging (MRI) data collected as part of the publicly available data set from the Multi-Ethnic Study of Atherosclerosis (MESA).

Additionally, we used these data to investigate the prevalence of thoracic aortic aneurysms (TAAs) in the general population, which is currently relatively poorly known. Identification of TAAs is hindered by the fact that such aneurysms are asymptomatic in over 95% of affected patients [12]. Additionally, many cases of fatal TAA rupture are likely misdiagnosed as myocardial infarction, thereby underestimating the true prevalence of TAAs. The MESA MRI dataset, representing a large cross section of the general population without diagnosed clinical cardiovascular disease, represents a suitable source to define this prevalence.

Methods

MESA was a multicenter trial initiated in 2000 that enrolled over 6,814 patients aged 45–84 without overt cardiovascular disease to investigate various risk factors for developing atherosclerosis over time. Details of this study protocol have been previously published [13]. Cardiac MRI scans were obtained as part of the
initial examination in 73% of the subjects enrolled in this study; 3,573 subjects had MRIs of the aorta. Aortic luminal diameters measured from these imaging studies were publicly reported. These 3,573 patients represent our study population. MESA reports the mean luminal dimensions of the ascending aorta at the level of the right main pulmonary artery.

Mean aortic diameter and standard deviations determined for various patient subgroups, separated by age, gender and ethnicity, have been previously described by Turkbey et al. [14] along with factors that influence aortic size, in their comprehensive paper. For our study we focused solely on the general distribution of sizes, in order to define frequency of each size category across all subjects and to plot an overall distribution curve. Statistical analysis was carried out using Stata (version 11, Stata Corp., College Station, Tex., USA).

To evaluate the risk of type A AAD at various aortic diameters, we compared the proportion of our population within defined aortic size brackets to the previously reported proportion of dissections [3] that occur within these ranges.

### Results

Our cohort was very similar in age to the IRAD cohort, however, as would be expected in a group of exclusive dissection patients, the IRAD cohort had more males and more hypertensive patients (table 1).

The distribution curve for the general population obtained from our MESA cohort resembles a normal distribution curve, but with a wider tail at the upper end (fig. 2a). In other words, the aorta can vary more widely at the large end than it can at the small end of diameters.

When the natural logarithm of diameter is used for the y-axis of the distribution curve, the curve resembles even more closely a normal distribution (fig. 2b). This qualifies the distribution of aortic size as a 'log-normal' distribution, like so many other biological phenomena [15]. Table 2 outlines the frequency of each size category and respective percentage of our total population.

Mean aortic diameter of our study population was 3.2 cm (SD 0.4 cm); 99.97% (n = 3,572) of individuals had an aorta <5.0 cm; only 1 subject, a male, had an aorta that was 5.0 cm. No patients had an aorta >5.0 cm. Nearly 80% of the subjects had an aorta <3.5 cm, with only 8 subjects with an aorta 4.5 cm and greater (0.22%, table 3). In plain words, the normal aorta was very small.

### Table 1. Clinical and demographic factors from the MESA and IRAD databases

<table>
<thead>
<tr>
<th>Variable</th>
<th>MESA</th>
<th>IRAD [3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in study, n</td>
<td>3,573</td>
<td>591</td>
</tr>
<tr>
<td>Age, years</td>
<td>60.7</td>
<td>60.8</td>
</tr>
<tr>
<td>Males, %</td>
<td>46</td>
<td>66</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>42</td>
<td>71</td>
</tr>
</tbody>
</table>

### Table 2. Aortic diameter in general population from the MESA database

<table>
<thead>
<tr>
<th>Aortic diameter, cm</th>
<th>Frequency, n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.5</td>
<td>2,830</td>
<td>79.21</td>
</tr>
<tr>
<td>3.5–3.9</td>
<td>642</td>
<td>17.97</td>
</tr>
<tr>
<td>4.0–4.4</td>
<td>93</td>
<td>2.60</td>
</tr>
<tr>
<td>≥4.5</td>
<td>8</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Fig. 1. Hypothesized role of bell curve characteristics in mitigating observation of some aortic dissections occurring at small aortic size. Note how small the ‘tails’ of such a curve are. Large aneurysms would reside far out in the tails. While dissections do occur at small dimensions, note how rapidly the at-risk group increases in number as the putative criterion diameter goes from $d_1$ to $d_2$. We anticipate that millions of Americans harbor small TAAs, making for a very large denominator of vulnerable patients, and a correspondingly low likelihood of dissection at small sizes. Reprinted with permission from Elefteriades and Farkas [8].
If we define an aortic aneurysm as 1.5× the mean diameter at that level, this gives us 1.5 × 3.2 cm = 4.8 cm. Therefore, with this definition, the prevalence of silent TAA in the general population would be even <0.22%. Alternatively, if we use a definition of aneurysm as an aorta ≥2 SD above the mean value, our data would indicate that 4.0 cm constitutes an aneurysm. With this definition, the prevalence of aneurysm in the general population would be 2.82%.

The IRAD study [3] consisted of 591 patients. Mean age was 60.8 years. The mean diameter at dissection was 5.3 cm. Fifty-nine percent of dissections occurred at sizes <5.5 cm, and 40% occurred at sizes <5.0 cm (table 3).

Figure 3 shows the distribution of aortic sizes from the database of dissected aortas from Pape et al. [3]. Table 3 shows the frequency of each size in the respective category and the subsequent percentages of that size over the total cohort of dissections. As can be seen, a substantial number of aortic dissections occurred at small sizes. However, this graph represents all patients presenting to many IRAD institutions, with no information on patients at risk in each size category. The patients at risk would include large populations in many countries in the catchment area of the many IRAD participating institutions. For the purposes of this study, we presume that the aortic size distribution in the populations at risk in the IRAD catchment areas is similar to our distribution from the MESA study. Both IRAD and MESA represent large, multiethnic populations and can fairly be considered to represent the distribution of aortic sizes in ‘humans’.

The information from the current study on the distribution of aortic sizes is combined with information from Pape et al. [3] to create a hypothetical estimate of relative risk of aortic dissection at various aortic sizes, as shown in table 4. The proportion of dissections in each aortic size range from IRAD is presented in line 1. The proportion of the population in each aortic size range from MESA (representing the ‘human’ population) is shown in line 2. The relative risk [calculated by dividing the proportion of dissections by the proportion of the population (line 1 divided by line 2)] is shown in line 3. Line 4 represents the

Table 3. Size distribution of dissected aortas from the IRAD study [3]

<table>
<thead>
<tr>
<th>Aortic diameter, cm</th>
<th>Frequency, n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.5</td>
<td>25</td>
<td>4.23</td>
</tr>
<tr>
<td>3.5–3.9</td>
<td>35</td>
<td>5.92</td>
</tr>
<tr>
<td>4.0–4.4</td>
<td>78</td>
<td>13.2</td>
</tr>
<tr>
<td>4.5–4.9</td>
<td>90</td>
<td>15.4</td>
</tr>
<tr>
<td>5.0–5.4</td>
<td>119</td>
<td>20.3</td>
</tr>
<tr>
<td>5.5–5.9</td>
<td>82</td>
<td>14.0</td>
</tr>
<tr>
<td>6.0–6.4</td>
<td>63</td>
<td>10.8</td>
</tr>
<tr>
<td>6.5–6.9</td>
<td>27</td>
<td>4.6</td>
</tr>
<tr>
<td>≥7.0</td>
<td>62</td>
<td>10.6</td>
</tr>
</tbody>
</table>

Please note that 76% of patients had aortas >4.5 cm.
relative risk compared to aortas ≤3.4 cm in size (number in each box in line 3 divided by the number in the first box in line 3). In essence, line 4 ‘normalizes’ the dissection risk relative to the smallest size range. Please note that the risk of aortic dissection for aortas ≥4.5 cm is 6,305.5 times greater than for aortas ≤3.4 cm.

### Discussion

The present study adds to our knowledge of the ‘normal’ size of the aorta in human beings, by taking advantage of the MESA study, which had accumulated accurate MRI information on aortic size in over 3,500 individuals without known cardiovascular disease. These data add to the relatively small number of studies in the literature regarding the size of the normal thoracic aorta.

**Normal Size of the Human Aorta**

We see that the ascending aorta is small, with a mean diameter of only 3.2 cm when not diseased. The maximum ascending aortic diameters among these thousands of individuals were only 4.9 cm in women and 5.0 in men. There was not a single patient among the thousands in MESA with an aorta exceeding 5 cm – a dimension that does not generate much enthusiasm at a center for thoracic aortic disease. Based on a current US population estimate of 315,000,000 people, our MESA-based calculations translate to about 168,000 individuals with aortas ≥4.8 cm and 88,000 individuals with an aorta of 5.0 cm. We see from these data that, like so many biological phenomena, aortic size follows a log-normal distribution, with a wider tail at the right side of the curve. That is to say, the aorta can only get so small (at the left end of the curve), but the aorta has more ‘freedom’ over a range of sizes at the upper end of the curve of aortic size.

**Occurrence of Aortic Dissections at Small Sizes – The ‘Aortic Size Paradox’ in Perspective**

The Pape et al. [3] study from IRAD, which showed that half of aortic dissections occurred at less than the common intervention criterion of 5.5 cm for the ascending aorta, raised some concern among the aortic community. But, showing excellent judgment, Pape et al. [3] recommended no change in intervention criteria based on their study.
In 2010, we expressed the opinion that, were population data available, the Pape et al. [3] findings would be mitigated by the finding of huge populations at risk in the small aortic size ranges [8]. That is, we felt that the denominator would likely be so large in the small size ranges that the number of observed dissections would represent only a very small percentage risk. This was based on the anticipation of a normal or log-normal distribution of aortic size (fig. 1, 2).

This suspicion is fully confirmed by the present investigation, which shows very powerfully the overwhelming impact of aortic size on risk of aortic dissection. Even a relatively mild dilatation of the ascending aorta to a size of 4.0–4.4 cm confers an 89-fold increase in risk of aortic dissection. And, an enlargement of the ascending aorta to 4.5 cm or greater confers a 348-fold increased risk of aortic dissection. These population-based studies confirm that aortic dissection at small aortic sizes is an extremely rare phenomenon.

However, it should be noted that at a diameter of 4.5 cm the relative risk of dissection jumps from 4.9 to 346; concurrently, the relative risk compared to aortas ≤3.4 cm in diameter jumps to over 6,000 times more likely. We have previously described ‘hinge points’ or critical sizes in aortic diameter at which the risk of rupture or dissection increases considerably [4]. The current analysis also finds a major hinge point in relative risk (at 4.5 cm; fig. 4).

### Difficulty in Ascertaining the Exact Aortic Size prior to Aortic Dissection

For most acute dissection patients, the only aortic size we have available is that measured on the CT scan done at the time of presentation with dissection. We do not generally have any available scan obtained just prior to the occurrence of dissection. In an animal model for AAD [16], we noted an abrupt (but mild) increase in aortic diameter at the moment of dissection.

Interestingly, Rylski et al. [17] recently looked at type A dissections in patients who had available CT scan imaging up to 2 years prior to dissection. In 27 patients with spontaneous dissections, the average size of the mid-ascending aorta 2 years before it dissected was 4.3 cm; but this diameter changed to an average of 5.2 cm at the time of dissection. (Of course, one cannot rule out the possibility that the aorta enlarged during the 2 years prior to dissection, thus provoking dissection at the larger size.)

These results in the context of the present study are thought-provoking in two aspects. First, the diameter of 4.5 cm in the general population is the diameter where we find in the present study that risk increases markedly — perhaps not to the point where one would extirpate the aorta prophylactically, but reasonably a point for the clinician to start intensive monitoring and risk factor (blood pressure) modification. Second, it is apparent that the geometry of the aorta changes (enlarges) at the time of dissection. Until now, most of the studies on aortic dissection report only size at the time of dissection. Except in rare cases with incidental scans available, it is usually unclear exactly what was the aortic size just before the dissection occurred.

### Limitations (and Strengths)

Ours is not a typical study. We attack an important issue (the aortic size paradox), which bears heavily on criteria for surgical intervention in ascending aortic aneurysm, by correlating information from two literature studies: the MESA study and the IRAD study. We apply a commonsense statistical approach to these data to reach some meaningful observations and conclusions of clinical importance.

Our study has multiple inherent limitations. The MESA population was not screened for cardiovascular disease. However, the fact that no aorta exceeded 5 cm provides powerful post hoc evidence that severe aneurysms simply did not exist in this ‘normal’ population. (It is possible that patients with enlarged aortas underwent surgery and were excluded from this population, but that possibility seems remote, given the relative rarity of tho-
Aortic Size Distribution in the General Population

Aortic dissection is an unpredictable and potentially catastrophic event. Until now, effective prevention still evades medical science, except via replacement of the enlarging aorta. The size of 5.0–5.5 cm for prophylactic surgical extirpation remains valid. Although dissections can occur at smaller sizes, the relative risk of dissection compared to the huge numbers of patients with small aneurysms is very low. To recommend surgery at smaller sizes would dangerously – and unnecessarily – expose individuals with minimal risk of dissection to the small but real risk of open-heart surgery. Vigilance should be augmented from the point that an aorta reaches 4.5 cm, with periodic imaging and risk factor modification (blood pressure control). We are hopeful (and confident) that further research into genetic markers, biochemical bloodborne markers, wall stress measurements, and shape indices will enhance surgical decision making in the future – above and beyond the effectiveness of size alone as a discriminator.

Conclusion

Aortic dissection is an unpredictable and potentially catastrophic event. Until now, effective prevention still evades medical science, except via replacement of the enlarging aorta. The size of 5.0–5.5 cm for prophylactic surgical extirpation remains valid. Although dissections can occur at smaller sizes, the relative risk of dissection compared to the huge numbers of patients with small aneurysms is very low. To recommend surgery at smaller sizes would dangerously – and unnecessarily – expose individuals with minimal risk of dissection to the small but real risk of open-heart surgery. Vigilance should be augmented from the point that an aorta reaches 4.5 cm, with periodic imaging and risk factor modification (blood pressure control). We are hopeful (and confident) that further research into genetic markers, biochemical bloodborne markers, wall stress measurements, and shape indices will enhance surgical decision making in the future – above and beyond the effectiveness of size alone as a discriminator.

Conflict of Interest

The authors have no conflicts of interest to disclose. There were no sources of funding.

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Erratum

The authors of the article entitled ‘Aortic size distribution in the general population: explaining the size paradox in aortic dissection’ [Cardiology 2015;131:265–272, DOI: 10.1159/000381281] wish to publish the following correction. On page 265, the first name of the 2nd author has been published incorrectly: Kahled should read Khaled. The correct author list should be as follows:

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