Relationship Between Abdominal Aortic Aneurysm Wall Compliance and Clinical Outcome: a Preliminary Analysis

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Background: Aortic compliance, as measured by the pressure-strain elastic modulus (Ep) and stiffness (B), may allow a more precise estimate of abdominal aortic aneurysm rupture risk than size alone.

Aim: To determine the relationships between AAA compliance, size, growth, and clinical outcome.

Methods: One-hundred and twelve patients with initially non-operated AAA (86 men, 26 women, mean age 73 years), recruited from five centres, underwent baseline compliance measurements and were then followed for a median of 7 (range 2-18) months; 85 patients underwent repeated measurements (median 3, range 2-5) 3-6-monthly over a median of 12 (range 3-18 months).

Results: Seven patients have ruptured and 16 have undergone repair of non-ruptured AAA. AAA that ruptured had significantly lower Ep and B (more compliant). In AAA that ruptured or required repair there was an inverse relationship between diameter and Ep and B. In those undergoing repeated measurements AAA expansion was only associated with a significant increase in Ep and B in non-operated patients.

Conclusions: Baseline AAA compliance was significantly related to rupture and the future requirement for operative repair. Failure of compliance to increase with size may be a marker for rapid growth, developmental symptoms and rupture.

Introduction

Ruptured abdominal aortic aneurysm (AAA) is associated with a 30-day combined community and hospital mortality of 90%. By contrast, the mortality associated with elective repair is currently 10% or less in many centres.1 The decision to operate on an asymptomatic AAA involves weighing the risk of rupture against the risk of operative repair for that individual patient. The risk of rupture is currently estimated primarily on the basis of maximal diameter and growth rate, although both variables are known to be inaccurate predictors of rupture. As no size of AAA appears to be entirely free from the risk of rapid expansion and rupture,2 a method which provides a more precise quantification of risk for individual patients is urgently required. It is hypothesised that compliance, which relates directly to aortic wall behaviour and composition, might provide such information. The aim of the present study was to investigate, for the first time, the relationship between AAA wall compliance, maximum diameter and growth rates in a series of patients, with initially non-operated and asymptomatic AAA.

Patients and Methods

One-hundred and twelve patients with non-operated AAA, recruited from five different centres, underwent baseline compliance measurements, and were followed for a median of 7 (range of 2-18) months. The mean age of the patients was 73 years. There were 86 men and 26 women. Patients were not operated on initially, either because of small size or because of co-morbidity which, in the opinion of their surgeon, precluded AAA repair. All patients gave fully informed consent and the study was approved by the local ethics committees. A subset of 85 patients underwent repeated compliance measurements (median 3, range 2-5) at 3-6-monthly intervals over a median follow-up period of 12 (range 3-18) months.

The decision to subsequently operate or not upon a
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patient in this study group was left entirely to the discretion of the consultant surgeons responsible, who were unaware of compliance data. Although it could be argued that stipulating criteria for operation would have allowed the end-points of the study to be defined more precisely, in the opinion of the authors and the relevant ethics committees this would have been unsatisfactory for two reasons. Firstly, at the outset of the study it was not possible to know whether compliance would or would not relate to future aneurysm behaviour. Secondly, any influence exerted by the authors on the decision to operate might have biased the results of the study. The requirement for surgery was precipitated by onset of symptoms (abdominal and/or back pain) in two cases, and in 14 cases because, in the opinion of the responsible consultant, the AAA had enlarged to a point where the benefits of repair outweighed the potential risks.

Compliance was measured by means of an electronic echo-tracking device (Diamove, Teltec, Lund, Sweden) interfaced with a B-mode real-time ultrasound scanner (EUB-240, Hitachi, Tokyo, Japan) fitted with a 3.5 MHz linear array transducer. An echo-tracking phase-locked loop circuit restored the position of an electronic gate relative to the moving echo and yielded the echo movement per unit time. The instrument was equipped with dual echo-tracking which made it possible to track simultaneously two separate echoes from opposing vessel walls. The difference between signals indicated instantaneously the change in vessel diameter. The calculated smallest detectable movement was 7.8 μm, the repetition frequency of the echo-tracking loops was 870 Hz, and the time resolution was therefore approximately 1.2 ms. The data acquisition unit comprised a 486 personal computer (Toshiba) linked to a 12-bit analogue-to-digital converter (Analogue Devices, Norwood, U.S.A.). Change in maximal AAA diameter with cardiac cycle was measured over an 11 s period.

Strain (fractional diameter change) was defined as:

\[
\text{Strain} = \frac{\text{maximal systolic diameter} - \text{maximal diastolic diameter}}{\text{maximal diastolic diameter}}
\]

The arterial wall distensibility was initially expressed as pressure strain elastic modulus (Ep) where:

\[
\text{Ep} = K \times \frac{\text{systolic pressure} - \text{diastolic pressure}}{\text{strain}}
\]

The constant K = 133.3 and allows Ep to be converted from mmHg to Newton (N/m²).

Because of the non-linear pressure-diameter relationship of the normal arterial wall, Ep is pressure dependent. Previous workers have observed a linear relation in vitro between the logarithm of relative pressure and distension ratio. This index is called stiffness (B) and appears to characterise the entire deformation behaviour of the arterial wall, without pressure dependence, within the physiological range. Stiffness may therefore be a more useful index of aortic compliance than Ep; although whether this relationship holds true for the human aneurysmal aorta in vivo is unknown. The higher Ep and B, the less distensible the artery and the lower the compliance.

For a more detailed discussion of these concepts the reader is referred to two recent reviews. Systolic and diastolic blood pressures were measured in the brachial artery in the usual way by auscultation following inflation and deflection of a sphygmomanometer. Brachial pressure is known to be lower than aortic pressure. However, previous authors have concluded that although Ep and B are consequently under-estimated, this is a systematic error that is likely to affect equally the members of any particular study group. Furthermore, if compliance is to prove a clinically useful variable worthy of routine measurement, its value must be established in relation to brachial pressure rather than a scientifically more robust but impracticable direct intra-arterial measurement of blood pressure. Mean arterial pressure (MAP) was diastolic pressure plus one-third pulse pressure.

Because variables were highly skewed, linear associations between pairs were assessed using Spearman’s rank correlation. Data was entered on the Edinburgh University mainframe computer for statistical analysis.

**Results**

Baseline compliance measurements, size and subsequent outcome

Seven patients have ruptured and 16 have undergone operative repair for non-ruptured AAA; two for symptoms (abdominal and/or back pain) and 14 due to increase in size. Seven patients have died of unrelated causes.

Patients who went on to rupture had a greater baseline maximal AAA diameter than those who were operated for non-rupture, who in turn had larger AAA than those who did not rupture or undergo repair. Patients who ruptured had lower baseline Ep and B than those who were operated for non-rupture, who in turn had lower baseline Ep and B than those who neither ruptured nor were operated (Table 1).
Table 1. Comparison of baseline size, $Ep$, and $B$ in those patients who went on to rupture, required operative repair of non-ruptured AAA, and those who did not.

<table>
<thead>
<tr>
<th>Baseline compliance measurements</th>
<th>Rupture ($n=7$)</th>
<th>Operated (non-rupture) ($n=16$)</th>
<th>Not operated or ruptured ($n=89$)</th>
<th>$p$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal diameter (mm)</td>
<td>54.9 (46.9–72.0)</td>
<td>49.2 (42.4–70.3)</td>
<td>45.0 (28.8–77.2)</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td>Strain – $Ep$ (N/m$^2$)</td>
<td>2.16 (1.59–3.72)</td>
<td>2.45 (1.22–7.58)</td>
<td>2.79 (0.55–9.46)</td>
<td>$p&lt;0.01$</td>
</tr>
<tr>
<td>Stiffness – $B$ (arbitrary units)</td>
<td>15 (9.1–23.0)</td>
<td>17.3 (9.9–51.5)</td>
<td>18.2 (4.0–71.6)</td>
<td>$p&lt;0.01$</td>
</tr>
</tbody>
</table>

* Kruskal–Wallis non-parametric ANOVA 3 column comparison of unpaired median values.

**Relationship between baseline compliance and size**

In patients who subsequently ruptured there was a non-significant inverse relationship between baseline maximal diameter and baseline $Ep$ (Spearman coefficient, $r = -0.25, p = 0.6$) and between baseline maximal diameter and baseline $B$ (Spearman coefficient, $r = -0.11, p = 0.84$).

Patients who underwent operative repair of non-ruptured AAA also demonstrated a non-significant inverse relationship between baseline maximal diameter and baseline $Ep$ (median 2.45, range 1.22–7.58, N/m$^2$) (Spearman coefficient, $r = -0.45, p = 0.074$) (Fig. 1), and between baseline maximal diameter and baseline $B$ (median 17.3, range 9.9–51.5, arbitrary units) ($r = -0.47, p = 0.067$) (Fig. 2).

By contrast, in the 89 patients who neither ruptured nor required operative repair ($n=89$), there was a significant positive correlation between baseline maximal diameter (median 45.0, range 28.8–77.2, mm) and baseline $Ep$ (Spearman coefficient, $r = 0.27, p = 0.01$) (Fig. 3).
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Fig. 4. Relationship between baseline maximal diameter and B in patients with AAA which did not rupture or require operative repair; Spearman coefficient, $r = 0.24$, $p = 0.018$.

and baseline Ep (median 2.79, range 0.55–9.46, N/m²) (Spearman coefficient, $r = 0.27$, $p < 0.01$) (Fig. 3); and between baseline maximal diameter and baseline B (median 18.2, range 4.0–71.6, arbitrary units) ($r = 0.24$, $p = 0.018$) (Fig. 4).

Change in size and compliance over time

In the subset of 85 patients undergoing repeated compliance measurements, two patients have ruptured, eight have undergone operative repair of non-ruptured AAA and four have died of unrelated causes. Due to small sample size, statistical analysis has been restricted to a comparison of the (non-rupture) operated group and the non-operated groups.

Although there was a significant increase in size in both the operated non-rupture and the non-operated groups over the period of the study, only the non-operated group demonstrated a significant increase in Ep and B; that is, an increase in stiffness (Table 2).

<table>
<thead>
<tr>
<th>Operated AAA</th>
<th>Baseline measurement</th>
<th>Final measurement</th>
<th>$p$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal diameter (mm)</td>
<td>48.1 (43.5–56.6)</td>
<td>53.1 (46.2–68.6)</td>
<td>$p = 0.03$</td>
</tr>
<tr>
<td>Strain Ep (N/m²)</td>
<td>2.85 (1.22–6.05)</td>
<td>3.44 (1.1–6.54)</td>
<td>$p = 0.74$</td>
</tr>
<tr>
<td>Stiffness B (arbitrary units)</td>
<td>18.6 (9.9–51.5)</td>
<td>20.45 (9.3–45.4)</td>
<td>$p = 0.84$</td>
</tr>
<tr>
<td>Non-operated AAA</td>
<td>44.3 (28.8–77.2)</td>
<td>49.6 (31.4–80.9)</td>
<td>$p = 0.01$</td>
</tr>
<tr>
<td>Maximal diameter (mm)</td>
<td>2.42 (0.55–9.23)</td>
<td>3.64 (0.95–8.65)</td>
<td>$p = 0.0038$</td>
</tr>
<tr>
<td>Stiffness B (arbitrary units)</td>
<td>18.1 (4.0–71.6)</td>
<td>25.2 (7.5–60.3)</td>
<td>$p = 0.002$</td>
</tr>
</tbody>
</table>

* Wilcoxon signed rank test for paired, non-parametric data.

Conclusions

Numerous attempts have been made to predict, on the basis of physical characteristics, which AAA will rupture and which are safe to observe. Previous work has focused upon absolute size (maximal anterior–posterior or transverse diameter, cross-sectional area), relative size (standardised on the basis of patient build, age and sex), shape (circular vs. elliptical cross-sectional profile on computed tomography), wall thickness and blistering and expansion rate. Aneurysm size and expansion may, in turn, be affected by other factors such as hypertension and continued smoking.

Unfortunately, the predictive value of these variables, while perhaps being useful in population studies, is insufficient to quantify risk on an individual patient basis. Rupture of small AAA, though uncommon, is well recognised, suggesting that other factors more directly related to aortic wall behaviour may be more important and worthy of study. However, to date, little work has been performed defining the mechanical properties of the aneurysm wall itself.

Aneurysmal dilation of the aorta is associated with a significant decrease in elastin and smooth muscle content and an increase in collagen and ground substance. In vitro studies comparing the tensile strength of excised normal and aneurysmal human aorta obtained at surgery or post-mortem have indicated that aneurysmal tissue is much less distensible; and that this loss of compliance is related to loss of elastin from the wall. Aortic compliance, as measured by Doppler ultrasound assessment of pulse wave velocity, is reduced in adults at increased risk of atherosclerosis and such measurements have been proposed as a useful screening test for premature vascular disease.

In this prospective study, baseline compliance measurements have been made in order to determine whether differences in compliance might predict rupture and/or the future requirement for operative repair.
intervention on account of symptoms or expansion. Both compliance and maximal diameter varied widely in the rupture, the non-rupture operated, and the non-rupture non-operated groups. The principal finding is that AAA which subsequently ruptured or required operative repair, while being significantly larger at baseline, possessed significantly lower Ep and B. In other words, size for size, AAA which rupture or require elective repair appear to be more compliant than those AAA that do not.

The fundamental question is, therefore, whether such compliance data can be used independently of diameter to predict which AAA are at risk of rupture. In this respect, interesting relationships between compliance and size in the different clinical groups were observed. The relationship between compliance and size in the non-operated, non-ruptured group was similar to that found in a previous retrospective study of 60 patients with non-operated, non-ruptured AAA. In these patients, as their AAA increases in size there is a significant increase in both Ep and B; that is, the aneurysm becomes stiffer and less compliant as it grows. By contrast, in patients who subsequently rupture or require operative intervention, Ep and B fail to increase or even fall as the AAA grows.

It is possible that a single baseline compliance measurement might be misleading if both size and compliance were to change between that time and the time the AAA ruptures or is repaired. For this reason, repeated measurements were performed in a subset of patients to determine whether a change in compliance over time might relate to future clinical outcomes. The principal finding is that the relationship between compliance and size observed in the clinical groups is also observed in individual AAAs over time. Thus, while there was a significant increase in size in both operated and non-operated AAA, only the non-operated AAAs demonstrated a significant increase in Ep and B. In the operated AAA, increasing size was not associated with a significant increase in stiffness.

Taken together, these preliminary data suggest that, while a single baseline compliance measurement may be able to distinguish those AAA that subsequently rupture or require operative repair, changes in compliance over time are likely to be a better predictor of future behaviour. In particular, failure of compliance to decrease with size, and/or an increase in the compliance of a large AAA over time, may be markers for above average growth, onset of symptoms, and rupture.

One might speculate that small AAA are more compliant than large AAA because they retain many of the features of the normal arterial wall in that a significant proportion of the wall still comprises elastin. As AAA enlarge, elastin is replaced with collagen and compliance decreases; that is, they become stiffer. Once AAA reach a certain size, which may vary considerably between different patients, it may be possible to differentiate AAA on the basis of compliance measurements into two types:

(a) Type I AAA. Further enlargement is accompanied by further increases in stiffness. This increase in stiffness is due to increasing collagen deposition and/or remodelling in the aortic wall which actually confers strength to the AAA such that the risk of rupture is, in fact, low.

(b) Type II AAA. Further enlargement is not associated with an increase in stiffness and, in fact, stiffness may even fall. This may be because of a failure to lay down and remodel collagen, leading to the production of an aortic wall which is weak or “thinning”. It is these AAA that may be at risk of rupture.

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References

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