Increased Peak Wall Stress, but Not Maximum Diameter, Is Associated with Symptomatic Abdominal Aortic Aneurysm

Begoña Soto a,b, Luis Vila a,c, Jaime F. Dilmé a,b,c, Jose R. Escudero a,b,c, Sergi Bellmunt d, Mercedes Camacho a,c,*

INTRODUCTION

An abdominal aortic aneurysm (AAA) is a progressive focal dilatation and weakening of the abdominal aorta and it is the most common type of arterial aneurysm. In adults, an aortic diameter > 3.0 cm is generally considered aneurysmal. The disease is progressive, with growth and rupture.1,2 A ruptured AAA is life threatening with a high mortality rate and requires immediate repair.3 Open surgery or endovascular repair are the only treatments currently available for AAA.

Although AAA are usually asymptomatic (aAAA), between 5 and 22% of patients manifest clinical symptoms such as abdominal or back pain, and are termed symptomatic AAA (sAAA).4 The presence of a symptomatic abdominal aortic aneurysm is generally a harbinger of rupture, and sAAA patients require urgent AAA repair.5 Regarding aAAA, the decision to proceed with surgical repair is generally determined by assessing the maximum AAA diameter (MD), which is routinely monitored by medical imaging.6 Elective repair is usually considered when the MD is greater than 55 mm. However, rupture of aneurysms less than 55 mm are greater in symptomatic than in asymptomatic AAA. However considering patients with a maximum diameter ≥ 65 mm alone, only PWS was useful in differentiating symptomatic from asymptomatic AAA.

WHAT THIS PAPER ADDS

Because the presence of symptoms is strongly associated with the risk of rupture, this fact was used to assess the differences between the most commonly used parameter, the AAA maximum diameter, and finite element analysis calculated PWS in identifying symptomatic patients. This study indicates that maximum diameter and PWS are greater in symptomatic than in asymptomatic AAA. However considering patients with a maximum diameter ≥ 65 mm alone, only PWS was useful in differentiating symptomatic from asymptomatic AAA.

Objective: Maximum diameter (MD) is the established rupture predictor for abdominal aortic aneurysm (AAA). However, biomechanical markers from finite element analysis (FEA) could be more accurate predictors for these patients. In this study, the association between peak wall stress (PWS) and MD with symptoms of AAA was evaluated.

Methods: Patients diagnosed with infrarenal non-ruptured AAA at the centre between 2009 and 2015 were included. Clinical data, morphological variables (including MD), and the biomechanical variables PWS and diameter normalised PWS (dnPWS) in symptomatic (sAAA) and asymptomatic AAA patients (aAAA) were included.

Results: A total of 170 patients were analysed, 153 aAAA and 17 sAAA. MD was significantly greater in sAAA patients than in aAAA patients (70.4 mm, 95% CI 66.4–86.0 vs. 59.1 mm, 95% CI 53.7–67.8, respectively; p = .002). PWS was also significantly higher in the sAAA group (324.6 kPa, 95% CI 217.4–399.5 vs. 199.2 kPa, 95% CI 165.6–239.5; p < .01). No differences in MD were found in patients with an AAA ≥ 65 mm (43 aAAA and 14 sAAA); however, both PWS (327.4 kPa, 95% CI 239.0–473.3 vs. 229.4 kPa, 95% CI 210.0 to 289.4; p = .020) and dnPWS (4.3, 95% CI 3.17–4.67 vs. 3.03, 95% CI 2.8–3.49; p = .004) were higher in sAAA than in aAAA.

Conclusions: This study suggests that MD and the biomechanical parameters obtained by finite element analysis are greater in sAAA than in aAAA. However, considering patients with MD ≥ 65 mm alone, only PWS, and particularly dnPWS, were able to differentiate sAAA from aAAA.

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Keywords: Abdominal aortic aneurysm, Morphological variables, Biomechanical variables, Finite element analysis, Symptomatic aneurysm

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diameter has been reported, suggesting that the risk of aneurysm rupture is not determined by MD alone.\textsuperscript{7,8}

Mechanisms leading to AAA rupture remain unclear. Many studies report that the difference between complicated AAA (sAAA and ruptured AAA) and aAAA is primarily biomechanical wall stress. Peak wall stress (PWS) evaluated using computer modelling through finite element analysis (FEA) is a useful parameter for predicting the risk of rupture,\textsuperscript{9–12} with PWS being greater in symptomatic or ruptured AAA than in asymptomatic intact AAA.

Since symptomatic aneurysms harbour an increased risk of rupture, the aim of this study was to compare the ability of biomechanical parameters from FEA and MD to differentiate between symptomatic and asymptomatic AAA patients.

**METHODS**

**Patients**

Between 2009 and 2015, consecutive patients diagnosed with infrarenal AAA were included in the study. The diagnosis of AAA was confirmed by computed tomography (CT) scan. Exclusion criteria included unsuitable computed tomography angiography (CTA) for FEA analysis, juxtagenual aneurysms (since the presence of adjacent visceral arteries on the imaging studies can complicate FEA analysis), myotic aneurysms, and ruptured aneurysms (confirmed by the presence of free blood in the abdominal space on CTA). Patients with symptoms were included in the sAAA non-ruptured group. sAAA was considered when the patient had an intact AAA on CT scanning and current onset back, abdominal, or groin pain not identified to be from other causes.\textsuperscript{5} To exclude other causes of pain, blood analysis, radiological, or ultrasound examinations were obtained when needed. An emergency physician also confirmed the differential diagnosis.

Only strictly necessary clinical data from patients were used, obtained from the informatics database of the hospital. All data were collected by the same investigator, and were stored on a computer using a personal key. The data included the clinical history of various comorbidities, including diabetes mellitus (DM, all types), systolic and diastolic blood pressure, dyslipidaemia (total cholesterol >200 mg/dL), cerebrovascular disease (history of stroke, transient ischaemic attack, or major neurological deficit), heart disease (history of myocardial infarction, angina pectoris, or previous coronary intervention), lung disease (chronic obstructive pulmonary disease), smoking (during the last year), and peripheral artery disease. Each patient’s weight and height were also recorded (see Table 1).

The protocol was approved by the institution’s review board (protocol code, IIBS-FIN-2013-89). As this was a retrospective case series analysis, informed consent was not deemed necessary.

The three dimensional AAA geometry was acquired from routine CTA imaging data. The lumen, intraluminal thrombus, and external wall data were acquired separately and semi-automatically. The program includes a manual correction feature if some special point is found, such as a penetrating ulcer or some other unusual anatomy. The resultant geometry is subdivided into multiple contiguous elements that form a fine mesh. The AAA is ready for wall stress computation after the appropriate material properties are set. The end result is aneurysm specific wall stress distribution.\textsuperscript{9,12}

In all cases, the segment from the infrarenal aorta to the iliac bifurcation was analysed. The morphological variables

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**Table 1. AAA demographics.**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>sAAA</th>
<th>p</th>
<th>Patients with MD ≥ 65 mm</th>
<th>aAAA</th>
<th>sAAA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>153</td>
<td>17</td>
<td>.29</td>
<td>43</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>74 (68–79)\textsuperscript{a}</td>
<td>77 (69–81)</td>
<td>.65</td>
<td>75 (67–80)</td>
<td>78 (72–83)</td>
<td>.74</td>
<td>.17</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>75 (70–85)</td>
<td>70 (61–80)</td>
<td>.69</td>
<td>73 (67–82)</td>
<td>67 (60–80)</td>
<td>.82</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 (1.65–1.74)</td>
<td>1.7 (1.66–1.71)</td>
<td>.69</td>
<td>1.7 (1.67–1.73)</td>
<td>1.7 (1.66–1.71)</td>
<td>.42</td>
<td></td>
</tr>
<tr>
<td>Sex, % (women)</td>
<td>3.9</td>
<td>5.9</td>
<td>.60</td>
<td>2.3</td>
<td>7.1</td>
<td>.99</td>
<td></td>
</tr>
<tr>
<td>CSBP (mmHg)</td>
<td>140 (130–146)</td>
<td>140 (138–141)</td>
<td>.92</td>
<td>140 (130–140)</td>
<td>140 (130–140)</td>
<td>.68</td>
<td></td>
</tr>
<tr>
<td>DSBP (mmHg)</td>
<td>80 (70–80)</td>
<td>70 (70–80)</td>
<td>.35</td>
<td>70 (70–80)</td>
<td>70 (70–80)</td>
<td>.61</td>
<td></td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>54.9</td>
<td>41.2</td>
<td>.41</td>
<td>55.8</td>
<td>35.7</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>HTN (%)</td>
<td>76.5</td>
<td>76.5</td>
<td>.76</td>
<td>69.8</td>
<td>71.4</td>
<td>.82</td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>21.6</td>
<td>17.6</td>
<td>.94</td>
<td>23.3</td>
<td>14.3</td>
<td>.73</td>
<td></td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>25.5</td>
<td>18.8</td>
<td>.78</td>
<td>2.9</td>
<td>15.4</td>
<td>.97</td>
<td></td>
</tr>
<tr>
<td>PAD (%)</td>
<td>37.9</td>
<td>38.5</td>
<td>.80</td>
<td>46.5</td>
<td>4.0</td>
<td>.99</td>
<td></td>
</tr>
<tr>
<td>BVD (%)</td>
<td>7.2</td>
<td>11.8</td>
<td>.85</td>
<td>7.0</td>
<td>14.3</td>
<td>.77</td>
<td></td>
</tr>
<tr>
<td>IHD (%)</td>
<td>26.8</td>
<td>35.3</td>
<td>.65</td>
<td>16.3</td>
<td>35.7</td>
<td>.24</td>
<td></td>
</tr>
<tr>
<td>COPD (%)</td>
<td>15.7</td>
<td>17.6</td>
<td>.88</td>
<td>18.6</td>
<td>21.4</td>
<td>.87</td>
<td></td>
</tr>
</tbody>
</table>

BVD = brain vascular disease; CSBP = chronic diastolic blood pressure; COPD = chronic obstructive pulmonary disease; CSBP = chronic systolic blood pressure; HTN = chronic hypertension; IHD = ischaemic heart disease; PAD = peripheral artery disease.

\textsuperscript{a} Non-normally distributed quantitative absolute data are expressed as median (25–75%).
determined were MD, maximum lumen diameter, maximum thickness of intraluminal thrombus, total volume of the aneurysm, total volume of lumen, and total volume of intraluminal thrombus.

The biomechanical variable determined was PWS: the maximal stress on the surface of the AAA wall based on aneurysm shape, diameter, and blood pressure values. The diameter normalised PWS (dnPWS), PWS divided by MD, was also analysed.

**Statistical analysis**

SPSS and Sigma-Plot software were used for statistical analysis. To compare the demographic variables between symptomatic and non-symptomatic patients, the Student t test was used for those continuous variables with a normal distribution and the Mann—Whitney U test was used for those continuous variables that did not have a normal distribution. To compare demographic dichotomous variables between symptomatic and non-symptomatic patients, the z test was used. To compare symptomatic and non-symptomatic patients with regard to morphological and FEA calculated parameters the Mann—Whitney U test was used because the data did not adjust to a normal distribution.

Receiver operating characteristic (ROC) curves were used to evaluate the capacity of morphological and biomechanical parameters to discriminate between symptomatic and asymptomatic patients. To compare the area under the curve (AUC), the method of Hanley and McNeil with the Bonferroni correction for multiple comparisons was used. In addition to the ROC study, to choose the cutoff point that identified sAAA, continuous value parameters were analysed using classification and a regression tree (CART). The CART analysis split the continuous data into segments that were as heterogeneous as possible, according to the dependent variable. For CART analysis, the symptomatic condition (positive) was considered as a dichotomous state variable, and based on data from the ROC curves; dnPWS was chosen as the test variable. A p value < .05 was considered significant.

To calculate the sample size, the results of the paper by Erhart et al. were taken into account. The ratio of asymptomatic/symptomatic patients in the database was 9:1. The common standard deviation was assumed to be 34. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two sided test, 153 subjects were necessary in the first group and 17 in the second group in order to reach 80% power to detect a difference greater than or equal to 25 units. GRANMO (7.12) software was used (https://www.imim.cat/ofertadeserveis/software-public/granmo).

**RESULTS**

Table 1 shows the patient demographic and clinical data. Of the 170 patients included in the study, 17 were symptomatic and 153 asymptomatic. Patient MD values ranged from 32.6 to 120 mm. With regard to demographic and clinical data, no significant differences were observed between symptomatic and asymptomatic patients, except for weight, which was slightly higher in the aAAA group.

As the presence of symptoms was clearly associated with large aneurysms, patients were stratified into two groups: small—medium diameter (MD < 65 mm), and large diameter (MD ≥ 65 mm). This arbitrary threshold diameter was used because the median of the distribution of MD for patients with MD > 55 mm was 65 mm. Nevertheless, only the large MD group could be studied because only three of 105 patients in the MD < 65 mm group were sAAA, so the statistic was not reliable in this group. Table 1 shows the demographic and clinical data of patients with MD ≥ 65 mm (57 patients: 43 aAAA and 14 sAAA); no statistically significant differences were observed between the two groups.

Table 2 shows morphological and FEA calculated parameters. When all patients were included in the statistics, the MD, lumen volume, AAA volume, intraluminal thrombus volume, PWS, and dnPWS were significantly greater in sAAA patients.

Since both MD and PWS were statistically different when comparing the sAAA and aAAA groups (Table 2), the predictive ability of these parameters and dnPWS using the ROC curve were compared. When all patients were included, the AUCs for the ROC curve based on MD, PWS, and dnPWS showed no significant differences (Fig. 1). Thus,

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Table 2. Morphological and FEA calculated parameters.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aAAA</td>
<td>sAAA</td>
<td>p</td>
<td>aAAA</td>
<td>sAAA</td>
<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>153</td>
<td>17</td>
<td></td>
<td>43</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD (mm)</td>
<td>59.1</td>
<td>53.7</td>
<td>.67</td>
<td>7.4</td>
<td>66.4</td>
<td>.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMD (mm)</td>
<td>38.2</td>
<td>32.9</td>
<td>.47</td>
<td>42.3</td>
<td>38.3</td>
<td>.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILTMD (mm)</td>
<td>23.4</td>
<td>15.6</td>
<td>.28</td>
<td>25.6</td>
<td>2.8</td>
<td>.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV (cm³)</td>
<td>68.6</td>
<td>47.1</td>
<td>.104</td>
<td>89.5</td>
<td>56.8</td>
<td>184.8</td>
<td>.030</td>
<td>114.3</td>
</tr>
<tr>
<td>AAVV (cm³)</td>
<td>178.2</td>
<td>134.0</td>
<td>234.0</td>
<td>233.5</td>
<td>201.8</td>
<td>455.0  </td>
<td>.003</td>
<td>333.7</td>
</tr>
<tr>
<td>ILTV (cm³)</td>
<td>79.9</td>
<td>5.0</td>
<td>111.4</td>
<td>155.8</td>
<td>86.5</td>
<td>241.6</td>
<td>.008</td>
<td>148.3</td>
</tr>
<tr>
<td>PWS (Kpa)</td>
<td>199.2</td>
<td>165.6</td>
<td>239.5</td>
<td>324.6</td>
<td>217.4</td>
<td>399.5</td>
<td>&lt;.001</td>
<td>229.4</td>
</tr>
<tr>
<td>dnPWS (Kpa/mm)</td>
<td>3.30</td>
<td>2.88</td>
<td>3.87</td>
<td>4.41</td>
<td>3.35</td>
<td>4.86</td>
<td>.003</td>
<td>3.03</td>
</tr>
</tbody>
</table>

AAAV = AAA volume; dnPWS = diameter-normalised peak wall stress; ILTMD = ILT maximum diameter; ILTV = ILT volume; LMD = lumen maximum diameter; LV = lumen volume; MD = maximum AAA diameter; PWS = peak wall stress.

* Non-normally distributed quantitative data are expressed as median (25–75%).
MD, PWS, and dnPWS were useful to predict sAAA and had similar statistical outcomes (Table 2 and Fig. 1).

The statistical analysis in the patient cohort who had an aneurysm with a MD ≥65 mm, as stated above, showed no differences in the demographic characteristics between sAAA and aAAA patients. Results in Table 2 show that, unlike when all patients were included, there were no statistical differences in the morphological parameters between sAAA and aAAA, while PWS and dnPWS were significantly greater in the sAAA group. The ROC curves of patients with a MD ≥ 65 mm showed that the AUCs of PWS and dnPWS were significantly greater than MD (p = .018 and p = .033, respectively, after Bonferroni correction) whereas there were no significant differences between PWS and dnPWS (Fig. 2). To find a cutoff point that allowed the classification of the sample, a CART analysis was performed in addition to the ROC study. The symptomatic condition was the dichotomous state variable and, based on data from the ROC curves of the patients with MD > 65 mm, dnPWS as the test variable was used.

When all patients were included, CART analysis classified patients into two categories: dnPWS ≤ 4.3 kPa/mm and dnPWS > 4.3 kPa/mm (Fig. 3). Furthermore, CART analysis using symptomatic condition as the dependent variable and dnPWS as the independent variable analysing only patients having an aneurysm with MD ≥ 65 mm, also classified patients into two categories: dnPWS ≤ 3.8 kPa/mm and dnPWS > 3.8 kPa/mm (Fig. 4).

**DISCUSSION**

One of the biggest challenges facing the vascular surgeon is the ability to predict the risk of rupture of a particular AAA given the associated high mortality rate. Several reports suggest biomechanical analysis is an effective tool for predicting the risk of AAA rupture. This fact was used to assess the differences between the most commonly used parameter, the AAA MD and FEA calculated PWS and dnPWS in identifying symptomatic patients. Biomechanical differences between aAAA and sAAA were found.

A meta-analysis published in 2010 by Malkawi et al. and another in 2014 by Khosla et al. suggested that PWS was significantly greater in patients with symptomatic or ruptured AAA than in those with an asymptomatic intact AAA. Khosla’s review included nine studies, with a combined population of 348 individuals: 204 with asymptomatic intact AAA and 144 with symptomatic/ruptured AAA. The main limitation of this analysis was the heterogeneity between the included studies regarding participant selection, the FEA software used and the FEA calculations applied. Consistently with these previous reports this study observed that PWS and dnPWS were significantly higher in the sAAA group. Of note, a large number of patients (153 aAAA and 17 sAAA) were included in the study and uniform criteria for patient inclusion and data collection were applied. However, although the series is large, the group of symptomatic AAA is relatively small. This low sAAA patient number may be related to strict inclusion criteria (see Methods). Ruptured AAA were not included in the study for two main reasons: FEA is difficult to perform in this group of patients and FEA is not validated for ruptured AAA because when this occurs, blood enters the abdominal space and the CTA structure and pressure on the aortic wall changes. In effect, in the study of Erhart et al., only nine of 15 patients with ruptured AAA were finally included in their analysis due to complex vessel morphology or contrast extravasation.

When all patients were included in the analysis, both MD and PWS or dnPWS were able to predict that an aneurysm was symptomatic, with PWS being a slightly better predictor parameter than dnPWS. These results are consistent with symptoms is strongly associated with the risk of rupture, but not Maximum Diameter, is Associated with Symptomatic Abdominal Aortic Aneurysm, European Journal of Vascular and Endovascular Surgery (2017), https://doi.org/10.1016/j.ejvs.2017.09.010
previous reports showing that both MD and PWS predicted rupture, although PWS was superior in differentiating patients who would present catastrophic outcomes.\textsuperscript{10,15–17} However, when only the most developed aneurysms were considered, the scenario changed dramatically: the MD completely lost its ability to predict sAAA while the PWS and the dnPWS (the latter being the better predictor) retained this ability. CART analysis showed that biomechanical analysis became more important when the AAA diameter was \( \geq 65\) mm, since it is the only data that differ between aAAA and sAAA. Nevertheless, it would have been even more valuable to predict sAAA in patients with MD \(< 55\) mm, the diameter at which surgery is recommended. In addition, when the patients were stratified into three groups, small MD \(< 55\), medium MD = (55–64.9 mm) and large MD \(\geq 65\) mm, in all three groups dnPWS best predicted the presence of symptoms in terms of AUCs (not shown). However, the limitation was that only two of 45 in the \(< 55\) mm group and one of 65 in the 55–65 mm group were sAAA, so the validity of the statistics is highly questionable in these groups.

It is interesting to note that only FEA showed differences between sAAA and aAAA in the group of large AAA. In routine clinical practice, every AAA with a MD \(\geq 65\) mm is considered for surgery. Although biomechanical parameters would not change the final indications, they would help clinicians limit indications in cases of complex anatomy, and in elderly patients or those with high comorbidity. These findings are also useful to prioritise those operations that may be considered urgent due to a high risk, and therefore an objective criterion is necessary. It was found that this criterion cannot be fully based on the MD but rather on the dnPWS, at least regarding AAA with a MD \(\geq 65\) mm. However, as in other studies, the main limitation of this work is the difficulty demonstrating that stress analysis is a valid tool to predict the risk of AAA rupture. Of course, additional studies would be desirable to find a threshold value to identify asymptomatic patients at increased risk of rupture. Follow-up studies would be necessary but are not an option in all patients because treatment is immediate after diagnosis by MD, it might be an option only in patients unsuitable for immediate surgery. A parameter to predict sAAA is of limited use as the symptoms themselves are predictive, the hypothesis and the putative usefulness of this work is that if a parameter can predict a high risk characteristic such as the presence of symptoms it will be able to predict AAA at risk in general. This study adds value in the sense that PWS and dnPWS predict sAAA. It is therefore legitimate to assume that these parameters can also predict the risk of rupture of any AAA. A limitation of this study is the possible selection bias because of its retrospective design with consecutive recruitment.

In conclusion, using the FEA model significant morphological and biomechanical differences between symptomatic and asymptomatic AAA were observed. However, when AAA patients with MD \(\geq 65\) mm were considered separately, the MD was unable to recognise sAAA, while PWS,
and particularly dnPWS, were able to do so. aAAA with increased dnPWS may be at a high risk of becoming symptomatic or even complicated cases, but further studies are needed based on individual follow-up to confirm this.

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CONFLICT OF INTEREST

None.

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REFERENCES


