Thrombus volume is similar in patients with ruptured and intact abdominal aortic aneurysms

Jonathan Golledge, MChir, FRACS (Vasc), FRCS, Vikram Iyer, MBBS (Hons), Julie Jenkins, RN, Barbara Bradshaw, RGN, Oliver Cronin, MBBS (Hons), and Philip J. Walker, FRACS (Vasc)

Townsville and Brisbane, Queensland, Australia

Objective: Most abdominal aortic aneurysms (AAAs) contain intraluminal thrombus (ILT), which has been demonstrated to contain proteolytic enzymes and proinflammatory cytokines implicated in AAA progression and rupture. In animal models, anticoagulants have been shown to limit AAA progression. Whether ILT plays a role in AAA rupture is unknown.

The aim of this study was to compare the volume of ILT in patients with ruptured and intact AAAs.

Methods: We matched by maximum axial diameter alone, on a 1:2 basis, 28 patients with ruptured AAAs and 56 patients with intact AAAs. Total infrarenal aortic volume and ILT volume were measured from computed tomography angiograms using a previously validated and reproducible semiautomated workstation protocol. Clinical risk factors were also recorded. The Mann-Whitney U test was used to compare ILT volumes between patients with ruptured and intact AAAs.

Results: Median (interquartile range [IQR]) maximum AAA diameter (84.0 [77.5-93.9] mm vs 82.6 [77.1-93.3] mm; P = .769) and median (IQR) total AAA volume (372.8 [277.4-486.1] cm³ vs 358.4 [289.1-563.4] cm³; P = .977) were similar in patients with ruptured and intact AAAs. Median (IQR) AAA ILT volume was similar in patients with ruptured (152.7 [84.8-252.4] cm³) and intact (180.1 [89.9-254.8] cm³; P = .414) AAAs.

Conclusions: This study suggests that ILT volume is not different in ruptured and intact AAAs.

Aortic dilatation and weakening, known as an aortic aneurysm, is an important cause of death in older adults due to aortic rupture. The prevalence of abdominal aortic aneurysms (AAAs) is ~2% to 5% in men and 1% in women aged >65 years, and in some countries, screening programs have been introduced to detect AAAs at an early stage.

There is considerable current interest in identifying medications that effectively limit AAA progression and avoid later complications of AAA, particularly AAA rupture. One suggested approach to the medical management of AAAs is that based on inhibiting thrombosis. Intraluminal thrombus (ILT) is present in most AAAs, and ILT volume has been shown to correlate with AAA size. ILT contains high concentrations of proteolytic enzymes and proinflammatory cytokines implicated in AAA rupture.

Antiplatelet and antithrombotic strategies have both been found to inhibit AAA progression in an autoimmune model of AAAs in which decellularized guinea pig aortas were transplanted into rats. One clinical study reported the association of aspirin prescription with reduced AAA progression in 148 patients with small AAAs.

In contrast to these data, ILT has also been suggested to physically protect against AAA rupture by decreasing aortic wall stress. ILT quantity would be expected to be different in ruptured and intact AAAs if it plays an important role in AAA rupture. Previous studies designed to compare ILT in intact and ruptured AAAs have provided conflicting results, perhaps due to difficulty comparing between AAAs of different sizes and absence of reproducible means to measure ILT quantity.

The aim of the current study was to compare AAA thrombus volume in intact and ruptured AAAs. Patients with ruptured and intact AAAs were matched for maximum AAA diameter, and infrarenal aortic thrombus volume was measured using a reproducible workstation protocol. The hypothesis being tested was that thrombus volume would be greater in ruptured than in intact AAAs.

METHODS

This study was granted ethics approval by the Human Research Ethics Committees of the Royal Brisbane and Women’s Hospital (RBWH) Health Service District and the Townsville Health Service District.
Patients. Participants were identified through retrospective analyses of the databases maintained by the Departments of Vascular Surgery at the RBWH and The Townsville Hospital (TTH). These databases include patients who have undergone treatment since 2002. Both hospitals are tertiary referral centers for vascular surgery in their regions. The RBWH is one of the largest teaching hospitals in Australia, serving a population of ~1 million and undertaking ~100 AAA repairs annually. TTH is the largest hospital in North Queensland, serving a population of ~400,000 and performing ~30 AAA repairs annually.

The inclusion criteria in the cohort with a ruptured AAA were a diagnosis of a ruptured AAA by a consultant vascular physician and the availability of a computed tomography angiogram (CTA) obtained after rupture but before any surgical intervention. A ruptured AAA was defined as an AAA associated with clear evidence of blood within the retroperitoneum or peritoneum on the CTA and at operation. Patients with symptomatic but intact AAAs were not included.

Patients with intact AAAs were identified from those undergoing elective surgical repair at the two hospitals involved. For inclusion, these patients had to have undergone a CTA and been able to be matched to one of the patients with ruptured AAAs.

Matching was based on maximum axial AAA diameter because AAA diameter is an important determinant of both AAA rupture risk and ILT volume.\(^7,31\) Matching by AAA diameter was performed by obtaining two patients with intact AAAs for every one with a ruptured AAA. Maximum AAA diameter was matched to within 1 mm.

**CTA protocol.** Multislice CTAs were performed under a set acquisition protocol as previously described at both centers.\(^7,31\) Iodixanol 300 contrast (100 mL; Bayer, Wayne, NJ) was delivered intravenously under a validated CTA protocol by an automatic injection driver system (MEDRAD, Warrendale, Pa.)\(^7,30,31\) A low-dose preliminary CT locator was set above the renal arteries, which triggered the CTA when the Hounsfield unit (HU) at the center of the aorta reached 130 after the delivery of the contrast agent.

**Assessment of AAA morphology and ILT volume.** Analysis was conducted using a Philips MxView Visualization Workstation at TTH by a single investigator (V.I.) using a previously validated protocol.\(^7,31\) Analysis was restricted to images of the infrarenal abdominal aorta, commencing at the origin of the lowest renal artery (excluding accessory arteries) and concluding at the aortic bifurcation. Maximum axial AAA diameter was recorded from two-dimensional axial slices using the largest of eight diameter measurements taken using electronic callipers. Images were assessed using the CTA viewer function. The aorta was scouted to find the region of maximal diameter by taking many measurements. Axial diameters were measured on a horizontal axial slice as previously described.\(^31\) The maximal diameter was recorded in millimeters (to the nearest 0.1 mm). ILT volume, total infrarenal aortic volume, and thrombus percentage were recorded using a previously validated technique, with an interobserver coefficient of variation of ~5%.\(^33,34\)

The intraobserver reproducibility was examined in the current study through assessment of the first 10 scans on two separate occasions. The mean coefficient of variation for thrombus and total aortic volume were <5%.

A volume of interest (VOI) was created around the infrarenal abdominal aorta for each slice, and the volumes were recorded using the “thrombus” and “total volume of aneurysm” HU settings. The settings in this study used HU parameters that have previously been validated to identify thrombus and contrast.\(^7,31\) ILT (center HU, 0; window width HU, 140) and total aneurysm volume (center HU, 1000; window width HU, 4000) were measured in this way. AAA thrombus percentage was calculated as the ratio of AAA thrombus to total infrarenal aortic volume presented as a percentage.

**Clinical risk factors.** Age at the date of the patient’s CTA and sex were recorded. Smoking was defined as ever or never smoked. The presence or absence of hypertension, ischemic heart disease, stroke, and chronic obstructive pulmonary disease was defined by history or current treatment for these conditions, taken from the patient’s medical record or preoperative interview. Medications recorded were aspirin, other antiplatelet agents, and statins. These were recorded from the departments’ AAA databases or from the preoperative notes found in the patients’ records.

**Statistical analysis and sample size calculation.** A previous study of patients with large AAAs demonstrated that mean (± standard deviation) thrombus volume was 97.6 ± 50 cm\(^3\).\(^36\) Based on demonstrating a 40% difference in thrombus volume at a power of 85%, we estimated that we required 28 cases and 56 controls (based on a one

---

**Table I.** Demographic and clinical risk factors in patients with ruptured and intact abdominal aortic aneurysms (AAAs)

<table>
<thead>
<tr>
<th>Clinical variable(^a)</th>
<th>Ruptured AAA</th>
<th>Intact AAA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>74.0 (67.5-80.0)</td>
<td>71.5 (65.3-77.0)</td>
<td>.083</td>
</tr>
<tr>
<td>Male sex</td>
<td>21 (75)</td>
<td>54 (96)</td>
<td>.003</td>
</tr>
<tr>
<td>Smoking</td>
<td>22 (84)(^b)</td>
<td>54 (96)</td>
<td>.056</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (81)(^b)</td>
<td>36 (64)</td>
<td>.131</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (15)(^b)</td>
<td>9 (35)</td>
<td>.937</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>11 (42)(^b)</td>
<td>29 (52)</td>
<td>.424</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)(^b)</td>
<td>5 (9)</td>
<td>.116</td>
</tr>
<tr>
<td>COPD</td>
<td>4 (15)(^b)</td>
<td>12 (21)</td>
<td>.520</td>
</tr>
<tr>
<td>Aspirin</td>
<td>13 (50)(^b)</td>
<td>29 (52)</td>
<td>.880</td>
</tr>
<tr>
<td>Other antiplatelet</td>
<td>4 (15)(^b)</td>
<td>16 (29)</td>
<td>.196</td>
</tr>
<tr>
<td>medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>13 (50)(^b)</td>
<td>38 (68)</td>
<td>.121</td>
</tr>
</tbody>
</table>

COPD, Chronic obstructive pulmonary disease.

\(^a\)Nominal variables are presented as numbers (%) and were compared using Pearson \(x^2\) test. Continuous variables are presented as median (interquartile range) and were compared using the Mann-Whitney \(U\) test.

\(^b\)\(n = 24\) (data unavailable for two patients).
case-to-two controls design) to identify this difference. We estimated that a 40% difference in thrombus volume would be readily detectable and of clinical significance. Data were entered into an Excel spreadsheet (Microsoft, Redmond, Wash) and statistically analyzed using SPSS software (SPSS Inc, Chicago, Ill).

Maximum axial diameter, total aneurysm volume, and thrombus volume were compared between groups by univariate tests to test the primary hypothesis. The distribution was initially assessed using Q-Q plots and the Kolmogorov-Smirnov test. Data were not normally distributed and were compared using the Mann-Whitney U test. Groups were also compared for confounding factors, including demographic factors and clinical variables, using the Pearson \( \chi^2 \) test and the Mann-Whitney U test. Significance was defined as \( P < .05 \).

### RESULTS

**Patient demographics and clinical factors.** We initially identified 34 patients with ruptured AAAs; however, only 28 could be matched one-to-two with 56 patients with intact AAAs. Six patients with ruptured AAAs were therefore excluded. These patients had very large AAAs (all \( \geq 98 \) mm), and patients with similar-diameter intact AAAs could not be identified. The demographic and clinical risk factors of the 28 patients with ruptured AAAs and 56 patients with intact AAAs are reported in Table I. Data, other than age and sex, were not recorded for two members of the rupture group. Seven patients (25%) with ruptured AAAs were women compared with only two patients (4%) with intact AAAs (\( P = .003 \)). Other demographic and clinical factors were similar in patients with ruptured and intact AAAs.

### Table II. Comparison of maximum axial diameter, total infrarenal aortic volume, and thrombus volume in intact and ruptured abdominal aortic aneurysms (AAAs)

<table>
<thead>
<tr>
<th>CTA measurement</th>
<th>Ruptured AAA</th>
<th>Intact AAA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial diameter, mm</td>
<td>84.00 (77.45-93.93)</td>
<td>82.55 (77.13-93.33)</td>
<td>.769</td>
</tr>
<tr>
<td>Total infrarenal aortic volume, cm(^3)</td>
<td>372.80 (277.40-486.05)</td>
<td>358.35 (289.08-563.35)</td>
<td>.977</td>
</tr>
<tr>
<td>AAA thrombus volume, cm(^3)</td>
<td>152.65 (84.75-252.43)</td>
<td>180.05 (89.90-254.78)</td>
<td>.414</td>
</tr>
<tr>
<td>AAA thrombus percentage</td>
<td>43.20 (26.76-61.27)</td>
<td>45.86 (35.95-58.48)</td>
<td>.662</td>
</tr>
</tbody>
</table>

CTA, Computed tomography angiography.

Continuous variables are presented as median (interquartile range) and were compared using the Mann-Whitney U test. AAA thrombus percentage represents the ratio of AAA thrombus to infrarenal aortic volume presented as a percentage.

Fig 1. Axial computed tomography angiogram (CTA) images show similarly sized (A and B) ruptured and (C and D) intact abdominal aortic aneurysms (AAAs) with similar intraluminal thrombus (ILT) volumes.
ILT thrombus volume in ruptured and intact AAAs. The CTA assessments of patients with ruptured and intact AAAs are reported in Table II. Maximum axial AAA diameter and total aneurysm volume were similar in patients with ruptured and intact AAAs, as was to be expected from the study design. Median ILT volume did not differ significantly between patients with ruptured AAAs (152.7 cm$^3$; interquartile range, 84.8-252.4 cm$^3$) and intact AAAs (180.1 cm$^3$; interquartile range, 89.9-254.8 cm$^3$; $P = .414$). The percentage of AAA thrombus was also similar in intact and ruptured AAAs (Table II). Example images showing these similarities are shown in Figs 1 and 2.

DISCUSSION

This study suggests that there is no difference in ILT volume between patients with ruptured and intact AAAs when they are matched for AAA diameter.

A literature search identified four studies that used CTA to compare ILT in patients with ruptured and intact AAAs. Pillari et al. assessed ILT location, arc, and ILT-to-lumen ratio, reporting that thrombus load increased disproportionately to aneurysm diameter in the 50-mm to 70-mm range, but that this trend reversed >70 mm, suggesting that thrombus failure was implicated in AAA rupture. The methods used in their study did not directly assess thrombus volume, measuring only thrombus thickness at the point of maximum axial AAA diameter, and contrast and noncontrast images were both used in the analysis. Thrombus thickness would be expected to vary considerably throughout the AAA and may be hard to examine accurately, particularly in thick-slice CT scans. The investigators did not report the reproducibility of their assessment method. Furthermore, the CT protocol used 10-mm slices scanned at 20-mm intervals, which may have influenced their ability to detect changes in thrombus thickness. Despite these limitations, their study was the first to assess the role of ILT in AAA rupture.

Mehard et al. and Siegel et al. both reported the association of a crescent of high attenuation identified on CTA, presumed to represent bleeding into the thrombus, with AAA instability and rupture. These studies also used contrast and noncontrast images for analysis, slice thickness and intervals that have now become antiquated, and thrombus volume was only recorded as a percentage of aneurysmal cross-sectional area at maximum anteroposterior, transverse, and longitudinal diameters, with no clear assessment of the reproducibility of their methods.

A different approach was used by Fillinger et al., who found that thrombus parameters measured using CTA were not related to rupture risk in an analysis of 100 ruptured and 100 intact AAAs. However, this study only used two-dimensional analysis of AAA and ILT geometry and conceded that further research was required using three-dimensional techniques to definitively evaluate the role of ILT in AAA rupture.

Hans et al. assessed ILT volume in 67 intact and 31 ruptured AAAs using AutoCAD2000 software (Autodesk Inc, San Rafael, Calif) to record four equidistant CTA images along the length of the aneurysm and to describe the location and volume of ILT. The investigators reported that the diameter and volume of ILT in ruptured AAAs was significantly greater than in intact AAAs but that the ILT-to-aneurysm ratio was not useful in the assessment of rupture risk. Their study had some limitations. Using four equidistant CTA images and extrapolating their data for three-dimensional analysis of thrombus volume could potentially result in significant error given the propensity for diameter asymmetry and irregular lumens in unstable AAAs.

One major limitation of all of the above studies is that patients with ruptured and intact AAAs were not matched for maximum AAA diameter. The latter is the best established predictor of AAA rupture and is also highly correlated with AAA thrombus volume.

The results of the current study may reflect the opposing actions of the effects of thrombus on the aortic wall. ILT has been described as having both biomechanically protective and biochemically destructive properties. Overall, the results of this current study do not favor a role for ILT in AAA rupture, assuming that the volume of ILT correlates with its postulated ability to alter rupture potential.
The current study has a number of limitations. First, the sample size was small but estimated to have sufficient power to detect a 40% difference between cases and controls. The study was underpowered to detect more subtle differences between cases and controls.

Second, women were more common among the patients with ruptured AAAs, in keeping with previous reports. This may have affected our findings; however, we have no reason to expect that the effect of ILT would be different in men and women.

Third, we did not measure other aspects of ILT, such as maximum thrombus thickness and thrombus location, which have previously been assessed in similar studies.

Fourth, because all CTAs undertaken in patients with ruptured AAAs were performed after rupture, it is impossible to be sure that the images were representative of the situation immediately before rupture. Changes in AAA size and thrombus volume might have occurred after AAA rupture and influenced the findings. Ideally, imaging should be obtained immediately before AAA rupture; however, this was not feasible.

Fifth, because we were unable to match some very large ruptured AAAs with similar-diameter intact AAAs, we had to exclude six patients from the current study. It is possible that the current results may not be representative of findings in patients with very large AAAs. Furthermore, exclusion of these patients reduced the power of the current study to assess our hypotheses.

Finally, an inherent selection bias is evident in patients with ruptured AAAs who are able to have preoperative CTAs because these ruptures are likely to represent the current study to assess our hypotheses.

Finally, because we were unable to match some very large ruptured AAAs with similar-diameter intact AAAs, we had to exclude six patients from the current study. It is possible that the current results may not be representative of findings in patients with very large AAAs. Furthermore, exclusion of these patients reduced the power of the current study to assess our hypotheses.

Fifth, because we were unable to match some very large ruptured AAAs with similar-diameter intact AAAs, we had to exclude six patients from the current study. It is possible that the current results may not be representative of findings in patients with very large AAAs. Furthermore, exclusion of these patients reduced the power of the current study to assess our hypotheses.

Finally, an inherent selection bias is evident in patients with ruptured AAAs who are able to have preoperative CTAs because these ruptures are likely to represent the current study to assess our hypotheses.

Finally, an inherent selection bias is evident in patients with ruptured AAAs who are able to have preoperative CTAs because these ruptures are likely to represent the current study to assess our hypotheses.

Finally, an inherent selection bias is evident in patients with ruptured AAAs who are able to have preoperative CTAs because these ruptures are likely to represent the current study to assess our hypotheses.

Finally, an inherent selection bias is evident in patients with ruptured AAAs who are able to have preoperative CTAs because these ruptures are likely to represent the current study to assess our hypotheses.

Finally, an inherent selection bias is evident in patients with ruptured AAAs who are able to have preoperative CTAs because these ruptures are likely to represent the current study to assess our hypotheses.

Finally, an inherent selection bias is evident in patients with ruptured AAAs who are able to have preoperative CTAs because these ruptures are likely to represent the current study to assess our hypotheses.

Finally, an inherent selection bias is evident in patients with ruptured AAAs who are able to have preoperative CTAs because these ruptures are likely to represent the current study to assess our hypotheses.

Finally, an inherent selection bias is evident in patients with ruptured AAAs who are able to have preoperative CTAs because these ruptures are likely to represent the current study to assess our hypotheses.


Submitted Jun 21, 2013; accepted Aug 21, 2013.