The influence of aneurysm size on perioperative cardiac outcome in elective open infrarenal aortic aneurysm repair

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Background: Abdominal aortic aneurysm (AAA) size and growth has been found to be associated with local generation of inflammation markers such as interleukin-6. Inflammation also seems to be important in perioperative adverse cardiac events. We hypothesized that patients with a large AAA are at increased risk for cardiac events.

Methods: Consecutive patients who underwent a computed tomography angiography scan before open elective infrarenal AAA repair between March 2000 and December 2005 at three hospitals were analyzed. All patients were screened for the clinical risk factors of age, gender, angina pectoris, myocardial infarction, heart failure, diabetes, stroke, renal failure, and chronic obstructive pulmonary disease, as well as for cardioprotective medication. Postoperative data on troponin release, creatine kinase/creatine kinase isoenzyme MB, and electrocardiogram were routinely collected on days 1, 3, 7, and 30. The main outcome measure was the combined end point of 30-day cardiovascular death and nonfatal myocardial infarction. Multivariate Cox regression analysis was used to evaluate the influence of AAA size on postoperative cardiac outcome.

Results: The study included 500 patients. Their mean age was 69.8 ± 9.5 years, and 431 (86%) were men. Thirty-one patients (6.2%) had perioperative cardiovascular complications, consisting of 15 (3.0%) cardiovascular deaths and 16 (3.2%) nonfatal myocardial infarctions. After correction for other risk factors, including age, Revised Cardiac Risk Index, medication use, duration of surgery, and intraoperative blood loss, AAA size was independently associated with perioperative nonfatal myocardial infarction and cardiovascular death (3.2% increase in risk for each millimeter added, 95% confidence interval 1.1% to 6.2%, \(P = .007\)).

Conclusion: A larger AAA size is independently associated with an increased incidence of perioperative cardiovascular complications after elective infrarenal AAA repair. (J Vasc Surg 2006;44:435-41.)

Abdominal aortic aneurysm (AAA) occurs frequently in the elderly population, with a 5% to 7% prevalence in men aged 65 to 74 years that increases to >10% in men >74 years old.1-3 The overall mortality from ruptured AAA remains high, at up to 75%, and preventive elective repair of large AAAs appears to be the best option.4 Perioperative cardiac complications of elective AAA repair remain a significant problem, however, despite recent perioperative advancements such as cardioprotective medication and improved anesthesiologic and surgical care.5,6

The pathophysiology of these perioperative adverse cardiac events is not entirely clear. Coronary plaque instability caused by inflammation that leads to thrombosis and myocardial infarction is a major cause of perioperative cardiac events, similar to myocardial infarctions occurring in the nonoperative setting.7 At least two studies evaluating the pathophysiology of perioperative myocardial infarction using noninvasive tests, coronary angiography, and autopsy results showed that coronary plaque rupture and thrombus formation occurred in about 50% of all fatal cases, and a sustained mismatch of oxygen supply and demand was responsible for the remaining half.8,9

It has been shown that AAAs might be an important source of circulating inflammatory markers such as interleukin (IL)-6, serum amyloid A, C-reactive protein (CRP), and high-sensitivity (hs) CRP. These inflammatory markers are also positively related to the abdominal aortic size.10-13 As was recently shown, the concentration of inflammatory markers such as IL-6 and hsCRP is predictive for adverse cardiac events in patients with peripheral arterial disease.14

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Competition of interest: none.

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Brady et al.\textsuperscript{15} also showed that AAA size is predictive for long-term cardiovascular mortality.

Because AAA size and growth seems to be related to the concentration of circulating proinflammatory markers and to long-term cardiac outcome, we hypothesized that patients with a large AAA might be more prone to adverse perioperative cardiac events after AAA repair than patients with small AAAs. We conducted the present study to evaluate this hypothesis.

METHODS

Patient population. The study population was composed of all consecutive patients who underwent a computed tomography angiography (CTA) scan before elective open infrarenal AAA repair between March 2000 and December 2005 at one of three hospitals (Erasmus University Medical Center in Rotterdam, Albert Schweitzer Hospital in Dordrecht, and Reinier de Graaf Hospital in Delft, the Netherlands). Surgical medical charts were screened retrospectively to identify patients.

A CTA scan of the AAA before surgical repair to measure the maximum diameter of the AAA was required to be included in this analysis. All CTA scans were scored, including maximum diameter, by the attending radiologist. In a weekly meeting of radiologists and vascular surgeons, the measurements of the AAAs were reviewed and adjusted, if necessary, after consensus was reached.

To obtain a more homogenous study population, patients with an inflammatory or myotic aneurysm were excluded from analysis. All operation reports were screened to make sure only patients requiring infrarenal aortic cross-clamping were included in the analysis. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center.

Perioperative cardiac risk assessment. All patients were screened for cardiac risk factors, including age, hypertension (ie, medical therapy to control hypertension), a history or presence of angina pectoris, previous myocardial infarction, heart failure, stroke, renal failure (ie, a serum creatinine of $>2.0$ mg/dL), and diabetes mellitus. Also noted were smoking status (never, current, or former) and the presence of chronic obstructive pulmonary disease (COPD). A patient was classified as having COPD at the preoperative screening visit according to symptoms and pulmonary function test (ie, forced expiratory volume of 1 second of $<70\%$ of maximal age and gender predictive value). Heart failure was scored according to the notes of the preoperative screening visits as well. Duration of surgery and intraoperative blood loss were noted in all patients.

All prescription and over-the-counter medications were noted on the day of admission and were classified as follows: statins, $\beta$-blockers, platelet aggregation inhibitors, angiotensin-converting enzyme inhibitors, calcium-channel blockers, diuretics, and nitrates. Patients unable to take oral medication perioperatively were switched to an intravenous formula. If no intravenous formula was available (ie, statins and angiotensin-converting enzyme inhibitors), oral medication was restarted as soon as possible after surgery.

Outcome. The main outcome measure was the combined end point of 30-day cardiovascular death and nonfatal myocardial infarction. Secondary 30-day all-cause mortality was analyzed. Cardiovascular death was defined as any death with a cardiovascular cause, including those deaths after a cardiac procedure, cardiac arrest, myocardial infarction, pulmonary embolus, stroke, or sudden deaths not ascribed to other causes. Myocardial infarction was defined as the presence of two of the following three criteria: (1) characteristic ischemic symptoms lasting $>20$ minutes, (2) electrocardiographic changes including acute ST elevation followed by appearance of Q waves or loss of R waves, new left bundle branch block, new persistent T wave inversion for at least 24 hours, or new ST segment depression which persists $>24$ hours, and (3) a positive troponin T (ie, $>0.10$ ng/mL) or peak creatinine phosphokinase-MB 8% of an elevated total creatinine phosphokinase with characteristic rise and fall.\textsuperscript{16} To assess cardiac complications during the postoperative period, blood and plasma samples for cardiac troponin T, creatinine phosphokinase levels, creatinine phosphokinase-MB levels, and electrocardiography were collected on 1, 3, 7 (or at the day of discharge), and 30 days after surgery.

Statistical analysis. Continuous variables were described as mean value (range), and categoric variables as percent frequencies. Linear regression analysis was used to explore the relation between aneurysm size and duration of surgery and blood loss. Kaplan-Meier survival curves were constructed to assess perioperative cardiovascular event-free and overall survival. The association of AAA size, cardiovascular risk factors, and medication use with perioperative cardiovascular complications and all-cause death was assessed via multivariate Cox regression analysis. All covariables associated with perioperative cardiac complications or all-cause mortality ($P < .20$ in univariate analysis) were included in the multivariate model.

The number of outcome events in the study was limited. Therefore, to avoid overfitting and to enable assessment of the relation between clinical risk factors and the perioperative composite end point, we used the Revised Cardiac Risk Index.\textsuperscript{17} The Revised Cardiac Risk Index identifies high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, insulin-dependent diabetes mellitus, and renal failure as the six predictors of major cardiac complications. Based on the presence of 0, 1, 2, or $\geq 3$ of these predictors, the rate of major cardiac complications was estimated to be 0.4%, 0.9%, 7%, and 11%, respectively, in the original study by Lee et al.,\textsuperscript{18} resulting in an excellent area under the curve (AUC) of 0.81. Receiver operating characteristic curve analysis was performed to calculate AUC values. The performance of risk models can be determined by the AUC, which indicates how well a model rank orders patients with respect to their outcomes, where 0.5 indicates no predictive value and 1.0 indicates perfect performance.\textsuperscript{16} The limit of statistical significance was set at $P = .05$ (two sided). All analysis was
Table I. Baseline characteristics, surgery, and medication use during hospitalization of all patients and in patients with or without perioperative events

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 500)*</th>
<th>Patients without events (n = 469)*</th>
<th>Patients with events (n = 31)*</th>
</tr>
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<tbody>
<tr>
<td><strong>Men</strong></td>
<td>431 (86)</td>
<td>404 (86)</td>
<td>27 (87)</td>
</tr>
<tr>
<td><strong>Age (mean ±SD)</strong></td>
<td>70 ± 9.5</td>
<td>70.3 (60-89)</td>
<td>73.5 (64-89)</td>
</tr>
<tr>
<td><strong>Median AAA size (mm, range)</strong></td>
<td>56 (42-110)</td>
<td>56 (42-110)</td>
<td>66 (47-95)</td>
</tr>
<tr>
<td><strong>Median duration of surgery (min, range)</strong></td>
<td>216 (120-535)</td>
<td>216 (120-500)</td>
<td>210 (140-535)</td>
</tr>
<tr>
<td><strong>Median blood loss (mL, range)</strong></td>
<td>2100 (400-18000)</td>
<td>2100 (400-18000)</td>
<td>3100 (2000-6500)</td>
</tr>
<tr>
<td><strong>Previous angina pectoris</strong></td>
<td>110 (22)</td>
<td>101 (22)</td>
<td>9 (29)</td>
</tr>
<tr>
<td><strong>Previous MI</strong></td>
<td>163 (33)</td>
<td>150 (32)</td>
<td>13 (42)</td>
</tr>
<tr>
<td><strong>Previous heart failure</strong></td>
<td>26 (5)</td>
<td>24 (5)</td>
<td>2 (7)</td>
</tr>
<tr>
<td><strong>CVA or TIA</strong></td>
<td>77 (15)</td>
<td>72 (15)</td>
<td>5 (16)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>48 (10)</td>
<td>45 (10)</td>
<td>3 (10)</td>
</tr>
<tr>
<td><strong>Renal failure</strong></td>
<td>28 (6)</td>
<td>24 (6)</td>
<td>4 (13)</td>
</tr>
<tr>
<td><strong>Systemic hypertension</strong></td>
<td>207 (42)</td>
<td>197 (43)</td>
<td>10 (33)</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>127 (25)</td>
<td>115 (25)</td>
<td>12 (39)</td>
</tr>
<tr>
<td><strong>Revised Cardiac Risk Index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 risk factor</td>
<td>203 (41)</td>
<td>195 (42)</td>
<td>8 (26)</td>
</tr>
<tr>
<td>2 risk factors</td>
<td>165 (33)</td>
<td>154 (33)</td>
<td>11 (36)</td>
</tr>
<tr>
<td>≥3 risk factors</td>
<td>132 (26)</td>
<td>120 (26)</td>
<td>12 (39)</td>
</tr>
<tr>
<td><strong>Platelet aggregation inhibitors</strong></td>
<td>178 (36)</td>
<td>170 (36)</td>
<td>8 (26)</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td>152 (31)</td>
<td>144 (31)</td>
<td>8 (26)</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>84 (17)</td>
<td>80 (17)</td>
<td>4 (13)</td>
</tr>
<tr>
<td><strong>Nitrates</strong></td>
<td>66 (13)</td>
<td>60 (13)</td>
<td>6 (19)</td>
</tr>
<tr>
<td><strong>β-blockers</strong></td>
<td>364 (73)</td>
<td>349 (74)</td>
<td>15 (48)</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>202 (40)</td>
<td>196 (42)</td>
<td>6 (19)</td>
</tr>
<tr>
<td><strong>Calcium antagonists</strong></td>
<td>157 (31)</td>
<td>147 (32)</td>
<td>10 (32)</td>
</tr>
</tbody>
</table>

MI, Myocardial infarction; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme.

*Data are numbers and percentages in parenthesis, except where indicated as ranges, and means ± SD.

performed using the statistical software SPSS 12.1 (SPSS Inc, Chicago, Ill) for Windows (Microsoft, Redmond, Wash).

RESULTS

Patient characteristics. The study included 500 patients with an infrarenal AAA. Their mean age was 70 ± 9.5 years, and 86% were men. The overall median maximum AAA diameter was 56 mm (range, 42 to 110 mm). According to the Revised Cardiac Risk index classification, almost half of the patients (41%) had one risk factor (ie, high-risk type of surgery), whereas 33% and 26% had two and three or more risk factors. Baseline clinical characteristics and medication use are presented in Table I. The median duration of surgery was 216 minutes, and median blood loss during surgery was 2100 mL. Neither duration of surgery (P = .78) nor blood loss during surgery (P = .13) was related to AAA size.

Perioperative cardiovascular outcome. Perioperative cardiac events occurred in 31 patients (6.2%), including cardiovascular death in 15 and nonfatal myocardial infarction in 16. In univariate analysis, AAA diameter and Revised Cardiac Risk Index were associated with worse outcome, and β-blocker therapy and statin therapy were associated with a reduced incidence of perioperative adverse cardiac events (Table II). In multivariate analysis, AAA size was associated with an increased incidence of perioperative cardiac events (3.2% increase in risk for each millimeter added; 95% confidence interval [CI], 1.1% to 6.2%, P = .007). Furthermore, age and a higher score of the Revised Cardiac Risk Index were associated with an increased risk of perioperative cardiac events (Table II).

ROC analysis showed an AUC of 0.60 for the Revised Cardiac Risk Index alone, but this AUC improved to 0.69 if AAA size was added to the model (P = .001). If age was also added to the model, the AUC further improved to 0.75 (P = .003). β-Blocker therapy and statin therapy were both associated with a reduced incidence of perioperative cardiac events in multivariate analysis (hazard ratio, 0.31; 95% CI 0.15 to 0.63; and hazard ratio, 0.40; 95% CI 0.16 to 0.95, respectively).

Perioperative all-cause mortality. Twenty-nine patients (5.8%) died during the first 30 days after AAA repair. Fifteen deaths (52%) were caused by cardiovascular complications, 4 (14%) by respiratory complications, 6 (21%) by multiorgan failure, and 4 (14%) by other complications. The results of univariate analysis are shown in Table III. The size of AAA was not significantly associated with perioperative all-cause death (P = .08) in univariate analysis. In multivariate analysis (Table III), AAA size was also not associated with an increase or reduction in perioperative all-cause mortality (adjusted odds ratio for every millimeter increase in size, 1.02; 95% CI 0.98 to 1.05; P = .35). Two or more clinical risk factors and increased age were associated with an increased incidence of 30-day mortality in multivariate analysis. Statin therapy and β-blocker therapy were associated with an approximate fourfold relative risk reduction (Table III).
DISCUSSION

This study showed an association between AAA size and perioperative cardiovascular complications after elective infrarenal AAA repair irrespective of other known factors influencing perioperative cardiovascular outcome. This study also showed a beneficial effect of both statin therapy and β-blocker therapy in patients undergoing open AAA repair.

The overall 30-day mortality rate of 5.8% is in line with other studies on open infrarenal AAA repair. Our study confirmed the observation from previous reports that approximately half of all perioperative deaths after AAA repair are attributable to cardiovascular complications. The 6.2% perioperative overall cardiac event rate of our study emphasizes the high cardiac risk for patients undergoing vascular surgery.
This high cardiac risk is explained by the high prevalence of asymptomatic coronary artery disease in AAA patients. As was shown by Hertzer et al in a study involving 1000 vascular surgical patients undergoing coronary angiography, >60% of patients with an AAA have some form of coronary artery disease. These lesions may cause a myocardial supply and demand imbalance owing to prolonged tachycardia and increased myocardial contractility, and thus are thought to be responsible for approximately half of all postoperative myocardial infarctions. This hypothesis has been confirmed in at least two studies using noninvasive tests, coronary angiography, and autopsy results.

The other 50% of myocardial infarctions might be caused by sudden rupture of so-called vulnerable coronary plaques. Surgery imposes extra myocardial workload, resulting in mechanical stress, stress-induced inflammation, and possibly spasms. This can cause vulnerable plaques to become unstable, leading to the cascade of plaque rupture, thrombus formation, myocardial ischemia, myocardial infarction, and eventually death.

Naghavi et al., in their extensive review on vulnerable plaques, reported that inflammation is one of the major criteria in the definition of vulnerable plaques. It is generally well accepted that inflammation is of imminent importance in the whole process. Therefore, most research has been focused on inflammation of coronary plaques as the ultimate trigger for vulnerable plaque rupture. This interest in inflammatory components has been justified in several population-based studies in which a positive relationship between inflammation markers and the occurrence of cardiovascular events was found.

In recent studies, the presence of an abdominal aortic aneurysm was positively related to circulating inflammatory markers. These inflammatory markers include IL-1β, IL-6, tumor necrosis factor-α, interferon-γ, CRP, and hsCRP. Importantly, both Jones et al. and Rohde et al. found a positive correlation between circulating IL-6 levels and AAA size. Vainas et al. found a similar correlation between hsCRP and AAA size. Also of importance is that they found CRP messenger RNA in AAA tissue.

From these observations, it might be hypothesized that aneurysmal tissue produces inflammatory markers: Patients with an AAA have a higher level of circulating inflammatory markers, and patients with a large AAA have a higher level of circulating inflammatory markers than patients with small AAAs. A different hypothesis might also be true, however: Patients with an elevated inflammatory status may be more prone to AAA development and growth than patients with a normal inflammatory status. Subsequently, patients with an elevated inflammatory status have a faster growing, larger AAA. Which hypothesis is true remains unknown, and further research in this area is required.

Large, prospective population-based studies have shown that circulating levels of hsCRP and IL-6 are related to long-term cardiac outcome. In a study by Ridker et al.,
IL-6 was a good predictor for myocardial infarction during a 6-year follow-up in 404 patients. Also supported by several clinical studies is the association of elevated hsCRP levels with long-term adverse cardiac events.

Because patients with large AAAs seem to have an elevated inflammatory status compared with patients with small AAAs, it might be hypothesized that patients with a large AAA are more prone to vulnerable plaque rupture than patients with a small AAA (Fig). This hypothesis was confirmed by Brady et al in a group of 2305 patients; AAA size was associated with a 34% increased risk for cardiovascular long-term mortality for every 0.8 cm added to AAA size. 15

The outcome of the UK Small Aneurysm Trial did not show a relation between AAA size and perioperative all-cause 30-day mortality. 25 Our study confirmed this observation: No association between AAA size and perioperative all-cause mortality was found. Unfortunately, the UK Small Aneurysm Trial did not report on cardiac death. It would be interesting to evaluate recent prospective trials on infra-renal abdominal aneurysm repair such as the UK Small Aneurysm Trial, the Dutch Randomised Endovascular Abdominal Aneurysm Repair such as the UK Small Aneurysm Trial did not report on cardiac death. It would be interesting to evaluate recent prospective trials on infra-renal abdominal aneurysm repair such as the UK Small Aneurysm Trial, the Dutch Randomised Endovascular Aneurysm Management Trial, 26 and Endovascular Aneurysm Repair-1 trial 27 for the relationship between AAA size and postoperative cardiac outcome. This study has several limitations owing to its retrospective nature. Autopsy was performed in only a few patients who died, and thus, misclassification of cause of death might have occurred. Also, there was no prespecified protocol for the measurement of the maximum abdominal aortic diameter and the measurement of this diameter was done on the basis of institutional common practice. Furthermore, no information on the inflammatory state of our study population (eg, IL-6 and high-sensitivity CRP levels) was available.

CONCLUSION

This study shows a clear association between AAA size and postoperative cardiac outcome, irrespective of other known risk factors. Future studies on the influence of AAA size on perioperative outcome should, if possible, also include the patients’ inflammatory status.

AUTHOR CONTRIBUTIONS

Conception and design: OS, NK, DP
Analysis and interpretation: OS, NK, DP
Data collection: OS, NK, MH, JL
Writing the article: OS, DP
Critical revision of the article: NK, MH, JL
Final approval of the article: OS, NK, MH, JL, DP
Statistical analysis: OS, NK
Obtained funding: Not applicable
Overall responsibility: DP

REFERENCES


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