C-Reactive Protein Levels and the Expansion of Screen-Detected Abdominal Aortic Aneurysms in Men

Paul Norman, MB, ChB, DS, FRACS; Carole A. Spencer; Michael M. Lawrence-Brown, MB, BS, FRACS; Konrad Jamrozik, MBBS, DPhil, FAFPH

Background—C-reactive protein (CRP) levels have been shown to predict a number of cardiovascular outcomes. CRP levels have also been found to be elevated in patients with abdominal aortic aneurysms (AAAs). The aim of this study was to assess the relation between CRP levels and rates of expansion of small AAAs.

Methods and Results—A cohort of men with small aneurysms was identified in a trial of screening with ultrasound scanning. After initial screening, men were rescanned at 6- to 12-month intervals. CRP levels were measured at the first follow-up visit. Rates of expansion and risk factors for expansion were assessed with the use of data from 545 men who attended for at least 1 scan after CRP levels were measured. These men were followed for a median of 48 (range, 5 to 69) months. The mean annual rate of expansion was 1.6 mm. The median CRP level was 2.6 mg/L in men with the smaller AAAs (30 to 39 mm, n=433) compared with 3.5 mg/L in men with larger AAAs (40 to 54 mm, n=112) (P=0.007). The multivariate age-adjusted logistic model confirmed initial aortic diameter to be the only factor associated with rapid expansion with an odds ratio of 7.2 (95% CI, 4.3,12.2) for an initial diameter of 40 to 54 mm relative to one of 30 to 39 mm.

Conclusions—Most small aneurysms expand slowly. CRP levels are elevated in larger aneurysms but do not appear to be associated with rapid expansion. The most useful predictor of aneurysmal expansion in men is aortic diameter. (Circulation. 2004;110:862-866.)

Key Words: aorta • aneurysm • proteins • risk factors

C-reactive protein (CRP) has been shown to be a strong predictor of various cardiovascular events.1–3 Although there is evidence that the levels of CRP and other inflammatory biomarkers are elevated in patients with aortic abdominal aneurysm (AAA), it is unclear whether the CRP level is of any prognostic significance in terms of rate of expansion.4–6 The detection of elevated levels of CRP in patients with large, symptomatic, or ruptured AAA is unlikely to change the treatment of such patients because they need repair of the AAA. However, it is in the management of small (30 to 54 mm in diameter) AAAs that CRP levels might be hypothesized to have a role. Aneurysms of this size are not uncommon, with a prevalence of ~6% in men and 1% in women >65 years of age.7,8 Although surgery is not indicated for these AAAs,9,10 a proportion will expand until they are large enough to warrant elective intervention before rupture occurs. Current practice is to monitor the diameter of small AAAs with periodic ultrasound or CT scanning, but our understanding of the natural history of these aneurysms is incomplete. Many small AAAs are remarkably stable, with some patients facing long and ultimately unnecessary periods of follow-up. Uncertainty surrounds the advice that should be given to individuals with a small AAA, particularly with regard to the likelihood that their AAA will expand to a dangerous size. The identification of any risk factors associated with greater rates of expansion may help in the planning of surveillance of AAAs, the identification of high-risk patients who may benefit from early intervention, and possibly the development of strategies to prevent expansion. We have used data from the Western Australian AAA Screening Study11 to test the hypothesis that the level of CRP predicts the rate of expansion of small AAAs.

Methods

The methods and initial results of the Western Australian trial of screening for AAA have been reported previously.11 The study was approved by the Human Research Ethics Committee of the University of Western Australia, and informed consent was obtained from all participants. Briefly, we invited a population-based random sample of men 65 to 83 years of age living in Perth, Western Australia, to attend for an ultrasound scan of their abdominal aorta. Men attending for scanning also completed a questionnaire on risk factors that included the Edinburgh Claudication Questionnaire12 and had their height, weight, blood pressure, and circumference at the
waist and hips recorded. Men were given the result of their scan in the form of a letter for their general practitioner as they left the clinic. Referral to a vascular surgeon was recommended for men with an aortic diameter of ≥50 mm.

All men with an infrarenal aortic diameter of ≥30 mm were invited to attend a follow-up study involving repeat ultrasound scans at intervals of 6 months if the initial diameter was ≥40 mm and 12 months if the initial diameter was 30 to 39 mm. At the first follow-up visit, in addition to an ultrasound scan, a sample of venous blood was obtained from all consenting men. C-reactive protein was measured by a high-sensitivity assay, with the use of the particle-enhanced immunonephelometry system on the BNII analyzer (Dade Behring).

Statistical Methods

The differences in cardiovascular risk factors between men who attended and those who did not were compared by means of t tests. Subsequent analysis of the data began with calculation of the change in size of the infrarenal aortic diameter and the time in months between the scan performed at the time of the CRP assay and latest scan for all men who attended at least 1 follow-up after venesection. These measurements were used to categorize AAAs into “rapid expanders” (≥3-mm expansion per year) and “slow expanders” (<3-mm expansion per year). Contingency tables were constructed with SAS software, in which rapid expanders were compared with slow expanders across a range of independent factors that we hypothesized may be associated with rates of expansion. These factors were age (in 5-year strata), initial aortic diameter, smoking status (categorized into lifelong nonsmokers, ex-smokers, and current smokers), hypertension (treatment for and measured), height, body mass index, history of coronary heart disease or stroke, presence of peripheral arterial disease (possible or positive Edinburgh Claudication Questionnaire), and level of CRP. The small number of missing values for categoric variables was set to “not present.” Definitions of categories for the variables are described in more detail elsewhere. Subjects were divided into 4 groups, based on aortic diameter at baseline (30 to 34, 35 to 39, 40 to 44, and 45 to 54 mm). However, because the rates of expansion (and levels of CRP) in the two smallest-diameter groups (30 to 34 and 35 to 39 mm) were almost identical—similarly for the two largest-diameter groups (40 to 44 and 45 to 54 mm)—we based the initial analysis on 2 groups: 30 to 39 mm and 40 to 54 mm. Possible bivariate interaction between CRP and diameter was subsequently explored in more detail by using the 4 groups of initial diameter. Because the distribution of CRP levels is skewed toward higher values, analysis was based on medians and quintiles, with differences in CRP levels in large and small AAAs assessed by the Mann-Whitney U test. All the factors mentioned above were initially included in the multivariate logistic regression, with the use of EGRET software. A reverse stepwise approach was used to obtain the most parsimonious model in which the outcome variable was rapid expander or slow expander.

At intervals of 4 months during the initial screening period and in the follow-up study, 10 subjects were selected at random for assessment of intra-rater and inter-rater agreement of aortic diameter measurements. Each man was scanned twice by each observer as well as by a senior vascular sonographer. All scans were performed with the operators blinded to previous aortic diameter measurements. Nonparametric tests and SPSS software were used to compare mean intra-rater and inter-rater differences in aortic diameter measurements. No significant differences were found between observers, with 95% of differences in each of anteroposterior and transverse diameters being <3 mm.

Results

Of 17 305 eligible men invited to a baseline scan between April 1996 and December 1998, 12 203 (70.5%) attended. Of these, 875 (7.2%) men were found to have an aortic diameter of between 29.5 mm (rounded up to 30.0 mm) and 54 mm at initial screening, with 686 (79%) subsequently attending for follow-up and 628 (72%) agreeing to venesection. Of the 628 men who underwent venesection, 83 did not attend for further scans and were therefore excluded from further analysis.

The analysis of rates of expansion and risk factors for expansion is based on 545 men who attended for at least 1 scan after CRP levels were measured. These men were followed for a median of 48 months (range, 5 to 69). The cardiovascular risk factor profile of these men is shown in Table 1. Comparison of the profiles of these men and those who did not attend reveal that both groups are similar, apart from a significantly larger initial aortic diameter in the nonattenders. Profiles were also compared for the various subgroups of attenders, being those with CRP levels, those without, and those who eventually dropped out during follow-up, with no significant differences being found (data not shown).

The mean annual rate of expansion rose from 1.3 mm in the group with the smaller AAA (30 to 39 mm initial diameter) to 3.0 mm in the group with the larger AAA (45 to 54 mm initial diameter) (Table 2). The distribution of CRP levels is shown in Figure 1. The median (interquartile range) CRP level was 2.6 mg/L (1.4 to 5.2) in men with the smaller AAAs (30 to 39 mm, n=433) compared with 3.5 mg/L (1.8 to 7.4) in men with larger AAAs (40 to 54 mm, n=112) (P=0.007).

There were 75 men with expansion of ≥3 mm per annum (rapid expanders) and 470 with expansion of <3 mm per annum (slow expanders). After adjusting for age, univariate analyses revealed a significant association between initial aortic diameter and an annual expansion rate of ≥3 mm (Table 3). There was no association with height, weight, hypertension, smoking status, evidence of peripheral vascular disease, or a history of cardiac or cerebrovascular disease.

### TABLE 1. Cardiovascular Risk Factors in 545 Men

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No. Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent claudication*</td>
<td>59 (11)</td>
</tr>
<tr>
<td>Body mass index ≥25.0</td>
<td>320 (59)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>81 (15)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>373 (68)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>91 (17)</td>
</tr>
<tr>
<td>History of</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>139 (26)</td>
</tr>
<tr>
<td>Angina</td>
<td>150 (28)</td>
</tr>
<tr>
<td>Stroke</td>
<td>59 (11)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>55 (10)</td>
</tr>
<tr>
<td>Hypertension (treatment for or measured)</td>
<td>248 (46)</td>
</tr>
</tbody>
</table>

*Possible or positive Edinburgh Claudication Questionnaire.

### TABLE 2. Annual Rate (in mm) of Aortic Expansion in 545 Men With Screen-Detected AAA

<table>
<thead>
<tr>
<th>Initial Aortic Diameter</th>
<th>No.</th>
<th>%</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39 mm</td>
<td>433</td>
<td>79</td>
<td>1.3</td>
<td>1.2</td>
<td>1.0</td>
<td>0–9.1</td>
</tr>
<tr>
<td>40–54 mm</td>
<td>112</td>
<td>21</td>
<td>3.0</td>
<td>2.7</td>
<td>2.2</td>
<td>0–17.0</td>
</tr>
<tr>
<td>Total</td>
<td>545</td>
<td>100</td>
<td>1.6</td>
<td>1.7</td>
<td>1.2</td>
<td>0–17.0</td>
</tr>
</tbody>
</table>
The multivariate age-adjusted logistic model confirmed initial diameter to be the only factor associated with expansion, with an odds ratio of 7.2 (95% CI, 4.3, 12.2), for an initial diameter of 40 to 54 mm relative to one of 30 to 39 mm. When initial diameter was treated as a continuous variable, a significant increase in risk was also seen (OR of 7.1 per 10 mm of initial diameter, data not shown). There was no obvious bivariate interaction between initial aortic diameters and levels of CRP and their relation with expansion (Figure 2).

**Discussion**

The present cohort consists only of men with small AAAs (30 to 54 mm). Although all men found to have an AAA at initial screening were invited to participate in the follow-up study, men with an AAA of ≥50 mm in diameter were also encouraged to see a vascular surgeon. The focus is therefore on small AAAs requiring surveillance rather than early surgery, and the only difference between men who did and did not attend for follow-up was initial aortic diameter. Our analysis confirms reports from other studies that the rates of expansion of small screen-detected AAA are very low (Table 1). The mean annual increase in aortic diameter was 1.3 mm for AAA in the 30- to 39-mm range, rising to 3.0 mm for AAA in the 40- to 54-mm range. For most individual patients, these increments are within measurement error for ultrasound scanning.

In the analysis of risk factors for aneurysmal expansion, we chose a categoric definition of expansion using as our threshold an increase of ≥3 mm per year, on the basis that this was >95% of measurement errors. Furthermore, sustained expansion at this rate is likely to be of clinical significance. By using data on a range of simple clinical factors, we found that the only variable independently associated with expansion was the initial aortic diameter (Table 3). The importance of initial aortic diameter in subsequent aneurysmal expansion has been shown in other population-based studies. We failed to confirm an independent association with smoking reported elsewhere. This may be due to the relatively small proportion of current smokers in our study. Because hypertension has been documented as a risk factor for AAA in several studies, it is surprising that hypertension is not a risk factor for expansion of small aneurysms. In the case of our study, it may be because the majority of men with hypertension are adequately treated, thereby minimizing the impact of this risk factor.

Inflammation is now considered to be of fundamental importance in the pathogenesis of occlusive atherosclerosis, and the role of inflammatory markers as predictors of future cardiovascular events has been established over the last decade. C-reactive protein appears to be the most useful of a wide range of markers studied to date. In view of the proteolysis, chronic inflammation, and cytokine activation seen in the walls of large AAAs, it is not surprising that the levels of circulating inflammatory markers are also increased in patients with AAA. Levels of CRP have been reported to be elevated in patients with both symptomatic and asymptomatic AAA and to be higher in patients with AAA than those with occlusive aortoiliac disease. Increased levels of circulating interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor-α, and interferon-γ have also been previously associated with AAAs.

It remains unclear whether the inflammation seen in the walls of AAAs plays a causal role in the expansion of small AAAs.
AAAs. Despite mounting evidence that the presence of an AAA is associated with increased levels of circulating inflammatory markers, the relation between these markers and the rate of expansion of AAAs has received very little attention. Aortic diameter is known to be the dominant predictor of both rate of expansion and risk of rupture. The levels of inflammatory markers appear to increase with increasing aortic diameter in both nonaneurysmal aortas and AAAs. However, Jones et al found that baseline IL-6 levels did not predict rates of expansion of AAAs in a subset of patients in the surveillance arm of the UK Small Aneurysm Trial. Similarly, we did not demonstrate any significant relation between CRP (a surrogate for IL-6) levels and rapid expansion (Table 3 and Figure 2). We did confirm that CRP levels are higher in larger AAAs, and the lack of association with expansion raises the possibility that inflammation (as manifested by elevated levels of inflammatory markers) is a response to expansion rather than the primary cause. In support of this is evidence that CRP is produced in the walls of some aneurysmal aortas, and large AAAs may be an important source of circulating IL-6. If inflammation is not a cause of aneurysmal expansion, then efforts to control inflammation pharmacologically are unlikely to be successful in reducing rates of expansion.

A larger study may have had the power to detect a statistically convincing relation between CRP levels and expansion. Although this would help clarify the causal role of inflammation in the progression of aneurysmal disease, it is doubtful whether CRP measurements will have a practical role in planning surveillance of small AAAs. Aortic diameter remains both the strongest and simplest predictor of expansion, and it is appropriate, for the time being, to base surveillance schedules for small asymptomatic AAAs on this measurement alone.

Acknowledgments

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References

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