Aortic aneurysms secrete interleukin-6 into the circulation

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Objective: **Circulating plasma interleukin-6 (IL-6) concentrations are elevated in patients with abdominal aortic aneurysms (AAAs) compared with controls. In vitro studies suggest that the aneurysm is the source of the IL-6. Because IL-6 is an independent risk factor for cardiovascular mortality, elevation of this cytokine may be significant in these patients, who represent a group at increased risk from cardiovascular death. The aim of this study was to directly measure in vivo aortic IL-6 concentrations, testing the hypothesis that aneurysms secrete IL-6 into the circulation.**

Methods: **Before endovascular aneurysm repair took place, blood was sampled from the entire length of the aorta in 27 patients with AAA and nine with thoracic aneurysms (TAs). A control group consisted of 15 patients without aneurysms undergoing angiography. Plasma IL-6 was determined using enzyme-linked immunosorbent assay, and high-sensitivity C-reactive protein (hs-CRP) was measured turbidimetrically. Aneurysm surface area was calculated from axial computed tomography scans.**

Results: **Mean IL-6 concentrations (pg/mL) were higher in the TA and AAA groups compared with controls (10.4 ± 3.7 and 4.9 ± 0.5 vs 2.7 ± 0.5, $P = .002$). There was a significant difference in plasma IL-6 concentration corresponding to aneurysm position in the AAA ($P = .002$) and TA ($P = .008$) groups, with both patterns conforming to a linear trend. This pattern was not observed in the control group, in which no significant difference in IL-6 concentrations was found throughout the aorta. Peak IL-6 occurred earlier in TAs compared with AAAs (descending aorta vs iliac artery) corresponding to aneurysm position ($P = .0007$). Linear regression revealed a positive correlation between aneurysm surface area and mean plasma IL-6 (Spearman's correlation, $P = .003$). The mean surface areas of the TAs, at 0.07 m^2 (interquartile range [IQR], 0.06 to 0.09), were higher than those of the AAAs at 0.03 m^2 (IQR, 0.02 to 0.04; $P = .002$). High-sensitivity CRP was within normal limits, and no significant differences were found between the AAA group and the controls.**

Conclusions: **Circulating IL-6 is elevated within the aorta in patients with aneurysms and corresponds to aneurysm position. Furthermore, aneurysm surface area and mean plasma IL-6 are correlated. In the absence of any evidence of systemic inflammation in the form of elevated hs-CRP, these data support the hypothesis that aneurysms secrete IL-6 into the circulation. This may contribute to the high cardiovascular mortality observed in patients with aneurysms. (J Vasc Surg 2007;45:350-6.)**

Clinical Relevance: **Abdominal aortic aneurysms (AAAs) are characterized histologically by widespread inflammation, with IL-6 playing a central role. IL-6 is secreted by AAAs in vitro, and elevated IL-6 is an independent risk factor for cardiovascular mortality. This may be clinically important in this group of patients with significant comorbidities at high risk of cardiovascular death. This study supports the hypothesis that aneurysms secrete IL-6 into the systemic circulation and suggests that the aneurysms may have more insidious effects upon cardiovascular health than solely that of rupture.**

Inflammation has emerged as a key process in the pathogenesis of abdominal aortic aneurysms (AAAs).[1,2] This has encouraged elucidation of the role of inflammatory cytokines in aneurysm disease. The current paradigm of aneurysm development suggests that inflammatory cells within the wall of the aneurysm produce cytokines that stimulate proteolytic enzymes such matrix metalloproteinases.[3] These enzymes promote the activation and release of subsequent cytokines, perpetuating a vicious cycle of chronic inflammation and extracellular matrix degradation that is the pathologic hallmark of aneurysms.[4]

The multifunctional cytokine interleukin-6 (IL-6) has been specifically implicated in aneurysm pathogenesis, contributing to both acute and chronic inflammatory processes. A body of circumstantial evidence suggests that AAAs secrete IL-6 into the circulation. It has been demon-

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Table I. Demographic and clinical characteristics of subjects*

	TA *n = 9 (%)*	*AAA* *n = 27 (%)*	*Control* *n = 15 (%)*	P
Demographics				
Age, years (range)	74 (62-80)	73 (58-91)	50 (32-74)	<.0001
Male sex	5 (56)	27 (100)	3 (20)	<.0001
Aneurysm diameter (mm)	57 (44-92)	64 (51-100)	—	—
Current smoker	3 (33)	8 (30)	5 (33)	0.96
Ex-smoker	4 (44)	17 (63)	2 (13)	0.008
Prevalent chronic diseases†				
Hypertension	8 (89)	18 (67)	5 (33)	0.017
Ischemic heart disease	4 (44)	13 (48)	0 (0)	0.005
Cerebrovascular disease	3 (33)	6 (22)	0 (0)	0.077
Diabetes mellitus	2 (22)	4 (15)	0 (0)	0.2
COPD	2 (22)	6 (22)	0 (0)	0.14
Chronic renal impairment	3 (33)	8 (30)	4 (27)	0.94
Medication				
Statin	6 (67)	22 (81)	5 (33)	0.0074
Aspirin	5 (56)	24 (89)	1 (7)	<.0001
NSAID	1 (11)	2 (7)	3 (20)	0.48

TA, Thoracic aneurysm; *AAA,* abdominal aortic aneurysm; *COPD,* chronic obstructive pulmonary disease; *NSAID,* Nonsteroidal anti-inflammatory drugs.
*Values for continuous variables are reported as mean (range) with comparisons by analysis of variance. Categoric variables expressed as n (%) and compared by χ^2 test.
†Definitions: *Hypertension,* Chronic treated hypertension; *ischemic heart disease,* history of angina, heart failure, previous myocardial infarction, or coronary artery bypass grafting; *cerebrovascular disease*, history of transient ischemic attack or cerebrovascular accident, or both; *diabetes*, controlled by diet, tablet, or insulin; *COPD,* evidence on lung function tests or treatment with bronchodilators; *chronic renal impairment*, chronic renal failure on urea and electrolytes or under treatment with renal physician for chronic renal failure.

strated that patients with AAA have higher venous IL-6 concentrations compared with controls,[5-8] and in vitro tissue culture models revealed that aneurysms actively secrete IL-6.[9,10]

It is plausible that IL-6 may play a far more critical and insidious role in the long-term fate of the patient with aneurysm disease. Elevated circulating IL-6 is an independent risk factor for future myocardial infarction and cardiovascular and all-cause mortality.[8,11] This may be relevant considering that two thirds of patients with AAA die from cardiovascular causes unrelated to their aneurysm.[12]

We hypothesized that IL-6 is secreted into the circulation by the aneurysm and, therefore, plasma levels will be higher downstream to the aneurysm. Because no direct evidence exists to support this hypothesis, we aimed to measure circulating IL-6 in vivo from several points within the aorta in patients with aneurysms.

METHODS

Patients. The study comprised three groups of patients, 27 with asymptomatic infrarenal aneurysms (AAAs) and nine with asymptomatic thoracic aneurysms (TA), all scheduled for elective endovascular aneurysm repair. The control group consisted of 15 patients undergoing diagnostic or interventional angiograms. The indications for angiograms were uterine artery embolization in 7, iliac and femoral angioplasty in 4, renal angiogram in 3, and femoral angiogram in 1. Patients were excluded if there was evidence of acute illness or infection, an active inflammatory condition, malignancy, or corticosteroid use. All patients undergoing aneurysm repair received a general anaesthetic, whereas angiography was performed under local anesthesia. Patient demographics are listed in Table I. The study was approved by the Wandsworth Local Ethics Committee, and patients gave written informed consent.

Blood collection. Before endovascular aneurysm repair or angiographic intervention occurred, a size 4F angiographic flush catheter (Cordis, Johnson & Johnson, Miami Lakes, Fla) was passed into the aorta through a femoral puncture. Blood was aspirated sequentially from several points within the aorta: ascending aorta (TA only), arch of aorta or thoracic aneurysm, descending aorta, proximal abdominal aorta (AAA and controls only), distal abdominal aorta, and external iliac artery. Positions were standardized by using the following anatomic landmarks identified on fluoroscopy: distal to the aortic valve (ascending aorta), proximal to the left subclavian artery (arch of aorta), proximal to the diaphragm (descending aorta), L2 lumbar vertebrae (proximal AAA) and L3 lumbar vertebrae (distal AAA), and distal to bifurcation (common iliac artery). A peripheral venous sample was also obtained from the antecubital fossa.

Samples were obtained before infusion of radiographic contrast medium and heparin, collected into ethylenediaminetetraacetic acid bottles, and immediately transported to the laboratory on ice. Samples were centrifuged for 10 minutes at 3000 rpm, and the plasma was stored in aliquots at −80°C.

Laboratory methods. Plasma samples were analyzed by a blinded observer in batches after one freeze–thaw episode. Plasma IL-6 concentrations were measured in duplicate using an enzyme-linked immunosorbent assay

Table II. Association between arterial interleukin-6 and high-sensitivity C-reactive protein concentrations and aortic location in patients with thoracic aneurysms, abdominal aortic aneurysms, and controls

	Interleukin-6 (pg/mL)			*hs-CRP (mg/L)*	
Aorta location	*TA n = 9*	*AAA n = 27*	*Control n = 15*	*AAA n = 25*	*Control n = 12*
Ascending	9.61 ± 3.55	—	—	—	—
Arch/TA	9.84 ± 3.48	4.70 ± 0.47	2.45 ± 0.50	4.79 ± 0.95	3.65 ± 1.02
Descending	11.20 ± 3.94	4.73 ± 0.48	2.65 ± 0.54	4.76 ± 0.94	3.62 ± 1.02
Proximal abdomen	—	5.00 ± 0.51	2.82 ± 0.59	4.80 ± 0.93	3.69 ± 1.03
Distal abdomen	10.61 ± 3.83	5.09 ± 0.50	2.80 ± 0.59	4.83 ± 0.95	3.65 ± 1.01
Iliac artery	10.53 ± 3.63	5.17 ± 0.46	2.54 ± 0.47	4.68 ± 0.89	3.52 ± 0.98
P	.008*	.002*	.26*	.24*	.21*
Mean concentration					
Aortic	10.36 ± 3.68	4.94 ± 0.48	2.65 ± 0.51	4.77 ± 0.93	3.62 ± 1.01
P		.002†		.44‡	
Venous	11.51 ± 4.02	5.34 ± 0.78	2.75 ± 0.64	5.23 ± 1.35	3.65 ± 1.21
P		.008†		.42‡	

TA, Thoracic aneurysm; *AAA*, abdominal aortic aneurysm; *hs-CRP*, high-sensitivity C-reactive protein.
Results expressed as mean ± SEM.
*One-way repeated measures analysis of variance.
†One-way analysis of variance.
‡Unpaired Student's *t* test.

(Quantikine HS, R&D Systems, Inc, Minneapolis, Minn). High-sensitivity C-reactive protein (hs-CRP) was determined by rate turbidimetry immunoassay (Synchron LX System, Beckman Coulter, Inc, Fullerton, Calif) as a baseline for systemic inflammation.

Thrombus content. Thrombus content of the aneurysm was estimated using computed tomography (CT) imaging. The percentage of the aortic cross-sectional area that the thrombus occupied was calculated at the level of maximum thrombus deposition.

Aneurysm surface area. The total surface area of aneurysmal aorta was calculated by summing the individual surface areas of 10-mm volume slices on axial CT scans at a CT workstation.

Statistical analysis. Categoric variables were compared by a χ^2 test. Normally distributed data were expressed as mean ± standard error. Nonparametric data were expressed as median ± interquartile range (IQR). Statistical analysis among the three groups was performed using one-way analysis of variance (ANOVA). Comparisons within groups were performed with repeated measures ANOVA. An unpaired Student's *t* test was used for comparison of means and a Mann-Whitney test for comparison of medians or ranked data. Statistical significance was set at $P < .05$. Statistical analysis was performed using Prism 4.0 (GraphPad Software, Inc, San Diego, Calif) and SPSS 12.0 (SPSS, Inc, Chicago, Ill) software.

RESULTS

Aortic interleukin-6. Mean aortic plasma IL-6 concentrations (pg/mL) were calculated from samples collected from all positions and were higher overall in patients with AAAs and TAs compared with controls (AAA, 4.94 ± 0.48; TA, 10.36 ± 3.68; controls 2.65 ± 0.51; $P = .002$). This relationship was unaltered after adjusting the data for age and sex ($P = .002$) and also remained significant after adjusting for 3-hydroxy-3 methyl-glutaryl-coenzyme A (statin) use.

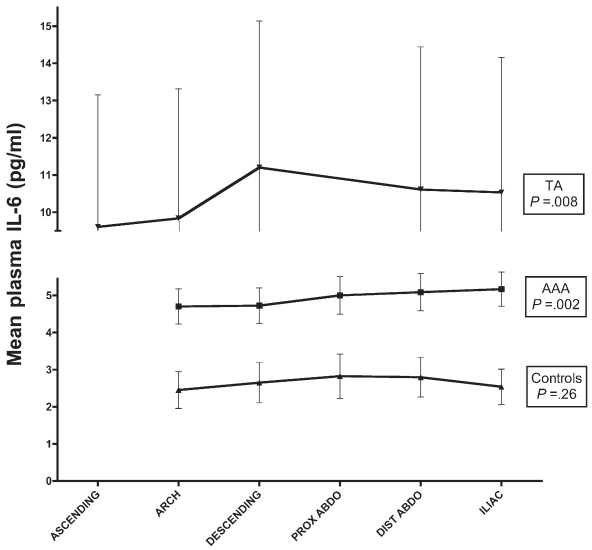

Fig 1. Variation in interleukin-6 *(IL-6)* concentrations with aorta position in thoracic aneurysms *(TA)*, abdominal aortic aneurysms *(AAA)*, and controls. Vertical axis, showing mean plasma IL-6 within the aorta, is interrupted between 5 and 10 pg/mL. Concentrations of aortic IL-6 increased significantly throughout the aorta in patients with TAs ($P = .008$) and AAAs ($P = .002$), corresponding to aneurysm position (repeated measures analysis of variance). This pattern was not observed in the control group. Results expressed as mean ± SEM.

Within both aneurysm groups, there was a significant difference in IL-6 with aortic position. Elevation in IL-6

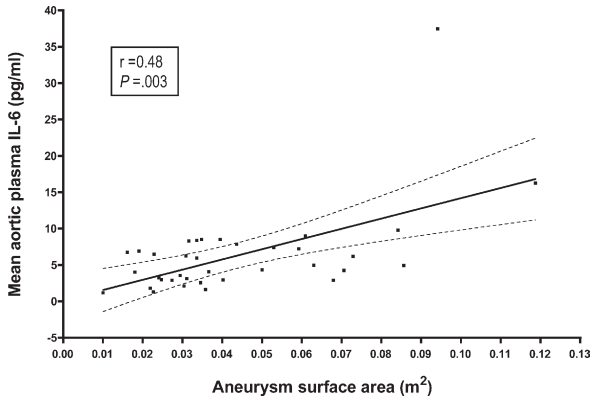

Fig 2. Correlation between mean aortic plasma interleukin-6 *(IL-6)* and aneurysm surface area in patients with thoracic and abdominal aortic aneurysms. The linear regression and 95% confidence interval are shown.

concentrations corresponded to aneurysm position (Table II). In the AAA group, there was a significant rise in IL-6 concentration distal to the aneurysm ($P = .002$) that followed a linear trend ($P < .001$, post-test for linear trend, Fig 1). The TA group also demonstrated a rise in IL-6 concentration corresponding to aneurysm position ($P = .008$), which corresponded to a linear trend ($P = .01$). Within the control group, there were no significant differences in IL-6 with aortic position and no linear trend.

The maximum plasma IL-6 level for each aneurysm patient was ranked according to aorta location. Comparison of these ranked data revealed that plasma IL-6 peaked earlier in the TA group than in the AAA group, corresponding to the anatomic position of the aneurysm (distal descending aorta vs iliac artery, $P = .0007$). Within the AAA group, six patients (22%) had aneurysmal extension into the common iliac arteries. Subgroup analysis of the AAA group, excluding the iliac aneurysms, did not alter the pattern of IL-6 with aorta position.

Systemic venous concentrations were significantly higher in the aneurysm groups ($P = .008$) and mirrored the arterial levels (Table II).

Aneurysm surface area. Fig 2 displays the linear regression line between mean aortic plasma IL-6 and aneurysm surface area (Spearman's rank correlation $r = 0.48$, $P = .003$). The mean aneurysm surface area in the TA group, 0.07 m^2 (IQR, 0.06 to 0.09) was also significantly higher than that in the AAA group, 0.03 m^2 (IQR, 0.02 to 0.04; $P = .0002$).

C-reactive protein. There was no significant difference in hs-CRP throughout the aorta in patients with AAAs and controls. Arterial and venous concentrations of CRP were higher in the AAA group, but this did not reach statistical significance.

The effect of thrombus. The mean thrombus burden was 56% of aneurysm cross-sectional area (range, 16% to 83%). Linear regression analysis failed to identify any correlation between thrombus and plasma IL-6, or thrombus and plasma CRP.

DISCUSSION

Aortic aneurysms as a source of circulating interleukin-6. Explants from AAAs have been to shown to secrete several cytokines, including tumor necrosis factor-α, interferon-γ, monocyte chemoattractant protein-1, and IL-1β, IL-6, and IL-8.[5,10,13-16] Interleukin-6 has emerged as the principal cytokine consistently associated with AAA, being secreted in vitro at higher levels than in both healthy controls and those with occlusive aortic disease.[5,9,10,17,18] Circulating levels of IL-6 have also been reported to be significantly higher in patients with AAAs than in controls.[5,6] Furthermore, these systemic concentrations have been correlated with aortic diameter in both patients with aneurysms[5,8] and in healthy subjects.[7] These data suggest that IL-6 may play a role in the early biologic processes of aortic dilatation that eventually leads to aneurysm development.

Jones et al[8] suggested that aneurysms secreted IL-6 into the circulation by observing that IL-6 was higher in the iliac arteries compared with the brachial arteries of patients with AAA.[8] Our results support and strengthen this hypothesis because they are the first, to our knowledge, to be based on direct measurements from within the aneurysm.

Overall levels of IL-6 were higher in the TAs compared with the AAAs. Although the mean maximum aneurysm diameter was higher in the AAAs (64 mm vs 57 mm), the total extent of aneurysmal disease in terms of surface area affected was approximately twofold higher in the TA group. Considering that we have demonstrated a correlation between mean plasma IL-6 and aneurysm surface area, it is interesting to note that this is the same order of magnitude difference seen in plasma IL-6 between the two groups. If the aneurysm does secrete IL-6 into the circulation, then a larger-volume aneurysm will provide a larger surface area, leading to higher concentrations of circulating IL-6.

In both the TA and AAA groups, levels of IL-6 were similar in the preaneurysm and first aneurysm positions. After this, a significant rise was noted in IL-6 corresponding to the second aneurysm position. In the AAA group the levels continued to rise, in the TA group they fell, perhaps because there was only one sample site after the aneurysm in the AAA group, whereas there were two in the TA group. The pattern of IL-6 elevation in both aneurysm groups conformed to a linear trend: IL-6 tended to increase overall throughout the length of the aorta. These patterns were not observed in the control group, which did not conform to a linear trend.

The CRP levels in the present study are within normal limits, indicating an absence of widespread inflammation. The elevated IL-6 concentrations observed in the aneurysm patients are therefore unlikely to simply reflect systemic inflammation and may be specifically due to the aneurysm. This hypothesis is further supported by the observation of

regional differences in IL-6 concentrations seen within the aorta corresponding to aneurysm position.

The IL-6 has several possible sources[9] because it is secreted by numerous cell types found within aneurysms.[20] The most obvious candidates are those cells present in the inflammatory infiltrate associated with the aneurysm wall, such as macrophages, B and T lymphocytes, and plasma cells.[1] Macrophages and neutrophils have also been identified in the intraluminal thrombus found within most aneurysms.[21] In addition, cells integral to the vascular wall of aneurysms, including fibroblasts, smooth muscle cells, and endothelial cells, have also been shown to secrete IL-6.

Interleukin-6 as an independent risk factor for cardiovascular mortality. Elevated circulating IL-6 has been identified as an independent risk factor for cardiovascular and all-cause mortality in elderly populations with cardiovascular disease[22,23] and for future myocardial infarction in young, apparently healthy controls.[11] In addition, the CC genotype, which predisposes to higher circulating levels of IL-6, was associated with a higher risk of cardiovascular and all-cause mortality in patients with aneurysms.[8]

Controversy exists about whether this association is a disease epiphenomenon or causal. It has been suggested that preclinical atherosclerosis acts as an inflammatory stimulus, with IL-6 a marker rather than cause of disease.[11] Conversely, it has been proposed that the relationship with mortality is not simply explained by the severity of concomitant disease, because elevated IL-6 has been associated with mortality independent of cardiovascular disease severity.[23]

Juvonen et al[6] reported higher levels of circulating IL-6 in AAA patients compared with those with coronary heart disease, suggesting that the elevated IL-6 was due to the aneurysm and independent of any coexisting coronary heart disease. In addition, Brady et al[24] reported a relationship between aneurysm diameter and cardiovascular mortality that was independent of atherosclerotic risk factors.[24] This group highlighted the fact that if the aneurysm wall was a source of IL-6, this could influence myocardial function, thrombosis, and inflammation.[24]

Proinflammatory cytokines have negative inotropic actions,[25,26] stimulate sympathetic and renin-angiotensin systems,[23] stimulate a prothrombotic state mediated by CRP,[23] and stimulate matrix metalloproteinases, leading to destabilization of atherosclerotic plaques. Because IL-6 is associated with numerous conditions characterized by tissue injury, this pathophysiologic mechanism may explain the excess risk of mortality associated with increasing circulating levels of inflammatory markers.[23] Elevated systemic IL-6 is therefore a plausible contributing factor in the high cardiovascular mortality observed in patients with AAA at all stages of the disease.[12,27,28]

Whether the elevated IL-6 identified in patients with TAs leads to a higher incidence of cardiovascular death than in patients with AAAs is a matter of conjecture. Bearing in mind perioperative mortality is higher in endovascular repair of TAs compared with AAAs, long-term survival rates of patients who have undergone endovascular repair of TAs are worse than that of AAAs. The largest series quote 1-year mortality of about 18% to 20%[29,30] for TA and 51% at 5 years,[30] compared with 1-year mortality of 7.4% after endovascular repair of AAA and 26% at 4 years.[31] Most deaths in both groups are due to acute cardiovascular events and are not aneurysm related.

Clinical relevance. Anecdotal evidence from the UK Small Aneurysm Trial supports our hypothesis. Patients who underwent early surgery had a 7.2% survival advantage at 8 years over those under surveillance, possibly owing to reduced temporal exposure to aneurysm-derived IL-6.[12] In addition, despite low perioperative mortality, the risk of death after endovascular repair of large AAA is approximately 8% at 1 year, with almost all deaths resulted from cardiovascular causes.[31] It remains to be seen whether aneurysm repair actually reduces circulating IL-6 concentrations and whether exclusion of the aneurysm by endovascular means would reduce circulating IL-6. This is clearly a key question and a prospective study is underway looking at this.

Statins are associated with a reduction in cardiovascular morbidity and mortality in patients with aneurysms,[32] and although their mechanism of action is almost certainly pleiotropic, they have been shown to reduce circulating IL-6.[33,34] As such, they form an integral part of the risk factor modification regimen that must complement the treatment of all patients with aneurysmal disease. This includes smoking cessation and the use of antihypertensive and antiplatelet medications.

Study limitations and considerations. As a major determinant of the acute phase response, IL-6 may be secreted in response to any stimuli resulting in tissue injury.[4,35] The aneurysm groups received general anesthesia, which may account for an acute rise in inflammatory markers. Evidence shows, however, that circulating IL-6 and CRP concentrations are similar to preoperative levels until at least 1 hour into a major operation,[36] and in the present study, blood was collected at the beginning of the procedure.

The principal limitation of the study was finding a suitable control group, matched for age, sex, and comorbidities, undergoing elective invasive vascular procedures allowing access to aortic circulation. However, when the data were corrected for age and sex, the presence of an aneurysm still had a significant effect on mean plasma IL-6 concentrations within the aorta.

As previously mentioned, certain drugs may influence IL-6 levels. Statins, in particular, have been shown to reduce IL-6 production from carotid plaques.[34] However, when the data were corrected for statin use, as well as age and sex, the relationship between mean plasma IL-6 and presence of aneurysm was not significantly affected. Other drugs more prevalent in the aneurysm groups include aspirin and antihypertensives such as angiotensin-converting enzyme inhibitors and β-blockers. In common with statins, there is good evidence that these drugs have a direct anti-inflammatory effect and reduce levels of IL-6[37,38] and therefore we would not expect their effect to negate our findings.

The aneurysm groups had a higher incidence of documented heart disease, and coronary plaques have been shown to express IL-6.[39] However, in contrast to acute coronary events in which circulating levels are elevated,[40] in quiescent coronary disease, as found in the aneurysm groups, circulating levels of IL-6 have been reported to be similar to that of healthy controls.[6]

Another potential criticism is that other manifestations of atherosclerotic burden such as peripheral artery disease could account for the elevated IL-6 observed. However, the proportion of patients with symptomatic peripheral artery disease was much higher in the control group (control, 27%; AAA, 15%; TA, 0%). Although more nonsmokers were in the control group, current smoking status has been shown to influence circulating IL-6,[11] and this was similar in all groups (control, 30%; AAA, 33%; TA, 33%).

CONCLUSION

The present study provides evidence supporting the theory that the aneurysm wall is a source of circulating IL-6. In addition to its role in aneurysm pathogenesis, aneurysm-derived IL-6 may stimulate distant systemic actions. Because circulating IL-6 has been identified as an independent risk factor for mortality, it is reasonable to suggest that the biologic effect of aneurysms may be more far-reaching and insidious regarding serious implications for cardiovascular health than the well-documented mortality associated with rupture and repair. It remains to be seen whether aneurysm repair reduces circulating levels of IL-6.

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AUTHOR CONTRIBUTIONS

Conception and design: MT, JD, AB
Analysis and interpretation: JD, GC, MT
Data collection: JD, EC, AB, IL, MT
Writing the article: JD, GC, EC, AB, IL, MT
Critical revision of the article: JD, MT, GC
Final approval of the article: MT, JD, GC, EC, AB, IL
Statistical analysis: JD, MT
Obtained funding: JD, MT
Overall responsibility: MT

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