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The Influence of Wall Stress on AAA Growth and Biomarkers

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Abstract *Objectives:* This study investigated the relation between abdominal aortic aneurysm (AAA) wall stress, AAA growth rate and biomarker concentrations. With increasing wall stress, more damage may be caused to the AAA wall, possibly leading to progression of the aneurysm and reflection in up- or downregulation of specific circulating biomarkers. Levels of matrix metalloproteinase-9, tissue inhibitor of matrix metalloproteinase-1, C-reactive protein and alpha 1-antitrypsin were therefore evaluated.
Methods: Thirty-seven patients (maximum AAA diameter 41–55 mm) with two, three or four consecutive computed tomography angiography (CTA) scans were prospectively included. Diameter growth rate in mm/year was determined between each pair of two sequential CTA scans. AAA wall stress was computed by finite element analysis, based on the first of the two sequential CTA scans only ($n = 69$ pairs). Biomarker information was determined in 46 measurements in 18 patients. The relation between AAA diameter and wall stress was determined and the AAA's were divided into three equally sized groups (relative low, medium and high stress). Growth rate and biomarker concentrations were compared between these groups. Additionally, correlation coefficients were computed between absolute wall stress, AAA growth and biomarker concentrations.

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Results: A relative low AAA wall stress was associated with a lower aneurysm growth rate. Growth rate was also positively related to MMP-9 plasma concentration ($r = 0.32$). The average MMP-9 and CRP concentrations increased with increasing degrees of relative wall stress, although the absolute and relative wall stress did not correlate with any of the biomarkers.
Conclusion: Although lower relative wall stress was associated to a lower AAA growth rate, no relation was found between biomarker concentrations and wall stress. Future research may focus on more and extensive biomarker measurements in relation to AAA wall stress.

Introduction

Incidence of abdominal aortic aneurysm (AAA) is increasing due to general aging of the population and an increase in the amount of screening programs.[1,2] If left untreated, an AAA will increase in size until rupture of the aortic wall occurs, causing a life-threatening hemorrhage. Growth rate of an AAA is generally defined as the change in maximum aortic diameter over a certain time period. Previous studies indicate that AAA growth rate increases with the diameter of the AAA.[3,4] However, this growth rate is not identical for all AAA's, as some AAA's remain stable for a considerable period of time, while others show a strong increase in diameter over a short period. Also, some AAA's tend to grow discontinuously, with alternating periods of growth and non-growth.[5,6]

Recently, multiple studies have focused on patient-specific AAA wall stress analyses.[7–11] Peak wall stress was found to be significantly higher for patients with symptomatic or ruptured AAA's than for asymptomatic aneurysms.[7,10] However, in these studies, the relation between wall stress and AAA growth rate was not investigated. With increasing wall stress, more damage may occur in the AAA wall, leading to degeneration of the wall and expansion of the aneurysm. Wall stress may thus have a prominent role in aneurysm growth and computing AAA wall stress may lead to a predictive model for AAA growth rate.

Circulating biomarkers are believed to reflect inflammation and degeneration in the AAA wall.[12] Matrix metalloproteinase-9 (MMP-9) is involved in the breakdown of the extracellular matrix and a higher plasma MMP-9 concentration was associated with AAA presence.[12] Additionally, MMP-9 significantly correlated with AAA growth rate.[13] The activity of MMP's is, amongst others, controlled by tissue inhibitor of the metalloproteinases-1 (TIMP-1). Although plasma concentrations of TIMP-1 were found to be significantly higher in AAA's than in healthy controls,[14] TIMP-1 levels were found to be lower in AAA wall tissue compared to healthy aortic tissue.[15] C-reactive protein (CRP) is a non-specific acute phase protein that is rapidly expressed in inflammation and has been previously linked to AAA size.[16] Recently, alpha 1-antitrypsin (α1-AT), an inhibitor of serine proteases such as trypsin and leukocyte elastase, was correlated with AAA growth.[17]

Summarizing, AAA's with a relative high wall stress may experience more damage to the AAA wall, possibly leading to faster expansion of the aneurysm. The amount of AAA wall damage may be reflected by up- or downregulation of specific circulating biomarkers. In this study, the relation between AAA wall stress, AAA growth rate, and biomarker concentrations was evaluated. First, the relation between the maximum diameter and wall stress was determined, and AAA's with relative high, medium and low wall stress, relative to their diameter, were identified. Prospective AAA diameter growth rate was determined and compared for each of the wall stress groups. The concentrations of MMP-9, TIMP-1, highly sensitive measured CRP (hs-CRP) and α1-AT were studied in relation to the computed wall stress and the prospective AAA growth rate.

Methods

Thirty-seven patients with asymptomatic AAA (initial maximum diameter 41–55 mm) from the Catharina Hospital Eindhoven (the Netherlands, $n = 19$) and the University Medical Center Maastricht (the Netherlands, $n = 18$) were prospectively included in the study. CTA scans were made with a 4-month interval until either the patient was eligible for surgery or the maximum of 4 consecutive CTA scans was reached. The patients were included for a 1-year follow-up with CTA, thereafter, regular ultrasound surveillance was continued. Blood pressures were measured within 30 min after the CTA scan. Growth in AAA diameter was determined as the change in maximum anterior–posterior diameter between two consecutive CTA measurements, and was converted to mm/year. Venous blood was drawn via an antecubital vein puncture and collected in SST (serum) and EDTA (plasma) buffered vacutainers®. Exactly 30 min after collection, the blood was centrifuged (15 min, 3000*g*, 4 °C) and multiple aliquots were stored at −80 °C, exactly 1 h after collection, until further analyses.

Patient demographical information (age, gender, hypertension, smoking, diabetes mellitus and statin use) was collected at every measurement and updated at each visit. Research approval was given by the local Medical Ethics Commissions of the hospitals involved. All patients signed informed consent prior to inclusion in the study.

Biomarker analysis

Biomarker analyses were only performed on the blood samples of the 18 patients from the University Medical Center Maastricht. Plasma levels of MMP-9 and TIMP-1 were determined in duplo by means of commercial available ELISA (GE Healthcare, Upsala, Sweden). The duplo concentration measurements results in two independent values, and whenever these values deviated less than 10% of each other, the values were averaged. Otherwise, the measurements were discarded in the analyses. The serological levels of α1-AT and hs-CRP were routinely

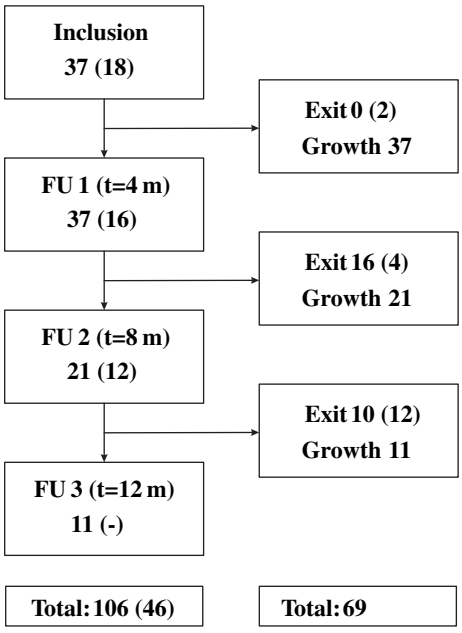

Figure 1 The patient flow chart indicating the number of patients with CTA at inclusion and at 4, 8 and 12-month follow-up. In brackets is indicated how many patients were included in the biomarker analysis. The right side indicates the number of patients who were lost between each follow-up and the number of AAA's used for growth analysis.

determined on the BN Prospec (Dade Behring Inc., Dearfield, USA).

Wall stress analysis

Automatic segmentation of the AAA's from the contrast enhanced CTA data was done as described previously.[11] No thrombus or calcifications were incorporated in the finite element model, but the relative thrombus volume[18] and calcification index[19] were determined for each model. The segmentation of the AAA wall was used as input to create a finite element mesh. A mesh typically consisted of approximately 30,000 quadratic 15-node tetrahedral elements, and a constant wall thickness of 2 mm was applied. A mesh refinement study was performed prior to the analyses and showed that the wall stress results changed less than 1% for an increasing number of elements.

The finite element software Sepran (Sepra, Delft, the Netherlands) was used to calculate AAA wall stresses. The governing equations of momentum and continuity were solved and the most distal and proximal planes of the models were constrained in all directions as essential boundary conditions. The nonlinear material model as proposed by Raghavan and Vorp (2000) was used to model the aortic wall behavior.[20] The patient group averaged systolic blood pressure of 140 mmHg (18.7 kPa) was applied to the inner wall of the finite element model. No cardiac triggering was applied in the CTA imaging protocol, therefore, the AAA geometry as derived from the CTA, was subjected to a time-averaged blood pressure. This results in initial stress in the AAA wall, which was accounted for using the backward incremental (BI) method.[21,22] The mean arterial pressure, as measured after the CTA scan, was used for that purpose.

Stresses, strains and displacements were calculated throughout the whole aneurysm model. In each node, maximum principal stress was computed. 99-Percentile wall stress in the AAA was used as stress measure, computed as the highest stress, after exclusion of 1% of the nodes in the mesh, with the highest stress. 99-Percentile wall stress showed to be more reproducible and less sensitive to geometrical variations than peak AAA wall stress.[11]

Data analysis

Based on the law of Laplace it may be expected that AAA wall stress generally increases with diameter. A regression model between the maximum AAA diameter and 99-percentile wall stress was therefore determined for all AAA models. The residuals of the regression model were normalized with the standard deviation of the model, and the AAA's were divided into three equally sized groups (relative high, medium and low stress), based on the

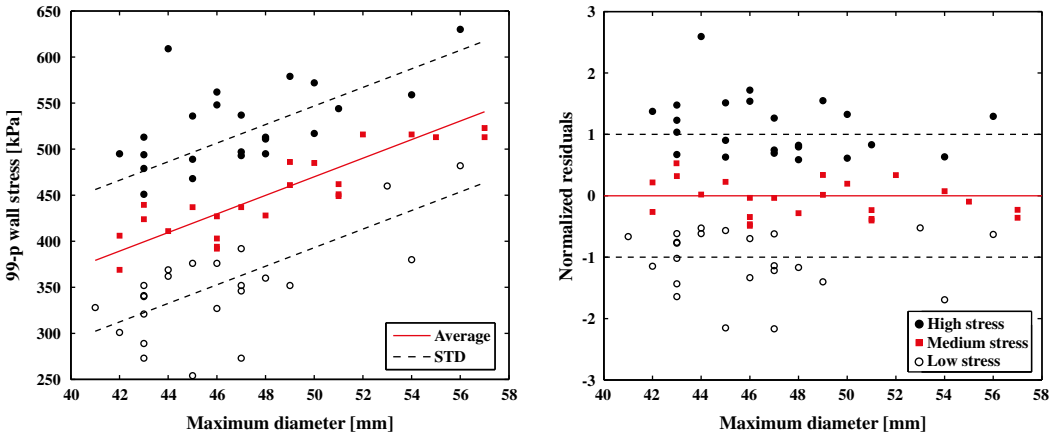

Figure 2 Regression model between maximum aortic diameter and 99-percentile wall stress (left, $r = 0.47$, p-value <0.01). The residuals of the regression model, divided by the standard deviation (right).

Table 1 Demographics for relative low, medium and high stress AAA's.

Relative wall stress	Low ($n = 23$)	Medium ($n = 23$)	High ($n = 23$)	p-Value
Gender (M:F)	23:0	23:0	18:5	<0.01
Age (mean(std)) years	73 (6)	72(6)	70 (6)	0.31[a]
Smoking (never:ex:current)	1:20:2	3:14:6	4:13:6	0.17
Hypertension[c]	11	13	16	0.50
Statin-use	13	7	13	0.20
Diabetes mellitus Type I	1	2	0	0.32
Max diameter (mean(std)) mm	46 (4)	49 (4)	47 (4)	0.14[a]
Relative thrombus volume (mean(std)) %	23 (29)	39 (29)	34 (30)	0.16[a]
Calcification index (mean (std)) %	20 (16)	19 (15)	13 (9)	0.24[a]
AAA growth rate (median (IQR)) mm/y	0 (3)	3 (7.5)	3 (8.3)	0.06[b]

Pearson chi-square test unless stated otherwise.
[a] Independent t-test.
[b] Kruskal–Wallis test.
[c] Hypertension is defined as a consistent blood pressure of at least 140 mmHg systolic or 90 mmHg diastolic.

normalized residuals. Patient demographics, relative thrombus volume,[18] calcification index[19] and prospective AAA growth were compared for each stress group. The log levels of MMP-9, TIMP-1, α1-AT and hs-CRP were compared between the high, medium and low stress AAA's, using ANOVA. As the biomarkers may influence each other on different levels, partial correlation coefficients were computed for both AAA growth rate and wall stress, in relation with log levels of the biomarkers. In that case, the strength of the relation between two variables is measured, after adjusting for the relations with other variables included in the evaluation. A p-value <0.05 was considered significant. The data analyses were performed with Statgraphics Centurion XV (StatPoint, Herndon, Virginia, USA).

Results

A total of 106 CTA scans were made (range 2–4 scans per patient). The median AAA diameter in these scans was 46 mm (range 41–57 mm). Of each pair of two sequential CTA scans, the diameter growth rate was determined and only the first of the two sequential scans was used for wall stress analyses, leaving in total 69 growth–stress comparisons in 37 patients (Fig. 1). During the study, four patients reached a diameter of 55 mm or more and were scheduled for aneurysm repair.

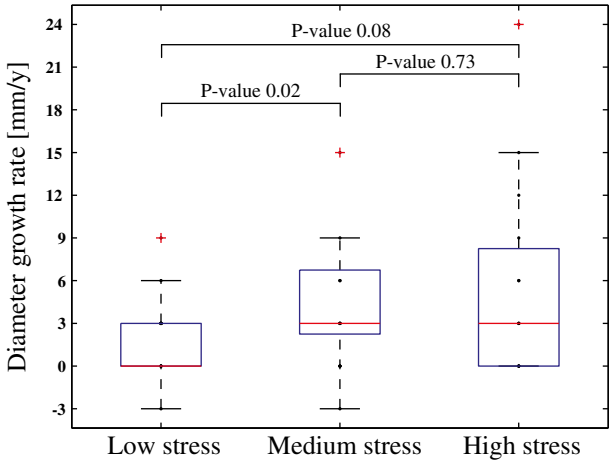

Figure 3 Box-and-Whisker plots of the AAA diameter growth rate for low, medium and high stress groups with the Kruskal–Wallis p-values. The Kruskal–Wallis test p-value was 0.06 for growth rate between all groups.

The left image of Fig. 2 shows the relation between the maximum AAA diameter and 99-percentile wall stress for the 69 measurements ($r = 0.47$, p-value <0.01). The residuals of the regression model were normalized by the standard deviation (STD) of the model and three equally sized groups were formed with relative low, medium and high stress (Fig. 2 right). The thresholds to form the groups were ± 0.5 STD.

Patient demographics of the three stress groups are summarized in Table 1. Gender was significantly different between the groups, as all female patients had a relative high AAA wall stress. The relative thrombus volume and calcification index were not significantly different between the groups (p-values 0.16 and 0.24, respectively). The AAA growth rate per group is displayed in the Box-and-Whisker plot in Fig. 3. The growth rate of the low stress group was significantly lower than of the medium stress group (Kruskal–Wallis p-value 0.02). The difference in growth rate between the low and high wall stress groups was close to significant (Kruskal–Wallis p-value 0.08).

Biomarker concentrations were determined in 18 patients, with total 46 measurements (see Fig. 1). Determined biomarker levels were inaccurate and discarded for 3 TIMP-1 measurements and the data of 6 hs-CRP and α1-AT analyses were missing. The log transferred biomarker concentrations for relative low, medium and high stress groups are given in Table 2. p-Values were computed with ANOVA. The mean plots of the MMP-9 and hs-CRP levels are displayed in Fig. 4. Although the average levels of MMP-9 and hs-CRP showed an increasing trend with relative wall stress, no significant differences were found in the log levels of any of the biomarkers between the three stress groups.

Partial correlations between absolute 99-percentile wall stress and the log levels of the biomarkers are shown in Table 3. Significant correlations between MMP-9 and TIMP-1

Table 2 Biomarker concentrations (median (IQR)) for low, medium and high stress AAA models (46 measurements in 18 patients). ANOVA *p*-values for the log levels of the biomarkers are given and the number of measurements are displayed below the concentration values.

Wall stress	Low	Medium	High	All	*p*-Value
MMP-9 (ng/mL)	34 (22–38) ($n = 18$)	43 (22–64) ($n = 16$)	49 (24–53) ($n = 12$)	41 (22–50) ($n = 46$)	0.52
TIMP-1 (ng/mL)	129 (109–159) ($n = 17$)	134 (98–163) ($n = 15$)	130 (91–151) ($n = 11$)	131 (98–163) ($n = 43$)	0.54
hs-CRP (mg/L)	2.3 (1.4–3.1) ($n = 14$)	3.3 (1.4–5.0) ($n = 17$)	3.7 (1.2–6.1) ($n = 9$)	3.0 (1.3–4.2) ($n = 40$)	0.67
α1-AT (g/L)	1.6 (1.2–1.8) ($n = 14$)	1.6 (1.5–1.8) ($n = 17$)	1.6 (1.5–1.8) ($n = 9$)	1.6 (1.5–1.8) ($n = 40$)	0.88

($r = -0.38$, *p*-value 0.03), MMP-9 and hs-CRP ($r = 0.32$, *p*-value 0.01), and between TIMP-1 and α1-AT ($r = -0.55$, *p*-value <0.01) were found. AAA wall stress did not correlate with any of the biomarkers.

Table 4 shows the partial correlations between AAA growth rate and log levels of the biomarkers. It must be noted that the correlation coefficients between the biomarkers mutually in Tables 3 and 4 do not exactly coincide due to the fact that partial correlations were computed. By doing so, the correlation between two variables is computed after adjusting for the relations with other variables included in the evaluation. Besides the previously found significant correlations between the biomarkers mutually, AAA growth rate showed to be significantly related to MMP-9 plasma concentration ($r = 0.32$, *p*-value <0.05). This was also significant for the univariate correlation between AAA growth rate and MMP-9 concentration ($r = 0.34$, *p*-value 0.02).

Discussion

In this study we hypothesized that in AAA's with high wall stress, relative to the diameter, the wall is more extensively damaged and degenerated than average. This could be reflected by increased AAA growth rate and up- or downregulation of specific biomarkers. The results showed that a relative medium or high wall stress could be associated with a higher growth rate, which was significant between the medium and low wall stress groups (*p*-value 0.02), and close to significant between the high and low wall stress groups (*p*-value 0.08). Although the average levels of MMP-9 and hs-CRP showed an increasing trend for increasing relative wall stress, none of the MMP-9, TIMP-1, α1-AT and hs-CRP concentrations were significantly different between the stress groups (Table 2). The average concentration of hs-CRP in the medium and high stress groups exceeded 3 mg/L, which was previously identified as threshold level between average and higher relative risk for future vascular events.[23] The growth rate in these groups was also higher than for the low stress group. A positive relation between MMP-9 concentration and AAA growth rate was found, but no correlation between absolute AAA wall stress and biomarkers could be identified.

The maximum aneurysm diameter and the corresponding 99-percentile wall stress showed a significant positive relation ($r = 0.47$, *p*-value <0.01). The relative low, medium and high wall stress groups as determined from this stress–diameter relation, did not show significant differences in age, smoking, hypertension, use of statins and diabetes mellitus. The maximum AAA diameter, relative thrombus volume and calcification index were also not different between the wall stress groups. The fact that all female patients resided in the high stress AAA group may be explained by geometrical differences in AAA's between men and women. Due to a smaller initial diameter, AAA's of equal size have a greater proportional dilatation in females than in males,[24] which generally results in a stronger curvature at inflection points on the wall surface. As in most cases high stress areas are situated at inflection points,[11] this can result in a higher 99-percentile wall stress. A larger patient population should be evaluated to elaborate on the differences in wall stress between male and female patients.

Between the biomarkers mutually, a positive correlation was found between hs-CRP and MMP-9 (Tables 3 and 4),

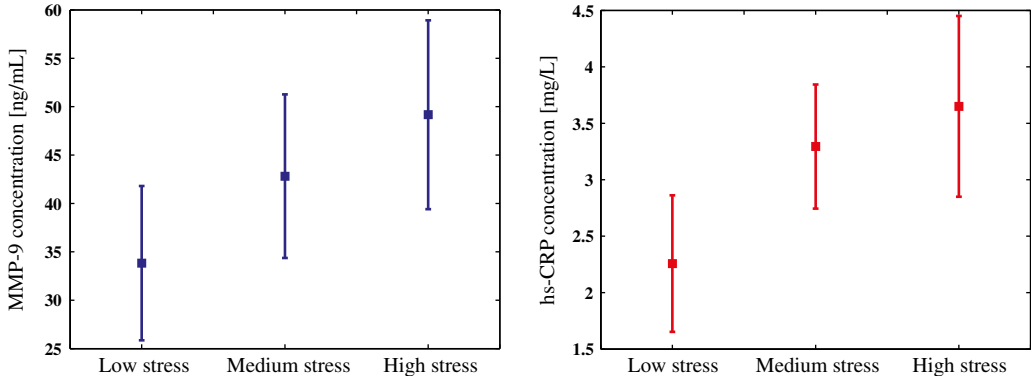

Figure 4 Means and Tukey HSD confidence intervals of the actual MMP-9 and hs-CRP concentrations for low, medium and high stress groups. ANOVA *p*-values were computed with log-transformed concentration (*p*-values 0.52 and 0.67, respectively).

Table 3 Partial correlation coefficient matrix between wall stress and log levels of MMP-9, TIMP-1, hs-CRP and α1-AT. The upper right part shows the correlation coefficients and the number of measurements, the lower left part shows the corresponding p-values. The * indicates a significant correlation.

	Stress	MMP-9	TIMP-1	hs-CRP	α1-AT
Stress	–	0.20 ($n = 46$)	0.06 ($n = 41$)	0.02 ($n = 39$)	0.05 ($n = 40$)
MMP-9	0.19	–	−0.38* ($n = 38$)	0.32* ($n = 36$)	−0.16 ($n = 37$)
TIMP-1	0.73	0.03	–	0.39 ($n = 32$)	−0.55* ($n = 33$)
hs-CRP	0.92	0.01	0.09	–	0.17 ($n = 39$)
α1-AT	0.77	0.37	< 0.01	0.32	–

Table 4 Partial correlation coefficient matrix between AAA growth and log levels of MMP-9, TIMP-1, hs-CRP and α1-AT. The upper right part shows the correlation coefficients and the number of measurements, the lower left part shows the corresponding *p*-values. The * indicates a significant correlation.

	AAA Growth rate	MMP-9	TIMP-1	hs-CRP	α1-AT
AAA Growth rate	–	0.32* ($n = 46$)	0.12 ($n = 41$)	0.06 ($n = 39$)	0.00 ($n = 40$)
MMP-9	<0.05	–	−0.39* ($n = 38$)	0.40* ($n = 36$)	−0.14 ($n = 37$)
TIMP-1	0.51	0.02	–	0.38 ($n = 32$)	−0.55* ($n = 33$)
hs-CRP	0.72	0.02	0.08	–	0.17 ($n = 39$)
α1-AT	0.99	0.42	<0.01	0.31	–

possibly reflecting the fact that both biomarkers respond to AAA related events; namely inflammation and matrix degradation. Furthermore, TIMP-1 was negatively correlated with MMP-9. Normally, TIMP-1 regulates the activity of MMP-9. This regulation may be disturbed in patients with AAA, resulting in a lower TIMP-1 concentration for higher MMP-9 levels. TIMP-1 and α1-AT were also negatively correlated. The pathophysiological meaning is not clear, but it was previously postulated that both MMP-9 and α1-AT positively correlated with AAA growth.[13,17] However, in the current study, only MMP-9 showed a positive correlation with AAA growth. Future research is required to establish the underlying relations between these biomarkers and their role in AAA pathophysiology.

This study is the first to couple AAA biomechanics and biomarker information. Nevertheless, some limitations and future research suggestions need to be mentioned. First, all measurements in this study are treated as individual and independent, although repeated measurements were performed in the patient group. It may well be that the stress and biomarker information is not independent per patient. The analyses are repeated with only one, randomly selected measurement per patient and the same trends were identified. However, no significant correlations could be found due to the small sample size. Also, ANOVA repeated measurement analyses were performed with all patients with three measurements. Again, the same trends were found, but due to the small sample size, no significance was reached in most cases. As the same trends were found, we are confident that the stress and biomarker measurements can be treated as independent measurements.

The AAA growth rate in this research was determined based on the maximum anterior-posterior diameter, which is currently the gold standard to determine the size of an AAA. The 3D models could be used to determine more sophisticated growth measures, based on the largest diameter perpendicular to the central axis or the AAA volume. However, these measures showed a considerable variation, in the same order as the growth rate itself. The determination of the maximum diameter is also subject to measuring errors and user variations. Future developments in 3D analysis tools may lead to more accurate and reproducible AAA growth rates.

Although it was previously shown that wall stress is a potentially better AAA rupture risk criterion than the maximum diameter,[7,10] AAA wall stress, as a stand-alone marker, may not be specific enough. Wall thickness variation, material heterogeneity, intraluminal thrombus and aortic calcifications are not included in the present simulations. Currently, no noninvasive techniques are available that can give information on the local wall thickness and material behavior. Implementation of thrombus and calcifications is debatable as the material properties, material model and interaction between thrombus, calcifications and AAA wall remain unknown.[18,19] Including these patient-specific factors may increase the specificity of wall stress simulations in the future.

Most biomechanical considerations of AAA's have focused on computing stresses acting on the aneurysm wall and not on the wall strength. This is, however, an equally important part in rupture risk prediction, since rupture occurs when the stresses exceed the strength of the wall. Information on the local wall constituents, for instance by means of MRI or advanced molecular imaging may substantially contribute to wall strength estimations and therefore to future AAA rupture risk analysis.

It must be noted that the relations found in this study only apply for AAA's with diameters between 40 and 55 mm, and cannot directly be extrapolated to smaller or larger AAA's. The current analysis was limited by a relative small patient group, representing AAA's with the most clinically relevant diameter. Extending the study with AAA's with

a wider range in diameter may give more insight in the general relations between wall stress, AAA growth and biomarkers.

Conclusion

To our knowledge, this is the first study that combines both circulating biomarker information and wall stress information with the prospective growth rate of AAA's. A relative medium or high wall stress was associated with a higher growth rate compared to a relative low wall stress (medium-low *p*-value 0.02, high-low *p*-value 0.08). The MMP-9 plasma concentration positively correlated to AAA growth rate (*p*-value <0.05). No correlation was found between absolute or relative wall stress and biomarker concentrations analyzed in this study, although the average concentrations of MMP-9 and hs-CRP showed an increase for higher relative wall stress. Further analysis is warranted to verify the relation between AAA wall stress, growth rate and biomarker concentrations.

Conflict of Interest/Funding

None.

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