Increased arterial stiffness in males with abdominal aortic aneurysm

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Abstract

Background: Abdominal aortic aneurysm (AAA), a localized dilatation of the abdominal aorta, has a prevalence of about 1.5%–3% among 65- to 70-year-old males in Europe. AAA confers an increased risk of developing major cardiovascular events in addition to the risk of aneurysm rupture. The aim of this study was to evaluate whether the arterial wall distensibility is altered in subjects with AAA.

Methods: Two hundred and eighty-four male subjects (182 with AAA and 102 controls) were enrolled in the study. Arterial wall distensibility was evaluated using non-invasive applanation tonometry to measure regional pulse wave velocity between the carotid and femoral arteries and the carotid and radial arteries. In addition, blood pressure was measured, and the pulse pressure waveform was analysed.

Results: Higher aortic augmentation index (25.1% versus 20.6%; \( p < .001 \)) and higher aortic pulse wave velocity (12.3 m/s versus 10.9 m/s; \( p < .001 \)) were demonstrated in the AAA cohort. The slightly higher arm pulse wave velocity in the AAA group (9.4 m/s versus 9.1 m/s; \( p < .05 \)) was abolished after adjusting for mean arterial blood pressure.

Conclusions: Males with AAA have decreased aortic wall distensibility and enhanced reflection waves in central aorta during systole. These results imply that increased arterial wall stiffness may be a contributing factor to the overall higher cardiovascular risk seen in patients with AAA.

Keywords
arteries, blood pressure, cardiovascular risk assessment, distensibility, pulse wave velocity

1 INTRODUCTION

An aneurysm is in general terms defined as a focal arterial dilatation comprising all three layers of the vessel wall with a diameter exceeding 50% of that of the adjacent normal segment (Kuivaniemi et al., 2015b). For aneurysms located within abdominal aorta (AAA), an absolute infrarenal diameter of at least 30 mm is traditionally required for the AAA diagnosis to be set (Kuivaniemi et al., 2015a; Svensjo et al., 2011; Wanhainen et al., 2001). The reported prevalence of AAA varies worldwide and is further affected by divergent traditions in diameter measurement techniques, but recent studies indicate that approximately 1.5%–3% of 65- to 70-year-old males in Europe develop an AAA (Benson et al., 2016; Hager et al., 2014; Wanhainen et al., 2016). AAA and atherosclerosis share many
common risk factors, including age, male gender, smoking and low HDL cholesterol even though atherosclerosis does not cause AAA per se (Nordon et al., 2010; Wanhainen et al., 2005).

Although AAA is usually asymptomatic, rupture has catastrophic consequences with a survival rate of only 10%-20% (Hultgren et al., 2016). Even in the absence of rupture, AAA increases the risk of developing other major cardiovascular events (Bath et al., 2015). The mechanisms underlying this increased risk are not fully understood, although genetic factors appear to contribute (Kuivaniemi et al., 2015). AAA is a disease with a predominance of male (4:1 ratio) (Lo & Schermerhorn, 2016; McPhee et al., 2007). Moreover, males with a family history of AAA exhibit a larger non-aneurysmal abdominal aortic diameter (Joergensen et al., 2014). Atherosclerosis develops more rapidly in AAA patients, suggesting an underlying pathology in the aortic wall that may extend beyond the aneurysm.

One consequence of accelerated vascular ageing is a more pronounced age-related decline in arterial wall distensibility, which increase central aortic blood pressure and left ventricular workload (Mikael et al., 2017). Arterial wall distensibility can be measured by a variety of invasive and non-invasive methods. Pulse wave velocity (PWV) and pulse wave analysis (PWA) are validated methods for determining regional arterial wall properties and predicting risk for future cardiovascular events (Lane et al., 2006; Laurent et al., 2006). Few studies have evaluated arterial wall distensibility in AAA, most often by measuring central arterial PWV in a limited number of male and female subjects compiled into one group. The results are conflicting, showing either increased (Durmus et al., 2014), unaltered (Bailey et al., 2014) or decreased (Lee & Park, 2013) carotid-femoral PWV in subjects with AAA.

It is still unclear whether males with AAA demonstrate high PWV and higher systolic reflection waves in aorta. Thus, the main objective of this study was to determine whether AAA is associated with decreased arterial wall distensibility.

2 | MATERIALS AND METHODS

2.1 | Study population

Participants included 307 males, 199 patients with AAA and 108 controls, ranging in age from 55 to 80 years. Subjects were recruited consecutively from a regional AAA ultrasound surveillance program or an ongoing AAA ultrasound-screening program at two neighbouring counties in the southern part of Sweden between 2011 and 2016. Exclusion criteria applied at the time of recruitment were cardiac arrhythmia, severe disability, advanced cancer and language barriers. Twenty-three subjects (17 AAA and 6 controls) were excluded after examinations due to poor quality of pulse wave recordings (n = 10), ongoing arrhythmia (n = 10) or hardware failure (n = 3). Thus, 182 AAA and 102 controls were enrolled. The males in the AAA cohort presented a maximum infrarenal aortic diameter measured according to the leading edge-to-leading edge (LELE) method ≥30 mm during their most recent clinical ultrasound examination. Their average maximal AAA diameter was 42 mm (range, 30–58 mm). The AAA diameter in 176 out of 182 cases was below the suggested intervention threshold of 55 mm, thus here regarded as a small AAA:s. The controls displayed an absolute infrarenal aortic diameter within the reference range, without any sign of ectasia, at their foregoing screening examination within the past five years. Prior to study entry, all subjects provided written informed consent. The study was approved by the regional ethical review board in Linköping, Sweden, and was conducted in accordance with principles stated in the Declaration of Helsinki.

Participants were asked to provide information about smoking status, cardiovascular diseases and current medications. Responses were compiled, and missing information was retrieved from individual medical records.

2.2 | Blood pressure and body measurements

Blood pressure was measured when subjects were in supine position. Upper-arm blood pressure was determined with an oscillometric device (Dinamap model PRO 200 Monitor, Critikon). After cuff deflation, systolic, diastolic, mean arterial pressure and heart rate appeared on the monitor. Ankle systolic blood pressure was measured during cuff deflation by detecting the return of the pulsatile blood flow with a Doppler device (in the dorsal pedal artery and later in the tibial posterior artery).

Body weight was determined without shoes and trousers and rounded down to the nearest 0.5 kg (SECA, model 877, Seca GmBH & Co). Height was measured and rounded to the nearest 0.5 cm.

2.3 | Pulse wave velocity and analysis

The SphygmoCor system (Model MM3, AtCor Medical) equipped with a Millar pressure tonometer was used to record the pulse pressure waveforms non-invasively. All waveforms were transferred online to a PC where the SphygmoCor software (version 8.0) was installed. Simultaneous electrocardiogram (ECG) allowed pulse wave velocity (PWV) to be calculated. The pulse transit time was determined by automatic analysis of the average delay from the R-wave of the ECG to the foot of the pulse wave, initially at the distal site and later at the proximal site, each for 10 s. The pulse travel distance between the two arterial sites was estimated on the body surface according to the subtraction method. In the present study, we obtained the carotid to the femoral PWV (abbreviated as PWVcf) and the carotid to the radial artery PWV (abbreviated as PWVcr).

Calculation of central aortic pressure and waveform was achieved from the calibrated radial pressure wave that was analysed with a generalized transfer function. Time to reflection (Tr) and augmentation index (Alx) were automatically calculated from the aortic waveform.
2.4 | Study protocol

All subjects were instructed to refrain from consuming alcohol for 12 hr and tobacco and caffeinated beverages for 4 hr prior to their visit. Height and weight were measured, followed by completion of the questionnaire. Vascular examinations were then performed with the subject in supine position in a quiet room with air temperature 22–24°C after 10 min of rest. The systolic upper-arm blood pressure was measured in each arm to exclude ipsilateral arterial occlusive disease in the proximal part of the upper extremity. The left arm was fixed as the standard reference arm for later measurements (except when systolic pressure was at least 10 mmHg higher on the right side). Systolic ankle pressure was measured bilaterally concomitantly with the left upper-arm pressure.

The distance from the suprasternal notch to each pulse recording site was measured on the body surface with a measurement stick. ECG leads were connected to the subject. A tonometer pencil probe was pressed alternately towards the left femoral and right carotid arteries, and later to the left radial and right carotid arteries. The oscillometric upper-arm blood pressure was recorded before and after the paired pulse wave recordings.

2.5 | Calculations and data analysis

The radial artery augmentation index (Per AIx) is defined as the radial artery pulse pressure at the second systolic peak (P2) divided by the pressure at the first systolic peak (P1).

\[
\text{Per AIx} \, (\%) = \frac{P2}{P1} \times 100.
\]

The aortic augmentation index (AIx) is defined as the increase of pressure over the first systolic shoulder due to wave reflection (aug), divided by pulse pressure (PP).

\[
\text{AIx} \, (\%) = 100 \times \frac{\text{aug}}{\text{PP}}.
\]

The left ventricular ejection time influences the amplitude of the late systolic pressure augmentation. Consequently, the augmentation index was also presented normalized to heart rate 75, abbreviated Per AIxHR75 and AIxHR75, respectively.

Pulse pressure (PP) is defined as:

\[
\text{PP} \, (\text{mmHg}) = \text{systolic blood pressure} - \text{diastolic blood pressure}.
\]

The systolic ankle-to brachial pressure index (ABPI) is calculated as:

\[
\text{ABPI} = \frac{\text{Ankle systolic pressure}}{\text{Brachial systolic pressure}}.
\]

The ankle brachial index value is presented as the average calculated ABPI on the right and left sides, respectively.

All reported data from the vascular examination are mean values from two separate recordings of acceptable technical quality.

2.6 | Statistics

Data were analysed using SPSS 25.0 for Windows (SPSS inc.). Values are presented as number of participants and per cent for categorical variables and as mean ± SD for continuous variables. Comparisons between two groups were performed using unpaired Student’s t test or non-parametric means test (Mann–Whitney U test). Moreover, analysis of covariance (ANCOVA) was run in order to compare means after adjustment for confounders. Additionally, bivariate associations between variables were evaluated using Pearson’s bivariate correlation. Logarithmic transformation was used for continuous variables with a non-normal distribution. \( p < .05 \) was considered significant.

3 | RESULTS

3.1 | Demographic data

Age, height and prevalence of diabetes mellitus were similar between groups, whereas weight and BMI were higher in the AAA cohort (\( p < .05 \); Table 1). Symptomatic ischaemic heart disease and cerebrovascular events were more often reported in the AAA group that included a higher number of current and former smokers (\( p < .001 \)). Circulatory levels of glycated haemoglobin A1c (\( p < .01 \)) and c-reactive protein (\( p < .001 \)) were higher in the AAA cohort than in the control group. Finally, a greater proportion of subjects in the AAA cohort were treated with anti-hypertensive drugs, aspirin (ASA) and statins (\( p < .001 \)).

3.2 | Pulse wave measurements and blood pressure

PWVcf was higher in AAA versus controls, 12.3 m/s versus 10.9 m/s (\( p < .001 \); Table 2). The difference persisted after adjusting for MAP and BMI 12.3 m/s and 11.1 m/s (\( p < .001 \)) in AAA and controls, respectively (Figure 1). Predominantly peripheral PWV, which was measured between the carotid and radial arteries (PWVcr), was slightly higher in AAA versus controls, 9.4 m/s versus 9.1 m/s (\( p < .05 \)), although this difference disappeared after adjusting for MAP and BMI. Consequently, the PWVcf/PWVcr ratio was significantly lower in controls than AAA. Analysis of the recorded radial arterial pulse pressure waveform showed a higher Per AIx and Per AIxHR75 (adjusted to a heart rate of 75) in AAA versus controls, 90.1% versus 83.1% (\( p < .001 \)). Derived aortic AIx and AIxHR75 were higher in AAA versus controls. Simultaneously,
TABLE 1  Characteristics of the study population

|                      | AAA (n = 182) | Control (n = 102) | p-value |
|----------------------|---------------|-------------------|---------|
| Age (years)          | 70.4 ± 3.9    | 70.3 ± 4.4        | NS      |
| Height (cm)          | 177.3 ± 6.1   | 177.1 ± 5.5       | NS      |
| Weight (kg)          | 87.1 ± 13.3   | 83.5 ± 11.8       | <.05    |
| BMI (kg/m²)          | 27.7 ± 4.1    | 26.6 ± 3.4        | <.05    |
| HR (beat/min)        | 60.3 ± 8.7    | 59.0 ± 9.3        | NS      |
| Smokers*, n (%)      |               |                   |         |
| Current              | 45 (26.6)     | 5 (5.2)           | <.001   |
| Former               | 108 (63.9)    | 31 (32.3)         | <.001   |
| Diabetes, n (%)      | 13 (7.1)      | 8 (7.8)           | NS      |
| IHD, n (%)           | 68 (37.4)     | 9 (8.8)           | <.001   |
| CVD, n (%)           | 28 (15.4)     | 2 (2.0)           | <.001   |
| HbA1c (mmol/mol)     | 41.9 ± 9.9    | 39.0 ± 7.1        | <.05    |
| ApoB/ApoA1           | 0.67 ± 1.07   | 0.72 ± 0.19       | <.05    |
| Creatinine (µmol/L)  | 86.9 ± 26.5   | 83.2 ± 15.1       | NS      |
| Hb (g/L)             | 146.0 ± 12.2  | 148.2 ± 9.6       | NS      |
| CRP (mg/L)           | 4.2 ± 6.2     | 2.4 ± 3.3         | <.001   |
| AHT, n (%)           | 125 (69.1)    | 43 (42.2)         | <.001   |
| β blockers, n (%)    | 74 (40.9)     | 17.0 (16.7)       | <.001   |
| Diuretics, n (%)     | 37 (20.4)     | 4 (3.9)           | <.001   |
| Ca antagonists, n (%)| 51 (28.2)     | 12 (11.8)         | <.001   |
| ACE inhibitors, n (%)| 82 (45.3)     | 32 (31.4)         | <.05    |
| Statin, n (%)        | 136 (75.1)    | 27 (26.5)         | <.001   |
| Aspirin, n (%)       | 110 (60.8)    | 18 (17.6)         | <.001   |

Note: Values are presented as mean ± SD for continuous variables and number of participants and per cent for categorical variables.

Abbreviations: ACE, angiotensin-converting enzyme; AHT, antihypertensive treatment; BMI, body mass index; CRP, C-reactive protein; CVD, history of symptomatic cerebrovascular disease; Hb, haemoglobin; HR, heart rate; IHD, history of ischaemic heart disease; NS, not significant.

Data are available in 169 AAA and 96 controls.a

a shorter time to reflection wave arrival (Tr) was observed in the central aorta of subjects with AAA (p < .001). Among blood pressure parameters, MAP and diastolic blood pressure were significantly higher in the AAA versus control group (p < .05). Males with AAA had a lower average ABPI than controls (p < .001). In addition, the number of males with ABPI < 0.9 (unilateral or bilateral) was higher in the AAA cohort compared with controls, 22 (12.1%) versus 2 (2.0%).

3.3  Correlations to pulse wave parameters

Pearson’s bivariate correlation analysis was performed between PWVcf, PWVcr, Aix75 and other selected parameters. With all subjects included, MAP (r = .31), pPP (r = .33), BMI (r = .27) and HR (r = .23) were correlated with PWVcf (Table 3). MAP also correlated with PWVcr (r = .35) and Aix75 (r = .37). In addition, Aix75 correlated with pPP (r = .29). None of the pulse wave variables correlated significantly with the maximum AAA diameter in the AAA cohort.
Further, the faster age-related stiffening of elastic arteries reduce pulse wave velocity (Ciurica et al., 1979; Sugawara et al., 2008). However, ageing impacting arterial geometry alters the regional hemodynamics while changed wall properties are expected to emerge within the aneurysmal segment of aorta. Ultrasonic echo-tracking shows that patients with AAA have higher aortic wall stiffness within the aneurysm (Sandgren et al., 1999). The enlargement and wall deformation within an aneurysm is thus supposed to affect the regional pressure wave propagation (Fujikura et al., 2007). It has been proposed that the presence of an aneurysmal dilatation invalidate the reliability of the PWV method as an instrument for evaluation of wall distensibility (Lee & Park, 2013). Interestingly, no association between the size of the aneurysm and PWV was found in neither the present or the study by Durmus et al., 2014 (Durmus, Kazaz, Altun & Cansu). Another factor that could have suppressed the expected link between AAA size and PWV is the flow stasis that facilitate development of intra-luminal thrombus formation (Salsac et al., 2004) that reduce the intra-luminal diameter within the aneurysm sack markedly in most larger AAA. Even in AAA with diameter <40 mm, a luminal reduction due to intra-luminal thrombus formation is seen in about 50% of all aneurysms (Behr-Rasmussen et al., 2014). According to the Moens–Kortweg equation, such a process is expected to set-off the influence seen on the pulse wave propagation speed due to outer arterial enlargement. It is reasonable to believe that the structural wall properties along aorta in the AAA group were far more important for the regional pressure wave propagation speed than the altered geometry in the aneurysmal zone (Cameron et al., 2018).

The calculation of the regional PWV is based on distance measurements on the body surface. A characteristic feature of the ageing process is a significant elongation of the aorta. A prerequisite for reliable comparison of PWV data between two groups is equal disagreement between true and estimated path length between the two pulse recording sites. By ageing, elongation primarily seems to affect ascending aorta, a segment that is excluded when measuring PWVcf (Ciurica et al., 1979; Sugawara et al., 2008). However, ageing may promote arterial elongation from the aortic arch to the proximal femoral artery, and clinically, the impression is that tortuosity occur due to wave reflection. The arterial pulse wave pressure that undergo deformation in peripheral direction is the result of a forward wave component from ventricular ejection, together with reflected waves. The observed higher central augmentation index in the AAA group may have consequences for the cardiac work, since amplified reflected waves in central aorta during late systole may increase left ventricular afterload (Nichols, 2011). Time to reflection (Tr) was shorter in the AAA group, a finding likely explained by their higher aortic PWV.

In theory, pulse wave velocity calculation assumes a straight tube, mechanically as well as geometrically homogeneous. Changed arterial geometry alters the regional hemodynamics while changed wall properties are expected to emerge within the aneurysmal segment of aorta. The main findings of this cross-sectional study are summarized as follows. Males with small AAA have both higher PWV and the systolic reflection wave amplification within aorta compared with age-matched controls. These data suggest that the vascular ageing process in their central arterial walls have progressed further versus controls. Furthermore, the maximal aneurysm diameter did not correlate with the recorded regional PWV.

In the present study, we determined the speed of the pulse wave along two arterial segments that cover predominantly elastic and muscular arterial segments, respectively. Ageing impacts arterial stiffness through loss of elastin, with age-related changes observed primarily in central arteries. The elastin to collagen ratios in the arterial walls of central and peripheral arteries differ, with central arteries containing a larger proportion of elastin (Nichols, 2011). Further, the faster age-related stiffening of elastic arteries reduce or even reverse the stiffness gradient between central and peripheral arteries seen in healthy younger subjects, thus resulting in faster central than peripheral artery PWV instead of the opposite (Länne et al., 1992, 1998; Lee & Oh, 2010; Sandgren et al., 1999). PWVcf is the gold-standard measurement in the evaluation of aortic wall distensibility through its proven association with incident cardiovascular disease (Laurent et al., 2006). The speed at which a pulse wave travels along arteries provides a measure of the arterial wall distensibility through the Moens–Kortweg equation (Callaghan et al., 1986). In the present study, unadjusted carotid-femoral PWV was markedly higher, and carotid-radial PWV slightly higher in the AAA cohort. Distending pressure is a well-known predictor of PWV, but also BMI is positively associated with PWVcf, primary due the link between overweight and conventional risk factors, but overestimation of the pulse path length from body-surface measurement can also contribute (Canepa et al., 2014). After adjusting for the slightly higher MAP and BMI seen in the AAA, the PWVcr difference between the two groups disappeared, whereas the difference in PWVcf between groups persisted (Figure 1). Along with PWVcf, higher ratio PWVcf/ PWVcr was found in AAA which underline the PWVcf finding. Actually, PWV ratio is better predictor of overall mortality than PWVcf alone, with potential to display vascular ageing in a more blood pressure-independent manner (Fortier et al., 1979). By pulse wave analysis, an overall measure of the general arterial condition is achieved that reflect both arterial structure, geometry and function. The arterial pulse wave pressure that undergo deformation in peripheral direction is the result of a forward wave component from ventricular ejection, together with reflected waves. The observed higher central augmentation index in the AAA group may have consequences for the cardiac work, since amplified reflected waves in central aorta during late systole may increase left ventricular afterload (Nichols, 2011). Time to reflection (Tr) was shorter in the AAA group, a finding likely explained by their higher aortic PWV.

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more often in cases with aneurysmal disease. If so, it would in fact diminishes the true difference in carotid-to-femoral PWV between the two groups.

AAA has historically been considered a focal manifestation of advanced atherosclerosis (Bailey et al., 2014; Nordon et al., 2009) studied central arteries using CT and suggest that AAAs are representative of a systemic vascular disease (Nordon et al., 2009). Higher PWV is usually correlated to more prominent atherosclerosis at different arterial sites of the arterial system (Kim & Kim, 2019). Whether regional arterial atherosclerosis or wall thickening directly suppresses the arterial wall distensibility or if the two conditions simple share many common risk factors are not fully elucidated. In the present study detailed evaluation of the participants atherosclerotic burden is lacking. However, higher prevalence of symptomatic ischaemic heart disease and ABPI < 0.9 in the AAA compared to the controls makes it reasonable to believe that the degree of arterial atherosclerosis differs between the two cohorts. As expected, a higher percentage of males in the AAA group were treated with statins, anti-platelet therapy and blood pressure-lowering agents (Table 1), drugs that should be considered in all patients with AAA according to current guidelines.

Use of anti-hypertensive drugs may affect arterial impedance. Beta-blockers reduce heart rate, which in turn can influence the viscoelastic properties of the arterial wall, increase wave reflections, and decrease aortic SBP and PP (Janić et al., 2014). Since the two study groups presented similar mean heart rate, it is unlikely that heart rate had any major impact on the comparison of pulse wave data. ACE inhibitors and calcium channel blockers may affect arterial stiffness and reduce PWV (Williams et al., 2006). However, despite higher use of these agents, AAA patients had significantly higher PWV compared with controls.

Another important factor to consider is the prevalence of diabetes mellitus (DM), a disease associated with higher arterial stiffness and thus increased PWV (Prener & Chirinos, 2015). However, there was no difference in the prevalence of DM between the AAA and control groups (Table 1). Although DM indeed is a risk factor for cardiovascular disease in general, less cases are found among those with AAA diagnosis. Instead, DM seems to have a protective effect on AAA, both through pathophysiological mechanisms and antidiabetics drugs (Raffort et al., 2018). Metformin prescription in AAA patients has also been shown to be associated with reduced AAA growth rate (Unosson et al., 2020).

4.1 | Study limitations

In the present study, the following limitations should be noted. The AAA group had (a) larger proportion of smokers and former smokers, and, as already mentioned, (b) were more often taking medication, and finally, (c) had likely more prominent atherosclerotic arteries. Thus, other factors than just absence or presence of aneurysm differed between the two groups. Nevertheless, we consider the selection of participants as representative for the AAA group and the general population, respectively. Moreover, as the study followed a cross-sectional design, no direct cause-and-effect associations can be derived.

5 | CONCLUSION

In conclusion, males with AAA have decreased aortic wall distensibility and enhanced systolic wave reflection back to central aorta. Our results suggest that arterial stiffness measurements may assist in the management of patients with AAA and identify patients with an enhanced overall cardiovascular risk. Moreover, the maximal aneurysm diameter does not correlate with the carotid-femoral PWV.

Nevertheless, longitudinal studies are needed before definite conclusions can be drawn about the prognostic role of PWV in the surveillance of AAA patients.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

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