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Impaired abdominal aortic wall integrity in elderly men carrying the angiotensin-converting enzyme D allele

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ABSTRACT

Objective: A polymorphism in the angiotensin-converting-enzyme gene (ACE I/D) has been associated with abdominal aortic aneurysm and a link between aortic aneurysm and aortic stiffness has been suggested. This study aimed to explore the links between ACE I/D polymorphism, circulating ACE, and abdominal aortic wall integrity as reflected by abdominal aortic wall stiffness.

Material: 212 men and 194 women, 70-88 years were studied.

Methods: Mechanical properties of the abdominal aorta were determined using Wall Track System, ACE-genotype using PCR, and circulating ACE level by ELISA.

Results: In men, pulsatile diameter change differed between genotypes (II 0.70, ID 0.55, DD 0.60 mm, $P=0.048$), while a tendency was seen for distensibility coefficient (DC) (II 10.38, ID 7.68, ID 8.79, $P=0.058$). Using a dominant model (II vs. ID/DD), men carrying the ACE D allele had lower pulsatile diameter change ($P=0.014$) and DC ($P=0.017$) than II carriers. Multiple regression analyses showed additional associations between the D allele and increased stiffness β , and reduced compliance coefficient.

Conclusion: Men carrying the ACE D allele have stiffer abdominal aortas compared to II carriers. Deranged abdominal aortic stiffness indicates impaired vessel wall integrity, which along with other local predisposing factors, may be important in aneurysmal disease.

KEY WORDS: arterial stiffness, distensibility, gene polymorphism, mechanical properties, aorta

INTRODUCTION

A genetic polymorphism in the ACE gene (ACE I/D polymorphism) has previously been associated with increased cardiovascular risk, with carriers of the ACE D allele being more susceptible.^{1,2} In addition, this polymorphism has been associated with abdominal aortic aneurysm (AAA),³⁻⁵ although this association has been questioned.⁶ The abdominal aorta is of particular interest as age- and gender-related changes are more pronounced at this site than other arteries⁷ and as the abdominal aorta is particularly prone to aneurysm formation.⁸ The mechanical properties of the abdominal aorta are measures of aortic wall integrity. Impaired wall integrity might, along with other local hemodynamic and inflammatory processes predispose to aneurysm formation. The aim of the study was to investigate the association between ACE I/D polymorphism, circulating ACE and the mechanical properties of the abdominal aorta in elderly men and women.

MATERIALS AND METHODS

Study population

Subjects were recruited from an ongoing longitudinal study of elderly people from a rural community in South East Sweden. All inhabitants aged 65-82 were invited to participate in the original study.⁹ A total of 876 individuals of the 1130 originally invited, agreed to participate.⁹ During a follow-up study, which was carried out between 2003 and 2005, we had the opportunity to perform a cross-sectional study in this population. A total of 123 individuals died before the follow-up study started. 452 of the remaining study population agreed to take part in the present study, of whom 23 subjects were excluded due to irregular heart rate (e.g. atrial fibrillation) with variable pressure pulses in the arteries, difficulties in obtaining a blood sample, or to hepatitis infection. In the remaining 429 subjects, the abdominal aorta was examined using ultrasound. Twenty-three of these were excluded due to low quality of the ultrasonic measurements, resulting in a final study population of 406 subjects (212 men and 194 women) aged 70-88.

Subjects were asked to refrain from tobacco, coffee and tea for at least four hours before the examination. All participants had a physical examination and were asked about cardiovascular risk factors, cardiovascular disease and medications. Individuals with a previous diagnosis of hypertension, or with a blood pressure of $\geq 140/90$ mmHg were defined as hypertensive. Diabetes mellitus was defined as a previous diagnosis of diabetes or a fasting plasma glucose of ≥ 7 mmol/L. Ischemic heart disease (IHD) was defined as history of angina pectoris or ECG-verified myocardial infarction. Individuals who stated that they smoked were classified as smokers. A diameter ≥ 30 mm of the abdominal aorta, a localized abdominal aortic dilatation or previous surgical repair was defined as abdominal aortic aneurysm (AAA). All participants gave their 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.

Blood samples were taken after an overnight fast and collected in pre-chilled plastic Vacutainer tubes (Terumo EDTA K-3). Plasma was prepared by centrifugation at 3000 g for 10 min at 4 °C. Blood and plasma were stored at -70 °C pending analysis. Fasting glucose, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were measured in plasma. Height and weight were recorded and used for calculation of body mass index (BMI) and body surface area (BSA).

Blood pressure measurements

Brachial blood pressure was measured with subjects in the supine position using an oscillometric technique (Dinamap model PRO 200 Monitor, Critikon, Tampa, FL, USA) after at least 15 min of rest. Systolic, diastolic and mean arterial pressures (MAP) were measured, and pulse pressure was calculated (systolic pressure – diastolic pressure).

Measurement of intima-media thickness and lumen diameter in the abdominal aorta

The abdominal aorta was examined approximately 3-4 cm proximal to the aortic bifurcation. The Wall Track System (WTS2; Pie Medical, Maastricht, The Netherlands) was used to determine lumen diameter, pulsatile diameter changes during the cardiac cycle, and intima-media thickness (IMT), as described previously.^{10, 11} An ultrasound scanner (Esaote AU5; Esaote Biomedica, Florence, Italy) equipped with a 7.5 MHz linear transducer or a 7.3 MHz curved transducer was used. All measurements were carried out by two experienced ultrasonographers on a single occasion, with subjects in the supine position, immediately following brachial blood pressure measurements. IMT of the posterior wall was measured in diastole. Diastolic and systolic lumen

diameter and pulsatile diameter change were determined between the posterior and the anterior wall. Mean values from three successive recordings were used.

Calculations

The compliance coefficient (CC) and the distensibility coefficient (DC) were calculated using the formulae¹²:

$$CC = \pi(2 \times D_{dia} \times \Delta D + \Delta D^2) / (4 \times \Delta P)$$

$$DC = (2 \times D_{dia} \times \Delta D + \Delta D^2) / (D_{dia}^2 \times \Delta P)$$

CC is expressed in mm²kPa⁻¹ and DC in 10⁻³kPa⁻¹. D_{dia} is the end diastolic diameter (mm), ΔD is the diameter change between diastole and systole (mm), and ΔP is the brachial pulse pressure (kPa).

CC is the absolute change in cross-sectional area during a cardiac cycle for a given increase in aortic pressure, assuming that the length of the vessel is not affected by the pulse wave. A decrease in CC indicates reduced vessel buffering capacity. DC is the relative change in aortic diameter during a cardiac cycle for a given increase in pressure and varies inversely with abdominal aortic stiffness.

There is a non-linear relationship between pressure and diameter change in the abdominal aorta, the vessel being very distensible at low pressures and small diameters and becoming gradually stiffer (less compliant) with increasing pressure and diameter.¹³ Stiffness β seems to be less dependent on pressure changes,¹³ and may be used as a complement to CC and DC. Stiffness β was calculated according to:^{13, 14}

$$Stiffness\beta = \ln(P_{sys} / P_{dia}) / (\Delta D / D_{dia})$$

P_{sys} and P_{dia} represent the systolic and diastolic brachial blood pressures in mmHg.

Blood pressure was measured in the brachial artery extrapolating this to the abdominal aorta, in order to calculate local aortic stiffness, distensibility and compliance. There is a good agreement between brachial and intra-arterial aortic systolic pressure.¹⁵ The diastolic pressure is higher in the brachial artery, leading to a slight systematic underestimation of aortic stiffness.¹⁵ However, as no age- or gender-related differences have been observed,¹⁵ this systematic bias should not affect comparative studies between groups or subjects.

ACE genotyping

Genomic DNA was isolated from peripheral blood using QIAmp DNA Mini Kit (QIAGEN, Hilden, Germany) following the manufacturer's instructions. ACE-genotype was determined using a previously described protocol.¹⁶

Angiotensin-converting enzyme assay

Plasma ACE levels were analysed using ELISA (Human ACE DuoSet, R&D Systems, Minneapolis, USA), following the manufacturer's instructions. All samples were analysed in duplicate and mean values were calculated. Duplicates where the variance from the mean value exceeded 15% were reanalysed.

Statistical analyses

The data are presented as mean values or number of subjects. Men and women were analysed separately as abdominal aortic wall mechanics is known to be gender-dependent¹⁷. Discrete variables were analysed using the χ^2 test. ONE-way ANOVA or student's *t*-tests were used to compare continuous data between groups, with adjustments for potentially confounding factors. Multiple regression analyses were made to assess the effect of ACE-genotype and ACE level on CC, DC and stiffness β , with adjustment for potentially confounding factors. The Hardy

Weinberg equilibrium was assessed by χ^2 test. *P*-values of <0.05 were considered statistically significant. Statistical analyses were carried out using SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Study population

Characteristics of the study population are shown in Table 1. 64% of the study population was on antihypertensive treatment (ACEi 20%, angiotensin II receptor blockers 4%, beta blockers 36%, calcium channel blockers 18% and diuretics 36%) and 23% were on statins (data not shown).

There were no significant differences in the medication between men and women (data not shown). Of the 429 subjects, 18 men (8%) and 2 women (1%) were affected by AAA. Ten of the men were excluded due to low quality of the ultrasonic measurements, leaving 8 men and 2 women with AAA in the final study population of 406 subjects.

Table 1 Characteristics of study population

	All	Men	Women	<i>P</i>
Number of subjects, n (%)	406	212 (52)	194 (48)	
Age, years (SD)	78.8 (3.5)	78.6 (3.1)	78.9 (3.8)	0.383
Body mass index, kg/m ² (SD)	26.3 (3.8)	26.0 (3.2)	26.5 (4.3)	0.197
Plasma glucose, mmol/L (SD)	5.7 (2.2)	5.8 (2.0)	5.7 (2.4)	0.491
Plasma LDL, mmol/L (SD)	3.1 (1.0)	3.0 (0.8)	3.3 (1.1)	<0.001
Plasma HDL, mmol/L (SD)	1.3 (0.3)	1.2 (0.3)	1.4 (0.4)	<0.001
Blood pressure, mmHg (SD)				
Systolic pressure	148 (23)	145 (22)	152 (24)	0.005
Diastolic pressure	75 (10)	76 (10)	74 (11)	0.107
Pulse pressure	73 (19)	69 (18)	78 (20)	<0.001
Mean arterial pressure	103 (16)	102 (15)	104 (17)	0.308
History, n (%)				
Ischaemic heart disease	89 (22)	56 (26)	33 (17)	0.022
Hypertension	337 (83)	168 (79)	169 (87)	0.035
Diabetes	87 (21)	49 (23)	38 (20)	0.387
Smoking	36 (9)	27 (13)	9 (5)	0.004

Values are mean (SD) or number of subjects (%).

P-values are men vs women

ACEi treatment

Treatment with ACEi was associated with higher levels of plasma ACE. Plasma ACE level was 308 ± 112 ng/ml in men taking ACEi and 184 ± 84 ng/ml in men who were not ($p < 0.001$). The corresponding ACE levels for women were 359 ± 186 ng/ml and 200 ± 94 ng/ml ($p < 0.001$). As ACEi treatment induces upregulation of ACE¹⁸, subjects who were on this treatment (43 men and 40 women) were excluded from the statistical analyses of ACE levels. Treatment with angiotensin II receptor blockers, beta blockers, calcium channel blockers, diuretics and statins had no effect on plasma ACE (data not shown).

Genotype frequency and association of ACE I/D gene polymorphism with circulating ACE

The frequency of the D allele was 0.50 (men 0.48, women 0.53). The genotype frequencies were in accordance with the Hardy Weinberg equilibrium. As shown in Figure 1, plasma ACE levels were influenced by ACE I/D polymorphism. The ACE D allele accounted for 17% (9% in men and 27% in women) of the variance in plasma ACE level. There was no difference in ACE level between men and women (data not shown).

Association of ACE I/D polymorphism with abdominal aortic wall mechanics

The characteristics of the study population according to ACE I/D polymorphism are shown in Table 2 (men) and Table 3 (women). In men, there was a significant difference in pulsatile diameter change ($p = 0.048$) between genotypes, and a tendency for DC ($p = 0.058$). Using a dominant model (II vs. ID//DD), men carrying the ACE D allele had lower pulsatile diameter change (ΔDiaSys) (ID/DD 0.57 mm vs II 0.70mm, $p = 0.014$) and DC (ID/DD 8.09 vs II 10.38, $p = 0.017$) than subjects carrying the II genotype. Excluding subjects with AAA had only little effect (DC $p = 0.036$). Using a recessive model (II/ID vs. DD), there were no differences in abdominal aortic wall mechanics in men (data not shown). In women, there was a difference in

age and frequency of IHD between genotypes, while there was no difference in abdominal aortic wall mechanics. In addition, more men with the II genotype were on statins than men with the D allele (II 31% vs ID/DD 17%, $p=0.024$) (data not shown). Subjects treated with other cardiovascular drugs (ACEi, angiotensin II receptor blockers, beta blockers, calcium channel blockers and diuretics) were evenly distributed between genotypes in men and women (data not shown).

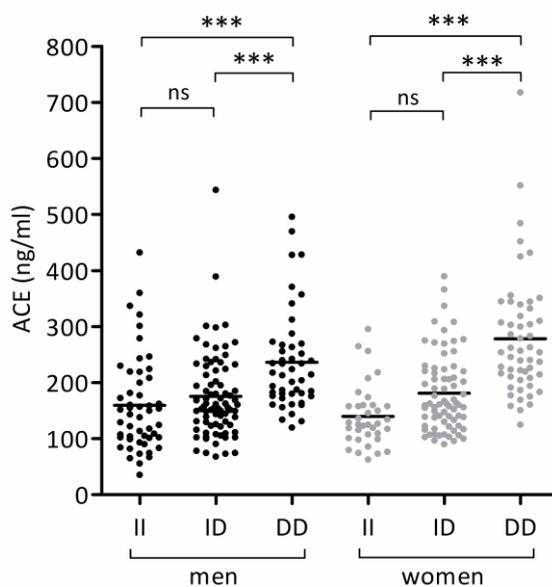


Figure 1. Plasma ACE level (ng/ml) according to ACE I/D polymorphism in men ● and women ●. Individuals treated with ACE inhibitors were excluded. *** $p<0.001$

Multiple regression analyses

Multiple regression analyses were used to further investigate the association between ACE level, ACE-genotype and aortic wall properties in men (Table 4). The presence of the D allele, circulating ACE level and potentially confounding factors (age, MAP, BMI, heart rate, LDL, C-reactive protein, diabetes mellitus, smoking and antihypertensive treatment) were included. There was a significant association between the presence of the D allele and reduced CC ($p=0.045$), reduced DC ($p=0.003$) and increased stiffness β ($p=0.048$), whereas no association was found

with ACE level. In addition, there was an association between MAP and both CC and DC ($p < 0.001$) and an association between BMI and CC, DC and stiffness β ($p < 0.001$).

Table 2 Characteristics according to ACE I/D polymorphism in men

	I/I	I/D	D/D	P	I/I	ID/DD	P
Number of subjects, n (%)	65 (31)	92 (43)	55 (26)		65 (31)	147 (69)	
Age, years (SD)	78.6 (3.4)	77.9 (3.1)	77.9	0.351	78.6 (3.4)	77.9 (3.0)	0.147
Body mass index, kg/m ² (SD)	26.1 (3.6)	26.0 (3.2)	26.0 (3.0)	0.960	26.1 (3.6)	26.0 (3.1)	0.781
Laboratory data (SD)							
Plasma glucose, mmol/L	6.1 (2.5)	5.8 (1.8)	5.5 (1.8)	0.243	6.1 (2.5)	5.7 (1.8)	0.191
Plasma LDL, mmol/L	2.8 (0.87)	3.0 (0.87)	3.0 (0.75)	0.398	2.8 (0.87)	3.0 (0.83)	0.179
Plasma HDL, mmol/L	1.2 (0.24)	1.2 (0.26)	1.3 (0.31)	0.065	1.2 (0.24)	1.2 (0.28)	0.322
Plasma ACE, ng/ml *	159 (85)	174 (76)	227 (80)	<0.001	159 (85)	194 (81)	0.013
Blood pressure, mmHg (SD)							
Systolic pressure	145 (23)	147 (22)	142 (20)	0.500	145 (23)	145 (22)	0.953
Diastolic pressure	75 (11)	78 (9)	73 (9)	0.041	75 (11)	76 (9)	0.471
Pulse pressure	70 (18)	69 (18)	69 (17)	0.887	70 (18)	69 (17)	0.636
Mean arterial pressure	102 (16)	104 (15)	100 (15)	0.421	102 (16)	102 (15)	0.707
Aortic wall properties (SD)							
Intima-media thickness, mm	0.54 (0.11)	0.56 (0.15)	0.55 (0.15)	0.713	0.54 (0.11)	0.55 (0.15)	0.458
Diastolic lumen diameter, mm	17.0 (3.0)	17.8 (3.3)	17.4 (2.8)	0.347 †	17.0 (3.0)	17.6 (3.1)	0.168 †
Systolic lumen diameter, mm	17.7 (3.0)	18.3 (3.3)	18.0 (2.7)	0.533 †	17.7 (3.0)	18.2 (3.1)	0.303 †
Pulsatile diameter change, mm	0.70 (0.40)	0.55 (0.31)	0.60 (0.37)	0.048 †	0.70 (0.40)	0.57 (0.34)	0.014 †
Compliance coefficient mm ² /kPa	2.21 (1.60)	1.84 (1.3)	1.87 (1.24)	0.150 ‡	2.21 (1.60)	1.85 (1.21)	0.061 ‡
Distensibility coefficient 10 ⁻³ /kPa	10.38 (7.94)	7.68 (5.37)	8.79 (6.76)	0.058 ‡	10.38 (7.94)	8.09 (5.93)	0.017 ‡
Stiffness β	24.9 (20.4)	29.9 (19.2)	29.5 (21.9)	0.385 §	24.9 (20.4)	29.7 (20.1)	0.129 §
History, n (%)							
Ischemic heart disease	21 (32)	22 (24)	13 (24)	0.433	21 (32)	35 (24)	0.196
Hypertension	52 (80)	74 (80)	42 (76)	0.827	52 (80)	116 (79)	0.857
Diabetes	20 (31)	20 (22)	9 (16)	0.161	20 (31)	29 (20)	0.079
Smoking	10 (15)	7 (8)	10 (18)	0.132	10 (15)	17 (12)	0.442

Values are mean (SD) or number of subjects (%)

* subjects treated with ACE inhibitors are excluded, † adjusted for age, MAP and BSA, ‡ adjusted for age and MAP, § adjusted for age

Table 3 Characteristics according to ACE I/D polymorphism in women

	I/I	I/D	D/D	P	I/I	ID/DD	P
Number of subjects, n (%)	46 (24)	89 (46)	59 (30)		46 (24)	148 (76)	
Age, years (SD)	79.1 (3.8)	78.8 (3.7)	77.3 (3.7)	0.029	79.1 (3.8)	78.2 (3.8)	0.180
Body mass index, kg/m ² (SD)	26.2 (4.6)	26.0 (4.3)	27.6 (3.7)	0.072	26.2 (4.6)	26.6 (4.2)	0.522
Laboratory data (SD)							
Plasma glucose, mmol/L	5.3 (1.2)	5.8 (2.7)	5.7 (2.8)	0.452	5.3 (1.2)	5.8 (2.7)	0.076
Plasma LDL, mmol/L	3.3 (0.95)	3.2 (1.15)	3.4 (1.0)	0.540	3.3 (0.95)	3.3 (1.11)	0.943
Plasma HDL, mmol/L	1.4 (0.45)	1.4 (0.34)	1.4 (0.35)	0.932	1.4 (0.45)	1.4 (0.35)	0.887
Plasma ACE, ng/ml *	141 (55)	181 (69)	272 (105)	<0.001	141 (55)	218 (96)	<0.001
Blood pressure, mmHg (SD)							
Systolic pressure	154 (26)	152 (24)	149 (24)	0.524	154 (26)	151 (24)	0.357
Diastolic pressure	76 (11)	74 (11)	73 (10)	0.525	76 (11)	74 (11)	0.282
Pulse pressure	79 (21)	78 (19)	76 (20)	0.700	79 (21)	77 (19)	0.575
Mean arterial pressure	107 (19)	103 (16)	103 (16)	0.335	107 (19)	103 (16)	0.141
Aortic wall properties (SD)							
Intima-media thickness, mm	0.56 (0.15)	0.61 (0.25)	0.63 (0.2)	0.294	0.56 (0.15)	0.61 (0.22)	0.075
Diastolic lumen diameter, mm	14.4 (2.8)	14.6 (2.9)	15.1 (2.3)	0.437 †	14.4 (2.8)	14.8 (2.6)	0.199 †
Systolic lumen diameter, mm	14.9 (2.9)	15.2 (2.8)	15.7 (2.3)	0.427 †	14.9 (2.9)	15.4 (2.6)	0.194 †
Pulsatile diameter change, mm	0.55 (0.31)	0.61 (0.33)	0.58 (0.33)	0.943 †	0.55 (0.31)	0.60 (0.33)	0.861 †
Compliance coefficient mm ² /kPa	1.38 (1.08)	1.44 (0.91)	1.50 (1.01)	0.921 ‡	1.38 (1.08)	1.46 (0.95)	0.687 ‡
Distensibility coefficient 10 ⁻³ /kPa	8.24 (5.40)	9.29 (6.63)	8.6 (6.12)	0.708 ‡	8.24 (5.40)	9.01 (6.41)	0.833 ‡
Stiffness β	29.2 (23.0)	24.8 (16.7)	28.4 (30.0)	0.313 §	29.2 (23.0)	26.3 (23.1)	0.633 §
History, n (%)							
Ischemic heart disease	13 (28)	9 (10)	11 (19)	0.027	13 (28)	20 (14)	0.020
Hypertension	41 (89)	78 (88)	50 (85)	0.785	41 (89)	128 (86)	0.640
Diabetes	7 (15)	21 (24)	10 (17)	0.422	7 (15)	31 (21)	0.393
Smoking	2 (4)	3 (3)	4 (7)	0.624	2 (4)	7 (5)	1.00

Values are mean (SD) or number of subjects (%)

* subjects treated with ACE inhibitors are excluded, † adjusted for age, MAP and BSA, ‡ adjusted for age and MAP, § adjusted for age

Table 4 Multiple regression analyses in men using compliance coefficient, distensibility coefficient and stiffness β as dependent variables

	Compliance coefficient			Distensibility coefficient			Stiffness β		
	B	SE of B	P	B	SE of B	P	B	SE of B	P
Presence of D allele	-0.48	0.238	0.045	-3.55	1.163	0.003	7.50	3.76	0.048
ACE, ng/ml	0.001	0.001	0.691	0.01	0.006	0.308	-0.02	0.02	0.329
Age, years	-0.02	0.034	0.552	-0.20	0.165	0.221	-0.01	0.53	0.993
Map, mmHg	-0.03	0.007	<0.001	-0.14	0.034	<0.001	0.15	0.11	0.187
Body mass index, kg/m ²	-0.18	0.033	<0.001	-0.79	0.163	<0.001	2.79	0.53	<0.001
Heart rate, beats/min	-0.02	0.010	0.061	-0.07	0.049	0.170	0.04	0.16	0.796
Plasma LDL, mmol/L	0.04	0.122	0.740	-0.37	0.596	0.531	1.62	1.93	0.403
C-reactive protein, mg/L	-0.001	0.006	0.819	0.02	0.030	0.588	-0.03	0.10	0.802
Diabetes mellitus	-0.20	0.290	0.492	-1.94	1.416	0.173	0.01	4.58	0.998
Smoking	-0.14	0.311	0.661	-0.81	1.523	0.593	2.57	4.92	0.603
Antihypertensive medication	0.13	0.215	0.543	-0.24	1.053	0.823	-1.64	3.40	0.630
<i>Adjusted r² of the model</i>	0.325			0.328			0.195		

Subjects treated with ACE inhibitors are excluded

B: regression coefficient, SE: Standard Error, Map: mean arterial pressure

DISCUSSION

In this study the impact of ACE I/D polymorphism and circulating ACE on abdominal aortic wall mechanics were examined. It is unknown whether the ACE I/D polymorphism acts in a dose-dependent, dominant or recessive manner. Our results indicate that the association between the ACE I/D polymorphism and abdominal aortic stiffness is independent of one or two copies of the D allele, suggesting a dominant pattern.

Men carrying the ACE D allele had lower pulsatile diameter changes and lower DC in the abdominal aorta. Multiple regression analyses showed additional associations between the D allele and CC as well as stiffness β , suggesting reduced buffering capacity as well as increased stiffness. In line with our findings, Mattace-Raso et. al. found lower DC in ID and DD carriers compared to II, while no difference was seen between ID and DD.¹⁹ In addition, an association between the ACE D allele and reduced CC has been reported²⁰.

A number of studies have examined the link between ACE I/D polymorphism and carotid-femoral pulse wave velocity (aortic PWV). Higher PWV has been reported in carriers of the I allele^{21, 22}, while others failed to identify any associations¹⁹. As PWV is measured between the carotid and femoral arteries, it reflects the mean arterial stiffness of several areas of the arterial tree. PWV may thus reflect aspects of vascular function other than those measured in our study. In addition, the elasticity of various arteries may differ, and genetic determinants may produce different outcomes depending on the artery studied²³.

Although age is considered a major determinant of arterial stiffness, our results did not show any association between age and CC, DC or stiffness β . This is probably due to the narrow age range in our study (70-88 years). In younger subject, there is a gender difference in abdominal aortic stiffness, with men having stiffer aortas than women of corresponding age.¹⁷ This study, however, did not find any gender-associated difference in abdominal aortic stiffness. The

calculated values of stiffness β were similar to previous findings in elderly men,¹⁷ suggesting that age-related changes in aortic wall properties accelerate in women after menopause. Furthermore, in accordance with previous data, BMI was shown to be a strong determinant of CC, DC and stiffness β ,²⁴ and there was a positive association between MAP and CC and DC, while stiffness β was less dependent of MAP.¹³

The abdominal aorta is the most common site for aneurysm formation⁸. Most of the abdominal aortic media lacks vasa vasorum and is instead supplied with oxygen and nutrients by diffusion from the bloodstream²⁵. Increased wall thickness, as a result of e.g. ageing, may therefore result in impaired nutrition of the abdominal aortic wall. In addition, as a consequence of pulse wave reflections from the periphery, the abdominal aorta is exposed to higher systolic and pulse pressures than other central arteries⁸. The mechanisms involved in aneurysm formation are largely unknown, however it has been argued that a combination of local hemodynamic factors, and factors affecting wall strength (genes, proteolytic activity, inflammation etc.) are of importance.⁸ We have previously reported an association of aneurysm-associated genetic variations on chromosome 9p21.3 with reduced abdominal aortic stiffness,²⁶ while this study showed higher stiffness in carriers of the D allele. Deranged abdominal aortic stiffness indicates impaired integrity of the aortic wall which might be important in aneurysmal disease.²⁷ As the ACE D allele is a common allele, it cannot be the sole factor responsible. However, together with other local factors, the ACE D allele may predispose to aneurysm formation.

The prevalence of AAA in our population (8% in men and 1% in women) was similar to other populations.⁸ The low prevalence of AAA made it impossible to explore the link between the ACE I/D polymorphism and AAA. Such link has on the other hand been identified by others.³⁻⁵

Previous experimental studies lend support to the suggestion that ACE has a role in aneurysm formation.^{28, 29} Accumulation of ACE has been reported in the abdominal aortic wall in patients with aneurysm,²⁸ and angiotensin II infusion induces AAA in mice.²⁹ It has been suggested that the increased stiffness seen in carriers of the D allele may be a consequence of exposure to higher levels of ACE.¹⁹ Previous studies have shown that 20-50% of the variation in ACE activity in the general population can be explained by ACE I/D polymorphism.^{30, 31} We³², and others³¹ have however shown large variations in ACE level even between those carrying the same genotype, and only 17% of the variation in circulating ACE was related to ACE I/D polymorphism in our elderly population. Interestingly, although the ACE D allele was associated with increased stiffness in the abdominal aorta in our study, we found no link between circulating ACE and aortic stiffness (Table 3). We do not yet know whether levels of circulating ACE correlate with the levels in the arterial wall. Therefore, although no connection between circulating ACE and aortic stiffness was seen, we cannot rule out a possible link between ACE level in the vessel wall and abdominal aortic stiffness. The ACE D allele may be in linkage disequilibrium with genetic variations in other genes, which in turn may influence aortic stiffness. ACE I/D polymorphism may thus represent a marker for another genetic polymorphism involved in the regulation of vessel wall mechanics.

This study provided evidence of an association between the ACE D allele and aortic stiffness in men, whereas no such association was found in women. This is interesting in the context of aneurysm formation, as AAA is more common in men.⁸ Previous studies investigating the link between the ACE I/D polymorphism and arterial stiffness have analysed mixed populations.¹⁹⁻²¹ The lack of association between the ACE D allele and aortic stiffness in women may therefore conceal the association in men, if mixed populations are studied.

Conclusions

This study shows an association between the ACE D allele and abdominal wall mechanics, with men carrying the ACE D allele having a stiffer abdominal aorta than II carriers. However, no association between circulating ACE level and aortic stiffness was found, suggesting that the effect of the D allele is due to factors other than elevated levels of circulating ACE. Increased abdominal aortic stiffness suggests impaired vessel wall integrity, which combined with local hemodynamic, inflammatory as well as other genetic factors may have an important role in aneurysm formation, and could possibly explain the previously reported association between the ACE I/D polymorphism and AAA.

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