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ORIGINAL RESEARCH

Determinants of Occurrence of Aortic Sclerosis in an Aging Population

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OBJECTIVES We sought to identify clinical, physiological, and biochemical correlates, including markers of endothelial dysfunction and of tissue nitric oxide (NO) responsiveness, of the presence of aortic sclerosis (ASc) in an aging population.

BACKGROUND Aortic sclerosis has been regarded predominantly as a precursor of hemodynamically significant aortic stenosis. However, ASc also represents an independent correlate of increased risk of cardiovascular morbidity and mortality; the basis of this association is incompletely understood. The assumption that the pathogenesis of aortic valve disease is similar to that of atherosclerosis has not been supported by recent studies; rather there has been increasing evidence of a pathogenetic role of inflammation and endothelial dysfunction. Furthermore, we have recently developed methodology for echocardiographic quantitation of early aortic valve disease.

METHODS Randomly selected subjects (n = 253) ages 51 to 77 years underwent transthoracic echocardiography; aortic valve ultrasonic backscatter score (AV_{BS}) was used to quantitate echogenicity of the aortic valve. Conventional coronary risk factors were identified. Integrity of NO generation/response was assessed via: 1) plasma asymmetric dimethylarginine concentrations, as a marker of endothelial dysfunction; 2) inhibition of platelet aggregation by the NO donor sodium nitroprusside, as a measure of tissue NO responsiveness and also a coronary prognostic marker; and 3) aortic augmentation index, as a measure of arterial stiffness/wave reflection. All putative correlations with AV_{BS} were examined by univariate and multiple linear regression analyses.

RESULTS On the basis of AV_{BS} scores, ASc was present in 19.4% of subjects. The AV_{BS} directly correlated with patients' age but inversely correlated with high-sensitivity C-reactive protein, creatinine clearance, and platelet NO responsiveness. On multiple linear regression, ASc was associated with impaired platelet NO responsiveness ($\beta = -0.16$, $p = 0.02$), advancing age ($\beta = 0.21$, $p = 0.003$), and low body mass index ($\beta = -0.23$, $p = 0.001$).

CONCLUSIONS Aortic sclerosis is associated with platelet NO resistance rather than conventional coronary risk factors: this might explain the increased thrombotic risk in ASc. (J Am Coll Cardiol Img 2009;2:919–27) © 2009 by the American College of Cardiology Foundation

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Aortic stenosis (AS) occurs as a result of a progressive increase in calcium deposition within the aortic valve, leading to increased stiffness and progressive narrowing of the valve. Hemodynamically significant AS occurs in approximately 2% of adults older than 65 years of age (1,2). The earlier stage of this process, known as aortic (valve) sclerosis (ASc)—which implies the presence of abnormal aortic valve morphology in the absence of marked obstruction—is even more common, affecting approximately 30% of adults older than age 65 (2,3).

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ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional
ACEI = angiotensin-converting enzyme inhibitor
ADMA = asymmetric dimethylarginine
AIIRB = angiotensin II receptor blocker
AIx = augmentation index
AS = aortic stenosis
ASc = aortic sclerosis
AVBS = aortic valve ultrasonic backscatter score
BMI = body mass index
BSA = body surface area
CrCl = creatinine clearance
CRP = C-reactive protein
hs-CRP = high-sensitivity C-reactive protein
LDL = low-density lipoprotein (cholesterol)
LV = left ventricular
NO = nitric oxide
SNP = sodium nitroprusside

The clinical significance of ASc extends beyond its status as a precursor of hemodynamically significant AS. A number of carefully conducted studies have established that ASc is an independent, incremental marker of risk of cardiac events and cardiovascular mortality (3,4). However there is current uncertainty concerning both the major biochemical mechanism(s) underlying the development/progression of ASc and its association with coronary events.

It has been previously suggested that the pathogenesis of AS involves an "atherogenesis-like process" (5). However, there is also evidence that atherogenesis is not the central pathogenic process in AS. Attempts to induce the development of AS via hypercholesterolemia alone in animal models have generally proved unsuccessful (6,7), whereas lipid-lowering therapy did not slow progression of AS in the SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) (8) or SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) studies (9).

It is theoretically possible that a combination of endothelial dysfunction (i.e., of both valve and vasculature) and redox stress might contribute both to development of ASc and to its associated cardiovascular risk. With regard to endothelial dysfunction, it has been recently shown that calcific nodule formation in cell culture of aortic valve fibroblasts is inhibited by nitric oxide (NO) (10). Clinically, we have also shown that advanced AS is associated with elevation of plasma concentrations of asymmetric dimethylarginine (ADMA) (11), a marker of endothelial dysfunction. Therefore, it is probable that endothelial dysfunction develops at some stage in the clinical course of AS and that NO is important for inhibition of development of valve calcification.

A phenomenon closely related to but not identical to endothelial dysfunction is NO resistance (12), which has been described extensively in the vasculature (13,14) and also in platelets (15). In both coronary arteries and platelets, this phenomenon of NO resistance is an independent marker of coronary event risk (13,16). Although the basis for NO resistance remains uncertain in the vasculature, the major underlying mechanism in platelets is incremental oxidative stress, with "scavenging" of NO by O_2^- anion (15). If NO resistance were associated with propensity for development of ASc, this would represent both a basis for calcification and a potential link to coronary risk.

Previous investigations have generally regarded ASc as a categorical variable. However, it is now possible to incorporate into analyses quantitation of ASc, with aortic valve backscatter (AV_{BS}) (17,18). We have recently evaluated the basis for the association between ASc development and increased AV_{BS} in a rabbit model of mild AS (19). In this model, the correlation between AV_{BS} and extent of valve calcification was strong ($R = 0.76$, $p < 0.001$). Hence, AV_{BS} reflects in part a quantitative measure of overall valve calcification. This technique therefore facilitates evaluation of disease severity and/or progression. In the current study, we used this technique to perform a cross-sectional population study evaluating biochemical and physiological correlates of the presence of ASc in aging individuals. In particular, we sought to identify the relative strengths of association of conventional coronary risk factors versus parameters of endothelial function/NO effect as correlates of the presence of ASc.

METHODS

Study subjects. The current investigation was a prospectively defined substudy of the North Western Adelaide Health Study (NWAHS). The NWAHS cohort participants were recruited by telephone to conduct the interviews and the Electronic White Pages as the sampling frame. Within each household, the person who had their birthday last and was 18 years and older was selected for interview and invited to attend the clinic for a biomedical examination. To minimize potential bias due to differing probabilities of selection in the sample, the data were weighted by region (western and northern health regions), age group, and sex. This cohort study did not recruit people residing in

institutions, such as nursing homes. However, people who had their own telephone number and were living in individual units attached to a nursing home were eligible to participate (20).

The current study population consisted of 255 consecutive, randomly selected subjects from the NWAHS cohort from 51 to 77 years of age (mean 63.4 ± 6 years), who had not previously undergone aortic valve replacement. Of 255 subjects screened, 2 subjects were excluded due to the presence of terminal cancer (n = 1) and dextrocardia (n = 1). Informed consent was obtained from all subjects before study. The study was approved by the Ethics of Human Research Committee of The Queen Elizabeth Hospital.

Doppler echocardiography. Complete transthoracic echocardiographic studies were performed in all subjects with a commercially available system (Vivid 5 [GE Vingmed, Horten, Norway], with a 2.5 MHz phased array probe). M-mode and 2-dimensional (2D) echocardiograms with Doppler analysis were obtained for all subjects. Left ventricular (LV) diameters and wall thicknesses were measured from 2D-guided M-mode echocardiography. Mean and peak pressure gradients across the aortic valve were calculated with the modified Bernoulli equation, with continuous-wave Doppler recordings from the highest velocity available from any view. The aortic valve area was computed with the continuity equation with standard methods.

Ultrasound backscatter data analysis. Aortic valve backscatter values were obtained for all subjects with methods as previously published (17). Briefly, 2D ultrasonic backscatter images of the aortic valves were obtained from standard parasternal long-axis views over 3 cardiac cycles with a zoom of 8 cm. Three consecutive scans were acquired for each study subject. Backscatter values from the blood pool in the LV outflow tract and aortic root were used as reference values. Calibrated backscatter values were obtained by subtracting the average blood pool value from the averaged backscatter values obtained from the aortic valves.

In all cases, valve morphology was categorized on the basis of visual assessment, as previously described (3,21). However, ASc was quantitated on the basis of AV_{BS} scores, and $AV_{BS} \geq 16$ dB was used as a definition of the presence of ASc (17).

Biochemical measurements. Blood was collected from all subjects into heparinized tubes and centrifuged at 4°C at 2,700 *g* for 20 min, and plasma was stored at −80°C until assay. Concentrations of ADMA in plasma were measured by high-performance liquid chromatography with the derivitization reagent AccQ-Fluor (Waters, Milford, Massachusetts) after solid phase extraction, as previously described (22). Lipid profile, high-sensitivity C-reactive protein (hs-CRP), serum creatinine, calcium, phosphate, and 1,25 dihydroxy cholecalciferol (vitamin D levels) were measured by a 125I radioimmunoassay (Immunodiagnostic Systems Ltd., Bolden, United Kingdom). Creatinine clearance (CrCl) was calculated according to the Cockcroft-Gault equation and indexed for body surface area (BSA) with the Dubois and Dubois formula.

Platelet responsiveness to NO. Blood was collected in plastic tubes containing 1:10 volume of acid citrate anticoagulant (2 parts of 0.1 mol/l citric acid to 3 parts of 0.1 mol/l trisodium citrate); acidified citrate was used to minimize deterioration of platelet function during experiments. Platelet aggregation in whole blood was examined with a dual-channel impedance aggregometer (model 560, Chrono-Log, Havertown, Pennsylvania). Aggregation was induced with adenosine 5′-diphosphate at a final concentration of 2.5 μmol/l. Aggregation was monitored continually for 7 min, and responses were recorded for electrical impedance (ohms). In control tests, physiologic saline was added in appropriate volumes. Platelet responsiveness to NO was evaluated via inhibition of aggregation in the presence of the NO donor, sodium nitroprusside (SNP) (10 μmol/l), as previously described (23).

Measurement of augmentation index. Pulse waveform analysis was performed noninvasively with a commercially available SphygmoCor system (AtCor Medical, Sydney, Australia), as previously described (24). All subjects were asked to lie down in a quiet room for 15 min before the procedure. Briefly, pulse waveform analysis was computed from the radial artery at the wrist and recorded by applanation tonometry with a high-fidelity micromanometer. Three recordings of 10 sequential waveforms were acquired for each subject; a validated, generalized transfer function was used to generate the corresponding central aortic pressure waveform, from which augmentation index (AIx) was derived. Only high-quality recordings with in-device quality index ≥90% were used. All augmentation indexes were corrected for a standard heart rate of 75 beats/min.

Statistical analyses. All data are expressed as mean ± SD unless otherwise stated. Normal distribution was tested for all continuous variables, and skewed data were normalized either by log or square root transformation. Comparisons between groups for normally distributed data were performed with

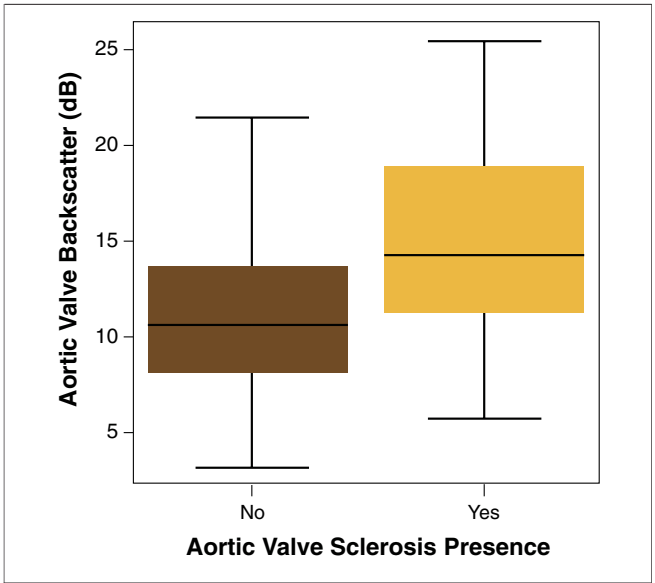

Figure 1. Correlation of AV_{BS} and Visual Assessment Score

Comparison of aortic valve backscatter scores (AV_{BS}) with visual assessment scores in subjects without and with aortic sclerosis. There was a significant difference in AV_{BS} between groups (11.2 ± 3.9 dB vs. 14.9 ± 4.5 dB, respectively, $p < 0.001$). Means and interquartile ranges are depicted. Whiskers represent minimum and maximum values.

nonpaired *t* tests and, comparisons for nonparametric data were made with the Mann-Whitney test. Correlations between transformed, continuous nonparametric data were made with linear regression. Stepwise multiple linear regression analyses were performed to assess independent predictors of AV_{BS} scores. Included variables to predict AV_{BS} sores were: age, sex, smoking history, previous ischemic events/angina, diabetes mellitus, hypercholesterolemia, hypertension, calculated CrCL, calcium-phosphate product (Ca_xPO_4) levels, vitamin D levels, body mass index (BMI), hs-CRP, AIx, ADMA concentrations, and platelet responses to SNP. Binary logistic backward regression analysis was also performed with the aforementioned variables but with the presence of ASc on backscatter as a categorical variable to evaluate whether presence of elevated AV_{BS} scores per se identified similar associations as those seen with stepwise multiple linear regression. All analyses were performed with SPSS version 13 software (SPSS, Chicago, Illinois), and a p value of <0.05 was considered to be statistically significant.

RESULTS

Subject characteristics. Mean AV_{BS} score was 12.2 ± 4.4 dB. In 19.4% of subjects, AV_{BS} was ≥16 dB, corresponding to the chosen definition of ASc (17). On visual assessment, aortic valve morphology was abnormal in 25.4% of subjects; such subjects had significantly higher ($p < 0.001$) AV_{BS} scores than those without visual assessment criteria for ASc (Fig. 1). Mean ejection fraction was 68.3 ± 8.6% (only 3 subjects had ejection fraction <40%); mean LV mass index was 113.27 ± 31.1 g/m^2; mean interventricular wall thickness was 1.04 ± 0.17 cm; mean aortic valve pressure gradient was 7 ± 3.8 mm Hg. There were no statistically significant echocardiographic differences between those with and those without ASc with respect to LV ejection fraction, LV mass index, interventricular wall thickness, and aortic valve pressure gradient. There were no subjects with bicuspid aortic valve.

Baseline clinical characteristics are summarized in Table 1 for subjects with and without ASc. Overall, there was a high proportion (30.8%) of obese subjects (BMI >30 kg/m^2). Multiple (≥3) coronary risk factors were present in 32% of subjects. One-third of subjects were on statin treatment with a similar proportion receiving angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (AIIRBs). Seventy-nine percent of hypertensive patients were receiving ACEI/AIIRBs, whereas 55% of hypercholesterolemic patients were treated with statins. There were statistically significant differences between those subjects with ASc and those without, with respect to age and BMI ($p < 0.05$ in both cases) only.

Biochemical data. Biochemical findings are summarized in Table 2. Plasma cholesterol concentrations were elevated beyond normal (>5.5 mmol/l) in 26.4% of subjects at entry. In general, renal function was well-preserved: there were no patients on dialysis, with only 2 subjects with CrCl <30 ml/min/1.73 m^2. Vitamin D levels were generally toward the lower end of the reference normal range for the laboratory assay (normal range 50 to 160 nmol/l) (25). Comparisons between subjects with and without ASc revealed that CrCl was significantly greater in subjects without ASc.

Endothelial function and platelet responsiveness to NO. Mean AIx was 27.6 ± 8.5% (normal range: 15 ± 16%), substantially greater than values for normal adults (26); these findings suggested increased arterial stiffness/wave reflection in this subject cohort. Similarly, mean platelet antiaggregatory response to SNP was a relatively low 33 ± 27% (normal range: 54 ± 24%), consistent with some degree of platelet resistance to NO (22). However, mean plasma ADMA concentrations were within

Table 1. Patient Characteristics: Clinical Data

Characteristic	No ASc (AV_{BS} Score <16 dB) (n = 204)	ASc (AV_{BS} Score ≥16 dB) (n = 49)	p Value
Age, mean ± SD (yrs)	63 ± 6.0	64.9 ± 9	0.045
BMI (kg/m^2)	28.5 ± 5.1	26.7 ± 4.2	0.019
Sex (% male)	42%	49%	0.372
History of hypercholesterolemia	61.8%	53.1%	0.565
Statin therapy	30.5%	38.8%	0.268
Previous angina/MI	11.9%	20.4%	0.114
ACEI/AIIRB therapy	34.8%	25%	0.193
Hypertension	44.1%	32.7%	0.146
Family history of CVD	51%	57.1%	0.439
Smoking	14.8%	12.2%	0.649
Diabetes mellitus	10.8%	10.2%	0.898
Subjects with >2 cardiovascular risk factors	31.5%	32.7%	0.879
History of CVA	3.5%	4.1%	0.835
Calcium supplementation	16.7%	16.7%	1
Vitamin D supplementation	2%	0%	0.327

ACEI = angiotensin-converting enzyme inhibitor; AIIRB = angiotensin II receptor blocker; ASc = aortic sclerosis; AV_{BS} = aortic valve ultrasonic backscatter; BMI = body mass index; CVA = cerebrovascular accident; CVD = cardiovascular disease; MI = myocardial infarction.

the previously described normal range (0.52 ± 0.08 μmol/l [normal range: 0.50 ± 0.08 μmol/l]) (22,27).

Univariate correlations with AV_{BS} scores. These are summarized in Table 3. There was a significant correlation between AV_{BS} scores and age. Although total cholesterol and low-density lipoprotein (LDL) levels did not correlate with AV_{BS} scores, high high-density lipoprotein levels were significantly associated with high AV_{BS} scores. There was a significant inverse correlation between calculated CrCL (corrected for BSA) and AV_{BS} scores. Although there was no correlation between AV_{BS} and calcium levels, there were borderline correlations between AV_{BS} and phosphate or Ca_xPO_4 levels. Importantly, there was no significant relationship between vitamin D levels and AV_{BS} scores.

BMI inversely correlated with AV_{BS} scores. There was also an inverse correlation between AV_{BS} scores and hs-CRP levels. With regard to parameters of endothelial function/NO responsiveness in this study population, there was no significant correlation between AV_{BS} scores and either AIx or plasma ADMA concentrations. However, there was a significant inverse correlation between platelet responsiveness to SNP and AV_{BS} scores.

Of interest, none of the "traditional" major coronary risk factors were significant correlates of AV_{BS} ($p > 0.2$ in all cases); nor did treatment

Table 2. Patient Characteristics: Baseline Biochemical Data

	No ASc (AV_{BS} Score <16 dB)	ASc (AV_{BS} Score ≥16 dB)	p Value
Total cholesterol (mmol/l)	5 ± 1	4.9 ± 1	0.774
LDL (mmol/l)	2.9 ± 0.9	2.8 ± 0.7	0.549
HDL (mmol/l)	1.3 ± 0.3	1.4 ± 0.4	0.126
Calcium (mmol/l)	2.2 ± 0.1	2.2 ± 0.1	0.7
Phosphate (mmol/l)	1 ± 0.2	1 ± 0.2	0.129
Ca_xPO_4	2.3 ± 0.4	2.3 ± 0.5	0.236
Vitamin D (nmol/l)	71.5 ± 22	79 ± 32	0.138
CrCL (indexed for BSA) (ml/min/1.73 m^2)	84.2 ± 22.7	76 ± 20	0.022
hs-CRP (mg/l)	3.5 ± 3.6	4 ± 5.6	0.576
AIx (%)	25.7 ± 8.1	24.3 ± 9.4	0.355
% platelet responsiveness to SNP	34.8 ± 27.5	26.6 ± 25.4	0.084
ADMA (μmol/l)	0.52 ± 0.08	0.52 ± 0.07	0.746

Expressed as mean ± SD.
ADMA = asymmetric dimethylarginine; AIx = augmentation index; BSA = body surface area; Ca_xPO_4= calcium-phosphate product; CrCL = creatinine clearance; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; SNP = sodium nitroprusside; other abbreviations as in Table 1.

Table 3. Univariate Correlates of AV_{BS} Scores

Parameter	p Value	β Coefficient
Age	0.005	0.18
HDL levels	0.016	0.154
CrCL indexed for BSA	0.001	−0.204
Phosphate levels	0.068	0.116
Ca_xPO_4	0.084	0.11
BMI	<0.001	−0.245
hs-CRP	0.028	−0.14
% platelet responsiveness to SNP	0.017	−0.162

Only parameters with $p < 0.1$ for correlation with AV_{BS} scores are shown. Data for HDL levels, BMI, hs-CRP, and % platelet responsiveness to SNP were transformed via log transformation to achieve normal distributions. Abbreviations as in Tables 1 and 2.

with either statins or ACEIs apparently interact with AV_{BS}.

There was a strong positive correlation between BMI and CrCl indexed for BSA, which persisted at $p = 0.001$ level even with calculation of CrCl with the modified diet in renal disease equation (28), where body weight is not a part of the equation ($p = 0.001$). These data therefore suggest strongly that, even after indexing for BSA, CrCl calculation is not a reliable estimate of renal function for obese subjects. This finding was recognized as having important implications in the multiple regression analyses, as regards interpretation of both BMI and CrCl data.

Stepwise multiple linear regression analyses. Table 4 documents results of stepwise multiple linear regression analysis. Advanced age was positively associated with high AV_{BS} scores ($\beta = 0.2$, $p = 0.004$), whereas platelet antiaggregatory responsiveness to SNP ($\beta = -0.16$, $p = 0.02$) and BMI ($\beta = -0.23$, $p = 0.001$) was negatively associated.

Binary logistic backward regression. Binary logistic backward regression analysis with the presence of ASc on backscatter as a categorical variable produced similar results but with weaker statistical power. Advanced age was positively (and significantly) associated with the presence of ASc ($p = 0.008$, $\beta = 0.08$, odds ratio: 1.1, 95% confidence interval: 1.02 to 1.15), whereas platelet antiaggregatory responsiveness to SNP ($p = 0.054$, $\beta = -0.122$, odds ratio: 0.885, 95% confidence interval: 0.781 to 1.002) and BMI ($p = 0.118$, $\beta = -4$, odds ratio: 0.018, 95% confidence interval: 0 to 2.776) tended to be negatively associated.

DISCUSSION

Previous evaluations of the epidemiology of ASc have been performed in a substantially larger population of aging individuals as components of the Cardiovascular Health Study (2,3,29). These investigations have focused on putative correlations between conventional coronary risk factors and the presence/development of ASc (2,3,29): in general significant correlations have been documented in the case of some but not all coronary risk factors. In contrast, the current study evaluated a substantially smaller subject cohort but had the advantage of quantitative rather than qualitative assessment of valve thickening, thus increasing the power of the study. Furthermore, the current study focused additionally on the premise that factors related to NO response at the level of the platelets and vasculature might predispose to development of ASc in humans, just as NO negatively modulates valve calcification in vitro (10).

The results of the current study are therefore important with regard to both positive and negative findings: platelet NO resistance was a significant correlate of ASc, whereas all conventional coronary risk factors did not approach such significant association.

Apart from the Cardiovascular Health Study (2,3,29), other investigations have examined determinants of progression of AS. In general, these investigations have considered patients in whom moderate AS was present at initial evaluation. Such studies tend to identify coronary risk factors, including male sex, as correlates of rapid progression (2,30–33)—apart from the finding that AS "progression" is seen to accelerate as the disease advances. In contrast, the study of Novaro et al. (29), the only previously reported investigation concerning correlates of ASc, found a weak correlation with elevation of LDL cholesterol and no association between ASc and other coronary risk factors. Furthermore, evaluation of aortic valve calcification within the MESA (Multi-Ethnic Study of Atherosclerosis) cohort (34,35) indicated that both diabetes and metabolic syndrome were correlates of de novo valve calcification but not of its progression.

The central methodology used in the current study was the quantitation of AV_{BS} with the defi-

Table 4. Variables Independently Associated With High AVBS Scores After Stepwise Multiple Linear Regression Analysis

Parameter	β Coefficient	p Value
BMI	−0.23	0.001
Age	0.20	0.004
Platelet responsiveness to SNP	−0.16	0.02

Abbreviations as in Tables 1 and 2.

nition of ASc chosen to be AV_{BS} ≥16 dB (16). This parameter had strong but incomplete concordance with visual assessment of valve morphology (Fig. 1) but had the advantage of substantially increasing the power of the study. For example, the association between platelet NO resistance and ASc was of borderline significance only on categorical analysis of AV_{BS} values (Table 2) but, with quantitative analysis, demonstrated statistically significant association both on univariate (Table 3) and on multivariate (Table 4) analyses.

In the current study, ASc was associated with platelet resistance to NO. This finding is of potential relevance to the association between ASc and thrombotic events (3,4,16). Furthermore, tissue resistance to NO might also contribute to the calcification process per se (9). The major biochemical mechanism underlying NO resistance is "scavenging" of NO by O_2^- anion (15), suggesting in turn incremental redox stress in association with ASc. Conversely, plasma concentrations of ADMA, which potentially can limit endogenous NO formation, were not elevated. This suggests that at the early stages of AS development, endothelial dysfunction might be limited to accelerated NO clearance by O_2^- anion; the previously observed elevation of ADMA levels (11) presumably develops only in patients with more advanced disease.

There was no association between presence of ASc and any of the coronary risk factors evaluated. Although these data are consistent with the low concordance between the presence of AS and coronary artery disease (36), they contrast to some extent with previous evaluations (30,32,36). In 2 previous studies (30,31), elevation of LDL cholesterol levels was associated with the presence of ASc. It is possible that the results might have been influenced by widespread pharmacotherapy, for example with statins, ACEI, and AIIRBs. However, overall these data suggest that pathogenetic factors for ASc differ from those for atherosclerosis.

It is also of some interest that the presence of ASc was not associated with increased AIx, a marker of arterial stiffness (as well as endothelial function) (37–39). Therefore, these findings tend to dissociate ASc from the arterial degenerative changes underlying systolic hypertension (40).

Although inflammatory activation is present as a component of histological appearances in ASc (41,42), plasma hs-CRP levels were not correlated with ASc in this study. These results are similar to those in a related recent evaluation (36). As regards the putative association between plasma vitamin D levels and ASc, this association has been evaluated to date only in advanced disease (42) and is most clearly evident in patients with chronic renal failure (43,44).

Advanced age was found to be an independent correlate of AV_{BS} values, consistent with the findings in the most recent study (36) and with previous reports in AS patients (1–3). The implication of this finding is that the biochemical nexus between advanced age and development of ASc remains to be identified.

Study limitations. The results of the study as regards renal dysfunction are somewhat equivocal. In the subject population examined, renal function was generally well preserved, but low CrCl was a univariate correlate of high AV_{BS} values. Creatinine clearance was "corrected" for BSA via the Dubois and Dubois formula, but a direct association between BMI and "corrected" CrCl persisted. Furthermore, CrCl was a strong inverse univariate correlate of AV_{BS}. Therefore, it is possible that some relationship between renal dysfunction and AV_{BS} has been obscured by inadequate correction for obesity. However, the overall conclusion from the current findings is that CrCl does not markedly affect development of ASc in a population with overall well-preserved renal function. Therefore, the finding that BMI inversely correlated with AV_{BS} scores might also be partially confounded by this interaction with renal function estimates. However, it remains possible, as suggested by previous studies in advanced AS (45), that there is a link between low BMI and propensity toward development of ASc.

It is also important to emphasize that the current negative results as regards the association between conventional coronary risk factors and the presence of ASc in no way invalidate the largely contrary findings of the larger Cardiovascular Health Study (2,3,29). Lack of demonstration of such associations might in part reflect type II error (in particular as regards diabetes mellitus, given the small proportion of diabetic subjects) and/or the influences of more extensive background pharmacotherapy. The results of the current study also do not in themselves validate increased backscatter as a marker either of risk of cardiac events or of a potentially accelerated rate of development of AS.

CONCLUSIONS

The presence of ASc in this aging population was associated with platelet NO resistance, a finding

that provides a potential mechanism for the propensity for acute coronary syndromes in this condition. In contrast, neither LDL elevation nor hypertension or any of the other "conventional" coronary risk factors examined was predictive of presence of ASc. This further emphasizes differences in risk factors for atheroma and for ASc. Both these positive and negative findings should be taken into account in planning interventions to improve outcomes in patients with early aortic valve disease.

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Key Words: aging ■ aortic valve sclerosis ■ endothelial function ■ nitric oxide ■ platelets.

▶ APPENDIX

For supplementary lists of clinical studies, please see the online version of this article.