JACC Vol. 29, No. 3
March 1, 1997:630–4

Clinical Factors Associated With Calcific Aortic Valve Disease

B. FENDLEY STEWART, MD, FACC, DAVID SISCOVICK, MD, MPH, BONNIE K. LIND, MS, JULIUS M. GARDIN, MD, FACC,* JOHN S. GOTTDIENER, MD, FACC,† VIVIENNE E. SMITH, MD,‡ DALANE W. KITZMAN, MD, FACC,§ CATHERINE M. OTTO, MD, FACC, FOR THE CARDIOVASCULAR HEALTH STUDY‖

Seattle, Washington; Orange, California; Washington, D.C.; Winston-Salem, North Carolina; and Albany, New York

Objectives. **The aim of this study was to determine the prevalence of aortic sclerosis and stenosis in the elderly and to identify clinical factors associated with degenerative aortic valve disease.**

Background. **Several lines of evidence suggest that degenerative aortic valve disease is not an inevitable consequence of aging and may be associated with specific clinical factors.**

Methods. **In 5,201 subjects ≥65 years of age enrolled in the Cardiovascular Health Study, the relation between aortic sclerosis or stenosis identified on echocardiography and clinical risk factors for atherosclerosis was evaluated by using stepwise logistic regression analysis.**

Results. **Aortic valve sclerosis was present in 26% and aortic valve stenosis in 2% of the entire study cohort; in subjects ≥75 years of age, sclerosis was present in 37% and stenosis in 2.6%. Independent clinical factors associated with degenerative aortic valve disease included age (twofold increased risk for each 10-year increase in age), male gender (twofold excess risk), present smoking (35% increase in risk) and a history of hypertension (20% increase in risk). Other significant factors included height and high lipoprotein(a) and low density lipoprotein cholesterol levels.**

Conclusions. **Clinical factors associated with aortic sclerosis and stenosis can be identified and are similar to risk factors for atherosclerosis.**

(J Am Coll Cardiol 1997;29:630–4)

Degenerative aortic valve disease, characterized macroscopically as increased leaflet thickness, stiffening and calcification, without commissural fusion, is common among the elderly, with echocardiographic evidence of calcification in 14% and moderate to severe valve obstruction in 5% of a randomly selected group of men and women aged 75 to 86 years (2). Milder degrees of aortic valve calcification are even more common, often designated as valve sclerosis on echocardiography.

Although the prevalence of aortic valve disease increases with age, several lines of evidence suggest that degenerative aortic valve disease is not simply a consequence of aging. Aortic valve disease is not seen universally among the elderly, as 25% to 45% of octogenarians have no evidence of aortic valve calcification (2,3). In addition, the early lesion of calcific aortic valve disease appears to involve an active process with some similarities to atherosclerosis, including lipid deposition (apo B, apo(a) and apo E), macrophage infiltration and production of osteopontin and other proteins (4–8), implicating atherosclerosis risk factors in the development of aortic valve disease. This possibility is supported by preliminary studies that have identified risk factors for calcific aortic stenosis including smoking, hypertension, hyperlipidemia, lipoprotein(a) [LP(a)] levels and diabetes (9–13). Some of these studies have been limited by a small sample size, possible selection bias and retrospective study designs. Among >500 elderly subjects in the Helsinki Aging Study (14), age, hypertension and body mass index were independent predictors of aortic valve calcification (14).

The Cardiovascular Health Study (CHS) is a prospective population-based study of the elderly that includes extensive clinical and echocardiographic data. The purpose of this study was to utilize the CHS data base to 1) determine the prevalence of aortic valve sclerosis and stenosis, and 2) identify clinical factors associated with degenerative aortic valve disease.

Methods

The CHS is a prospective, longitudinal study of 5,201 men (n = 2,239) and women (n = 2,962) ≥65 years of age randomly selected from households identified on Medicare eligibility lists

From the Departments of Medicine, Epidemiology and Biostatistics, University of Washington, Seattle, Washington; *Division of Cardiology, University of California Irvine, Orange, California; †Division of Cardiology, Georgetown University Hospital, Washington, D.C.; §Cardiology Section, Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina; and ‡Division of Cardiology, Albany Medical College, Albany, New York. ‖A complete list of investigators for the Cardiovascular Health Study appears in Reference 1. This study was supported in part by Contracts NO1-HC85079 through HC-850086 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Manuscript received June 17, 1996; revised manuscript received November 8, 1996, accepted November 26, 1996.

Address for correspondence: Dr. Catherine M. Otto, Division of Cardiology, Box 356422, Department of Medicine, University of Washington, Seattle, Washington 98195-6422. E-mail: cmotto@u.washington.edu.

Published by Elsevier Science Inc.

0735-1097/97/$17.00
PII S0735-1097(96)00563-3

Abbreviations and Acronyms

CHS = Cardiovascular Health Study
HDL = high density lipoprotein
HDLc = high density lipoprotein cholesterol
LDL = low density lipoprotein
LDLc = low density lipoprotein cholesterol
Lp(a) = lipoprotein(a)
2D = two-dimensional

in four communities in the United States: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Allegheny County, Pennsylvania. Of 9,078 eligible persons, 5,201 (57%) agreed to participate. The study was approved by the institutional review board at each participating center, and clinically important findings were communicated to both the participants and their physicians. Study design and objectives have been published previously (1). In brief, the baseline examination, conducted in 1989 to 1990, consisted of an extensive medical history, physical examination, 12-lead electrocardiogram, spirometry, and echocardiography. Laboratory evaluation included serum chemistry determinations, an oral glucose tolerance test and assessment of levels of fasting plasma lipids (derived beta-quantification), Lp(a) and hemostatic factors (fibrinogen, factors VII and VIII).

Echocardiography protocol. Echocardiographic studies were technically adequate in 5,176 (>99%) of subjects and were recorded on super-VHS tape with use of a Toshiba SSH-160A cardiac ultrasound machine as previously described (15). Two-dimensional (2D) assessment of the aortic valve was performed from the parasternal long- and short-axis and apical long-axis views. Videotapes were sent to the Echocardiography Reading Center (located at the University of California, Irvine), where abnormalities of the aortic valve were coded as aortic stenosis, bicuspid aortic valve, aortic sclerosis, aortic valve vegetation or prosthetic aortic valve. Sclerosis was defined as increased echogenicity and leaflet thickness without restriction of leaflet motion. Aortic stenosis was defined as thickened leaflets with reduced systolic opening on 2D imaging and an increased anterograde velocity (≥2.5 m/s by continuous wave Doppler ultrasound) across the valve.

For this substudy, aortic valve morphology was reanalyzed in detail by two of us (B.F.S., C.M.O.) without knowledge of the Reading Center coding. A total of 201 studies were selected by the Coordinating Center to include all 92 coded as aortic stenosis and 109 not coded as aortic stenosis (randomly selected). On review of the original videotapes, each valve leaflet was graded on a scale of 0 (normal) to 3+ (severe) for leaflet thickening and calcification. A total valve score was calculated as the sum of the individual leaflet scores divided by the number of leaflets. This score was used to classify the aortic valve as normal or abnormal (score ≥0.25).

Agreement between the Reading Center coding and the reanalysis of aortic valve morphology in 201 subjects was assessed after exclusion of poor quality studies (n = 4) and cases with an aortic valve replacement (n = 8). Leaflet thickening or calcification was confirmed in 27 (73%) of 37 aortic valves originally classified as sclerotic and in 70 (80%) of 87 classified as stenotic. Of valves originally classified as neither sclerotic or stenotic, 65 (84%) of 77 did not demonstrate significant leaflet thickening or calcification. Of the 12 discrepant cases, only 1 had more than mild leaflet change (score ≥1.0). There was no evidence of subvalvular obstruction on any of 201 reviewed studies. Given the good agreement between the initial Reading Center coding and the reanalysis (kappa = 0.62), the Reading Center coding was used for all subsequent analyses in order to take advantage of the large sample size.

Table 1. Prevalence of Aortic Valve Abnormalities by Echocardiography

	Aortic Valve Abnormality			
	None	Sclerosis	Stenosis	Valve Replacement
All subjects	3,736 (72%)	1,329 (26%)	88 (2%)	23 (0.4%)
Women	2,249 (76%)	641 (22%)	43 (1.5%)	12 (0.4%)
Men	1,487 (67%)	688 (31%)	45 (2%)	11 (0.5%)
65–74 years old	2,684 (78%)	697 (20%)	43 (1.3%)	16 (0.5%)
Women	1,654 (82%)	344 (17%)	20 (1.0%)	9 (0.4%)
Men	1,030 (73%)	353 (25%)	23 (1.6%)	7 (0.5%)
75–84 years old	962 (62%)	542 (35%)	37 (2.4%)	7 (0.5%)
Women	546 (66%)	259 (31%)	22 (2.7%)	3 (0.4%)
Men	416 (58%)	283 (39%)	15 (2.1%)	4 (0.6%)
85+ years old	90 (48%)	90 (48%)	8 (4%)	0 (0%)
Women	49 (56%)	38 (43%)	1 (1%)	0
Men	41 (41%)	52 (52%)	7 (7%)	0

Data are expressed as number (%) of subjects.

Statistical analyses. Bivariate analysis was performed by using unpaired *t* tests and chi-square analysis with the significance level set at 0.01. Independent risk factors for aortic valve sclerosis or stenosis were determined by stepwise logistic regression analysis. Statistical analysis was performed by using SPSS/PC plus V4.0 (SPSS Inc., 1990) and EGRET (Statistics and Epidemiology Research Corp., 1990) with default settings. A p value of 0.01 was used for entry into the logistic regression analysis.

Results

Prevalence of aortic sclerosis and stenosis. Table 1 shows the prevalence of sclerosis and stenosis on 2D echocardiography for the total study group and by gender and age groups. The variables chosen for analysis were based on our hypothesis that aortic valve disease has risk factors similar to those of atherosclerosis. To exclude subjects with rheumatic or congenital aortic valve disease, we excluded from the analysis subjects coded as having aortic valve replacement (n = 23), mitral

Table 2. Bivariate Relations of Clinical Variables to Aortic Valve Abnormalities

	Normal (n = 3,709)	Sclerosis/ Stenosis (n = 1,405)	p Value
A. Continuous Variables			
Age (yr)	72.0 ± 5.2	74.7 ± 6.1	<0.0001
Height (cm)	164.8 ± 9.5	165.2 ± 9.7	NS
Weight (kg)	73 ± 14.6	71.7 ± 13.8	NS
Waist circumference (cm)	93.7 ± 13.1	94.0 ± 12.3	NS
Hip circumference (cm)	101.9 ± 10.0	100.7 ± 8.8	0.0002
Fibrinogen (mg/dl)	319.2 ± 63.7	324.0 ± 70.3	NS
Factor VII (%)	126.4 ± 33.0	123.4 ± 36.6	0.009
Factor VIII (%)	121.6 ± 37.1	122.9 ± 38.4	NS
Cholesterol (mg/dl)	214.9 ± 39.0	214.3 ± 39.7	NS
Triglycerides (mg/dl)	141.3 ± 74.3	145.9 ± 89.0	NS
HDL (mg/dl)	54.5 ± 15.8	52.3 ± 15.4	<0.0001
LDL (mg/dl)	132.8 ± 35.6	133.9 ± 35.9	NS
Lp(a) (mg/dl)	50.7 ± 48.5	62.3 ± 71.4	<0.001
Fasting glucose (mg/dl)	109.2 ± 31.7	112.5 ± 40.7	0.007
Fasting insulin (μU/ml)	16.4 ± 19.7	17.8 ± 32.9	NS
2-h insulin (μU/ml)	86.1 ± 65.0	79.6 ± 58.4	0.002
2-h glucose (mg/dl)	146.2 ± 56.4	150.7 ± 62.5	NS
Albumin (g/dl)	4.0 ± 0.3	4.0 ± 0.3	NS
Potassium (mEq/liter)	4.2 ± 0.4	4.2 ± 0.4	NS
Uric acid (mg/dl)	5.6 ± 1.5	5.8 ± 1.6	0.0003
Creatinine (mg/dl)	1.0 ± 0.3	1.1 ± 0.4	<0.0001
Systolic BP (mm Hg)	134.9 ± 21.2	138.0 ± 22.1	<0.0001
Diastolic BP (mm Hg)	70.3 ± 11.3	69.7 ± 12.0	NS
B. Categoric Variables			
Smoking			
Never	1,707 (47%)	608 (44%)	NS
Past	1,526 (42%)	607 (44%)	
Present	422 (12%)	162 (12%)	
Hypertension*			
No	2,068 (57%)	710 (52%)	0.001
Yes	1,584 (43%)	668 (48%)	
Diabetes*			
No	3,301 (90%)	1,241 (89%)	NS
Yes	382 (10%)	148 (11%)	
Estrogen use†			
No	1,928 (86%)	607 (90%)	NS (0.016)
Yes	300 (14%)	67 (10%)	
Coronary heart disease‡			
No	2,838 (77%)	987 (70%)	<0.0001
Yes	871 (23%)	418 (30%)	

*Self-reported. †Among women (n = 2,943) only. ‡Coronary heart disease was defined by physician diagnosis of myocardial infarction, angina, angioplasty, coronary artery bypass grafting or by silent myocardial infarction on electrocardiography. Data are expressed as mean value ± SD or number (%) of subjects. BP = blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; Lp(a) = lipoprotein(a).

stenosis or mitral valve replacement, or both (n = 37), bicuspid aortic valve (n = 4) or aortic valve endocarditis (n = 2) and those with inadequate echocardiographic data (n = 25). Factors associated with the presence of degenerative aortic valve disease, defined as stenosis or sclerosis, based on bivariate analysis are shown in Table 2. Note the associations of aortic sclerosis or stenosis with age, hip circumference, coagulation factors (factor VII), serum high density lipoprotein (HDL) and Lp(a) levels, fasting glucose and 2-h insulin levels, serum creatinine and systolic blood pressure.

Table 3. Clinical Factors Associated With Aortic Stenosis or Sclerosis by Stepwise Multiple Logistic Regression

Variable	p Value	Odds Ratio	95% Confidence Limits
Age	<0.001	2.18*	2.15, 2.20
Male gender	<0.001	2.03	1.7, 2.5
Lp(a)	<0.001	1.23†	1.14, 1.32
Height (cm)	0.001	0.84‡	0.75, 0.93
History of hypertension	0.002	1.23	1.1, 1.4
Present smoking	0.006	1.35	1.1, 1.7
LDLc (mg/dl)	0.008	1.12†	1.03, 1.23

*± 75th vs. 25th percentile. †± 10-year increase. ‡± 10-unit increase. LDLc = low density lipoprotein cholesterol; Lp(a) = lipoprotein(a).

Multiple logistic regression analysis. Continuous variables that competed for entry into the multiple logistic regression model included age, height, weight, waist and hip circumference, average systolic and diastolic blood pressure, heart rate, factors VII and VIII, fibrinogen, triglycerides, HDL cholesterol (HDLc), LDL cholesterol (LDLc), Lp(a), glucose, insulin, albumin, potassium, uric acid and creatinine. Categoric variables that competed for entry included gender, smoking (past, present, never), congestive heart failure (none, possible, definite), coronary heart disease and self-reported histories of hypertension, diabetes and estrogen use.

The results of the stepwise multiple logistic regression are shown in Table 3. The odds ratio and associated 95% confidence intervals were estimated to assess the magnitude of the association between these factors and the presence of aortic sclerosis or stenosis. The odds ratio was 2.18 for each 10-year increase in age. Male gender was associated with a twofold excess risk. Relative to never smoking, present smoking was associated with a 35% increase in risk. Lp(a) was strongly associated with an increased risk of aortic valve disease. A history of hypertension conveyed a 20% excess risk. The odds ratio associated with increases in LDLc from the 25th to 75th percentile level was significant but small. Exclusion of participants with aortic stenosis from the multivariate analysis did not significantly alter the findings.

Discussion

Echocardiographic data from the Cardiovascular Health Study have confirmed that aortic valve disease is common in the elderly. Approximately one in four subjects had visually apparent leaflet thickening or calcification, or both, and the prevalence increased with advancing age. These results are in agreement with the older Helsinki Aging Study (2) in which aortic valve calcification was found in >50% of subjects aged 75 to 86 years. Aortic valve sclerosis and stenosis were both considered to represent calcific valve disease because substan-

tial clinical and histopathologic data (2–10) suggest that these conditions represent different stages of the same disease process.

Predictors of aortic valve disease. It is unlikely that degenerative aortic valve disease is merely related to age-associated "wear and tear." The multivariate analysis is most helpful in evaluating associations with aortic valve disease, as bivariate analysis fails to incorporate interactions among the clinical variables (thus accounting for the apparent differences between the bivariate and multivariate analyses). Stepwise logistic regression analysis identified eight independent predictors of aortic valve disease. Age was not an unexpected predictor, having been noted in previous studies. In addition to age, we hypothesized that atherosclerosis risk factors would also be risk factors for degenerative aortic valve disease. This hypothesis was based on several lines of evidence including 1) the similarities between early lesions of aortic valve disease and atherosclerosis, including lipid deposition (6); 2) the association between aortic valve lesions and hyperlipidemia (16,17) or elevated LP(a) levels (9); and 3) the location of the focal changes of sclerosis on the aortic side of the leaflets (18), suggesting endothelial injury from low shear stress and high tensile stress as possible initiating factors in the disease process (19,20). Endothelial injury and disruption could then lead to inflammatory cell infiltration and lipid deposition analogous to the early atherosclerotic process (4,21).

Previous studies of degenerative aortic valve disease have found associations with atherosclerosis risk factors, but the significant factors have varied among studies. Aronow et al. (11) studied a very elderly population with 2D echocardiography and found an association between aortic valve disease and hypertension, diabetes, hypercholesterolemia and low HDLc. In the Helsinki Aging Study (14), hypertension, age and a low body mass index were independent predictors of aortic valve calcification; cholesterol, smoking and diabetes were not. The Jichi Medical School study (9) identified an association between Lp(a) levels and aortic valve sclerosis. The current study, the largest study to date examining this question, shows that age, gender, height, hypertension, smoking, Lp(a) and LDLc are independent predictors of degenerative aortic valve disease. The magnitude of the risk conveyed by these factors is particularly high for age, male gender, hypertension, smoking and Lp(a), with only a small increase in risk evident for elevations of LDLc (Table 2). In general, the magnitude of the association is similar to that for coronary artery disease risk factors in the elderly (22).

Mechanism of association. Potential explanations for the association of these clinical factors with aortic valve disease include the possibility that hypertension results in abnormally high tensile stress on the aortic leaflets. Alternatively, turbulent flow patterns associated with high volume flow rates may lead to low shear stress, resulting in endothelial injury and disruption as is seen in atherosclerotic lesions (18,23). Elevated levels of LDLc and Lp(a) may facilitate lipid deposition after endothelial injury from any cause. Smoking may increase the risk for aortic valve disease through mechanisms analogous to those postulated for atherosclerosis, including adverse effects on endothelial permeability and lipoprotein oxidation (23).

The explanation for an inverse association between height and aortic valve disease is not as readily apparent. Lindroos et al. (14) found an inverse relation between aortic valve calcification and body mass index, and they postulated that the relation might be mediated through osteoporosis. Loss of height in osteoporosis is well described (24), again raising the possibility of an association between degenerative aortic valve disease and osteoporosis. Other possibilities include hemodynamic and shear stress effects related to the length of the peripheral vasculature.

Study limitations. The major limitations of this study are that it is a cross-sectional analysis and includes only subjects ≥65 years of age, which may bias the results against an even stronger relation between these risk factors and aortic valve disease. In addition, the time available for echocardiographic evaluation of the aortic valve was limited and quantitative Doppler data were not available. On the other hand, echocardiography readers did not know the clinical and risk factor status, and the subjects were not highly selected. Agreement between the Reading Center coding of aortic valve morphology and a detailed rereview of a subset of the studies was not perfect, but the differences are unlikely to have affected the results given the large sample size and, in any case, would bias the results against observing significant associations.

Summary. In summary, several clinical factors associated with degenerative aortic valve disease have been identified, including age, gender, Lp(a), LDLc, hypertension and smoking. Although these clinical factors also have been associated with atherosclerosis, other factors must be important for the development of significant aortic valve disease because only 50% of patients with severe aortic stenosis also have significant coronary artery disease (25–27). Further understanding of both the cellular and molecular mechanisms involved in the pathogenesis of degenerative aortic valve disease and the risk factors for this disease may lead to interventions that prevent or delay disease progression. In addition, studies to determine whether control of risk factors prevents aortic valve disease appear to be warranted.

References

1. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1:263–76.
2. Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. J Am Coll Cardiol 1993;21:1220–5.
3. Pomerance A, Darby AJ, Hodkinson HM. Valvular calcification in the elderly: possible pathogenic factors. J Gerontol 1978;33:672–5.
4. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis: histologic and immunohistochemical studies. Circulation 1994;90:844–53.
5. O'Brien KD, Kuusisto J, Reichenbach DD, et al. Osteopontin is expressed in human aortic valvular lesions. Circulation 1995;92:2163–8.
6. O'Brien KD, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a) and E accumulate in the morphologically early

lesion of degenerative valvular aortic stenosis. Arterioscler Thromb Vasc Biol 1996;16:523–32.
7. Olsson M, Rosenqvist M, Nilsson J. Expression of HLA-DR antigen and smooth muscle cell differentiation markers by valvular fibroblasts in degenerative aortic stenosis. J Am Coll Cardiol 1994;24:1664–71.
8. Olsson M, Dalsgaard C-J, Haegerstrand A, Rosenqvist M, Ryden L, Nilsson J. Accumulation of T lymphocytes and expression of interleukin-2 receptors in nonrheumatic stenotic aortic valves. J Am Coll Cardiol 1994;23:1162–70.
9. Gotoh T, Kuroda T, Yamasawa M, et al. Correlation between lipoprotein(a) and aortic valve sclerosis assessed by echocardiography (the JMS Cardiac Echo and Cohort Study). Am J Cardiol 1995;76:928–32.
10. Mohler ER, Sheridan MJ, Nichols R, Harvey WP, Waller BF. Development and progression of aortic valve stenosis: atherosclerosis risk factors—a causal relationship? A clinical morphologic study. Clin Cardiol 1991;14: 995–9.
11. Aronow WS, Schwartz KS, Koenigsberg M. Correlation of serum lipids, calcium, and phosphorus, diabetes mellitus and history of systemic hypertension with presence or absence of calcified or thickened aortic cusps or root in elderly patients. Am J Cardiol 1987;59:998–9.
12. Hoagland PM, Cook EF, Flatley M, Walker C, Goldman L. Case-control analysis of risk factors for presence of aortic stenosis in adults (age 50 years or older). Am J Cardiol 1985;55:744–7.
13. Deutscher S, Rockette HE, Krishnaswami V. Diabetes and hypercholesterolemia among patients with calcific aortic stenosis. J Chronic Dis 1984;37: 407–15.
14. Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikilä J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. Eur Heart J 1994;15:865–70.
15. Gardin JM, Wong ND, Bommer W, et al. Echocardiographic design of a multicenter investigation of free-living elderly subjects: the Cardiovascular Health Study. J Am Soc Echocardiogr 1992;5:63–72.
16. Záhor Z, Czabanová V. Experimental atherosclerosis of the heart valves in rats following a long-term atherogenic regimen. Atherosclerosis 1977;27:49–57.
17. Sprecher DL, Schaefer EJ, Kent KM, et al. Cardiovascular features of homozygous familial cholesterolemia: analysis of 16 patients. Am J Cardiol 1984;54:20–30.
18. Thubrikar MJ, Aouad J, Nolan SP. Patterns of calcific deposits in operatively excised stenotic or purely regurgitant aortic valves and their relation to mechanical stress. Am J Cardiol 1986;58:304–8.
19. Sauren AAHJ, Kuijpers W, Van Steenhoven AA, Veldpaus FE. Aortic valve histology and its relation with mechanics: preliminary report. J Biomech 1980;13:97–104.
20. Thubrikar MJ, Nolan SP, Aouad J, Deck JD. Stress sharing between the sinus and leaflets of canine aortic valves. Ann Thorac Surg 1986;42:434–40.
21. Stein PD, Sabbah HN, Pitha JV. Continuing disease process of calcific aortic stenosis: role of microthrombi and turbulent flow. Am J Cardiol 1977;39: 159–63.
22. Psaty BM, Koepsell TD, Manolio TA, et al. Risk ratios and risk differences in estimating the effect of risk factors for cardiovascular disease in the elderly. J Clin Epidemiol 1990;43:961–70.
23. O'Brien KD, Chait A. The biology of the artery wall in atherogenesis. Med Clin North Am 1994;41–67.
24. Kiebzak GM. Age-related bone changes. Exp Gerontol 1991;26:171–87.
25. Exadactylos N, Sugrue DD, Oakley CM. Prevalence of coronary artery disease in patients with isolated aortic valve stenosis. Br Heart J 1984;51: 121–4.
26. Vandeplas A, Willems JL, Piessens J, De Geest H. Frequency of angina pectoris and coronary artery disease in severe isolated valvular aortic stenosis. Am J Cardiol 1988;62:117–20.
27. Georgeson S, Meyer KB, Pauker SG. Decision analysis in clinical cardiology: when is coronary angiography required in aortic stenosis? J Am Coll Cardiol 1990;15:751–62.