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Correlates of Aortic Distensibility in Chronic Aortic Regurgitation and Relation to Progression to Surgery

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Aortic distensibility decreases with increasing age. Patients with chronic aortic regurgitation eject a large stroke volume into the proximal aorta. A decrease in distensibility of the aorta may impose a higher afterload on the left ventricle and may contribute to deterioration of left ventricular function over time. Accordingly, aortic distensibility was measured in 33 patients aged 13 to 73 years who had chronic isolated aortic regurgitation with minimal or no symptoms.

Ascending aortic diameter was measured 4 cm above the aortic valve by two-dimensional echocardiography and pulse pressure was measured simultaneously by sphygmomanometry. Aortic distensibility was calculated as (Change in aortic diameter between systole and diastole/End-diastolic diameter)/Pulse pressure. Left ventricular systolic wall stress and mass were derived from standard M-mode echocardiographic measurements. Left ventricular volumes and ejection fraction were measured by radionuclide ventriculography.

Aortic distensibility decreased logarithmically with increasing age ($r = -0.62$, $p < 0.001$) and also correlated inversely with systolic wall stress, left ventricular mass and end-diastolic volume. Patients who eventually underwent aortic valve replacement for symptoms of left ventricular dysfunction had significantly lower aortic distensibility than did those who did not yet require valve replacement: 0.09 ± 0.08 vs. $0.22 \pm 0.19 \times 1/100$ (1/mm Hg) ($p < 0.05$).

Thus, the reduced aortic distensibility that occurs with increasing age may contribute to the gradual left ventricular dilation and dysfunction seen in patients with chronic aortic regurgitation.

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Patients with chronic aortic regurgitation experience a gradual deterioration in left ventricular performance over time (1–4). The causes of this gradual decline are not well defined. The altered loading conditions imposed on the left ventricle in aortic regurgitation are due to increased preload and afterload—the latter contributing to increased end-systolic wall stress (5,6). During ejection of the left ventricular stroke volume, the proximal aorta distends and this aortic distension decreases the impedance to outflow from the left ventricle. In aortic regurgitation, a very large stroke volume is ejected into the proximal aorta. One would suspect that stiffening (a decrease in distensibility) of the aorta would result in increased impedance to left ventricular ejection with resultant increases in systolic wall stress of the left ventricle. It has been noted (7) that patients with chronic aortic regurgitation usually experience a deterioration of left ventricular function in the 4th decade, at a time when aortic distensibility is decreasing (8–16). Increased systolic wall stress and end-diastolic volume have been associated with an increased need for valve replacement (17). Therefore we hypothesized that decreasing aortic distensibility with age may contribute to the deterioration of the left ventricle as manifested by increased systolic wall stress and preload (left ventricular end-diastolic volume).

Accordingly, patients of various ages with aortic regurgitation were studied to determine if aortic distensibility correlated with left ventricular wall stress and volumes and whether it predicted future need for aortic valve replacement.

Methods

Study patients (Table 1). Thirty-three patients with chronic isolated aortic regurgitation were studied. All patients were in New York Heart Association functional class I or early class II on entering the study (18). The patients were predominantly male (29 of 33) and ranged in age from

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Table 1. Clinical Characteristics of 33 Patients With Chronic Aortic Regurgitation

Age (yr)	40 ± 15
Gender	29M, 4F
Duration of AR (yr)	16 ± 14
LV EDVI (ml/m²)	157 ± 72
LV ESVI (ml/m²)	56 ± 33
LV SVI (ml/m²)	101 ± 43
LV EF (%)	64 ± 9
LV/RV stroke count ratio	4.1 ± 1.6
Systolic wall stress (dynes/cm²)	74 ± 25
LV mass (g)	400 ± 151
Ao distensibility (1/mm Hg) × 10^{-2}	0.17 ± 0.16
Etiology of AR	
Rheumatic	5
Congenital	17
s/p commissurotomy	4
s/p endocarditis	1
Traumatic	1
Unknown	5

Ao = aortic; AR = aortic regurgitation; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; F = female; LV = left ventricular; M = male; RV = right ventricular; s/p = status post; SVI = stroke volume index.

13 to 73 years. The estimated duration of aortic regurgitation ranged from <1 year to 49 years. A subset of 20 of these patients formed part of a previously reported study of hydralazine therapy (6) and the other 13 patients were followed up but not randomized to treatment with hydralazine or placebo. Patients were included in this present study when two-dimensional echocardiograms became available as part of the previously reported study. The 11 patients taking hydralazine at the time of the echocardiogram did not differ from the other 22 patients with respect to age, left ventricular end-diastolic volume index, ejection fraction, systolic wall stress, left ventricular mass, systolic or diastolic blood pressure or aortic distensibility. All 33 patients were in sinus rhythm, had a characteristic diastolic murmur of aortic regurgitation on physical examination, had preserved left ventricular ejection fraction and were not considered a surgical candidate at the time of study.

All patients underwent 1) two-dimensional and M-mode echocardiography for measurement of aortic root size and left ventricular dimensions and wall thickness, and 2) radionuclide angiographic measurements for left ventricular end-diastolic and end-systolic volumes, ejection fraction and regurgitant index (left ventricular/right ventricular stroke count ratio). No other cardiac disease was known to be present; specifically, no patient had hemodynamically significant aortic stenosis, coronary artery disease or peripheral vascular disease.

Sixteen healthy normal volunteers without hypertension or other medical diseases also underwent simultaneous two-dimensional echocardiography of the aortic root and blood pressure measurement. All patients signed consent forms that were approved by the Institutional Review Board at Oregon Health Sciences University on March 1, 1982.

Echocardiography. All patients underwent standard two-dimensional and M-mode echocardiography with use of Hewlett-Packard model Sonos 500. Measurements of the aortic root diameter were made 4 cm above the aortic valve. The end-diastolic measurements were made at the onset of the R wave and end-systolic measurements at the peak of the T wave on the electrocardiogram (ECG) with the light pen quantification system. This system has been electronically calibrated. The mean of three separate measurements of end-diastolic and end-systolic diameter was used in the calculation of aortic distensibility. Intraobserver and interobserver correlations were r = 0.91, SEE = 0.28 cm and r = 0.89, SEE = 0.26 cm, respectively. Left ventricular wall thickness and chamber measurements were made in standard fashion (19) without knowledge of the patient's age or the results of radionuclide measurements of left ventricular volume or function. Left ventricular mass and systolic wall stress were calculated as previously described (20,21).

Radionuclide left ventriculography. All patients with aortic regurgitation underwent radionuclide ventriculographic assessment of left ventricular end-diastolic and end-systolic volumes and ejection fraction as previously described (6,22). The whole body radiation dose was 0.32 rem. Left ventricular end-diastolic and end-systolic volumes have been shown (6) to correlate well with angiographic measurements of left ventricular volume in our laboratory. The left ventricular/right ventricular stroke count ratio was measured as previously described (23), without knowledge of the echocardiographic measurements of aortic distensibility.

Aortic distensibility. Aortic distensibility was calculated in the study patients and the normal control group as [(End-systolic diameter minus End-diastolic aortic diameter)/(End-diastolic diameter)]/Pulse pressure (24–26). Pulse pressure was measured by sphygmomanometry as systolic minus diastolic blood pressure. Diastolic pressure was taken at the fourth Korotkov sound (27).

Statistical analysis. Correlations among age, aortic distensibility, left ventricular ejection fraction, volumes and systolic wall stress were made by regression analysis. Differences between groups were determined by an unpaired *t* test. Variables predicting aortic valve replacement or changes in end-diastolic volume index and systolic blood pressure were assessed by stepwise logistic regression analysis. All data are expressed as mean values ± SD. A p value < 0.05 was considered significant.

Results

The left ventricular end-diastolic volume index was large but the left ventricular ejection fraction was preserved (Table 1). The left ventricular/right ventricular stroke count ratio (an estimate of the severity of aortic regurgitation) was markedly elevated as were systolic wall stress and left ventricular mass.

Aortic distensibility. There was a significant inverse correlation between aortic distensibility and age in both the

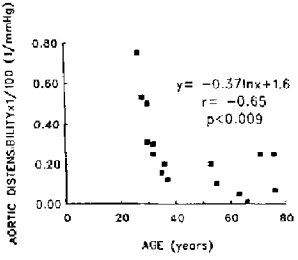

Figure 1. Relation between aortic distensibility and age in 16 normal subjects.

normal control group ($r = -0.65$, $p < 0.009$; Fig. 1) and the group with aortic regurgitation ($r = -0.62$, $p < 0.001$; Fig. 2). Aortic distensibility decreased logarithmically with advancing age (Fig. 1). After 40 years of age, distensibility of the proximal ascending aorta appeared to remain relatively constant in both patients and control subjects. There were also significant but modest inverse logarithmic correlations between aortic distensibility and systolic wall stress ($r = -0.58$, $p < 0.0001$), left ventricular mass ($r = -0.64$, $p < 0.0001$) and left ventricular end-diastolic and end-systolic volumes ($r = -0.47$, $p < 0.007$ and $r = -0.41$, $p < 0.016$, respectively). There was no significant correlation between aortic distensibility and ejection fraction, stroke volume index or left ventricular/right ventricular stroke count ratio. There were nine patients with a systolic blood pressure between 140 and 168 mm Hg initially and six patients with systolic pressure >140 mm Hg at follow-up.

Aortic valve replacement (Table 2). The patients with aortic regurgitation were then classified into two subgroups: 1) the 11 patients who subsequently underwent aortic valve

Figure 2. Relation between aortic distensibility and age in 33 patients with aortic regurgitation.

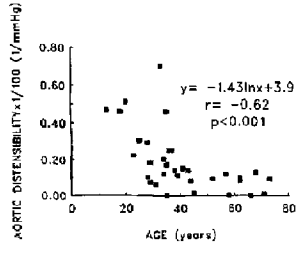

Table 2. Characteristics of Patients With and Without Subsequent Valve Replacement

	No AVR (n = 22)	AVR (n = 11)	p Value
Age (yr)	38 ± 17	44 ± 13	0.15
Duration of AR (yr)	13 ± 13	21 ± 15	0.13
LV EDVI (ml/m^2)	136 ± 42	199 ± 99	<0.05
LV ESVI (ml/m^2)	47 ± 20	74 ± 45	<0.05
LV SVI (ml/m^2)	87 ± 23	125 ± 60	<0.05
LV EF (%)	64 ± 12	64 ± 8	0.90
LV/RV stroke count ratio	3.9 ± 1.4	4.6 ± 1.5	0.31
Systolic wall stress (dynes/cm^2)	69 ± 25	85 ± 22	0.08
LV mass (g)	463 ± 152	534 ± 142	0.15
Ao distensibility ($1/mm\ Hg) \times 10^{-2}$	0.22 ± 0.19	0.09 ± 0.08	<0.05

AVR = aortic valve replacement; other abbreviations as in Table 1.

replacement within 7 years for symptoms of left ventricular dysfunction, and 2) the 22 patients who did not. The mean total duration of follow-up was 61 ± 11 months. In the 11 patients who underwent valve replacement, the decision to recommend the procedure was made by the individual physicians caring for the patients. All 11 patients had clear documentation of symptoms referable to left ventricular dysfunction or substantial decreases in left ventricular ejection fraction, or both, prompting valve replacement. None had endocarditis at the time of clinical deterioration. There was no significant difference at baseline between the groups with and without valve replacement in age, duration of aortic regurgitation, left ventricular ejection fraction, left ventricular/right ventricular stroke count ratio or left ventricular mass (Table 2). However, the group undergoing aortic valve replacement had a significantly lower aortic distensibility and a larger left ventricular end-diastolic volume, end-systolic volume and stroke volume. This group also tended to have a higher left ventricular systolic wall stress ($p = 0.08$ [NS]). Systolic blood pressure was higher in the patients with than in the patients without valve replacement (136 ± 9 and 123 ± 16 mm Hg, respectively, $p < 0.05$) and diastolic blood pressure tended to be lower in the valve replacement group (55 ± 22 vs. 62 ± 11 mm Hg, respectively, $p = 0.22$). Thus, pulse pressure was larger in the group with than in the group without valve replacement (80 ± 18 vs. 63 ± 18 mm Hg, respectively, $p < 0.02$).

Predictors of need for aortic valve replacement. Stepwise logistic regression analysis revealed that left ventricular end-diastolic volume index and systolic blood pressure were the two variables that predicted the need for valve replacement; no other variable provided additional independent information. However, two variables predicted end-diastolic volume index: aortic distensibility and diastolic blood pressure. These two variables correlated inversely with end-diastolic volume index, were the only two variables that independently predicted it and, together, accounted for 51% of the variability in this index. In addition, aortic distensibility and diastolic blood pressure were the only two variables that independently predicted systolic blood pressure.

Discussion

Aortic distensibility changes in aortic regurgitation. This study demonstrated a significant inverse relation between distensibility of the proximal ascending aorta and age in this group of nearly asymptomatic patients with chronic aortic regurgitation. Aortic distensibility also correlated inversely with left ventricular end-diastolic and end-systolic volumes as well as systolic wall stress and left ventricular mass. These observations suggest that decreases in aortic distensibility that usually occur with increasing age (8–16) may adversely effect left ventricular systolic wall stress and ventricular volume. A similar change in aortic distensibility with increasing age was observed in the normal healthy volunteers. In addition, the 11 patients with aortic regurgitation undergoing aortic valve replacement for left ventricular dysfunction had lower aortic distensibility than did the other patients with aortic regurgitation. This finding also suggests that decreased aortic distensibility contributes to the increased afterload imposed on the left ventricle during systole. The decreased aortic distensibility results in a more rapid pulse wave velocity so that the reflected wave may arrive back at the aortic root at a time when systolic ejection is still occurring, thus increasing afterload (28). This increase in afterload may contribute to the increasing end-diastolic volume and systolic wall stress that have been shown (17) to be indicators of high risk for eventual valve replacement. The square of the correlation coefficients (r^2) would suggest that the changes in aortic distensibility might be responsible for 22% and 34%, respectively, of the changes observed in end-diastolic volume index and systolic wall stress.

End-diastolic volume index and systolic blood pressure were found to be independent predictors of the subsequent need for valve replacement. Because progressive enlargement of the left ventricle is one of the major clinical criteria on which clinicians base decisions to recommend valve replacement, the predictive value of end-diastolic volume index for valve replacement might be expected. Aortic distensibility and diastolic blood pressure provided independent information predicting both end-diastolic volume index and systolic blood pressure. Thus, lower aortic distensibility predicted higher end-diastolic volume and higher systolic blood pressure in this group of patients with nearly asymptomatic aortic regurgitation. This finding that aortic distensibility has independent predictive value for end-diastolic volume index and systolic blood pressure supports the hypothesis that decreasing aortic distensibility (increased stiffness) contributes to hemodynamic deterioration in these patients.

Systolic blood pressure was higher and diastolic blood pressure tended to be lower in the group with valve replacement. Consequently pulse pressure was also greater in this group. The higher systolic blood pressure may be due in part to a stiffer aorta, that is, decreased aortic distensibility (28), in this group.

Possible mechanisms of changes in aortic distensibility. Previous investigators (8–16) have shown that aortic distensibility varies with age. Fragmentation of the circumferential layers of elastic tissue and its replacement with collagen fibers has been observed with increasing age (29). With increasing age the ascending aorta tends to dilate (30) and become thicker (9). The dilation would result in higher circumferential wall stress and the thickening of the aortic wall would tend to normalize the wall stress (9). Also the large stroke volume that occurs in patients with aortic regurgitation may contribute to excessive stress on the ascending aortic wall. This could compromise the vasa vasorum blood supply and damage the medial layer of the artery as described in hypertension (31,32). The increased "stiffness" of the aortic wall in this study may be due to 1) a decrease in the elastin/collagen ratio, 2) the increase in the wall thickness of the aorta with increasing age (9), or 3) dilation of the aorta (30). Also, the aorta may be becoming more atherosclerotic with calcification. There is more elastin than collagen in the thoracic aorta (33). Aging alters the histologic structure of the arterial wall (29,34) and thus may modify the dynamic response of the artery to changes in arterial pressure that occur during the cardiac cycle.

Limitations of study. The accuracy of measurements of aortic diameter with ultrasound is limited principally by the quality of the image. Interobserver and intraobserver variability with respect to these echocardiographic aortic measurements was sufficient to allow measurement of changes in aortic diameter between diastole and systole. Similar kinds of errors for these aortic dimension measurements also occur with invasive techniques (9,12–14). Newer imaging techniques such as nuclear magnetic resonance imaging or intravascular echocardiography with improved spatial resolution may improve the accuracy of aortic dimension measurements (35). In addition, the distensibility of the proximal ascending aorta measured at one location in one dimension may not be representative of multiple measurements that characterize the total aortic distensibility. The measurement of pulse pressure by sphygmomanometry was used as an approximation of central aortic pulse pressure. Peripheral amplification of systolic pressure and peripheral reduction in diastolic pressure may have resulted in an overestimation of pulse pressure. However, peripheral amplification of pulse pressure decreases with age (8) even though the aortic wall gets stiffer with age (36). This paradox may be due to increasingly uniform stiffness in the arterial tree as a whole. As the level of aortic stiffness increases toward the stiffness level of the peripheral arteries, pressure wave reflections may be decreased. These wave reflections are the cause of the peripheral amplification (36,37). End-diastolic pressure was obtained at the fourth Korotkov sound because this sound has been found to correlate with end-diastolic pressure in patients with aortic regurgitation (27).

The measurements of left ventricular volumes by radionuclide angiography are subject to errors due to differences in attenuation of the 140 keV photons between patients and

in computer edge detection. However, the reproducibility of the measurements of left ventricular volume (28) was sufficient for the purposes of this study. Indeed, the correlations between end-diastolic volume and aortic distensibility are highly significant even though both measurements may be subject to various errors in measurement.

The timing of aortic valve replacement could have affected some of the results of this study. The individual physicians caring for the patients recommended surgery on the basis of symptoms referable to left ventricular dysfunction or substantial decreases in left ventricular ejection fraction, or both. However, the timing of valve replacement is, at present, controversial (17,39–42). The group with aortic valve replacement tended to be older than the group not undergoing valve replacement, but this difference did not achieve statistical significance, possibly because of the relatively small number of patients. The hypothesis of this study would suggest that, in fact, the patients requiring valve replacement should have been older because aortic distensibility decreases with age, especially around the age of 40 years. The duration of aortic distensibility also tended to be longer in the patients undergoing valve replacement.

Conclusions. This study demonstrates a decrease in aortic distensibility with increasing age in patients with aortic regurgitation that is similar to that seen in normal patients. In patients with aortic regurgitation, decreased aortic distensibility appears to be a factor related to increases in left ventricular size, function and systolic wall stress. These variables in turn appear to be important predictors in the gradual deterioration that occurs in patients with chronic aortic regurgitation. Our observation that patients who required valve replacement had lower aortic distensibility supports this possibility.

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