Valvular Heart Disease

Systemic Arterial Response to Exercise in Patients With Aortic Valve Stenosis

Warren K. Laskey, MD; William G. Kussmaul III, MD; Abraham Noordergraaf, PhD

Background—Systemic arterial hemodynamics play an important role in the assessment of the severity and hemodynamic consequences of aortic valve stenosis (AVS).

Methods and Results—Systemic vascular resistance, total arterial compliance, effective arterial elastance, and aortic characteristic impedance were derived from high-fidelity catheter recordings of ascending aortic pressure and blood flow velocity at rest and with supine bicycle exercise in 18 patients with AVS and 11 control subjects. Mean aortic pressure was similar between groups. At rest, systemic vascular resistance (AVS patients, 1426±318 dynes·s·cm⁻⁵; control subjects, 107±228 dynes·s·cm⁻⁵; P<0.01), arterial elastance (AVS patients, 1.38±0.36 mm Hg/mL; control subject, 0.99±0.15 mm Hg/mL; P<0.002), and aortic characteristic impedance (AVS patients, 107±23 dynes·s·cm⁻⁵; control subjects, 76±30 dynes·s·cm⁻⁵; P<0.01) were increased, whereas total arterial compliance was lower (AVS patients, 0.737±0.19×10⁻³ cm²/dyne; control subjects, 1.155±0.27×10⁻³ cm²/dyne; P<0.001) in AVS. With exercise, total arterial compliance increased in control subjects (rest, 1.155±0.27×10⁻³ cm²/dyne; exercise, 1.421±0.49×10⁻³ cm²/dyne; P<0.05) but did not change in AVS patients (rest, 0.737±0.19×10⁻³ cm²/dyne; exercise, 0.769±0.21×10⁻³ cm²/dyne; P=0.2). Arterial elastance increased on exercise in AVS patients (rest, 1.38±0.36 mm Hg/mL; exercise, 1.57±0.44; P<0.01). Aortic characteristic impedance remained elevated on exercise (AVS patients, 122±30 dynes·s·cm⁻⁵; control subjects, 80±43 dynes·s·cm⁻⁵; P=0.01). Stroke flow increased significantly in both AVS patients (rest, 229±69 mL/s; exercise, 256±78 mL/s; P<0.01) and control subjects (rest, 230±37 mL/s; exercise, 406±69 mL/s; P<0.001), although the increment was much attenuated in AVS. On multiple regression, the increase in stroke flow was related to the decrease in systemic vascular resistance (P=0.03), increase in total arterial compliance (P=0.03), and decrease in arterial elastance (P=0.02).

Conclusions—These results indicate a pressure-independent increase in the steady and pulsatile components of the arterial load in patients with AVS under resting conditions. Persistent “stiffening” of the arterial system is an important contributor to the diminished stroke output response to exercise in AVS. (Circulation. 2009;119:996-1004.)

Key Words: aorta □ elasticity □ stenosis □ valves

The systemic arterial response to exercise in humans has been studied under a wide variety of conditions. Common to all conditions, albeit to varying extents, is systemic arterial vasodilation.1–3 Generally represented by systemic vascular resistance (SVR), systemic arterial vasodilation represents the opposition to steady arterial flow. However, under pulsatile flow conditions, the total opposition to forward flow is represented by the frequency-dependent vascular hydraulic load or input impedance spectrum.4,5 Changes in the steady and pulsatile components of the vascular hydraulic load have been reported in a variety of cardiovascular disease states under resting conditions.6–8 However, information is scarce on these measures in patients with valvular heart disease in general and in patients with aortic valve stenosis (AVS) in particular. Given the emphasis on and prognostic importance of exercise-related symptoms in patients with AVS,9–11 further information in this setting is needed.

Clinical Perspective p 1004

Recently, attempts have been made to quantify arterial compliance, a measure of the pulsatile component of the arterial vascular hydraulic load, in patients with AVS and to relate compliance to circulatory performance.12,13 However, the dependence of arterial compliance on arterial pressure, intrinsic arterial wall pathology, age, and other clinical conditions is likely to confound any association between compliance and ventricular performance. Likewise, studies of patients in the resting state provide no insight into the behavior of compliance on exercise or the clinical and hemodynamic significance of physiological perturbations in

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compliance. The purpose of the present study was to more fully characterize the systemic arterial hemodynamic response to exercise in patients with AVS and to compare this response with a control group of subjects without cardiovascular disease.

Methods

Patient Population

The patient population for this study comprised 29 subjects referred for diagnostic cardiac catheterization and angiography as part of their clinical evaluation. Eighteen subjects had clinically (ie, symptomatic) and hemodynamically significant AVS. Eleven patients, defined as the control group, were found to be free of detectable cardiovascular disease. All 29 patients were selected from a larger population of patients with a variety of cardiovascular conditions referred to our laboratory for diagnostic cardiac catheterization who underwent supine bicycle exercise as part of their evaluation. For purposes of the present study, the groups were chosen so that their age and sex distributions were similar. All patients with AVS had an angiographically determined left ventricular ejection fraction >0.55, no significant degree of aortic valve insufficiency on aortic root angiography, and no significant obstructive coronary artery disease on coronary angiography. All patients were in sinus rhythm. Vasoactive medications, when prescribed, were withheld for at least 12 hours before the procedure. Outpatient medical therapy consisted of diuretics (n=12 AVS), nitrates (n=11 AVS, 11 control subjects), calcium channel antagonists (n=10 control subjects), digoxin (n=4 AVS), or angiotensin-converting enzyme inhibitors (n=12 AVS).

Study Protocol

Hemodynamic evaluation was performed with a high-fidelity, multisensor catheter as previously described.14–16 Patients were studied under supine, resting conditions and during supine bicycle exercise beginning at an external workload of 25 W. Patients exercised for 3 to 5 minutes or until the development of symptoms (fatigue or dyspnea). Data reported here represent steady-state conditions (consecutive unchanging pulmonary artery oxygen saturation determinations obtained from a balloon flotation catheter inserted into the pulmonary artery). All data were recorded continuously on magnetic tape for subsequent offline analysis. All patients gave written consent for the exercise portion of the procedure in accordance with guidelines established by the University of Pennsylvania Committee on Studies Involving Human Beings. All patients successfully completed the study protocol, and no complications were encountered.

Data Processing and Analysis

Ascending aortic pressure, blood flow velocity, and surface ECG signals were recorded on magnetic tape as previously described.14–16 The analog signals were taken directly from tape, low-pass filtered at 50 Hz (24 dB per octave), and automatically digitized at 4-ms intervals with a 12-bit analog-to-digital converter interfaced to a microcomputer. The instantaneous blood flow velocity signal was scaled to the simultaneously obtained thermodilution cardiac output, performed in triplicate, thereby allowing calculation of blood flow. In patients with AVS, the ascending aortic pressure and velocity waveforms may vary as a function of the location of the proximal pressure sensor within the region of pressure recovery.17 Therefore, beats were chosen for analysis if peak ascending aortic pressure exhibited <5-mm Hg variation over the interval examined and if little variation occurred in the configuration of the velocity waveform (minimal early diastolic dip, flat late diastolic segment, and easily identifiable peak). This was generally not difficult in the resting state when catheter translational motion was minimal (Figure 1). An average of 12 beats (range, 8 to 15 beats) per subject were stored and signal averaged for subsequent analysis of the resting data (Figure 2). Under exercise conditions, 15 to 30 beats were reviewed for stability of the ascending aortic and velocity waveforms. Beats were chosen for analysis when the ascending aortic pressure exhibited <10-mm Hg variation (respiratory effect) over the segment chosen for analysis and the simultaneously obtained velocity signal exhibited the same qualitative characteristics as required at rest. No attempts were made to reposition the catheter during exercise. An average of 15 beats (range, 10 to 30 beats) per subject were stored and signal averaged for subsequent analysis of the exercise data. Figure 3A and 3B illustrates exercise data from 2 subjects.

Estimation of Total Arterial Compliance

Total arterial compliance (TAC) was assessed with 2 independent methodologies as previously described.18 Method 1 (TAC-1), using analysis of the diastolic decay of the ascending aortic pressure, assumes that it follows the monoexponential function $P(t) = P_0 e^{-t/\tau}$, where $P_0$ is the dicrotic notch pressure, $t$ is time at any point in diastole, and $\tau$ is the time constant of the arterial system expressed as
the product of the SVR, R, and the arterial compliance. Arterial compliance is then derived from the natural log transform of the above relationship when the slope is equal to \(-1/\tau\). Because \(\tau = RC\), where \(C\) is arterial compliance, \(C = \pi/\tau\). Only beats with a least-squares-derived \(r \geq 0.95\) (for the semilog fit to a linear relationship) were used for analysis. Method 2 (TAC-2) uses derivation of the aortic input impedance spectrum from simultaneous ascending aortic pressure and velocity signals. Only beats with a stable ascending aortic velocity waveform were used for this analysis. We report arterial compliance at the first harmonic of the fundamental frequency because in a linear system compliance is frequency independent and the low-frequency components of the input impedance are of greater physiological importance. When the impedance modulus was less than aortic characteristic impedance (\(Z_c\); see below) at the selected frequency, a solution for arterial compliance does not exist, and these data points are missing.

An additional, albeit indirect, measure of arterial distensibility, effective arterial elastance (\(E_a\)), was estimated as previously described from the relationship \(E_a = R/T\), where \(R\) is the total arterial resistance (SVR) and \(T\) is the cardiac period. A significant linear
relationship ($r=0.95$) between the mean ascending aortic pressure and the end-systolic ascending aortic pressure was verified in all subjects, allowing substitution of mean pressure for end-systolic pressure$^{18}$ in this calculation.

$Z_c$, a direct measure of intrinsic aortic distensibility, was calculated as previously described.$^{14}$ Only beats with stable ascending aortic velocity waveforms were chosen for analysis. A minimum of 5 consecutive beats was required for analysis. In cases in which multiple moduli of the amplitudes of flow harmonics $>4$ Hz fell below the sensitivity of the recording system,$^{14}$ $Z_c$ could not be calculated. This was true in 1 subject in each group under resting conditions and in 3 AVS patients and 1 control subject under exercise conditions.

### Statistical Analysis

Continuous data are summarized as mean±SD. Intergroup comparisons were accomplished with an ANCOVA, with subject age as a covariate, and Fisher’s protected least-significant-difference post hoc testing. Rest-exercise comparisons within each group were accomplished with paired $t$ tests. Least-squares linear regression was used to examine the bivariate relationship between selected continuous variables. Multiple linear regression was used to examine the contribution of pulsatile and nonpulsatile components of the vascular hydraulic load to the change in stroke output on exercise. A value of $P<0.05$ was considered statistically significant. All analyses were performed with Statview version 5.0 (SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

In the 18 patients with AVS, age ranged from 43 to 75 years with a mean of 53±7 years ($P=0.045$ versus AVS). Seven men and 4 women were included in the control group and 13 men and 5 women in the AVS group ($P=NS$ for difference in proportions). The mean Gorlin-derived aortic valve area in the patients with AVS was 0.65±0.22 cm$^2$. AVS patients presented with dyspnea on effort ($n=16$), angina ($n=3$), or syncope ($n=1$).

Table 1 details the circulatory response to exercise. Heart rate, mean aortic pressure, and cardiac output all increased significantly from rest to exercise in both groups. The relative increase in cardiac output was significantly lower in patients with AVS ($30±10%$; control subjects, $70±30%$; $P<0.001$). In contrast to the control group in whom the increases in both heart rate (rest, 73±12 bpm; exercise, 104±14 bpm; $P<0.001$) and stroke volume (rest, 92±12 mL; exercise, 118±20 mL; $P=0.01$) contributed to the increased cardiac output, the increased cardiac output on exercise in AVS patients was due predominantly to the increase in heart rate (rest, 78±13 bpm; exercise, 105±13 bpm; $P<0.001$); the stroke volume response was flat (rest, 76±23 mL; exercise, 74±23 mL; $P=NS$). However, stroke flow (stroke volume divided by the systolic ejection time) increased significantly in both AVS patients (rest, 229±69 mL/s; exercise, 256±78 mL/s; $P=0.002$) and control subjects (rest, 230±37 mL/s; exercise, 406±69 mL/s; $P<0.001$), although the increase in stroke flow with exercise was significantly less in AVS (AVS patients, 26±31 mL/s; control subjects, 107±71 mL/s; $P<0.001$).

Table 2 details the systemic arterial hemodynamics at rest and with exercise. It can be seen that, overall, patients with AVS at rest are characterized by higher SVR (AVS patients, 1425±317 dynes·s·cm$^{-5}$; control subjects, 1107±227 dynes·s·cm$^{-5}$; $P=0.007$) and lower TAC-1 (AVS patients, 0.737±0.19×10$^{-3}$ cm$^3$/dyne; control subjects, 1.155±0.27×10$^{-3}$ cm$^3$/dyne; $P<0.001$) at similar levels of mean aortic pressure (AVS patients, 97±15 mm Hg; control subjects, 95±7 mm Hg; $P=0.7$). Consistent with the difference in TAC-1, similar findings were reached with analyses of TAC-2 and Ea (Table 2). Aortic characteristic impedance at rest also was significantly higher in AVS (AVS patients, 107±23 dynes·s·cm$^{-5}$; control subjects, 76±30 dynes·s·cm$^{-5}$; $P=0.007$).

The systemic arterial response to exercise in patients with AVS differed from control subjects (Figure 4 and Table 2). Although SVR decreased significantly with exercise in both groups, the SVR on exercise remained higher in patients with AVS (AVS patients, 1189±242 dynes·s·cm$^{-5}$; control subjects, 723±158 dynes·s·cm$^{-5}$; $P<0.001$), and the percentage decrease in resistance on exercise was significantly attenuated (AVS patients, 16±10%; control subjects, 34±11%; $P=0.002$). Control subjects exhibited increases in both measures of TAC on exercise. Patients with AVS exhibited no significant change in either measure of TAC. Ea, significantly higher in patients with AVS at rest (AVS patients, 138.0±35 mm Hg/mL; control subjects, 98.0±15 mm Hg/mL; $P=0.002$), increased further with exercise (in contrast to control subjects) and remained higher than in control patients during exercise (AVS patients, 157.5±44 mm Hg/mL; control subjects, 93.0±18 mm Hg/mL; $P<0.001$). Importantly, mean ascending aortic pressure increased to a similar degree, and to a similar final level, in each group. Characteristic impedance did not significantly change on exercise in either group, although $Z_c$ remained higher in AVS (AVS patients, 122±30 dynes·s·cm$^{-5}$; control subjects, 80±42 dynes·s·cm$^{-5}$; $P=0.01$).

### Relationship Between Components of the Arterial Hydraulic Load

TAC-1 and TAC-2 were significantly correlated within each group under both resting and exercise conditions (Figure 5) and in the combined population ($r=0.93$, $P<0.001$). No significant relationship was found between mean ascending aortic pressure over the range of aortic pressures encountered and TAC-1, TAC-2, Ea, or $Z_c$. In the combined population, statistically significant associations were identified between SVR and Ea ($r=0.80$, $P<0.001$), TAC-1 ($r=-0.74$, $P<0.001$), and TAC-2 ($r=-0.75$, $P<0.001$). Similar statistically significant (inverse) relationships were found between Ea and TAC-1 ($r=-0.76$, $P<0.001$) and TAC-2 ($r=-0.71$, $P<0.001$) in the combined population. No significant association was found between TAC (r=0.31, P=0.2), Ea ($r=0.22$, P=0.3), or $Z_c$ ($r=0.11$, P=0.6) and age.

### Cardiac and Stroke Output Response to Exercise

As noted above, the cardiac output, stroke volume, and stroke flow response to exercise was significantly attenuated in AVS patients. On multiple linear regression, the increase in stroke flow was significantly (model $R^2=0.96$) related to the de-
crease in SVR ($P<0.03$), increase in TAC-2 ($P<0.03$), and decrease in Ea ($P<0.02$).

**Discussion**

In this study, we observed significant differences in systemic arterial hemodynamics between patients with AVS and a control group of patients without cardiovascular disease. Independently derived measures of resting TAC revealed significant differences between groups at similar mean aortic pressures. With exercise, each group exhibited systemic arterial vasodilation, albeit to a lesser degree in AVS. In contrast to control subjects, patients with AVS exhibited minimal change in TAC and an increase in Ea on exercise. Finally, the increase in stroke output/flow on exercise was significantly attenuated in AVS patients compared with control subjects. These findings suggest that at equivalent levels of distending aortic pressure, the arterial system is “stiffer” at rest and during exercise in patients with AVS and that the diminished stroke output response to exercise in patients with AVS is closely associated with these abnormal responses in the steady and pulsatile components of the vascular load.

The response to exercise in patients with AVS has been the subject of ongoing interest for $50$ years. It is now recognized that the onset of effort-related symptoms represents a critical point in the natural history of AVS.9,10 The majority of studies of the effects of exercise in patients with AVS were directed toward a description of the central hemodynamic alterations (ie, intracardiac filling pressures, valvular hemodynamics, and cardiac output).19–25 A common theme among

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**Table 1. Aortic Pressures, Heart Rates, and Cardiac Output at Rest and With Exercise**

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<td>111</td>
<td>8.6</td>
<td>12.4</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>96±7</td>
<td>128±10</td>
<td>79±8</td>
<td>106±8†</td>
<td>142±13†</td>
<td>88±8†</td>
<td>73±12</td>
<td>104±14*</td>
<td>7.1±1.4‡</td>
<td>12.2±2.5§‡</td>
</tr>
</tbody>
</table>

R indicates rest; X, exercise; AoP, aortic pressure; m, mean; s, systolic; d, diastolic; HR, heart rate; and CO, cardiac output.

For rest versus exercise comparisons, *$P<0.001$; †$P<0.01$. For AVS versus control comparisons, ‡$P<0.01$; §$P<0.001$. 
these exercise studies is a blunted cardiac/stroke output response. In general, this blunted stroke response has been attributed to abnormal left ventricular filling dynamics, although the role of increased afterload has been much discussed. More recently, there has been increased interest in the relationship between systemic arterial hemodynamics and measures of stenosis severity and ventricular function. The latter studies were performed under resting conditions; thus, extrapolation to the exercise state is problematic.

Fundamental to any interpretation of acute or chronic alterations in arterial distensibility is an understanding of the clinical and hemodynamic factors that modify arterial compliance. Thus, it is important to emphasize that our 2 study groups had similar (mean and systolic) arterial pressures, an absence of significant angiographic coronary heart disease, preserved left ventricular systolic function, similar gender mix, and similar age distribution. Each of these factors has been associated with decreased arterial distensibility. Thus, any differences between the present groups in measures of arterial stiffness or distensibility likely reflect fundamental alterations in arterial structure, function, or both. Because of the importance of accurate characterization of arterial distensibility, we chose to analyze the latter using multiple independent methodologies. The internal consistency of the data speaks strongly to the presence of a stiffer arterial system in patients with AVS, at rest and with exercise.

Our data are in agreement with the observations of Briand et al despite the different methodologies used in the 2 studies. However, in the present study, with little meaningful intergroup difference in age, with matched ascending aortic pressures, and with the finding of increased aortic characteristic impedance in AVS, conclusions relating to a primary reduction in systemic arterial compliance in AVS are further strengthened. The present study extends the findings and implications of reduced resting arterial compliance by...
observing an attenuated decrease in the steady component of the hydraulic load and a discordant response (compared with the control group) in the pulsatile component of the load on exercise. It would appear as though the “coupling” between the steady (resistance) and pulsatile (compliance) components of the vascular load observed in control patients is “uncoupled” in the setting of AVS. This discordant response in the steady and pulsatile components of the vascular load suggests that the “handicapped” arterial system in AVS makes a strong effort to preserve aortic pressure to protect perfusion to critical vascular beds. Finally, observations on the importance of the pulsatile component of the load to ventricular output at rest12 are extended in the present study to the exercise setting and underscore the contribution of pulsatile arterial hemodynamics to the stroke output response to exercise.

Study Limitations

Theoretical and experimental limitations to the assessment of the “true” TAC preclude precision in the estimation of this parameter.36 However, over the range of aortic pressures encountered in this population, No dependence of the arterial compliance on mean, systolic, or diastolic aortic pressure was observed. The concordant behavior of the TAC, estimated with multiple independent methodologies, further strengthens our observations. Although there are strong epidemiologically derived associations between large-scale variations in age and arterial stiffness,37–39 the extent of decrease in compliance is less certain over the smaller range of ages observed in the present study. Furthermore, statistical adjustment for the age difference between groups did not alter the magnitude, direction, or significance of the observed changes in vascular properties in AVS.

Assessment of arterial distensibility with 3 independent methodologies (TAC-1, TAC-2, and Ea) yielded numerically different, although highly correlated, estimates. Directionally similar changes with exercise in these measures in the control group also support the reliability of the conclusions. Finally, the observation of an increased Zc in AVS provides further substantiation of a reduction in arterial compliance.

The technical difficulties encountered in signal acquisition for these analyses are well known. Excessive noise in the recording system and unstable catheter position resulted in
the inability to calculate all data points in all patients (see Methods). The effect of such missing data on our conclusions is difficult to estimate. However, the comparisons reported possessed sufficient (posthoc) statistical power to result in meaningful inferences. We assumed a flat velocity profile in the region of the ascending aorta where the velocity probe was situated. This assumption may not be valid in this setting regardless of the quality and stability of the velocity signal.

By selecting patients for study with preserved left ventricular systolic function, no obstructive coronary artery disease on angiography, and no aortic regurgitation, we attempted to avoid these known confounders of not only an abnormal response to exercise but altered arterial compliance. Thus, although the present data may be regarded as a “best-case scenario,” arterial compliance would likely be further reduced in the presence of such comorbidities. In addition, we recognize that, overall, ours is a relatively young population.

Arterial compliance is further reduced with advanced age; thus, the impact of altered compliance on exercise performance in elderly patients with AVS is likely to be even more clinically relevant than reported here.

We recognize the many factors affecting circulatory performance in patients with AVS. For purposes of the present study, we chose to focus on the systemic arterial circulation, as allowed by the methodology used. We also make the distinction between TAC and local aortic compliance. At the input to the arterial system, where these measurements were obtained, the correlation between Zc and TAC is likely to be good because a large portion of the total compliance is located within the central arteries.

Conclusions
In symptomatic patients with AVS, TAC is reduced at rest and SVR is increased compared with control subjects at the same aortic pressure. With exercise, control subjects show a consistent tendency to further increase compliance and reduce SVR. In contrast, patients with AVS exhibit further stiffening of the arterial system on exercise. Such an abnormal response in vascular hydraulic load would explain in part the reduced cardiac and stroke output on exercise and, quite likely, the development of effort-related symptoms.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

The determinants of the increase in cardiac output with exercise in patients with aortic valve stenosis (AVS) are identical to those in normal individuals and consist of chronotropic competence, increased contractility, adequate ventricular filling, and a reduction in the resistance to forward flow. The last, called vascular hydraulic load, is made up of steady and pulsatile (frequency-dependent) components. Although it is commonly believed that the valvular stenosis itself is mainly responsible for the opposition to forward flow, valvular hemodynamics are, in fact, a function of the arterial vascular hydraulic load. Using high-fidelity catheter-tip manometry and velocimetry during diagnostic cardiac catheterization, we studied the steady (systemic vascular resistance) and pulsatile (arterial compliance and aortic impedance) components of the arterial load in 18 patients with clinically significant (symptomatic) AVS at rest and with supine exercise and compared the response to that of a control group free of cardiovascular disease. We identified increases in systemic vascular resistance and aortic characteristic impedance and diminished total arterial compliance in patients with AVS at rest. With exercise, in contrast to the control subjects, patients with AVS exhibited blunted systemic vasodilation and further decreases in arterial compliance. The stroke output response in control subjects was significantly greater than in AVS and was directly and significantly related to the decrease in systemic vascular resistance and input impedance and the increase in arterial compliance. Taken together, these findings indicate that the “downstream” properties of the arterial circulation (ie, distal to the aortic valve) directly influence the exercise response in patients with AVS. In addition, the potential for therapeutic manipulation of “afterload” in patients with AVS rests on the increased “stiffness” of the arterial system in AVS.
