Impact of Vascular Adaptation to Chronic Aortic Regurgitation on Left Ventricular Performance

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Background—This investigation was designed to test the hypothesis that vascular adaptation occurs in patients with chronic aortic regurgitation to maintain left ventricular (LV) performance.

Methods and Results—Forty-five patients with chronic aortic regurgitation (mean age 50±14 years) were studied using a micromanometer LV catheter to obtain LV pressures and radionuclide ventriculography to obtain LV volumes during multiple loading conditions and right atrial pacing. These 45 patients were subgrouped according to their LV contractility (Ea) and ejection fraction values. Group I consisted of 24 patients with a normal Ea. Group IIa consisted of 10 patients with impaired Ea values (Ea <1.00 mm Hg/mL) but normal LV ejection fractions; Group IIb consisted of 11 patients with impaired contractility and reduced LV ejection fractions. The left ventricular-arterial coupling ratio, Ea/Ees, where Ees was calculated by dividing the LV end-systolic pressure by LV stroke volume, averaged 1.60±0.91 in Group I. It decreased to 0.91±0.27 in Group IIa (P<0.05 versus Group I), and it decreased further in Group IIb to 0.43±0.24 (P<0.001 versus Groups I and IIa). The LV ejection fractions were inversely related to the Ea values in both the normal and impaired contractility groups (r=−0.48, P<0.05 and r=−0.56, P<0.01, respectively), although the slopes of these relationships differed (P<0.05). The average LV work was maximal in Group IIa when the left ventricular-arterial coupling ratio was near 1.0 because of a significant decrease in total arterial elastance (P<0.01 versus Group I). In contrast, the decrease in the left ventricular-arterial coupling ratio in Group IIb was caused by an increase in total arterial elastance, effectively double loading the LV, contributing to a decrease in LV pump efficiency (P<0.01 versus Group IIa and P<0.001 versus Group I).

Conclusions—Vascular adaptation may be heterogeneous in patients with chronic aortic regurgitation. In some, total arterial elastance decreases to maximize LV work and maintain LV performance, whereas in others, it increases, thereby double loading the LV, contributing to afterload excess and a deterioration in LV performance that is most prominent in those with impaired contractility. (Circulation. 1999;99:1027-1033.)

Key Words: regurgitation • ventricles • contractility • arteries • elasticity

The development of significant aortic regurgitation into the left ventricle (LV) results in both pressure and volume overloads that can lead to the chronic condition of afterload excess.1,2 The LV attempts to compensate for these alterations in load by hypertrophy of myocytes in series and parallel to normalize the increased stresses.3,4 Although aortic regurgitation may be tolerated for decades with normal LV performance and a lack of symptoms, there is approximately a 4% per year progression to symptoms or resting LV dysfunction requiring surgical correction.5,6 While the LV undergoes these changes, it does not operate independently. The LV is coupled to the arterial system, which may also adapt to aortic regurgitation and, thereby, contribute to LV afterload. This vascular adaptation may be assessed using the concept of total arterial elastance,7−9 which incorporates all elements of vascular load.

Using this concept of total arterial elastance, several studies have analyzed vascular adaptation in animals and in a variety of pathophysiologic conditions in humans.10−16 However, no study has used this conceptual framework to assess whether vascular adaptation occurs in patients with chronic aortic regurgitation. The application of this conceptual framework may provide insight into the pathophysiologic processes that occur beyond LV chamber and myocardial adaptation in response to aortic regurgitation; this application may also shed light on potential mechanisms of deterioration in LV performance and response to therapeutic interventions. Accordingly, the purpose of this investigation was to use the concept of total arterial elastance to examine the arterial system in patients with aortic regurgitation to test the hypothesis that vascular adaptation occurs in this disease process to maintain LV performance.

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Methods

Patients

The study population consisted of 45 patients with chronic aortic regurgitation. Thirty-nine of these patients were men and 6 were women, with an age range of 29 to 78 years (mean 50 ± 14 [SD] years). They were drawn from a larger group of 51 consecutive patients with chronic aortic regurgitation referred for cardiac catheterization to establish the hemodynamic significance of their aortic valve disease. Six of these 51 patients were not included in this investigation because of concomitant aortic stenosis or coronary artery disease, technical difficulties with data acquisition, or patient refusal. Of the remaining 45 patients, 11 were in NYHA clinical class I, 18 were in clinical class II, 9 were in clinical class III, and 5 were in clinical class IV. Ten patients were taking no medication, whereas digoxin (n = 15), diuretics (n = 17), and/or calcium channel blockers (n = 11) were being prescribed in 35 patients. All patients provided written, informed consent for this investigation on forms approved by the Human Studies Committees at the University of Michigan or VA Medical Centers, Ann Arbor, Mich.

Protocol

All medications were stopped 24 to 48 hours before cardiac catheterization. After a diagnostic cardiac catheterization documented normal coronary anatomy, each patient entered the protocol. A bipolar pacing catheter was placed in the right atrium to maintain a constant heart rate throughout the protocol. Through the right femoral artery, a precalibrated, micromanometer LV catheter (Millar Instruments) was positioned to measure LV pressures. In vivo red blood cell labeling with 30 mCi of 99mTc was performed for gated equilibrium radionuclide ventriculography. Then, simultaneous micromanometer LV pressures and radionuclide ventriculograms were acquired under control conditions and during multiple, additional LV loading conditions produced by steady-state infusions of methoxamine or nitroprusside with heart rate held constant by right atrial pacing. The methoxamine infusion was adjusted to achieve a variable increase in LV systolic pressure of 20 to 50 mm Hg, and the nitroprusside infusion was adjusted to achieve a variable decrease in LV systolic pressure of 20 to 40 mm Hg. A stable hemodynamic condition was considered present when the micromanometer LV systolic pressure varied ±10 mm Hg.

Hemodynamics

The LV pressure waveforms were acquired at 100 mm/s paper speed and included an electrocardiographic lead and micromanometer LV pressures on 40 and 200 mm Hg scales. These hemodynamic measurements were recorded for 10 to 20 cardiac cycles at the beginning, middle, and end of each radionuclide acquisition. Then, these LV pressure waveforms were averaged to obtain an average LV pressure waveform to match with the corresponding radionuclide LV volume data for each loading condition. The LV pressure waveforms were digitized using a Calcomp 9100 inductance digitizing surface (resolution 0.2 mm) beginning at the peak of the R-wave of the simultaneously recorded ECG. The program developed in this laboratory yields instantaneous LV pressures at a variable sampling frequency.17 Interpolation of the LV pressure data was conducted to guarantee isochronicity of the LV pressure values with the mid-point of each radionuclide frame throughout the cardiac cycle.

Radionuclide Ventriculography

Gated equilibrium radionuclide ventriculograms were obtained for 30 ms frames throughout the cardiac cycle for 250 cardiac cycles. During the mid-point of each radionuclide acquisition, a 2 mL blood sample was drawn and later counted for 2 minutes. The time delay was recorded for decay correction. At the completion of the protocol, a distance measurement was obtained for attenuation correction. Absolute radionuclide LV volumes were calculated frame-by-frame from background-subtracted hand-drawn region-of-interest LV count data that were standardized for frame duration, number of cardiac cycles acquired, decay-corrected blood sample counts, and attenuation.18,19

Data Analysis

Radionuclide LV ejection fraction was calculated as LV stroke volume divided by end-diastolic volume. In addition, we also calculated LV regurgitant index. Right ventricular (RV) stroke counts were obtained using a modification of the method described by Madahhi and co-workers,20 which we have used in other investigations.21–23 We used it in this investigation to calculate LV regurgitant index (RI) as:

\[ RI = \frac{(LVEDC - LVESC)/(RVEDC - RVEweg)}{EDC} \]

where EDC is end-diastolic counts and ESC is end-systolic counts.

The corresponding micromanometer LV pressures and radionuclide LV volumes for each loading condition were plotted to obtain multiple pressure-volume loops for each patient. The maximal pressure-volume ratio for each pressure-volume loop was subjected to linear regression analysis to obtain a slope (Ees) reflecting LV chamber elastance, a relatively load-independent index of LV contractility.24–26 To obtain total arterial elastance (Ea), LV end-systolic pressure (Pes) was divided by radionuclide LV stroke volume. The LV end-systolic pressure (Pes) was defined as the LV pressure at the maximum pressure-volume ratio during the baseline hemodynamic condition. The left ventricular-arterial coupling ratio was then defined as the ratio of Ees to Ea.

Two important assumptions were inherent in these calculations. First, consistent with the data from Sunagawa and colleagues,7,8 concerning isolated left heart preparations and with the results from the theoretic studies of Burkhoff and Sugawa,9 we assumed that maximal LV work would occur when Ees equaled Ea. Second, we also assumed that Ees reflected total arterial load, as shown in the studies of Latham and colleagues,11 in normotensive and hypertensive nonhuman primates and by Kelly and co-workers,13 in normotensive and hypertensive patients.

To assess LV mechanical (pump) efficiency, LV stroke work was obtained by calibrated planimetry of the pressure-volume loop. The result was then multiplied by 0.0136 to convert from mm Hg/mL to grams per meter. The LV pressure-volume area was obtained by calibrated planimetry of the area enclosed by Ees, the diastolic curve, and the systolic portion of each pressure-volume loop.7 The ratio of external work to the pressure-volume area is reflective of LV pump efficiency, that is, the efficiency of converting the total energy available to the LV into external work. It is important to recognize that, although the LV pressure-volume area has a linear relationship with myocardial oxygen consumption,9 this relationship has a variable MVO2 axis offset as a result of basal metabolism and the energy costs of excitation-contraction coupling, which are not reflected in the pressure-volume area. Thus, LV pump efficiency cannot be assumed to be synonymous with myocardial efficiency.

Statistical Analysis

All data are expressed as the mean ± SD. The patients with aortic regurgitation were subgrouped according to whether or not their LV contractility (Ees) and ejection fraction values were normal or abnormal. Data from a previous group of control subjects was used to establish normal Ees values ≥1.00 mm Hg/mL, whereas LV ejection fraction was considered to be normal when it was ≥0.45 by radionuclide ventriculography.27,28 Accordingly, all Group I patients had normal Ees values, whereas all patients in Group II had impaired LV contractility. Group II patients were further subdivided into those with normal LV ejection fractions (IIa) and those with abnormal LV ejection fractions (IIb). Data were compared between these 3 subgroups using ANOVA. Then, t tests with a Bonferroni correction were used to identify specific differences between subgroups. Continuous variables were com-
Results

Aortic Regurgitation Subgroups

Of the 45 patients with chronic aortic regurgitation, 24 were in Group I, 21 were in Group II, with 10 in Group IIa and 11 in Group IIb. The baseline hemodynamic data for these 3 subgroups are shown in the Table. There were no significant differences in the average heart rates or LV end-diastolic and peak systolic pressures. In contrast, there was an increase in the LV end-diastolic volumes from a mean of 202±78 mL in Group I to 383±155 mL in Group IIa (P<0.001 versus Group I) and to 514±282 mL in Group IIb (P<0.001 versus Group I). Similarly, there was an increase in the average LV end-systolic volumes from 84±37 mL in Group I to 179±92 mL in Group IIa (P<0.001 versus Group I) and to 347±207 mL in Group IIb (P<0.001 versus Group I and P<0.05 versus Group IIa). The average LV ejection fraction values in Groups I, IIa, and IIb were similar; but, by subgroup definition, it was largest in Group IIa. The LV pump efficiency (SW/PVA) values are shown for the patients with chronic aortic regurgitation in Groups I (solid bars), IIa (striped bars), and IIb (crosshatched bars). Note that despite no significant further change in LV contractility from Group I to IIa, there was a significant decrease in total arterial elastance in Group IIa in comparison to Group I, with an increase in total arterial load on the LV in Group IIb. This resulted in a decrease in the left ventricular-arterial coupling ratios, maximization of LV work in Group IIa, and marked decrease in LV work and pump efficiency in Group IIb. Significant differences are noted.

Left Ventricular Chamber Performance

The LV contractility index, Ees, averaged 2.15±1.49 mm Hg/mL in Group I, which, by subgroup definition, exceeded the average value in Group II (0.62±0.23 mm Hg/mL in IIa and 0.47±0.27 mm Hg/mL in IIb).

Figure 1. The average LV contractility (Ees, mm Hg/mL), total arterial elastance (Ea, mm Hg/mL), left ventricular-arterial coupling (Ees/Ea), LV work (SW, g/m), and LV pump efficiency (SW/PVA) values are shown for the patients with chronic aortic regurgitation in Groups I (solid bars), IIa (striped bars), and IIb (crosshatched bars). Note that despite no significant further change in LV contractility from Group I to IIa, there was a significant decrease in total arterial elastance in Group IIa in comparison to Group I, with an increase in total arterial load on the LV in Group IIb. This resulted in a decrease in the left ventricular-arterial coupling ratios, maximization of LV work in Group IIa, and marked decrease in LV work and pump efficiency in Group IIb. Significant differences are noted.
from 0.61±0.12 in Group I to 0.50±0.11 in Group IIa (P<0.05 versus Group I) and further to 0.45±0.23 in Group IIb (P<0.01 versus Group IIa and P<0.001 versus Group I).

These data are also illustrated in Figure 1. The ratio of LV work to pressure-volume area, a measure of LV pump efficiency, and the left ventricular-arterial coupling ratio, Ees/Ea, had a curvilinear relationship over a wide range of coupling ratios (Figure 2). It is evident that, in patients with aortic regurgitation, LV pump efficiency falls dramatically as the left ventricular-arterial coupling ratio declines below 1.0, which is represented primarily by our patients in Group IIb. The relationship between LV ejection fraction and left ventricular-arterial coupling was similar, that is, as the Ees/Ea ratio fell below 1.0, LV ejection fraction declined sharply.

To further examine this relationship, the LV ejection fractions were compared with the total arterial elastance values; and no significant relationship was observed (y=−0.036x+0.56, r=−0.22, P=0.14) between these variables in the total population. However, when the aortic regurgitation patients were divided into those with and without normal contractility, significant relationships between the LV ejection fraction and Ea values were evident in each of these 2 groups (Figure 3). In the normal contractile group (Group I), there was an inverse relationship between the LV ejection fraction and Ea values (y=−0.049x+0.66, r=−0.48, P<0.05). In the impaired contractile group (Group II), a similar relationship was established (y=−0.10x+0.54, r=−0.56, P<0.01), but the slope of this relationship was more steep (P<0.05). Thus, there was evidence that LV performance in each contractile group was dependent on arterial load across the full continuum of total arterial elastance values.

To further examine these interactions, normalized LV work values were also plotted against the left ventricular-arterial coupling ratios (Figure 4). The solid line represents the theoretic relationship between normalized LV work and the left ventricular-arterial coupling ratio.9 Accordingly, maximum LV work would theoretically occur when the LV chamber elastance and total arterial elastance values are coupled at an Ees/Ea ratio of 1.0. The normalized LV work values in control subjects over a wide range of LV loading conditions fall on this theoretic relationship in the higher left
ventricular-arterial coupling ratios >1.0. The aortic regurgitation patients in Group I, who had normal LV contractility and ejection fraction values, also fell in the higher range of left ventricular-arterial coupling ratios consistent with LV operating between maximal work and efficiency similar to a normal heart. However, in Group IIa, there was a decline in the left ventricular-arterial coupling ratio to ≈1.0 to maximize LV work in line with the theoretic framework. As the Eₐ/Eₑ ratio deteriorated in Group IIb, falling below a coupling ratio of 1.0, normalized LV work also deteriorated.

Discussion

The data in this investigation indicate that LV contractility and left ventricular-arterial coupling are similar to those in a normal heart in a range that attempts to maintain mechanical efficiency while accommodating to the increased demands for LV work with the development of aortic regurgitation. When LV contractile dysfunction supervenes, the arterial system may also adapt with a reduction in total arterial elastance to maintain left ventricular-arterial coupling near a ratio of 1.0 to maximize LV work. However, in some patients with aortic regurgitation, total arterial elastance may increase, providing an additional arterial load on the LV, effectively double loading the LV and reducing the left ventricular-arterial coupling ratio below the critical value of 1.0. This leads to a reduction in LV work, pump performance, and pump efficiency. Thus, these data indicate that adaptation of the arterial system is heterogeneous and may assist the LV in optimizing work and maintaining LV performance in some patients with aortic regurgitation, but it may also contribute to afterload excess and the impairment of LV pump performance in others with this disease process, most prominently those with impaired contractility.

The left ventricular-arterial coupling concept proposed by Sunagawa and colleagues provides a convenient theoretical framework within which LV performance can be evaluated through the interaction of the LV with the arterial system. This framework predicts that the transfer of energy from the LV to the arterial system, that is, the performance of external work, is maximal when these 2 elastances are equal. Thus, by standardizing LV work to the maximal theoretic value, the effects of aortic regurgitation on LV work and pump efficiency can be examined over a range of contractile states and coupling ratios. The data in this investigation suggest that the left ventricular-arterial coupling ratio remains unaffected and energy transfer from the LV to the arterial remains high, but not maximal, with development of aortic regurgitation similar to that in a normal human heart. However, with progression to LV contractile dysfunction, the left ventricular-arterial coupling ratio may decline to maximize LV work and maintain LV performance. Part of this adaptation is a reduction in total arterial elastance, which offsets the decline in LV chamber performance. This is consistent with prior investigations examining the individual components of arterial load in animals and humans. In experimental aortic regurgitation, it has been reported that increased circumferential distensibility of the aorta results in decreased characteristic impedance. In humans with chronic aortic regurgitation, it has been reported that vascular compliance may either be increased or decreased, depending on the calculation methodology; vascular resistance is usually less than normal, although standard methods of calculating vascular resistance in aortic regurgitation may obscure this beneficial vascular response. Thus, vascular adaptation in aortic regurgitation may contribute to preservation of LV performance.

These data are consistent with previous observations in normal human subjects reported from this laboratory, but they contrast with data from patients with dilated congestive cardiomyopathy studied by Asanoi and colleagues and others. In hypertensive, cardiomyopathic, or mitral regurgitation patients, there is a relative increase in total arterial elastance as LV chamber performance deteriorates with these disease processes; this may contribute to worsening LV dysfunction. Nevertheless, although there may be a decrease in total arterial elastance in some patients with aortic regurgitation, in others, the arterial system may not be capable of this kind of adaptation. In these patients, double loading of the LV may cause deterioration in LV performance, manifested by a reduction in LV work and pump efficiency and, thereby, contributing to the state of afterload excess. This contrasts with the effects of double loading of the LV in patients with aortic stenosis. Carroll and colleagues found that double loading of the LV with aortic stenosis and systemic hypertension did not affect LV performance in any substantive manner. Thus, in contrast to other disease processes, the arterial system may undergo a heterogeneous adaptation in aortic regurgitation.

This may also have significant implications for understanding the development of symptoms and resting LV dysfunction requiring surgical intervention and the benefits of vasodilator therapy. In the asymptomatic patient with aortic regurgitation, the development of symptoms or resting LV dysfunction occurs in approximately 4% of patients per year. Predictors of progression to surgery include large LV volumes, a relatively low LV ejection fraction, and an elevated end-systolic stress. Because these parameters were found predominantly in our Group II patients, these data suggest that maladaptation of the arterial system may represent one possible hemodynamic mechanism for the development of clinical indicators for surgery in these patients. Burkhoff and Sagawa have also demonstrated within this theoretical framework that in the depressed contractile state, a heart is more susceptible to an increase in total arterial elastance. Therefore, an increase in Eₑ in patients with aortic regurgitation and contractile dysfunction would predict a greater reduction in LV performance. In our patient population, there was a steeper, more inverse relationship between LV ejection fraction and Eₑ in the patients with impaired contractility compared with those with normal contractility manifesting their sensitivity to afterload excess in line with theoretic predictions. Reversal of this kind of vascular maladaptation may explain the observations of Bonow and colleagues, who described improvement in LV dysfunction after surgical intervention when surgery was performed in a timely fashion. In addition, the long-term benefit observed with vasodilator therapy in asymptomatic patients with moderate-to-severe aortic regurgitation may be related to optimization of total arterial elastance through a reduction in
vascular resistance, which may, in a parallel fashion, prevent or delay maladaptation of the arterial system.

One potential limitation of this approach is that total arterial elastance incorporates vascular resistance, vascular compliance, and characteristic impedance into a single measure of total arterial load. One benefit of this approach, however, is the ability to couple total arterial elastance to LV chamber elastance, because both are measured in the pressure-volume plane. This concept provides a better appreciation of the interaction of the LV and arterial system in aortic regurgitation. Further, it has been recognized that changes in total arterial elastance reflect corresponding and proportionate changes in the 3 specific parameters that characterize the arterial system. Another potential benefit to this approach is that it obviates the question of how resistance and compliance should be calculated in aortic regurgitation. Nevertheless, the specific parameters that are altered, and to what extent, cannot be ascertained from this approach. Another potential limitation is that we could not totally exclude residual vasodilator drug effects on arterial elastance. Although we discontinued all medications 24 to 48 hours before the study, some residual effects may have persisted. Nevertheless, these residual effects should have been minimized and were present in only 11 of the 45 patients studied.

In conclusion, the data in this investigation suggest that adaptation of the arterial system is important in some patients with chronic aortic regurgitation to maintain LV work and performance by optimizing coupling of the arterial system to the LV, while maladaptation of the arterial system, which leads to double loading of the LV, may occur in others and contribute to afterload excess and the development of LV pump dysfunction requiring surgical intervention.

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