Chronic Pressure-Overload Hypertrophy Attenuates Vortex Formation Time in Patients With Severe Aortic Stenosis and Preserved Left Ventricular Systolic Function Undergoing Aortic Valve Replacement

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Objective: **Transmitral blood flow produces a vortex ring that enhances the hydraulic efficiency of early left ventricular (LV) filling. The effect of pressure-overload hypertrophy on the duration of LV vortex ring formation (vortex formation time [VFT]) is unknown. The current investigation tested the hypothesis that chronic LV pressure-overload hypertrophy produced by severe aortic stenosis (AS) reduces VFT in patients with preserved LV systolic function undergoing aortic valve replacement.**

Design: **Observational study.**

Setting: **Veterans Affairs Medical Center.**

Participants: **After the Institutional Review Board's approval, 8 patients (7 men and 1 woman; age, 62 ± 5 y; and ejection fraction, 59% ± 5%) with AS (peak pressure gradient, 81 ± 22 mmHg; aortic valve area, 0.78 ± 0.25 cm^2) scheduled for aortic valve replacement were compared with 8 patients (all men; age, 63 ± 3 y; and ejection fraction, 60% ± 7%) without AS undergoing coronary artery bypass graft surgery.**

Interventions: **None.**

Measurements and Main Results: **Under general anesthesia, peak early LV filling (E) and atrial systole (A) blood flow velocities and their corresponding velocity-time integrals were obtained using pulse-wave Doppler echocardiography to determine E/A and atrial filling fraction (β). Mitral valve diameter (D) was calculated as the average of minor and major axis lengths obtained in the midesophageal bicommissural and long-axis transesophageal echocardiography imaging planes, respectively. Posterior wall thickness (PWT) was measured at end-diastole using M-mode echocardiography. VFT was calculated as $4 \times (1-\beta) \times SV/\pi D^3$, where SV = stroke volume measured using thermodilution. Systemic and pulmonary hemodynamics, LV diastolic function, PWT, and VFT were determined during steady-state conditions 30 minutes before cardiopulmonary bypass. Early LV filling was attenuated in patients with AS (eg, E/A, 0.77 ± 0.11 compared with 1.23 ± 0.13; β, 0.43 ± 0.09 compared with 0.35 ± 0.02; $p < 0.05$ for each). LV hypertrophy was observed (PWT, 1.4 ± 0.1 cm compared with 1.1 ± 0.2 cm; $p < 0.05$) and VFT was lower (3.0 ± 0.9 *v* 4.3 ± 0.5; $p < 0.05$) in patients with versus without AS. Linear regression analysis showed a significant correlation between VFT and PWT ($VFT = -2.57 \times PWT + 6.81$; $r^2 = 0.345$; $p = 0.017$).**

Conclusion: **The results indicated that pressure-overload hypertrophy produced by AS reduced VFT in patients with normal LV systolic function undergoing aortic valve replacement.**

KEY WORDS: aortic stenosis, coronary artery disease, pressure-overload hypertrophy, transmitral blood flow velocity, vortex formation time

THE PHYSICS OF fluid movement plays an essential, although somewhat underappreciated, role in left ventricular (LV) filling. A 3-dimensional rotational body of fluid (known as a "vortex ring") is generated whenever fluid moves through an orifice,[1-3] such as when blood enters the LV across the mitral valve inlet during early filling.[4-7] This vortex ring enhances transfer of volume and momentum from the left atrium to the LV,[8,9] directs blood flow to areas beneath the mitral valve leaflets (anterior > posterior),[6,10] and facilitates the continuous circulation of blood in the LV apex.[11] These actions not only improve the efficiency of early LV filling,[12,13] but also enhance the dynamics of the subsequent ejection by assuring adequate filling of the outflow tract[14] and prevent stagnation of blood in the LV apex.[15]

The duration of LV vortex formation correlates with the rate and extent of LV relaxation, the magnitude of mitral annular excursion during diastole, the maximum left atrial-LV pressure gradient, and the minimum LV diastolic pressure.[2,8,16] This phenomenon has been quantified using a dimensionless variable termed "vortex formation time" (VFT).[7] Consistent with results in vitro,[3,17] VFT values between 3.3 and 5.5 were observed in healthy volunteers with normal LV function, whereas VFT ranged between 1.5 and 2.0 in patients with dilated cardiomyopathy.[7] These data suggested that pathologic conditions may profoundly depress vortex formation and that measurement of VFT may provide important information about diastolic transmitral flow efficiency. Indeed, subsequent studies demonstrated that replacement of the native mitral valve with a prosthesis,[10,18] exposure to cardiopulmonary bypass and cardioplegic arrest,[19] elevated LV afterload,[20] and LV diastolic dysfunction[14] also affect VFT. The effects of chronic LV pressure-overload hypertrophy on VFT have not been examined. The current investigation tested the hypothesis that LV pressure-overload hypertrophy produced by aortic stenosis (AS) reduces VFT in patients undergoing aortic valve replacement.

METHODS

The Institutional Review Board of the authors' institution approved the protocol. Written informed consent was waived because a pulmonary artery catheter and transesophageal echocardiography (TEE) are used routinely in each patient undergoing cardiac surgery. Patients with preoperative ejection fraction greater than 50% undergoing aortic valve

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replacement for severe AS or those without aortic valve disease undergoing coronary artery bypass graft (CABG) were included. Patients with known contraindications for the use of intraoperative TEE and those older than 80 years of age were excluded. Patients with other valvular disease, those undergoing repeat median sternotomy or emergency surgery, and those with thoracic aortic disease were excluded. Patients with atrial fibrillation, atrial flutter, or other supraventricular tachyarrhythmias also were excluded.

Each patient received intravenous midazolam (1-3 mg) and fentanyl (50-150 μg) for conscious sedation. Intravenous and radial artery catheters were inserted using local anesthesia (1% lidocaine). Supplemental oxygen (2-4 L/min per nasal cannula) was provided. A pulmonary artery catheter was inserted using local anesthesia (1% lidocaine) under sterile conditions through the right internal jugular vein with or without ultrasound guidance at the discretion of the attending anesthesiologist. Anesthesia was induced using intravenous etomidate (0.3 mg/kg), fentanyl (3-5 μg/kg), and rocuronium (1 mg/kg) and was maintained using inhaled isoflurane (end-tidal concentration of 0.5%-1.0%) in 100% oxygen, intravenous fentanyl (2-3 μg/kg/h), intravenous propofol (25 μg/kg/h), and intravenous rocuronium (0.05 mg/kg) titrated to effect using neuromuscular monitoring. The stomach was suctioned using an oral-gastric tube, and an omniplane TEE probe (Model X7-2t, Philips, Bothell, WA) was placed into the esophagus and advanced into the stomach using the standard technique.

Each patient underwent a comprehensive TEE examination following American Society of Echocardiography/Society of Cardiovascular Anesthesiologists guidelines.[21] LV diastolic function was determined using analysis of the transmitral and pulmonary venous blood flow velocity waveforms. Pulse-wave Doppler sample volumes were placed at the tips of the mitral leaflets and within the left superior pulmonary vein (1.5 cm from the left atrial orifice) to measure transmitral and pulmonary venous blood flow velocities, respectively, in the midesophageal 4-chamber TEE imaging plane. The peak early LV filling and atrial systole blood flow velocities (E and A, respectively) and the corresponding velocity-time integrals (VTI-A and VTI-E, respectively) were used to determine E/A and atrial filling fraction (β; VTI-A/[VTI-E + VTI-A]), respectively, with the echocardiography equipment's integrated software package (iE33, Philips Ultrasound, Bothell, WA). The ratio of peak pulmonary venous systolic and diastolic blood flow velocity also was determined following published recommendations.[22] The lengths of the mitral valve major and minor axes were determined in the midesophageal bicommissural and long-axis TEE imaging planes, respectively.[21] The maximum opening of the mitral leaflets during early LV filling was determined by visual inspection of slow-motion images immediately after the T-wave of the simultaneously recorded continuous electrocardiogram. The integrated "caliper" function of the echocardiography equipment's software was used to determine the distance between the mitral leaflets in each view. The average of the minor and major axis lengths was used to calculate mitral valve diameter (D) and area. Posterior wall thickness (PWT) at end-diastole was measured using M-mode echocardiography in the transgastric short-axis plane; the posterior papillary muscle and associated chordal structures were excluded. Cardiac output was determined using thermodilution; stroke volume was calculated as the ratio of cardiac output to heart rate. All quantitative echocardiography measurements and thermodilution cardiac output were performed in triplicate during end-expiration. VFT was calculated as $4 \times (1-\beta) \times SV/\pi D^3$, where SV = stroke volume measured using thermodilution.[7] The comprehensive TEE examination and all other TEE measurements described earlier were stored on the equipment's hard drive and the hospital's computerized patient record system following institutional practice. Systemic and pulmonary hemodynamics, LV diastolic function, PWT, and VFT were determined during steady-state conditions 30 minutes before initiation of cardiopulmonary bypass in each patient.

A power analysis indicated that a group size of $n \geq 8$ was required for a minimal difference in VFT of 20% (α error < 0.05; β error $< 20\%$) with a power of 95%. Data were analyzed using analysis of variance followed by the Bonferroni modification of the Student t test.[23] Linear regression analysis was used to determine the relationship between VFT and PWT (StatPlus:macLE, AnalystSoft, Vancouver, British Columbia, Canada). The null hypothesis was rejected when $p < 0.05$. All data are presented as mean ± standard deviation.

RESULTS

With the exception of weight, no differences were observed in demographic, historic, and medication data between patients with versus without AS (Table 1). Heart rate and rate-pressure product were elevated significantly ($p < 0.05$), and stroke volume was reduced ($p < 0.05$) in the presence compared with the absence of AS (Table 2). Patients with AS had peak and mean pressure gradients across the valve of 81 ± 22 mmHg and 49 ± 13 mmHg, respectively, concomitant with a valve area of 0.78 ± 0.25 cm^2. Aortic regurgitation was absent in all the patients. LV diastolic dysfunction was observed in patients with versus without AS (E/A, 0.77 ± 0.11 compared with 1.23 ± 0.13; E-wave deceleration time and slope, 292 ± 100 ms and 189 ± 72 cm/s^2, respectively, compared with 160 ± 28 ms and 396 ± 69 cm/s^2, respectively; β, 0.43 ± 0.09 compared with 0.35 ± 0.02; $p < 0.05$ for each parameter) concomitant with greater LV hypertrophy (PWT, 1.4 ± 0.1 cm compared with 1.1 ± 0.2 cm; $p < 0.05$). No differences in the ratios of peak systolic-to-diastolic pulmonary venous blood flow velocity were observed between groups. Mitral valve diameter and area also were similar between groups. Pressure-overload hypertrophy resulting from AS reduced VFT (3.0 ± 0.9 with v 4.3 ± 0.5 without AS; $p < 0.05$). Linear regression analysis demonstrated a significant correlation between VFT and PWT ($VFT = -2.57 \times PWT + 6.81$; $r^2 = 0.345$; $p = 0.017$).

DISCUSSION

The current results demonstrated that pressure-overload hypertrophy resulting from severe AS reduced VFT in patients with preserved LV systolic function undergoing aortic valve replacement. These findings indicated that pressure-overload hypertrophy adversely affected diastolic transmitral flow efficiency by reducing the duration of vortex ring formation. This observation suggested an additional mechanism by which pressure-overload hypertrophy impaired early LV filling. LV stroke volume and atrial filling fraction were lower in the presence compared with the absence of AS, and these differences were responsible for the observed changes in VFT because mitral valve diameter was similar between groups. AS causes progressive LV hypertrophy as an adaptive response to chronically elevated LV end-systolic wall stress.[24] Myocyte diameter increases, causing pronounced LV wall thickening without substantial LV chamber dilatation. Interstitial fibrosis invariably accompanies this compensatory LV remodeling.[25,26] Increases in LV torsion and delays in apical recoil also occur in patients with pressure-overload hypertrophy resulting from AS.[27,28] Apical untwisting is observed immediately before early LV filling in healthy individuals; prolonged apical recoil blunts early LV filling and contributes to diastolic dysfunction in patients with pressure-overload hypertrophy.[28,29] These features combine to produce LV diastolic dysfunction characterized by delayed LV relaxation and