Left Ventricular Remodeling and Improvement in Diastolic Function After Balloon Aortic Valvuloplasty for Congenital Aortic Stenosis

Kevin G. Friedman, MD; Doff B. McElhinney, MD; Steven D. Colan, MD; Diego Porras, MD; Andrew J. Powell, MD; James E. Lock, MD; David W. Brown, MD

Background—In congenital aortic stenosis, chronic pressure load has detrimental effects on left ventricular (LV) systolic and diastolic function. Reduction in LV pressure load with balloon aortic valvuloplasty (BAVP) may improve diastolic function.

Methods and Results—Echocardiographic and catheterization data for 25 consecutive patients undergoing BAVP for congenital aortic stenosis were retrospectively analyzed. Median age at BAVP was 11.5 years (3.2–40.1). LV end-diastolic pressure was elevated (≥15 mm Hg) in 72% of patients, with a median of 17 mm Hg (range, 9–24). With BAVP, median aortic stenosis gradient was reduced from 63 mm Hg (range, 44–105) to 30 mm Hg (range, 10–43). Aortic regurgitation increased from trivial (none to mild) to mild (trivial to moderate). Pre-BAVP early diastolic mitral inflow velocity/tissue Doppler early diastolic velocity (E/E′) correlated with LV end-diastolic pressure (r=0.52, P=0.007). On follow-up echocardiography (median, 11 months after BAVP), aortic stenosis gradient was lower (P<0.001) and degree of AR was higher (P=0.01) compared with pre-BAVP echocardiograms. LV end-diastolic volume z-score increased (P=0.02), LV mass was unchanged, and LV mass:volume decreased (P=0.002). Mitral annular and septal E′ (P<0.001) were higher and E/E′ was lower after dilation (10.8 versus 14.2, P<0.001). Lower pre-BAVP E/E′ and lower pre-BAVP LV mass z-score were associated with lower post-BAVP E/E′.

Conclusions—After BAVP, LV remodeling characterized by an increase in EDV and decrease in LV mass:volume improve in most patients. Risk factors for persistent diastolic dysfunction include higher pre-BAVP LV mass z-score and worse pre-BAVP diastolic function. (Circ Cardiovasc Interv. 2012;5:00-00.)

Key Words: congenital heart disease balloon aortic valvuloplasty diastolic function echocardiography remodeling diastolic function

Aortic valve stenosis (AS) imposes a chronic pressure load on the left ventricle (LV). The myocardial response to chronic pressure load has been well described in adult patients with calcific AS. In response to chronic pressure loading, the LV remodels and develops concentric hypertrophy.1–3 This initially adaptive response allows for peak systolic wall stress to remain normal and for systolic function to be preserved early in the course of the disease, but concentric remodeling is the substrate for later development of diastolic dysfunction.4–8 Later in the disease course, the deleterious effects of concentric hypertrophy and associated myocardial fibrosis become apparent with the development of both systolic and diastolic dysfunction.9–13 In adults with calcific AS, removal of LV pressure load with aortic valve replacement leads to partial, but not complete, halting or, in some cases, reversal of the maladaptive processes of concentric hypertrophy and myocardial fibrosis and to an improvement in diastolic function.14–16

The myocardial response to chronic pressure load in children is also characterized by concentric hypertrophy, myocardial fibrosis, and impaired diastolic function,17–20 although it has been less well described than in adults. The time course, pathophysiology, and risk factors for progression of diastolic dysfunction may be different in younger AS patients.21 The response of the LV myocardium in younger patients with congenital AS to removal of pressure load via balloon aortic valvuloplasty (BAVP) has only been described in the immediate post-BAVP period.17 The aim of this study is to characterize the medium-term effect BAVP on LV remodeling and diastolic function in patients with congenital AS.
WHAT IS KNOWN

- Chronic pressure load on the left ventricle due to aortic stenosis results in ventricular hypertrophy, myocardial fibrosis, and abnormal myocardial mechanics.
- These processes can result in both systolic and diastolic dysfunction.

WHAT THE STUDY ADDS

- Diastolic function and noninvasive measures of left atrial pressure improve in the majority of patients after effective relief of aortic stenosis with balloon aortic valvuloplasty.

Methods

Patients

We retrospectively reviewed the records all patients $\geq$ 3 years of age undergoing BAVP for isolated congenital AS at our institution from January 2006 through June 2011. Patients with complete echocardiographic assessment of diastolic function, including mitral inflow pulsed Doppler, tissue Doppler imaging (TDI), pulmonary vein Doppler, and left atrial volume measurement, both within 1 month before catheterization and 6 to 24 months after catheterization, were included. Forty-two patients underwent BAVP in this time period and met inclusion criteria, 25 of whom had both pre- and post-BAVP echo data available and were included in the analysis. Patients with structural heart disease apart from patent foramen ovale, bicommissural aortic valve, and aortic coarctation were excluded. Additionally, patients who underwent any cardiac surgery requiring cardiopulmonary bypass (before catheterization or after catheterization and before follow-up echocardiogram) were excluded to avoid the confounding effect of cardiopulmonary bypass on myocardial function.

Catheterizations

Hemodynamic data were collected retrospectively from reports produced at the time of the catheterization. Hemodynamic data, including ordinal AR grade (0 = none, 1 = trivial, 2 = mild, 3 = moderate, 4 = severe) and peak-to-peak AS gradient, before and after intervention, were included in the analysis. Patients with structural heart disease from patent foramen ovale, bicommissural aortic valve, and aortic coarctation were excluded. Additionally, patients who underwent any cardiac surgery requiring cardiopulmonary bypass (before catheterization or after catheterization and before follow-up echocardiogram) were excluded to avoid the confounding effect of cardiopulmonary bypass on myocardial function.

Echocardiograms

All patients had a precatheaterization (within 1 month of catheterization) and at least 1 postcatheterization echocardiogram (between 6 and 24 months after catheterization) included in the analysis. For patients with multiple post-BAVP echocardiograms, the most recent echocardiogram up to 24 months after BAVP was used in the analysis.

The following LV variables and Z-scores for each variable were recorded from reports produced at the time of the study: end-diastolic volume (EDV), mass, mass:volume, ejection fraction (EF), end-systolic stress, velocity of circumferential fiber shortening, and sphericity index. LV EDV was calculated using the 5/6 area-length formula and LV mass using volumetric 2D measurements. Maximum instantaneous AV gradient from the apical imaging window or mean AV gradient from the suprasternal notch imaging window (whichever was higher) and qualitative aortic regurgitation grades (0–4) on an ordinal scale were collected.

Diastolic function assessment included pulsed Doppler of the mitral inflow, TDI, and left atrial volume for both the pre- and post-BAVP echocardiograms. All measurements of diastolic variables were retrospectively remeasured by a single echocardiographer (K.F.) from images obtained at the time of the study. Conventional pulsed Doppler indices of diastolic function, including peak early (E) and late (A) diastolic transmitral velocities, E:A ratio, A-wave duration, and E-wave deceleration time were measured from the spectral Doppler signal of the mitral valve inflow. Pulsed-wave TDI velocities were obtained from the lateral mitral annulus and the interventricular septum from the apical 4-chamber view. TDI measurements for each of the myocardial segments included peak early diastolic velocity (E’) and peak late diastolic velocity (A’). Only tracings that demonstrated a clear E’ were used. Each TDI velocity was measured on 3 consecutive cardiac cycles, and the average of these values was used for the analysis. Peak early diastolic mitral inflow velocity (E) + early septal diastolic velocity (E’/E) was calculated. Left atrial volumes were calculated using the prolate-ellipse formula.

Statistical Analysis

Means and standard deviations were used to express measures of central tendency, and dispersion for echocardiographic data and median and range were used for catheterization data. Associations between predilation echocardiographic and predilation hemodynamic data were evaluated using Pearson correlation coefficients. Receiver-operator curves were constructed to asess the ability of pre-BAVP E/E’ to predict LVEDP measured at catheterization. Paired t tests were used to compare pre- and post-BAVP echocardiographic variables. Factors associated with elevated postdilation E/E’ ($\geq$12) were sought, using Fisher exact test or Mann-Whitney test as appropriate. All statistical analysis were 2-sided, and type I error was controlled at a level of 0.05. Analyses were performed with SPSS (version 16.0, SPSS Inc, Chicago, IL).

Results

Demographic and clinical data for the 25 patients meeting inclusion criteria are shown in Table 1. Median age at catheterization was 11.5 years. All patients had either a bicommissural (60%) or unicommissural (40%) aortic valve. Nine patients (39%) underwent prior BAVP, with 4 patients having undergone prior BAVP twice and 5 patients having a single prior BAVP. Median residual AS gradient after BAVP in these 9 patients was 20 mm Hg (range, 20–43). Six patients (24%) previously underwent coarctation repair, none of whom had significant residual arch obstruction. Blood pressure at most recent evaluation was within normal range in all patients.

Median pre-BAVP LVEDP was 17 mm Hg, with the majority of patients (18 patients, 72%) having a LVEDP $\geq$15 mm Hg (Table 2). Pre-BAVP E/E’ correlated with LVEDP ($r=0.57,$
Table 2. Catheterization Data

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>17 (10–27)</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>17 (9–24)</td>
</tr>
<tr>
<td>LV end-diastolic pressure &gt;=15 mm Hg, n (%)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Mean PA pressure, mm Hg</td>
<td>24 (14–35)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, Wood Units</td>
<td>1.5 (0.2–6.9)</td>
</tr>
<tr>
<td>Pre-BAVP AR grade*</td>
<td>1 (0–2.5)</td>
</tr>
<tr>
<td>Post-BAVP AR grade*</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Pre-BAVP AS gradient, mm Hg</td>
<td>63 (44–105)</td>
</tr>
<tr>
<td>Post-BAVP AS gradient, mm Hg</td>
<td>30 (10–43)</td>
</tr>
<tr>
<td>AS gradient reduction, mm Hg</td>
<td>30 (15–75)</td>
</tr>
<tr>
<td>AS gradient reduction, %</td>
<td>54 (27–83)</td>
</tr>
</tbody>
</table>

LV indicates left ventricle; PA, pulmonary artery; BAVP, balloon aortic valvuloplasty; AR, aortic regurgitation; and AS, aortic stenosis.

Values are expressed as median (range) unless otherwise shown.

*AR ordinal grading system: 0 = none, 1 = trivial, 2 = mild, 3 = moderate, 4 = severe.

\( P=0.007 \) (Figure 1). \( E/E' >12 \) predicted LVEDP \( \geq 18 \text{ mm Hg} \), with 86% sensitivity and 78% specificity (Figure 2). Six patients (24%) had PVR >2 Wood Units (WU), with 5 having mildly elevated PVR between 2 and 3 WU and 1 patient having significantly elevated PVR at 6.9 WU. Significant AR before BAVP was rare, with 14 patients (56%) having trivial or less AR and only 1 patient having more than mild AR.

BAVP resulted in a median AS gradient reduction of 54% and a reduction in peak-to-peak gradient to \( \leq 45 \text{ mm Hg} \) in all patients (Table 2). On post-BAVP angiography, 18 patients (72%) had mild or less AR, 5 (20%) had mild to moderate AR, and 2 (8%) had moderate AR.

At a median follow-up time of 11 months after BAVP (range, 6–23 months), echocardiography showed lower AS gradient (\( P<0.001 \)) and higher AR grade (\( P=0.01 \)) than before BAVP (Table 3). After BAVP, LV EDV (\( P=0.004 \)) and LV EDV (\( P=0.02 \)) z-score were higher (\( P=0.02 \)), LV mass was unchanged, and LV mass:volume was lower (\( P=0.002 \)) than before BAVP. Most patients (72%) had an increase in LVEDV z-score, with 9 patients (36%) having a marked increase (more than 2 z-score units). Greater than mild AR on follow-up echo was associated with both higher LVEDV z-score at follow-up (\( P=0.002 \)) and larger increase in LVEDV z-score between catheterization and follow-up (\( P=0.009 \)). The majority of patients (80%) had a decrease in LV mass:volume z-score. Greater than mild AR on follow-up echo was associated with a higher percentage decrease in LV mass:volume (\( -33\% \text{ versus } -7\% \), \( P=0.027 \)). Residual AS gradient was not associated with the magnitude of change in LV mass:volume.

Comparison of pre- and post-BAVP diastolic function parameters showed higher mitral annular E’ (\( P=0.004 \)) and septal E’ (\( P<0.001 \)) and lower E/E’ after BAVP (\( P<0.001 \)) (Table 3). Before BAVP, septal E’ and mitral annular E’ z-scores were abnormally low (z-score \( \leq -2 \)) in 18 (72%) and 19 (76%) patients, respectively. After BAVP, the majority of patients had normalization of septal E’ and mitral annular E’, with only 6 patients (24%) having z-score \( \leq -2 \) for each value. Pre-BAVP E/E’ was elevated (\( \geq 12 \)) in 16 patients (64%), whereas after BAVP only 5 patients (20%) continued to have elevated E/E’ (Figure 3). No differences were found in mitral inflow spectral Doppler derived variables, including E:A and mitral E-wave deceleration time, or in left atrial volume before and after BAVP.

In univariate analysis, factors associated with E/E’ \( \geq 12 \) at follow-up included higher pre-BAVP LV mass (163 g versus 77 g, \( P=0.006 \)), pre-BAVP LV mass z-score (2.7 versus 1.7, \( P=0.03 \)), higher pre-BAVP E/E’ (16.9 versus 12.7, \( P=0.035 \)), and higher LV mass z-score at follow-up (2.6 versus 1.7, \( P=0.05 \)). There was a trend toward higher residual peak-to-peak AS gradient immediately after BAVP being associated with E/E’ \( \geq 12 \) at follow-up (36 versus 29 mm Hg, \( P=0.07 \)). Age at
intervention, need for previous BAVP, pre-BAVP AS gradient, duration of post-BAVP at follow-up echocardiogram, and AR grade after BAVP were not associated with post-BAVP E/E’.

Residual AS gradient at follow-up was associated with magnitude of decrease in E/E’. Patients with AS gradient ≤40 mm Hg on follow-up echocardiography had a median decrease in E/E’ of 30% compared with 14% in patients with AS gradient >40 mm Hg (P=0.011) (Figure 4).

### Discussion

In this study, we show that diastolic dysfunction and elevated left heart filling pressures are common in patients with congenital AS and that echocardiographic measures of diastolic function and LVEDP improve after BAVP. In the majority of patients, diastolic function and echocardiographic estimate of LVEDP (E/E’) improve after removal of pressure load, but a minority have significant ongoing elevation of E/E’ and evidence of persistent diastolic dysfunction. Factors associated with ongoing elevation of E/E’ are higher pre- and post-BAVP LV mass and higher E/E’ before BAVP. Additionally, this study describes LV remodeling after BAVP, which is characterized primarily by an increase in LV EDV and decrease in LV mass:volume without a change in LV mass.

Our results agree with previous studies showing diastolic dysfunction in children with left heart obstructive lesions. Lam et al. reported on 23 patients with congenital AS and showed that they have more echocardiographic evidence of diastolic dysfunction and elevated LVEDP than patients with aortic coarctation or control subjects. de Kort et al reported echocardiographic diastolic function data on 9 children before and shortly after BAVP (1–4 days after catheterization), using TDI and strain imaging, and showed that values

---

**Table 3. Echocardiographic Data**

<table>
<thead>
<tr>
<th>Anatomic variables</th>
<th>Pre-BAVP</th>
<th>Post-BAVP</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>89 (±42)</td>
<td>113 (±44)</td>
<td>0.004</td>
</tr>
<tr>
<td>LV end-diastolic volume z-score</td>
<td>-0.1 (±1.6)</td>
<td>0.9 (±1.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>106 (±48)</td>
<td>113 (±51)</td>
<td>0.24</td>
</tr>
<tr>
<td>LV mass z-score</td>
<td>1.7 (±1.4)</td>
<td>1.8 (±1.9)</td>
<td>0.82</td>
</tr>
<tr>
<td>LV mass:volume</td>
<td>1.3 (±0.3)</td>
<td>1.0 (±0.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>LV mass:volume z-score</td>
<td>2.4 (±2.2)</td>
<td>1.0 (±1.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>70 (±6)</td>
<td>65 (±5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak aortic stenosis gradient, mm Hg</td>
<td>64 (±15)</td>
<td>37 (±8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic regurgitation grade*</td>
<td>2 (0–2.5)</td>
<td>2.5 (1–4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Diastolic parameters

| Mitral inflow E:A | 2.2 (±0.7) | 2.1 (±0.9) | 0.53 |
| Mitral inflow E:A z-score | 0.1 (±1.1) | -0.2 (±1.4) | 0.47 |
| Abnormal mitral inflow E:A | 2 (8%) | 2 (8%) | 0.99 |
| Mitral inflow E-wave decel time, ms | 136 (±26) | 141 (±44) | 0.68 |
| Mitral inflow E-wave decel time z-score | -0.3 (±0.8) | -0.3 (±1.2) | 0.90 |
| Mitral annular E’, cm/s | 12.1 (±2.4) | 14.3 (±2.6) | 0.004 |
| Mitral annular E’ z-score | -2.1 (±0.8) | -1.3 (±1.0) | 0.006 |
| Septal E’, cm/s | 8.4 (±1.6) | 10.0 (±1.9) | <0.001 |
| Septal E’ z-score | -2.4 (±0.8) | -1.6 (±1.0) | 0.001 |
| E/E’ | 14.2 (±4.9) | 10.8 (±3.4) | <0.001 |
| Left atrial volume, mL/m² | 19 (±7) | 20 (±6) | 0.37 |
| LV sphericity index | 0.66 (±0.09) | 0.69 (±0.07) | 0.17 |
| VCFc, circ - s⁻¹ | 1.25 (±0.17) | 1.12 (±0.11) | 0.008 |
| End-systolic stress, g/cm² | 31 (±13.3) | 40 (±8) | 0.001 |

BAVP indicates balloon aortic valvuloplasty; LV, left ventricle; E, early diastolic pulsed Doppler mitral inflow velocity; A, late diastolic pulsed Doppler mitral inflow velocity; decel, deceleration; E’, early diastolic tissue Doppler velocity; and VCFc, heart rate–corrected velocity of circumferential fiber shortening.

Values are expressed as mean (±SD).

* Aortic regurgitation ordinal grading system: 0=none, 1=trivial, 2=mild, 3=moderate, 4=severe.
improved after BAVP in most cases. Unique from previous studies, this study examines diastolic function over a longer follow-up period (6–24 months), which allows for LV remodeling to occur after BAVP. Additionally, we are able to identify factors associated with persistent diastolic dysfunction after BAVP.

Despite low residual AS gradients in the vast majority of patients, LV mass did not change after BAVP. Yet, diastolic function and E/E’ improve, suggesting the hypertrophy alone is not entirely responsible for diastolic dysfunction in this population. In addition to ventricular hypertrophy, possible mechanisms for diastolic dysfunction in this population include impaired active relaxation due to alterations in calcium handling24–26 and myocardial fibrosis6,7,12,27,28 secondary to chronic pressure load.

Despite substantial relief of LV pressure load in all patients, 20% of patients continued to have echocardiographic evidence of impaired diastolic function and elevated left atrial pressure. The association between higher pre- and post-BAVP LV mass z-score and higher post-BAVP E/E’ suggests that there may be a subset of patients in whom longer duration of LV pressure load has lead to myocardial changes, including hypertrophy and myocardial fibrosis,13,29,30 as well as alterations in active relaxation24–26 that are less reversible. Future studies are needed to identify mechanisms of impaired diastolic function in this population more precisely and to determine their reversibility.31 Severe, and in some cases, irreversible diastolic heart failure, has been described in a small number of patients with congenital AS who underwent BAVP as infants.32 As patients who have undergone BAVP as children are now increasing reaching their 3rd and 4th decades of life, long-term clinical follow-up will establish how many of these patients have persistent diastolic dysfunction and if these abnormalities will lead to development of symptoms of diastolic heart failure or decreased exercise capacity. Current approaches to the timing of BAVP and effectiveness of therapy have focused primarily systolic function and on the degree of AS and AR.31 A future approach using not only the degree of aortic valve disease and systolic function but also diastolic function, particularly signs of less reversible changes and evidence of myocardial fibrosis, in timing of intervention may improve management.

Limitations of this study include the retrospective design and small cohort size, which may limit ability to identify all factors associated with changes in diastolic function after BAVP. The retrospective nature of the study resulted in variable post-BAVP follow-up periods with range of 6 to 24 months. Patients under 3 years of age were excluded due to the wide variability in the quality and reproducibility of diastolic function measures in this age range and lack of normative data in infants and young children. Follow-up LVEDP was estimated as elevated or normal using E/E’ ≥12 rather than measured invasively, because few patients in this cohort had repeat catheterizations within this time frame. Last, although degree of post-BAVP AR grade did not have an influence on diastolic function in this cohort, the study design and small cohort patients did not allow us to definitively determine the effect of AR and mixed aortic valve disease on diastolic function.

Conclusions
After BAVP, LV remodeling characterized by an increase in LV EDV and decrease in LV mass:volume occurs and echocardiographic measures of diastolic function and LVEDP improve in the majority of patients. Risk factors for persistently elevated E/E’ after BAVP include higher LV mass z-score and higher pre-BAVP E/E’.

Sources of Funding
This study was supported by the Hinden Family Foundation. Dr Friedman is supported by an NIH training grant (T32 HL 007572–28).

Disclosures
None.

References
7. Piper C, Schultheiss HP, Akdemir D, Rudolf J, Horstkotte D, Pauschinger M. Remodeling of the cardiac extracellular matrix differs between...


Left Ventricular Remodeling and Improvement in Diastolic Function After Balloon Aortic Valvuloplasty for Congenital Aortic Stenosis

Kevin G. Friedman, Doff B. McElhinney, Steven D. Colan, Diego Porras, Andrew J. Powell, James E. Lock and David W. Brown

_Circ Cardiovasc Interv_. published online June 26, 2012;
_Circulation: Cardiovascular Interventions_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/early/2012/06/26/CIRCINTERVENTIONS.112.968958

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Interventions_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Interventions_ is online at:
http://circinterventions.ahajournals.org//subscriptions/