Spontaneous Regression of Left Ventricular Dilation in Children with Restrictive Ventricular Septal Defects

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Objectives To test the hypothesis that left ventricular (LV) dilation associated with pressure-restrictive ventricular septal defect (VSD) often remains stable or regresses spontaneously, calling into question the role of interventional management for such defects.

Study design We analyzed 96 serial echocardiograms from 33 unoperated patients with a moderate-to-large VSD with LV dilation (LV end-diastolic dimension [LVED] z score >2.0) at enrollment who were followed for more than 2 years. Records of 125 surgical patients also were reviewed. Patients were evaluated for evidence of persistent or progressive LV dilation; signs or symptoms of congestive heart failure (CHF), failure to thrive (FTT), or pulmonary hypertension (PAH); as well as acquired ventricular outflow obstruction or aortic regurgitation. LVED z scores at enrollment versus latest follow-up were compared using paired t tests. A random-effects model with random intercept and slope was fitted to account for repeated observations for each patient.

Results Mean age at enrollment was 4.6 ± 3.2 years, and mean follow-up was 7.8 ± 4 years (range, 2.8 to 22 years), during which mean LVED z score decreased from 3.0 ± 0.6 to 1.2 ± 1.3 ($P < .01$). LVED z score decreased in 29 of the 33 patients, and decreased to <2 in 26 of these 29 (79%).

Conclusions Most patients with pressure-restrictive VSD with moderate-to-severe LV dilation without CHF, FTT, or PAH will experience spontaneous resolution of LV dilation and can avoid cardiac surgery or catheter-based intervention. *(J Pediatr 2007;150:583-6)*

Ventricular septal defect (VSD) is the most common congenital cardiac malformation.[1] Large, unrestrictive VSD(s) associated with congestive heart failure (CHF) and failure to thrive (FTT), not responsive to anticongestive therapy during early infancy, require surgery. Patients with unrestrictive VSD with associated pulmonary hypertension (PAH) need surgery within the first 2 years of life to avoid irreversible pulmonary vascular disease.[2,3]

The natural history of VSD may follow various pathways,[4] including spontaneous decrease in defect size or the development of a right ventricular (RV) or LV outflow tract obstruction, pulmonary vascular obstructive disease, aortic regurgitation, or bacterial endocarditis. Most VSDs are small and pressure-restrictive and are asymptomatic during infancy. Even with large defects, initially manifesting with significant left-to-right shunts and symptoms of CHF, subsequent spontaneous decrease in defect size may result in decreased shunting, remission of symptoms, and pressure restriction that protects the pulmonary vascular bed from significant hypertension.[5,6]

Most centers reserve intervention for large defects, but in some centers surgery may be recommended for even relatively small and pressure-restrictive defects, with the rationale of avoiding late progressive LV dysfunction secondary to chronic ventricular dilation, despite the absence of PAH.[7,8] Prevention of aortic valve prolapse and prevention of bacterial endocarditis are cited as additional reasons for closing small defects. The recent introduction of investigational implantable devices for VSD closure has raised the possibility that size criteria for intervention for VSD will be further relaxed as perceived risks associated with defect closure decrease.[9]

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CHB	Complete heart block	NHS-II	Natural History Study of Congenital Heart Disease-II
CHF	Congestive heart failure		
FTT	Failure to thrive	PAH	Pulmonary hypertension
LV	Left ventricular	RV	Right ventricular
LVED	Left ventricular end-diastolic dimension	VSD	Ventricular septal defect

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Based on extensive clinical experience with children and young adults with VSD, we hypothesized that LV dilation associated with pressure-restrictive VSD and no symptoms or evidence of PAH often remains stable or spontaneously regresses, calling into question the interventional management strategies for such defects.

METHODS

Echocardiographic and clinical databases of the Division of Pediatric Cardiology, Morgan Stanley Children's Hospital and the Weill-Cornell Children's Hospital of New York-Presbyterian Hospital were searched for patients with a diagnosis of moderate to large perimembranous and/or muscular VSD with LV dilation, defined as an LV end-diastolic dimension (LVED) *z* score ≥2.0 at the time of enrollment, who had serial clinical and echocardiographic follow-up for more than 2 years. Exclusion criteria included: clinical evidence of CHF, FTT, PAH (estimated systolic pressure in the main pulmonary artery ≥30 mm Hg, based on measurement of systemic blood pressure and continuous wave Doppler estimation of peak instantaneous systolic pressure difference across the VSD and/or continuous wave Doppler estimation of peak instantaneous systolic pressure difference between the right ventricle and right atrium. The latter is calculated from the velocity of a detectable jet of tricuspid regurgitation), RV or LV outflow tract obstruction, aortic valve prolapse or insufficiency at the time of enrollment, coarctation of the aorta, and atrioventricular canal type, doubly committed subarterial, or malalignment conoventricular VSD.

Serial measurements of ventricular dimensions, systolic performance, and estimated RV and pulmonary arterial systolic pressure, along with surveillance for the development of aortic regurgitation and/or ventricular outflow tract obstruction, were reviewed retrospectively from the echocardiographic and clinical records. Ventricular dimensions and systolic shortening were assessed using m-mode echocardiography. In this study, VSD diameters were not assessed and Doppler estimates of Qp/Qs were not obtained. Doppler waveforms of LV and RV diastolic filling were recorded on all echocardiographic studies.

The LVED *z* scores at the time of enrollment and at the time of most recent follow-up were compared using paired *t* tests. A random-effects model with random intercept and slope was fitted to the data to account for repeated observations from each patient.

RESULTS

A total of 82 patients with restrictive VSD and LVED > 1 standard deviation above the mean for body surface area, without evidence of CHF, PAH, or FTT, were identified between 1993 and 2003. Twelve of these patients underwent cardiac surgery without longitudinal follow-up. In addition, during this time period, another 113 patients underwent surgical repair of VSD due to unrestrictive defects with CHF or FTT. A total of 70 patients with restrictive VSD and LVED > 1 standard deviation above the mean were followed longitudinally; 58 of these patients had an isolated perimembranous defect. Ten patients had a muscular VSD, and 2 patients had a perimembranous VSD with accessory muscular defects. No patient in the series underwent complete spontaneous complete closure of the defect during the course of follow-up. In addition, no patient developed clinically detectable subpulmonary or subaortic stenosis during follow-up, and no patient developed clinically significant aortic regurgitation or aortic valve prolapse. One patient was successfully treated for *Streptococcus viridans* subacute bacterial endocarditis, without sequelae. No patient had segmental LV wall dysfunction on 2-dimensional imaging, and all patients maintained normal LV shortening fractions throughout follow-up.

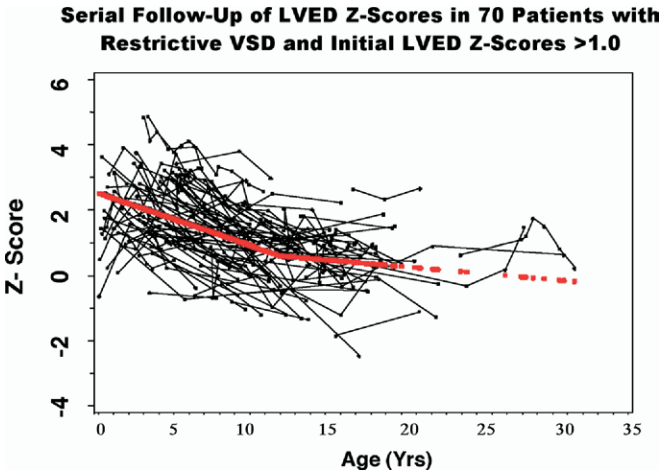

Figure 1. A random-effects model with random intercept and slope was fitted to the data to account for the repeated observations from each individual. Based on the graphical display, a linear decline in LVED dimension *z* score, with an inflection at age 12 years, was observed. Age 12 years was close to the 3rd quartile of age. The estimated rate of decline in *z* score was 0.16 per year (95% confidence interval [CI] = 0.13, 0.19). After age 12, the rate of decline in *z* score decreased by 0.12 per year (95% CI = 0.06, 0.18) per year, resulting in a decline of 0.04 per year. Therefore, we can conclude that *z* score declined with age and that the rate of decline before age 12 differed from that after this age ($P < .001$).

Of the 70 patients with LVED *z* score >1.0, the mean age at the time of enrollment was 4.9 ± 3.9 years, with a mean period of follow-up of 7.3 ± 4.2 years. LVED *z* scores for this entire population decreased significantly over the study period, at a rate of decline of 0.16/year until age 12, when the rate of decline changed to 0.04/year (Figure 1). LVED dimension was >2 standard deviations above the mean ($z > 2.0$) in 33 of the 70 subjects at the time of initial examination. The mean follow-up period for this subgroup of subjects was 7.8 ± 4 years (range, 2.8 to 22 years), during which there was a significant decrease in LVED *z* score, from 3.0 ± 0.6 to 1.2 ± 1.3 ($P < .01$). Two of these patients had an increased LVED *z* score and 2 patients had an unchanged LVED *z* score during the course of follow-up; the remaining 29 patients experienced a spontaneous decrease in LVED *z* score (Figure 2). Seven of the 33 patients (21%) had an LVED z score ≥2.0 at the time of the most recent follow-up. Similarly, of the 37 patients initially presenting with LVED

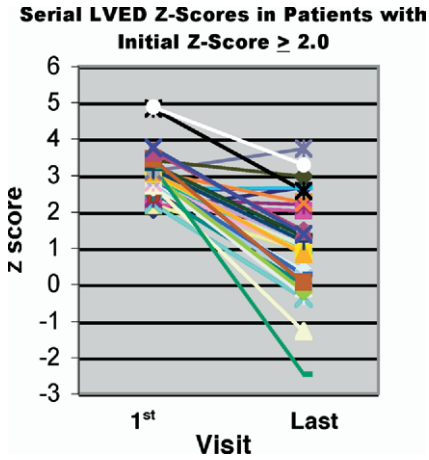

Figure 2. LVED at the first evaluation versus the most recent evaluation for subgroup of 33 patients with LVED z score >2.0 at enrollment. The mean follow-up for this subgroup of subjects was 7.8 ± 4 years (range, 2.8 to 22 years), during which there was a significant decrease in LVED z score, from 3.0 ± 0.6 to 1.2 ± 1.3 ($P < .01$). Two patients demonstrated increased LVED z score over the course of follow-up.

z score of 1 to 2, 2 had an increased LVED z score, 1 had no change in LVED z score, and 34 had a decreased LVED z score over the course of follow-up. LV shortening fraction was normal in all patients at the time of enrollment (38.4% ± 2.7%) and remained normal at the time of most recent evaluation (37.8% ± 3.7%) (P = not significant). Similarly, LV diastolic performance, judged on the basis of E/A ratios calculated from transmitral pulsed Doppler transmitral waveform, was normal (E/A > 1) on all of the echocardiograms reviewed at enrollment and at final follow-up during the study period. Doppler tissue imaging velocities were not routinely measured during the study period.

DISCUSSION

This study demonstrates that the great majority of patients with a moderately large VSD and a volume-overloaded left ventricle without PAH, clinical evidence of CHF, or FTT remain clinically stable and experience a progressive spontaneous decrease in LVED. LV dilation was resolved without intervention in 79% of patients with dilation secondary to restrictive VSD without PAH, CHF, or FTT. Although 12 patients underwent surgery for isolated findings of VSD and LV dilation, without serial follow-up, we were unable to define specific findings predictive of whether these patients would have experienced a spontaneous decrease in the degree of LV dilation. The rare patient who presents with isolated membranous VSD and LV dilation with serial follow-up over 2 years or longer demonstrating progressive LV dilation should be considered for surgery.

Although some observers have suggested that patients with LV dilation risk progressive diminution of systolic performance, the incidence of this problem has not been defined. Kertesz et al[10] investigated LV dilation in children with complete heart block (CHB) and found that LVED stress was normal, even though shortening fraction and velocity of circumferential fiber shortening were increased. They were unable to demonstrate a change over time in LV mass, volume, geometry, loading conditions, or systolic function. They did not find an association between LV dilation and deterioration in pump function. LVED stress analysis was not routine in our laboratory during the time frame of our study.

The Natural History Study-II (NHS-II) demonstrated a 30-year survival of 87% in patients with VSD.[11] The most powerful predictor of survival was the severity of symptoms at the time of enrollment. More than 94% of patients presenting with trivial to moderate defects were in New York Heart Association class I at 20- to 30-year follow-up. The life expectancy of this group of patients was the same as that of age-matched normal controls.

Although data from NHS-II demonstrated that surgery for VSD decreases risk of bacterial endocarditis (to 7.3 cases per 10,000 patient-years from 18.7 per 10,000 patient-years), the risk is not completely eliminated.[12] Similarly, surgical repair of VSD does not resolve the risk of aortic regurgitation or ventricular outflow obstruction in postoperative patients.[13] Careful surveillance for aortic valve prolapse should obviate the potential for severe cryptogenic aortic regurgitation among these patients. The potential for aortic insufficiency is not a rationale for closing all VSDs, regardless of size or position.

No series of patients with restrictive VSDs has demonstrated late CHF in middle age or beyond. Neumayer et al[14] reviewed a series of adult patients with small VSDs and found that although most patients remained asymptomatic, ~25% developed significant complications, including bacterial endocarditis, aortic regurgitation, and acquired arrhythmias. It should be emphasized that this group did not did not consist exclusively of patients with restrictive VSDs. Patients with pulmonary pressures up to 40 mm Hg were included. Such patients normally would have undergoned surgical closure at an early age and were not considered in our study. In addition, more than 25% of the patients in this study had additional cardiovascular lesions, which may have contributed to their late problems. Aortic regurgitation developed in 37 patients, 12 of whom had congenitally abnormal valves, although others had VSDs that were in a position below the aortic valve that predisposed them to this problem. Several of their patients had coarctation of the aorta, which involves an entirely different approach and prognosis. Some had rhythm disturbances that may not have been attributable to VSD, and others had cardiomyopathies not necessarily related to VSD. We do not consider this study to present compelling evidence for recommending the closure of uncomplicated restrictive perimembranous VSD, because such patients were not analyzed separately.

Surgical closure of VSD is associated with a risk of late rhythm disturbances, including heart block.[15-17] Moeller et al[16] described several patients who suffered late, sudden, unexpected death, presumably from arrhythmia post surgical repair. The risk of CHB associated with catheter-based device treatment of perimembranous VSD has not yet been fully

defined; however, initial experience has found this complication in some cases (K. Lock, AGA Medical, personal communication). On the basis of these early reports and other potential complications, the criteria for device closure of restrictive perimembranous VSD must be strictly defined in order to avoid unnecessary interventions. Given the expectation of naturally decreasing defect size and the long life expectancy of this group of patients, the risk of CHB is disconcerting. We believe that evidence-based management dictates that asymptomatic patients with pressure-restrictive VSD be followed clinically, without being subjected to the early or late risks, discomfort, and psychological and financial costs of cardiac surgery or therapeutic catheterization.

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