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Doppler Echocardiographic Assessment of Impaired Left Ventricular Filling in Patients With Right Ventricular Pressure Overload Due to Primary Pulmonary Hypertension

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In patients with primary pulmonary hypertension, competition between the right and left ventricles for the limited pericardial space results in distortion of left ventricular geometry reflected in displacement of the ventricular septum toward the left ventricular cavity. Left ventricular shape is most dramatically deranged at end-systole and early diastole, suggesting the possibility that the distribution of left ventricular diastolic filling might be altered. To investigate this hypothesis, nine patients with primary pulmonary hypertension and nine normal individuals were studied with echocardiographic techniques. Left ventricular isovolumic relaxation time was significantly prolonged in patients with primary pulmonary hypertension by comparison with normal individuals (129 ± 36 versus 53 ± 9 ms, $p < 0.005$) and the fraction of the transmitral flow velocity integral occurring in the first half of diastole was significantly less than in normal individuals (38 ± 14% versus 70 ± 9%, $p < 0.005$). Measurement of fractional changes in short-axis left ventricular cavity area similarly demonstrated that in patients with primary pulmonary hypertension fractional early diastolic cavity expansion (32 ± 11%) was significantly less than in normal individuals (78 ± 9%, $p < 0.005$).

In patients with primary pulmonary hypertension, the ventricular septum was abnormally flattened toward the left ventricular cavity at end-systole (normalized septal curvature 0.04 ± 0.19) and remained that way throughout early diastolic filling but returned toward normal at end-diastole (normalized septal curvature 0.68 ± 0.19, $p < 0.005$). Thus, in patients with primary pulmonary hypertension end-systolic and early diastolic deformation of the left ventricle by septal flattening toward the left ventricular cavity is associated with relative underfilling of the left ventricle in early diastole and redistribution of left ventricular filling into late diastole. The reliance on late diastolic filling and atrial systole to maintain left ventricular preload in primary pulmonary hypertension may have important implications for the use of vasodilators in this disease.

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Distortion of the left ventricular cavity by leftward displacement of the ventricular septum has been studied in a variety of conditions associated with right ventricular pressure overload (1–7) and volume overload (8–12). Attention has focused on the transseptal pressure gradient as an important hemodynamic determinant of this abnormal septal configuration (4,5,11,12). Recently, we and others (13) studying patients with right ventricular pressure overload have noted abnormal transmitral flow velocity profiles in these patients, suggesting that left ventricular filling dynamics may be influenced by the altered left ventricular geometry.

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Patients with primary pulmonary hypertension offer the unique opportunity to study left ventricular filling dynamics in a cohort of individuals with marked right ventricular pressure overload and an intrinsically normal left ventricle. Accordingly, we undertook this study to characterize the abnormalities in left ventricular filling dynamics in primary pulmonary hypertension and to investigate their relation to the geometric distortion of the left ventricle seen in this disease. Because vasodilator therapy, which is employed in this disease (14–16), can profoundly influence left ventricular preload, an awareness and an understanding of the abnormalities in left ventricular filling dynamics in this disease may have particular clinical significance.

Methods

Study group. Nine patients (aged 13 to 55 years, mean 38 ± 15) with unexplained pulmonary hypertension under-

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went a thorough evaluation to exclude secondary causes of pulmonary hypertension (14,15). No patient had clinical evidence for left ventricular or coronary artery disease. While taking no cardiac medications, these nine patients underwent right heart catheterization to characterize their hemodynamic status (Table 1) within 24 hours of their Doppler echocardiographic examination. Nine normal individuals (aged 16 to 60 years, mean 36 ± 12) without evidence for myocardial or valvular disease by pulsed Doppler or two-dimensional echocardiography served as control subjects.

Pulsed Doppler and echocardiographic examinations. *Echocardiography.* Two-dimensional echocardiograms from standard left parasternal and apical windows, derived M-mode echocardiograms and pulsed Doppler recordings were obtained using a Diasonics CV 400 sector scanner interfaced with a 3.5 MHz mechanical transducer while the subjects had sinus rhythm and were breathing quietly in the left lateral recumbent position. Short-axis two-dimensional echocardiographic images of the left ventricular cavity at the level of the mitral leaflet tips were obtained by angling the transducer from base to apex so that mitral leaflet excursion was maximized and further apical angulation resulted in disappearance of the mitral leaflets. Symmetry of the medial and lateral aspects of the mitral leaflets was required to ensure that the imaging plane was orthogonal to the long axis of the left ventricle. All studies were recorded on 0.5 inch (1.27 cm) videotape for subsequent real-time playback or stop-frame analysis. Stop-frame images during the cardiac cycle were selected for analysis based on the position of the mitral leaflet tips and identified as follows: 1) End-systole: the frame just before mitral valve opening; 2) end of early diastolic filling: the frame in which mitral leaflets drift back to a midposition after their initial opening excursion; and 3) end-diastole: the frame in which mitral leaflets close after their reopening with atrial systole.

Left ventricular cavity area was determined by tracing the internal interface of the left ventricular endocardium with the blood pool using a digitizing video screen interfaced with a computerized graphics analyzer (Digisonics) and the internally generated calibrations displayed on the echocardiogram.

Table 1. Hemodynamic Profile of Patients With Primary Pulmonary Hypertension

	Average	Range
Mean pulmonary artery pressure (mm Hg)	61 ± 20	46 to 115
Mean right atrial pressure (mm Hg)	5 ± 5	1 to 17
Cardiac output (liters/min)	3.1 ± 0.5	2.4 to 4.2
Pulmonary vascular resistance (Wood units)	18 ± 8	13 to 38
Mean pulmonary capillary wedge pressure (mm Hg)	9 ± 4	1 to 12

The aortic and mitral valve excursions were recorded by M-mode echocardiography simultaneously with limb lead II of the electrocardiogram at a sweep speed of 50 mm/s. The difference between the time from the onset of the QRS complex to the opening of the mitral valve and the time from the onset of the QRS complex to the closure of the aortic valve (representing the interval between aortic valve closure and mitral valve opening) divided by the square root of the cycle length was computed as the rate-corrected isovolumic relaxation time.

Pulsed Doppler echocardiography. Sampling for pulsed Doppler measurements was performed with a cursor positioned within the 80° two-dimensional sector scan at varying range gates to a maximal depth of 16 cm with a sample volume length of 4.1 mm. Doppler output (filtered with a 400 Hz high pass filter) produced an audio signal as well as a spectral display derived by fast Fourier transform analysis. To record transmitral inflow the transducer was positioned in the apical window to obtain a standard four chamber view of the heart with clear visualization of the ventricular apex, mitral leaflet excursions and left atrium. The pulsed Doppler cursor was aligned parallel to the long axis of the left ventricle, running from the ventricular apex to the midpoint of the mitral orifice, and the sample volume was positioned at or just distal to the mitral anulus. Minor adjustments of transducer angulation were permitted to ensure that the interrogating Doppler beam was parallel to mitral inflow. Such optimal positioning of the Doppler beam was considered to have been achieved when 1) a relatively pure tone audio signal was appreciated, 2) a reproducible display of the flow velocity envelope with minimal (<0.5 kHz maximal width) spectral broadening could be recorded, and 3) maximal peak flow velocities were obtained. No correction was attempted for the angle between the Doppler cursor and the apparent direction of mitral inflow and in all cases that angle was estimated to be less than 20°. In no subject did the recorded Doppler frequency shifts exceed the Nyquist limit for the range gate utilized to record mitral inflow. The transmitral flow velocity profiles were recorded with a simultaneous limb lead II electrocardiogram at 50 mm/s. The transverse diameter of the mitral anulus measured from its lateral and medial inner edges just proximal to the insertion of the mitral leaflets was obtained from the same four chamber echocardiographic image of the heart at the times of maximal mitral leaflet excursion in early and late diastole. Assuming circular geometry of the mitral anulus the cross-sectional area could thus be derived as $\pi \times (\text{diameter}/2)^2$.

Measurements and calculations. Change in short-axis left ventricular cavity area during *early* diastolic filling (ΔE) was calculated from the difference between short-axis cavity area at the end of early diastolic filling and end-systole. Change in cavity area over the *late* diastolic filling period (ΔA) was calculated from the difference between cavity area

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at end-diastole and at the end of early diastolic filling. The fractional change in left ventricular cavity area during early diastolic filling was calculated as the ratio $\Delta E/(\Delta E + \Delta A)$, and the fractional change in left ventricular cavity area during late diastolic filling was calculated as $\Delta A/(\Delta E + \Delta A)$.

The degree of distortion of the ventricular septum was quantified by measuring its radius of curvature (5,10) from the short-axis images of the left ventricular cavity at the level of the mitral leaflet tips. The shape of the septum at this level was found to be characteristic of its shape along its entire length by examining serial short-axis planes at more caudad and cephalad levels. After tracing the internal left ventricular endocardial interface of the ventricular septum, two chords subtending different parts of the arc were constructed and perpendicular bisectors of these chords erected. The intersection of these perpendicular bisectors defined the center of curvature of the septal arc and the distance from this point to the arc defined the septal radius of curvature (R). When septal curvature was convex with respect to the left ventricular cavity its radius of curvature was determined relative to a center of curvature in the right ventricle and assigned a negative value. An idealized radius of curvature (R_i), normalized for left ventricular cavity area, was computed assuming idealized cavity area to be perfectly circular; thus $R_i = (\text{cavity area}/\pi)^{1/2}$. In order to arrive at an index of septal distortion and left ventricular deformation that varied as a continuous variable passing through zero rather than infinity, normalized septal curvature (R_i/R) was calculated (5). Values approaching unity represent a nearly circular left ventricular short-axis profile, whereas values approaching zero represent flattening of the ventricular septum toward the left ventricular cavity. Negative values represent increasing degrees of reversal of septal curvature with the ventricular septum appearing convex with respect to the left ventricular cavity.

Measurements from the Doppler flow velocity profile (17,18) of transmitral flow were made with the aid of a digitizing tablet interfaced with a computerized graphics analyzer and the internally generated calibrations provided with the Doppler spectra which are solved for velocity. Peak velocities in early and late diastole were determined from the midpoint of the Doppler spectral envelope at the times of maximal Doppler shift in early and late diastole, respectively. Peak filling rate in early diastole was calculated as the product of peak velocity of transmitral flow in early diastole and mitral anular area at the time of maximal mitral leaflet opening in early diastole (18). Peak filling rate in late diastole was calculated as the product of peak velocity of transmitral flow in late diastole and mitral anular area at the time of maximal mitral leaflet opening in late diastole.

Quantitative determination of the distribution of flow velocity within the diastolic filling period was obtained by tracing a continuous line through the midpoint of the gray scale spectral display (approximating instantaneous modal velocity) of the transmitral flow velocity profile and determining the integral of the profile. Taking the time interval from the beginning to the end of the transmitral flow velocity profile as the diastolic filling period, measurements of the fraction of the flow velocity integral falling within the first and second halves of the diastolic filling period were determined.

Statistical methods. Where appropriate, the data were analyzed with the Student's paired or unpaired *t* test. If comparisons among multiple groups were required the significance level was adjusted according to the Bonferroni method (19), a probability value of less than 0.05 being considered statistically significant. Linear regression analysis by the least squares method was also employed. Values are reported as the mean ± 1 SD.

Results

Transmitral flow velocity profiles (Fig. 1). *In the nine normal individuals*, left ventricular isovolumic relaxation time ranged from 41 to 70 ms (mean 53 ± 9). After opening of the mitral valve, the Doppler-derived transmitral flow velocity waveform was characterized by peak flow velocities in early diastole (during rapid diastolic filling) of 62 ± 10 cm/s (range 45 to 80) and peak flow velocities in late diastole (during atrial systole) of 39 ± 13 cm/s (range 18 to 57). In each subject peak flow velocities in late diastole were less than those in early diastole resulting in a ratio of late to early diastolic peak flow velocities of 0.6 ± 0.2 (range 0.4 to 0.9). In each subject the majority of transmitral flow velocity fell within the first half of the diastolic filling period; hence, the fraction of the flow-velocity integral occurring in the first half of the diastolic filling period ranged from 0.52 to 0.86 (mean 0.70 ± 0.09).

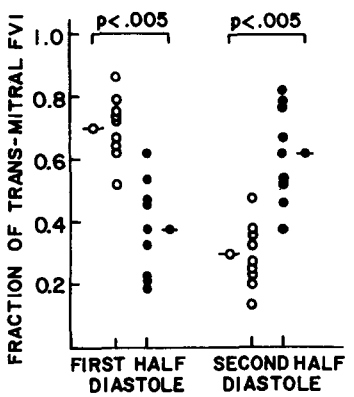


Figure 1. Distribution of the transmitral flow-velocity integral (FVI) within the first and second halves of diastole. Patients with primary pulmonary hypertension (**solid circles**) have a significantly lower fraction of total diastolic filling occurring in the first half of diastole by comparison with normal individuals (**open circles**) in whom the major portion of left ventricular filling occurs in early diastole.

By contrast, in the nine patients with primary pulmonary hypertension, rate-corrected left ventricular isovolumic relaxation time was significantly prolonged when compared with the value in normal subjects, ranging from 58 to 181 ms (mean 129 ± 36, $p < 0.005$). After isovolumic relaxation, transmitral flow velocity waveforms were characterized by peak flow velocities in early diastole of 27 ± 11 cm/s (range 12 to 44) and peak flow velocities in late diastole of 47 ± 15 cm/s (range 20 to 70). The ratio of late to early diastolic peak flow velocities in these nine patients was 2.1 ± 1.0 (range 0.8 to 3.9), which was significantly higher than the value in the normal subjects ($p < 0.005$). Similarly, the fraction of the flow velocity integral falling in the first half of the diastolic filling period (0.38 ± 0.14, range 0.19 to 0.62) was significantly less in patients with primary pulmonary hypertension than in normal subjects ($p < 0.005$).

Early and late peak diastolic filling rates (Fig. 2). Doppler-derived peak diastolic filling rates provided further evidence for impaired early diastolic filling and redistribution of left ventricular filling into late diastole in patients with primary pulmonary hypertension. In the nine normal subjects peak filling rates during late diastolic filling (155 ± 69 ml/s, range 60 to 264) were less than peak filling rates during early diastolic filling (219 ± 83 ml/s, range 140 to 405), resulting in a ratio of late to early diastolic peak filling rates of 0.7 ± 0.2 (range 0.3 to 1.0). By contrast, in the nine patients with primary pulmonary hypertension, peak filling rates in late diastole (125 ± 65 ml/s, range 42 to 224) were generally greater than peak filling rates in early diastole (70 ± 36 ml/s, range 29 to 144). The resultant ratio of late to early diastolic peak filling rates in patients with primary pulmonary hypertension (2.2 ± 1.4, range 0.5 to 5.2) was significantly greater ($p < 0.01$) than that for normal individuals.

Fractional changes in left ventricular cavity area (Fig. 3). Analysis of the fractional change in short-axis left ventricular cavity area during diastole provided a measure of relative left ventricular filling in early and late diastole independent of the analysis of Doppler derived flow velocity waveforms. Whereas in normal subjects the fractional increase in left ventricular cavity area attributable to early diastolic filling was 0.78 ± 0.09 (range 0.67 to 0.96), in patients with primary pulmonary hypertension the early diastolic fractional increase in left ventricular cavity area was significantly less, 0.32 ± 0.11 (range 0.12 to 0.45, $p < 0.005$). Thus, in contrast to normal individuals, patients with primary pulmonary hypertension showed a reduced proportion of total left ventricular diastolic cavity expansion occurring in early diastole with a reciprocal increase in the proportion of left ventricular cavity expansion occurring in late diastole.

Time course of distortion in ventricular septal geometry (Fig. 4 and 5). The temporal distribution of left ventricular filling during diastole was related to the changes in ventricular septal geometry by measuring normalized septal curvature (Fig.4). At end-systole the ventricular septum

Figure 2. Peak left ventricular filling rates (PFR) in early and late diastole. **A,** Patients with primary pulmonary hypertension (PPH) show higher peak filling rates in late diastole than in early diastole, which is an inversion of the relation found in normal individuals. **B,** The ratio of late to early peak diastolic filling rates is significantly greater in patients with primary pulmonary hypertension than in normal individuals, reflecting the redistribution of ventricular filling to late diastole in patients with primary pulmonary hypertension.

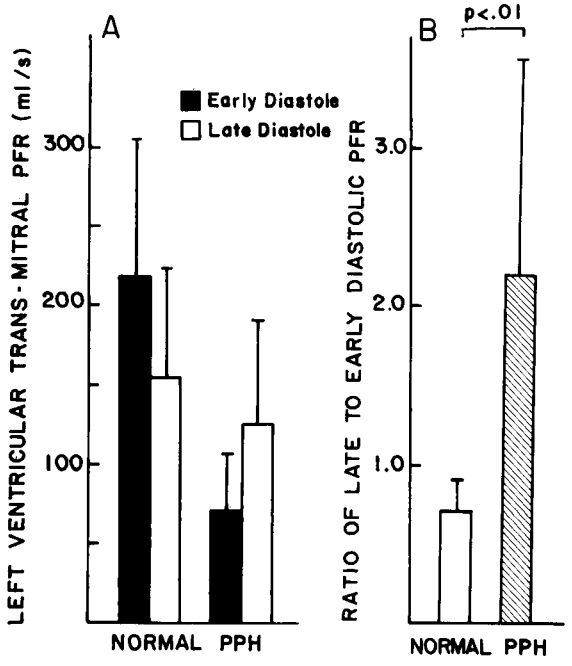
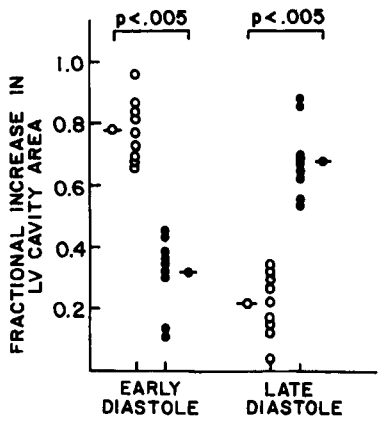


Figure 3. Fractional increases in left ventricular (LV) cavity area during early and late diastole. Patients with primary pulmonary hypertension (**solid circles**) exhibit significantly greater late diastolic fractional increases in left ventricular cavity area when compared with normal individuals (**open circles**). Whereas in normal individuals the major increase in cavity area occurs in early diastole, in patients with primary pulmonary hypertension late diastolic cavity expansion exceeds early diastolic cavity expansion.



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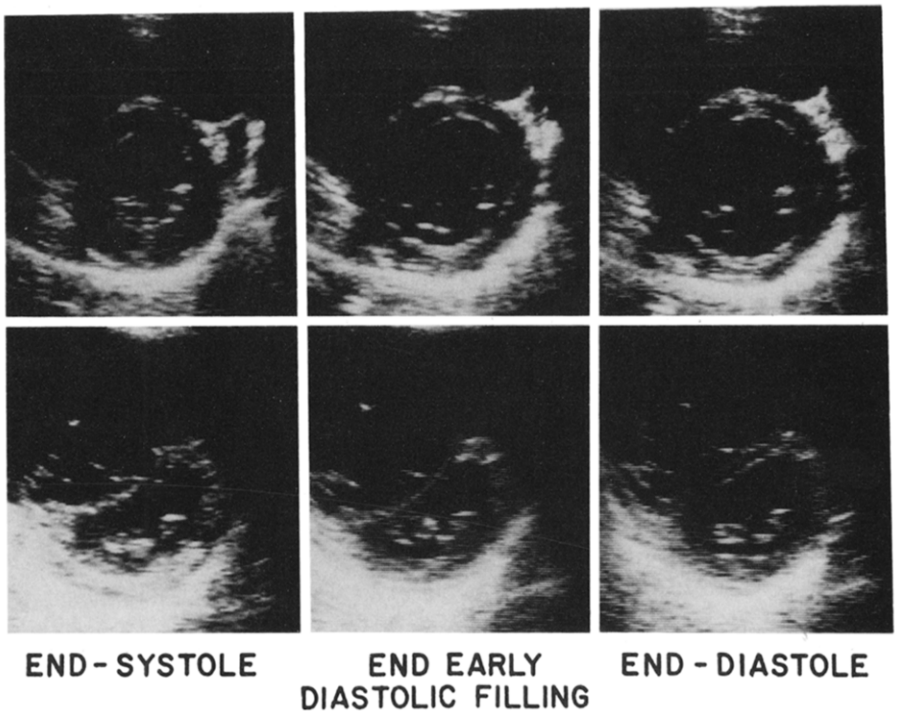


Figure 4. Stop-frames of two-dimensional echocardiograms obtained in the short-axis plane at the level of the tips of the mitral valve leaflets in a normal individual (**upper panels**) and in a patient with primary pulmonary hypertension (**lower panels**). At end-systole the ventricular septum is markedly flattened toward the center of the left ventricular cavity in the patient with primary pulmonary hypertension by comparison with the pattern of ventricular septal curvature seen in the normal individual. At the end of early diastolic filling, whereas the normal individual exhibits a significant increase in left ventricular cavity area and maintenance of the relatively circular configuration of the left ventricle, the patient with primary pulmonary hypertension shows little change in cavity area and persistent bulging of the ventricular septum into the left ventricular cavity. At end-diastole the ventricular septum in the patient with primary pulmonary hypertension has shifted away from the left ventricular cavity though its curvature is still reduced compared with the normal individual and appears flattened relative to curvature of the left ventricular free wall. By comparison with the stop-frame image obtained at the end of the early diastolic filling period there has been a significant increase in cavity area for the patient with primary pulmonary hypertension.

was flattened toward the center of the left ventricular cavity in all patients with primary pulmonary hypertension. In six of these nine patients the ventricular septum was without curvature and in an additional patient the ventricular septum was convex with respect to the left ventricular cavity. The normalized septal curvature was 0.04 ± 0.19 (range −0.32 to 0.43). At the end of the early diastolic filling period the ventricular septum remained flattened toward the left ventricular cavity in all patients, and normalized septal curvature (−0.09 ± 0.40, range −0.52 to 0.64) was not significantly changed with respect to the end-systolic configuration for the group as a whole. In four of the nine patients the ventricular septal distortion was more marked by comparison with the end-systolic configuration and appeared convex with respect to the left ventricular cavity. In three of the nine patients the ventricular septum remained flat and in the two remaining patients ventricular septal curvature had become less abnormal in configuration but remained flattened in appearance. At end-diastole the ventricular septal configuration returned to a more normal shape in all patients, and normalized septal curvature (0.68 ± 0.19, range 0.30 to 0.94) was significantly increased compared with measurements obtained at the end of the early diastolic filling period ($p < 0.005$) (Fig. 5).

In the normal subjects, there were no significant changes in normalized septal curvature comparing images obtained at end-systole, at the end of early diastolic filling and at end-diastole. Throughout the diastolic filling period normalized ventricular septal curvature ranged from 0.92 ± 0.08 to 0.98 ± 0.06, reflecting a nearly circular profile of the left ventricular cavity and no flattening of the ventricular septum toward the left ventricular cavity.

Discussion

Alterations of ventricular septal geometry in right ventricular pressure overload. In this study of patients with severe right ventricular pressure overload due to primary pulmonary hypertension we have demonstrated that the left ventricle is distorted from its usual circular configuration by flattening of the ventricular septum toward the center of the left ventricle. Utilizing normalized septal curvature as an index of this abnormal septal flattening (and in some instances reversal of septal curvature), we found that the distortion of the left ventricular cavity is established at end-systole before the onset of transmitral inflow and persists throughout the early diastolic filling period. During the late diastolic filling period this distortion becomes less marked as the ventricular septum becomes less flattened and normalized septal curvature increases from near zero (flat sep-

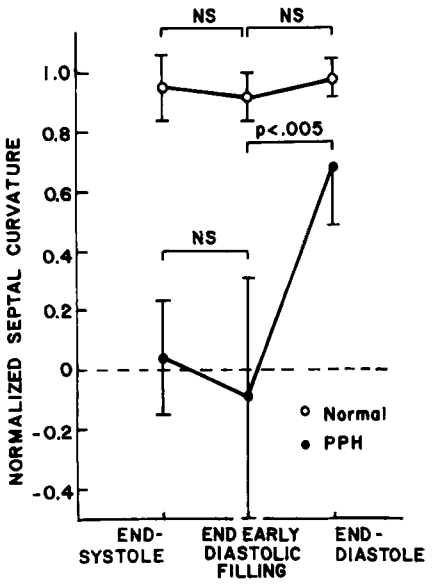


Figure 5. Normalized ventricular septal curvature in normal individuals and patients with primary pulmonary hypertension (PPH) throughout the diastolic filling period. In normal individuals the left ventricle assumes a relatively circular profile with normalized septal curvature approaching unity throughout the diastolic filling period. In these individuals there are no significant changes in septal geometry from end-systole, through the end of the early diastolic filling to end-diastole. In contrast, at the onset of diastole, patients with primary pulmonary hypertension exhibit marked leftward displacement of the ventricular septum resulting in flattening of the septum or reversal of its curvature (Fig. 4) and a normalized septal curvature approaching zero. Throughout the early diastolic filling period left ventricular geometry remains distorted and normalized septal curvature remains near zero, concomitant with decreased early diastolic filling (Fig. 1 and 2). By contrast, during the late diastolic filling period there is a significant increase in the normalized septal curvature resulting in a rightward shift of the ventricular septum and relative normalization of ventricular geometry (Fig. 4) concomitant with increased late diastolic filling (Fig. 1 and 2). NS = not significant by paired comparison with measurement at preceding point in the cardiac cycle.

tum with no curvature) at the end of early diastolic filling to 0.68 (a curvature closer to the value of unity found in normal individuals) at end-diastole.

Impact of early diastolic ventricular septal displacement on left ventricular filling. We hypothesized that the pattern of left ventricular filling might be altered by these geometric changes and in particular that early diastolic filling might be compromised. Our results show that the left ventricular isovolumic relaxation period is significantly prolonged in these patients, resulting in a delay in onset of transmitral inflow. Other authors (20,21) have emphasized that the isovolumic relaxation time is influenced not only by the rate of left ventricular pressure decline, and hence left ventricular relaxation, but also by the magnitude of the pressure drop and the timing of aortic valve closure. In our patients with primary pulmonary hypertension as well as in our normal subjects, systemic arterial pressures were normal and aortic valve disease was absent so that the observed prolongation in the isovolumic relaxation period truly reflects a decrement in the rate of left ventricular pressure decay in patients with primary pulmonary hypertension relative to normal subjects.

Pulsed Doppler-derived left ventricular peak filling rates in these patients with primary pulmonary hypertension were generally lower than measurements obtained from normal individuals, reflecting the reduced pulmonary blood flow characteristic of these patients with pulmonary vascular obstruction. Whereas late diastolic filling contributed 30% of total diastolic filling in normal individuals, in patients with primary pulmonary hypertension late diastolic filling accounted for more than 60% of total diastolic filling. This observation suggests that in patients with right ventricular pressure overload due to primary pulmonary hypertension the ventricular septum is flattened at end-systole and the persistence of this distortion of the left ventricular cavity throughout early diastole is reflected in a relative redistribution of left ventricular filling from early to late diastole.

Previous studies of diastolic interdependence of the ventricles. The abnormal pattern of ventricular septal motion seen in primary pulmonary hypertension was described by Goodman et al. (1) using M-mode echocardiography; they also noted a reduction in the mitral valve EF slope, suggesting the possibility of altered early diastolic filling of the left ventricle. Postmortem (22) and two-dimensional echocardiographic techniques (5,7) used to evaluate patients with right ventricular pressure overload (some of whom had primary pulmonary hypertension), have also characterized the pattern of abnormal septal curvature observed in the present study and demonstrated a significant linear correlation between end-systolic normalized septal curvature and relative right ventricular systolic pressure (5). Krayenbuehl et al. (3), in a micromanometric cineangiographic study of patients with chronic pulmonary hypertension due to primary or secondary pulmonary vascular disease, observed leftward septal displacement (reduced end-diastolic left ventricular minor axis in the left anterior oblique projection) in association with increased left ventricular end-diastolic pressures at low normal end-diastolic volumes in 6 of 10 subjects. They concluded that the apparent decreased left ventricular compliance was attributable to this abnormal interaction between the ventricles by way of the septum.

Several authors (4,9–12) studying right ventricular overload states associated with abnormal septal motion have considered the leftward septal shift to be primarily a diastolic phenomenon with restoration to more normal septal curvature in systole (9). Several of these investigators (4,11,12) postulated that the reversal or reduction in the transseptal pressure gradient (between the left and the right ventricles) during diastole resulted in the leftward shift of the ventricular septum. The findings in the present study are in general

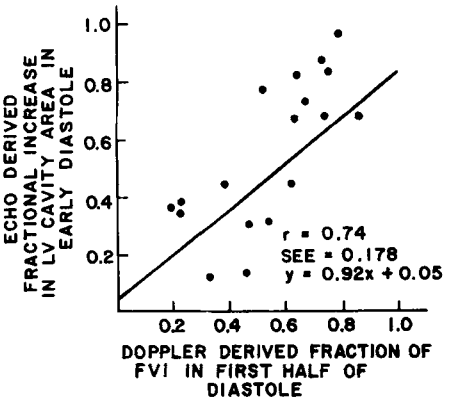
agreement with these observations; however, in our patients with predominant right ventricular *pressure* overload the maximal distortion in septal curvature was established at *end-systole* before the onset of left ventricular diastolic filling and persisted throughout early diastolic filling. In several of the foregoing studies (9–11) volume overload of the right ventricle predominated and may have resulted, therefore, in leftward septal shift limited to diastole. In a closed chest, open pericardium canine model, Visner et al. (23) acutely created peak right ventricular systolic pressures of 68 ± 9 mm Hg by pulmonary artery constriction and found the greatest reductions in ventricular septum to left ventricular free wall dimension to occur during isovolumic relaxation and early diastole, in agreement with our present findings. Similarly, in a study of children with right ventricular systolic hypertension, King et al. (5) demonstrated greater loss of normalized septal curvature at end-systole by comparison with end-diastole. Recently, Agata et al. (6), using two-dimensional echocardiography, demonstrated that patients with right ventricular volume overload had flattening and leftward displacement of the ventricular septum at end-diastole but not at end-systole, whereas patients with right ventricular pressure overload displayed abnormal leftward septal displacment at end-systole with lesser degrees of distortion at end-diastole. In a group of patients with right ventricular pressure and volume load, Minagoe et al.(13) identified a subset of patients with abnormal end-systolic and end-diastolic septal geometry in whom late diastolic transmitral flow velocities exceeded early diastolic transmitral flow velocities. Their results are similar to our own showing redistribution of left ventricular filling to late diastole in patients with right ventricular pressure overload.

Other mechanisms for the redistribution of left ventricular filling to late diastole. We have postulated that early diastolic distortion of the left ventricle by the flattening of the ventricular septum in right ventricular pressure overload results in reduced early diastolic left ventricular filling and compensatory increases in late diastolic filling at a time when septal geometry is less deranged. Other mechanisms for ventricular diastolic interdependence, including changes in compliance of the common septal wall and interactions between the ventricles through shared circumferential muscle fibers (24,25) may also be operative. Because we do not have detailed pressure-volume data in our patients with primary pulmonary hypertension we cannot assess the role that apparent changes in left ventricular chamber compliance may have played in the redistribution of diastolic filling from early to late diastole (26–29), though it is tempting to speculate that chamber compliance may be disproportionately decreased in early diastole at the time when septal deformation is most marked.

Alternatively, one might reason that because pulmonary venous return is reduced in primary pulmonary hypertension the distortion in ventricular shape in this disease might result from rather than cause the abnormal left ventricular filling pattern. By this argument the series relation between the right and left heart pumps rather than their anatomic juxtaposition and mechanical interaction would explain our findings. Three observations in our patients make this hypothesis unlikely: 1) although left ventricular peak filling rates are reduced consequent to pulmonary vascular obstruction in this disease, this does not account for the disproportionate reduction in early peak filling rates relative to late peak filling rates; 2) abnormal ventricular septal flattening occurs before mitral valve opening and thus cannot be the result of underfilling of the left ventricle; and 3) distortion of the left ventricle is regional, manifested as flattening of the ventricular septal curvature with preservation of free wall curvature, which would be difficult to explain solely on the basis of decreased pulmonary venous return. Addressing this issue by comparing the effects of pulmonary artery constriction and vena caval occlusion in a canine model, Visner et al. (23) concluded that the ventricular septal shift during acute right ventricular hypertension due to pulmonary artery constriction could not result simply as a passive response to reduced left ventricular input.

Methodologic considerations. Several limitations inherent in the analysis of the short-axis left ventricular echocardiogram and the interpretation of Doppler-derived flow velocities in the assessment of diastolic function should be recognized. In this study we assumed that diastolic volume changes were reflected in short-axis area changes. An analysis of true left ventricular volume was not attempted because a practical geometric model for computing left ventricular volume from the distorted shape of the left ventricle in primary pulmonary hypertension is not readily available.

Figure 6. Least squares linear regression of Doppler-derived fraction of transmitral flow-velocity integral (FVI) occurring in the first half of diastole versus echocardiographically determined fractional increase in left ventricular (LV) cavity area in early diastole. A linear relation between the Doppler estimate and the echocardiographic estimate of fractional left ventricular filling is demonstrated (with correlation coefficient = 0.74).



Similarly, septal curvature was only quantitated in the short-axis plane although in each patient the shape of the septum at the level of the mitral leaflet tips was found to be characteristic of the septum along its length by examining serial short-axis planes at more caudad and cephalad levels. The Doppler technique measures blood flow velocity, not volumetric flow, and peak flow rates at selected times in diastole were derived assuming that the mitral anulus was circular and that it adequately reflected the effective cross-sectional flow area for the spatial distribution of transmitral flow velocities. Utilizing these assumptions other investigators (17,18) have validated this technique for quantitating transmitral volumetric flow (17) and have found good correlations with angiographically determined diastolic filling rates (18). Quantitation of the transmitral flow velocity integral as well as Doppler derived peak filling rates have also been found to closely reflect variables of fractional diastolic filling and peak filling rates determined by radionuclide blood pool scintigraphy (30,31). Because we did not measure ventricular volume in our patients we did not follow the convention adopted by others (18,31) of normalizing Doppler derived peak filling rates by left ventricular end-diastolic volume. Because the primary goal of our investigation was to compare relative left ventricular filling and filling rates in early and late diastole, normalization for end-diastolic volume was not necessary.

Despite the limitations of our echocardiographic and Doppler techniques, these two methods of assessing diastolic function independently demonstrated that patients with primary pulmonary hypertension have an abnormal redistribution of left ventricular filling from early to late diastole. When data from normal individuals and patients with primary pulmonary hypertension were pooled, there was a linear correlation ($r = 0.74$) between the Doppler-derived fraction of transmitral flow velocity integral occurring in the first half of diastole and the echocardiographically determined fractional increase in left ventricular cavity area in early diastole (Fig. 6), demonstrating that these independent methods of assessing patterns of left ventricular filling yield quantitatively comparable results.

Clinical implications. Using Doppler echocardiographic techniques we have demonstrated a marked redistribution of left ventricular filling from early to late diastole in patients with right ventricular pressure overload due to primary pulmonary hypertension. This alteration in diastolic filling pattern appears to coincide with the marked ventricular septal flattening that is present before the onset of transmitral inflow and persists throughout the early diastolic filling period. This dependence on late diastolic filling to achieve adequate left ventricular preload may be of particular significance in patients who develop arrhythmias that result in loss of the late diastolic "booster effect" of atrial systole or who develop sinus tachycardia with resultant disproportionate abbreviation of the available diastolic filling period. In addition, current therapy for primary pulmonary hypertension (15,16) relies heavily on vasodilator therapy, which may profoundly influence left ventricular preload. Even small reductions in left ventricular filling pressures may result in inadequate diastolic loading, given the abnormalities we have demonstrated in left ventricular filling dynamics. On the other hand, vasodilator-mediated decreases in pulmonary vascular resistance resulting in augmented pulmonary blood flow *without* concomitant reductions in pulmonary artery pressure might result in increased volume loading of the left ventricle at a time when early filling dynamics are still impaired because of flattening of the ventricular septum toward the left ventricular cavity. Thus the demonstration in this study of altered left ventricular filling dynamics in primary pulmonary hypertension should attract attention to the potential for adverse effects of vasodilator therapy on diastolic loading of the left ventricle in this disease.

References

1. Goodman DJ, Harrison DC, Popp RL. Echocardiographic features of primary pulmonary hypertension. Am J Cardiol 1974;33:438–43.
2. Pearlman AS, Clark CE, Henry WL, Morganroth J, Itscoitz SB, Epstein SE. Determinants of ventricular septal motion. Influence of relative right and left ventricular size. Circulation 1976;54:83–91.
3. Krayenbuehl HP, Turina J, Hess O. Left ventricular function in chronic pulmonary hypertension. Am J Cardiol 1978;41:1150–8.
4. Tanaka H, Tei C, Nakao S, et al. Diastolic bulging of the interventricular septum toward the left ventricle. An echocardiographic manifestation of negative interventricular pressure gradient between left and right ventricles during diastole. Circulation 1980;62:558–63.
5. King ME, Braun H, Goldblatt A, Liberthson R, Weyman AE. Interventricular septal configuration as a predictor of right ventricular systolic hypertension in children: a cross-sectional echocardiographic study. Circulation 1983;68:68–75.
6. Agata Y, Hiraishi S, Misawa H, Takanashi S, Yashiro K. Two-dimensional echocardiographic determinants of interventricular septal configurations in right or left ventricular overload. Am Heart J 1985;110:819–25.
7. Handa S, Miyamori R, Ohnishi S, et al. Left ventricular geometry and contraction in patients with primary pulmonary hypertension (abstr). Circulation 1985;72(suppl III):III-411.
8. Kerber RE, Dippel WF, Abboud FM. Abnormal motion of the interventricular septum in right ventricular volume overload. Circulation 1973;48:86–96.
9. Weyman AE, Wann S, Feigenbaum H, Dillon JC. Mechanism of abnormal septal motion in patients with right ventricular volume overload. A cross-sectional echocardiographic study. Circulation 1976;54:179–86.
10. Brinker JA, Weiss JL, Lappe DL, et al. Leftward septal displacement during right ventricular loading in man. Circulation 1980;61:626–33.
11. Guzman PA, Maughan WL, Yim FCP, et al. Transseptal pressure gradient with leftward septal displacement during the Mueller manoeuvre in man. Br Heart J 1981;46:657–62.
12. Kingma I, Tyberg JV, Smith ER. Effects of diastolic transseptal pressure gradient on ventricular septal position and motion. Circulation 1983;68:1304–14.
13. Minagoe S, McKay CR, Chandraratna PAN. Doppler echocardiographic left ventricular filling dynamics in patients with right ventricular overload (abstr). Circulation 1985;72 (suppl III):III-352.

14. Rich S, Brundage BH. Primary pulmonary hypertension. JAMA 1984;251:2252–4.

15. Rich S, Brundage BH, Levy PS. The effect of vasodilator therapy on the clinical outcome of patients with primary pulmonary hypertension. Circulation 1985;71:1191–6.

16. Packer M. Vasodilator therapy for primary pulmonary hypertension. Ann Intern Med 1985;103:258–70.

17. Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones QA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. Circulation 1984;70:425–31.

18. Rokey R, Kuo LC, Zoghbi WA, Limacher WC, Quinones MA. Determination of parameters of left ventricular diastolic filling with pulsed Doppler echocardiography: comparison with cineangiography. Circulation 1985;71:543–50.

19. Godfrey K. Comparing the means of several groups. N Engl J Med 1985;313:1450–6.

20. Benchimol A, Ellis JG. A study of the period of isovolumic relaxation in normal subjects and in patients with heart disease. Am J Cardiol 1967;19:196–206.

21. Gamble WH, Shaver JA, Alvares RF, Salerni R, Reddy PS. A critical appraisal of diastolic time intervals as a measure of relaxation in left ventricular hypertrophy. Circulation 1983;68:76–87.

22. Kieffer RW, Hutchins GM, Moore GW, Bulkley BH. Reversed septal curvature. Association with primary pulmonary hypertension and Shone syndrome. Am J Med 1979;66:831–5.

23. Visner MS, Arentzen CE, O'Connor MJ, Larson EV, Anderson RW. Alterations in left ventricular three-dimensional dynamic geometry and systolic function during acute right ventricular hypertension in the conscious dog. Circulation 1983;67:353–65.

24. Ross J Jr. Acute displacement of the diastolic pressure-volume curve of the left ventricle: role of the pericardium and the right ventricle. Circulation 1979;59:32–7.

25. Bove AA, Santamore WP. Ventricular interdependence. Prog Cardiovasc Dis 1981;23:365–88.

26. Taylor RR, Covell JW, Sonnenblick EH, Ross J Jr. Dependence of ventricular distensibility on filling of the opposite ventricle. Am J Physiol 1967;213:711–8.

27. Bemis CE, Serur JR, Borkenhagen D, Sonnenblick E, Urschel CW. Influence of right ventricular filling pressure on left ventricular pressure and dimension. Circ Res 1974;34:498–504.

28. Stool EW, Mullins CB, Leshin SJ, Mitchell JH. Dimensional changes of the left ventricle during acute pulmonary arterial hypertension in dogs. Am J Cardiol 1974;33:868–75.

29. Kelly DT, Spotnitz HM, Beiser GD, Pierce JE, Epstein SE. Effects of chronic right ventricular volume and pressure loading on left ventricular performance. Circulation 1971;44:403–12.

30. Spirito P, Maron BJ, Bonow RO. Noninvasive assessment of left ventricular diastolic function: Comparative analysis of Doppler echocardiographic and radionuclide angiographic techniques. J Am Coll Cardiol 1986;7:518–26.

31. Friedman B, Drinkovic N, Miles H, Stipp V, Mazzoleni A, DeMaria AN. Assessment of left ventricular diastolic function: comparison of Doppler and blood pool scintigraphy (abstr) Circulation 1985;72(suppl III): III-429.