Factors Related to End-Systolic Volume Are Important Determinants of Peak Early Diastolic Transmitral Flow Velocity

Michael Courtois, MA; Carol J. Mechem, RN; Benico Barzilai, MD; and Philip A. Ludbrook, MB, BS, FRACP

Background. Three important determinants of left ventricular (LV) peak early diastolic filling rate, which is related directly to the magnitude of the transmitral pressure difference, are the rate of LV isovolumic pressure fall (T1/2), left atrial (LA) pressure at mitral valve opening (X1), and end-systolic volume (ESV).

Methods and Results. To delineate the relative degrees to which these factors contribute to the magnitude of peak early diastolic filling rate, we measured LA and regional intra-LV pressures with micromanometers, LV volume with contrast angiography, and peak transmitral flow velocity (E) with transesophageal Doppler echocardiography in 16 anesthetized closed-chest dogs. E did not correlate significantly with either X1 (r = -0.255) or T1/2 (r = -0.281). Multivariate analysis, with E entered as the dependent variable and X1 and T1/2 as independent variables, also failed to reach significance (R = 0.310). E correlated significantly with ESV (r = -0.633, p < 0.009). Using multivariate analysis, the major determinants of ESV were found to be LV contractility (+dP/dt), afterload (aortic diastolic pressure, Aodis), and preload (end-diastolic volume, EDV) (R = 0.848, p < 0.001). E correlated significantly with two of the determinants of ESV (+dP/dt and Aodis) (R = 0.906, p < 0.001); however, the addition of EDV did not significantly improve the multivariate relation (R = 0.911). To determine whether X1 or T1/2 would add significantly to the above multivariate relation, these factors were entered individually along with +dP/dt and Aodis, as third independent variables. Neither the addition of X1 (R = 0.906) or T1/2 (R = 0.926) resulted in a significant improvement in the prediction of E.

Conclusions. Our observations confirm the importance of factors related to ESV as important determinants of early diastolic filling. These relations suggest that the process of early diastolic function is intimately related to systolic function. (Circulation 1992;85:1132-1138)

KEY WORDS • echocardiography, transesophageal • echocardiography, Doppler • pressure gradients • ventricle • diastole

The traditional concept of early diastolic left ventricular (LV) filling portrays the relaxing ventricles as being distended during early diastole by venous pressure: "As soon as systole is over and the ventricular pressures fall again to their low diastolic values, the high pressures in the atria immediately push the atrioventricular valves open and allow blood to flow rapidly into the ventricles."1 Thus, early filling is thought to be determined primarily by filling load and the rate of ventricular relaxation. Over the past decades, evidence has accumulated indicating that ventricular ejection is also an important determinant of subsequent early diastolic filling. Several studies indicate that the ventricle exerts a suction effect that actively contributes to the generation of the early diastolic transmitral pressure difference that acts to fill the ventricular chamber,2-5 and that the magnitude of this suction effect is related to elastic potential energy stored in the myocardium when the end-systolic volume (ESV) achieved by the contracting ventricle is below equilibrium volume.6-8

Because ESV should be determined by LV contractility, the load against which the LV is ejecting (afterload), and the end-diastolic volume (EDV) (preload), the present study was carried out both to assess the degree to which these three factors actually determine ESV in the intact canine and the degree to which peak transmitral flow velocity (E) is related to these three factors, along with filling load and relaxation rate. Transmitral flow velocity was obtained by transesophageal Doppler echocardiography; filling load was estimated by left atrial (LA) pressure at the time of mitral valve opening; myocardial relaxation was approximated by T1/2, an index of the rate of LV isovolumic pressure decline; LV contractility was estimated by the peak rate of change of LV pressure during isovolumic contraction;
LV afterload was approximated by aortic diastolic pressure \( \text{Ao}_{\text{min}} \); and preload was measured as EDV obtained by contrast angiography.

**Methods**

Sixteen mongrel dogs of either sex weighing 27–34 kg (29±0.6 kg) were sedated with morphine (1 mg/kg s.c.) 30 minutes before induction of general anesthesia with sodium pentothal (12.5 mg/kg i.v.) and \( \alpha \)-chloralose (100 mg/kg i.v.). Previous experience in our laboratory indicated that this anesthetic regimen is accompanied by a relatively wide range of LV ejection (ejection fraction [EF], 56±10%; range, 42–69%) and loading (mean aortic pressure, 90±17 mm Hg; range, 71–119) states. These variations are probably attributable to differing effects of the anesthetic agents and/or variables such as circulating catecholamine levels in individual animals. In fact, a wide range of loading conditions (\( \text{Ao}_{\text{min}} \) of 66–130 mm Hg) has been reported to be a common finding in normal dogs. Thus, it was anticipated that interventions to alter loading conditions would not be needed.

Each dog was intubated and ventilated with room air with use of a Harvard respirator. The left common carotid artery, the right femoral artery, and the right and left femoral veins were isolated, and a valved sheath (USCI, Hemaqut 8F) was placed in each. A bolus injection of heparin sodium (4,000–5,000 USP units) was then administered intravenously. A Swan-Ganz thermodilution catheter (model 93A-131-7F, American Edwards) was directed under fluoroscopy from the left femoral vein to the inferior vena cava. A micromanometric catheter (model 484A-8F, Millar Instruments) was directed from the right femoral artery to the aortic arch, and a second micromanometric catheter with dual sensors (3-cm spacing) (model SPC 771-7F, Millar Instruments) was directed from the left carotid artery into the LV apex so that the distal transducer was placed as close to the LV apex as possible without inducing ectopy. A third micromanometer was positioned in the left atrium by puncture of the interatrial septum by using a Mullins transeptal catheter introducer set (8F, USCI) and a Brockenbrough needle (18 gauge, USCI) as described previously.

To record LV pressures referenced solely to atmospheric pressure rather than to an external fluid-filled transducer signal, which is highly dependent on the height of the external transducer relative to the height of the heart, the micromanometers were placed in a dry, graduated cylinder immersed in a water bath and warmed between 36 and 38°C, corresponding to the temperature of the animal. Because this position could be most easily standardized in each animal, the LV apical pressure signal was selected as the “standard,” and all other high-gain pressure signals were aligned with it during late diastasis (Figure 1). In the presence of rapid heart rates, alignment of pressures was accomplished during the long diastatic period occurring after premature ventricular contractions that produced a compensatory pause. At the conclusion of the experiment, the zero baseline of the LV apical transducer was confirmed by replacing the dual sensor catheter in the graduated cylinder. In no case did the signal drift >1.0 mm Hg from the original zero baseline. Equal sensitivity of the three high-gain micromanometers was assured by simultaneously subjecting them to identical pressures via a y-connector attached to a mercury manometer.

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**FIGURE 1.** Record of simultaneous pressure measurements obtained from the micromanometric pressure transducer recordings. Measurements included peak aortic pressure (AOP) and end-diastolic pressure (LAP) during left ventricular (LV) systole (\( X_{\text{min}} \)); the upslope and height of the left atrial V wave (V); the first crossover point (\( X_i \)) of LAP and LV pressures (LVP); the maximum forward (LAP>LVP) early transmural pressure gradient measured between the LA transducer and the LV apical transducer; the maximum early diastolic intraventricular pressure gradient measured between the midventricular and apical transducers; the height and slope of the LV F wave (F); and LV end-diastolic pressure. ECG, electrocardiogram.

**FIGURE 2.** Record of a time–velocity profile obtained with transesophageal Doppler. The ultrasound system used in this study enables the Doppler signals to be inverted for viewing convenience, thus they appear above rather than below the baseline. Measurements included peak velocity of the early diastolic filling wave (E) and peak velocity of the late diastolic filling wave (A). ECG, electrocardiogram; LVP, left ventricular pressure.
Catheters produced identical signals over a range of 0–22 mm Hg.

A low-gain pressure signal from the aortic micromanometer (100 mm Hg=10.0 cm) and the three high-gain pressure signals from the LA and LV sensor catheters (20 mm Hg=16 cm) were transmitted to a photographic recorder (model 1508B, Honeywell Visicorder). The LV apical high-gain signal was also transmitted to a heat-sensitive recorder (model 77500B, Hewlett-Packard) interfaced with an ultrasound imaging system. This facilitated precise alignment of the transmitial pressure waveforms and the Doppler time-velocity profiles. Transmitral Doppler recordings were made with a transeosophageal two-dimensional phased-array echocardiographic 5-MHz transducer with pulsed Doppler capabilities (model 77020A, Ultrasound System, Hewlett-Packard). Pressure and Doppler recordings were made at a chart speed of 100 mm/sec. Left ventriculograms were recorded at 30 frames/sec in the left lateral projection after the acquisition of hemodynamic and transmitial flow velocity data; 22 ml of nonionic contrast medium (Omnipaque 350, Winthrop) was injected by a power injector at a rate of 11 ml/sec through the low-gain micromanometer–angiographic pigtail catheter that was advanced from its position in the aortic arch into the LV after high-gain pressure–flow recordings. Core body temperature was maintained with use of a circulating water (38°C) heating pad and was monitored continuously via the Swan-Ganz catheter thermistor. In no case did the temperature drop below 36°C. Arterial blood gases were assessed periodically, and ventilator rate and volume were adjusted accordingly.

**Data Analysis**

All volume, hemodynamic, and Doppler flow velocity measurements were recorded during brief apnea with the animal in the supine position. Pressure and flow–velocity measurements from five consecutive beats were averaged for each animal. The following measurements were obtained from the micromanometer pressure transducer recordings (Figure 1): peak aortic pressure and Aopeak; minimum pressure after the LA C wave (nadir of X' descent); upslope and height of the LA V wave; first crossover pressure point of atrial and ventricular pressures (Xv); maximum forward (LA pressure>LV pressure) early transmitial pressure gradient measured between the LA and LV apical transducers immediately before LV minimum pressure (LVmin); maximum early diastolic intraventricular pressure gradient measured between the midventricular and apical transducers (MIVP); minimum LV apical pressure during early diastole; height and slope of the LV F wave; LV end-diastolic pressure recorded from the LV apical transducer; and height of the LA pressure a wave. A waveform analysis program was used to determine peak positive (+dP/dt) and negative (−dP/dt) rates of LV pressure change from analog LV pressure data recorded on an FM tape recorder system (model 3968A, Hewlett-Packard) that were subsequently transferred off-line into a computer (5600M computer system, Hewlett-Packard) and digitized at a rate of 800 Hz. LV isovolumic relaxation was assessed with use of the least-squares method, using pressure points digitized every 2.5 msec starting at peak −dP/dt (t=0) and ending 5 mm Hg above end-diastolic pressure based on a model of exponential decay with variable asymptote:14

\[
P(t)=Ae^{-bt}+C .
\]

The time for LV pressure at t=0 to decrease by half (T1/2) was computed from this formula.15,16

Peak transmitial flow velocity was obtained from the Doppler time-velocity profile (Figure 2). LV ESV and EDV and EF were calculated from LV contrast ventriculograms using standard techniques.17 Ventriculographic volumes were calibrated using the known distance between the sensors of the dual sensor micromanometer as the absolute reference to calculate the magnification factor.

**Table 1. Individual Data Points for the 21 Reported Variables**

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<th>Aopeak (mm Hg)</th>
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TMPapex, peak early diastolic transmittal pressure gradient measured from the left atrial (LA) to the left ventricular (LV) apex; MVPapex, maximum early diastolic pressure gradient measured between the LV apical and midventricular transducers; HR, heart rate; A0 dias, peak aortic pressure; AOA0 dias, end-diastolic aortic pressure; X1, first crossover point of LA and LV pressure signals; Vheight, height of the LA pressure V wave; Vslope, upslope of the LA pressure V wave; T1/2, isovolumic relaxation constant; +dP/dt, peak positive rate of LV pressure increase; −dP/dt, peak negative rate of LV pressure decline; EDP, LV end-diastolic pressure; LVmin, minimum LV pressure; X’min, minimum LA pressure during LV systole; E, peak early diastolic flow velocity; Fheight, height of the LV rapid filling pressure wave from minimum LV pressure to the top of the F wave; Fslope, upslope of LV pressure F wave; ESV, LV end-systolic volume; EDV, LV end-diastolic volume; EF, ejection fraction; A, peak velocity of late diastolic flow; bpm, beats per minute.

Bivariate and multiple regression linear correlation coefficients were calculated using the STATWORKS statistics package (Cricket Software, Philadelphia, Pa.). A probability value of less than 0.05 was considered significant. To test whether the partial regression coefficient calculated for a given independent variable is significantly different from zero and whether it contributes significantly to the multiple regression after controlling for the effects of the other independent variables, the t ratio was used18 as

\[ t_j = b_j / \text{SE}_{bj} \]

\[ \text{SE}_{bj} = \sqrt{\frac{\text{SS}_{\text{res}}}{\text{SS}_j (1 - R^2_j)}} \]

where \( b_j \) is the partial regression coefficient of variable \( j \); \( \text{SE}_{\text{res}} \) is the standard error of the \( j \)th coefficient; \( \text{SS}_{\text{res}} \) is the standard error of estimate; \( \text{SS}_j \) is the sum of squares of variable \( j \); and \( R_j \) is the multiple correlation between variable \( j \), used as a dependent variable, and the remaining independent variables. All data are reported as mean±SD.

Results

The individual data, means, and standard deviations for the 21 reported variables (\( n = 16 \)) are found in Table 1. Bivariate and multivariate correlations of early diastolic flow velocity with LA pressure at the time of mitral valve opening and with the rate of LV isovolumic pressure fall. The traditional view1 of early diastolic filling predicts that E should be determined primarily by filling load and the rate of ventricular relaxation. As noted in Table 2, E did not correlate significantly with either X1 (\( r = -0.225 \)) or \( T_{1/2} \) (\( r = -0.281 \)). Multivariate analysis with E entered as the dependent variable and \( X_1 \) and \( T_{1/2} \) as independent variables also failed to reach significance (\( R = 0.310, NS \)). See Table 3.

Bivariate correlation between E and ESV and multivariate correlation between E and the determinants of ESV. According to the suction model of ventricular filling, early diastolic filling rate is related to ESV. As shown in Table 2, E correlated significantly with ESV (\( r = 0.633, p < 0.009 \)).

The primary determinants of ESV are expected to be LV contractility (+dP/dt), the load against which the LV is ejecting (AO dias), and LV preload (EDV). To test this relation, we performed a multivariate analysis with ESV as the dependent variable and +dP/dt, AO dias, and EDV as independent variables. This relation was significant (\( R = 0.848, p < 0.001 \)). Calculation of t ratios indicates that all three variables add significantly to the relation. No significant interrelations existed between any of the three independent variables. See Table 3.

To assess whether the determinants of ESV also determine E, we entered E as the dependent variable into a multiple regression with +dP/dt, AO dias, and EDV as independent variables. This relation was highly significant (\( R = 0.911, p < 0.001 \)); however, the t ratio indicated that EDV did not contribute significantly to the correlation. No significant relations were found between the independent variables. See Table 3.
The multiple regression of E with +dP/dt and Aodias alone was highly significant ($R=0.906, p<0.001$). See Table 3.

Addition of $X_1$ and $T_{1/2}$ to the multivariate relation between E and +dP/dt and Aodias. To determine whether $X_1$ and/or $T_{1/2}$ would add significantly to the above multivariate relation, these factors were entered individually as independent variables. The addition of $X_1$ did not improve the above relation ($R=0.906, p<0.001$). $X_1$ appeared to be loading dependent, as indicated by a significant relation with Aodias ($r=0.664, p<0.005$). See Table 3.

The addition of $T_{1/2}$ also did not improve the overall regression coefficient ($R=0.926, p<0.001$). The t ratio indicates that $T_{1/2}$ does not contribute significantly to the variability of E. See Table 3.

Significant bivariate correlations of E with other measured parameters. E correlated significantly with EF ($r=0.782, p<0.001$) and with both of the measured intracardiac pressure gradients TMP apex (peak early diastolic transmural pressure gradient measured from the LA to the LV apex) ($r=0.716, p<0.002$); and MIVP ($r=0.682, p<0.004$) (see Table 2). E was also found to correlate significantly with LV min ($r=0.537, p<0.032$) and with the height and slope of the LV F wave ($r=0.814, p<0.001; r=0.679, p<0.004$, respectively). Finally, E correlated significantly with the height and slope of the LA V wave ($r=0.639, p<0.008; r=0.630, p<0.009$, respectively).

Discussion

In this study, a significant correlation was observed between E and ESV, and ESV was found to be strongly related to LV contractility, afterload, and preload. However, when these three independent variables were entered as predictors of E, it was found that preload (EDV) did not contribute significantly to the relation. Knowledge of LV contractility and afterload in the normal ventricle yielded a relatively accurate prediction of E ($R=0.906$), probably because, taken together, these two factors are strongly related to myocardial shortening and thus to the storage of elastic energy in the normal ventricle. Related to this was the apparently incongruous finding that although E is strongly related to these two determinants of ESV (contractility and afterload), E is only weakly related to ESV itself ($r=0.633$). This suggests that contractility and afterload may be determinants of some other factor affecting E independent of ESV, such as ventricular shape change and torsion.19,20

Contrary to other reports, either alone or together, $X_1$ and $T_{1/2}$ were not significantly related to E.10,12,21,22

Common among studies identifying $X_1$ as a significant factor contributing to peak early diastolic flow is the
large magnitude of the change in LA loading conditions produced by the various interventions used. It may be that within the range of LA loading found in this study, X₁ may not exert a significant influence. Because our anesthetic regimen includes premedication of the dogs with morphine sulphate, an agent known to increase venous capacitance and thereby reduce preload,23 factors related to systolic shortening and subsequent ventricular recoil may dominate the determination of peak early diastolic filling velocity.

Although T₁₂ was also found to be unrelated to E, this should not be interpreted to indicate that the rate of myocardial inactivation is unrelated to early diastolic filling. As has been shown, dramatically slowed rates of myocardial relaxation are often associated with certain myocardial disease states,24 indicating that a state of residual crossbridge attachment may exist at the time of mitral valve opening. Such a condition would certainly lead to decreased rate of early diastolic filling. Enhancement of the rate and extent of myocardial inactivation under conditions such as exercise may also lead to increased recoil and filling.25 Again, the results of this study indicate that, for this group of animals and by using this experimental preparation, the extent of ejection is a more important determinant of early diastolic filling rate than the rate of isovolumic pressure fall.

As shown in Table 2, E was also found to correlate directly with EF, with both of the measured intracardiac pressure gradients T₁₂s, and MIVP, and with the heights and slopes of both the LA V and LV F waves. E also correlated inversely with LV minimum pressure.

The reason for the significant relation between E and EF appears to be clear. Because high rates of early diastolic filling tend to be present in highly dynamic ventricles exhibiting small ESVs, EF should be expected to be related to E. That EF is related to peak filling has previously been demonstrated using radio- nuclide angiography.26

The bivariate correlations between E and T₁₂s, LVmin, and MIVP are also expected. The driving force for ventricular filling is the transmitral pressure gradient. Because LVmin is a major determinant of the transmitral pressure gradient,12 the inverse relation between E and LVmin is reasonable. We have previously presented data that indicate that the MIVP is related to recoil of the ventricular walls during early diastole.9 Because storage of elastic energy at end systole and subsequent recoil during early diastole are strongly related to E, the relation between E and MIVP is also expected.

The correlation between E and the height and slope of the LV pressure F wave is also predictable. The F wave has been demonstrated to be related to the pressure impact created when early diastolic flow decelerates by colliding against the ventricular walls.27 Thus, it is reasonable to expect that in the normal LV, the height and steepness of the F wave should be closely related to the peak velocity of early transmitral flow.

The relation between E and the height and slope of the LA pressure V wave was also anticipated. The steep fall in LA pressure after atrial systole (X descent) has long been attributed to “pulling down” of the mitral valve ring during LV systole.28 This piston-like action of the mitral valve lowers LA pressure, generating a pressure gradient between the LA and the lungs that aids in filling the LA during LV systole. Thus, highly dynamic ventricles, which tend to display high early diastolic transmitral filling rates (as demonstrated by the strong correlation between E and EF), would also tend to generate large pressure gradients between the LA and the lungs during LV systole. Consequently, the velocity of the blood entering the LA during the ventricular systolic phase would also tend to be higher in more dynamic ventricles. Because the LA V wave, like the LV F wave, is related to deceleration of flow, the V waves in these dynamic hearts should be steep and large. That V₁₂s and V₈early are related to E because of covariance with the dynamics of LV systole is supported by the observation that, as calculated from the data in Table I, both of these variables evidenced significant bivariate correlations with EF (r=0.730, p<0.001; r=0.765, p<0.001, respectively).

Conclusions

Our observations underscore the importance of factors related to myocardial shortening as important determinants of early diastolic filling. Peak early diastolic filling rate is strongly related to LV contractility and afterload (R=0.906). Because the variability of a dependent variable accounted for by the independent variables is equal to R², these two factors accounted for 82% of the variability associated with E. LA pressure at the time of mitral valve opening and the rate of isovolumic pressure decline, when added to these two factors, did not significantly improve the prediction of E. These relations are consistent with the hypothesis that the process of early diastolic function is intimately related to systolic function: that the normal heart fills during early diastole under the influence of rapid ventricular expansion via elastic recoil.

Acknowledgment

The authors thank Donna Marquart, RT, for her technical assistance.

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*Circulation*. 1992;85:1132-1138
doi: 10.1161/01.CIR.85.3.1132

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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