Estimation of diastolic intraventricular pressure gradients by Doppler M-mode echocardiography

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Greenberg, Neil L., Pieter M. Vandervoort, Michael S. Firstenberg, Mario J. Garcia, and James D. Thomas. Estimation of diastolic intraventricular pressure gradients by Doppler M-mode echocardiography. Am J Physiol Heart Circ Physiol 280: H2507–H2515, 2001.—Previous studies have shown that small intraventricular pressure gradients (IVPG) are important for efficient filling of the left ventricle (LV) and as a sensitive marker for ischemia. Unfortunately, there has previously been no way of measuring these noninvasively, severely limiting their research and clinical utility. Color Doppler M-mode (CMM) echocardiography provides a spatiotemporal velocity distribution along the inflow tract throughout diastole, which we hypothesized would allow direct estimation of IVPG by using the Euler equation. Digital CMM images, obtained simultaneously with intracardiac pressure waveforms in six dogs, were processed by numerical differentiation for the Euler equation, then integrated to estimate IVPG and the total (left atrial to left ventricular apex) pressure drop. CMM-derived estimates agreed well with invasive measurements (IVPG: $y = 0.87x + 0.22$, $r = 0.96$, $P < 0.001$, standard error of the estimate = 0.35 mmHg). Quantitative processing of CMM data allows accurate estimation of IVPG and tracking of changes induced by β-adrenergic stimulation. This novel approach provides unique information on LV filling dynamics in an entirely noninvasive way that has previously not been available for assessment of diastolic filling and function.

Diastole; hemodynamics; ventricles

NORMAL DIASTOLIC FUNCTION of the left ventricle can be defined as the ability of the ventricle to adequately fill under low filling pressures. Diastolic dysfunction is present in a number of cardiac diseases and often precedes left ventricular systolic dysfunction, leading to symptoms of heart failure in patients with preserved systolic function. Whereas regional pressure differences between the left ventricle, the left ventricular outflow tract, and the aorta during ejection have been recognized for some time (10), the importance of regional pressure differences within the ventricle during diastole has only recently gained attention. Although the presence of such intraventricular pressure differences between the left ventricular base and apex during early diastole was first reported in canine models by Ling et al. (9) in 1979 and Falsetti et al. (4) in 1980, the possible clinical implications of these observations have not been fully appreciated. Falsetti et al. (4) also observed a gradual increase in the magnitude of the intraventricular pressure differences with graded infusions of isoproterenol and a decrease of these intraventricular pressure differences with propranolol. Courtois et al. (2) found in an animal model that these intraventricular diastolic pressure differences disappeared during ischemia induced by coronary occlusion. More recently, Smiseth et al. (13) demonstrated a relationship between early filling and the pressure difference between the left ventricular apex and outflow tract. Work from this group has also demonstrated that the delay of apical filling in acute ischemic failure was attributed to a decrease in the intraventricular driving pressure (15). Whereas these findings suggest the critical importance of the diastolic intraventricular pressure gradients in assuring adequate left ventricular filling, this information can only be obtained currently during invasive left heart catheterization with careful pressure measurements in the left atrium (LA) and multiple points in the left ventricle, a very impractical procedure for diagnosis and follow-up of patients in the clinical setting.

In recent years, color Doppler M-mode echocardiography has been proposed as a new and promising approach to evaluate left ventricular diastolic function noninvasively. Color Doppler M-mode provides velocity information, not only at a single point as seen with traditional pulsed Doppler methods, but along the entire inflow tract from the LA across the mitral valve into the left ventricle and this throughout the entire diastolic filling period. Several studies (1, 3, 5, 14, 16, 18) observed differences in the left ventricular inflow patterns as detected by color Doppler M-mode echocardiography in different disease states and physiological conditions. Multiple parameters have been proposed to describe these differences in filling patterns, but all of these proposed methods have the following similar disadvantages: 1) only a very limited amount of the...
velocity information available is used, 2) some measurements are difficult and rather subjective, and 3) the methods are only indirectly related to diastolic function. We (7) recently developed a novel concept to calculate transmitral pressure differences across a normal mitral valve incorporating the inertial forces into the unsteady flow form of the Bernoulli equation by using the full digital velocity map. In this study, we extend this concept and apply basic hydrodynamic principles to the noninvasively obtained spatiotemporal velocity distribution of left ventricular inflow to calculate intraventricular pressure gradients. This approach provides unique information on left ventricular filling dynamics in an entirely noninvasive way that has never been available before.

Glossary

\[ \mathbf{v} \] Three-component vector of local blood velocity

\[ P \] Local pressure

\[ \mathbf{B} \] Body forces (such as gravity) acting on the fluid

\[ \rho \] Blood density, 1.05 g/cm\(^3\)

\[ \mu \] Blood viscosity, 0.02 cm\(^2\)/s

\[ s \] Distance along the central streamline from the left atrium to left ventricle

\[ \partial \mathbf{v} / \partial t \] Partial derivative of velocity with respect to time

\[ \partial \mathbf{v} / \partial s \] Partial derivative of velocity with respect to space (left atrium to left ventricle)

\[ \partial P / \partial s \] Partial derivative of pressure with respect to space

\[ \Delta P_{IV} \] Doppler-derived instantaneous intraventricular pressure difference

\[ \Delta P_{MV} \] Instantaneous transmitral pressure difference derived from Doppler measurements

\[ \Delta P_{IV} \] Instantaneous total pressure difference derived from Doppler measurements

\[ v_N \] Nyquist velocity

\[ PRF \] Pulse-repetition frequency

\[ P_{LA}(t) \] Instantaneous left atrial pressure (catheter)

\[ P_{base}(t) \] Instantaneous basal left ventricular pressure (catheter)

\[ P_{apex}(t) \] Instantaneous apical left ventricular pressure (catheter)

\[ \Delta P_T \] Instantaneous total pressure difference based on catheter measurements

\[ \Delta P_{MV} \] Instantaneous transmitral pressure difference based on catheter measurements

\[ \Delta P_{IV} \] Instantaneous intraventricular pressure difference based on catheter measurements

METHODS

Theoretical Background

Fluid dynamics of diastolic intraventricular flow. Three-dimensional (3-D) flow across a normal mitral valve, from the LA to the left ventricular apex (LVapex), is governed by the Navier-Stokes equations for incompressible fluid as shown in Eq. 1, where \( \mathbf{v} \) is a three-component vector of local blood velocity, \( P \) is the local pressure, \( \mathbf{B} \) represents body forces (such as gravity) acting on the fluid, and \( \rho \) and \( \mu \) are blood density and viscosity, respectively. Note that Eq. 1 is the differential form of the continuity equation

\[ \nabla \cdot \mathbf{v} = 0 \]

\[ -\nabla P + \mathbf{B} + \mu \nabla^2 \mathbf{v} = \rho \left( \frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v} \right) \]

(1)

This complex set of coupled differential equations can be simplified by the following assumptions: 1) the viscous term, \( \mu \nabla^2 \mathbf{v} \), is very small and can be neglected (19, 22); and 2) the gravitational force is balanced by hydrostatic buoyancy, and thus \( \mathbf{B} = 0 \). If we consider flow along a streamline, this becomes the one-dimensional Euler equation as shown in Eq. 2, where the vector notation has been dropped as the focus has shifted to the velocity in one direction

\[ \frac{\partial P}{\partial s} = -\rho \left( \frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v} \right) \]

(2)

Integrating the Euler equation along an inflow streamline, from the LV base (LVbase) to apex, yields the nonsteady Bernoulli equation, a noninvasive estimate of the intraventricular pressure difference as shown in Eq. 3

\[ \Delta \hat{P}_{IV}[t] = \int_{\text{base}}^{\text{apex}} \frac{\partial P}{\partial s} ds \]

(3)

The instantaneous pressure difference is the sum of convective and inertial components.

Animal Model

After approval by the institutional review board, simultaneous pressure and velocity data were obtained from six adult mongrel dogs, which were anesthetized with pentobarbital sodium (25 mg/kg iv), intubated, and ventilated with the use of room air. A peripheral vein, the right internal jugular vein, and the right femoral artery were cannulated for administration of medication and hemodynamic monitoring. Pulmonary artery pressure and arterial pressure were measured using fluid-filled catheters and monitored throughout the experiments. After a midline sternotomy was performed, the sternum was split widely and the heart suspended in a pericardial cradle, ensuring an adequate echocardiographic imaging window.

High-fidelity pressure measurements. In the first experiment, we used a combination of single- and dual-sensor micromanometer catheters (Millar Instruments; Houston, TX) to obtain pressure measurements from the LA, LVbase, and LVapex. A catheter with dual pressure sensors separated by 5 cm was used to record the intraventricular pressures. The catheters were positioned so that the spacing between the LA and LVbase sensors was ~2 cm. This was achieved by advancing the dual catheter 1 cm past an initial position, where the pressure signal from the proximal sensor switched from LA to LV, and then pulling back 1 cm on the single-sensor catheter from a similar initial position. In the subsequent experiments, we used a multisensor catheter with 5-cm spacing between LV pressure measurements and 2-cm spacing between the sensors for the LA and LVbase pressures. Before introduction, the catheters were immersed in a saline solution for over 1 h to minimize “drift” and calibrated relative to atmospheric pressure, 20 and 100 mmHg, respec-
tively. To account for hydrostatic pressure differences, LA and LV pressures were aligned during a long diastolic time interval on a postextrasystolic beat. The pressure signals were amplified by using a universal amplifier (Gould; Valley View, OH) with a flat frequency response up to 500 Hz. LA and LV pressures were digitized at 1,000 Hz by using a multifunction data-acquisition card (model AT-MIO-16, National Instruments; Austin, TX) and transferred for storage on a 486/50 personal computer (Gateway; N. Sioux City, SD) with the use of a custom-designed acquisition program developed in the LabView (National Instruments) environment.

Doppler ultrasound measurements. Velocity estimation is made in color Doppler echocardiography by comparing the phase shifts in a series of ultrasound pulses by using autocorrelation techniques along the scanline (8). Visualization of the spatial distribution is provided as an overlay of color-encoded velocity data over structural information. In contrast to the low temporal resolution of two-dimensional (2-D) color imaging (10–20 Hz), color M-mode directs successive pulses in a constant direction, allowing the velocity along a single scanline to be recorded at 200 Hz. Color Doppler imaging obtained using this M-mode format provides the spatial velocity distribution along the Doppler scanline (y-axis) and its temporal changes during the cardiac cycle (x-axis).

A 5-MHz imaging transducer (3.7-MHz Doppler frequency) was used with an echocardiograph (Sonos model 1500, Hewlett-Packard; Andover, MA) equipped with digital storage and retrieval capabilities. From the apical scanning window, the Doppler cursor was aligned in parallel with diastolic inflow with the use of 2-D color Doppler flow imaging. Color Doppler M-mode velocity maps were stored on optical disk, allowing digital processing of the color Doppler velocity information. The velocity data were aligned with the pressure waveforms using a timing marker signal that was generated within the data-acquisition program and stored with both the hemodynamic signals and the color Doppler M-mode images.

The velocity data were stored in the Hewlett-Packard digital storage and retrieval image format with 5-ms temporal resolution (200 Hz) resulting from the selection of the fastest sweep speed setting from the echocardiograph. The velocity resolution of this system is dependent on the Nyquist velocity ($v_N$), which is determined by the system for settings of imaging depth and the pulse-repetition frequency (PRF). In this experiment PRF typically varied between 5 and 7.5 kHz, depending on imaging depth, leading to a UN between 48 and 81 cm/s. This system stores Doppler data with an 8-bit value: 5 bits for the velocity and 3 bits for the variance. The 5-bit encoding allows 32 possible values within the range of ±vN. Therefore, in this experiment, velocity resolution was 3–4 cm/s. The diastolic filling velocity distribution across the mitral valve has a spatial resolution of ~0.5 mm.

Data Analysis

Data were obtained from 10 cardiac cycles under baseline hemodynamic conditions in all 6 animals and from an additional 10 cardiac cycles in 4 animals after intravenous administration of isoproterenol (0.1 µg·kg⁻¹·min⁻¹).

Calculation of the Invasive Pressure Differences

Instantaneous transmitral pressure differences ($\Delta P_{MV}$) were computed from the direct measurements of LV apical and basal pressures ($\Delta P_{MV}[t] = P_{LA}[t] - P_{base}[t]$). The intraventricular pressure difference ($\Delta P_{IV}$) was computed from the direct measurements of LV apical and basal pressures ($\Delta P_{IV}[t] = P_{base}[t] - P_{apex}[t]$) in the same cardiac cycles. The total pressure difference ($\Delta P$) is the sum of the transmitral and intraventricular pressure gradients ($\Delta P_{MV} + \Delta P_{IV}$) during early filling and the time from mitral valve opening (pressure crossover) to the peak filling pressure differences ($\Delta P_{MV}[\text{max}]; \Delta P_{IV}[\text{max}]$). We also measured the mitral and intraventricular pressure differences at the maximum total pressure difference ($\Delta P_{MV}[\Delta P_{MT\text{max}}]; \Delta P_{IV}[\Delta P_{MT\text{max}}]$) to calculate the relative contribution of the transmitral and intraventricular pressure differences to the total pressure difference.

Calculation of the Noninvasive Pressure Differences

Preprocessing of color Doppler M-mode images. Assuming that the Doppler M-mode cursor closely approximates an inflow streamline, the color-coded Doppler velocity map provides the spatiotemporal velocity distribution ($v[s,t]$) along an inflow streamline from the LVbase to LVapex. The velocity distribution was extracted from the raw image file by using a customized analysis program developed in LabView (National Instruments). The program allows the user to identify regions within the image where the flow velocities have aliasing outside of $v_N$. With these regions identified, an unaliasing algorithm is used to convert the color scale into true velocities given the Nyquist limit stored with the image. Final calibration of the velocity distribution is based on the spatial and temporal resolution coded in the header of the raw image file.

As shown in Eq. 3, the instantaneous value of the intraventricular pressure difference ($\Delta P_{IV}$) is calculated by integration of the pressure gradient ($\partial P/\partial s$) between the LVbase and LVapex. Pressure differences between the LA and LVapex and LVbase ($\Delta P_{MT}$ and $\Delta P_{MV}$) are computed by varying the limits of integration in $\Delta P_{IV}$ in Eq. 3. The pressure gradient is computed as the product of blood density ($\rho$) with the sum of the convective ($v \cdot \delta P/\delta s$) and inertial components ($\partial v/\partial t$). These partial derivatives of the velocity distribution with respect to space ($s$) and time ($t$) are evaluated by convolving $v[s,t]$ with Sobel operators as shown in Eqs. 4 and 5.

$$\frac{\partial v[s,t]}{\partial t} = v[s,t] \otimes \begin{bmatrix} 1 & 2 & 1 \\ 0 & 0 & 0 \\ -1 & -2 & -1 \end{bmatrix}$$

An example of the simultaneous Doppler velocity and intracardiac pressure data acquired in this experiment is shown in Fig. 1. After the Doppler scanline was positioned (Fig. 1, left), the spatiotemporal velocity distribution (Fig. 1, middle) was acquired with color-coded blood flow velocities on a 5-bit scale such that zero velocity is black, velocities toward the transducer are red/yellow, and velocities away from the transducer are blue/cyan. The maximum, or Nyquist, velocity was held constant in this experiment at ±81 cm/s. The simultaneous intraventricular and LA pressure measurements (Fig. 1, right) are aligned with the use of a timing marker and electrocardiogram waveforms.

After extraction of the early filling wave, the pressure gradient ($\partial P/\partial s$) is calculated using the one-dimensional Euler equation as shown in Fig. 2. A noninvasive Doppler estimate of the $\Delta P_{IV}$ is computed by integration of the pres-
Fig. 1. Left: two-dimensional echocardiographic (ECG) sector image showing the position of the scanline from the left ventricular apex (LV apex), across the mitral valve (MV), and into the left atrium (LA). Middle: color Doppler M-mode spatiotemporal velocity distribution of diastolic inflow in two cardiac cycles, each with early (E) and atrial (A) filling waves. Right: simultaneous intraventricular pressure measurements for these cardiac cycles after alignment with the velocity distribution.

pressure gradient, $\partial P/\partial s$, over the range in depth ($\Delta s = 5$ cm) corresponding to the distance between the transducers located on the catheter at the LV base and apex.

**Statistical Analysis**

The estimates of the magnitude of the peak intraventricular ($\Delta P_{IV\text{max}}$) and total pressure ($\Delta P_{T\text{max}}$) differences were compared with the directly measured maximum pressure differences ($\Delta P_{IV\text{max}}$, $\Delta P_{T\text{max}}$) by using linear regression analysis and by paired $t$-tests. The timings of the peak intraventricular and total pressure differences were also compared with the directly measured maximum pressure differences. The errors ($\epsilon$) between the measured and computed maximum pressure difference magnitudes of intraventricular error ($\epsilon_{IV}$) and total error ($\epsilon_{T}$) and temporal locations ($\Delta t_{IV}$ and $\Delta t_{T}$) were assessed with the use of paired $t$-tests.

In addition to comparing the maximum pressure differences, the instantaneous pressure difference waveforms were also compared to assess the accuracy of the methodology throughout diastole. The mean error ($\epsilon_{M}$) and mean absolute error ($\Delta \epsilon$) were computed during early filling ($\epsilon_{E}$, $\Delta \epsilon_{E}$) and throughout diastole ($\epsilon_{E\rightarrow A}$, $\Delta \epsilon_{E\rightarrow A}$) for both the intraventricular and total pressure differences.

The intraventricular pressure differences were also compared with standard indices of diastolic function. $\Delta P_{IV\text{max}}$ was compared with Doppler early and atrial filling velocities ($E$, $A$, and $E/A$), peak negative first derivative of pressure development over time ($dP/dt$) and the relaxation time constant ($\tau$) by linear regression analysis. Statistical significance was defined at $P < 0.05$. Data are expressed as means ± SD.

**Numerical Simulation**

A central assumption of our methodology is that the color Doppler M-mode cursor lies along a streamline of flow. Because this clearly cannot hold in all situations throughout diastole, we felt it incumbent to determine the sensitivity of our results to this assumption with a numerical simulation. We therefore analyzed a previously described 3-D finite element simulation of flow across the mitral valve (7). By using cross-sectional geometry obtained by echocardiography, we designed (with the use of Ansys/Flotran) a simplified axisymmetric model of the LA, mitral valve, and the LV. The simulated mitral valve and LV diameters were 3 and 6 cm, respectively. Simulated pulsatile flow resulted in a solution providing spatiotemporal velocity and pressure data in a series of 2-D images with 5-ms temporal resolution. The spatiotemporal velocity distribution along particular scanlines and axial flow streamlines were extracted and used to compute the pressure differences by using the Euler equation. Spatiotemporal velocity distributions were extracted from the model to assess the effects of the approximation of inflow streamlines by a simulated scanline. To assess the importance of scanline placement in the flow distribution, the estimated intraventricular pressure drop was compared with the true drop for parallel scanline displacements of 0–1.5 cm from the midline and misalignments of 0–30° from the LV long axis.

**RESULTS**

Under baseline conditions, the $\Delta P_{IV\text{max}}$ by direct catheter measurement was $1.80 \pm 0.47$ mmHg. This

**Fig. 2.** Graphical solution to the one-dimensional Euler equation. The pressure gradient ($\partial P/\partial s$) is computed from the color Doppler M-mode velocity distribution ($v$) and its partial derivatives in time ($\partial v/\partial t$) and space ($\partial v/\partial s$). Spatiotemporal velocity distribution of $E$ filling ($\omega$) shows diastolic inflow propagating from the LA to the LV apex. Spatial range, or image width, is 5 cm and the temporal range, or image height, is 300 ms. Acceleration ($\partial^2 v/\partial t^2$ or $\partial^2 v/\partial s^2$) is color coded in yellow, whereas deceleration ($-\partial v/\partial t$ or $-\partial v/\partial s$) is coded in blue. Brightness of the color display indicates the magnitude of acceleration or deceleration. Acceleration of the $E$ wave, as indicated by the yellow region in the $\partial v/\partial t$ image, is followed by a period of deceleration shown in blue. $\partial v/\partial s$ also provides a similar pattern, with acceleration of blood from the LA through the MV and deceleration within the ventricle.
represented 71.1 ± 12.6% of the [ΔP_T]_max, which was 2.58 ± 0.66 mmHg. The percentage of the intraventricular pressure difference at the time of peak total pressure difference (ΔP_IV)[ΔP_IV(T)max] was slightly less (68.1 ± 12.1%).

The average noninvasive estimate of the [ΔP_IV]_max for the baseline data was 1.77 ± 0.53 mmHg, representing 68.0 ± 7.2% of the [ΔP_T]_max. Again the percentage of the intraventricular pressure difference at the time of peak total pressure difference was slightly less (66.1 ± 7.8%). Linear regression analysis comparing catheter (x) and Doppler-derived (y) measurements demonstrated significant agreement for both intraventricular [y = 0.97x + 0.031, r = 0.84, standard error of the estimate (SEE) = 0.34 mmHg, P < 0.001] and total [y = 1.06x – 0.12, r = 0.95, SEE = 0.31 mmHg, P < 0.001] maximum pressure differences. Figure 3A demonstrates this agreement at baseline between invasive and noninvasive measurements of the intraventricular pressure difference. A paired t-test demonstrated that the difference, or ε, between invasive and noninvasive estimates of both the intraventricular (ε_IV = [ΔP_IV]_max – [ΔP_IV]_max = 0.03 ± 0.29 mmHg) and total (ε_T = [ΔP_T]_max – [ΔP_T]_max = −0.04 ± 0.23 mmHg) pressure differences were not significantly different from zero. The standard deviations of these differences provide an indication of the unsigned scatter in the error. The time to peak filling pressure differences was also measured and used to compute the temporal errors (Δt) between the invasive and noninvasive measures for both the maximum total

Δt_T = t(ΔP_T)max – t(ΔP_T)max = 0.012 ± 0.045 s

and intraventricular pressure differences

Δt_IV = t(ΔP_IV)max – t(ΔP_IV)max = −0.018 ± 0.023 s

After we administered isoproterenol to four of the six animals, the invasive measurement of the maximum total and intraventricular pressure difference increased significantly (ΔP_IV)max, 2.82 ± 0.42 to 5.32 ± 1.52 mmHg; [ΔP_IV]_max, 1.89 ± 0.3 to 4.43 ± 1.29 mmHg; P < 0.01). The relative contribution of the intraventricular pressure difference to the total difference also increased significantly from 68.0 ± 12.1% at baseline to 83.3 ± 5.3% during isoproterenol infusion. These changes were also tracked well by the noninvasive Doppler-derived estimates. The errors between the Doppler-derived estimates and catheter measurements were not significantly different (ε_T, −0.04 ± 0.23 at baseline vs. −0.12 ± 0.49 mmHg with isoproterenol; ε_IV, 0.03 ± 0.29 at baseline vs. 0.35 ± 0.49 mmHg with isoproterenol). Data from both conditions (baseline and isoproterenol) were compared with the simultaneously measured pressure differences by catheter using linear regression analysis. Figure 3B demonstrates the relationship for the combined intraventricular pressure differences at both conditions. Linear regression results for each animal (animals 1, 2, 3, and 6) are provided along with the overall relationship of [ΔP_IV]_max versus [ΔP_IV]_max, y = 0.87x + 0.22, SEE = 0.35 mmHg, r = 0.96, P < 0.001.

In addition to comparing the peak pressure differences, the instantaneous estimates of intraventricular (ΔP_IV(t)) and total (ΔP_T(t)) pressure differences throughout diastole were also evaluated and compared with the catheter-based waveforms. The ε and Δ during early filling and throughout diastole were computed for both the intraventricular and total pressure differences. The ΔP_IV(t) closely tracked the catheter-based...
The diagnosis of LV diastolic dysfunction remains a challenge in clinical practice. The most complete information on LV relaxation and compliance can be obtained from intraventricular pressure measurements combined with simultaneous volume measurements to reconstruct pressure-volume loops. Because this requires an invasive procedure with high-fidelity pressure measurements in the LV and tedious tracing of ventricular contours on angiograms to obtain LV volume estimates, this is rarely performed in clinical practice. The most commonly used technique to assess LV diastolic function clinically is the pulsed-Doppler measurement of the LV inflow velocities at the level of the mitral valve. Although characteristic inflow patterns have been described, this method is limited because the transmitral velocity profile is also affected by several parameters other than LV diastolic function.

**DISCUSSION**

The maximum intraventricular pressure difference ($\Delta P_{IV}$) was related to standard Doppler indices of diastolic filling ($E$, $y$ [cm/s] = 8.394$x$ + 29.0, $r = 0.84$; $E/A$, $y$ [dimensionless] = 0.36$x$ + 1.003, $r = 0.68$) as well as the maximal rate of pressure decrease over time ($-dP/dt_{max}$) ($y$ [mmHg/s] = 238.4$x$ + 577.7, $r = 0.51$) and $\tau$ ($y$ [ms] = $-11.2x + 90.2$, $r = 0.54$).

**Numerical Simulation**

Figure 5 demonstrates the impact of scanline misalignment from the midline streamline of the inflow tract. For parallel displacement as great as 0.9 cm, the mean squared error in estimation remains <0.26 mmHg, with a correlation between predicted and actual pressure drop of $r = 0.93$ (see Fig. 5A). Given that the simulated mitral valve orifice was 3 cm, the scanline can be placed within the central 60% of the valve [(2 × 0.9 cm)/3 cm] to achieve this result. Similarly, Fig. 5B shows that for angular misalignments as great as 20°, the mean squared error remains <0.18 mmHg, with a correlation of $r = 0.95$.
such as heart rate, atrioventricular conduction interval, and left atrial pressure.

The use of color Doppler M-mode echocardiography to assess LV inflow was introduced by Brun et al. (1) in 1992 and has been shown to provide information on LV diastolic function in addition to traditional measurements of the transmitral pulsed-Doppler velocity profile. Stugaard et al. (16) noticed a significant change in the color Doppler M-mode inflow pattern with delayed apical filling during ischemia caused by balloon occlusion of the left anterior descending coronary artery. We hypothesized that color Doppler M-mode profiles, representing flow velocities within the ventricle between base and apex, could provide information on intraventricular pressure gradients.

The presence of these intraventricular gradients during early diastole was first reported by Ling et al. (9) in an animal model. Falsetti et al. (4) showed an increase in intraventricular gradients during β-stimulation and a decrease in the magnitude of the intraventricular gradients during β-blockade, suggesting the close linkage between the LV rate of relaxation and intraventricular pressure gradients. Courtois et al. (2) subsequently showed the disappearance of these intraventricular gradients in an ischemic model during left anterior descending occlusion. Smiseth et al. (13) showed in both animals and humans that the pressure gradient between the ventricular apex and outflow tract strongly correlated with peak early transmirtal flow and stroke volume. These observations suggest the critical importance of intraventricular pressure gradients to ensure efficient LV diastolic filling and its close linkage with more traditional parameters of LV diastolic function.

In this study, we propose a novel concept to apply basic hydrodynamic principles to the color Doppler M-mode spatiotemporal velocity distribution to reconstruct noninvasively the intraventricular pressure gradients present between LV base and apex during diastole. Color Doppler echocardiography is usually used in a qualitative way to assess normal and abnormal blood flows in the cardiac chambers. Although quantitative algorithms have been developed using color Doppler images to calculate cardiac output (17, 20) or to quantify severity of regurgitant valves (12, 21), these are relatively simplistic. This study uses the local spatial and temporal velocity distribution measured by color Doppler M-mode echocardiography to calculate local pressure gradients using the Euler equation, integration of which allows us to calculate a pressure difference between two points along the inflow tract. In this study we focused on the intraventricular component of the filling gradient, integrating the pressure gradient between the base and apex of the left ventricle and comparing the results of this estimate with direct catheter measurement. This Doppler-derived pressure difference closely matched the invasive measurement. The magnitude and timing of these noninvasively reconstructed pressure gradients between the LA and different levels in the ventricle closely matched the invasive measurements and also correspond well with data previously published in the literature. We also showed that this approach not only provides accurate information under baseline conditions but is also able to detect relatively small changes in transmirtal and intraventricular gradients induced by pharmacologically altering LV relaxation. During isoproterenol infusion, we observed an increase in the reconstructed intraventricular gradients, similar to observations of Falsetti et al. (4) and consistent with the finding by Brun et al. (1) of increased flow propagation into the left ventricle in patients during intracoronary dobutamine infusion.

This new application of color Doppler M-mode echocardiography allows us to reconstruct small intraventricular pressure gradients completely noninvasively, thus avoiding the risk and expense of a cardiac catheterization. This method also enables us to detect changes in these small intraventricular gradients induced by changing LV relaxation and is therefore a promising tool that may help us understand and evaluate the complex phenomena underlying LV filling. This new method is particularly attractive because it can provide much more information than could ever be obtained during an invasive procedure. Because color Doppler M-mode velocities are measured as a continuum between the LA and the LV apex at 0.5-mm spatial resolution, the derived pressure gradient distribution along a scanline (\( P/dx \)) can be integrated over space to produce a pressure map. This pressure information can be displayed in a surface plot where pressure (relative to LA pressure) is graphed (z-axis) from the LA to the LV apex (y-axis) throughout the early diastolic filling wave (x-axis) (Fig. 6). This type of information on LV filling pressures has never been available before to researchers or clinicians and opens up entirely new perspectives to evaluate LV diastolic filling and function.

![Fig. 6. Relationship between the derived intraventricular pressure distribution (surface with red and blue representing positive and negative pressure differences, respectively) and the direct catheter pressure differences between the LA and the LV base (white) and apex (green).](image-url)
The time required for the color Doppler M-mode image analysis and extraction of pressure waveforms is ~1 min using the customized software we developed. The processing time is much quicker (a few seconds) after the semiautomatic preprocessing of the color Doppler M-mode data. The preprocessing step requires the user to identify regions within the color Doppler M-mode image where aliasing has occurred. By using this information, the software performs an unaliasing procedure and provides \( v(s,t) \) for the calculation of \( dP/ds \) by using the Euler equation. With known locations for the spatial sample points (depths corresponding to LA, LV\textsubscript{base}, and LV\textsubscript{apex} pressure transducer locations), transmitral and intraventricular pressure difference waveforms are instantly calculated. Because there is a potential of clinical application of this method, we have extended this methodology to allow pressure differences to be calculated from digital echocardiographic images collected by a variety of equipment, including Acuson and ATL. For these sources, however, a color lookup table is generated from the color bar to provide quantitative velocity data because current implementations of the DICOM (digital imaging and communications in medicine) standard do not provide information to calculate the velocity associated with this mapping.

The accuracy of pressure difference estimates results in part from the accuracy of color Doppler M-mode velocity data used in the noninvasive calculation of pressure differences. Shandas et al. (11) compared ultrasound color Doppler imaging to the reference standard laser Doppler velocimetry technique, establishing the accuracy of using models of steady and pulsatile flow acceleration. By using data from this paper, we estimate the standard error between laser and color Doppler to be 6.8 cm/s, nearly equal to the resolution of color Doppler with a Nyquist velocity of 81 cm/s. In addition to this velocity resolution, the temporal and spatial resolutions of color Doppler M-mode images are important as they determine the degree of accuracy for the partial derivative terms of the Euler equation. The accuracy of the pressure estimate is also related to the degree to which the ultrasound scanline approximates an inflow streamline through the center of the mitral valve. We have shown through the computational model described in this paper that accurate results are achieved when the scanline is placed within the central 60% of the valve orifice (\( \epsilon < 0.26 \text{ mmHg}, r = 0.93 \)) or when an angular misalignment is made up to 20° (\( \epsilon < 0.18 \text{ mmHg}, r = 0.95 \)).

Pressure difference estimates can be made reproducibly using this technique. The average absolute difference in the noninvasive peak intraventricular pressure differences calculated by two users was only 0.05 mmHg. This small degree of variability between users is due to the limited steps required to compute the noninvasive pressure differences from color Doppler M-mode images, namely selecting aliased regions and defining spatial locations (or transducer positions) over which the pressure gradient is integrated.

**Limitations**

A critical assumption of our methodology is that of scanline alignment with a streamline of flow. Given the complex 3-D geometry of the LV inflow tract, no straight line could ever be expected to coincide with a streamline throughout diastole. However, simplifications such as this are commonly made in medical measurements (the Gorlin and simplified Bernoulli equations, to name two), and it is reassuring that our numerical analysis suggests relatively little sensitivity of our results to precise alignment of the scanline. Indeed, the error remains relatively small (mean squared error <0.26 mmHg) when the scanline is over halfway to the edge of the valve or misaligned by up to 20°. Of particular concern is the presence of vortices that form at the leaflet tips. However, these form outside the central flow region and thus should not greatly impact our recordings. The fact that these vortices grow throughout diastole may explain why our results in early diastole are somewhat better than atrial filling.

The numerical model used to evaluate the impact of scanline misalignment is also a simplification of the 3-D/4-D actual valvular geometry by using 2-D cross-sectional geometry obtained by echocardiography. Limitations of the modeling tools available also required that ventricular cavity was not dynamically changing during diastole. Whereas the resulting spatiotemporal velocity distributions were somewhat representative of actual color Doppler M-mode images, actual fluid-structure interactions may provide a step in realizing a more accurate model.

Other noninvasive imaging modalities may offer the possibility to acquire 3-D velocity data and calculate pressure differences on the basis of a less simplified version of the Navier-Stokes equations. Whereas real-time 3-D echocardiographic assessment of flow velocities is possible, the necessary tradeoffs result in a greatly decreased temporal resolution (10 frames/s). Magnetic resonance imaging techniques such as phase encoding and particle tracking have been utilized to determine ventricular flow characteristics including streamline assessment, but these procedures are generally not available and also have tradeoffs in terms of temporal resolution. More advanced models of ventricular filling utilizing interactions between structural mechanics and fluid dynamics may provide a less simplified analysis of potential errors in our methodology.

Hemodynamic data were available only at three points within the LV inflow tract, and thus we were able to assess the ability of color M-mode to measure pressure differences within the ventricle rather than true spatial pressure gradient. Future work with the multisensor Millar catheter may refine this validation, but this remains fundamentally an issue of an inadequate gold standard against which to compare our noninvasive findings. These results were obtained in canine model with open chest and open pericardium and thus full validation in humans in a clinical setting awaits further work.
In conclusion, it is very encouraging that though sophisticated, through very straightforward application of basic hydrodynamic principles to color Doppler M-mode data, we are able to measure accurately and noninvasively intraventricular pressure differences throughout diastole. The potential for applying this approach in physiological research and clinical practice appears very significant, because noninvasive diastolic filling gradients have previously been available with only the most meticulous invasive technique.

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