

Physiologic Determinants of Mitral Inflow Pattern Using a Computer Simulation: Insights into Doppler Echocardiography in Diverse Phenotypes

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Background: Although echo Doppler recordings of mitral inflow patterns are often employed clinically to identify “diastolic dysfunction,” abnormal flow profiles may be seen in a diverse set of disorders in which the specific physiologic determinants are not well defined. *Methods:* We used a validated cardiovascular simulation model to assess the effects of four hemodynamic parameters on Doppler measures of LV filling: (1) total blood volume, (2) diastolic stiffness (LV Beta), (3) systemic vascular resistance (SVR), and (4) pulmonary vascular resistance (PVR). In each simulation, we calculated instantaneous flow through the mitral valve as a function of time. *Results:* Increases in blood volume led to an increase in the E:A ratio and a decrease in deceleration time (DT), such that for every 100 mL of volume, DT decreased by ~3 ms. Increases in LV Beta increased the E:A ratio and decreased DT such that for every 0.005 mmHg/mL increase in LV Beta, DT decreased by ~8 ms. While changes in SVR did not significantly alter the Doppler pattern, increases in PVR effected a prolongation of DT and an impaired relaxation E:A pattern. Increasing blood volume and LV Beta simultaneously was additive, while increasing PVR attenuated the effect of increasing volume on the E:A ratio. *Conclusions:* Computer simulations demonstrate that both blood volume and LV stiffness significantly impact the mitral inflow profile indicating that both filling pressure and intrinsic properties of the ventricle are contributors. These data confirm that there are multiple determinants of the Doppler mitral inflow pattern and suggest a new approach toward understanding complex physiologic interactions. (ECHOCARDIOGRAPHY, Volume 26, February 2009)

heart failure, Doppler echocardiography, mitral flow profile, computer simulation

Heart failure in the setting of a preserved ejection fraction (HFPEF) is a common and heterogeneous clinical disorder with a diverse set of related underlying clinical comorbidities.^{1,2} Patients with this disorder tend to be elderly and female and often have associated conditions such as diabetes, hypertension, and/or ventricular hypertrophy,³ all of which can result in an abnormal Doppler flow profile in the

presence or absence of a clinical syndrome of heart failure. While it is well recognized that Doppler measures of filling dynamics are “load dependent,” Doppler echocardiography has become the most commonly employed clinical tool to identify patients with “diastolic dysfunction,” which is a presumed requisite for the development of diastolic heart failure.⁴⁻⁶

Because of the difficulty in experimentally determining the effect of isolated changes in physiological parameters on the Doppler mitral inflow variables, we used a validated, computer-based mathematical simulation of the circulatory system to further evaluate the individual effect of various physiologic variables on Doppler mitral inflow patterns.⁷ We hypothesized that distinctly different intrinsic

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and extrinsic variables would affect the mitral inflow pattern in similar ways and that a computer simulation model would assist in delineating the effect of each individual variable. Additionally, by demonstrating that the computer model can mimic certain clinical situations, we aim to demonstrate the utility of the model for studying complex pathophysiology.

Methods

We used a previously described, validated, mathematical computer model of the circulatory system to investigate cardiac function.⁷⁻⁹ The model is a computer program based on experimental data. It utilizes a time-varying elastance model of contraction which relates instantaneous ventricular pressure to instantaneous volume.⁷ The program allows individual variation of hemodynamic parameters (e.g., heart rate, stressed blood volume, systemic vascular resistance, and contractility). The output is displayed as a pressure-volume loop plotted between the end-systolic and end-diastolic pressure (EDP) volume relationships. In addition, numerical data are obtained, including blood pressure, stroke volume, ejection fraction, left ventricular pressure, and instantaneous flow through the mitral and aortic valves. Transvalvular mitral flow is displayed as E- and A-waves, representing passive filling (E) and atrial contraction (A), similar to the appearance on Doppler echocardiography.

We modeled the effect of four hemodynamic variables: blood volume (indexed by stressed

volume, the relevant volume for initiating an increase in pressure in the filling chamber), LV diastolic stiffness (indexed by stiffness constant LV β), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR), on deceleration time (DT), peak E- and A-wave velocities, and the E:A ratio. In each simulation, we calculated instantaneous flow through the mitral valve as a function of time by varying the four aforementioned physiologic parameters individually with all other variables remaining constant to achieve an incremental change in stroke volume of 5 mL between values of 45 mL and 75 mL. In order to determine the effects of multiple physiologic variables, we modeled the combinations of increasing LV volume plus LV β as well as LV volume plus PVR on the E:A ratio.

The computer-generated output of the mitral flow profiles was analyzed. Peak E- and A-wave velocities and E:A ratios were calculated. Deceleration time was determined by approximating the downslope of the E-flow curve and extrapolating to the x-axis, using the first 35 time points (at 5 ms intervals) after the peak of the E-wave (see Fig. 1).

Results

The changes in Doppler flow profiles as a result of modifications of each of the four hemodynamic parameters are shown in Table I. Specific mitral flow profiles are shown graphically in Figure 2. Increases in blood volume led to an increase in end-diastolic pressures (EDP), an

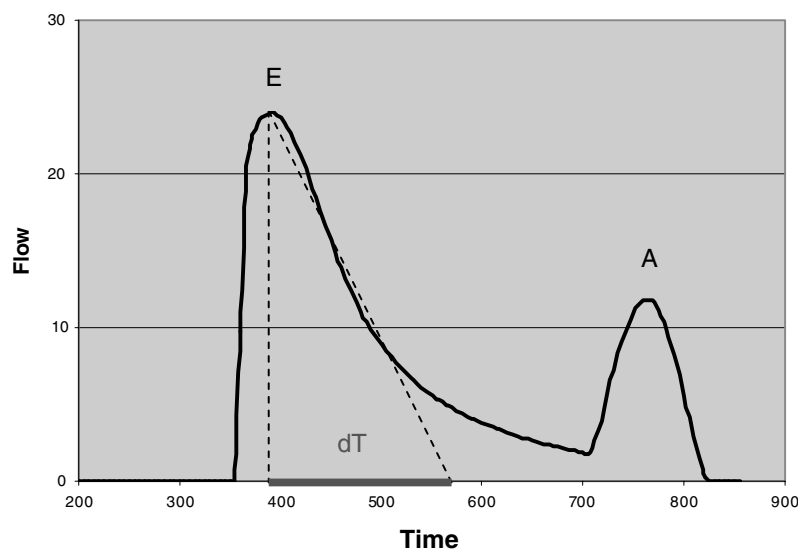


Figure 1. Typical Doppler flow profile as generated from program output. E = peak early flow; A = peak flow with atrial contraction; dT = deceleration time.

TABLE I
Effect of Changes in Physiologic Parameters on the E:A Ratio and Deceleration Time

	Stroke Volume (mL)	Blood Pressure (mmHg)	Cardiac Output (L/min)	End-Diastolic Pressure (mmHg)	E:A Ratio	Deceleration Time (ms)
BV (mL)						
-390	45	85/42	3.1	4	0.45	205
-250	55	105/52	3.9	7	0.71	198
-50	65	124/62	4.6	13	1.29	196
+300	75	143/72	5.2	21	3.68	183
SVR (Dynes)						
4545	45	203/156	3.1	16	1.39	182
2918	55	170/114	3.8	15	1.50	188
1734	65	135/73	4.6	14	1.51	193
882	75	100/31	5.3	13	1.42	200
PVR (Dynes)*						
655.5	45	87/43	3.1	4	0.45	201
395.8	55	105/52	3.8	7	0.69	195
153.0	65	125/62	4.6	13	1.29	196
LV β						
0.058	45	86/43	3.2	4	4.46	160
0.046	55	105/53	3.9	7	2.77	174
0.037	65	123/62	4.5	13	1.70	191
0.028	75	144/72	5.3	21	0.97	210

Hemodynamic output from program with parameters [blood volume (BV), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), LV β] adjusted to achieve stroke volume changes of 10 mL increments between 45 mL and 75 mL. *For PVR, further decreases beyond those to achieve SV of 65 did not affect an increase in SV.

increase in the E:A ratio, and a decrease in deceleration time (Table I). Specifically, the E:A waveform changed from A dominance at low central blood volumes to E dominance at high central blood volumes (Fig. 2), and the deceleration time decreased such that on average for every added 100 mL of blood volume, DT decreased by 3 ms. Similarly, increases in LV diastolic stiffness (LV β) resulted in an increased EDP, increased E:A ratio, and decreased deceleration time. A reversal of the E:A waveform was again noted, and deceleration time changed such that on average for every 0.005 mmHg/mL increase in LV β , DT decreased by 8 ms. A comparison of the effects of blood volume and LVB on the E:A ratio is shown in Figure 3. Alterations in SVR did not significantly affect EDP, the E:A ratio, or the deceleration time. Increases in PVR did not result in marked changes in the deceleration time but were associated with a reversal of the E:A waveform from E predominance to A predominance as PVR was increased.

The E:A ratios derived from altering two parameters simultaneously (stressed blood volume plus LV β and stressed blood volume plus PVR) are displayed in Figure 4. At low volumes, LV β had little effect on the E:A ratio, while

at high volumes, LV β increased the E:A ratio in a manner additive to that seen with increased volume alone. PVR also had little effect on the E:A ratio at low volumes. At high volumes, increases in PVR attenuated the volume-dependent increase in the E:A ratio.

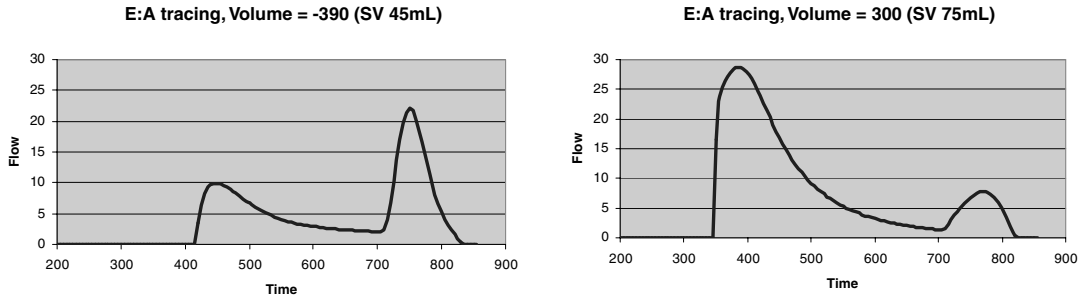
Discussion

These data demonstrate the ability of a computer simulation of the cardiovascular system to mimic mitral inflow patterns observed clinically. We found that changes in factors extrinsic to the heart (blood volume, PVR) as well as intrinsic myocardial properties (left ventricular stiffness) affect the mitral flow profile, findings which are concordant with conclusions derived from in vivo measurements.

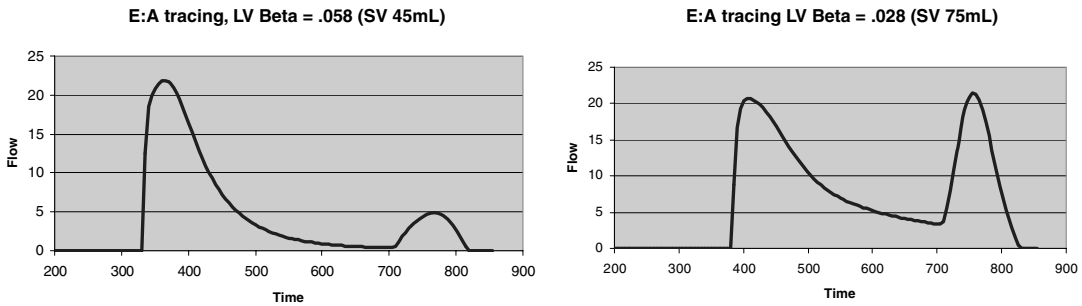
Loading Conditions

A number of clinical scenarios, including cirrhosis, chronic renal failure, and pulmonary hypertension, illustrate the effect of loading conditions on Doppler flow¹⁰⁻¹⁸ and may be mimicked using the simulator. In cirrhotic patients, who typically have a volume overloaded, low-resistance state,^{15,16} abnormal mitral flow profiles have been observed.¹⁰⁻¹² While

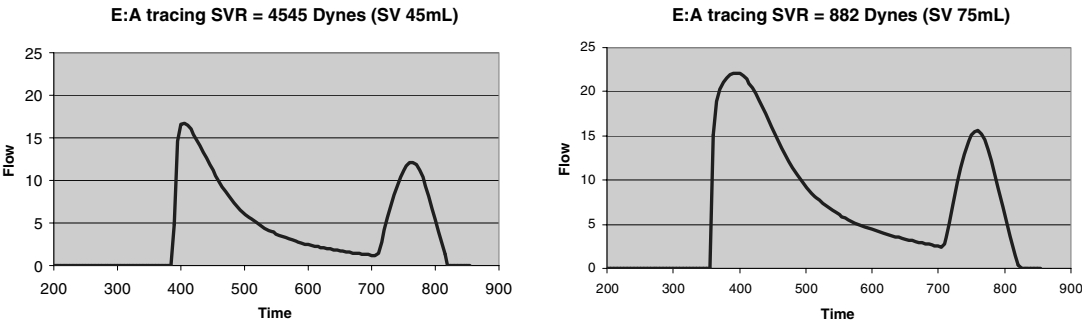
Volume



LV Beta



SVR



PVR

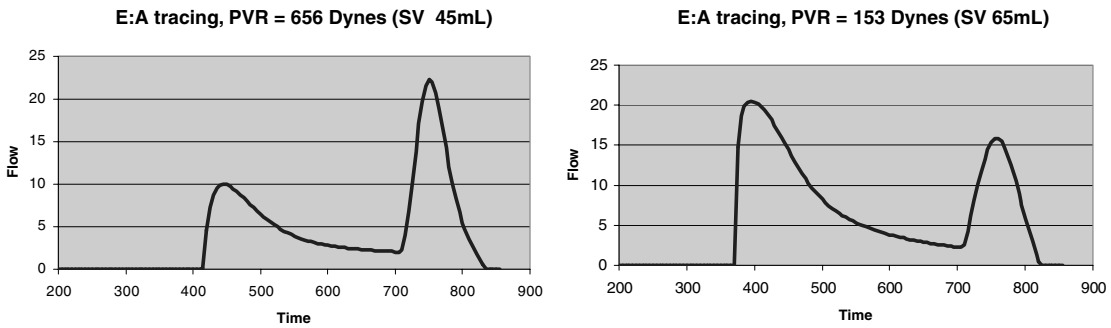


Figure 2. Mitral flow tracings obtained by varying blood volume, LV β , SVR, and PVR to achieve either high or low stroke volumes. The greatest change is seen with alterations in either blood volume or intrinsic stiffness (LV β). Of note, decreasing LV β or increasing stressed blood volume leads to increased stroke volume. Increases in pulmonary vascular resistance alter the mitral flow pattern as well, while systemic vascular resistance exerts little effect.

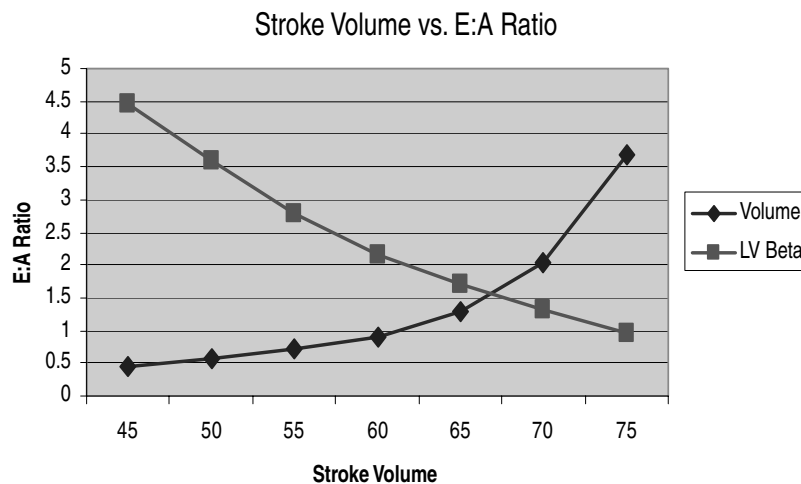


Figure 3. Comparison of changes in the E:A ratio with alterations in blood volume and LV β . Both parameters affect the E:A ratio, albeit in an opposite manner.

some have speculated that such echocardiographic findings are due to intrinsic myocardial abnormalities such as fibrosis and hypertrophy,¹⁰ our findings suggest that observed changes in the Doppler flow profile may also simply be the result of changes in blood volume in the absence of altered intrinsic ventricular stiffness. Among cirrhotics who have a normal or reduced effective blood volume as indexed by plasma renin activity (PRA),¹¹ those with a high PRA (e.g., effective hypovolemia) demonstrated an impaired relaxation pattern while those with a low PRA (e.g., hypervolemia) demonstrated a pseudonormal mitral Doppler pattern. Furthermore, after transjugular intrahepatic portosystemic shunt (TIPS), a procedure which rapidly shifts blood into the central circulation,^{11,19,20} marked changes in Doppler flow patterns were observed in those patients with effective hypovolemia with a shift from an impaired relaxation to a pseudonormal pattern. The dependence on ventricular loading conditions of Doppler flow in cirrhosis is further demonstrated by the difference between E:A ratios in patients with mild ascites compared to those with tense ascites; one study found that while the former group had an A dominant (“impaired relaxation”) flow tracing, the latter had an E:A ratio similar to that of controls.¹⁰ Tense ascites may increase effective intravascular volume, which is supported by the observation that central venous pressure is higher in this condition than in mild ascites.²¹ Collectively, these results suggest that abnormal Doppler patterns seen in cirrhotics are at least in part a result of loading conditions.

In chronic renal failure (CRF), a condition characterized by volume overload, abnor-

mal mitral flow profiles have been observed as well.^{13–16,22} Specifically, one study of CRF patients on chronic renal replacement therapy (CRRT) found that abnormal mitral flow profiles prehemodialysis normalized postdialysis,¹⁵ while another demonstrated reduction of the E:A ratio in patients who had been dialyzed greater than 1 kg.²² We observed similar patterns with changes in volume using the simulator.

In pulmonary hypertension, where increased volume loading to the right ventricle and elevated PVR result in a shift of the interventricular septum with concomitant under-filling of the left ventricle, Doppler flow profiles are frequently abnormal.^{23–25} Echocardiographic findings in pulmonary hypertension typically include an impaired relaxation pattern (with A-wave predominance) as well as a prolongation of the deceleration time.²⁶ Supportive evidence for a significant role of an elevated PVR on mitral flow profiles was demonstrated by an elegant study in which Doppler flow was recorded pre- and postsurgery for chronic thromboembolic pulmonary hypertension (CTEPH).²³ Prior to surgery, patients demonstrated a dominant A-wave pattern on Doppler echocardiography. Following thrombectomy, the mean E:A ratio reversed, appearing to normalize with the removal of the cause of increased PVR.²³ These results are concordant with our findings, which demonstrated that increasing pulmonary resistance leads to the reversal of the E:A pattern, without changing intrinsic properties of the myocardium. Of note, the simulator also allowed us to alter both volume and PVR simultaneously, which demonstrated that increased pulmonary resistance

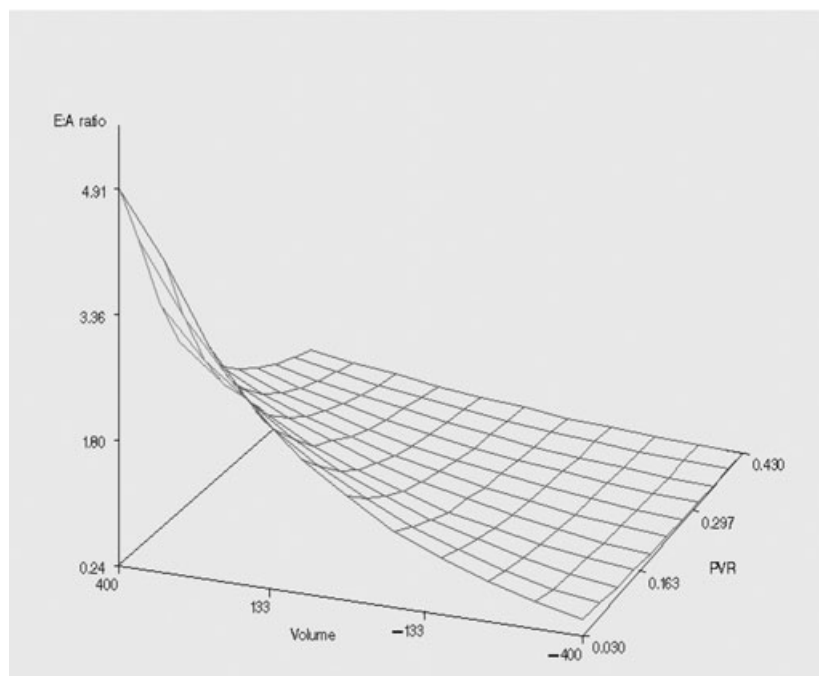
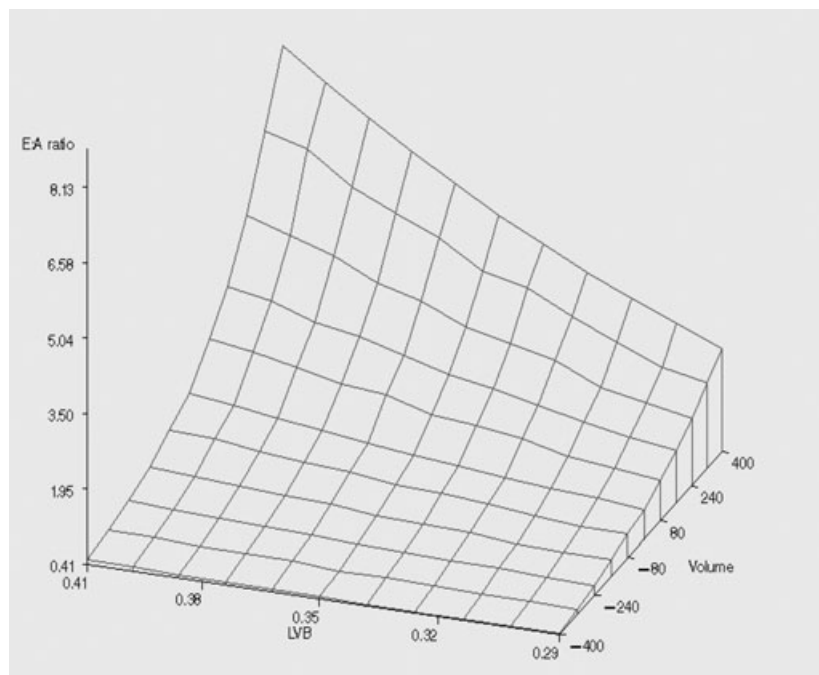


Figure 4. Three-dimensional plot of E:A ratios during simulation of two variables simultaneously. **Upper graph:** stressed blood volume plus LV β ; **lower graph:** stressed blood volume plus pulmonary vascular resistance (see the text for details).

attenuates the volume-dependent increase in the E:A ratio.

Intrinsic Ventricular Stiffness

Variations in LV intrinsic myocardial stiffness (e.g., as indexed by the parameter β) also

demonstrated a significant effect on mitral flow profiles in our study to a degree equivalent to if not greater in magnitude than changes in blood volume. Specifically, we found that in altering blood volume the deceleration time changed by an average of 7.3 ms for every 10 mL change in stroke volume (between 45 and 75 mL), while in altering LV β the deceleration time changed by

an average of 16.7 ms for every 10 mL change in SV. The effect of volume and LV β appears to be additive, as demonstrated by our analysis (Fig. 4).

The changes in mitral flow seen with variations in LV β are similar to altered echocardiographic patterns seen in disease processes intrinsic to the myocardium such as restrictive, infiltrative, or hypertrophic cardiomyopathies.^{25,27-31} In cardiac amyloidosis, for example, Doppler flow patterns correlate with disease severity, with abnormal relaxation seen early, followed by pseudonormalization and then restrictive filling as symptoms progress.²⁹ Patients with hypertrophic cardiomyopathy often exhibit an impaired relaxation pattern with prolonged deceleration time and a larger contribution of atrial systole to ventricular filling.³² In constrictive pericarditis a restrictive filling pattern may be present, with a shortened deceleration time and reduced A-wave velocity.³¹

Limitations

The use of computer modeling to simulate the cardiovascular system has been previously validated^{7,8} and has special utility in situations where it is not feasible to perform experiments in humans or where individual control over physiologic parameters cannot be obtained. However, as the experiments were done using a simulator, our results should not be considered the same as actual measurements. Our model changed only one or two variables at a time, whereas the situation in vivo is more complex. Whether more complex changes in physiologic variables have an additive, negative, or synergistic effect on Doppler flow profiles is not addressed by these data. Additionally, we did not model the effect of the loading conditions on newer measures of diastolic function including tissue Doppler or flow propagation velocity. Recent data suggest that even these variables are also dependent on loading conditions, reducing their specificity for identifying intrinsic ventricular stiffness,³³ though they clearly perform better than traditional mitral Doppler inflow patterns for identifying diastolic dysfunction.³⁴

Conclusions

Using a validated computer-based mathematical model of the cardiovascular system, we demonstrated that both blood volume and intrinsic LV stiffness significantly impact mitral

inflow patterns. Additionally, we found that isolated increases in PVR can cause an impaired relaxation pattern on mitral inflow Doppler profiles. These data confirm that there are multiple determinants of the Doppler mitral inflow pattern and suggest a new approach toward understanding complex physiologic interactions that account for abnormal Doppler flow profiles.

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