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Evaluation of LV Diastolic Function From Color M-Mode Echocardiography

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OBJECTIVES This study evaluated early diastolic filling dynamics using a semiautomated objective analysis of filling velocities obtained from color M-mode echocardiography.

BACKGROUND Diastolic function can be evaluated from color M-mode echocardiography by measuring the early diastolic flow propagation velocity (Vp) from the slope of a single linear approximation of an isovelocity contour. However, this method has limitations and may not accurately represent diastolic filling.

METHODS We used a semiautomated objective analysis of color M-mode echocardiograms from a development cohort of 125 patients with varying diastolic function to quantify left ventricular filling velocities. Early diastolic filling was not accurately described with a single propagation velocity; instead, the rapid initial filling velocity abruptly decelerated to a slower terminal velocity. Then, we evaluated a new measure of diastolic function in a separate group of 160 patients.

RESULTS Compared with normal filling, diastolic dysfunction with restricted filling had a lower initial velocity (53 ± 21 cm/s vs. 87 ± 29 cm/s, $p < 0.001$), and the deceleration point occurred closer to the mitral annulus (2.4 ± 0.6 cm vs. 3.1 ± 0.7 cm, $p < 0.05$). The product of the initial velocity and the distance to the deceleration point from the mitral annulus, indicating the strength of the early filling (Vs), was progressively reduced with diastolic dysfunction. In a separate validation cohort of 160 patients, Vs better recognized diastolic dysfunction (classified by reduced diastolic intraventricular pressure gradient, elevated pulmonary capillary wedge pressure, or elevated B-type natriuretic peptide) than Vp did.

CONCLUSIONS Early diastolic flow propagation occurs with an initial rapid velocity that abruptly decelerates to a terminal velocity. With diastolic dysfunction, the initial velocity is slower and the deceleration point occurs closer to the mitral annulus than with normal filling. A new parameter that combines these 2 effects (Vs) provides a more accurate assessment of diastolic function than the conventional propagation velocity. (J Am Coll Cardiol Img 2011;4:37–46) © 2011 by the American College of Cardiology Foundation

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Left ventricular (LV) diastolic function can be noninvasively evaluated from LV filling dynamics determined by Doppler echocardiography (1–3). Color M-mode (CMM) echocardiography provides a spatiotemporal map of the velocities of the blood flow along the scan line from the mitral annulus to the LV apex (4,5). The current method of analyzing this data is to calculate the propagation velocity (Vp) of the inflow jet traveling toward the apex during early diastole (1–3,5–11). Vp is measured as the slope of a linear approximation of an isovelocity contour. Vp is reduced in patients with diastolic dysfunction, and the ratio of peak transmitral E-wave velocity (E) to Vp is elevated when left atrial pressure is increased (3,12–16).

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ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CMM = color M-mode

E = E-wave inflow velocity

HCM = hypertrophic cardiomyopathy

IVPD = intraventricular pressure difference

LV = left ventricular

PCW = pulmonary capillary wedge

Vp = propagation velocity

Vs = early filling strength

There are several potential limitations to the use of Vp as a measure of LV diastolic function. First, in many situations, the isovelocity contour may not be accurately described by a straight line (17–19). Thus, assignment of a single slope (i.e., Vp) may not be accurate. Furthermore, Vp is subject to variation based on how the isovelocity contour is determined (1,17,20). Finally, Vp has been found to be normal in patients with hypertrophic cardiomyopathy (HCM) who have diastolic dysfunction apparent by other methods (21).

Under normal circumstances, early diastolic filling results from a progressive pressure gradient from the left atrium (3,22) that extends toward the LV apex. With diastolic dysfunction, the magnitude of the pressure gradient is reduced, and it does not extend as deeply into the left ventricle (9). Thus, we hypothesized that: 1) with diastolic dysfunction, the initial Vp of the filling wave is reduced; and 2) it would decelerate to a lower velocity prior to reaching the apex. In contrast, in normal subjects, the initial velocity would be higher and deceleration would occur closer to the LV apex.

Accordingly, we evaluated early diastolic filling using CMM echocardiograms from 125 patients with a range of diastolic function. Consistent with our hypothesis, we found that the early diastolic flow velocities were not accurately described by a single slope. We used this information to develop a new metric of early diastolic filling that more accurately recognized diastolic dysfunction. We then tested this new measure in a second cohort of 160 patients.

METHODS

Echo Doppler. Echo Doppler examinations were completed using an iE33 ultrasound imaging system with a multiple frequency transducer (Philips Medical Systems, Andover, Massachusetts). Standard 2-dimensional images were obtained in the parasternal long and short axes and in the apical 4- and 2-chamber views. Pulsed-wave Doppler tracings of mitral valve inflow were recorded at the leaflet tips. A CMM ultrasound was obtained in the apical long-axis view with a sweep speed of 100 mm/s with a scale that optimized visualization of the isovelocity color contour as judged by the recording sonographer. Recordings of the septal and lateral mitral annular velocities were averaged. The LV volumes and Doppler tracings were analyzed using a digital echocardiography workstation as previously described (23,24).

Brief description of the automated algorithm. An automated data analysis algorithm was developed to examine the CMM echocardiograph images. Original CMM images were analyzed in MATLAB (The Mathworks, Natick, Massachusetts) using in-house developed image processing algorithms. The algorithm is used to crop a region of interest (Fig. 1B) and the velocity color scale region. With this information, a point-by-point velocity reconstruction is completed on the region of interest (see the Online Appendix for additional information).

The image was reconstructed using a dealiasing technique similar to that used by Thomas et al. (25) and Rovner et al. (26) (Fig. 1D). Using image-processing tools, the E-wave velocity field was reduced to a series of 27 isovelocity contours evenly spaced between 45% and 55% of the peak E-wave transmitral velocity shown in Figure 1E. The reconstructed velocity contours are shown in Figure 1F with the 45% to 55% isovelocity contours shown from light to dark.

Ensemble contour methodology. A smoothing spline was fit to the series of isovelocity contours and is referred to as the ensemble contour in the remaining analysis (see the Online Appendix for additional information).

Change-point methodology. Previous observations of a change in slope or curvilinear isovelocity contour (17–19) are consistent with an abrupt

Figure 1. Color M-Mode Echocardiography Analysis Method Overview

Color M-mode echocardiogram analysis of a restrictive filling patient. **(A)** Original image. **(B)** Extracted region of interest (ROI). **(C)** ROI after a point-by-point velocity reconstruction. **(D)** Antialiased ROI. **(E)** ROI displaying isovelocity contours from 45% to 55% of the E-wave peak transmitral velocity. **(F)** Isovelocity contours shown from **light** to **dark. Arrows** in **E** and **F** indicate the deceleration point location. **(G)** Initial **(pink)** and terminal **(green)** propagation velocities.

deceleration of the LV filling wave. We used a statistical change-point analysis method (27,28) on the derivative of the ensemble contour (Figs. 2D and 2I) to objectively determine the deceleration point. The method is based on a cumulative sum of the difference between the value of interest (x_i) and the mean value ($\bar{x}$). Equation 1 displays the cumulative sum equation:

$$Cumulative\ Sum_i = Cumulative\ Sum_{i-1} + (x_i - \bar{x})$$

The waveform produced by the output of the cumulative sum equation was plotted to determine the significance of the change throughout the signal (Figs. 2E and 2J). The peaks within this cumulative sum waveform were sorted according to their magnitude. The peak with the highest magnitude signifies the most statistically significant change and was labeled as the deceleration point.

Pressure calculations. The 1-dimensional incompressible Euler equation, shown in Equation 2, where p is the pressure, ρ is constant blood density, and ν is velocity, was used to calculate the relative pressures within the region of interest from the reconstructed velocity field. The pressure at each point along a scan line was calculated relative to the position of the mitral annulus just prior to mitral valve opening by calculating the line integral between them (9,29,30).

$$\frac{\partial p}{\partial s} = -\rho\left(\frac{\partial v}{\partial t} + \nu\frac{\partial v}{\partial s}\right)$$

From the relative pressures, the peak diastolic intraventricular pressure difference (IVPD) from the left atrium to the LV apex was calculated similar to the calculations of Greenberg et al. (30) and Rovner et al. (26). This method has been validated by comparison to direct measurements with micromanometers (9,30). The IVPD provides a measure of the strength of LV diastolic suction (9). We used an IVPD of 2.2 mm Hg as the lower limit of normal based on the observations of the IVPD in healthy volunteers by Yotti et al. (9).

Early filling velocity strength. We observed that early filling is characterized by a point at which the Vp abruptly decelerates, indicating that a single straight line is not an accurate approximation for the Vp parameter. The ensemble contour was divided at the deceleration point into 2 segments: the initial

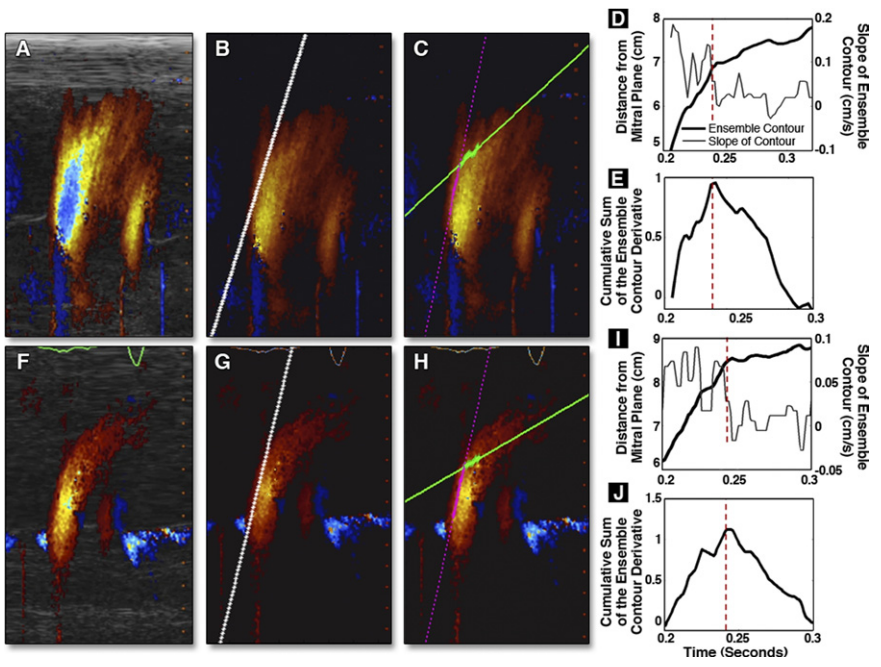

Figure 2. Propagation Velocities and Deceleration Point Location

(A, F) Color M-mode echocardiograms of a normal **(top)** and restrictive filling **(bottom)** patient. **(B, G)** Dealiased region of interest displaying conventional propagation velocity. **(C, H)** Dealiased region of interest displaying initial and terminal propagation velocities, deceleration point located at their intersection. **(D, I)** Ensemble contour and ensemble contour slope. **(E, J)** Cumulative sum calculated from ensemble contour slope. **Vertical dotted line** represents deceleration point time.

propagation region and the terminal propagation region. A line was fit to the ensemble contour for each filling region to calculate the propagation velocities before (initial Vp) and after the deceleration point (terminal Vp), as shown in Figure 2C and 2H as the 2 intersecting lines where the junction is the deceleration point.

We calculated the distance from the position of the mitral annulus just prior to the opening of the mitral valve to the deceleration point, L_i. The product of this distance and the initial Vp represents the strength of early filling (Vs).

$$V_s = \text{InitialVp} \cdot L_i$$

Patient population. Two independent groups of patients were used in this study: a development cohort consisting of 125 patients and a validation cohort consisting of 160 patients. These were selected from patients undergoing clinically indicated comprehensive echocardiography and Doppler evaluation at the Wake Forest University Baptist Medical Center. The study was conducted according to protocols approved by the Virginia Tech and Wake Forest University Baptist Medical Center institutional review boards.

Diastolic dysfunction stages were assigned based on the mitral valve inflow, tissue Doppler mitral annular velocities, and conventional Vp measured according to the American Society of Echocardiography guidelines (3).

DEVELOPMENT COHORT. The patients in the development cohort were selected to create 5 equally sized categories. Due to the wide range of ages, the healthy filling category was divided into 2 categories: the first group was <30 years of age, and the second group was ≥30 years of age. The remaining 3 categories were composed of 25 patients with each of the 3 stages of diastolic dysfunction: delayed relaxation filling (stage 1); pseudonormal filling (stage 2); and restrictive filling (stage 3) (Table 1). Seventeen patients from the development cohort were randomly selected for the assessment of parameter reproducibility. The patients were analyzed 3 independent times by 3 different observers to assess the interobserver and intraobserver variability.

VALIDATION COHORT. The patient population for the validation cohort consisted of 160 patients, including 10 patients with HCM (Table 2). It is important to note that development cohort CMM data included only good image quality scans and that CMM images with merged E and A waves

Table 1. Clinical Characteristics of the Testing Cohort

Diastolic Dysfunction Stage	Number of Patients	Age (yrs)	E/A*	E/E′†	Ejection Fraction
0—Healthy, age <30 yrs	25	24.36 ± 4.25	1.98 ± 0.69	6.53 ± 1.47	0.57 ± 0.05
0—Healthy, age >30 yrs	25	47.36 ± 14.33	1.54 ± 0.31	7.88 ± 2.66	0.62 ± 0.05
1—Delayed relaxation	25	68.32 ± 9.62	0.79 ± 0.11	13.00 ± 4.22	0.57 ± 0.13
2—Pseudonormal	25	66.20 ± 12.94	1.58 ± 0.31	16.40 ± 5.27	0.40 ± 0.15
3—Restrictive filling	25	59.44 ± 18.50	2.91 ± 1.02	18.77 ± 7.38	0.28 ± 0.08

Patients are classified based on clinically diagnosed diastolic dysfunction stage. Values represent mean ± SD. *E-wave to A-wave transmitral velocity ratio. †E-wave transmitral to E-wave mitral annulus velocity ratio.

were not included. The validation cohort's CMM selection criteria were less strict, and patients with fair to poor image quality and merged E and A waves were included in the analysis. Other analysis of observations in some of the validation patient population has been previously published by Brucks et al. (31).

Each of these patients had a clinically indicated echo-Doppler examination. Fifty-six of these patients had undergone cardiac catheterization with measurement of the pulmonary capillary wedge (PCW) within 2 days of the echocardiography; 117 of the patients had a serum B-type natriuretic peptide (BNP) determination on the same day as the echo. In the validation cohort, we assessed the ability of CMM parameters to recognize diastolic dysfunction defined in 3 different ways. These included: 1) elevated mean PCW pressure >18 mm Hg; 2) elevated serum BNP >100 pg/ml (31–33); and 3) reduced IVPD <2.2 mm Hg, indicating reduced LV suction (9).

Statistical analysis. Data are expressed as mean ± SD. We analyzed statistical significance among groups using a 1-way analysis of variance and the Tukey-Kramer honest significant difference test.

The squared correlation coefficient, R^2, was used to compare a single linear fit and the combined initial and terminal fit of the leading edge of the early filling wave (Table 3).

The ability to distinguish patients with diastolic dysfunction from normal filling was analyzed by

Table 2. Clinical Characteristics of the Validation Cohort

Subset With IVPD Measurement

n	Age, yrs	Sex, n (%)		EF <0.4, n (%)	Diastolic function, n (%)	
160	57 ± 13	Male	92 (58)	29 (18)	Normal	52 (33)
		Female	68 (42)		Impaired relaxation	51 (32)
					Pseudonormal filling	26 (16)
					Restricted filling	24 (15)
					Not determined	7 (4)

Subset With BNP Measurement

n	Age, yrs	Sex, n (%)		EF <0.4, n (%)	Diastolic function, n (%)	
117	58 ± 14	Male	61 (52)	25 (21)	Normal	40 (34)
		Female	56 (48)		Impaired relaxation	43 (37)
					Pseudonormal filling	18 (15)
					Restricted filling	15 (13)
					Not determined	1 (0.9)

Subset With PCW Pressure Measurement

n	Age, yrs	Sex, n (%)		Period Between Echo and Catheterization, h	EF <0.4, n (%)	Diastolic Function, n (%)	
56	56 ± 19	Male	38 (68)	20 ± 15	14 (25)	Normal	20 (36)
		Female	18 (32)			Impaired relaxation	8 (14)
						Pseudonormal filling	9 (16)
						Restricted filling	13 (23)
						Not determined	6 (11)

BNP = B-type natriuretic peptide; EF = ejection fraction; IVPD = intraventricular pressure difference; PCW = pulmonary capillary wedge.

Table 3. Coefficient of Determination of Linear and 2-Stage Initial and Terminal Contour Fits

Diastolic Dysfunction Stage	Linear Fit R^2 Value	Initial and Terminal Fit R^2 Value	p Value
Healthy, age <30 yrs	0.77	0.84	0.0098
Healthy, age >30 yrs	0.77	0.87	0.0328
Delayed relaxation	0.76	0.84	0.0461
Pseudonormal	0.82	0.89	0.0716
Restrictive filling	0.78	0.84	0.1065

receiver-operator characteristic curves. The diagnostic ability of the parameters was assessed by comparing the area under the receiver-operator characteristic curves with the method of DeLong et al. (34) using MedCalc Statistical Software (MedCalc Software bvba, Mariakerke, Belgium). JMP Statistical Discovery Software (SAS Institute Inc., Cary, North Carolina), was used for the other statistical analyses.

RESULTS

Analysis of the development cohort. The isovelocity contours were not linear as the 2-stage initial and terminal fit provided considerably better fits than a single linear approximation (Table 3). This nonlinearity was also present by visual inspection. Because the slope abruptly decreased at the discontinuity point, we termed this the deceleration point. Using a change-point analysis, the location of the deceleration point occurred furthermost into the LV for healthy patients and patients with delayed relaxation filling (3.1 ± 0.7 cm and 3.3 ± 0.8 cm, respectively) and progressively decreased with increased diastolic dysfunction (2.4 ± 0.6 cm for restrictive filling), shown in Figure 3A.

The inflow wave was split into an initial and terminal section before and after the deceleration point. The initial Vp progressively decreased with diastolic dysfunction shown in Figure 3B. The terminal Vp was lower than the initial Vp and was similar in normal subjects and patients with increasing diastolic dysfunction shown in Figure 3C. Because both the initial Vp and the distance to the deceleration point decreased with increasing diastolic dysfunction, we calculated their product as a potential new diastolic parameter. This product indicates the strength of the initial flow propagation (Vs) and represents the magnitude of LV suction. Vs was progressively decreased with increasing diastolic dysfunction (Fig. 4B). In the development cohort, Vs was better at distinguishing patients with diastolic dysfunction from normal subjects than conventional Vp (Fig. 5).

The variability of repeated measures of Vs was 9.9% for intraobserver and 13.8% for interobserver. Additional analysis of the intraobserver and interobserver variability values of Vs parameter, deceler-

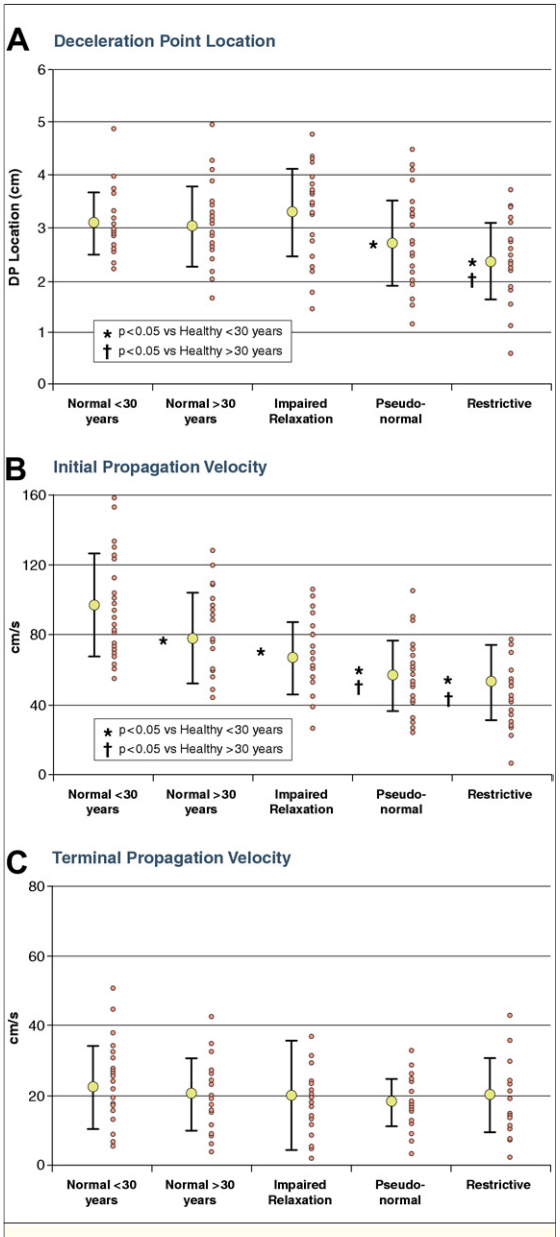

Figure 3. DP Location and Initial and Terminal Propagation Velocities

The distance into the left ventricle where the velocity deceleration point (DP) occurs is progressively decreased with more severe diastolic dysfunction, as is the initial propagation velocity. In contrast, the terminal propagation velocity is similar in all groups.

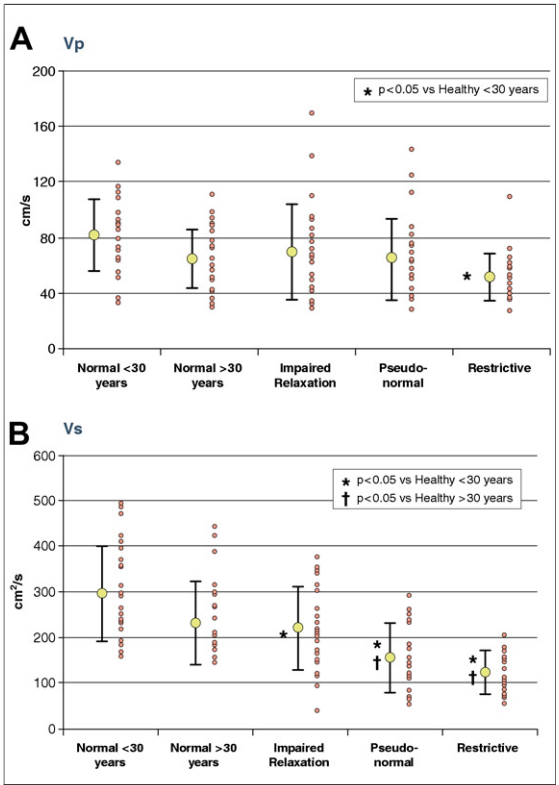

Figure 4. Conventional Vp and Vs

The conventional flow propagation velocity (Vp) is reduced from normal <30 years in patients with restricted filling patterns. The early filling strength (Vs) progressively declines with increasing diastolic dysfunction.

ation point location, and initial Vp and terminal Vp values are in the Online Appendix. The variability of all parameters was calculated from a single beat for each patient and does not include beat-to-beat variability.

Analysis of the validation cohort. In the validation cohort, Vs was consistently better at recognizing diastolic dysfunction than conventional Vp whether diastolic dysfunction was defined as a reduced IVPD, elevated PCW pressure, or elevated BNP (Fig. 6). The pairwise agreement of the 3 measures of diastolic dysfunction was: IVPD versus BNP = 57%; PCW versus BNP = 55%; PCW versus IVPD = 65%.

We separately analyzed 10 patients with HCM who had abnormal diastolic filling patterns and 50 normal subjects with normal filling pattern. We found that Vs (area under the curve [AUC] = 0.76) was superior to conventional Vp (AUC = 0.58, p = 0.022) in detecting the 7 patients with HCM who had diastolic dysfunction (IVPD <2.2 mm Hg).

DISCUSSION

Color M-mode echocardiography provides a spatiotemporal map of early diastolic filling. Conventionally, this has been evaluated by calculating the slope of an isovelocity contour representing the Vp. Using an objective quantitative analysis of the CMM data, we found that a single slope does not accurately represent the Vp for normal subjects or patients with diastolic dysfunction. Instead, the flow propagation is characterized by a more rapid initial slope indicating rapid flow propagation that abruptly slows after a deceleration point. In the presence of diastolic dysfunction, the initial slope is reduced and the deceleration point moves progressively closer to the mitral annulus. The product of the initial slope and the distance to the deceleration point (Vs) provides a measure of the strength of early diastolic LV suction and may provide a better measure of diastolic function than the conventional Vp.

Under normal circumstances, early diastolic filling results from a progressive pressure gradient from the left atrium (4,22) that extends most of the way to the LV apex. This results in a rapid initial Vp that extends 3.1 ± 0.7 cm from the mitral annulus toward the LV apex. With diastolic dysfunction, the magnitude of the pressure gradient is reduced, and it does not extend as deeply into the left ventricle (9). Thus, we observed with diastolic dysfunction that the initial Vp is reduced and that filling wave decelerates to a lower velocity closer to the mitral annulus. After termination of the pressure gradient, the terminal Vp is reduced to similar levels in all subjects regardless of diastolic function.

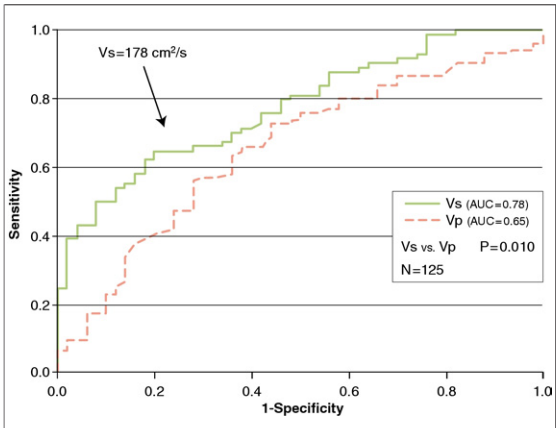

Figure 5. Development Cohort ROC Curves

Receiver-operator characteristic (ROC) curves displaying the ability of Vp and Vs to discriminate normal subjects from subjects with abnormal diastolic filling patterns. Vs performs better than Vp.

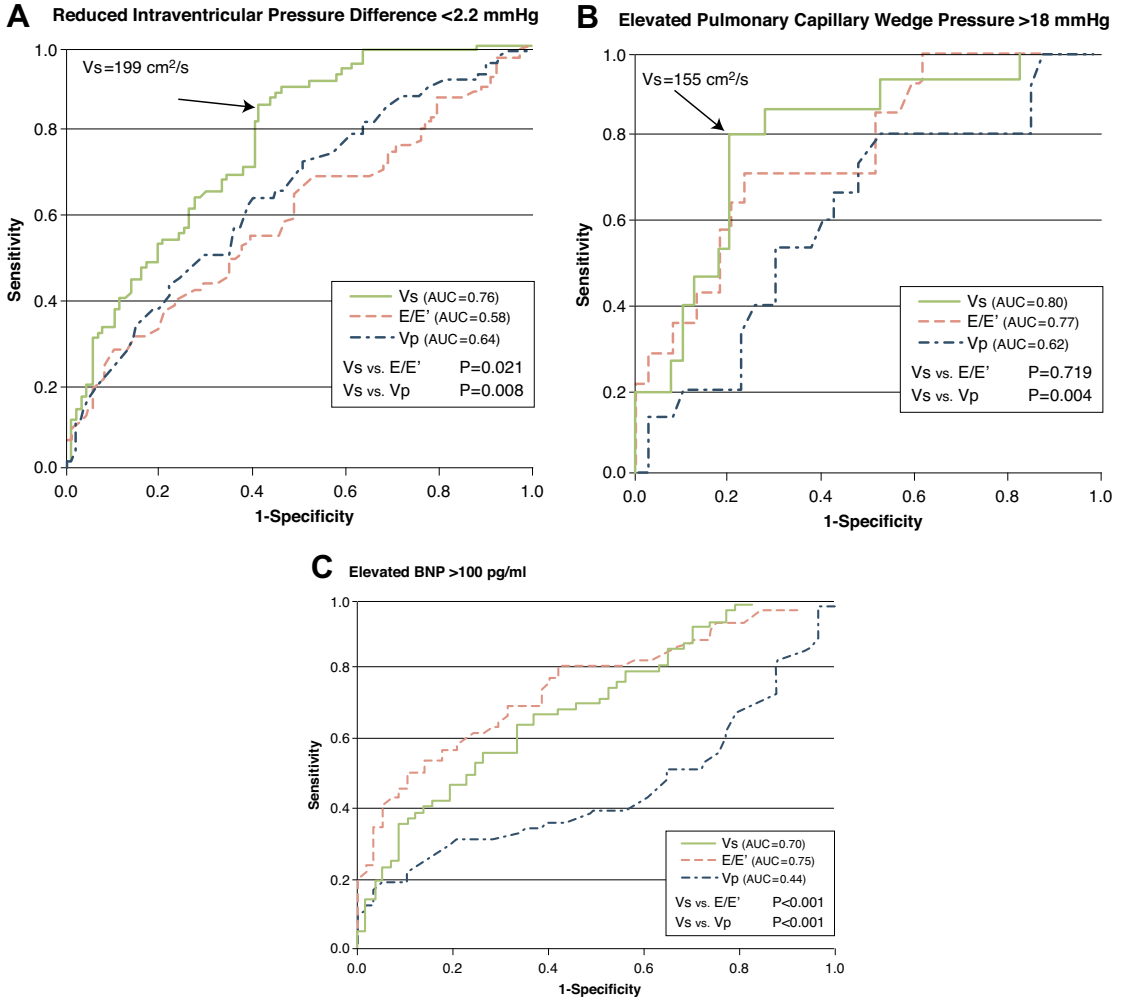

Figure 6. Validation Cohort ROC Curves

ROC curves displaying the ability of color M-mode parameters to detect diastolic dysfunction recognized as: **(A)** a reduced intraventricular pressure gradient <2.2 mm Hg, **(B)** an elevated pulmonary capillary wedge pressure >18 mm Hg, and **(C)** an elevated B-type natriuretic peptide >100 pg/ml. Regardless of how diastolic dysfunction is defined, Vs was superior to Vp. BNP = B-type natriuretic peptide; E = E-wave inflow velocity; other abbreviations as in Figures 4 and 5.

This terminal Vp may represent slower inertial flow in the absence of a pressure gradient. The terminal Vp may also be reduced due to deviation of flow from the M-mode scan line.

Propagation velocity is conventionally calculated as the linear slope of an isovelocity contour from the mitral annulus to 4 cm into the LV as recommended by the American Society of Echocardiography (3). Patients with normal filling display a deceleration point that occurs 3.1 ± 0.7 cm from the annulus. Accordingly, the initial Vp and conventional Vp for normal filling are similar. In contrast, in restrictive filling, the deceleration point occurs closer to the mitral annulus (2.4 ± 0.6 cm). Thus, in this circumstance, the conventional Vp will be determined by both the initial Vp and the terminal Vp, further decreasing the conventional Vp below the initial Vp alone. Clinically, Vp may be measured using only the initial linear portion. In patients with impaired filling and a short distance to the deceleration point, this will produce a higher value for Vp and potentially fail to recognize diastolic dysfunction.

The conventional Vp is frequently normal in severely hypertrophied ventricles that have clear evidence of diastolic dysfunction (3). Accordingly, we assessed the new Vs parameter in 10 patients with HCM and found that its performance was superior to conventional Vp in accurately detecting diastolic dysfunction in HCM. These results should be interpreted with caution because of the small sample size.

Study limitations. We analyzed the degree of diastolic dysfunction in the development cohort based on the mitral inflow and tissue Doppler. In the validation cohort, we used BNP, IVPD, and invasively determined PCW pressure to provide 3 independent means of recognizing diastolic dysfunction. However, none of these standards is a perfect method of evaluating LV diastolic dysfunction. Increased BNP values are correlated with diastolic dysfunction (32); however, BNP values can be influenced by other factors (35). The IVPD provides another objective measure of the degree of diastolic dysfunction. We used a method to calculate the IVPD that has been validated by comparison to micromanometer pressure measurements (9,30). However, the values are not completely independent of the echocardiography analysis because relative pressures were calculated from CMM using the Euler relationship. The PCW measurements were not performed simultaneously with the echocardiograms, thus diminishing the accuracy of the measurement in assessing diastolic dysfunction at the time of the echo-Doppler examination. The limited agreement of the 3 methods of evaluating diastolic dysfunction may indicate that diastolic function is a complex process that cannot be evaluated by a single parameter. Despite the potential limitations of the 3 methods of independently defining diastolic function, we found that Vs consistently performed better than Vp. This suggests that Vs provides a superior method of recognizing diastolic dysfunction from CMM echocardiography.

We used an algorithm to analyze a single beat of previously acquired clinical studies. It is possible that the algorithm could be implemented online as data are being acquired and applied to multiple beats. This has the potential to improve its accuracy. Although we used a quantitative analysis algorithm, the initial Vp and the distance to the deceleration point can be recognized by visual inspection (Fig. 2).

In the development cohort, we included only patients with high-quality CMM images. However, in the evaluation cohort, we did not exclude patients based on the quality of the images. This demonstrates the robustness of the analysis algorithm and the potential utility of Vs.

CONCLUSIONS

The propagation of flow into the LV in early diastole does not have a single velocity. The initial rapid flow velocity suddenly slows at a deceleration point. Diastolic dysfunction is characterized by a reduction of the initial Vp and the deceleration point occurring closer to the mitral annulus. The product of these 2 parameters, Vs, which reflects the strength of early diastolic filling, provides a more accurate assessment of diastolic function than conventional measurement of Vp from CMM echocardiography.

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Key Words: diastole ■ echocardiography ■ heart failure ■ imaging.

▶APPENDIX

For detailed methodology and analysis information, please see the online version of this article.