Left Ventricular Velocity of Propagation: A Useful Non-Invasive Measurement When Assessing Hemodynamic Alterations in Pulmonary Arterial Hypertension

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Abstract

Background: Left ventricular (LV) velocity of propagation (Vp) has been shown to be inversely related to the LV relaxation time constant. We sought to examine Vp from a group of chronic pulmonary hypertension (cPH) patients and compare these values to Vp obtained in normal individuals and patients with known LV diastolic dysfunction (LVDD).

Methods: Echo-Doppler data and Vp measurements were retrospectively collected from all patients. The studied population was divided into four groups. Group I comprised of 15 patients with normal LV diastole, group II included 27 patients with stage 1 LVDD, group III was made up of 27 patients with stage 2 LVDD, and group IV included 66 patients with cPH.

Results: In the cPH population studied, patients had smaller end-diastolic LV cavities with the highest Vp values but their early mitral inflow to Vp ratios were not different from healthy controls. In addition, Vp values and pulmonary wedge capillary pressures were significantly associated in patients with LV dysfunction or pulmonary hypertension (P < 0.01).

Conclusions: LVVp might be a useful non-invasive measurement to be routinely obtained in cPH patients as it probably not only reflects the compressive forces being exerted on the LV, known to increase Vp, but also might be quite useful for the non-invasive assessment of pulmonary capillary wedge pressures in these patients.

Keywords: Cardiac hemodynamics; Echo-Doppler; Left ventricle; Right ventricular dysfunction; Relaxation; Propagation velocity

Introduction

The physiology of normal left ventricular (LV) early-diastolic filling not only is regulated by indices of active relaxation and passive chamber stiffness, but also by principles of fluid dynamics [1-3]. Even though elastic recoil and myocardial relaxation rate determine LV early-diastolic performance, the integrity of LV synchrony and geometry is essential to maintain the effect of their timely action on early-diastolic LV filling [4]. These factors are not only prime determinants of LV pressure decay during isovolumic relaxation and immediately after mitral valve opening, but they also instigate the generation of a sufficient intra-ventricular pressure gradient, which enhances efficient early-diastolic LV filling [4]. Accurate non-invasive echo-Doppler assessments of LV diastolic abnormalities have important therapeutic and prognostic implications. However, at times it remains a potential challenge for many cardiologists, particularly when evaluation of LV relaxation using standard Doppler echocardiographic parameters is hindered by their preload dependency [5].

Color M-mode of the mitral inflow displays color-coded mean velocities of the blood column as it propagates from the left atria to LV. This velocity of propagation (Vp) not only is inversely related to the LV relaxation time constant, but also is a largely preload independent index of LV diastolic performance [6-12]. Color M-mode Vp data have been studied both in animals and humans [13] and found particularly useful to identify patients with varying degrees of LV diastolic dysfunction (LVDD) [12-16].

Both magnitude and vector of the pressure gradient formation are dependent on LV geometry. Specifically, apical to base negative gradient formation is enhanced in small ellipsoidal LV cavities and corresponding Vp values higher than in normal sized ventricles, as blood redistribution by vortex formation and propagation requires that the LV diameter sufficiently exceeds the mitral diameter [17-20].

Since the pressure-overloaded right ventricle (RV), as a result of pulmonary arterial hypertension (PAH), not only is known to significantly alter LV geometry [21], but also impair
LV filling based on cardiac magnetic resonance data [22], we sought to study if there were any differences in Vp values obtained from PAH patients when compared to patients with normal LV diastolic function as well as with patients with stage 1 and 2 LVDD.

Methods

Population studied

Study approval was obtained from the University of Cincinnati IRB Office (protocol number 12061302) and since this was a retrospective study, there was no need to obtain a written consent.

For the purpose of this study, our echocardiographic database at the University of Cincinnati was queried for transthoracic echocardiograms in which color M-mode acquisition was performed across the mitral valve from the four-chamber apical view. Consecutive studies were reviewed and for final inclusion into the study, all patients had to be in normal sinus rhythm at the time of the examination. In addition, a complete spectral Doppler study was needed to examine LV diastolic function in accordance with American Society of Echocardiography guidelines [16, 23]. In contrast, data from patients with atrial fibrillation, frequent premature or atrial contraction beats were excluded. Patients with LVDD stage 3 were also excluded, as most of subjects falling into this category have significant LV systolic dysfunction which could be an important cofounder in our study.

Echocardiographic studies

Two-dimensional echocardiographic studies were performed using commercially available systems (Vivid 7 and 9; GE Medical Systems, Milwaukee, WI, USA). Images were obtained in the parasternal and apical views with the patient in the left lateral decubitus position and in the subcostal view with the patient in the supine position using a 3.5 MHz transducer. Standard two-dimensional, color, pulsed, and continuous-wave Doppler data were digitally acquired in gently held end-expiration, and saved in regular cine loop format for subsequent offline analysis.

The following parameters were measured. 1) LV end-systolic and end-diastolic volumes were traced from the apical four-chamber view in accordance to published data, while ejection fraction calculations were done using the Simpson’s rule algorithm [23]. 2) Mitral inflow velocities were obtained using pulsed-wave Doppler examination at a sweep speed of 100 mm/s from the apical four-chamber view by placing the sample volume at the tips of the mitral leaflets and peak early-diastolic (E-wave) velocity was measured as previously described [16]. 3) In terms of tissue Doppler imaging (TDI) of the lateral portion of the mitral annulus (MA), early-diastole (E’) and late-diastole (A’) velocities were measured by placing the sample volume at the junction where the mitral valve plane intersects the LV free wall using images obtained from the apical four-chamber view. LV diastolic pressures were estimated using the mitral valve inflow E/mitral annular TDI E’ ratio [16]. Finally, LV diastolic function was classified as normal, impaired relaxation, or pseudonormal pattern following published recommendations [16]. 4) Color M-mode acquisitions were made from the four-chamber view during transthoracic apical imaging. Direction of the inflowing blood is identified by placing a large color box from the mitral valve to the apex and care is taken to assure that the scan line goes through the center of the mitral valve and along the central part of the blood column (staying within the 60% central part of the mitral orifice and limiting misalignment to < 20° is acceptable) [8, 9]. Gain is set at sub-saturation levels and the Nyquist range limit is adapted to ±75% of the spectral E velocity to obtain overflow (“aliasing”). Switching to M-mode and with the chart recorder set at a sweep rate of 100 mm/s, an M-mode spatio-temporal velocity map with the shape of a “flame” is displayed, as shown in Figure 1.

From the Vp data then the following quantitative information was obtained. First, a Vp value between 55 and 45 cm/s is used to define impaired relaxation in the young, and mid-aged
Results

The study population included 135 patients that were divided into four groups. Group I included 15 patients with a normal LV diastolic function (mean age 41 ± 11 years, 60% males). Group II consisted of 27 patients classified as LVDD stage 1 (mean age 59 ± 12 years, 67% males). Group III included 27 patients classified as LVDD stage 2 (mean age 57 ± 13 years, 54% females). Group IV was composed of 66 patients with known chronic PAH by prior heart catheterization (mean age 57 ± 13 years, 83% females). None of the individuals of groups I, II and III had any grade of PAH. While patients in group I were younger any other three groups, as expected, there was no statistical difference in terms of age between the two LVDD and PAH groups (P > 0.05). Furthermore, most of the patients in both groups I and II were males while females predominated in groups II and IV. Finally, there was no statistical difference in terms of body surface area (BSA) among the studied groups (group I: 1.96 ± 0.33; group II: 1.98 ± 0.24; group III: 2.11 ± 0.38; group IV: 2.01 ± 0.31; P = 0.067).

With regard to the relevant echocardiographic data collected for this study as seen in Table 1, the largest end-systolic as well as end-diastolic LV volumes were found in group III patients. Similarly, the smaller end-diastolic LV volumes were noted in PAH (group IV) patients. Also, LV ejection fraction (EF) was lowest in group III and IV when compared to the other two groups. Finally, both MA E/A’ and MV E/MA E’ ratios were used to confirm the LVDD classification.

Table 1. Relevant Echocardiographic Data of the Studied Population

| Variables          | Group I (n = 15) | Group II (n = 27) | Group III (n = 27) | Group IV (n = 66) | P-value |
|--------------------|-----------------|------------------|-------------------|------------------|---------|
| LVESV (cm³)        | 40 ± 15         | 40 ± 27          | 73 ± 54           | 34 ± 17          | < 0.01  |
| LVEDV (cm³)        | 119 ± 30        | 112 ± 30         | 145 ± 66          | 81 ± 35          | < 0.01  |
| LVEF (%)           | 67 ± 7          | 67 ± 13          | 57 ± 13           | 59 ± 9           | < 0.01  |
| MA E/A ratio       | 1.3 ± 0.3       | 0.8 ± 0.1†       | 1.7 ± 0.7§        | 1.2 ± 0.6        | < 0.01  |
| MV E/MA E’ ratio   | 7 ± 3           | 9 ± 3            | 17 ± 6β           | 10 ± 12          | < 0.01  |

LV: left ventricle; LVESV: LV end-systolic volume; LVEDV: LV end-diastolic volume; LVEF: LV ejection fraction; MA: mitral annulus; MV: mitral valve. †Bonferroni test indicates significant differences (P < 0.05) between group II and groups I, III, IV. §Group III and group II. βGroup III and groups I, II, IV and §Group IV and groups I, II, II.

Discussion

Our study is firstly, to our knowledge, aimed directly at comparing Vp values obtained from a heterogeneous group of PAH patients to Vp values acquired from patients with both normal and abnormal LV diastolic function (stages 1 and 2). From our analysis, we found that the highest Vp values are recorded from PAH patients while the lowest Vp values were seen in LVDD patients.

On a typical color M-mode tracing, Vp data are displayed along a scan line with a temporal resolution of 5 ms, a spatial resolution of about 1 mm, and a velocity resolution equal to the forward plus the reversed Nyquist limit divided by 32 [12]. In

Statistical analysis

All echocardiographic parameters were calculated using the commercially available software Merge Cardio Workstation (Merge Healthcare). Continuous variables were compared between all groups using one-way analysis of variance (ANOVA) with Bonferroni correction, assuming equal variances. In addition, simple linear regression analysis was the preferred method to determine the association between continuous variables. A P-value of less than 0.05 was considered statistically significant. All statistics were calculated in MedCalc Software bvba Version 14.12.0 (Belgium).
a typical color M-mode tracing while the patient is in normal sinus rhythm, the first wave propagates from the atria to the ventricular apex corresponding to early filling and a second wave follows atrial contraction. The magnitude of these velocities is highest above the valve leaflet tips and decreases as flow approaches the apex, as shown by the change in encoding color. Additionally, in normal ventricles, the spatial position of the maximal velocity is closer to the ventricular apex for the early filling wave than it is for the atrial contraction wave, suggesting that intraventricular pressure gradients during early filling produce a suction force that accelerates flow beyond the valve orifice [12, 14].

The utility of color M-mode interrogation across the mitral valve depicting Vp data has been useful in terms of assessing LV diastolic function. Initial validation data, published by Garcia et al, demonstrated that color M-mode Doppler Vp data not only were unaffected by preload alterations, but also mainly dependent on LV relaxation [13]. Furthermore, Stewart and associates analyzing color M-mode propagation velocities in patients with varying degrees of LVDD found that early-diastolic flow propagation occurs with an initial rapid velocity that abruptly decelerates to a terminal velocity [15]. Most im-

Figure 2. (a) Box plot representation of Vp values from all four groups. Bonferroni test indicates significant differences (P < 0.05) between: (#) PAH and control, LVDD 1, LVDD 2 and (%) control and LVDD 1, LVDD 2 groups. (b) Box plot representation of PCWP values from all four groups. Bonferroni test indicates significant differences (P < 0.05) between: (^)LVDD 2 and control, LVDD 1, PAH and (*) LVDD 1 and control, PAH groups.
Figure 3. Representative color M-mode Vp images for the four studied groups.

Figure 4. Scatter plot graphs showing the relationship between Vp and PCWP for all study groups.
portantly, they also noted that with LVDD the initial velocity is slower and the deceleration point occurs closer to the MA than with normal filling.

Even though the American Society of Echocardiography identified Vp not only as a semiquantitative marker of LVDD, but also in its use in conjunction with mitral E as useful in predicting LV filling pressures in a previous publication [5], the new guidelines point out that Vp though reliable as an index of LV relaxation in patients with depressed LV systolic function and dilated LV was not so useful in patients with normal LV systolic function [16]. Furthermore, the American Society of Echocardiography has now issued some comments regarding Vp due to lower feasibility and reproducibility as well as problems with angulation between M-mode cursor and flow that might lead to erroneous measurements.

Notwithstanding Vp values have not been previously compared between PAH and patients with LVDD, our laboratory has used color M-mode to study if there were any differences between the temporal onset of the Vp signal between individuals with normal pulmonary artery systolic pressures and patients with chronic PAH [30]. In this study, we found that chronic PAH not only disrupted RV and LV diastolic Vp signal distribution, but also their temporal occurrence. These findings implied the presence of significant interventricular diastolic dysynchrony as a result of PAH.

From a mechanistic point of view RV remodeling is known to occur as a result of an increased afterload in PAH. During this adaptive process RV hypertrophy initially occurs, followed by RV dilation [31]. Once the RV dilates not only RV contractility is compromised, but also this causes further RV dilatation due to tricuspid regurgitation. Since the RV and LV do not function in isolation and share a common pericardial sac and interventricular septum, the leftward ventricular septal bowing that occurs with PAH not only leads to LV underfilling [32, 33], but also impaired LV contractility occurs through ventricular interdependence [32]. Reduction in early LV diastolic filling velocity documented by cardiac magnetic resonance imaging has been clearly shown as a result of an abnormal intraventricular septal deformation toward the LV cavity [34, 35]. Our group has previously shown that this abnormal systolic eccentricity motion is the best echocardiographic predictor of PH [36]. Therefore, the results of the present study seem to align with the known functional and anatomical changes occurring as a result of PAH resulting in significantly higher Vp values. In fact, we have previously described a case report of a patient with severe PAH whose propagation velocity was almost perpendicular after Valsalva, resembling the propagation velocity profile of patients with constrictive pericarditis [37].

The presence of both RV systolic and diastolic dysynchrony has been shown to occur in PAH patients [30, 38, 39]; however, LV diastolic flows have not been either well studied or characterized. Therefore, these results underscore the need to broaden our attention when studying the effects of PAH, so that we can better understand our findings in lieu of clinical symptoms and overall prognosis.

The following limitations need to be acknowledged. First, this was a retrospective study; however, the main goal was attained. Second, a small number of patients were included for analysis. However, the main purpose of this study was to determine if there were any difference in Vp values from PAH patients when compared to patients with normal LV diastolic function as well as with patients with stage 1 and 2 LVDD and this was demonstrated. Third, based on the pre-specified exclusion criteria no assumptions can be made on how atrial fibrillation or frequent ectopy could affect the reliability of our study findings. Fourth, RV dimensions were not available from the patients with LVDD to make any potential correlations between right-sided chamber size and Vp values. Even though color M-mode is only known to assess parameters in two dimensions and at first glance might be considered inadequate to describe diastolic flows, as these flows occur as vortices and consequently would be better assessed using a three-dimensional mode; the intent of this work was to evaluate the influence of PAH on LV diastolic Vp. Future studies should now determine the relationship that might exist between Vp and right-sided cavity sizes as a result of PAH. Fifth, lack of invasive hemodynamic data might be considered as a limitation. However, the main study goal was met. With these results we can now propose future studies that should address if potential correlations can be drawn between invasive hemodynamic data and echocardiographic color M-mode Vp values. It can also be argued that we lack sequential echocardiographic studies on PAH patients to validate the utility of Vp findings over time. Finally, some might argue that intraobserver as well as interobserver variability results were not obtained. Even though we have previously published these results for color M-mode Vp measurements for both RV and LV [30], we do acknowledge the potential limitation of using color M-mode to study diastolic flows.

**Conclusion**

In summary, this study suggests that PAH patients show significantly higher Vp values when compared to patients with

Table 2. Simple Linear Regression Analysis to Determine the Association Between Important Echocardiographic Variables

| Variables               | Group I            | Group II           | Group III           | Group IV           |
|-------------------------|--------------------|--------------------|--------------------|--------------------|
| Vp vs. PCWP             | -0.8213 (0.46)     | -1.4200 (< 0.01)   | -1.5520 (< 0.01)   | -3.2673 (< 0.01)   |
| Vp vs. MV E/MA E' ratio | 1.1685 (0.22)      | 0.8431 (0.12)      | 0.2637 (0.64)      | -0.2192 (0.18)     |
| Vp vs. MA E'            | -0.5117 (0.56)     | 1.9742 (0.02)      | 2.2038 (0.29)      | 0.1049 (0.41)      |
| MV E/Vp vs. MV E/MA E' ratio | 0.1188 (< 0.01) | 0.1416 (< 0.01) | 0.1257 (< 0.01) | 0.0146 (< 0.01) |

Vp: velocity of propagation; PCWP: pulmonary capillary wedge pressure; MA: mitral annulus; MV: mitral valve.
both, normal and abnormal LV diastolic function (stages 1 and 2). These results not only might reflect the compressive forces being exerted on the LV by the dilated and hypertrophied RV, known to increase Vp but also might be useful for non-invasive assessment of PCWP in PAH patients. Additional prospective studies are now warranted to assess its clinical utility.

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Conflicts of Interest

The authors report no conflicts of interest.

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