Usefulness of Echocardiography/Doppler to Reliably Predict Elevated Left Ventricular End-Diastolic Pressure in Patients With Pulmonary Hypertension

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The ability of echocardiography (echo)/Doppler to predict elevated left ventricular (LV) end-diastolic pressure (EDP) specifically among patients with pulmonary hypertension is not well defined. This was a retrospective analysis of 161 patients referred to a specialized pulmonary hypertension clinic. A model based on an American Society of Echocardiography (ASE)/European Association of Echocardiography (EAE) joint statement was evaluated, and a new model was developed using univariate linear regression and multivariable logistic regression for potentially better prediction of elevated LVEDP. The study cohort had a median pulmonary arterial pressure was 34.0 mm Hg and pulmonary vascular resistance was 3.7 Wood units; 81 patients (51%) had LVEDP >15 mm Hg on invasive testing. Doppler E/A, E/e′ (septal, lateral, and average), e′/a′ (lateral and average), and left atrial volume and diameter all had significant correlation with LVEDP ($p < 0.05$). The ASE/EAE model performed poorly (sensitivity 54% and specificity 66%) for detecting elevated LVEDP. Only echo/Doppler grade 3 diastolic dysfunction had an LVEDP significantly different from other grades (grade 0 to 2, median 15 mm Hg, interquartile range 13 to 22 mm Hg; grade 3, median 22 mm Hg, interquartile range 19 to 32 mm Hg; $p < 0.01$). An experimental model was statistically significant in its prediction of elevated LVEDP (area under the receiver operating characteristic curve 0.7, $p < 0.001$) but demonstrated poor performance (sensitivity 67% and specificity 61%). In conclusion, numerous echo/Doppler measurements correlate with elevated LV filling pressure. However, both the ASE/EAE model and our experimental model had poor test performance that did not permit confident identification of elevated LVEDP. © 2016 Elsevier Inc. All rights reserved. **(Am J Cardiol 2016;■:■−■)**

Among patients with pulmonary hypertension (PH), echocardiography (echo)/Doppler has received considerable attention as a noninvasive technique to help estimate left ventricular (LV) filling pressures as a means to monitor volume status and to distinguish between pre- and post-capillary hypertension.[1−6] The accuracy of echo/Doppler for determination of LV filling pressures specifically among patients with PH has not been addressed. This study examines the clinical utility of echo/Doppler to determine both the grade of LV diastolic dysfunction and the presence of significantly elevated LV end-diastolic pressures (EDPs) using a model based on established guidelines.[7] In addition, the study sought to define any significant correlations between echo/Doppler and elevated LVEDP and to attempt to create a more robust model for the prediction of elevated LVEDP among patients with advanced PH.

Methods

The University of Michigan Health System Pulmonary Hypertension Program is a tertiary/quaternary care multidisciplinary program for the diagnosis and management of patients with known or suspected PH. Consecutive patients enrolled in the PH program for invasive, catheter-based assessment of PH during a 2-year interval from August 2012 to August 2014 were retrospectively identified. Inclusion criteria consisted of invasive determination of LVEDP and/or pulmonary capillary wedge pressure (PCWP), comprehensive transthoracic echo/Doppler within a 3-month interval of heart catheterization, normal sinus rhythm at the time of echo/Doppler, and no change in diuretic therapy or change in medical management of PH between the time of echo/Doppler and the time of invasive hemodynamic assessment. Patients were excluded from analysis if echo/Doppler was incomplete or of inadequate image quality for reasonable analysis. Patient characteristics were obtained from retrospective chart review. The study was evaluated and approved by the University of Michigan Institutional Review Board.

Clinically indicated right and left heart catheterizations were performed by interventional cardiologists. Hemodynamic data obtained from heart catheterization included chamber pressures, cardiac output, and cardiac index by Fick method, pulmonary vascular resistance, and systemic vascular resistance. PH was defined as a mean pulmonary artery pressure >25 mm Hg and elevated LV filling pressure as LVEDP >15 mm Hg; PCWP was used if LVEDP was not reported.

Clinically indicated echocardiograms were performed by a trained sonographer using current-generation equipment

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See page 5 for disclosure information.

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and digitally archived in standard DICOM format. Measurements of chamber size and LV diastolic function were performed by a single investigator (DMC) with oversight and verification by a second investigator with advanced experience and expertise in echo/Doppler (DSB). All measurements were made from digitally stored images using standard software (Synapse Cardiovascular; Fujifilm Medical Systems USA, Inc., Stamford, Connecticut). Left atrial (LA) diameter was obtained from 2-dimensional imaging in the parasternal long-axis view; single-plane LA volume was obtained from the 4-chamber view using the method of stacked disks. Mitral inflow velocities (E and A waves) and E-wave deceleration time were obtained using pulse-wave Doppler in the 4-chamber view. Lateral and septal mitral annular diastolic velocities (e′, a′) were obtained using Doppler tissue imaging.

Point data are presented as number and percent; comparisons between groups were made using the chi-square tests. Continuous data were evaluated for normal distribution using the Shapiro-Wilk test; data are shown as median and interquartile range, and comparisons between groups were evaluated using the Mann-Whitney *U* test. The 2009 ASE/EAE guidelines[8] were used to predict elevated LVEDP (defined as >15 mm Hg). In patients with normal ejection fraction (EF), E/e′ and LA volume were measured; in patients with depressed EF, E/A, E/e′, and E wave deceleration time were measured. The predictions were compared with the invasive measurements, and test characteristics (sensitivity, specificity, PPV, NPV) were determined. The 2009 ASE/EAE guidelines[8] were also used to define LV diastolic dysfunction grade for each patient as normal, grade 1, 2, or 3 LV diastolic dysfunction based on the following echo variables: e′, LA volume, E/A, E wave deceleration time, and E/e′. The Mann-Whitney *U* test was used to compare the distribution of LVEDP between groups.

In addition, a new model was developed in an attempt to improve performance compared with the 2009 ASE/EAE guidelines. First, correlations between echo/Doppler variables (mitral valve inflow velocities [E wave, A wave, E/A], structural indexes [LA diameter, LA volume], and mitral annular tissue velocities [e′, a′, E/e′, e′/a′; septal, lateral, and average]) and LVEDP were tested using simple linear regression. Variables with a significant correlation ($p < 0.05$) then were included in a multivariate binary logistic regression analysis for prediction of elevated LVEDP; variables were added sequentially in order of most significant correlation. Receiver operating characteristic curves (ROC) for each of these models were analyzed, and the discriminant factor for optimal sensitivity and specificity were determined using the Youdon index. All statistical evaluations were performed using IBM SPSS (version 22; IBM, Armonk, New York) and Microsoft Excel (version 15; Microsoft, Redmond, Washington).

Results

Of 469 patients who underwent assessment of invasive hemodynamics during the 2-year study interval, 258 underwent echo/Doppler assessment within 3 months. Of those, 51 were excluded due to changes in either PH medications or diuretic regimen, 40 were excluded due to poor echo/Doppler image quality or incomplete studies and 6 were excluded due to absence of sinus rhythm at the time of echo, yielding a final cohort of 161 patients.

Characteristics of the 161 patients are listed in Table 1. Excluded patients had a median mean PAP of 38 mm Hg (interquartile range [IQR] 26.5 to 46.5, $p = 0.9$), median pulmonary vascular resistance of 3.9 Wood units (IQR 2.3 to 7.0, $p = 0.2$), and Fick cardiac index of 2.8 mL/m^2 (2.4 to 3.2, $p = 0.9$); these were not significantly different from included patients. Median time between echocardiogram and catheterization was 23 days (IQR 7.5 to 41.5). Echo/Doppler data based on LVEDP are listed in Table 2.

The study first examined the performance of the 2009 ASE/EAE guidelines for the prediction of elevated LVEDP. Note was made of poor test performance with test characteristics listed in Table 3. In addition, the relevance of the assigned grade of LV diastolic dysfunction was assessed by comparing LVEDP for each diastolic grade (Figure 1). Significant overlap was observed in LVEDP between diastology grades, and with the exception of grade 3 diastolic dysfunction, there was no statistically significant difference in LVEDP between diastology grades (grade 0 to 2 median 15 [IQR 15 to 22]; grade 3 median 22 [IQR 19 to 32]; $p < 0.01$).

Data were reanalyzed with the goal of creating a new model with possibly better test performance for predicting elevated LVEDP. The linear regression analysis demonstrated numerous variables with significant but weak correlations (Table 4). Binary logistic regression of models with sequentially added variables showed improved model performance over individual variables and over the 2009 ASE/EAE guidelines (ROCs shown in Figure 2). The model with the best performance was a 3-variable model: score = (1.5 × LA diameter) + (1.7 × E/A) + (1.1 × E/e′ septal); ROC shown in Figure 3. Test characteristics of the model with the largest AUC is listed in Table 3.

Discussion

There is interest in using echo/Doppler to distinguish between pre- and post-capillary PH. Tissue Doppler imaging and mitral valve inflow velocities have been shown to have significant correlation to elevated filling pressures in patients with PH.[3–5] In 2008, Willens et al[6] showed that E/e′ and E/A had excellent test performance in predicting elevated LVEDP in a composite cohort of left-sided heart failure and group 1 patients with PH, although this was a small cohort (n = 44) with only half being patients with PH. In 2012, Optowosky et al[4] developed a simple model to identify pre-capillary PH that had very reasonable test performance; however, a recent study published by D'Alto et al[1] reported a lower ROC for this model. In the same study, a new model was developed, with an ROC of 0.756, sensitivity of 77.5%, and specificity of 67.9% (n = 152), which was interpreted as being reasonable test performance.[1]

The present study first examined the performance of a model based on ASE/EAE guidelines to grade diastolic dysfunction and predict elevated LVEDP. It would be expected that ascending grades of diastolic dysfunction would be associated with increasingly elevated LVEDP. However, this was only the case in grade 3 diastolic dysfunction that demonstrated a statistically significant difference in LVEDP