Echocardiographic Assessment of Pulmonary Hypertension in Patients with Advanced Lung Disease


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Doppler echocardiography is commonly used to estimate systolic pulmonary artery pressure and to diagnose pulmonary hypertension, but data relating to its utility in patients with advanced lung disease are limited. In a cohort study of 374 lung transplant candidates, the performance characteristics of echocardiography compared with right heart catheterization in the determination of systolic pulmonary artery pressure and diagnosis of pulmonary hypertension were investigated. The prevalence of pulmonary hypertension was 25% in the study population. Estimation of systolic pulmonary artery pressure by echocardiography was possible in 166 patients (44%). The correlation between systolic pulmonary artery pressure estimated by echocardiography and measured by cardiac catheterization was good (r = 0.69, p < 0.0001). However, 52% of pressure estimations were found to be inaccurate (more than 10 mm Hg difference compared with measured pressure), and 48% of patients were misclassified as having pulmonary hypertension by echocardiography. Sensitivity, specificity, and positive and negative predictive values of systolic pulmonary artery pressure estimation for diagnosis of pulmonary hypertension were 85%, 55%, 52%, and 87%, respectively. In conclusion, despite a statistically significant correlation with directly measured values, estimation of systolic pulmonary artery pressure by echocardiography is frequently inaccurate in patients with advanced lung disease and leads to considerable overdiagnosis of pulmonary hypertension.

Keywords: pulmonary hypertension; echocardiography; cardiac catheterization; lung disease

Pulmonary hypertension (PH) is a common feature signaling the advanced stages of diseases of the pulmonary vasculature, parenchyma, and airways. Detection of the presence of PH provides valuable prognostic information and dictates the need for such therapies as vasodilators and supplemental oxygen (1–3). Moreover, the magnitude of PH influences decisions on the appropriateness of surgical options for treatment of advanced lung disease. In this regard, the presence of significant PH often prompts consideration of lung transplantation in the appropriate setting (4). Conversely, PH is considered a contraindication to lung volume reduction surgery for advanced emphysema (5).

Although pulmonary artery pressures and other cardiac hemodynamic parameters can be accurately assessed by right heart catheterization (RHC), a simple, reliable, and noninvasive method to estimate pulmonary artery pressures and diagnosis of PH in patients with advanced lung disease is preferable. Doppler echocardiography (DE) has gained popularity in the last 2 decades for noninvasive estimation of systolic pulmonary artery pressure (sPAP) from the peak velocity of a tricuspid regurgitant jet. Studies in patients with cardiac disease have revealed a significant statistical correlation between sPAP estimated by DE and that measured by RHC (6–9). However, in patients with chronic pulmonary disease, DE has been reported to perform variably in the assessment of sPAP (10–12). Despite a close correlation between DE-estimated and directly measured sPAP, several studies have revealed that such estimations were possible in only a minority of patients with chronic lung disease (11–14). More importantly, by focusing exclusively on the correlation between estimated and measured pressures, previous studies have largely ignored the important issue of the true accuracy of DE estimation of sPAP. That is, if DE were to consistently overestimate or underestimate sPAP by a constant value, correlation would be high, but the accuracy of the estimation would be dictated by the magnitude of discrepancy. It is the accuracy of estimation that defines the clinical utility of DE in such circumstances as evaluation of patients for lung volume reduction surgery or lung transplantation.

Patients with advanced lung disease referred for lung transplantation at our center are required to undergo both DE and RHC as part of their evaluation. Using this large cohort of patients, the aim of this study was to examine the performance characteristics of DE in estimating sPAP and detecting the presence of PH.

METHODS

Consecutive patients with advanced lung disease who underwent an evaluation for lung transplantation between January 1991 and December 2000 were screened. The study population included all patients who had DE and RHC within 72 hours of each other during a formal evaluation process. DE was typically performed 24–48 hours before RHC according to our transplant evaluation protocol. The studies were performed independently by operators who had no knowledge of the results of the other study. The clinical status and treatment of these patients were unaltered during the evaluation period.

DE Technique

DE was performed using conventional clinical echocardiographic equipment (Hewlett-Packard 2500 or 5500 models; Hewlett-Packard, Palo Alto, CA) with 2.5- or 3.5-MHz transducers. Transthoracic Doppler and two-dimensional images were obtained from parasternal long- and short-axis, apical four-chamber, and subcostal four-chamber views. Echocardiograms were reviewed to assess the pericardium, valvular anatomy and function, left- and right-sided chamber size, and cardiac function. Right ventricular size and function were evaluated qualitatively. Tricuspid regurgitant flow was identified by color flow Doppler techniques, and the maximum jet velocity was measured by continuous wave Doppler without the use of intravenous contrast. Right ventricular systolic pressure was estimated based on the modified Bernoulli equation and was considered to be equal to the sPAP in the absence of right ventricu-
lar outflow obstruction: \( sPAP \) (mm Hg) = right ventricular systolic pressure + trans-tricuspid gradient + right atrial pressure (RAP) where trans-tricuspid gradient is \( 4v^2 \) (\( v \) = peak velocity of tricuspid regurgitation, m/second) (7, 9, 15).

RAP was empirically estimated as 15 mm Hg before 1997. Since 1997, RAP was estimated to be 5, 10, or 15 mm Hg based on the variation in the size of inferior vena cava with inspiration as follows (16): complete collapse, RAP = 5 mm Hg; partial collapse, RAP = 10 mm Hg; and no collapse, RAP = 15 mm Hg.

RHC

A balloon-tipped, flow-directed pulmonary artery catheter was introduced via the right femoral vein or right internal jugular vein using the Seldinger technique under local anesthesia. Patients were commonly premedicated with diazepam 5 mg by mouth to treat procedure-related anxiety, but conscious sedation was not typically employed. The following measurements were obtained in duplicate: RAP, pulmonary artery systolic and diastolic pressures, pulmonary artery occlusion pressure, and cardiac output.

Definitions and Statistical Analysis

PH was defined in this study as a sPAP of greater than or equal to 45 mm Hg. This value was chosen based on the criteria established by the World Health Organization Symposium on Primary Pulmonary Hypertension (1998), which defines mild PH as a sPAP of 40–50 mm Hg. Moreover, the value of 45 mm Hg is clinically relevant as patients with emphysema and sPAP above this value are excluded from lung volume reduction surgery in the National Emphysema Treatment Trial (5).

We assessed the capacity of DE to estimate sPAP and diagnose PH in three ways. First, to examine the overall relationship of DE-estimated sPAP to RHC measurements, we compared the results as continuous variables using Pearson and intraclass correlation methods. Second, we calculated the “accuracy” of DE-estimated sPAP, defined as the percentage of studies that fell within 10 mm Hg of the pressure measured directly by RHC. Third, using RHC as the gold standard, we calculated the sensitivity, specificity, and positive and negative predictive values of two methods of diagnosing PH by DE: (1) an estimation of sPAP by trans-tricuspid gradient method and (2) the presence of qualitative right ventricular structural or functional abnormalities. By the former method, a DE-estimated sPAP equal to or exceeding 45 mm Hg was considered to be positive for the diagnosis of PH. By the latter method, the presence of any one of the following findings was considered as a positive study: right ventricular hypertrophy, dilation, or systolic dysfunction.

To determine whether estimation of RAP by DE impacted significantly on the accuracy of sPAP estimation, DE-derived sPAP estimates were recalculated by using the actual RAP measured by RHC in the formula, and the correlation coefficients and accuracy were recalculated.

Results are expressed as means ± SD or as percentages. Comparisons of percentages among disease subpopulations were made by a chi-square test. In all analyses, a \( p \) value of 0.05 or less was considered significant. All statistical comparisons were performed using STATA version 7.0 (STATA Corp., College Station, TX).

This research protocol was granted exempt status by the Institutional Review Board of the Office of Regulatory Affairs at the University of Pennsylvania.

RESULTS

During the study period, 592 consecutive patients underwent a formal evaluation for lung transplantation. Three hundred and seventy-four patients had DE and RHC within 3 days of each other. This group forms the study population. The clinical characteristics of study patients are shown in Table 1. Two hundred fifty-three patients (68%) had obstructive lung disease; 106 patients (28%) had interstitial lung disease, and 15 patients (4%) had pulmonary vascular disease. By RHC, 94 patients (25%) had PH, whereas 280 patients (75%) did not. The prevalence of PH was 18% among the obstructive lung disease population, 59% among those with interstitial lung disease, and 100% among those with pulmonary vascular disease.

Estimation of sPAP by DE was possible in 166 (44%) of the 374 patients (Figure 1). Patients with RHC-confirmed PH were more likely to have an estimated sPAP by DE compared with patients without PH (64% versus 38%, \( p < 0.0001 \)). Estimation of sPAP was achieved less frequently in patients with obstructive lung diseases compared with those with interstitial lung diseases or pulmonary vascular disease (estimation possible in 38%, 54%, and 67%, respectively; \( p = 0.008 \)). Similarly, the likelihood of estimating sPAP was significantly lower in patients with marked air trapping, defined as a residual volume exceeding 150% of predicted, compared with those without air trapping of this magnitude (40% versus 56%, \( p = 0.007 \)).

![Figure 1](image-url)
Correlation and Accuracy

In the subset of 166 patients in whom sPAP could be estimated by DE, there was a strong correlation between sPAP estimated by DE and that measured by RHC (r = 0.69, p < 0.0001 by Pearson correlation) (Figure 2). Likewise, the intraclass correlation was strong (r = 0.60, p < 0.0001).

We observed a significant discrepancy between RAP estimated by DE and measured by RHC (15 ± 1 versus 8 ± 5 mm Hg, p < 0.001). The magnitude of this discrepancy was not affected by the method of estimating RAP (universal assumption of an RAP of 15 mm Hg versus estimation of RAP by the pattern of inferior vena caval collapse). To determine whether the estimation of RAP by DE impacted significantly on the correlation between estimated and measured sPAP, the actual RAP measurements obtained by RHC were used to recalculate DE-estimated sPAP values. The correlation coefficient improved only slightly when RAP measured by RHC was substituted for that estimated by DE and DE sPAP was recalculated (r = 0.74, p < 0.0001).

Despite a statistically significant correlation between sPAP estimated by DE and that measured by RHC, DE-estimated sPAP was accurate (within 10 mm Hg of RHC measurement) in only 48% (95% CI, 40 to 56%) of the studies. Moreover, 47 of 166 (28%) studies revealed a difference between DE-estimated and RHC-measured sPAP of more than 20 mm Hg, and in 15 studies (9%), the difference was more than 30 mm Hg. The accuracy of DE was higher in patients with obstructive lung disease compared with those with interstitial lung disease and pulmonary vascular disease (56% versus 37% versus 20%, p = 0.018). The accuracy of DE was not different in patients with or without PH as determined by RHC (50% versus 47%, p = 0.89). However, in patients without PH, DE was more likely to overestimate sPAP, whereas in those with PH, DE was as likely to overestimate as underestimate sPAP (Figure 3). When DE-estimated sPAP was recalculated using RAP measured by RHC rather than estimated RAP, the overall accuracy of DE improved only modestly (55% accuracy compared with 48% when estimated RAP was used).

Conversely, when estimated sPAP was 45 mm Hg or more by DE, it was accurate in only 31% of the studies compared with 72% of studies in which estimated sPAP was less than 45 mm Hg (p < 0.0001). Importantly, 48 of 99 patients (48%) with sPAP of 45 mm Hg or more by DE did not have PH by RHC (Figure 1). In all but four of these false-positive cases, the difference in sPAP obtained by the two methods was more than 10 mm Hg.

Diagnosis of PH by DE

We first examined the performance characteristics of DE-estimated sPAP in establishing or excluding a diagnosis of PH, using RHC as the gold standard (Table 2). PH was considered to be present by DE when the estimated sPAP was 45 mm Hg or

TABLE 2. SENSITIVITY, SPECIFICITY, AND POSITIVE AND NEGATIVE PREDICTIVE VALUES OF DOPPLER ECHOCARDIOGRAPHY FINDINGS FOR DIAGNOSIS OF PULMONARY HYPERTENSION

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Finding</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
<td>sPAP</td>
<td>85% (73–93%)</td>
<td>55% (45–64%)</td>
<td>52% (41–62%)</td>
<td>87% (76–94%)</td>
</tr>
<tr>
<td></td>
<td>RV findings¹</td>
<td>82% (73–89%)</td>
<td>57% (51–62%)</td>
<td>39% (32–46%)</td>
<td>90% (85–94%)</td>
</tr>
<tr>
<td>OLD</td>
<td>sPAP</td>
<td>76% (50–93%)</td>
<td>65% (54–75%)</td>
<td>32% (18–48%)</td>
<td>93% (83–98%)</td>
</tr>
<tr>
<td></td>
<td>RV findings</td>
<td>84% (67–95%)</td>
<td>56% (49–62%)</td>
<td>22% (15–30%)</td>
<td>96% (91–99%)</td>
</tr>
<tr>
<td>ILD</td>
<td>sPAP</td>
<td>85% (68–95%)</td>
<td>17% (5–39%)</td>
<td>60% (44–74%)</td>
<td>44% (14–79%)</td>
</tr>
<tr>
<td></td>
<td>RV findings</td>
<td>76% (61–87%)</td>
<td>53% (40–67%)</td>
<td>57% (43–69%)</td>
<td>74% (58–86%)</td>
</tr>
</tbody>
</table>

* Defined as the total group of patients for whom the DE finding could be ascertained (n = 166 patients for whom sPAP could be estimated and n = 372 patients for whom RV could be visualized).

¹ RV findings are defined as the presence of RV dilation, hypotrophy, or systolic dysfunction.

Definition of abbreviations: ILD = interstitial lung disease; NPV = negative predictive value; OLD = obstructive lung disease; PPV = positive predictive value; RV = right ventricular; sPAP = systolic pulmonary artery pressure.
more. For the entire group of 166 patients for whom DE-estimated sPAP could be determined, the sensitivity, specificity, and positive and negative predictive values of estimated sPAP in diagnosing PH were 85% (95% CI, 73 to 93%), 55% (95% CI, 45 to 64%), 52% (95% CI, 41 to 62%), and 87% (95% CI, 76 to 94%), respectively.

Next, the performance characteristics of DE-identified right ventricular abnormalities as a surrogate diagnostic marker of PH were examined (Table 2). The right ventricle was adequately visualized in 372 of the 374 patients. When applied to this group, the sensitivity, specificity, and positive and negative predictive values of right ventricular abnormalities in diagnosing PH were 82% (95% CI, 73 to 89%), 57% (95% CI, 51 to 62%), 39% (95% CI, 32 to 46%), and 90% (95% CI, 85 to 94%), respectively. The utility of using right ventricular findings in patients in whom sPAP could not be estimated was then specifically scrutinized (Figure 1). In 208 patients in whom sPAP could not be estimated, right ventricular findings were present in 88 (42%), but only 29 of these 88 (33%) patients had PH by RHC. In 120 patients who had no right ventricular findings, 115 (96%) did not have PH by RHC. Thus, the finding of right ventricular abnormalities led to considerable overdiagnosis of PH, but the absence of these abnormalities reliably excluded PH.

Finally, we calculated the performance characteristics of DE-estimated sPAP and right ventricular abnormalities in establishing a diagnosis of PH for each of the two main disease subgroups: obstructive lung disease and interstitial lung disease (Table 2). Similar to the group as a whole, the specificity of these DE parameters was generally lower than their sensitivity, a discrepancy that was particularly apparent in relationship to DE-estimated sPAP among the interstitial lung disease group. The positive predictive value of DE studies was low in both disease subgroups. In contrast, the negative predictive value of DE studies exceeded 90% in the obstructive lung disease group, whereas corresponding values were lower and more variable in the interstitial lung disease population. The universal prevalence of PH among patients with pulmonary vascular disease precluded calculation of all but sensitivity in this group, which was 100% for DE-estimated sPAP and 93% for the presence of right ventricular abnormalities.

DISCUSSION

In this study, we investigated the value of DE as a noninvasive means of estimating sPAP and establishing or excluding a diagnosis of significant PH in a large cohort of patients with advanced lung disease of various etiologies. We demonstrated a reasonably strong and statistically significant correlation between DE-estimated sPAP and RHC-measured sPAP. Despite this significant correlation, several important limitations of DE were identified. First, sPAP estimation by DE was possible in less than one-half of all patients. Second, there was a discordance of greater than 10 mm Hg between estimated and measured sPAP in 52% of patients, and in 28%, the discordance was greater than 20 mm Hg. Third, DE-estimated sPAP was associated with a poor positive predictive value for the diagnosis of PH, with confirmation of PH by RHC in only one-half of those patients in whom DE suggested its presence. Reliance on findings of right ventricular abnormalities did not enhance the poor positive predictive value of DE.

The technique employed in this study to estimate sPAP by DE involves calculation of the trans-tricuspid gradient from measurement of the peak velocity of the tricuspid regurgitation jet using the modified Bernoulli equation (6, 7, 9, 15). Right ventricular pressure and, indirectly, sPAP are then determined by adding an estimated RAP to the calculated trans-tricuspid gradient. The success and accuracy of this technique are dependent on the ability to identify and precisely measure the velocity of the tricuspid regurgitant jet and, therefore, are influenced by factors altering the position of the heart in relationship to the DE probe, such as obesity and hyperinflated lungs. Intraobserver and interobserver variability and limitations in the estimation of RAP also impact the accuracy of this technique. The use of this technique has been most extensively and convincingly validated in patients with cardiac disease. In three of the largest studies, encompassing a total of over 250 patients, sPAP could be estimated in 59–87% of patients, and the correlation with measured sPAP was excellent, with a correlation coefficient of 0.93–0.97 (6, 7, 9).

In contrast to these studies, we have focused on a population with advanced pulmonary disease, comprised chiefly of patients with severe chronic obstructive pulmonary disease and interstitial lung diseases. Our study comprises the largest cohort of patients with pulmonary disease studied to date and both corroborates and extends observations made in previous smaller series. We have demonstrated that both the likelihood of estimating a sPAP and the correlation with measured sPAP are lower in this population compared with those with cardiac disease. Regarding the first issue, we were able to estimate sPAP in only 44% of patients. It is likely that factors related to pulmonary disease contributed significantly to this. Specifically, changes associated with chronic obstructive pulmonary disease, including marked increase in intrathoracic gas, expansion of the thoracic cage, and alterations in the position of the heart, adversely influence the ability to detect and measure the velocity of the tricuspid regurgitant jet. Our demonstration that the likelihood of obtaining a DE-estimated sPAP was significantly lower in the subset of patients with obstructive lung disease and those with a residual volume exceeding 150% of predicted support this claim. The 38% success rate in estimating sPAP in patients with obstructive lung disease falls within a range documented in several previous studies. In a study of 100 patients with chronic obstructive pulmonary disease, Tramarin and colleagues obtained estimates by DE in only 30% (12). Bach and associates documented a success rate of 26% among 207 patients with advanced chronic obstructive pulmonary disease undergoing evaluation for lung volume reduction surgery (11). In contrast, Laaban and colleagues obtained estimates of sPAP in 66% of 41 patients with severe chronic obstructive pulmonary disease (10). Whether changes in chest wall configuration and cardiac orientation also limit DE estimation of sPAP in patients with interstitial lung diseases remains unclear.

Although we documented a statistically significant correlation between DE-estimated sPAP and measured values by RHC, the correlation coefficient of 0.69 was well below that reported in studies involving cardiac patient populations. This suggests that there is greater variability between estimated and measured pressures in patients with lung disease, again likely due to factors specific to this patient population that limit accurate visualization and measurement of the velocity of the tricuspid regurgitant jet. Three previous studies involving patients with pulmonary disease have found similar correlation coefficients, in the range of 0.65–0.73 (10–12). One additional study documented a correlation coefficient of 0.92, but sPAP was determined by DE in only 24% of patients, suggesting that the patients in whom pressures were estimated may have been meticulously selected (13). In contrast to these previous studies that focused largely on definition of a correlation coefficient as a means of characterizing the variability between estimated and measured pressures, we have attempted to provide a more clinically relevant parameter by determining the frequency with which estimated sPAP fell within 10 mm Hg of the actual value. We found that DE provided an
appears to be of greatest utility as an adjunctive means of excluding significant PH in patients with obstructive lung disease, particularly in situations in which sPAP cannot be estimated.

One potential limitation of our study is that DE and RHC were not performed simultaneously but rather within a 3-day window. In a study by Currie and colleagues, 43 patients underwent RHC and both simultaneous and sequential DE, with an average of 3 days separating the two DE studies (7). Notably, the trans-tricuspid gradients were not significantly different between the two DE studies, but the correlation between DE and RHC pressures dropped slightly over time ($r = 0.97$ for simultaneous DE and 0.87 for delayed DE). This study suggests that separation of RHC and DE by up to 3 days has at best a minimal impact. Furthermore, all patients in our study were clinically stable and observed daily with no changes in any medications made during their evaluation period.

In conclusion, estimation of sPAP by DE is frequently inaccurate (i.e., discrepant by at least 10 mm Hg) in patients with underlying advanced lung disease. In light of the poor positive predictive value of DE-estimated sPAP and of findings of right ventricular abnormalities in this population, reliance on this non-invasive technique can potentially lead to overdiagnosis of PH. When the exact magnitude of PH is of critical importance, such as in the assessment of patients for lung volume reduction surgery or lung transplantation, echocardiographic findings suggestive of PH should be confirmed by RHC.

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References


