Pulmonary Circulation

Validity of algorithm for estimating left sided filling pressures on echocardiography in a population referred for pulmonary arterial hypertension

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Abstract
The determination of LV filling pressure is integral to the diagnosis of pulmonary arterial hypertension (PAH). The American Society of Echocardiography (ASE) has devised algorithms for their estimation. We aimed to test these algorithms in a population referred for suspected PAH. In our retrospective study, we evaluated the accuracy of the ASE Algorithms compared to right heart catheterization done within three months, in patients seen during 2006–2014. All echocardiograms were classified as showing normal, elevated or indeterminate filling pressures. Those with indeterminate pressures were excluded. We evaluated the diagnostic properties of this algorithm to predict a pulmonary artery wedge pressure (PAWP) and left ventricular end diastolic pressure (LVEDP) >15 mmHg. A total of 94 patients were included. The ASE algorithms yielded indeterminate results in 50 (53.2%) patients. This occurred more commonly in older patients and patients with cardiovascular comorbidities. The algorithm had a high sensitivity for predicting an elevated PAWP at 89.5% (95% confidence interval [CI] = 66.9–98.7) and an elevated LVEDP at 100% (95% CI = 76.8–100). The algorithm had a negative predictive value of 81.8% and 100% for predicting an elevated PAWP (95% CI = 52.4–94.8) and LVEDP, respectively, but a poor positive predictive value. The ASE algorithm for predicting LV filling pressures often cannot be applied in populations with suspected PAH. When they are interpretable, they have a high negative predictive value for elevated PAWP and LVEDP. We recommend caution when using these algorithms in populations with suspected PAH.

Keywords
echocardiography, pulmonary hypertension, left-sided filling pressure

Date received: 30 January 2017; accepted: 9 October 2017

Pulmonary Circulation 2017; 8(1) 1–7
DOI: 10.1177/2045893217740471

Introduction

Pulmonary arterial hypertension (PAH) is a rare, progressive disease affecting the small pulmonary arteries, resulting in increased resistance to flow in the pulmonary circulation, and leading to right-sided heart failure and death.[1] Hemodynamically, PAH is defined as a mean pulmonary artery pressure (mPAP) $\geq$25 mmHg, mean left atrial pressure $\leq$15 mmHg, and a pulmonary vascular resistance (PVR) $>$3 Wood Units (WU) on cardiac catheterization.[2]

Although mortality remains high, it has substantially improved since the introduction of pulmonary vasodilator therapy.[3,4] However, pulmonary vasodilator therapy can be hazardous in populations with elevated left ventricular (LV) filling pressures secondary to left-sided heart disease.[5,6] Therefore, ruling out elevated LV filling pressures is essential in determining candidacy for therapy. Although the gold standard for their measurement remains cardiac catheterization, it is invasive and not without risk of

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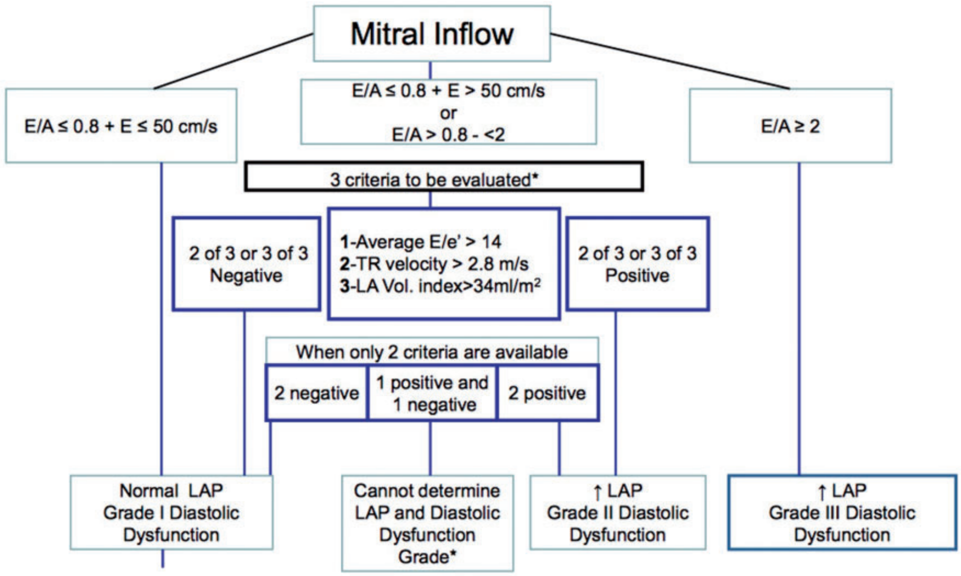

Fig. 1. Algorithm as defined by the ASE to estimate filling pressures for normal ejection fraction. Figure reproduced from Nagueh et al.[10] LA, left atrium; TR, tricuspid regurgitation; E, mitral inflow E velocity; e', tissue doppler mitral annular e' velocity.

complications.[7,8] Transthoracic echocardiography (TTE) is an invaluable tool for the detection and evaluation of PAH. It is the established screening test for PAH, and is non-invasive and widely available.[9] The American Society of Echocardiography (ASE) has recently revised their algorithm for estimating LV filling pressure on the basis of echocardiography.[10] This algorithm has not been validated in a population where PAH is expected to be prevalent. As it is widely used in echocardiographic laboratories, it is important to determine whether this algorithm is helpful or misleading in a population undergoing evaluation for suspected PAH. In our study, we investigated the accuracy of the 2016 ASE algorithm for predicting elevated left-sided pressures in a population referred for evaluation of PAH.

Methods

Study design and population

This was a single-center retrospective study involving patients referred to our tertiary pulmonary hypertension center between January 2006 and June 2014. A structured chart review was undertaken to identify all patients that had a complete TTE with assessment of LV filling pressures within three months of a diagnostic right heart catheterization (RHC). Patients were evaluated by experienced pulmonary hypertension (PH) specialists and classified using the World Health Organization (WHO) classification scheme for PH, according to previously published recommendations.[11] All clinic charts for the study cohort were reviewed by authors (EL, JS, LA, TA, NB) to obtain complete demographic data. Age, gender, BMI, established WHO group, and risk factors for elevated LV filling pressures were recorded for all patients. These risk factors included a history of hypertension, atrial fibrillation, diabetes mellitus, congestive heart failure, and coronary artery disease.[12] This study was approved by the Research Ethics Review Board at the University of British Columbia, Vancouver, British Columbia (H14-01309).

Echocardiography

Patients had a complete TTE at their initial clinic visit as per our standard pattern of practice. We included only patients with normal LV systolic function, defined by an LV ejection fraction (LVEF) >40%. For all included patients, the echocardiograms were reviewed by level 3 trained echocardiographers and the estimated LV filling pressures were assigned according to the 2016 ASE Guidelines (Fig. 1).

Among other parameters, the ASE algorithm for estimating LV filling pressures takes into account: (1) mitral inflow velocity obtained by pulsed-wave Doppler in the apical four-chamber view; (2) LV tissue Doppler velocity at the mitral valve annulus; (3) LA volume index; and (4) tricuspid regurgitation velocity. Fig. 2 illustrates examples of acquisition of these parameters. All measurements were performed according to established echocardiography guidelines.[10] For each echocardiogram, if the measured parameters were discordant and a conclusion on the status of the LV filling pressure could not be reached, the filling pressure was classified as indeterminate. Otherwise, LV filling pressures were classified as normal or elevated, according to the 2016 ASE recommendations for evaluation of left ventricular diastolic function on echocardiography.

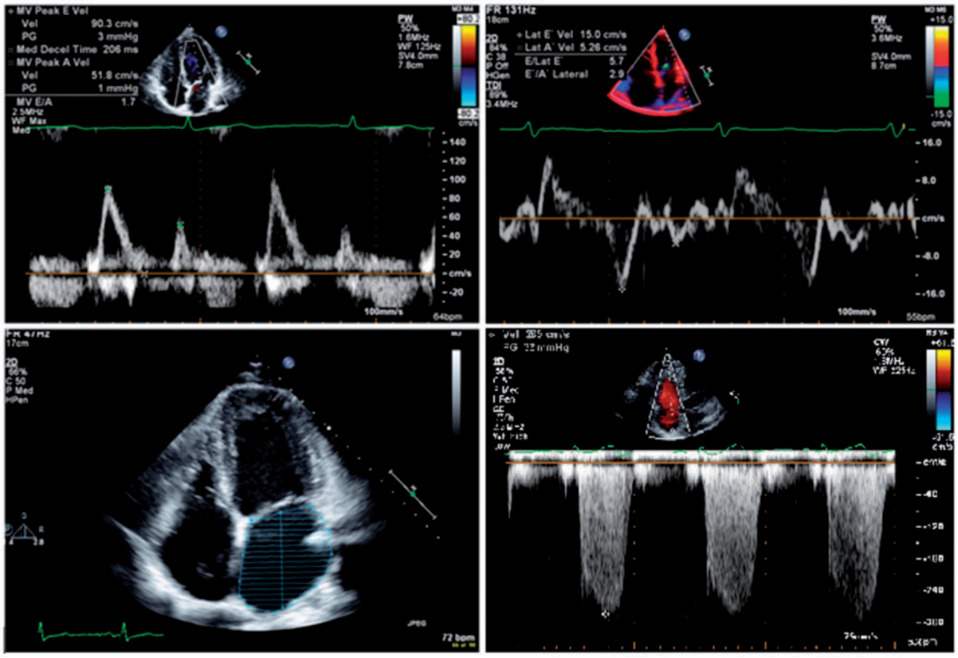

Fig. 2. Illustration of measurements taken to estimate left sided filling pressures. Top left: Mitral inflow velocity obtained by pulsed-wave (PW) Doppler in the apical four-chamber view, the optimal alignment is achieved by color flow imaging; Top right: LV tissue Doppler velocity at the medial and lateral triscupid valve annulus. Bottom left: LA volume in apical four-chamber view. Bottom right: Tricuspid regurgitation signal.

Cardiac catheterization

As per standard PH evaluation,[13] the subset of patients seen at our clinic suspected to have PAH were referred for left and RHCs, which were performed simultaneously. We included only patients who underwent catheterization for PH, but a mPAP of >25 mmHg was not an inclusion criterion for this study. At our institution, all catheterizations were performed by experienced operators with an annual experience of >200 procedures. The procedure was performed using a 7-F balloon-tipped triple lumen pulmonary artery catheter. The zero level was set at the mid-axillary line. Right atrial, right ventricular, pulmonary artery, and pulmonary artery wedge pressures (PAWP) were recorded. All pressures were measured at end expiration from manual review of tracings. The PAWP was measured as the mean over the entire cardiac cycle rather than the mean of the a-wave, as used in some other centers. Left heart catheterization for measurement of left ventricular end-diastolic pressure (LVEDP) was often done to confirm the PAWP, if the operator felt necessary. Left heart catheterizations were used liberally at our institution and were generally performed if this was the patient's first cardiac catheterization, especially if the patient had risk factors for left heart disease. It was also performed if the PAWP tracing was felt to be suboptimal. All pressure measurements were performed at end-expiration. Cardiac output was obtained by the thermodilution and the indirect Fick method, at the discretion of the operator. Nitric oxide and fluid challenge tests were performed if appropriate. Elevated LV filling pressures were defined as >15 mmHg for both PAWP and LVEDP.

Statistical analysis

Key clinical characteristics are presented as means and standard deviations with 95% confidence intervals (CI) for continuous variables and percentages for categorical variables. They were compared for patients with normal LV filling pressures, elevated LV filling pressures, and indeterminate LV filling pressures.

The primary outcome of interest was the agreement between LV filling pressure measurements taken by PAWP or LVEDP and estimation of LV filling pressure by the ASE algorithm. Sensitivity and specificity with associated 95% CIs were calculated for both PAWP and LVEDP. Positive predictive values (PPV), negative predictive values (NPV), likelihood ratios, and accuracy rates of the algorithm for each of these variables were also determined. A Kappa (κ) statistic was calculated for each of PAWP and LVEDP for further reliability and agreement analysis. Statistical analyses were performed using IBM SPSS for Windows (IBM SPSS Statistics, Armonk, NY, USA).

Results

A total of 94 patients satisfied inclusion criteria for this study. Patient characteristics are presented in Table 1. Only one patient had a LVEF in the range of 40–50%.

Table 1. Baseline demographic data.

	Normal (n = 11)	Elevated (n = 30)	Indeterminate (n = 50)	P value (normal vs. elevated)
Age (±SD)	50.2 (15.8)	71.2 (10.5)	61.9 (14.7)	<0.001
Female gender (%)	45.5	66.7	74.0	0.2
BMI (±SD)	26.3 (3.8)	29.0 (6.6)	27.5 (6.5)	0.2
WHO Classification				
I (%)	45.5	30.0	48.0	0.4
Idiopathic (%)	9.1	13.3	28.0	
Connective tissue disease (%)	27.3	6.7	18.0	
Portopulmonary (%)	0	6.7	2.0	
Congenital heart disease (%)	0	6.7	2.0	
PVOD (%)	9.1	0	0	
II (%)	0	56.7	24.0	0.001
III (%)	45.5	43.3	42.0	0.9
IV (%)	27.3	6.7	8.0	0.08
V (%)	0	3.3	0	0.6
Co-morbidities				
HTN (%)	18.2	66.7	50.0	0.05
Afib (%)	18.2	60.0	18.0	0.02
DM (%)	9.1	30.0	12.0	0.2
CAD (%)	0	10.0	20.0	0.3
CHF (%)	0	30.0	2.0	0.04
Prior smoking (%)	18.2	50.0	48.0	0.07
Hx of DVT/PE (%)	27.3	10.0	8.0	0.2
Baseline NYHA (±SD)	2.5 (0.9)	2.9 (0.5)	2.8 (0.6)	0.1
Echo				
PASP (mmHg) (±SD)	43.6 (28.5)	62.0 (17.5)	66.5 (23.8)	0.02
RV dysfunction				
Normal (%)	6 (54.5)	15 (50.0)	23 (46.0)	0.8
Mild (%)	2 (18.2)	13 (43.3)	14 (28.0)	0.1
Moderate–severe (%)	3 (27.3)	2 (6.7)	13 (26.0)	0.08
Cath				
sPAP (mmHg) (±SD)	55.5 (30.0)	64.6 (19.7)	72.7 (26.7)	0.3
dPAP (mmHg) (±SD)	20.1 (8.3)	24.3 (8.3)	28.1 (12.4)	0.2
mPAP (mmHg) (±SD)	33.6 (15.2)	41.2 (11.8)	46.0 (16.7)	0.1
Fick CO (L/min) (±SD)	5.5 (2.5)	4.1 (1.8)	4.0 (1.2)	0.05
TD CO (L/min) (±SD)	5.1 (1.0)	4.8 (2.2)	4.6 (1.4)	0.6
PAWP (mmHg) (±SD)	11.8 (3.6)	17.3 (7.2)	15.4 (9.3)	0.02
LVEDP (mmHg) (±SD)	8.7 (2.0)	16.3 (5.7)	14.7 (6.4)	0.002
Mean RAP (mmHg) (±SD)	7.8 (3.5)	11.4 (6.1)	9.7 (6.7)	0.08
Mean time from echo to catheterization (days) (±SD)	48.5 (31.7)	37.8 (26.5)	30.5 (19.5)	0.3

BMI, body mass index (kg/m^2); CAD, coronary artery disease; NYHA, New York Heart Association function status; PASP, pulmonary artery systolic pressure; RV, right ventricle; sPAP, systolic pulmonary arterial pressure; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; CO, cardiac output; TD, thermodilution; PAWP, pulmonary arterial wedge pressure; RAP, right atrial pressure.

All others had LVEFs ≥50%. In our study, 11 (11.7%) patients were determined to have normal filling pressures, 30 (31.9%) had elevated filling pressures, and 50 (53.2%) were classified as indeterminate. Patients with elevated or indeterminate filling pressures were older, with respective mean ages of 71.2 and 61.9 years, compared to 50.2 years for normal LV filling pressures ($P = 0.002$).

As expected, a higher prevalence of risk factors for WHO Group 2 PH were noted in the elevated filling pressure group, compared to normal LV filling pressures.

Table 2. Categorical data for PAWP and LVEDP and filling pressures.

	PAWP		LVEDP	
	Elevated	Normal	Elevated	Normal
ASE				
Elevated	17	14	14	15
Normal	2	9	0	7
Indeterminate	14	34	16	26
Total	33	57	30	48

ASE, American Society of Echocardiography filling pressures; PAWP, pulmonary artery wedge pressure; LVEDP, left ventricular end diastolic pressure.

Table 3. Diagnostic properties of PAWP and LVEDP.

	PAWP	LVEDP
Prevalence	45.24 (29.85–61.33)	38.89 (23.14–56.54)
Sensitivity	89.47 (66.86–98.70)	100 (76.84–100)
Specificity	39.13 (19.71–61.46)	31.82 (13.86–54.87)
Diagnostic Accuracy	61.90 (46.81–75.00)	58.33 (42.20–72.86)
Positive Predictive Value	54.84 (45.81–63.56)	48.28 (41.23–55.39)
Negative Predictive Value	81.82 (52.44–94.84)	100 (N/A)
Positive Likelihood Ratio	1.47 (1.02–2.11)	1.47 (1.10–1.95)
Negative Likelihood Ratio	0.27 (0.07–1.10)	0 (N/A)
Kappa K (p-value)	0.2711 ($P > 0.20$)	0.2663 ($P > 0.20$)

All reported values represent % and 95 CIs except for the likelihood ratios and Kappa statistic.

Significantly more atrial fibrillation, hypertension and congestive heart failure was observed in the elevated compared to normal filling pressure group. There was a trend towards a higher prevalence of diabetes in the elevated filling pressure group, but this did not meet statistical significance.

Echocardiographic and hemodynamic characteristics are also included in Table 1. By RHC, PAWP and LVEDP was obtained in 94 of 94 (100%) and 80 of 94 (85.1%) patients, respectively. As expected, our data showed a correlation between PAWP and LVEDP ($R^2 = 0.17$). There was higher PAWP in patients with echo-derived elevated filling pressures compared to echo-derived normal filling pressures (17.3 mmHg vs. 11.8 mmHg, $P = 0.02$). This association was stronger for LVEDP (16.3 mmHg vs. 8.7 mmHg, $P = 0.002$). The mean PAWP in the indeterminate filling pressures group was high and comparable to the elevated filling pressures group (15.3 mmHg vs. 17.3 mmHg). This was also the case with LVEDP (14.7 mmHg vs. 16.3 mmHg). There appeared to be more moderate or severe RV dysfunction for those with normal filling pressures, but this trend did not reach statistical significance (27.3% vs. 6.7%, $P = 0.08$). The ASE algorithm was more likely to give indeterminate results when moderate or severe RV dysfunction was present, when compared to mild or no RV dysfunction (72% vs. 51%, $P = 0.1$).

Table 2 demonstrates how patients were classified by echocardiography and cardiac catheterization. Sensitivity and specificity analysis for the ASE algorithm in predicting elevated filling pressures for PAWP and LVEDP and their associated diagnostic properties are illustrated in Table 3. The sensitivity of the ASE algorithm in predicting a PAWP >15 mmHg was high at 85.5%. Similarly, the sensitivity for predicting LVEDP >15 mmHg was 100%. The specificity of the ASE algorithm is poor at predicting both elevated PAWP and LVEDP (39.1% and 31.8%, respectively). There were no statistically significant differences in the calculated sensitivities and specificities for PAWP and LVEDP.

Discussion

In our retrospective analysis, we evaluated the ability of the most recent ASE algorithm for evaluating LV filling pressures to predict an elevated PAWP or LVEDP on a cardiac catheterization done within three months of echocardiography in a population referred for suspected PAH. The ASE algorithms often yielded indeterminate results. suggesting they are of limited utility in real world populations undergoing evaluation for PAH.

There are a number of reasons why the ASE algorithm may perform sub-optimally in populations with a high prevalence of PAH. First, high tricuspid regurgitation velocity is one of the criteria used by the ASE algorithm to identify elevated LV filling pressures (Fig. 1). While high velocity of the tricuspid regurgitation jet would be expected to result from elevated LV filling pressures in passive WHO Group 2 pulmonary hypertension, this of course would not hold true for PAH. Second, other parameters used in the ASE algorithm could possibly be influenced by PAH. For example, the pressure overloaded right ventricle may affect the septal tissue Doppler mitral annular velocity. Other echocardiographic scores and equations have been developed to assess LV filling pressures in populations with PAH.[14,15] However, this algorithm is in routine clinical use and thus required validation in populations suspected of having PAH. A recent meta-analysis of 24 studies performed by Sharifov et al. calls into question the reliability of the E/e' ratio in estimating LV filling pressures.[16] Our study gives similar findings. A recent study published by Cameron et al. used the ASE algorithm to predict left-sided filling pressures, initially with the 2009 algorithms, but they also reanalyzed their data using the 2016 algorithm.[17,18] Similarly, they found the algorithm to perform unreliably. Their reported sensitivity and specificity were 50.6% and 66.5% for predicting an elevated filling pressure, respectively.

We found that the negative predictive value the ASE algorithms for predicting elevated LV filling pressures to be high when PAWP and LVEDP is used as the gold standard. Therefore, it appears that clinicians can be reasonably confident in a finding of normal LV filling pressure on echocardiography. However, this NPV needs to be interpreted in light of the high number of indeterminate results. The lower PPV shows that a finding of elevated filling pressure is not sufficient in confirming those who truly have a high LV filling pressures. Given the low NPV and the high proportion of indeterminate results, we would not recommend applying this algorithm to patients being evaluated for PAH.

This study is not without limitations. First, RHC and echocardiography did not occur simultaneously, and it is possible that the status of a patient's LV filling pressures may have changed between the time of echocardiography and the time of catheterization. However, the mean time between echocardiography and RHC was relatively short at 35 days. While it is possible that diuretic doses may have changed in a minority of patients between the echocardiogram and RHC, the pattern of practice in our clinic is not to routinely alter diuretic dosing in this time interval. It is therefore unlikely that the volume status of the patient changed substantially. This time delay was similar to the delays seen in other comparable studies.[14,17] Additionally, it is important to stress that a normal filling pressure does not rule out WHO group 2 PH, as a well diuresed patient can have normal LV filling pressures even in the presence of substantial left heart disease. Furthermore, our sample size was relatively small. Larger multicenter studies should be considered to evaluate the echocardiographic estimation of LV filling pressures in the context of suspected PAH. Lastly, we did not follow these patients' disposition over time as our primary objective was to determine the accuracy of this echocardiographic tool.

Conclusions

The ASE algorithm for estimating LV filling pressures often yields indeterminate results in patients referred for suspected PAH. However, the finding of normal LV filling pressures using these algorithms is very likely to predict a normal PAWP and LVEDP on cardiac catheterization. A finding of elevated LV filling pressures does not correlate strongly with elevated PAWP or LVEDP on catheterization. Multicenter studies should be performed to further evaluate and refine echocardiographic algorithms for estimating LV filling pressures in patients with suspected PAH.

Acknowledgements

An abstract of these results was previously presented at the 2015 American Thoracic Society Conference in Denver. The authors thank the Center for Health Evaluation and Outcome Sciences (CHEOS) and Dr. Joseph Puyat for their assistance with the statistical analysis and data presentation.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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