Accuracy and Diagnostic Performance of Doppler Echocardiography to Estimate Mean Pulmonary Artery Pressure in Heart Failure

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Abstract

BACKGROUND. Multiple Doppler Echocardiography (DE) algorithms have been proposed to estimate mean pulmonary artery pressure (PAP_M) and assess pulmonary hypertension (PH) likelihood. We assessed the accuracy of 4 different DE approaches to estimate PAP_M in patients with heart failure (HF) undergoing near-simultaneous right heart catheterization (RHC), and compared their diagnostic performance to identify PH with recommendation-advised tricuspid regurgitation peak velocity (TRV_{max}). METHODS. PAP_M was retrospectively assessed in 112 HF patients employing 4 previously validated DE algorithms. Association and agreement with invasive PAP_M were assessed. Diagnostic performance of DE methods vs. TRV_{max}=2.8m/sec to identify invasive PAP_M [?] 25mmHg were compared. RESULTS. All DE algorithms demonstrated reasonable association (r = 0.41 to 0.65; p<0.001) and good agreement with invasive PAP_M, with relatively lower mean bias and higher precision observed in algorithms that included TRV_{max} or velocity time integral. All methods demonstrated strong ability (AUC=0.70-0.80; p<0.001) to identify PH but did not outperform TRV_{max} (AUC=0.84; p<0.001). Echocardiographic estimates of right atrial pressure were considered in 3 of 4 DE algorithms and falsely elevated in as many as 30% of patients. CONCLUSIONS. Echocardiographic estimates of PAP_M demonstrate reasonable accuracy to represent invasive PAP_M and strong ability to identify PH in HF. However, even the best performing algorithm did not outperform recommendation-advised TRV_{max}. The additional value of echocardiographic estimates of right atrial pressure may need to be re-evaluated.

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DECLARATIONS

Ethics approval and consent to participate : The study was approved by the ethics committee at Karolinska Institutet, Sweden (DNR 2008/1695-31). All patients provided written informed consent

Consent for publication : Not Applicable

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ABSTRACT

BACKGROUND. Multiple Doppler Echocardiography (DE) algorithms have been proposed to estimate mean pulmonary artery pressure (PAP_M) and assess pulmonary hypertension (PH) likelihood. We assessed the accuracy of 4 different DE approaches to estimate PAP_M in patients with heart failure (HF) undergoing near-simultaneous right heart catheterization (RHC), and compared their diagnostic performance to identify PH with recommendation-advised tricuspid regurgitation peak velocity (TRV_{max}).

METHODS. PAP_M was retrospectively assessed in 112 HF patients employing 4 previously validated DE algorithms. Association and agreement with invasive PAP_M were assessed. Diagnostic performance of DE methods vs. TRV_{max}=2.8m/sec to identify invasive PAP_M [?] 25mmHg were compared.

RESULTS. All DE algorithms demonstrated reasonable association (r = 0.41 to 0.65; p<0.001) and good agreement with invasive $PAP_{M,}$ with relatively lower mean bias and higher precision observed in algorithms that included TRV_{max} or velocity time integral. All methods demonstrated strong ability (AUC=0.70-0.80; p<0.001) to identify PH but did not outperform TRV_{max} (AUC=0.84; p<0.001). Echocardiographic estimates of right atrial pressure were considered in 3 of 4 DE algorithms and falsely elevated in as many as 30% of patients.

CONCLUSIONS . Echocardiographic estimates of PAP_M demonstrate reasonable accuracy to represent invasive PAP_M and strong ability to identify PH in HF. However, even the best performing algorithm did not outperform recommendation-advised TRV_{max}. The additional value of echocardiographic estimates of right atrial pressure may need to be re-evaluated.

INTRODUCTION

Pulmonary hypertension (PH) is common in heart failure (HF)[1] and is associated with poor prognosis.[2] Passive downstream elevations in left heart pressures often combined with pulmonary arteriolar remodeling are seen both in HF with preserved (HFpEF) and reduced ejection fraction (HFrEF) and carry therapeutic implications.[3] PH is defined as per current recommendations as a mean pulmonary artery pressure (PAP_M) [?] 25mmHg at rest, measured during right heart catheterization (RHC).[4] Although definite PH diagnosis necessitates an invasive evaluation of PAP_M,Doppler echocardiography (DE) is routinely employed to screen for PH and evaluate hemodynamic severity during follow-up. Multiple approaches to estimate PAP_M using DE have been previously proposed.[5-11] Most algorithms incorporate elements of Doppler analysis obtained from tricuspid regurgitation (TR),[5 8 9 11] pulmonary regurgitation (PR)[7] or flow across the right ventricular outflow tract (RVOT)[6 12] into empirical relationships to obtain PAP_M. However, the accuracy of these approaches to estimate invasive PAP_M in the specific setting of heart failure has not been studied. Further, current ESC recommendations do not advise use of any DE algorithms to assess PAP_Mbut instead recommend the use of tricuspid regurgitation peak velocity (TRV_{max}) cut-off >2.8m/sec to assign PH probability.[4] Availability of alternative echocardiographic approaches that represent invasive PAP_M could potentially replace TRV_{max}during screening, and may even obviate the need for invasive assessment. Studies directly comparing diagnostic performance of the recommended TRV_{max} cut-off and echocardiographic PAP_M algorithms to identify PH are few.[13]

With this background, we aimed to study the feasibility and accuracy of 4 different DE methods to estimate PAP_M in a retrospective analysis of HF subjects undergoing near-simultaneous RHC. Further, we wished to compare the diagnostic performance of these algorithms with recommendation-based TRV_{max} to identify PH.

METHODS

STUDY POPULATION. Echocardiographic examinations of consecutive patients with clinically judged HF referred for RHC to the Karolinska University Hospital between 2014 to 2018 were retrospectively reviewed. All subjects were hemodynamically stable during assessment and medical therapy was suitably titrated. Patients in atrial fibrillation or with significant arrhythmias and/or poor echocardiographic image quality precluding accurate measurement were excluded. Thereafter, subjects with isolated pre-capillary alterations on right heart catheterization were excluded from the analysis. The study was approved by the local ethics committees (Karolinska: DNR 2008/1695-31) and all patients provided written informed consent.

ECHOCARDIOGRAPHIC EVALUATION. All patients underwent comprehensive echocardiography employing a Vivid E9 ultrasound system (GE Ultrasound, Horten, Norway) by a single experienced echocardiographer (AV) in keeping with current recommendations.[14] 2D gray-scale images were acquired at 50-80 frames/sec and Doppler tracings were recorded using a sweep speed of 100mm/sec. Three consecutive heart cycles were acquired in sinus rhythm. TR was measured with Continuous wave Doppler, considering the most optimal signal obtained from multiple echocardiographic windows. PR was obtained with Continuous wave Doppler from the parasternal short-axis view at the level of the semi-lunar valves. Right ventricular outflow tract (RVOT) flow was obtained by placing a 5-mm Pulsed Doppler signal in the right ventricular outflow tract just proximal to the pulmonic valve. All images were subsequently exported and analyzed offline (EchoPAC PC, version 11.0.0.0 GE Ultrasound, Waukesha, Wisconsin) by an experienced, credentialed echocardiographer blinded to catheterization data.

A summary of approaches employed to evaluate PAP_M are illustrated in Figure 1. Broadly, PAP_M was evaluated using 4 algorithms taking into consideration 3 different approaches employing TR- ,[5 8] PR- ,[7] and RVOT acceleration time ($RVOT_{AT}$).[6] Applying the approach postulated by Aduen et al., [5]PAP_M was estimated by adding TR mean pressure gradient to recommended estimates of right atrial pressure (RAP) obtained from inferior vena cava (IVC) size and collapsibility.[14]The second approach adopted from Chemla et al. incorporated estimated systolic pulmonary artery pressure (PAP_S) obtained by adding the gradient corresponding with peak TR velocity (TRV_{max}) to IVC-estimated RAP to calculate PAP_M using the rela-

tionship PAP_M = 0.61 x PAP_S + 2 mm Hg.[8] In the third approach (Abbas and colleagues), PAP_M was estimated by adding gradients obtained from peak PR velocity to corresponding IVC-estimated RAP.[7] Finally, in the fourth approach proposed by Dabestani et al, $RVOT_{AT}$ was defined during systole as time in milliseconds from beginning of flow to peak velocity. PAP_{mean} was then calculated as PAP_{mean} = 90 - (0.62 x $RVOT_{AT}$) when AT < 120msec and 79 – (0.45 x $RVOT_{AT}$) when AT [?] 120msec.[6]

INVASIVE EVALUATION. Echocardiographic examinations were followed by RHC within a 1-hour period. Pharmacological status was unaltered between echocardiography and catheterization. RHC was performed by experienced operators blinded to echocardiography examinations using a 6F Swan Ganz catheter employing jugular or femoral vein access. After suitable calibration with the zero-level set at the mid-thoracic line, pressure measurements were taken from the right atrium (RA), right ventricle (RV) and pulmonary artery (PA) during end-expiration. Five to 10 cardiac cycles were acquired and all pressure tracings were stored and analyzed offline using a standard hemodynamic software package (WITT Series III, Witt Biomedical Corp., Melbourne, FL).

STATISTICAL ANALYSIS. Normality was tested using the Shapiro-Wilk test and visually reaffirmed using QQ plots. Continuous variables were expressed as mean +- SD for parametric variables or median (interquartile range) for non-parametric variables and categorical variables were expressed as numbers and percentage. Correlations between Doppler PAP_M approaches and corresponding invasive measurements were performed using the Pearson's 2-tailed test (correlation between 2 continuous variables). Accuracy was defined as the difference of the mean bias and precision as the spread of data points between echocardiographic and invasive measurements on Bland-Altman analysis. Receiver operating characteristics (ROC) curve was employed to illustrate diagnostic potential of both TRV_{max} and echocardiographic algorithms. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were measured. IBM SPSS statistics version 23.0 was employed for analysis.

RESULTS

STUDY POPULATION . Of 212 enrolled in the study, 45 patients with atrial fibrillation and 46 with pacemaker therapy were first excluded. Nine patients were subsequently excluded after RHC revealed isolated pre-capillary alterations. Ultimately, 112 patients (60 +- 16 years; 46% Female) were included in the analysis. Baseline characteristics are presented in Table 1. All subjects demonstrated signs and symptoms of HF, elevated NTproBNP and objective evidence of LV systolic and/or diastolic function. Echocardiographic and invasive data of the cohort is presented in Table 2. LV EF was reduced (< 50%) in 55 (49%) of the patients. Patients had elevated filling pressures represented by elevated mitral E/e', dilated LA volumes and elevated PA systolic pressure. Further, the cohort demonstrated elevated PA systolic, diastolic, mean pressures (PAP_S, PAP_D and PAP_M respectively), mean pulmonary capillary wedge pressures ($PAWP_M$) and increased pulmonary vascular resistance (PVR) on RHC. Sixty-five patients (58%) demonstrated PH, as defined by PAP_M [?] 25mmHg.

FEASIBILITY AND ACCURACY OF DOPPLER PAP_M ALGORITHMS. Echocardiographic assessment of PAP_M was most feasible employing the approach considering $RVOT_{AT}$introduced by Dabestani et al[12] (86% of patients could have PAPm assessed using this method), followed by TR-derived assessments by Chemla et al[8] (84%) and Aduen et al[5] (81%). PAP_M estimated using the PR-derived approach (Abbas et al[7]) was least feasible of the 4 methods (53%). All echocardiographic PAP_Malgorithms demonstrated a moderately significant correlation with invasive variables (r = 0.41 to 0.65; p < 0.001 for all) (Figure 2). The method proposed by Aduen et al[5]demonstrated the strongest relationship (r = 0.65; p < 0.001), comparable with how recommendation-based TRV_{max} (r = 0.64; p < 0.001) correlated with PAP_M. Agreement between each echocardiographic approach and RHC was studied using Bland-Altman analysis (Figure 3). Echocardiography demonstrated good accuracy to represent invasive pressures in the methods employing TR gradients (Aduen et al[5] and Chemla et al[8]), as seen in relatively low bias between echocardiography and RHC (bias = +2.4 and -2.4mmHg respectively). Moderate precision was observed with limits of agreement (mean value + 1.96 x SD) in the range of +-20mmHg for both methods. Relatively higher systematic error between diagnostic modalities was observed for approaches by Dabestani et al[12] (that employed $RVOT_{AT}$)

that overestimated invasive measurements (bias = +4.2mmHg) and Abbas et al[7] (that employed PR peak velocity) that underestimated invasive measurements (bias = -6.1mmHg). Relatively wider limits of agreement were seen in both algorithms (Figure 3).

DIAGNOSTIC PERFORMANCE OF ECHOCARDIOGRAPHIC ALGORITHMS TO ASSIGN PH PROBABILITY. Recommendation-based TRV_{max}demonstrated strong discriminatory ability to identify invasive PAP_M [?] 25mmHg (AUC = 0.84, CI 0.76 to 0.91; $p < 0.001$). All echocardiographic approaches demonstrated moderate to strong discrimination (AUC range 0.70 to 0.80; $p < 0.001$ for all) with the Chemla et al algorithm[8]demonstrating strongest diagnostic performance (AUC = 0.80, CI 0.71 to 0.89; $p < 0.001$) (Figure 4). Sensitivity, Specificity, PPV and NPV of TRV_{max} and algorithms to identify invasive PAP_M [?] 25mmHg are presented in Table 3. The recommended TRV_{max} cut-off of 2.8m/sec demonstrated 83% sensitivity and 61% specificity to identify PAP_M [?] 25mmHg. At a cut-off of 25mmHg, PAP_M derived by Aduen et al[5] and Dabestani et al[12]demonstrated low specificity (38% and 35% respectively) and Abbas et al,[7] low sensitivity (48%). The only algorithm to show comparable, strong, balanced sensitivity and specificity was that proposed by Chemla et al[8] (78% sensitivity and 67% specificity).

ACCURACY OF ECHOCARDIOGRAPHIC RIGHT ATRIAL PRESSURE ESTIMATES. Echocardiographic RAP employing IVC size and collapse were incorporated to calculate PAP_M in all DE algorithms with the exception of the approach postulated by Dabestani et al.[10] In 107 subjects (96%) with interpretable images, RAP estimated by IVC was elevated (8 or 15mmHg) in 78% subjects (n = 83, RAP = 8mmHg in 43 and 15mmHg in 40 subjects). However false positives were frequent, as seen in 12 of 40 patients (30%) with significantly elevated RAP estimated by echocardiography (15mmHg) that had normal invasive RAP ([?]7mmHg).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the accuracy of multiple echocardiographic algorithms to estimate PAP_M and study diagnostic performance to identify PH in the specific setting of HF. All 4 DE algorithms demonstrated reasonable association with RHC and good agreement on Bland-Altman analysis, with generally lower bias seen in methods interrogating the TR signal. Of the 4 methods, the Chemla et al algorithm demonstrated comparable diagnostic performance with TRV_{max}, both when employing ROC and sensitivity analysis. However, none of the DE algorithms outperformed $TRV_{max.}$

The accuracy of DE to estimate pulmonary artery pressures has been a matter of debate. Earlier studies suggest that DE frequently over- or underestimates invasive pulmonary pressures and should not be relied upon.[15] [16] More recent studies, however, have emphasized results of Bland-Altman analyses that display low bias between echocardiographic PAP_M and RHC, suggesting that Doppler estimates are highly accurate.[17] Our data suggests that accuracy of DE estimates may also vary based on approach utilized. Minimal bias was observed in methods that incorporated TRV_{max}, corroborating an earlier study employing high-fidelity catheters that suggests that such an approach, despite being routinely used as an estimate of PAP_S, provides the most accurate estimate of $PAP_{M.}$[18]Higher systemic bias with RHC and lower precision reflected in wider limits of agreement employing both PI (Abbas et al[7]) and $RVOT_{AT}$ (Dabestani et al[12]) seen in this study may, at least in part, be attributable to smaller patient cohorts (n = 23 and 39 respectively) and less severe clinical presentations in the original studies. As seen in the Bland-Altman plots, a greater dispersion of points is observed at higher mean values of $PAP_{M,}$ suggesting that these methods may be less reliable in the setting of severe PH. The cohort examined by Abbas et al demonstrated a PAP_M = 25 (range 10-57) mmHg and $PAWP_M$ =15 (range 2-38) mmHg, suggesting a milder hemodynamic presentation compared with the present cohort.[7] Dabestani et al do not present corresponding values in their cohort, but suggest a PAP_M range that is relatively lower than that in our study with lower PH cut-off (20mmHg).[12] Additionally, the empirical algorithms presented using this method may demonstrate limited utility in the setting of severely elevated $PAP_{M,}$ as alluded to in certain comparative studies evaluating multiple echocardiographic approaches.[13]

Importantly, despite displaying relatively lower precision and agreement with invasive measurements, both the above-mentioned methods demonstrated good diagnostic ability to identify PH in our cohort. Unin-

terpretable TR signals are frequent in HF,[19] have been reported in as many as 39% of subjects and may present a limitation to echocardiographic evaluation of PH.[20] In our study, TRV_{max} could not be adequately assessed in 14% and VTI in 19% of patients, suggesting a potential diagnostic role for methods that do not necessitate TR jet interrogation.

Early identification of PH in HF has direct consequences on treatment and prognosis. Despite reasonable diagnostic ability demonstrated by all echocardiographic algorithms, only the approach postulated by Chemla et al[8] demonstrated diagnostic ability comparable with recommended 2.8m/sec TRV_{max} cut-off in both ROC and sensitivity analysis. However, none of the methods outperformed $TRV_{max.}$ This finding is contrary to a recent comparative report where the chosen DE algorithms showcased generally superior performance as compared with TRV_{max}.[13]The authors suggest in the abovementioned study that DE algorithms that consider estimates of right atrial pressure in addition to TRV_{max} demonstrate generally stronger correlation with invasive measurements and superior diagnostic performance when compared with TRV_{max}. This was substantiated by data from their study where right atrial pressure > 15mmHg estimated by echocardiography demonstrated highest odds ratio for invasively confirmed PH. In the setting of HF, echocardiographic estimates of right atrial pressure are frequently falsely elevated and sole reliance on the IVC to estimate RAP may be misleading.[21] In our study, 30% of patients with echocardiographically estimated RAP_M = 15mmHg demonstrated normal corresponding invasive pressures, suggesting that these estimates are frequently inaccurate and may not necessarily contribute to stronger performance of derived PAP_M variables as suggested in certain derivation cohorts[7] and the comparative study.[13] Echocardiographic estimates of RAP_M have been incorporated into empirical derivations of PAP_M in all but one selected PAP_Malgorithms in this study. This may play a role in the observed lower performance when compared with TRV_{max} alone, but needs to be further examined.

The use of fluid-filled catheters instead of high-fidelity manometer-tipped catheters for pressure measurement might introduce additional error and may be considered a limitation in this study. Retrospective analysis of echocardiographic data did not permit a closer inspection factors leading to lower feasibility of certain algorithms included in this comparative analysis. Finally, we did not employ agitated saline bubble contrast to strengthen TR jet signal as this is not part of routine protocol in our laboratory.

CONCLUSIONS

In the setting of HF, echocardiographic estimates of PAP_M are highly feasible, demonstrate reasonable association and good agreement with invasive measurements. Despite displaying strong ability to identify PH, none of the methods outperformed recommendation-proposed TRV_{max} cut-off >2.8m/sec.

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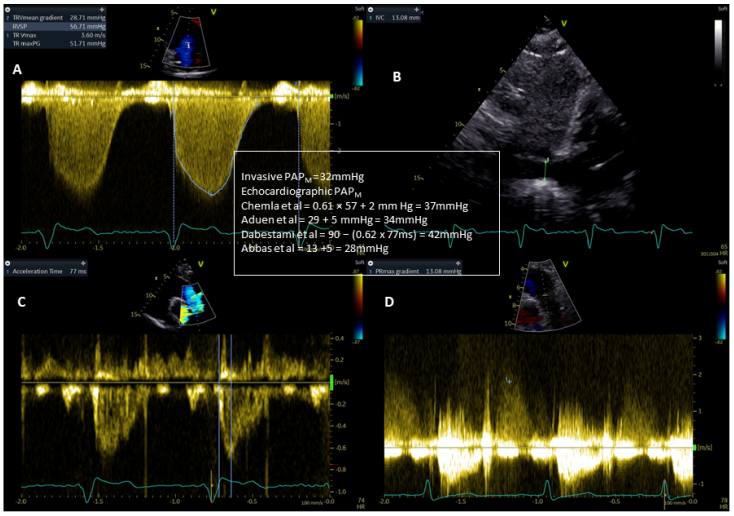

Figure 1. Echocardiographic evaluation of PAP$_M$. A) CW Doppler spectrum of TR velocity for TRVmax (Chemla et al) and TR mean gradient (Aduen et al), B) IVC size and collapse to estimate RAP (Chemla et al, Aduen et al, Abbas et al), C) RVOT acceleration time assessed by PW Doppler (Dabestami et al), D) PR peak gradient assessed by CW Doppler (Abbas et al). Corresponding values of PAP$_M$ in a subject with invasive PAP$_M$ = 32mmHg provided.

FIGURE 2

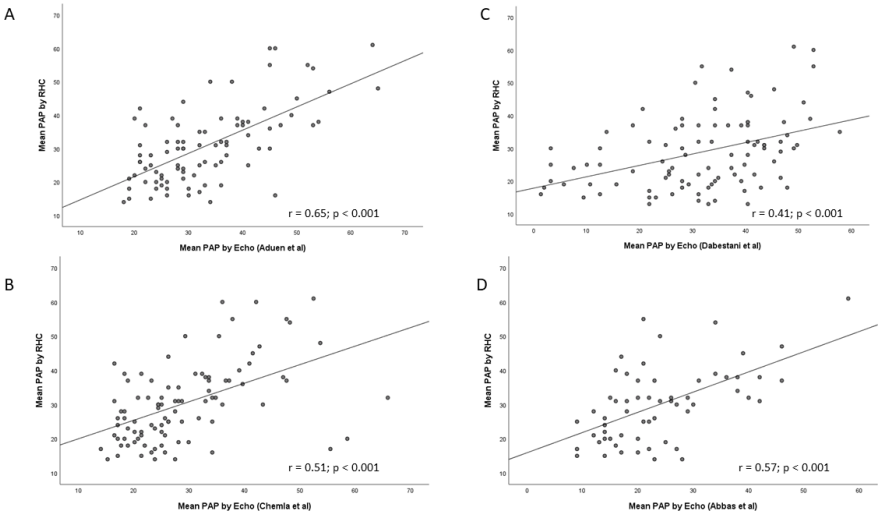

FIGURE 3

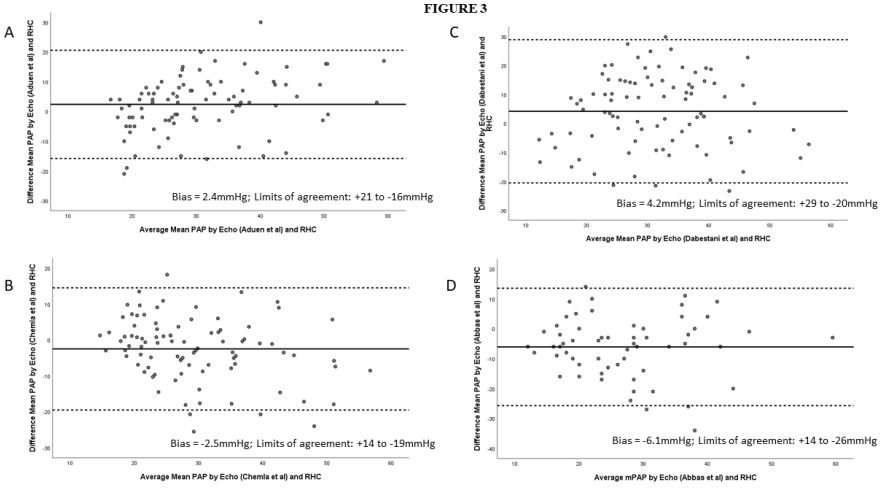

FIGURE 4