Echocardiographic evaluation of systolic and mean pulmonary artery pressure in the follow-up of patients with pulmonary hypertension

Stylianos A. Pyxaras1*, Bruno Pinamonti1, Giulia Barbati1,2, Sara Santangelo1, Matej Valentincic1, Francesca Cettolo1, Gabriele Secoli1, Silvia Magnani1, Marco Merlo1, Francesco Lo Giudice1, Andrea Perkan1, and Gianfranco Sinagra1

1Cardiovascular Department, Pulmonary Hypertension Division, University Hospital of Trieste, Via Valdoni 7, 34149, Trieste, Italy; and 2Department of Environmental Medicine and Public Health, University of Padua, Padua, Italy

Received 30 April 2011; accepted after revision 6 July 2011; online publish-ahead-of-print 4 August 2011

Aims
To identify a correction of the modified Bernoulli formula used to estimate systolic and mean pulmonary artery pressure [sPAP and mPAP, respectively: sPAP = 4 × TRv (tricuspid regurgitation velocity)² + RAP (right atrial pressure); and mPAP = 0.61sPAP + 2], applicable in the follow-up of pulmonary hypertension (PH) patients.

Methods and results
From January 1979 to December 2009, 60 patients with precapillary (class I and IV) and ‘out of proportion’ PH were consecutively enrolled in the PH Registry of Trieste. All patients underwent both echocardiographic and right heart catheter evaluation. We used a simple-linear-regression method in order to compare sPAP and mPAP Doppler-estimated values with the respective right-heart catheterization invasive variables. The comparison of the estimated with the traditional modified Bernoulli formula echo-Doppler data and the effective invasive values confirmed a significant association between them (for sPAP P < 0.001; for mPAP P = 0.006). Simple-linear-regression-derived formulas were sPAP = 1.07 × (4TRv² + RAP) + 7.4 (1) and mPAP = 1.1 × (0.61sPAP + 2) + 2.5 (2). These regression-corrected formulas were validated in an external population of PH patients.

Conclusion
Our data suggest that formulas (1) and (2) could be more reliable with respect to the traditional modified Bernoulli equation, when estimating echocardiographically sPAP and mPAP in patients with PH confirmed by right-heart catheterization.

Keywords
Pulmonary hypertension • Echocardiography • Non-invasive haemodynamic assessment

Introduction
Pulmonary hypertension (PH), a pathophysiological and haemodynamic condition characterized by a variable aetiology and clinical presentation, is frequently recognized during an echocardiographic Doppler examination, even before its definitive diagnosis by means of right-heart catheterization; its presence is usually associated with increased morbidity and mortality.1-16 Furthermore, its presence is a relatively common haemodynamic finding in patients who have left-sided heart disease. In fact, some of these patients with systolic and/or diastolic left ventricular (LV) cardiomyopathic processes may develop secondary PH, which is associated with relevant clinical and prognostic consequences.

Estimated systolic and mean pulmonary artery pressure (sPAP and mPAP, respectively) are the two main echocardiographic variables currently used in the non-invasive evaluation of patients with PH; they both derive by the modified Bernoulli formula (sPAP = 4vTR² + RAP and mPAP = 0.61sPAP + 2 mmHg).17,18 Still, echo-Doppler evaluation of sPAP and mPAP is not always reliable in evaluation in PH patients, with frequent cases of under- or over-estimation in these values with respect to the invasive data at right-heart catheterization.19,20 Therefore, PH cannot be reliably defined by a cut-off value of Doppler-derived sPAP.1

In this study, we sought to identify a corrected-regression formula based on echo-Doppler data for the sPAP and mPAP estimation. Our main goal was to correct the non-invasive diagnostic
method (i.e. echo-Doppler examination) applied after the baseline diagnosis of PH made with invasive means (i.e. right-heart catheterization), as indicated by current guidelines. 

Methods

Study population
From January 1979 to December 2009, 60 patients with precapillary (class I and IV) and 'out of proportion' PH were consecutively enrolled in the PH Registry of Trieste. The choice to enrol patients with precapillary PH along with the 'reactive' PH forms was dictated by the well-known and established similarities of the latter to Class I histopathological changes; in fact, every 'reactive' form is characterized by a fixed structural obstructive remodelling of the pulmonary artery resistance vessels, due to several pathogenic factors, that include vasoconstrictive reflexes, endothelial dysfunction of pulmonary arteries, and proliferation of vessel wall cells. A 'reactive' PH form implies the presence of a trans-pulmonary gradient >12 mmHg, along with a mPAP > 25 mmHg, both measured during right-heart catheterization; these forms make part of PH class II forms (clinical classification). All patients underwent both echocardiographic transthoracic and right heart catheter (Swan–Ganz catheter—Edward’s Lifesciences) evaluation at baseline evaluation. Both invasive and non-invasive diagnostic evaluation at baseline occurred within 12 h since hospital admission.

The right atrial pressure (RAP) was echocardiographically estimated from evaluation of the inferior vena cava during respiration. From a subcostal window, a segment of the inferior vena cava is imaged during quiet respiration. A 5 mmHg value was attributed as RAP if the inferior vena cava diameter was normal (1.5–2.5 cm), and the segment adjacent to the right atrium collapses by at least 50% with respiration. When this decrease was <50%, a 10 mmHg value of RAP was estimated. If the inferior vena cava diameter was over 2.5 cm and the respiration-induced collapse was <50%, the RAP was estimated as 15 mmHg. Finally, when also hepatic vein dilation was added, the RAP was estimated as 20 mmHg. None of our patients was receiving any specific anti-PH drug therapy at baseline evaluation.

Statistical analysis
Summary statistics of clinical and instrumental variables were expressed as mean and standard deviation or count and percentage, as appropriate. Comparison between group of patients were made by the ANOVA test on continuous variables—using the Brown–Forsythe statistic when the assumption of equal variances did not hold—and the χ² test for discrete variables.

Simple-linear-regression models were used to calibrate echocardiographic estimation of sPAP and mPAP with respect to the real values of right-heart catheterization. The Pearson correlation, the Lin concordance correlation and the Bland–Altman correlation coefficients with the catheter data were computed for the proposed corrected and the classical formulas, both on the initial and on the validating sample. As it is well known, the Pearson correlation coefficient evaluates the linear association between two variables, in the sense of the regression towards the mean, but a systematic variation between the two series of measures could not be evaluated. Moreover, in our case, due to the fact that simple-linear-regression was applied to calibrate classical formulas, we expected no difference between Pearson coefficients calculated with classical and modified formulas, both in the initial and in the validating sample. The Lin concordance correlation coefficient was computed in order to evaluate the accuracy and reproducibility of measures (i.e. how much the couple of points were far from the bivector line in the scatter plot). Finally, the Bland–Altman correlation was computed as the Pearson correlation coefficient between two derived series (the differences and the means of the two variables) in order to evaluate the grade of independence between bias and mean.

Results
Demographic, clinical, echo-Doppler and haemodynamic characteristics of our total PH population and within subgroups are listed at Table 1.

Of note, no significant differences were found within subgroups, regarding echo-Doppler-estimated and haemodynamically measured sPAP and mPAP values. The ‘reactive’ PH patient subgroup was characterized by relatively more dilated left atria and ventricles, with respect to Class I and IV subgroups (left atrium diameter 50 ± 8 mm vs. 34 ± 9 and 39 ± 8 mm, respectively, P < 0.001; LV end-diastolic diameter 56 ± 16 mm vs. 41 ± 9 and 44 ± 8 mm, respectively, P = 0.002; LV indexed end-diastolic volume 81 ± 12 mL/m² vs. 13 ± 20 and 24 ± 23 mL/m², respectively, P = 0.001; LV indexed end-systolic volume 45 ± 21 mL/m² vs. 6.7 ± 13 and 10 ± 11 mL/m², respectively, P = 0.001); they also had more frequently abnormal diastolic LV function, as documented by either echo-Doppler and/or invasive parameters (E/A 2.0 ± 1.6 vs. 1.0 ± 0.6 and 0.6 ± 0.5, respectively, P = 0.006; PCWP 25 ± 7 mmHg vs. 10 ± 5 and 11 ± 6 mmHg, respectively, P < 0.001). Increased pulmonary vascular resistances were confirmed during right-heart catheterization (836 ± 680 dyne.s/cm5), with significantly higher values documented in the Class I subgroup (1009 ± 733 dyne.s/cm5), followed by the Class IV subgroup (526 ± 147 dyne.s/cm5) and the ‘reactive’ subgroup (324 ± 128 dyne.s/cm5; P = 0.049).

There was a statistically significant correlation between echo-Doppler-estimated and invasively determined sPAP and mPAP values (respectively: r = 0.457, P = 0.002; r = 0.451, P = 0.006), when the ‘traditional’ modified Bernoulli equation was used, but with an underestimation of both sPAP and mPAP by Doppler formula (Figure 1A and B): linear slopes derived by the regression models were in fact, respectively, 1.07 (P < 0.001) and 1.1 (P = 0.006).

The simple-linear-regression models permitted the correction of the above-mentioned equations, resulting in the new, modified versions (the lines depicted in Figure 1A and B):

\[ s\text{PAP} = 1.07 \times (4vTR^2 + \text{RAP}) + 7.4 \text{mmHg} \]  

(1)

and

\[ m\text{PAP} = 1.1 \times (0.61s\text{PAP} + 2 \text{mmHg}) + 2.5 \text{mmHg}. \]  

(2)

Subsequently, we sought to validate the (1) and (2) corrected equations for other forms of PH. To do that, we randomly selected 29 patients with a PH data at both echo-Doppler and right-heart catheterization evaluation. These 29 subjects were all admitted in our Cardiovascular Department and had different clinical forms of PH, excluding patients belonging to Class I, IV or ‘reactive’ forms. This external validation allowed us to verify that correlation coefficients higher than 0.65 for the corrected equations were.
obtained (respectively for sPAP and mPAP: \( r = 0.690, P < 0.001; \) 
\( r = 0.692, P < 0.001, \) Figure 2A and B); difference between these correlation coefficients with respect to those obtained in the original study sample could be considered as statistically significant, taking into account the difference in sample size (\( z\)-test \( \geq 1.64 \) in both cases)
From the theory of the Pearson correlation coefficient, the Lin concordance correlation coefficient and the Bland–Altman correlation coefficient, to obtain a better agreement between two series of measurements, increasing values for Pearson and Lin and decreasing values for Bland–Altman have to be observed. In our data, as expected, due to the fact that we used simple-linear-regression to calibrate classical formulas, we have no difference between Pearson correlations calculated with classical and modified formulas, both in the initial and in the validating sample; instead, using the modified formulas, increasing values for Lin and decreasing values for Bland–Altman both in the initial and in the validating sample were obtained (Table 2).

No significant difference between estimated and measured RAP was found by the simple-linear-regression method. Furthermore, the method used in our study to echocardiographically assess the RAP had a significant correlation to the cath measured RAP (correlation between estimated and measured RAP: \( P < 0.001, r = 0.64 \)).

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were all calculated for both the equations, considering a 25 and a 40 mmHg cut-off, respectively, for the echocardiographically estimated mPAP and sPAP, as proposed by the current ESC Guidelines.1 These values are reported in Table 3.

### Discussion

Current international guidelines on PH state that right-heart catheterization is required to confirm the diagnosis of PH at baseline evaluation and to assess the severity of the haemodynamic impairment, and that it should also be repeated 3–4 months after the initiation or changes of drug treatment, and in cases of clinical worsening. Still, even at experienced centres, right-heart catheterization procedures have considerable morbidity and mortality rates,25 while relatively not-important complications extend hospital admission duration, with an impact on both the patient quality of life and an adjunctive economic burden.

On the other hand, several studies sought to determine the accuracy of echo-Doppler non-invasive PH evaluation generally with disappointing results.19,20 Most recently, Fisher et al concluded their study on estimating PAP in patients with emphysema using Doppler echocardiography, demonstrating very weak correlations of echocardiographic pressure estimated values with the respective ones derived invasively.20 Also, in a recent review article, Celermajer and Marwick underline that under- and over-estimations of tricuspid gradients are well known to occur, with a standard error for the estimate of Doppler-TR-derived pressure calculation that ranges from 5 to 9 mmHg. They also suggest large-scale reconsideration for both current cut-off values of PH and measurement techniques used in echocardiographic evaluation.19
Table 3  Comparison between ‘classical’ and modified formulas for estimated systolic and mean pulmonary artery pressures for sensitivity, specificity, positive predictive value and negative predictive values in the study population and the external validating sample

<table>
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<th>mPAP, 25 mmHg</th>
<th>sPAP, 40 mmHg</th>
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<tr>
<td></td>
<td>Initial sample</td>
<td>Validating sample</td>
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<tr>
<td></td>
<td>Classical formula</td>
<td>Modified formula</td>
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<tr>
<td>Sensitivity (%)</td>
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<tr>
<td>Specificity (%)</td>
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<tr>
<td>PPV (%)</td>
<td>97</td>
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<td>NPV (%)</td>
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mPAP, mean pulmonary arterial pressure; NPV, negative predictive value; PPV, positive predictive value; sPAP, systolic pulmonary arterial pressure.

The main result of the present study was that our simple regression Equations (1) and (2), by multiplying to a superior to 1 factor (1.07 and 1.1, respectively) and by adding an intercept correction value (7.4 and 2.5 mmHg, respectively), incrementally correct the traditional Bernoulli formula, thus confirming that in our PH population the application of the Bernoulli equation underestimated somehow both sPAP and mPAP values. This conclusion is in accordance with the positive value of the suggested standard error by Celermajer and Marwick, regarding RV pressure estimated values with Doppler-TR-derived calculations. Furthermore, RAP-echocardiography-derived values were demonstrated to be frequently underestimated, especially in PH patients, who notoriously have elevated PAP values.19

The three subgroups of PH patients enrolled in the present study showed significant differences in terms of left ventricular dilatation, left atrial diameter, atrial fibrillation, pulmonary capillary wedge pressure and pulmonary vascular resistances (Table 1). This result is driven principally by the implicit difference of the ‘reactive’ PH subgroup that, by definition, is characterized by left cardiac involvement and, thus, more dilated left heart chambers and higher left atrial filling pressures. In addition, pulmonary vascular resistances measured during right heart catheterization were higher in the first patient subgroup (class 1 PH), were the pulmonary vasculature is directly and primitively compromised. At the same instance, mPAP and sPAP were not significantly different within groups, a finding that is consistent with the overall population’s homogeneity, that is due to the disease’s defining character and severity in all patient types, principally determined by the presence of elevated pulmonary pressure values.

Of note, in our data, only two patients of the study population had a mPAP < 25 mmHg and a sPAP < 40 mmHg. For this reason, specificity values are near to zero; instead, sensitivity values are very high. Also in the external validating sample, only two patients had a mPAP < 25 mmHg, while six of them had a sPAP < 40 mmHg. Thus, to extensively evaluate differences in sensitivity, specificity, PPV and NPV values across our modified equations, larger and more balanced samples are needed.

Conclusions

The (1) and (2) simple-linear-regression-derived equations could be more calibrated with respect to the traditional modified Bernoulli equation, when echocardiographically estimating sPAP and mPAP. These resulted applicable in different classes of PH patients, as validated by an external PH population.

Right-heart catheterization remains essential for the baseline diagnostic confirmation of PH.

Further studies in larger PH populations should be made to confirm broader use of formulas (1) and (2).

Conflict of interest: none declared.

References


