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Early View

Research letter

Non-invasive *versus* invasive pressure/flow relationship of the pulmonary circulation: bias and error

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Non-invasive vs invasive pressure/flow relationship of the pulmonary circulation: bias and error

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Testing the pulmonary circulation in dynamic conditions has been proposed in the recent years as a mean to provide additional insights into patients' symptoms and disease severity, complementing diagnostic evaluations at rest [1-6]. As pulmonary vascular haemodynamics can be described as a function of flow, resistance and left atrial pressure, it has been suggested that pressure-flow relationship of the pulmonary circulation can discriminate normal from abnormal behaviors, the latter consistent with cardiac, pulmonary, or pulmonary vascular disease [4].

Echocardiography can provide an accurate noninvasive estimate of pulmonary haemodynamics, but may suffer of limited precision [7-9]. Although this tool is particularly suitable for population studies (being non-invasive and with no systematic bias), it has insufficient precision for clinical decision making that does not obviate the need for invasive confirmation. Indeed, while accuracy and precision of echocardiography have been repeatedly proven for measurements at rest [7-9], much less evidence is available regarding exercise data [10-13], with only one report focusing also on pressure-flow relationship [11]. Thus, although the theoretical advantage of using a non-invasive approach by echocardiography cannot be denied, there is paucity of information on whether it might provide adequate estimates of pressure-flow relationships during exercise.

Aim of the present study was to compare echocardiographic estimates and invasive measurements of pressure-flow relationship for the pulmonary circulation. In particular, and in keeping with analyses of data obtained in resting conditions [7-9], we hypothesized that exercise stress echocardiography would be rather accurate as compared with invasive measurements, but might suffer of limited precision.

We included patients undergoing a clinically indicated right heart catheterization (RHC), that was immediately followed by invasive hemodynamic evaluation as well as by echocardiographic evaluation during exercise. The analysis was approved by the local ethics committees and patients gave consent for the use of their data for research purposes. Patients were recruited in two centers (Erasme Hospital and Istituto Auxologico Italiano) who followed the same protocol described below.

We excluded patients who did not had a good quality tricuspid regurgitant jet signal at Doppler echocardiography, thus precluding pulmonary artery pressure (PAP) estimation.

Zero reference was placed at midthoracic level [1]. Upon completion of resting hemodynamic measurements, the patients' feet were placed on the pedals and, after a 2-minute rest, subjects were asked to exercise in the supine position. Workload was increased in a stepwise manner every 2 to 3 minutes by 5 to 30 Watts, according to subject's exercise capacity, in order to achieve at least 3 steps of exercise, and measurements were taken during the last minute of each step [1,3,5]. Invasive hemodynamic recordings were analyzed offline by two operators blinded to patients' clinical characteristics and echocardiographic data. Pressure values were averaged over several heart beats (at least 8) and over several respiratory cycles [1].

Methodology for stress echocardiographic assessment of the pulmonary circulation during exercise has been previously described [2,14]. In brief, subjects exercised in supine (Erasme) or semi-supine (Auxologico) position. Workload was increased in a stepwise manner every 2 to 3 minutes (Erasme) or using a ramp protocol (Auxologico), with measurements taken every 2 to 3 minutes. All echocardiographic measurements were performed offline by a single operator, blinded to patients' clinical characteristics and RHC data.

Mean PAP was plotted against cardiac output and the linear regression slope relating these two variables throughout the exercise test (P/Q slope) was calculated both for RHC and for echocardiographic data [1,4,14]. Also the ratio between mean PAP and cardiac output at peak exercise (TPR at peak) was computed [1,3].

Accuracy and precision of echocardiographic estimates of pressure-flow relationships of the pulmonary circulation, compared with invasive measurements, were evaluated through Bland–Altman analysis. The bias, standard deviation of the difference, and 95% limits of agreement were reported. All data analyses were performed using R Core Team software (2016), Vienna, Austria.

After having excluded 20 subjects (n=18 with suboptimal tricuspid regurgitation signal and n=2 with severe tricuspid regurgitation precluding PAP estimation by echocardiography; 80% of without pulmonary hypertension, PH, at rest), our final population consisted of 60 subjects (73% females). All of the included subjects had at least three pairs of pressure and flow invasive measurements and echocardiographic estimates, including peak values.

Sixty-three percent of patients had PH at rest, which was pre-capillary in 61% of cases. Nevertheless, when considering also patients without PH at rest, more than half of the patients (55%) suffered from left heart failure, with a preserved left ventricular ejection fraction in 70% of cases. Only 7% of patients were on permanent atrial fibrillation. Twenty-seven percent of patients had a chronic obstructive pulmonary disease (GOLD 1-2 in 63% of cases).

Echocardiographic estimates of P/Q slope and TPR at peak were significantly correlated with invasive measurements (R^2=0.38 and 0.56 respectively, $p<0.001$). The mean differences between echocardiographic estimates and invasive measurements of TPR at peak and P/Q slope were -0.4 and 1.2 mmHg/L/min, respectively (figure 1). However, the 95% limits of agreement for echocardiographic estimates of TPR at peak and P/Q slope were quite large (5.7 and 8.2 mmHg/L/min, respectively). These results were consistent also when separately analyzing the subgroup of patients (n=30) undergone both exercise echocardiography and exercise RHC in the supine position, which included 90% of patients with PH at rest (mean difference between echocardiographic estimates and invasive measurements of TPR at peak and P/Q slope: -0.9 and

1.4 mmHg/L/min, respectively; 95% limits of agreement for echocardiographic estimates of TPR at peak and P/Q slope: 7.6 and 11.3 mmHg/L/min, respectively).

Echocardiographic estimates of P/Q slope and of TPR at peak were more imprecise and inaccurate in patients with obesity or with lung disease (n=26). The mean differences between echocardiographic estimates and invasive measurements of TPR at peak and P/Q slope were -0.8 and 2.2 mmHg/L/min in patients with obesity or lung disease, and 0.3 and -0.1 mmHg/L/min in patients without these comorbidities. The 95% limits of agreement for echocardiographic estimates of TPR at peak and P/Q slope were 10.9 and 7.7 mmHg/L/min in patients with obesity or lung disease, and 4.8 and 3.6 mmHg/L/min in patients without these comorbidities.

Furthermore, after subdividing the population by the median of the difference between invasive measurement and echocardiographic estimate, P/Q slope resulted more imprecise in patients with obesity ($p<0.001$), in those with higher mean PAP values ($p<0.01$), lower cardiac index ($p<0.05$) and higher pulmonary vascular resistance ($p<0.01$). TPR resulted more imprecise in patients with higher mean PAP ($p=0.06$) and higher pulmonary vascular resistance ($p<0.01$).

When considering the subgroup of patients (n=22) without PH at rest, the mean differences between echocardiographic estimates and invasive measurements of TPR at peak and P/Q slope were 0.8 mmHg/L/min for both variables, while the 95% limits of agreement for echocardiographic estimates of TPR at peak and P/Q slope were 1.9 and 2.9 mmHg/L/min, respectively.

Our study provides one of the first evaluations of the accuracy and precision of echocardiographic estimates of pressure-flow relationships of the pulmonary circulation during exercise, as compared to RHC. In keeping with previous analyses [11,12], non-invasive pressure-flow relationships seem to have a reasonably good agreement with invasive measurements. However, some aspects deserve attention. First, our data show that echocardiography provides an imprecise estimate of pressure-flow relationships of the pulmonary circulation not only at rest but also during exercise. Many possible explanations have been already proposed to account for the imprecision of Doppler echocardiography at rest, which is mirrored by dispersion of individual points at Bland-Altman plot [7-9,11]. These may include suboptimal quality of Doppler signals, imprecise estimation of right atrial pressure, as well as the reliance on few Doppler signal recordings (in inspiration or in expiration) according to the acoustic window available rather than based on an average over several respiratory cycles. All these factors are likely to hold true also for exercise evaluations, and might be particularly relevant for patients predisposed to have huge intrathoracic pressure swings, such as obese patients and patients with lung disease, as well as for patients with higher PAP values. Indeed, the 95% limits of agreement for echocardiographic estimates were quite large , especially when considering that the cut-off value to separate normal from abnormal responses has been suggested to be about 3 mmHg/L/min for both variables [2,5,6]. Even if echocardiography seemed to perform slightly better in the subgroup of patients without PH at rest (95% limits of agreement for echocardiographic estimates: ±2.9 for P/Q slope and ±1.9 for TPR at peak), its imprecision might render its interpretation questionable also in these most delicate cases [15]. Furthermore, PAP estimation was not possible in one fourth of consecutively evaluated patients, including a large number of patients with normal pulmonary hemodynamics at rest. Overall, our data suggest a bias towards echocardiographic overestimation of pressure-flow relationships of the pulmonary circulation. The bias was minimal for TPR at peak but possibly relevant for P/Q slope, which incorporates multiple points and might thus be more prone to accumulation of errors.

Some limitations of our work should be acknowledged. First, this study was conducted on a relatively small number of highly-selected patients, i.e. patients with a clinical indication to undergo RHC after a thorough clinical evaluation. However, proposing RHC for research purposes only in this context would be deemed unethical [1]. Half of patients had exercise echocardiography in the semi-supine position. However, body position seemed not to relevantly affect our results. In this regard, it has been previously shown that neither maximal exercise capacity [16,17] nor P/Q slope relationship [17] might be relevantly affected by body position. Finally, both exercise echocardiography and exercise RHC are time-consuming techniques, whose analysis was conducted blindly and rigorously, eventually providing results which are coherent with what should have been expected based on previous suggestions.

In conclusion, our results suggest that, when adequate tricuspid regurgitant jet signal is present, exercise echocardiography can provide imprecise but rather accurate and sensitive estimates of pressure-flow relationships of the pulmonary circulation, as compared with RHC under exercise. Such an intrinsic imprecision of echocardiography, therefore, should probably limit its use in the assessment of the pulmonary circulation in clinical practice.

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REFERENCES

1. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, Garcia G, Grünig E, Howard L, Humbert M, Lau E, Laveneziana P, Lewis GD, Naeije R, Peacock A, Rosenkranz S, Saggar R, Ulrich S, Vizza D, Vonk Noordegraaf A, Olschewski H. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. Eur Respir J. 2017 Nov 22;50(5). pii: 1700578. doi: 10.1183/13993003.00578-2017
2. Rudski LG, Gargani L, Armstrong WF, Lancellotti P, Lester SJ, Grünig E, D'Alto M, Åström Aneq M, Ferrara F, Saggar R, Saggar R, Naeije R, Picano E, Schiller NB, Bossone E. Stressing the Cardiopulmonary Vascular System: The Role of Echocardiography. J Am Soc Echocardiogr. 2018 May;31(5):527-550.e11
3. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, Lador F, Jaïs X, Parent F, Günther S, Humbert M, Simonneau G, Chemla D. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J. 2015 Sep;46(3):728-37
4. Naeije R, Vanderpool R, Dhakal BP, Saggar R, Saggar R, Vachiery JL, Lewis GD. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. Am J Respir Crit Care Med. 2013 Mar 15;187(6):576-83
5. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail. 2010 Sep;3(5):588-95
6. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, Cunningham TF, Hardin KM, Baggish AL, Ho JE, Malhotra R, Lewis GD. Pulmonary Capillary Wedge Pressure Patterns During Exercise Predict Exercise Capacity and Incident Heart Failure. Circ Heart Fail. 2018 May;11(5):e004750
7. D'Alto M, Romeo E, Argiento P, D'Andrea A, Vanderpool R, Correra A, Bossone E, Sarubbi B, Calabrò R, Russo MG, Naeije R. Accuracy and precision of echocardiography versus right

heart catheterization for the assessment of pulmonary hypertension. Int J Cardiol. 2013 Oct 9;168(4):4058-62

8. Rich JD, Shah SJ, Swamy RS, Kamp A, Rich S. Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice. Chest. 2011 May;139(5):988-993
9. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med. 2009 Apr 1;179(7):615-21
10. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation. 2017 Feb 28;135(9):825-838.
11. Claessen G, La Gerche A, Voigt JU, Dymarkowski S, Schnell F, Petit T, Willems R, Claus P, Delcroix M, Heidbuchel H. Accuracy of Echocardiography to Evaluate Pulmonary Vascular and RV Function During Exercise. JACC Cardiovasc Imaging. 2016 May;9(5):532-43
12. van Riel AC, Opotowsky AR, Santos M, Rivero JM, Dhimitri A, Mulder BJ, Bouma BJ, Landzberg MJ, Waxman AB, Systrom DM, Shah AM. Accuracy of Echocardiography to Estimate Pulmonary Artery Pressures With Exercise: A Simultaneous Invasive-Noninvasive Comparison. Circ Cardiovasc Imaging. 2017 Apr;10(4). pii: e005711
13. Kovacs G, Maier R, Aberer E, Brodmann M, Scheidl S, Hesse C, Troester N, Salmhofer W, Stauber R, Fuerst FC, Thonhofer R, Ofner-Kopeinig P, Gruenig E, Olschewski H. Assessment of pulmonary arterial pressure during exercise in collagen vascular disease: echocardiography vs right-sided heart catheterization. Chest. 2010 Aug;138(2):270-8. doi: 10.1378/chest.09-2099. Epub 2010 Apr 23.

14. Argiento P, Chesler N, Mulè M, D'Alto M, Bossone E, Unger P, Naeije R. Exercise stress echocardiography for the study of the pulmonary circulation. Eur Respir J. 2010 Jun;35(6):1273-8

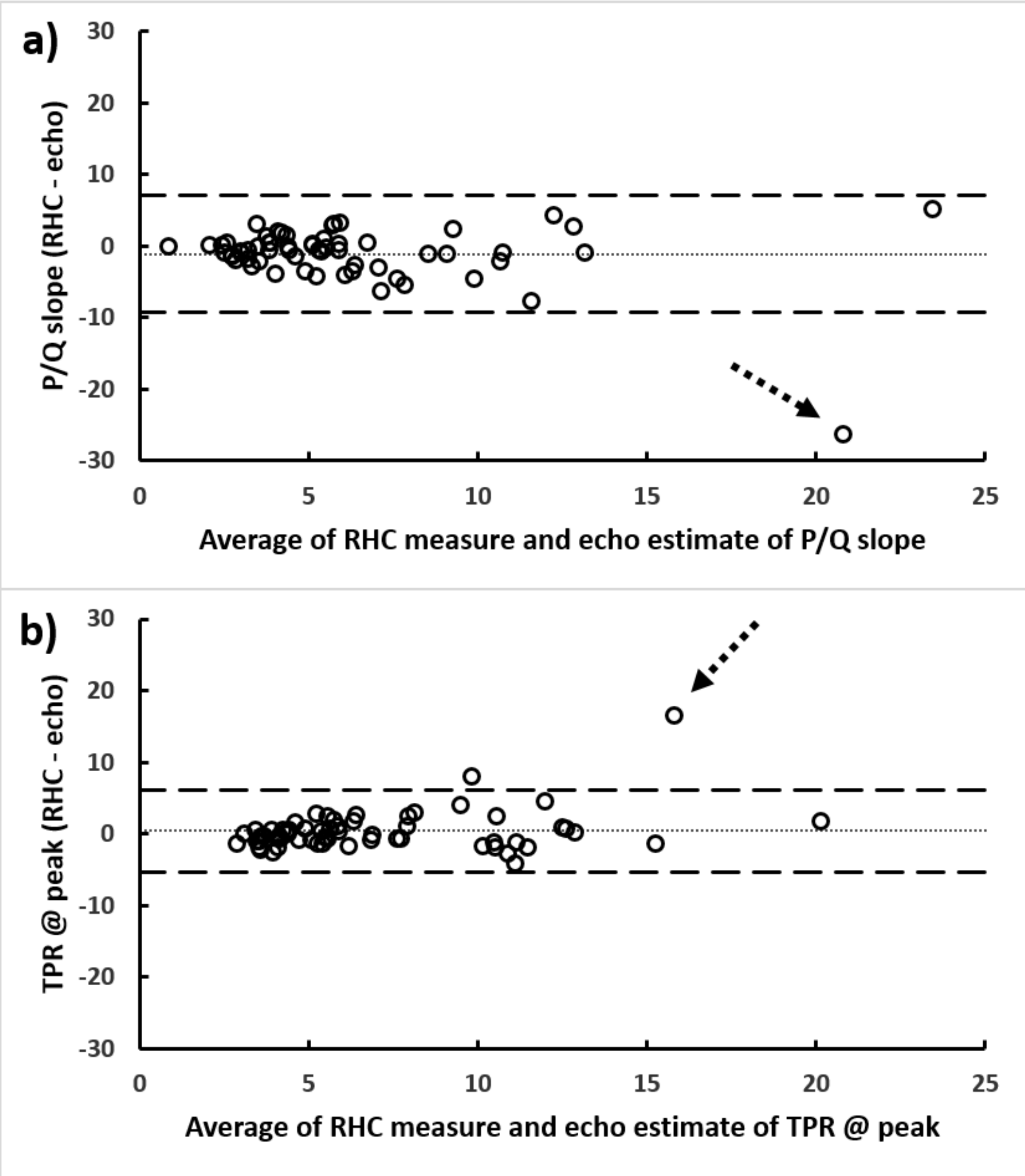
15. Vachiery JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, Coghlan G, Chazova I, De Marco T. Pulmonary hypertension due to left heart disease. Eur Respir J 2019; pii:1801897

16. Reddy YNV, Olson TP, Obokata M, Melenovsky V, Borlaug BA. Hemodynamic Correlates and Diagnostic Role of Cardiopulmonary Exercise Testing in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2018 May 21. pii: S2213-1779(18)30203-8

17. Forton K, Motoji Y, Deboeck G, Faoro V, Naeije R. Effects of body position on exercise capacity and pulmonary vascular pressure-flow relationships. J Appl Physiol (1985). 2016 Nov 1;121(5):1145-1150

FIGURE LEGEND

Figure 1. Bland-Altman plots representing the bias and limits of agreement of echocardiographic estimates as compared with invasive measurements of: A) total pulmonary vascular resistance at peak exercise and B) the regression slope between mean pulmonary artery pressure and cardiac output. Dashed line: 95% limits of agreement; dotted line: bias; the arrows indicate outliers. P/Q slope=regression slope between mean pulmonary artery pressure and cardiac output; RHC=right heart catheterization; TPR=total pulmonary vascular resistance.


a)
P/Q slope (RHC - echo)
Average of RHC measure and echo estimate of P/Q slope
b)
TPR @ peak (RHC - echo)
Average of RHC measure and echo estimate of TPR @ peak