Determinants of pulmonary artery hypertension at rest and during exercise in patients with heart failure

Gabriele Tumminello†, Patrizio Lancellotti‡, Mathieu Lemperre, Vincent D’Orio, and Luc A. Pierard*

Department of Cardiology, University Hospital Sart Tilman, B-4000 LIEGE, Belgium

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KEYWORDS
Heart failure; Pulmonary artery hypertension; Mitral regurgitation; Exercise.

Aims Pulmonary hypertension, a marker of poor prognosis in heart failure, may develop or increase during exercise. We sought to examine the determinants of pulmonary hypertension at rest and during exercise in heart failure patients.

Methods and results Forty-six patients with left ventricular (LV) dysfunction (ejection fraction: 30 ± 6%) underwent a semi-recumbent, incremental bicycle exercise Doppler echocardiography. LV systolic and diastolic function, pulmonary artery systolic pressure (PASP), functional mitral regurgitation (MR), and left atrial volume were quantified at rest and during exercise. Wide changes in PASP at exercise were unrelated to PASP at rest (r = 0.12). Independent predictors of PASP at rest were left atrial volume (P = 0.006), E-wave velocity (P = 0.02), mitral tenting area (P = 0.005), and mitral effective regurgitant orifice (ERO) (P = 0.02). The incidence of dyspnoea was similar in patients with and without moderately severe pulmonary hypertension at baseline. At peak exercise, LV ejection fraction (P = 0.03) and mitral ERO (P = 0.038) were independently associated with PASP. Patients with a larger exercise increase in PASP (>60 mmHg) interrupted frequently exercise for dyspnoea (70 vs. 27%; P = 0.04). A larger rise in mitral regurgitant volume during exercise emerged as the single determinant of exercise-induced increases in PASP.

Conclusion In patients with HF, left atrial volume, mitral deformation, and mitral regurgitant orifice correlated with pulmonary pressure at rest, whereas dynamic MR and limited contractile reserve correlated with pulmonary pressure at exercise. The magnitude of pulmonary pressure during exercise in these patients mainly depends on dynamic MR.

Introduction
Pulmonary hypertension is frequent in patients with heart failure, contributes to exercise intolerance and is associated with a worse outcome. The degree of pulmonary hypertension is not independently related to the severity of left ventricular (LV) systolic dysfunction but is associated with LV diastolic filling abnormalities and with the quantified degree of functional mitral regurgitation (MR). Several histological changes develop in the pulmonary circulation: medial hypertrophy of arterioles, intimal fibroproliferation, and arteriolization of pulmonary veins. These changes depend on the chronicity and the severity of the hypertension and may be initially reversible.

Pulmonary artery systolic pressure (PASP) increases with exercise but the level of increase is highly variable in relation to the respective contribution of recruitment of the pulmonary bed, increased pulmonary resistance, reduced compliance, and increase in left atrial pressure. Reliable estimation of both PASP and LV diastolic pressure can be obtained non-invasively during exercise by Doppler echocardiography.

In this study, we examined patients with heart failure due to LV systolic dysfunction by exercise Doppler echocardiography and we sought to analyse the determinants of pulmonary hypertension during exercise and of exercise-induced changes in PASP.

Methods
Study population
For a period of 8 months, all patients referred to our stress echo laboratory were prospectively screened according to the following inclusion criteria: LV ejection fraction ≤ 45%, at least mild MR, capability to perform a semi-supine exercise Doppler echocardiographic test, clinical stability since at least 1 month. Thirty-seven of the 83 patients who fulfilled the following criteria were excluded: technically inadequate echocardiogram (n = 4), history of myocardial infarction <6 months (n = 18), structurally abnormal mitral valve (n = 5), atrial fibrillation (n = 3), and evidence of inducible ischaemia (n = 7). The final study concerned 46 patients with a mean age of 66 ± 10 years (range 45-80 years).

All patients were in New York Heart Association functional class II (25 patients) or III (21 patients). The site of previous myocardial
infarction was anterior in 19 patients, inferior in 23, and both anterior and inferior in four. A history of systemic arterial hypertension was noted in 19 patients and six were diabetic. Seven patients had previously been submitted to surgical revascularization. Medications included angiotensin-converting enzyme-inhibitor in 39 patients, beta-blockers in 34, diuretics in 21, spironolactone in 14, and nitrate in nine. All patients gave their informed consent and the protocol was approved by the Local Ethics Committee.

**Exercise echocardiography**

Beta-blockers were stopped 24 h before the test. A symptom-limited graded bicycle exercise test was performed in the semisupine (45 degrees) position on a tilting exercise table, keeping the legs at the seat level. The same position was maintained throughout the entire examination period to minimize the influence on the venous return. After an initial workload of 25 W maintained for 3 min, the workload was increased every 2 min by 25 W. Blood pressure and a 12-lead electrocardiogram were recorded every 2 min. Two-dimensional and Doppler echocardiographic recordings were available throughout the test. The presence of inducible myocardial ischaemia was excluded by the use of adenosine sestamibi single-photon emission computed tomography, as described previously.

**Echocardiographic measurements**

Echocardiographic examinations were performed using a Vivid 7 imaging device (General Electric Healthcare, Little Chalfont, UK). All echocardiographic and Doppler data were obtained in digital format and stored on optical discs for offline analysis. All measurements were averaged over three cardiac cycles. Quantification of MR was performed by both the quantitative Doppler method using mitral and aortic stroke volumes and the proximal isovelocity surface area method as previously described. The results of the two methods were averaged allowing calculation of regurgitant volume and the effective regurgitant orifice (ERO). The test area was obtained from the parasternal long-axis view at mid-systole and was measured as the area enclosed between the annular plane and mitral leaflets. From the mitral inflow, the E- and A-wave velocities, E-wave deceleration time, and E/A ratio were measured. LV end-diastolic and end-systolic volumes and left atrial volume were measured by the biplane Simpson disk method. PASP was estimated from the systolic tricuspid pressure gradient (in mmHg), using the simplified Bernoulli equation: \( \Delta P = 4V^2 \), where \( V \) = maximal tricuspid regurgitant velocity in m/s, adding an assumed right atrial pressure of 10 mmHg. Colour-tissue Doppler imaging was performed in the apical views (two-, three-, and four-chamber view) to assess longitudinal myocardial regional function. The sector size and depth were optimized to obtain the highest possible frame rate. Regional pulsed-wave Doppler velocity profiles were reconstructed and computer-analysed offline. Peak velocities during early (E) and late (A') diastole obtained at the level of septal, lateral, inferior, and anterior mitral annulus were measured separately and averaged. The E/E' ratio was calculated. All echocardiographic parameters were obtained at rest and at peak exercise.

**Statistical analysis**

The sample size used was limited according to a screening period corresponding to the contemporary presence of the first authors in the stress echo laboratory. Data are expressed as mean ± SD. Student's paired or unpaired t-test was used to compare measurements obtained at rest and during exercise. Categorical variables were compared with Fisher's exact test. A value of \( P < 0.05 \) was considered significant. Linear regression analysis was applied to study the correlation between PASP at rest and at exercise and different parameters. To evidence the co-factors most predictive for the development of pulmonary artery hypertension during exercise, a multiple regression analysis including all continuous variables was performed (STATISTICA version 6). Moderately severe pulmonary hypertension at rest was defined as PASP ≥ 50 mmHg and as PASP ≥ 60 mmHg at exercise. The reliability of quantitative assessment of MR has been previously evidenced: an excellent correlation was found between two observers in the evaluation of the MR during exercise (\( r = 0.98 \) and \( r = 0.94 \) for the PISA method and Doppler method, respectively).

**Results**

**Characteristics: baseline and exercise**

All the 46 patients performed the exercise test without chest pain, ST-segment depression, or echocardiographic evidence of inducible ischaemia. Mean LV ejection fraction was 35 ± 6%. The mean calculated PASP was 31 ± 11 mmHg, with a wide range of variation (12–68 mmHg). Heart rate and systolic blood pressure increased significantly from rest to peak exercise (75 ± 13 vs. 110 ± 12 b.p.m.; 128 ± 18 vs. 158 ± 22 mmHg, both \( P < 0.0001 \)). LV end-diastolic volume remained unchanged during exercise (165 ± 40 vs. 154 ± 27 ml/m²; \( P = \text{ns} \)), whereas end-systolic volume decreased significantly (from 116 ± 33 to 94 ± 22 ml/m²; \( P < 0.0001 \)) and ejection fraction increased (from 30 ± 6 to 38 ± 6%; \( P < 0.0001 \)). Mitral regurgitant volume and the ERO increased significantly (from 19 ± 11 to 35 ± 18 ml and from 12 ± 6 to 18 ± 11 mm², both \( P < 0.0001 \)). The PASP also increased significantly (from 31 ± 11 to 52 ± 18 mmHg; \( P < 0.00001 \)), range 18–98 mmHg.

**Determinants of PASP at rest**

Baseline haemodynamic characteristics are shown in Table 1. Several parameters obtained at rest correlated significantly with the degree of pulmonary hypertension in univariate analysis: Indices of LV diastolic function (left atrial volume and E-wave velocity), severity of MR (regurgitant volume, ERO, and tenting area), and LV volumes.

In multivariable analysis, left atrial volume (\( P = 0.006 \)), E-wave velocity (\( P = 0.02 \)), mitral valve tenting area (\( P = 0.005 \)), and mitral ERO (\( P = 0.02 \)) remained significant (Table 1). Moderately severe pulmonary hypertension (PASP ≥ 60 mmHg) was observed in 10 patients. The incidence of exercise-limiting dyspnoea was similar in patients with (four of 10, 40%) and without (15 of 36, 44%) marked pulmonary hypertension at rest.

**Determinants of PASP during exercise**

The haemodynamic and Doppler echocardiographic variables obtained during exercise are shown in Table 2. LV volumes at peak stress correlated positively with PASP at exercise. A negative correlation was found with the LV ejection fraction. The severity of MR at exercise and of geometric deformation of the mitral valve correlated with PASP. Indices of LV diastolic function (E velocity, E/E', and left atrial volume) also correlated with PASP. Multivariable analysis of the determinants of exercise PASP showed the ERO (\( P = 0.008 \)) calculated during exercise to be the most important predictor. Low LV ejection fraction was also found to be predictive (\( P = 0.03 \) (Table 2).

The comparison between patients with and without PASP ≥ 60 mmHg at exercise is presented in Table 3. Patients with moderately severe pulmonary hypertension at exercise were more frequently limited by dyspnoea.
Several variables measured during exercise were different between the two groups. Marked pulmonary hypertension at exercise was associated with lower LV systolic function, a higher degree of MR, a lower LV ejection fraction, and a higher E/E' ratio. Left atrial volume was not significantly different between the two groups.

Determinants of exercise-induced changes in PASP

The level of PASP at rest did not correlate with exercise-induced increase in PASP (r = 0.12) (Figure 1). The increase in MR severity (Δ regurgitant volume) and the rise in LV systolic function during exercise correlated with the increase in PASP during exercise (Table 4). Under multivariable analysis, an increase in regurgitant volume emerged as the single independent predictor of PASP changes (P = 0.01).

Discussion

The present study shows that, in patients with heart failure and LV systolic dysfunction, (i) the degree of pulmonary hypertension in resting conditions is independently related to left atrial volume, to mitral valvular deformation, as assessed by the tenting area, and to the mitral regurgitant orifice but is not related to the severity of LV systolic dysfunction, (ii) PASP at exercise is independently related to the severity of MR as measured by the regurgitant orifice during exercise, (iii) the increase in PASP during exercise is unrelated to the level of pulmonary pressure at rest, (iv) dynamic MR, as determined by the increase in regurgitant volume, is the major determinant of a large exercise-induced increase in PASP, and (v) exercise-limiting dyspnoea is not predictable by the level of PASP at rest but relates to moderately severe pulmonary hypertension during exercise.
Figure 1  Correlation between PASP at rest and exercise-induced variation in PASP (APASP).

Table 4  Correlations between clinical, haemodynamic, and echocardiographic variables and exercise-induced increase in PASP (APASP).

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<td>ΔSystolic arterial pressure (mmHg)</td>
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r² = 0.81

Abbreviations as in Table 1.

Pulmonary hypertension at rest in patients with heart failure

In the present work, we assumed that the pressure gradient across the entire pulmonary circulation was due to occlusive resistance. In this way, PASP must equal the sum of the left atrial pressure as downstream end of the pulmonary vasculature and the product of vascular resistance and flow as input impedance. Therefore, pulmonary hypertension may result from increased pulmonary venous pressure, enhanced resistance, elevated cardiac output, or a combination of these mechanisms. As a matter of fact, pulmonary hypertension is a frequent complication of chronic heart failure, and the degree of pulmonary hypertension was previously found to be associated to the severity of functional MR as measured by ERO and to a LV restrictive filling pattern characterized by a high E/A ratio and in particular by a short deceleration time. Our findings do not contradict these observations, though the selected independent variables were different. The stronger independent parameter correlated with PASP was left atrial volume, a marker of chronic diastolic dysfunction and of chronic MR. Although a correlation was found between PASP and both ERO and regurgitant volume, multivariable analysis selected the ERO as independent parameter.

In contrast to Enriquez-Sarano et al., we did not observe in our study group a correlation between PASP and a short deceleration time of the E-wave velocity. The two populations differed in several aspects: we excluded patients in NYHA class IV, unable to exercise and those in atrial fibrillation. Left atrial volume was higher in their study: 111 ± 52 vs. 68 ± 24 mL in ours. Left atrial volume reflects the chronicity and the magnitude of the increased LV filling pressure and has been found to be a robust predictor of cardiovascular outcomes in retrospective and prospective studies.11-13 Enlarged left atrium has a lower load dependency because of increased fibrosis and lower elastic recoil.

The ratio of early transmitral velocity to tissue velocity (E/E'), a marker of increased LV diastolic pressure, did not correlate with PASP at rest. This may be due to the medical treatment of our patients in class II or III; 85% of them received an ACE-inhibitor and 74% a beta-blocker.

Pulmonary hypertension during exercise

During exercise, physiological increases in pulmonary arterial pressure are mechanically limited owing to recruitment and distension of the pulmonary circulation while blood flow increases. During effort, a dramatic increase in pulmonary artery pressure may theoretically result from an apparent increase both in pulmonary resistance as a result of the linear relationship between resistance and flow in the face of a fully distended circuit14 and in left atrial pressure.15 Previous studies have evidenced absent or minimal changes in pulmonary vascular resistance in HF patients during exercise.1 A rise in left atrial pressure may be due to LV systolic dysfunction and/or diastolic dysfunction16 and/or MR.17 Our findings suggest that these three phenomena may play a role. Lower LV ejection fraction, a greater degree of MR, and higher E/E' correlated with estimated PASP. Multivariable analysis indicated that LV systolic dysfunction and the severity of functional MR were the independent determinants of PASP at exercise and that exercise-induced increase in regurgitant volume was the single independent determinant of a high increase in PASP during exercise.

Our patients did not develop definite evidence of exercise-induced ischaemia. A low contractile reserve and increased LV dyssynchrony during exercise may result in reduced LV systolic function and in turn reduced mitral valve closing force. A more spherical LV18 and increased mitral valve deformation at exercise19 contribute to increased tethering forces. Both effects—increase in tethering of the mitral leaflets and decrease in LV force available to close them—result in dynamic exacerbation of functional ischaemic MR.
Limitation of exercise capacity

Patients with heart failure are frequently limited by exertional fatigue, dyspnea, or both. The normal pulmonary circulation is a low-pressure and resistance system with thin-walled vessels. When chronic pulmonary venous hypertension develops, histological changes are observed in the arteries, capillaries, and veins. Medial hypertrophy develops in arterioles and veins; the thickness of the alveolar-capillary membrane increases and lung lymphatic vessels dilate, permitting a high lymphatic output of transudated fluid. In addition, the left atrium also dilates and becomes more compliant. These adaptive mechanisms support our observations, indicating that increased PASP at rest is not the primary cause of exercise-limiting dyspnea in stable patients with chronic heart failure. In contrast, compensatory mechanisms may be overwhelmed at exercise in some patients, leading to an acute rise in left atrial pressure transmitted to the pulmonary circulation, generating exercise-limiting dyspnea. A major mechanism of this symptom in the setting of LV systolic dysfunction appears to be dynamic ischemic MR, sensitive to limited contractile reserve and to changes in LV size, loading, and function. In some patients, the clinical presentation may progress to acute pulmonary edema.20

The absence of relationship between PASP at rest and exercise-induced increase in PASP strengthens the clinical importance of dynamic exercise testing in heart failure patients and the role of exercise Doppler echocardiography in this setting.

Limitations

Several limitations should be acknowledged. Patients in NYHA class IV were excluded. The analysis of tissue Doppler imaging parameters was performed offline. As a result, E/E' ratio appears to be higher than previously reported.21 No evaluation of strain and strain rate parameters was performed to differentiate passive motion from active motion. Although the Doppler methods performed to quantify MR have some pitfalls, the two quantitative methods used in this study have been validated at rest and during exercise in our institution.8 We did not perform invasive measurement of neither PASP nor cardiac output at rest and during exercise, excluding assessment of pulmonary vascular resistance as an indicator of input impedance. However, the assessment of PASP by Doppler echocardiography has been found reliable and reproducible.22 We used a similar estimation of right atrial pressure at rest and at exercise, thus missing the potential influence of exercise-induced increase in right atrial pressure.

Conclusions

The PASP does not predict limiting symptoms and changes during exercise. At rest, PASP appears to relate to the chronicity and severity of heart failure in terms of larger left atrial volume, severity of MR, and mitral valvular deformation dependent on LV remodeling. The level of PASP at exercise relates to reduced LV systolic function and to severity of MR, whereas the increase in PASP relates to dynamic MR. A high exercise-induced level of PASP is associated with exercise-limited dyspnea and relates to dynamic MR. Thus, the findings of this study suggest that resting identification of pulmonary hypertension does not provide enough information and should better be combined with dynamic evaluation by exercise testing.

Conflict of interest: none declared.

References

Clinical vignette

A large mediastinal tumour?

Marc Dewey* and Bernd Hamm

Department of Radiology, Charité, Medical School, Freie Universität und Humboldt-Universität zu Berlin, Charitéplatz 1, 10117 Berlin, Germany

*Corresponding author. Tel: +49 30 4505 27996; fax: +49 30 4505 27996. E-mail address: marc.dewey@charite.de

A 72-year-old man with increasing shortness of breath and atypical angina pectoris received a chest radiograph (Panels A and B) as part of his routine work-up. The posterior (Panel A) and lateral (Panel B) views showed a large (8×5 cm²) mediastinal tumour posterior to the heart (arrows). Differential diagnoses in this situation included a tumour, e.g. arising from the oesophagus or the lungs, a lymphoma, an aortic aneurysm, a pericardial cyst, and gastric herniation. Consequently performed multislice computed tomography showed an oval-shaped cystic lesion immediately lateral to the oesophagus and the descending aorta and posterior to the heart (3D reconstruction, arrows in Panel C). Magnetic resonance imaging (Panel D) demonstrated a lipid-water level (sagittal orientation, arrow; L, lipid; W, water) within the cyst. Thus, a lymphatic origin from the thoracic duct was the most likely cause of this large mediastinal cyst, and a potentially life-threatening carcinosomatous or vascular tumour could be excluded.

A colour version of this figure is available at European Heart Journal online.