

Pulmonary Artery Pressure and Right Ventricular Function during Exercise

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SUMMARY

Background

The physiological behavior of pulmonary artery pressure during exercise has not been precisely established yet. There is lack of agreement in the published literature about the abnormal values of pulmonary artery pressure (PAP) during exercise in the absence of mitral valve disease. Indeed, the last guidelines do not recommend using mean pulmonary artery pressure value ≥ 30 mmHg during exercise to define pulmonary hypertension. There is scarce information about the hemodynamic and functional response of the right ventricle (RV) during exercise and if it is useful to discriminate between a physiological or abnormal response of the pulmonary artery pressure.

Objective

To determine the behavior of PAP during exercise and to compare the echocardiographic parameters of systolic and diastolic RV function in relation to PAP levels.

Material and Methods

A total of 94 patients without significant heart disease were included. Systolic pulmonary artery pressure (SPAP) at rest and maximum exercise during exercise stress echocardiography was adequately measured in all patients. The population was divided into two groups according to the value of pulmonary artery pressure during exercise: A) PAP < 50 mmHg (56) B) PAP ≥ 50 mmHg (38). We also compared the variables of RV systolic function (S-wave measured by tissue Doppler imaging) and diastolic function (using pulsed Doppler echocardiography in the inlet tract and tissue Doppler echocardiography in the lateral wall).

Results

During exercise, 40% of the analyzed population reached a PAP ≥ 50 mmHg. This value was associated with greater age, female gender and elevated values of SPAP at rest. The parameters of RV diastolic function did not present significant differences. The group with PAP ≥ 50 mmHg during exercise presented a less increase in the S-wave measured by tissue Doppler imaging as an expression of a compensatory reduced RV contractile performance.

Conclusions

A high percentage of the population developed PAP ≥ 50 mmHg during exercise. The variables of RV diastolic function did not show significant differences and the group with PAP ≥ 50 mmHg during exercise presented compensatory reduced RV contractile performance as an expression of subclinical dysfunction.

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Key words >

Non-compaction cardiomyopathy; cardiac magnetic resonance imaging; trabeculations; cardiomyopathies; echocardiogram.

Abbreviations >

RV:	Right ventricle	SPAP:	Systolic pulmonary artery pressure
LV:	Left ventricle	TDI:	Tissue Doppler imaging
PH:	Pulmonary hypertension		

BACKGROUND

The importance of the evaluation of the pulmonary circulation has increased during the last years due to progress in understanding the pathophysiology

of the diseases involved, in the number and quality of the diagnostic tools and of the new therapeutic schemes developed in the treatment of pulmonary hypertension (PH).

The physiological values of resting systolic (SPAP), diastolic (DPAP) and mean pulmonary arterial pressure (MPAP) range between 15 and 35, 6 and 12 and 10 and 18 mmHg, respectively. These values vary according to age, height above sea level and hemodynamic conditions. The advent and improvement of non-invasive techniques as Doppler echocardiography allows the estimation of pulmonary artery pressures with a good correlation with the values obtained with right heart catheterization. 1

The definition of PH is based on hemodynamic criteria and established in the presence of a resting mean pulmonary arterial pressure ≥ 25 mmHg. The last guidelines do no longer use the definition of PH on exercise as a mean PAP >30 mmHg due to the conflicting information available. In addition, the different catheterization laboratories use dissimilar quantification parameters in subjects without left heart valve diseases.2

Pulmonary hypertension occurs due to pathological lesions affecting the distal pulmonary arteries (group I) or to different pathological conditions affecting the pulmonary vascular resistance or hemodynamics (groups II-III-IV-V). The presence PH aggravates the prognosis of the associated disease (heart failure, pulmonary thromboembolism, among others) and the early diagnosis allows us to improve patients' prognosis. (3)

In patients with mitral valve disease, SPAP values > 60 mmHg during exercise are useful to define the prognosis and indicate surgery.i,4 In special subgroups of patients with pulmonary arterial hypertension (scleroderma), increased values of pulmonary artery pressure (PAP) during exercise determine the outcomes during follow-up.ii,5

During exercise, PAP increases due to several mechanisms, such as greater pulmonary flow, changes in vascular resistances, increased mean left atrial pressure and abnormalities in gas exchange. These conditions explain in part the differences to define the values of normal PAP during exercise in subjects without heart disease.

Different values in terms of absolute and percentage numbers have been used to define the diagnosis of exercise-induced pulmonary hypertension.iii,6 However, the definition should include a pathophysiological definition associated to abnormalities of the loading conditions of the pulmonary circulation rather than an absolute value of PAP. In this sense, the right ventricle may provide some answers to this issue. The evaluation of the parameters of systolic and diastolic function during exercise might discriminate between physiological and pathological values of pulmonary pressures.

OBJECTIVE

To determine the behavior of PAP during exercise and to compare the echocardiographic parameters of systolic and diastolic RV function in relation to PAP levels.

MATERIAL AND METHODS

From March 1, 2008 to April 30, 2009, 94 consecutive patients referred to our echo stress laboratory underwent exercise stress echocardiography. All patients had adequate tricuspid regurgitation signal to measure resting SPAP and during exercise and were included in this study. The

population selected presented low pretest probability for the development of exercise-induced myocardial ischemia. The exclusion criteria were the following: intermediate or high pretest probability of coronary artery disease (previous angina, history of a positive functional test or electrocardiographic changes); left ventricular (LV) systolic dysfunction with an ejection fraction $< 45\%$ (using the biplane Simpson's method); history of acute myocardial infarction (AMI) and myocardial revascularization (< 12 months); significant heart valve disease; advanced lung diseases (chronic obstructive pulmonary disease, pulmonary fibrosis); significant resting pulmonary hypertension (SPAP > 45 mmHg); functional class III-IV dyspnea and low exercise capacity (≤ 300 kg).

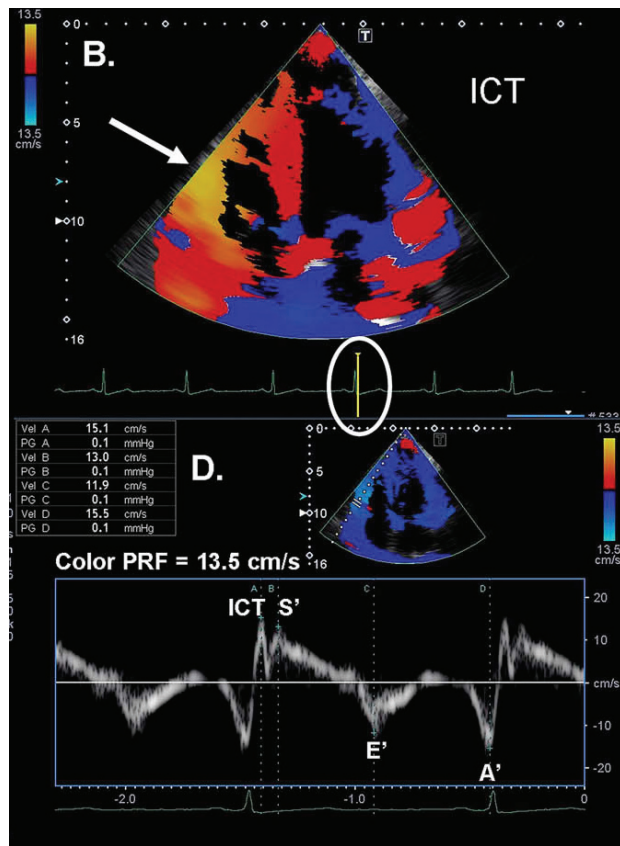
The study was performed by an operator with experience in analyzing wall motion and estimating intracardiac flows during exercise. Echocardiographic examination was performed with a Vivid 5 ultrasound machine using a 2.5 MHz transducer with the patient in the left lateral decubitus position on a semi supine exercise echocardiography table.

Systolic PAP was determined following the international recommendations, adding the systolic pressure gradient across the tricuspid valve ($4 \times$ maximum velocity of the tricuspid valve regurgitant jet²) and the right atrial pressure (estimated by the diameter and inspiratory collapse of the inferior vena cava < 17 mm and $>50\%$, respectively) at rest and in the last minute of maximum exercise. The experience in measuring SPAP is high and this parameter is feasible to determine during exercise. Right atrial pressure value during exercise was assumed similar to that at rest due to technical difficulties to measure it during the maximum exercise and immediately after.

The following parameters were measured in the LV: systolic function (ejection fraction using the biplane Simpson's method), wall thickness, wall motion, diastolic function (E-wave, A-wave and E/A ratio) and the presence of heart valve diseases. The RV was evaluated at rest and during exercise by measuring baseline telediastolic diameter, qualitative systolic function and diastolic function (using pulsed Doppler echocardiography in the inflow tract to quantify E-wave, A-wave and E/A ratio). Pulsed tissue Doppler imaging (TDI) was recorded at the RV basal lateral wall using the software provided by the machine. Systolic function (S-wave), diastolic function (E-wave, A-wave, E/A ratio) and the ratio between the E-wave measured at the inflow tract and the E-wave measured by TDI (E/E'ratio) at rest and at the last minute of exercise with a sweep speed of 50 ms. We used TDI based on the experience of the center with the management of the technique and the high feasibility and reproducibility of the method (Figure 1)..

Exercise stress echocardiography was performed with continuous 12-lead electrocardiographic monitoring, and blood pressure measurements, beginning with a 150 kgm load and increasing 150 km every 2 minutes. Exercise was carried out using a bicycle ergometer in the semi supine position. Images were acquired at rest and at the last minute of maximum exercise (4- and 2- chamber views, apical long-axis view and parasternal short-axis view). The reasons to stop the study were: lower limb muscle fatigue, hypertension (systolic blood pressure > 240 mmHg and diastolic blood pressure > 100 mmHg); angina, significant arrhythmias, symptomatic hypotension (systolic blood pressure < 90 mmHg), heart failure, development of intermediate to high risk myocardial ischemia and achievement of maximum heart rate. We also determined the maximum load achieved, if the patient has exercised to a sufficient level, the presence

Fig. 1. Tissue Doppler imaging analysis of low diastolic and systolic velocities of the RV.



of hemodynamic changes, ECG abnormalities and arterial oxygen saturation.

The population was classified into two groups according to the value of PAP during exercise:

- A) PAP <50 mmHg
- B) PAP ≥50 mmHg

The value of PAP of 50 mmHg during exercise was based on previous studies demonstrating these average levels in non-athletes healthy subjects and on the hemodynamic projection of a MPAP ≥ 30 mmHg used as a previous definition of PH.iv,7 Values of SPAP of 60 mmHg during exercise were not considered, as these values have been determined in athletes, in populations above sea level, in patients with heart failure and scleroderma. The hemodynamic projections of systolic pressure of 60 mmHg estimate a MPAP > 35 mmHg.v,8

$$MPAP: OPAP + 1/3 (SPAP - DPAP)$$

Statistical analysis

We used the t test for the analysis of continuous variables with normal distribution and the chi-square test for dichotomous variables. We defined an alpha error < 0.05.

RESULTS

In this observational, prospective and consecutive study, 94 patients were included. All patients had adequate quantification of SPAP at rest and during exercise and a low pretest probability of coronary artery disease.

The initial evaluation included 116 patients; 22 patients (18%) were excluded due to inadequate tricuspid regurgitation signal (10 patients), inappropriate determination during exercise (9 patients) and low functional capacity (3 patients).

Mean age was 59 years, 55% were men, 39% had hypertension, 6% were diabetics, 27% were current smokers, 6% had a previous myocardial infarction and 8% presented dyspnea.

The echocardiogram reported LV hypertrophy in 21%, an average ejection fraction of 59% (preserved LV systolic function), normal RV systolic function and normal RV diameter in 100% of patients, and low-risk myocardial ischemia in 6%. The average resting and exercise values of SPAP were 32.9 and 49 mmHg, respectively.

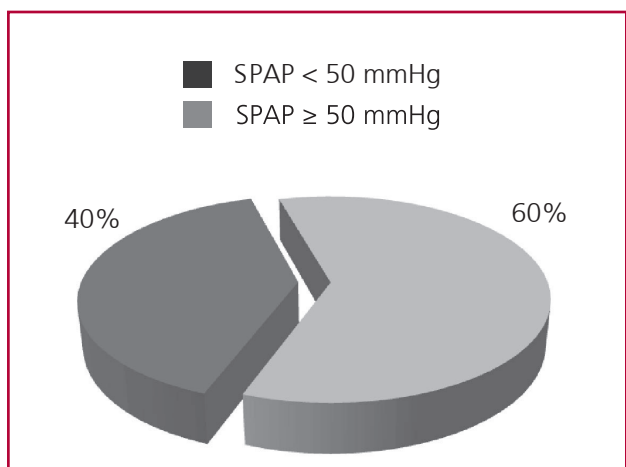
During exercise, 40% of patients (n = 38) developed PAP ≥ 50 mmHg. The baseline characteristics and the echocardiographic parameters were compared between both groups. The average PAP during exercise was 43 mmHg (group a) and 59 mmHg (group b); 7 patients reached a value > 70 mmHg (7%) (Figure 2).

Patients in group B were older (56 vs. 63 years, p < 0.0008); there were more women (30 vs. 58%, p < 0.007) and had higher resting values of SPAP (29 vs. 37, p < 0.001). These findings are similar to those previously reported.vi,9

There were no significant differences in the final load achieved (600 vs. 544 kgm), presence of cardiovascular risk factors (hypertension, dyslipemia, diabetes and smoking habits) history of myocardial infarction, angina, dyspnea, systemic blood pressure values reached (systolic blood pressure of 153 mmHg vs. 154 mmHg, and diastolic blood pressure of 86 mmHg vs. 85 mmHg) and LV ejection fraction. Qualitative right ventricular ejection fraction at rest and during exercise was normal in both groups (Table 1).

Pulsed Doppler echocardiography and in the RV inflow tract and TDI at rest did not show significant differences between both groups (E: 0.5 vs. 0.52; A: 0.39 vs. 0.42; E/A ratio: 1.28 vs. 1.20; S-wave: 14 vs. 13; E-wave: 11 vs. 12; A-wave: 14 vs. 15; E/A ratio: 0.9 vs. 0,8). Similarly, there were no significant differences in the parameters evaluated in both studies during

Fig. 2. Results of pulmonary artery pressure during exercise.



exercise (E: 0.65 vs. 0.65; A: 0.49 vs. 0.48; E/A ratio: 1.36 vs. 1.33; and E-wave: 22 vs. 21; A-wave: 27 vs. 24; E/A ratio: 0.83 vs. 0.93). However, we observed significant differences in the proportional increase of the S-wave measured by TDI in group A (19.7 vs. 17; $p < 0.001$).

Right ventricular end-diastolic pressure, expressed by the E/E' ratio, did not show significant differences between rest (3.57 vs. 4) and exercise (3.29 vs. 3.8) (Table 2).

The presence of a less increase in a parameter of RV systolic function measured by TDI (S-wave) in group B might be a sign of pathophysiological abnormality during exercise which might represent an important pathophysiological value related to the definition of exercise-induced pulmonary hypertension.

physiological or pathological status.

Previous studies evaluating patients with heart failure undergoing exercise stress echocardiography determined parameters of LV diastolic function (E/E' ratio) as an expression of elevated end-diastolic pressure and prognostic markers.^{vii,10} We did not find that this parameter correlates with increased PAP during exercise.

Right ventricular systolic and diastolic function during exercise has received little attention and there is scarce information available in patients with pulmonary hypertension. Probably, the pathophysiological concept of estimating the value of PAP should focus on the hemodynamic impact on the

Resting variables	TOTAL (94)	SPAP <50 (56)	SPAP ≥50 (38)	P value
Age (years)	59	56	63	<0.0008
Gender (n) male	55		39	16
female	39	17	22	<0.0007
HT (n)	37	19	18	NS
Diabetes (n)	6	2	4	NS
Dyslipemia (n)	42	21	21	NS
Smoking habits (n)	26	17	9	NS
AMI (n)	6	3	3	NS
Angina (n)	3	2	1	NS
Dyspnea (n)	8	5	3	NS
LVEF (%)	59	60	58	NS
Rest SPAP (mmHg)	32.9	29	37	<0.01
Sufficient test(%)	47	45	55	NS

Table 1. Baseline clinical and echocardiographic characteristics of the selected population.

DISCUSSION

The definition of exercise-induced pulmonary hypertension is still controversial and the last European guidelines do not support its measurement as a diagnostic criteria any more. The different opinions and dissimilar definitions in the cardiology community are due to the use of absolute values, to the attempt to unify criteria and to the extrapolation of data to the entire population.

At present, we recognize that an absolute number of PAP does not allow a precise discrimination between the different physiological and pathological status of the pulmonary circulation during exercise. Multiple variables have demonstrated changes of the absolute values reached during exercise: age, gender, resting SPAP, height above sea level and load achieved. These differences determined that no definition for PH on exercise as assessed by right cardiac catheterization can be provided at the present time.

The values of PAP on exercise obtained by different authors in the absence of heart valve disease vary between 40 and 60 mmHg among very different populations. The maximum values may reach 80 mmHg and there are no variables that allow us to discriminate when these numbers represent a

Table 2. Comparative analysis of the different variables related to the groups.

Resting variables	SPAPS<50	SPAP ≥50	P value
Normal RVSF (%)	100	100	NS
E-wave	0.50	0.52	NS
A-wave	0.39	0.43	NS
E/A	1.28	1.20	NS
TDI. S	14	13	NS
TDI. E	11	12	NS
TDI. A	14	15	NS
TDI. E/A	0.9	0.8	NS
E/E'	3.57	4	NS
Effort variables			
Onda E	0,65	0,65	NS
Onda A	0,49	0,48	NS
E/A	1,36	1,33	NS
DT. S	19,7	17	<0,01
DT. E	22	21	NS
DT. A	27	24	NS
DT. E/A	0,83	0,93	NS
E/E'	3,29	3,8	NS

RV produced by PAP during exercise.

Previous publications measured blood flow at the RV outflow tract as a manifestation of stroke volume in order to diagnose pathological pulmonary vascular responses during exercise as an indicator of elevated pulmonary resistance. However, this parameter should be interpreted considering the range of heart rate achieved, the loading conditions of right-sided heart chambers, the technical difficulties in the quantification and the partial analysis of phenomenon that involves more than the vascular tone (increased pulmonary flow, pulmonary venous hypertension, hypoxia, among others).

We chose pulsed tissue Doppler imaging on the free wall of the RV to evaluate systolic and diastolic function based on the fact that it is less influenced by loading conditions and on the high reproducibility at rest and during exercise. Pulsed-wave TDI is used to measure low-frequency Doppler systolic and diastolic velocities that reflect longitudinal RV myocardial motion.^{viii,11} The limitations of this technique are the different values depending on the age, the difficulties in determining radial contraction and the need for experienced operators.

Our population has a higher number of subjects (40%) with PAP ≥ 50 mmHg during exercise compared to the cutoff point established to define the diagnosis; 7% of patients reached a value > 70 mmHg. Higher values of PAP on exercise have been described in special populations (heart failure, scleroderma, high altitude, athletes, advanced age, among others).

Our findings about an exaggerated response related to age, female gender and elevated resting SPAP are consistent with the literature. Several mechanisms may be proposed to justify this response in advanced age and female populations: increased vascular resistance, interstitial fibrosis and greatest prevalence of left ventricular diastolic dysfunction. We did not detect variations in transvalvular mitral flow suggestive of LV diastolic dysfunction during exercise; on the other hand, a reduced group of subjects developed myocardial ischemia.

High resting SPAP were more frequent in group B as a consequence of the definition using absolute values (≥ 50 mmHg). Some laboratories use percentage increases ($>50\%$) related to resting parameters to establish the presence of exercise-induced PH.

Group B presented a less increase in the S-wave measured by tissue Doppler imaging as an expression of a compensatory reduced RV contractile performance, indicating a pathophysiological response to the exaggerated increase in PAP. In other words, the development of PAP on exercise ≥ 50 mmHg produces a reduced compensatory longitudinal contraction of the RV.

The most interesting aspect of PAP on exercise is to determine the real clinical significance of this condition and the cutoff point of the definition. A longitudinal, long-term follow-up might identify if these patients have high-risk to develop pulmonary

hypertension in the future and whether it represents an adaptive response of the RV and pulmonary circulation to exercise or is a simple variant of a physiological entity without clinical involvement.

This study arises several questions about the cutoff point used to define the groups with and without pulmonary hypertension during exercise, the absence of parameters of RV diastolic dysfunction and the scarce influence of the loading conditions. Interpreting these findings is the main challenge, as the impact on the RV may indicate an abnormal response of the pulmonary circulation during exercise. Further studies are necessary to define PH on exercise more accurately and to establish its real prognosis.

Study Limitations

One of the main limitations of the study is that the values of right atrial pressure during exercise were extrapolated with the resting values due to technical difficulties in evaluating the inferior vena cava at peak exercise. These data might underestimate the value of PAP on exercise.

We did not measure PAP by right heart catheterization to compare it with the echocardiographic data. We know that the correlation between both methods is good at rest but lower during exercise lower.

The cutoff point of 50 mmHg for PAP during exercise used to classify the groups of patients is dissimilar in the published studies with values ranging from 40 to 60 mmHg.^{ix,12}

We could not measure PAP in each exercise stage and correlate TDI with TAPSE during exercise due to technical issues.

CONCLUSIONS

A high percentage of the population developed PAP ≥ 50 mmHg during exercise. The variables of RV diastolic function did not show significant differences and the group with PAP ≥ 50 mmHg during exercise presented compensatory reduced RV contractile performance as an expression of subclinical dysfunction.

RESUMEN

Comportamiento de la presión pulmonar y función del ventrículo derecho intraesfuerzo

Introducción

El comportamiento fisiológico de la presión pulmonar durante el ejercicio continúa sin establecerse con precisión. La literatura es discordante con respecto a los valores considerados patológicos de presión pulmonar intraesfuerzo (PPI) en ausencia de valvulopatía mitral e incluso, las últimas guías no recomiendan utilizar la presión pulmonar media ≥ 30 mmHg con el esfuerzo para definir hipertensión pulmonar. Es escasa la información disponible en relación a la respuesta hemodinámica y funcional del ventrículo derecho (VD) con el esfuerzo y tampoco sobre el hecho de si podría discriminar entre una respuesta fisiológica o patológica de la presión pulmonar.

Objetivo

Determinar el comportamiento de la PPI y comparar los parámetros ecocardiográficos de función sistólica y diastólica del VD en relación a sus niveles.

Material y métodos

estimar presión pulmonar sistólica (PPS) basal y en máxima carga durante el eco-estrés en ejercicio. De acuerdo al valor de presión pulmonar con el ejercicio, la población fue estratificada en dos grupos: a) $PI < 50$ mmHg / Hg (56) y b) $PI \geq 50$ mm. (38) Se compararon las variables de función sistólica (onda S del Doppler tisular) y diastólica (Doppler pulsado en tracto de entrada y Doppler tisular de pared lateral) del VD.

Resultados

El 40% de la población analizada alcanzó una $PPI \geq 50$ mm/Hg y se relacionó con mayor edad, sexo femenino y valores elevados de PPS basal. Los parámetros de función diastólica del VD no demostraron diferencias significativas. El grupo con $PPI \geq 50$ mmHg presentó un menor incremento de la onda S del Doppler tisular como expresión de una disminución de la respuesta compensadora contráctil del VD.

Conclusiones

Un porcentaje elevado de la población estudiada desarrolló una $PPI \geq 50$ mmHg. En relación al VD, no se observaron diferencias significativas en las variables de función diastólica y el grupo con $PPI \geq 50$ mmHg presentó una menor respuesta sistólica compensadora con las cargas, como expresión de disfunción sub-clínica.

Palabras clave > Hipertensión pulmonar - Ergometría - Ventrículo derecho - Fisiología cardiovascular

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