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Power of resting echocardiographic measurements to classify pulmonary hypertension patients according to European society of cardiology exercise testing risk stratification cut-offs

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A B S T R A C T

Background: Right ventricular function is the major determinant of morbidity and mortality in pulmonary arterial hypertension (PAH). The ESC risk assessment strategy for PAH is based on clinical status, exercise testing, NTproBNP, imaging and haemodynamics but does not include right ventricular function. Our aims were to test the power of resting echocardiographic measurements to classify PAH patients according to ESC exercise testing risk stratification cut-offs and to determine if the classification power of echocardiographic parameters varied in chronic thrombo-embolic pulmonary hypertension (CTEPH).
Methods: We prospectively and consecutively recruited 46 PAH patients and 42 CTEPH patients referred for cardio-pulmonary exercise testing and comprehensive transthoracic echocardiography. Exercise testing parameters analyzed were peak oxygen consumption, percentage of predicted maximal oxygen consumption and the slope of ventilation against carbon dioxide production. Receiver operator characteristic curves were used to determine the optimal diagnostic cut-off values of echocardiographic parameters for classifying the patients in intermediate or high risk category according to exercise testing.
Results: Measurements of right ventricular systolic function were the best for classifying in PAH (area under the curve 0.815 to 0.935). Measurements of right ventricular pressure overload (0.810 to 0.909) were optimal for classifying according to exercise testing in CTEPH. Measurements of left ventricular function were of no use in either group.
Conclusions: Measurements of right ventricular systolic function can classify according to exercise testing risk stratification cut-offs in PAH. However, this is not the case in CTEPH where pressure overload, rather than right ventricular function seems to be linked to exercise performance.

1. Introduction

Pulmonary arterial hypertension (PAH) is a disease of very poor prognosis, defined by right heart catheterization as increased mean pulmonary arterial pressure ≥25mmHg , pulmonary vascular resistance >3 wood units and pulmonary capillary wedge pressure ≤15 mm Hg at rest, in the absence of other causes of precapillary PH such as PH due to lung diseases, chronic thromboembolic pulmonary hypertension (CTEPH) or other rare diseases [1]. It is essential to risk stratify patients to optimize treatment and care. In 2015, the European society of cardiology (ESC) published a risk assessment classification with various cut-offs in clinical signs and symptoms, cardio-pulmonary exercise testing (CPET), NTproBNP plasma levels, hemodynamics and imaging (right atrial area and pericardial effusion) [1]. There is no mention of right ventricular (RV) parameters although RV dysfunction is considered as the major determinant of morbidity and mortality factor in pulmonary hypertension [2, 3, 4]. However, resting transthoracic echocardiography is a reliable, non-invasive technique that can be done at the patient's bedside. Furthermore, the ESC recommends transthoracic echocardiography at regular intervals for follow-up in PAH.

Abbreviations: CPET, cardio-pulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; ESC, European Society of Cardiology; PAH, pulmonary arterial hypertension; (L/R) V, left/right ventricle; AUC, area under the curve; ROC, receiver operator characteristic (curve); VE, minute ventilation; VCO2, carbon dioxide production; VO2, oxygen consumption.

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The association between ESC cut-offs as assessed by exercise testing and resting echocardiographic parameters has never been investigated.

No risk assessment strategy exists in the other pulmonary hypertension groups, CTEPH in particular. It is already known that there are major differences between groups. Indeed we have previously shown that significant differences in exercise gas exchanges exist between PAH and CTEPH and that there seems to be a disconnection between exercise performance (ventilatory efficiency) and disease severity in CTEPH [5]. More recently we showed that resting RV function was associated with exercise performance in PAH but not in CTEPH [6].

In view of this, our primary aim was to determine the echocardiographic measurements that have the highest power to classify PAH patients according to ESC CPET risk stratification cut-offs.

Our secondary aim was to determine if the power of these echocardiographic parameters varied between PAH and CTEPH, to approach the association between resting RV parameters and exercise performance in both groups.

2. Methods

2.1. Study population

One hundred and twenty consecutive patients were prospectively recruited, between November 2013 and July 2014 at the Hammersmith Hospital, London, UK. Criteria for inclusion were pre-capillary pulmonary hypertension diagnosed by right heart catheterization and sinus rhythm. Only patients that the Hammersmith Hospital pulmonary hypertension team considered required regular follow-up trans-thoracic echocardiography and CPET were invited to participate, and among these patients, only those with both procedures performed within a month of each-other with no change in treatment during this time were included.

Patients were categorized into precapillary pulmonary hypertension groups according to the ESC guidelines for the treatment and diagnosis of pulmonary hypertension [1]. Pulmonary hypertension was suspected on non-specific symptoms (shortness of breath, fatigue, weakness, angina, dry cough, syncope) associated with physical signs (left parasternal lift, accentuated second heart sound, pansystolic murmur of tricuspid regurgitation, elevated jugular venous pressure). Patients then had an electrocardiogram, a chest radiograph and transthoracic echocardiography. If pulmonary hypertension was suspected with transthoracic echocardiography (peak tricuspid regurgitation velocity ≥2.9 m/s or <2.9 m/s with other pulmonary hypertension signs), patients then had pulmonary function tests, ventilation/perfusion lung scan and high-resolution contrast enhanced computed tomography to identify lung diseases or thromboembolic disease. Definite diagnosis was then made with right heart catheterization. Pre-capillary pulmonary hypertension was defined as mean PAP ≥25 mm Hg, pulmonary wedge pressure ≤15 mm Hg and pulmonary vascular resistance >3 wood units. The classification of PAH and CTEPH were defined in accordance with ESC guidelines [1]. Exclusion criteria were incomplete data on echocardiogram (suboptimal imaging), complete bundle branch block (which alters timings of the cardiac cycle), presence of a pacemaker or defibrillator and groups of pulmonary hypertension other than PAH and CTEPH.

In the PAH group, 6 patients were treated with Sildenafil, 1 with Ambrisentan, 4 with Bosentan, 1 with Diltiazem, 10 with Sildenafil + Ambrisentan, 1 with Sildenafil + Treprostinil, 1 with Sildenafil + Epoprostenol, 7 with Sildenafil + Bosentan, 1 with Sildenafil +Veletri + Bosentan, 1 with Sildenafil + Epoprostenol + Bosentan. 13 received no treatment. In the CTEPH group, 10 patients were treated with Sildenafil, 2 with Ambrisentan, 2 with Bosentan, 1 with Tadalafil, 3 with Ambrisentan + Sildenafil, 3 with Bosentan + Sildenafil, 1 with Sildenafil + Bosentan + Veletri. 20 received no treatment.

Patients consented to use of their medical data; the study was approved by the hospital's ethics committee. The investigation conformed to the principles of the Declaration of Helsinki.

2.2. Echocardiographic measurements

A senior echocardiographer accredited by the British Society of Echocardiography performed a comprehensive transthoracic echocardiography with a Philips (Andover, MA, USA) iE33 probe S5-1 (30 patients), GE (GE Healthcare, Holten, Norway) vivid 7 probe M4S (22 patients), vivid 9 probe M5Sc (22 patients), and Toshiba Artida Aplio (Toshiba Medical Systems Europe BV, Zoetermeer, The Netherlands) probe PST-30B (14 patients).

The left heart was assessed according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations for cardiac chamber quantification by echocardiography in adults [7]. The following measurements were recorded: biplane LV ejection fraction, LV end-diastolic diameter, LV end-systolic diameter and averaged septal and lateral mitral E/e′. The right heart was assessed according to the American Society of Echocardiography right heart assessment guidelines [8]. The following measurements were recorded: RV fractional area change, RV basal diameter, RV length, peak tricuspid regurgitation velocity, pulmonary acceleration time, tricuspid tissue Doppler Imaging S′ wave, TAPSE, right atrial area (then indexed to body surface area calculated by the Mosteller equation from height and weight) RV myocardial performance index, LV systolic and diastolic eccentricity index.

Images centered on the RV acquired from the apical four chamber view were used to acquire right ventricular longitudinal strain. Images were optimized for speckle-tracking by decreasing the depth to improve spatial resolution, and narrowing the sector width to increase frame rate. The off-line analysis was performed at the acquisition frame rate using a single vendor independent computer analysis system specific for 2D RV Speckle-tracking (Epsilon Imaging/Echo Insight version 2.2.2.837, Michigan, USA) Speckle-tracking was performed by manually tracing the endocardial border of the RV at end diastole. The tracking was then assessed by the software and visually by the reader. Adjustments were made when necessary. Both global right ventricular longitudinal strain, therefore including both the RV free wall and the interventricular septum and free-wall right ventricular longitudinal strain were recorded.

2.3. CPET data collection

CPET was performed on a stationary cycle ergometer according to the recommendations of the American College of Chest Physicians, [9] using a breath-by breath system Master Screen CPX; Jaeger; Hoechberg, Germany). Patients wore a face mask and were supervised by an experienced physiologist and physician. The patients were monitored during a 3 min upright rest period; a 3 min unloaded pedaling period and then during the exercise phase when the work load increased at a rate to achieve a loaded period of 10 min. The exercise continued until the symptom-limited maximum. Arterial blood pressure, 12-lead ECG and peripheral oxygen saturation were continuously recorded. The breath-by-breath measurements were ventilation (VE), CO_2 production (VCO_2) and oxygen consumption (VO_2).

PeakVO_2 is the peak oxygen uptake measured during the test divided by the patient's weight and is expressed in mL/min/kg. Maximum workload is the maximum load in watts that the patient reaches. VO2max defines the maximal aerobic capacity. Predicted VO2max is calculated from the ECSC (European coal and steel community) 1993 formula which includes height, weight, age and gender. VE/VCO_2 slope is an index of ventilatory efficiency. It is the slope measured by the linear regression equation plotting VE against VCO_2 before the respiratory compensation point. It reflects the increase in VE per unit increase of VCO_2. (Normal value <30) [9].

According to the ESC 2015 guidelines, PAH patients are considered at intermediate risk for clinical worsening or death (5–10%) for peakVO2 = 11–15 mL/min/kg, percentage predicted VO2max =– 65%, VE/VCO2slope = 36–44.9. There are considered at high risk (>10%) for peakVO_2 <11 mL/min/kg, percentage predicted VO2max <35%, VE/VCO2 slope ≥45 [1].

2.4. Statistical analysis

Data were analyzed using IBM SPSS Statistics 21(Chicago, Illinois).

The distribution of the data was assessed by visual review when plotted as a histogram, with normality further confirmed using the Shapiro–Wilk test. Summary statistics for normally distributed data are given as the mean ± standard deviation, with the median ± interquartile range given for non-parametric data. The unpaired student t-test was used to compare normally distributed continuous variables between PAH and CTEPH groups. Non-normally distributed variables were compared with the Mann Whitney U test. The Chi-squared test was used to assess differences in categorical variables between groups. All tests were two-tailed and the cut-off for statistical significance was 0.05. Receiver operator characteristic (ROC) curves were used to determine the optimal diagnostic cut-off values of echocardiographic parameters for classifying the patients in intermediate or high risk category according to ESC CPET classification [1].

All the echocardiographic parameters collected were tested.

3. Results

3.1. Population

One hundred and twenty patients were prospectively recruited. Thirty-two patients were excluded for inadequate imaging or because they did not qualify for PAH or CTEPH diagnosis. (Fig. 1) Patients' baseline characteristics are presented in Table 1.

In the CTEPH group, there was a higher proportion of men, patients were older and had a higher body mass index than in the PAH group. There were no significant differences in RV function, LV systolic or diastolic function or in exercise performance between groups.

3.2. PAH

In PAH we found that RV parameters approaching systolic function (global right ventricular longitudinal strain, free-wall right ventricular longitudinal strain, RV fractional area change, TAPSE and tricuspid S′ wave in tissue Doppler imaging) had an excellent ability to classify

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