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Prognostic relevance of pulmonary arterial compliance after therapy initiation or escalation in patients with pulmonary arterial hypertension

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ABSTRACT

Background: Conventional hemodynamic parameters are considered to be the gold standard indices of outcome in pulmonary arterial hypertension (PAH); on the contrary, few data support the hypothesis that the pulsatile component of right ventricular afterload provides important prognostic information. The aim of the study was to investigate the prognostic significance of pulmonary arterial compliance (PCa) after therapy initiation or escalation in PAH patients.

Methods: A cohort of 419 consecutive PAH patients (308 naive and 111 prevalent) underwent right heart catheterisation (RHC) prior to initiating or escalating PAH-targeted therapy. RHC was repeated in 255 patients (61%) after 4 to 12 months of therapy as 62 patients (15%) died and 102 (24%) did not undergo a follow-up RHC within the first year.

Results: After the follow-up RHC, 63 patients died over a median follow-up period of 39 months. At multivariate analysis, age > 50 years old, male gender, etiology associated with systemic sclerosis, persistence of WHO class III/IV, and reduced PCa at follow-up RHC were the independent parameters significantly associated with poor prognosis. At ROC analysis, the optimal cut-off point of PCa to predict survival was 1.4 mL/mmHg (AUC 0.73, sensitivity 81.8%, specificity 58.8%).

Conclusions: In PAH patients hospitalized to initiate or to escalate PAH-specific therapy, failure to improve PCa after therapy is a strong hemodynamic predictor of poor prognosis.

1. Introduction

The identification of clinically relevant prognostic predictors is a key objective for clinicians involved in the care of patients with pulmonary arterial hypertension (PAH). Hemodynamic parameters are of paramount importance to predict the outcome in PAH. The National Institutes of Health (NIH) registry was the first to show the impact of baseline hemodynamic parameters on outcome, demonstrating that increased right atrial pressure (RAP), increased mean pulmonary artery pressure (PAP), and reduced cardiac index are independently associated with an increased mortality [1]. Since then, right heart hemodynamic parameters have been confirmed in several studies as robust independent prognostic factors [2–7]. Importantly, follow-up hemodynamic evaluations were also found to provide relevant information to assess the risk of PAH patients; as a matter of fact, follow-up data provided a more reliable prognostic estimation than baseline data in several studies [3,8]. Of note, all such studies evaluated conventional right heart hemodynamic parameters, i.e. parameters that represent the static component of right ventricular (RV) afterload.

More recently, data are accumulating in the literature, suggesting that the pulsatile component of RV afterload may provide important prognostic information in heart failure with reduced left ventricular systolic function, in heart failure with preserved left ventricular systolic function, and in PAH as well [9–12]. However, in the only previous study performed in adult PAH patients, the number of patients included was too small to perform multivariable analysis [13]. In addition, the prognostic significance of the changes in pulmonary compliance (PCa) determined by PAH-targeted treatments has never been assessed.

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Therefore, we retrospectively evaluated a cohort of incident and prevalent PAH patients, who were hospitalized to perform right heart catheterization and either initiate or tailor medical therapy, with the aim to investigate the prognostic significance of right heart hemodynamic parameters obtained after therapy, focusing on the role of PCa.

2. Methods

2.1. Patients

The study includes 419 PAH patients diagnosed according to guidelines recommendations [14], aged >18 years old, admitted to four referral centers for pulmonary hypertension in Italy from 2004 to 2012 (Catania, Napoli, Pavia, Rome). These centers share the same clinical approach and collect prospectively the clinical and hemodynamic data. Incident cases were patients from whom clinical and hemodynamic data were collected at the moment of the diagnosis before any specific treatment; prevalent cases were patients from whom baseline data were collected at a follow-up hospitalization, because their clinical conditions were considered unsatisfactory and required repeat right heart catheterization and escalation of targeted therapy. After 1 year from the baseline evaluation, a subgroup of 255 patients underwent a second evaluation and were followed for survival until the end of the observation period (December 2014).

The investigation conforms to the principles outlined in the Declaration of Helsinki. All patients signed an informed consent to collect data for scientific purpose, and subsequently the Ethical Committee gave the approval for the analysis (prot. 424/12 EC Rome).

2.2. Right heart catheterization

Right heart catheterization (RHC) was performed by insertion of a balloon-tipped catheter in the pulmonary artery via the internal jugular vein or the femoral vein. The following hemodynamic parameters were measured or calculated: pulmonary capillary wedge pressure; systolic, diastolic, and mean pulmonary artery pressure; right atrial pressure; cardiac output, calculated by thermodilution or by the Fick method in case of severe tricuspid regurgitation and in the presence of systemic-to-pulmonary shunts; cardiac index, obtained dividing cardiac output by the body surface area; pulmonary vascular resistance (PVR), calculated as (mean pulmonary artery pressure − pulmonary capillary wedge pressure) / cardiac output, PCa calculated as stroke volume / pulse pressure. All pressures were recorded during several respiratory cycles. Zero reference was set at midthoracic level. In each patient, cardiac output was determined using the same technique in the baseline and in the follow-up RHC.

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as absolute and relative frequencies. Comparisons between groups of quantitative and qualitative variables were done with the two-sample *t* test, Wilcoxon rank-sum (Mann–Whitney) test, and Fisher exact test, when appropriate.

Cumulative survival was calculated on the basis of Kaplan–Meier estimates; the relative risk of dying (hazard ratio, HR) and its 95% confidence interval (95%CI) were computed using Cox model. Survival was estimated from time of enrolment with all-cause mortality as the end point. Variables significantly associated with the death in univariate analysis were entered into a multiple Cox model. The stepwise procedure was performed with the backward selection method in order to estimate the final model. The optimal PCa cut-off value for predicting survival was identified with ROC curve analysis and sensitivity, specificity, positive and negative predictive values accordingly calculated after logistic regression. Calibration and discrimination were evaluated with Hosmer–Lemeshow statistics, calibration slope, and Brier score. All tests were two-sided, and a p of <0.05 was considered statistically significant. Data handling and analyses were done with STATA version 13.1 software (College Station, Texas 77845, USA).

3. Results

3.1. Patient characteristics and follow-up

Patient disposition is shown in Fig. 1. The baseline clinical, hemodynamic, and echocardiographic characteristics of the study population ($n = 419$) are summarized in Table 1. There were 308 incident patients and 111 prevalent patients. Most of the patients had idiopathic PAH (260, 62%), or PAH associated with connective tissue disease (106, 25%), patients in functional class III/IV were the majority (244, 58%). The hemodynamic pattern was consistent with severe pulmonary vascular disease.

Within the first year, 62 patients died (15%) and 102 patients (24%) did not perform RHC, thus 255 patients (61% of the original cohort) underwent the second invasive evaluation within 1 year (median interval time = 8 months). During the subsequent follow-up period (median 39 months), 63 patients died. The baseline clinical and hemodynamic characteristics of the 255 patients are shown in Table 2 and are similar to those of the general population. Table 3 shows the therapy of this cohort of patients at baseline and at the follow-up catheterization. There was a small proportion of patients that had no specific PAH treatment at follow-up (8.2%). These patients were responders to nitric oxide and did not receive specific PAH treatments but only calcium antagonists. After therapy initiation or escalation, mean PAP and PVR were significantly lower, CI and PCa were significantly higher, RAP and functional class showed a marginal nonsignificant improvement (Table 2). Interestingly, the change in PCa from baseline to control RHC (mean ± SD) was not statistically different in incident vs prevalent patients (respectively, 1.38 ± 0.93 vs 1.43 ± 0.96 mL/mmHg, $p = 0.695$); the change in PCa from baseline to control RHC was significantly greater in WHO class I–II vs WHO class III–IV patients (0.55 ± 1.39 vs 0.21 ± 0.97 mL/mmHg, $p = 0.041$).

3.2. Prognostic impact of baseline variables

Table 4 shows the baseline clinical and hemodynamic parameters that were associated with prognosis at univariate analysis: age, PAH associated with systemic sclerosis, WHO class III/IV and CI; PCa approached statistical significance ($p = 0.054$). Table 4 also shows the three parameters that were independently related to poorer survival at multivariate analysis, i.e. etiology associated with systemic sclerosis, WHO class III/IV and a reduced cardiac index.

3.3. Prognostic importance of hemodynamic parameters after therapy

Table 5 shows the follow-up clinical and hemodynamic parameters which were associated with prognosis at univariate analysis: age, etiology associated with systemic sclerosis, persistence of WHO class III/IV, mPAP, PVR, and PCa. Table 5 also shows the parameters that were independently related to poorer survival at multivariate analysis, i.e. age > 50 years old, male gender, etiology associated with systemic sclerosis, persistence of WHO class III/IV, and reduced PCa, which was the only hemodynamic parameter independently related to prognosis at multivariate analysis. In addition, since the changes in PCa from baseline to control RHC were greater in WHO class I–II vs WHO class III–IV patients, we also tested whether there was an interaction between PCa and WHO functional class and the result was negative (p value for interaction = 0.558, indicating that the prognostic significance of PCa was similar in WHO class I–II and in WHO class III–IV patients).

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