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Early View

Research letter

Pulmonary haemodynamics and mortality in chronic hypersensitivity pneumonitis

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Title: Pulmonary haemodynamics and mortality in chronic hypersensitivity pneumonitis

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To the Editor:

Chronic hypersensitivity pneumonitis (CHP) is a common interstitial lung disease (ILD) frequently associated with lung fibrosis[1]. Among patients with CHP, the degree of pulmonary function impairment and the extent of fibrosis are known predictors mortality[2, 3]. In other forms of ILD, such as idiopathic pulmonary fibrosis (IPF) and sarcoidosis, abnormal pulmonary haemodynamics measured during resting supine right heart catheterization (RHC) are additionally associated with poor prognosis[4–7]. In CHP however, the prognostic value of RHC is unknown.

We recently found that pulmonary hypertension (PH), defined by a mean pulmonary arterial pressure (mPAP) ≥25 mmHg at RHC, is a prevalent feature of CHP[8]. In the current report, we extend our analysis evaluating the association between pulmonary haemodynamics and mortality in this population.

This was an observational study, assessing mortality rates of a previously published cohort of CHP patients that underwent a standardized PH assessment protocol, including RHC[8]. As previously reported[8], data were collected between August 2011 and February 2013 at the ILD Outpatient Clinic of the Federal University of São Paulo, Brazil. 1023 consecutive outpatients with ILD were evaluated during the study period to identify those with CHP without relevant comorbidities or postcapillary PH (n=47). Mortality rates were assessed up to June 2016. Data are presented as mean±SD or median [interquartile range] for normally and non-normally distributed variables, respectively, based on the Shapiro-Wilk statistic. Comparisons between survivors and non-survivors were made using t-test for normally or Mann–Whitney test for non-normally distributed variables. Categorical variables were compared using Chi-squared and Fisher exact tests. *Receiver operating characteristics* (ROC) curves were used to obtain the best hemodynamic

cut-offs for prognostication. Cox proportional hazards and Kaplan–Meier cumulative survival analyses were performed following standard procedures. Correlation analysis between forced vital capacity (FVC) and arterial oxygen saturation (SaO_2) vs. pulmonary vascular resistance (PVR) and pulmonary vascular compliance (PVC) were performed to examine the association between ILD severity and pulmonary vascular dysfunction. $p<0.05$ was considered significant.

The study sample (n=47) included 25 non-PH and 22 pre-capillary PH patients[8], with 12 subjects having severe pre-capillary PH, defined by mPAP >35 mmHg or mPAP ≥25 mmHg associated with a cardiac index (CI) <2.5 L/min/m^2[9]. Median follow-up was 40 [29-46] months. Overall mortality was 45% (n=21/47); 1-year, 2-year and 3-year mortality rate was 13% (n=6/47), 21% (n=10/47) and 36% (n=17/47), respectively. Among severe PH patients, 1-year, 2-year and 3-year mortality rate was 33% (n=4/12), 42% (n=5/12) and 58% (n=7/12), respectively. The mean age was 57±13 years for non-survivors and 64±9 years for survivors (p=0.06), without gender differences between these groups (76 vs. 77% females, p=0.61). FVC and SaO_2 for non-survivors vs. survivors were 44±4 vs. 72±18% predicted (p<0.01) and 89 [84-94] vs. 95 [93-96]% (p<0.01), respectively. Time from CHP diagnosis was 10 [1-25] months for non-survivors and 36 [9-82] months for survivors (p=0.03).

At resting RHC, non-survivors had elevated mPAP, elevated transpulmonary gradient (TPG), elevated diastolic pulmonary gradient (DPG), elevated PVR and decreased PVC compared to survivors (28±7 vs. 24±5 mmHg, p=0.05; 19±7 vs. 14±4 mmHg, p=0.01; 12±5 vs. 8±4 mmHg, p=0.02; 4.1±1.8 vs. 2.8±0.9 WU, p=0.01; and 3.0 [1.8-4.0] vs. 4.2 [2.9-4.8] mL/mmHg, p=0.07, respectively). There were no differences for CI between survivors and non-survivors (2.7±0.4 vs. 2.7±0.5 L/min/m^2, p=0.89).

By *ROC* curve analysis, the optimal cut-off points to separate non-survivors from survivors was 24 mmHg for mPAP (AUC 0.66, p=0.07), 15 mmHg for TPG (AUC 0.71, p=0.01), 10 mmHg for DPG (AUC 0.69 p=0.02), 3.3 WU for PVR (AUC 0.71, p=0.01) and 3.6 mL/mmHg for PVC (AUC 0.69, p=0.03). After adjusting for age, gender and time from CHP diagnosis, a TPG ≥15 mmHg (HR 4.72, 95% CI 1.47-15.16, p=0.01), a PVR ≥3.3 WU (HR 3.23 95% CI 1.29-8.09, p=0.01) and a PVC ≤3.6mL/mmHg (HR 3.52 95% CI 1.41-8.80, p=0.01) remained predictors of mortality. By Kaplan Meier survival curve analysis, the aforementioned PVR and PVC thresholds dichotomized non-survivors from survivors starting at 6 months following RHC (figure 1). The coefficient of determination (R^2) between FVC (% predicted) and PVR, and between FVC (% predicted) and PVC was 0.32 ($p<0.01$) and 0.15 ($p<0.01$), respectively. The coefficient of determination between SaO_2 and PVR, and SaO_2 and PVC was 0.47 ($p<0.01$) and 0.31 ($p<0.01$), respectively.

In sum, we found that abnormal pulmonary haemodynamics at RHC are associated with mortality in patients with CHP. These findings suggest that pulmonary vascular dysfunction, characterized by elevated PVR and decreased PVC, has negative long-term prognostic implications in CHP.

In patients with sarcoidosis and IPF, PVR >3WU[7] and >6.23 WU[6], respectively, have been associated with worse survival. Additionally, minor elevations of mPAP were also found to predict patients' outcomes in IPF[4, 5]. In the current study, mPAP per se was not a strong predictor of mortality; however, patients with PVR ≥3.3 WU encountered a more than 3-fold increased mortality rate compared to patients with PVR <3.3WU, despite a similar CI. These observations might be indicative of a yet preserved relationship between the right ventricle (RV)

contractility and the afterload, before pulmonary pressures significantly increase and/or the RV becomes dysfunctional[10], as is the case for early stages of pulmonary vascular disease[11].

Along this lines, the PVC optimal cut-off value of 3.6 mL/mmHg to separate non-survivors from survivors was much higher than that previously reported in pulmonary arterial hypertension (PAH)[12, 13]. Mahapatra et al.[12] and Campo et al[13] identified that PVC values of 0.83 mL/mmHg and 1.25 mL/mmHg were associated with mortality in patients with idiopathic PAH and scleroderma-related PAH, respectively. Therefore, our PVC findings likely reflect early pulmonary vascular stiffness[14, 15] and ultimately suggest that PVC is clinically relevant to the pathophysiology of ILD.

Taken together, our data add to the framework of understanding the prognostic role of pulmonary vascular insufficiency in ILD, indicating that a mildly increased RV afterload impacts patient´s clinical outcome in CHP. Our findings, therefore, should be helpful when risk stratifying patients with CHP and determining the optimal therapeutic strategy, including referral or prioritization for lung transplantation.

Interestingly, the hemodynamic measurements predicting mortality in the present study were not entirely justified by the severity of the parenchymal lung disease, given the weak/moderate coefficient of determination between FVC and PVR/PVC. Additionally, SaO_2 explained <50% of the observed pulmonary vascular dysfunction. Therefore, the elevated PVR and decreased PVC of CHP non-survivors are likely a consequence of multiple pathophysiologic mechanisms converging to pulmonary vascular remodelling, such as chronic inflammation, distortion of the lung microcirculation (likely enhanced by CHP bronchiolocentric pattern), hypoxic vasoconstriction and endothelial and vascular smooth muscle cell dysfunction.

The current study is limited by the small sample size and relatively low number of events. However, to the best of our knowledge, this is the largest cohort of patients with CHP reported to date prospectively evaluated with invasive haemodynamics and with long-term follow-up, and as such, the current data provides important insight into the prognostic role of pulmonary vascular dysfunction in this population.

In conclusion, indices of pulmonary vascular dysfunction are associated with mortality in CHP, providing therefore valuable prognostic information. In addition to the identification of decreased FVC and SaO_2, which were also associated with mortality, the identification of an elevated PVR and decreased PVC should be helpful when accessing prognosis in CHP and determining prioritization or referral for lung transplantation.

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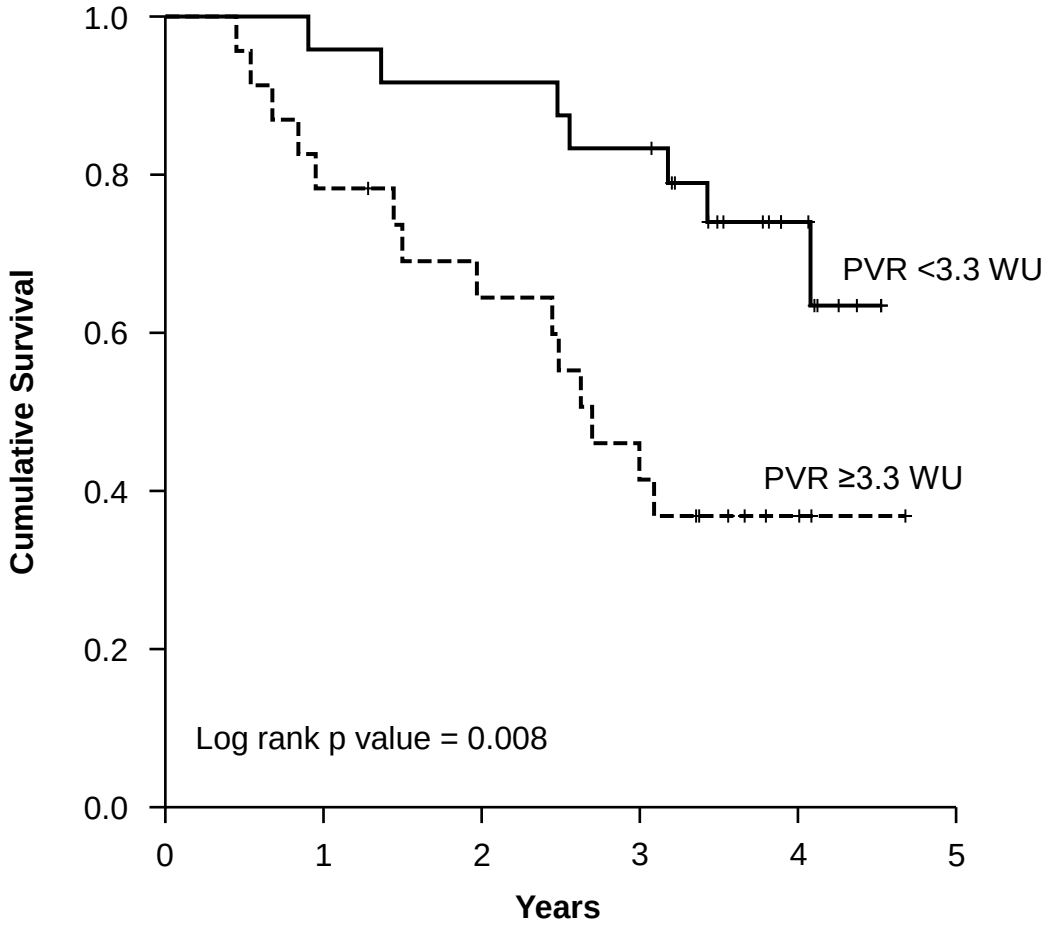
Figure 1. Kaplan Meier survival curves for pulmonary vascular resistance (PVR) and pulmonary vascular compliance (PVC) in patients with chronic hypersensitivity pneumonitis

A.



B.