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Prognostic relevance of right heart reverse remodeling in idiopathic pulmonary arterial hypertension

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KEYWORDS:
idiopathic pulmonary arterial hypertension; right heart remodeling; echocardiography; morbidity-mortality; clinical worsening

BACKGROUND: Right ventricular (RV) failure is a major determinant of symptoms and shortened survival in pulmonary arterial hypertension (PAH). This study assessed the prognostic relevance of increased right heart (RH) dimensions determined by echocardiography and RH reverse remodeling (RHRR) with targeted therapies in idiopathic PAH (IPAH).

METHODS: The study prospectively monitored 102 therapy-naïve IPAH patients for the presence of clinical worsening. Baseline evaluation included RH catheterization and echocardiography. RHRR at the 1-year follow-up was defined by a decrease in RV end-diastolic area, right atrial area, and the left ventricular systolic eccentricity index.

RESULTS: At the 1-year follow-up, 18 of 102 patients (17.6%) presented with RHRR. A decrease in pulmonary vascular resistance was the only independent determinant of RHRR. The 94 surviving patients were monitored for 995 ± 529 days. RHRR was an independent prognostic factor and significantly improved the power of the prognostic model based on traditional clinical and hemodynamic parameters. The respective event-free survival rates at 1, 3, and 5 years were 94%, 94%, and 94% in patients with RHRR and 75%, 55%, and 24% in those without RHRR ($p = 0.0001$). Interestingly, RHRR was able to further stratify patients' risk assessment through the Registry to Evaluate Early And Long-term PAH Disease Management risk score.

CONCLUSIONS: RHRR after 1 year of treatment is an independent predictor of prognosis in IPAH. The likelihood of RHRR is proportional to decreased pulmonary vascular resistance.

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Right ventricular (RV) function is a major determinant of symptoms and outcome in severe pulmonary hypertension (PH).[1,2] The RV basically adapts to increased afterload in PH by an increased contractility with preserved dimensions (homeometric adaptation), relying also on increased dimen-

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sions (heterometric adaptation) when this systolic function increase becomes insufficient to preserve RV-arterial coupling.[2–4] RV failure in severe PH thus inevitably results in increased RV dimensions, which may occur in the presence of otherwise unchanged pulmonary hemodynamics or exercise capacity.[5] Reversing RV dimensions back to normal should therefore be a therapeutic preoccupation in the care of severe PH.

Echocardiographic imaging is an essential component of current multimodality assessment of RV-arterial coupling in severe PH.[6] In the present study, we reassessed efficacy of targeted therapies in reversing increased right heart (RH) dimensions in patients with PAH. We defined RH reverse remodeling (RHRR) by simple and commonly used echocardiographic parameters as a decrease in RV end-diastolic area (RVEDA), right atrial (RA) area, and left ventricular systolic eccentricity index (LV-EIs). Each of these echocardiographic measures has been shown to be a predictor of outcome in severe PH.[2,3] We hypothesized that RHRR, defined by a decrease in RVEDA, RA area, and LV-EIs at 1 year after institution of targeted therapies in idiopathic PAH (IPAH), would be associated with an improved survival.

Methods

Population and study design

The study enrolled and prospectively monitored 102 consecutive treatment-naïve IPAH patients referred to the Pulmonary Hypertension Unit (Policlinico Umberto I, Sapienza University of Rome, Italy) from January 2009 to December 2011. In accordance with guidelines, the diagnosis of IPAH relied on RH catheterization showing precapillary PH (mean pulmonary artery pressure [mPAP] $>$ 25 mm Hg, pulmonary artery wedge pressure [PAWP] $<$ 15 mm Hg) and the use of an algorithm including respiratory function tests, perfusion lung scan, computed tomography scan, and echocardiography.[7] The baseline evaluation at the time of diagnosis included medical history, physical examination, a nonencouraged 6-minute walk test (6MWT), RH catheterization, and echocardiographic assessment. The patients were treated in agreement with the recommendations of the European Respiratory Society/European Society of Cardiology guidelines available at the start of the study,[8] which were less insistent on earlier combinations of drugs than in the 2015 update.[6] Thus, combination therapy was not started unless clinical worsening (CW) was present.

During the first year of follow-up, 8 patients died. The 94 surviving patients were re-evaluated at 1 year (physical examination, 6MWT, RH catheterization, and echocardiographic assessment) and monitored for CW until December 2015 (Figure 1).

CW was defined as a reduction in exercise capacity (–15% compared with the previous 6MWT, confirmed by 2 tests done $\leq$ 2 weeks) plus worsening in World Health Organization (WHO) Functional Class, or non-elective hospitalization for PAH (need for intravenous diuretic or inotropic drugs, need for new PAH therapies, lung transplantation, or septostomy), or all-cause mortality.

All patients were prospectively monitored with monthly telephone calls and clinical examinations every 1 to 3 months for the presence of CW, which was evaluated by 2 physicians (V.C.D., P.R.) blinded to the echocardiographic results. The first episode of CW was taken into consideration for the analysis.

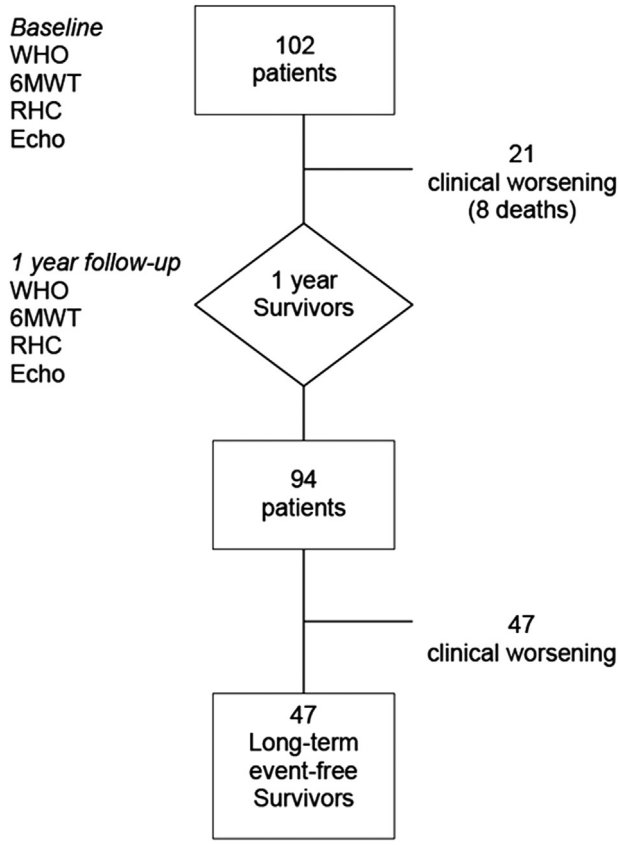

Figure 1 Study design. 6MWT, 6-minute walk test; RHC, right heart catheterization; WHO, World Health Organization Functional Class.

The investigation conformed with the principles outlined in the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board for Human Studies of the Policlinico Umberto I, Sapienza University of Rome (Protocol No. 42412). All patients were included in the study after informed consent signature.

RH catheterization

Pulmonary vascular pressures were measured in triplicate at end-expiration using triple-lumen balloon-tipped thermodilution Swan-Ganz catheters, as previously described.[9] Cardiac output was measured by thermodilution.

Echocardiographic assessment

Baseline echocardiographic studies were performed within 24 hours of the RH catheterization. All echocardiographic data were acquired using commercially available equipment (Vivid S6, GE) in the standard views. Standard M-mode, 2-dimensional, and Doppler images were obtained during breath hold at end expiration. Measurements were obtained from the mean of 3 consecutive beats in accordance with the American Society of Echocardiography Guidelines.[10]

The following standard parameters and derived measures were considered in the analysis: RA area, RVEDA, RV end-systolic area (RVESA), RV fractional area change % [RVFAC = (RVEDA – RVESA)/RVEDA $\times$ 100], tricuspid annular plane systolic