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Signs of Right Ventricular Deterioration in Clinically Stable Patients With Pulmonary Arterial Hypertension

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BACKGROUND: Even after years of stable response to therapy, patients with idiopathic pulmonary arterial hypertension (IPAH) may show an unexpected clinical deterioration due to progressive right ventricular (RV) failure. Therefore, the aim of this study was to assess in 5-year clinically stable patients with IPAH whether initial differences or subsequent changes in RV volumes precede late clinical progression.

METHODS: Included were 22 clinically stable patients with IPAH as reflected by stable or improving New York Heart Association functional class II-III and exercise capacity during 5 years of follow-up. Twelve patients subsequently remained stable during a total follow-up of 10 years, whereas 10 other patients showed late progression leading to death or lung transplantation after a follow-up of 8 years. All patients underwent right-sided heart catheterization and cardiac MRI at baseline and at 1½, 3½, 6½, and, if still alive, 10 years follow-up.

RESULTS: Baseline hemodynamics were comparable in both groups and remained unchanged during the entire follow-up period. Baseline RV end-systolic volume (RVESV) was higher and RV ejection fraction (RVEF) was lower in late-progressive patients. Late-progressive patients demonstrated a gradually increased RV end-diastolic volume and RVESV and a decline in RVEF, whereas long-term stable patients did not show any RV changes.

CONCLUSIONS: In patients with stable IPAH for 5 years, subsequent late disease progression is preceded by changes in RV volumes. The results indicate that monitoring RV volumes anticipates clinical worsening, even at a time of apparent clinical stability.

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ABBREVIATIONS: 6MWT = 6-min walk test; CMR = cardiac MRI; CO = cardiac output; EDV = end-diastolic volume; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RHC = right-sided heart catheterization; RV = right ventricular; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; SV = stroke volume

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In patients with pulmonary arterial hypertension (PAH), increased pulmonary vascular resistance (PVR) and pulmonary artery pressure ultimately result in right ventricular (RV) failure and death.[1] Various effective medical therapies have become available allowing prolonged clinical stability and survival. Although a small group of patients may survive longer than 5 years after diagnosis, overall long-term mortality rates are high.[2,3] Much is known about the predictors of short-term survival, but predictors of ultimate clinical deterioration in patients with an initially favorable treatment response have not been identified. A clinically stable condition, defined as a stable New York Heart Association (NYHA) functional class II-III and 6-min walk test (6MWT),[4] was not associated with better long-term survival,[5,6] which might be explained by current medical therapies successfully improving 6MWT and cardiac output (CO) but not necessarily slowing RV failure progression.[7,8] If the RV has adverse remodeling during a stable condition, assessment of RV remodeling parameters might predict ultimate disease progression. Therefore, the aim of the present study was to assess whether initial differences or subsequent changes in RV volumes precede clinical deterioration in patients with idiopathic PAH (IPAH) or heritable PAH (HPAH) with a proven 5-year stable clinical condition.

Materials and Methods

Patients

At the VU University Medical Center, patients received a diagnosis of PAH according to guidelines, including a right-sided heart catheterization (RHC).[9] This retrospective analysis of an ongoing prospective study assessed the clinical value of cardiac MRI (CMR) in PAH. During patient selection, we were unaware of RHC and CMR results. Inclusion criteria were (1) diagnosis of IPAH or HPAH; (2) age ≥ 18 years; (3) proven clinically stable condition during the first 5 years of follow-up defined as a stable NYHA functional class II-III and no reduction in the 6MWT ≥ 15%[4]; (4) CMR, RHC, 6MWT, and NYHA class at baseline and at regular follow-up intervals; and (5) a total follow-up period of 10 years. Therefore, patients with IPAH or HPAH diagnosed between February 1999 and February 2004 were selected and followed until February 2013. The local medical ethics committee approved the study without requirement of a consent statement because the study did not fall within the scope of the Medical Research Involving Human Subjects Act (approval number 2012288).

Application of PAH-targeted medical therapies was performed in-line with guidelines[9] and according to availability in The Netherlands. Before 2002, all patients in NYHA functional class III and IV were started on prostacyclins. After 2002, patients in NYHA class II-III were treated with oral medical therapy comprising endothelin receptor antagonists, phosphodiesterase 5 inhibitors, or both either as single-agent therapy or in combination, whereas patients in NYHA class IV received prostacyclins with or without additional oral medical therapies. All patients received anticoagulation and diuretics.

Right-Sided Heart Catheterization

Hemodynamic assessment was performed with a 7F balloon-tipped flow-directed Swan-Ganz catheter (Baxter Healthcare Corp) as described previously.[8]

Cardiac MRI

CMR was performed on a 1.5-T Sonata or Avanto scanner (Siemens Corporation). CMR data acquisition and postprocessing were performed according to our routine protocol.[8] Briefly, during postprocessing using dedicated software, a blinded observer assessed the left ventricular (LV) and RV volumes, mass, and function by manual delineation of the endocardial and epicardial contours on short-axis images. Disc summation was performed according to Simpson's rule. Stroke volume (SV) was calculated as end-diastolic volume (EDV) − end-systolic volume. Ejection fraction was calculated as (SV/EDV) × 100%. Ventricular relative wall thickness was calculated as ventricular mass divided by EDV.[10] Ventricular volumes and masses were indexed to body surface area.

6-Min Walk Test

The 6MWT was performed according to American Thoracic Society guidelines.[11]

Statistical Analysis

Data are presented as mean ± SD unless stated otherwise. Unpaired Student *t* tests or Mann-Whitney tests were used to compare continuous variables, and log-linear analysis was performed to compare categorical variables between the two groups at baseline. Linear mixed model analysis was applied to assess the differences between the groups over time. Interaction statistics are presented. Residuals were normally distributed for every tested parameter. Model fit was evaluated, and when necessary, random effects of time variables were corrected for intercepts, slopes, or both. A sensitivity analysis was performed to test whether missing values influenced the results. Data were analyzed using SAS, version 9.2 (SAS Institute Inc) and SPSS, version 20.0 (IBM) software. $P < .05$ was considered significant.

Results

Patient Selection

Between 1999 and 2004, 48 of 58 patients were selected. Exclusion reasons were no regular CMR due to logistics (n = 4) or claustrophobia (n = 1), follow-up in another hospital (n = 2), development of LV failure (n = 1), and a positive vasodilator challenge (n = 2).[9] Twenty-two patients clinically stable for 5 years after diagnosis were enrolled (Fig 1).

Twelve of these 22 patients remained clinically stable during the remaining years of follow-up (median, 10 years; interquartile range, 10-11 years) and were labeled as "stable" patients. The other 10 patients showed late clinical disease progression defined as progression to NYHA functional class IV and a reduction in 6MWT > 15%[4] after 5 years of initial clinical stability. Patients labeled as "progressive" ultimately either died due to cardiopulmonary causes (n = 6) or underwent lung transplantation (n = 4) by a median of 8 years