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Prognostic Value of Cardiac Magnetic Resonance Imaging for Idiopathic Pulmonary Arterial Hypertension Before Initiating Intravenous Prostacyclin Therapy

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Background: Because few have reported the prognostic significance of cardiac magnetic resonance imaging (CMR) for idiopathic pulmonary arterial hypertension (IPAH), in this study we evaluated the value of CMR measurements as a prognostic predictor of IPAH before starting intravenous prostacyclin therapy.

Methods and Results: A total of 121 consecutive CMR studies for evaluating right ventricular (RV) function were reviewed. Forty-one patients were diagnosed with IPAH and served as the study group. Factors, such as age, sex, New York Heart Association functional class (NYHAFC), 6-min walk test, plasma brain natriuretic peptide level, serum uric acid level and CMR measurements were analyzed as predictors of first hospitalization and death. The mean follow-up period was 1,350±769 days. Nine patients were hospitalized because of heart failure, and 4 patients died from cardiopulmonary causes. The univariate analyses suggested that the left ventricular (LV) mass index, the left and right ventricular end-diastolic volume indices (LVEDVI, RVEDVI), the LV and RV end-systolic volume indices (LVESVI, RVESVI) and NYHAFC predicted the risk for hospitalization and that RVEDVI, RVESVI and NYHAFC predicted mortality. The multivariate analyses suggested that RVEDVI and NYHAFC are independent predictors of both hospitalization and mortality. The effects of RVEDVI and NYHAFC on hospitalization were not substantially affected by the concomitant medication.

Conclusions: In IPAH patients, the RVEDVI predicts both hospitalization for right heart failure and mortality before initiating intravenous prostacyclin therapy. (*Circ J* 2012; **76:** 1737–1743)

Key Words: Clinical outcome; Idiopathic pulmonary arterial hypertension; Magnetic resonance imaging

Idiopathic pulmonary arterial hypertension (IPAH) is a life-threatening chronic disorder that affects the pulmonary circulation and has an unknown etiology. Elevated pressure and resistance in the pulmonary vessels lead to progressive right heart failure, which results in functional limitations and ultimately the death of most patients.[1–3] The prognosis is poor; without specific treatment, the 1-, 3- and 5- year survival rates are 68, 48 and 34%, respectively.[4] Thus, monitoring right ventricular (RV) function is of great importance. Cardiac magnetic resonance imaging (CMR) is a noninvasive, 3-dimensional tomographic technique that enables visualization of the detailed morphology of the heart and accurate measurement of the RV volume, myocardial mass and transvalvular flow.[5–8] It can also determine whether impaired RV diastolic function results from pulmonary hypertension. However, few studies have reported the prognostic significance of CMR measurements.[9,10] Furthermore, to the best of our knowledge, the association between hospitalization for heart failure because of IPAH and CMR results has not been discussed in the literature. The purpose of this historical cohort study was to evaluate the value of CMR measurements as a prognostic predictor of IPAH before starting intravenous prostacyclin therapy.

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Methods

Patients

Our hospital is a pulmonary hypertension referral center in Japan. We performed a retrospective review of CMR results

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Table 1. Patients' Characteristics

Characteristic	Value
Demographic variables	
Total number	41
Age (years)	39±14
F/M	29 (71%)/12 (29%)
CMR measurements	
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.3±0.8
SVI (ml/m^2)	37±14
RVMI (g/m^2)	39±18
LVMI (g/m^2)	50±15
RVEF (%)	32±12
LVEF (%)	56±9
RVEDVI (ml/m^2)	123±43
RVESVI (ml/m^2)	86±39
LVEDVI (ml/m^2)	61±30
LVESVI (ml/m^2)	30±15
Functional status	
NYHAFC II, III, IV	20 (49%), 18 (44%), 3 (7%)
6MWT (m) (n=28)*	358±98
Biochemical markers	
Plasma BNP (pg/ml)	236±331
Serum uric acid (mg/dl)	6.9±2.4
Medication use	All follow-up duration/before CMR
Intravenous prostacyclin	14 (34%)/0 (0%)
Endothelin-receptor antagonists	22 (54%)/9 (22%)
Sildenafil	36 (88%)/18 (44%)
Calcium antagonists	9 (22%)/9 (22%)

*Of all the eligible patients, only 28 had a 6MWT within 1 week of the CMR examination without changing therapy.
CMR, cardiac magnetic resonance imaging; SVI, stroke volume index; RVMI, right ventricular (RV) mass index; LVMI, left ventricular (LV) mass index; RVEF, RV ejection fraction; LVEF, LV ejection fraction; RVEDVI, RV end-diastolic volume index; RVESVI, RV end-systolic volume index; LVEDVI, LV end-diastolic volume index; LVESVI, LV end-systolic volume index; NYHAFC, New York Heart Association functional class; 6MWT, 6-min walk test; BNP, brain natriuretic peptide.

Table 2. Right Heart Catheterization Measurements

Characteristic	Value
Mean PAP (mmHg)	51±14
Systolic PAP (mmHg)	80±22
Diastolic PAP (mmHg)	31±11
Mean right atrial pressure (mmHg)	6.8±4.0
PVR index ($dyne\ s \cdot cm^{-5} \cdot m^{-2}$)	737±504
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.2±0.7
SVI (ml/m^2)	33±12
Heart rate (beats/min)	72±13
Mixed venous O_2 saturation (%)	64±8

PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SVI, stroke volume index.

from 122 consecutive examinations of patients who were either suspected of having pulmonary arterial hypertension (PAH) or who had been diagnosed with PAH between September 2003 and September 2010 at our institute. Of the 122 examinations, 41 patients were diagnosed with IPAH and served as the study group. The diagnosis of IPAH was based on a mean pulmonary arterial pressure (PAP) >25 mmHg at rest, pulmonary capillary wedge pressure (PCWP) <15 mmHg, and an elevated pulmonary vascular resistance (PVR) in a patient with no identifiable underlying causes (such as familial PAH, drug- or toxin-induced PAH, connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis, pulmonary hypertension owing to lung disease/hypoxia, chronic thromboembolic pulmonary hypertension or pulmonary hypertension with unclear multifactorial mechanisms).[11,12]

To prevent the potential risk of damaging the intravenous prostacyclin equipment in the magnetic resonance imaging (MRI) scanner rooms, CMR was not performed for patients who had started prostacyclin treatment. Accordingly, all of the IPAH patients in this study were examined before starting intravenous prostacyclin therapy. Each patient's status was scored according to their New York Heart Association functional class (NYHAFC) at the time of the CMR examination. According to clinical guidelines, patients with a positive acute vasodilator challenge during right heart catheterization were treated with calcium antagonists;[13] 9 patients (22%) had been treated with an endothelin-receptor antagonist, 18 (54%) had been treated with sildenafil, and 9 (22%) had been treated with calcium antagonists before the CMR assessment. The study protocol was approved by the institutional review board.

Endpoint Determination

The follow-up data were retrospectively collected from medical charts, and the end of data collection was March 31, 2011. The following endpoints were used in this historical cohort study: (1) the date of the first hospitalization for right heart failure; (2) the date of the last clinical visit; (3) death; and (4) March 31, 2011. Clinical follow-up visits were performed at regular intervals (1–3 months) at the outpatient clinic.

CMR Imaging

The CMR scans were obtained using a 1.5-Tesla clinical scanner (Signa TwinSpeed, GE Healthcare, Milwaukee, WI, USA). For the RV volume measurements, contiguous transverse images were acquired through the entire RV using a 2D cine, steady-state, free-precession technique with prospective ECG gating. Each cross-sectional image was obtained while the patient held a single breath. Each cross-sectional image used the following parameters: repetition time=3.2 ms, echo time=1.6 ms, flip angle=45°, bandwidth=125 kHz, field of view=350×350 mm^2, matrix size=224×192, slice thickness=10 mm without a gap and 20 phases during 1 cardiac cycle. The in-plane spatial resolution was 1.6×1.8 mm^2. The CMR examination time was approximately 30 min and included short-axis images of the left ventricle (LV) to evaluate LV function after obtaining transverse images of the RV. The CMR functional parameters were calculated on a workstation (Advantage Workstation, GE Healthcare). The endocardial borders of all of the images at end-diastole and end-systole were manually traced by a radiologist with 10 years of experience with CMR. The end-diastolic volume, end-systolic volume, and ejection fraction (EF) were automatically calculated using Simpson's rule with commercially available analysis software (Mass Analysis Plus version 4.0, Medis, Leiden, the Netherlands). The incorporation of the trabeculae carneae into the RV volume followed the rules that are generally used in ultrasound methods. Fewer than 15 min were required for the RV volume measurement. The cardiac output was determined by multiplying the stroke volume by the heart rate. The measures were indexed by

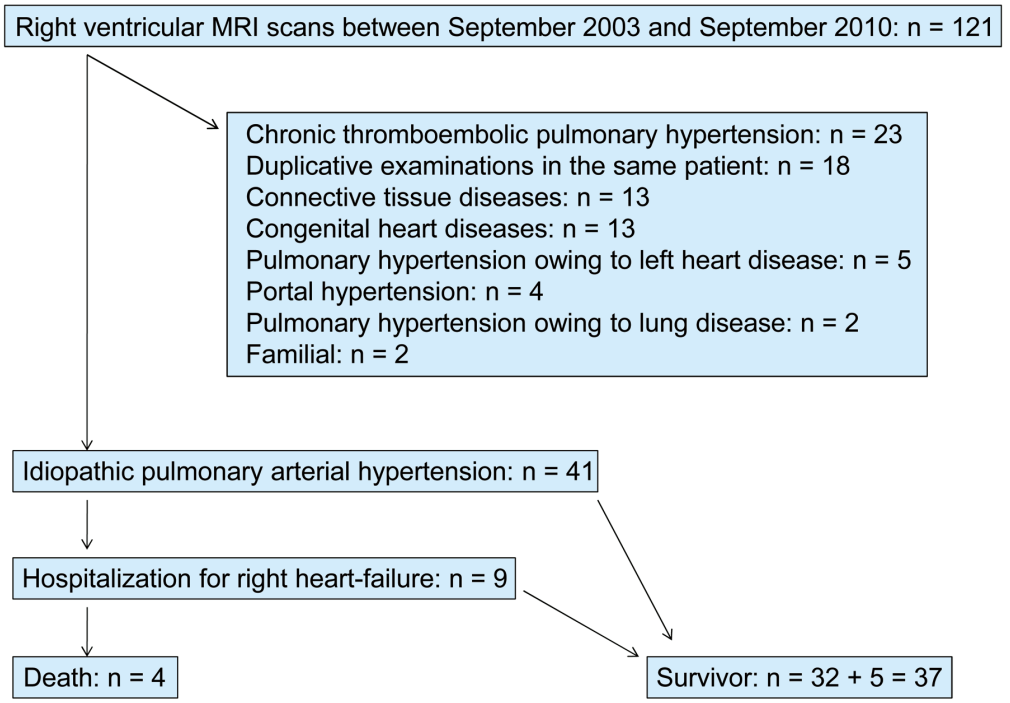

Figure. Study profile.

correcting for the patient's body surface area. The RVEF and LVEF were determined by dividing the systolic volume by the right and left end-diastolic volumes, respectively.

Right Heart Catheterization

A diagnostic right-heart catheterization was performed using a balloon-tipped, flow-directed 7F Swan-Ganz catheter. The patient was stable, lay supine, and breathed room air. The PAP, right atrial pressure, PCWP, cardiac output, PVR index and mixed venous oxygen saturation were measured. Blood was sampled with the catheter positioned inside the main pulmonary artery. The arterial oxygen saturation was measured using blood sampled from the radial or femoral artery. The cardiac output was assessed using the Fick method, and the PVR was calculated using the following formula: (mPAP−PCWP)/cardiac output. All of the eligible patients had right-heart catheterization examinations within 6 months of their CMR examinations.

Statistical Analysis

All data are expressed as the mean±standard deviation (SD). The hazard ratios of the factors potentially associated with a first hospitalization (primary endpoint) or death after hospitalization (secondary endpoint), such as age, sex, NYHAFC, biochemical markers and the CMR measures, were calculated using a Cox proportional-hazards model. First, the hazard ratio and 95% confidence interval (CI) for each factor were estimated using a univariate model. The following variables were tested: age, sex, the NYHAFC, the distance in a 6-min walk test (6MWT), the plasma brain natriuretic peptide (BNP) level,[14] the serum uric acid level,[15] the cardiac index, the stroke volume index (SVI), the RV mass index (RVMI), the LV mass index (LVMI), RVEF, LVEF, the RV end-systolic volume index (RVESVI), the RV end-diastolic volume index (RVEDVI), the LV end-systolic volume index (LVESVI) and the LV end-diastolic volume index (LVEDVI). Catheterization was not performed on the same day as the CMR examination, so the right heart catheterization variables were not tested. To examine the robustness of the univariate results, multivariate Cox regression analyses with step-wise variable selection were performed. A multivariate Cox model with time-dependent covariates was also used to evaluate the effects of any concomitant medications during the follow-up period.

We added exploratory analyses with respect to the endpoint of clinical worsening, including all clinical events (additional therapies in response to clinical worsening, hospitalization and death) with a univariate Cox regression model.

All of the confidence intervals were estimated at the 95% confidence level, and significance was set at a $P<0.05$ (2-tailed). All of the data were analyzed using a commercially available software program (SAS version 9.1, Cary, NC, USA).

Results

Patients' Characteristics

The patients' demographic and baseline CMR data are summarized in **Table 1**. The right heart catheterization measurements collected within 6 months of each CMR examination are also shown in **Table 2**. Over a mean follow-up period of 1,350±769 (range: 196–2,654) days, 9 of the 41 patients were hospitalized for right heart failure; 4 of the 9 hospitalized patients died and none died from non-cardiopulmonary causes (**Figure**). In 29 patients (71%), the medical therapy was changed because of clinical worsening. Intravenous prostacyclin, endothelin-receptor antagonists and sildenafil were added in 14, 13 and 18 patients, respectively (**Table 1**). All the patients were

Table 3. Univariate Analysis of Factors With Cox Regression Model for Hospitalization and Mortality

	Hospitalization for right HF				Mortality			
	HR	95%CI Lower	95%CI Upper	P value	HR	95%CI Lower	95%CI Upper	P value
Demographic variables								
Age (year)	1.01	0.97	1.05	0.716	1.04	0.98	1.12	0.193
Sex (M/F)	2.00	0.54	7.48	0.301	2.36	0.33	16.73	0.392
CMR measurements								
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	0.81	0.33	1.98	0.645	0.46	0.09	2.43	0.358
SVI (ml/m^2)	1.01	0.97	1.05	0.645	0.98	0.91	1.06	0.681
RVMI (g/m^2)	0.96	0.88	1.06	0.444	0.96	0.88	1.05	0.401
LVMI (g/m^2)	1.07	1.02	1.12	0.008*	1.03	0.97	1.10	0.386
RVEF (%)	0.97	0.92	1.03	0.351	0.96	0.87	1.05	0.369
LVEF (%)	0.95	0.88	1.02	0.175	0.97	0.86	1.08	0.527
RVEDVI (ml/m^2)	1.02	1.00	1.03	0.012*	1.02	1.00	1.04	0.028*
RVESVI (ml/m^2)	1.02	1.00	1.03	0.014*	1.03	1.00	1.05	0.021*
LVEDVI (ml/m^2)	1.03	1.00	1.05	0.019*	1.00	0.95	1.04	0.932
LVESVI (ml/m^2)	1.04	1.00	1.07	0.027*	1.00	0.92	1.08	0.907
Functional status								
NYHAFC	4.61	1.69	12.55	0.003*	6.23	1.29	30.13	0.023*
6MWT (m)	1.00	0.99	1.01	0.467	1.00	0.98	1.02	0.799
Biochemical markers								
Plasma BNP (pg/ml)	1.00	1.00	1.00	0.129	1.00	1.00	1.00	0.197
Serum uric acid (mg/dl)	1.25	0.98	1.59	0.075	1.38	0.95	2.00	0.087

*P<0.05.
HF, heart failure; HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

Table 4. Multivariate Analysis of the Factors for Hospitalization Using a Cox Regression Model

	Hospitalization for right HF			
	HR	95%CI Lower	95%CI Upper	P value
RVEDVI (ml/m^2)	1.02	1.00	1.03	0.010*
LVEDVI (ml/m^2)	1.02	1.00	1.05	0.052
NYHAFC	7.66	2.05	28.61	0.002*

*P<0.05.
Abbreviations as in Tables 1,3.

Table 5. Multivariate Analysis of the Factors for Mortality Using a Cox Regression Model

	Mortality			
	HR	95%CI Lower	95%CI Upper	P value
RVEDVI (ml/m^2)	1.03	1.00	1.05	0.020*
NYHAFC	21.85	1.46	328.14	0.023*

*P<0.05.
Abbreviations as in Tables 1,3.

Table 6. Univariate Analysis of the Therapies Using Cox Regression Models for Hospitalization and Mortality

Therapy	Hospitalization for right HF				Mortality			
	HR	95%CI Lower	95%CI Upper	P value	HR	95%CI Lower	95%CI Upper	P value
Intravenous prostacyclin	2.87	0.77	10.72	0.117	2.09	0.29	14.90	0.461
Endothelin-receptor antagonists	0.52	0.14	1.96	0.334	0.23	0.02	2.24	0.207
Sildenafil†	–	–	–	(0.994)	–	–	–	(0.996)
Calcium antagonists	1.02	0.21	4.92	0.981	1.18	0.12	11.36	0.885

†All hospitalized or deceased patients were treated with sidenafil.
Abbreviations as in Table 3.

treated with oral anticoagulants.

Predictors of Hospitalization for Right Heart Failure or Mortality

The univariate Cox regression analyses suggested that LVMI, LVEDVI, LVESVI, RVEDVI, RVESVI and NYHAFC were associated with the time to hospitalization (primary endpoint) in the IPAH patients and that RVEDVI, RVESVI and NYHAFC were associated with the time to death (secondary endpoint) (Table 3). The RVEDVI was closely related to the RVESVI, and the LVEDVI was closely related to the LVESVI and LVMI; therefore, multivariate Cox regression analyses were performed using RVEDVI, LVEDVI and NYHAFC as predictors of the hazard of hospitalization and RVEDVI and

Table 7. Multivariate Cox Model for Hospitalization With Time-Dependent Covariates

Therapy/Variable	Hospitalization for right HF			
	HR	95%CI		P value
		Lower	Upper	
Intravenous prostacyclin				
RVEDVI (ml/m²)	1.02	1.01	1.04	0.008*
NYHAFC	5.02	1.17	21.54	0.030*
Time-dependent covariate (intravenous prostacyclin)	4.60	0.96	21.92	0.055
Endothelin-receptor antagonists				
RVEDVI (ml/m²)	1.02	1.01	1.03	0.005*
NYHAFC	9.24	2.16	39.43	0.003*
Time-dependent covariate (endothelin-receptor antagonists)	2.47	0.47	12.98	0.286
Sildenafil†				
RVEDVI (ml/m²)	1.02	1.00	1.03	0.009*
NYHAFC	5.21	1.51	18.02	0.009*
Time-dependent covariate (sildenafil)†	–†	–†	–†	(0.995)†
Calcium antagonists				
RVEDVI (ml/m²)	1.02	1.00	1.03	0.009*
NYHAFC	8.01	2.11	30.49	0.002*
Time-dependent covariate (calcium antagonists)	0.52	0.10	2.70	0.438

*P<0.05. †Because of a high percentage of patients treated with sildenafil (88%), it was impossible to evaluate the effect of sildenafil by means of multivariate Cox model with time-dependent covariate.
Abbreviations as in Tables 1,3.

NYHAFC as predictors of mortality. The multivariate analyses using step-wise variable selection showed that the RVEDVI and NYHAFC were independent predictors of the hazards of both hospitalization and mortality (Tables 4,5).

There was no significant relationship between the endpoints and the type of therapy (ie, intravenous prostacyclin, endothelin-receptor antagonist, sildenafil and calcium antagonists; Table 6). Furthermore, the effects of RVEDVI and NYHAFC on hospitalization were not substantially changed in a time-dependent Cox model with additional adjustments for any concomitant medications during the follow-up period (Table 7). However, because of the large percentage of patients treated with sildenafil (88%), it was impossible to evaluate the effects of sildenafil using this statistical model.

Results of Exploratory Data Analyses

Clinical worsening, including all clinical events (additional therapies in response to clinical worsening, hospitalization and death), occurred in 32 of 41 patients. In the univariate Cox regression model, there was no significant association between clinical worsening and any variables including age, sex, NYHAFC, 6MWT, BNP level, serum uric acid level and CMR measurements.

Discussion

In this study, we investigated the prognostic significance of CMR measurements in patients with IPAH before initiating intravenous prostacyclin therapy. We found that increased RVEDVI and NYHAFC were associated with both hospitalization for right heart failure and mortality.

In our study, we only focused on patients with IPAH. Some previous studies have included multiple types of PAH patients (category 1 of the Venice or Dana Point classification[11]) in their cohorts and subsequent analyses. Although this approach may be appropriate for some therapeutic studies,[16] the validity of this practice is questionable when evaluating prognostic factors.[17] It is well known that survival curves are not comparable across all subgroups of category 1 PAH,[18] and therefore it should not be assumed that the prognostic variables will be identical in the various populations.

Compared with other diagnostic tools, the advantages of CMR are its noninvasiveness, non-ionizing safety, excellent spatial and temporal resolution, and repeatability. CMR is more reproducible than echocardiography when measuring RV function.[19] There have been few previous studies that have addressed the relationships between CMR measures and clinical outcomes in IPAH patients. Previous studies have demonstrated that an increased RVEDVI, a large right atrium, and a low RVSVI are associated with a poor prognosis.[9,20,21] However, to the best of our knowledge, the associations between hospitalization for heart failure because of IPAH and the CMR results have not yet been reported. We found that the RVEDVI and RVESVI were associated with both hospitalization for right heart failure and mortality. This finding is clinically important because CMR provides a direct RV parameter for predicting early RV failure (before the initiation of intravenous prostacyclin therapy). Measures of increased RVEDVI and RVESVI could be used to predict treatment failure and, thus, could offer an opportunity to change the patient's treatment or add the patient to the transplant list before RV failure leads to death.[9] It is well known that the RV compensates for increased afterload via enlargement and hypertrophy. At some point, the RV is unable to further adapt to the increased afterload, and RV failure occurs, leading to hospitalization for heart failure or imminent death.

A previous study enrolling 64 IPAH patients revealed a significantly better survival in the patients with RVEDVI <84 ml/m² than in those with RVEDVI ≥84 ml/m².[9] In our post hoc analysis by means of a Cox regression, treating the RVEDVI as a binary variable, no event was observed in patients with RVEDVI <84 ml/m² during a longer mean follow-up period (32±16 vs. 45±26 months), which is consistent with the previous finding; however, we did not observe enough events in the

patients with RVEDVI ≥84 ml/m^2 to establish a significant difference between the groups (**Figure S1**). Thus, in the statistical analyses presented here, we treated each factor (eg, RVEDVI) as a continuous variable to avoid the loss of information associated with creating binary variables.

In our study, the NYHAFC was an independent predictor of both hospitalization and mortality. Previous studies have reported that this classification is a prognostic factor for mortality in IPAH patients.[22–24] Sitbon et al have reported that the survival of primary pulmonary hypertension patients treated with intravenous prostacyclin is associated with the NYHAFC at baseline,[23] and our results are consistent with that.

Our univariate analyses also found that LVEDVI, LVESVI and LVMI were associated with hospitalization; however, these 3 parameters were not associated with mortality. The reason for the discrepancy in P-values between hospitalization and death events may have been related to the difference in the numbers of events; that is, the statistical power of the death-event data (4 events) is lower than that of the hospitalization-event data (9 events). In the multivariate model, these 3 parameters did not predict our patients' prognoses, which may have been related to the strong effect of the RVEDVI on the severity of the IPAH. Additional large-scale studies are warranted.

The exploratory analyses showed no significant association between clinical worsening (all clinical events, including additional therapies, hospitalization and death) and any variables in our study. One explanation is that too many events (32 out of 41 patients) may have resulted in a low statistical power in the exploratory analyses of our patient population. Furthermore, hospitalization and death were more clinically relevant than the total of all clinical events (new additional therapies, hospitalization and death) and would have a higher power to detect associations between the MRI findings and the patients' prognoses in this study.

Study Limitations

First, this was an observational study with a cohort limited to a 45-month period. Second, our single measurement of the CMR parameters at the time of study entry and our inability to evaluate the longitudinal trends in these parameters may have led to an underestimation of the relationships between the CMR measures and our endpoints because of regression-dilution bias. Third, because our study had an observational design, the IPAH therapies were not controlled. However, there was no significant relationship between the endpoints and the medications used. Furthermore, the effects of RVEDVI and NYHAFC on hospitalization were consistent when the concomitant medications were included as time-dependent covariates. Finally, our data were obtained from a single center and should be evaluated in other centers.

Conclusions

In IPAH patients, the RVEDVI obtained from CMR measurements predicts both hospitalization for right heart failure and mortality before initiating intravenous prostacyclin therapy.

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Disclosures

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Supplementary Files

Supplementary File 1

Figure S1. Kaplan-Meier plots showing survival in patients with IPAH categorized according to RVEDVI <84 ml/m^2 or ≥84 ml/m^2.

Please find supplementary file(s);
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