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RESEARCH ARTICLE

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Clinically important changes in right ventricular volume and function in pulmonary arterial hypertension assessed with cardiac magnetic resonance imaging

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Abstract

Right ventricular (RV) dilatation predicts clinical worsening in pulmonary arterial hypertension (PAH) and RV volumes can be measured with high precision using cardiovascular magnetic resonance imaging. In regular follow-up of patients and in studies of improvement in RV function, knowledge of clinically significant changes of RV volumes and function are of relevance. Patients with PAH were followed with cardiovascular magnetic resonance imaging and clinical assessment at 6-month intervals. Changes in RV volumes associated with changes in clinical status were assessed. Twenty-five patients with PAH (Group 1) were included and examined every 6 months for 2.5 years, with a total of 107 MRI scans. For a step change in WHO functional class, the associated change in RV volume was 11% (confidence interval 7%−14%, $p < 0.0001$) and in stroke volume 9% (confidence interval 3%−15%, $p = 0.003$). This study found an 11% change in RV volume to be clinically significant. The combination of clinically significant changes and the known precision in the measurements enables individualized follow-up of RV-function in PAH. To our knowledge, this study is the first to use repeated assessments to suggest clinically significant changes of RV volume based on changes in clinical presentation.

KEYWORDS
magnetic resonance imaging, minimal clinically important difference, right ventricle

INTRODUCTION

Pulmonary arterial hypertension (PAH) is one of the subgroups of the pulmonary hypertensive spectrum of diseases that is modifiable by specific PAH therapy. Since the introduction of targeted treatments, morbidity and mortality in PAH has reduced.[1] Increased pulmonary vascular resistance (PVR) is central in PAH and is the result of a series of pulmonary vascular changes. Clinical manifestations of PAH (such as WHO FC), as well as measurements of right ventricular (RV) function, are closely related to survival.[2–4]

PVR, RV contraction, and RV filling all affect the blood flow through the lungs.[5] PVR can be reduced with targeted PAH therapy, including phosphodiesterase-5-inhibitors, endothelin receptor antagonists, and prostacyclin analogs.[1]

Targeting RV contraction has recently received more attention in PAH but currently treatment improving RV relaxation has not received much attention.[6]

To target either PVR, RV contraction, or RV relaxation, it is important to characterize the reproduction of the measurements and to know the clinically significant changes in the measurements. PVR is measured invasively and is predictive of survival, but its reproducibility is not well established and its role as a surrogate for short-term clinical events is small.[7] RV dilatation is associated with poorer survival and its reproducibility with cardiovascular magnetic resonance imaging (CMR) is known,[8] but a clinically significant change is not yet established. Impaired RV relaxation is a part of the reduced RV function in PAH and is associated with worse survival.[9] The reproducibility of ventricular filling using CMR is known,[10] but its relation to clinical presentation is not.

This study hypothesizes that RV volumes and function are related to clinical presentation of PAH, enabling values of clinically significant changes to help guide targeted therapy intensity. In addition, with increased availability of MR facilities, to optimize future intervention studies.

METHODS

Inclusion of patients

Patients were included at a specialized reference center for pulmonary hypertension and were asked for participation at either their regular assessment visit or if they were newly diagnosed with PAH, thus representing a random sample of patients. Inclusion criteria were diagnosis of PAH according to the European guidelines,[11] age ≥ 18 years and cardiac sinus rhythm. Exclusion criteria were implants incompatible with magnetic resonance imaging. The Ethics Committee for the Capital Region of Denmark approved the study (protocol number H-2-2014-079) and all participants provided written informed consent.

Protocol, clinical, and paraclinical assessment

At scheduled semiannual visits, patients attended CMR with concomitant WHO FC assessment, recording of medication status, and blood samples with measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP). A 6-min walking test (6MWT) was scheduled within 2 days of the visit. Functional class assessment was done immediately before the CMR session and was evaluated by the same physician for all visits. There was no planned treatment intervention and patients attended normal scheduled follow-up at our expert center with any treatment alterations and interventions guided by the current guidelines.

CMR and image analysis

The same CMR protocol was used at all visits and was completed by the same operator for all the scans. CMR has good to excellent intra- and interobserver variability for LV- and RV volumes.[12] The patients were instructed to hold their breath at end expiration for 8−10 s and SSFP cine-imaging was performed (8 mm contiguous slices, no-gap, echo time 1.57 ms.; resolution matrix 192 × 192; field of view 300−340 mm; typical voxel size 1.8 × 1.8 × 8.0; flip angle 69° with retrospective ECG-gating), providing long-axis views of the heart as well as whole-heart axial and short-axis cine for RV and left ventricular (LV) assessment. At the final part of the session, the patients were instructed to breathe freely during the free-breathing phase-contrast flow CMR sequences (echo time 2.8 ms; resolution matrix 256 × 256; field of view 320 mm; voxel size 1.3 × 1.3 × 5.0 mm; flip angle 30°; receiver bandwidth 543 Hz/Px; 4 averages, phases 50; and slice thickness 5 mm with retrospective ECG-gating and image averaging) of the aortic (valve level and sino-tubular junction) and pulmonary (trunk and left and right main pulmonary arteries) vessels, which were all acquired consecutively in the listed order. The same 1.5 Tesla magnetic resonance scanner (1.5 T MAGNETOM Espree; Siemens) was used for all scans and the patients were examined supinely positioned with chest (6-channel) phase array coil and back surface coils.

Images were analyzed with CMR-focused software (CVI42; Circle Cardiovascular Imaging Inc.). The trans-axial cine images were used for RV assessment as the atrioventricular border is easier to determine. In a dilated RV, in- or exclusion of volume at the atrioventricular border can have a greater impact.[13] Long axis views of the RV help with the identification of valvular borders. RV volumes were measured by delineating the endocardial border with a smooth contour in all phases of the cardiac cycle, including the trabeculae in the blood pool in accordance with recommendations.[14] For assessment of RV mass, an epicardial contour was drawn along the RV free wall. The septum was assigned to the LV in which the mass

also was measured by delineating the epicardial border. LV end-diastolic and end-systolic volume were measured by manual threshold segmentation in all phases of the cardiac cycle, excluding papillary muscles from the volume, as previously explained.[8] A three-chamber view eased identification of LV volume in the LV outflow tract and at the atrio-ventricular border. Volumetric stroke volume (SV) was calculated as the difference between end-diastolic and end-systolic volume. SV and cardiac output were also calculated from the flow CMR images by tracing the vascular border in the flow and magnitude images, accounting for the movement of the vessel and systolic dilatation. Background correction was applied by encircling a large area of no-flow and forwarding it to all phases. The software handled all the summations of measurements from the images.

Statistics

To determine clinically significant changes, an anchor-based method was applied using changes in WHO FC as an anchor, as this reflects patient-perceived functional capacity. R[15] was used for all calculations and statistical illustrations. Due to the repeated measurements design, a mixed model approach using the gls-function in the nlme package[16] was used to calculate changes in RV end-diastolic volume, SV, peak filling, and peak emptying rates associated with a change in WHO FC as assessed at every visit. Unstructured patient correlation was accounted for by the model using the CorSymm-function and any difference in variance at each scan was accounted for with the varIdent-function. Calculations were made both with and without adjustments for age, sex, body mass index, and intensity of targeted therapy or vasoreactivity testing status.

Emptying and filling rates in the RV and LV were calculated as the derivative of the volume−time relationship during the full cardiac cycle. Peak emptying rate was calculated as the maximal negative rate in the systolic phase of the time–volume curve, and peak filling rate was defined as the maximal positive rate in early diastole. Measurements were calculated as the mean of the three maximal values, respectively, to minimize the effect of extreme values due to measurement error in the endocardial delineations.

A p-value < 0.05 was considered significant. In the calculations, SV from volumetric assessment of the LV is used due to being the highest reproducible measurement of SV in PAH.[8]

RESULTS

Patient demographics

The study included 25 patients with PAH (Group I). The included patients had idiopathic and heritable PAH and no patients had drug or toxin-induced PAH or any associated form such as connective tissue disease or congenital heart disease. The patients were scanned at 6-month intervals for a total of 6 (9 patients), 5 (5 patients), 4 (1 patient), 3 (5 patients), 2 (4 patients) times, and 1 (1 patient) time, totaling 107 scans over 2.5 years and a total follow-up of 494 person-months. Since one patient did not have follow-up scans during the study period, this patient did not contribute to follow-up data but remained in the study in compliance with the protocol. During the study period, two patients died (after participating in two scans respectively), one was lung transplanted (also after participating in two scans) and one withdrew from the study due to being uncomfortable during the scan after participating in three scans. Sex distribution was 64% (16) women and 36% (9) men. The mean age at inclusion was 45.5 (SD 14.9) years, median NT-proBNP was 18 pmol/L (interquartile range 10−68) with no change during the study period ($p = 0.19$), 6MWD was 522 m (SD 165) with no change during the study period ($p = 0.88$) and 10 patients were in WHO FC I, 9 in II, 5 in III and 1 in WHO FC IV. See Table 1 for a more detailed description of the patient population, including the most recent right heart catheterization data. Follow-up right heart catheterization was not routinely performed during the study period. Changes in targeted therapy during the study period are included in Table 2. For CMR variables at inclusion and their changes over the study period, see Table 3.

The relationship between changes in RV and stroke volume with functional class

During follow-up in the study period, 9 occasions occurred of one-step increase in WHO FC, 58 occasions unchanged, 13 occasions of one-step decrease, and one occasion each for two- and three-step decrease in WHO FC.

For a step change in WHO FC, the associated change in RVEDV was 11% (confidence interval [CI] 7%−14%, $p < 0.0001$) and in SV 9% (CI 3%−15%, $p = 0.003$); see Table 4 and Figure 1a,b. When the values for the three-step change in WHO FC were removed from the calculations to test for the effect of the most extreme value, the associated change in RVEDV corresponding to a step-change in WHO FC was 9% (CI 5%−13%, $p < 0.0001$). The results were recalculated including

TABLE 1 Patient demographics and cardiac function at inclusion

Patients (*n*)	25
Idiopathic or heritable PAH (*n*)	25
Vasoreactivity (*n*)	7
Age (years)	45.5 (SD 14.9)
Sex, F/M	16 (64%)/9 (36%)
BSA (m^2)	1.87 (SD 0.20)
BMI (kg/m^2)	24.89 (SD 4.23)
WHO FC (I/II/III/IV)	10/9/5/1
Mono or combination therapy	
None	2
Mono	5
Dual	11
Triple	7
Medication	
Sildenafil	19
Tadalafil	1
Bosentan	6
Macitentan	5
Selexipag	1
Treprostinil	9
Iloprost	2
Nifedipin	7
6MWD (m)	523 (SD 165)
Median observation time (months)	24 [IQR 13–24]
Patient observation time (months)	494
Right heart catheterization	
Time from most recent right heart catheterization[a]	2.2 years [IQR 3.4–0.6]
Mean pulmonary artery pressure (mmHg)	46 (SD 11)
Pulmonary capillary wedge pressure (mmHg)	10 (IQR 10–13)
Pulmonary vascular resistance (Wood units)	8.1 (SD 4.2)
Right atrial pressure (mmHg)	7.9 (SD 2.5)
Cardiac index ($L/min/m^2$)	2.9 (SD 0.9)

Abbreviations: 6MWD, 6-min walking distance, BMI, body mass index; BSA, body surface area; ERA, endothelin receptor antagonist; WHO FC, World Health Organization Functional Class.

[a]Not routinely repeated unless clinical deterioration.

TABLE 2 Changes in PAH-targeted therapy during the study period.

Change in targeted PAH therapy	Patients (*n*)
Unchanged	9
Initiation of or increases in the concentration of Treprostinil infusion	6
Initiation of endothelin receptor antagonist	5
Initiation of or increases in PDE5-inhibitor	6
Discontinued inhaled Iloprost	2
Initiated inhaled Iloprost	1
Double lung transplantation and thereafter discontinued PAH-targeted therapy	1

Abbreviation: PAH, pulmonary arterial hypertension.

TABLE 3 Cardiovascular magnetic resonance imaging variables at baseline and changes per scan during the study period.

	Baseline	Change per scan	*p*
RVEDV (ml)	232 (60)	2.6	0.009
RVESV (ml)	144 (56)	−2.4	<0.001
RVSV (ml)	89 (26)	1.5	0.03
RVEF (%)	40 (11)	0.5	0.06
RV mass (g)	72 (25)	−0.7	0.27
LVEDV (ml)	131 (33)	−0.4	0.51
LVESV (ml)	51 (13)	−0.2	0.60
LVSV (ml)	80 (23)	−0.1	0.81
LVEF (%)	61 (7)	0.2	0.38
LV mass (g)	105 (25)	1.5	0.02
Pulmonary artery CO (L/min)	5.52 (SD 1.63)	0.2	<0.001
Aorta ST-junction CO (L/min)	5.02 (SD 1.41)	0.2	<0.001

Note: Values are presented as mean with standard deviation.

Abbreviations: CO, cardiac output; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricular; RV, right ventricular; ST, sino-tubular; SV, stroke volume.

adjustments for age, sex, body mass index, and intensity of targeted therapy with a resulting 9% (CI 5%–13%), $p < 0.0001$, associated change in RVEDV for a step-change in WHO FC. Adjustment for vasoreactivity status instead of the intensity of targeted therapy in the above model resulted in a 12% (CI 8%–15%), $p < 0.0001$ change in RVEDV for a step-change in WHO FC.

TABLE 4 The associated changes of right ventricular end-diastolic volume (RVEDV) and stroke volume (SV) with change in WHO functional class (WHO FC) during follow-up

	Intercept (confidence interval)	For change in WHO FC (confidence interval)	*p*
RVEDV	102.1% (99.7−104.5)	+10.6% (7.0−14.3)	<0.0001
SV	101.9% (98.5−105.3)	−9.0% (−14.9 to −3.2)	0.003

Note: When removing the values for the patient improving three functional classes (the most extreme value), the associated change in RVEDV corresponding to a step change in WHO FC was 9% (CI 5%−13%, $p < 0.0001$). When including adjustments for age, sex, body mass index, and intensity of targeted therapy, the associated change in RVEDV corresponding to a step change in WHO FC was 9% [CI 5%−13%], $p < 0.0001$.

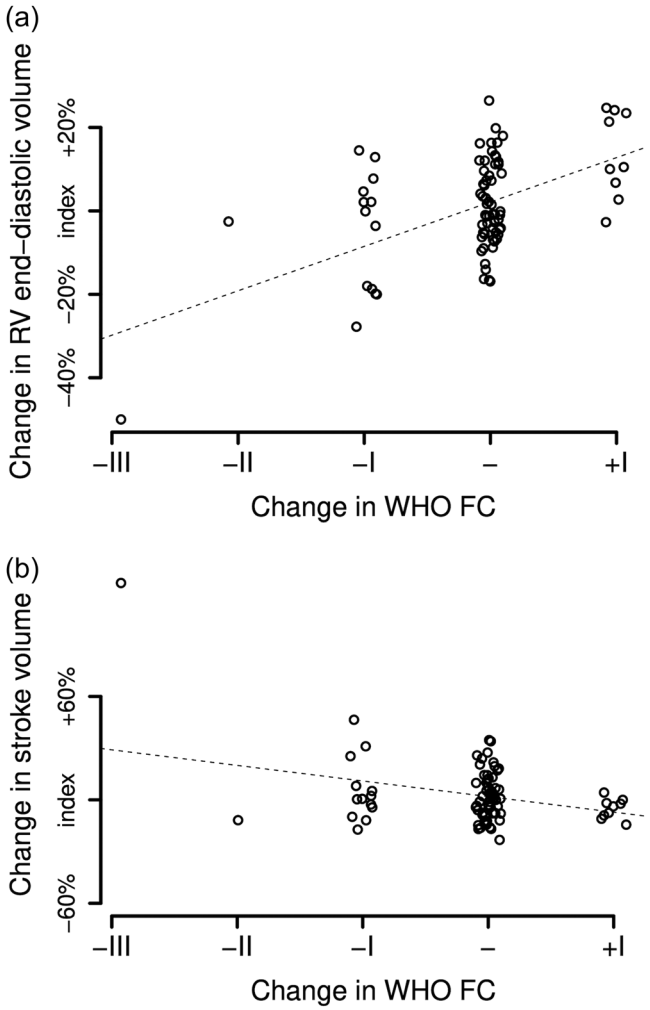

FIGURE 1 Changes in right ventricular end-diastolic volume (a) and stroke volume (b) were significantly associated with changes in WHO FC. Dotted line indicates the regression line with values presented in Table 4. WHO FC, World Health Organization Functional Class.

For 6MWD, a calculated change by 100 m was significantly associated with a change in RVEDV of 5% (CI 1%−9%, $p = 0.01$). Every 100% change in NT-proBNP (log-transformed in the analysis) was associated with a 6% change in RVEDV. Overall, NT-proBNP had a log-linear relationship to RV ejection fraction.

Peak filling and emptying rates during the study period and their association with functional class

Mean peak filling rate in the RV for the population did not change significantly throughout the study period (mean 110 ml/s/m^2 with 2 ml/s/m^2 increase, $p = 0.08$, at every 6-month scan). RV peak filling rate showed a U-shape relationship to changes in functional class, with increases in peak filling rate associated with both gradual improvement and gradual worsening of functional class (see Figure 2a). When calculating a linear relationship between changes in WHO FC and RV peak filling rate, there was no significant association (4% [CI −10% to 20%] increase in RV peak filling rate for every step-change in functional class, $p = 0.54$).

Peak emptying rate in the RV did not change significantly between the scans (mean 189 ml/s/m^2 with −1 ml/s/m^2 change at every 6-month scan, $p = 0.47$). For a step-change in WHO FC there was no significant change in RV peak emptying rate (mean 8% [CI −1% to 16%], $p = 0.08$) (see Figure 2b).

In the left ventricle (LV), the peak filling rate reduced slightly but significantly throughout the study period for the population (mean 138 ml/s/m^2 with a change of −2 ml/s/m^2 per 6-month interval scan, $p = 0.04$). For every step worsening of functional class, there was an associated significant reduction in LV peak filling rate (−10% [CI −18% to −1%], $p = 0.02$) (see Figure 2c)

Peak emptying rate in the LV did not change significantly between the scans (mean 196 ml/s/m^2 with −2 ml/s/m^2 per 6-month interval scan, $p = 0.34$) and there was no significant association between changes in functional class and changes in LV peak emptying rate (−1% [−5% to 4%], $p = 0.68$) (see Figure 2d).

DISCUSSION

In this study, changes in RV volumes were associated with changes in patient WHO functional class in PAH. RV function is reflected in patients' physical functional

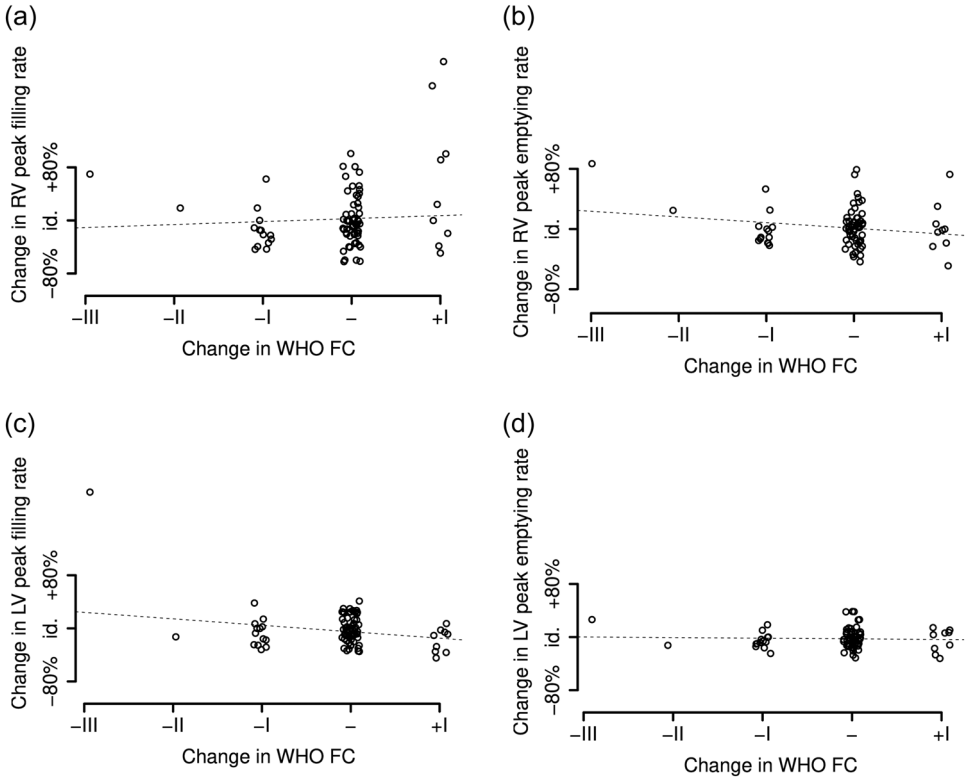

FIGURE 2 Changes in right ventricular peak filling rate (a), peak emptying rate (b), left ventricular peak filling rate (c), and peak emptying rate (d) in relation to changes in WHO FC. Right ventricular peak filling rate shows a "U" form relationship with changing functional class. "id.", index value. Dotted line indicates the regression line with values presented in the Results section.

capacity and this study suggests that a change in RV end-diastolic volume of 11% can be seen as clinically significant. RV end-diastolic volume for the study population increased modestly but significantly at every scan and LV peak filling rate decreased also modestly but significantly throughout the study period. RV peak filling rate, representing a measurement of diastolic function, showed a U-shaped relationship with changes in patient functional class.

RV dilatation is a sign of disease progression and is associated with poorer survival.[17,18] Ideally, PVR should be measured to follow the remodeling of the pulmonary vasculature and disease progression. However, PVR is a composite of three different measurements (mean pulmonary artery pressure, pulmonary artery wedge pressure, and cardiac output), each measurement with its difficulties and caveats, including variations in cardiac output measurements and the requirement for uniform reading of the pressure measurements according to the respiratory cycle.[19] Furthermore, the PVR does not necessarily reflect the state of the circulation, as it is the contractile force of the heart that ultimately results in a sufficient circulating blood volume. However, right heart catheterization is still required for the PAH diagnosis and is included as a recommendation in regular follow-up assessments as a part of the decision regarding alterations in PAH-targeted therapy.

Recently, a meta-analysis of CMR in PAH demonstrated that even small changes in RV volumes and function predict both clinical worsening and mortality, further strengthening the potential role of CMR both in the clinical setting and clinical trials.[18] Additionally, follow-up studies have shown increased survival associated with improvements in RV size and function.[20,21] To establish CMR as a tool in the management of patients with PAH, it is important to know the clinical implications of changes in measurements of RV size and function, when it is measured accurately with CMR. Both measurements of reproducibility and demonstration of what are clinically significant changes in RV size and function are required in the clinical assessment of PAH patients and when planning clinical trials that use CMR measures as clinical endpoints.

After the diagnosis of PAH is established, a baseline risk assessment predicts the prognosis for survival and suggests treatment intensity, and the patient is scheduled for regular reassessments. A panel of observations and measurements will be repeated at each follow-up to see if the patient is stable or deteriorating. However, it can be difficult to judge if a change in, for instance, NT-proBNP

reflects a consistent change or is an expression of normal variation, and it can be challenging to judge if there has been a reported change in WHO functional class.[22] Although all the measurements are associated with fluctuations, the sum of measurements predicts survival in PAH.[23] To further add to the complexity, comorbidities may also affect measurements that are not disease-specific, such as the 6MWD-test, or WHO functional class in PAH patients with a lung disease such as chronic obstructive pulmonary disease.

Risk assessment in PAH can be based on available calculators such as the REVEAL risk assessment calculator[24] or according to the European Society of Cardiology and European Respiratory Society guidelines for diagnosis and treatment of pulmonary hypertension.[11] There is the added value of CMR in risk assessment in PAH[20] and there is potential benefit in using CMR in the follow-up of individual patients. Disease-specific surrogate measurements for morbidity and mortality with known precision in the measurements and known clinical implications should be an essential aid for the physician treating PAH. Assessment of the RV using CMR fulfills many of these goals.

The peak filling rate of the RV in this study showed a similar pattern as the E/A ratio known from echocardiography as a method to assess diastolic function. This illustrates the difficulties in the assessment of diastolic function when filling pressures are not known. In the LV, however, there was a linear relationship, but the LV in PAH is dependent on the function of the RV. If RV function improves, LV filling and volume increase, probably without reaching the levels of increased filling pressures associated with the upslope of the U-shaped association.

Previous studies have found that progressive RV dilatation precedes clinical worsening and is associated with increased mortality and that worsening of RV diastolic function is also associated with increased mortality, but few studies have focused on clinically significant changes in PAH. For stroke volume, a clinically significant change of 10 ml has been suggested[25] and for 6MWD there is a suggested clinically significant change of 33 m.[26] NT-proBNP has in a previous study showed a log-linear relationship with RV ejection fraction[27] and this was also seen in our study (see Figure 3).

The figure illustrates the potential difficulty in following RV function using NT-proBNP, as NT-proBNP levels relatively abruptly increase first at very low levels of RV ejection fraction. Also, the figure shows that the range of NT-proBNP levels can spread over all risk category limits in the European Guidelines on Pulmonary Hypertension Risk Assessment Table at the same level of RV ejection fraction, making it difficult to use NT-proBNP independently as a risk indicator. Even though NT-proBNP in combination with WHO FC and 6MWD has shown to identify patients at low risk of mortality in PAH, the role of NT-proBNP as a quick test in risk assessment is debated.[28] The limited availability can be held against widespread use of CMR, but CMR is being used more extensively not least in PH centers. CMR excels in the known precision in the measurements of cardiac function and in the emerging knowledge of how large changes that are clinically important in PAH. A recent example of the applicability of CMR measurements as an endpoint in clinical trials is a study evaluating the effect of macitentan, a PAH-targeted medication, on RV function measured as SV.[29] The study was stopped after a prespecified interim analysis after the inclusion of only 42 patients as the primary endpoint had been met and the study was declared positive. The authors concluded that the effect of macitentan resulted in both a statistically and a clinically relevant increase in SV.

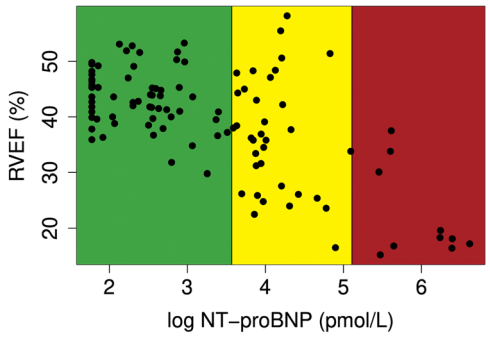

FIGURE 3 NT-proBNP and right ventricular ejection fraction have a log-linear relationship, making it presumably difficult to judge right ventricular status from NT-proBNP measurements as increases are seen mainly at very low right ventricular ejection fractions. Colors represent limits of NTproBNP-levels from the 2015 European Guidelines on Pulmonary Hypertension Risk Assessment Table. Green represents the limits of the low-risk category, yellow intermediate, and red the high-risk category. The purpose of the color overlay is to illustrate that a right ventricular ejection fraction of, for example, 35% can have corresponding NT-proBNP levels in both the low-risk and high-risk categories.

Limitations to this study include sample size and that the patients included are restricted to idiopathic and heritable PAH. The sample size is one part of the calculation to judge if a study is sufficiently powered to evaluate the desired endpoint, with the other two being the reproducibility of the measurement and the desired difference to measure. With the high reproducibility in the measurements, the sample size in this study was sufficient to show that changes in clinical parameters,

such as functional class, were significantly associated with changes in RV function. The suggested clinically important differences would have to be validated in other populations (including, e.g., PAH associated with systemic sclerosis and congenital heart disease) to have wider applicability, possibly including a wider array of tests as anchors such as the REVEAL Risk Calculator or the ESC/ERS risk stratification model. However, it does not currently have practical implications on how large the clinically significant changes are, as long as they are smaller than the reproducibility of the measurement, which for RV end-diastolic volume has been a suggested 14% and for stroke volume 11%.[8] Another current limitation for the wider applicability for measurement of RV filling is the time-consuming work of delineating ventricular volumes for the full cardiac cycle, but future technical improvements in image analysis should presumably make the process more automated and faster.

CMR studies have been considered time-consuming, and this can be true for a comprehensive CMR protocol. However, after revising the CMR protocol to focus on important measurements in a follow-up setting in PAH, a clinically relevant study, including initial scouting images (5 min), transversal assessment of RV-volumes (8−10 min), and cardiac output (2 min), can be done in well under half an hour. The examination is noninvasive, radiation-free and the following image analysis by an experienced reader should take less than 15 min. Such a routine could be planned in relation to patients attending regular follow-up in the daily clinical setting. Based on the above discussion, a suggested target could be to achieve at least a 14% reduction in RV volume and an 11% improvement in stroke volume with an escalation of targeted therapy intensity. An alternative goal could be RV volume and stroke volume within these values at serial assessments—in essence, stable RV function. For validation of these hypotheses on clinical impact, larger long-term studies would be needed.

In conclusion, this study adds to the current knowledge of RV function in PAH that changes in WHO functional class are associated with an 11% change in RV end-diastolic volume using transversal images in the studied population. Furthermore, this study shows how the filling of the right ventricle changes in accordance with changes in WHO functional class, mimicking the pattern seen in echocardiography in the assessment of diastolic function.

The practical applicability of the findings in this study is in combining the reproducibility and clinically significant changes in the measurement of RV end-diastolic volume and SV. Any change in the follow-up assessment of a patient with PAH that is greater than these limits would then be considered to be both statistically significant and clinically important.

AUTHOR CONTRIBUTIONS

Christoffer Göransson participated in the design of the study; acquired and analyzed the data and drafted the manuscript. Niels Vejlstrup design idea, interpreted the results, and revised the manuscript. Jørn Carlsen design idea, included patients, interpreted the results, and revised the manuscript. All authors reviewed, revised, and approved the manuscript for submission.

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CONFLICT OF INTEREST

Jørn Carlsen is a member of an advisory board for Janssen Cilag, and the institution has received research grants and advisory/speaker fees. In addition, the institution has received fees from United Therapeutics for clinical trials and Astra Zeneca and Ferrer for speaker fees.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The Ethics Committee for the Capital Region of Denmark approved the study (protocol number H-2-2014-079) and all participants provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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