Early View

Original research article

Right atrial function is associated with RV diastolic stiffness: RA-RV interaction in pulmonary arterial hypertension

Jeroen N. Wessels, Sophia A. Mouratoglou, Jessie van Wezenbeek, M. Louis Handoko, J. Tim Marcus, Lilian J. Meijboom, Berend E. Westerhof, Harm Jan Bogaard, Gustav J. Strijkers, Anton Vonk Noordegraaf, Frances S. de Man

Please cite this article as: Wessels JN, Mouratoglou SA, van Wezenbeek J, *et al.* Right atrial function is associated with RV diastolic stiffness: RA-RV interaction in pulmonary arterial hypertension. *Eur Respir J* 2021; in press (<https://doi.org/10.1183/13993003.01454-2021>).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Right atrial function is associated with RV diastolic stiffness: RA-RV interaction in pulmonary arterial hypertension

Jeroen N. Wessels, MD¹; Sophia A. Mouratoglou, MD, PhD¹; Jessie van Wezenbeek, MSc¹; M. Louis Handoko, MD, PhD²; J. Tim Marcus, PhD³; Lilian J. Meijboom, MD, PhD³; Berend E. Westerhof PhD⁴; Harm Jan Bogaard, MD, PhD¹; Gustav J. Strijkers, PhD⁵; Anton Vonk Noordegraaf, MD, PhD¹; Frances S. de Man, PhD¹

¹Pulmonary Medicine, ²Cardiology, ³Radiology and Nuclear medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

⁴Cardiovascular and Respiratory Physiology, Faculty of Science and Technology, Technical Medical Centre, University of Twente, Enschede, The Netherlands

⁵Dept of Biomedical Engineering and Physics, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Corresponding author

Frances de Man, PhD

Amsterdam UMC, Vrije Universiteit Amsterdam

Pulmonary Medicine

Amsterdam Cardiovascular Sciences

De Boelelaan 1117

1081 HV Amsterdam, The Netherlands

fs.deman@amsterdamumc.nl

Tel: +31 20 44 41883

Fax: +31 20 44 44328

Abstract

Background

Pulmonary arterial hypertension (PAH) patients have altered right atrial (RA) function and right ventricular (RV) diastolic stiffness. This study assessed the impact of RV diastolic stiffness on RA-RV interaction.

Methods

Low or high end-diastolic elastance (E_{ed}) PAH patients ($n=94$) were compared to controls ($n=31$). Treatment response was evaluated in $n=62$ patients. RV and RA longitudinal strain, RA emptying and RV filling were determined and diastole was divided in a passive and active phase. Vena cava backflow was calculated as RV active filling-RA active emptying; RA stroke work as RA active emptying*RV end-diastolic pressure.

Results

With increased E_{ed} , RA and RV passive strain were reduced while active strain was preserved. In comparison to controls, patients had lower RV passive filling, but higher RA active emptying and RA stroke work. RV active filling was lower in high E_{ed} patients, resulting in higher vena cava backflow. Upon treatment, E_{ed} reduced in half of high E_{ed} patients, which coincided with larger reductions in afterload, RV mass and vena cava backflow and greater improvements in RV active filling and stroke volume in comparison to patients in whom E_{ed} remained high.

Conclusions

In PAH, RA function is associated with changes in RV function. Despite increased RA stroke work, severe RV diastolic stiffness is associated with reduced RV active filling and increased vena cava backflow. In 50% of high baseline E_{ed} patients, diastolic stiffness remains high, despite treatment. E_{ed} reduction coincided with a large reduction in afterload, increased RV active filling and decreased vena cava backflow.

Introduction

Right ventricular (RV) adaptation is essential in pulmonary arterial hypertension (PAH) patients, since RV failure is the main determinant of symptoms and mortality [1]. One of the hallmarks of ventricular adaptation, hypertrophy, comes at the cost of ventricular stiffening, which is exacerbated by changes in collagen deposition and titin phosphorylation [2, 3]. Some stiffening may be beneficial, since it prevents overt dilatation of the right ventricle, but excessive stiffening may have detrimental effects. The degree of RV diastolic stiffness is associated with other parameters of disease severity and is a predictor of mortality [4, 5]. It may also affect right atrial (RA) function, as was recently suggested by correlations of RV diastolic stiffness with vena cava backflow and RA longitudinal strain [6, 7]. However, it is unclear whether changes in RA function reflect impaired RA contraction, or develop as a (potentially reversible) consequence of RV diastolic stiffness. We used an integrative approach combining RA and RV strain measurements with pressure-volume analysis in PAH patients before and after treatment to assess RA-RV interaction and vena cava backflow at different gradations of RV diastolic stiffness to answer the following questions:

- Are changes in RA function a consequence of RV diastolic stiffness or do they reflect impaired RA contraction?
- To what extent is severe RV diastolic stiffness reversible and does reversal lead to improvement of RA-RV interaction and reduction of vena cava backflow?

Methods

Study subjects

Idiopathic, hereditary or connective tissue disease (CTD) associated PAH patients diagnosed between December 2002 and May 2019 at the Amsterdam University Medical Center, The Netherlands (a tertiary referral center for PAH) were evaluated for eligibility (supplemental figure 1). Patients (n=178) had undergone cardiac magnetic resonance imaging (CMR) within two weeks of right heart catheterization at baseline and at follow-up. Medication use at baseline, poor quality RV pressure curves or CMR image were exclusion criteria (n=84). This resulted in n=94 patients who were divided in two subgroups based on median end-diastolic elastance (E_{ed}), with high E_{ed} identifying PAH patients with severe RV diastolic stiffness. The median E_{ed} of 0.63 mmHg/ml closely corresponds to the optimal cut-off for survival prediction [5]. Subjects who had dyspnea or a positive mutation carrier status, but normal pulmonary artery pressures, were included as controls (n=31). None of these had pulmonary or cardiovascular disease, diabetes or systemic hypertension. Treatment response was evaluated in n=62 patients after a median follow-up of 11 months (interquartile range 6-13 months). Due to the retrospective character of this study using data obtained for clinical purposes, the medical ethics review committee of the VU Medical Center did not consider this study to fall within the scope of the Medical Research Involving Human Subjects Act. Therefore, no additional approval was required (approval number 2012288).

Pressure-volume analysis

Right heart catheterization was performed using a balloon-tipped, flow directed 7.5F triple lumen Swan-Ganz catheter (Edwards Lifesciences LLC, Irvine, CA, USA). Cardiac output (CO) was

measured by direct Fick or thermodilution method. All pressure curve analyses were performed by one researcher (JNW). Derivation of end-systolic elastance (E_{es}) in PAH patients was done according to the single-beat method [8], using systolic pulmonary artery pressure (sPAP) to estimate end-systolic pressure [9]. A sine wave was fitted over the RV pressure curve using the isovolumic contraction period (from end-diastole to the point of maximal rate of pressure rise [dP/dt_{max}]) and the isovolumic relaxation period (from minimal dP/dt to start diastole). The point of end-diastole was identified using the R-wave of the ECG and, when needed, shifted manually to the point before the upslope of the ascending limb. RV iso-volumic pressures were averaged over >10 heart beats. Beats with significant catheter artifacts were excluded. Arterial elastance (E_a) was calculated as systolic pulmonary artery pressure /stroke volume and RV-arterial coupling as E_{es}/E_a [10]. E_{ed} was derived by fitting a curve through (0,0), the beginning diastolic and the end-diastolic points on the pressure-volume curve. E_{ed} is the slope of this curve at end-diastolic volume [4, 5]. We estimated RA stroke work by multiplying RA active emptying volume with RV end-diastolic pressure (unit: ml*mmHg).

Cardiac magnetic resonance

All images were acquired on a 1.5T Avanto or Sonata scanner equipped with a 6-element phased array coil (Siemens Medical Solutions, Erlangen, Germany). Images were analyzed as previously described [11]. RV volume was also measured during atrial diastasis, just before the start of atrial contraction. Because a stack of images through the atria was not available (the typical protocol for a short axis stack is to start just above the tricuspid valve), RA volume was determined by applying the area-length method on the four-chamber view. This method results in an underestimation of the volume [12], but it correlates excellently with the volume determined on a transverse stack of slices in 42 pulmonary hypertension patients

(supplemental figure 2). We added the difference between the two methods to the four-chamber volume to derive accurate RA volumes. RA volumes were measured in three phases (maximal, diastasis and minimal). RA passive emptying was defined as the difference between RA maximal and RA diastasis volume; RA active emptying as the difference between RA diastasis and RA minimal volume [7, 13]. RV passive and active filling were calculated similarly. We derived vena cava backflow by subtracting RV active filling from RA active emptying. A detailed description of the cardiac phases and corresponding volumes is given in figure 1. To measure the possible impact of tricuspid regurgitation (TR), we estimated TR volume by subtracting LV from RV stroke volume [14].

Strain analysis

Strain analysis was performed by CMR feature tracking using commercially available software (Circle CVI42®). RV longitudinal strain was determined on a four-chamber view by drawing epicardial and endocardial contours in the end-diastolic phase (L0), excluding trabeculations. The analysis included only the RV free wall [15]. Similarly, right atrial longitudinal strain was determined by drawing contours in the phase with maximal RA volume (L0). The automated feature tracking was visually checked and corrections to the initial contours were made if deemed necessary. Both RA and RV strain were divided in a passive and active phase [13]. Representative examples of contouring, feature tracking and division of strain in three phases are given in figure 1.

Statistical analysis

Statistical analyses were performed using R version 3.6.1 (<https://cran.r-project.org/>). Distribution of all variables was visually checked using histograms and qqplots (rcompanion; <https://CRAN.R-project.org/package=rcompanion>). Data are reported as mean±standard deviation or median [interquartile range] depending on distribution. Categorical variables are reported as absolute numbers and relative frequencies (percentage). Non-normally distributed variables were normalized by logarithmic transformation. N-terminal pro brain natriuretic peptide (NT-proBNP) could not be normalized and was compared with a Wilcoxon's test. Comparison of multiple groups was done with analysis of variance (ANOVA) and post-hoc Tukey's test to correct for the family-wise error-rate. Differences between baseline and follow-up measurements were tested with a paired t-test for continuous variables and Fisher's exact test for categorical variables. All statistical tests were done with rstatix (<https://CRAN.R-project.org/package=rstatix>), Visualization of data with ggplot2 (<https://CRAN.R-project.org/package=ggplot2>). To visualize the RA and RV strain curve over one cardiac cycle, the mean strain values for all patients who had 30 CMR phases was used (other patients had 20-29 phases). These 56 patients were representative for the full cohort (supplemental table 1). Furthermore, patients with follow-up (n=62) were representative for the full cohort (supplemental table 1). Patients with E_{ed} at baseline >0.63 mmHg/ml were divided in two groups at follow-up based on the improvement of E_{ed} to <0.63 mmHg/ml. Approximately half of the patients had a large and significant improvement in E_{ed} from 0.92 [0.88-1.15] to 0.37 [0.31-0.46] mmHg/ml ($p<0.001$). In the other half, E_{ed} did not change. Changes in hemodynamic

and CMR parameters in these groups were compared with repeated measures ANOVA and post-hoc pairwise t-tests with Bonferroni correction.

Results

Baseline characteristics

The study population consisted of 63 idiopathic, 9 hereditary and 25 CTD-PAH patients. Patients were 58 ± 18 years old and predominantly female (65%). On average, the E_{ed} in patients (0.70 ± 0.41 mmHg/ml) was 3.5 times that of controls (0.20 ± 0.08 mmHg/ml), indicating significant RV diastolic stiffness. Patients were divided in a low E_{ed} and high E_{ed} group, based on the median value of 0.63 mmHg/ml. A comparison of baseline variables in both patient groups and controls is given in table 1.

RV and RA passive strain reduced in high E_{ed} patients, active strain preserved

We evaluated the association between strain patterns and RV diastolic stiffness (figure 2). The atrium and ventricle are oppositely directed, but the pattern is very similar. RA reservoir and passive strain in high E_{ed} patients were strongly reduced in comparison to low E_{ed} patients (supplemental figure 3). There were no differences in RA active strain. RV global longitudinal strain was slightly lower in high E_{ed} patients. The RV passive strain was reduced to a similar degree as RA passive strain, with the strongest reduction in patients with severe RV diastolic stiffness. RV active strain did not differ between the groups. A comparison of the whole PAH cohort with the control group is given in supplemental table 2. In addition to the differences between low and high E_{ed} patients, RA passive strain was lower in low E_{es}/E_a patients when

compared to high E_{es}/E_a patients (supplemental figure 4). There was no difference in RA active strain. RV global longitudinal and passive strain were slightly lower in low E_{es}/E_a patients, but RV active strain was not. To assess the possible impact of TR on RA volumes and strain, TR volume was correlated to RA maximal volume (Pearson $R=0.24$, $p=0.02$). There were no correlations between TR volume and RA strain parameters (data not shown).

High RA active emptying and vena cava backflow in high E_{ed} patients

To further evaluate the consequences of RV diastolic stiffness for RA-RV interaction, RA passive and active emptying and RV passive and active filling were determined (figure 3). While there were no differences in RA passive emptying, RA active emptying was higher than controls in both low and high E_{ed} patients. RA stroke work was approximately 3-fold greater in low E_{ed} patients and 4-fold greater in high E_{ed} patients, compared to controls (figure 3C). RV passive filling was markedly reduced in all PAH patients. RV active filling on the other hand, was preserved in low E_{ed} , but reduced in high E_{ed} patients. Vena cava backflow was negligible in controls, but present in low E_{ed} patients. In high E_{ed} patients the backflow was almost twice of that in low E_{ed} patients. In other words, the surplus of RA active emptying results in a significant portion of backward flow into the caval veins (figure 3F). RV active filling was moderately correlated to stroke volume (Pearson $R=0.42$, $p<0.001$). There were no differences in RV active filling or vena cava backflow between low and high E_{es}/E_a patients (supplemental figure 5). Vena cava backflow was lower in CTD-PAH patients, but a similar pattern was observed for E_{ed} groups (supplemental figure 6).

Treatment response

Almost a third of patients received monotherapy (31%), 63% received oral combination therapy and 6% received triple therapy. The changes in hemodynamic and CMR parameters for the PAH cohort are shown in supplemental table 3. As expected, pulmonary vascular resistance (PVR) dropped from 9.6 [6.8-12.9] to 4.7 [3.7-7.1] mmHg/L/min ($p<0.001$), mean pulmonary artery pressure decreased by 10 mmHg (95% CI: 6-13; $p<0.001$), cardiac index increased by 0.7 L/min (95% CI: 0.5-0.9; $p<0.001$) and RV stroke volume index increased by 6 ml (95% CI: 4-8; $p<0.001$). The E_{ed} decreased by almost 40%, but did not normalize. Passive filling of the right ventricle did not increase significantly, but active filling did. Backflow to the caval veins decreased substantially.

Severe RV diastolic stiffness improves in half of the patients

To identify which factors are associated with improvement of severe RV diastolic stiffness, we classified baseline high E_{ed} patients as responders when they converted to a low E_{ed} (<0.63 mmHg/ml) at follow-up or as non-responders when the E_{ed} remained elevated. Convergence to a low E_{ed} could not be explained by differences in gender or treatment, but it did coincide with greater reduction in afterload (E_a reduction of $48\pm17\%$ in responders vs. $13\pm34\%$ non- E_{ed} responders; p -interaction <0.001), greater improvement in RV stroke volume index ($47\pm25\%$ vs. $16\pm28\%$; p -interaction=0.003) and greater reduction in RV mass ($15\pm31\%$ vs. $2\pm28\%$; p -interaction=0.051), see figure 4. Furthermore, the change in afterload (E_a) was correlated with the change in E_{ed} , RV mass, RV active filling and vena cava backflow (figure 5).

RA-RV interaction improves in E_{ed} responders

RA reservoir and passive strain improved in E_{ed} responders, while RA active strain did not change (figure 6). In non- E_{ed} responders, there was no change in any of the RA strain parameters. RV global longitudinal strain improved in E_{ed} responders, but not in non- E_{ed} responders (table 2). RV passive and active strain did not change significantly in either group. RA passive emptying and RV passive filling did not change after treatment, RA stroke work did not change significantly and active emptying remained elevated in both groups. However, in E_{ed} responders, RV active filling increased by 19 ml (95% CI: 12-25; $p=0.003$). This was associated with a normalization of vena cava backflow (figure 7) while non- E_{ed} responders had no improvement in RV active filling or vena cava backflow. In summary, approximately half of patients with a high E_{ed} at baseline had a favorable response. RA active emptying became more efficient (increased forward flow, decreased backward flow) since the RV became less stiff (figure 8).

Discussion

By combining measurements of RV diastolic stiffness, RV filling, RA and RV longitudinal wall motion and RA stroke work in PAH patients and controls, we were able to demonstrate that:

- 1) RA function is associated with RV diastolic stiffness. RV passive filling is reduced in all patients while increased RA stroke work and active emptying preserve RV active filling in mild, but not in severe RV diastolic stiffness patients. The surplus of RA active emptying results in significant vena cava backflow.
- 2) Half of the severe RV diastolic stiffness patients have a relevant reduction in RV diastolic stiffness in response to treatment, which coincided with a large reduction in afterload, improvement of RV stroke volume and reduction in RV mass. In these patients, RV active filling increased and vena cava backflow normalized.

Importance of RA parameters

Both RA pressure and volume parameters are used for risk stratification of PAH patients [16]. We believe RA parameters are important not because they reflect RA failure, but because they are a consequence of RV diastolic stiffness. RA function has recently been assessed by speckle-tracking echocardiography studies [17-21], which showed decreased RA reservoir and passive strain, while active strain was either preserved or increased. Also, RA passive emptying was lower, while active emptying was higher in PAH [20, 21]. The RA strain pattern in the present study and another recent CMR feature tracking study [13], is in accordance with the echocardiography studies. Recently, a relation between RV diastolic dysfunction and RA function has been suggested [7, 22]. The peak early diastolic strain rate was associated with RV

end-diastolic pressure, E_{ed} , Tau and E_a [22]. CMR feature tracking RA strain in all three cardiac phases was correlated with E_{ed} and end-diastolic pressure [7]. Our study is the first to directly compare RA and RV strain patterns. We found that the RV strain pattern is in accordance with RA strain, suggesting a strong interaction between the ventricle and atrium. Furthermore, in high E_{ed} patients both RV and RA strain patterns are more severely affected than in low E_{ed} patients.

Atrial contraction compensates for loss of passive RV filling

Despite high RV end-diastolic pressure, RA stroke work in PAH was high enough (3-4x that of controls) to induce increased RA active emptying. RV passive filling was strongly reduced, while active filling was preserved in low E_{ed} but not in high E_{ed} patients. With higher E_{ed} , increasingly more backflow occurs [6]. In other words: because of RV diastolic stiffness, the atrium has to contract harder against a higher afterload, whereby substantial backflow to the caval veins occurs. We speculate that this mechanism is probably sufficient to preserve RV filling, preload and stroke volume in most patients, but in severe RV diastolic stiffness this mechanism may fall short. RA-RV uncoupling may occur, as suggested by a weak correlation between RV active filling and stroke volume. From clinical observations this is evident in patients with PAH and atrial fibrillation. As soon as they convert from sinus rhythm to atrial fibrillation, their symptoms may worsen tremendously. Therefore, rhythm control is essential in these patients. Furthermore, severe RV diastolic stiffness patients have high vena cava backflow which may induce congestive hepatopathy or the cardiorenal syndrome.

Changes in E_{ed} in relation to RV filling

After initiating treatment, we saw a relevant improvement of RV diastolic stiffness in half of patients (figure 8B). Their afterload decreased by 48%, RV stroke volume improved by 47% and there was a larger decrease of RV mass in this group. Afterload reduction is an important goal of therapy since it may induce a decrease in RV mass. The improvement in E_{ed} may partly be a consequence of decreased RV mass like described before [5]. However, intrinsic changes in RV myocardium like collagen deposition and sarcomeric stiffening may also play a role [3]. As a consequence of the large reduction in E_{ed} (approximately 50-90%), RV active filling improved and backflow to the caval veins diminished. The other half of patients had an unfavorable response (figure 8C). Their afterload and RV stroke volume only showed a small, non-significant improvement and their RV mass and E_{ed} did not decrease significantly. RV active filling did not improve and vena cava backflow remained substantial. Although fibrosis and sarcomeric stiffening have been implicated in RV stiffening [4], we were not able to investigate this in the current study. Further research is needed to elucidate these different phenotypes of RV diastolic stiffness and their clinical consequences.

Limitations

This was a single center study involving three patients groups: idiopathic, hereditary and CTD-PAH. Although there are important differences between these groups, E_{ed} was not different. Vena cava backflow was lower in CTD-PAH, but the distribution across E_{ed} groups was similar. As a stack of images through the atria was not available in all patients, we determined atrial volumes on the four-chamber view. Although this results in an underestimation of the volumes,

we were able to correct for this by measuring the difference in a set of patients in which we did have a stack of images through the atria. RA volumes may have been influenced by tricuspid regurgitation, but none of the patients had severe TR and the prevalence of mild and moderate TR was similar in low and high E_{ed} groups. TR may also induce vena cava backflow, but this is only of significance in a small minority of patients, and very small in comparison with the backflow during atrial contraction [6]. We included patients who were diagnosed between 2002 and 2019. Treatment strategies were therefore subject to changing guidelines over time. Relatively few patients received parenteral prostacyclins, which might have influenced the treatment response. However, since we compared treatment responders with non-responders (irrespective of specific PAH medication), it will not impact our results. E_{es} and E_{ed} measurements were based on a single-beat method. E_{ed} has only been validated in an animal model, but it is an often used and valued measure of RV stiffness. Pressures were measured through fluid-filled catheters, but since E_{ed} is a relative measure, this does not lead to artifacts. Pressures were averaged over at least 10 heart beats to minimize the influence of respiration.

Conclusion

In PAH, RA function is associated with changes in RV function. Severe RV diastolic stiffness is associated with reduced RV active filling and increased vena cava backflow, while RA stroke work and active emptying are increased. In 50% of high baseline E_{ed} patients, diastolic stiffness remains high, despite treatment. E_{ed} reduction coincided with a large reduction in afterload, increased RV active filling and decreased vena cava backflow.

Acknowledgements

None.

Sources of funding

HJB, AVN, and FSdM were supported by the Netherlands CardioVascular Research Initiative: the Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development, and the Royal Netherlands Academy of Sciences (CVON-2012-08 PHAEDRA, CVON-2018-29 PHAEDRA-IMPACT and CVON-2017-10 Dolphin-Genesis). AVN and FSdM were further supported by The Netherlands Organization for Scientific Research (NWO-VICI: 918.16.610, NWO-VIDI: 917.18.338). FSdM was supported by the Dutch Heart Foundation Dekker senior post-doc grant (2018T059).

Disclosures

HJB and AVN were supported by research grants from Actelion, GSK and Ferrer (Therabel).

References

1. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, et al. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. *J Am Coll Cardiol*. 2013;62(25 Suppl):D22-33.
2. Rain S, Andersen S, Najafi A, Gammelgaard Schultz J, da Silva Goncalves Bos D, Handoko ML, et al. Right Ventricular Myocardial Stiffness in Experimental Pulmonary Arterial Hypertension: Relative Contribution of Fibrosis and Myofibril Stiffness. *Circ Heart Fail*. 2016;9(7).
3. Rain S, Bos Dda S, Handoko ML, Westerhof N, Stienen G, Ottenheijm C, et al. Protein changes contributing to right ventricular cardiomyocyte diastolic dysfunction in pulmonary arterial hypertension. *J Am Heart Assoc*. 2014;3(3):e000716.
4. Rain S, Handoko ML, Trip P, Gan CT, Westerhof N, Stienen GJ, et al. Right ventricular diastolic impairment in patients with pulmonary arterial hypertension. *Circulation*. 2013;128(18):2016-25, 1-10.
5. Trip P, Rain S, Handoko ML, van der Bruggen C, Bogaard HJ, Marcus JT, et al. Clinical relevance of right ventricular diastolic stiffness in pulmonary hypertension. *Eur Respir J*. 2015;45(6):1603-12.
6. Marcus JT, Westerhof BE, Groeneveldt JA, Bogaard HJ, de Man FS, Vonk Noordegraaf A. Vena cava backflow and right ventricular stiffness in pulmonary arterial hypertension. *Eur Respir J*. 2019;54(4).
7. Tello K, Dalmer A, Vanderpool R, Ghofrani HA, Naeije R, Roller F, et al. Right ventricular function correlates of right atrial strain in pulmonary hypertension: a combined cardiac magnetic resonance and conductance catheter study. *Am J Physiol Heart Circ Physiol*. 2020;318(1):H156-H64.
8. Trip P, Kind T, van de Veerdonk MC, Marcus JT, de Man FS, Westerhof N, et al. Accurate assessment of load-independent right ventricular systolic function in patients with pulmonary hypertension. *J Heart Lung Transplant*. 2013;32(1):50-5.
9. Tello K, Richter MJ, Axmann J, Buhmann M, Seeger W, Naeije R, et al. More on Single-Beat Estimation of Right Ventriculoarterial Coupling in Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med*. 2018;198(6):816-8.
10. Brener MI, Burkhoff D, Sunagawa K. Effective Arterial Elastance in the Pulmonary Arterial Circulation: Derivation, Assumptions, and Clinical Applications. *Circ Heart Fail*. 2020;13(3):e006591.
11. van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol*. 2011;58(24):2511-9.
12. Li W, Wan K, Han Y, Liu H, Cheng W, Sun J, et al. Reference value of left and right atrial size and phasic function by SSFP CMR at 3.0 T in healthy Chinese adults. *Sci Rep*. 2017;7(1):3196.
13. Leng S, Dong Y, Wu Y, Zhao X, Ruan W, Zhang G, et al. Impaired Cardiovascular Magnetic Resonance-Derived Rapid Semiautomated Right Atrial Longitudinal Strain Is Associated With Decompensated Hemodynamics in Pulmonary Arterial Hypertension. *Circ Cardiovasc Imaging*. 2019;12(5):e008582.
14. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30(4):303-71.
15. Marcus JT, Gan CT, Zwanenburg JJ, Boonstra A, Allaart CP, Gotte MJ, et al. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *J Am Coll Cardiol*. 2008;51(7):750-7.
16. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology

(AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J*. 2015;46(4):903-75.

17. Alenezi F, Mandawat A, Il'Giovine ZJ, Shaw LK, Siddiqui I, Tapson VF, et al. Clinical Utility and Prognostic Value of Right Atrial Function in Pulmonary Hypertension. *Circ Cardiovasc Imaging*. 2018;11(11):e006984.

18. Bhawe NM, Visovatti SH, Kulick B, Kolas TJ, McLaughlin VV. Right atrial strain is predictive of clinical outcomes and invasive hemodynamic data in group 1 pulmonary arterial hypertension. *Int J Cardiovasc Imaging*. 2017;33(6):847-55.

19. D'Alto M, D'Andrea A, Di Salvo G, Scognamiglio G, Argiento P, Romeo E, et al. Right atrial function and prognosis in idiopathic pulmonary arterial hypertension. *Int J Cardiol*. 2017;248:320-5.

20. Meng X, Li Y, Li H, Wang Y, Zhu W, Lu X. Right atrial function in patients with pulmonary hypertension: A study with two-dimensional speckle-tracking echocardiography. *Int J Cardiol*. 2018;255:200-5.

21. Querejeta Roca G, Campbell P, Claggett B, Solomon SD, Shah AM. Right Atrial Function in Pulmonary Arterial Hypertension. *Circ Cardiovasc Imaging*. 2015;8(11):e003521; discussion e.

22. Richter MJ, Fortuni F, Wiegand MA, Dalmer A, Vanderpool R, Ghofrani HA, et al. Association of right atrial conduit phase with right ventricular lusitropic function in pulmonary hypertension. *Int J Cardiovasc Imaging*. 2020;36(4):633-42.

Figure legends

Figure 1. Example of RA & RV volume and strain in a healthy control and a PAH patient.

A+B) RA + RV volume and strain throughout the cardiac cycle in a healthy control. C+D) RA + RV volume and strain throughout the cardiac cycle in a PAH patient. The inset shows RA endo- and epicardial contours drawn at end-systole and maximal negative strain at end-diastole. RV contours were drawn at end diastole, while maximal negative strain (GLS) was reached at end-

systole. RA indicates right atrial; RV, right ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; GLS, global longitudinal strain.

Figure 2. Mean RA and RV strain curves during one cardiac cycle.

Mean RA and RV longitudinal strain curves with 95% confidence intervals; control (n=20), low E_{ed} (n=28) and high E_{ed} (n=28). p-interaction represents the interaction between patient group and CMR phase. RA indicates right atrial; RV, right ventricular; CMR, cardiac magnetic resonance; E_{ed}, end-diastolic elastance; RMANOVA, repeated measures analysis of variance.

Figure 3. RA emptying, RV filling and vena cava backflow

Data are presented as mean $\pm$ SEM. p-values were calculated with Tukey's post-hoc analysis and family-wise correction for multiple testing. A) RA passive emptying was similar in all groups. B) RA active emptying was much higher in all patients. C) RA stroke work was estimated by multiplying RA active emptying with the end diastolic pressure. D) RV passive filling was strongly reduced in all patients. E) RV active filling was preserved in low E_{ed} patients, but lower in high E_{ed} patients. F) Vena cava backflow represents the difference between RA active emptying and RV active filling. RA indicates right atrial; RV, right ventricular.

Figure 4. Changes in afterload, stroke volume and RV mass after the start of treatment.

Patients with high E_{ed} at baseline either improved to <0.63 mmHg/ml (green; E_{ed} responders) or remained high at >0.63 mmHg/ml (red; non E_{ed} -responders). Dots and whiskers represent mean $\pm$ SEM. p-values were determined through pairwise t-test with Bonferroni correction. p-interaction values represent repeated measures analysis of variance. A) E_a improved in the E_{ed} responders. B) RV stroke volume index improved significantly in E_{ed} responders, while there was no change in non-responders. C) The change in RV mass index was stronger in patients in E_{ed} responders. E_{ed} indicates end-diastolic elastance; E_a , arterial elastance; BL, baseline; FU, follow-up.

Figure 5. Correlations between change in afterload at follow-up and several RV parameters.

RV indicates right ventricle; Eed, end-diastolic elastance; Ea, arterial elastance. R values represent Spearman correlations.

Figure 6. Changes in RA reservoir, passive and active strain after the start of treatment.

Patients with high E_{ed} at baseline either improved to <0.63 mmHg/ml (green; E_{ed} responders) or remained high at >0.63 mmHg/ml (red; non E_{ed} -responders). Dots and whiskers represent mean $\pm$ SEM. p-values were determined through pairwise t-test with Bonferroni correction. p-interaction values represent repeated measures analysis of variance. A) RA reservoir strain improved in E_{ed} responders. B) RA passive strain improved significantly in E_{ed} responders, while there was no change in non E_{ed} -responders. C) RA active strain did not change in any of the groups. E_{ed} indicates end-diastolic elastance; RA, right atrial; BL, baseline; FU, follow-up.

Figure 7. Changes in RA active emptying, RV active filling and backflow after the start of treatment.

Patients with high E_{ed} at baseline either improved to <0.63 mmHg/ml (green; E_{ed} responders) or remained high at >0.63 mmHg/ml (red; non E_{ed} -responders). Dots and whiskers represent mean $\pm$ SEM. p-values were determined through pairwise t-test with Bonferroni correction. p-interaction values represent repeated measures analysis of variance. A) RA active emptying did not change in any of the groups. B) RV active filling improved significantly in E_{ed} responders, while there was no change in non E_{ed} -responders. C) Vena cava backflow normalized in E_{ed} responders, while it did not change in non E_{ed} -responders. E_{ed} indicates end-diastolic elastance; RA, right atrial; RV, right ventricular; BL, baseline; FU, follow-up.

Figure 8. Treatment response in patients with severe RV diastolic stiffness

A) In PAH patients with severe RV diastolic stiffness, RV active filling was reduced even though RA stroke work was enhanced. Consequently, there was substantial backflow to the caval veins. B) Half of patients showed a favorable response. RV afterload was lowered with increase in stroke volume. RV mass decreased with a corresponding decrease in RV diastolic stiffness. RV active filling improved tremendously and vena cava backflow normalized. In

other words, with improvement of RV compliance, RA efficiency improved. C) Approximately $\frac{1}{2}$ of patients did not have a significant decrease of RV mass or RV diastolic stiffness. In these patients, RV active filling remained low and vena cava backflow substantial. PAH indicates pulmonary arterial hypertension; RV, right ventricular; RA, right atrial; SV, stroke volume.

Table 1: Patient characteristics

Variable	Control (n=31)	PAH Low E _{ed} (n=47)	PAH High E _{ed} (n=47)	p Value
Age, y	43±14	55±18*	59±18*	<0.001
Female, n (%)	20 (65%)	29 (62%)	32 (68%)	0.81
NYHA 1/2/3/4	16/11/4/0	3/19/22/3*	1/14/28/4*	<0.001
NTproBNP, pg/ml (n=121)	38 [19.5-58.5]	443 [233-1366]*	2052 [1100-3281]*†	<0.001
Catheterization				
Heart rate, bpm	75±12	79±13	81±14	0.15
mPAP, mmHg	15±4	46±11*	56±16*†	<0.001
PAWP, mmHg	8±3	9±3	9±3	0.33
Cardiac index, L/min/m ²	3.6±1.0	2.7±0.8*	2.4±0.9*	<0.001
PVR, mmHg/L/min	1.0 [0.7-1.5]	7.5 [4.9-9.7]*	11.1 [7.2-15.4]*†	<0.001
mRAP, mmHg	4 [3-6]	6 [4-9]*	8 [4-11]*	0.001
RVEDP, mmHg	8 ± 4	14 ± 6*	18 ± 8*†	< 0.001
SvO ₂ , %	76±5	65±8*	60±12*†	<0.001
CMR				
RVEDV index, ml/m ²	66±13	82±21*	83±23*	<0.001
RVESV index, ml/m ²	27±7	50±22*	57±20*	<0.001
SV index, ml/m ²	39±8	32±8*	27±9*†	<0.001
RVEF, %	60±6	41±13*	33±10*†	<0.001
RV mass index, g/m ²	21±5	46±14*	53±17*†	<0.001
RA max vol index, ml/m ²	48 [43-56]	68 [57-89]*	78 [62-95]*	<0.001
TR volume, ml No/<30ml/30-59ml/>59ml	24/7/0/0	27/19/1/0	26/20/1/0	0.38
Pressure-volume analysis				
E _{es} , mmHg/ml (n=119)	NA	0.45 [0.34-0.74]*	0.52 [0.38-0.83]*	<0.001
E _a , mmHg/ml (n=123)	NA	1.23 [0.94-1.70]*	1.85 [1.40-2.40]*†	<0.001
E _{es} /E _a (n=119)	NA	0.42 [0.26-0.61]*	0.30 [0.23-0.42]*	<0.001
E _{ed} , mmHg/ml (n=119)	0.20 [0.15-0.24]	0.39 [0.24-0.52]*	0.93 [0.78-1.14]*†	<0.001

Data presented as mean±SD or median [IQR] when data was not normally distributed. The E_{ed} could not be determined in three patients. PAH indicates pulmonary arterial hypertension; NYHA, New York Heart Association; NT-proBNP, N-terminal pro brain natriuretic peptide; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; mRAP, mean right atrial pressure; RVEDP, right ventricular end-diastolic pressure; SvO₂, mixed venous oxygen saturation; CMR, cardiac magnetic resonance; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; SV, stroke volume; RVEF, right ventricular ejection fraction; TR, tricuspid regurgitation; E_{es}, end-systolic elastance; E_a, arterial elastance; E_{ed}, end-diastolic elastance.

*p<0.05 vs control, †p<0.05 vs low E_{ed}

Table 2: Treatment response of high E_{ed} patients, divided in patients with improvement of E_{ed} and patients in whom the E_{ed} remained high

Variable	E _{ed} improved (n=14)		E _{ed} stable > 0.63 (n=12)		p-int
	Baseline	Follow-up	Baseline	Follow-up	
Female, n (%)	10 (71%)		8 (67%)		1
ERA/PDE5i/double/triple	2/1/8/3		3/3/6/0		0.33
Catheterization					
mPAP, mmHg	58±20	43±17	53±8	49±10	0.052
Cardiac index, L/min/m ²	2.1±0.7	3.1±0.7 [†]	2.3±0.7	2.4±0.7	0.020
PVR, mmHg/L/min	11.9 [8.2-15.5]	4.5 [3.7-7.3] [†]	12.7 [8.1-14.9]	8.5 [5.9-11.7]	0.14
mRAP, mmHg	5.0 [3.3-10.5]	4.0 [3.3-6.0]	10.0 [5.0-15.0]	8.5 [5.8-10.2]	0.85
RV EDP, mmHg	17.4±9.1	11.1±5.1	18.1±5.7	17.4±4.4	0.08
CMR					
RVEDV index, ml/m ²	82±24	77±23	74±19	70±24	0.89
RVESV index, ml/m ²	57±22	42±16	47±17	41±21	0.10
SV index, ml/m ²	24±7	35±11 [†]	26±7	29±7	0.003
RVEF, %	31±9	47±10 [†]	37±12	44±12	0.014
RV mass index, g/m ²	57±19	45±13	46±7	44±11	0.051
RA max vol index, ml/m ²	76 [60-86]	63 [57-71]	80 [72-97]	75 [64-106]	0.26
Pressure-volume					
E _{es} , mmHg/ml	0.69 [0.40-0.84]	0.26 [0.18-0.48]	0.55 [0.40-0.83]	0.52 [0.40-0.86]	0.15
E _a , mmHg/ml	2.28 [1.77-2.63]	0.89 [0.76-1.29] [†]	1.77 [1.61-2.24]	1.55 [1.22-1.96]	<0.001
E _{es} / E _a	0.29 [0.23-0.34]	0.36 [0.16-0.58]	0.32 [0.24-0.41]	0.39 [0.25-0.63]	0.83
E _{ed} , mmHg/ml	0.92 [0.88-1.15]	0.37 [0.31-0.46] [†]	1.02 [0.81-1.42]	0.82 [0.74-0.97]	<0.001
Strain analysis					
RA reservoir strain, %	13.3±4.2	18.3±4.5*	11.2±4.9	15.7±5.9	0.83
RA passive strain, %	-4.4±2.0	-9.3±4.0 [†]	-4.2±3.3	-6.8±4.7	0.11
RA active strain, %	-9.1±3.7	-9.7±3.3	-7.4±4.0	-9.2±4.0	0.52
RV GLS, %	-12.6±3.4	-18.2±3.9 [†]	-14.2±5.0	-16.9±4.7	0.21
RV passive strain, %	5.9±3.1	8.6±3.4	5.8±3.2	8.0±3.9	0.74
RV active strain, %	7.0±3.4	9.8±3.4	8.4±4.5	9.2±4.5	0.32
RA-RV interaction					
RA passive emptying, ml	23±10	22±9	22±9	23±13	0.57
RA active emptying, ml	37±12	34±11	37±18	39±17	0.24
RV passive filling, ml	31±21	33±18	37±19	40±26	0.85
RV active filling, ml	14±11	33±16 [†]	13±15	16±14	0.053
RA stroke work, ml*mmHg	634±365	409±275	691±464	709±421	0.073
Vena cava backflow, ml	23±17	1±12 [†]	22±15	20±17	0.013

Data presented as mean±SD or median [IQR] when data was not normally distributed. P-values represent the interaction of time and group as determined with repeated measures ANOVA.

E_{ed} indicates end-diastolic elastance; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase 5 inhibitor; double, combination of ERA and PDE5i; triple, combination of ERA, PDE5i and prostacyclin agonist; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; mRAP, mean right atrial pressure; RV, right ventricular; EDP, end-diastolic pressure; CMR, cardiac magnetic resonance; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; SV, stroke volume; RVEF, right ventricular ejection fraction; RA, right atrial; E_{es}, end-systolic elastance; E_a, arterial elastance; GLS, global longitudinal strain.

*p<0.05 in comparison with baseline, after Bonferroni correction for multiple testing

†p<0.01 in comparison with baseline, after Bonferroni correction for multiple testing

SUPPLEMENTAL MATERIAL

Right atrial function is associated with RV diastolic stiffness: RA-RV interaction in pulmonary arterial hypertension

Jeroen N. Wessels, MD; Sophia A. Mouratoglou, MD, PhD; Jessie van Wezenbeek, MSc; M. Louis Handoko, MD, PhD; J. Tim Marcus, PhD; Lilian J. Meijboom, MD, PhD; Berend E. Westerhof PhD; Harm Jan Bogaard, MD, PhD; Gustav J. Strijkers, PhD; Anton Vonk Noordegraaf, MD, PhD; Frances S. de Man, PhD

Supplemental table 1. Comparison of patients with 30 CMR phases and patients with follow-up to the overall cohort

	All PAH patients (n=97)	Baseline PAH with 30 CMR phases (n=56)	Patients with follow-up (n=62)
Age, y	57.5 ± 17.9	57.4 ± 16.8	54.1 ± 18.1
Female, n (%)	63 (65%)	33 (59%)	41 (66%)
NYHA 1/2/3/4	4/33/53/7	2/22/29/3	4/27/29/2
NTproBNP, pg/ml	1367 [360-2809]	1122 [372-2368]	1290 [396-2327]
Right heart catheterization			
Heart rate, bpm	80 ± 14	76 ± 11	79 ± 12
mPAP, mmHg	51 ± 15	51 ± 15	53 ± 14
PAWP, mmHg	9 ± 3	9 ± 3	9 ± 3
CI, L/min/m ²	2.6 ± 0.9	2.7 ± 0.9	2.5 ± 0.8
PVR, mmHg/L/min	8.9 [6.1-11.9]	8.3 [5.8-11.2]	9.5 [6.9-12.6]
mRAP, mmHg	6 [4-10]	6 [4-9]	6 [4-10]
SvO ₂ , %	62 ± 10	63 ± 11	63 ± 9
Cardiac magnetic resonance			
RV EDV index, ml/m ²	82 ± 22	83 ± 21	82 ± 20
RV ESV index, ml/m ²	54 ± 21	53 ± 20	53 ± 19
RV ejection fraction, %	37 ± 12	38 ± 12	36 ± 11
RV mass index, g/m ²	49 ± 16	50 ± 15	50 ± 15
Pressure-volume analysis			
Ees, mmHg/ml	0.48 [0.35-0.77]	0.47 [0.34-0.73]	0.51 [0.38-0.82]
Ea, mmHg/ml	1.57 [1.14-2.11]	1.52 [1.11-2.05]	1.69 [1.23-2.15]
Ees/Ea	0.35 [0.24-0.54]	0.31 [0.25-0.54]	0.31 [0.23-0.52]
Eed, mmHg/ml	0.63 [0.40-0.99]	0.64 [0.42-1.02]	0.64 [0.42-1.02]
Strain and RV filling			
RA reservoir strain, %	14.3 ± 5.1	15.2 ± 5.2	14.5 ± 5.0
RA passive strain, %*	-5.6 ± 3.4	-5.8 ± 3.5	-5.8 ± 3.6
RA active strain, %	-9.0 ± 4.0	-9.7 ± 4.1	-9.1 ± 3.8
RV global longitudinal strain, %	-15.1 ± 4.7	-15.5 ± 4.7	-15.0 ± 4.9
RV passive strain, %	7.3 ± 3.6	7.6 ± 4.0	7.4 ± 3.7
RV active strain, %	8.0 ± 3.5	8.0 ± 3.7	7.9 ± 3.7
RV passive filling volume, ml	33 ± 19	36 ± 20	34 ± 19
RV active filling volume, ml	22 ± 17	22 ± 14	20 ± 16

There are no differences between baseline patients with 30 CMR phases or patients with follow-up measurements and the overall cohort. PAH indicates pulmonary arterial hypertension; CMR, cardiac magnetic resonance; NYHA, New York Heart Association functional class; NTproBNP, Nterminal pro brain natriuretic peptide; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; mRAP, mean right atrial pressure; SvO₂, mixed venous oxygen saturation; EDV, end-diastolic volume; ESV, end-systolic volume; RV, right ventricular; Ees, end-systolic elastance; Ea, arterial elastance; Eed, end-diastolic elastance; RA, right atrial

Supplemental table 2: Longitudinal strain, right atrial emptying and right ventricular filling

Variable	Control (n=31)	PAH patients (n=97)	p-Value
RA reservoir strain, %	19.1 ± 4.3	14.3 ± 5.1	< 0.001
RA passive strain, %	-12.4 ± 3.3	-5.6 ± 3.4	< 0.001
RA active strain, %	-7.5 ± 2.8	-9.0 ± 4.0	0.019
RV GLS, %	-23.6 ± 3.6	-15.1 ± 4.7	< 0.001
RV passive strain, %	15.1 ± 3.2	7.3 ± 3.6	< 0.001
RV active strain, %	8.9 ± 3.2	8.0 ± 3.5	0.16
RA passive emptying volume, ml	25 ± 9	23 ± 10	0.39
RA active emptying volume, ml	22 ± 8	38 ± 14	< 0.001
RV passive filling volume, ml	48 ± 19	33 ± 19	< 0.001
RV active filling volume, ml	24 ± 13	22 ± 17	0.38
Vena cava backflow, ml	-2 ± 14	17 ± 19	< 0.001

Data presented as mean ± SD. PAH indicates pulmonary arterial hypertension; RA, right atrial; RV, right ventricular; GLS, global longitudinal strain.

Supplemental table 3. Change in hemodynamics and CMR variables after treatment

	Baseline PAH (n=62)	Follow-up PAH (n=62)	p-Value
ERA	na	10 (16%)	
PDE5i	na	6 (10%)	
ERA + PDE5i	na	39 (63%)	
Triple therapy	na	4 (6%)	
Calcium channel blocker	na	3 (5%)	
Right heart catheterization			
Heart rate, bpm	79 ± 13	75 ± 11	0.015
mPAP, mmHg	53 ± 14	43 ± 12	< 0.001
PAWP, mmHg	9 ± 3	9 ± 3	0.187
CI, L/min/m ²	2.5 ± 0.8	3.2 ± 0.9	< 0.001
PVR, mmHg/L/min	9.6 [6.8-12.9]	4.7 [3.7-7.1]	< 0.001*
mRAP, mmHg	6 [4-11]	6 [4-8]	0.001
SvO ₂ , %	63 ± 9	70 ± 7	< 0.001
E _{es} , mmHg/ml (n=53)	0.48 [0.37-0.82]	0.41 [0.21-0.75]	<0.053*
E _a , mmHg/ml (n=58)	1.73 [1.23-2.16]	0.92 [0.76-1.46]	<0.001*
E _{es} /E _a (n=53)	0.31 [0.23-0.48]	0.42 [0.22-0.66]	0.32*
E _{ed} , mmHg/ml (n=53)	0.64 [0.38-0.95]	0.39 [0.28-0.71]	0.004*
Cardiac magnetic resonance			
RVEDV index, ml/m ²	82 ± 20	76 ± 19	0.003
RVESV index, ml/m ²	54 ± 19	42 ± 17	< 0.001
Stroke volume index, ml/m ²	28 ± 9	34 ± 9	< 0.001
RVEF, %	36 ± 11	47 ± 11	< 0.001
RV mass index, g/m ²	50 ± 15	42 ± 12	< 0.001
RA max volume index, ml/m ²	74 [64-89]	67 [56-79]	0.002*
RA passive emptying, ml	22.9 ± 9.1	21.1 ± 9.9	0.13
RA active emptying, ml	40.0 ± 11.4	35.9 ± 12.9	0.009
RV passive filling, ml	34.1 ± 19.1	37.9 ± 21.2	0.10
RV active filling, ml	19.7 ± 15.5	27.2 ± 14.9	0.002
Vena cava backflow, ml	20.1 ± 15.5	8.0 ± 17.1	<0.001

Treatment modalities consisted of mono-, double- or triple therapy or calcium channel blocker. PAH indicates pulmonary arterial hypertension; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase-5 inhibitor; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; mRAP, mean right atrial pressure; SvO₂, mixed venous oxygen saturation; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular endsystolic volume; RVEF, right ventricular ejection fraction; RV, right ventricular.

*paired t test after logarithmic transformation

Supplemental figure 1. Flowchart of patient selection

PAH indicates pulmonary arterial hypertension; RHC, right heart catheterization; CMR, cardiac magnetic resonance imaging; FU, follow-up; RV, right ventricular; Eed, end-diastolic elastance.

Supplemental figure 2. Correlations of RA volume determined on the four-chamber view or transverse stack slices
 RA volumes were lower when determined on the four-chamber view, but correlated excellent with the volumes determined on a stack of slices. RA indicates right atrium; 4CH, four-chamber

A) Right atrial strain

B) Right ventricular strain

Supplemental figure 3. Quantification of RA and RV strain in the three cardiac phases

A) RA strain (mean $\pm$ SEM) divided in three phases. B) RV strain (mean $\pm$ SEM) divided in three phases. p values represent ANOVA test. RA indicates right atrial; RV, right ventricular; ANOVA, analysis of variance; Eed, end-diastolic elastance.

*p < 0.05 vs control

#p < 0.05 vs low Eed

A) Right atrial strain

B) Right ventricular strain

Supplementalfigure4.RA and RV strain inpatients with low vs high Ees/Ea

A) RA strain (mean $\pm$ SEM) divided in three phases. B) RV strain (mean $\pm$ SEM) divided in three phases. p values represent ANOVA test. RA indicates right atrial; RV, right ventricular; ANOVA, analysis of variance; Ees, end-systolic elastance; Ea, arterial elastance.

*p < 0.05 vs control

†p < 0.05 vs low Ees/Ea

Supplementalfigure 5. RA emptying, RV filling and vena cava backflow in patients with low vs high Ees/Ea

Data are presented as mean $\pm$ SEM. p-values were calculated with Tukey's post-hoc analysis and family-wise correction for multiple testing. Patients were divided based on the median Ees/Ea (0.35) in a low and high Ees/Ea group. A) RA passive emptying is similar in all groups. B) RA active emptying is much higher in all patients. C) RA stroke work was estimated by multiplying RA active emptying with the end-diastolic pressure. D) RV passive filling is strongly reduced in all patients. E) RV active filling does not differ between patients with low and high Ees/Ea. F) Vena cava backflow represents the difference between RA active emptying and RV active filling. RA indicates right atrial; RV, right ventricular; Ees, end-systolic elastance; Ea, arterial elastance.

Supplemental figure 6. Comparison of RA emptying, RV filling and backflow in idiopathic/hereditary PAH and CTD-PAH with low or high Eed

RV active filling and vena cava backflow are lower in CTD-PAH patients, but show the same distribution with high vena cava backflow in high Eed patients. RA indicates right atrial; CTD, connective tissue disease; PAH, pulmonary arterial hypertension; RV, right ventricular

*p<0.05 vs control