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

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Despite increased RA stroke work in PAH patients, severe RV diastolic stiffness is associated with lower RV active filling and high vena cava backflow. Upon treatment, severe RV diastolic stiffness and RA–RV interaction improve in only ~50% of patients. https://bit.ly/31qai5Z

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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 PAH patients with low or high end-diastolic elastance (E_{ed}) (n=94) were compared with controls (n=31). Treatment response was evaluated in 62 patients. RV and RA longitudinal strain, RA emptying and RV filling were determined and diastole was divided into a passive and active phase. Vena cava backflow was calculated as RA active emptying−RV active filling and 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 patients with high E_{ed}, resulting in higher vena cava backflow. Upon treatment, E_{ed} was reduced in ~50% of the patients with high E_{ed}, 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 with 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 patients with high baseline E_{ed}, diastolic stiffness remained high, despite treatment. A reduction in E_{ed} 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, given that 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 because 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: 1) Are changes in RA function a consequence of RV diastolic stiffness or do they reflect impaired RA contraction? 2) 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

Patients with idiopathic, hereditary or connective tissue disease (CTD)-associated PAH diagnosed between December 2002 and May 2019 at a tertiary referral centre for PAH (Amsterdam University Medical Center, The Netherlands) were evaluated for eligibility (supplementary figure S1). Patients (n=178) had undergone cardiac magnetic resonance imaging (CMR) within 2 weeks of right heart catheterisation 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 94 eligible patients, who were divided into 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^{-1} closely corresponds to the optimal cut-off for survival prediction [5]. Subjects who had dyspnoea 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 62 patients after a median follow-up of 11 months (interquartile range 6–13 months). Owing 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 catheterisation was performed using a balloon-tipped flow-directed 7.5 F triple lumen Swan-Ganz catheter (Edwards Lifesciences LLC, Irvine, CA, USA). Cardiac output was measured by direct Fick or thermodilution method. All pressure curve analyses were performed by one researcher (JNW). End-systolic elastance (E_{es}) in PAH patients was derived according to the single-beat method [8], using systolic pulmonary artery pressure 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 isovolumic pressures were averaged over >10 heartbeats. Beats with significant catheter artefacts 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 start-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 by RV end-diastolic pressure (unit: mL·mmHg^{-1}).

Cardiac magnetic resonance

All images were acquired on a 1.5 T Avanto or Sonata scanner equipped with a six-element phased array coil (Siemens Medical Solutions, Erlangen, Germany). Images were analysed 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 correlated excellently with the volume determined on a transverse stack of slices in 42 patients with pulmonary hypertension (supplementary figure S2). 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, and 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 left ventricular from RV stroke volume [14].

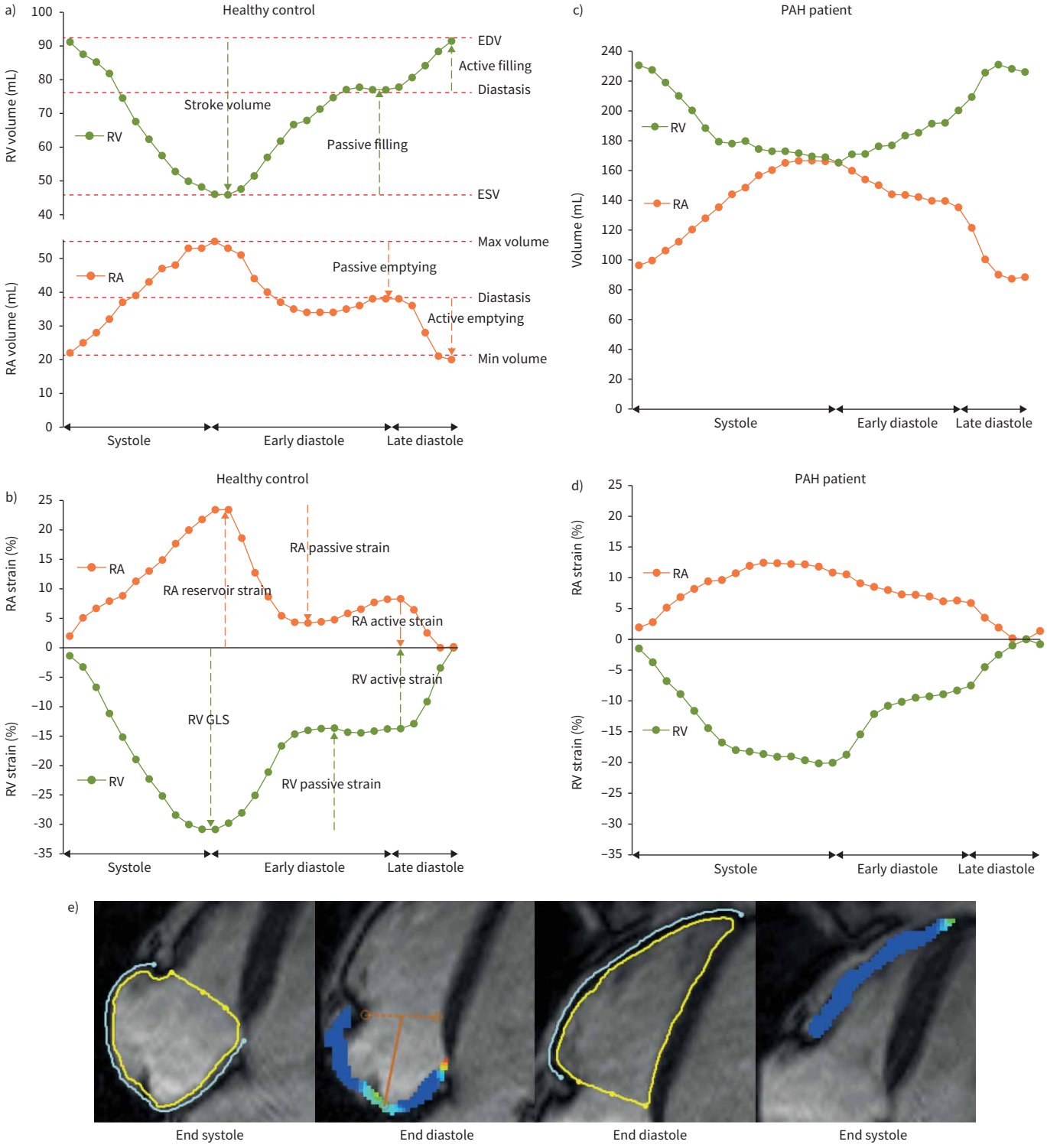

FIGURE 1 Example of right atrial (RA) and right ventricular (RV) volume and strain in a healthy control and a patient with pulmonary arterial hypertension (PAH). a, b) RA and RV volume and strain throughout the cardiac cycle in a healthy control. c, d) RA and RV volume and strain throughout the cardiac cycle in a PAH patient. e) RA endo- and epicardial contours drawn at end systole and maximal negative strain (global longitudinal strain (GLS)) at end diastole (left panels). RV contours were drawn at end diastole, while maximal negative strain (GLS) was reached at end systole (right panels). EDV: end-diastolic volume; ESV: end-systolic volume.

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, RA 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±SD or median (interquartile range) depending on distribution. Categorical variables are reported as n (%). Non-normally distributed variables were normalised by logarithmic transformation. N-terminal pro-brain natriuretic peptide could not be normalised and was compared with a Wilcoxon's test. Comparison of multiple groups was done with 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) and

TABLE 1 Patient characteristics

Variable	Control	PAH low E_{ed}	PAH high E_{ed}	p-value
Subjects, n	31	47	47	
Age, years	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^{-1} (n=121)	38 (19.5–58.5)	443 (233–1366)*	2052 (1100–3281)*,#	<0.001
Catheterisation				
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^{-1}·m^{-2}	3.6±1.0	2.7±0.8*	2.4±0.9*	<0.001
PVR, mmHg·L^{-1}·min^{-1}	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
S_{vO_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 maximum volume index, mL·m^{-2}	48 (43–56)	68 (57–89)*	78 (62–95)*	<0.001
TR volume, mL No/<30 mL/30–59 mL/>59 mL	24/7/0/0	27/19/1/0	26/20/1/0	0.38
Pressure-volume analysis				
E_{es}, mmHg·mL^{-1} (n=119)	NA	0.45 (0.34–0.74)*	0.52 (0.38–0.83)*	<0.001
E_a, mmHg·mL^{-1} (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^{-1} (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 (interquartile range) when data were not normally distributed. PAH: pulmonary arterial hypertension; E_{ed}: end-diastolic elastance; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-brain natriuretic peptide; mPAP: mean pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; mRAP: mean right atrial pressure; RVEDP: right ventricular end-diastolic pressure; S_{vO_2}: 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. *: p<0.05 *versus* control; #: p<0.05 *versus* low E_{ed}.

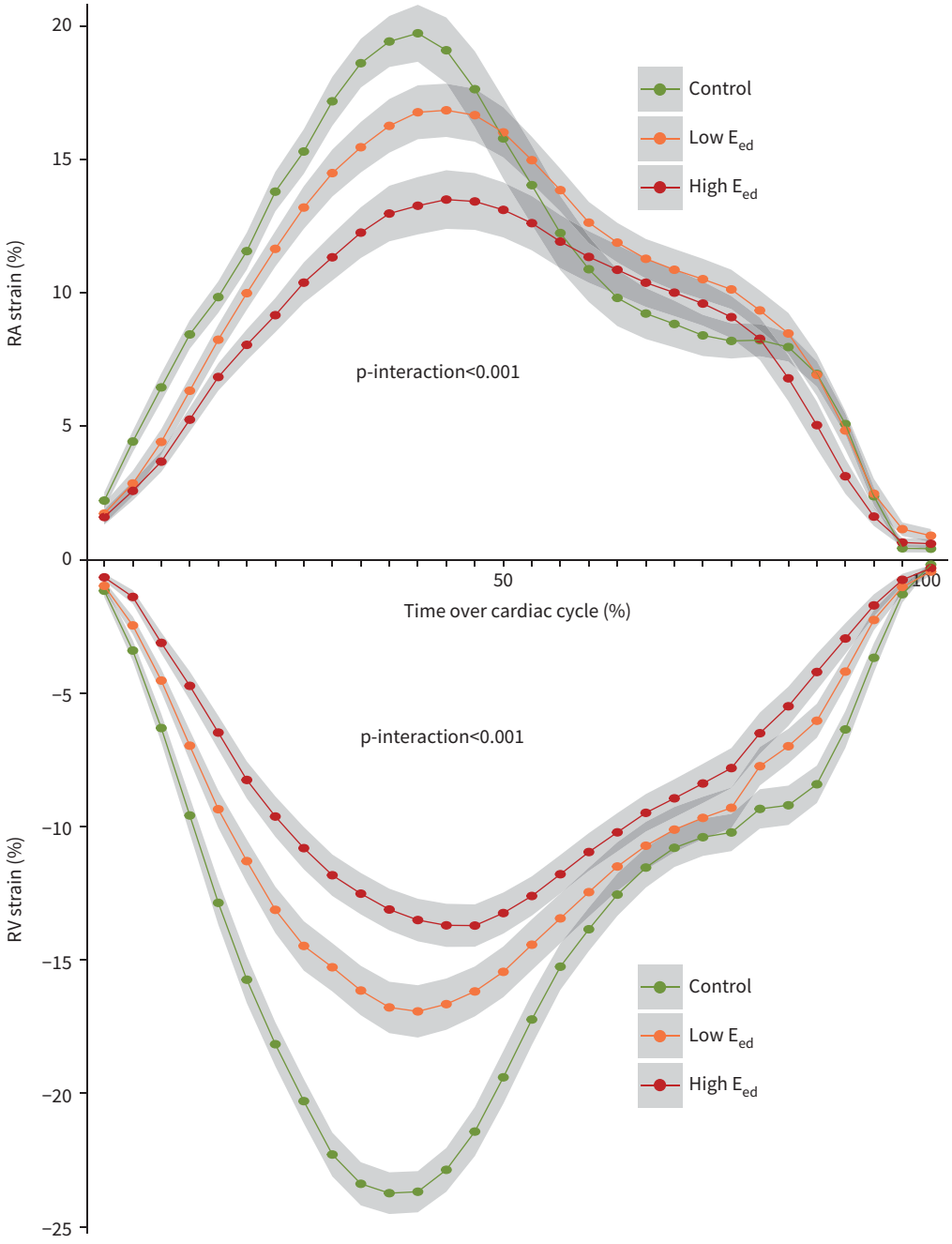

FIGURE 2 Mean right atrial (RA) and right ventricular (RV) longitudinal strain curves during one cardiac cycle. Control, n=20; low end-diastolic elastance (E_{ed}) (<0.63 mmHg·mL^{-1}), n=28; high E_{ed} (>0.63 mmHg·mL^{-1}), n=28. Shaded region represents 95% CI. p-interaction represents the interaction between patient group and cardiac magnetic resonance imaging phase assessed by repeated measures ANOVA.

visualisation of data with ggplot2 (https://cran.r-project.org/package=ggplot2). To visualise 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 of the full cohort (supplementary table S1). Furthermore, patients with follow-up (n=62) were representative of the full cohort (supplementary table S1). Patients with baseline E_{ed} >0.63 mmHg·mL^{-1} were divided into two groups at follow-up based on the improvement of E_{ed} to <0.63 mmHg·mL^{-1}. About 50% of the patients had a large and significant improvement in E_{ed} from 0.92 mmHg·mL^{-1} (0.88–1.15 mmHg·mL^{-1}) to

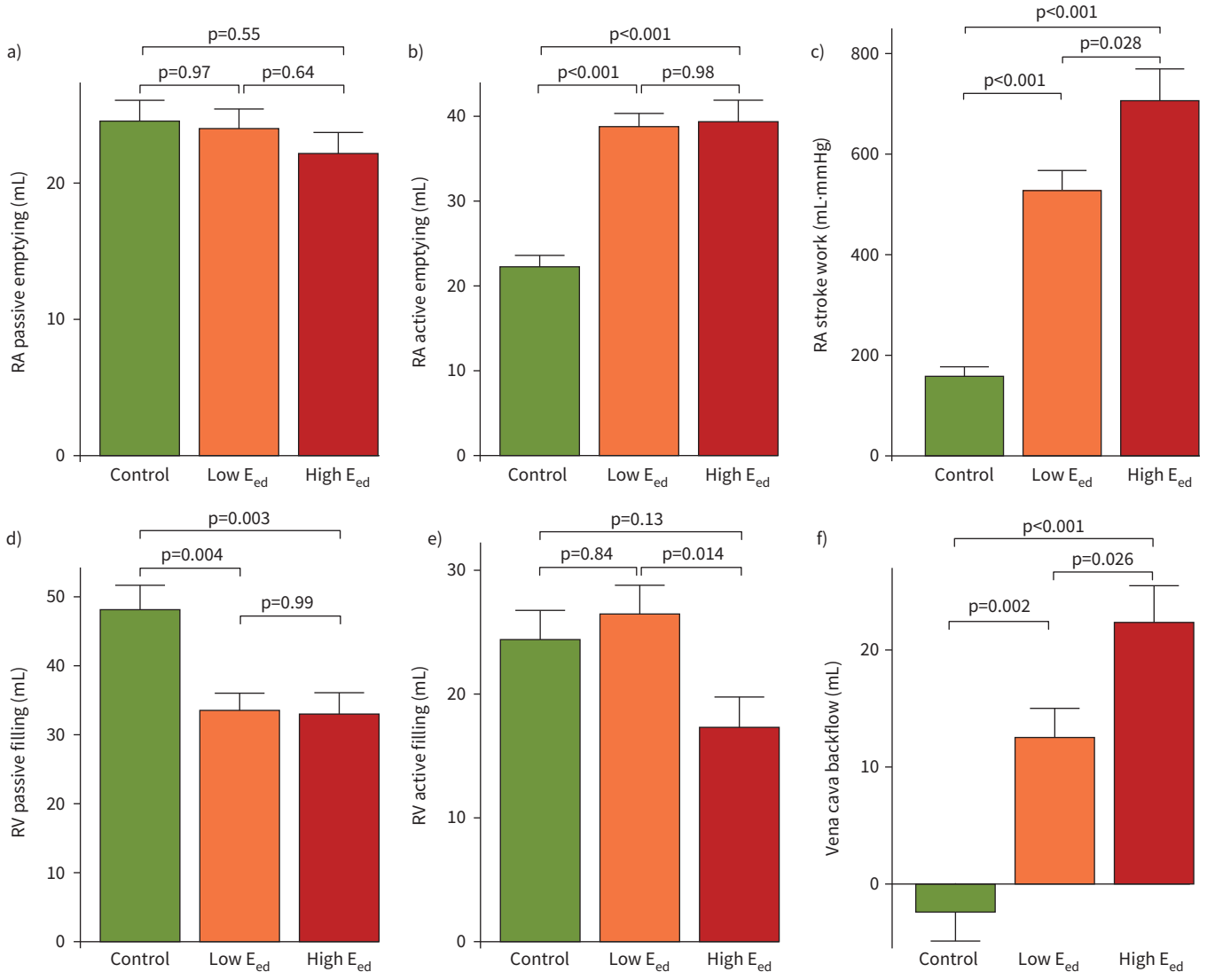

FIGURE 3 Right atrial (RA) emptying, right ventricular (RV) filling and vena cava backflow. Data are presented as mean±SEM. p-values were calculated with Tukey's *post hoc* analysis and family-wise correction for multiple testing. a) RA passive emptying was similar in all groups. b) RA active emptying was much higher in all patients with pulmonary arterial hypertension. 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 patients with low end-diastolic elastance (E_{ed}) (<0.63 mmHg·mL^{-1}), but lower in patients with high E_{ed} (>0.63 mmHg·mL^{-1}). f) Vena cava backflow represents the difference between RA active emptying and RV active filling.

0.37 mmHg·mL^{-1} (0.31–0.46 mmHg·mL^{-1}) (p<0.001). In the remaining patients, E_{ed} did not change. Changes in haemodynamic 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 patients with idiopathic PAH, nine with hereditary PAH and 25 with CTD-PAH. Patients were 58±18 years old and predominantly female (65%). On average, the E_{ed} in patients (0.70±0.41 mmHg·mL^{-1}) was 3.5 times that of controls (0.20±0.08 mmHg·mL^{-1}), indicating significant RV diastolic stiffness. Patients were divided into low E_{ed} and high E_{ed} groups, based on the median value of 0.63 mmHg·mL^{-1}. A comparison of baseline variables in both patient groups and controls is given in table 1.

RV and RA passive strain reduced in patients with high E_{ed}, 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 patients with high E_{ed} were strongly reduced in comparison to those with low E_{ed} (supplementary figure S3). There were no differences in RA active strain. RV global longitudinal strain was slightly lower in patients with high E_{ed}. 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 supplementary table S2. In addition to the differences between patients with low and high E_{ed}, RA passive strain was lower in patients with low E_{es}/E_a than in those with high E_{es}/E_a (supplementary figure S4). There was no difference in RA active strain. RV global longitudinal and passive strain were slightly lower in patients with low E_{es}/E_a, 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 patients with high E_{ed}

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 that in controls in patients with both low and high E_{ed}. RA stroke work was approximately three-fold greater in patients with low E_{ed} and four-fold greater in patients with high E_{ed}, compared to controls (figure 3c). RV passive filling was markedly reduced in all PAH patients. RV active filling, by contrast, was preserved in patients with low E_{ed}, but reduced in those with high E_{ed}. Vena cava backflow was negligible in controls, but present in patients with low E_{ed}. In patients with high E_{ed}, the backflow was almost twice that in patients with low E_{ed}. 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 patients with low and high E_{es}/E_a (supplementary figure S5). Vena cava backflow was lower in CTD-PAH patients, but a similar pattern was observed for E_{ed} groups (supplementary figure S6).

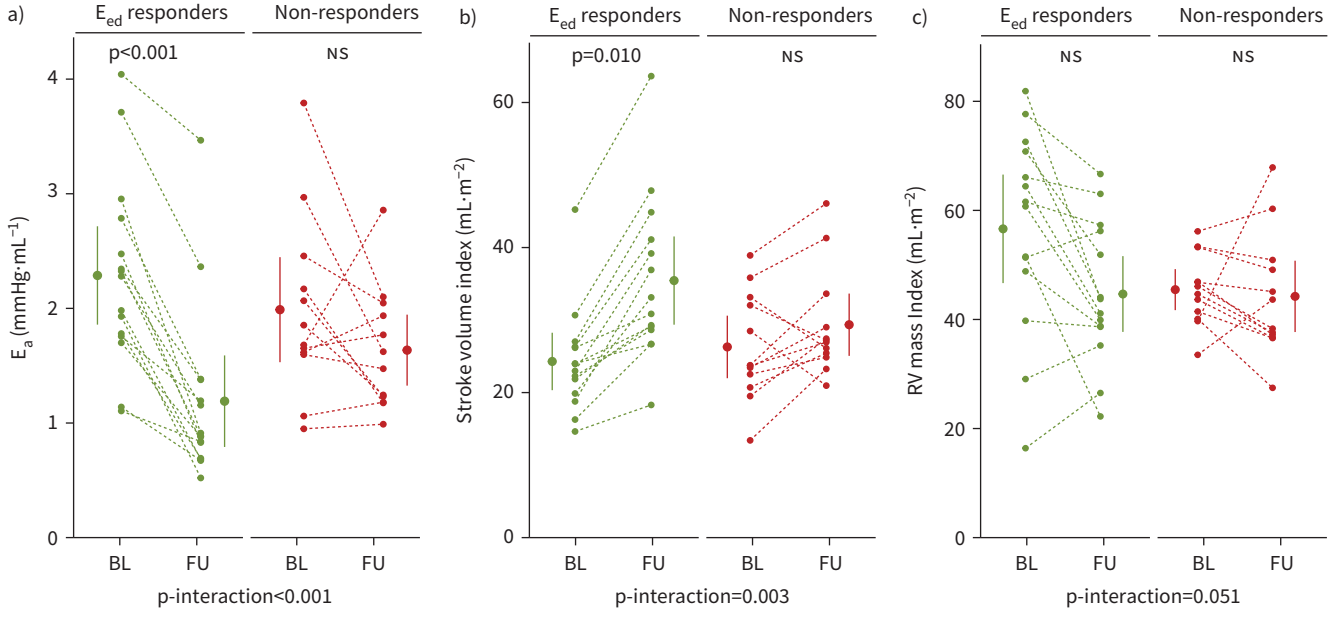

FIGURE 4 Changes in afterload, stroke volume and right ventricular (RV) mass after the start of treatment. Patients with high baseline end-diastolic elastance (E_{ed}) either improved to <0.63 mmHg·mL^{-1} (green; E_{ed} responders) or remained high at >0.63 mmHg·mL^{-1} (red; non-responders). Dots and whiskers represent mean±SEM. p-values were determined through pairwise t-test with Bonferroni correction. p-interaction values represent repeated measures ANOVA. a) Arterial elastance (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 E_{ed} responders. BL: baseline; FU: follow-up; NS: nonsignificant.

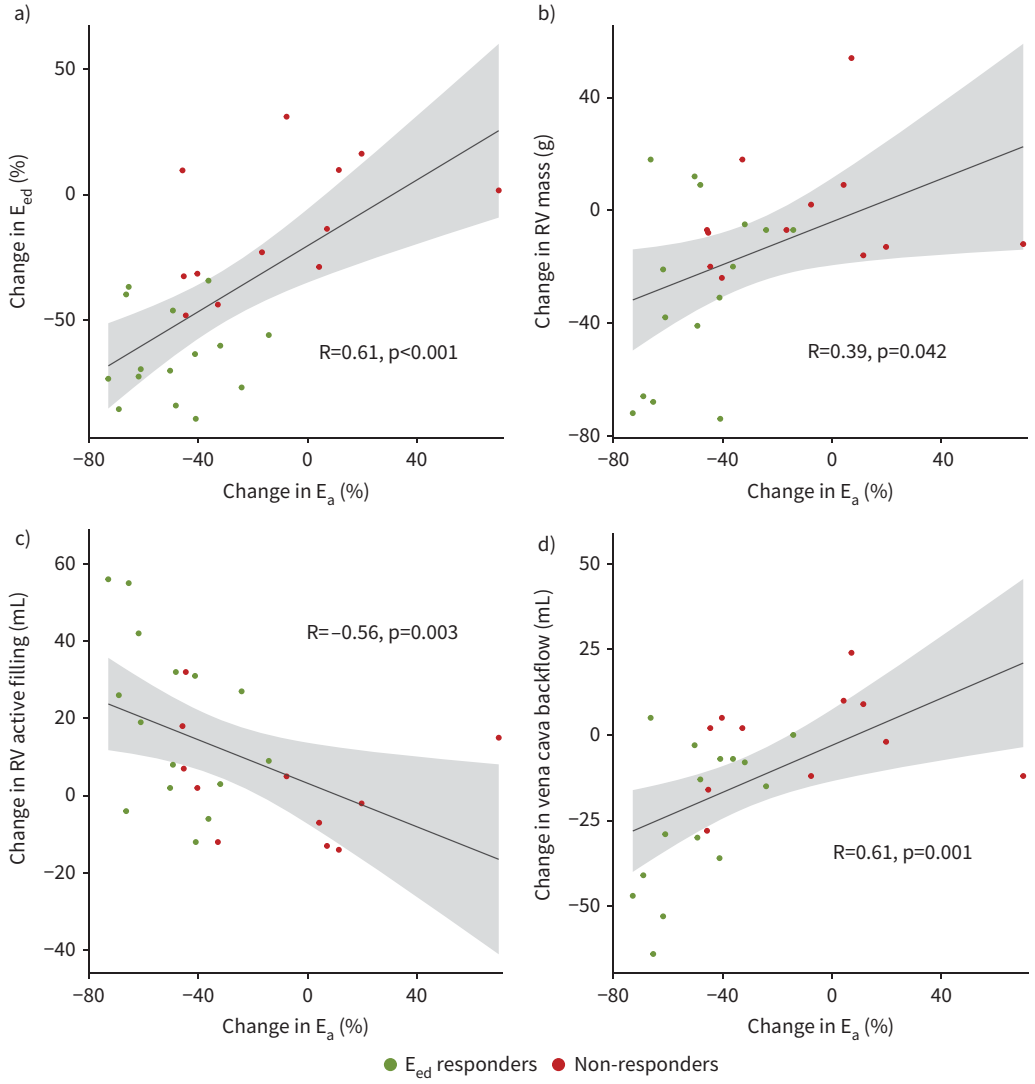

FIGURE 5 Correlations between change in afterload (arterial elastance (E_a)) at follow-up and several right ventricular (RV) parameters. a) End-diastolic elastance (E_{ed}), b) RV mass, c) RV active filling and d) vena cava backflow. R-values represent Spearman correlations.

Treatment response

Almost a third of patients (31%) received monotherapy, 63% received oral combination therapy and 6% received triple therapy. The changes in haemodynamic and CMR parameters for the PAH cohort are shown in supplementary table S3. As expected, pulmonary vascular resistance dropped from 9.6 mmHg·L^{-1}·min^{-1} (6.8–12.9 mmHg·L^{-1}·min^{-1}) to 4.7 mmHg·L^{-1}·min^{-1} (3.7–7.1 mmHg·L^{-1}·min^{-1}) (p<0.001), mean pulmonary artery pressure decreased by 10 mmHg (95% CI 6–13 mmHg, p<0.001), cardiac index increased by 0.7 L·min^{-1} (95% CI 0.5–0.9 L·min^{-1}, p<0.001) and RV stroke volume index increased by 6 mL (95% CI 4–8 mL, p<0.001). The E_{ed} decreased by almost 40%, but did not normalise. 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 ~50% of patients

To identify which factors are associated with improvement of severe RV diastolic stiffness, we classified patients with a high baseline E_{ed} as responders when they converted to a low E_{ed} (<0.63 mmHg·mL^{-1}) 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 E_a (reduction of 48±17% in responders *versus* 13±34% in non-E_{ed} responders, p-interaction<0.001), greater improvement

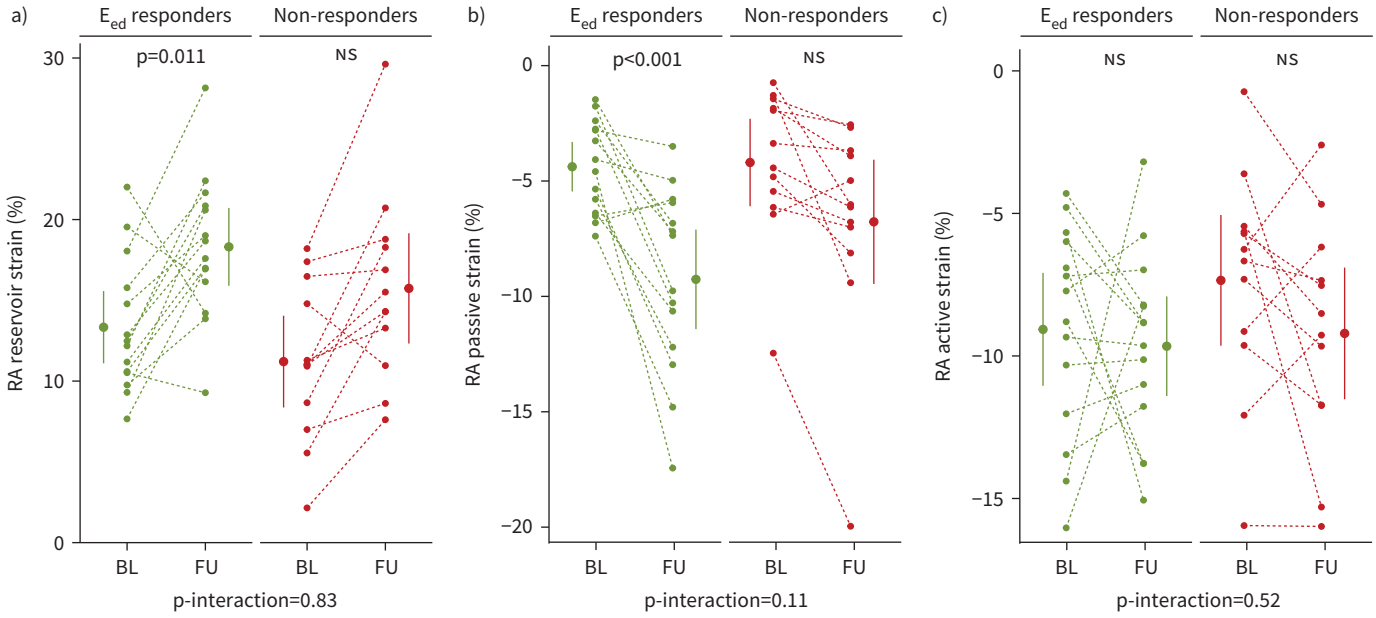

FIGURE 6 Changes in right atrial (RA) reservoir, passive and active strain after the start of treatment. Patients with high baseline end-diastolic elastance (E_{ed}) either improved to <0.63 mmHg·mL^{-1} (green; E_{ed} responders) or remained high at >0.63 mmHg·mL^{-1} (red; non-responders). Dots and whiskers represent mean±SEM. p-values were determined through pairwise t-test with Bonferroni correction. p-interaction values represent repeated measures ANOVA. 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-responders. c) RA active strain did not change in either of the groups. BL: baseline; FU: follow-up; NS: nonsignificant.

in RV stroke volume index (47±25% *versus* 16±28%, p-interaction=0.003) and greater reduction in RV mass (15±31% *versus* 2±28%, p-interaction=0.051) (figure 4). Furthermore, the change in E_a 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 mL, p=0.003). This was associated with a normalisation of vena cava backflow (figure 7) while non-E_{ed} responders had no improvement in RV active filling or vena cava backflow. In summary, ~50% of the patients with a high E_{ed} at baseline had a favourable response. RA active emptying became more efficient (increased forward flow, decreased backward flow) as 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 the following: 1) RA function is associated with RV diastolic stiffness, with RV passive filling reduced in all patients while increased RA stroke work and active emptying preserve RV active filling in patients with mild, but not severe, RV diastolic stiffness. The surplus of RA active emptying results in significant vena cava backflow. 2) Approximately 50% of the patients with severe RV diastolic stiffness have a relevant reduction in RV diastolic stiffness in response to treatment, which coincides 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 normalised.

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

TABLE 2 Treatment response of patients with high E_{ed}, categorised as patients with improvement of E_{ed} and patients in whom E_{ed} remained high

Variable	E_{ed} improved (n=14)		E_{ed} stable >0.63 (n=12)		p-interaction
	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
Catheterisation					
mPAP, mmHg	58±20	43±17	53±8	49±10	0.052
Cardiac index, $L{\cdot}min^{-1}{\cdot}m^{-2}$	2.1±0.7	3.1±0.7**	2.3±0.7	2.4±0.7	0.020
PVR, $mmHg{\cdot}L^{-1}{\cdot}min^{-1}$	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
RVEDP, mmHg	17.4±9.1	11.1±5.1	18.1±5.7	17.4±4.4	0.08
CMR					
RVEDV index, $mL{\cdot}m^{-2}$	82±24	77±23	74±19	70±24	0.89
RVESV index, $mL{\cdot}m^{-2}$	57±22	42±16	47±17	41±21	0.10
SV index, $mL{\cdot}m^{-2}$	24±7	35±11**	26±7	29±7	0.003
RVEF, %	31±9	47±10**	37±12	44±12	0.014
RV mass index, $g{\cdot}m^{-2}$	57±19	45±13	46±7	44±11	0.051
RA maximum volume index, $mL{\cdot}m^{-2}$	76 (60–86)	63 (57–71)	80 (72–97)	75 (64–106)	0.26
Pressure–volume					
E_{es}, $mmHg{\cdot}mL^{-1}$	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, $mmHg{\cdot}mL^{-1}$	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}, $mmHg{\cdot}mL^{-1}$	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 (interquartile range) when data were not normally distributed. p-values represent the interaction of time and group as determined with repeated measures ANOVA. E_{ed}: 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; RVEDP: right ventricular 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; RV: right ventricular; 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.

studies [17–21], which showed decreased RA reservoir and passive strain, while active strain was either preserved or increased. RA passive emptying was also lower in PAH, while active emptying was higher [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. A relation between RV diastolic dysfunction and RA function has recently 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 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 was in accordance with RA strain, suggesting a strong interaction between the ventricle and atrium. Furthermore, both RV and RA strain patterns were more severely affected in patients with high E_{ed} than low E_{ed}.

Atrial contraction compensates for loss of passive RV filling

Despite high RV end-diastolic pressure, RA stroke work in PAH was high enough (3–4× that of controls) to induce increased RA active emptying. RV passive filling was strongly reduced, while active filling was

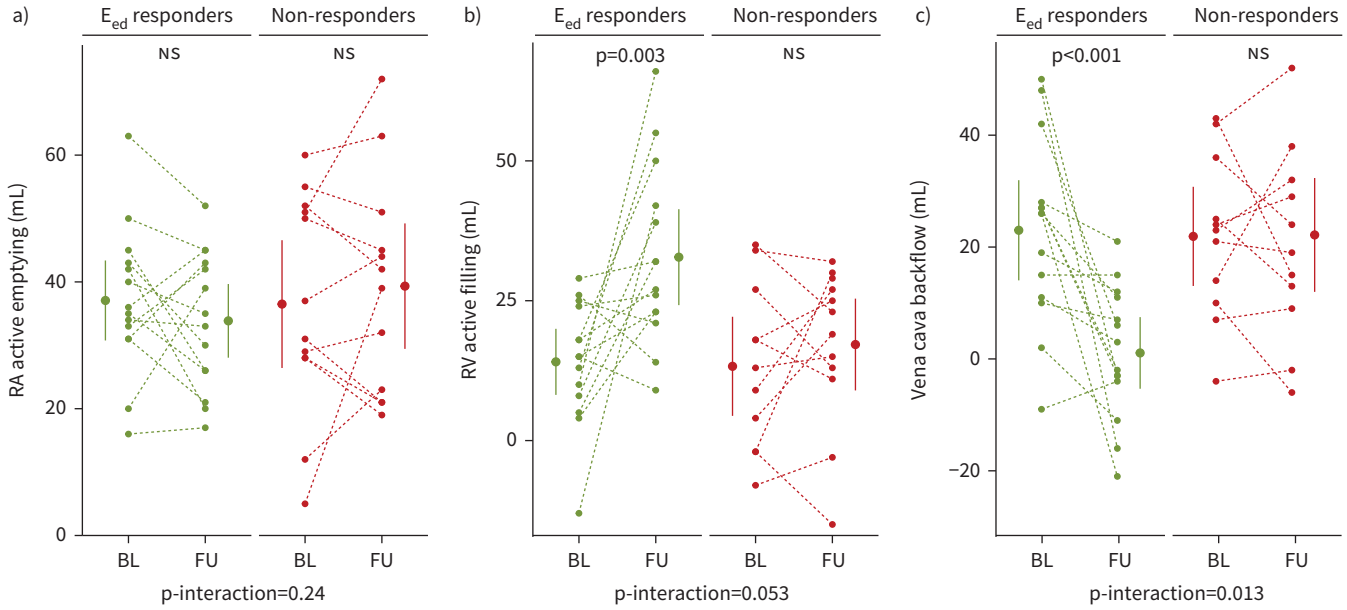

FIGURE 7 Changes in right atrial (RA) active emptying, right ventricular (RV) active filling and backflow after the start of treatment. Patients with high baseline end-diastolic elastance (E_{ed}) either improved to <0.63 mmHg·mL^{-1} (green; E_{ed} responders) or remained high at >0.63 mmHg·mL^{-1} (red; non-responders). Dots and whiskers represent mean±SEM. p-values were determined through pairwise t-test with Bonferroni correction. p-interaction values represent repeated measures ANOVA. a) RA active emptying did not change in either of the groups. b) RV active filling improved significantly in E_{ed} responders, while there was no change in non-responders. c) Vena cava backflow normalised in E_{ed} responders, while it did not change in non-responders. BL: baseline; FU: follow-up; NS: nonsignificant.

preserved in patients with low E_{ed} but not high E_{ed}. 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, patients with severe RV diastolic stiffness have high vena cava backflow, which may induce congestive hepatopathy or cardiorenal syndrome.

Changes in E_{ed} in relation to RV filling

After initiating treatment, we saw a relevant improvement of RV diastolic stiffness in ~50% of the 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 because it may induce a decrease in RV mass. The improvement in E_{ed} may partly be a consequence of decreased RV mass, as 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} (~50–90%), RV active filling improved and backflow to the caval veins diminished. The other ~50% of the patients had an unfavourable response (figure 8c). Their afterload and RV stroke volume only showed a small, nonsignificant 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-centre 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. Because a stack of images

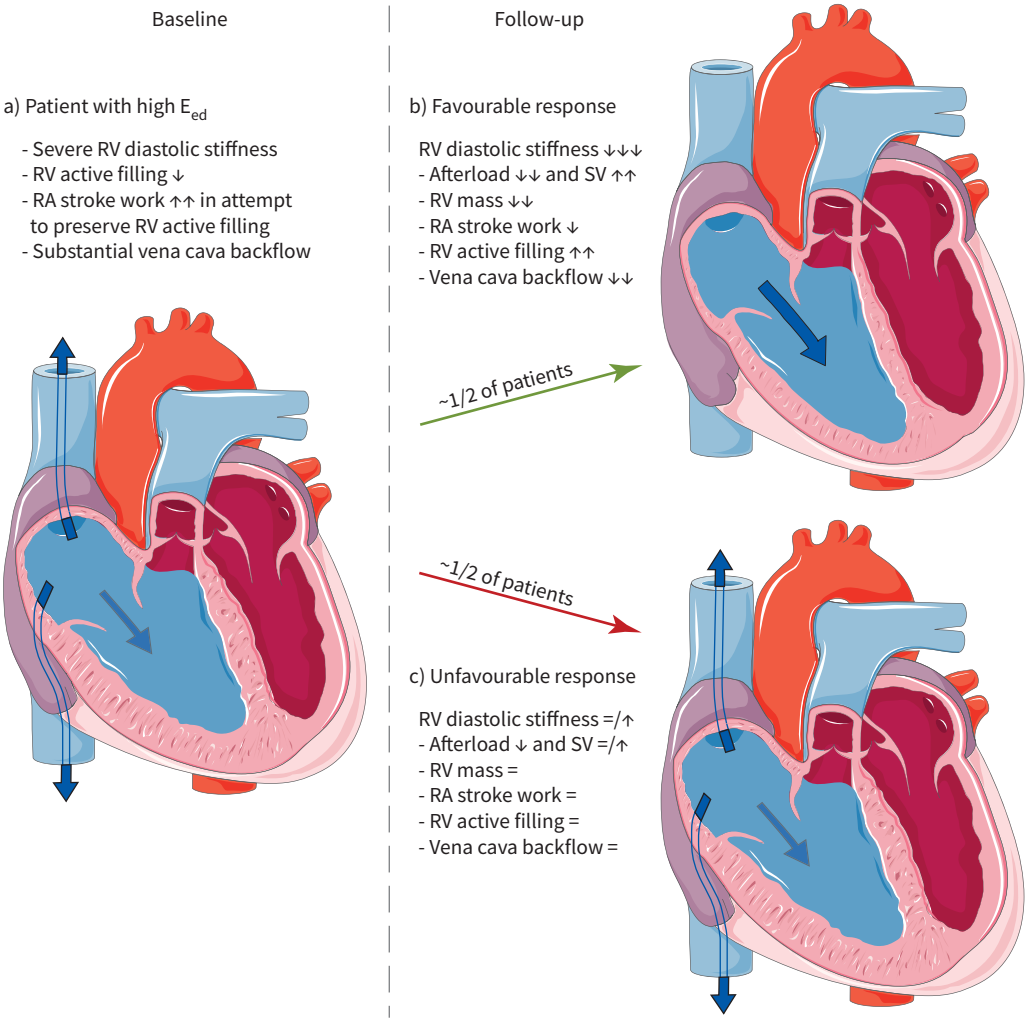

FIGURE 8 Treatment response in patients with severe right ventricular (RV) diastolic stiffness. a) In pulmonary arterial hypertension (PAH) patients with severe RV diastolic stiffness, RV active filling was reduced even though right atrial (RA) stroke work was enhanced. Consequently, there was substantial backflow to the caval veins. b) Approximately 50% of the patients showed a favourable response. RV afterload was lowered with increase in stroke volume (SV). RV mass decreased with a corresponding decrease in RV diastolic stiffness. RV active filling improved tremendously and vena cava backflow normalised. In other words, with improvement of RV compliance, RA efficiency improved. c) Approximately 50% of the 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.

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 volume, we were able to correct for this by measuring the difference in a set of patients for whom we did have a stack of images through the atria. RA volumes may have been influenced by TR, but none of the patients had severe TR and the prevalence of mild and moderate TR was similar between 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, because we compared treatment responders with non-responders (irrespective of specific PAH medication), this will not have affected 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 because E_{ed} is a relative measure, this does not lead to artefacts. Pressures were averaged over at least 10 heartbeats to minimise 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 patients with high baseline E_{ed}, 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.

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