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Balloon pulmonary angioplasty improves right atrial reservoir and conduit functions in chronic thromboembolic pulmonary hypertension

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Aims Right atrial (RA) function largely contributes to the maintenance of right ventricular (RV) function. This study investigated the effect of balloon pulmonary angioplasty (BPA) on RA functions in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) using cardiac magnetic resonance imaging (CMRI).

Methods and results CMRI and RV catheterization were performed before BPA sessions and at the follow-up periods in 29 CTEPH patients. Reservoir [RA longitudinal strain (RA-LS)], passive conduit [RA early LS rate (LSR)], and active (RA late LSR) phases were assessed by using cine CMRI and a feature-tracking algorithm. The relationships between the changes in RA functions and in brain natriuretic peptide (BNP) were evaluated in both the dilated and non-dilated RA groups. RA-LS (32.4% vs. 42.7%), RA LSR (6.3% vs. 8.3%), and RA early LSR (-2.3% vs. -4.3%) were improved after BPA, whereas no significant change was seen in RA late LSR. The changes in RA peak LS and in RA early LSR were significantly correlated with the changes in BNP (ΔRA-LS: r = -0.63, ΔRA-early LSR: r = 0.65) and pulmonary vascular resistance (PVR) (ΔRA-LS: r = -0.69, ΔRA-early LSR: r = 0.66) in the nondilated RA group.

Conclusion The RA reservoir and passive conduit functions were impaired in inoperable CTEPH, whereas RA active function was preserved. BPA markedly reversed these impaired functions. The improvements in RA reservoir and conduit functions were significantly correlated with the changes in BNP levels and PVR in CTEPH patients with normal RA sizes.

Keywords right atrial function • chronic thromboembolic pulmonary hypertension • balloon pulmonary angioplasty • cardiac magnetic resonance imaging

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4) is characterized by organized thrombotic obliteration of major vessels, resulting in right ventricular (RV) dilatation and dysfunction.[1,2] Recently, balloon pulmonary angioplasty (BPA) has been recommended as a first-line treatment option in CTEPH patients who are unsuitable for pulmonary endarterectomy.[3–5] BPA dilates multiple thrombotic lesions, dramatically reduces pulmonary arterial pressure and subsequent RV afterload in patients with inoperable CTEPH. BPA has previously been shown to markedly reduce RV afterload, resulting in improved exercise tolerance and overall survival in inoperable CTEPH patients.[6,7]

The right atrium (RA) has three functions: reservoir, passive conduit, and active contractile of these phasic functions.[8,9] With advances in cardiac magnetic resonance imaging (CMRI) and speckle-tracking

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echocardiography, it has become possible to determine reproducible assessment of RA size and function. Recent clinical studies have demonstrated that RA reservoir and active conduit functions were impaired in pulmonary arterial hypertension (PAH, WHO Group 1) independent of RA size and pressure and probably reflected right heart failure (RHF) and overload. In addition, impaired reservoir function predicted clinical worsening of pulmonary hypertension.[8–11] However, little is known about RA function in CTEPH patients. Moreover, it remains uncertain whether impaired RA function is reversible after reduction of RV afterload after a series of BPA in patients with inoperable CTEPH.

The study aim was to evaluate the effect of BPA on RA functions in patients with inoperable CTEPH using CMRI.

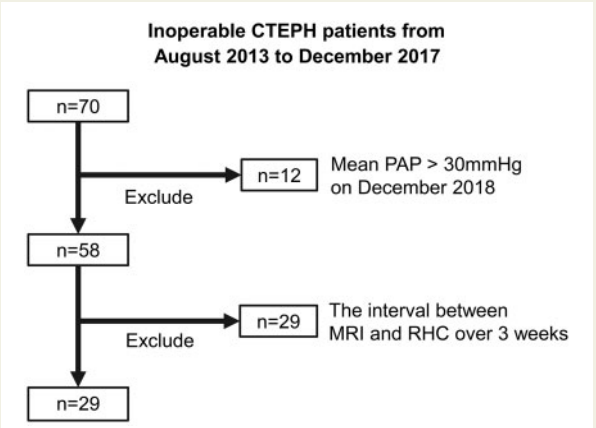

Figure 1 Patients' flow diagram. MRI, magnetic resonance imaging; PAP, pulmonary arterial pressure.

Methods

Study population

This prospective observational study was approved by the institutional review board of Kyushu university hospital (No. 29-526). In our hospital, a specialized pulmonary circulation team, including interventional cardiologists, surgeons, and radiologists, evaluate the operability for pulmonary endarterectomy. Seventy patients with a diagnosis of inoperable CTEPH from August 2013 to December 2017 were screened in this study. First, 12 patients who could not achieve mean pulmonary artery pressure (mPAP) ≤30 mmHg on December 2018 were excluded from this study. Second, 29 patients who could not undergo magnetic resonance imaging (MRI) and right heart catheterization (RHC) before first BPA within 3 weeks were excluded from this study. Consequently, 29 patients were enrolled in this study, and written informed consent was obtained from each patient (*Figure 1*). In addition, control data of CMRI was obtained from 15 healthy subjects with similar age and sex to those of the enrolled CTEPH patients.

We analysed the following demographic data: New York Heart Association functional class, 6-min walk distance (6MWD), and laboratory data, including brain natriuretic peptide (BNP).

Right heart catheterization

All CTEPH patients underwent the first MRI and RHC before the first BPA session, including RHC immediately before the first BPA. RHC provided right atrial pressure (RAP), mPAP, and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was calculated by the thermodilution method. Pulmonary vascular resistance (PVR) was calculated as (mPAP - PCWP)/CO.

Cardiac magnetic resonance imaging

Post-operative haemodynamic measurements were repeated on a day between 1 month and 6 months after the last BPA session. All CMRI examinations were performed with the patient in a supine position by using a 3.0T MRI system (Ingenia 3.0T CX; Philips Medical Systems, Best, The Netherlands) with a dS Torso coil using electrocardiographic gating. The cine-images in axial-view and four-chamber-view of 20 cardiac phases/RR intervals were obtained by steady-state free precession sequences. The imaging parameters were as follows: repetition time = 2.7 ms, echo time = 1.37 ms, flip angle = 45°, slice thickness = 8 mm, field of view = 380 mm × 435 mm, acquisition matrix = 176 × 142, and reconstruction matrix = 512 × 512.

RA strain analysis

The RA strain and strain rate (SR) were analysed by an in-house-developed off-line feature-tracking application that had been validated in previous clinical studies[12–14] following the method from a previously published paper (*Figure 2*).[8] For RA deformation, the RA endocardial border was traced at the ventricular end-diastole in the apical four-chamber view. The software then tracks points along the endocardial border throughout the cardiac cycle and derives the longitudinal strain (LS) and longitudinal SR (LSR). Three different phases of the RA strain function can be defined (*Figure 2*): (i) reservoir function, which reflects the ability of the RA to distend, is determined by the peak RA LS and LSR during RV systolic phase; (ii) conduit function, which reflects the passive emptying phase of the RA as a result of tricuspid valve opening and RV relaxation, is determined by the bottom of the RA early LSR during the RV diastolic early phase; and (iii) active contraction is determined by the bottom of the RA late LSR during the RV diastolic late phase.[8]

RA and RV volumes were measured on the basis of axial images, as previously reported.[15] End-diastolic volume and end-systolic volume were measured manually, and stroke volume and ejection fraction (EF) were calculated on a workstation (IntelliSpace Portal, Philips Healthcare, Best, Netherlands). The maximum and minimum phases of RA and end-diastolic and end-systolic phases of RV were identified visually on those images that showed the largest and smallest cavity areas.

After comparison of RA functions among before BPA, after BPA, and controls, sub-analysis was performed to assess the clinical significance of RA strain regardless of RA volume. We classified our cohort into two groups on the basis of RA size before BPA.[16] Then, we determined if there were correlations between the before and after BPA change and the BNP changes in RA functions.

To evaluate the reliability of the strain analysis, RA strain and RA SR measurements were tested for intra-observer reproducibility by having one observer perform all cardiac magnetic resonance strain analyses on 10 randomly selected patients from the before and after BPA groups (five from each) and then blindly repeating the analysis on a separate occasion. Inter-observer reproducibility was evaluated by a second observer blinded to the clinical and experimental data who performed RA strain and RA SR analyses on the same 10 patients. The intra- and inter-observer reproducibility of the strain and SR measurements were evaluated by the intra-correlation coefficient (ICC).

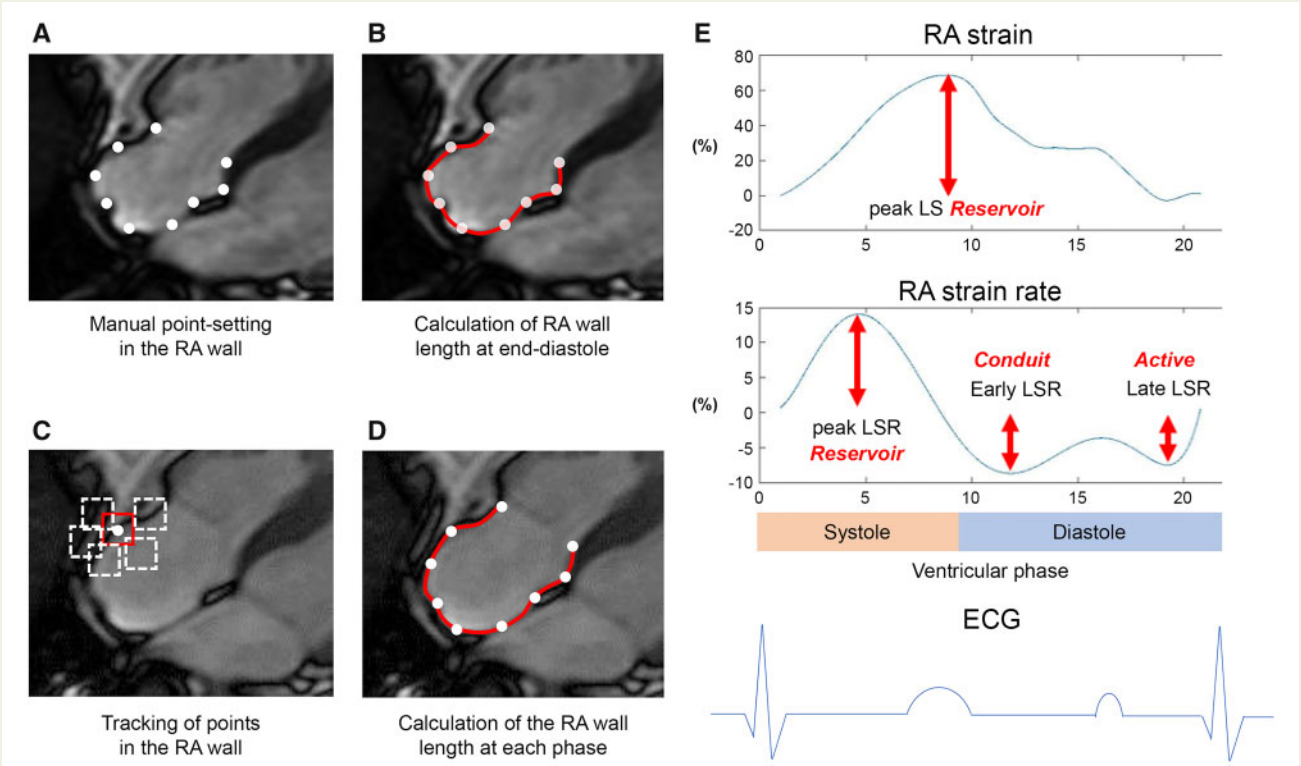

Figure 2 Semi-automatic right atrium strain analysis. (*A*) Manual point-setting (white dots) in the RA wall at end-diastole. (*B*) Calculation of RA wall length (red solid line) at end-diastole. (*C*) Tacking of points in the RA wall with the local template matching technique. The square template size and square search area are configured for 50 × 50 pixels in size. (*D*) The longitudinal lengths of RA walls through a cardiac cycle (red solid line). (*E*) Representative RA strain and strain rate with the electrocardiogram (ECG).

Statistical analysis

JMP Pro version 14.2.0 (SAS Institute Inc., NC, USA) and GraphPad Prism version 6.0 (GraphPad Software, Inc., CA, USA) were used for statistical analysis. The Shapiro–Wilk test was applied to test for normally distributed data. We performed a two-tailed paired Student's *t*-test (normally distributed variables) or the Mann–Whitney U test (non-parametric variables) to compare pre- and post-operative haemodynamic measurements. The before BPA, after BPA, and control RA parameters were compared by using one-way repeated analysis of variance with the Tukey's *post hoc* test for multiple comparisons (normally distributed variables) or the Kruskal–Wallis test with the Steel–Dwass test (non-parametric variables). The associations between the change in RA function vs. the changes in RA volume, haemodynamic parameters measured by catheterization, BNP, and the 6MWD were tested by linear regression. All data are presented as the mean ± standard deviation. A *P*-value of <0.05 was considered to be indicative of statistical significance.

The inter-study variability was assessed by ICC. Agreement was considered excellent for ICC >0.74, good for ICC = 0.60–0.74, fair for ICC = 0.40–0.59, and poor for ICC <0.40.

Results

Study population

The interval between RHC and CMRI was 5 ± 5 days, and the interval between the before and after BPA dataset was 505 ± 412 days. Haemodynamic and CMRI parameters and laboratory data before and after BPA are shown in *Table 1*. The patients before BPA showed pulmonary hypertension (PH) (mean PAP: 38.4 ± 10.3 mmHg and PVR: 7.4 ± 4.1 Wood units) with preserved cardiac index (3.0 ± 0.8 L/min/m^2). BPA significantly reduced the mean PAP and PVR (24.4 ± 4.2 mmHg and 3.5 ± 0.9 Wood units) without significant changes in the cardiac index (3.2 ± 0.7 L/min/m^2). Although the RAP before BPA was within the normal upper limit (5.4 ± 3.0 mmHg), BPA significantly reduced the RAP (3.9 ± 1.7 mmHg). BPA significantly reduced heart rate (70.4 ± 12.0 vs. 62.9 ± 11.0 bpm; $P < 0.001$). Additionally, BPA significantly reduced plasma BNP levels (110.7 ± 160.9 vs. 21.9 ± 18.0 pg/mL; P<0.001) and increased the 6MWD (382 ± 87 vs. 451 ± 94 m; P<0.001). CMRI indicated that RA volumes and RV volumes were significantly reduced by BPA.

RA strain analysis

As shown in *Figure 3*, compared with the controls, the CTEPH patients before BPA had significantly impaired RA reservoir function, as reflected by reduced peak LS (Control: 41.2% ± 5.8% vs. before BPA: 32.4% ± 12.9%, $P < 0.05$) and peak LSR (Control: 9.2% ± 1.9% vs. before BPA: 6.3% ± 2.7%, $P < 0.05$). BPA improved the impaired peak LS (42.7% ± 10.9%) and peak LSR (8.3% ± 1.9%). There were no significant differences in peak LS and LSR between after BPA patients and controls. Similarly, compared with the controls, the RA passive conduit as reflected by RA early LSR was impaired in the

Table 1 Patient characteristics

CTEPH patients ($n = 29$)			
Age (years)		61 ± 11	
Sex (male/female)		5/24	
Number of BPA sessions		3.5 ± 2.0	
	Before BPA	After BPA	*P*-value
WHO functional class (I/II/III/IV)	0/6/22/1	3/23/3/0	<0.001
RAP (mmHg)	5.4 ± 3.0	3.9 ± 1.7	<0.01
Mean PA pressure (mmHg)	38.4 ± 10.3	24.4 ± 4.2	<0.001
Cardiac index (L/min/m^2)	3.0 ± 0.8	3.2 ± 0.7	NS
PVR (Wood Units)	7.4 ± 4.1	3.5 ± 0.9	<0.001
BNP (pg/mL)	110.7 ± 160.9	21.9 ± 18.0	<0.001
Six-minute walk distance (m)	382 ± 87	451 ± 94	<0.001
Pulmonary vasodilator			
PDE5i, sGC	7	3	
ERA	23	7	
Prostanoid	11	4	
Cardiac MRI			
RA maximum volume (mL/m^2)	67.4 ± 28.8	50.4 ± 14.4	<0.01
RA minimum volume (mL/m^2)	40.7 ± 26.6	26.0 ± 10.5	<0.01
RA ejection fraction (%)	42.0 ± 9.8	49.3 ± 10.2	<0.001
RV end-diastolic volume (mL/m^2)	113.2 ± 34.0	92.7 ± 19.2	<0.001
RV end-systolic volume (mL/m^2)	73.2 ± 37.3	51.0 ± 15.7	<0.001
RV ejection fraction (%)	38.8 ± 13.3	45.8 ± 7.7	<0.001
Heart rate (bpm)	70.4 ± 12.0	62.9 ± 11.0	<0.001
Echocardiography			
Tricuspid regurgitation			
Trivial/mild/moderate/severe	9/10/5/5	11/16/2/0	

BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; ERA, endothelin receptor antagonist; NS, not significant; PA, pulmonary artery; PDE5i, phosphodiesterase type 5 inhibitor; sGC, soluble guanylyl cyclase stimulator.

CTEPH before BPA patients (Control: -5.3% ± 1.9% vs. before BPA: -2.3% ± 2.0%). BPA significantly improved the impaired RA early LSR (-4.3% ± 2.3%). There were no significant differences in the RA early LSR between the after BPA patients and controls. On the other hand, there were no significant differences in the active function and RA late LSR among the before BPA patients, after BPA patients, and controls (before BPA: -4.3 ± 3.6; after BPA: -5.3 ± 2.2; Controls: -5.5 ± 4.5; $P = 0.40$). These results suggested that BPA normalized the impaired RA reservoir and conduit functions, whereas the RA active function was similar among the controls and inoperable CTEPH patients before and after BPA.

Correlations between ΔBNP and ΔRA functions in dilated and non-dilated RA groups

Our cohort was divided into the dilated RA group (RA maximum volume index ≥ 70 mL/m^2 or minimum volume index ≥ 35 mL/m^2 in females, maximum volume index ≥ 75 mL/m^2, or minimum volume index ≥ 45 mL/m^2 in males before BPA)[16] and the non-dilated group and then performed a sub-analysis to evaluate the clinical usefulness of the RA strain regardless of the RA volume. There were no significant differences between the dilated RA group and non-dilated group before BPA in RA peak LS (28.8% ± 11.8%, 36.1 ± 12.8%; $P = 0.19$), RA peak LSR (5.5% ± 2.7%, 7.2% ± 2.4%; $P = 0.21$), RA early LSR (-1.9% ± 1.9%, -2.6% ± 2.0%; $P = 0.31$), and RA late LSR (-3.9% ± 4.0%, -4.6% ± 3.2%; $P = 0.35$). In the dilated RA group, ΔBNP was significantly correlated with ΔRA volumetric parameters (ΔRA maximum volume: $r = 0.66$, $P < 0.05$; RA minimum volume: $r = 0.69$, $P < 0.05$; ΔRAEF: $r = -0.74$, $P < 0.01$) (*Table 2*) but was not correlated with Δstrain parameters. On the other hand, only ΔRA peak LS and ΔRA early LSR, which represent the RA reservoir and conduit functions, were significantly correlated with ΔBNP in the non-dilated RA group (ΔRA peak LS: $r = -0.63$, $P < 0.05$; ΔRA early LSR: $r = 0.65$, $P < 0.05$). The same trend as observed for ΔBNP was observed for ΔPVR, which correlated with ΔRA volume in the dilated RA group (ΔRA maximum volume: $r = 0.60$, $P < 0.05$; RA minimum volume: $r = 0.62$, $P < 0.05$; ΔRAEF: $r = -0.74$, $P < 0.01$) and with the ΔRA reservoir and conduit functions in the non-dilated RA group (ΔRA peak LS: $r = -0.69$, $P < 0.05$; ΔRA peak LSR: $r = 0.59$, $P < 0.05$; ΔRA early LSR: $r = 0.66$, $P < 0.05$). Δ6MWD was not correlated with these parameters in both groups.

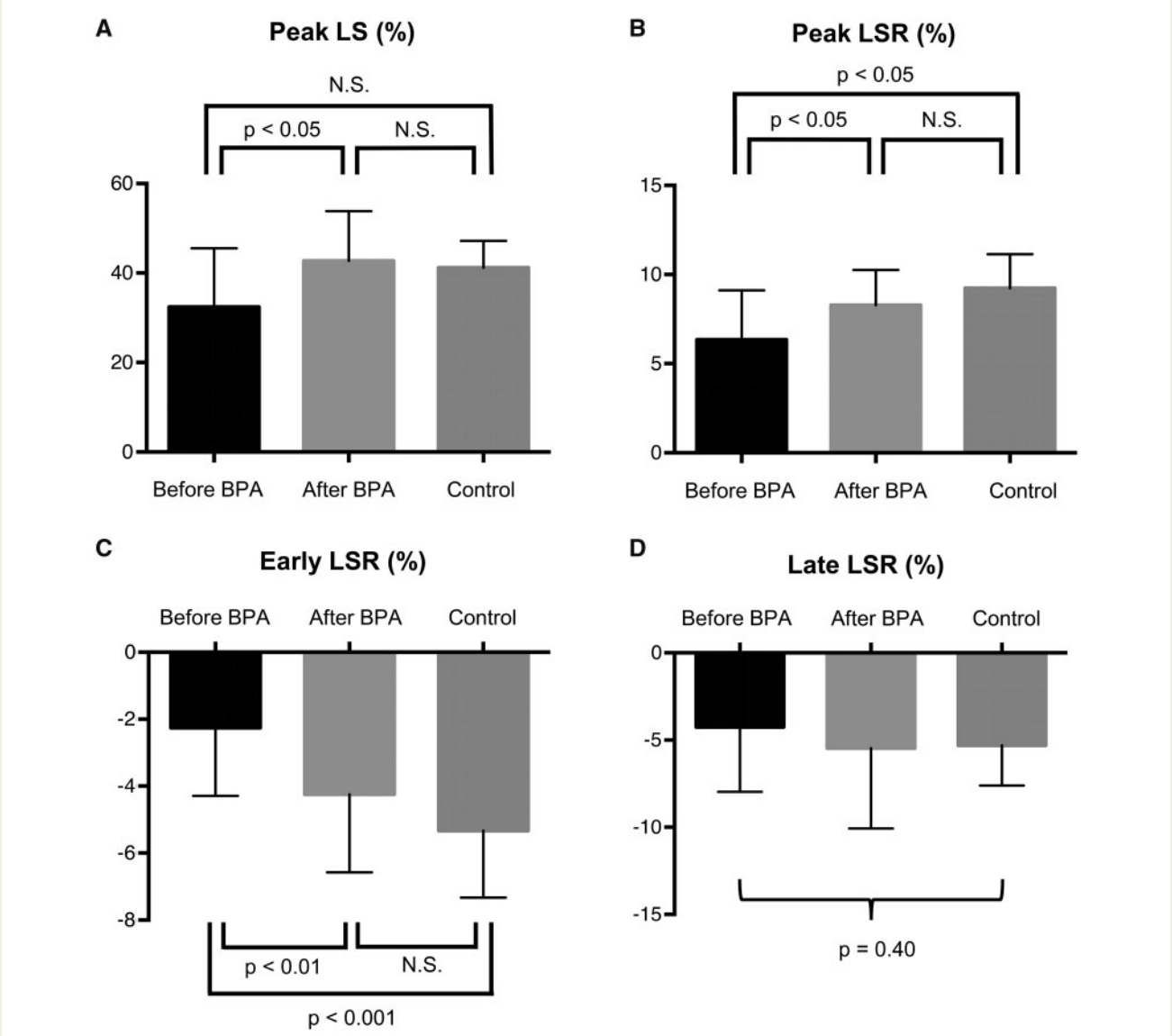

Figure 3 Comparison of right atrium functions among pre-BPA, post-BPA, and control groups. (*A*) Peak LS. (*B*) Peak LS rate. (*C*) Early LSR. (*D*) Late LSR. LS, longitudinal strain; LSR, longitudinal strain rate.

Reliability of strain analysis

Table 3 presents the intra- and inter-observer reproducibility of the measurements. All of the ICCs were high.

Discussion

This CMRI study on the RA functions in CTEPH demonstrated that (i) RA reservoir and conduit functions were impaired in CTEPH and significantly improved after BPA, whereas no significant change was found in the RA active function; (ii) In the non-dilated RA group, the changes in RA reservoir and conduit functions between the before and after BPA patients were significantly correlated with the changes in PVR and BNP levels, which reflected the disease severity in CTEPH.

Effect of BPA on RA dysfunctions in inoperable CTEPH

Regarding the strain functions, there was an improvement in the RA reservoir and conduit functions, whereas active function did not change significantly after BPA. These results were consistent with those of a previous report in which it was found that RA reservoir and conduit functions were impaired in PAH, whereas there was no significant difference in RA active function between the normal subjects and PAH patients. Previous studies have demonstrated that RA

Table 2 Pearson's correlation coefficients between ΔBNP and Δstrain or Δvolume in the dilated RA group and non-dilated RA group

	Dilated RA group ($n = 14$)		Non-dilated RA group ($n = 15$)	
	ΔBNP	ΔPVR	ΔBNP	ΔPVR
ΔRA peak LS	NS	NS	-0.63*	-0.69*
ΔRA peak LSR	NS	NS	NS	-0.59**
ΔRA early LSR	NS	NS	0.65**	0.66**
ΔRA late LSR	NS	NS	NS	NS
ΔRA maximum volume	0.66**	0.60**	NS	NS
ΔRA minimum volume	0.69**	0.62**	NS	NS
ΔRA EF	-0.74#	-0.74#	NS	NS

BNP, brain natriuretic peptide; LS, longitudinal strain; LSR, longitudinal strain rate; NS, not significant.
*$P < 0.01$.
**$P < 0.05$.

Table 3 Intra- and inter-observer reproducibility of the measurements

Parameters	Intra-observer ICC (95% CI)	Inter-observer ICC (95% CI)
Peak LS (%)	0.96 (0.84–0.99)	0.94 (0.77–0.98)
Peak LSR (%)	0.98 (0.90–0.99)	0.87 (0.56–0.97)
Early LSR (%)	0.91 (0.69–0.98)	0.96 (0.83–0.99)
Late LSR (%)	0.97 (0.89–0.99)	0.96 (0.86–0.99)

reservoir and conduit functions were hampered in PAH, and our results are consistent with those.[8] The RA active function compensates against the decline of reservoir and conduit functions to maintain RV diastolic filling.[8,17] As RV dysfunction increases, the rate of active function in RV diastolic filling becomes larger; however, the RA active function is preserved unless RHF becomes considerably more severe.[8] A decline in RA active function due to severe RA impairment or atrial fibrillation worsens prognosis. Most of the CTEPH patients in this study had a normal mean RA pressure and a cardiac index with normal levels, so they did not have critical RHF. Thus, the patients' backgrounds might have influenced the negative results of RA active function.

In our study, RA-LSR and RA early LSR normalized after BPA. To the best of our knowledge, this is the first study to prove the reversibility of RA dysfunction after treatment. BPA reportedly improved pulmonary haemodynamics, exercise tolerance, and clinical outcomes.[4–7] This amelioration of RA functions might have contributed to the improvement in clinical outcomes in CTEPH. Further study would be needed to determine if RA dysfunctions can predict re-exacerbation of CTEPH and hospitalization due to RHF over the long term.

Atrial arrhythmia is common after PEA (pulmonary endarterectomy). In a previous study, 24.2% of patients developed atrial arrhythmia after PEA, and the development of atrial arrhythmia was associated with a longer length of stay and a higher number of post-operative complications.[18] Conversely, atrial arrhythmia was not observed after BPA in our study. This could represent a major advantage of BPA over PEA. There is a great possibility that it influences RA function because atrial fibrillation is associated with the decline of pump function. Further investigation comparing the effects of BPA and PEA on RA function is required in the future.

In our study, BPA reduced HR in CTEPH patients after BPA. The change of HR has the potential to affect RA functions, especially reservoir function. However, as shown in *Figure 4*, no significant correlations were noted between the change of HR and those of RA functions. This suggests that the reduction of heart rate had little effect on RA functions after BPA.

The degree of TR was improved after BPA in 41% (12/29) of patients. We divided our study cohort into two groups based on the improvement of TR after BPA and analysed the changes of RA functions in each group. As shown in *Table 4*, RA reservoir and conduit functions were recovered after BPA in both the improved and nonimproved TR groups. Therefore, only some of the changes of RA functions after BPA were attributable to the improvement of TR.

RA dysfunction in small RA volume

An increase in RA minimum volume is a predictor of poor prognosis in PH.[11] However, Querejeta Roca *et al.*[8] demonstrated that RA reservoir and conduit functions were impaired not only in an RA dilated group but also in an RA non-dilated group in PH. In our study, the ΔRA reservoir and conduit functions were significantly correlated with ΔBNP and ΔPVR in patients with small RA size, whereas the ΔRA volumes were associated with ΔBNP in patients with dilated RA. BNP and PVR have been shown to be significant predictors of outcome in PH and useful for assessing the procedural success of BPA in CTEPH.[19,20] RA reservoir and passive conduit functions may be non-invasive measures of recovery from RHF and pulmonary haemodynamics as BPA treatment effects in patients with normal RA size. On the other hand, Δ6MWD did not correlate with any ΔRA volumes and functions. The ceiling effect is important when

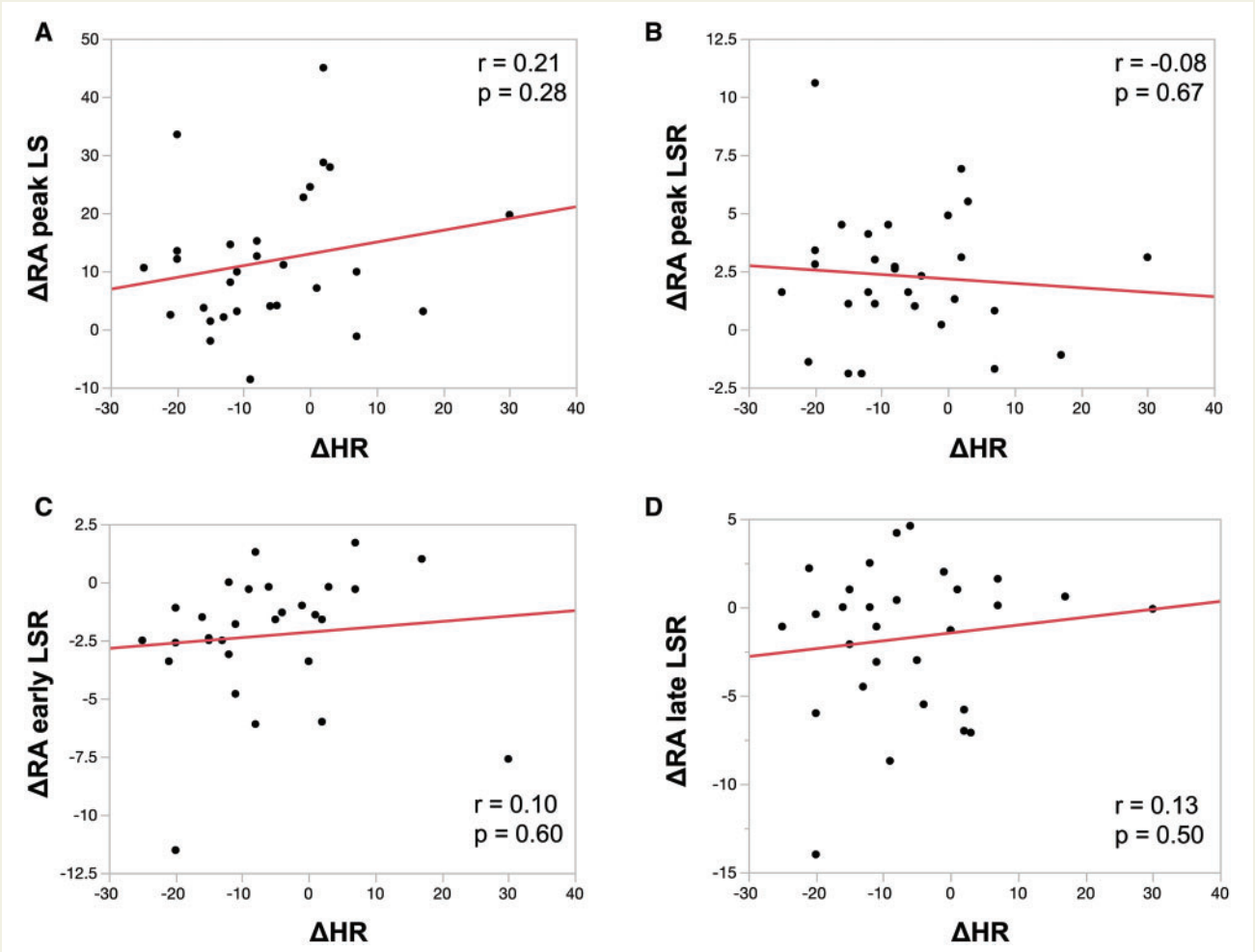

Figure 4 Correlations between the changes in heart rate and those in RA functions. (*A*) Peak LS. (*B*) Peak LS rate. (*C*) Early LSR. (*D*) Late LSR. LS, longitudinal strain; LSR, longitudinal strain rate.

Table 4 RA functional parameters before and after BPA in the improved ($n = 12$) and non-improved TR groups ($n = 17$)

Parameter	Before BPA	After BPA	*P*
Improved TR group			
RA LS (%)	24.5 ± 11.8	40.5 ± 10.8	<0.01
RA LSR (%)	4.5 ± 2.6	7.5 ± 1.6	<0.01
RA early LSR (%)	-2.1 ± 1.8	-4.5 ± 2.2	<0.01
RA late LSR (%)	-3.0 ± 2.7	-5.8 ± 4.3	<0.01
Non-improved TR group			
RA LS (%)	36.9 ± 9.7	44.5 ± 10.8	<0.05
RA LSR (%)	7.5 ± 1.9	8.8 ± 2.0	<0.05
RA early LSR (%)	-2.4 ± 2.1	-4.1 ± 2.4	<0.05
RA late LSR (%)	-4.9 ± 3.8	-5.3 ± 4.7	NS

evaluating the improvement after treatment by the 6MWD. Reportedly, it is difficult to decide on changes in the walking distance in patients with baseline 6MWD >450 m.[21] In the present study, six patients had baseline 6MWD ≥450 m before BPA.

Feature tracking MRI assessment

In this study, we used feature-tracking MR, which was developed in-house, instead of speckle-tracking ultrasonography (US). Both techniques can assess expansion and contraction of the myocardium and their results correlate highly, but feature-tracking MRI has higher reproducibility so it is a valid alternative to speckle-tracking US, especially in patients with suboptimal echo quality.[22] The characteristics and benefits of our feature-tracking MRI have been proven previously,[12–14] and high reproducibility was proven in the present study's RA assessment (*Table 3*).

Study limitations

This study had several limitations that should be considered when interpreting the results. First, the size of our study was small, so a larger-scale study might be needed. Second, we analysed RA strain by using in-house developed software, which has been validated for left and RV analysis, but this is the first application for RA. However, we

verified its accuracy and its high inter- and intra-observer reproducibility in this study. Additionally, no validated software was commercially available for dedicated RA analysis by deformation imaging at the time of this study.

Recently, it was reported that significant backward flow in the vena cava was observed in PAH as a consequence of impaired RV filling.[23] Investigations related to the vena cava flow and the relationship between RA function and vena cava flow are of interest because backward flow in the vena cava occurred mostly during atrial contraction and could influence active function. Thus, future studies regarding this relationship are needed.

Conclusions

Impairment of RA reservoir and conduit functions were shown to be reversible after BPA in patients with inoperable CTEPH. RA reservoir and conduit functions could serve as novel indices of the BPA treatment effect, especially in patients with CTEPH but without RA dilation.

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Conflict of interest: none declared.

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