HOKKAIDO UNIVERSITY

Title	Right atrial volume and phasic function in pulmonary hypertension
Author(s)	Sato, Takahiro; Tsujino, Ichizo; Oyama-Manabe, Noriko et al.
Citation	International journal of cardiology, 168(1), 420-426 https://doi.org/10.1016/j.ijcard.2012.09.133
Issue Date	2013-09-20
Doc URL	https://hdl.handle.net/2115/53617
Type	journal article
File Information	Int J Cardiol_168(1)_420-426.pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Title: Right atrial volume and phasic function in pulmonary hypertension

Names and affiliations of authors:

Takahiro Sato, M.D.[*], Ichizo Tsujino, M.D., Ph.D.[*], Noriko Oyama-Manabe, M.D., Ph.D.[†], Hiroshi Ohira, M.D., Ph.D.[*], Yoichi M. Ito, Ph.D.[‡], Asuka Yamada, M.D.[*], Daisuke Ikeda, M.D., Ph.D.[*], Taku Watanabe, M.D., Ph.D.[*], Masaharu Nishimura, M.D., Ph.D.[§]

[*]First Department of Medicine and [†]Department of Diagnostic and Interventional Radiology, Hokkaido University Hospital; [‡]Department of Biostatistics and [§]First Department of Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Total word count: 5058 words

Corresponding author:

Ichizo Tsujino M.D., Ph.D.

First Department of Medicine, Hokkaido University Hospital

North 14, West 5, Kita-ku, Sapporo 060-8648, Japan

FAX: +81-11-706-7899, Tel: +81-11-706-5911, E-mail: itsujino@med.hokudai.ac.jp

ABSTRACT

Background

Few studies have focused on right atrial (RA) structure and function in pulmonary hypertension (PH). We sought to evaluate RA volume and phasic function using cardiac magnetic resonance (CMR), and to examine their clinical relevance in PH.

Methods

We prospectively studied 50 PH patients and 21 control subjects. RA volume and indices of phasic function (reservoir volume, ejection fraction [EF], and conduit volume) were evaluated by CMR.

Results

Maximum RA volume index was significantly higher in PH patients (56 [44-70] ml/m^2) than in controls (40 [30-48] ml/m^2) ($p<0.001$). Reservoir volume index was significantly lower in PH than in controls ($p<0.001$), but conduit volume index was higher in PH than in controls ($p=0.008$). RA EF was similar when comparing the two groups ($p=0.925$). Interestingly, RA EF was increased in PH patients with WHO functional class III patients as compared with controls ($p<0.001$) but was reduced in advanced PH patients with WHO functional class IV ($p<0.01$). Maximum RA volume and RA EF significantly correlated with pulmonary hemodynamic indices, atrial and brain natriuretic hormone levels, and CMR-derived right ventricular indices. By contrast, RA reservoir volume correlated with cardiac index and 6-minute walk distance.

Conclusions

PH is associated with increased size, decreased reservoir function, and increased conduit function of the right atrium. RA systolic function indicated by RA EF increases in patients with mild to moderate PH but decreases in patients with advanced PH. Varying associations between RA indices and conventional PH indices suggest their unique role in the management of PH.

(249 words)

Key Words: pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, magnetic resonance imaging

Introduction

Pulmonary hypertension (PH) is defined by a resting mean pulmonary artery pressure (PAP) ≥ 25 mmHg(1). An increase in PAP causes right ventricular (RV) and right atrial (RA) pressure-overload, leading to right heart failure and premature death. An increase in RA pressure is associated with poor prognosis in patients with PH(2) and thus, accurate evaluation of RA structure and function is potentially critical in the management of PH.

To date, limited attention has been paid to the right atrium in PH. This is partly because of technical difficulties in assessing RA morphology. However, recent advances in cardiac magnetic resonance (CMR) have enabled precise and reproducible assessment of the volume of the right atrium. For example, Jarvinen et al. validated the accuracy of CMR in the measurement of human RA dimension using cadaveric atrial casts(3). They also assessed phasic function of the right atrium using CMR(4). Previous studies of the right atrium have been conducted mostly in healthy subjects or in patients with congenital heart disease(5, 6) and not in PH patients. Thus, details regarding the impact of PH on RA morphology remain incompletely investigated.

The atria provide three functions during the cardiac cycle – namely, reservoir, conduit, and contractile functions(3, 4, 7, 8). Coordination of these phasic functions plays an important role for the maintenance of overall cardiac function(9). In the case of the left atrium, its phasic functions are reportedly impaired in various cardiovascular diseases(10-12). However, only a small number of studies have addressed the impact of PH on the phasic functions of the right atrium(13, 14).

The present study sought to evaluate the volume and phasic function of the right atrium in PH patients using CMR. This study also addressed the possible clinical relevance of measuring RA size and function by comparing RA parameters with established clinical indices of PH.

Methods

In this single-center, case-control, prospective, observational study, subjects who met the entry criteria [mean PAP of ≥25 mm Hg and pulmonary capillary wedge pressure (PCWP) of ≤ 15 mm Hg] were consecutively enrolled between December 2009 and September 2011. Exclusion criteria consisted of any myocardial, valvular, or systemic diseases that might exclusively affect cardiac morphology and function, unstable PH condition that required treatment modifications, and inability to obtain or analyze electrocardiogram (ECG)-gated CMR images. Patients with atrial fibrillation/flutter were excluded based on the last criterion. Age- and gender-matched subjects who did not have cardiac and/or respiratory diseases were recruited as control subjects.

Patients with PH underwent right heart catheterization (RHC), CMR, a 6-minute walk test, and measurement of serum atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels within a 1-week interval during which they were clinically stable. RHC measurements included PAP, PCWP, RV end-diastolic pressure (EDP), RA pressure, and cardiac output (CO). CO was measured by the thermodilution method, and the mean of three or more measurements was used as representative data.

All subjects gave informed written consent to participate, and the study protocol was approved

by the ethics committee of the Hokkaido University Graduate School of Medicine. The present study complied with the Declaration of Helsinki.

CMR imaging

CMR studies were performed using a 1.5-Tesla Philips Achieva magnetic resonance imaging system (Philips Medical Systems, Best, The Netherlands) with a cardiac five-channel coil, equipped with Master gradients (maximum gradient amplitude, 33 mT/m; maximum slew rate, 100 mT/m/msec). Imaging was performed with breath-holding in expiration, using a vector-cardiographic method for ECG-gating. PH patients receiving domiciliary oxygen therapy underwent CMR while being administered the same amount of oxygen that they typically used at rest. From the coronal localizing images, an orthogonal stack of axial slices was planned to cover the heart from a level just below the diaphragm to the bronchial bifurcation, covering the heart in diastole. A total of about 12 axial slices were acquired using a steady-state free precession pulse sequence (repetition time = 2.8 msec, echo time = 1.4 msec, flip angle= 60, acquisition matrix= 192 x 256, field of view= 380 mm, slice thickness= 10 mm, 0 mm inter-slice gap, 20 phases/cardiac cycle). A slice thickness of 10 mm was greater than the recommended thickness(15), but we adopted it to minimize the number of image acquisitions of the enlarged heart and to reduce the frequency and duration of breath-holding. Breath-holding time for each image acquisition was 10-15 s, which varied depending on the heart rate.

CMR images were evaluated using commercially available software (Extended MR Work Space:

ver. 2.6.3, Philips Medical Systems, Amsterdam, The Netherlands). RA and left atrial (LA) volumes were measured using cine axial images obtained from coronal and sagittal scout images to cover the whole heart (Fig 1). Time-volume curves of the right and left atria were constructed by plotting each instantaneous atrial volume against the R wave at which acquisition was performed. The volume cycle was reconstructed from 20 consecutive atrial volumes. The section was planimetered with a mouse-derived cursor, and simultaneous volumes were totaled given the total cavity volume at every time phase from the contiguous axial view. The inlets of the superior and inferior vena cava and the coronary sinus were excluded from the RA volume. The pulmonary vein inlets were excluded from the LA volume. The volumes of the right and left atrial appendages were included in atrial chamber volumes.

The atrial volume cycle and measurements are shown schematically in Figure 2. As has been documented in previous reports(3, 4), the atrial maximum and minimum volumes were determined from this volume-time curve. The atrial reservoir volume was defined as the difference between the atrial maximum volume and the smallest atrial volume in mid-diastole. The atrial stroke volume was defined as the decrease in atrial volume at end-diastole. If the atrial volume-time curve was continuously down-sloping during diastole, the reservoir volume was considered to be the volume decrease before the final 200 msec of the cardiac cycle, and the atrial stroke volume was defined as the volume reduction over the remaining cardiac cycle. The atrial ejection fraction (EF) was the ratio of atrial stroke volume to the volume at the onset of atrial systole. The atrial conduit volume was calculated as the difference between the RV stroke volume and the sum of RA reservoir and stroke volumes.

RV and left ventricular (LV) volumes were similarly measured using cine axial and short axis images obtained from coronal and sagittal scout images, and manual tracing of RV and LV endocardial borders of contiguous axial slices at end-diastole and end-systole allowed for calculation of RV and LV EF. RV EF was measured in transaxial orientation, as Alfakih et al. had demonstrated that the transaxial orientation resulted in better observer variability when compared with the short axis orientation(16). Endocardial and epicardial ventricular borders were manually contoured for quantification of the volume of RV and LV wall. The interventricular septum was regarded as a part of LV wall. RV and LV mass were calculated by multiplying each wall volume by 1.05.

Pericardial effusion was evaluated using T2 weighted four-chamber views of the heart taken at end-diastole. The presence of pericardial effusion was classified as none, partial or circumferential.

Statistical analysis

Atrial and ventricular volumes and ventricular mass were indexed by body surface area. Categorical variables are expressed as percentages, and continuous variables are expressed as mean ± SD for those normally distributed or otherwise as medians and interquartile ranges (IQR). Departures from normality were detected with the Shapiro-Wilk statistic. Differences of measurements between the control group and either PH group or pulmonary arterial hypertension (PAH) group were assessed with the chi-square test, Student's *t* test, or the Wilcoxon test as appropriate. Differences in RA size and phasic function among controls and PH patients with different functional class were assessed by analysis of

variance, followed by the post hoc Tukey-Kramer test. RA indices were also compared between PH patients who were receiving any of the PAH-specific vasodilator(s), i.e., endothelin receptor blockers, phosphodiesterase 5 inhibitors or oral/intravenous prostacyclin, and those who were not. Further, RA indices were compared among PH patient groups treated by different treatment regimens.

Correlations of RA CMR parameters with other parameters were assessed using Spearman's rho test. Multivariate regression analysis of four RV parameters (RV EDP, RV EDV, RV mass index, and RV EF) and CMR-derived RA indices was also conducted.

All statistical analyses were performed using JMP® Version 9 (SAS Institute, Inc., Cary, NC), and p values less than 0.05 were considered statistically significant.

Reproducibility and reliability of the CMR measurements of the right atrium

The intraobserver agreement for measurements was assessed by comparing the measurements of repeated analysis in five randomly chosen control subjects and in 10 randomly chosen PH patients (T.S.). The interobserver agreement was assessed using the same patients (n=15) by comparing the results measured by T.S. and those obtained by a second, experienced cardiologist (I.T.). The second cardiologist was not aware of the CMR measurements of the first examiner. Bland-Altman analysis and intraclass correlations (ICC) between the two measurements were used to assess reproducibility.

Results

A total of 51 Japanese patients met the entry criteria. One patient had organic tricuspid valve disease and was excluded according to the pre-specified exclusion criteria. Twenty-one age- and gender-matched healthy controls were also enrolled. There were no significant demographic differences between the 50 PH patients and the 21 control subjects (Table 1). Table 2 shows the characteristics of the PH patients.

Comparison of CMR measurements

All participants were in sinus rhythm during the CMR image acquisitions. When compared with control subjects, PH patients exhibited greater RA maximum and minimum volume index (Table 3). PH patients exhibited smaller reservoir volume index and greater conduit volume index than controls, but RA EF was similar between the two groups. RV end-diastolic and end-systolic volume index and RV mass index were significantly greater in PH patients than in controls. RV EF was significantly lower in PH patients than in controls. There was no difference in the heart rate between the two groups (PH, 67 ± 10/min; controls, 63 ± 8/min, p=0.126).

Comparison of the RA indices of 26 PAH patients with those of the control subjects similarly showed greater RA volume (PAH 55 (46-70) ml/m^2, p=0.0001 vs controls), smaller RA reservoir volume index (PAH 9 ± 4 ml/m^2, p=0.0005 vs controls), greater RA conduit volume index (PAH 18 ± 8 ml/m^2, p=0.0027 vs controls), and similar RA EF (34 ± 7%, p=0.95) in PAH patients as compared with controls.

Figure 3 shows RA indices of controls and PH patients with different World Health

Organization-functional class (WHO-FC). RA maximum volume index was greater in PH patients with WHO-FC III or IV than in controls (Figure 3A). By contrast, RA reservoir volume index was reduced in PH patients with WHO-FC III or IV as compared with less advanced PH patients (Figure 3B). RA EF was significantly higher in PH patients with WHO-FC III than in controls, whereas it was conversely decreased in PH patients with WHO-FC IV as compared with PH patients with WHO-FC II or III (Figure 3C).

There were no significant differences in any of the RA indices between PH patients who were on PAH-specific vasodilators (n = 29) and PH patients who were not (n = 21) (Table 4). Also, no differences in RA indices were found among four patient groups treated by different regiments, i.e., beraprost (oral prostanoid monotherapy) (n=7), phosphodiesterase 5 inhibitor with or without beraprost (n=5), endothelin receptor antagonist with or without beraprost (n=9), and other regimens (n=8) (Table 4).

Correlations between CMR indices of the right atrium and other clinical parameters (Table 5)

Maximum RA volume index significantly correlated with mean PAP, RV EDP, mean RA pressure, RV EDV index, RV mass index, RV EF, and serum ANP and BNP levels. Similarly, RA EF significantly correlated with mean PAP, RV EDP, PVR, RV EDV index, RV mass index, RV EF, and serum ANP and BNP levels. RA reservoir volume index significantly correlated with mean PAP, cardiac index (CI), PVR, RV EF, serum ANP levels, and 6-minute walk distance. RA conduit volume index correlated with CI and RV EDV index.

Multivariate regression analysis of RA indices with RV parameters (Table 6)

RA indices (i.e., outcome variables) were associated with RV parameters (i.e., explanatory variables) in a varying manner. For example, RA maximum volume index was independently associated with RV EDP, RV EDV index and RV mass index. Further, RA reservoir volume index was positively associated with RV EF, but RA EF was negatively associated with RV mass index.

Reproducibility and reliability

Bland-Altman analysis of the intraobserver variability of CMR-derived RA indices showed low mean differences and limits of agreement (maximum RA volume, -0.1±6.4 ml; minimum RA volume, 1.9±8.4 ml; RA reservoir volume, -0.3±5.5 ml; RA conduit volume, 1.6±6.3 ml; RA EF, -1.9±5.2%) (Figure 4). ICCs were greater than 0.85 for all five measurements (maximum RA volume, 0.998; minimum RA volume, 0.995; RA reservoir volume, 0.887; RA conduit volume, 0.957; RA EF, 0.967). Regarding the interobserver variability, Bland-Altman analysis showed similarly small mean differences and limits of agreement (maximum RA volume, -4.8±20 ml; minimum RA volume, 0.3±10.2 ml; RA reservoir volume, 0.0±9.2 ml; RA conduit volume, 3.3±16.6 ml; RA EF, 2.4±7.4%) (Figure 4). ICCs were acceptably high for all measurements (maximum RA volume, 0.984; minimum RA volume, 0.994; RA reservoir volume, 0.816; RA conduit volume, 0.737; RA EF, 0.909).

Discussion

The present CMR study on the RA volume and phasic function in PH demonstrated that 1) RA volume was increased in PH patients than in controls; 2) reservoir volume was decreased, whereas conduit volume was increased in PH patients than in controls; 3) RA EF was similar when comparing PH and control groups; however, 4) RA EF was increased in mild to moderate PH patients whereas it was conversely decreased in advanced PH patients; 5) maximum RA volume and RA EF significantly correlated with pulmonary hemodynamic measurements, serum ANP/BNP levels, and RV morphology and function; in contrast, RA reservoir volume correlated with CI and 6-minute walk distance**;** 6) maximum RA volume was independently associated with three RV indices (RV EDP, RV EDV index and RV mass index). Alternatively, RA reservoir volume and RA EF were associated with RV EF and RV mass index, respectively, in the multivariate analysis.

Only a few human studies have investigated RA volume in PH. In 2008, an echocardiographic study by Willens et al. demonstrated that RA volume was higher in PH patients than in controls(17). RA dilatation in PH was also shown in another echocardiographic report by Cioffi et al.(13). However, in these previous studies, RA volume was calculated based on two-dimensional echocardiographic measurements and multiple mathematical assumptions. Also, the diagnosis of PH was made by echocardiography alone without RHC, hampering the accuracy of the diagnosis of PH itself. In the present study, we used ECG gated three-dimensional CMR imaging, which has established accuracy and reproducibility in the volumetric analysis of the cardiac chambers(3, 4). Also, the diagnosis of PH was made by RHC in our study. Thus, the present study validated increased RA volume in PH patients relative to control patients

with superior accuracy and reliability.

Phasic functions of the right atrium in PH have been investigated in echocardiographic studies. For example, increase in the systolic function of the right atrium has been documented by two-dimensional measurements(13), by Doppler methods(17), and by pulsed tissue Doppler imaging(14). The increased RA EF in PH patients with WHO-FC III seen in the present study is consistent with these prior observations. Likewise, the RA EF in the 26 PAH patients was greater than that of controls. Interestingly, however, RA EF was even lower in PH patients with WHO-FC IV when compared with less advanced PH patients. With regards to reservoir function, Willens et al. reported a significantly smaller reservoir volume in PH patients compared with controls(17). This is consistent with findings from the present study, in which there was an approximately 40% decrease in reservoir volume in PH patients relative to controls. A recent animal study reported increased RA conduit function in a PH model(18), but no such studies have been performed in humans. Thus, the present study is the first to demonstrate a significant increase in RA conduit function in PH patients, although the clinical implication of this finding remains to be elucidated.

Alterations of the RA measurements of PH patients (i.e., increased size, reduced reservoir volume, and systolic function increased in mild to moderate cases whereas reduced in advanced cases) can be explained by the Frank-Starling law. First, reduced reservoir volume can be interpreted as a decrease in early diastolic emptying of the right atrium, leading to increased volume at the onset of RA systole. In fact, RA size at the onset of systole (pre-atrial contraction volume) was about 1.5 times greater in PH patients than in controls in this study. This increase in RA size could subsequently lead to compensatory

enhancement of atrial contraction through Frank-Starling mechanics. Indeed, this compensatory response has been documented in the left atrium(8, 10-12). Also, as was seen in PH patients with WHO-FC IV, a further increase in RA volume was associated with decreased RA EF. This non-linear relationship between volume and systolic function has been documented in a recent three-dimensional echocardiographic study of the left atrium(19). However, various cardiac and non-cardiac factors affect RA size and function, particularly in cases of advanced PH. Thus, additional studies are needed to further clarify the association between RA size and function in PH.

Correlation analysis in this study suggested that CMR-derived RA indices may have differing clinical relevance. For example, RA size seems to reflect right heart pressure overload and subsequent RV remodeling and dysfunction. In fact, maximum RA volume index significantly correlated with mean PAP and RV indices, such as RV volume, mass index, and EF. Similarly, RA EF correlated with mostly the same parameters that correlated with RA maximum volume index, suggesting that RA EF may also be a marker of pressure overload, remodeling, and dysfunction of the right ventricle. By contrast, RA reservoir volume index may be a "functional" index, because it significantly correlated with CI and 6-minute walk distance, but correlated weakly, if at all, with PAP and RV indices. In this regard, a recent report by Kasikcioglu et al. documented a significant correlation between LA reservoir function and exercise capacity(20), suggesting a possible link between atrial reservoir function and overall cardiac performance.

For the purpose of identifying major determinants of altered RA volume and function, we selected indices that are likely to affect RA indices and used them as explanatory variables in multivariate

regression analysis. The results suggested that the changes in RA volume and phasic function depend on RV morphology/function in a varying manner. For example, RA volume seems to increase in response to elevated RV EDP and RV hypertrophy (increased RV EDV and RV mass). In contrast, RA reservoir function was suggested to decrease along with decreased RV EF, independent of other RV parameters. Of note, however, is that this multivariate regression analysis did not include clinical parameters, such as age, sex and comorbid diseases. Larger studies with more participants are needed to further clarify the determinants of RA volume and function.

There are several limitations to this study that merit discussion. First, this study included PH patients with diverse etiologies, which might have significantly affected the results. In fact, it is well known that patient characteristics are different between patients with PAH and patients with chronic thromboembolic pulmonary hypertension. Thus, we compared RA indices between controls and PAH patients and found results similar to those seen in the overall analysis. Even so, larger studies with controlled enrollment of PH patients with different etiologies and stages are needed to further clarify this issue. Second, varying treatment regiments might have also influenced the results. Indeed, some PH-specific vasodilators can affect cardiac function(21). There were no differences in RA indices between PH patients who were on PAH-specific vasodilators and those who were not, or among PH patients treated with different regimens. However, the number of patients in each group was small and the possible influence of varied treatment cannot be excluded. Third, the methods of measuring RA volume applied in this study have not been widely used. However, intra- and interobserver reproducibility analysis were

favorable. Also, the CMRI-based methodology itself is commonly used in the volmetry of other cardiac chambers. Even so, a small error in RA measurements could be clinically significant and, thus, cautious interpretation of the RA indices is warranted. Fourth, three to four episodes of breath-holdings were required to cover the entire heart during the CMR image acquisition, which can result in slice misregistration. To minimize this inaccuracy, the radiologist assessed for overlap of the slices and decided which slices should be used. Fifth, CMR does not necessarily allow precise assessment of atrial systolic and diastolic function. Recordings of pressure-volume loops during alterations of both preload and afterload are required for such evaluation. Lastly, and most importantly, the present observational study does not allow true clinical implication of measuring RA size and function. The clinical relevance of RA volumetry will be addressed in long-term prospective studies including our ongoing follow-up study.

In conclusion, the present volumetric CMR study demonstrated increased volume and altered phasic function of the right atrium in PH patients when compared with healthy controls. Also, different correlation patterns between CMR-derived RA indices and other clinical parameters have suggested that the clinical relevance of each RA index can vary. Additional long-term studies are warranted to further characterize the clinical application of the measurement of RA volume and function in PH.

Acknowledgements

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology(22)

Conflict of Interest: none declared

References

1. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2009;54(1 Suppl):S55-66. Epub 2009/07/09.

2. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115(5):343-9. Epub 1991/09/01.

3. Jarvinen VM, Kupari MM, Hekali PE, Poutanen VP. Right atrial MR imaging studies of cadaveric atrial casts and comparison with right and left atrial volumes and function in healthy subjects. Radiology. 1994;191(1):137-42. Epub 1994/04/01.

4. Jarvinen VM, Kupari MM, Poutanen VP, Hekali PE. Right and left atrial phasic volumetric function in mildly symptomatic dilated and hypertrophic cardiomyopathy: cine MR imaging assessment. Radiology. 1996;198(2):487-95. Epub 1996/02/01.

5. Riesenkampff E, Mengelkamp L, Mueller M, Kropf S, Abdul-Khaliq H, Sarikouch S, et al. Integrated analysis of atrioventricular interactions in tetralogy of Fallot. Am J Physiol Heart Circ Physiol. 2010;299(2):H364-71. Epub 2010/05/25.

6. Tsao CW, Josephson ME, Hauser TH, O'Halloran TD, Agarwal A, Manning WJ, et al. Accuracy of electrocardiographic criteria for atrial enlargement: validation with cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2008;10:7. Epub 2008/02/15.

7. Stefanadis C, Dernellis J, Toutouzas P. A clinical appraisal of left atrial function. Eur Heart J. 2001;22(1):22-36. Epub 2001/01/03.

8. To AC, Flamm SD, Marwick TH, Klein AL. Clinical utility of multimodality LA imaging: assessment of size, function, and structure. JACC Cardiovasc Imaging. 2011;4(7):788-98. Epub 2011/07/16.

9. Matsuda Y, Toma Y, Ogawa H, Matsuzaki M, Katayama K, Fujii T, et al. Importance of left atrial function in patients with myocardial infarction. Circulation. 1983;67(3):566-71. Epub 1983/03/01.

10. Spencer KT, Mor-Avi V, Gorcsan J, 3rd, DeMaria AN, Kimball TR, Monaghan MJ, et al. Effects of aging on left atrial reservoir, conduit, and booster pump function: a multi-institution acoustic quantification study. Heart. 2001;85(3):272-7. Epub 2001/02/17.

11. Cioffi G, Mureddu GF, Stefenelli C, de Simone G. Relationship between left ventricular geometry and left atrial size and function in patients with systemic hypertension. J Hypertens. 2004;22(8):1589-96. Epub 2004/07/17.

12. Gottdiener JS, Kitzman DW, Aurigemma GP, Arnold AM, Manolio TA. Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons > or =65 years of age (the cardiovascular health study). Am J Cardiol. 2006;97(1):83-9. Epub 2005/12/27.

13. Cioffi G, de Simone G, Mureddu G, Tarantini L, Stefenelli C. Right atrial size and

function in patients with pulmonary hypertension associated with disorders of respiratory system or hypoxemia. Eur J Echocardiogr. 2007;8(5):322-31. Epub 2006/08/01.

14. Shiina Y, Funabashi N, Lee K, Daimon M, Sekine T, Kawakubo M, et al. Right atrium contractility and right ventricular diastolic function assessed by pulsed tissue Doppler imaging can predict brain natriuretic peptide in adults with acquired pulmonary hypertension. Int J Cardiol. 2009;135(1):53-9. Epub 2008/09/17.

15. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E, Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized P. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. J Cardiovasc Magn Reson. 2008;10:35. Epub 2008/07/09.

16. Alfakih K, Plein S, Bloomer T, Jones T, Ridgway J, Sivananthan M. Comparison of right ventricular volume measurements between axial and short axis orientation using steady-state free precession magnetic resonance imaging. J Magn Reson Imaging. 2003;18(1):25-32. Epub 2003/06/20.

17. Willens HJ, Fertel DP, Qin J, Labrador E, Lowery MH. Effects of age and pulmonary arterial hypertension on the different phases of right atrial function. Int J Cardiovasc Imaging. 2008;24(7):703-10. Epub 2008/05/06.

18. Voeller RK, Aziz A, Maniar HS, Ufere NN, Taggar AK, Bernabe NJ, Jr., et al.

Differential modulation of right ventricular strain and right atrial mechanics in mild vs. severe pressure overload. Am J Physiol Heart Circ Physiol. 2011;301(6):H2362-71. Epub 2011/09/20.

19. Anwar AM, Geleijnse ML, Soliman OI, Nemes A, ten Cate FJ. Left atrial Frank-Starling law assessed by real-time, three-dimensional echocardiographic left atrial volume changes. Heart. 2007;93(11):1393-7. Epub 2007/05/16.

20. Kasikcioglu E, Oflaz H, Akhan H, Kayserilioglu A, Umman B, Bugra Z, et al. Left atrial geometric and functional remodeling in athletes. Int J Sports Med. 2006;27(4):267-71. Epub 2006/03/31.

21. Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: results of a 1-year, prospective, randomized, placebo-controlled study. Circ Heart Fail. 2011;4(1):8-17. Epub 2010/11/03.

22. Coats AJ, Shewan LG. Statement on authorship and publishing ethics in the international journal of cardiology. Int J Cardiol. 2011;153(3):239-40. Epub 2011/11/24.

Figure legends

Fig 1. Representative CMR images for the measurement of right atrial volume

Representative axial CMR images taken at the end diastole are shown. Endocardial contours of RA were manually traced using commercially available software (Extended MR Work Space: ver. 2.6.3, Philips Medical Systems, Amsterdam, The Netherlands). The tracing was performed at 20 phases in a cardiac cycle, and the right atrial volume at each phase was calculated using the same software. Note that the right atrial appendage was included in the right atrial cavity (left top panel), and the coronary sinus (left bottom panel) and the inferior vena cava (right bottom panel) were excluded from the right atrial cavity. CMR, cardiac magnetic resonance; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle

Fig 2. Schematic time-volume curve of atrium

Schematic time-volume curve and volumetric measurements are shown. See text for details of each measurement.

Fig 3. Comparison of right atrial size and phasic function in controls and pulmonary hypertension patients with different functional class

Analysis of variance indicated significant differences in right atrial maximal volume index (Panel A, $p<0.0001$), reservoir volume index (Panel B, $p<0.0001$), ejection fraction (Panel C, $p<0.0001$),

and conduit volume index (Panel D, p=0.016) among controls, pulmonary hypertension patients with WHO functional class II, III or IV. Results of post-hoc Tukey-Kramer test are shown in each panel. WHO-FC: World Health Organization-functional class

Fig 4. Bland-Altman analyses between intraobserver and interobserver measurements of the RA cardiac magnetic resonance-derived parameters

A. **Analyses between intraobserver RA measurements**

Small mean differences and limits of agreement (RA maximum volume, -0.1±6.4 ml; RA minimum volume, 1.9±8.4 ml; RA reservoir volume, -0.3±5.5 ml; RA conduit volume, 1.6±6.3 ml; RA ejection fraction, -1.9±5.2%) are shown. RA, right atrial

B. **Analyses between interobserver RA measurements**

Small mean differences and limits of agreement (RA maximum volume, -4.8±20 ml; RA minimum volume, 0.3±10.2 ml; RA reservoir volume, 0.0±9.2 ml; RA conduit volume, 3.3±16.6 ml; RA ejection fraction, 2.4±7.4%) are shown. RA, right atrial

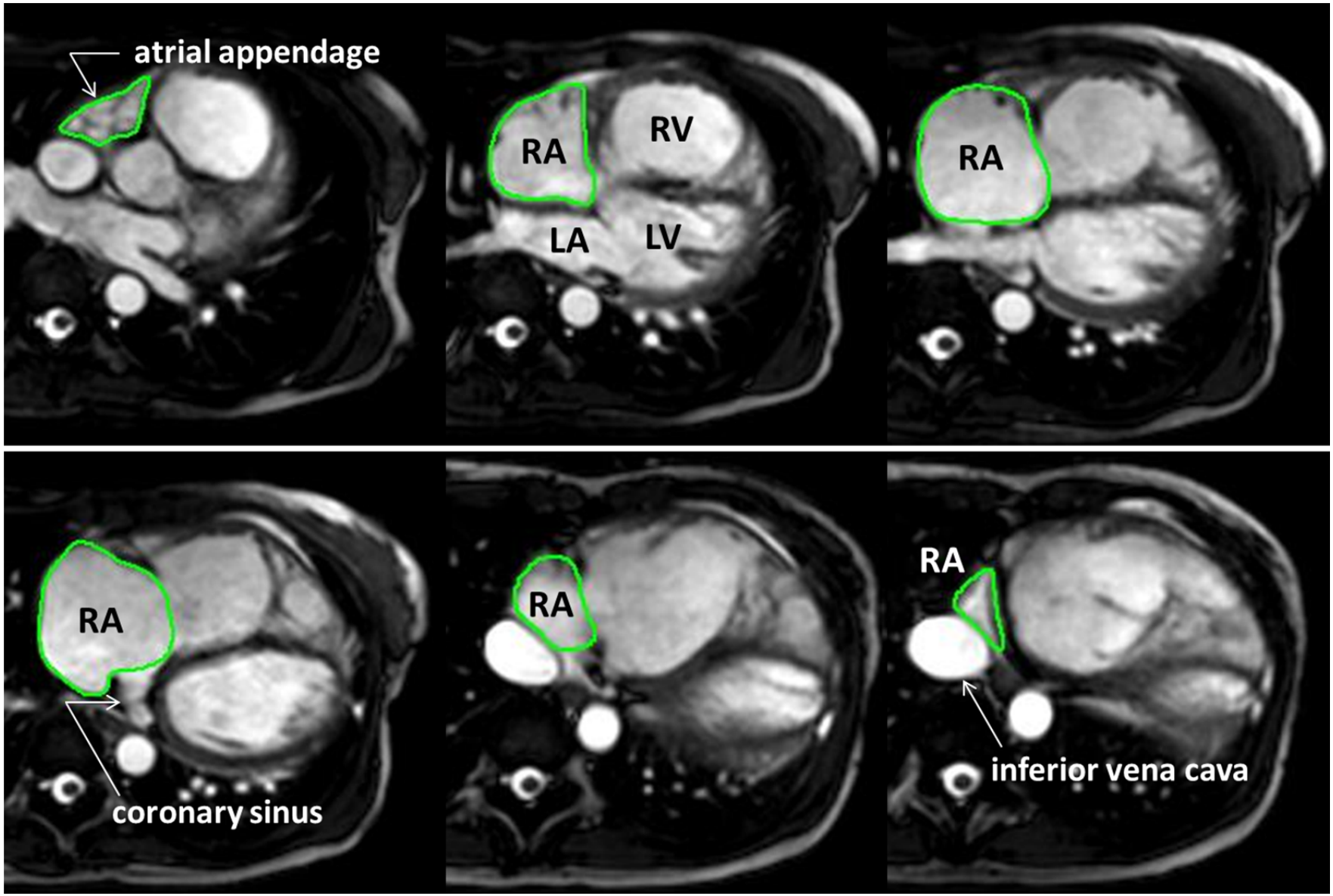

atrial appendage
RA
RV
LA
LV
RA
RA
coronary sinus
RA
RA
inferior vena cava

Figure 2

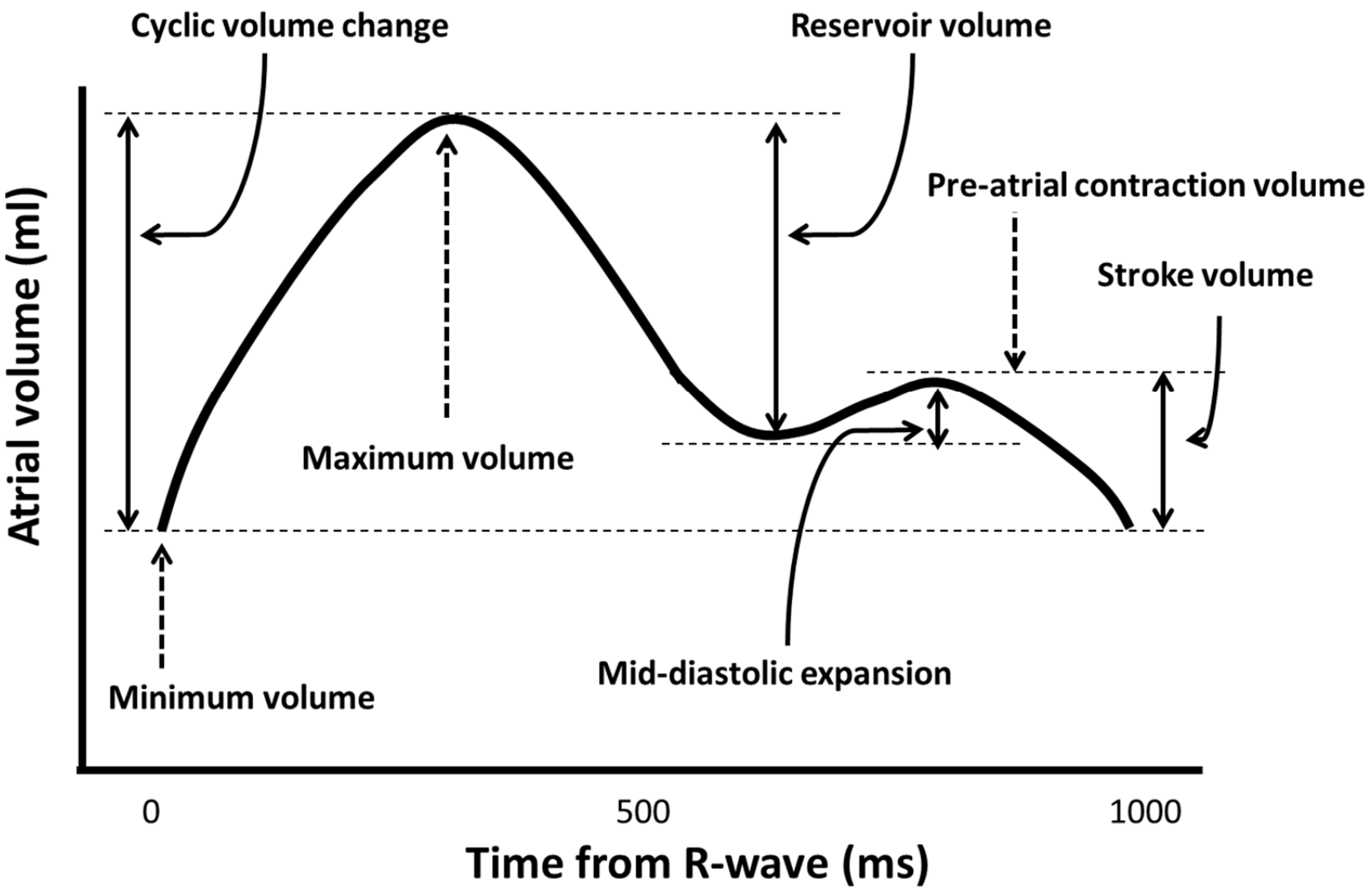

Cyclic volume change
Reservoir volume
Pre-atrial contraction volume
Stroke volume
Maximum volume
Minimum volume
Mid-diastolic expansion
Atrial volume (ml)
0
500
1000
Time from R-wave (ms)

Figure 3

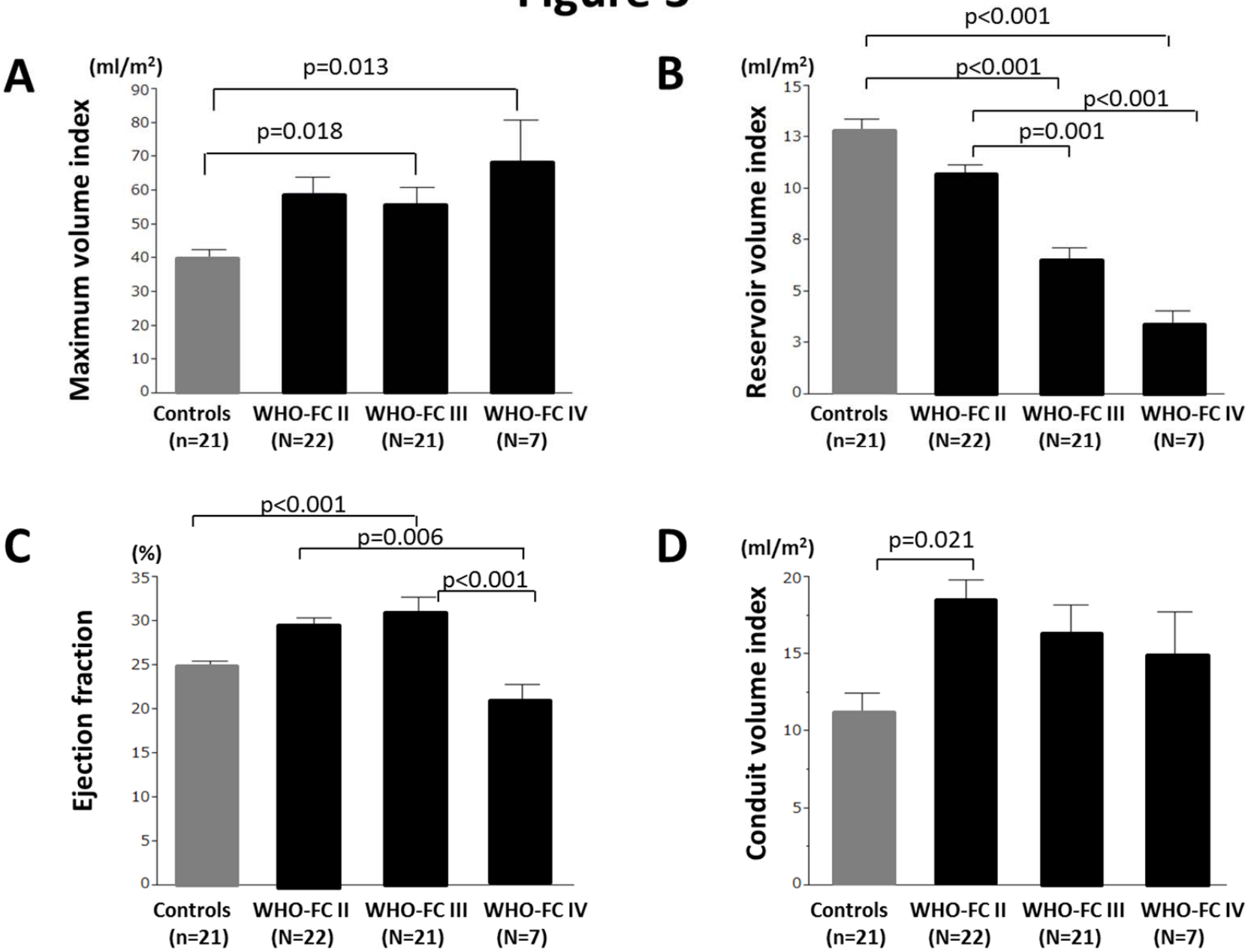

A
(ml/m²)
Maximum volume index
p=0.013
p=0.018
Controls (n=21)
WHO-FC II (N=22)
WHO-FC III (N=21)
WHO-FC IV (N=7)
B
(ml/m²)
Reservoir volume index
p<0.001
p<0.001
p<0.001
p=0.001
C
(%)
Ejection fraction
p<0.001
p=0.006
p<0.001
D
(ml/m²)
Conduit volume index
p=0.021

Figure 4

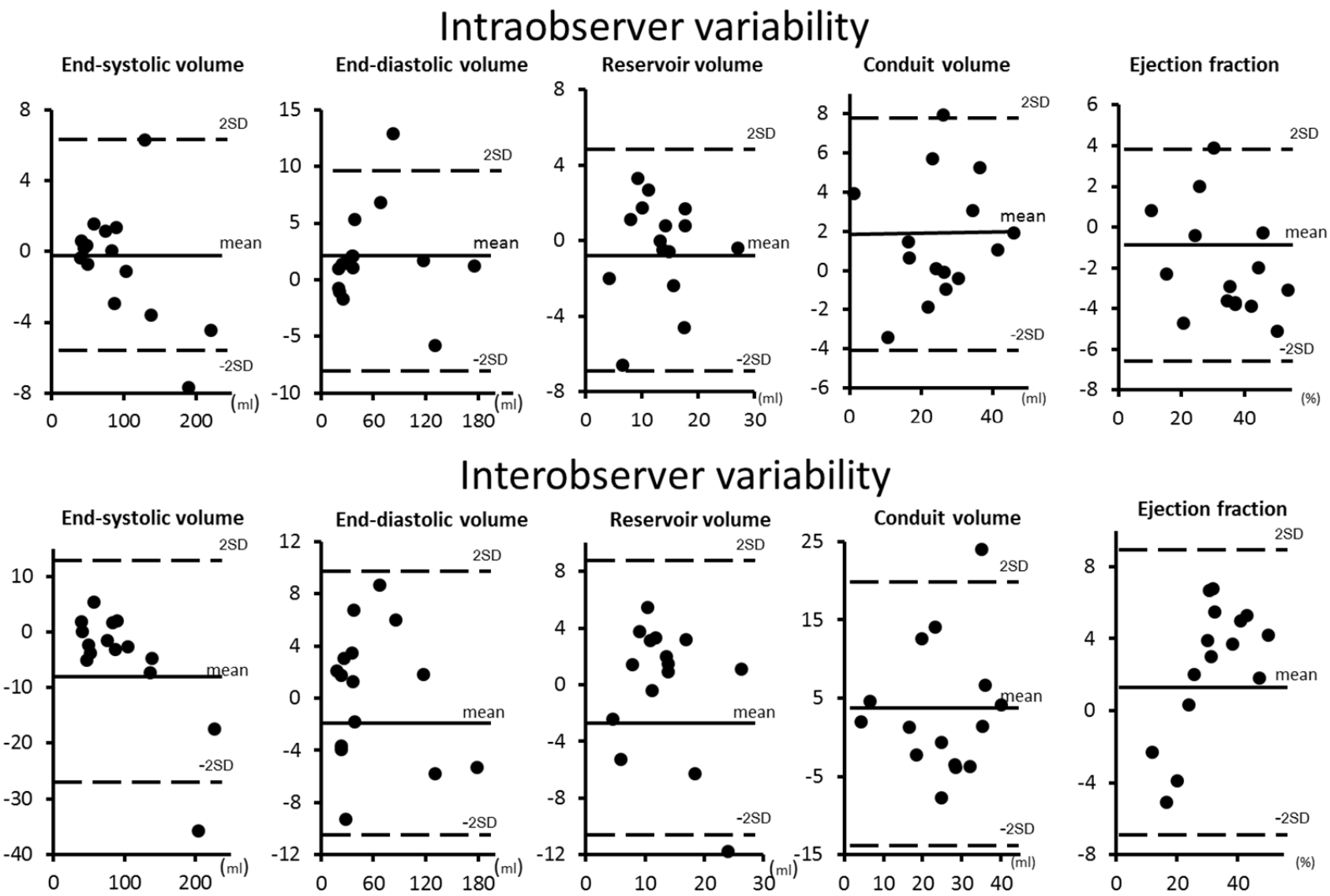

Intraobserver variability
End-systolic volume
End-diastolic volume
Reservoir volume
Conduit volume
Ejection fraction
2SD
mean
-2SD
(ml)
(%)
Interobserver variability
End-systolic volume
End-diastolic volume
Reservoir volume
Conduit volume
Ejection fraction
2SD
mean
-2SD
(ml)
(%)

Table 1. Demographics of participants

	Healthy controls (N=21)	Patients with PH (N=50)	P value
Age	45 ± 8	51 ± 15	0.090
Sex (male/female)	6/15	14/36	0.867
Height (cm)	1.61 ± 0.08	1.57 ± 0.07	0.052
Weight (kg)	58 ± 11	56 ± 11	0.415
Body surface area (m^2)	1.58 ± 0.16	1.55 ± 0.16	0.408
Smoking (none/past/current)	0/1/0	35/12/3	0.065
Systolic systemic blood pressure (mmHg)	115 ± 12	115 ± 22	0.985
Diastolic systemic blood pressure (mmHg)	69 ± 12	65 ±14	0.309
Hypertension	1	3	0.836
Hyperlipidemia	1	6	0.331
Diabetes mellitus	0	1	0.514

PH: pulmonary hypertension

Table 2. Characteristics of patients with pulmonary hypertension

Diagnosis	
Pulmonary arterial hypertension	26 (52%)
Pulmonary veno-occlusive disease	2 (4%)
Pulmonary hypertension due to lung diseases and/or hypoxia	7 (14%)
Chronic thromboembolic pulmonary hypertension	12 (24%)
Others	3 (6%)
WHO-functional class	
II	22 (44%)
III	21 (42%)
IV	7 (14%)
Use of pulmonary hypertension-specific vasodilators	
Beraprost	21 (42%)
Sildenafil/tadalafil	11/0 (22%/0%)
Bosentan/ambrisentan	14/1 (28%/2%)
Intravenous epoprostenol	4 (8%)
Combination therapy	18 (36%)

None	21 (42%)
Domiciliary oxygen therapy	27 (54%)
PH patients with/without either pulmonary hypertension-specific vasodilators or domiciliary oxygen therapy	**39 (76%) / 11 (24%)**
6-minute walk distance (m) *	380 ± 131
Atrial natriuretic peptide (pg/ml) †	45 (15 – 96)
Brain natriuretic peptide (pg/ml)	39 (19 – 185)
Pulmonary hemodynamics	
Systolic pulmonary artery pressure (mmHg)	63 (49 – 77)
Diastolic pulmonary artery pressure (mmHg)	24 (20 – 28)
Mean pulmonary artery pressure (mmHg)	39 (32 – 46)
Pulmonary capillary wedge pressure (mmHg)	8 ± 3
Right ventricular end-diastolic pressure (mmHg)	9 ± 4
Mean right atrial pressure (mmHg)	6 ± 3
Cardiac index (L/min/m^2)	2.7 (2.3 – 3.3)
Pulmonary vascular resistance (dyne· s· cm^{-5})	541 (405 – 797)

*Not performed in five patients with WHO functional class IV, †Not obtained in four patients.

Table 3. Comparison of CMR measurements between healthy controls and patients with pulmonary hypertension

	Healthy controls (N=21)	Patients with PH (N=50)	P value
Right atrial measurements			
Maximum volume index (ml/m^2)	40 (30 - 48)	56 (44 – 70)	<0.001
Minimum volume index (ml/m^2)	20 (15 – 25)	30 (23 – 46)	<0.001
Cyclic volume change index (ml/m^2)	23 ± 8	21 ± 6	0.170
Reservoir volume index (ml/m^2)	13 ± 4	8 ± 4	<0.001
Mid-diastolic expansion index (ml/m^2)	2.4 (1.7 – 2.8)	1.1(0 – 1.8)	<0.001
Pre-atrial contraction volume index (ml/m^2)	29 (23 - 36)	49 (37 - 62)	<0.001
Stroke volume index (ml/m^2)	10 ± 3	16 ± 6	<0.001
Conduit volume index (ml/m^2)	11 ± 7	18 ± 11	0.008
Fractional emptying (%)	51 ± 6	41 ± 10	<0.001
Ejection fraction (%)	34 ± 4	33 ± 9	0.925
Right ventricular measurements			
End-diastolic volume index (ml/m^2)	64 (53 - 79)	99 (82 – 134)	<0.001

End-systolic volume index (ml/m^2)	31 (25 - 41)	63 (48 – 94)	<0.001
Mass index (g/m^2)	19 (17 - 21)	38 (30 – 50)	<0.001
Ejection fraction (%)	53 (46 - 55)	39 (32 – 46)	<0.001
Left atrial measurements			
Maximum volume index (ml/m^2)	35 (30 - 45)	33 (29 – 38)	0.100
Minimum volume index (ml/m^2)	17 (15 - 22)	16 (13 – 19)	0.338
Reservoir volume index (ml/m^2)	12 ± 3	8 ± 3	<0.001
Stroke volume index (ml/m^2)	10 ± 3	10 ± 3	0.777
Conduit volume index (ml/m^2)	12 ± 6	17 ± 6	0.002
Ejection fraction (%)	36 ± 4	38 ± 7	0.202
Left ventricular measurements			
End-diastolic volume index (ml/m^2)	51 (47 - 61)	59 (53 – 67)	0.034
End-systolic volume index (ml/m^2)	19 (15 – 23)	22 (19 – 30)	0.016
Mass index (g/m^2)	44 (48 – 52)	52 (44 - 60)	0.173
Ejection fraction (%)	64 ± 5	60 ± 10	0.046
Pericardial effusion	21/0/0	30/11/9	0.003
(no/partial/circumferential)			

PH: pulmonary hypertension

Table 4. Comparison of RA indices among PH patients receiving different treatment regimens

	Treated by PAH-specific vasodilators			Regimens of PAH-specific vasodilator therapy				
	yes	no	p	Berapro-st alone	PDE 5 inhibitor with or without Berapro-st	ERA with or without Berapro-st	Other regimens	p
n	29	21		7	5	9	8	
Maximum volume index (ml/m^2)	55 (44 - 67)	62 (35 - 75)	0.828	52 (44 - 56)	55 (43 - 93)	52 (38 - 61)	65 (50 - 86)	0.331
Reservoir volume index (ml/m^2)	7 (5 - 12)	7 (4 - 11)	0.615	5 (2- 10)	7 (2 -13)	7 (6 - 13)	10 (7 – 14)	0.231
Ejection fraction (%)	28 (23 - 32)	29 (24 - 34)	0.658	26 (22 - 38)	29 (23 - 39)	30 (26 - 31)	28 (17 – 32)	0.865
Conduit volume	18	14	0.077	16	22	19	19	0.865

index (ml/m^2)	(12 - 24)	(7 - 21)	(12 - 23)	(14 - 30)	(12 - 28)	(16 - 22)

RA, right atrial; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; ERA, endothelin receptor antagonist

Table 5. Correlations between CMR-derived RA indices and other clinical parameters

	RA maximum volume index (ml/m^2)	**RA reservoir volume index (ml/m^2)**	**RA ejection fraction (%)**	**RA conduit volume index (ml/m^2)**
Mean pulmonary artery pressure (mmHg)	$\rho=0.38^*$	$\rho=-0.31^*$	$\rho=-0.39^*$	$\rho=0.25$
RV end-diastolic pressure (mmHg)	$\rho=0.38^*$	$\rho=-0.04$	$\rho=-0.34^*$	$\rho=-0.06$
Mean right atrial pressure (mmHg)	$\rho=0.33^*$	$\rho=-0.01$	$\rho=-0.20$	$\rho=-0.04$
Cardiac index (L/m^2)	$\rho=-0.04$	$\rho=0.39^*$	$\rho=0.23$	$\rho=0.30^*$
Pulmonary vascular resistance ($dyne\cdot s\cdot cm^{-5}$)	$\rho=0.28$	$\rho=-0.37^*$	$\rho=-0.33^*$	$\rho=0.038$
RV end-diastolic volume index (ml/m^2)	$\rho=0.51^*$	$\rho=-0.14$	$\rho=-0.32^*$	$\rho=0.37^*$
RV mass index (g/m^2)	$\rho=0.58^*$	$\rho=-0.14$	$\rho=-058^*$	$\rho=0.03$
RV ejection fraction (%)	$\rho=-0.32^*$	$\rho=0.39^*$	$\rho=0.56^*$	$\rho=0.09$

Atrial natriuretic peptide (pg/ml)	ρ=0.46*	ρ=-0.33*	ρ=-0.54*	ρ=0.13
Brain natriuretic peptide (pg/ml)	ρ=0.48*	ρ=-0.23	ρ=-0.53*	ρ=0.13
6-minute walk distance (m)	ρ=-0.11	ρ=0.32*	ρ=0.03	ρ=-0.10

CMR: cardiac magnetic resonance, RA: right atrial, RV: right ventricular, * $p<0.05$

Table 6. Multivariate regression analysis of RA indices and RV parameters

RA maximum volume index (ml/m^2)			
Explanatory variables	**Estimates**	**Confidential interval**	**P value**
RV end-diastolic pressure (mmHg)	1.7	0.27 – 3.13	0.021
RV end-diastolic volume index (ml/m^2)	0.28	0.13 – 0.42	<0.001
RV mass index (g/m^2)	0.36	0.04 – 0.67	0.026
RV ejection fraction (%)	0.33	-0.33 – 0.98	0.323
RA reservoir volume index (ml/m^2)			
Explanatory variables	**Estimates**	**Confidential interval**	**P value**
RV end-diastolic pressure (mmHg)	0.06	-0.27 – 0.40	0.693
RV end-diastolic volume index (ml/m^2)	0.02	-0.02 – 0.05	0.294
RV mass index (g/m^2)	-0.01	-0.08 – 0.07	0.836
RV ejection fraction (%)	0.16	0.01 – 0.31	0.037
RA ejection fraction (%)			
Explanatory variables	**Estimates**	**Confidential interval**	**P value**
RV end-diastolic pressure (mmHg)	-0.04	-0.60 – 0.52	0.88
RV end-diastolic volume index (ml/m^2)	0.01	-0.04 – 0.07	0.613

RV mass index (g/m^2)	-0.19	-0.31 – -0.07	0.003
RV ejection fraction (%)	0.25	-0.01 – 0.51	0.054

RA conduit volume index (ml/m^2)

Explanatory variables	**Estimates**	**Confidential interval**	**P value**
RV end-diastolic pressure (mmHg)	-0.4	-0.99 – 0.18	0.166
RV end-diastolic volume index (ml/m^2)	0.14	0.08 – 0.20	<0.001
RV mass index (g/m^2)	0.07	-0.06 – 0.20	0.295
RV ejection fraction (%)	0.58	0.31 – 0.85	<0.001

Outcome variables: RA maximum volume index, RA reservoir volume index, RA ejection fraction, and RA conduit volume index. RV: right ventricular, RA: right atrial