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ORIGINAL ARTICLE

Usefulness of three-dimensional echocardiography in assessing right ventricular function in patients with primary pulmonary hypertension

Makoto Amaki[1], Satoshi Nakatani[1,2], Hideaki Kanzaki[1], Shingo Kyotani[1], Norifumi Nakanishi[1], Chiaki Shigemasa[3], Ichiro Hisatome[4] and Masafumi Kitakaze[1]

Although right ventricular (RV) function is an important determinant of morbidity and mortality in patients with primary pulmonary hypertension (PPH), there have been no clinically validated quantification methods to date. The first derivative of RV pressure (d*P*/d*t*) is a good index of contractility, but it depends on preload. d*P*/d*t* divided by end-diastolic volume (EDV), that is, d*P*/d*t*/EDV, on the other hand, is an index of contractility relatively independent of preload. However, the measurement of accurate RV EDV is difficult because of RV complex geometry. Real-time three-dimensional (3D) echocardiography allows us to measure ventricular volume irrespective of its shape. To investigate the clinical feasibility and significance of 3D echocardiography in evaluating RV function in patients with PPH by measuring RV EDV and d*P*/d*t*/EDV, 13 patients with PPH (41 ± 20 years, four men) underwent echocardiography, a 6-min walk distance (mWD) test and blood sampling within 1 week of invasive hemodynamic measurements. RV d*P*/d*t* was estimated from a continuous wave Doppler-determined tricuspid regurgitant velocity. RV EDV was measured by both two-dimensional (2D) biplane Simpson method (EDV_{2D}) and real-time 3D echocardiography (EDV_{3D}). RV d*P*/d*t*/EDV was calculated using EDV_{2D} and EDV_{3D}. EDV_{3D} showed better correlations than EDV_{2D} with the invasive and non-invasive parameters of RV function, suggesting the validity of volume measurement by 3D echocardiography. RV d*P*/d*t*/EDV_{3D} correlated well with disease severity, whereas d*P*/d*t* and d*P*/d*t*/EDV_{2D} did not. In patients with PPH, 3D-echocardiography-determined RV d*P*/d*t*/EDV and EDV seem to be potential markers of disease severity.

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INTRODUCTION

Primary pulmonary hypertension (PPH) is an uncommon but progressive disease characterized by elevated pulmonary artery pressure with pathological changes in precapillary pulmonary artery.[1] In the 1990s, treatment with a continuous intravenous infusion of epoprostenol was shown to improve the symptoms and prognosis of PPH. However, prognosis of the disease still remains poor. Right ventricular (RV) function is an important determinant of morbidity and mortality in patients with PPH.[2,3] Right heart catheterization parameters, such as cardiac index, right atrial pressure and pulmonary artery pressure, correlate well with prognosis of PPH patients,[3,4] and are the standard for assessing the severity and prognosis of PPH.[2,3] However, catheter examination is a high-risk procedure for PPH patients and therefore is not suitable for repeated assessment. On the other hand, the first derivative of RV pressure (d*P*/d*t*), which can be estimated using continuous-wave Doppler echocardiography, is known to be a good index of contractility, but it is preload dependent.[5] In contrast, d*P*/d*t* divided by end-diastolic volume (EDV), d*P*/d*t*/EDV, is an index of contractility that is relatively independent of preload.[6] It is but not routinely used in the assessment of RV function, because the complexity of RV geometry hampers accurate measurement of RV volume. Real-time three-dimensional (3D) echocardiography allows us to measure RV volume irrespective of its shape.[7–9]

The purpose of this study was to determine the clinical significance of 3D-echocardiography-determined RV d*P*/d*t*/EDV by comparing it with invasive measurements in patients with PPH.

[1]Division of Cardiology, National Cardiovascular Center, Osaka, Japan; [2]Division of Functional Diagnostics, Department of Health Sciences, Osaka University Graduate School of Medicine, Osaka, Japan; [3]Division of Regenerative Medicine and Therapeutics, Department of Genetic Medicine and Regenerative Medicine and Therapeutics, Institute of Regenerative Medicine and Biofunction, Tottori University Graduate School of Medical Science, Tottori, Japan and [4]Division of Molecular Medicine and Therapeutics, Department of Multidisciplinary Internal Medicine, Tottori University Faculty of Medicine, Tottori, Japan
Correspondence: Dr S Nakatani, Division of Functional Diagnostics, Department of Health Sciences, Osaka University Graduate School of Medicine, 1-7 Yamada-oka, Suita, Osaka 565-0871, Japan.
E-mail: nakatani@sahs.med.osaka-u.ac.jp
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METHODS

Patient population

We studied 20 consecutive patients with PPH who had been referred to our hospital. PPH was diagnosed according to the criteria established by the National Heart, Lung and Blood Institute for the PPH patient registry.[4]

Seven patients were excluded from the analysis for the following reasons. In four patients, the heart size exceeded the pyramidal scan volume of 3D echocardiography. In three patients, continuous-wave Doppler flow profile was not satisfactory enough to determine d*P*/d*t*. As a result, the study subjects consisted of 13 patients (average age: 42 ± 16 years, four men).

Study protocol

Patients received echocardiography, unencouraged 6-min walk distance (6 mWD) test and blood sampling for brain natriuretic peptide (BNP) within 1 week of right heart catheterization. The study protocol was approved by our ethical committee and informed consent was obtained from each patient.

Hemodynamic studies

A7 F Goodtec Thermodilution Catheter (Goodman Co., Nagoya, Japan) was used to measure right-heart hemodynamics. Measurements included heart rate, mean right atrial pressure, mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure (PCWP) and mixed venous oxygen saturation (SvO_2). Cardiac output (CO) was obtained using the calculated Fick method, and cardiac index (CI) was determined. Pulmonary vascular resistance (PVR) was calculated by using the formula PVR=80×(mPAP−PCWP)/CO.

Echocardiographic measurements

Two-dimensional (2D) and real-time 3D echocardiograms were performed using a commercially available ultrasonograph (iE33, Philips Medical System, Best, The Netherlands). Each patient was examined in a supine position. Real-time 3D echocardiographic images were acquired in a transthoracic apical full-volume mode using a matrix-array transducer (X4, 2–4 MHz, Philips Medical System). The 3D images were stored in a compact disk for off-line analysis.

2D echocardiographic assessment of RV EDV and the right atrial area

Right ventricular EDV_{2D} was measured using 2D echocardiography by the modified Simpson method, tracing the endocardium of the right ventricle at four- and two-chamber views at end-diastolic phase. For both apical views, end-diastolic frames were selected as those captured at the peak of the R wave.

3D echocardiographic assessment of RV end-diastolic volume

Using the full-volume data obtained by 3D echocardiography, RV EDV_{3D} was measured with a commercially available software (3DQ advance QLAB v4.1, Philips Medical System). Care was taken to include the entire RV cavity within the pyramidal scan volume. The 3D volume dataset was first displayed in three different cross-sections that could be modified interactively. The anatomically correct four- and two-chamber views were displayed simultaneously. Markers were then placed onto the tricuspid annulus and the apex. Using these markers, endocardial contours were traced automatically by the software at end-diastole with the papillary muscles included in the RV cavity. By rotating and scanning the three different cross-sections, manual correction was applied if needed.

Doppler echocardiography

Right ventricular d*P*/d*t* was estimated from continuous-wave Doppler-determined tricuspid regurgitant velocity.[5] The continuous-wave Doppler flow profile of tricuspid regurgitation was obtained with the Doppler beam parallel to the direction of the regurgitant jet, with the aid of color Doppler echocardiography at the apical view. Recordings were carried out at a speed of 100 mm s^{-1}. Similar to left-ventricular d*P*/d*t* estimation using mitral regurgitation, RV d*P*/d*t* was calculated using the interval between 1 and 3 m s^{-1} on the tricuspid regurgitation velocity spectrum.

Right-ventricular d*P*/d*t*/EDV was calculated using both EDV_{2D} and EDV_{3D}. RV d*P*/d*t*, RV EDV_{2D}, RV EDV_{3D}, RV d*P*/d*t*/EDV_{2D} and RV d*P*/d*t*/EDV_{3D} were compared with conventional prognostic markers of PPH.

Interobserver and intraobserver variability

To determine the interobserver variability in the 2D and RT3D evaluations of RV EDV, all measurements were repeated by a second observer, who was blinded to the values obtained by the first observer. Interobserver variability was calculated for each patient as the absolute difference between the two observers, expressed as percentage of their mean. To assess intraobserver variability, all measurements were repeated using the stored images 1 month later by an observer who was blinded to the results of the previous measurements. Intraobserver variability was calculated as the difference between the two measurements, and expressed as percentage of their mean.

Statistical analysis

All analyses were performed using JMP statistical software (a business unit of SAS, version 5.1.1, SAS Inc., Cary, NC, USA). Data were summarized as mean ± s.d. for continuous variables and the number of subjects (%) for categorical variables. For all statistical assessments, *P*-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Baseline demographic features, the plasma BNP levels, 6-mWD results and hemodynamic characteristics of the 13 patients are shown in Table 1. Most of the patients were women, and their New York Heart Association (NYHA) classes were II–III. Continuous intravenous epoprostenolol infusion was given to 39% of the patients. Bosentan, an orally active dual endothelin-receptor antagonist, was given to 46%, and Beraprost sodium was given to 46% of the patients. Mean pulmonary artery pressure, measured by catheter examination, ranged from 42 to 74 mm Hg. CI, measured using the calculated Fick formula,

Table 1 Clinical features, exercise capacity and hemodynamic characteristics

	Mean ± s.d. or n *(%)*
Age (years)	42 ± 17
Male gender (*n* (%))	4 (27)
Body surface area (cm^2)	1.52 ± 0.12
NYHA (n (%))	
II	7 (54)
III	6 (46)
Medication (n (%))	
Continuous epoprostenolol infusion	5 (39)
Bosentan	6 (46)
Beraprost sodium	6 (46)
Furosemide	7 (54)
BNP (pg per 100 ml)	195 ± 140
6-min walk distance (m)	445 ± 75
Mean heart rate (beats per min)	76.8 ± 32
Mean PA pressure (mm Hg)	53.2 ± 10.1
Mean RA pressure (mm Hg)	6.2 ± 4.4
PVR (dyne×s cm^{-5})	1280 ± 400
Cardiac index (l min^{-1})	2.0 ± 0.4
Mixed venous O_2 saturation (%)	59.1 ± 18.3

Abbreviations: BNP, brain (B-type) natriuretic peptide; NYHA, New York Heart Association functional class; PA, pulmonary artery; RA, right atrial; PVR, pulmonary vascular resistance.

Table 2 Echocardiographic features

Variable	
EDV_{2D} (ml)	104.4 ± 32
EDV_{3D} (ml)	84.7 ± 23
d*P*/d*t* (mm Hg s^{-1})	625 ± 124
d*P*/d*t*/EDV_{2D} (mm Hg s ml^{-1})	6.6 ± 2.8
d*P*/d*t*/EDV_{3D} (mm Hg s ml^{-1})	7.8 ± 1.9
Tricuspid regurgitation grade	2.3 ± 1.0
(RV−RA) pressure gradient (mm Hg)	78.3 ± 37

Abbreviations: EDV_{2D}, end-diastolic volume measured by two-dimensional echocardiography; EDV_{3D}, end-diastolic volume measured by three-dimensional echocardiography; RV–RA: right ventriculo-atrial.

Table 3 Correlation coefficient

	CI	*mRAP*	*SvO_2*	*BNP*	*6 mWD*
EDV_{2D}	NS	0.70**	NS	0.58*	NS
EDV_{3D}	−0.69**	0.65*	−0.70**	NS	NS
d*P*/d*t*	NS	NS	NS	NS	NS
d*P*/d*t*/EDV_{2D}	NS	NS	NS	NS	NS
d*P*/d*t*/EDV_{3D}	0.60*	−0.55*	NS	−0.61*	NS

Abbreviations: 6 mWD, 6-min walk distance; CI, cardiac index; EDV_{2D}, end-diastolic volume measured by two-dimensional echocardiography; EDV_{3D}, end-diastolic volume measured by three-dimensional echocardiography; mRAP, mean right atrial pressure; SvO_2, mixed venous oxygen saturation.
*$P<0.05$, **$P<0.01$.

ranged from 1.4 to 2.7 l/min. The distance of 6-min walk was shorter in patients with class III, compared with those with NYHA class II (370 ± 28 vs 491 ± 21 m, $P<0.01$). CI was smaller and PVR and BNP were larger in patients with NYHA class III, but the difference was not significant. Echocardiographic measurements are shown in Table 2. EDV measured by 2D echocardiography was significantly larger than that measured by 3D echocardiography ($P<0.05$).

Relationship between echocardiographic parameters and hemodynamics

The correlation coefficients between echocardiographic measurements and hemodynamics, both plasma BNP levels and 6 mWD are listed in Table 3. EDV_{3D} showed better correlations with the hemodynamics compared with EDV_{2D}. EDV_{2D} had significant correlations with mean RAP and plasma BNP levels, but not with CI and SvO_2. RV d*P*/d*t* and d*P*/d*t*/EDV_{2D} were not correlated with any of those measurements. However, RV d*P*/d*t*/EDV_{3D} showed a good correlation with the invasive and the non-invasive parameters of RV function (Table 3).

Reproducibility

The interobserver variability was 25 ± 13% of the measured EDV_{2D}, ranging between 5 and 55% between patients, and 11 ± 8% of the measured EDV_{3D}, ranging between 3 and 23% ($P<0.05$ between techniques). The intraobserver variability was 21 ± 8% of the measured EDV_{2D}, ranging between 11 and 41% between patients, and 9 ± 5% of the measured EDV_{3D}, ranging between 3 and 19% between patients ($P<0.05$ between techniques).

DISCUSSION

In this study, we found 3D-echocardiography-derived RV EDV and d*P*/d*t*/EDV showed a good correlation with indices of the cardiac function compared with those determined by 2D echocardiography.

Assessment of severity and the prognosis of PPH patients with conventional echocardiographic indices

Earlier investigators showed the clinical significance of 2D echocardiographic parameters in patients with PPH. Increasing severity of pericardial effusion was found to be associated with prognosis of PPH.[10] Another study showed pericardial effusion and indexed RA were independently associated with the mortality.[11] However, these parameters simply reflect the end stage of RV failure. It is important to assess the disease status and the effect of the therapy in the management of PPH. Therefore, quantitative analysis of RV function is necessary in the clinical setting. Our findings shed light on the possibility of determining the severity of PPH non-invasively.

Index of RV systolic function

There have been several methods for assessing RV function. The conductance catheter is a frequently used instrument to assess RV function.[12,13] Conductance-derived pressure–volume data are preload-independent measurements of RV contractile function. However, conductance catheterization is invasive and not cost-effective. Therefore, they are predominantly used as a research tool for assessment of ventricular function. Attempt has been made to measure RV function by echocardiography, but the simple M-mode or 2D echocardiographic indices cannot be reliably applied for assessing the RV function because of RV complex geometry.[14] Other non-invasive methods, such as MRI, can be used accurately to measure end-diastolic and end-systolic volumes and calculate the ejection fraction,[15,16] but these methods are time consuming and cannot be performed at the bedside.

Left-ventricular d*P*/d*t* has been well established as an index of contractility and is known to correlate well with the prognosis of left-ventricular dysfunction.[17] There have been few studies on Doppler-derived RV d*P*/d*t*. Anconina *et al.*[18] measured the mean rate of right ventriculo-atrial pressure gradient and showed good correlation with invasively determined maximal d*P*/d*t*. We have previously reported that non-invasive measurement of RV peak-positive d*P*/d*t* by echocardiography correlated well with that derived by catheterization irrespective of the level of right atrial pressure.[19] However, d*P*/d*t* is dependent on preload,[5] and may overestimate the contractility in RV dilatation accompanied by PPH.

Measuring 3D-echocardiography-derived RV d*P*/d*t*/EDV

In this study, we analyzed RV d*P*/d*t* divided by RV EDV obtained by 3D echocardiography. As RV EDV has been shown to be a marker of preload,[20,21] RV d*P*/d*t* divided by RV EDV should be a marker of preload-independent RV function. We have shown that RV d*P*/d*t*/EDV_{3D} correlated well with both invasively and non-invasively derived RV function indices.

Although there are many parameters that relate to the severity and prognosis of PPH, no single parameter can be the gold standard. We used invasive measurements as the next best standard and investigated the correlations. The correlation coefficients were not so high, but we believe that RV d*P*/d*t*/EDV_{3D} was still clinically useful because no other parameters were good enough to assess the severity of the disease.

Study limitations

Measuring RV volume by 3D echocardiography is challenging in the severely enlarged RV, especially in patients in the end stage. In our study, we could not measure RV volume in 4 out of 20 patients by 3D echocardiography, because the RV size exceeded the scan volume. It is a major limitation of this study. The latest version of the 3D

ultrasound equipment provides us the wider scan area, which may increase the clinical applicability.

d*P*/d*t* is also affected by afterload. However, in patients with PPH, pulmonary artery pressure is elevated, and the timing of the opening of pulmonary valve is delayed. Therefore, the influence of afterload can be neglected.

Medical therapy also could have affected the result. However, the number of patients with oral medication or with intravenous epoprostenolol infusion was too small to investigate the effect.

In this study, all patients had echocardiography and 6-mWD test within 1 week of catheterization. In addition to the scarcity of PPH itself, this strict criterion was also partly the reason why the number of the patients was small.

Our study population consisted of rather severe PPH patients. It is a limitation of this study that we did not have patients with mild-to-moderate PPH among our study subjects. We believe that our method is applicable even to those with milder disease. It is warranted to conduct larger trials to extend these findings to patients with a different stage of disease.

Clinical implications

By using our index, we could estimate the catheterization-derived RV function in patients with PPH non-invasively. It is useful in a setting where the patient condition is unstable and the catheter examination is extremely dangerous. It is also useful when a new drug is administered and the catheter-derived index is needed for repeated assessment of the drug effect.

CONCLUSION

In patients with PPH, 3D-echocardiography-determined RV EDV and d*P*/d*t*/EDV correlated well with prognostic markers of PPH, including CI, mean right atrial pressure and BNP. 3D-echocardiography-determined RV d*P*/d*t*/EDV seems to be a potential marker of disease severity, and may be useful in assessing therapeutic effects and the prognosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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