Echocardiographic surrogates of right atrial pressure in pulmonary hypertension

Ryo Watanabe, Hirohisa Amano, Shigeru Toyoda, Masashi Sakuma

Shichiro Abe, Toshiaki Nakajima, Teruo Inoue

The Department of Cardiovascular Medicine, Dokkyo Medical University School of Medicine, Mibu, Japan

For correspondence: Hirohisa Amano, MD, PhD

Department of Cardiovascular Medicine

Dokkyo Medical University School of Medicine

880 Kitakobayashi, Mibu, Tochigi 321-0293, Japan

TEL: 81-282-87-2146

FAX: 81-282-86-5633

E-mail: amano@dokkyomed.ac.jp

Abstract

Right atrial pressure (RAP), a representative parameter of right heart failure, is very important for prognostic evaluation and risk assessment in pulmonary hypertension. However, its measurement requires invasive cardiac catheterization. In this study, we determined the most accurate echocardiographic surrogate of catheterization-based RAP. In 23 patients with pulmonary hypertension, a total of 66 cardiac catheterization procedures were performed along with 2-dimensional echocardiography. We evaluated tricuspid E/A, E', A' and E/E', and estimated RAP by the respirophasic variation of the inferior vena cava diameter (eRAP-IVCd) as possible surrogates of catheterization-based RAP. In simple linear regression analysis, E/A (R=0.452, P=0.0001) and eRAP-IVCd (R=0.505, P<0.0001) were positively correlated with catheterization-based RAP, whereas A' (R=-0.512, P<0.0001) was negatively correlated with RAP. In multiple regression analysis, A' was the most significant independent predictor of catheterization-based RAP (R=-0.375, P=0.0007). In 16 patients who had multiple measurements, there were a total of 43 measurements before and after medication changes. The absolute change in catheterization-based RAP was negatively correlated with the percent change in A'. Receiver operating characteristic curve analysis indicated that the optimal cut-off value of A' to predict a catheterization-based RAP>10 mmHg was 11.3 cm/s (area under the curve=0.782, sensitivity=0.70, specificity=0.78). The echocardiographic parameter, A', was the best surrogate of catheterization-based RAP.

Key words: right atrial pressure, cardiac catheterization, echocardiography, A', pulmonary hypertension

Introduction

Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) over 25 mmHg. Pathophysiological deterioration of pulmonary hypertension can cause an increase in PAP over the long-term, and subsequent continuous right heart overload leads to right heart failure. The presence of the right heart failure greatly contributes to the prognosis of patients with pulmonary hypertension [1, 2]. In patients who have right heart failure, decreased cardiac output causes PAP to reach a limit or even decrease because PAP is greatly affected by cardiac output [3]. A paradoxical decrease in the mPAP, often seen in patients with advanced-stage pulmonary hypertension, is due to this pathophysiological mechanism. Right atrial pressure (RAP) is a representative parameter of right heart failure, but its measurement requires invasive cardiac catheterization. On the other hand, several studies have estimated RAP in pulmonary hypertension using echocardiographic parameters [2, 4-7]. Two-dimensional (2D) echocardiography is a simpler, noninvasive and less expensive method that is frequently performed, even in outpatient clinics; thus, the American Society of Echocardiography (ASE) has suggested several right heart function parameters [4]. In the present study, we assessed the relationship between several echocardiographic right heart function parameters and catheterization-based RAP to determine the most accurate echocardiographic surrogate.

Methods

Subjects

Subjects included 23 patients (6 males and 17 females aged 59±17 years old) with pulmonary hypertension. Pulmonary hypertension was diagnosed using right cardiac catheterization and pulmonary angiography based on the 2012 guidelines of the Japanese Circulation Society (JCS 2012). Basal diseases were idiopathic pulmonary artery hypertension in 11 patients and chronic thromboembolic pulmonary hypertension in 12. The severity of dyspnea based on the World Health Organization (WHO) functional classification was class II in 17 patients, class III in 4 and class IV in 2. This study was approved by the ethics committee of Dokkyo Medical University, and all patients provided written informed consent before participation.

Methods

In the 23 patients enrolled, a total of 66 cardiac catheterization procedures were performed (16 patients underwent multiple procedures with a maximum of 7 procedures per patient) (Table 1). 2D echocardiography was also performed within several days of each cardiac catheterization procedure. Patients were on the following medications at the time of the 66 measurements: none in 10 measurements, prostacyclin (prostaglandin I2, PGI2) drugs alone in 11, phosphodiesterase 5 (PDE-5) inhibitors alone in 2, endothelin (ET) receptor antagonists alone in 1, PGI2 plus PDE-5 inhibitors in 12, PGI2 plus ET receptor antagonists in 4, PGI2 plus PDE-5 inhibitors plus ET receptor antagonists in 25, and a PGI2+ET receptor antagonist plus a soluble guanylate cyclase (sGC) stimulant in 1 (Table 1). In this study, patients with atrial fibrillation were not included.

Right cardiac catheterization

Right cardiac catheterization was performed using a 6F Swan-Ganz catheter (Fukuda Denshi, Tokyo, Japan) via the right femoral approach. All of the measurements were performed at the end-expiratory phase. We measured RAP, systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), pulmonary capillary wedge pressure (PCWP) and cardiac output (CO). The CO was measured more than 3 times by the thermodilution method, and 3 measurements that agreed within 10% were averaged.

The mPAP was calculated as: mPAP=[dPAP+1/3(sPAP-dPAP)], and the pulmonary vascular resistance (PVR) as: PVR=(mPAP–PCWP)/CO×80 (dyne·sec·cm^{-5}).

2D echocardiography

Transthoracic echocardiography was performed, and the images were analyzed by two experienced echocardiographers using commercially-available equipment (Vivid 7, GE Medical Systems, Horton, Norway). Right ventricular diastolic inflow was recorded at the tricuspid valve leaflet in the apical view using pulsed Doppler. The peak early diastolic flow velocity (E), E-wave deceleration time and peak atrial systolic flow velocity (A) were determined based on the blood flow patterns, and the ratio of the E-wave to A-wave (E/A) was calculated. The early diastolic (E') and atrial systolic tricuspid annular motion velocity (A') were determined at the tricuspid annular septum in the four-chamber apical view using tissue Doppler imaging, and the E to E' ratio (E/E') was calculated. These parameters were determined by recording 3 cardiac cycles

under stable conditions, and the mean of the measurements was used for analysis. In addition, the inferior vena cava (IVC) diameter was measured in the image from the subxiphoid approach, and we estimated RAP (eRAP) using the respirophasic variation of the IVC diameter (eRAP-IVCd) (Table 2) [4]. In this study, we selected the following 5 parameters as possible surrogates of catheterization-based RAP: E/A, E', A', E/E' [4], and eRAP-IVCd [2].

Statistical analysis

Data are expressed as the mean ± standard deviation and n (%). All statistical analyses were performed using statistical software (Stat Mate IV, ATMS, Tokyo, Japan). Intra-group comparisons for continuous variables were performed using a paired t test. The correlation between catheterization-based RAP and each of the five echocardiographic variables was determined by simple linear regression analysis. Multiple regression analysis was performed to assess the independent correlation of RAP measured by right heart catheterization with the echocardiographic right heart function parameters. Receiver operating characteristic (ROC) curve analysis was performed to predict a catheterization-based RAP>10 mmHg using A', and sensitivity, specificity and area under the curve (AUC) were calculated. P values < 0.05 were considered significant.

Results

Cardiac catheterization and echocardiographic parameters for the 66 measurements are shown in Table 3. The average RAP measured by cardiac catheterization was 6.6±3.5 mmHg. Among the 5 echocardiographic parameters assessed, E/A (R=0.452, P=0.0001) and eRAP-IVCd (R=0.505, P<0.0001) were positively correlated with catheterization-based RAP, whereas A' (R=-0.512, P<0.0001) was negatively correlated with RAP in simple linear regression analysis. However, E' and E/E' were not correlated with catheterization-based RAP (Table 4, Fig. 1-A). In multiple regression analysis, A' was the most significant independent predictor of catheterization-based RAP (R=-0.375, P=0.0007) (Table 5).

In the 16 patients who had multiple measurements to assess the effects of new or additional medical treatments, we assessed the relationship between the change in catheterization-based RAP and that in A'. In case of measurements more than 3 times, the changes in the most recent 2 measurements were evaluated. There were a total of 43 measurements before and after medication changes. New or additionally prescribed drugs included PGI2 drugs in 11 patients, PDE-5 inhibitors in 10, ET receptor antagonists in 19, an sGC stimulant in 1, a PGI2+ET receptor antagonist in 1, and a PDE-5 inhibitor plus ET receptor antagonist in 1. Simple linear regression analysis showed that the change in catheterization-based RAP (value after treatment–baseline value: mmHg) was negatively correlated with the percent change in A' ([value after treatment–baseline value]×100/baseline value; %) (Fig 1-B).

Finally, ROC curve analysis using the 66 measurements indicated that the optimal cut-off value of A' to predict a catheterization-based RAP>10 mmHg was 11.3 cm/s (AUC=0.782, sensitivity=0.70, specificity=0.78) (Fig. 2).

Discussion

The major finding of the present study is that among several echocardiographic parameters, A' was the most powerful surrogate of catheterization-based RAP in patients with pulmonary hypertension.

Right heart catheterization is essential to confirm the diagnosis of pulmonary hypertension, assess right heart function or the severity of hemodynamic impairment and perform vasoreactivity testing of the pulmonary circulation in selected patients. Although these procedures have low morbidity and mortality rates when performed at expert centers [8], the risk increases in patients with severe pulmonary hypertension (WHO or NYHA class IV) [9, 10]. In addition to cardiac catheterization, magnetic resonance imaging and radionuclide angiography are also available to assess right heart function. However, these modalities require large facilities and are expensive. In contrast, 2D echocardiography is a simpler, noninvasive and less expensive method that is frequently used to assess right heart function, and this method can even be used in outpatient clinics [11, 12].

We have been investigating surrogate echocardiographic parameters as an alternative to various indices measured by cardiac catheterization or radionuclide angiography for hemodynamic assessment in patients with pulmonary hypertension. Our previous results showed that the best surrogate of catheterization-based PAP was an echocardiographic parameter, (PEP/AcT)/(PEP+ET), where PEP was pre-ejection

period, AcT was acceleration time, and ET was ejection time [13]. In addition, the best echocardiographic alternative to right ventricular ejection fraction measured by radionuclide angiography was right ventricular Tei index [14]. In the present study, we focused on RAP, because the recent European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines indicated that comprehensive prognostic evaluation and risk assessment for pulmonary hypertension should be based on RAP. In these guidelines, patients with an RAP>14 mmHg were considered high risk (estimated 1-year mortality>10%), and those with an RAP of 8-14 mmHg were considered moderate risk (estimated 1-year mortality of 5-10%) [2]. Thus, RAP is considered the most important cardiac catheterization parameter to predict the prognosis of pulmonary hypertension, and we attempted to find the best echocardiographic surrogate of RAP.

In the present study, we selected 5 echocardiographic parameters as possible surrogates for catheterization-based RAP. Four of these surrogates (E/A, E', A' and E/E'), are recommended as indices of right ventricular diastolic function in the ASE guidelines [4]; and the fifth surrogate, eRAP-IVCd, is strongly recommended as an index of catheterization-based RAP in the ESC/ERS guidelines [2]. Simple regression analysis showed that E/A, A' and eRAP-IVCd were correlated with RAP. However, multiple regression analysis showed that A' was the most significant independent predictor of catheterization-based RAP. In addition, the absolute change in catheterization-based RAP was negatively correlated with the percent change in A'. Thus, we believe that A' is the best surrogate of catheterization-based RAP in patients with pulmonary hypertension. A' is thought to reflect atrial contraction [15], and it is strongly affected by preload in the right as well as left ventricle in healthy subjects [16].

In pediatric patients with congenital heart disease, A’ was strongly correlated with right ventricular end-diastolic pressure [17]. There is also a report that among various echocardiographic parameters, tricuspid annular E/E' was the best index of RAP in patients with cardiovascular disease who had an elevated RAP (>10 mmHg) [7]. E/E’ was also correlated with right ventricular end-diastolic pressure in pediatric patients with congenital heart disease [17]. In contrast, the results of the present study showed that E/E’ was not correlated with catheterization-based RAP in pulmonary hypertension patients with an average RAP of 6.6±3.5 mmHg. The discrepancy between the present study and other studies might be due to differences in baseline characteristics, such as age, the baseline level of RAP, or the type of disease present (i.e., cardiovascular disease, congenital heart disease or pulmonary hypertension). In our study, we measured eRAP-IVCd using the respirophasic variation in IVC diameter because it is recommended as a possible surrogate of catheterization-based RAP in the ASE guidelines [4]. eRAP-IVCd has been shown to discriminate among patients with an RAP of 3, 8 and 15 mmHg, and this parameter has a great advantage in that the IVC diameter can be simply measured from a subcostal window. However, the disadvantages are that it does not accurately reflect RAP when the IVC is collapsed in ventilator-dependent patients, and it is less reliable for intermediate values of RAP. Our results suggest that A’ is a better surrogate of catheterization-based RAP than eRAP-IVCd.

Finally, using ROC curve analysis, we determined that the optimal cut-off value of A’ was 11.3 cm/s to predict a catheterization-based RAP>10 mmHg. An RAP>10 mmHg has been shown to predict mortality in patients with pulmonary hypertension

[18]. Our results suggest that pulmonary hypertension should be treated to obtain an A' value >11.3 cm/s.

Study limitations

The present study has several potential limitations. First, the study included a small sample of 66 measurements in 23 patents, and the sample included multiple measurements (maximum of 7 measurements) in 16 patients. In the future, we need to investigate the relationship between catheterization-based RAP and the echocardiographic parameter, A', in a larger number of patients. In addition, we need to evaluate the relationship between A' and the therapeutic efficacy of the drugs used to treat pulmonary hypertension. Second, in the present study, there was a time lag of several days between right heart catheterization and echocardiography. To obtain more precise information on the relationships between invasive RAP and noninvasive A', the simultaneous measurement of both parameters is required. Finally, in the present study, patients had either thromboembolic or idiopathic pulmonary hypertension. Since diastolic pulmonary artery pressure is commonly higher in thromboembolic than idiopathic pulmonary hypertension, this could potentially lead to a difference in right heart hemodynamics and RAP. Therefore, additional evaluation is needed separately in each type of pulmonary hypertension.

Clinical implications/conclusion

In the present study, we found that an echocardiographic parameter, A' was a better surrogate of catheterization-based RAP than eRAP-IVCd, which has been

recommended by the ESC/ERS guidelines. At the present time, right heart catheterization is essential for the diagnosis and treatment of pulmonary hypertension; however, 2D echocardiography should be considered as a method to assess right heart function because it is a simpler, less invasive and less expensive. We believe that the present study provides novel insight into pulmonary hypertension that can be used in routine clinical practice.