Accuracy of Doppler echocardiography in the assessment of pulmonary arterial hypertension in patients with congenital heart disease

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Abstract. – BACKGROUND AND OBJECTIVES: Pulmonary arterial hypertension (PAH) is a major cause of morbidity and mortality among patients with congenital heart disease (CHD). Earlier diagnosis of PAH would be of great benefit for the estimation of the CHD, the grasp of the indications for surgery and prognosis.

PATIENTS AND METHODS: We assessed the diagnostic accuracy of Doppler echocardiography (D-ECHO) in detecting PAH in patients with CHD and the value of estimation about ventricular morphology and function of PAH-CHD patients. 123 CHD patients evaluated for suspected PAH were prospectively recruited. D-ECHO was performed and estimated right ventricular systolic pressure (RVSP) was measured to screen for PAH. Subsequently, pulmonary hemodynamic parameters were measured by right heart catheterization (RHC) for definitive diagnosis of PAH.

RESULTS: RHC identified 66/123 (54%) patients with PAH. The noninvasive cut-point was: estimated right ventricular systolic pressure (RVSP) > 36.5 mm Hg by D-ECHO. D-ECHO classified 107 subjects correctly (sensitivity 89.4%, specificity 84.2%). The area under receiver-operating characteristic curve (AUC) was 0.96 for D-ECHO. A positive significant correlation ($r = 0.853$, $p < 0.01$) was found between RVSP measured by D-ECHO and systolic pulmonary arterial pressure (sPAP) measured by RHC. In addition, D-ECHO showed higher RVSP, left ventricular internal diameter (LV), right atrial diameter (RA), right ventricular internal diameter (RV), left ventricular end-diastolic diameter (EDD), left ventricular diastolic end-diastolic volume (EDV) and mitral velocity A wave (AMV) values in the PAH-CHD group than in the CHD group ($p < 0.05$).

CONCLUSIONS: D-ECHO is not only an important noninvasive diagnostic technique for PAH-CHD patients, but also a tool which can indicate the ventricular remodeling and diastolic dysfunction induced by PAH to some extent.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease with poor survival and a major subgroup is PAH due to congenital heart disease (CHD) with systemic-to-pulmonary shunt[1]. This shunting may lead to extensive histological changes in the distal pulmonary arteries resulting in an irreversible increase in pulmonary vascular resistance (PVR). The development of PAH in patients with CHD is associated with increased mortality and high morbidity, reflected in a substantial increase in health service utilization[2,3]. Patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) are often accompanied by hemodynamic abnormalities and postoperative low cardiac output, which are the major complications leading causes of death[4,5]. Therefore, earlier diagnosis of PAH would be of great benefit for the estimation of the CHD, the grasp of the indications for surgery and prognosis. Right heart catheterization (RHC) is the gold standard method for diagnosis of PAH and an important tool for testing the eligibility of patients with CHD to undergo operations for correction of heart defects. However, it is an invasive test and not always practical for repeated ongoing evaluation[3]. Thus, accurate noninvasive assessment of PAH is desirable both for diagnostic purposes and to assess response to

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therapy. Doppler echocardiography (D-ECHO) has become the most important and routinely applied noninvasive imaging technique for the diagnosis and follow-up of patients with CHD and is recommended as the initial noninvasive modality in the screening and evaluation of PAH[6,7]. The aim of this study was to assess the diagnostic accuracy of D-ECHO in detecting PAH in patients with CHD and the value of estimation about ventricular morphology and function of PAH-CHD patients.

Patients and Methods

Patients

Approval for the protocol was obtained from the Institutional Review Board of the West China Hospital of Sichuan University. Written informed consent was obtained from all subjects. One hundred and twenty three CHD participants evaluated for suspected PAH, who were admitted in West China Hospital of Sichuan University between January 2010 and January 2012, were prospectively included in this study. None of the patients reported a family history of PAH. All patients had D-ECHO and RHC within 72 hours of each other during a formal evaluation process. D-ECHO was typically performed 24-48 hours before RHC. The studies were performed independently by operators who were blind to the results of the other study.

Doppler Echocardiography

Complete 2-dimensional and Doppler echocardiography was recorded using various models of commercially available echocardiographic equipment. Patients were placed in the left lateral decubitus position, and standard parasternal and four-chamber apical views were obtained by two independent operators. Any discrepancies were resolved by discussion with a third operator to reach a final consensus. The RVSP was estimated by adding the right atrial pressure (RAP) to the transtricuspid pressure gradient (TPG)[8-10]. The TPG was calculated from the peak TR velocity using the modified Bernoulli equation: TPG (mmHg) = $4V^2$, where V = highest continuous wave Doppler measurement of the TR velocity (m/sec) in the parasternal short axis and four-chamber apical views. RAP was estimated to be 5, 10, or 15 mm Hg based on the variation in the size of inferior vena cava[11]: complete collapse, RAP = 5 mm Hg; partial collapse, RAP = 10 mm Hg; and no collapse, RAP = 15 mm Hg. RVSP was considered to be equal to the sPAP in the absence of right ventricular outflow obstruction. Measurement of cardiac morphology and function indicators include: right atrial diameter (RA), right ventricular internal diameter (RV), left atrial internal diameter (LA), left ventricular internal diameter (LV), left ventricular end-diastolic diameter (EDD), left ventricular diastolic end-diastolic volume (EDV), ejection fraction (EF), interventricular septum (IVS), mitral velocity E wave (EMV), mitral velocity A wave (AMV).

Right Heart Catheterization

Under local anesthesia, a multilumen thermodilution catheter (Swan-Ganz CCO catheter, 774HF75; Edwards Lifesciences, Irvine, CA, USA) was inserted via the right internal jugular vein and positioned 10-15 cm distal to the pulmonary valve. Mean pulmonary artery pressure (mPAP), systolic pulmonary arterial pressure (sPAP), central venous pressure (CVP) and pulmonary capillary wedge pressure were measured using this catheter. Characterized by abnormal pressure in the pulmonary arteries, PAH is defined as an elevated mPAP of 25 mmHg or higher and a pulmonary wedge pressure of 15 mm Hg or lower[12]. Both children and adults with CHD can experience PAH[13-17].

Statistical Analysis

Continuous data were presented as mean ± standard deviation (SD). Categorical data were presented as frequency and percent. Student's *t* test and chi-square test was used when appropriate. We assessed the capacity of D-ECHO to estimate sPAP and diagnose PAH in two ways. First, to examine the overall relationship of estimated right ventricular systolic pressure (RVSP) to RHC measurements, we compared the results as continuous variables using Pearson correlation analyses. Second, using RHC as the gold standard, we calculated the sensitivity, specificity, and positive and negative predictive values of the method of diagnosing PAH by D-ECHO: estimation of sPAP by trans-tricuspid gradient method. By the method, a RVSP equal to or exceeding 40 mm Hg was considered to be positive for the diagnosis of PAH. SPSS software version 18.0 was used in statistical evaluation of the above data. A 2-sided value of $p < 0.05$ was considered statistically significant.

Results

The demographic character of study subjects and comparison of study groups for echocardiographic measurements are summarized at Table I. The study enrolled 123 individuals, including 66 patients with CHD-PAH (group1) (17 patients with ventricular septal defects, 18 patients with patent ductus arteriosus, 24 patients with atrial septal defects, 2 patients with atrial septal defects and patent ductus arteriosus, 5 patients with ventricular septal defects and patent ductus arteriosus) and 57 patients with CHD (group 2) (14 patients with ventricular septal defects, 7 patients with patent ductus arteriosus, 33 patients with atrial septal defects, 2 patients with atrial septal defects and ventricular septal defects, 1 patient with atrial septal defects and ventricular septal defects and patent ductus arteriosus).

The 2 groups did not differ significantly in terms of age, gender, LA, IVS, and EF (Table I). Doppler echocardiographic records showed higher RVSP, LV, RA, RV, EDD, EDV and AMV values in the CHD-PAH group than in the CHD subjects. EMV values decreased in the CHD-PAH group ($p < 0.05$, Table I).

Figure 1 shows the correlation between the RVSP (50.3±26.1 mm Hg) measured by Doppler echocardiography and sPAP (51.0±32.9 mm Hg) measured by right-heart catheterization. A strong correlation was found (r = 0.853, $p < 0.01$). A similar but relatively weak positive correlation was also observed between RVSP and mPAP by RHC (r = 0.790, $p < 0.01$) (Figure 2). However, a significant discrepancy between RVSP measured by Doppler echocardiography and sPAP by RHC in patients with PAH was found (66.4±26.3 mm Hg VS 72.1±32.3 mm Hg, $p = 0.035$), which was also observed between RVSP and mPAP by RHC (66.4±26.3 mm Hg VS 45.9±22.1 mm Hg, $p < 0.01$).

As a screening test, Doppler echocardiography had a sensitivity of 89.4%, and a specificity of 84.2%, whereas its positive and negative predictive values were 86.8% and 87.3% (Table II). A ROC analysis was conducted to determine the most significant RVSP measured by Doppler echocardiography for PAH. The area under the ROC curve by ROC analysis was 0.96 for estimated RVSP ($p < 0.01$, Figure 3). This generated a cutoff value for RVSP of 36.5 mmHg. This cutoff level had a specificity of 84.2% and a sensitivity of 93.9% (Figure 3).

Table I. The demographic character of study subjects and comparison of study groups for echocardiographic measurements and right heart catheterization hemodynamics.

	CHD-PAH (n=66)	CHD (n=57)	*p*-value
Male (%)	20 (30.3)	15 (26.3)	0.625**
Age (± SD)	26.86 (± 15.3)	21.97 (± 14.4)	0.072
Doppler echocardiography Measurements			
RVSP (mm Hg)	33.02 (± 18.6)	11.14 (± 3.7)	0.000*
LV (mm)	43.89 (± 10.7)	39.93 (± 8.2)	0.025*
LA (mm)	31.65 (± 9.0)	30.39 (± 7.0)	0.391
RV (mm)	23.26 (± 7.2)	21.04 (± 4.5)	0.040*
RA (mm)	39.32 (± 11.1)	34.05 (± 8.1)	0.003*
IVS (mm)	8.58 (± 2.5)	8.51 (± 2.1)	0.875
EDD (mm)	48.59 (± 13.4)	44.37 (± 9.8)	0.047*
EDV (ml)	112.39 (± 79.0)	87.61 (± 41.8)	0.029*
EF (%)	64.29 (± 8.1)	61.42 (± 11.4)	0.115
EMV (m/s)	0.90 (± 0.4)	1.02 (± 0.2)	0.030*
AMV (m/s)	0.83 (± 0.3)	0.68 (± 0.1)	0.001*
Right-Heart Catheterization Hemodynamics			
SPAP (mm Hg)	72.14 (± 32.3)	26.42 (± 2.3)	0.000*
MPAP (mm Hg)	45.91 (± 22.1)	16.05 (± 2.8)	0.000*

CHD: congenital heart disease; PAH: Pulmonary arterial hypertension; RVSP: estimated right ventricular systolic pressure; RA: right atrial diameter; RV: right ventricular internal diameter; LA: left atrial internal diameter; LV: left ventricular internal diameter; EDD: left ventricular end-diastolic diameter; EDV: left ventricular diastolic end-diastolic volume; EF: ejection fraction; IVS: interventricular septum; EMV: mitral velocity E wave; AMV: mitral velocity A wave; SPAP: systolic pulmonary arterial pressure; MPAP: mean pulmonary arterial pressure. *$p \leq 0.05$ (Student's t test). **Pearson's χ^2 test.
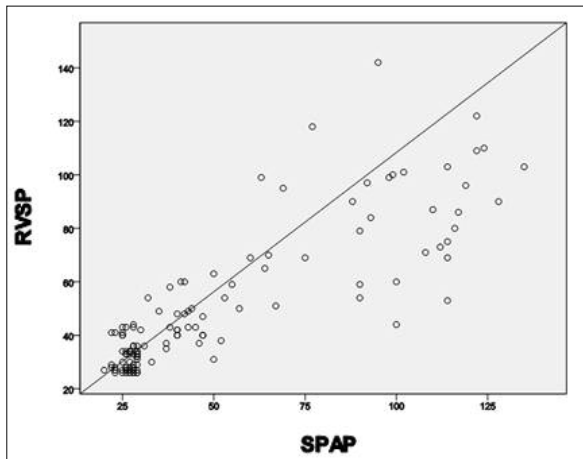
Figure 1. Relationship between RVSP estimated by D-ECHO and sPAP by RHC (r = 0.853, $p < 0.01$).

Discussion

The development of PAH in patients with CHD is associated with increased mortality and high morbidity[2,3,18]. While successful early closure of a cardiac defect prevents the development of PAH, and advances in paediatric cardiology and surgery have led to a marked decrease in the prevalence of PAH-CHD in western countries, the number of patients with CHD surviving into adulthood has increased[19,20]. However, not all patients have a fully successful repair and many continue to suffer from residual lesions and potentially serious sequelae into adulthood. Depending on their age at closure, even patients who have had a full repair of their cardiac defect

Table II. PAH RHC and D-ECHO cross tabulation.

|		PAH (RHC)		
		Yes	No	Total
PAH (D-ECHO)	Yes	59 (a)	9 (b)	68
	No	7 (c)	48 (d)	55
	Total	66	57	123

Sensitivity (%) = a/(a+c)×100%; specificity (%) = d/(b+d)×100%; positive predictive value (%) = a/(a+b)×100%; negative predictive value (%) = d/(c+d)×100%; D-ECHO, Doppler echocardiography; RHC, right heart catheterization; PAH, pulmonary arterial hypertension.

are at risk of developing PAH. In addition, there remains a population of patients with left-to-right shunts who are not diagnosed until childhood or even into adulthood at an advanced stage. In these patients, changes to the pulmonary vasculature have already occurred, and PAH has, to a greater or lesser degree, already developed, which have a very important significance for the surgery program selection and prognosis of CHD. At present, right heart catheterization is the gold standard for the definitive diagnosis of PAH[21]. Although right heart catheterization could assess pulmonary arterial pressure and cardiac output accurately, it is not routinely used because of its invasiveness and complications.

In this study we investigated the value of D-ECHO as a noninvasive means of estimating sPAP and establishing or excluding a diagnosis of significant PAH in a cohort of patients with
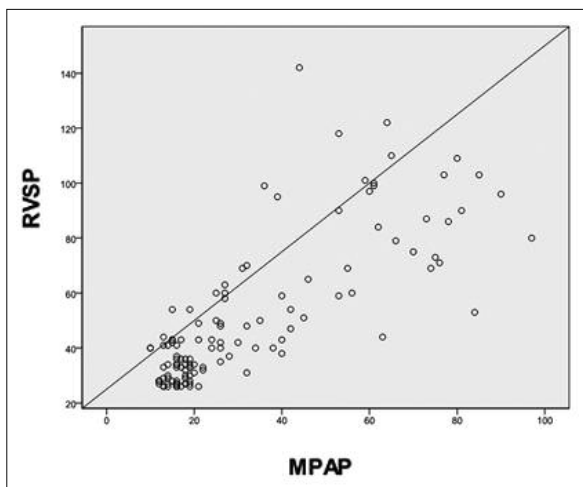
Figure 2. Relationship between RVSP estimated by D-ECHO and mPAP by RHC (r = 0.790, $p < 0.01$).
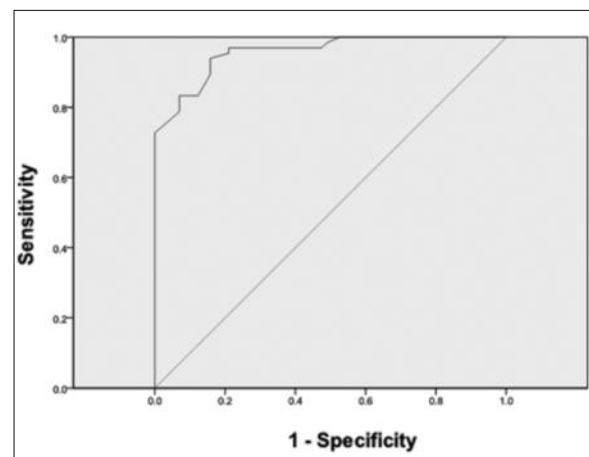
Figure 3. Receiver-operating characteristic curves for the diagnosis of PAH in patients with CHD using Doppler echocardiography-estimated RVSP. Areas under the curves (AUC) were calculated by the trapezoidal rule.

CHD of various etiologies. We demonstrated a statistically significant correlation between RVSP and RHC-measured sPAP. Despite this significant correlation, the discordance was found between RVSP and sPAP by RHC in patients with PAH, which was also observed between RVSP and mPAP by RHC. Doppler echocardiography has been proposed as a screening tool to diagnose elevated PAH; however, the assessment of PAH by this test relies on measurement of the tricuspid regurgitation jet to provide an indirect measurement of the RVSP. The absence of this jet does not exclude PAH and there is significant variability among investigators in technique and interpretation of results[22,23]. These patterns of inconsistency required RHC to confirm or dismiss the diagnosis of PAH with certainty. In current study, D-ECHO had a sensitivity of 89.4%, and a specificity of 84.2%, whereas its positive and negative predictive values were 86.8% and 87.3%. This method had high positive likelihood ratio (5.7) and great area under the ROC curve (95.8%). A lower RVSP cutoff (such as RVSP 36.5 mm Hg) could serve better to increase the specificity (93.9%) of this test, however sensitivity would be reduced to 84.2%.

PAH often leads to progressive right heart failure, low cardiac output and right atrial pressure increased[4], which are the major complications leading causes of death. Therefore, concerning about changes of ventricular function is of great significance clinically. D-ECHO has been considered to be useful in assessing atrium and ventricle size and function as well as evaluating left-side valvular disease, a cause of secondary PAH[24,25]. Do et al[26] concluded that the RA size measured by echocardiography is strongly correlated to invasive parameters of RV diastolic filling and predicts high RV end-diastolic pressure. This study assessed the value of estimation about ventricular morphology and function of PAH-CHD patients by D-ECHO. LV, RA, RV, EDD, EDV and AMV values were significantly higher in the CHD-PAH group than in the CHD group, EMV values decreased in the CHD-PAH group. Our data indicates that the PAH might not only contribute to the expansion and remodeling of right ventricular diameter, but also the increase of left ventricular end-diastolic diameter and the decrease of the left ventricular diastolic function. The EF levels showed no statistically significant difference between the groups (Table I). Although EF is recognized to indicate systolic function effectively, however, is not sensitive to reflect the impact on left ventricular caused by PAH[27].

Conclusions

Our data revealed a strong correlation between Doppler echocardiographic assessment and direct hemodynamic measurement of pulmonary artery pressures in patients with congenital heart disease. Doppler echocardiography is highly sensitive and specific in detecting clinically significant pulmonary hypertension. It may be useful for first-line surveillance in patients in whom PAH is suspected, although the confirmation of PAH should be based on right heart catheterization. The combination of Doppler echocardiography with other noninvasive methods may increase the diagnostic accuracy, but evidence-based medical studies of such a combination are rare, and should be the next direction for future study of diagnostic modalities for Doppler echocardiography. The emergence of a variety of new ultrasound technology makes it possible to accurately evaluate ventricular function. With the continuous development of ultrasound technology, the method of evaluation of ventricular morphology and function will be more diverse and complete, so as to provide richer clinical information.

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