Utility of Echocardiography Versus BNP Level for the Prediction of Pulmonary Arterial Pressure in Patients With Pulmonary Arterial Hypertension

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SUMMARY

Recent advances in the treatment of pulmonary arterial hypertension provide a rational basis for earlier, noninvasive diagnosis of pulmonary arterial hypertension. However, the reliability of transthoracic echocardiography, plasma BNP levels, and other parameters for the diagnosis of pulmonary arterial hypertension remains unclear. Thus, the purpose of this study was to determine the utility of these modes of investigation for the prediction of pulmonary arterial pressure as compared with the current gold standard, Swan-Ganz catheterization.

Among 46 PAH patients, 37 had connective tissue diseases, while the remainder had primary pulmonary arterial hypertension, chronic pulmonary thromboembolism, and interstitial pneumonitis. Systolic pulmonary arterial pressure calculated by transthoracic echocardiography was significantly correlated with systolic pulmonary arterial pressure measured using a Swan-Ganz catheter ($r = 0.51$, $P < 0.01$). Plasma BNP concentration did not correlate with systolic pulmonary arterial pressure ($r = 0.10$, NS) in the overall patient population. However, when we excluded left ventricular heart failure and left ventricular hypertrophy, BNP concentration was correlated with systolic pulmonary arterial pressure ($r = 0.508$, $P < 0.05$). Among other variables tested, ECG electrical axis was correlated with pulmonary arterial pressure ($r = 0.46$, $P < 0.05$) but uric acid, lactate dehydrogenase, %DLCO, enhanced IIP sound, and pulmonary artery enlargement on chest x-ray did not correlate with pulmonary arterial pressure.

These data suggest that echocardiography is the noninvasive modality of choice for the assessment of pulmonary arterial hypertension. Plasma BNP level also predicts pulmonary arterial pressure, when left ventricular heart failure and cardiac hypertrophy are excluded. (Int Heart J 2010; 51: 343-347)

Key words: Pulmonary arterial hypertension, Connective tissue disease, Swan-Ganz catheterization, Transthoracic echocardiography, B-type natriuretic peptide

Measurement of pulmonary arterial pressure (PAP) in patients with pulmonary arterial hypertension (PAH) is critical for diagnosis and for the assessment of response to therapy. Although the current gold standard for the assessment of PAP is via Swan-Ganz (S-G) catheterization, this procedure is invasive and associated with a small but significant risk of serious complications. Further, noninvasive assessment of PAH in high risk patients, such as those with connective tissue disease, pulmonary thromboembolism,¹⁾ and interstitial pneumonia, enables early detection and treatment of PAH, thereby improving outcomes.²⁻⁹⁾ However, the optimal method for the noninvasive assessment of PAH remains unclear. Thus, the purpose of this study was to determine the utility of various modes of investigation such as transthoracic echocardiography (TTE), plasma BNP levels, and other clinical and laboratory parameters for the prediction of PAP as compared with the current gold standard, S-G catheterization.

METHODS

This was a retrospective, noninterventional study of PAH patients who were hospitalized in the Cardiovascular Department of Gunma University Hospital, Japan, for any period of time between February 1995 and March 2008.

Of the 200 patients enrolled, 46 patients were eligible for final analysis. PAH was diagnosed according to guidelines from the American College of Chest Physicians. Patients were excluded from analysis if they did not satisfy diagnostic criteria or if there were insufficient data available for analysis.

Patient data were collected by review of the clinical charts. Data collected from the charts included clinical symptoms according to WHO functional class, 6-minute-walk capacity, blood gas analysis, electrocardiographic (ECG) parameters (axis, bundle branch block, height of pII, sinus rhythm, atrial fibrillation), chest x-ray (CXR) parameters (width of pulmonary artery, level of ground glass shadow), TTE data, S-G catheterization data, respiratory function test results (%DLCO and %vital capacity), requirement for home oxygen therapy, and data from various imaging studies, including thallium

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scintigraphy, magnetic resonance imaging, coronary angiography, and left ventriculography.

Laboratory testing data were also collected, including but not limited to titers of uric acid, lactate dehydrogenase, anti-nuclear antibody, anti-DNA antibody, anti-U1-RNP antibody, anti-Sm antibody, anti-SS-A antibody, anti-SS-B antibody, anti-Scl antibody, anti-centromere antibody, anti-Jo-1 antibody, anti-mitochondria antibody, anti-smooth muscle antibody, RP-3-ANCA (c-ANCA), MPO-ANCA (p-ANCA), anti-cardiolipin antibody, anti-beta2-GPI antibody, anti-microsomal antibody, antithyroglobulin antibody, RAHA antibody, rheumatism factor, and CH 50.

Transthoracic echocardiography data were evaluated for right ventricular systolic pressure, pulmonary vascular resistance, tricuspid regurgitation-pressure gradient (TR-PG), aortic dimension, left atrial dimension, left ventricular end-diastolic dimension, left ventricular internal dimension in systole, ejection fraction, E wave, A wave, E/A ratio, S/D ratio, deceleration time, and left ventricular wall motion in TTE.

S-G catheterization data were evaluated for mean pulmonary capillary wedge pressure, systolic pulmonary arterial pressure (systolic PAP-SG), mean PAP-SG, right ventricular pressure, right atrial pressure (RAP), cardiac index, and change in pulmonary vascular resistance in response to nitric oxide.

Medication profiles were reviewed for the use of prednisolone, beraprost sodium, bosentan hydrate, sildenafil citrate, warfarin potassium, aspirin, cilostazol, ticlopidine hydrochloride, sarpogrelate hydrochloride, furosemide, spironolactone, nifedipine, verapamil hydrochloride, amlodipine besilate, angiotensin II receptor blocker, digoxin, and epoprostenol sodium.

PAP-TTE was calculated by Bernoulli's principle as follows: PAP-TTE = TR-PG + RAP.

Statistical analysis: Statistical analysis was performed using the SPSS statistical program (version 14.0, Chicago, IL, USA). Linear regression analysis was applied to determine the correlation between PAP measured by S-G catheter and other parameters. All statistical tests were evaluated at a significance level of 0.05.

RESULTS

Baseline characteristics are summarized in the Table. The average age of the study population was 64.1 ± 12.3 years. Of the 46 patients with PAH, 12 were male (26.1%). PAH was attributed to connective tissue disease in 16 patients (34.8%), and to chronic pulmonary thromboembolism in 9 patients (20%), interstitial pneumonia in 4 patients (8.7%), and chronic obstructive pulmonary disease in 1 patient (2.2%).

Of the 16 patients with connective tissue disease, 14 (30.4%) had systemic sclerosis, 2 (4.3%) had systemic lupus erythematosus, 1 (2.2%) had dermatomyositis, and 2 (4.3%) had Sjogren syndrome. This includes 2 patients (4.3%) with both systemic sclerosis and Sjogren syndrome, and 1 patient (2.2%) with both systemic sclerosis and dermatomyositis. None of the patients had polyarteritis nodosa, mixed connective tissue disease, or rheumatoid arthritis.

Specific medications used by a proportion of the study population included prednisolone ($n = 10$, 21.7%); beraprost sodium ($n = 26$, 56.5%); bosentan hydrate ($n = 7$, 15.2%); sildenafil citrate ($n = 1$, 2.2%); warfarin potassium ($n = 17$,

Table. Baseline Characteristics

<i>n</i> = 46	
Age	64.07 $\pm$ 12.28 SD
Gender (men) (%)	12 (26.1)
Connective tissue disease (%)	16 (34.8)
Systemic sclerosis (%)	14 (30.4)
Systemic lupus erythematosus (%)	2 (4.3)
Polyarteritis nodosa (%)	0 (0)
Mixed connective tissue disease (%)	0 (0)
Dermatomyositis (%)	1 (2.2)
Rheumatoid arthritis (%)	0 (0)
Sjogren syndrome (%)	2 (4.3)
More than two diseases (%)	3 (6.5)
Chronic pulmonary thromboembolism (%)	9 (20.0)
Interstitial pneumonia (%)	4 (8.7)
Chronic obstructive pulmonary disease (%)	1 (2.2)
Cardiac medications	
prednisolone (%)	10 (21.7)
beraprost sodium (%)	26 (56.5)
bosentan hydrate (%)	7 (15.2)
sildenafil citrate (%)	1 (2.2)
warfarin potassium (%)	17 (37.0)
aspirin (%)	9 (37.0)
cilostazol (%)	1 (2.2)
ticlopidine hydrochloride (%)	1 (2.2)
sarpogrelate hydrochloride (%)	2 (4.3)
furosemide (%)	20 (43.5)
spironolactone (%)	9 (19.6)
nifedipine (%)	4 (8.7)
verapamil hydrochloride (%)	1 (2.2)
amlodipine besilate (%)	6 (13.0)
angiotensin II receptor blocker (ARB) (%)	12 (26.1)
digoxin (%)	7 (15.2)
epoprostenol sodium (%)	1 (2.2)

Figure 1. Correlation between systolic PAP as calculated by TR-PG on TTE and systolic PAP as measured by S-G catheter. Systolic PAP as calculated by TTE correlates with PAP-SG ($r = 0.505$, $P < 0.01$).

37.0%); aspirin ($n = 9$, 19.6%); cilostazol ($n = 1$, 2.2%); ticlopidine hydrochloride ($n = 1$, 2.2%); sarpogrelate hydrochloride ($n = 2$, 4.3%); furosemide ($n = 20$, 43.5%); spironolactone (n

Figure 2. Correlation between BNP and PAP-SG. **A:** There is no significant correlation between BNP and PAP-SG ($r = 0.101$, $P = 0.631$). **B:** There is a correlation between BNP and PAP-SG, when left ventricular heart failure and left ventricular hypertrophy are excluded.

= 9, 19.6%); nifedipine ($n = 4$, 8.7%); verapamil hydrochloride ($n = 1$, 2.2%); amlodipine besilate ($n = 6$, 13.0%); ARBs ($n = 12$, 26.1%); digoxin ($n = 7$, 15.2%), and epoprostenol sodium ($n = 1$, 2.2%).

Figure 1 illustrates the correlation between systolic PAP as calculated by assessing the TR-PG by TTE and the systolic PAP measured by S-G catheterization; systolic PAP calculated by TTE was correlated with systolic PAP-SG ($r = 0.505$, $P < 0.01$).

Figure 2A illustrates the correlation between BNP and PAP measured by S-G catheter; there was no significant correlation between BNP and PAP-SG ($r = 0.101$, NS).

However, when we excluded left-ventricular heart failure with a left ventricular ejection fraction of less than 51% (mean 47.8%) ($n = 3$) and diastolic dysfunction ($n = 4$), and severe left ventricular hypertrophy ($n = 2$), BNP was correlated with PAP-SG ($r = 0.508$, $P = 0.044$) (Figure 2B). There was no significant correlation between PAP-SG and uric acid, LDH,

Figure 3. Correlation between ECG axis and PAP-SG. ECG axis correlates with PAP-SG ($r = 0.604$, $P = 0.029$).

%DLCO, IIP sound, or posteroanterior distance on CXR.

Figure 3 shows the correlation between ECG axis and PAP-SG. ECG axis was correlated with PAP-SG ($r = 0.604$, $P = 0.029$).

DISCUSSION

Measurement of PAH: Several strategies have been employed for the assessment of PAH, including noninvasive (eg, laboratory tests, ECG, CXR, blood gas analysis, TTE, chest CT, chest MRI, respiratory function tests, pulmonary scintigraphy) and invasive methods (eg, S-G catheterization, pulmonary artery angiography, pulmonary biopsy). For example, characterization of PAH patients by laboratory testing can reveal polycythemia, transaminitis, and elevations in atrial natriuretic peptide, BNP, and uric acid. Furthermore, ECG may demonstrate right ventricular hypertrophy, while CXR may show bilateral central PA dilatation and peripheral PA shrinkage as well as dilatation of the right atrium and right ventricle, and arterial blood analysis often shows hypocapnia (or hypercapnia if concomitant pulmonary disease is present). TTE is a particularly useful modality for the assessment of PAH, revealing dilatation of the right ventricle and right atrium and shifting of the septal wall toward the left ventricle, and providing an indirect assessment of PAP through measurement of the peak gradient of tricuspid regurgitation. Use of chest CT or MRI in patients with PAH can also demonstrate dilatation of the right atrium, right ventricle, and pulmonary artery, as well as thrombus in the pulmonary artery or extensive pulmonary artery disease. Respiratory function testing often reveals a restrictive disorder in the context of idiopathic pulmonary artery hypertension or familial pulmonary artery hypertension and can document an obstructive disorder in those with COPD. Pulmonary scintigraphy can sometimes reveal the cause of PAH, while S-G catheterization, the gold standard for the diagnosis of PAH, can evaluate pulmonary capillary wedge pressure, systolic PAP, mean PAP, right ventricular pressure, RAP, cardi-

ac index, and pulmonary vascular resistance. By contrast, pulmonary artery angiography can reveal morphological changes in the pulmonary vessels, and pulmonary biopsy can provide a pathologic diagnosis and grading of the severity of PAH.

While invasive testing provides the best assessment of PAH, it also carries a higher risk of complications. Thus, establishment of valid and reliable noninvasive measurement would be of benefit for the initial diagnosis and serial monitoring of PAH.

BNP: Previous studies have reported that the BNP level may predict outcomes and/or right ventricular failure in various patient populations, including those with primary pulmonary hypertension (PPH) and pulmonary thromboembolism.¹⁰⁻¹²⁾ However, it is also well known that the BNP level is high in patients with left ventricular heart failure and left ventricular hypertrophy. The amount of BNP elevation is less than seen with processes leading to left ventricular heart failure.¹³⁾ Therefore, when a PAH patient has left ventricular heart failure, the BNP level may become higher than that expected by PAP. For example, one patient in the present study had relatively low systolic PAP-SG (34 mmHg) but high BNP (1590 pg/mL). This patient had a low ejection fraction (40%). BNP did not correlate with PAP in the overall patient population (Figure 2A). However, when we excluded left ventricular heart failure and left ventricular hypertrophy, BNP correlated with PAP-SG. Our data suggest clinicians should be careful when using BNP as an estimate of PAP, if the patient has left ventricular heart failure and left ventricular hypertrophy.

ECG: A previous study reported that right ventricular hypertrophy is present in 87% of patients with PAH, while a right axis shift is seen in 79% of patients with PAH.¹⁴⁾

ECG findings suggestive of PAH include: 1) right-axis deviation; 2) a tall R wave and small S wave with an R/S ratio > 1 in lead V1; 3) a qR complex in lead V1; 4) an rSR' pattern in lead V1; 5) a large S wave and small R wave with an R/S ratio < 1 in lead V5 or V6; and 6) an S1, S2, S3 pattern. In the present study, changes in the ECG axis were correlated with PAP-SG.

TTE: PAP can be calculated from TR-PG using Bernoulli's principle ($PAP = TR-PG + RAP$). TR-jet was analyzed in 39 patients.^{15,16)}

Several groups have described the correlation between data from TTE and S-G catheterization. Although one study failed to demonstrate a significant correlation ($r = 0.31$), most other studies have demonstrated a correlation ($r = 0.78-0.95$) between data from TTE and S-G catheterization,^{15,17,18)} which is consistent with findings from the present study. Further, some studies have reported that the pulmonary arterial diastolic pressure correlates with PAP-SG ($r = 0.92$).¹⁹⁾ When comparing PAP measurements determined by TTE to those determined by S-G catheterization, values may vary by as much as 3 to 38 mmHg.^{15,20,21)} For example, in one study, TTE underestimated PAP by an average of 11 mmHg¹⁵⁾ and by more than 20 mmHg in 31% of patients. Two other studies describe even larger discrepancies (> 100 mmHg) in PAP measurements.^{20,21)} The sensitivity and specificity of TTE or a diagnosis of PAH ranges from 0.79-1.0 and 0.60-0.98, respectively.²²⁾

At our institution, we assign a value of 10 mmHg for RAP within the Bernoulli principle formula ($PAP-TTE = TR-PG + RAP$). However, even when assigning this value, TTE still overestimated PAP. Regardless, TTE remains a useful mo-

dalities for the diagnosis of PAH by virtue of its noninvasive methodology. Other studies have suggested that exercise Doppler echocardiography is also useful for the diagnosis of PAH,²³⁾ but this methodology was not investigated in the present study.

Limitations: There are several notable limitations to this study. First, this was a nonrandomized retrospective study. Second, the study population consisted of patients admitted to the Department of Cardiology at our institution, which may result in selection bias. Third, the study population was relatively small, and further study in a larger group of patients is required to verify the present findings.

Conclusions: These data suggest that TTE is still the noninvasive modality of choice for the assessment of PAP, but that it may also overestimate PAP compared with the assessment by S-G catheter. Plasma BNP levels were also a good predictor of elevated PAP, when left ventricular heart failure and left ventricular hypertrophy were excluded.

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