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Noninvasive Differential Diagnosis Between Chronic Pulmonary Thromboembolism and Primary Pulmonary Hypertension by Means of Doppler Ultrasound Measurement

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Objectives. **The purpose of this investigation was to differentiate chronic pulmonary thromboembolism (CPTE) from primary pulmonary hypertension (PPH) by using noninvasive Doppler ultrasound techniques.**

Background. **A recent investigation in our laboratory has indicated that the pulmonary artery (PA) pressure waveform conveys significant information that can be used to differentiate CPTE from PPH. Pulse pressure was markedly larger in CPTE than in PPH, indicating that the major occlusive site is central in CPTE and peripheral in PPH.**

Methods. **In 19 patients with CPTE and 16 patients with PPH, we estimated PA systolic pressure and diastolic pressure from the velocities of tricuspid regurgitation and pulmonary regurgitation, respectively.**

Results. **Estimated systolic pressure was not significantly different between CPTE and PPH (mean [±SD] 81 ± 20 and 79 ± 21 mm Hg, respectively, p = NS). Pulse pressure normalized by systolic pressure was higher in CPTE than in PPH (0.82 ± 0.05 vs. 0.63 ± 0.10, respectively, p < 0.01). Pulse pressure normalized by mean pressure was also higher in CPTE than in PPH (1.65 ± 0.30 vs. 0.94 ± 0.25, respectively, p < 0.01). Receiver operating characteristic analysis indicated that pulse pressure normalized by systolic pressure separated CPTE from PPH, with a sensitivity of 0.95 and a specificity of 1.00. Pulse pressure normalized by mean pressure also separated them, with a sensitivity of 0.95 and a specificity of 1.00.**

Conclusions. **Normalized pulse pressures estimated from Doppler ultrasound measurements enable us to noninvasively differentiate between CPTE and PPH.**

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A recent investigation in our laboratory (1) has indicated that the pulmonary artery (PA) pressure waveform conveys significant information that can be used to differentiate chronic pulmonary thromboembolism (CPTE) from primary pulmonary hypertension (PPH). The key to differentiating between the two diseases is the relative magnitude of pulse pressure to mean pressure. The pulse pressure was markedly larger in CPTE than in PPH, indicating that the major occlusive site is central in CPTE and peripheral in PPH. Because PA pressure may be noninvasively estimated by using Doppler echocardiography from the regurgitant flow of the pulmonary and tricuspid valves (2,3), it is conceivable that the pulsatility of the PA pressure waveform may be identified from those noninvasively obtained data. The purposes of this investigation were to derive indexes of pulsatility of PA pressure using Doppler echocardiography and to examine their significance in diagnosing CPTE and PPH.

We approximated PA systolic pressure by measuring regurgitant flow across the tricuspid valve, using a modified Bernoulli equation (4). We also approximated diastolic pressure by measuring regurgitant flow across the pulmonary valve. The results indicated that, despite such approximations of PA systolic and diastolic pressures, estimated pulsatility was markedly more increased in CPTE than in PPH, suggesting the usefulness of the proposed noninvasive technique in differentiating CPTE from PPH.

Methods

Study subjects. This was a retrospective, unblinded study. Between 1988 and 1996, 61 patients were admitted to the National Cardiovascular Center, Suita, Japan, for evaluation of symptomatic pulmonary hypertension (New York Heart Association functional class II through IV) with no known causes other than CPTE and PPH. Of these, 26 patients were

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Abbreviations and Acronyms

CPTE = chronic pulmonary thromboembolism
PA = pulmonary artery
PPH = primary pulmonary hypertension
PR = pulmonary regurgitation/regurgitant
RA = right atrium/atrial
ROC = receiver operating characteristic
RV = right ventricle/ventricular
TR = tricuspid regurgitation/regurgitant

excluded either because peak PA pressure estimated by tricuspid regurgitation (TR) did not exceed 50 mm Hg or because the recording of pulmonary regurgitant (PR) jet was unavailable. We did not routinely record PR flow. No patients were excluded because of poor quality Doppler measurements. Pulmonary hypertension might be more severe in the PPH group, because right atrial (RA) pressure was slightly higher (9.5 vs. 6.1 mm Hg). Clinical diagnoses for these patients were based on the following criteria: CPTE was diagnosed when pulmonary arteriography revealed opacification of filling defects and when areas of ventilation-perfusion mismatch typical of regionally impaired pulmonary perfusion were identified by standard radioisotope imaging. No history of acute episodes of chest pain or dyspnea, or both, was required for the diagnosis. The diagnosis of PPH was made after echocardiography, cardiac catheterization and arteriography; ventilation-perfusion scanning and pulmonary function testing assisted in excluding other known causes of pulmonary hypertension. We excluded from the PPH group patients with signs of collagen vascular disease, positive antinuclear antibody, history of drug abuse, use of diet pills or history of liver disease. There were 19 patients with CPTE (11 men and 8 women, age 28 to 64 years [mean ± SD 55 ± 14]) and 16 patients with PPH (5 men and 11 women, age 19 to 61 years [mean ± SD 37 ± 15]). This resulted in a larger proportion of female ($p < 0.05$) and younger ($p < 0.01$) patients in the PPH group, as reported (5). All patients in both groups had normal sinus rhythm. The protocol was in accordance with Institutional Guidelines for Human Research, and each patient gave written, informed consent for the diagnostic procedures required by Doppler ultrasound measurement, which stated that the results of the examination can be used for the retrospective study.

Doppler examination. Differences between CPTE and PPH, in terms of dynamic-mechanical properties of the PA system, would be more evident in the pressure waveform than in the mean pressure, granted that the mean pressure reflects the level of total arterial resistance (1). Thus, we focused on the systolic, diastolic and pulse pressure values. We approximated these values by means of Doppler ultrasound measurements, with some variability in measurements.

We recorded Doppler flow velocities of both TR and PR to estimate PA systolic and diastolic pressure, respectively. Regurgitant flow was quantified using a continuous wave Doppler method with a 2.5-MHz transducer (Toshiba, model 160A, Tokyo). We chose this method because the regurgitant flow velocity could cause aliasing with pulsed-wave Doppler measurements in these patients. Each patient was examined in the supine position by trained clinicians who had no knowledge of the clinical diagnosis. Guided by color-encoded Doppler flow mapping, the continuous wave Doppler beam was orientated as parallel as possible to the direction of the TR and PR jets. Then, minor manipulations of the transducer were performed to obtain the highest velocity. Using a modified Bernoulli equation (4), we approximated peak systolic pressure from the measured peak TR velocity on the assumption that RA pressure was zero. We also approximated diastolic pressure from the velocity of PR flow at the moment of its abrupt deceleration in late diastole, on the assumption that right ventricular (RV) diastolic pressure was zero. If abrupt deceleration was not obvious, we approximated it from PR flow at the moment of the R wave. Because the absolute pressure value varied depending on the severity of disease, we normalized pulse pressure by either peak pressure or mean pressure in establishing indexes for differentiating CPTE from PPH. We obtained mean pressure by adding one-third of the value of pulse pressure to the estimated diastolic pressure.

Statistical analysis. Pooled data are expressed as the mean value ± SD. Differences between the two groups were compared by using the unpaired *t* test. A p value < 0.05 was considered significant. Performance of each index in differentiating between CPTE and PPH was assessed with receiver operating characteristic (ROC) curve analysis (6). In this report, sensitivity stands for the ratio of the number of patients correctly diagnosed as having CPTE to the total number of patients with CPTE. Specificity stands for the ratio of the number of patients correctly diagnosed as having PPH to the total number of patients with PPH. We calculated the combinations of sensitivity and specificity for cutoff values at the midpoints of the ranges between adjacent pulsatility index values.

Results

Shown in Figure 1 are the scheme of PA and RV pressure waves (central panels) and representative recordings of TR (right panels) and PR (left panels) measured by continuous wave Doppler methods. The flow velocities of PR at end-diastole are lower in CPTE (top, left panel) than in PPH (bottom, left panel), even if those recordings of TR are comparable.

Basic PA hemodynamic variables are summarized in Table 1. There were no significant differences in heart rate or PA systolic pressure between patients with CPTE and those with PPH. In contrast, diastolic and mean pressure were significantly higher in the PPH group than in the CPTE group. This resulted in a higher pulse pressure in CPTE than in PPH.

Shown in Figure 2 are normalized pulse pressure values in patients with CPTE and those with PPH. Pulse pressure normalized by systolic pressure was significantly higher in the CPTE group than in the PPH group (0.82 ± 0.05 vs. 0.63 ±

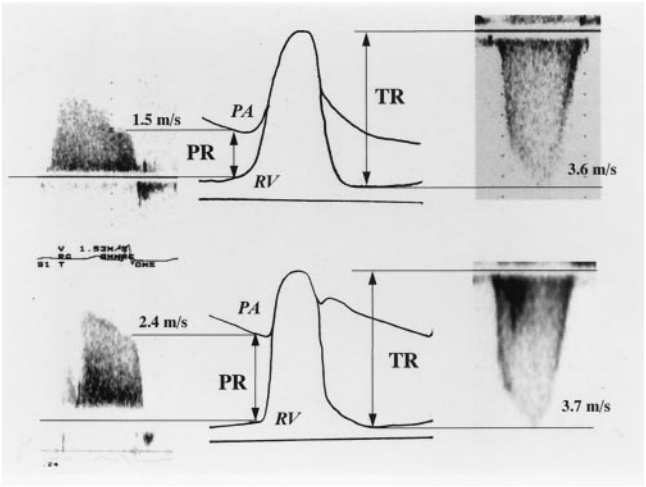


Figure 1. Continuous Doppler measurements in representative cases with the scheme of PA and RV pressure waveforms **(center).** The **top panels** are from a patient with CPTE. The **bottom panels** are from a patient with PPH. The **right panels** are the continuous Doppler measurements of TR. The **left panels** are the continuous Doppler measurements of PR. Although the Doppler flow velocities of TR are comparable between CPTE and PPH, those of PR are lower in CPTE than in PPH. The peak pressure gradient (TR) across the tricuspid valve during systole is defined as a measure of PA systolic pressure. We also approximated diastolic pressure (PR) from the velocity of PR flow at the moment of its abrupt deceleration in late diastole. If the abrupt deceleration was not identifiable, we approximated it from PR flow at the moment of the R wave.

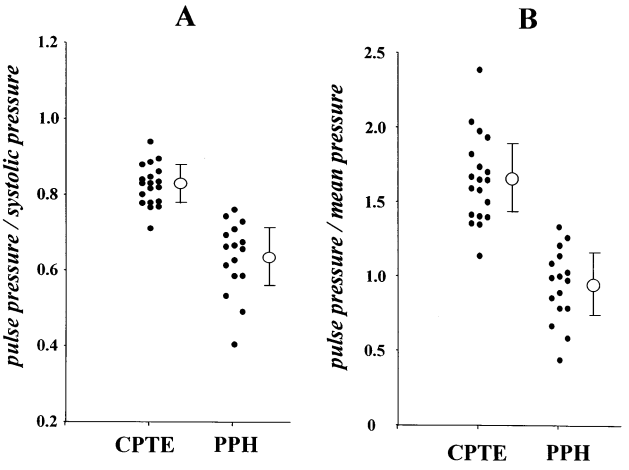


Figure 2. Normalized pulse pressure obtained by two methods. Estimated pulse pressure was normalized by either systolic pressure **(A)** or mean pressure **(B).** Both indexes differentiated CPTE from PPH reasonably well, with minimal overlap. **Solid circles** = individual data; **open circles** = mean values; **bars** = SD.

0.10, $p < 0.01$) (Fig. 2A), with a few overlap cases. Pulse pressure normalized by mean pressure was also significantly higher in the CPTE group than in the PPH group (1.65 ± 0.30 vs. 0.94 ± 0.25, $p < 0.01$) (Fig. 2B).

We evaluated the sensitivity and specificity of normalized pulse pressure in differentiating CPTE from PPH. ROC curves of these indexes are shown in Figure 3. Pulse pressure normalized by systolic pressure separated CPTE from PPH reasonably well, with a sensitivity of 0.95 and a specificity of 1.00 at the cutoff value of 0.77 (Fig. 3A). Similarly, pulse pressure normalized by mean pressure separated CPTE from PPH reasonably well, with a sensitivity of 0.95 and a specificity of 1.00 at the cutoff value of 1.35 (Fig. 3B).

Table 1. Heart Rate and Pulmonary Artery Hemodynamic Variables in Patients With Chronic Pulmonary Thromboembolism and Primary Pulmonary Hypertension

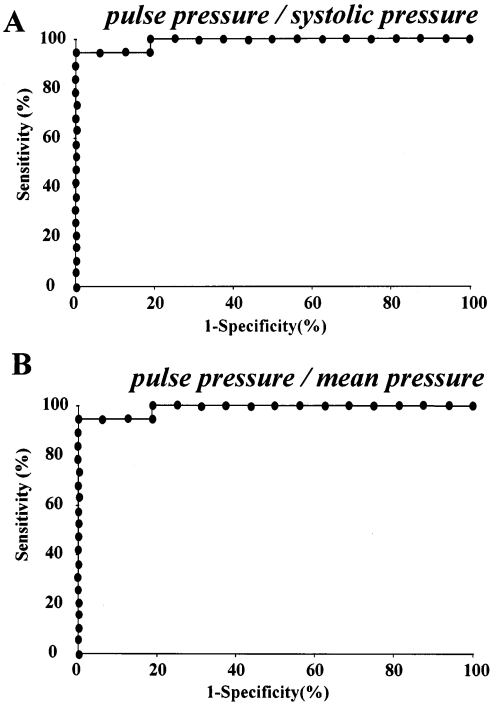
	CPTE Group	PPH Group	p Value
Heart rate (beats/min)	79 ± 15	81 ± 11	NS
Pulmonary artery pressure (mm Hg)			
Systolic	81 ± 20	79 ± 15	NS
Diastolic	14 ± 5	27 ± 3	< 0.01
Mean	41 ± 10	54 ± 9	< 0.01
Pulse	67 ± 18	52 ± 21	< 0.05

Pulmonary artery pressure values were estimated by continuous Doppler ultrasound measurements. CPTE = chronic pulmonary thromboembolism; PPH = primary pulmonary hypertension.

Discussion

We demonstrated in this study that CPTE could be differentiated from PPH on the basis of PA pressure pulsatility

Figure 3. ROC curve of normalized pulse pressure indexes in differentiating CPTE from PPH. Pulse pressure normalized by systolic pressure separated CPTE from PPH with a sensitivity of 0.95 and a specificity of 1.00 at the cutoff value of 0.77 **(A).** Pulse pressure normalized by mean pressure separated CPTE from PPH with a sensitivity of 0.95 and a specificity of 1.00 at the cutoff value of 1.35 **(B).**



estimated with Doppler ultrasound measurements. This method is completely noninvasive and can be applied to virtually all patients with pulmonary hypertension. In current practice, because the results of ventilation-perfusion radioisotope scanning might be unsatisfactory for establishing an accurate differential diagnosis in some patients (7), the use of pulmonary arteriography has been necessary at the expense of possibly serious and sometimes fatal complications (8). The clear separation between patients with CPTE and those with PPH in this study, with a relatively small sample size, indicates, if proven true in a larger group, that Doppler ultrasound measurement would be an additional diagnostic tool in differentiating between CPTE and PPH.

Mechanistic consideration. In CPTE, thrombi are lodged in the proximal arteries and result in stenosis of large arteries and possibly in stiffening of the arterial wall (9). Narrowing of the arterial segments increases resistance of the segments, and stiffening of the arterial segments increases characteristic impedance of the segments. Both changes increase apparent proximal arterial resistance (10). Pulmonary peripheral resistance is relatively normal. Thus, the ratio of proximal resistance (characteristic impedance) to peripheral resistance increases in CPTE, which would make pulse pressure large relative to mean pressure. Indeed, various investigators have shown, in the systemic arterial system, that decreased arterial compliance and increased characteristic impedance result in widening pulse pressure (11–14).

In contrast, in PPH, the peripheral arteries are preferentially involved and the resistance of peripheral arterial segments is increased without comparable changes in proximal arterial resistance (10). The ratio of proximal resistance (characteristic impedance) to peripheral resistance decreases in PPH, which, in turn, increases mean arterial pressure without comparable increases in pulse pressure.

Although the difference in pathologic findings seems to be the major cause of the difference in pulsatility, because of the retrospective study design, we could not rule out the possibility that the larger degree of PR in the CPTE group might result in larger pulsatility.

Pressure indexes derived from Doppler ultrasound measurements. Doppler flow velocity measurements have often been used for noninvasive measurements of cardiac chamber pressure (15,16). This has been accomplished by making use of the small regurgitation jet across the cardiac valves. Considering that patients with pulmonary hypertension usually have both TR and PR, it is relatively easy to record these regurgitant flow velocities in such patients. Strictly speaking, we can estimate the pressure gradient across valves, but not the absolute pressure values. The TR flow velocity provides the systolic pressure gradient between the RV and the RA. Because RA pressure is usually low, the peak pressure gradient approximated the absolute peak PA pressure. The PR flow velocity gives the diastolic pressure gradient between the PA and the RV. Because RV pressure is low in diastole, the pressure gradient at end-diastole is likely to reflect the absolute value of PA diastolic pressure. Using invasive recordings of mean RA pressure (6.1 ± 1.9 [CPTE] and 9.5 ± 2.6 [PPH] mm Hg, $p = 0.01$) and of RV end-diastolic pressure (9.1 ± 3.4 [CPTE] and 11.3 ± 3.9 [PPH] mm Hg, p = NS), pulsatility indexes obtained after adding these pressure values (either average or individual values) resulted in similar sensitivity (0.95) and specificity (0.94) in differentiating CPTE from PPH. To summarize, the use of pressure gradients across the tricuspid and pulmonary valves, as substitutes for absolute systolic and diastolic pressures, respectively, seems reasonable for our purpose. In our patient group, pulmonary diastolic pressure itself estimated by Doppler ultrasound measurements could separate CPTE and PPH reasonably well (sensitivity 0.89, specificity 1); this might not hold, however, if patients with more various systolic pressure values were included.

Study limitations. There are several limitations of this study. First, the PPH group consisted of more women and younger patients. The pulsatility indexes, however, were not different between men and women and did not correlate with age in either CPTE or PPH (data not shown). In addition, in normal subjects, changes in pulsatility with age were relatively small (17). These data indicate that age and gender did not affect pulsatility indexes much. Furthermore, although CPTE and PPH could be differentiated based on age and gender to some degree (sensitivity 0.89, specificity 0.75), pulsatility indexes provided much better differentiation between the two groups.

Second, we retrospectively analyzed only a limited number of patients. Performance of the indexes in differentiating between CPTE and PPH depends on the patient group. To generalize the results of this study, prospective studies involving many patients are essential, although accentuated pulsatility in CPTE and attenuated pulsatility in PPH seem to remain useful, as the results reflect the unique mechanical characteristics of PAs in patients with CPTE and PPH.

Many investigators have suggested that the pathophysiology of CPTE and PPH may overlap to a certain extent (9,18). We clinically diagnosed CPTE only when we could document thrombi in the PA with arteriography, and PPH was diagnosed by exclusion. Thus, PPH might include those patients with minute thrombi undetectable by arteriography. Although the clinical diagnosis generally relies on functional rather than pure etiologic aspects of disease, the former is important as it may indicate the possibility for surgical intervention (19).

Although both TR and PR flow velocities were not measured simultaneously, all patients were in sinus rhythm and the pressure differences among beats were minor. Also, because perfect alignment of the Doppler beam to the flow direction is impossible, the measured flow velocity was minimally, but to varying degrees, underestimated. Marked elevation of mean RA pressure and RV end-diastolic pressures caused deviations in absolute pressure values. Nevertheless, the fact that normalized pulse pressure differentiated CPTE from PPH reasonably well indicates that the pulse pressure indexes have significant clinical values regardless of such errors in pressure estimation.

Conclusions. Doppler echocardiography may offer a new approach to the differential diagnosis between patients with

CPTE and those with PPH with moderate to severe pulmonary hypertension.

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