

## Pulmonary Hypertension

# Pulmonary Artery Reflection for Differentially Diagnosing Primary Pulmonary Hypertension and Chronic Pulmonary Thromboembolism

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<b>OBJECTIVES</b>	The purpose of this investigation was to differentiate chronic pulmonary thromboembolism (CPTE) from primary pulmonary hypertension (PPH) by means of the indexes of pulmonary arterial reflection.
<b>BACKGROUND</b>	These differences in the primary lesions would make pulmonary artery reflection occur earlier in CPTE than in PPH. Although the analysis of pulsatility of pulmonary arterial pressure is useful in the differential diagnosis of PPH and CPTE, it is not known whether the analysis of pulmonary artery reflection can differentiate CPTE from PPH.
<b>METHODS</b>	Since CPTE predominantly involves the proximal arteries, whereas PPH involve the peripheral arteries, we hypothesized that patients with CPTE have a large augmentation index and a short inflection time. For this study, we enrolled 62 patients who had CPTE (31 patients) and PPH (31 patients). We measured pulmonary arterial pressure using a fluid filled system that included a balloon-tipped flow directed catheter. To quantify the pulmonary artery reflection, we used the augmentation index and inflection time.
<b>RESULTS</b>	The augmentation index was markedly higher in CPTE than it was in PPH ( $27.4\% \pm 15.2\%$ [SD] and $-25.1\% \pm 26.9\%$ , respectively, $p < 0.001$ ) and was diagnostic in separating the two groups. Inflection time separated the two groups reasonably well ( $97 \pm 20$ ms and $210 \pm 49$ ms, respectively, $p < 0.001$ ).
<b>CONCLUSIONS</b>	The analysis of pulmonary arterial reflection is useful in the differential diagnosis of CPTE and PPH. (J Am Coll Cardiol 2001;38:214–8) © 2001 by the American College of Cardiology

The augmentation index (i.e., the magnitude of the secondary rise in pressure relative to pulse pressure) and the inflection time (i.e., the period from the onset of the pressure increase after diastole to the inflection point) give information on the magnitude and return time of reflected waves, respectively (1–3). The distance of the reflection site and the pulse wave velocity then determines the inflection time. When the reflection is large, such as when an embolus is present, the augmentation index will be large, and the inflection time is determined by the location of the embolus. Differential diagnosis between chronic pulmonary thromboembolism (CPTE) and primary pulmonary hypertension (PPH) remains a clinical challenge. In particular, the correct diagnosis of CPTE is a prerequisite for life-saving surgical procedures (4). Chronic pulmonary thromboembolism predominantly involves the proximal arteries, that are usually stiff (i.e., have a pulse wave velocity), whereas in PPH the periphery is involved with relatively compliant arteries. Therefore, we hypothesized that pulmonary artery (PA) reflections would return with greater magnitude, producing

an increased augmentation index and with shorter inflection time. The results of our study, indeed, indicate that this is the case and that this information can be used in differentiating CPTE and PPH.

## METHODS

**Study subjects.** The study group consisted of 62 consecutive patients who were admitted to the National Cardiovascular Center, Osaka, Japan, because of symptomatic pulmonary hypertension (New York Heart Association class II to IV) between January 1997 and May 2000 and who were subsequently diagnosed as having CPTE or PPH. Chronic pulmonary thromboembolism was diagnosed when thromboembolism was positively diagnosed by means of both pulmonary angiography and radioisotope ventilation-perfusion imaging in patients with a clinical history compatible with CPTE. Primary pulmonary hypertension was a diagnosis of exclusion made when other possible etiologies of pulmonary hypertension (i.e., secondary causes), such as mitral valve diseases, congenital heart disease, left ventricular failure and CPTE were excluded. We excluded patients with signs of collagen vascular disease from the PPH group, positive antinuclear antibody, history of drug abuse, use of diet pills or history of liver disease. The protocol was in

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**Abbreviations and Acronyms**

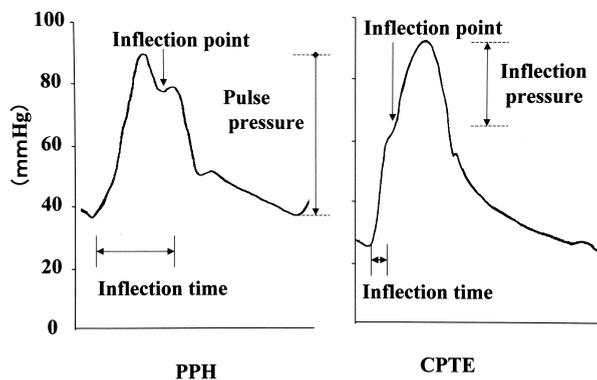
CPTE = chronic pulmonary thromboembolism  
 PA = pulmonary artery  
 PPH = primary pulmonary hypertension

accordance with Institutional Guidelines for Human Research, and each individual provided a written statement of informed consent for diagnostic and therapeutic procedures required for examination, which stated that the results of the examination could be used for the study.

**Measurement of hemodynamic variables.** We obtained hemodynamic variables in the supine position. Pulmonary arterial pressure was measured at end-expiration during a short episode of breath-holding using a fluid-filled system that included a balloon-tipped flow directed catheter (7F Swan-Ganz catheter) in the main PA. A hard copy was made of the pressure tracing using a chart recorder (Nihon Koden, Surgical Monitoring System, Tokyo, Japan) at a paper speed of 100 mm/s. We determined cardiac output using the Fick principle based on oximetry.

We compared tracings of systolic, diastolic, mean and pulse pressures in patients with CPTE and PPH. Pulmonary pressure at inflection point dividing into an early and late systolic phase was used as inflection pressure (1-3). The inflection point in the pulmonary pressure divides systole in an early and late phase (Fig. 1). We divided the PA pressure waveform into three subgroups (A, B and C), according to classification by Murgu et al. (1-3). The augmentation index was defined as the ratio of inflection pressure to pulse pressure in subgroup A and B, and as the ratio of minus inflection pressure to pulse pressure in subgroup C. We used inflection time ( $\Delta tp$ ) as the time interval between onset of systolic pressure waveform and inflection point (1-3).

**Statistical analysis.** Values are expressed as mean  $\pm$  one SD. Differences in the mean values between the two groups were compared by unpaired *t* test. Categorical variables were



**Figure 1.** Pulmonary arterial pressure tracings in representative cases. The left panel is from a patient with primary pulmonary hypertension (PPH). The right panel is from a patient with chronic pulmonary thromboembolism (CPTE). Inflection time is by far larger in PPH than it is in CPTE. Inflection time, inflection point and inflection pressure are indicated.

**Table 1.** Baseline Characteristics of Patients

Variables	PPH	CPTE	P Value
Men/number	13/31	13/31	1.00
Age (yr)	39.4 $\pm$ 12.6	49.8 $\pm$ 11.1	0.001
Heart rate (beats/min)	83.4 $\pm$ 12.1	73.9 $\pm$ 11.1	0.002
Cardiac output (l/min)	3.2 $\pm$ 1.2	3.4 $\pm$ 1.0	0.501
Mean blood pressure (mm Hg)	82.0 $\pm$ 11.5	87.0 $\pm$ 8.2	0.057

CPTE = chronic pulmonary thromboembolism; PPH = primary pulmonary hypertension.

compared using the chi-squared test. A p value of <0.05 was considered significant.

**RESULTS**

**Baseline clinical characteristics.** The baseline clinical characteristics of the study group are summarized in Table 1. There were 31 patients with CPTE (13 men and 18 women) whose average age was 39.4  $\pm$  12.6 years (range: 26 to 67 years). The rest of the patients had PPH (13 men and 18 women). Their average age was 49.8  $\pm$  11.1 years (range: 19 to 63 years). Medical therapy for pulmonary hypertension included loop diuretics (n = 38), digoxin (n = 33), warfarin (n = 29), calcium channel antagonists (n = 9) and beraprost sodium (oral prostaglandin I<sub>2</sub> derivative) (n = 28). Four of the 31 patients with CPTE and five of the 31 with PPH were taking calcium channel antagonists (p = NS). Thirteen of those with CPTE and 15 with PPH were taking beraprost sodium (p = NS). Although the distribution of gender, cardiac output and mean blood pressure were similar, there were significant differences in the mean age and heart rate.

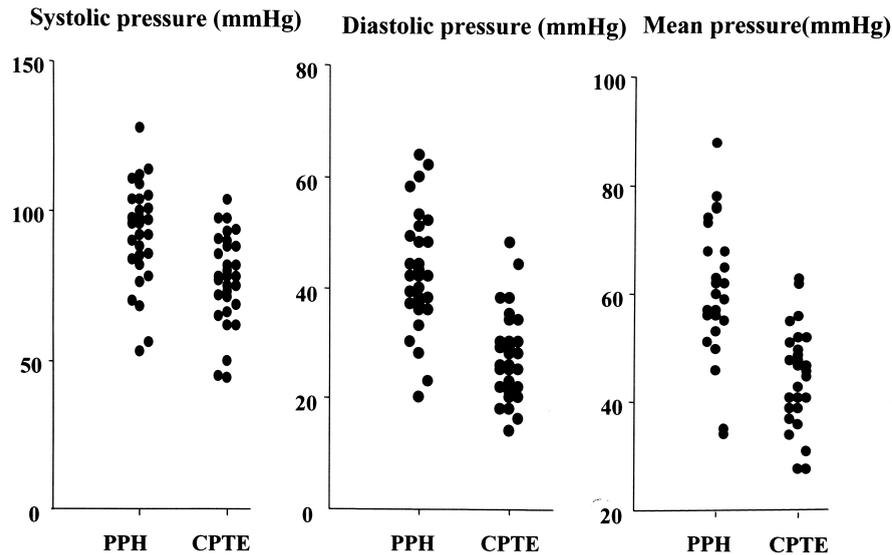
**Pulmonary hemodynamic variables.** The pulmonary hemodynamic variables characteristic of the study group are summarized in Table 2. Systolic, diastolic and mean pressures and total pulmonary resistance in the PA were higher in patients with PPH than in patients with CPTE. There were significant differences in augmentation indexes and inflection time between the two groups.

Figure 1 illustrates the waveforms of PA pressure in the case of CPTE (right panel) and in PPH (left panel). Although heart rates are similar in the two cases, inflection point occurs much earlier in CPTE than in PPH. As a result, inflection time is, by far, shorter in CPTE than in PPH.

**Table 2.** Pulmonary Hemodynamic Variables

Variables	PPH	CPTE	p Value
Systolic pressure (mm Hg)	97.2 $\pm$ 16.6	77.1 $\pm$ 14.8	< 0.001
Diastolic pressure (mm Hg)	42.6 $\pm$ 10.5	27.4 $\pm$ 7.9	< 0.001
Mean pressure (mm Hg)	60.5 $\pm$ 11.5	44.7 $\pm$ 8.7	< 0.001
Total pulmonary resistance (u)	21.1 $\pm$ 9.3	14.8 $\pm$ 7.0	0.002
Augmentation index (%)	-25.1 $\pm$ 26.9	27.4 $\pm$ 15.2	< 0.001
Inflection time (ms)	210 $\pm$ 49	97 $\pm$ 20	< 0.001

CPTE = chronic pulmonary thromboembolism; PPH = primary pulmonary hypertension.

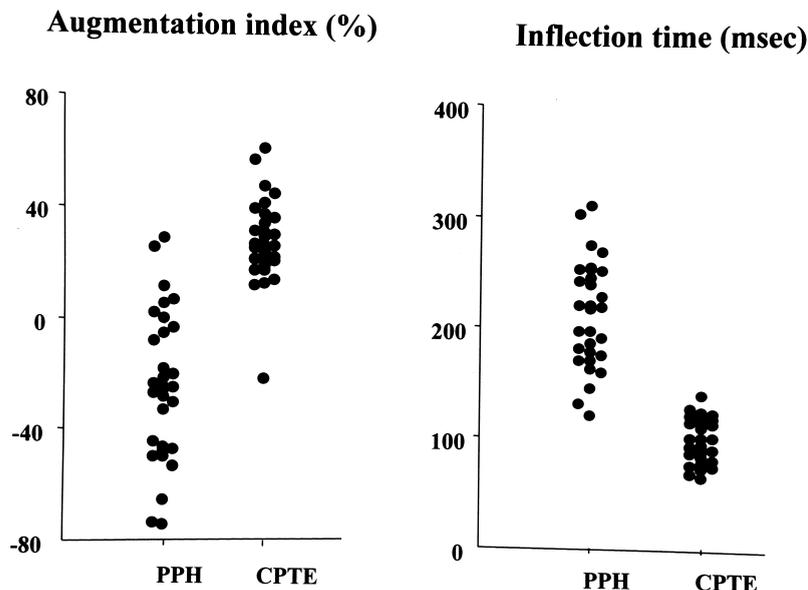


**Figure 2.** Pulmonary hemodynamic variables in primary pulmonary hypertension (PPH) and in chronic pulmonary thromboembolism (CPTE). The closed circles represent individual data.

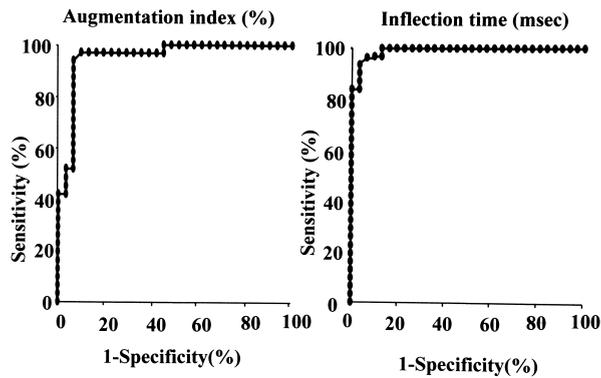
Figure 2 illustrates the pooled data representing pulmonary hemodynamics. Systolic PA pressure was statistically lower in CPTE than in PPH ( $77.1 \pm 14.8$  and  $97.2 \pm 16.6$  mm Hg, respectively,  $p < 0.001$ ) (Fig. 2). Diastolic PA pressure was lower in CPTE than in PPH ( $27.4 \pm 7.9$  and  $42.6 \pm 10.5$  mm Hg, respectively,  $p < 0.001$ ) (Fig. 2). Mean PA pressure was also significantly lower in CPTE than in PPH ( $44.7 \pm 8.7$  and  $60.5 \pm 11.5$  mm Hg, respectively,  $p < 0.001$ ) (Fig. 2). Despite these significant differences in pulmonary hemodynamics, none of them were remarkably capable of separating these two groups.

Figure 3 illustrates the comparison of the two reflection indexes we proposed for differentiating between CPTE and

PPH. As shown in the left panel of Figure 3, the augmentation index was significantly higher in CPTE than in PPH ( $27.4 \pm 15.2$  and  $-25.1 \pm 26.9$ , respectively,  $p < 0.001$ ). It separated the two groups reasonably well. The receiver operating characteristic analysis indicated that the sensitivity of augmentation index to differentiate CPTE from the combined group of CPTE and PPH was 0.94, when the cutoff value was chosen as 12% (5). The specificity for excluding CPTE from the combined group of CPTE and PPH was 0.94 (Fig. 4, left panel). The right panel of Figure 3 illustrates the inflection time of pulmonary arterial pressure. Inflection time was significantly shorter in CPTE than in PPH ( $97 \pm 20$  and  $210 \pm 49$ , respectively,  $p < 0.001$ ).



**Figure 3.** Comparison of pulmonary artery reflection between primary pulmonary hypertension (PPH) and chronic pulmonary thromboembolism (CPTE). The closed circles represent individual data.



**Figure 4.** Receiver operating characteristic curve of augmentation index and inflection time in differentiating chronic pulmonary thromboembolism from primary pulmonary hypertension.

It separated the two groups reasonably well. The receiver operating characteristic analysis indicated that sensitivity of inflection time to differentiate CPTE from the combined group of CPTE and PPH was 0.93 when the cutoff value was chosen as 122 ms. The specificity for excluding CPTE from the combined group of CPTE and PPH was 0.97 (Fig. 4, right panel).

## DISCUSSION

We have shown that, although conventional variables of pulmonary arterial pressure failed to differentiate between CPTE and PPH, waveform analysis focusing on pulmonary arterial reflection made it possible to differentiate CPTE from PPH.

**Clinical implications in differentially diagnosing CPTE and PPH on the basis of the pulmonary arterial reflection.** In clinical settings, the etiological diagnosis of pulmonary hypertension remains a challenge. Noninvasive techniques such as radioisotopic ventilation and perfusion scanning and computed tomography have been extremely useful in the differential diagnosis of pulmonary hypertension. They could, however, sometimes fail in the diagnosis and necessitate study by angiography (6). Although pulmonary angiography is a well-established technique in evaluating PA disease, it could occasionally lead to sudden cardiovascular collapse and even death (7). Thus, there are obvious needs to develop tools to help in the etiological diagnosis of severe pulmonary hypertension. We have demonstrated in a previous study that the pulsatility analysis of the pulmonary arterial pressure waveform provides useful information in differentiating between CPTE and PPH (8). As the measurement of PA pressure by a balloon-tipped flow directed catheter is a relatively safe procedure as compared with pulmonary angiography, the waveform analysis focusing on pulmonary arterial reflection added to pulsatility analysis on the pulmonary arterial pressure waveform might help in differentiating between CPTE and PPH.

**Differing severity of pulmonary hypertension between CPTE and PPH.** In this investigation, although cardiac output was similar, the PA pressure was significantly higher in PPH than in CPTE. The severity of pulmonary hypertension may influence on augmentation index or inflection time. Therefore, we separately analyzed the diagnostic significance of PA reflection in the subgroups with a similar degree of pulmonary hypertension, whose mean PA pressures was >40 mm Hg in CPTE and was <60 mm Hg in PPH (CPTE: n = 23, PPH: n = 16). Mean pressures and total pulmonary resistance in the PA were similar for PPH and CPTE (53.4 mm Hg  $\pm$  10.0 mm Hg vs. 48.4 mm Hg  $\pm$  6.4 mm Hg, p = NS, 18.1 U  $\pm$  8.3 U vs. 16.3 U  $\pm$  7.4 U, p = NS). The results indicated that the augmentation index was markedly higher for CPTE than for PPH (26.1%  $\pm$  15.0% and -28.5%  $\pm$  31.1%, respectively, p < 0.001). Inflection time also separated the two groups (95.3  $\pm$  19.8 and 216  $\pm$  55.0, respectively, p < 0.001). These results were in line with those obtained from the total group. Thus, the severity of pulmonary hypertension did not appear to significantly modulate the basic characteristics of the PA reflection of CPTE or PPH.

**Study limitations.** There are several limitations in the study. We analyzed only a limited number of patients. To generalize the results of this study, prospective studies involving many patients are essential. Nevertheless, waveform analysis focusing on pulmonary arterial reflection in CPTE would be expected to remain a useful, valid observation as it is based on the fundamental mechanical characteristics of CPTE and PPH.

We used a fluid filled catheter to record pulmonary arterial pressure. Although a high-fidelity catheter (tip) manometer is preferred (9,10), the harmonic concept of the PA waveform is so low that, when carefully filled, the fluid-filled system can be used.

**Conclusions.** In conclusion, pulmonary arterial pressure waveform analysis can offer an additional new approach in the differential diagnosis that would help to discriminate between CPTE and PPH.

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