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Dilatation of Bronchial Arteries Correlates With Extent of Central Disease in Patients With Chronic Thromboembolic Pulmonary Hypertension

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Background Dilatation of the bronchial arteries is a well-recognized feature in patients with chronic thromboembolic pulmonary hypertension (CTEPH). The purpose of the current study was to use computed tomography (CT) to assess the relationship between dilated bronchial arteries and the extent of thrombi, and to evaluate the predictive value of the former for surgical outcome.

Methods and Results Fifty-nine patients with CTEPH and 16 with pulmonary arterial hypertension (PAH) were retrospectively evaluated. The total cross-sectional area of bronchial arteries was measured by CT and its relationship with the central extent of thrombi or surgical outcome was assessed. The total area of the bronchial arteries in CTEPH patients was significantly larger than that in PAH patients (median [range], 6.9 [1.7–29.5] mm^2 vs 3.2 [0.8–9.4] mm^2), with the total area of bronchial arteries correlating with the central extent of thrombi. In patients who had undergone pulmonary thromboendarterectomy (PTE) (n=22), the change in PaO_2 after surgery had a tendency to correlate with the total area of the bronchial arteries.

Conclusion The total cross-sectional area of the bronchial arteries correlated with the extent of central disease in patients with CTEPH, and it might predict gas exchange improvement after PTE. (*Circ J* 2008; **72:** 1136–1141)

Key Words: Bronchial artery; Chronic thromboembolic pulmonary hypertension; Pulmonary circulation; Pulmonary embolism

In patients with chronic thromboembolic pulmonary hypertension (CTEPH), dilatation of the bronchial arteries (BAs) is a well-recognized feature on conventional angiography[1] and computed tomography (CT) angiography[2,3] As the finding of dilated BAs is rarely seen in patients with idiopathic pulmonary arterial hypertension (PAH) or acute pulmonary embolism, it has been suggested that this feature could help distinguish patients with CTEPH from those with other diseases causing pulmonary hypertension[1,3,4]

The presence of dilated BAs represents increased systemic collateral blood supply[1,2] and it plays a important role in maintaining the viability of ischemic lung parenchyma after pulmonary artery occlusion[5] However, the mechanisms of bronchial arterial development are not well understood. It is thought that both hemodynamic and nonhemodynamic factors might be involved[6] In a canine model, Rehulova et al showed that the development of collateral bronchopulmonary circulation depended on the size of the occluded branch of the pulmonary arteries[7] In patients with CTEPH, the location of thrombi varies between individuals, but to our knowledge no study has evaluated the relationship between the location of thrombi and the dilatation of BAs in humans.

Previous studies showed a lower postoperative mortality rate and lower postoperative pulmonary vascular resistance (PVR) after pulmonary thromboendarterectomy (PTE) in patients with dilated BAs according to the preoperative evaluation, compared with patients without dilated BAs[8,9] Those studies classified patients into 2 groups, with (≥1.5 mm) or without (<1.5 mm) dilated BAs. Ley et al showed a correlation between the cross-sectional area of BAs assessed by CT angiography and the bronchopulmonary shunt volume assessed by magnetic resonance imaging[2] Those results prompted us to use the cross-sectional area of the BAs, instead of their diameters, for assessment of the relationship with surgical outcome after PTE, as the bronchopulmonary shunt volume may contribute directly to supporting ischemic parenchymal tissue caused by occlusion of the pulmonary arteries.

The purpose of our study was to use CT angiography to assess the relationship between the cross-sectional area of the BAs and the central extent of thrombi, as well as to evaluate the predictive value of dilated BAs for surgical outcome.

Methods

Study Population

For this retrospective study, we searched the computer database of Chiba University Hospital to identify patients

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with CTEPH (n=74) and PAH (n=19) who had undergone CT angiography between January 2002 and August 2007. All patients, except 1 with PAH, had undergone right-heart catheterization. The diagnosis of CTEPH or PAH was made on the basis of multiple diagnostic tests, including a detailed history, physical examination, pulmonary function testing, perfusion scanning, CT scanning, echocardiogram, right-heart catheterization and serologic tests.

Fourteen patients (11 with CTEPH, 3 with PAH) were excluded because of suboptimal contrast material delivery for evaluation of the BAs. Four patients with CTEPH were also excluded because the duration between CT angiography and right-heart catheterization was more than 3 months. Finally, 59 patients with CTEPH (CTEPH group) and 16 patients with PAH (PAH group: 8 with idiopathic PAH, 4 with PAH associated with collagen vascular disease, 2 with arterial septal defect and 2 with PAH associated with portal hypertension) were evaluated. Right-heart catheterization and selective pulmonary angiography were performed in all patients of the CTEPH group.

Twenty-four patients in the CTEPH group had undergone PTE; 2 of them died in the early postoperative period, and the remainder, except 1 patient (n=21), underwent post-operative CT angiography within 3 months (median [range], 1 [1–3]) after PTE. Postoperative blood gas analyses were performed for all patients and compared with preoperative blood gas levels.

As for the control of the total area of the BAs, we evaluated 12 patients who had acute pulmonary thromboembolism (APTE), whose thrombi were treated and resolved almost completely (post-APTE group).

The Human Subject Committee of Chiba University approved the study, and written informed consent was given by all patients at the time of diagnosis.

CT Protocol

All CT scans were obtained with a 16-row multidetector CT scanner (LightSpeed Ultra16; General Electric Medical Systems, Milwaukee, WI, USA) with 1.25-mm slice thickness. Patients were injected with 100 ml of contrast material with 350 mg of iodine/ml at 3 ml/s. All CT examinations were performed for a normal workup to diagnose or evaluate CTEPH or PAH, with a scanning delay of 20–30 s for optimal pulmonary artery visualization.

Image Interpretation

CT images were reviewed by 2 investigators using a cine-mode display on a computer workstation, and final evaluations were achieved by consensus. All BAs arising from the descending aorta in each patient as depicted by CT angiography were identified. At the mediastinal window setting of the axial images, right and/or left BAs were identified as contrast material-enhanced round or curvilinear structures (Fig 1). Their diameters were measured at the most proximal site from their origin. We calculated the cross-sectional area of each BA based on its diameter, and then summed the cross-sectional areas in each patient to yield the total area of the BAs.

The CTEPH group was divided into 3 subgroups, main type, lobar type and segmental type, according to the most proximal location of thrombi observed on CT angiography. The main type (n=9) was defined as thrombi of main arteries with or without more distal thrombi location, the lobar type (n=29) was defined as thrombi of lobar arteries with or without more distal thrombi location, and the segmental type (n=21) was defined as thrombi in segmental arteries or distal location.

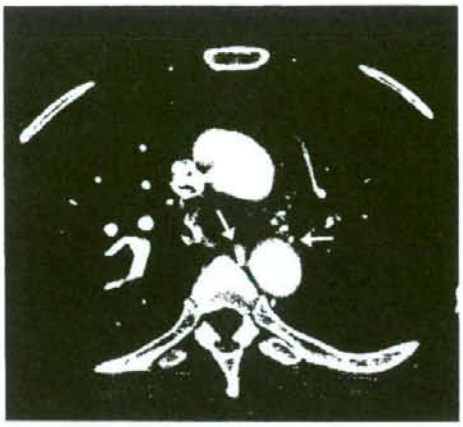

Fig 1. Computed tomography angiography in a patient with chronic thromboembolic pulmonary hypertension shows dilated bronchial arteries (arrows).

We also evaluated pulmonary infarction by the peripheral scar score as described by Heinrich et al.[9] In short, CT scan images at the lung window settings were analyzed for peripheral, irregular, wedge-shaped or linear densities. By adding up the number of involved lobes (lingual was regarded as a lobe), the peripheral scar score was obtained up to a maximum score of 6.

Statistical Analysis

Group comparisons were performed by Mann-Whitney U-test or 1-way analysis of variance on ranks (Kruskal-Wallis method) with post-hoc test using the Steel-Dwass method. When data were normally distributed with constant variance, correlations were measured using Pearson's correlation. Otherwise, the Spearman rank sum correlation was used. Comparison of the total areas of the BAs between before and after PTE was performed by Wilcoxon matched-pairs signed-ranks test. For all comparisons, a p-value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Clinical and Hemodynamic Characteristics of the Patients

Table 1 summarizes the clinical and hemodynamic data from the 75 patients included in the current study. No statistical significant differences were found in terms of age, mean pulmonary artery pressure, cardiac index and PVR among the groups and subgroups.

Comparisons Between Patient Groups

The median total area of the BAs in the CTEPH group was significantly larger than that in the PAH group and the post-APTE group (Fig 2a; median [range], 6.9 [1.7–29.5] mm^2 vs 3.2 [0.8–9.4] mm^2 vs 2.0 [0.9–5.1] mm^2). When the CTEPH group was divided into 3 subgroups according to the most proximal location of thrombi, the median total area of the BAs in the segmental type was significantly smaller than in the other 2 types (Fig 2b). No significant difference in

Table 1 Clinical and Hemodynamic Characteristics of the 75 Patients in the Present Study

	PAH group (n=16)	CTEPH group				p value*
		All (n=59)	Main (n=31)	Lobar (n=18)	Segmental (n=13)	
Age (year)	50.4±16.6 (17–69)	54.9±12.2 (34–78)	60.2±9.4 (43–71)	53.7±12.6 (34–72)	54.4±12.4 (36–78)	NS
Sex (M/F)	2/14	16/43	6/3	8/21	2/19	
Mean pulmonary artery pressure (mmHg)	42.7±9.84 (26–55)	44.5±12.9 (23–71)	48.6±12.4 (32–70)	43.2±12.8 (23–71)	44.6±13.4 (23–71)	NS
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.73±0.53 (2.15–4.31)	2.56±0.63 (1.44–4.35)	2.36±0.91 (1.44–4.35)	2.46±0.54 (1.61–3.54)	2.79±0.58 (1.82–4.24)	NS
Pulmonary vascular resistance ($dynes \cdot s^{-1} \cdot cm^{-5}$)	694±202 (343–947)	828±425 (289–2,285)	986±467 (515–1,699)	839±468 (289–2,285)	746±368 (316–1,950)	NS

Data are mean ± SD (range), unless otherwise stated.
**Study groups were analyzed by Kruskal-Wallis test.*
PAH, pulmonary atrial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; NS, not significant.

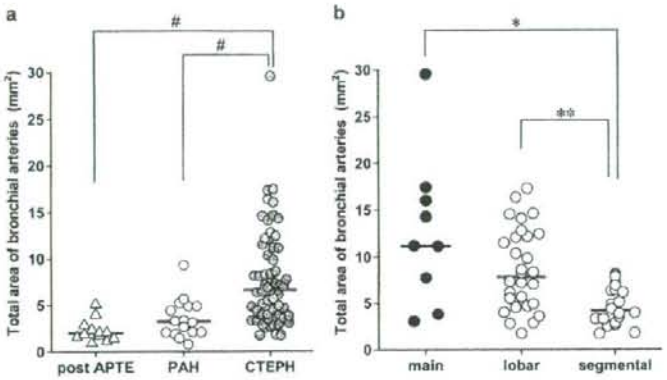

Fig 2. (a) Total area of the bronchial arteries in the post-APTE, PAH and CTEPH groups. (b) Comparison of the total area of the bronchial arteries in the 3 CTEPH subgroups according to the location of thrombi. Bars indicate median. #p<0.001, *p<0.01, **p<0.001. APTE, acute pulmonary thromboembolism; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension.

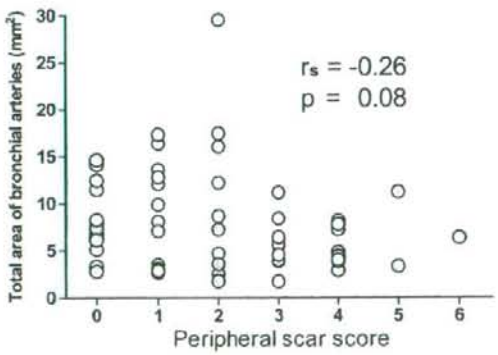

Fig 3. Correlation between peripheral scar score and total area of the bronchial arteries in the chronic thromboembolic pulmonary hypertension group.

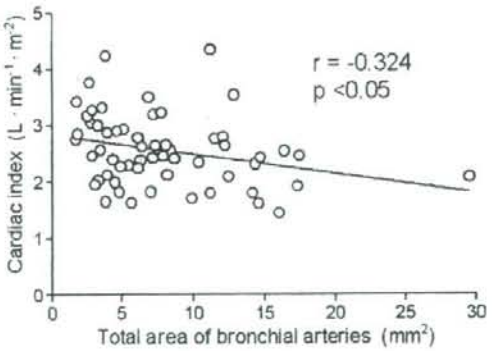

Fig 4. Correlation between the total area of the bronchial arteries and cardiac index in chronic thromboembolic pulmonary hypertension group.

total area of the BAs was observed between the PAH group and the segmental type of CTEPH. In the CTEPH group, the total area of the BAs showed a slight correlation with the peripheral scar score, but it did not reach statistical significance (Fig 3; r=–0.26, p=0.08).

Correlation With Total Area of BAs and Preoperative Hemodynamics

The total area of the BAs was significantly correlated with the preoperative cardiac index (Fig 4; r=–0.32, p<0.05). No significant correlation was found between the total area of the BAs and preoperative mean pulmonary artery pressure (r=–0.05, p=0.72) or PVR (r=0.12, p=0.37).

Table 2 Surgical Outcomes of Patients Undergoing PTE (n=22) and Correlation With Total Area of Bronchial Arteries

		Total area of bronchial arteries	
		r value	p value
Postoperative mean pulmonary artery pressure (mmHg)	26.5±12.5 (12–58)	−0.23	0.30
Postoperative cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.79±0.51 (1.85–3.63)	0.02	0.92
Postoperative pulmonary vascular resistance ($dynes \cdot s^{-1} \cdot cm^{-5}$)	388±348 (132–1,168)	−0.23	0.29
%reduction in pulmonary vascular resistance (%)	55±31 (−25–90)	0.16	0.47
Change in PaO_2 after PTE (mmHg)	14.1±13.6 (−10.9–44.3)	0.40	0.06
Change in $AaDO_2$ after PTE (mmHg)	−19.9±14.5 (−53.6–4.43)	−0.26	0.25

Data are mean±SD (range), unless otherwise stated.
PTE, pulmonary thromboendarterectomy; PaO_2, arterial oxygen tension; $AaDO_2$, alveolar-arterial oxygen pressure difference.

Correlation of Total Cross-Sectional Area of BAs With Outcome and its Change After PTE

Twenty-two patients (10 men, 12 women), mean 51.5 years (range, 18–69 years), underwent PTE and postoperative right-heart catheterization, and the relationship between the total cross-sectional area of the BAs and surgical outcome was evaluated. In this subgroup, the median total area of the BAs was 14.8 mm^2 (range, 3.6–29.5 mm^2). Every patient, except 1, had at least 1 BA with a diameter ≥1.5 mm. Based on the location of thrombi, 7 patients were classified as main type of CTEPH, 14 as lobar type, and only 1 patient was classified as the segmental type. Table 2 summarizes the surgical outcomes of the 22 patients. The total area of the BAs showed a slight correlation with changes in PaO_2, but it did not reach statistical significance (r=0.40, p=0.06). Other parameters regarding surgical outcome showed no correlation with the total area of the BAs. The total area of the BAs after PTE was significantly reduced compared with before PTE (Fig 5; median [range], 7.7 [2.3–18.9] mm^2 vs 11.2 [3.6–17.5] mm^2).

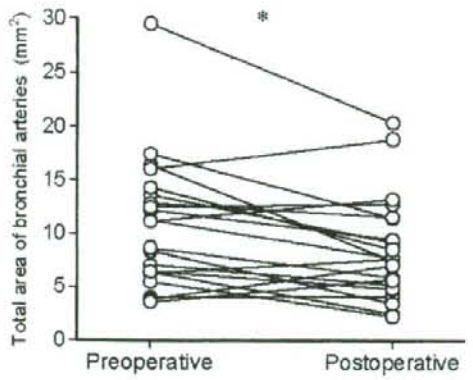

Fig 5. Comparison of the total area of the bronchial arteries before and after pulmonary thromboendarterectomy. *p<0.05.

Discussion

The current study demonstrated that the location of thrombi is related to the total cross-sectional area of the BAs in CTEPH patients. Although the BAs in the CTEPH patients were significantly dilated compared with those in the PAH patients, there was no significant difference in the total area of the BAs in the segmental type of CTEPH group and those in the PAH group. We also showed that the total area of the BAs in patients with CTEPH significantly decreased after PTE and might predict surgical outcome. With the advances in CT, the potential of CT angiography for diagnosing CTEPH has been demonstrated by a number of studies.[10–13] Moreover, CT angiography is also being recognized as a useful test for evaluating the development of systemic collateral supply to the lung.[2–4,8,9,14] Remy-Jardin et al showed that multidetector row helical CT angiography depicts the BAs more precisely than conventional angiography.[14] Therefore, in the present study we also used multidetector row helical CT angiography to evaluate the dilatation of the BAs.

Consistent with previous studies,[2–4,8,9,15] dilated BAs were frequently seen in the patients with CTEPH in the present study. The total area of the BAs in the CTEPH patients was significantly larger than that in the PAH patients. In the CTEPH group, as in earlier studies,[8,9] we did not find any significant correlation between the total area of the BAs and the preoperative mean pulmonary artery pressure or the PVR, meaning that the severity of pulmonary hypertension was not a stimulus for the development of dilated BAs. However, the total area of the BAs was negatively correlated with the cardiac index. Although the onset of CTEPH is difficult to detect, disease duration might correlate with the development of dilated BAs. On the other hand, reduction in the cardiac index occurs in the symptomatic and decompensated phase of pulmonary hypertension,[16] so disease duration might lead to this negative correlation between the total area of the BAs and cardiac index.

Of the CTEPH subgroups, the total area of the BAs in the segmental type was significantly smaller than in the other types. To our knowledge, this is the first study to investigate the correlation between BA enlargement and the central extent of thrombi in humans. The inverse relationship between the total area of the BAs and the peripheral scar score, possibly representing prior pulmonary infarction, might support this finding. One study using a dog model showed that the BAs did not become enlarged upon embolization of muscular arteries or arterioles, although enlargement occurred when the elastic branches of the pulmonary arteries were occluded.[7] This suggests that occlusion of the pulmonary arteries at the proximal sites of bronchopulmonary arterial anastomoses might open them up. In humans, preexisting bronchopulmonary arterial anastomoses are commonly seen slightly proximal to the lobular arteries.[17] The pressure gradient between the systemic arteries and the pulmonary arteries distal to the site of occlusion would increase when small distal arteries and arterioles are unaffected in patients with main or lobar type of CTEPH, and it would result in systemic arterial blood flow increasing in ischemic areas. Another possibility for the development of

systemic arterial supply to an occluded lung, related to the location of thrombi, is hyperplasia of the pulmonary artery vasa vasorum, which is of bronchial arterial origin[6,17] In addition, the extent of central disease per se may lead to nonhemodynamic factors, including pro- and anti-angiogenic factors. Our previous study showed that monocyte chemoattractant protein-1 is produced in endothelial cells, mononuclear cells, and smooth muscle cells in the fibrinous portion adjacent to the vascular lumen in endarterectomized tissue[18] Herve and Fadel speculated that macrophages infiltrating the wall of an occluded pulmonary artery stimulate proliferation of the vasa vasorum and lead to delivery of bone marrow-derived endothelial progenitor cells for local vasculogenesis within the nonresolving clots[6] Other nonhemodynamic factors that are elevated in patients with CTEPH, such as endothelin-1[19] might play a role in development of dilated BAs.

We also showed that the total area of the BAs was significantly reduced after PTE. However, the total area of the BAs after PTE was greater compared with that in the post-APTE group. A certain number of thrombi remained after PTE, which would keep the BAs dilated. Fadel et al showed that in piglets revascularization after a period of left pulmonary artery occlusion normalized the systemic blood flow to the left lung[20] Our finding is consistent with their experimental model and we believe that reduction in the total area of the BAs after PTE can prevent hemoptysis, a life-threatening complication of CTEPH.

When we divided the CTEPH group into main type, lobar type and segmental type based on the most proximal location of thrombi, we did not find any significant difference between the total area of the BAs in the segmental type of CTEPH and that in PAH. Some previous studies have indicated that the finding of dilated BAs can help distinguish CTEPH from idiopathic PAH[3] or APTE;[4] however, those studies made no mention of the central extent of thrombi in the CTEPH patients. Although dilatation of the BAs is a common finding in CTEPH, it seems to be relatively limited to the central type of CTEPH.

Although it did not reach statistical significance (p=0.06), the change in PaO_2 after PTE moderately correlated with the total area of the BAs. In patients without lung disease, the bronchial circulation supplying the systemic arterial flow is estimated to be 1% of cardiac output[21] In CTEPH patients, this bronchopulmonary shunt volume can increase up to approximately 30% of cardiac output[1,2] Some animal models have confirmed that bronchial circulation supports ischemic parenchymal lung tissue[5] Besides that support, prolonged lung ischemia damages the pulmonary endothelium and leads to increasing permeability in the lung[22] In that condition, ischemic–reperfusion injury after PTE could happen to varying degrees. Development of bronchial circulation was shown to attenuate ischemic–reperfusion lung injury in some experimental models[23–25] and our data also suggest a supportive role of the BAs in the ischemic lung and their importance for gas exchange after PTE.

We did not find any other relationships between surgical outcomes, including %reduction in PVR, and the total area of the BAs. Kauczor et al found a lower postoperative mortality rate in patients with dilated BAs after PTE[8] In our study, only 2 patients died during the early postoperative period, so we did not evaluate the mortality rate. Heinrich et al reported that the postoperative PVR was significantly lower in patients with dilated BAs than in those without;[9] they classified patients into 2 groups, with (≥1.5 mm) and without (<1.5 mm) dilated BAs. In our study, as 23 of 24 patients undergoing PTE had BAs ≥1.5 mm, it is likely that we performed surgery only for the relatively central type of CTEPH and assessed only the patients with dilated BAs, and thus we could not apply their criterion for determining any correlation between postoperative PVR and bronchial arterial dilatation.

The major difference between the current study and earlier studies is that we used the total cross-sectional area of the BAs to evaluate the development of the systemic collateral supply instead of their diameters. Evaluation of bronchial arterial dilatation in CTEPH is intended for assessment of the role of systemic circulation to the lung, so a method of quantifying the systemic collateral supply would be desirable. In our study we could determine a relationship between the total cross-sectional area of the BAs and the central extent of thrombi or the increase in PaO_2 after PTE, and we believe that it is reasonable to use the total area of the BAs to assess the role of systemic circulation to the lung in patients with CTEPH.

Study Limitations

First, none of our patients underwent conventional angiography of the BAs or measurement of the bronchopulmonary shunt volume, so we could not confirm the accuracy of our findings with a "gold standard". Second, the CT protocol was optimal for pulmonary artery visualization because all CT examinations were performed for a normal workup to diagnose or evaluate CTEPH or PAH. However, we could depict the BAs sufficiently for evaluation, except for 14 cases. Third, the number of patients in each group was small. Larger studies are needed to confirm the relationship between dilated BAs and the central extent of thrombi or surgical outcomes after PTE.

In conclusion, the total cross-sectional area of the BAs correlated with the extent of central disease in patients with CTEPH and it might be useful for predicting gas exchange improvement after PTE.

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Survival and Quality of Life for Patients With Peripheral Type Chronic Thromboembolic Pulmonary Hypertension

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Background The validity of pulmonary thromboendarterectomy for treatment of relatively peripheral type of chronic thromboembolic pulmonary hypertension (CTEPH) remains uncertain. The survival and quality of life (QOL) of patients with relatively peripheral type of CTEPH was investigated at follow up.

Methods and Results Between April 1999 and March 2006, 83 consecutive patients with CTEPH were evaluated for surgical indication and underwent computed tomography angiography. The extent of central disease was scored (ie, CD score), and a CD score of ≤1 was judged as relatively peripheral disease. Forty-three patients were excluded from surgery, and 40 patients, including 14 cases of relatively peripheral disease, underwent surgery. Long-term survival and QOL scores at follow up (1–3 years) were compared between the surgically and medically treated groups of relatively peripheral disease. Survival curves between the 2 treatment groups were not significantly different (p=0.78) because of high operative mortality (21.4%). However, improvement in physical functioning, role function (physically related), general health perception (as assessed by the Medical Outcome Study Short Form 36), and baseline dyspnea index were significantly higher in the group treated surgically compared with the medically treated group.

Conclusions Pulmonary thromboendarterectomy offers better QOL even in those patients with relatively peripheral type of CTEPH, although operative mortality must be reduced. (*Circ J* 2008; **72:** 958–965)

Key Words: Chronic thromboembolic pulmonary hypertension; Prognosis; Quality of life

Chronic thromboembolic pulmonary hypertension (CTEPH) is a relatively rare disease. Its natural history and etiology remain unclear[1–5] There have been a number of reports that pulmonary thromboendarterectomy (PTE) is an effective modality for treatment in selected patients with CTEPH[1–3,6–11] However, the hemodynamic benefit varies according to the location and extent of the thromboembolic occlusion, and Bergin and colleagues reported that the computed tomography (CT) angiographic extent of central disease (ie, CD score) is related to a low pulmonary vascular resistance (PVR) after surgery[12] Our preliminary data also showed high operative mortality with CD scores of 0 (25%) and 1 (20%), compared with those with a CD score of ≥2 (7.7%), so we classified those patients with a CD score of ≤1 as having relatively peripheral type CTEPH. The cause of operative death was related to residual pulmonary hypertension as a result of failure to remove a distal obstruction. New guidelines have recommended a post-surgical estimated reduction in PVR of >50%[10] The validity of PTE might be limited to central-type patients, especially in institutions in which the operation is performed infrequently.

The prognosis of CTEPH in the medically treated group had been thought to be poor[13–15] but Ono et al reported that oral beraprost sodium improved their survival[16] Recently, there have been some reports about improved 6-min walk distance and pulmonary hemodynamics after epoprostenol[17,18] sildenafil[19] and bosentan[20–22] in patients with CTEPH. These new drugs might improve vascular remodeling, and may offer improved survival in patients with relatively peripheral type CTEPH, in whom we predicted a poor reduction in PVR after surgery. We retrospectively tested the validity of PTE from the aspects of survival and quality of life (QOL) at long-term follow up in patients with relatively peripheral type CTEPH.

Methods

Patients

Between April 1999 and March 2006, a total of 83 patients admitted consecutively to Chiba University Hospital were diagnosed as having CTEPH and evaluated for surgical indication. CTEPH was defined as having a mean pulmonary arterial pressure (P_{PA}) of ≥25 mmHg with normal wedge pressure in patients who had dyspnea on exertion during a period of more than 6 months. In addition, lung

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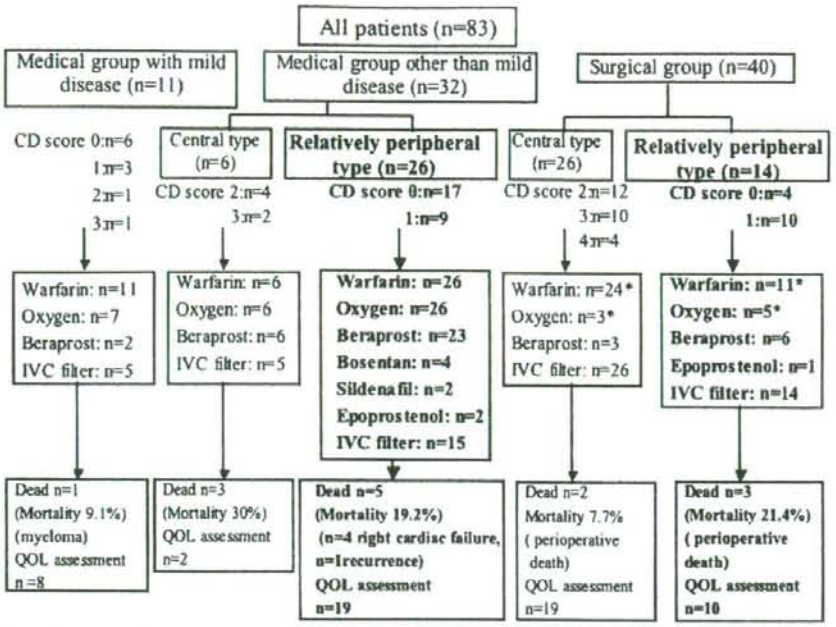

Fig 1. Algorhythm of management and course for chronic thromboembolic pulmonary hypertension (CTEPH). IVC, inferior vena cava filter; CD score, central disease score; QOL, quality of life. *Patients who died in hospital were excluded.

perfusion scans were required to demonstrate a segmental or larger defect concomitant with a normal ventilation scan. Finally, chronic thromboembolic findings were confirmed by pulmonary angiography[23]

The population studied comprises more female patients (n=56) than male patients (n=27). Duration from the symptom onset to cardiac catheterization was 34±37 months. Age at catheterization varied from 18 to 78 years, with a mean± SD of 54±13 years. Altogether, 33 patients (39.8%) had a history of deep vein thrombosis, 27 (32.5%) revealed abnormalities in the screening for coagulopathy, and 19 (24.1%) had antiphospholipid antibodies. Mean P_{PA}, cardiac index and PVR were 44.1±11.7 mmHg, 2.59±0.54 $L \cdot min^{-1} \cdot m^{-2}$, and 876±303 dynes $\cdot s^{-1} \cdot cm^{-5}$, respectively. Arterial oxygen tension (PaO_2) was 58.6±10.7 torr. Patients were classified according to criteria of the New York Heart Association as either functional class I (n=2), II (n=22), III (n=55), or IV (n=4). Forty patients underwent PTE (Fig 1). Forty-three patients were excluded from surgery because of: a mild disease (mean P_{PA} ≤30 mmHg) (n=11); relatively peripheral type of thrombi (n=26); aged >70 years (n=3); having an associated disease (n=2); and too severe (n=1) (Fig 1).

Helical CT Angiography and CD Score

CT angiography was performed with a Somatom Plus 4 (Siemens, Forcheim, Germany) between 1999 and 2001, and the scanning parameter setting was 2-mm collimation. From 2002, the LightSpeed Ultra (GE Medical Systems, Milwaukee, WI, USA) was used, and the scanning parameter settings changed to 8×1.25 mm between January 2002 and December 2002, and to 16×1.25 mm between January 2003 and 2006, according to hardware and software modifications[24]

By the method of Bergin et al, central arteries were defined as vessels proximal to the segmental branches and were divided into 4 portions[12] These portions included the right and left main pulmonary arteries proximal to the upper lobe branches, and the right and left descending portions of the central arteries between the upper lobes and the segmental branches. Disease within central vessels was identified by the presence of abnormal tissue lining the arterial wall or by irregularity of the intimal surface. The CD score was quantified by adding up the number of abnormal central portions in each patient up to a maximum score of 4. Two investigators retrospectively calculated the scores independently by workstation, and if the score differed, it was changed to either 1 score up or down by consensual agreement of the 2 investigators. The inter-observer agreement between the 2 investigators was also confirmed by Kendall's rank correlation coefficient for concordance for the first 22 patients (concordance=0.92, $p<0.01$, n=22).

Study Group

Relatively Peripheral Type In the surgically treated group, 14 cases were classified as relatively peripheral type (CD score ≤1), and 26 cases in the medically treated group (other than mild disease) were enrolled in the study as relatively peripheral type (Fig 1).

Central Type and Mild Disease Twenty-five surgically treated patients who were classified as central type (CD score ≥2), as well as 6 patients who had central type but were medically treated for other reasons, served as central type. Eleven patients excluded from surgery because of mild disease (mean P_{PA} ≤30 mmHg) were also analyzed (ie, mild disease) (Fig 1).

Table 1 Clinical Characteristics of Subgroups

	Relatively peripheral type		Central type	
	Treated surgically	Treated medically	Treated surgically	Treated medically
N	14	26	26	6
Age at diagnosis (years)	53.1±10.1	51.2±13.2	52.2±12.4	60.5±19.1
F/M	10/4	23/3	12/14	5/1
Duration of symptoms (months)	55.6±43.7*	33.1±27.9*	40.6±43.3	19.2±19.2
Mean P_{PA} (mmHg)	50.1±11.2	44.9±9.4	46.9±10.8††	44.0±10.7***
PVR (dynes·s^{-1}·cm^{-5})	972±310	868±453	904±367**	734±377***
PaO_2 (torr)	54.9±9.8	57.9±10.5	59.3±8.3**†	47.4±9.8***†
NYHA functional class I/II/III/IV	0/2/11/1	0/5/20/1	0/5/20/1**	0/2/3/1

Values are presented as the mean±SD.
*p=0.054 by unpaired t-test, **,***,†p<0.01 by unpaired t-test or chi-square test.
Duration of symptoms, duration from symptom onset to cardiac catheterization; P_{PA}, pulmonary arterial pressure; PVR, pulmonary vascular resistance; NYHA, New York Heart Association.

Measurements

At least 3 months after an acute episode, pulmonary hemodynamics, cardiac output by thermodilution technique, and blood gases were measured with the patient in a supine position while breathing air. The cardiac index was calculated as cardiac output divided by body surface area. PVR was calculated conventionally as the ratio of the difference between mean P_{PA} and pulmonary wedge pressure to cardiac output. The data of initial diagnosis were evaluated in 79 of 83 patients, and 4 surgically treated patients were re-examined just before surgery and their data were evaluated for pre-operative data. Cardiorespiratory variables were also measured after surgery.

Criteria for PTE

The selection criteria for PTE were slightly modified from those defined by Moser and colleagues[2] Our criteria were: (1) Mean P_{PA} of >30 mmHg, resulting in calculated PVR of >300 dynes·s^{-1}·cm^{-5}, even after oral anticoagulant therapy for >6 months; (2) WHO functional class of ≥3; (3) Thrombi defined as accessible to current surgical techniques (ie, presence at main, lobar or segmental arteries); and (4) Absence of severe associated disease[8,9] For patients with relatively peripheral type in whom we might be able to access a few thrombi, the patient's willingness for surgery despite the high operative mortality at the time was the most important indication. Median sternotomy under cardiopulmonary bypass with deep hypothermia and circulatory arrest technique has been performed. Since 1999, 40 operated patients were enrolled in this study. An inferior vena cava filter was inserted in all patients pre-operatively. Home oxygen therapy and beraprost sodium were also used for patients in whom PVR was insufficiently reduced by surgery.

Treatment in Medically Treated Patients With Relatively Peripheral Type

All patients received warfarin therapy and home oxygen therapy. We used beraprost sodium in patients with symptomatic CTEPH, including 23 of 26 patients with a CD score of ≤1. Three patients had severe flush and refused this treatment. More recently, bosentan (n=4), sildenafil (n=2), as well as epoprostenol (n=2), were also used in progressive patients even after beraprost sodium therapy. An inferior vena cava filter was inserted in 15 of such patients. Change in QOL at follow up was demonstrated before additional treatments in 24 patients and after additional treatments in 2 patients (ie, one for bosentan, the other for sildenafil).

Assessment of QOL

Patients were asked to complete a self-administered questionnaire, which included health-related QOL scores, as set by the Medical Outcome Study Short Form 36 (SF-36),[25–27] and the baseline dyspnea index;[28] within 2 weeks after the date of baseline right heart catheterization. We also sent out questionnaires to patients between 12 and 36 months of follow up after the date of diagnosis for medically treated cases or after surgery. Both questionnaires were collected from 58 (85.3%) of 68 patients after excluding 5 postoperative deaths and 6 deaths that occurred within 1 year of medical therapy, as well as 4 survivors with <1 month of follow-up. Ten patients did not return their questionnaires.

Investigation of Long-Term Outcome

We contacted all of the 83 patients and/or their families by mail or telephone in October 2006. Sixty-nine patients survived and 14 patients had died. Survival time was calculated from the initial date of diagnosis by right heart catheterization in the medical group, and was calculated from the date of surgery in the surgical group.

The Human Subject Committee at Chiba University approved the study, and written, informed consent was obtained from each patient at the time of diagnosis.

Statistical Analysis

Cardiorespiratory variables and QOL before and after surgery or at follow up were compared using the 2-tailed paired t-test. Log rank test was used to compare the survival curves between groups. Comparisons of 2 groups were analyzed by unpaired t-test and chi-square test, where appropriate. Pearson's correlation coefficient was also used to compare postoperative QOL with postoperative parameters. A p-value of <0.05 was considered significant.

Results

Baseline Characteristics of Relatively Peripheral Type

The mean age of the surgical and medical groups at diagnosis was similar. The duration of symptoms from the onset of symptoms to diagnosis for the surgically treated group was slightly longer than that for the medical group (55.6± 43.7 vs 33.1±27.9 months, p=0.054). Pulmonary hemodynamics and blood gasses were similar between the 2 groups (Table 1).

Baseline Characteristics of Central Type

For patients with central type, the PaO_2 in the surgical

Table 2 Comparisons of Pre and Post Data and Surgical Outcome Stratified by Relatively Peripheral and Central Types

		Relatively peripheral type	*Central type*
N		*14*	*26*
Mean P_{PA} (mmHg)	*Pre*	*50.1±11.2†*	*46.9±10.8****
	Post	*31.1±14.3*,†*	*21.0±8.5*,****
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	*Pre*	*2.50±0.50†*	*2.46±0.79*
	Post	*2.91±0.48†*	*2.81±0.57*
PVR ($dynes \cdot s^{-1} \cdot cm^{-5}$)	*Pre*	*972±310†*	*904±367****
	Post	*515±417*,†*	*259±188*,****
PaO_2 (torr)	*Pre*	*54.9±9.8††*	*59.4±8.3****
	Post	*72.9±15.0††*	*76.7±10.5****
NYHA functional class I/II/III/IV (n)	*Pre*	*0/2/11/1*	*0/5/20/1*
	Post	*1/6/4/0*	*6/15/3/0*
Decrease in mean P_{PA} (mmHg)		*16.2±14.0*	*24.8±13.3*
Decrease in PVR ($dynes \cdot s \cdot cm^{-5}$)		*405±243*	*619±418*
Percentage decrease in PVR (%)		*47.8±25.9***	*66.3±24.1***
Increase in PaO_2 (torr)		*15.1±17.7*	*16.8±13.5*
Mortality (%)		*21.4*	*7.7*

Values are presented as the mean±SD.
**p<0.05, **p=0.05 between relatively peripheral and central types by unpaired t-test.*
****,†p<0.01, ††p<0.05 between pre-operative and postoperative data by 2-tailed paired t-test.*
Pre, pre-operative; Post, postoperative; Decrease in mean P_{PA}, Pre mean P_{PA}-Post mean P_{PA}; Decrease in PVR, Pre PVR-Post PVR; Percentage decrease in PVR, [Pre PVR−Post PVR]×100(%)/Pre PVR; Increase in PaO_2, Post PaO_2-Pre PaO_2. Other abbreviations see in Table 1.

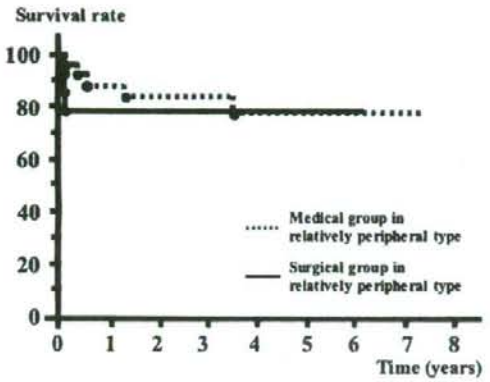

Fig 2. Comparison of survival curves between medically treated and surgically treated groups in relatively peripheral type. There was no statistically significant difference between the 2 groups (p=0.78, Log rank test).

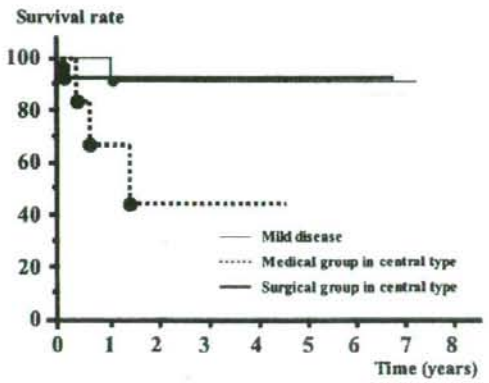

Fig 3. Comparisons of survival curves in mild disease, medical (medically treated group with central type for other reasons) and surgically treated group with central type. Medical group with central type showed significantly poorer survival compared with mild disease (p=0.039, Log rank test) or surgically treated group with central type (p=0.014, Log rank test).

group was significantly higher than in the medical group (Table 1).

Surgical Outcome

In 14 patients with relatively peripheral type, 3 patients died in hospital because of residual pulmonary hypertension during the early postoperative period within 1 month after surgery (operative mortality 21.4%). In 26 patients with central type, 2 patients died (7.7%) in hospital: 1 from residual pulmonary hypertension and the other from pulmonary hemorrhage (Fig 1).

In both relatively peripheral and central types, pulmonary hemodynamics improved significantly, but postoperative mean P_{PA} and PVR were significantly higher in patients with relatively peripheral type. Although there were no significant differences between them in terms of improvement in mean P_{PA}, PVR and PaO_2, the percentage decrease in PVR was significantly smaller in patients with relatively peripheral type (Table 2).

Survival Analysis of Patients With Relatively Peripheral Type

In 26 medically treated patients with relatively peripheral type, 5 died during follow up (1–42 months), 4 patients died of right cardiac failure, and one of recurrence, and all patients continued to need oxygen therapy (Fig 1). No death was observed during follow up in the 11 survivors of the surgically treated group. Six of 11 patients did not need oxygen therapy at follow up. Fig 2 shows the Kaplan–Meier survival curves from the operation date in the surgical group and the diagnosis date in the medical group to the time of death or last follow up in the 40 patients with relatively

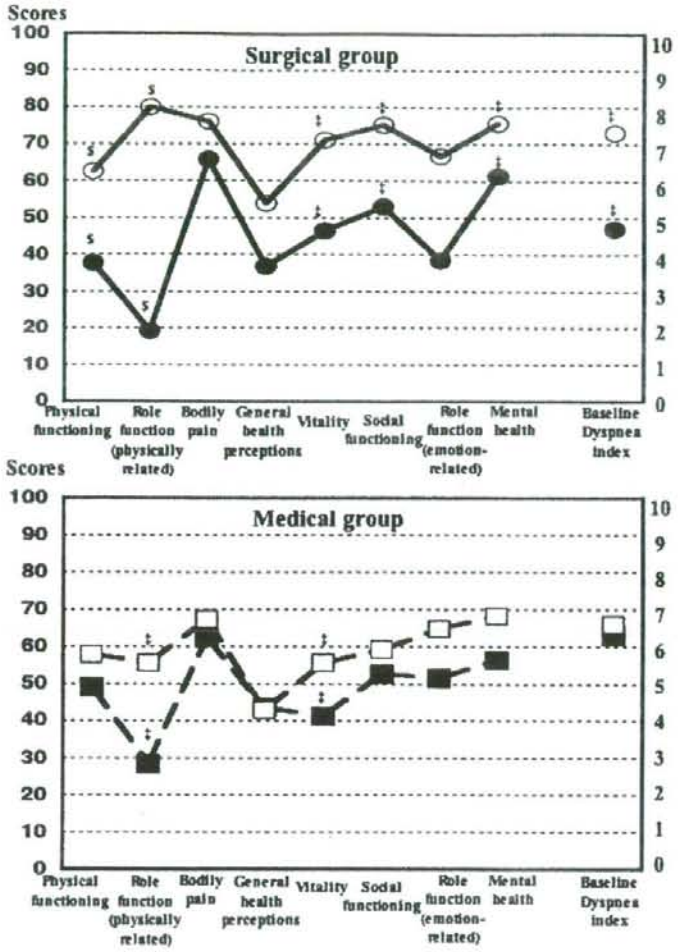

Fig 4. (Top) Comparisons of the SF-36 scores and baseline dyspnea index at pre-treatment and at follow up in the surgical group in relatively peripheral type. Pre-treatment in the surgical group (n=14, solid circles), at follow up in the surgical group (n=10, open circles); ‡p<0.05, §p<0.01 between pre-treatment and at follow up by paired t-test. (Bottom) Comparisons of the SF-36 scores and baseline dyspnea index at pre-treatment and at follow up in the medically treated group in relatively peripheral type. Pre-treatment in medical group (n=26, solid squares), at follow up in the medical group (n=19, open squares); ‡p<0.05, §p<0.01, between pre-treatment and at follow up by paired t-test.

peripheral type. In survivors, the time since the operation date or the diagnosis date to last follow up was an average of 3.9±2.0 (median 4.1, range 1–7) years. The initial decline in the surgical group represents in-hospital deaths. No statistically significant difference was found in the survival curves between the 2 groups (p=0.78). The 6-year survival rates in the surgically and medically treated groups were 78.6% and 77.6 %, respectively.

Survival Analysis in Others

Fig 3 shows the Kaplan–Meier survival curves for the groups mild disease, medical (medically treated group with central type for other reasons), and surgically treated with central type. The 6-year survival rate in the surgically treated group was 92.3%. The medical group with central type showed a significantly poorer survival rate compared with the mild disease group (p=0.039) or surgical group with central type (p=0.014). In 11 patients with mild disease, none died of CTEPH, although 1 patient died of multiple myeloma (Fig 1). In the medical group with central type, 3 patients died (2 of right cardiac failure and 1 of hemoptysis). In the surgical group with central type, all survived except 2 patients from peri-operative deaths. Only 3 patients needed oxygen therapy at follow up (Fig 1).

QOL at Follow up in Patients With Relatively Peripheral Type

QOL was reassessed at follow up (range 1.0–3.3, median 1.8 years) in 19 of 26 medically treated patients and in 10 of 11 post-surgery survivors (Fig 1). In the surgical group, 5 of 8 SF-36 and baseline dyspnea index scores improved significantly at follow up, but in the medical group only 2 SF-36 scores improved (Fig 4). Improvement in the scores of physical functioning (27.0±24.9 vs 2.7±18.0, p<0.01), role function (physically related) (60.0±44.4 vs 20.8±32.4, p<0.05), general health perception (20.2±26.0 vs –3.6±13.3, p<0.01), and baseline dyspnea index (6.3±2.3 vs –0.2±2.4, p<0.01) were significantly greater in the surgically treated group than in the medically treated group.

QOL at Follow up in Others

QOL was reassessed at follow up in 19 of 24 survivors in

Table 3 Correlations of SF-36 Scores and Baseline Dyspnea Index With Post PVR, Percentage Decrease in PVR in Relatively Peripheral Type (n=10)

	PVR (r-value)	*Decrease in PVR (%) (r-value)*
Physical functioning	*–0.88***	*0.84***
Role function (physically related)	*–0.31*	*0.48*
Bodily pain	*–0.54*	*0.65**
General health perceptions	*–0.75***	*0.90***
Vitality	*–0.56*	*0.68**
Social functioning	*–0.40*	*0.63**
Role function (emotion-related)	*–0.24*	*0.51*
Mental health	*–0.51*	*0.68**
Baseline dyspnea index	*–0.93***	*0.92***

Abbreviations see in Table 2.
*Expressed as Pearson's r-value, *p<0.05, **p<0.01.*

the surgical group with central type, and in 8 of 10 survivors in the mild disease group (Fig 1). However, QOL was reassessed in only 2 patients in the medical group with central type because 3 patients had died and another did not complete the questionnaire. In the surgically treated group with central type, 7 of 8 SF-36 scores and baseline dyspnea index improved at follow up. In the mild disease group, 5 of 8 SF-36 scores improved significantly at follow up.

Prediction of QOL at Follow up in the Surgically Treated Group

In patients with relatively peripheral type, physical functioning (r=–0.88, p<0.01) and general health perception (r=–0.75, p<0.01) of the SF-36 and baseline dyspnea index (r=–0.93, p<0.01) at follow up significantly correlated with postoperative PVR, and 6 of the SF-36 scores and baseline dyspnea index at follow up significantly correlated with a percentage decrease in PVR (Table 3). In all cases that included central type, physical functioning (r=–0.69, p<0.01), role function (physically related) (r=–0.38, p=0.049), general health perceptions (r=–0.45, p=0.018), role function (emotion-related) (r=–0.39, 0.045) of SF-36 and baseline dyspnea index (r=–0.68, p<0.01) at follow up significantly correlated with postoperative PVR. Similarly, 6 of the SF-36 scores and baseline dyspnea index at follow up correlated with a percentage decrease in PVR.

Discussion

PTE did not offer a survival benefit for patients with relatively peripheral type because of high operative mortality, but did result in significantly better QOL. The 6-year survival rate for the surgically treated group was 78.6% for relatively peripheral type and 92.3% for central type, values which are close to that obtained by Archibald et al's study (ie, 75% 6-year survival rate)[29] However, medical treatment offered better survival for patients with relatively peripheral type and with a mean P_{PA} of >30 mmHg when compared with previous reports[13–15]

Several issues need to be considered when interpreting the results. We used CT angiography to classify the patients, which was then confirmed by selective pulmonary angiography. We agree that selective pulmonary angiography is a gold standard technique for diagnosing CTEPH[23] Yet, the mortality of patients with visible thrombi in a central pulmonary (ie, CD score=1) by CT was similar to that of patients with a score of 0. Hence, we then classified those patients with a CD score of ≤1 as having relatively peripheral type by CT findings only. Only 1 patient had thrombi limited to subsegmental arteries, and the other patients had at least surgically accessible thrombi in 1 of the segmental arteries, even in the medical group with relatively peripheral type. High operative mortality and the report of improved survival by beraprost sodium allowed us to legally choose medical treatment in these marginal cases.

Although we cannot ignore the fact that the medical group had more peripheral thrombi (ie, CD score of 0) or subsegmental thrombi compared with the surgical group with relatively peripheral type, survival curves were similar between the medical and surgical groups when only those patients with a CD score of 0 were selected (p=0.61, 6-year survival 75% vs 81.4%). Improvements in physical functioning and general health perception of SF-36, as well as in the baseline dyspnea index, were significantly greater in the surgical group than in the medical group, even in those patients with a CD score of 0.

In their study, Thistlethwaite and colleagues divided patients into 4 groups, according to intraoperative classification[30]: type 1, fresh thrombus in the main-lobar pulmonary arteries; type 2, intimal thickening and fibrosis proximal to segmental arteries; type 3, disease within distal segmental arteries only; type 4, distal arteriolar vasculopathy. In the present series, all patients with central type (CD score ≥2) had type 1 or 2, whereas of the patients with relatively peripheral type, 2 patients with a CD score of 0 were type 3, and 1 patient with a CD score of 1 was type 4. Type 4 disease might be more common in the medical group with relatively peripheral type.

Despite a mean P_{PA} of >30 mmHg, the 6-year survival rate was 77.6% for the medically treated group with relatively peripheral type, which was better than that of previous reports[13–15] Ono et al reported a 5-year survival rate of 76% for the beraprost group and 46% for the conventional group[16] In the present series, most of the patients received beraprost sodium and a few patients were given bosentan, sildenafil, or PGI2. Recent developments in the medical treatment for pulmonary arterial hypertension may also offer improved survival for patients with relatively peripheral type CTEPH.

In the surgical group, improvement in QOL at follow up was significant for patients with either central or relatively peripheral type. These results are similar to those of Archibald and colleagues[29] whose study showed that postoperative patients had significantly better SF-36 scores (except for mental health) compared with those of pre-operative patients. In addition, for those with relatively peripheral type, 6 of 11 survivors after the survey did not need oxygen therapy, but all medically treated patients needed to con-

tinue oxygen therapy. Surgery offered better QOL even in relatively peripheral type patients with CTEPH.

In the present study, QOL at follow up correlated with postoperative PVR and a percentage decrease in PVR. Hoeper recommended that an estimated reduction in PVR of >50% could be indicated for surgery?[20] In the present study, when patients were divided into 2 groups (ie, sufficiently improved group and modestly improved group) according to percentage decrease in PVR >50%, the sufficiently improved group showed significantly better QOL scores in physical functioning (p=0.01), role function (physically related) (p=0.045), general health perceptions (p=0.019), social functioning (p=0.017), role function (emotion-related) (p<0.01), mental health (0.03), and baseline dyspnea index (p=0.03) than those in the modestly improved group at follow up. Furthermore, the number of patients with a percentage decrease in PVR was significantly smaller in patients with relatively peripheral type compared with those with central type. To achieve better QOL at follow up in patients with relatively peripheral type CTEPH, a reduction in PVR by sufficient PTE could be of major importance.

We recently reported that the D allele carrier in angiotensin-converting enzyme (ACE) gene polymorphism might be a poor prognostic factor for CTEPH?[31] In the present series, ACE-ID genotypes were determined in 29 of 32 medically treated patients other than those in the mild disease group. Of 7 patients with II genotype type, no patient died, whereas of 16 with ID or DD genotypes, 6 died. All 7 patients with II genotype were classified as having relatively peripheral type. ACE gene polymorphism might also be associated with a better prognosis for patients with relatively peripheral type in the present series.

We have also reported the change in health-related QOL scores in medically treated patients. Although the data were limited in survivors with relatively peripheral type at follow up ≤3 years, SF-36 scores did not decrease, and role function (physically related) and vitality significantly improved. Medical treatment that includes beraprost sodium might offer better QOL even in relatively peripheral type patients with a mean P_{PA} of >30 mmHg.

The limitations of the study are that it was retrospective and that the number of patients in each subcategory was small. Unconfirmed and insufficient data regarding medical treatment for CTEPH ethically prevented us from randomizing the patients into medical and surgical groups, even those patients with relatively peripheral type. Large randomized studies using beraprost sodium, bosentan, or sildenafil in inoperable patients will be warranted. Recently, between 2003 and December 2006, the mortality in our series decreased to 9.1% compared with the rate of 19.0% between 1999 and 2002. Ogino et al also reported decreased mortality (8.0%) in CTEPH in Japan[32]

However, the mortality rate of 21.4% for patients with relatively peripheral type is high. In agreement with us, Hoeper et al have also reported that a pre-operative PVR value of >900 $dyn \cdot s^{-1} \cdot cm^{-5}$ is a risk factor for surgery?[20] In patients with relatively peripheral type, all who had a pre-operative PVR value of ≤900 $dyn \cdot s^{-1} \cdot cm^{-5}$ survived, but all who had a pre-operative PVR value of >900 $dyn \cdot s^{-1} \cdot cm^{-5}$ did not (n=3).

Recent improvements in surgical skill and management in Japan can be expected to further decrease operative mortality, even in patients with relatively peripheral type. But until then caution should be exercised when evaluating relatively peripheral type patients with a PVR value of >900 $dyn \cdot s^{-1} \cdot cm^{-5}$.

In conclusion, this is the first study to investigate the change in QOL at follow up in patients with CTEPH, and PTE was found to result in significantly better QOL compared with medical treatment, even for patients with relatively peripheral type, although it must be emphasized that a reduction in operative mortality is essential.

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Letter to the Editor

Quantitative evaluation of chronic pulmonary thromboemboli by multislice CT compared with pulsed Tissue Doppler Imaging and its relationship with brain natriuretic peptide

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Abstract

Purpose: Chronic pulmonary arterial thromboembolism (CPATE) often causes right ventricular (RV) pressure overload but the relationship between the degrees of CPATE and RV pressure overload is not clear. To quantify the degrees of CPATE and RV pressure overload, we performed multislice computed tomography (CT) and Tissue Doppler Imaging (TDI) and compared the two modalities.

Materials and methods: Sixteen consecutive subjects (4 men, 12 women; age 27–72 with proven CPATE underwent CT. The right vascular obstruction index (VOI), the left VOI, and the total VOI (TVOI) were determined using the scoring system of Qanadli. The early systolic myocardial velocity (Sw) and diastole myocardial velocity (Ew) at the tricuspid annulus and the early diastolic tricuspid inflow (*E*) were obtained by TDI in the apical four chamber view; RV systolic pressure (RVSP) was estimated by pressure gradient of tricuspid valve regurgitation. *E*/Ew was calculated as the parameter of RV diastolic function.

Results: The right VOI was 23 ± 10%, the left VOI was 18 ± 10%, and TVOI was 41 ± 14%. The means with ranges of Sw, Ew, *E*/Ew, RVSP, and brain natriuretic peptide (BNP) were 10.7 (range 7.7–14.6) cm/s, 7.7 (range 4.2–10.6) cm/s, 5.0 (range 2.2–8.1), 55 (range 26–90) mm Hg, and 50.3 (range 12.2–165) pg/ml, respectively. The correlation coefficients between Sw, Ew, *E*/Ew, RVSP, and BNP and either larger of right or left side (LVOI) and TVOI were 0.041, −0.163 (Sw vs. LVOI, TVOI), −0.153, −0.232 (Ew vs. LVOI, TVOI), 0.145, 0.241 (*E*/Ew vs. LVOI, TVOI), 0.255, 0.401 (RVSP vs. LVOI, TVOI), and 0.192, 0.170 (BNP vs. LVOI, TVOI), respectively. The correlation coefficient between RVSP and BNP was 0.390.

Conclusions: TVOI was better correlated with RVSP ($R=0.401$) than the other parameters (Sw, Ew, *E*/Ew, and BNP), and this was similar to the degree that BNP was correlated with RVSP ($R=0.390$). TVOI can be a better indicator of RVSP than LVOI. CT VOI may be a useful parameter to assess CPATE morphologically.

Keywords: Chronic pulmonary thromboemboli; Multislice CT; Pulsed Tissue Doppler Imaging; Brain natriuretic peptide

1. Introduction

Chronic pulmonary arterial thromboembolism (CPATE) often causes right ventricular (RV) pressure overload [1] and RV pressure overload has a strong association with increased mortality of patients with pulmonary hypertension [2–8]. But the relationship between the degrees of CPATE and RV pressure overload is not clear. In this study, to quantify the degrees of CPATE, we performed multislice computed tomography (CT) and estimated the results using CT vascular obstruction index (VOI) by the method of Qanadli which is widely used to assess acute pulmonary arterial thromboembolism [9]. We applied this index to the assessment of CPATE.

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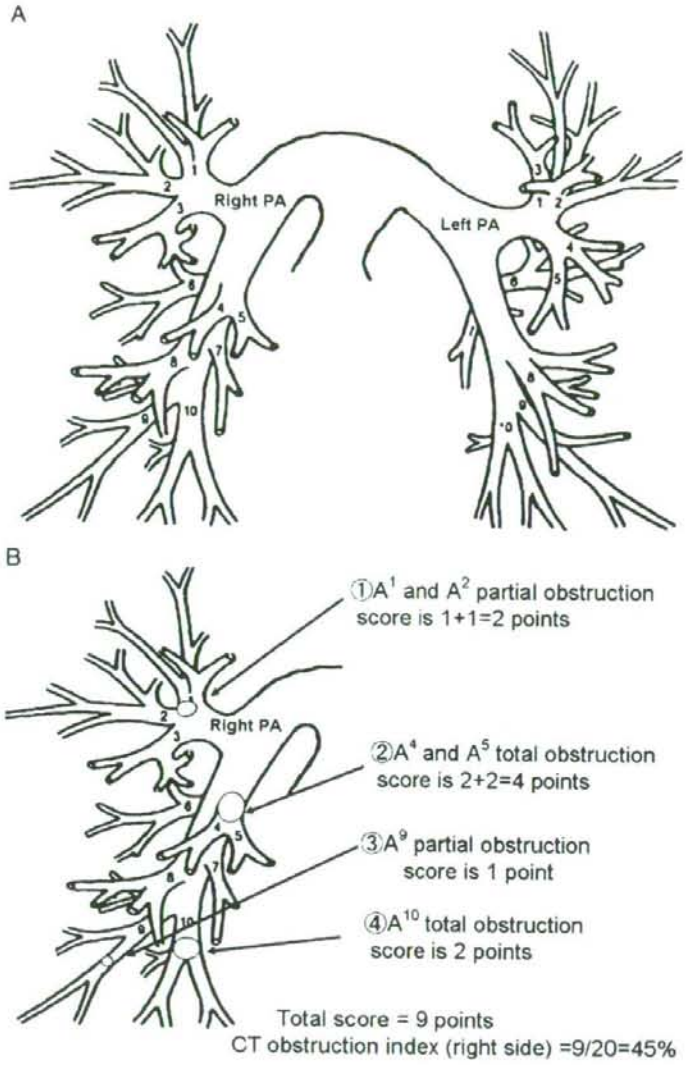

Fig. 1. (Modified figure from Ref. [9]) Schema of measurement of CT vascular obstruction index (VOI) for pulmonary arterial (PA) thromboembolism. The following scores are assigned in the scoring system of Qanadli: the score is equal to 0 when no thrombus is observed, the score is equal to 1 when a partially occlusive thrombus is observed, and the score is equal to 2 when there is total occlusion. A: To define the CT VOI according to Qanadli, the PA tree of each lung was regarded as having 10 segmental arteries (three to the upper lobes, two to the middle lobe and to the lingula, and five to the lower lobes). B: Measurement of PA thromboembolism in the right PA in schema. Pink circles indicate thrombi. For example, if the A1 and A2 segments of the right PA are partially obstructed the score of this thrombus is calculated as 1 + 1 = 2 points. If A4 and A5 segments of right PA are totally obstructed the score of the thrombus is calculated as 2 + 2 = 4 points. If there is a thrombus which partially blocks the A9 segment of the right PA, the score of this thrombus is 1 point. If the thrombus totally blocks the A10 segment of the right PA, the score of this thrombus is 2 points. As a result, the total score of the right side in this case is calculated as 9 points and CT VOI of right side is calculated as 9/20 = 45%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We also used pulsed Tissue Doppler Imaging (TDI) echocardiography to evaluate RV function. Both the systolic and diastolic function of the right heart is an important factor of prognosis in the patients with CPATE [10]. Pulsed TDI has been widely used to estimate LV systolic function [11–14], and now it can be applied to assessment of RV diastolic function [15].

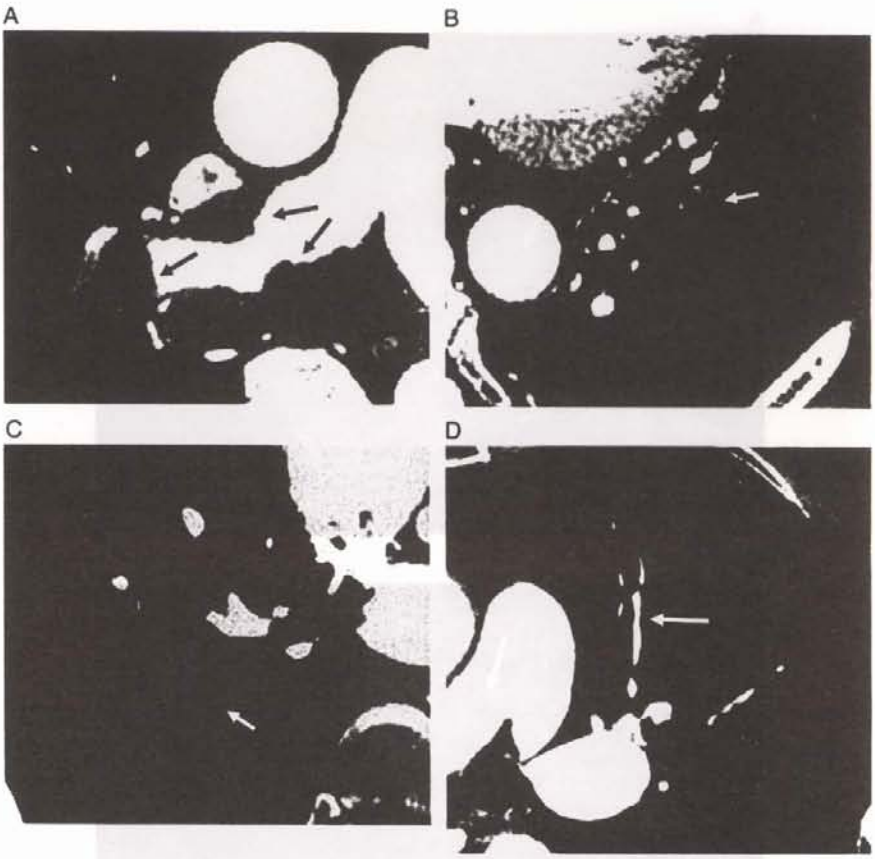

Fig. 2. Actual measurement of CT vascular obstruction index (VOI) for pulmonary arterial (PA) thromboembolism using axial source images of enhanced multislice CT. A: There are thrombi (arrows) which partially block the right main PA. We counted the thrombi distally from the segmental arteries. In this case the obstruction score was 20 points. B: There is a thrombus (arrow) which totally blocks the A8 and A9 segments of the left PA; the score of the thrombus was calculated as 2 + 2 = 4 points. C: There is a thrombus (arrow) partially blocking the A10 segment of right PA; the score of the thrombus was 1 point. D: There were intimal irregularities (arrow) in the PA and the findings were diagnosed as the presence of a partial obstructions; the score of each thrombus was calculated as 1 point.

Therefore we compared the two modalities and determined its relationship with brain natriuretic peptide (BNP).

2. Materials and methods

2.1. Multislice CT

Sixteen consecutive subjects (4 men, 12 women; age 27–72) with proven CPATE underwent multislice CT (Light Speed Ultra 16, GE). Twenty-five seconds after contrast injection, the thorax was scanned and 1.25 mm CT slices were acquired. Using the CT data, pulmonary arterial thromboembolism was quantified using the CT vascular obstruction index (VOI) proposed by Qanadli. This method has been used for evaluating acute pulmonary thromboembolism. We used this method to determine the right, left, and total VOI.

To define the CT VOI by the method of Qanadli, the arterial tree of each lung was regarded as having 10 segmental arteries (three to the upper lobes, two to the middle lobe and to the lingula, and five to the lower lobes) (Fig. 1A). VOI is the percentage of vascular obstruction of the pulmonary arterial tree caused by pulmonary embolism using the scoring system of Qanadli. The presence of an embolus is scored 1 point, and emboli on the most proximal arterial level were scored a value equal to the number of segmental arteries arising distally. To provide additional information about the residual perfusion distal to the embolus, a weighting factor was assigned to each value, depending on the degree of vascular obstruction. This factor was equal to 0 when no thrombus was observed; 1, when a partially occlusive thrombus was observed; and 2, when there was total occlusion. Thus, the maximal CT vascular obstruction score is 40 per patient. An isolated subsegmental

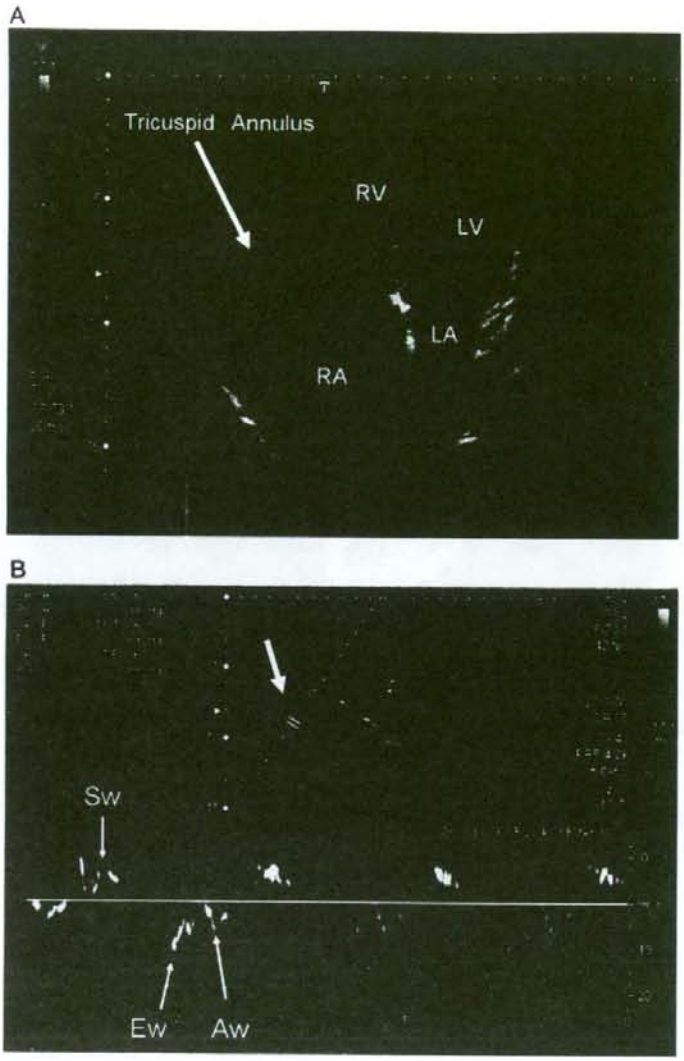

Fig. 3. These are examples of Doppler tissue images recording at the tricuspid annulus in the apical four chamber view (A). By putting a reference point on the tricuspid annulus on A, we could obtain a clear spectral Doppler recording of myocardial velocity at the tricuspid annulus (B). The early systolic velocity (Sw) and diastole myocardial velocity (Ew) at the tricuspid annulus can be observed in B. Sw was identified as the peak systolic velocity, Ew was identified as the early diastolic velocity, and Aw was identified as the late diastolic wave. RV, RA, LV, and LA indicate the right ventricle, right atria, left ventricle and left atria, respectively.

embolus was considered to be a partially occluded segmental artery and was assigned a value of 1.

The percentage of vascular obstruction was calculated by dividing the patient score by the maximal total score and by multiplying the result by 100. Therefore, the CT VOI can be expressed as: $\Sigma(nd)/40 \times 100$, where n is the value of the proximal thrombus in the pulmonary arterial tree equal to the number of segmental branches arising distally (minimum, 1; maximum, 20), and d is the degree of obstruction (minimum, 0; maximum, 2).

2.2. Pulsed Tissue Doppler Imaging by echocardiography

For all 16 patients with CPATE, we also measured pulsed TDI echocardiography (Aplio 80 SSA-770A, Toshiba). The early systolic velocity (Sw) and diastolic myocardial velocity (Ew) at the tricuspid annulus and the early diastolic tricuspid inflow (E) were obtained by TDI in the apical four chamber view, and RV systolic pressure (RVSP) was estimated by pressure gradient of the tricuspid valve regurgitation. E/Ew was calculated as the parameter of RV diastolic function.

2.3. Brain natriuretic peptide

A high level of plasma BNP has a strong association with increased mortality rate in patients with pulmonary hypertension [15–19]. We measured BNP within 48 h after pulsed TDI.

3. Results

3.1. Multislice CT

Measurement of PA thromboembolism in the right PA is shown in Fig. 1B, and the actual measurement of CT VOI for PA thromboembolism using axial source images of enhanced multislice CT are shown in Fig. 2.

In MSCT, the right VOI was 23±10%, the left VOI was 18±10% and TVOI was 41±14%.

An example of TDI recording at the tricuspid annulus is shown in Fig. 3. By putting a reference point on the tricuspid annulus we could obtain a spectral Doppler recording of myocardial velocity at the tricuspid annulus (Fig. 3B). The Sw and Ew at the tricuspid annulus can be observed in Fig. 3B. Sw was identified as the peak systole velocity and Ew was identified as the early diastolic velocity and Aw was identified as the late diastolic wave.

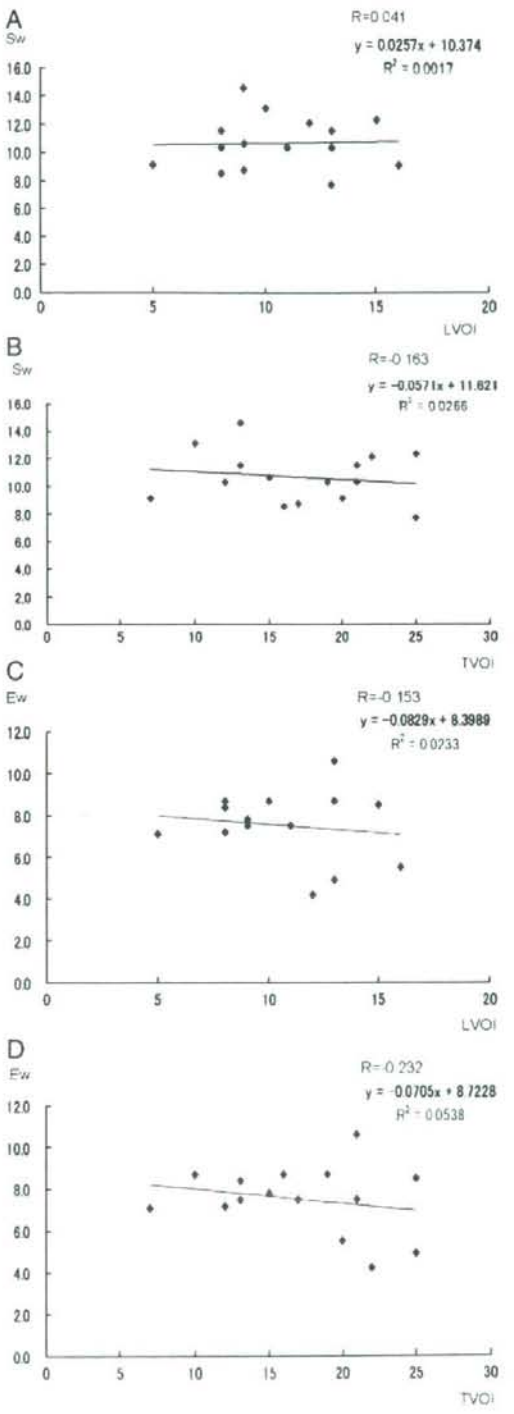

Fig. 4. Relationship between either larger of right or left side vascular obstruction index (VOI) (LVOI) and total VOI (TVOI) using the scoring system of Qanadli by multislice CT and several parameters indicating right ventricular (RV) function acquired by pulsed Tissue Doppler Imaging (TDI) and brain natriuretic peptide (BNP) (pg/ml). Several parameters indicating RV function acquired by TDI including the early systolic velocity (Sw) and diastolic myocardial velocity (Ew) at the tricuspid annulus, the early diastolic tricuspid inflow (*E*) in the apical four chamber view, and RV systolic pressure (RVSP) (mm Hg) were estimated by pressure gradient of tricuspid valve regurgitation. *E*/Ew was calculated as the parameter of RV diastolic function. A: Relationship of LVOI and Sw. There was no significant correlation between LVOI and Sw ($y=0.0257x+10.374$, $R^2=0.0017$, $R=0.041$, P=not significant (NS)). B: Relationship of TVOI and Sw. There was no significant correlation between TVOI and Sw ($y=-0.0571x+11.621$, $R^2=0.0266$, $R=-0.163$, P=NS). C: Relationship of LVOI and Ew. There was no significant correlation between LVOI and Ew ($y=-0.0829x+8.3989$, $R^2=0.0233$, $R=-0.153$, P=NS). D: Relationship of TVOI and Ew. There was no significant correlation between TVOI and Ew ($y=-0.0705x+8.7228$, $R^2=0.0538$, $R=-0.232$, P=NS). E: Relationship of LVOI and *E*/Ew. There was no significant correlation between LVOI and *E*/Ew ($y=0.0815x+4.1694$, $R^2=0.021$, $R=0.145$, P=NS). F: Relationship of TVOI and *E*/Ew. There was no significant correlation between TVOI and *E*/Ew ($y=0.0757x+3.741$, $R^2=0.0581$, $R=0.241$, P=NS). G: Relationship of LVOI and RVSP. There was no significant correlation between LVOI and RVSP ($y=2.0195x+33.149$, $R^2=0.065$, $R=0.255$, P=NS). H: Relationship of TVOI and RVSP. There was a weak but significant positive correlation between TVOI and RVSP ($y=1.7563x+24.803$, $R^2=0.1612$, $R=0.401$, $P<0.05$). I: Relationship of LVOI and BNP. There was no significant correlation between LVOI and BNP ($y=2.8757x+21.291$, $R^2=0.037$, $R=0.192$, P=NS). J: Relationship of TVOI and BNP. There was no significant correlation between TVOI and BNP ($y=1.4221x+27.504$, $R^2=0.029$, $R=0.170$, P=NS). K: Relationship of RVSP and BNP. There was a weak but significant positive correlation between RVSP and BNP ($y=0.7387x+12.58$, $R^2=0.1518$, $R=0.390$, $P<0.05$).

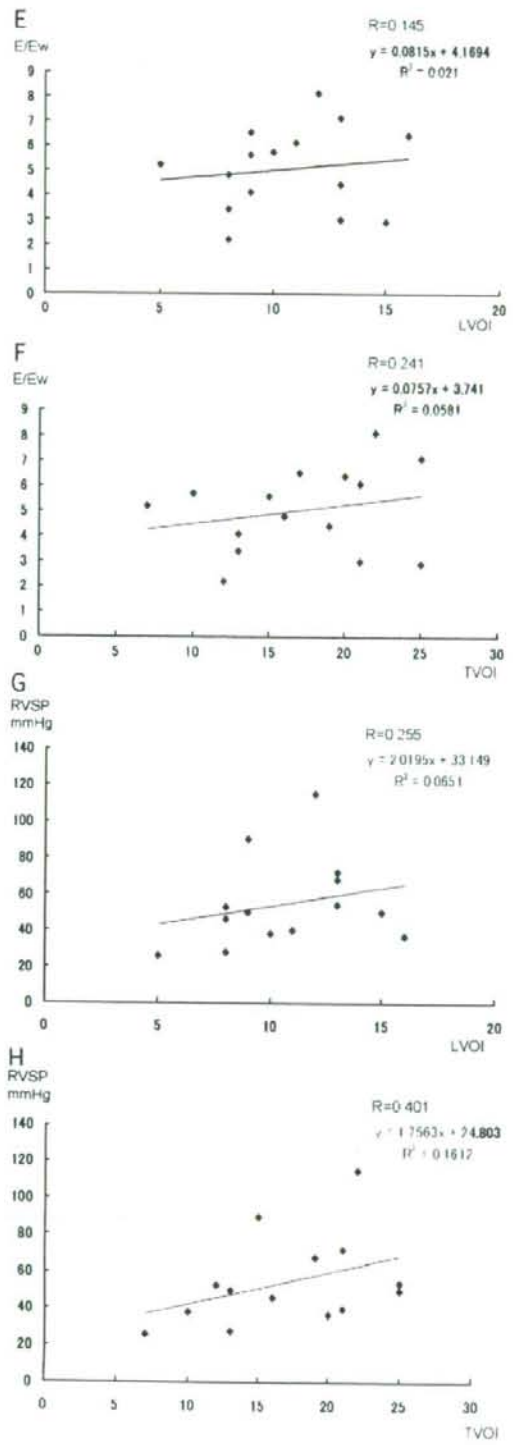

Fig. 4 (*continued*).

In TDI, Sw, Ew, *E*/Ew, and RVSP ranged 7.7–14.6 cm/s (mean 10.7), 4.2–10.6 cm/s (mean 7.7), 2.2–8.1 (mean 5.0), and 26–90 mm Hg (mean 55), respectively.

In TDI, the mean of Sw, Ew, *E*/Ew, and RVSP were 10.7 (7.7–14.6) cm/s, 7.7 (4.2–10.6) cm/s, 5.0 (2.2–8.1), and 55