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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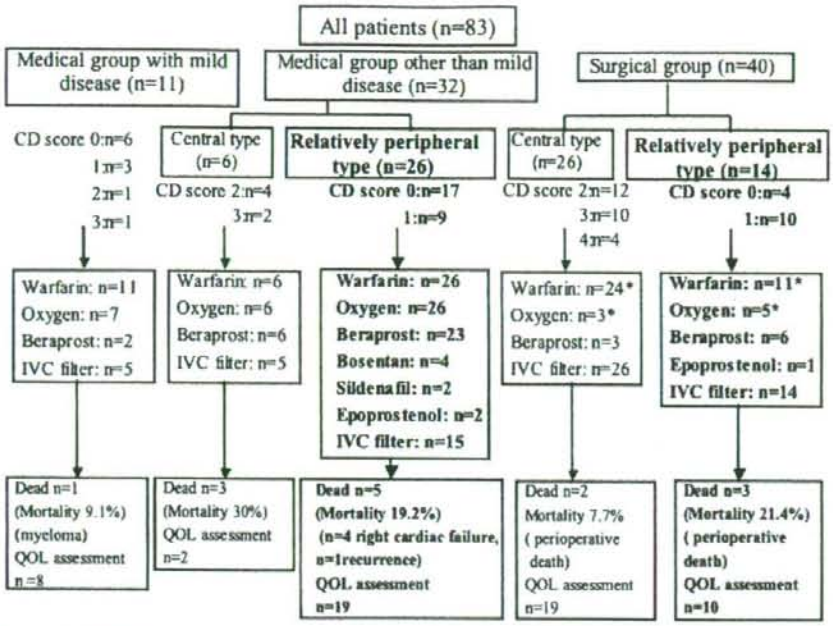

Fig 1. Algorhythm of management and course for chronic thromboembolic pulmonary hypertension (CTEPH). IVC, inferior vena cava filter; CD score, central disease score; QOL, quality of life. *Patients who died in hospital were excluded.

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.

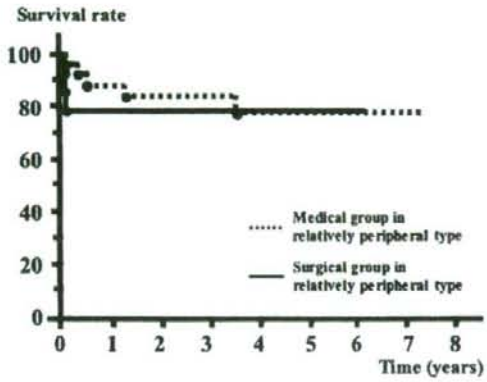

Fig 2. Comparison of survival curves between medically treated and surgically treated groups in relatively peripheral type. There was no statistically significant difference between the 2 groups (p=0.78, Log rank test).

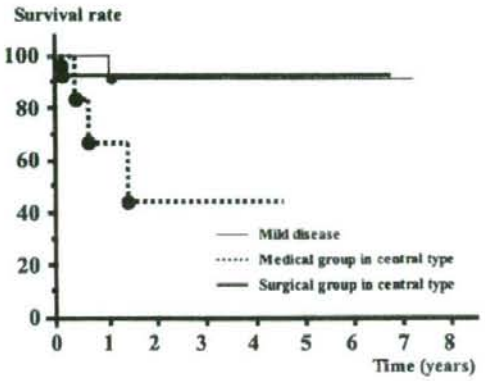

Fig 3. Comparisons of survival curves in mild disease, medical (medically treated group with central type for other reasons) and surgically treated group with central type. Medical group with central type showed significantly poorer survival compared with mild disease (p=0.039, Log rank test) or surgically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

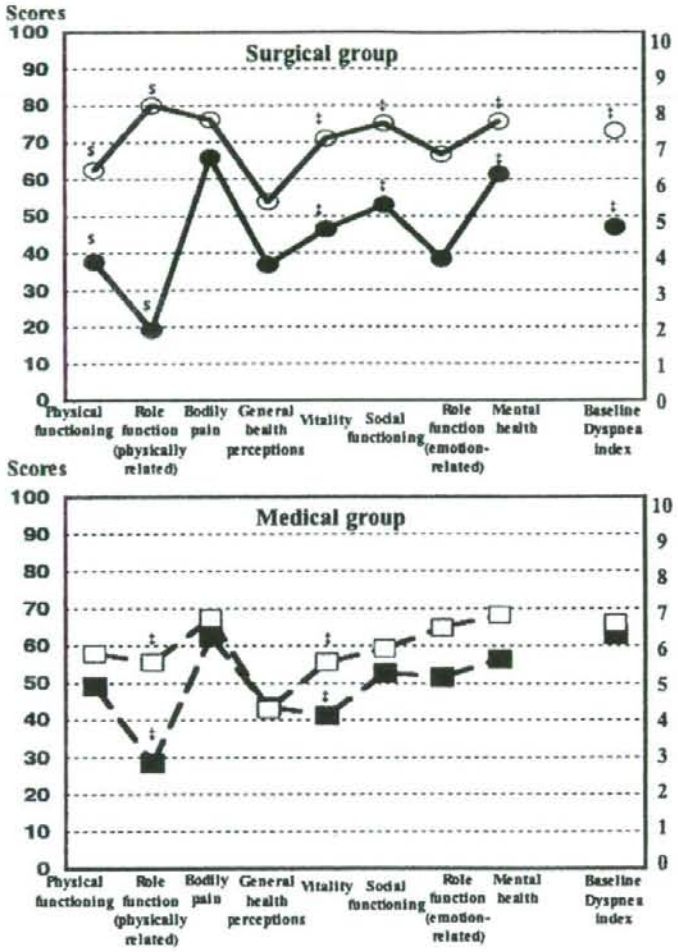

Fig 4. (Top) Comparisons of the SF-36 scores and baseline dyspnea index at pre-treatment and at follow up in the surgical group in relatively peripheral type. Pre-treatment in the surgical group (n=14, solid circles), at follow up in the surgical group (n=10, open circles); †p<0.05, ‡p<0.01 between pre-treatment 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 (Table3). 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.

Acknowledgment

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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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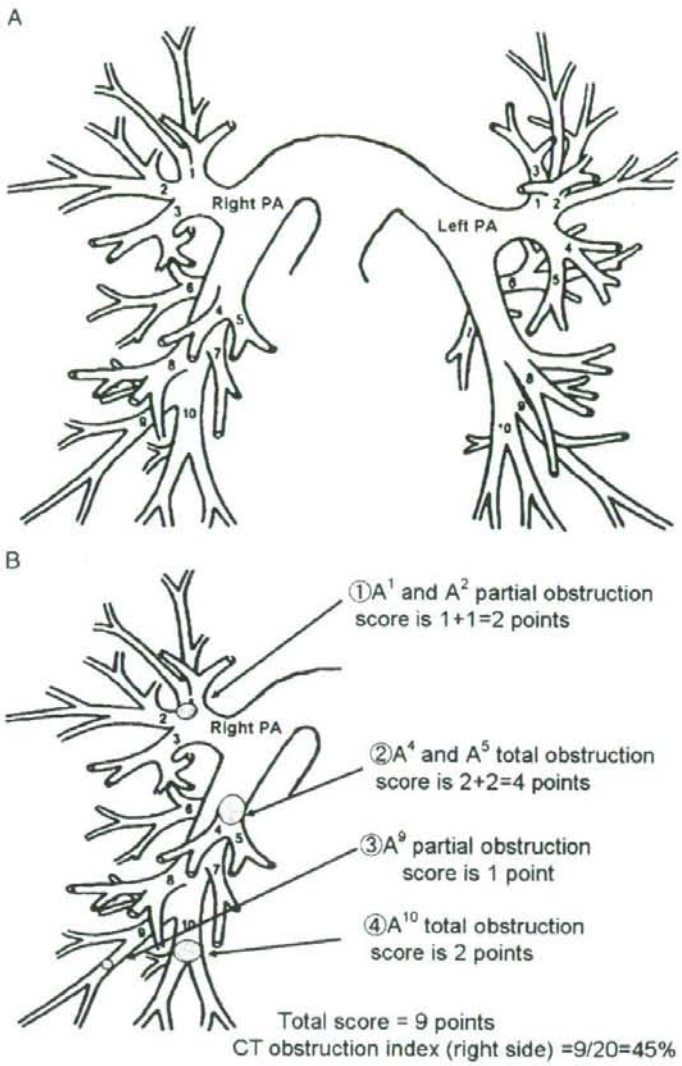

Fig. 1. (Modified figure from Ref. [9]) Schema of measurement of CT vascular obstruction index (VOI) for pulmonary arterial (PA) thromboembolism. The following scores are assigned in the scoring system of Qanadli: the score is equal to 0 when no thrombus is observed, the score is equal to 1 when a partially 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].

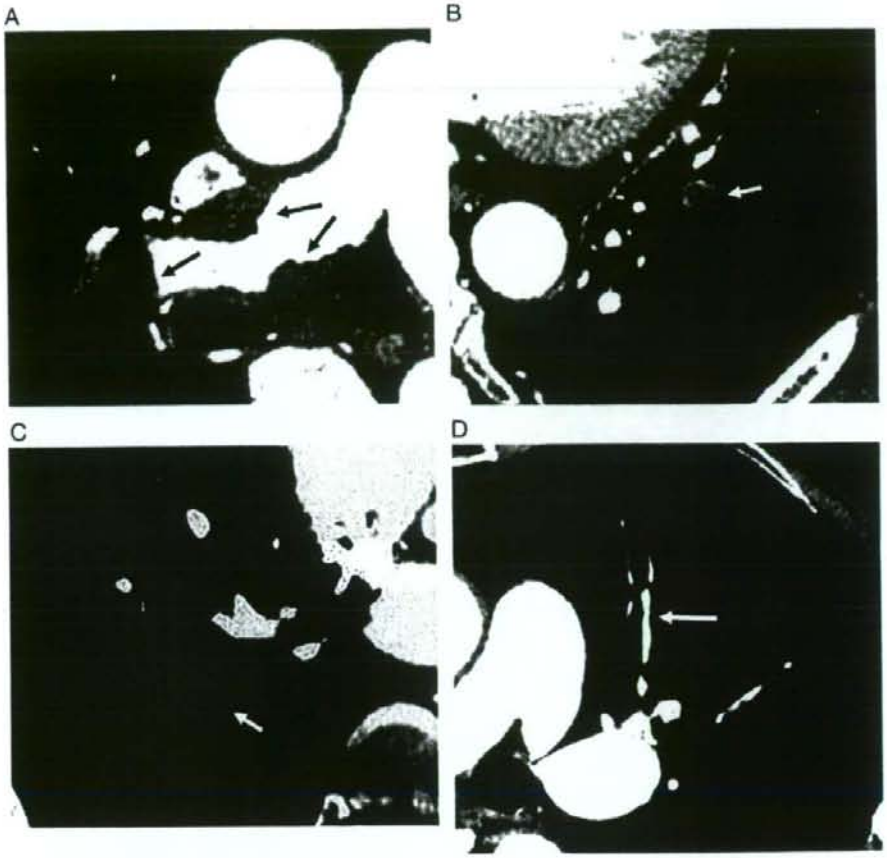

Fig. 2. Actual measurement of CT vascular obstruction index (VOI) for pulmonary arterial (PA) thromboembolism using axial source images of enhanced multislice CT. A: There are thrombi (arrows) which partially block the right main PA. We counted the thrombi distally from the segmental arteries. In this 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

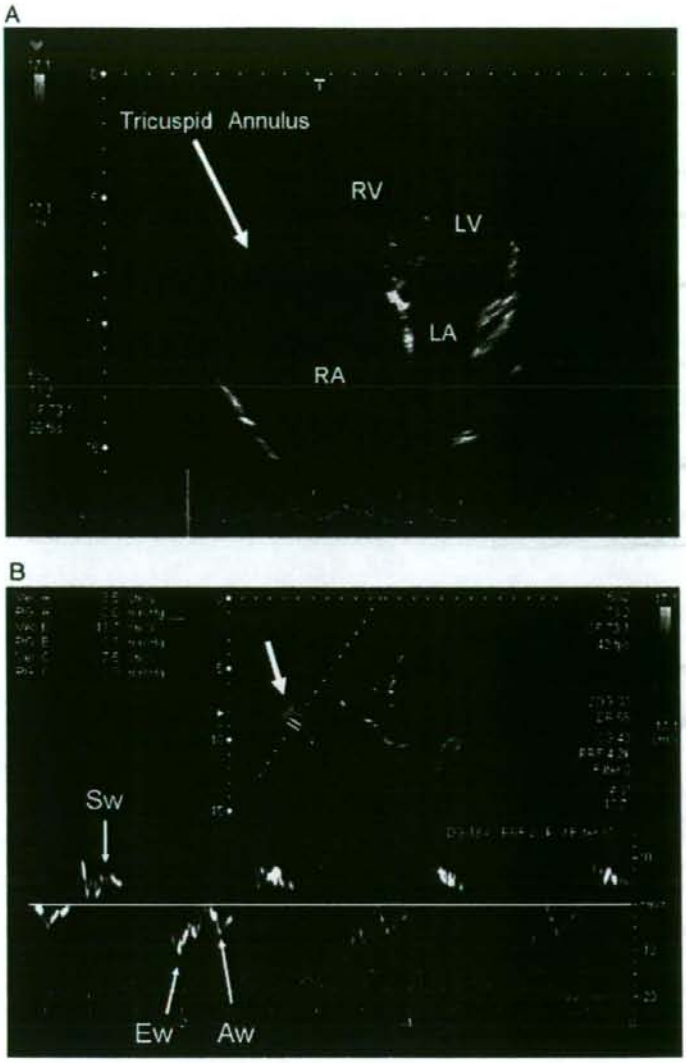

Fig. 3. These are examples of Doppler tissue images recording at the tricuspid annulus in the apical four chamber view (A). By putting a reference point on the tricuspid annulus on A, we could obtain a clear spectral Doppler recording of myocardial velocity at the tricuspid annulus (B). The early systolic 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.

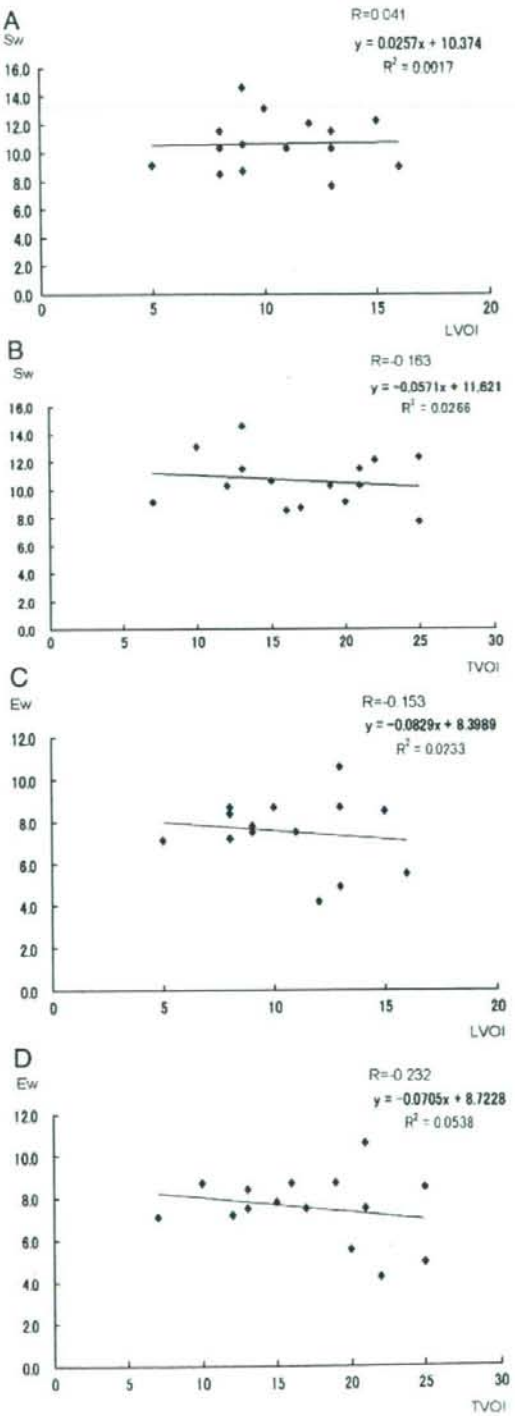

Fig. 4. Relationship between either larger of right or left side vascular obstruction index (VOI) (LVOI) and total VOI (TVOI) using the scoring system of Qanadli by multislice CT and several parameters indicating right ventricular (RV) function acquired by pulsed Tissue Doppler Imaging (TDI) and brain 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 ($y=0.7387x+12.58$, $R^2=0.1518$, $R=0.390$, $P<0.05$).

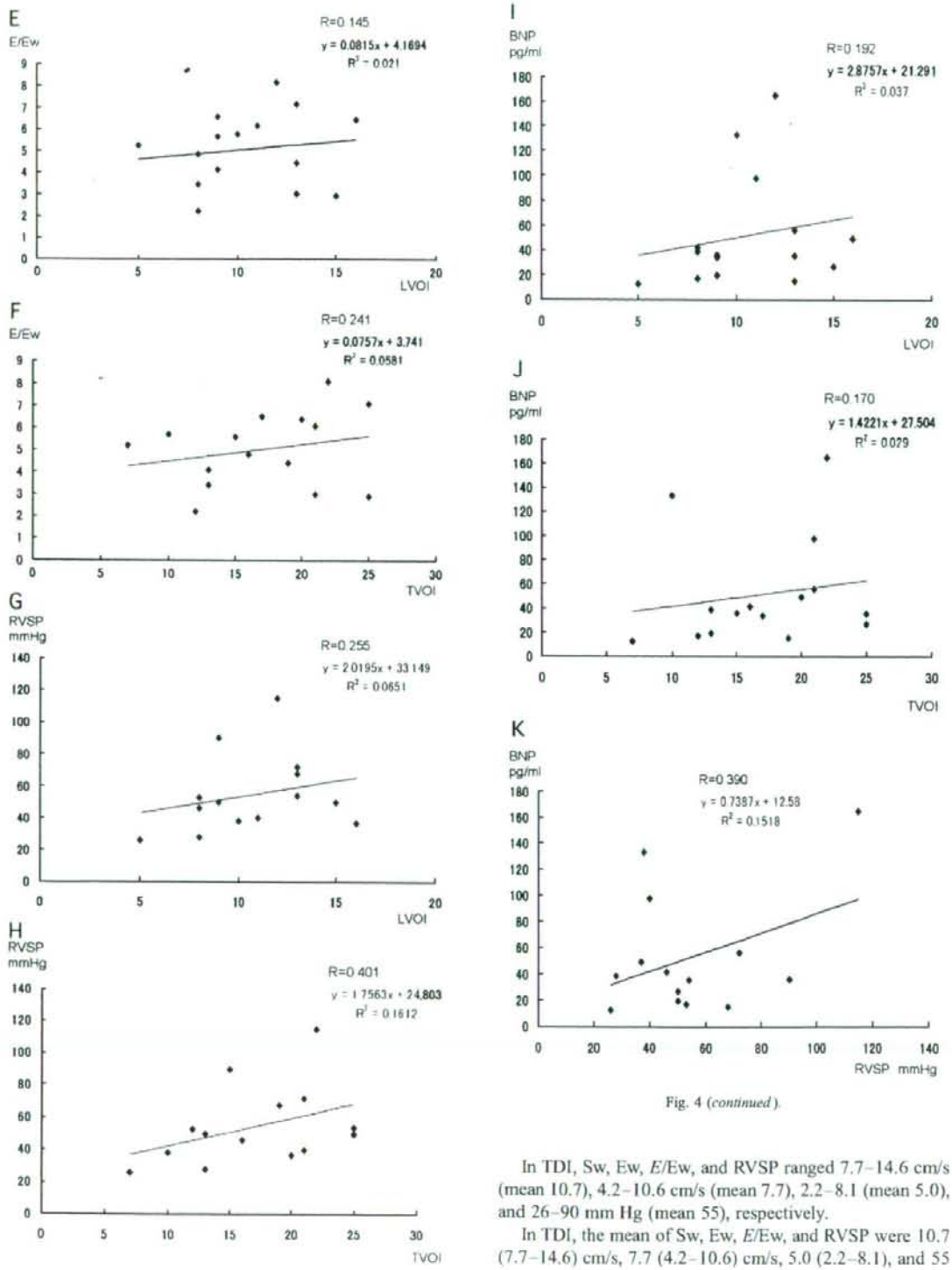

Fig. 4 (*continued*).

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

(26–90) mm Hg, respectively. The mean of BNP was 50.3 (12.2–165) pg/ml.

Relationship between either larger of right or left side (LVOI) or TVOI, and Sw, Ew, *E*/Ew, RVSP, and BNP were represented in Fig. 4A–J.

The relationship of LVOI and Sw is presented in Fig. 4A. 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]).

The relationship of TVOI and Sw is presented in Fig. 4B. There was no significant correlation between TVOI and Sw ($y=-0.0571x+11.621$, $R^2=0.0266$, $R=-0.163$, $P=$NS).

The relationship of LVOI and Ew is presented in Fig. 4C. There was no significant correlation between LVOI and Ew ($y=-0.0829x+8.3989$, $R^2=0.0233$, $R=-0.153$, $P=$NS).

The relationship of TVOI and Ew is presented in Fig. 4D. There was no significant correlation between TVOI and Ew ($y=-0.0705x+8.7228$, $R^2=0.0538$, $R=-0.232$, $P=$NS).

The relationship of LVOI and *E*/Ew is presented in Fig. 4E. There was no significant correlation between LVOI and *E*/Ew ($y=0.0815x+4.1694$, $R^2=0.021$, $R=0.145$, $P=$NS).

The relationship of TVOI and *E*/Ew is presented in Fig. 4F. There was no significant correlations between TVOI and *E*/Ew ($y=0.0757x+3.741$, $R^2=0.0581$, $R=0.241$, $P=$NS).

The relationship of LVOI and RVSP is presented in Fig. 4G. There was no significant correlation between LVOI and RVSP ($y=2.0195x+33.149$, $R^2=0.065$, $R=0.255$, $P=$NS).

The relationship of TVOI and RVSP is presented in Fig. 4H. There was a weak but significant positive correlation between TVOI and RVSP ($y=1.7563x+24.803$, $R^2=0.1612$, $R=0.401$, $P<0.05$).

The relationship of LVOI and BNP was represented in Fig. 4I. There was no significant correlation between LVOI and BNP ($y=2.8757x+21.291$, $R^2=0.037$, $R=0.192$, $P=$NS).

The relationship of TVOI and BNP is presented in Fig. 4J. There was no significant correlation between TVOI and BNP ($y=1.4221x+27.504$, $R^2=0.029$, $R=0.170$, $P=$NS).

The relationship of RVSP and BNP is presented in Fig. 4K. There was a weak but significant positive correlation between RVSP and BNP ($y=0.7387x+12.58$, $R^2=0.1518$, $R=0.390$, $P<0.05$).

4. Discussion

We assessed the morphological changes of CPATE using multislice CT and measured RV function using pulsed TDI; BNP concentration was also measured. The relationship between the various morphological and functional parameters and also their relationship to BNP concentration was determined. VOI determined by CT was better correlated with RVSP than the other parameters (Sw, Ew, and *E*/Ew) measured by pulsed TDI, or with BNP. CPATE is caused by obstruction of the large pulmonary arteries due to acute and recurrent pulmonary emboli, and how these blood clots are dispersed within the vessels [20]. In cases of CPATE, resorption of blood clots by local fibrinolysis with complete restoration of the pulmonary artery bed does not occur, and the emboli evolve to an organized clot inside the pulmonary artery. Abnormalities in hemostasis or fibrinolysis and recurrent emboli are possible culprits. The pulmonary arterial bed becomes occluded, resulting in remodeling of small pulmonary arteries and abnormal vascular reactivity with endothelial dysfunction even in the vessels with no occlusion [17,21]. This phenomenon is similar to that encountered in primary pulmonary hypertension. Therefore, the vascular resistance in the no obstructed vascular bed is also an important factor for the prognosis of CPTAE.

BNP regulates pulmonary arterial pressure and it is one of the widely used markers for the prognosis of patients with CPATE [18,19,22]. Actually in this study, there was a weak but significant positive correlation between BNP and RVSP ($R=0.390$, $P<0.05$). But TVOI was better correlated with RVSP ($R=0.401$) than the other parameters assessed (Sw, Ew, *E*/Ew, and BNP) and to the same degree that BNP correlated with RVSP ($R=0.390$).

Therefore, VOI may also be a useful parameter to assess CPTAE morphologically as well as acute pulmonary arterial thromboembolism.

Conversely we can suggest that CT VOI and RV pressure overload do not correlate well with each other. As we mentioned above, vascular remodeling in the pulmonary arteries, such as enlargement of the vessel or occurrence of collateral arteries, may influence the pulmonary artery systolic pressure [23]. In addition, CPATE does not always cause RV pressure load and sometimes it may cause RV volume load. Because of the limited sample size in this study, further studies are needed to compare CT VOI with pulsed TDI and BNP in a larger population.

5. Conclusions

CT TVOI was better correlated with RVSP ($R=0.401$) than the other parameters assessed (Sw, Ew and *E*/Ew, and BNP) and to the same degree that BNP correlated with RVSP ($R=0.390$). TVOI could reflect RVSP more than LVOI. CT VOI also may be a useful parameter to assess CPATE morphologically as well as for acute pulmonary arterial thromboembolism.

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Doppler imaging predicts cardiac events in chronic pulmonary thromboembolism

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Abstract

Purpose: We evaluated whether right ventricular (RV) diastolic dysfunction assessed by pulsed tissue Doppler imaging (TDI) predicts cardiac events in patients with chronic pulmonary thromboembolism (CPTE).

Materials and methods: In 63 consecutive patients with CPTE, early diastolic myocardial velocity (Ea) at the tricuspid annulus by TDI and early diastolic tricuspid inflow (E) by conventional pulsed Doppler were obtained, and E/Ea was calculated as an indicator of RV diastolic dysfunction. Brain natriuretic peptide (BNP) and other echo parameters were also obtained. A cardiac event (rehospitalization caused by congestive heart failure or cardiac death) was the study endpoint. Incidence of cardiac events was determined over a 374±451 day follow-up period.

Results: In the follow-up period twelve patients had cardiac events. We divided patients into group A with cardiac events and group B without events. E/Ea was significantly increased in group A as compared with group B (8.3±4.1 vs. 5.7±2.6, $p<0.01$). BNP was higher in group A than group B (221±191 vs. 121±140 mg/dl, $p<0.05$), and in addition E/Ea was significantly positively correlated with BNP ($r=0.48$, $p<0.001$). A logistic regression model for predicting cardiac events was constructed and E/Ea was associated with an increased incidence of cardiac events (relative risk = 1.33, 95% CI 1.00–1.75).

Conclusion: Elevated values of E/Ea obtained by TDI may predict cardiac events in patients with CPTE. BNP may also be a significant predictor.

Keywords: Doppler imaging; Cardiac events; Chronic pulmonary thromboembolism; E/Ea; Right ventricular diastolic dysfunction

1. Introduction

Right ventricular (RV) dysfunction is an important cause of mortality and morbidity in patients with chronic pulmonary thromboembolism (CPTE) [1] Chronic pulmonary hypertension (PH) induces RV remodeling, including hypertrophy and dilation [2]. The severity of pulmonary thromboembolism is dependent on embolus size and cardiopulmonary status [2]. Indeed, several studies show that a poor prognosis in patients with PH can be attributed to right heart failure. Fortunately, recent advances in the treatment of PH, including iloprost infusion therapy, endothelin antagonists, and sildenafil have improved disease prognosis [3,4]. Generally, evaluation of RV dysfunction is difficult because of complex RV morphology, and standard Doppler echocardiographic evaluation of RV function has several limitations based upon technological considerations.

Interestingly, in animal studies of chronic RV pressure overload RV systolic function may be preserved even though

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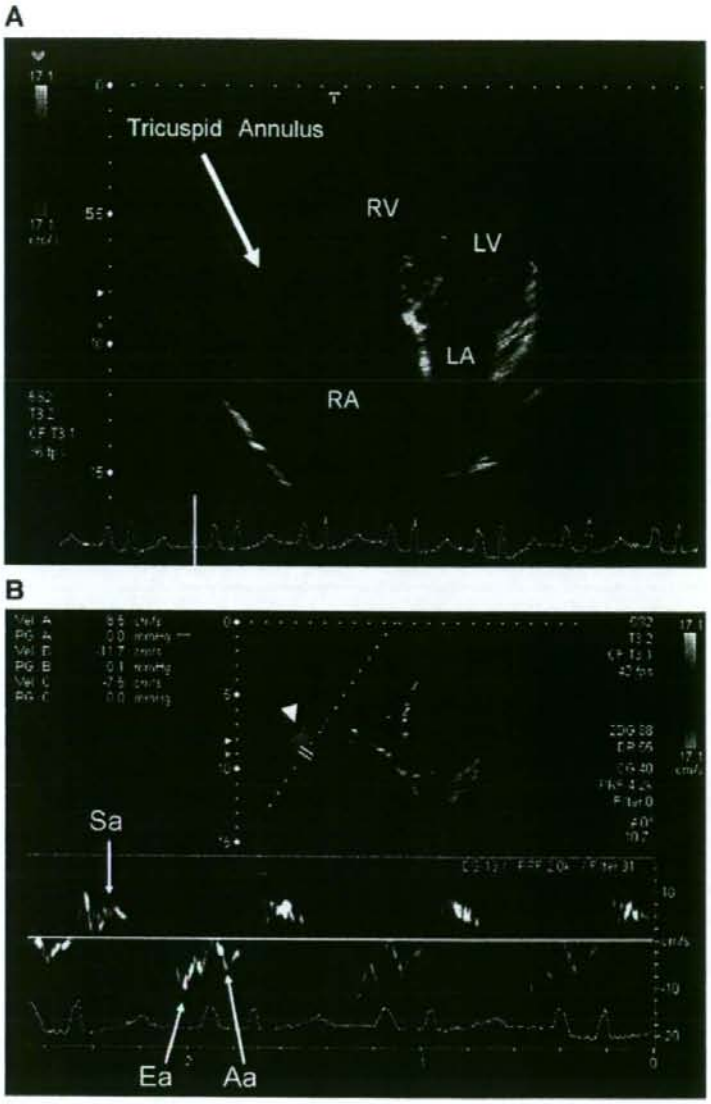

Fig. 1. A) Pulsed tissue Doppler image recording with reference point at the tricuspid annulus (arrowhead). RV = right ventricle; RA = right atrium; LV = left ventricle; LA = left atrium. B) Spectral Doppler recording at the tricuspid annulus (arrow). Sa = early systolic velocity; Ea = early diastolic velocity; Aa = late diastolic wave.

diastolic function is impaired [5,6]. These experimental findings indicate that not only RV systolic function but also RV diastolic function should be assessed in clinical settings. Tissue Doppler imaging (TDI) provides a useful technology that derives measurements of contraction and relaxation velocities directly from the myocardium. TDI is also a simple, noninvasive, and repeatable method that can be used to assess both systolic and diastolic function [7–13].

It is known also that plasma brain natriuretic peptide (BNP) levels [14–22] increase in proportion to the degree of RV dysfunction in PH [23,24], and that elevated BNP is also associated with a poor prognosis in patients with PH [25]. BNP is elevated in conditions with ventricular volume and pressure overload, and levels have been shown to correlate with mean pulmonary arterial pressure, pulmonary vascular resistance, and RV end diastolic diameter in patients with PH [23].

Accurate prediction of mortality is of critical importance in the treatment of patients with CPTE. In this study, we evaluated whether RV diastolic dysfunction assessed by

Table 1
Group A and group B measurements

	Group A with cardiac event ($n=12$)	Group B without cardiac event ($n=51$)	p value
E/Ea	8.3±4.1	5.7±2.6	$p<0.01$
Age	50.6±9.6	54.7±13	n.s
Male/female	1/11	18/33	n.s
BNP (pq/ml)	221±191	121±140	$p<0.05$
PASP (mmHg)	86±26	65±40	n.s
CO (l/min)	3.7±0.8	4.1±1.2	n.s

BNP = brain natriuretic peptide.
PASP = pulmonary arterial systolic pressure.
CO = cardiac output.

pulsed TDI may predict cardiac events in patients with CPTE, and also determined the role of BNP levels and other echo parameters [24,25].

2. Materials and methods

2.1. Study population

From April 2006 to March 2007, 63 consecutive patients with CPTE (male 19 and female 44 mean age 55±13 years) were enrolled. CPTE was confirmed by multislice computed tomography as the presence of thrombi in the pulmonary arterial lumen. All patients received anticoagulant treatment for at least 6 months, but none had a thromboendarterectomy procedure. PH was defined as presence of an estimated pulmonary artery systolic pressure (PASP) by echocardiography in excess of 40 mmHg. Echocardiographic examination was performed after informed consent. All patients were selected after exclusion of presence of 1) moderate or severe left-sided valvular disease; 2) any type of cardiomyopathy; 3) absence of normal sinus rhythm; 4) history of myocardial infarction or evidence of ischemic heart disease; 5) intracardiac shunt; 6) technical inadequacy of echocardiograms.

2.2. Echocardiography

A complete 2-dimensional and pulsed tissue Doppler echocardiographic examination was performed using Aplio80 SSA-770A (Toshiba Medical Systems, Tokyo, Japan) and a PST-30BT probe (2.8–4.4 MHz). All measurements were made by one of the authors. Early diastolic myocardial velocity (Ea) at the tricuspid annulus by TDI and early diastolic tricuspid inflow (E) by conventional pulsed Doppler were obtained from an apical four chamber view (Fig. 1A, B) We measured these values in triplicate at end expiration and at an angle as close to parallel to the direction of blood flow as possible. No angle corrections of the Doppler signal were applied. RV E/Ea was calculated and used as a parameter of RV diastolic dysfunction.

Other echo parameters, including estimated PASP and cardiac output (CO) (l/min) were also obtained. The systolic transtricuspid pressure gradient was calculated using a simple Bernoulli equation (pressure gradient $=4\times V^2$), where V represents the maximal regurgitant velocity in m/s. To estimate right atrial pressure, measurements of inferior vena cava diameters were made from long-axis subxiphoid views using the caval respiratory index as described by Kircher et al. [26]. The estimated PASP was calculated as the sum of the transtricuspid gradient and the estimated RA pressure. CO was calculated from the velocity time integral (VTI), the cross-sectional area of the conduit from which VTI was obtained, and the heart rate.

Table 2
Logistic regression analysis

	Odds ratio	CI 95%	p value
Age (year)	0.99	0.93–1.07	n.s
Male sex	0.20	0.019–2.17	n.s
E/Ea	1.33	1.00–1.75	$p<0.05$
BNP (pq/ml)	1.00	0.99–1.00	n.s
PASP (mmHg)	1.01	0.99–1.03	n.s
CO (l/min)	0.76	0.30–1.95	n.s

CI = confidence intervals; and n.s = not significant; other abbreviations as shown in Table 1.

2.3. Serum BNP

BNP levels were measured within 48 h after echocardiographic examination. Blood samples to measure the BNP level were obtained from the antecubital vein in the supine position after a resting period of 30 min just after echocardiographic examination. The BNP levels were measured using a chemiluminescent enzyme immunoassay (SRL, Inc. Tokyo, Japan).

2.4. Statistical analysis

Variables were presented as mean ± SD except for duration of the follow-up period, where the median and range was employed. Student's t test was used to estimate differences between group A and group B. The relationship between BNP and E/Ea was estimated by simple linear regression analysis. Factors associated with cardiac events were assessed using a logistic regression model. Differences were

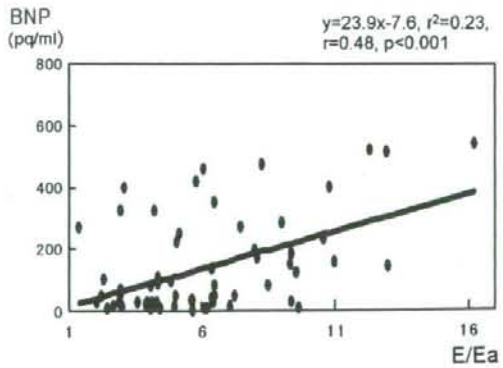

Fig. 2. Relationship of plasma BNP levels to E/Ea.

considered statistically significant if the p value was less than 0.05 with 95% confidence intervals. Event free survival rates of the two groups using the appropriate cut-off points of RV E/Ea were compared by Kaplan–Meier.

2.5. Study end point

A cardiac event (rehospitalization caused by decompensated congestive heart failure [CHF] or cardiac death) was defined as the study end point. A 374±451 day (median 212, range 31–2492) follow-up period was carried out, and the incidence of cardiac events was evaluated during this time.

3. Results

Of the total of 63 patients 12 experienced cardiac events during the follow-up period, with 11 rehospitalizations for CHF and 1 cardiac death. These 12 patients were designated as group A and the 51 patients without cardiac events as group B.

As shown in Table 1, there were no significant differences in age, the ratio of males to females, or estimated PASP and CO between the groups. However levels of E/Ea and serum BNP were significantly higher in group A than in group B (8.3±4.1 vs. 5.7±2.6, $p<0.01$, and 221±191 vs. 121±140 mg/dl, $p<0.05$, respectively). These findings suggest the presence of RV diastolic dysfunction. A logistic regression model for predicting cardiac events was constructed using age, male sex, estimated PASP, CO, BNP and E/Ea. In this model only E/Ea was associated with an increased incidence of cardiac events (relative risk=1.33, 95%CI 1.00–1.75) (Table 2).

Although BNP levels did not prove to be significant in the logistic regression analysis, as shown in Fig. 2 there was a weak but significant positive correlation between BNP and E/Ea ($y=23.9\times-7.6$, $r^2=0.23$, $r=0.48$, $p<0.001$). This finding suggests that BNP levels may have some prognostic value of their own.

We also assessed E/Ea and cardiac events using appropriate cut-off points. The best cut-off point for RV E/Ea was 7.0 for prediction of cardiac events, with a sensitivity of 60% and a specificity of 75% (data not shown). We divided the 63 patients into two groups (E/Ea<7.0 vs. E/Ea≧7.0) and compared event free survival rates by Kaplan–Meier. As shown in Fig. 3, event free survival rates in the E/Ea≧7.0 group were much lower than those in the E/Ea<7.0 group ($p<0.001$).

In this study, the inter- and intraobserver variabilities (error) for measurement of the Doppler velocity recording were 5.0% and 4.0%, respectively (data not shown).

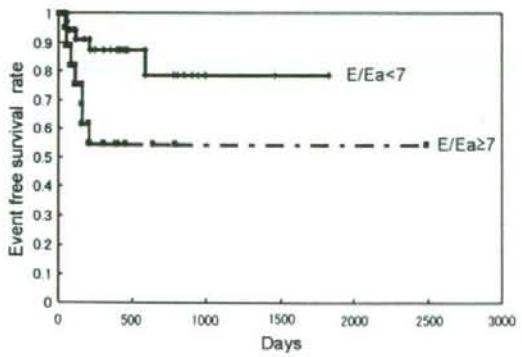

Fig. 3. Event free survival rate during patient follow-up for E/Ea<7 vs. ≧7.

4. Discussion

4.1. RV function and TDI

Right heart failure, hypotension, and cardiogenic shock have been confirmed as the most significant prognostic indicators of outcome in patients with PH [27–29]. Indeed, several studies show that poor prognosis in patients with PH can be attributed to right heart failure. According to Poiseuille's law, the circulatory system may be considered as a hydraulic pump composed of a right heart pump linked in series to a left heart pump. Left heart output cannot exceed right heart output, which allows for the functional integration of both pumps as a single hydraulic unit. In this respect, RV function is important in maintaining CO in patients with PH.

A number of studies have reported that not only RV systolic dysfunction but also RV diastolic dysfunction contribute to the RV dysfunction syndrome. However extensive assessment of PH-induced RV dysfunction remains difficult using conventional echocardiography. The accuracy of RV systolic and diastolic functional assessment is limited by the complex anatomy and geometry of the RV.

The myocardial performance index (MPI) and the identical Tei index are often applied as indexes of combined ventricular systolic and diastolic function [30]. Yeo et al. found that the RV MPI was a useful predictor of adverse outcome in patients with primary PH [31], and RV MPI is another potential indicator of prognosis in patients with systemic lupus erythematosus and PH [32]. Increased values of RV MPI result from prolongation of RV isovolumic relaxation time (IVRT) in patients with pulmonary thromboembolism [30] and the duration of RV IVRT becomes prolonged with disease progression in subjects with PH.

In patients with acute pulmonary thromboembolism the most striking difference, as compared with patients having CPTE, is marked prolongation of IVRT, measured by putting a reference point at the tricuspid annulus as represented in Fig. 1A. Interestingly, RV ejection fraction values are similar in acute pulmonary thromboembolism and CPTE, but RV MPI in acute pulmonary thromboembolism is much higher than in CPTE. This may indicate that the degree of RV diastolic dysfunction in acute RV overloading is actually more severe than during the chronic process that characterizes CPTE. On the other hand, the presence of RV diastolic function in chronic PH may suggest a poor prognosis.