(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

Yumi Shiina, Nobusada Funabashi *, Kwangho Lee, Masao Daimon, Tai Sekine, Miyuki Kawakubo, Yukiko Sekine, Maiko Takahashi, Rei Yajima, Yu Wakatsuki, Nobuhiro Tanabe, Takayuki Kuriyama, Issei Komuro

Department of Cardiovascular Science and Medicine, Chiba University Graduate School of Medicine, Inohana 1-8-1, Chuo-ku, Chiba City, Chiba 260-8670, Japan

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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

* Corresponding author. Tel.: +81 43 222 717; fax: +81 43 226 2096.
E-mail address: nobusada@w8.dion.ne.jp (N. Funabashi).

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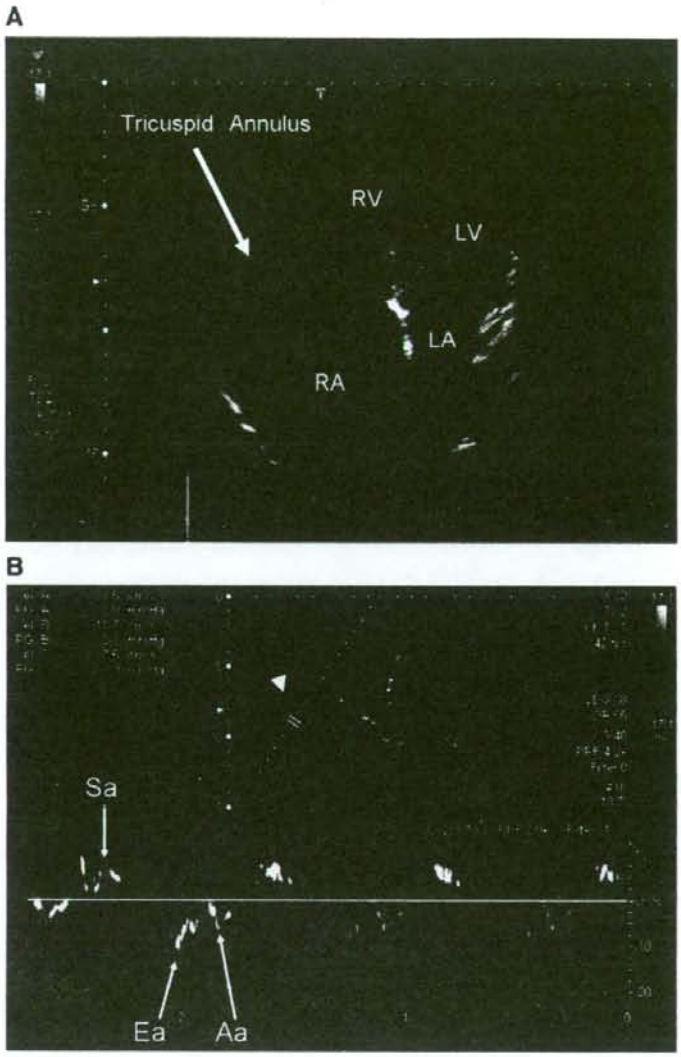

Fig. 1. A) Pulsed tissue Doppler image recording with reference point at the tricuspid annulus (arrowhead). RV = right ventricle; RA = right atrium; LV = left ventricle; LA = left atrium. B) Spectral Doppler recording at the tricuspid annulus (arrow). Sa = early systolic velocity; Ea = early diastolic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

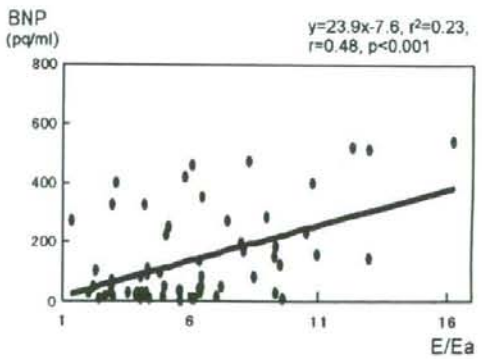

Fig. 2. Relationship of plasma BNP levels to E/Ea.

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).

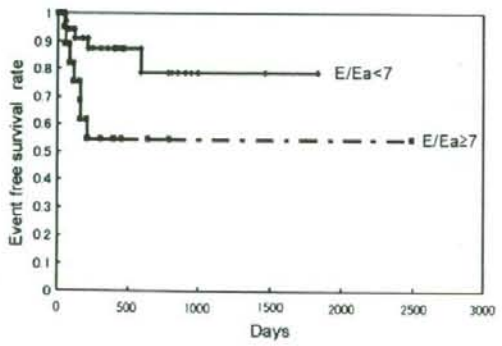

Fig. 3. Event free survival rate during patient follow-up for E/Ea <7 vs. ≧7.

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.

RV MPI is a useful assessment, but it is also complicated, and using the MPI is not a simple matter in routine echocardiograpic examinations. Interestingly, it has been reported that there is a significant relationship between RV E/Ea and MPI. RV MPI has also proven to be useful for the serial evaluation of patients with various heart diseases.

Pacileo et al. have reported values for E/Ea in the fetus that did not change significantly throughout gestation [33]. Ea and early systolic velocity (Sa) were significantly lower in fetuses with heart failure than in control fetuses, and E/Ea clearly distinguished fetuses with heart failure from controls [34]. Recent studies have demonstrated that E/Ea can correct for the influence of relaxation on E and that E/Ea relates strongly to RV filling pressure. The E/Ea ratio has also been reported to correlate with right atrial pressure [35]. Nagueh et al. found that an E/Ea ratio >6 had a sensitivity of 79% and a specificity of 73% for detecting a mean right atrial pressure >10 mmHg.

In an *in vitro* study Boissiere et al. reported that E/Ea, IVRT, and the RV Tei index were significantly increased in rats with PH induced by monocrotaline compared with controls [36]. These authors maintained that TDI was an accurate means of assessing both RV diastolic and RV global dysfunction. However conventional echocardiography did not prove to be very useful in highlighting RV diastolic abnormalities in PH groups. On the other hand, the combination of conventional pulsed Doppler and TDI was helpful in studying RV filling pressure increases in rats with severe PH.

BNP is elevated in conditions with ventricular volume and pressure overload. BNP has been shown to correlate with mean pulmonary arterial pressure and pulmonary vascular resistance in patients with PH, whether primary or secondary [37]. In patients with right ventricular pressure overload, including primary PH and thromboembolism, BNP levels were significantly higher than in controls. BNP is also a predictor of mortality in patients with primary PH [25]. Furthermore, BNP levels also correlate with mean pulmonary arterial pressure, RV end diastolic pressure, and total pulmonary vascular resistance [37,38].

Understanding the natriuretic peptide pathway and the mechanisms that cause an increase in BNP in RV pressure overload may be of value in evaluating treatment strategies and in monitoring clinical progress. BNP is produced mainly in ventricular cardiomyocytes, and its production is increased in response to ventricular volume or pressure overload. Stretching of ventricular walls causes activation of the BNP gene [39]. It is well known that RV overload increases atrial natriuretic peptide and BNP expression in both RV and atrial tissue [40,41]. Elevated BNP levels are not only associated with raised central venous pressure caused by volume overload, but are also affected by blood pressure, age, salt intake and renal function [42]. Elevation of BNP may play a therapeutic role when cardiac function deteriorates and may help to maintain renal function and sodium balance.

In the present study, there was a good correlation between RV E/Ea and BNP levels. However from the standpoint of cardiac events, RV E/Ea was a more accurate indicator than BNP. Whereas BNP levels are affected by volume overload in general or by renal dysfunction, increases in RV E/Ea provide information about global RV function, particularly diastolic function, in chronic RV hypertrophy. We observed that RV E/Ea is a useful predictor of cardiac events in patients with CPTE, however in evaluating the severity of disease in patients with CPTE, both RV function as assessed by TDI and measurement of BNP levels are useful.

4.2. Study limitations

First, the value of this study is limited by the lack of a reference standard for MPI using E/Ea in patients with PH. Next, we assessed only RV longitudinal contraction. Further studies that include both longitudinal and radial strain imaging may provide additional information. Patients with atrial fibrillation were excluded in our study, however it is known that the combination of atrial fibrillation and PH represents a more serious condition [43], suggesting that further examinations in this group may be needed.

We have, however, demonstrated that TDI examination of hearts of patients with CPTE is feasible and reproducible, and that it allows direct imaging of myocardial dynamics. We believe that these data represent important information for the quantitative assessment of RV function in patients with CPTE.

5. Conclusions

This study demonstrates a clinically important application of TDI derived tricuspid annular velocities in patients with CPTE. RV E/Ea obtained by pulsed TDI, suggesting RV diastolic dysfunction, may predict cardiac events in patients with CPTE.

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Venous Thromboembolism

— Deep Vein Thrombosis With Pulmonary Embolism, Deep Vein Thrombosis Alone, and Pulmonary Embolism Alone —

Masahito Sakuma, MD; Mashio Nakamura, MD*; Norikazu Yamada, MD*; Satoshi Ota, MD*; Kunio Shirato, MD**; Takeshi Nakano, MD*; Masaaki Ito, MD**; Takao Kobayashi, MD†

Background There are few data on the differences between deep vein thrombosis (DVT) with pulmonary embolism (PE) (Group A) and without PE (Group B), and no recent data on the incidence of PE and DVT in Japan.
Methods and Results The symptoms and findings of the lower extremities and risks for venous thromboembolism were compared between Groups A and B, and the numbers of new patients with PE and those with DVT in 2006 were calculated. DVT was found equally in left and right legs in Group A, but more frequently in left legs than in right legs in Group B. Proximal thrombus was more frequent in Group A than in Group B, and the number of cases of symptoms resulting from DVT was less in Group A than in Group B. Proximal DVT, DVT in the right leg, no symptoms, and younger age were related to the presence of PE. The calculated number of new patients with PE per year was 7,864 (3,492 cases in 1996), and that with DVT per year was 14,674.
Conclusion DVT in patients with PE and those without PE differed in the site and symptoms. The calculated number of new patients with PE per year doubled in 1 decade in Japan. (*Circ J* 2009; **73:** 305–309)

Key Words: Deep vein thrombosis; Incidence; Pulmonary embolism; Symptoms; Venous thromboembolism

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are thought to be the same disease with different presentation, and both have been handled as venous thromboembolism (VTE). Most cases of PE originate from DVT, so VTE is an important concept. However, there are no data on whether DVT with PE and DVT without PE have the same characteristics.

We reported the incidence of PE in 1996, 2000, and 2004[1–3] In 2004, 2 guidelines for VTE were published in Japan[4,5] generating increased interest in VTE.

The main purpose of this study was to clarify the different characteristics of DVT in cases with and without PE. The second purpose was to assess the recent incidence of PE and DVT in Japan.

Methods

The present study was approved by the Ethics Committee of Mie University. In July 2006, we sent questionnaires to the clinical departments (all departments of internal medicine, all departments of surgery, pediatrics, obstetrics and gynecology, orthopedics, otorhinolaryngology, ophthalmology, dermatology, and urology) of university schools of medicine or medical colleges and to hospitals with more than 100 beds in Japan. Based on the responses to the questionnaires, we assessed prospectively the number of new patients with PE from August 1, 2006 to September 30, 2006. The number of patients with PE (or DVT) per year was calculated as: the number of patients with PE (or DVT) per year = the number of patients with PE (or DVT) per 2 months × 6/the response rate[1–3]

PE was definitely diagnosed by (1) enhanced computed tomography, (2) pulmonary angiography, (3) pulmonary perfusion scintigraphy and/or pulmonary ventilation scintigraphy, (4) magnetic resonance imaging, or (5) autopsy. DVT was definitely diagnosed by (1) enhanced computed tomography, (2) venous ultrasonography, (3) contrast venography, (4) magnetic resonance venography, or (5) radioisotope venography. Major surgery was defined as abdominal surgery and/or surgery of more than 45 min duration within the previous 3 months[6–8] Immobilization was defined as strict bed rest for more than 3 continuous days within the previous 3 months[8]

We divided cases of VTE into 3 groups: DVT with PE, DVT alone, and PE alone.

Statistical Analysis

Analyses were performed using SPSS 15.0 (SPSS Inc, Chicago, IL, USA). All continuous variables were analyzed by Mann-Whitney test, and expressed as mean ± standard deviation. Non-ordinal categorical data were analyzed using the chi-square test. Multiple comparisons were performed using Bonferroni's modification. Potential risk factors for VTE were assessed using multiple logistic regression and the results were presented as estimated odds ratio (OR) with the corresponding 95% confidence intervals (CI). All significant tests were 2-tailed.

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*Division of Internal Medicine, Onagawa Municipal Hospital, Onagawa, *Department of Cardiology, Mie University Graduate School of Medicine, Tsu, **Division of Internal Medicine, Saito Hospital, Ishinomaki and †Hamamatsu Medical Center, Hamamatsu, Japan*
Mailing address: Masahito Sakuma, MD, Division of Internal Medicine, Onagawa Municipal Hospital, 51-6 Horikiriyama, Washinokamihama, Onagawa 986-2243, Japan

Table 1 Patients' Backgrounds

	DVT with PE	*DVT alone*	*PE alone*
With patient profile (n)	*210*	*420*	*140*
Gender (M/F)	*87/123*	*140/280*	*44/96*
Age (years)	*63.9±15.5*	*66.3±15.9*	*67.6±15.0*
BMI (kg/m²)	*23.7±3.8[a]*	*23.3±4.2[b]*	*23.2±3.8[c]*

[a]n=199, [b]n=392, [c]n=129.
DVT, deep vein thrombosis; PE, pulmonary embolism; BMI, body mass index.

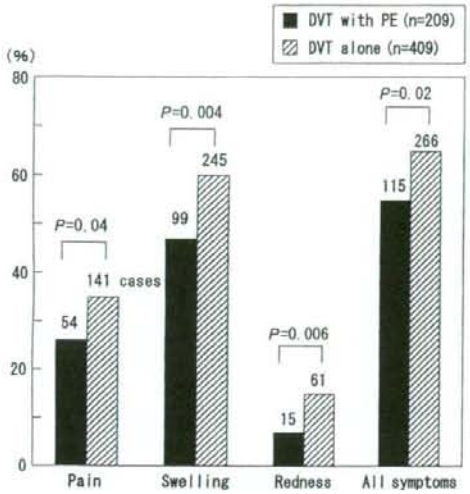

Fig 1. Symptoms of deep vein thrombosis (DVT). The number of cases is shown on each bar. PE, pulmonary embolism.

Results

Incidence of VTE

A total of 6,122 questionnaires were sent; 17 institutes were excluded from our analysis because they had closed or merged. We received 1,635 valid replies, giving a response rate of 26.8% (1,635/6,105). The number of patients newly diagnosed with PE was 351 during the 2 months of the present period, and that with DVT was 655. The estimated number of new patients with PE per year was 7,864 (95% CI: 6,572–9,155) and the incidence of PE was 61.9 (95% CI: 51.7–72.1) patients per 1,000,000 people per year in Japan. The estimated number of new patients with DVT per year was 14,674 (95% CI: 12,466–16,883) and the incidence of DVT was 115.5 (95% CI: 98.2–132.9) patients per 1,000,000 people per year in Japan.

Characteristics of DVT in Patients With and Without PE

Available cases with a detailed profile were 210 with both DVT and PE, 420 with DVT alone, and 140 with PE alone (**Table 1**). Symptoms resulting from DVT were more frequent in patients without PE, compared with those with PE (**Fig 1**). DVT was equally found in the left and right legs

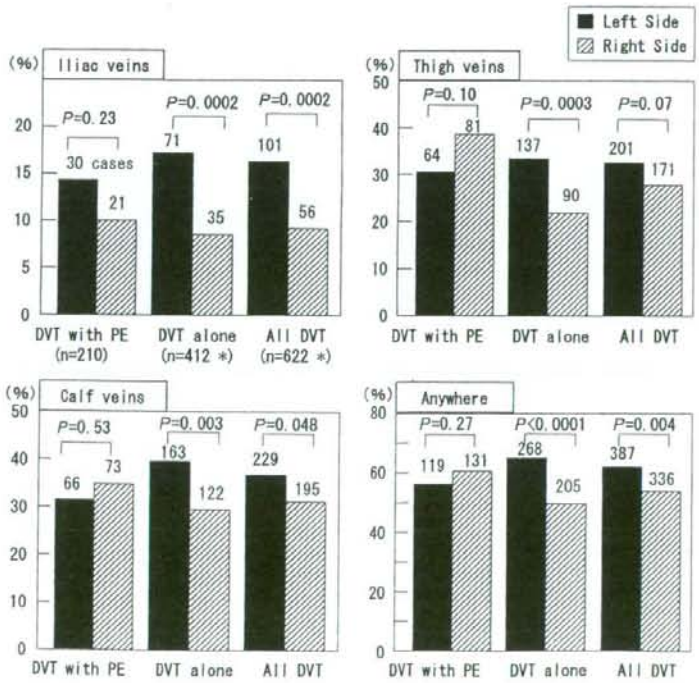

Fig 2. Location of deep vein thrombosis (DVT). The number of cases is shown on each bar. *Seven cases with DVT only in the upper extremities and one without data on DVT site were excluded. PE, pulmonary embolism.

Table 2 Diagnostic Techniques for DVT

	DVT with PE (n=210)	DVT alone (n=413*)	P value
Venous ultrasonography	132 (63%)	303 (73%)	0.008
CT	143 (68%)	180 (44%)	<0.0001
Contrast venography	18 (9%)	50 (12%)	0.22
MR venography	7 (3%)	22 (5%)	0.32
RI venography	3 (1%)	5 (1%)	1.00

CT, computed tomography; MR, magnetic resonance; RI, radioisotope. Other abbreviations see in Table 1.
**Seven cases with DVT only in the upper extremities were excluded.*

Table 3 Risk Factors for Venous Thromboembolism

	DVT with PE (n=210)	DVT alone (n=420)	PE alone (n=140)	P value
Prolonged immobilization	57 (27%)	101 (24%)	30 (21%)	0.46
Recent major surgery	54 (26%)	121 (29%)	40 (29%)	0.70
Cancer	48 (23%)	81 (19%)	23 (16%)	0.32
Recent major trauma and/or fracture	22 (11%)	47 (11%)	15 (11%)	0.96
Central venous catheter	7 (3%)	34 (8%)	9 (6%)	0.06
Pregnancy or postpartum	4 (2%)	14 (3%)	2 (1%)	0.34
Heart failure*	5 (2%)	22 (5%)	14 (10%)	0.009
Respiratory failure	5 (2%)	14 (3%)	8 (6%)	0.37
Cerebrovascular disease	10 (5%)	28 (7%)	8 (6%)	0.62
Connective tissue disease and/or steroid use	5 (2%)	11 (3%)	5 (4%)	0.79
Benign, large abdominal tumor	2 (1%)	9 (2%)	1 (1%)	0.33
No potential risk factors	42 (20%)	66 (16%)	28 (20%)	0.30

**P=0.10 between DVT with PE and DVT alone, P=0.003 between DVT with PE and PE alone. P=0.07 between DVT alone and PE alone. Abbreviations see in Table 1.*

Table 4 Multivariate Logistic Analysis of Relation to Presence of PE in Patients with DVT

	OR (95% CI)	P value
Age (10-year increments)	0.87 (0.77–0.99)	0.03
Male	1.12 (0.76–1.66)	0.57
No symptoms of DVT	2.05 (1.39–3.02)	0.0003
Right DVT	1.98 (1.22–3.19)	0.005
Left DVT	0.99 (0.61–1.60)	0.97
Proximal DVT[a]	1.79 (1.18–2.71)	0.006
BMI	1.03 (0.99–1.08)	0.16
Prolonged immobilization	1.2 (0.78–1.86)	0.41
Recent major surgery	0.83 (0.54–1.28)	0.40
Cancer	1.08 (0.68–1.70)	0.75
Recent major trauma and/or fracture	0.85 (0.46–1.54)	0.58
Central venous catheter	0.44 (0.19–1.00)	0.05
Pregnancy or postpartum	0.37 (0.10–1.32)	0.12
Heart failure	0.59 (0.20–1.68)	0.32
Respiratory failure	0.58 (0.18–1.92)	0.37
Cerebrovascular disease	0.66 (0.28–1.55)	0.34
Connective tissue disease and/or steroid use	1.48 (0.54–4.02)	0.45
Benign, large abdominal tumor	–	1.00

[a]Including IVC, iliac vein, and thigh veins.
OR, odds ratio; CI, confidence interval; IVC, inferior vena cava. Other abbreviations see in Table 1.

of patients with PE, but more frequently in the left than in the right leg of patients without PE (**Fig 2**). Proximal thrombus from the inferior vena cava to the popliteal vein was more frequent in patients with PE than in patients without PE (68% [142/210] vs 58% [240/412]; P=0.02).

Relationship Between Symptoms of DVT and Age

Leg swelling (presence, 64.7±16.0 years; absence, 66.5±15.7; P=0.10) and redness (presence, 63.0±15.7 years; absence, 65.9±15.9; P=0.09) were found regardless of age in patients with DVT. Younger patients complained more about leg pain (complaint, 61.2±15.7 years; no complaint, 67.4±15.6; P<0.0001). All findings for DVT (objective or subjective) were greater in younger patients (presence, 64.4±15.8 years; absence, 67.4±15.9; P=0.007).

*Diagnostic Techniques for DVT (**Table 2**)*

Venous ultrasonography was used more frequently and CT less frequently in patients without PE than in patients with PE. Contrast venography was used in only approximately 10% of patients.

Risk Factors for VTE and Relationship to Presence of PE

There were no differences in the risk factors, except heart

Table 5 Management of Venous Thromboembolism

	[1]DVT with PE (n=210)	[2]DVT alone (n=420)	[3]PE alone (n=140)	P value*		
				1 vs 2	1 vs 3	2 vs 3
Heparin	175 (83%)	243 (58%)	106 (76%)	<0.0001	0.30	0.0005
Warfarin	162 (77%)	282 (67%)	86 (61%)	0.03	0.006	0.66
Anticoagulation						
Heparin → warfarin	136 (65%)	173 (41%)	69 (49%)	<0.0001	0.02	0.30
Heparin alone	39 (19%)	70 (17%)	37 (26%)	1.00	0.26	0.04
Warfarin alone	26 (12%)	109 (26%)	17 (12%)	<0.0001	1.00	0.003
Thrombolysis	58 (28%)	55 (13%)	38 (27%)	<0.0001	1.00	0.006
IVC filter	110 (52%)	93 (22%)	22 (16%)	<0.0001	<0.0001	0.35

**All P-values by chi-square analysis among 3 groups (1, 2 and 3) were less than 0.05. Multiple comparisons were performed using Bonferroni's modification.*
Abbreviations see in Tables 1, 4.

failure, among the 3 groups (patients with DVT and PE, those with DVT alone, and those with PE alone) (**Table 3**). Patients with DVT and PE were younger than those with DVT alone (63.9±15.5 years vs 66.3±15.9; P=0.04). PE was found in 30.5% of females with DVT and in 38.3% of males with DVT (P=0.053). Proximal DVT, DVT in the right leg, no symptoms, and younger age were independently related to the presence of PE in patients with DVT (**Table 4**).

Management of VTE (Table 5)

Heparin and thrombolysis were used less frequently in patients with DVT alone. Implantation of an inferior vena cava filter and chronic use of warfarin were more frequent in patients with DVT and PE. When limited to cases of DVT, inferior vena cava filters were used more often in cases of proximal DVT (OR, 3.51; 95% CI, 2.33–5.27; P<0.0001) and PE (OR, 3.71; 95% CI, 2.56–5.37; P<0.0001). Antiplatelet agents were administered in 8 patients (4%) with DVT and PE (aspirin in 8, ticlopidine in 2; 2 cases used both antiplatelet agents), 44 with DVT alone (aspirin in 36, ticlopidine in 6, cilostazol in 1, sarpogrelate in 1), and 9 (6%) with PE alone (aspirin in 8, ticlopidine in 1, beraprost in 2; 2 cases used 2 antiplatelet agents).

For DVT, catheter therapy was performed in 9 patients with DVT and PE, and in 8 patients with DVT alone. Surgery was performed in 3 patients with DVT and PE, and in 1 patient with DVT alone. On the other hand, for PE, catheter therapy was performed in 13 patients with DVT and PE, and in 7 patients with PE alone. Surgery was performed in 4 patients with DVT and PE, and in 4 patients with PE alone.

Discussion

Characteristics of DVT With and Without PE

DVT in patients with PE and those without PE differed in the site and symptoms. In particular, DVT was equally found in the left and right legs of patients with PE, but more frequently in the left than in the right leg in those without PE. Moreover, cases of symptoms resulting from DVT were less frequent in the presence of PE than in the absence of PE.

Ileofemoral DVT tends to occur in the left leg;[9–12] whereas femoropopliteal DVT occurs equally in the right and left legs, and most are contiguous to calf thrombosis?[9–12] Those previous reports and the present results suggest that DVT without PE is related to ileofemoral DVT, and that DVT with PE is related to femoropopliteal DVT.

DVT is more common on the left side;[13] as observed in all of the present cases of DVT. In the present study, DVT with PE had no statistical difference in the rate of potential risk factors compared with DVT without PE.

Free-floating venous thrombi have a close relationship with PE compared with occlusive (no free-floating) thrombi;[14] and the previous reports suggest that free-floating venous thrombi cause less symptoms from DVT than occlusive DVTs![14,15] On the other hand, most cases of symptomatic DVT have extensive occlusive proximal thrombi?[9,16] The development of symptoms of DVT is thought to depend on the extent of thrombosis, the adequacy of collateral vessels, and the severity of associated vascular occlusion and inflammation![17] Leg edema is much more likely in contiguous thrombosis rather than with an isolated thrombus![18] DVT with PE has fewer symptoms, as shown in the present study, and resembles free-floating DVT.

Relationship to Presence of PE in Patients With DVT

Proximal DVT, DVT in the right leg and no symptoms of DVT were identified as independent of the presence of PE. Proximal DVT is often associated with acute PE![19–23] Embolic risk is low in calf-only DVT, but elevated in calf DVT with proximal (thigh) involvement![19] DVT in the right iliac vein is easily torn off and PE easily occurs because the right iliac vein is not compressed, unlike the left iliac vein. Most cases of DVT with no symptoms do not receive treatment and in such cases the DVT is found after PE occurs, which suggests that DVT showing few symptoms is a potential risk for PE. One of the candidate DVT is free-floating thrombi, but further study is needed to clarify this. Older patients with DVT have fewer symptoms and less incidence of PE; they may have fewer symptoms of PE and not be diagnosed as such, even if they have PE, but the real reason is unknown.

In the present study, the incidence of DVT was the same for the right and left legs in patients with PE, but multivariate logistic analysis revealed that DVT in the right leg was a risk for PE, because the left leg was prominent in all patients with DVT.

Diagnostic Techniques for DVT

Venous ultrasonography was used more frequently and CT less frequently in patients without PE than in patients with PE. Venous ultrasonography is noninvasive and convenient, and many diagnostic strategies for DVT use this method?[5,24] CT has been used more recently for the diagnosis of PE in recent years;[25] as its sensitivity for PE is not inferior to ventilation-perfusion lung scanning?[26] CT has the merit that DVT is diagnosed at the same time, so many doctors in Japan may choose venous ultrasonography as the initial diagnostic method in patients suspected of having DVT, and CT in patients suspected of having PE.

Management of VTE

Heparin and thrombolysis were used less frequently in patients with DVT alone. Chronic use of warfarin was more frequent in patients with DVT and PE. Moreover, warfarin was used first more frequently without heparin in cases of DVT alone.

Implantation of an inferior vena cava filter was more frequently performed in patients with DVT and PE. When limited to cases of DVT, inferior vena cava filters were more frequently used in proximal DVT with PE. Recurrence of PE in a patient with PE would increase mortality, so inferior vena cava filters are used to prevent recurrent PE in patients with both DVT and PE.

Incidence of VTE

The calculated number of new patients with PE per year was 3,492 cases in 1996[1] and 7,864 in 2006 in the present study. The calculated number of new patients with PE per year increased 2.25-fold in 1 decade in Japan. These results are similar to the prevalence of PE estimated by the Ministry of Health, Labour and Welfare in Japan (3,000 patients in 1996 and 7,000 in 2005)[27,28] The vital statistics were 1,410 deaths from PE in 1996, and 1,900 deaths in 2006[29,30] Annual deaths from PE increased 1.35-fold in 1 decade, which was lower than the increment of diagnostic patients during the same period.

The calculated number of new patients with DVT per year was 14,674 in 2006, which is similar to the prevalence reported in 2005 (16,000 cases[28]).

Study Limitations

One limitation of the present study is the low response rate. Response rates for questionnaires regarding less common diseases are low in general. The response rate in studies on the incidence of PE performed by us was 40.7% in 1996, 30.6% in 2000, 29.8% in 2004, and 26.8% in the present study.

Our results may be affected by the timing of the diagnosis and examination of VTE. Moreover, symptoms of PE may mask symptoms of DVT, despite this being a prospective study. Therefore, additional examinations are necessary to confirm the present results.

Conclusion

DVT in patients with and without PE differs in its site and symptoms. The calculated number of new patients with PE per year doubled over 1 decade in Japan.

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肺血栓塞栓症／深部静脈血栓症の院内発症予防ガイドライン公開後の評価ならびに改定と普及・推進に関する研究

主任研究者　中野　赳