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.

References

[1] Gomez A, Bialostozky D, Zajarias A, et al. Right ventricular ischemia in patients with primary pulmonary hypertension. J Am Coll Cardiol 2001;38:1137–42.
[2] Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001;37:183–8.
[3] Wilkins MR, Paul GA, Strange JW, et al. Sildenafil versus endothelin receptor antagonist for pulmonary hypertension (SERAPH) study. Am J Respir Crit Care Med 2005;171:1292–7.
[4] Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. Eur Respir J 2004;24:353–9.
[5] Gaynor SL, Maniar HS, Bloch JB, Steendijk P, Moon MR. Right atrial and ventricular adaptation to chronic right ventricular pressure overload. Circulation 2005;112:212–8.
[6] Leeuwenburgh BP, Steendijk P, Helbing WA, Baan J. Indexes of diastolic RV function: load dependence and changes after chronic RV pressure overload in lambs. Am J Physiol Heart Circ Physiol 2002;282:H1350–8.
[7] Parisi M, Galderisi M, Sidiropulos M, et al. Early detection of biventricular involvement in myotonic dystrophy by tissue Doppler. Int J Cardiol 2007;118:227–32.

[8] Karamitsos TD, Karvounis HI, Dalamanga EG, et al. Early diastolic impairment of diabetic heart: the significance of right ventricle. Int J Cardiol 2007;114:218–23.
[9] Vitarelli A, Conde Y, Cimino E, et al. Quantitative assessment of systolic and diastolic ventricular function with tissue Doppler imaging after Fontan type of operation. Int J Cardiol 2005;102:61–9.
[10] Schneider C, Bahlmann E, Malisius R, Hertting K, Antz M, Kuck KH. Tissue velocity imaging during dobutamine stimulation for assessment of myocardial viability: segmental analysis in patients after myocardial infarction. Int J Cardiol 2006;110:15–21.
[11] Dagdelen S, Yuce M, Emiroglu Y, et al. Correlation between the tissue Doppler, strain rate, strain imaging during the dobutamine infusion and coronary fractional flow reserve during catheterization: a comparative study. Int J Cardiol 2005;102:127–36.
[12] Gardiner HM, Pasquini L, Wolfenden J, et al. Myocardial tissue Doppler and long axis function in the fetal heart. Int J Cardiol 2006;113:39–47.
[13] Ogata H, Nakatani S, Ishikawa Y, et al. Myocardial strain changes in Duchenne muscular dystrophy without overt cardiomyopathy. Int J Cardiol 2007;115:190–5.
[14] Kyrzopoulos S, Adamopoulos S, Parissis JT, et al. Levosimendan reduces plasma B-type natriuretic peptide and interleukin 6, and improves central hemodynamics in severe heart failure patients. Int J Cardiol 2005;99:409–13.
[15] Talvani A, Rocha MO, Cogan J, et al. Brain natriuretic peptide measurement in Chagas heart disease: marker of ventricular dysfunction and arrhythmia. Int J Cardiol 2005;100:503–4.
[16] Ben Driss A, Tabet JY, Meurin P, et al. Role of B-type natriuretic peptide and echocardiographic indices in predicting the development of acute heart failure following beta-blocker uptitration in chronic heart failure patients with left ventricular systolic dysfunction. Int J Cardiol 2007;115:257–8.
[17] Hammerer-Lercher A, Pölzl G, Falkensammer G, et al. B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide are comparably useful for disease monitoring in heart failure. Int J Cardiol 2006;106:415–7.
[18] Thomas MD, Fox KF, Coats AJ. Redefining heart failure. Int J Cardiol 2006;112:139–41.
[19] Hogenhuis J, Jaarsma T, Voors AA, Hillege HL, Lesman I, van Veldhuisen DJ. Correlates of B-type natriuretic peptide and 6-min walk in heart failure patients. Int J Cardiol 2006;108:63–7.
[20] Conen D, Jander N, Trenk D, Neumann FJ, Mueller C. The use of B-type natriuretic peptides in the detection of myocardial ischemia in settings with rapid access to coronary angiography. Int J Cardiol 2007;119:416–8.
[21] Vorlat A, Claeys MJ, Bosmans JM, Van Hoof V, Vrints CJ. B-type natriuretic peptide and assessment of jeopardised myocardium in acute myocardial infarction. Int J Cardiol 2007;114:46–9.
[22] Falkensammer G, Lechleitner P, Hammerer-Lercher A, Theurl A, Puschendorf B, Mair J. B-type natriuretic peptide and N-terminal pro brain natriuretic peptide are related to systolic and diastolic left ventricular function assessed by radionuclide ventriculography. Int J Cardiol 2005;105:340–1.
[23] Kruger S, Graf J, Merx MW, et al. Brain natriuretic peptide predicts right heart failure in patients with acute pulmonary embolism. Am Heart J 2004;147:60–5.
[24] Tulevski II, ten Wolde M, van Veldhuisen DJ, et al. Combined utility of brain natriuretic peptide and cardiac troponin T may improve rapid triage and risk stratification in normotensive patients with pulmonary embolism. Int J Cardiol 2007;116:161–6.
[25] Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 2000;102:865–70.
[26] Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. Am J Cardiol 1990;66:493–6.
[27] Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386–9.
[28] Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993;341:507–11.
[29] Urokinase pulmonary Embolism Trial (UPET). Urokinase pulmonary embolism trial. Phase 1 results: a cooperative study. JAMA 1970;214: 2163–72.
[30] Hsiao SH, Lee CY, Chang SM, Yang SH, Lin SK, Huang WC. Pulmonary embolism and right heart function: insights from myocardial Doppler tissue imaging. J Am Soc Echocardiogr 2006;19:822–8.
[31] Yeo TC, Dujardin KS, Tei C, Mahoney DW, McGoon MD, Seward JB. Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. Am J Cardiol 1998;81:1157–61.
[32] Gin PL, Wang WC, Yang SH, Hsiao SH, Tseng JC. Right heart function in systemic lupus erythematosus: insights from myocardial Doppler tissue imaging. J Am Soc Echocardiogr 2006;19:441–9.
[33] Pacileo G, Paladini D, Russo MG, Pisacane C, Santoro G, Calabro R. Echocardiographic assessment of ventricular filling pressure during the second and third trimesters of gestation. Ultrasound Obstet Gynecol 2000;16:128–32.
[34] Aoki M, Harada K, Ogawa M, Tanaka T. Quantitative assessment of right ventricular function using Doppler tissue imaging in fetuses with and without heart failure. J Am Soc Echocardiogr 2004;17:28–35.
[35] Nageh MF, Kopelen HA, Zoghbi WA, Quinones MA, Nagueh SF. Estimation of mean right atrial pressure using tissue Doppler imaging. Am J Cardiol 1999;84:1448–51.
[36] Boissiere J, Gautier M, Machet MC, Hanton G, Bonnet P, Eder V. Doppler tissue imaging in assessment of pulmonary hypertension-induced right ventricle dysfunction. Am J Physiol Heart Circ Physiol 2005;289:H2450–5.
[37] Yap LB. B-type natriuretic peptide and the right heart. Heart Fail Rev 2004;9:99–105.
[38] Ishii J, Nomura M, Ito M, et al. Plasma concentration of brain natriuretic peptide as a biochemical marker for the evaluation of right ventricular overload and mortality in chronic respiratory disease. Clin Chim Acta 2000;301:19–30.
[39] Hama N, Itoh H, Shirakami G, et al. Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. Circulation 1995;92:1558–64.
[40] Doyama K, Fukumoto M, Takemura G, et al. Expression and distribution of brain natriuretic peptide in human right atria. J Am Coll Cardiol 1998;32:1832–8.
[41] Mukoyama M, Nakao K, Hosoda K, et al. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest 1991;87:1402–12.
[42] Montorsi P, Tonolo G, Polonia J, Hepburn D, Richards AM. Correlates of plasma atrial natriuretic factor in health and hypertension. Hypertension 1987;10:570–6.
[43] Tongers J, Schwerdtfeger B, Klein G, et al. Incidence and clinical relevance of supraventricular tachyarrhythmias in pulmonary hypertension. Am Heart J 2007;153:127–32.

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.

(Received April 16, 2008; revised manuscript received August 21, 2008; accepted September 11, 2008; released online December 18, 2008)
*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.

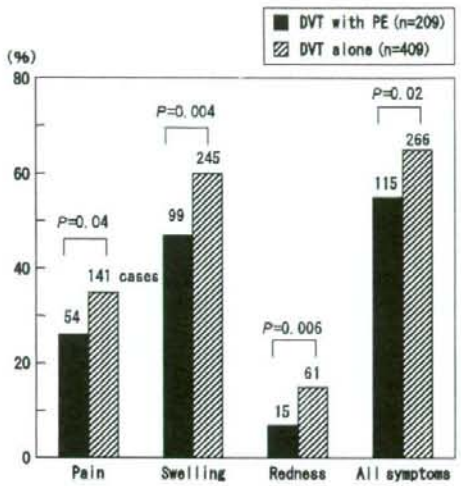

Fig 1. Symptoms of deep vein thrombosis (DVT). The number of cases is shown on each bar. PE, pulmonary embolism.

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

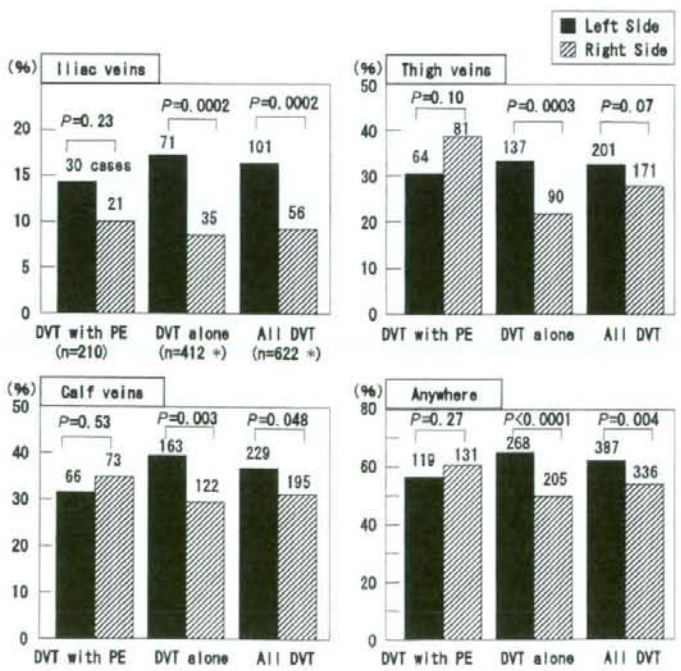

Fig 2. Location of deep vein thrombosis (DVT). The number of cases is shown on each bar. *Seven cases with DVT only in the upper extremities and one without data on DVT site were excluded. PE, pulmonary embolism.

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.

Acknowledgment

This study was partly supported by a grant from the Japanese Ministry of Health, Labor and Welfare for Blood Coagulation Abnormalities.

References

1. Kumasaka N, Sakuma M, Shirato K. Incidence of pulmonary thromboembolism in Japan. *Jpn Circ J* 1999; **63:** 439–441.
2. Kitamukai O, Sakuma M, Takahashi T, Kagaya Y, Watanabe J, Shirato K. Incidence and characteristics of pulmonary thromboembolism in Japan 2000. *Intern Med* 2003; **42:** 1090–1094.
3. Sugimura K, Sakuma M, Shirato K. Potential risk factors and incidence of pulmonary thromboembolism in Japan: Results from an overview of mailed questionnaires and matched case-control study. *Circ J* 2006; **70:** 542–547.
4. Editorial Committee on Japanese Guideline for Prevention of Venous Thromboembolism. Japanese Guideline for Prevention of Venous Thromboembolism. Medical Front International Ltd, Tokyo, 2004 (in Japanese).
5. The Japanese Circulation Society. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2004). *Circ J* 2004; **68**(Suppl): IV-1079–IV-1134 (in Japanese).
6. Nicolaides A, Breddin H, Fareed J, Goldhaber S, Haas S, Hull R, et al. Prevention of venous thromboembolism: International Consensus Statement: Guidelines compiled in accordance with the scientific evidence. *Int Angiol* 2001; **20:** 1–37.
7. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism. *Arch Intern Med* 1999; **159:** 445–453.
8. Quinn DA, Thompson BT, Terrin ML, Thrall JH, Athanasoulis CA, McKusick KA, et al. A prospective investigation of pulmonary embolism in women and men. *JAMA* 1992; **268:** 1689–1696.
9. Cogo A, Lensing AW, Prandoni P, Hirsh J. Distribution of thrombosis in patients with symptomatic deep vein thrombosis: Implications for simplifying the diagnostic process with compression ultrasound. *Arch Intern Med* 1993; **153:** 2777–2780.
10. Nylander G, Olivercrona H. The phlebographic pattern of acute leg thrombosis within a defined urban population. *Acta Chir Scand* 1976; **142:** 505–511.
11. Stamatakis JD, Kakkar VV, Lawrence D, Bentley PG. The origin of thrombi in the deep veins of the lower limb: A venographic study. *Br J Surg* 1987; **65:** 449–451.
12. Nicolaides AN, Kakkar VV, Field ES, Renney JT. The origin of deep vein thrombosis: A venographic study. *Br J Radiol* 1971; **44:** 653–663.
13. Ouriel K, Green RM, Greenberg RK, Clair DG. The anatomy of deep venous thrombosis of the lower extremity. *J Vasc Surg* 2000; **31:** 895–900.
14. Norris CS, Greenfield LJ, Herrmann JB. Free-floating ileofemoral thrombus: A risk of pulmonary embolism. *Arch Surg* 1985; **120:** 806–808.
15. Baldridge ED, Martin MA, Welling RE. Clinical significance of free-floating venous thrombi. *J Vasc Surg* 1990; **11:** 62–67.
16. Markel A, Manzo RA, Bergelin RO, Strandness ED Jr. Pattern and distribution of thrombi in acute venous thrombosis. *Arch Surg* 1992; **127:** 305–309.
17. Kearon C. Natural history of venous thromboembolism. *Circulation* 2003; **107**(Suppl): I-22–I-30.
18. Hill SL, Holtzman GI, Martin D, Evans P, Toler W, Goad K. The origin of lower extremity deep vein thrombi in acute venous thrombosis. *Am J Surg* 1997; **173:** 485–490.
19. Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis? *Ann Intern Med* 1981; **94:** 439–444.
20. Ferris EJ. Peripheral deep venous thrombosis and pulmonary thromboembolism: Correlative diagnostic evaluation. *Int Angiol* 1983; **2:** 85–98.
21. Dorfman GS, Cronan JJ, Tupper TB, Messersmith RN, Denny DF, Lee CH. Occult pulmonary embolism: A common occurrence in deep vein thrombosis. *Am J Roentgenol* 1987; **148:** 263–266.
22. Hiusman MV, Buller HR, ten Cate JW, van Roven EA, Vreeken J, Kersten MJ, et al. Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. *Chest* 1989; **95:** 498–502.
23. Monreal M, Ruiz J, Olazabal A, Arias A, Roca J. Deep venous thrombosis and the risk of pulmonary embolism: A systematic study. *Chest* 1992; **102:** 677–681.
24. Zieler BK. Ultrasonography and diagnosis of venous thromboembolism. *Circulation* 2004; **109**(Suppl): I-9–I-14.
25. Sakuma M, Okada O, Nakamura M, Nakanishi N, Miyahara Y, Yamada N, et al. Recent developments in diagnostic imaging techniques and management for acute pulmonary embolism: Multicenter registry by the Japanese Society of Pulmonary Embolism Research. *Intern Med* 2003; **42:** 470–476.
26. Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. *JAMA* 2007; **298:** 2743–2753.
27. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. Patient survey 1996. Tokyo, 1998.
28. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. Patient survey 2005. Tokyo, 2007.
29. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor and Welfare. Vital statistics of Japan 1996. Tokyo, 2008.
30. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor and Welfare. Vital statistics of Japan 2006. Tokyo, 2008.

平成十九～二十年度　厚生労働科学研究費補助金　地域医療基盤開発推進研究事業

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