A 56-year-old man was referred to our hospital because of an abnormality on his 12-lead electrocardiography. He was able to exercise regularly without any symptoms. The 12-lead electrocardiography demonstrated poor R progression and negative T waves in leads V_{4-6}. Echocardiography demonstrated preserved systolic function (left ventricular ejection fraction 56%), but the anterior-septal wall motion was mildly reduced. There was no valvular heart disease. A coronary angiography and a coronary multislice computed tomography (Aquilion 64, Toshiba, Tokyo, Japan)[1,2] revealed an anomalous origin of the left anterior descending artery (LAD) from the pulmonary artery. The markedly dilated right coronary artery (RCA) and the left circumflex artery (LCX), originating from the normal sinus of Valsalva, supplied the LAD through an abundance of prominent collaterals (Figure A Left, B). A right heart catheterization demonstrated a left-to-right shunt, with oxygen step-up (4%) between the right ventricular outflow tract and the pulmonary artery. The pulmonary/systemic flow ratio (Qp/Qs) was estimated to be 1.20. Myocardial perfusion scintigraphy (Multispect 3, Siemens Medical Systems, Chicago IL, USA)[3] with 99mTc-sestamibi showed a decreased uptake from the anterior-septal lesion to the apex (Figure C Upper). Surgical correction was performed by bypassing the LAD and ligation of the anomalous origin (Figure A Right). Postoperative myocardial scintigraphy showed recovery of myocardial perfusion in the LAD territory (Figure C Lower). Although the patient has been well during the 6-month follow-up period, improvement of electrocardiographic abnormality and mildly reduced wall motion was still insufficient. Therefore, 2.5 mg/day of enalapril was continued to promote left ventricular reverse remodeling.

An anomalous origin of the left coronary artery arising from the pulmonary artery is a rare congenital abnormality affecting 1 in 300,000 live births, and accounts for 0.5% of cases of congenital heart disease. Hypoperfusion occurs as pulmonary arterial pressure diminishes after birth and flow in the left coronary artery reverses. Perfusion of the anterior wall is therefore dependent on the development of collaterals from the RCA. If surgical correction is not performed, approximately 80–90% of affected infants will die due to heart failure or sudden cardiac death during the first year of life.[4,5]

The chronic phase of this malformation is characterized by considerable risk of death due to chronic myocardial ischemia and/or sudden death. Survival to adulthood is unusual, and patients older than 50 years are rare.[6,7] Previously, only one elderly Bland–White–Garland syndrome patient without any symptoms was reported by Ichikawa et al.[8] Surgical repair was not performed on that patient. In the present case, the LCX arose from the left sinus of Valsalva; thus perfusion of the lateral wall was preserved before surgical correction. Sufficient collateral flow from the RCA and LCX to the LAD and minimal coronary steal into the pulmonary artery might have masked symptoms in this patient. Fortunately, mitral valve function was also preserved. However, myocardial perfusion imaging clearly demonstrated serious myocardial ischemia from the anterior-septal wall to the apex of the left ventricle.

Currently, surgical intervention immediately after diagnosis, with the aim of repairing the abnormal coronary circulation system, is considered the appropriate treatment for Bland–White–Garland syndrome.[9] Improvement of left ventricular function after successful re-establishment of the coronary circulation has been consistently documented.[10] In consistent with previous reports, recovery of myocardial perfusion in the LAD territory was confirmed in the present case after bypass of the LAD and ligation of the anomalous origin.

Although asymptomatic Bland–White–Garland syndrome is rare presentation in adulthood, especially in patients greater than 50 years of age, awareness of this congenital abnormality is important. Surgical correction should be considered even in asymptomatic patients, so as to prevent irreversible damage to the myocardium and subsequent complications, including severe heart failure and sudden death.

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Original Article

Trends in Coronary Risk Factors Among Patients with Acute Myocardial Infarction Over the Last Decade: The Yamagata AMI Registry

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Aim: Recently, there has been an increase in the prevalence of coronary risk factors, such as diabetes and dyslipidemia, in Japan; however, it is unclear whether this has resulted in an increased incidence of acute myocardial infarction (AMI). We investigated the relationship between risk factors changes and AMI incidence in a Japanese population.

Methods: Trends in AMI incidence (per 100,000 person-years) were examined using data from the Yamagata AMI Registry from 1993 to 2007. We included 6,222 patients with a first-ever AMI (4175 men). The prevalence of coronary risk factors was investigated in three age groups of AMI patients (<65, 65-74, and ≥75 years) for the periods 1993-1997, 1998-2002, and 2003-2007. Coronary risk factors were further compared between recently registered AMI patients and 2,400 age-matched controls.

Results: The age-adjusted incidence of AMI increased significantly in men, but not in women. Younger men particularly showed a significant increase in the incidence of AMI. The prevalence of hypertension and diabetes increased in both genders; however, the prevalence of treatment for risk factors was significantly lower in men than women. Younger men showed significant increases in obesity and hypertriglyceridemia. Consequently, risk factors associated with the metabolic syndrome had accumulated among younger men. We revealed that hypertension, diabetes, hypercholesterolemia and current smoking were independent risk factors for AMI.

Conclusions: The incidence rate for AMI increased significantly in men, especially younger men. Preventive care for risk factors associated with metabolic syndrome, in addition to conventional risk factors, may be required in younger men.

J Atheroscler Thromb, 2010; 17:989-998.

Key words; Acute myocardial infarction, Coronary risk factor, Metabolic syndrome

Introduction

Coronary heart disease (CHD) is a major cause of death in developed countries[1]. Mortality due to acute myocardial infarction (AMI) is much lower in Japan than in Western countries[2, 3], and has decreased further with advances in treatment[4, 5]. However, recently, the prevalence of AMI has increased in Japan, and AMI is therefore becoming one of the most important causes of death[6]. The Hisayama study, a community-based cohort study, previously revealed that the age-adjusted incidence of AMI had not

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Received: December 10, 2009
Accepted for publication: April 7, 2010

changed[7]; however, a recent AMI registry study from 1990 to 2001 reported that the age-adjusted incidence of AMI had increased by 7-8% annually[8].

Previous studies indicated differences in coronary risk factors between Western and Asian countries[9-11]. A recent Japanese case-control study showed that hypercholesterolemia was an independent coronary risk factor in men, but not in women, and that obesity was not associated with AMI[12]; however, there have been marked increases in the prevalence of obesity, diabetes mellitus and hypercholesterolemia[7, 13], due to the westernization of dietary habits in Japan[14-17]. Furthermore, metabolic syndrome has gained attention as a novel cardiovascular risk factor[18-24], and its prevalence is also reported to have increased in Japan[25]. At present, there is little information on the relationship between recent changes in coronary risk factors and the incidence of AMI in Japan. In the present study, we investigated the trends in coronary risk factors among patients with a first-ever AMI who were registered between 1993 and 2007. The prevalence of risk factors was further compared between recently registered AMI patients and an age-matched general population.

Methods

Study Population

Yamagata Prefecture is located in the northern part of the main island of Japan. In the 2005 census, the population was 1,216,000 and the proportion of people ≥65 years old was higher than the average for Japan (25.5% vs. 20.1%). Since 1993, a multicenter project on the surveillance of AMI has been conducted as the Yamagata AMI Registry[5, 26, 27]. The clinical characteristics of AMI patients admitted to all hospitals belonging to the Yamagata Medical Association between 1993 and 2007 were investigated. A diagnosis of AMI required that the "definite criteria of AMI", as described in the World Health Organization MONICA Project[1], be satisfied. Of the 6,957 consecutive patients who were registered in Yamagata Prefecture from 1993 to 2007, 6,222 patients with a first-ever AMI were included in the present study. The observation period of 15 years was sub-divided into three intervals, 1993-1997 (n=1,827), 1998-2002, (n=1,999) and 2003-2007 (n=2,396). In addition, the enrolled patients were categorized into three groups by age at onset of AMI (younger, <65 years old; early elderly, 65-74 years old; late elderly, ≥75 years old).

Data Collection

Standard data were collected prospectively and entered into a computer database. These data included details of clinical presentation (age, gender, date and time of onset of AMI, time of admission to hospital), personal and family medical history, as well as coronary risk factors. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Obesity was defined as BMI ≥25 kg/m^2 for both genders. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or current use of antihypertensive drugs. Hypercholesterolemia was defined as a serum total cholesterol concentration ≥220 mg/dL and/or current use of lipid-lowering drugs. Diabetes mellitus was defined as a fasting blood glucose concentration ≥126 mg/dL, a non-fasting blood glucose concentration ≥200 mg/dL, and/or the use of antidiabetic drugs (any oral hypoglycemic agent or insulin). A family history of CHD and current cigarette smoking status were verified by a self-reported questionnaire and by interviewing the family.

Fasting blood samples were obtained during hospitalization. Low-density lipoprotein (LDL) cholesterol concentrations were calculated using the Friedwald formula when the triglyceride concentration was 400 mg/dL or less. Hypertriglyceridemia was defined as a triglyceride concentration ≥150 mg/dL and low high-density lipoprotein (HDL) cholesterol was defined as a HDL cholesterol concentration <40 mg/dL if male or <50 mg/dL if female. Metabolic syndrome was defined according to the modified National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines and criteria[28]. Patients were deemed to have metabolic syndrome if three or more of the following five criteria were satisfied: obesity, hypertriglyceridemia, low HDL cholesterolemia, high blood pressure, and high fasting glucose, as previously reported[29]. In this study, BMI was used to define obesity because waist circumference measurements were not available.

Statistical Analysis

To calculate the incidence rates for AMI per 100,000 person-years during the three time intervals, the annual population of Yamagata Prefecture was used as the denominator. To adjust for patient age, the Japanese population, as determined by the 2005 census, was used as the standard population. In addition, a case-control study was performed, comparing coronary risk factors during 2003-2007 between AMI patients and 2,400 age-matched control subjects who were enrolled in the Takahata study in 2005. The Takahata study has been described in detail elsewhere[29, 30]. To adjust for the age of subjects, we used standardized incidence ratios.

Table 1. Clinical characteristics of the study population

	Men				Women			
	1st (93'-97') n=1,202	2nd (98'-02') n=1,322	3rd (03'-07') n=1,651	p value for trend	1st (93'-97') n=625	2nd (98'-02') n=677	3rd (03'-07') n=745	p value for trend
Age (years)	65.8±12.5	66.5±12.2	67.1±12.8*	0.0253	73.9±10.2	74.8±11.1	76.8±10.8**††	<0.0001
Number of AMI (/year)	240.4±8.5	264.4±33.8	330.2±28.1**††	0.0004	125.0±10.4	135.4±18.6	149.0±16.9	0.0902
Age-adjusted incidence rates for AMI (/10^5 person-years)	42.7±1.0	42.5±5.0	50.1±3.8*†	0.0099	20.7±2.3	19.5±2.0	18.9±1.8	0.4352
Incidence rates for AMI (/10^5 person-years)								
<64 years old	19.3±1.2	21.1±4.4	28.5±2.6**††	0.0011	3.9±0.8	4.1±0.9	3.9±0.3	0.8842
65-74 years old	125.2±7.8	127.5±9.0	132.2±15.7	0.6238	47.5±11.8	41.6±4.5	39.8±4.5	0.2965
>75 years old	172.8±18.8	157.6±27.3	189.8±28.9	0.1755	105.0±12.6	98.9±12.8	98.4±13.0	0.6736
Coronary risk factors and treatment Obesity, BMI ≥25 (%)	26.1	27.8	31.6**†	0.0124	27.4	24.6	29.2	0.2760
Hypertension (%)	51.0	54.2	58.3**†	0.0008	60.7	62.6	69.2**†	0.0037
Receiving medication (%)	85.3	84.5	85.9	0.7285	91.8	94.2	93.8	0.3933
Diabetes mellitus (%)	20.6	24.6*	30.3**††	<0.0001	24.0	32.4**	33.0**	0.0009
Receiving medication (%)	54.1	58.0	65.1**	0.0159	73.0	78.9	78.4	0.4087
Hypercholesterolemia (%)	32.2	29.1	34.6††	0.0085	35.2	35.0	39.1	0.2299
Receiving medication (%)	45.6	38.2	46.8†	0.0582	51.9	50.0	59.3	0.1555
Family history (%)	25.4	22.6	15.5**††	<0.0001	18.1	20.5	10.8**††	0.0007
Current smoker (%)	60.2	56.8	55.4*	0.0517	10.3	10.0	8.9	0.6963

$^{*}p<0.05$, $^{**}p<0.01$ compared with the 1st period; $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$ compared with the 2nd period.
AMI, acute myocardial infarction; BMI, body mass index.
Incidence rates were age-adjusted to the Japanese population using data from the 2005 census.

Categorical variables were analyzed using the chi-square test. Continuous variables are presented as the means ± SD. Differences among groups were analyzed by analysis of variance (ANOVA) with the Scheffe post hoc test. Multivariate logistic regression analysis was used to evaluate the relationship between coronary risk factors and the development of AMI. A value of $p<0.05$ was considered significant.

Results

The clinical characteristics of the 6,222 patients enrolled in the study are summarized in **Table 1**. The female patients were, on average, about 10 years older than the male patients, and the age at onset of AMI was also significantly higher in female patients. There were increases in the numbers of male patients and in the age-adjusted incidence rate of AMI among male patients. Although the incidence rate of AMI increased with advancing age, it was not increased in elderly patients during the three time periods; in contrast, there was a significant increase among younger male patients.

As shown in the lower panel of **Table 1**, significant increases in the prevalence of hypertension and diabetes mellitus were observed in both genders. In contrast, there were significant increases in the prevalence of obesity and hypercholesterolemia among males, but not among females. A decrease in the proportion of AMI patients with a family history was observed in both genders during the third period (2003-2007) (**Table 1**). While the prevalence of treatment for hypertension was relatively high in both genders, the prevalence of the control of diabetes and hypercholesterolemia was still insufficient (**Table 1**). In males, the prevalence of treatment for each risk factor was approximately 10% lower than in females. Despite decreases in the proportion of current smokers among male patients, the proportion of male smokers was about six times greater than the proportion of female smokers (**Table 1**).

To evaluate the prevalence of coronary risk factors among AMI patients, the prevalence of each risk factor was compared between AMI patients during the third period (2003-2007) and the Japanese general population. AMI patients had a higher prevalence of

Table 2. Comparison of clinical risk factors between patients with AMI in the third period (2003–2007) and age-adjusted control subjects

	Men					Women				
	3rd (03'-07') n=1,651	Takahata n=1,054	odds ratio	95% CI	p value	3rd (03'-07') n=745	Takahata n=1,346	odds ratio	95% CI	p value
Obesity, BMI ≥25 (%)	31.6	28.7	1.15	0.96-1.37	0.1235	29.2	30.9	0.92	0.73-1.15	0.4735
Hypertension (%)	58.3	47.2	1.56	1.33-1.83	<0.0001	69.2	46.0	2.63	2.17-3.19	<0.0001
Diabetes mellitus (%)	30.3	9.1	4.34	3.42-5.49	<0.0001	33.0	6.0	7.65	5.81-10.06	<0.0001
Hypercholesterolemia (%)	34.6	22.1	1.87	1.56-2.23	<0.0001	39.1	33.2	1.29	1.06-1.57	0.0091
Current smoking (%)	55.4	31.3	2.73	2.31-3.22	<0.0001	8.9	1.6	6.26	3.76-10.42	<0.0001
Multivariate analysis										
Hypertension (%)			1.32	1.10-1.60	0.0035			2.13	1.64-2.77	<0.0001
Diabetes mellitus (%)			4.02	3.06-5.29	<0.0001			6.77	4.67-9.80	<0.0001
Hypercholesterolemia (%)			1.64	1.33-2.02	<0.0001			0.95	0.73-1.24	0.7148
Current smoking (%)			3.25	2.66-3.96	<0.0001			7.57	4.33-13.24	<0.0001

Age-adjusted control subjects were enrolled in the Takahata study in 2005.
Multivariate logistic regression analysis adjusted for patient age.

hypertension, diabetes, hypercholesterolemia and current smoking than age-adjusted control subjects enrolled in the Takahata study (**Table 2**). The odds ratios for diabetes and current smoking were especially high among women. Although obesity (BMI ≥25) increased among male patients during the third period, obesity was not a significant risk factor either in males or females. In multivariate logistic regression analysis adjusted for patient age, hypertension, diabetes, and current smoking were independent risk factors for AMI in both genders. Hypercholesterolemia was an independent risk factor for AMI among men, but not among women.

Surprisingly, more than 70% of younger male patients were current smokers, and the proportion of smokers was unchanged, except among early elderly men (**Fig. 1**). Younger female patients were also more likely to be smokers than elderly female patients. Younger male patients showed increases in the prevalence of hypertension and diabetes, increases in BMI and a decrease in the proportion with a family history of MI. Younger male patients showed a greater increase in triglyceride levels, while HDL and LDL cholesterol levels were unchanged. An increase in the prevalence of diabetes was observed for most patients, except younger female patients.

As shown in **Fig. 1**, younger men showed significant increases in the prevalence of hypertension and diabetes, as well as in BMI and triglyceride levels during the third period (2003–2007). Consequently, the number of risk factors associated with metabolic syndrome increased among younger and early elderly men (**Table 3**). In contrast, there was no significant change in the number of risk factors among women.

The prevalence of risk factors associated with metabolic syndrome was compared within each age group, between AMI patients during the third period (2003–2007) and the Japanese general population. Early elderly male patients had a higher prevalence of hypertension, diabetes, and low HDL cholesterolemia than control subjects (**Table 4**); however, younger male patients had a higher prevalence of all coronary risk factors associated with metabolic syndrome than control subjects. Multivariate regression analysis revealed that hypertension, diabetes and low HDL cholesterolemia were independent risk factors for AMI among younger and early elderly men. Further, BMI was an independent risk factor for AMI among younger men, but not among early elderly men. In contrast, BMI was not an independent risk factor for AMI among younger and early elderly women (**Table 5**). Younger male patients showed a significant increase in serum triglyceride levels and the prevalence of obesity during the third period. In addition, male patients with AMI aged <40 years showed significant increases in BMI (**Fig. 2**) and the prevalence of obesity (1st, 37%; 2nd, 62%; 3rd, 68%, respectively, $p<0.05$). Consequently, there was an accumulation of risk factors associated with metabolic syndrome among younger men. Furthermore, there were differences between younger and early elderly male patients in the proportion receiving medical treatment. **Fig. 3** demonstrates that the prevalence of treatment for hypertension and diabetes was significantly lower among younger men and, in contrast to the changes observed for elderly patients, this did not improve at all during the three time periods.

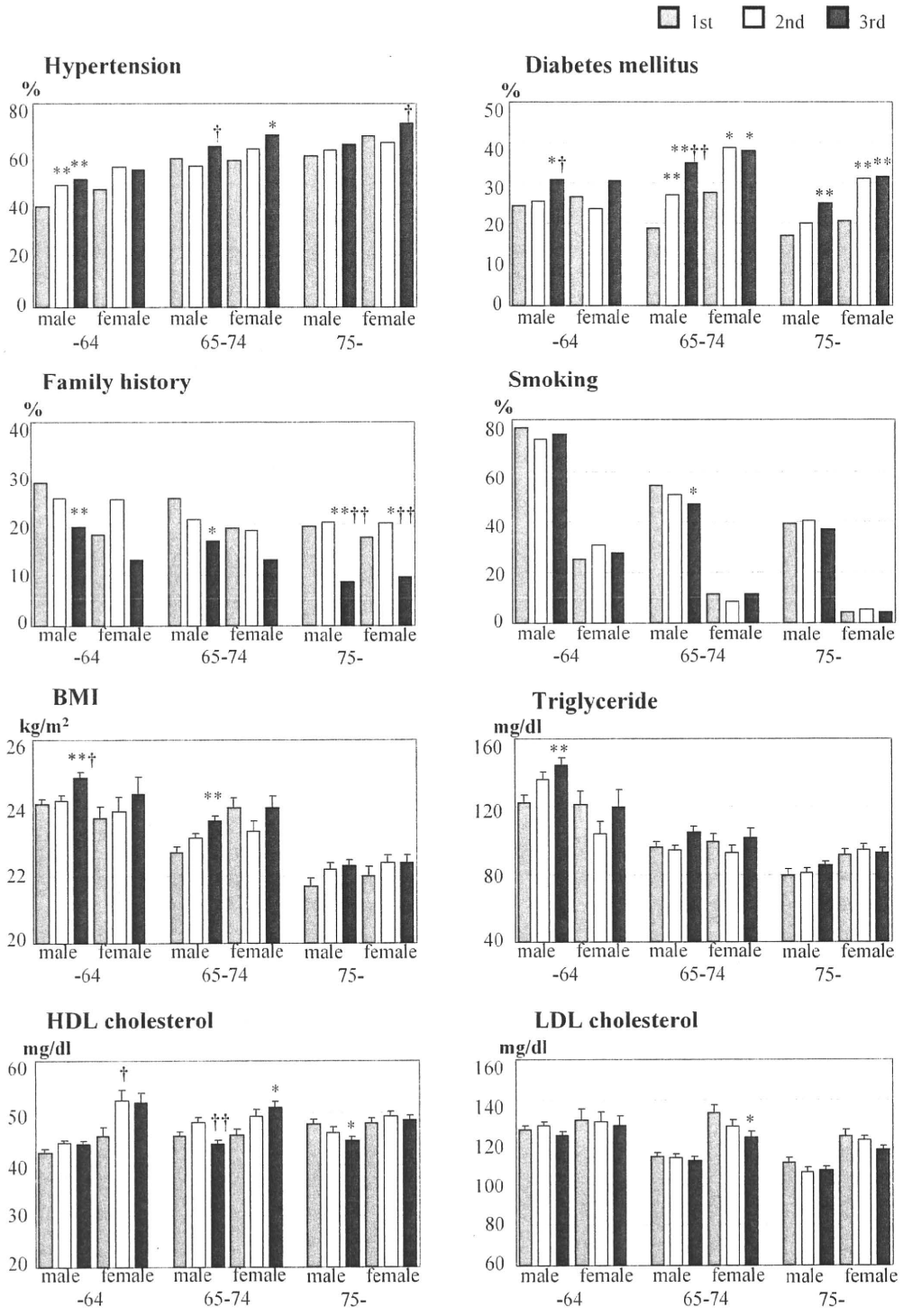

Fig. 1. Trends in coronary risk factors and lipid profiles among AMI patients.

Bars indicate the prevalence of coronary risk factors and the lipid profiles during hospitalization in the three age groups (<65, 65-74, ≥75 years old), for both genders, during the three time periods. Continuous variables are presented as the mean ± SE. $^{*}p<0.05$, $^{**}p<0.01$ compared with 1st period; $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$ compared with 2nd period.

Table 3. Trends in the number of risk factors associated with metabolic syndrome

	1st (93'-97')	2nd (98'-02')	3rd (03'-07')	*p* value for trend
Men	1.60±1.18	1.74±1.19	1.87±1.19**	<0.0001
<64 years old	1.71±1.23	1.97±1.24*	2.02±1.26**	0.0017
65-74 years old	1.54±1.17	1.57±1.14	1.94±1.13**††	<0.0001
>75 years old	1.42±1.05	1.58±1.09	1.56±1.08	0.4022
Women	2.04±1.10	2.08±1.14	2.12±1.20	0.6639
<64 years old	2.02±1.07	1.93±1.09	1.98±1.29	0.9013
65-74 years old	2.13±1.09	2.07±1.20	2.15±1.27	0.8721
>75 years old	1.96±1.13	2.14±1.13	2.14±1.15	0.3688

*$p<0.05$, **$p<0.01$ compared with 1st period; †$p<0.05$ compared with 2nd period.

Table 4. Comparison of risk factors associated with metabolic syndrome between younger and early elderly male patients with AMI during the third period (2003-2007) and control subjects

	Younger men					Early elderly men				
	3rd (03'-07') (*n*=653) 54.1±7.9y	Takahata (*n*=491) 54.9±6.4y	odds ratio	95% CI	*p* value	3rd (03'-07') (*n*=461) 69.6±2.8y	Takahata (*n*=394) 69.4±2.8y	odds ratio	95% CI	*p* value
Univariate analysis										
BMI (kg/m²)‡	24.9±3.5	23.6±3.0	1.50	1.29-1.68	<0.0001	23.6±2.9	23.5±2.9	1.06	0.92-1.22	0.4606
Hypertension (%)	50.4	40.6	1.49	1.15-1.92	0.0022	63.4	55.4	1.40	1.04-1.87	0.0244
Diabetes mellitus (%)	31.1	7.5	5.54	3.81-8.06	<0.0001	35.2	10.7	4.55	3.12-6.63	<0.0001
Hypertriglyceridemia (%)	34.8	27.1	1.44	1.10-1.87	0.0070	16.4	16.5	0.99	0.68-1.45	0.9572
Low HDL cholesterolemia (%)	36.4	11.4	4.44	3.20-6.16	<0.0001	38.4	10.4	5.37	3.65-7.90	<0.0001
Metabolic syndrome (%)	35.2	11.8	4.05	2.90-5.65	<0.0001	31.5	9.9	4.18	2.78-6.30	<0.0001
Multivariate analysis										
BMI (kg/m²)‡			1.23	1.04-1.45	0.0140					
Hypertension (%)			1.36	1.00-1.84	0.0474			1.41	1.01-1.96	0.0432
Diabetes mellitus (%)			5.27	3.37-8.24	<0.0001			4.13	2.68-6.36	<0.0001
Hypertriglyceridemia (%)			0.79	0.56-1.10	0.1646					
Low HDL cholesterolemia (%)			4.11	2.80-6.04	<0.0001			5.44	3.58-8.28	<0.0001

BMI, body mass index; HDL, high density lipoprotein
‡Data represent odds ratio corresponding to 1SD increase in BMI level

Discussion

The present study showed that the age-adjusted incidence of AMI increased in male patients. Younger men in particular showed a significant increase in the incidence of AMI during 2003-2007. In contrast, there was no increase in the incidence of AMI among females during the observation periods. There was a significant increase in the prevalence of metabolic syndrome among younger male patients compared with other age groups, as well as a greater increase in the number of risk factors associated with metabolic syndrome. These results suggested that an increase in the prevalence of risk factors associated with metabolic syndrome may be related to the increased incidence rate for AMI among younger men.

Increased Incidence of AMI Among Male Patients

An increased number of AMI was observed among male patients (**Table 1**). In contrast, the number of AMI did not increase and the age at onset increased significantly among women. There was no significant change in the age-adjusted incidence rate of AMI among women in the present study, which is consistent with the findings of the Hisayama study[7]. Another AMI registry study reported that the age-adjusted incidence rate increased by 7.6% among men and by 8.3% among women, between 1990 and 2001[8]. In contrast, the present study demonstrated that the age-adjusted incidence rate for AMI increased

Table 5. Comparison of risk factors associated with metabolic syndrome between younger and early elderly female patients with AMI during the third period (2003-2007) and control subjects

	Younger women					Early elderly women				
	3rd (03'-07') (n=87) 54.1±7.9y	Takahata (n=692) 54.9±6.4y	odds ratio	95% CI	p value	3rd (03'-07') (n=168) 69.6±2.8y	Takahata (n=479) 69.4±2.8y	odds ratio	95% CI	p value
Univariate analysis										
BMI (kg/m^2)*	24.4±4.2	23.4±3.5	1.07	1.01-1.15	0.0307	24.0±3.8	24.1±3.3	0.99	0.38-1.05	0.8321
Hypertension (%)	54.1	29.7	2.80	1.76-4.44	<0.0001	67.9	50.1	2.11	1.43-3.09	0.0001
Diabetes mellitus (%)	30.6	4.3	9.72	5.40-17.52	<0.0001	38.2	6.1	9.58	5.87-15.64	<0.0001
Hypertriglyceridemia (%)	15.3	12.3	1.29	0.65-2.55	0.4667	19.1	15.9	1.25	0.76-2.06	0.3807
Low HDL cholesterolemia (%)	50.7	18.1	4.67	2.80-7.78	<0.0001	49.2	22.3	3.37	2.24-5.07	<0.0001
Metabolic syndrome (%)	39.7	6.9	8.83	4.92-15.83	<0.0001	43.4	14.6	4.47	2.85-7.02	<0.0001
Multivariate analysis										
BMI (kg/m^2)*			1.00	0.92-1.09	0.9786					
Hypertension (%)			2.14	1.17-3.90	0.0131			1.82	1.14-2.90	0.0118
Diabetes mellitus (%)			6.92	3.14-15.28	<0.0001			7.19	4.11-12.55	<0.0001
Low HDL cholesterolemia (%)			2.35	1.23-4.49	0.0099			2.91	1.85-4.60	<0.0001

BMI, body mass index; HDL, high density lipoprotein
*Data represent odds ratio corresponding to 1SD increase in BMI level

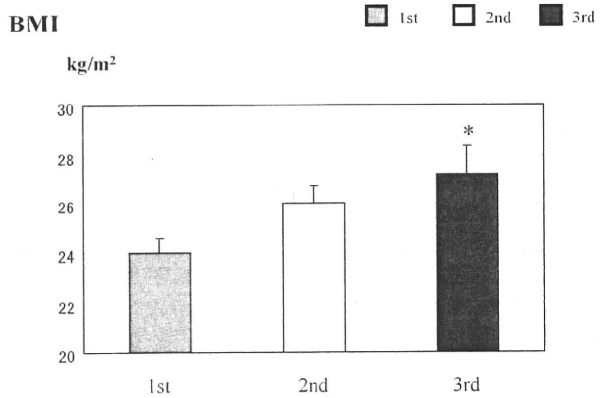

Fig. 2. Trends in BMI among male patients with AMI aged <40 years.

Bars indicate BMI during hospitalization among male AMI patients aged <40 years, during the three time periods. Continuous variables are presented as the mean±SE. *p<0.05 compared with 1st period.

only among men and was much higher than in women. Younger men in particular showed a significant increase in the incidence rate of AMI, which was seven times greater than in women during 2003-2007 (**Table 1**). These findings are not likely to be explained only by the influence of aging of the general population. We hypothesized that changes in the prevalence of risk factors, due to the westernization of dietary habits and changes in lifestyle, may have influenced the recent incidence rates of AMI.

Changes in the Prevalence of Coronary Risk Factors in AMI Patients

There were differences in the trends in coronary risk factors between men and women. Both showed a similar magnitude of increase in the prevalence of hypertension and diabetes; however, only younger men showed a significant increase in the prevalence of obesity and in serum triglyceride levels during 2003-2007 (**Fig. 1**). Consequently, the proportion of patients with metabolic syndrome increased among younger and early elderly men (**Table 3**). Several studies have demonstrated that metabolic syndrome is a significant risk factor for the development of AMI[18-24], but it had a weak or no association with CHD in the elderly[31], which is consistent with the findings of the present study.

In the present study, AMI patients of both genders showed a higher prevalence of hypertension, diabetes and hypercholesterolemia, and a higher incidence of current smoking than age-adjusted control subjects, which was consistent with the findings of the Framingham study[32]. Recently, a large Japanese case-control study demonstrated that hypertension, diabetes, current smoking, family history, and hypercholesterolemia were all independent risk factors for AMI[12]; however, only current smoking, diabetes and, hypertension were identified as independent risk factors in women in their study. Therefore, it was suggested that

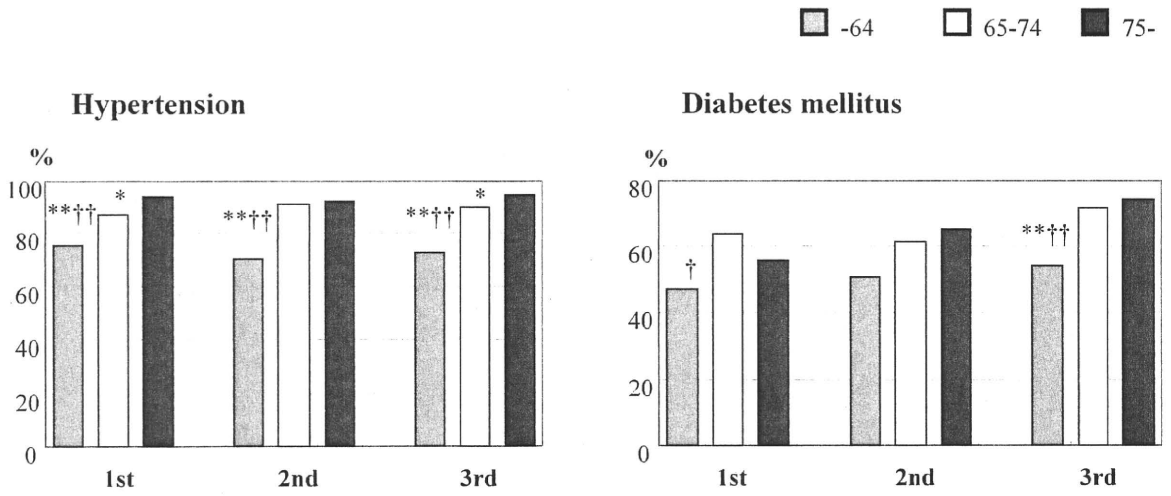

Fig. 3. Comparison of the proportions of male patients receiving medical treatment.

Bars indicate the proportions of male patients in the three age groups (<65, 65–74, ≥75 years old), receiving medical treatment for hypertension and diabetes during the three time periods. $^{*}p<0.05$, $^{**}p<0.01$ compared with late elderly patients; $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$ compared with early elderly patients.

hypercholesterolemia was an independent coronary risk factor in men, but not women, which is consistent with the results of the present study.

Previous studies reported that obesity and low HDL cholesterolemia were independent risk factors among younger male patients[33-35], which is consistent with our findings. In particular, male patients with AMI aged <40 years showed significant increases in BMI and the prevalence of obesity (**Fig. 2**).

Although the incidence of current smoking decreased during 2003–2007 in male patients (**Table 1**), it was significantly higher than in age-adjusted control subjects (**Table 2**). Surprisingly, the incidence of current smoking in female AMI patients was about six times higher than in age-adjusted control subjects, whereas it was lower than in male AMI patients. Thus, the prevalence of smoking has decreased in men, but not in women. Notably, the prevalence of smoking was significantly higher in younger women than in elderly patients. These results suggest that current smoking is an important risk factor for AMI, which is consistent with the findings from a previous study[12, 32, 36].

During 2003–2007, there was a significant decrease among both genders in the proportion of AMI patients with a family history (**Table 1**). This does not mean there was a decrease in the number of AMI patients with a family history, but rather that there was an increase in the number without a family history. In addition, the impact of lifestyle-related factors on the development of AMI may have become relatively more important in recent years[14-17, 23].

Insufficient Treatment of Coronary Risk Factors

Female AMI patients were 8–10 years older than male patients (**Table 1**). A previous study also reported that women develop CHD about 10 years later than men[37]. In general, menopause is a risk factor among females, which contributes to gender differences[38, 39]; however, it has been suggested that the difference in the age at onset is largely explained by the higher number of risk factors at younger ages in men than women[37]. The age at onset increased significantly in women in the present study. Since the number of female patients did not increase, despite an increase in the aging population, it is suggested that medical treatment may have partly contributed to suppressing the incidence of AMI in women. In fact, the proportion of patients receiving medical treatment for each risk factor was approximately 10% higher in women than men (**Table 1**). Although the proportion of patients receiving treatment for hypertension reached 94% in female patients, the proportions receiving treatment for diabetes and hypercholesterolemia remained suboptimal at 78% and 59%, respectively. In order to reduce the age-adjusted incidence of AMI in women, improved rates of treatment for diabetes and hypercholesterolemia, as well as increased rates of smoking cessation, are required.

In contrast to women, there was an accumulation of coronary risk factors and an increased incidence of AMI in male patients. Particular attention should be paid to the increased incidence of AMI among younger men, who showed a greater increase

in the prevalence of the metabolic syndrome than other age groups (**Table 4**), and also had a markedly high incidence of current smoking (**Fig. 1**), which did not decrease over the three time periods. Furthermore, the proportion of patients receiving treatment for each coronary risk factor was significantly lower in younger male patients than other age groups (**Fig. 3**). Therefore, control of the risk factors associated with metabolic syndrome, in addition to conventional risk factors, such as hypercholesterolemia, and increased rates of smoking cessation, are required to decrease the incidence of AMI among men.

In conclusion, the age-adjusted incidence of AMI increased in male patients, but not in female patients. In particular, younger men have shown a significant increase in the incidence of AMI recently. The control of conventional coronary risk factors is still thought to be insufficient, in both men and women, to contribute to a decrease in the incidence of AMI. In addition, preventive care for metabolic syndrome may be required in younger men.

Acknowledgements

We thank the investigators who participated in this multicenter survey of AMI in Yamagata Prefecture, Japan. This work was supported by a Grant-in-Aid from the Global COE Program of the Japan Society for the Promotion of Science, and by a grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 21590923 and No. 21790700).

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Low Wall Velocity of Left Atrial Appendage Measured by Trans-Thoracic Echocardiography Predicts Thrombus Formation Caused by Atrial Appendage Dysfunction

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Background: Atrial fibrillation is associated with ischemic stroke because of thrombi that form within the left atrial appendage (LAA). The aim of this study was to develop a new parameter for LAA function that is easily performed using transthoracic echocardiography (TTE).

Methods: TTE and transesophageal echocardiography were performed in 106 patients with stroke. LAA wall motion velocity (TTE-LAWV) was measured using Doppler tissue imaging at the LAA tip.

Results: TTE-LAWV was significantly lower in patients with atrial fibrillation and LAA thrombus than in those with atrial fibrillation and no LAA thrombus and in sinus rhythm (7.5 ± 1.9 vs 10.0 ± 3.4 and 13.8 ± 5.7 cm/s, respectively, $P < .05$). TTE-LAWV was significantly correlated with LAA emptying flow velocity ($R = 0.462$, $P < .05$). The multivariate logistic regression analysis showed that TTE-LAWV < 8.7 cm/s was an independent predictor of LAA thrombus formation (odds ratio, 9.473; 95% confidence interval, 1.172-76.55; $P < .05$).

Conclusion: TTE-LAWV can noninvasively evaluate LAA dysfunction and assist in the detection of LAA thrombus. (J Am Soc Echocardiogr 2010;23:545-52.)

Keywords: Left atrial appendage wall motion, Left atrial appendage thrombus, Noninvasive

The National Institute of Neurological Disorders and Stroke has characterized cardioembolic stroke as an important clinical issue because it is the most common cause of death in patients with acute ischemic stroke.[1,2] It is well known that the left atrial appendage (LAA) is a major thromboembolic source in patients with stroke and atrial fibrillation (AF).[3-5] Many clinical reports have shown a close relation between LAA thrombus formation and left atrial mechanical remodeling on the basis of findings from transesophageal echocardiography (TEE).[6-9] It was reported that the presence of spontaneous echocardiographic contrast (SEC) or LAA peak flow velocity measured by TEE is useful for the detection of LAA dysfunction, which causes LAA thrombus formation.[10,11] However, TEE may not be performed for screening to quantify the risk for stroke in patients with AF, because it is a semi-invasive procedure. Although transthoracic echocardiography (TTE) can be widely used for screening because of its noninvasive nature, it is thought to be difficult to detect LAA thrombus and evaluate LAA dysfunction on TTE. Doppler tissue imaging (DTI) reflects regional myocardial function. Recently, DTI was also reported to be useful for evaluation of LAA function.[12] In that study, using DTI with TEE, it was shown that LAA dysfunction plays a role in LAA thrombus formation.

We hypothesized that DTI velocity from the LAA on TTE (TTE-LAWV) is a feasible parameter for the risk stratification of patients with AF. In the present study, we compared TTE-LAWV with conventional markers of LAA dysfunction and investigated whether TTE-LAWV could predict thrombus formation.

METHODS

Study Patients

We performed TTE and TEE in 106 patients referred for the treatment of acute cerebral infarction. TTE and TEE were done within 7 days of onset (mean, 6 ± 1 days). We excluded patients with malignant disease (n = 6), chronic disseminated intravascular coagulation (n = 3), failure of TEE (n = 5), and failure of TTE-LAWV measurement (n = 10). The admission assessment included determining the risk factors for cerebral infarction,[13,14] clinical ischemic stroke category (National Institute of Neurological Disorders and Stroke[1]), and disease severity using the National Institutes of Health Stroke Scale.[15]

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This work was supported by a grant-in-aid from the Global COE program of the Japan Society for the Promotion of Science and by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan (grants 19790513, 19790515, and 20590813).

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0894-7317/$36.00

doi:10.1016/j.echo.2010.02.006

Abbreviations

AF = Atrial fibrillation

LAA = Left atrial appendage

LAA eV = LAA emptying flow velocity

LAD = Left atrial dimension

LAWV = LAA peak wall velocity

ROC = Receiver operating characteristic

SEC = Spontaneous echocardiographic contrast

TEE = Transesophageal echocardiography

TTE = Transthoracic echocardiography

We defined patients who had no histories of AF and no documented AF on continuous electrocardiographic monitoring during hospitalization as the sinus rhythm group, patients who had histories of AF before admission and/or continuously documented AF on continuous electrocardiographic monitoring during hospitalization as having chronic AF, and patients who had AF at admission and recovered to normal sinus rhythm during hospitalization and/or showed sinus rhythm at admission and documented transient AF on continuous electrocardiographic monitoring during hospitalization as having paroxysmal AF. Six patients (6%) had paroxysmal AF (all were in sinus rhythm at the time of TEE), and 48 patients (45%) had chronic AF. Previous anticoagulation before onset was performed in 2 patients with paroxysmal AF (33%) and 25 patients (52%) with chronic AF. Patients with paroxysmal AF and those with chronic AF were defined as the AF group.

The study subjects were classified into 3 groups on the basis of the presence of AF and LAA thrombus (group A: patients in sinus rhythm [n = 52]; group B: patients with AF and no LAA thrombi [n = 29]; and group C: patients with AF and LAA thrombi [n = 25]). We compared between transthoracic and transesophageal parameters among the 3 groups retrospectively. The local ethics committee approved the study protocol, and informed consent was given by all subjects.

Echocardiography

TTE was done using a Hewlett-Packard Sonos 7500 ultrasound instrument equipped with a sector transducer (carrier frequency, 2.5 or 3.75 MHz) (Hewlett-Packard Corporation, Palo Alto, CA). A 5-MHz phased-array multiplane probe was used for TEE. We examined the following parameters and findings using standard views and techniques: left atrial dimension (LAD), left ventricular end-diastolic dimension, left ventricular percentage fractional shortening measured by TTE, and the presence of an atrial septal aneurysm, a patent foramen ovale, SEC, or LAA thrombus evaluated by TEE.[16-18] LAA thrombus was diagnosed when a fixed or mobile echogenic mass could be clearly differentiated from the wall of the left atrium or LAA.[19] In patients with AF, echocardiographic measurements were obtained as the mean of 5 consecutive cardiac cycles. All findings were evaluated by two independent experienced echocardiologists who did not know the patients' clinical and other characteristics, and all echocardiographic measurements obtained by the two echocardiologists had good reproducibility.

TEE-LAWV, defined as LAA peak wall velocity, was measured using tissue Doppler with the sample volume placed at the LAA tip by TEE, as reported previously.[20] Peak wall velocity within each RR interval at diastole was obtained by scanning the appendage at 0°, 30°, 60°, and 90° and was averaged. We could also observe the LAA from parasternal the short-axis view on TTE and measure TTE-LAWV using a similar method as for TEE-LAWV measurement (Figure 1). We could evaluate TTE-LAWV in most patients (92%), except those with poor echocardiographic image quality due to obesity, chronic obstructive pulmonary disease, or emaciation.

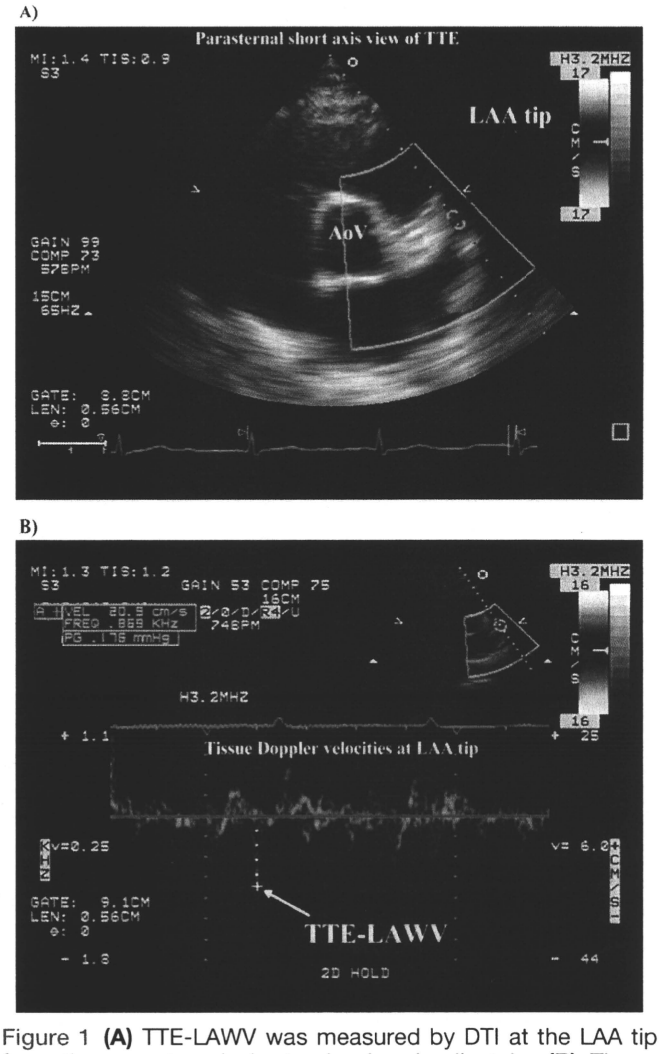

Figure 1 **(A)** TTE-LAWV was measured by DTI at the LAA tip from the parasternal short-axis view in diastole. **(B)** Tissue Doppler velocities were obtained, and the peak wall velocity of downward atrial waveform within each RR interval was averaged. *AoV*, Aortic valve.

LAA emptying flow velocity (LAA eV) was assessed using pulsed-wave Doppler with the sample volume placed 1 cm distal from the mouth of the appendage by TEE. Peak flow velocity within each RR interval at diastole was obtained by scanning the appendage at 0°, 30°, 60°, and 90° and was averaged.[21] We analyzed the correlations between TTE-LAWV and other conventional parameters.

Aortic and Carotid Echocardiographic Studies

Aortic images were obtained after the cardiac examination by TEE. The prevalence of protrusion ≥5 mm and/or mobile plaques in the arch were examined.[22]

Bilateral carotid artery imaging was performed with a 7.5-MHz linear transducer connected to a Sonos 7500 system. The carotid intima-media thickness without protruding atheromatous plaques was measured at end-diastole according to the method reported by

Pignoli et al[23] and was obtained as the mean of the bilateral common carotid arteries.

Hemostatic Markers

Blood samples were collected to determine the serum hemostatic marker levels at the time of the echocardiographic studies. Antithrombin III, fibrinogen, fibrin-monomer, plasminogen, α_2-plasmin inhibitor, fibrinogen degradation products, and D-dimer were assessed. General biochemical parameters were measured using routine laboratory methods.

Statistical Analysis

Results are expressed as mean ± SD for continuous variables and as percentages of the total number of patients for categorical variables. Skewed variables are shown as medians and interquartile ranges. Statistical analysis was conducted using StatView version 5.0 (SAS Institute Inc, Cary, NC). Patient characteristics, echocardiographic parameters, and hemostatic markers were compared among groups A, B, and C using Student's t test for unpaired continuous variables and the χ^2 test for categorical variables. If data were not distributed normally, the Mann-Whitney U test was used. P values $< .05$ were considered significant. Receiver operating characteristic (ROC) curves were constructed to determine the relevant TTE-LAWV cutoff values for predicting LAA thrombus on the basis of the optimal sensitivity and specificity. Bland-Altman analysis was performed to provide an analysis of agreement between TTE-LAWV and TEE-LAWV. To determine independent predictors of the presence of LAA thrombus for all patients, logistic regression analysis was performed. Significant variables selected in univariate logistic regression analysis ($P < .05$) were entered into the multivariate analysis. The intraobserver reliability and the interobserver reliability of TTE-LAWV and TEE-LAWV were assessed in 10 patients by two echocardiologists, each repeated once. By intraclass correlation coefficient, the mean intraobserver reliabilities of TTE-LAWV and TEE-LAWV were 98.6% and 98.1%, respectively. The mean interobserver reliabilities of TTE-LAWV and TEE-LAWV were 98.9% and 97.6%, respectively.

RESULTS

Patient's Characteristics

There were no significant differences among the 3 groups in sex distribution; the prevalence of hypertension, diabetes mellitus, and hyperlipidemia; history of previous stroke; and the use of oral antiplatelet medications (Table 1). Group C was significantly older than group A. The incidence of cardioembolic stroke was significantly higher in patients with AF (groups B and C) compared with patients in sinus rhythm (group A). Moreover, patients with AF and thrombi (group C) had a higher incidence of cardioembolic stroke compared with patients with AF without thrombi (group B). $CHADS_2$ scores were significantly higher in group C than in group B. Medication with anticoagulants was significantly higher in groups B and C than in group A (Table 1).

Echocardiographic Parameters

LAA thrombi were not detected in group A patients. There were no significant differences in the presence of atrial septal aneurysm, patent foramen ovale, and significant aortic or carotid atherosclerotic plaques among the 3 groups. Groups B and C had significantly larger LADs and smaller left ventricular percentage fractional shortening compared with group A (Table 2). Groups B and C had significantly smaller LAA eV, a higher prevalence of SEC, smaller TEE-LAWV, and smaller TTE-LAWV compared with group A (Table 2). Furthermore, group C had a significantly higher prevalence of SEC, smaller TEE-LAWV, and smaller TTE-LAWV compared with group B (Table 2). As shown in Figure 2, TTE-LAWV decreased with advancing $CHADS_2$ score. This result suggested that LAA function was impaired in patients with higher thromboembolic risks.

Table 1 Comparison of clinical characteristics among 3 groups

Variable	Group A (n = 52)	Group B (n = 29)	Group C (n = 25)
Age (y)	67 ± 15	71 ± 13	76 ± 10*
Men/women	35/17	20/9	16/9
Heart rate (beats/min)	73 ± 13	82 ± 12*	81 ± 17*
Hypertension	40 (71%)	22 (76%)	18 (72%)
Diabetes mellitus	15 (29%)	12 (41%)	8 (32%)
Hyperlipidemia	30 (58%)	8 (28%)	6 (24%)
Current smoking	29 (56%)	15 (52%)	12 (48%)
Previous stroke	12 (23%)	3 (10%)	7 (28%)
Atrial fibrillation	0 (0%)	29 (100%)	25 (100%)
National Institutes of Health Stroke Scale score	4.0 (0.5-8)	4.0 (2-10)	5.5 (2-14)
$CHADS_2$ score	1.9 ± 0.9	2.2 ± 1.4	3.0 ± 1.4*†
National Institute of Neurological Disorders and Stroke clinical category			
Cardioembolic stroke	3 (6%)	11 (38%)*	23 (92%)*†
Atherothrombotic stroke	12 (23%)	5 (17%)	0 (0%)
Lacunar stroke	9 (17%)	3 (10%)	2 (8%)
Others or undetermined	28 (54%)	10 (35%)	0 (0%)*†
Medication before onset			
Antiplatelets	20 (38%)	12 (41%)	9 (36%)
Anticoagulants	4 (8%)	15 (52%)*	12 (48%)*
Prothrombin time–international normalized ratio	1.41 ± 0.39	1.51 ± 0.34*	1.55 ± 0.4*

Data are expressed as mean ± SD or as number (percentage). Group A included patients with sinus rhythm, group B included patients with AF without thrombi, and group C included patients with AF with thrombi.
*$P < .05$ versus group A.
†$P < .05$ versus group B.

Blood Markers

There were no significant differences in hemostatic markers between group A and group B (Table 2). However, group C had higher levels of hemostatic markers such as fibrinogen, α_2-plasmin inhibitor, and C-reactive protein compared with groups A and B.

There was no significant difference in prothrombin time-international normalized ratio between patients with LAA thrombi and patients without LAA thrombi who were taking warfarin (1.55 ± 0.40 vs 1.52 ± 0.33, $P = .745$; Table 3).

Table 2 Comparison of echocardiographic findings and blood markers among 3 groups

Variable	Group A (n = 52)	Group B (n = 29)	Group C (n = 25)
LAD (mm)	34 ± 5	46 ± 8*	46 ± 9*
LV end-diastolic diameter (mm)	46 ± 6	49 ± 7*	48 ± 6
LV fractional shortening (%)	37 ± 6	34 ± 8	32 ± 8*
LAA eV (cm/s)	70 ± 12	58 ± 14*	16 ± 10*†
SEC	1 (2%)	11 (38%)*	19 (76%)*†
LAA thrombus	0 (0%)	0 (0%)	25 (100%)*†
Atrial septal aneurysm	5 (10%)	1 (3%)	0 (0%)
Patent foramen ovale	3 (6%)	3 (10%)	2 (8%)
Aortic plaque‡	4 (8%)	4 (14%)	3 (12%)
Aortic IMT (mm)	2.8 ± 1.3	3.0 ± 1.5	3.3 ± 1.8
Carotid plaque§	9 (17%)	4 (24%)	2 (8%)
Carotid IMT (mm)	0.8 ± 03	0.8 ± 0.1	0.7 ± 0.2
TEE-LAWV (cm/s)	16.5 ± 8.5	10.9 ± 4.4*	7.1 ± 1.4*†
TTE-LAWV (cm/s)	13.8 ± 5.7	10.0 ± 3.4*	7.5 ± 1.9*†
TTE-LAWV < 8.7 cm/s	3 (6%)	10 (34%)*	18 (72%)*†
Blood markers			
C-reactive protein (mg/dL)	0.2 (0.1-0.8)	0.1 (0.1-1.2)	2.1 (0.2-5.6)*†
Antithrombin III (%)	102 ± 23	98 ± 21	102 ± 22
Fibrinogen (mg/dL)	395 ± 115	423 ± 182	535 ± 242*†
Fibrin-monomer (mg/mL)	5.5 (3.3-8.5)	5.5 (2.9-9.6)	5.8 (2.8-13.5)
Plasminogen (%)	94 ± 18	91 ± 13	96 ± 16
α_2-plasmin inhibitor (%)	101 ± 14	105 ± 14	116 ± 18*†
D-dimer (mg/ml)	1.3 (0.5-3.1)	1.5 (0.5-4.3)	1.7 (0.8-4.7)
Fibrinogen degradation products (mg/mL)	4.7 (3.5-6.2)	3.9 (2.9-6.8)	5.3 (3.9-9.4)

Data are expressed as mean ± SD, as number (percentage), or as median (interquartile range).
*P < .05 versus group A.
†P < .05 versus group B.
‡Protruding >5 mm and/or mobile plaques in the aortic arch.
§Protruding plaque with >50% luminal stenosis in the common and/or proximal internal carotid artery.

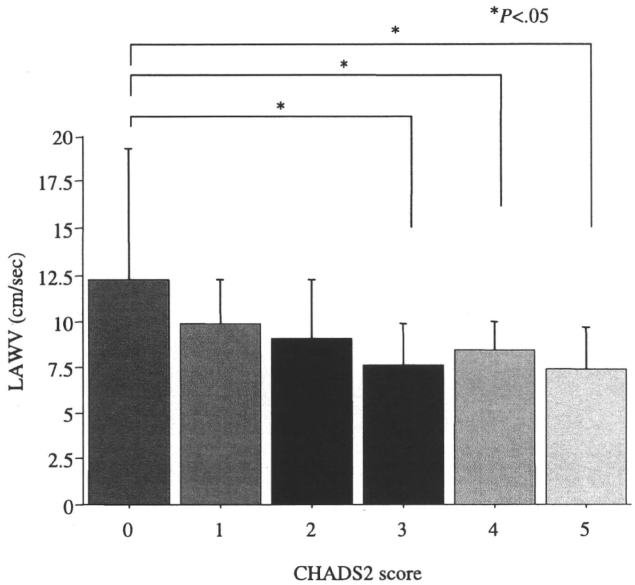

Figure 2 Association between LAWV and $CHADS_2$ score.

Table 3 Value of TTE-LAWV in patients with and without oral anticoagulation with warfarin

	Warfarin		No warfarin	
Variable	LAA thrombus (n = 12)	No LAA thrombus (n = 19)	LAA thrombus (n = 14)	No LAA thrombus (n = 61)
Prothrombin time–international normalized ratio	1.55 ± 0.40	1.52 ± 0.33	—	—
TTE-LAWV (cm/s)	6.9 ± 1.5	11.2 ± 4.7*	8.4 ± 2.1	13.0 ± 5.6†

Data are expressed as mean ± SD.
*P < .05 versus LAA thrombus with oral warfarin.
†P < .05 versus LAA thrombus without oral warfarin.

Evaluation of LAA Dysfunction by TTE-LAWV

We investigated the relationship between TTE-LAWV and previously reported left atrial functional parameters, such as LAA eV and TEE-LAWV. Figure 3 shows representative waveforms of TTE-LAWV and TEE-LAWV among the 3 groups. We found that the waveform of TTE-LAWV was quite similar to that of TEE-LAWV, like a specular image. TTE-LAWV was significantly correlated with TEE-LAWV (R = 0.682, P < .01; Figure 4A). The Bland-Altman plot also showed good agreement of LAWV assessment between TTE and TEE (Figure 4B). There was also a significant correlation between TTE-LAWV and LAA eV (R = 0.462, P < .05; Figure 4C). We measured LA emptying volume and LA ejection fraction in 67 patients. TTE-LAWV was significantly correlated with left atrial emptying volume and left atrial ejection fraction (Supplemental Figure 1).

LAA Dysfunction and LAA Thrombus

The ROC curve for TTE-LAWV as a predictor of LAA thrombus formation is shown in Figure 5. The area under the ROC curve was 0.815. The optimal TTE-LAWV for predicting LAA thrombus was determined as those with the largest sum of sensitivity plus specificity on the ROC curve; TTE-LAWV < 8.7 cm/s had sensitivity of 77% and specificity of 76% (Figure 5). Low TTE-LAWV (<8.7 cm/s) was observed in 31 of 106 study patients (29%). There were 3 patients with low TTE-LAWV in group A, 10 in group B, and 18 in group C. Low TTE-LAWV was observed in 72% of patients with LAA thrombi. We compared the ROC curves obtained by TTE-LAWV, TEE-LAWV, LAA eV, and LAD (Figure 5). TTE-LAWV was not inferior to conventional parameters for predicting LAA thrombus.

Logistic regression analysis was performed to identify independent predictors of the presence of LAA thrombus (Table 4). In univariate logistic regression analysis, age, $CHADS_2$ score, LAD, LAA eV < 20 cm/s, SEC, and TTE-LAWV < 8.7 cm/s were significantly associated with LAA thrombus formation. In multivariate logistic regression analysis, TTE-LAWV < 8.7 cm/s was an independent predictor of LAA thrombus formation (Table 4).

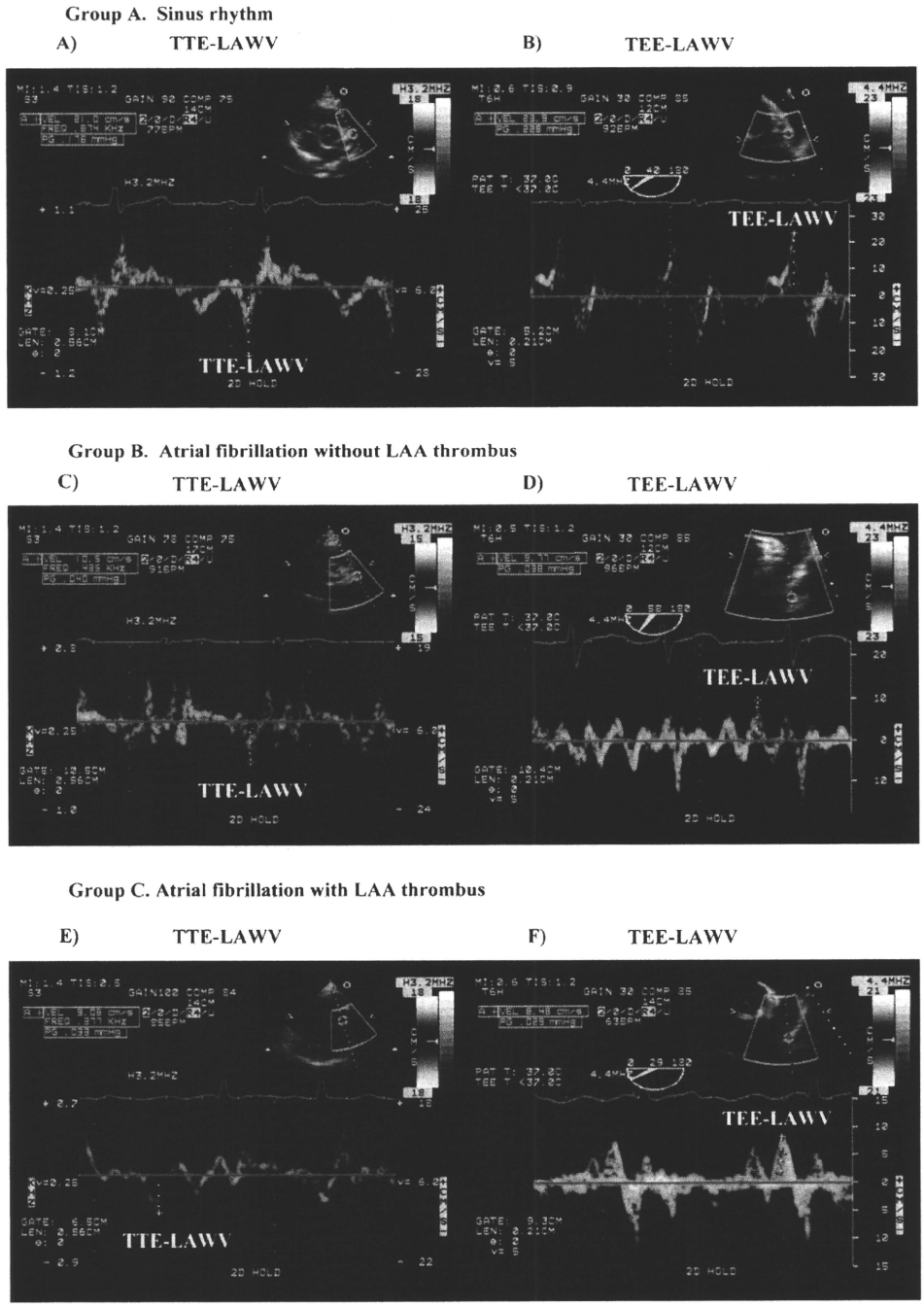

Figure 3 Representative waveforms of TTE-LAWV and TEE-LAWV among 3 groups. **(A)** Waveform of TTE-LAWV in group A. **(B)** Waveform of TEE-LAWV in group A. **(C)** Waveform of TTE-LAWV in group B. **(D)** Waveform of TEE-LAWV in group B. **(E)** Waveform of TTE-LAWV in group C. **(F)** Waveform of TEE-LAWV in group C. The waveform of TTE-LAWV was quite similar to that of TEE-LAWV, like a specular image.

DISCUSSION

The present study demonstrated that TTE-LAWV was well correlated with the conventional parameters that reflect LAA dysfunction. Low TTE-LAWV may be a promising noninvasive marker for LAA dysfunction, which causes thrombus formation.

Many clinical studies have shown that TEE parameters indicating LAA dysfunction can predict LAA thrombus formation.[6-9] A reduction in LAA eV or the development of SEC reflects atrial mechanical remodeling and thrombus formation.[24,25] Kamp et al[8] reported that the presence of SEC and low LAA eV were reliable markers for risk stratifying patients with AF for thromboembolism. Because these established predictors of LAA thrombus were evaluated by TEE, it might be difficult to apply to all patients with AF as screening for the presence of LAA dysfunction in clinical practice. Although it was reported that increased LAD, decreased fractional shortening, and increased transmitral inflow velocities (E/A) were useful predictors of LAA thrombus,[26,27] these transthoracic parameters were not

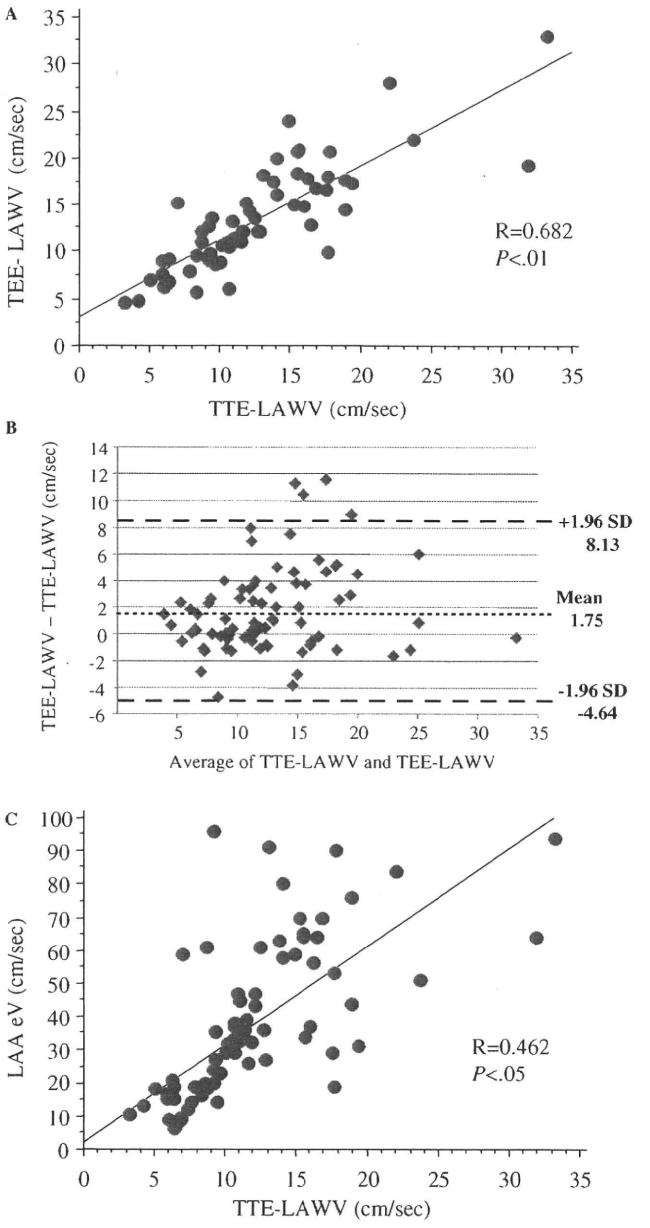

Figure 4 **(A)** Relationship of TEE-LAWV and TTE-LAWV. TTE-LAWV was significantly correlated with TEE-LAWV (R = .682, P < .01). **(B)** Bland-Altman plot comparing TTE-LAWV and TEE-LAWV (mean difference, 1.75 cm/s; limits of agreement, −4.64 to 8.13 cm/s). **(C)** Relationship of LAA eV and TTE-LAWV. TTE-LAWV was also significantly correlated with LAA eV (R = .462, P < .05).

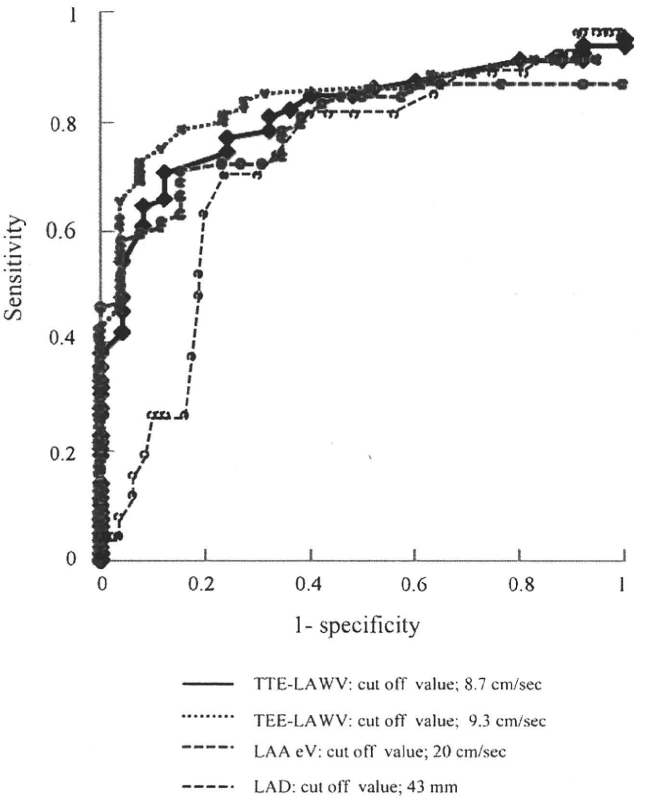

Figure 5 ROC curve analysis for TTE-LAWV, TEE-LAWV, LAA eV, and LAD.

Table 4 Univariate and multivariate logistic regression analyses for LAA thrombus formation

Variable	Risk ratio	95% confidence interval	P
Univariate analysis			
Age (per 1-SD increase)	2.261	1.134-4.420	.019
$CHADS_2$ score (per 1-SD increase)	1.878	1.032-3.417	.016
LAD (per 1-SD increase)	2.282	1.363-3.833	.002
LAA eV < 20 cm/s	12.30	3.669-28.93	<.001
SEC	14.81	5.032-43.56	<.001
TTE-LAWV < 8.7 cm/s	17.47	5.279-57.82	<.001
Multivariate analysis			
Age (per 1-SD increase)	1.149	0.439-3.054	.766
$CHADS_2$ score (per 1-SD increase)	1.302	0.606-2.802	.499
LAD (per 1-SD increase)	0.706	0.330-1.499	.362
LAA eV < 20 cm/s	1.468	0.224-9.615	.689
SEC	2.280	0.528-9.844	.269
TTE-LAWV < 8.7 cm/s	9.473	1.172-76.55	.035

specific, and their predictive values were much lower compared with transesophageal parameters. Recently, it was reported that DTI patterns from the LAA measured by TEE were useful for risk assessment of thromboembolism.[12,20] Therefore, DTI is thought to be a clinically applicable and reliable imaging technique that affords a quantitative assessment of regional LAA systolic function.

As shown in Figures 1 and 3, we could successfully evaluate LAWV using TTE. We found that there were significant correlations between TTE-LAWV and LA functional parameters obtained by TEE, such as TEE-LAWV (Figure 4A) and LAA eV (Figure 4C). Figure 5 demonstrates that the ROC curves of TTE-LAWV and TEE-LAWV were quite similar. This result suggests that our measuring method using TTE can evaluate the wall velocity of the LAA properly. The $CHADS_2$ score is a risk stratification system for patients with nonvalvular AF.[13] It was reported that high-risk patients defined according to the $CHADS_2$ scheme had a high rate of ischemic stroke despite receiving warfarin.[14] Figure 2 demonstrates that LAWV decreased with advancing $CHADS_2$ score in patients with AF. This result suggests that the endothelial dysfunction caused by aging, the prevalence

of hypertension, and diabetes mellitus may reduce LAA function, which is involved in LAA thrombogenesis.

Patients with LAA thrombi had greater increases in fibrinogen, α_2-plasmin inhibitor, and fibrinogen degradation products compared with those without (Table 2). We and others have reported that elevated levels of coagulation markers such as fibrinogen and fibrin-monomer are useful for the risk stratification of prognoses and outcomes in patients with ischemic stroke.[28,29] In the present study, TTE-LAWV was weakly correlated with fibrinogen ($R = -0.240$, $P = .017$). LAA dysfunction may be associated with systemic hypercoagulable state and long-term ischemic stroke recurrence.

There were no significant differences in sensitivity, specificity, and area under the ROC curve for predicting LAA thrombus between all patients (n = 106) and those with cardioembolic (n = 35) or cryptogenic (n = 2) stroke (sensitivity, 77% vs 80%; specificity, 76% vs 70%; area under the ROC curve, 0.815 vs 0.752). We thought that LAWV could evaluate the LAA dysfunction that was independent of stroke subtypes and useful for risk stratification of thromboembolism as a screening tool in patients with ischemic stroke.

Recently, Sallach et al[30] reported that DTI velocities of the LAA walls (anterior, posterior, and apical) evaluated by TTE are useful in determining the severity of LAA SEC and detecting LAA thrombi in patients with AF. Because their results are consistent with those of the present study, it is suggested that TTE-LAWV may be a promising way to detect LAA dysfunction.

This study had several limitations. First, this study included various stroke subtypes. Second, patients were anticoagulated with a lower limit of therapeutic range in this study. Poor anticoagulation might influence the echocardiographic findings, such as the prevalence of LAA thrombus and SEC. Third, the number of subjects was relatively small. Fourth, we did not measure the other LAA wall velocities, such as anterior, posterior, and lateral. However, a previous study demonstrated that DTI velocities of the LAA tip were very similar to that of LAA anterior, posterior, and lateral walls.[30]

In conclusion, low TTE-LAWV may be a reliable noninvasive marker of LAA dysfunction and predict LAA thrombus formation. TTE-LAWV may be useful for the risk stratification of systemic embolism, including cardioembolic stroke.

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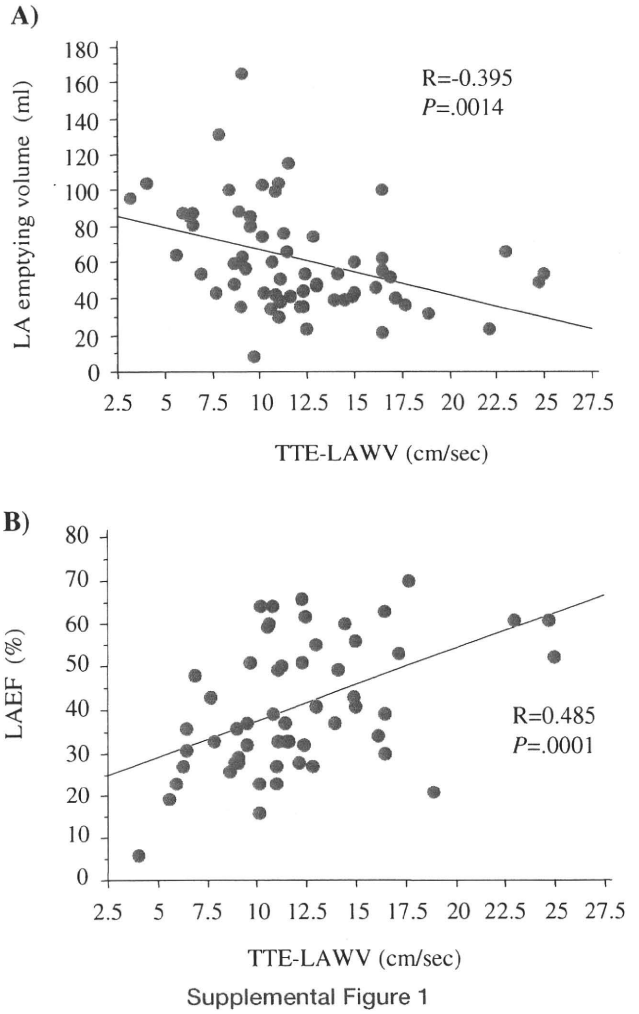

Supplemental Figure 1