原 著

Relationship between Doppler Echocardiographic Findings and the Incidence of Heart Failure in Patients with Left Ventricular Diastolic Dysfunction

Naoki Isobe*, Hiroshi Kamiyama**,
Shigeru Oshima*, Koichi Taniguchi*

Abstract

Mitral annular velocity in early diastole (E') gradually decreases following exacerbation of left ventricular (LV) diastolic dysfunction. Patients with an E' ≤ 5cm/s may have LV diastolic dysfunction similar to those with the ratio of the mitral E velocity to E' (E/E') ≥15. An E/A >1 obtained by Doppler evaluation of transmitral inflow is considered to indicate greater LV diastolic dysfunction, if E' is low. This study was designed to investigate whether echocardiographic Doppler studies predict the development of heart failure (HF). The present study group comprised 159 subjects of 2040 underwent echocardiographic studies who had an E' ≤5cm/s, normal systolic function and sinus rhythm. Subjects were divided into 2 groups based on whether they had evidence of heart failure during 18 months follow-up (HF group and non-HF group). Eleven percent of the subjects were in HF group. Twenty five percent of the subjects with an E/E' ≥ 15 were in HF group, as were 32% of those with an E/A >1. Furthermore, subjects with an E/E' ≥ 15 and an E/A >1 had a higher incidence (5 of 11 patients, 45%) of heart failure. Tissue Doppler and pulse Doppler studies may provide useful information about whether patients with preserved LV systolic function are susceptible to developing heart failure in the elderies.

Key words; tissue Doppler, pulse Doppler, left ventricular diastolic dysfunction, heart failure

*Division of Cardiology, Gunma Prefectural Cardiovascular Center, Maebashi, Japan
**Department of Cardiology, Isesaki-Sawa Medical Association Hospital, Isesaki, Japan

Introduction

Epidemiologic studies have revealed that left ventricular (LV) systolic function is preserved or minimally impaired in 40% of patients with heart failure patients[1~3]. This type of heart failure is mainly due to diastolic dysfunction and is termed diastolic heart failure[4]. Doppler echocardiographic studies and tissue Doppler imaging are noninvasive techniques for evaluating LV function. It is already known that an E/A ratio [ratio of the peak velocity of early diastolic filling (E) to that of atrial filling (A)] less than 1 indicates LV abnormal relaxation. Furthermore, as LV relaxation worsens, the E/A ratio becomes greater than 1, and pseudonormalization occurs[5]. Early diastolic myocardial velocity (E') on tissue Doppler imaging reflects myocardial relaxation[6,7] and is relatively load-independent[6]. E' derived from the motion velocity of the LV posterior wall is closely related to the time constant of relaxation[7] and gradually decreases following worsening of LV relaxation[8]. Wang et al[9] reported that when the E' is ≤5cm/s, the hazard ratio for cardiac death is significantly in-

creased compared to patients with an E'>5cm/s. In addition, the ratio of E to E'(E/E') correlates well with the mean LV diastolic pressure, and an E/E'>15 identifies patients with an increased mean LV diastolic pressure[10]. This study was designed to investigate whether echocardiographic Doppler studies predict the development of heart failure (HF) in patients with an E'≤5cm/s and preserved LV systolic function.

Methods

A. Subject selection

Of 2040 subjects underwent echocardiographic studies, 165 subjects who satisfied following the criteria were recruited in this study: (1) E'≤5cm/s obtained in the lateral mitral annulus; (2) LV ejection fraction ≥50%; (3) sinus rhythm; (4) free from valvular heart disease, severe mitral annular calcifications and constrictive pericarditis; (5) asymptomatic or had well-controlled heart failure (New York Heart Association functional class grade I or II). They were followed for 18 months, however, 3 subjects who underwent heart surgery (ie, coronary artery bypass grafting) or percutaneous coronary intervention and 3 subjects who had their medications changed during the follow-up period were excluded. We divided the remaining 159 patients [60 men, 99 women; age (mean±SD), 73±9 years] into 2 groups based on whether they had evidence of heart failure during follow-up (HF group and non-HF group). We explained the details of the study to all the patients and they gave informed consent.

B. Echocardiography

Echocardiography was performed using an ultrasonic sector scanner with 2.5-MHz transducers before the study entry. Standard parasternal long- and short-axis views and apical 2- and 4-chamber views were obtained in all of the patients. The left atrial dimension was measured on the M-mode echocardiogram derived from the 2-dimensional images. The LV ejection fraction was calculated by the modified Simpson's method. The LV filling velocities were recorded with pulse Doppler echocardiography by an apical approach. The sample volume was set at the level of the mitral leaflet tip in diastole. The peak velocity of early diastolic filling (E) and atrial filling (A) and their ratio (E/A) were determined. Doppler tissue imaging of the mitral annulus was acquired from the apical 4-chamber view, using a sample volume placed in the lateral mitral valve annulus. The peak velocities at early diastole (E') were measured and the ratio of E to E' (E/E') were calculated. The measurements were performed at end-expiration.

C. Outcome evaluations

The development or exacerbation of heart failure was defined as developing effort intolerance and dyspnea, especially in combination with venous congestion and pulmonary edema.

D. Statistical analysis

Data are expressed as mean±SD. Comparisons between 2 groups were performed by a 2-way ANOVA and post hoc testing. Categorical variables were compared using the chi-square test or the Fisher exact test, when appropriate. Probability values of less than 0.05 were considered significant.

Results

Seventeen subjects (11%) developed heart failure during the follow-up period (group HF) (**Table 1**). They were significantly older than subjects who were free of any evidence of heart failure (non-HF group). Patients with hypertrophic cardiomyopathy or chronic kidney disease, a medical history of heart failure were more frequent in HF group subjects than in non-HF group. No statistically significant differences between 2 groups in the prevalence of hypertension with or without hypertrophy, or coronary artery disease. Subjects in group HF had significantly higher use of diuretics than those in group non-HF. Rates of use of angiotensin-converting enzyme inhibitors or angiotensine II receptor blockers and β-blockers were similar between the 2 groups. There were no significant differences between the 2 groups in systoric or diastolic blood pressure or body weight (**Table 2**).

On the echocardiographic examinations in the HF subjects, LV mass index was significantly ($p<0.05$)

Table 1 Clinical characteristics and medication of the heart failure and non-heart failure groups

	HF (n=17)	Non-HF (n=142)	p value
Age (years)	79±6	72±9	<0.05
Male gender	9 (53%)	51 (36%)	NS
HT with LVH	9 (53%)	52 (37%)	NS
HT without LVH	0 (0%)	18 (13%)	NS
CAD	2 (12%)	30 (21%)	NS
HCM	5 (29%)	9 (6%)	<0.01
CKD	6 (35%)	20 (14%)	<0.05
History of HF	6 (35%)	8 (6%)	<0.005
Arrhythmia	0 (0%)	11 (8%)	NS
ECG abnormalities	1 (6%)	8 (6%)	NS
Free from CD	0 (0%)	14 (10%)	NS
Medications			
ACEI or ARB	13 (76%)	93 (65%)	NS
β-blocker	4 (24%)	29 (20%)	NS
Diuretics	9 (53%)	11 (8%)	<0.0001
No medication	2 (12%)	39 (27%)	NS

HT, hypertension; LVH, left ventricular hypertrophy; CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; CKD, chronic kidney disease; HF, heart failure; ECG, electrocardiogram; CD, cardiac disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2 Hemodynamics and Doppler-echocardiographic data in the heart failure and non-heart failure groups

	HF (n=17)	Non-HF (n=142)	p value
SBP (mmHg)	131±18	133±10	NS
DBP (mmHg)	79±10	79±6	NS
Body weight (kg)	53±9	54±9	NS
LAD (mm)	41±5	40±6	NS
LVDd (mm)	42±8	43±6	NS
LVMI (g/m^2)	152±52	124±33	<0.05
LVEF (%)	67±13	68±8	NS
E' (cm/s)	4.0±0.8	4.6±0.7	<0.01
E/E'	19±7	13±6	<0.05
E/A	0.96±0.35	0.70±0.25	<0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure; LAD, left artial dimension; LVDd, left ventricular end-diastolic dimension; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; E, early diastolic transmitral inflow velocity; E', early diastolic mitral annular velocity; E/A, ratio of early to late transmitral inflow velocity.

Table 3 Tissue Doppler and pulse Doppler findings in the heart failure and non-heart failure groups

	Patients	HF (n=17)	Non-HF (n=142)
E/E'≤8	18	0 (0%)	18 (100%)
8<E/E'<15	97	6 (6%)	91 (94%)
E/E'≥15	44	11 (25%)	33 (75%)
E/A≤1	140	11 (8%)	129 (92%)
E/A>1	19	6 (32%)	13 (68%)

larger, E' was significantly ($p<0.01$) lower, and E/E' and E/A were significantly ($p<0.05$) higher than in the non-HF group. No statistically significant differences in LA or LV dimension or LV ejection fraction were found between the 2 groups. With respect to the pulse Doppler and tissue Doppler findings (**Table 3**), patients with an E/E' ≤ 8 were free of heart failure. Patients with an E/E' ≥ 15 developed heart failure more frequently than in patients with 8<E/E'<15 ($p<0.005$) or patients with an E/E' ≤ 8 ($p<0.05$). Patients with an E/A>1 developed heart failure more frequently than those with an E/A ≤ 1 ($p<0.01$). When combining the results of E/E' with those of E/A (**Fig. 1**), patients with an E/E' ≥ 15 and an E/A>1 had a significantly higher incidence (5 of 11 patients, 45%) of heart failure than with showing 8<E/E'<15 and an E/A ≤ 1 ($p<0.001$) or those with an E/E' ≤ 8 and an E/A ≤ 1.

Discussion

Of patients with an E' ≤ 5cm on tissue Doppler imaging, even those with normal LV systolic function, 11% developed heart failure within 18 months. In the patients with an E' ≤ 5cm and an E/E' ≥ 15 or an E/A>1, the incidence of heart failure was approximately 2- or 3-fold higher than in other subjects, respectively. Furthermore, in patients with an E' ≤ 5cm, an E/E' ≥ 15 and an E/A>1, the incidence of heart failure was approximately 4-fold higher than in other subjects. It is believed that E' is positively correlated with LV relaxation[6,7] and E/E' is positively correlated with LV filling pressure[10]. In the setting of a reduced E', patients with an E/E' ≥ 15 are believe to have reduced LV myocardial relaxation and

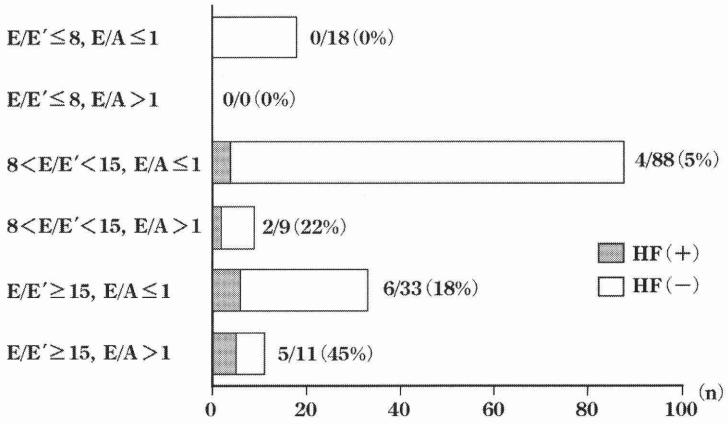

Figure 1 Combination of the results of E/E' ratio with E/A ratio.

elevated LV filling pressures. In this condition, patients with an E/A>1, which is considered to represent a pseudonormalization pattern, are believed to have markedly reduced LV myocardial relaxation. Consequently, we demonstrated that it is possible to determine the incidence of heart failure in patients with LV diastolic dysfunction based on the combination of tissue Doppler and pulse Doppler findings. Because the incidence of diastolic heart failure increases as the patients grow older[3,4], the incidence of diastolic heart failure will increase in the future.

A. Measurement of E' on tissue Doppler echocardiography

The E' wave on tissue Doppler imaging generally is measured in the septal or/and lateral mitral annular region from the apical approach. Peverill et al[11] reported that E' is not only of different magnitudes at the septal and lateral sites, but is not closely correlated. Generally, the lateral velocity exceeds the septal velocity for E'. The septal mitral annulus is influenced by the tricuspid and aortic annulus because it is connected to them by collagen fibers and is influenced by the right ventricle. Therefore, in the present study, we used the lateral annular velocity.

B. Limitations of tissue Doppler and pulse Doppler study

It is impossible to estimate the LV diastolic function accurately in patients with valvular heart disease[12] or constrictive pericarditis[13~15] because these disorders influence transmitral flow and mitral annular velocity. Patients with atrial fibrillation were excluded in the present study because of a lack of a transmitral A-wave. It is reported that the mean E' and E/E' in atrial fibrillation, similar to sinus rhythm, correlate with LV relaxation and LV filling pressure, respectively.[16] Therefore, we believe that tissue Doppler or pulse Doppler studies may be applied to patients with atrial fibrillation to estimate the LV diastolic function.

Conclusions

Patients with an E/E' ≥ 15 and E/A>1 had a significantly higher incidence (5 of 11 patients, 45%) of heart failure. Tissue Doppler and pulse Doppler studies provide useful information concerning whether patients are susceptible to the development of heart failure, even if their LV systolic function is not impaired.

Acknowledgements

We thank Hiroyuki Toide, Yasuyuki Kobayashi, Hiroki Okaniwa, Hiroko Maruyama, Eri Arai, and Rumi Higuchi of Echo Laboratory in Gunma Prefectural Cardiovascular Center for their excellent echocardiographic recordings.

References

1) Tsutsui H, Tsuchihashi M, Takeshita A: Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function. Am J Cardiol 2001; 88: 530–3.
2) Cleland JG, Swedberg K, Follath F, et al: The EuroHeart

Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003; 24: 442–63.
3) Aurigemma GP, Gaasch WH: Clinical practice. Diastolic heart failure. N Engl J Med 2004; 351: 1097–105.
4) Zile MR, Brutsaert DL: New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002; 105: 1387–93.
5) Klein AL, Hatle LK, Burstow DJ, et al: Doppler characterization of left ventricular diastolic function in cardiac amyloidosis. J Am Coll Cardiol 1989; 13: 1017–26.
6) Nagueh SF, Middleton KJ, Kopelen HA, et al: Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997; 30: 1527–33.
7) Oki T, Tabata T, Yamada H, et al: Clinical application of pulsed Doppler tissue imaging for assessing abnormal left ventricular relaxation. Am J Cardiol 1997; 79: 921–8.
8) Sohn DW, Chai IH, Lee DJ, et al: Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997; 30: 474–80.
9) Wang M, Yip GW, Wang AY, et al: Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. J Am Coll Cardiol 2003; 41: 820–6.
10) Ommen SR, Nishimura RA, Appleton CP, et al: Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000; 102: 1788–94.
11) Peverill RE, Gelman JS, Mottram PM, et al: Factors associated with mitral annular systolic and diastolic velocities in healthy adults. J Am Soc Echocardiogr 2004; 17: 1146–54.
12) Ohte N, Narita H, Akita S, et al: Striking effect of left ventricular high filling pressure with mitral regurgitation on mitral annular velocity during early diastole. A study using colour M-mode tissue Doppler imaging. Eur J Echocardiogr 2002; 3: 52–8.
13) Garcia MJ, Rodriguez L, Ares M, et al: Differentiation of constrictive pericarditis from restrictive cardiomyopathy: assessment of left ventricular diastolic velocities in longitudinal axis by Doppler tissue imaging. J Am Coll Cardiol 1996; 27: 108–14.
14) Oki T, Tabata T, Yamada H, et al: Right and left ventricular wall motion velocities as diagnostic indicators of constrictive pericarditis. Am J Cardiol 1998; 81: 465–70.
15) Ha JW, Oh JK, Ling LH, et al: Annulus paradoxus: transmitral flow velocity to mitral annular velocity ratio is inversely proportional to pulmonary capillary wedge pressure in patients with constrictive pericarditis. Circulation 2001; 104: 976–8.
16) Sohn DW, Song JM, Zo JH, et al: Mitral annulus velocity in the evaluation of left ventricular diastolic function in atrial fibrillation. J Am Soc Echocardiogr 1999; 12: 927–31.