Prognostic Value of Left Atrial Appendage Function in Patients With Dilated Cardiomyopathy

Takahide Ito, MD; Michihiro Suwa, MD; Ayaka Kobashi, MD;
Hatsumi Yagi, MD; Yoshiaki Otake, MD; Yuzo Hirota, MD

The purpose of the present study was to determine whether parameters of left atrial appendage (LAA) function, assessed by transesophageal echocardiography (TEE), could predict the clinical outcome in patients with dilated cardiomyopathy (DCM). Fifty-five patients (20 had ischemic cardiomyopathy; mean age, 56 ± 14 years) who underwent TEE to evaluate LAA function from 1992 to 1996 were studied. After a mean follow-up period of 34 ± 13 months, 16 patients died; the cause was cardiac in 14 and noncardiac in 2. Patients who died of cardiac cause had a lower LAA emptying velocity than survivors (38 ± 18 vs 54 ± 18 cm/s, $p=0.01$). There were, however, no significant differences between survivors and nonsurvivors with regard to the maximal LAA area (4.3 ± 1.3 vs 4.5 ± 0.9 cm², $p=0.55$), minimal LAA area (2.4 ± 1.1 vs 2.9 ± 1.1 cm², $p=0.13$), and LAA ejection fraction (46 ± 16 vs $36 \pm 18\%$, $p=0.05$). On the Cox proportional hazards model analysis, LAA emptying velocity <50 cm/s (chi-square 5.9, $p=0.02$), LAA ejection fraction $<43\%$ (chi-square 5.6, $p=0.02$), female gender (chi-square 5.2, $p=0.02$), pulmonary artery wedge pressure ≥ 14 mmHg (chi-square 4.8, $p=0.03$), E/A ratio ≥ 1.3 (chi-square 4.6, $p=0.03$), deceleration time <148 ms (chi-square 4.6, $p=0.03$), and cardiothoracic ratio $\geq 54\%$ (chi-square 4.3, $p=0.04$) were significantly related to cardiac death. The stepwise multivariate analysis revealed that LAA emptying velocity (chi-square 6.1, $p=0.01$) and gender (chi-square 5.4, $p=0.02$) were the independent predictors for outcome. In conclusion, the parameters of LAA function may be useful predictors of the clinical outcome in patients with DCM. (*Jpn Circ J* 2000; 64: 340–344)

Key Words: Atrial function; Dilated cardiomyopathy; Transesophageal echocardiography

Previous clinical and experimental data have shown that the left atrial appendage (LAA) acts as a buffer against atrial pressure increase during heart failure because the LAA has greater distensibility compared with the body of the left atrium.^{1–5} In addition, the LAA may contribute considerably to left ventricular filling because it accounts for up to 20% of the whole atrial volume⁶ and contracts more vigorously than the other parts of the atrium.^{4–7} Therefore, the role of the LAA in maintaining normal cardiac function should not be disregarded.

Dilated cardiomyopathy (DCM) is generally considered to have a poor prognosis and numerous studies have attempted to define the prognostic factors.^{8–11} It has been reported that patients with DCM and poor LAA function have a higher New York Heart Association (NYHA) functional class, elevated left ventricular filling pressures, and a restrictive filling pattern on Doppler echocardiography,^{12,13} all of which are important predictors of early cardiac death or the need for heart transplantation.^{14–16} However, the prognostic significance of LAA function remains to be elucidated, although there is increasing understanding of the pathophysiological role of this structure. In the present study, therefore, we examined whether parameters of LAA function, assessed by transesophageal echocardiography

(TEE), could predict clinical outcome in patients with ischemic or nonischemic DCM.

Methods

Patients

Fifty-five patients with DCM who were admitted between March 1992 and November 1996 were studied. There were 46 men and 9 women, aged 56 ± 14 (mean $\pm$ SD) years. The diagnosis of DCM was based on M-mode and two-dimensional echocardiography, revealing dilatation of the left ventricle (left ventricular end-diastolic dimension ≥ 60 mm) associated with diffuse depression of systolic function (left ventricular fractional shortening $<25\%$), and no segments of cardiac hypertrophy (left ventricular wall thickness <12 mm). Patients with more than grade II mitral regurgitation, atrial fibrillation, atrioventricular block, or renal failure (serum creatinine level ≥ 2 mg/dl) were excluded. Among the 55 patients, 35 were diagnosed as having idiopathic cardiomyopathy and 20 had ischemic cardiomyopathy. Among the latter group of patients, 14 had a history of myocardial infarction.

Echocardiography

All patients gave us informed consent before the induction of echocardiography, which was performed after stabilizing each patient with adequate medical therapy. Immediately before the TEE procedure, comprehensive transthoracic M-mode, two-dimensional, and Doppler echocardiography were performed. The left atrial dimension, left ventricular end-diastolic/end-systolic dimension, and the left ventricular fractional shortening were measured

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The Third Division, Department of Internal Medicine, Osaka Medical College, Takatsuki, Osaka, Japan

Mailing address: Takahide Ito, MD, The Third Division, Department of Internal Medicine, Osaka Medical College, 2-7 Daigaku-cho, Takatsuki City, Osaka 569-8686, Japan. E-mail: in3016@poh.osaka-med.ac.jp

Fig 1. Transesophageal echocardiography (longitudinal views). Left atrial appendage (LAA) emptying wave recorded by the pulsed-Doppler method (Left), and the maximal- (LAAMax) and minimal- (LAAMin) appendage areas calculated using planimetry (Right). The small arrow indicates the peak velocity point of the LAA emptying wave at atrial systole (LAAEV). LA, left atrium.

in the standard manner.¹⁷ Mitral flow velocities were obtained in the four-chamber view with the pulsed-Doppler sample volume placed at the tip of the mitral leaflets. The peak velocities of early filling (E) and atrial filling (A) waves were measured, and their ratio (E/A) was calculated. Deceleration time was also obtained by extrapolating the initial slope of E wave deceleration to the baseline.

TEE was performed using a Toshiba SSH-140A device equipped with a 5-MHz biplane transducer (Model PEF-507SB, Toshiba Medical Co, Japan). The echocardiographic probe was inserted into the esophagus under local pharyngeal anesthesia with the patient in the left lateral decubitus position. A one-lead electrocardiogram was displayed on the monitor during the procedure.

The LAA was visualized in the longitudinal view and appendage flow velocities were recorded by placing the pulsed Doppler sample volume 1–2 cm inside the LAA outlet. Then the LAA emptying velocity at atrial systole was measured (Fig 1). The LAA filling velocity was approximately equal to the emptying velocity, and so was not assessed separately in this study. Using computer-assisted planimetry, the LAA area immediately before the P wave (LAAMax) and just after the QRS complex (LAAMin) on the displayed electrocardiogram were measured (Fig 1). The LAA ejection fraction (LAAEF) was calculated from the following equation:

$$\text{LAAEF (\%)} = 100 \times (\text{LAAMax} - \text{LAAMin}) / \text{LAAMax}$$

For all measurements of Doppler variables, 3 consecutive beats were analyzed and averaged.

Hemodynamic Study

Of the 55 patients, 45 underwent both right and left heart catheterization prior to TEE. Nine patients who had previously been diagnosed as idiopathic DCM received only right heart catheterization at bedside. A balloon-tipped pulmonary artery catheter was inserted via the femoral or internal jugular vein and advanced into the pulmonary artery, where the mean pulmonary artery wedge pressure was recorded at end-expiration with the reference level at midchest.

Follow-up

The follow-up period was defined as beginning on the

day after TEE and ending on the most recent date or with death. The duration of follow-up was 34 ± 13 (mean $\pm$ SD) months. The cause of death was determined on the basis of hospital records and information from attending physicians, or through interviewing the patient's family by phone.

Statistical Analysis

The continuous and discrete variables between 2 groups were compared using the unpaired t test and chi-square test, respectively. The survival curves were assessed by the Kaplan-Meier method. Survival between 2 groups was compared using the logrank test. Cox proportional hazards model analysis (both univariate and multivariate) was performed to find which clinical and echocardiographic variables were significantly related to adverse outcome. In this model, chi-square analysis was utilized to assess the relative predictive power. The cut-off points was set at the median value of each variable, except for the NYHA functional class (I–II vs III–IV), gender (male vs female), and etiology (idiopathic vs ischemic). Variables found to be significant on univariate analysis were entered into a multivariate analysis. All data were expressed as the mean $\pm$ SD, and a p value less than 0.05 was considered significant.

Results

Clinical and Echocardiographic Features of Surviving and Nonsurviving Patients

During a follow-up period of up to 5 years, 16 of the 55 patients died. The cause of death was progressive heart failure in 12 (9 with idiopathic DCM and 3 with ischemic DCM), sudden death in 2 (one with idiopathic and the other with ischemic), and noncardiac death in 2 (both ischemic). Therefore, the following comparisons were obtained between surviving patients (n=39) and those who died from progressive or sudden heart failure (n=14).

Table 1 shows the clinical data of the patients divided into the 2 groups. There was no significant difference between survivors and nonsurvivors with regard to age, gender distribution, heart rate, etiology of cardiac disease or cardiac medications, but the latter group tended to be more symptomatic with a greater cardiothoracic ratio. The left atrial dimension, left ventricular end-diastolic/end-systolic dimension, and the left ventricular fractional short-

Table 1 Clinical and Echocardiographic Data of the Study Patients Except Those Who Died of Noncardiac Causes

Variable	Total group (n=53)	Survivors (n=39)	Nonsurvivors (n=14)	p value
Clinical data				
Age (years)	56±14	55±14	59±18	0.4
Male/female	45/8	35/4	10/4	0.10
Etiology (idiopathic/ischemic)	35/18	25/14	10/4	0.61
NYHA functional class (I–II/III–IV)	17/36	15/24	2/12	0.10
Cardiothoracic ratio (%)	54±4	53±4	57±4	0.00
Medication				
Digoxin	46 (87%)	33 (85%)	13 (93%)	0.39
ACE inhibitors	40 (75%)	29 (74%)	11 (79%)	0.75
Diuretics	37 (70%)	24 (62%)	13 (93%)	0.29
Nitrates	30 (57%)	20 (51%)	10 (71%)	0.19
Hemodynamic data (n=52)				
Heart rate (beats/min)	82±15	81±15	83±14	0.78
Pulmonary artery wedge pressure (mmHg)	14±8	13±9	18±8	0.08
Trans thoracic echocardiographic data				
LA dimension (cm)	4.3±0.6	4.2±0.6	4.4±0.7	0.41
LV end-diastolic dimension (cm)	6.5±0.6	6.5±0.6	6.6±0.6	0.88
LV fractional shortening (%)	16±6	16±6	15±6	0.62
E/A	1.3±0.6	1.2±0.7	1.7±1.0	0.04
Deceleration time (ms)	148±51	157±52	120±35	0.02
Parameters of LAA function				
LAA emptying velocity (cm/s)	50±19	54±18	38±18	0.01
LAA maximal area (cm ²)	4.4±1.2	4.3±1.3	4.5±0.9	0.55
LAA minimal area (cm ²)	2.5±1.1	2.4±1.1	2.9±1.1	0.13
LAA ejection fraction (%)	43±17	46±16	36±18	0.05

NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; LA, left atrial; LV, left ventricular; E/A, peak velocity ratio of early to atrial filling wave; LAA, left atrial appendage.

Table 2 Cox Proportional Hazards Model Analysis of Overall Mortality: Univariate Analysis

Variable	chi-square	95% CI	p value
Age ≥56 years	2.0	0.7–7.4	0.16
Gender, female	5.2	1.2–14.5	0.02
NYHA functional class III–IV	2.9	0.8–16.6	0.09
Etiology, idiopathic	1.3	0.2–1.6	0.25
Cardiothoracic ratio ≥54%	4.3	1.1–11.0	0.04
Pulmonary artery wedge pressure ≥14 mmHg	4.8	1.1–11.8	0.03
LV fractional shortening <16%	0.5	0.2–2.0	0.48
E/A ≥1.3	4.6	1.1–11.9	0.03
Deceleration time <148 ms	4.6	1.1–12.0	0.03
LAA emptying velocity <50 cm/s	5.9	1.4–18.3	0.02
LAA maximal area ≥4.4 cm ²	1.6	0.7–6.8	0.2
LAA minimal area ≥2.5 cm ²	1.4	0.6–6.9	0.2
LAA ejection fraction <43%	5.4	1.3–17.2	0.02

CI, confidence interval; other abbreviations as in Table 1.

Fig 2. Kaplan-Meier curves of survival for cardiac death in 53 patients with dilated cardiomyopathy, who were divided into 2 groups by the median value (50 cm/s) of the left atrial appendage emptying velocity (LAAEV). Numerals indicate the number and proportion of patients who survived.

ening were comparable between the 2 groups. The E/A ratio was higher, deceleration time was shorter, and the LAA emptying velocity was lower in patients who died than in surviving patients. The maximal/minimal LAA area was larger and LAA ejection fraction was lower in nonsurvivors, although these differences were not significant.

Prognostic Significance of LAA Function

Table 2 shows the results of Cox proportional hazards model analysis for the risk of cardiac death. Cardiothoracic ratio, LAA emptying velocity, LAA ejection fraction, gender, E/A ratio and the deceleration time were significantly related to the outcome. Stepwise multivariate analysis revealed that LAA emptying velocity (chi-square 6.1, $p=0.01$) and gender (chi-square 5.4, $p=0.02$) were the only significant predictors of cardiac death.

To further evaluate the prognostic significance of LAA function, we compared the survival of patients with an LAA emptying velocity <50 cm/s and those with an LAA emptying velocity ≥ 50 cm/s (Fig 2). The former group of patients had significantly reduced survival, with a median follow-up (34 months) survival rate of 69% compared with 96% in the latter group ($p<0.01$).

Discussion

The present study showed that the parameters of LAA function are important predictors of the clinical outcome in patients with ischemic or nonischemic DCM. Patients with a lower LAA emptying velocity had higher cardiac mortality than those with a higher LAA emptying velocity. Moreover, the patients who died tended to have a larger LAA and a lower LAA ejection fraction.

We also observed that female gender was one of the strongest predictor of adverse outcome. Limited data exist with regard to the relationship between gender and mortality in patients with DCM¹⁸ and the precise reason for the higher mortality rate in women is currently unknown, but in the present study can be mostly attributed to the fact that the patient population was relatively selective.

Mechanisms

In an experimental study, Hoit et al found that simultaneous volume loading of both the left atrium and the LAA caused a more rapid increase in atrial pressure than appendage pressure, with the appendage showing greater distensibility.¹ They, and others^{2,3} also observed that the pressure increase in the left atrium was larger in dogs with a resected LAA than in dogs with an intact appendage. These findings suggest that the LAA may act as a buffer against pressure increases in the atrial cavity, thereby preventing the development of pulmonary congestion. This concept is supported by some recent clinical studies, in one of which we demonstrated that after optimal treatment of heart failure, the size of the LAA decreased to a greater extent than the left atrium.⁴ Moreover, Tabata et al showed that in patients undergoing cardiac surgery, the pressure-volume relationship for the left atrium shifted upward and to the left after clamping the neck of the LAA.⁵

The LAA acts as a booster pump and contributes considerably to left ventricular filling. In an experimental study, Hondo et al observed that during volume loading, the LAA showed greater fractional shortening than the atrial body.⁶ We recently reported that after cardioversion of atrial fibrillation, the LAA emptying velocity increased over the next

week along with the atrial filling fraction of the Doppler transmitral flow curve, with the former showing greater recovery.⁷

It has been reported that the left ventricular filling parameters on Doppler echocardiography are important markers for predicting cardiac mortality in DCM.¹⁴⁻¹⁶ Patients with a restrictive filling pattern have a higher NYHA functional class, diminished exercise capacity, and a worse prognosis compared with those with a nonrestrictive pattern, irrespective of left ventricular systolic function.^{14,16} We recently reported that patients with a decreased LAA emptying velocity had a higher E/A ratio and a shorter deceleration time,¹² implying a worse cardiac status with a stiff ventricle and impaired atrial function.^{13-16,19} Indeed, in the present study, the E/A ratio was higher and the deceleration time was shorter in nonsurvivors. Therefore, restrictive physiology, as well as an abnormally functioning LAA, may affect the prognosis.^{14,16}

Study Limitations

The parameters of LAA function are partially dependent on age,²⁰ heart rate^{4,21} and loading conditions.^{4,13,22} but it is difficult to control these factors in a clinical study. In addition, the LAA parameters can change during long-term medical therapy. We also used the more troublesome TEE, compared with the transthoracic method, and this may lower the significance of the LAA parameters in predicting the prognosis of DCM, although in the present study the LAA parameters were more valuable than the clinically useful conventional indices, such as transmitral E/A ratio and deceleration time.

We used multiple parameters of LAA function to assess prognosis. A recent autopsy study showed that the LAA has multiple lobes²³ which may preclude accurate estimation of its area. Therefore, emptying velocity is more likely to be representative of LAA function.

Finally, this study focused on patients with heart failure and left ventricular systolic dysfunction. Therefore, the results cannot be generalized to heart failure patients who predominantly have left ventricular diastolic dysfunction.

Conclusions

We determined whether the parameters of LAA function could predict mortality in patients with ischemic or nonischemic DCM. Patients with a lower LAA emptying velocity had a worse outcome compared with those with a higher LAA emptying velocity, indicating that LAA function is useful for predicting the clinical outcome in these patients.

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