The Mitral L Wave

— A Marker of Advanced Diastolic Dysfunction in Patients With Atrial Fibrillation —

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Background The prominent mid-diastolic filling wave (mitral L wave) indicates advanced diastolic dysfunction in patients in sinus rhythm. The aim of the present study was to determine the clinical implications of the mitral L wave in patients with atrial fibrillation (AF).

Methods and Results Ninety-nine consecutive non-valvular chronic persistent AF patients were enrolled. The mitral L wave was defined as a distinct mid-diastolic flow velocity following the E wave with a peak velocity >20 cm/s. The prevalence of the L wave in AF patients (34/99, 34%) was significantly higher than that observed in patients in sinus rhythm during the same study period (23/946, 2.4%, $p<0.001$). Patients with AF and L wave were older, more frequently female and had a slower heart rate, shorter isovolumic relaxation times, larger E wave velocities and lower early diastolic mitral annulus velocity (E') resulting in the higher E/E' compared to those without L waves. The left atrial volume index was significantly larger in patients with an L wave. The Valsalva maneuver decreased, and leg elevation increased, the amplitude of the L wave in the subset of patients who received these procedures.

Conclusions The appearance of the mitral L wave in AF is relatively common, and its presence indicates advanced diastolic dysfunction, including elevated filling pressures and distended noncompliant LA. (*Circ J* 2007; 71: 1244–1249)

Key Words: Atrial fibrillation; Diastolic function; Mitral L wave

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia, with a reported incidence of 0.4% to 1% in general population^{1,2}. The prevalence of AF increases with age, reaching 8% in those older than 80 years³. It has been estimated that 2.2 million people in United States of America and 4.5 million in the European Union have paroxysmal or persistent AF¹. AF is associated with an increased risk of stroke, heart failure and all-cause mortality². It is an extremely costly public health problem, which is accompanied by a remarkable social burden⁴. Thus, early detection of left ventricular (LV) dysfunction in patients with AF is important in predicting which patients are at high risk of developing heart failure and in providing therapeutic intervention to reduce the future incidence of heart failure and its accompanied medical and social costs. AF is associated with diastolic dysfunction, even in the presence of a normal LV ejection fraction, resulting in a considerable risk of diastolic heart failure^{2,5,6}. The precise assessment of diastolic dysfunction in AF is extremely difficult because irregular RR intervals produce constantly changing loading conditions and the applicability of standard Doppler echocardiographic criteria for the diastolic dysfunction is hampered by the lack of late filling wave (A wave) from atrial contraction⁷. Averaging some diastolic in-

dices using Doppler echocardiography in multiple consecutive heart beats is tedious and cumbersome, and its routine application is often difficult in busy clinical scenarios^{8,9}.

In sinus rhythm, mitral inflow velocities usually consist of 2 forward flow velocities: the early rapid filling wave (E wave) and A wave. However, mitral inflow may have additional forward flow during mid-diastole. The prominent mid-diastolic filling wave, which has been described as a mitral L wave, is rarely encountered in sinus rhythm, but its existence has been reported as indicating advanced diastolic dysfunction with elevated LV filling pressures^{10–13}. We often observed distinct forward flow immediately after the E wave in patients with AF (Fig 1). We hypothesized that this wave might be a marker of advanced diastolic dysfunction in patients with chronic persistent AF. Thus, the aim of the present study was to determine the incidence of the mitral L wave and its clinical implication in patients with chronic persistent non-valvular AF.

Methods

Study Population

From November 2005 to October 2006, we consecutively enrolled 99 patients with chronic persistent non-valvular AF who underwent 2-dimensional (2D) and Doppler transthoracic echocardiographic studies. Nine hundred and forty-six patients in sinus rhythm, who underwent echocardiographic studies with the same ultrasound machine during the same study period, were identified and the prevalence of the mitral L wave was determined in our echocardiographic laboratory. Patients with mitral valvular abnormalities,

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Fig 1. Representative cases associated with (A, B) or without (C) mitral L wave in patients with atrial fibrillation. Right panel shows mitral annular velocity.

paroxysmal AF and other rhythm disturbances were excluded. The present study complied with the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained in all patients.

Clinical Data

Patient medical records were reviewed for demographic data, cardiovascular risk factors, medication use and heart failure status at the time of echocardiography. Hypertension was defined as ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic pressure on more than one determination and/or if the patient was treated with antihypertensive medication. Diabetes mellitus was diagnosed as a fasting glucose level of more than 126 mg/dl and/or continuous hypoglycemic treatment. Hypercholesterolemia was defined as fasting total cholesterol > 220 mg/dl and/or treatment with lipid-lowering drugs. Coronary artery disease was defined as a history of myocardial infarction, coronary revascularization or significant stenosis ($> 50\%$ diameter stenosis) of the major coronary artery using coronary angiography. The prevalence of heart failure at the time of index echocardiography was determined from clinical records, including chest X-ray, patient history and physical examination, and was verified independently by one cardiologist blinded to L wave status.

Echocardiography

M-mode, 2D and Doppler echocardiography were performed using a commercially available ultrasound system (Vivid 7, GE Healthcare, Milwaukee, MI, USA). The 2D harmonic parasternal long-axis view was acquired to obtain a maximized LV cavity dimension to take wall thickness and chamber diameter measurements perpendicular to the walls at the level of chordae tendineae. LV end-diastolic and end-systolic dimensions, and interventricular and posterior wall thicknesses were measured using M-mode echocar-

diography. LV mass was derived from the Devereux and Reichek formula.¹⁴ The 2D harmonic imaging was also performed from the apical window to obtain apical 4- and 2-chamber views. For both apical views, end-diastolic and end-systolic frames were selected and endocardial contours, including the papillary muscles in the LV cavity, were traced manually. LV volume and ejection fractions were calculated using a modified biplanar Simpson's formula.¹⁵ Left atrial (LA) volume was measured with the modified biplanar area-length method.¹⁵ From the mitral inflow velocities, the following variables were measured: peak velocity of the E wave, its acceleration and deceleration time, and time interval between the peak of the R wave on electrocardiogram and the onset of E velocity. The mitral L wave was verified as a distinct forward flow velocity after the E wave with a peak velocity > 20 cm/s.^{11–13} Tissue Doppler imaging (TDI) was used to measure the mitral annular velocity. For the TDI, the filter setting was lowered, and the Nyquist limit was adjusted (range: 16–20 cm/s). Gain was minimized to allow a clear tissue signal with minimal background noise. From the apical 4-chamber view, a 6-mm sample volume of TDI was placed at the septal corner of the mitral annulus. Peak systolic (S') and early diastolic (E') annular velocity and the time interval between the R wave to the onset of E' were measured. All Doppler measurements were recorded with simultaneous electrocardiography at a sweep speed of 50 to 100 mm/s. Doppler data were averaged on 6 to 8 consecutive beats. To evaluate the effect of preload alteration on the L wave profile, the mitral inflow filling pattern was also observed during a Valsalva maneuver in 8 patients and leg elevation in 7 patients with mitral L wave, respectively.

Statistical Analysis

Continuous data are presented as mean $\pm$ SD, and categorical data as number and percentage. Comparison be-

Table 1 Clinical Characteristics in Study Patients

	Patients with L wave (n=34)	Patients without L wave (n=65)	p value
Age	81±8	73±9	<0.001
Sex (M/F)	11/23 (32%)	51/14 (78%)	<0.001
BSA (m ²)	1.50±0.23	1.61±0.20	<0.05
Medication			
ACEI/ARB	6 (18%)	21 (32%)	NS
-blocker	9 (26%)	20 (31%)	NS
Ca antagonist	11 (32%)	15 (23%)	NS
Digitalis	18 (53%)	27 (42%)	NS
Diuretics	17 (50%)	22 (34%)	NS
Risk factor			
HT	19 (56%)	41 (63%)	NS
HL	13 (38%)	12 (18%)	<0.05
DM	11 (32%)	19 (29%)	NS
Smoking	6 (18%)	11 (17%)	NS
Proven CAD	5 (15%)	7 (11%)	NS
BNP (pg/ml)	570±485 (15)	279±204 (23)	<0.05

BSA, body surface area; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HT, hypertension; HL, hypercholesterolemia; DM, diabetes mellitus; CAD, coronary artery disease; BNP, brain natriuretic peptide.

Table 2 Echocardiographic Findings in Patients With and Without Mitral L Wave

	Patients with L wave (n=34)	Patients without L wave (n=65)	p value
HR (beats/min)	71±17	82±17	<0.005
IVS (mm)	11±2	11±2	NS
PW (mm)	10±2	10±2	NS
LVDd (mm)	48±7	48±9	NS
LVDs (mm)	31±7	32±10	NS
LAD (mm)	53.7±8.9	49.1±8.2	<0.05
LVEDVI (ml/m ²)	40.6±14.0	41.9±17.1	NS
LVESVI (ml/m ²)	18.3±10.4	19.5±13.9	NS
LVEF (%)	56.7±14.1	56.8±14.3	NS
LVMI (g/m ²)	125±30	111±32	<0.05
% of LVH	85%	43%	<0.001
LAVI (ml/m ²)	92.9±48.0	72.7±45.7	<0.05
E velocity (cm/s)	93±20	82±17	<0.01
S' velocity (cm/s)	4.4±1.0	4.8±1.2	NS
E' velocity (cm/s)	5.4±1.4	6.7±2.0	<0.001
E/E'	18.0±4.9	13.2±4.4	<0.001
% of E/E' >15	71%	31%	<0.01
DcT/√R-R (ms)	167±43	176±47	NS
IVRT/√R-R (ms)	104±17	114±16	<0.01
(R-E'/√R-R)-(R-E/√R-R)	3.8±23.6	-18.5±38.8	<0.005
PAP (mmHg)	44.9±13.6 (28)	35.8±8.6 (47)	<0.001

HR, heart rate; IVS, interventricular septum; PW, posterior wall; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LAD, left atrial diameter; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; LAVI, left atrial volume index; DcT, deceleration time of the E wave velocity; IVRT, isovolumic relaxation time; PAP, pulmonary artery pressure.

tween patients with mitral L wave and those without an L wave was analyzed using the t-test for continuous variables or Fischer exact test for dichotomous variables. A p value <0.05 was considered statistically significant. Multivariable linear regression analysis was used to test for independent associations between the mitral L wave and various parameters, including age, sex, heart rate, LV volume and mass, LA volume, isovolumic relaxation time, deceleration time of the E wave and E/E'. The event-free survival curve was assessed using a Kaplan-Meier analysis.

Results

Of 99 non-valvular chronic persistent AF patients, 34

(34%) showed a mitral L wave. Its incidence was significantly higher than that observed in patients with sinus rhythm who underwent echocardiographic examination during the same period (2.4%, 23/946, p<0.001). Table 1 shows the clinical characteristics of 34 AF patients with an L wave and 65 AF patients without. Patients with an L wave were older and more frequently female. The prevalence of heart failure at the time of echocardiographic examination tended to be higher in patients with an L wave compared to those without (44% vs 23%, p<0.053). No significant differences in cardiac medications were noted between the 2 groups. The B-type natriuretic peptide (BNP) was measured on the same day as the echocardiographic examination for 38 out of 99 AF patients. The BNP level was significantly

Fig2. Effect of Valsalva maneuver (Upper panel) and leg elevation (Lower panel) on the profile of mitral L wave. Valsalva maneuver produced prolongation of the deceleration time of the E wave and a reduction in the amplitude of the mitral L wave. In contrast, leg elevation produced a shortened deceleration time and augmented the amplitude of the mitral L wave.

higher in patients with an L wave compared to patients without (570 ± 485 pg/ml vs 279 ± 204 pg/ml, $p < 0.05$).

Table 2 shows the echocardiographic variables of the 2 groups. No significant difference in wall thickness, LV diameter, LV volume and LV ejection fraction was noted between 2 groups. The LA volume index was significantly larger in patients with an L wave. Patients with an L wave had a slower heart rate, shorter isovolumic relaxation times and larger E wave velocities. The deceleration time of the E wave did not differ between the 2 groups. Pulmonary arterial pressure, predicted from tricuspid regurgitation velocity, was analyzed in 75 patients. Among them, pulmonary arterial pressure was significantly higher in 28 patients with an L wave than for the 47 patients without. E' was significantly lower in patients with an L wave, resulting in a higher E/E' ratio compared to those without L waves (18.0 ± 4.9 vs 13.2 ± 4.4 , $p < 0.001$). An E/E' ratio greater than 15 was observed in 71% of patients with an L wave in contrast to 31% in those without ($p < 0.01$). The RR interval corrected time difference between the onset of the E wave and E' was also prolonged in patients with an L wave. The average amplitude of the mitral L wave in 34 AF patients with a mitral L wave was 26.7 ± 5.5 cm/s. No significant correlation was noted between the amplitude of the L wave and E/E' or LA volume. However, a weak but significant correlation was noted between the amplitude of the mitral L wave and plasma BNP level ($r = 0.49$, $p < 0.05$, $n = 15$).

Multivariable linear regression analysis showed that the mitral L wave was associated with heart rate ($p = 0.0011$), female gender ($p = 0.0289$), E/E' ($p = 0.0311$) and deceleration time of the E wave ($p = 0.0464$).

The Valsalva maneuver and leg elevation was performed in a subset of patients with L wave to determine the effect of preload alteration on LV inflow velocity profile (Fig 2). Valsalva maneuver significantly decreased the amplitude of the L wave (from 28.4 ± 3.7 cm/s to 7.6 ± 8.3 cm/s, $p < 0.001$) in all 8 patients who underwent this procedure. The reduction of the amplitude of the E wave velocity (from 98.8 ± 18.3 cm/s to 89.8 ± 16.2 cm/s, $p < 0.005$) and prolonged deceleration time of the E wave (from 159 ± 18 ms to 231 ± 39 ms,

Fig3. Kaplan-Meier event free survival between patients with mitral L wave and those without.

$p < 0.001$) was also observed. Leg elevation produced an augmentation of the L wave (from 28.4 ± 3.7 cm/s to 33.2 ± 4.5 cm/s, $p < 0.05$) in 6 of 7 patients who received this procedure, the deceleration time of the E wave did not change considerably (from 159 ± 18 ms to 161 ± 25 ms, $p = \text{NS}$).

Complete follow up data were available in 91 AF patients. During a mean of 5.7 months (range 3 days to 12 months), 9 cardiac events (1 cardiac death and 8 heart failures necessitating hospitalization) developed, including 6 patients with an L wave and 3 without. Kaplan-Meier analysis showed significantly higher event rates in patients with an L wave compared to those without L wave (6 month event rate; 18% vs 6%, log-rank, chi-square 4.06, $p < 0.05$, Fig 3).

Discussion

The present study demonstrates that the prevalence of a mitral L wave in patients with AF is relatively common and often associated with higher E/E' , elevated BNP level and enlarged LA volumes, reflecting a more advanced stage of diastolic dysfunction. Thus, the identification of a mitral L

wave is a simple and novel method for detecting advanced diastolic abnormalities in patients with AF.

Assessment of Diastolic Function in AF

AF is the most common sustained arrhythmia in the elderly, and is associated with an increased risk of heart failure and cardiovascular mortality.² Non-invasive estimation of LV function, especially LV filling pressure, is therefore important in selecting patients who need aggressive intervention. Additionally, it can be used to determine high risk patients who may develop heart failure. LA dilatation is usually a hallmark of long-standing elevated LV filling pressures.^{6,16–18} However, patients with AF commonly have a dilated left atrium, hence the use of LA dimensions or volumes may not allow for good discrimination between elevated and normal LV filling pressures. The assessment of diastolic function using conventional Doppler mitral flow and pulmonary vein flow indices in AF is often difficult because of the altered left chamber loading conditions due to beat-to-beat irregularity and loss of atrial contraction. Although a previous study reported that mitral annulus velocity is useful in the detection of impaired LV relaxation and estimation of LV filling pressure even in patients with AF, it requires averaging the values in multiple cardiac cycles.⁵ Nagueh et al and Chirillo et al independently developed equations that predict LV filling pressure in patients with AF, but those equations were not easily adaptable for routine use in daily clinical practice.^{19,20}

Current Study

Although the reported incidence is low (1%), mitral L wave in sinus rhythm has been reported to be associated with elevated filling pressures, delayed myocardial relaxation and a slow heart rate.^{11–13} This unique mitral inflow velocity pattern indicates advanced diastolic dysfunction. We found the incidence of mitral L wave in AF (34%) is significantly higher than that observed in patients with sinus rhythm (2.4%) during the same study period. Patients with AF and L waves were older, more frequently female and experienced LV hypertrophy at higher rates. They had a slower heart rate, larger LA volume, shorter isovolumic relaxation times, larger E wave velocities and lower E', resulting in the higher E/E' compared to those without L waves. The genesis of a mitral L wave is thought to be the result of: (1) delayed and prolonged LV relaxation; and/or (2) elevated LA pressure.¹³ The extension of the relaxation phase creates a mid-diastolic pressure gradient across the mitral valve with resultant additional ventricular filling.¹⁰ Even after initial rapid LV filling, LA pressure can remain elevated during mid-diastole as pulmonary venous flow fills a distended noncompliant LA. Either condition or both could produce a pressure gradient between LA and LV during mid-diastole, resulting in mid-diastolic LV filling. The Valsalva maneuver decreased L wave amplitude, and leg elevation increased L wave amplitude in a subset of patients in the present study. Preload-dependent characteristics were in agreement with previous studies.^{11–13} Because LA compliance is severely depressed in AF with dilated LA, the reestablishment of the elevation of LA pressure over LV pressure during mid-diastole is likely to be a more plausible explanation of the genesis of a mitral L wave in AF. Thus, the appearance of an L wave in AF is also a maker of advanced diastolic dysfunction. In contrast to the other Doppler diastolic indices, the identification of a mitral L wave is relatively easy and does not require a tedious cal-

culation process. As a result, it has the potential for assessing LV diastolic function in patients with AF.

The present study also demonstrates that patients with a mitral L wave were associated with higher subsequent cardiac event rates, especially the recurrence of congestive heart failure. However, a relatively shorter follow-up period and timing of the examination should be addressed in the present study. Echocardiographic examination was performed at the time of the attending physician's request and, thus, not systematically performed. Some patients still had symptoms of heart failure at the time of the examination, irrespective of heart failure treatment. The determination of the prognostic value of the mitral L wave just before the hospital discharge in a larger population and longer follow-up period merits further study. Experimental and clinical studies have demonstrated that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers may prevent LA remodeling due to a decrease atrial pressure and reduced fibrosis.^{2,21} Although statistically not significant, patients with a mitral L wave had taken less ACEIs/angiotensin receptor blockers compared to those without in the present study. Further study is needed to determine whether ACEIs/angiotensin receptor blockers will decrease the incidence of mitral L waves in patients with AF.

Study Limitations

There were some limitations in the present study. Invasive measurements of LV filling pressure or pulmonary arterial pressure were not performed in this study. However, the accuracy of E/E' for predicting LV filling pressure and pulmonary capillary wedge pressure has been validated.^{22–25} Similar to previous studies, several standard Doppler diastolic indices were calculated by averaging the values in multiple cardiac cycles. This would produce some variability in the measurements. As with previous studies, the mitral L wave was defined as a distinct forward flow velocity after the E wave with a peak velocity >20 cm/s in the present study.^{11–13} In addition to its arbitrary cut-off values, the beat-to-beat variability of the loading condition and diastolic time interval in AF affects the appearance and degree of the mitral L wave. Thus, we might underestimate its true incidence because a faster heart rate can make the amplitude of mitral L wave <20 cm/s or may mask the existence of the mitral L wave in some cases.

In conclusion, the mitral L wave is relatively common in patients with chronic persistent non-valvular AF, and reflects elevated LV filling pressure and enlarged noncompliant LA. Thus, the detection of mitral L waves is a simple and useful finding for diagnosing advanced diastolic dysfunction in patients with AF.

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