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Triphasic mitral inflow velocity with mid-diastolic flow: The presence of mid-diastolic mitral annular velocity indicates advanced diastolic dysfunction☆

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Abstract Mitral inflow filling pattern usually consists of 2 forward flow velocities in sinus rhythm: early rapid filling (*E*) and late filling with atrial contraction (*A*). However, additional mid-diastolic flow velocity may be present resulting in triphasic mitral inflow filling pattern. When mitral inflow is triphasic, mitral annulus velocity recorded by tissue Doppler imaging (TDI) frequently demonstrates a mid-diastolic component (*L′*). The significance of *L′* has not been explored previously. The purpose of this study was to explore possible mechanisms and clinical implications of triphasic mitral inflow with or without *L′* using TDI and proBNP. Of 9004 patients who underwent transthoracic echocardiography from March to November 2003, 83 (0.9%) patients (33 male, 50 female; mean age, 63 ± 10 years) with a triphasic mitral inflow velocity pattern, including mid-diastolic flow velocity of at least 0.2 m/s, and sinus rhythm were prospectively identified in our clinical echocardiography laboratory. Peak velocity of *E*, mid-diastolic (*L*), and *A*, and deceleration time (DT) of the *E* wave velocity were measured. Diastolic mitral annular velocities were measured at the septal corner of the mitral annulus by TDI from the apical 4-chamber view. ProBNP was measured at

Abbreviations: *A*, peak filling velocity of mitral inflow during atrial contraction; *E*, peak filling velocity of mitral inflow during early diastole; *E′*, early diastolic mitral annular velocity; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; *L′*, mid-diastolic component of mitral annular velocity; proBNP, N-terminal pro-brain natriuretic peptide; TDI, tissue Doppler imaging.

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the time of echocardiogram using a quantitative electrochemiluminescence immunoassay. Mean heart rate was 54 ± 6 beats/min (range, 40–67). Mean left ventricular (LV) ejection fraction (EF) was 64 ± 13% and LV systolic dysfunction (EF < 40%) was present in only 6 (7%). Patients were classified into 2 groups: group 1 ($n = 47$) included those who had L' and group 2 ($n = 36$) included those without L'. Group 1 patients had significantly higher peak velocity (35 ± 14 vs 26 ± 6 cm/s, $p = 0.0002$) and TVI (35 ± 14 vs 26 ± 6 cm/s, $p = 0.0002$) of L, E/E' (18 ± 8 vs 14 ± 6, $p = 0.02$), and left atrial volume index (42 ± 14 vs 34 ± 10 ml/m^2, $p = 0.0037$). E' (4.7 ± 1.3 vs 6.2 ± 2.3 cm/s, $p = 0.001$) and A' (6.2 ± 2.0 vs 8.6 ± 3.4 cm/s, $p = 0.0006$) were significantly lower in group 1 compared with those of group 2. ProBNP was significantly higher in group 1 (847 ± 1461 vs 438 ± 1039 pmol/l, $p = 0.0012$) and it was above normal in all except in 1 patient of group 1. In conclusion, the presence of L' in subjects with triphasic mitral inflow velocity pattern with mid-diastolic flow is associated with higher E/E', elevated proBNP and enlarged left atrium indicating advanced diastolic dysfunction with elevated filling pressures. This unique mitral annular velocity pattern should be helpful in identifying the patients with advanced diastolic dysfunction and increased LV filling pressures.

Introduction

Diastole consists of 3 phases: early rapid filling, diastasis, and atrial contraction. Because diastasis is the quiescent phase characterized by an overall balance of forces and an absence of an atrioventricular pressure gradient, mitral inflow velocities obtained by pulsed wave Doppler echocardiography usually consist of 2 forward flow velocity peaks in sinus rhythm: early diastolic peak from early rapid filling (E) and late filling peak from atrial contraction (A). However, mitral inflow may have additional forward flow velocity during mid-diastole.[1,2] The prominent mid-diastolic filling wave, which has been described as an L wave,[1] is rarely encountered and the mechanism and its clinical implications are still elusive.

Tissue Doppler imaging (TDI) is a recent Doppler application that allows direct measurement of myocardial velocities. Previous studies suggested that early diastolic mitral annular velocity (E') recorded by TDI is a simple and reliable non-invasive index of left ventricular (LV) relaxation[3–6] with a significant inverse correlation between E' and τ.[4,5] It is also useful in estimating LV filling pressure.[6,7] When mitral inflow is triphasic, mitral annulus velocity recorded by TDI frequently demonstrates a mid-diastolic component (L'). However, the significance of L' has not been explored previously. Recently, N-terminal pro-brain natriuretic peptide (proBNP), a peptide hormone secreted from the cardiac ventricles in response to increased pressure and volumes, has been shown as a good predictor of high LV end-diastolic pressure (LVEDP) in patients with LV systolic dysfunction.[8] However, no data are available regarding TDI and proBNP in patients with triphasic mitral inflow with mid-diastolic flow. The purpose of this study was to explore possible mechanisms and clinical implications of triphasic mitral inflow with or without L' using TDI and proBNP.

Methods

Study population

Of 9004 patients who underwent transthoracic echocardiography from March to November 2003, 83 (0.9%) patients (33 male, 50 female; mean age, 63 ± 10 years) with a triphasic mitral inflow velocity pattern, including mid-diastolic flow velocity of at least 0.2 m/s, and sinus rhythm were prospectively identified in our clinical echocardiography laboratory. Patients were classified into 2 groups: group 1 ($n = 47$) included those who had L' and group 2 ($n = 36$) included those without L'. Comprehensive echocardiographic evaluation of systolic and diastolic functions was performed. Clinical data were obtained from clinical notes. *This study was approved by Institutional Review Board.*

Two-dimensional and Doppler echocardiography

Two-dimensional and Doppler echocardiography was performed with a commercially available echocardiographic unit equipped with an imaging transducer having both pulsed wave and tissue Doppler capability. The ejection fraction (EF) was calculated with 2-dimensional echocardiography,

with a modification of the method of Quinones et al.[9] Left atrial volume was measured with the modified biplane area-length method.[10,11] From the apical window, the pulsed Doppler sample volume was placed at the mitral valve tips, and 5–10 cardiac cycles were recorded. From the mitral inflow velocities, the following variables were measured: peak velocity and time velocity integral of early (*E*), mid-diastolic (*L*), and late (*A*) filling, and deceleration time (DT) of the *E* wave velocity. TDI was used to measure mitral annular velocities, *E′*, *A′*, and *L′* (Fig. 1). For TDI, the filter setting was lowered, and the Nyquist limit was adjusted (range, 15–20 cm/s). Gain was minimized to allow for a clear tissue signal with minimal background noise. From the apical 4-chamber view, a 2- to 3-mm sample volume of TDI was placed at the septal corner of the mitral annulus. Measurements were recorded with simultaneous electrocardiography at a sweep speed of 50–100 mm/s. Mitral inflow filling pattern was also observed during Valsalva maneuver to evaluate the effects of preload.

Measurement of NT proBNP

Blood samples for proBNP analysis were drawn *immediately after echocardiographic study*, and kept at 4 °C and analyzed within 4 h of sampling. Before analysis, each tube was inverted several times to ensure homogeneity. The whole blood was then analyzed in triplicate by electrochemiluminescence immunoassay method for proBNP (Elecsys proBNP, Roche Diagnostics, Basel, Switzerland).

Results

Clinical characteristics

The mean heart rate of 33 men and 50 women (mean age, 63 ± 10 years) at the time of the echocardiogram was 54 ± 6 beat/min (range, 40–67). Systolic and diastolic blood pressures at the time of the examination were 139 ± 22 and 80 ± 14 mmHg, respectively. However, a history of hypertension was present in 52 (63%) of 83 patients. Most common associated conditions were coronary artery disease ($n = 23$), hypertrophic cardiomyopathy ($n = 16$), and end-stage renal failure ($n = 10$). Of 83 patients, 14 patients (17%) presented as a congestive heart failure. Two patients had paroxysmal atrial fibrillation.

Echocardiography

LV end-diastolic and end-systolic dimensions and EF were 51 ± 7 mm, 34 ± 8 mm, and 64 ± 13%,

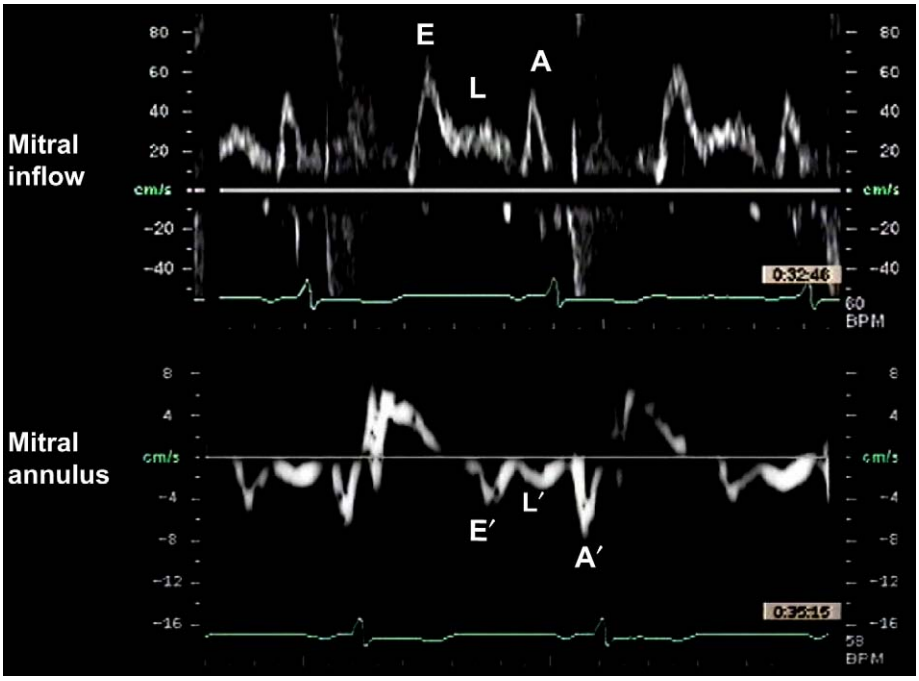

Figure 1 Mitral inflow and annulus velocity pattern in a patient with triphasic mitral inflow with prominent mid-diastolic filling (*L*). *E*, peak velocity of mitral inflow early filling; *E′*, early diastolic mitral annular velocity; *A*, peak velocity of mitral inflow late filling during atrial contraction; *A′*, late diastolic mitral annular velocity; *L′*, mid-diastolic mitral annular velocity.

respectively. The thickness of the ventricular septum and the posterior wall was 11 ± 3 and 10 ± 2 mm, respectively. Mean LV mass was 216 ± 73 g. LV hypertrophy, defined as an LV mass index of more than 116 g/m^2 in men and more than 104 g/m^2 in women,[12] was noted in 54 patients (65%). Mean left atrial volume index was 39 ± 13 ml/m^2. Left atrial volume index was above normal, greater than 23 ml/m^2 in 75 (90%) of 83 patients. LV systolic dysfunction, an EF of less than 40%, was present in 6 (7%) of 83 patients. Patients were classified into 2 groups: group 1 ($n = 47$) included those who had L' and group 2 ($n = 36$) included those without L'. There were no significant differences in age, gender, heart rate, *systolic and diastolic blood pressures*, LV end-diastolic, end-systolic dimensions, EF and LV mass index. Left atrial volume and left atrial volume index of group 1 were significantly larger than those of patients of group 2 (left atrial volume, 68 ± 23 vs 55 ± 18 ml, $p = 0.01$; left atrial volume index, 42 ± 14 vs 34 ± 10 ml, $p = 0.0037$) (Tables 1 and 2). Group 1 patients had significantly higher peak velocity (35 ± 14 vs 26 ± 6 cm/s, $p = 0.0002$) and TVI (6.2 ± 3.2 vs 4.6 ± 1.1 cm, $p = 0.0079$) of L. E' (4.7 ± 1.3 vs 6.2 ± 2.3 cm/s, $p = 0.001$) and A' (6.2 ± 2.0 vs 8.6 ± 3.4 cm/s, $p = 0.0006$) were significantly lower in group 1 compared with that of group 2. E/E' was significantly higher in patients of group 1 compared with that of group 2 (18 ± 8 vs 14 ± 6, $p = 0.02$) (Table 3). Normal filling pressure, estimated as an E/E' ratio less than 8, was observed in only 3 (3.6%) patients but none of the patients from group 1. E/E' ratio more than 15 was observed in 30 (64%) of 47 patients of group 1 and 13 (36%) of 36 patients of group 2. E' was less than 0.1 m/s in all except in 2 patients and these patients were from group 2. Valsalva maneuver performed in 81 patients unmasked a delayed relaxation pattern in 69 (85%).

Table 1 Comparison of clinical variables between patients with or without mid-diastolic mitral annular velocity (L')

	Group 1 ($n = 47$)	Group 2 ($n = 36$)	p Value
Age (years)	62 ± 11	65 ± 9	0.12
Gender (M/F)	15/32	18/18	0.1
BSA (m^2)	1.61 ± 0.16	1.66 ± 0.17	0.19
Hypertension	26 (62%)	26 (72%)	0.38
Diabetes mellitus	10 (24%)	11 (31%)	0.56
Systolic BP (mmHg)	140 ± 23	139 ± 20	0.81
Diastolic BP (mmHg)	81 ± 12	79 ± 17	0.58
HR (beat/min)	54 ± 6	52 ± 6	0.11

M, male; F, female; BSA, body surface area; BP, blood pressure; HR, heart rate.

Table 2 Echocardiographic variables between patients with or without mid-diastolic mitral annular velocity (L')

	Group 1 ($n = 47$)	Group 2 ($n = 36$)	p Value
LVEDD (mm)	50 ± 6	52 ± 7	0.31
LVESD (mm)	34 ± 8	34 ± 8	0.81
LV EF(%)	63 ± 15	64 ± 10	0.67
IVS (mm)	12 ± 4	11 ± 2	0.09
PW (mm)	10 ± 2	10 ± 2	0.77
LVMI (g/m^2)	136 ± 44	129 ± 40	0.45
LAV (ml)	68 ± 23	55 ± 18	0.01
LAVI (ml/m^2)	42 ± 14	34 ± 10	0.0037

LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; EF, ejection fraction; IVS, interventricular septum; PW, posterior wall; LVMI, left ventricular mass index; LAV, left atrial volume; LAVI, left atrial volume index.

Plasma level of proBNP

ProBNP was normal, defined as ≤20 pmol/l, in only 7 (7%) of 83 patients and it was significantly higher in group 1 (847 ± 1461 vs 438 ± 1039 pmol/l, $p = 0.0012$) when compared with that of group 2. All except 1 patient of group 1 had elevated proBNP.

Table 3 Mitral inflow and annular velocities and proBNP between patients with or without mid-diastolic mitral annular velocity (L')

	Group 1 ($n = 47$)	Group 2 ($n = 36$)	p Value
E (m/s)	0.77 ± 0.22	0.79 ± 0.20	0.68
A (m/s)	0.60 ± 0.26	0.65 ± 0.18	0.35
E/A	1.5 ± 0.6	1.3 ± 0.5	0.22
DT (ms)	192 ± 46	192 ± 45	0.97
L (m/s)	0.35 ± 0.14	0.26 ± 0.06	0.0002
TVI of L	6.2 ± 3.2	4.6 ± 1.1	0.0079
E' (cm/s)	4.7 ± 1.3	6.2 ± 2.3	0.001
A' (cm/s)	6.2 ± 2.0	8.6 ± 3.4	0.0006
E/E'	18 ± 8	14 ± 6	0.02
ProBNP (pmol/l)	847 ± 1461	438 ± 1039	0.0012

E, mitral early diastolic filling velocity; A, mitral late diastolic filling velocity; DT, deceleration time of E wave; L, mitral mid-diastolic filling velocity; TVI, time velocity integral; E', early diastolic mitral annular velocity; A', mitral annular velocity during atrial contraction.

Discussion

Although the presence of L′ is relatively uncommon, the novel finding of this study is that the presence of *L′* in subjects with triphasic mitral inflow velocity pattern with mid-diastolic flow is associated with higher *E*/*E′*, elevated proBNP and enlarged left atrium indicating advanced diastolic dysfunction with elevated filling pressures. To the best of our knowledge, this study is the largest and first study which provided proBNP level and the importance of mid-diastolic mitral annulus velocity in patients with triphasic mitral flow.

Previous studies on the mechanism of triphasic mitral inflow with mid-diastolic filling produced conflicting results. Keren et al.,[1] who studied 12 healthy volunteers using M-mode and Doppler echocardiography, concluded that mid-diastolic flow arises from the reestablishment of a positive transmitral pressure gradient due to left atrial filling from the pulmonary veins. Smiseth and Thompson[13] also suggested that mid-diastolic filling is driven by the momentum of the blood that enters the atrium from the pulmonary veins, because of the small transmitral pressure gradient during diastasis. In contrast, Hatle[2] described a mid-diastolic increase in forward mitral flow velocity in a patient with marked LV hypertrophy and suggested that a prominent mid-diastolic flow was the result of markedly prolonged relaxation that lowers LV diastolic pressure during mid-diastole. However, few data are available regarding TDI and proBNP.

Associated clinical conditions

Most of the patients with triphasic mitral inflow velocity pattern have underlying cardiovascular diseases, such as hypertension, hypertrophic cardiomyopathy, or ischemic heart disease suggesting that triphasic flow is not a normal phenomenon. Based on surrogate markers, most patients with triphasic mitral inflow appeared to have elevated filling pressures.

Effect of myocardial relaxation

Early diastolic mitral annular velocity recorded by TDI has been correlated with τ[5] and is thought to reflect myocardial relaxation. Mitral annulus velocity was shown to be relatively preload independent, especially in patients with impaired relaxation.[14] Therefore, early diastolic mitral annular velocity, a noninvasive surrogate of myocardial relaxation, is well suited for assessing the underlying mechanism of triphasic mitral inflow with mid-diastolic filling. When myocardial relaxation is normal, *E′* is usually 0.1 m/s or greater. In this study, *E′* was less than 0.1 m/s in all except in 2 patients, which suggests impaired myocardial relaxation in patients with a triphasic mitral inflow pattern. This finding was further confirmed by the Valsalva maneuver, which unmasked a delayed relaxation pattern in most of these patients.

Effect of preload

ProBNP, a peptide hormone secreted from the cardiac ventricles in response to increased pressure and volumes, has been shown as a good predictor of high LVEDP in patients with LV systolic dysfunction.[8] In this study, more than 90% of patients had above normal range of proBNP level. In addition, it is significantly higher in patients with *L′*, suggesting LV filling pressures are elevated in these patients. The results of the Valsalva maneuver which unmasked delayed relaxation pattern in 85% of the patients also indicate that elevated filling pressure contributes to the triphasic mitral inflow pattern. Increased *E*/*E′* also substantiated the importance of increased preload in producing the triphasic mitral inflow pattern in these patients.

Underlying mechanism of *L′* is not clear. Frommelt et al. have shown that prolonged LV pressure decrease into mid-diastole was preceded by mid-diastolic mitral annular motion toward the ventricle.[15] Thus, mid-diastolic mitral annular motion, a delayed wave of active relaxation, may create a diastolic suction effect in mid-diastole and leads to mid-diastolic inflow across the mitral valve.

Study limitations

In this study, we do not have invasive hemodynamic correlation of our findings. However, previous investigations have shown that an *E*/*E′* ratio of more than 15 identified increased LV filling pressure.[6,7] In addition, elevated proBNP in the presence of normal systolic function is specific for the prediction of elevated LV end-diastolic and filling pressures.[16] *In this study, we do not have controls*.

We conclude that the presence of *L′* in subjects with triphasic mitral inflow velocity pattern with mid-diastolic flow is associated with higher *E*/*E′*, elevated proBNP and enlarged left atrium *suggesting* advanced diastolic dysfunction with elevated filling pressures. This unique mitral annular velocity

pattern should be helpful in identifying the patients with advanced diastolic dysfunction and increased LV filling pressures *and complimentary to the other measures of diastolic function*.

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