

Prognostic Significance Of Left Ventricular Diastolic Dysfunction With Preserved Systolic Function Following Acute Myocardial Infarction

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Summary:

Background : The contribution of diastolic dysfunction in patients with preserved left ventricular (LV) systolic function to impaired functional status and cardiac mortality in myocardial infarction (MI) is unknown.

Materials and Methods : Assessment of LV diastolic function was performed by Doppler analysis of the mitral and pulmonary venous flow and the propagation velocity of early mitral flow by color M-mode Doppler echocardiography in 150 consecutive patients at day 5-7 following their first acute MI.

Results : Patients were classified into four groups: group A: preserved LV systolic and diastolic function (n=59); group B: LV systolic dysfunction with preserved diastolic function (n=8); group C: LV diastolic dysfunction with preserved systolic function (n=49); group D: combined LV systolic and diastolic dysfunction (n=33). The cardiac mortality rate at 6 months was significantly higher in groups C (12%) and D (36%) compared to A (2.5%) ($p < 0.01$). Multivariate regression analysis identified LV diastolic dysfunction ($p = 0.001$), Killip class $\geq II$ ($p = 0.005$), and age (0.007) as predictors of cardiac death or readmission due to heart failure.

Conclusion : The presence of LV diastolic dysfunction is associated with increased morbidity and mortality following acute MI.

Key Words: Prognosis. Diastolic. Myocardial infarction

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Introduction:

Both the extent of left ventricular (LV) systolic dysfunction and LV dilation are well known predictors of outcome after acute myocardial infarction (MI) [1, 2]. Recently, it has become increasingly clear that abnormalities of diastolic function contribute significantly to symptoms of congestive heart failure, and gives prognostic information in patients with heart failure [3, 4]. Pulsed Doppler echocardiography of transmitral inflow and pulmonary venous flow has become well accepted as a reliable and useful noninvasive tool to estimate filling pressures, and to diagnose patients with diastolic dysfunction [5-7]. Recently, color M-mode has also been found to provide information on LV relaxation, which may be useful in identification of pseudonormal transmitral LV filling pattern [8, 9]. Systolic and diastolic dysfunctions frequently coexist in patients with MI even though both isolated systolic and diastolic dysfunction can be identified [10,11]. The restrictive LV filling pattern characterized by shortened deceleration time (DT) of the early diastolic filling wave, and increased ratio of peak velocity of early and late filling wave (E/A ratio), has been associated with high filling pressures, LV remodeling, congestive heart failure, and poor

prognosis following MI [12, 13]. Additionally, a filling pattern of impaired relaxation during the acute phase of MI has been associated with in-hospital heart failure [14]. Information on the long term prognostic significance of impaired relaxation or pseudonormal-restrictive filling pattern is limited following acute MI. Furthermore, the prognostic implications of LV diastolic dysfunction in patients with preserved systolic function is unknown in acute MI.

The primary objective of the present study was to determine the prognostic significance of LV diastolic dysfunction in patients with preserved systolic function after acute MI. Secondly, to determine the prognostic value of a normal, an impaired relaxation, or a pseudonormal-restrictive LV filling pattern.

Methods:

We prospectively studied 150 patients from a total population of 172 patients who were admitted to the coronary care unit of Baghdad teaching hospital with acute MI, defined as (1) creatine kinase ≥ 100 U/L or (2) electrocardiographic evidence of MI (ST elevation > 1 mm in 2 limb leads or 2 contiguous chest leads or subendocardial pattern) and (3) typical chest pain on presentation. Echocardiography was performed at day 5-7 after admission in all patients. Clinical status was evaluated daily during hospitalization. At every

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follow-up visit (1, 3 and 6 months) an evaluation of the functional status of the patients was performed according to the New York Heart Association heart failure classification. Readmission to hospital due to heart failure and death was noted during follow-up.

Echocardiography: Two-dimensional, color M-mode, pulsed Doppler, and color flow Doppler echocardiographic examinations were performed with a standard cardiac ultrasound unit. LV volumes and ejection fraction (EF) were obtained by Simpson's method, and the means of three measurements were used [15]. Doppler measurements were calculated from an average of five consecutive cardiac cycles in patients with sinus rhythm while an average of ten was used in patients with atrial fibrillation. Color M-mode Doppler echocardiography was performed from the apical four-chamber view. The propagation velocity of early transmitral flow (V_p) was measured and the ratio of E-wave peak velocity to V_p (E/ V_p) was calculated. Mitral regurgitation was evaluated and graded in all patients.

Exercise Test: A symptom-limited treadmill test was performed 5-7 days after admission according to the Bruce protocol. ST segment deviations were measured 60 ms after the J point. Horizontal or descending ST depressions > 1 mm were considered significant. Based on previous echocardiographic studies, together with current recommendations for identifying LV diastolic dysfunction and diastolic heart failure, the patients were assigned into four groups according to the ejection fraction (EF) and the Doppler analysis of the mitral and pulmonary venous flow [7, 12, 16,17]. Doppler measurements of the pulmonary venous flow, and assessment of the E/ V_p ratio were used to detect pseudonormalization of the mitral Doppler inflow profile [6, 8, 9, 16]. The LV filling pattern was classified according to table 1. LV systolic dysfunction was defined as LV ejection fraction (LVEF) of less than 50% [17]. Patients assigned to group A were patients with normal LV systolic and diastolic function; group B were patients with LV systolic dysfunction (isolated) with normal LV diastolic function; group C were patients with LV diastolic dysfunction with normal systolic function; group D were patients with combined LV systolic and diastolic dysfunction.

Statistical Analysis: All results were expressed as mean \pm 1 standard deviation. χ^2 was used for comparison between groups for categorical data. Differences between mean values in patients groups were compared by univariate analysis of variance. Survival, free of cardiac event (death or readmission to hospital with congestive heart failure) was estimated using the Kaplan-Meier method, where time to first event was entered in the analysis. Univariate and multivariate regression

analysis using the Cox proportional hazards model were used to identify predictors of cardiac events. P values < 0.05 were considered to be significant.

Results:

Group Characteristics: Basic characteristics for the 150 patients are shown in table 2. No differences were noted between groups regarding gender, systolic blood pressure, arterial hypertension, diabetes mellitus, administration of thrombolytic therapy, infarct localization, Q-wave myocardial infarction, inducible ischemia, use of beta-blocking agents, aspirin, calcium channel blockers, or nitrates. (table 2). Age and heart rate were significantly higher in groups C and D compared to A (table 2). The use of diuretics (51 vs. 26%, respectively) and angiotensin converting enzyme inhibitors (ACE-I) (61 vs. 25%, respectively) were more frequently used in group D compared to C. Echocardiographic variables of LV systolic and diastolic function of the groups and the incidence of mitral regurgitation are shown in table 3. Killip class \geq II was noted in 7 patients in group A, 3 in group B, 21 in group C, and 30 in group D, respectively (group C and D vs. A, $p < 0.05$). During the out-of-hospital phase, NYHA functional class \geq II was noted in 10 patients of group A, 1 patient of group B, 31 patients of group C, and 29 of group D (group C and D vs. A, $p < 0.05$).

LV Filling Pattern: The LV filling patterns were classified according to table 1 in the 150 patients. In 68 patients LV filling was normal, 34 patients had a filling pattern of impaired relaxation, and in 48 patients filling was pseudonormal or restrictive.

Clinical Outcome: Follow-up period was 6 months. During this period, 24 patients (16%) died of cardiac causes (11 patients from sudden death, 13 of progressive heart failure including 3 patients with myocardial re-infarction). Readmission to hospital due to heart failure occurred in 19 patients (12.6%) during follow-up. The 6-months cardiac mortality was 2, 14, 39 % in group A, C, and D, respectively. The cardiac-event-free rate at 6 months was 97% in group A, 98% in group B, 78% in group C, and 49% in group D (group C and D vs A, $p < 0.0001$)(group C vs D, $p < 0.02$). The cardiac-event-free rate at 6 months was 51% in patients with LV diastolic dysfunction with LVEF $< 50\%$ and 82 % in patients with LV diastolic dysfunction with LVEF $\geq 50\%$. The cardiac-event-free rate at 6 months was 95% in the normal filling group, 80% in the impaired relaxation group (compared to normal filling group, $p < 0.02$) and 55% in the pseudonormal-restrictive LV filling group (compared to normal filling group, $p < 0.0001$). The survival rates were also significantly different between patients with impaired relaxation and pseudonormal-restrictive LV filling ($p < 0.01$). Using a stepwise multivariate Cox proportional hazards analysis, the presence of LV diastolic dysfunction

(impaired relaxation or pseudonormal-restrictive LV filling), Killip class \geq II, and age were identified

as independent predictors of cardiac events.

Table 1: Definitions of LV filling patterns

	Relaxation			
	Normal	Impaired	Pseudonormal	Restrictive
E-wave deceleration time, ms	140-240	>240	140-240	<140
E/A ratio	≥ 0.8	<0.8	1-2	>1.5
Isovolumetric relaxation time, ms	<100	≥ 100	<100	<100
Pulmonary S/D ratio	>1.0	>1.0	<1.0	<1.0
PA – MA	<0	<0	≥ 0	≥ 0
E/Vp	<1.5	<1.5	≥ 1.5	≥ 1.5

PA-MA= Pulmonary venous A duration minus mitral A duration.

Impaired transmitral filling pattern was considered in patients with isovolumetric relaxation time \geq 100 ms or E-wave deceleration time \geq 240 ms and E/A ratio <0.8.

Table 2: Clinical characteristics in patients with normal diastolic function and preserved systolic function (group A), isolated systolic dysfunction (group B), isolated diastolic dysfunction (group C), and combined systolic and diastolic dysfunction (group D).

	Group A N=59	Group B N=8	Group C n=49	Group D n=33
Age, years	59 \pm 10	62 \pm 9	68 \pm 12*	66 \pm 12*
Gender (male/female)	41/18	6/2	36/13	21/12
Diabetes mellitus	5(8)	0(0)	6(12)	5(15)
Arterial hypertension	11(19)	2(25)	16(33)	12(36)
Smoker(current or previous)	48(81)	7(88)	43(88)	30(90)
Anterior myocardial infarction	25(42)	4(50)	20(41)	18(55)
Q-wave myocardial infarction	19(32)	2(25)	12(24)	13(39)
Heart rate, beats/min	70 \pm 12	79 \pm 13*	75 \pm 17	86 \pm 19*
Thrombolytic therapy	39(66)	6(75)	25(51)	21(64)
Beta-blocking agents	40(68)	6(75)	30(61)	15(45)
ACE-I	6(10)	2(25)	14(28)	21(64)*
Nitrates	8(14)	3(38)	12(24)	14(42)
Diuretics	6(10)	2(25)	11(22)	14(42)*
Inducible ischemia on exercise ECG	23(39)	2(25)	15(31)	6(18)

Data are presented as mean \pm SD and percentage of patients.

* p<0.001 versus group A.

Table 3: Echocardiographic characteristics in patients with normal diastolic function and preserved systolic function (group A), isolated systolic dysfunction (group B), isolated diastolic dysfunction (group C), and combined systolic and diastolic dysfunction (group D).

	Group A n=59	Group B n= 8	Group C n=49	Group D n=33
E/A ratio	1.21 \pm 0.42	0.92 \pm 0.30	0.97 \pm 0.46*	1.30 \pm 0.65
Deceleration time, ms	179 \pm 28	176 \pm 22	231 \pm 57*	162 \pm 65*
Isovolumetric relaxation time, ms	71 \pm 20	77 \pm 17	76 \pm 31	83 \pm 33
S/D ratio	1.30 \pm 0.13	1.11 \pm 0.10	0.97 \pm 0.18*	0.83 \pm 0.20

PA – MA, ms	27±13	25±10	1±18*	-14±19*
E / Vp	1.19±0.22	1.22±0.11	1.79±0.69*	2.51±0.83*
End diastolic volume index, ml/m ²	64±15	88±20*	61±16	86±29*
End systolic volume index, ml/m ²	28±10	53±16*	27±12	55±22*
EF, %	59±7	40±5*	58±7	35±8*
Mitral regurgitation				
Grade I-II	11(19)	3(38)	5(10)	10(30)
Grade III-IV	0(0)	2(25)	4(8)	7(21)

Data are presented as mean± SD and percentage of patients. * p<0.001 versus group A.

PA-MA= pulmonary venous A duration minus mitral A duration; S/D ratio= ratio between peak systolic and diastolic pulmonary venous flow velocity.

Figures in parenthesis are percentages.

Discussion:

The clinical and prognostic implications of LV diastolic dysfunction in patients with preserved systolic function after MI are not well documented. In the present study, about one third of a consecutive population with MI showed Doppler echocardiographic signs of LV diastolic dysfunction despite preserved systolic function, which was associated with increased risk of death and congestive heart failure. Furthermore, multivariate regression analysis identified the presence of LV diastolic dysfunction as the most powerful predictor of cardiac death or development of heart failure following acute MI. Previous studies concluded that as many as 30-40% of patients presenting with clinical heart failure had normal or near normal LV systolic function [3,4]. In the present study, patients with isolated diastolic dysfunction demonstrated a 6-months mortality rate of 14% and a combined cardiac event rate of 22%. Furthermore, our patients with combined systolic and diastolic dysfunction demonstrated an attenuated cardiac mortality of 36% and a combined 6-months event rate of 49%. Patients with either isolated diastolic dysfunction or combined systolic and diastolic dysfunction demonstrated higher Killip and NYHA classes compared to patients with preserved systolic and diastolic LV function. It is shown that patients with preserved systolic and diastolic LV function had an excellent prognosis. Isolated systolic dysfunction seems to be a rare condition. As LV diastolic dysfunction is shown to precede systolic dysfunction in various cardiac conditions, it is most likely that patients with systolic dysfunction have some degree of diastolic dysfunction. The results show that patients with combined systolic and diastolic dysfunction have a higher risk of adverse outcome compared to those with isolated diastolic dysfunction. However, LV diastolic dysfunction was found to be the best predictor of combined outcome. This finding can be explained by the presence of more advanced LV diastolic dysfunction in patients with simultaneous systolic dysfunction. Previous studies have shown

that patients with a restrictive LV filling pattern and the presence of impaired relaxation are related to LV dilatation and have a higher risk of cardiac death and development of heart failure [10, 14, 15] in MI. The restrictive LV filling pattern has primarily been demonstrated in patients with an LVEF <45% [10, 14]. In agreement with these observations, we found that a pseudonormal-restrictive LV filling pattern was associated with decreased LVEF and poor outcome. Additionally, we found that patients with an impaired relaxation LV filling pattern had higher cardiac event rate compared to patients with a normal LV filling pattern. The possible explanation for these findings may be the elevated LV filling pressures often found in patients with pseudonormal-restrictive LV filling patterns and in some patients with impaired relaxation [6, 8, 16]. The Doppler measurements of LV filling could be affected by several factors including age, heart rate, rhythm, loading conditions, mitral regurgitation and medical treatment. Blood pressure was comparable between groups and thus seems to be of less importance. The age and heart rate were significantly higher in patients of group C and D compared to group A, which might influence the echocardiographic measurements upon which the grouping of patients was based. The E/A ratio is known to decrease and the isovolumetric relaxation time and DT increase with age resulting in an impaired relaxation filling pattern. Therefore, some patients might be placed into groups C and D due to higher age alone. However, heart rate was significantly higher in groups C and D compared to A, resulting in shortening of the isovolumetric relaxation time, and thereby having an opposite effect on this parameter with respect to the influence of increasing age. Therefore, we believe that the differences in heart rate and age are unlikely to have misclassified a significant number of patients in group C and D with respect to A. LV filling may be different in patients with atrial fibrillation compared to sinus rhythm; however, both DT and Vp have been validated in patients with atrial fibrillation [18].

Moderate to severe mitral regurgitation was more frequently seen in groups C and D compared to A. Mitral regurgitation might result in increased atrial filling pressure, which would result in the development of pseudonormal or restrictive LV filling pattern. As no patient with moderate to severe mitral regurgitation was found in group A, the problem of misclassification of a patient with a pseudonormal LV filling pattern into group A seems minimal. Medical treatment might affect the Doppler measurements and thereby influence the predefined subdivision of patients. In addition, we cannot control the variables of treatment which might affect LV function and outcome. No difference was noted between groups A and C, and it is therefore unlikely that it would affect the main results of the present study. Finally, echocardiography was performed 5-7 days after MI, when the patients were hemodynamically stable without intravenous medication such as nitroglycerine and inotropics, which would have affected the measurements to a considerable degree. In conclusion, the identification of LV diastolic dysfunction by Doppler and color M-mode echocardiography in patients with preserved systolic function seems to identify patients at increased risk of cardiac morbidity and mortality.

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