



Echocardiographic evaluation of diastolic function of left ventricle among post myocardial infarction patients

^{*1} Sasikumar Perumal, ² Sureshkumar Krishnan, ³ Ravikumar Padmanaban, ⁴ Ravikumar Padmanaban, ⁵ Karthick Kuppan, ⁶ Shankar Radhakrishnan

^{1, 2, 3, 4, 5} Assistant Professor, Department of Internal Medicine, Government Medical College, Dharmapuri, Tamil Nadu, India

⁶ Associate Professor, Department of Preventive Medicine, VMKVMCH, Salem, Tamil Nadu, India

Abstract

Background: The overall cardiovascular mortality in India is increasing with an increase in the incidence and prevalence of heart failure. In recent years, LV diastolic dysfunction has been related to development of heart failure, progressive LV dilatation, and mortality after myocardial infarction. Pulsed Doppler echocardiography has become well accepted as a reliable and useful non-invasive method for assessment of LV diastolic function. Mitral and pulmonary venous flow velocities assessed by Doppler are used for the evaluation of LV filling pressure, relaxation, and chamber stiffness in establishing diagnosis and prognosis.

Aim: To assess the left ventricular diastolic function among post MI patients using echocardiogram.

Methodology: A cross-sectional study was conducted for a period of one year in the medicine department at Dharmapuri medical college hospital. Patients with a history of previous episode of myocardial infarction in the age group of 30 – 55 years were included in the study. Patients with known history of diabetes and hypertension were excluded from the study. A total of 220 patients with the above mentioned inclusion criteria were enrolled for our study. All the basic blood and urine examination was conducted to assess their sugar levels, renal functions and the lipid parameters. ECG was taken for all the subjects. Two-dimensional echocardiography was videotaped by use of the parasternal long-axis view, multiple short-axis views, and apical 2-, 4-, and long-axis views. The systolic and diastolic functions were assessed using the echocardiogram.

Results: Among the various site of infarct inferior wall followed by anterior wall MI were found to be more common among the study subjects and in 18% of the patients there was a combination of both anterior and lateral wall and anterior and inferior wall MI. In our study among the 220 patients 65 patients showed features of diastolic dysfunction in echocardiogram with a prevalence of 29.5% among which type I dysfunction found to be more common followed by type II and only one patient had type IV diastolic dysfunction.

Conclusion: The prevalence of diastolic dysfunction is much more common than the systolic dysfunction among the coronary artery disease patients and it is increasing among elderly. Echocardiography being a non-invasive and cost-effective tool compared to angiogram or other radioisotope studies can be used periodically among the post MI patients to identify the diastolic dysfunction at an early stage and plan appropriate interventions.

Keywords: echocardiogram, left ventricle diastolic function, myocardial infarction

Introduction

The overall cardiovascular mortality in India is increasing with an increase in the incidence and prevalence of heart failure. The largest group of patients with heart failure is composed of those with coronary artery disease and previous myocardial infarctions ^[1]. Heart failure (HF) is a frequent complication of myocardial infarction (MI). Several factors, such as recurrent myocardial ischemia, infarct size, ventricular remodelling, stunned myocardium, mechanical complications, and hibernating myocardium influence the appearance of left ventricular systolic dysfunction with or without clinical HF after MI ^[2-4] of note, the relevance of each factor responsible for HF after MI depends on the time to the establishment of cardiac dysfunction following coronary occlusion.

Patients with signs of HF on admission to the hospital are usually elderly, with recurrent ischemia and diabetes. In this

setting, ventricular function is related to pre-existent comorbidities that reduce tolerance to ischemic injury. On the other hand, development of HF during one's hospital stay is usually related to infarct size, mechanical complications, or myocardial stunning. Finally, some patients will develop HF only after being discharged from the hospital. In this setting, myocyte loss, hibernating myocardium, and ventricular remodelling are the principal causes of heart failure. Among these factors, ventricular remodelling is the most important. Left ventricular (LV) systolic function is a well-established predictor of morbidity and mortality following acute myocardial infarction ^[5, 6]. In recent years, LV diastolic dysfunction has been related to development of heart failure, progressive LV dilatation, and mortality after myocardial infarction ^[7, 8].

Left ventricular (LV) function is traditionally divided into

systole and diastole, describing ventricular emptying and filling. Acute myocardial infarction (AMI) is characterized by loss of contractile tissue and changes of ventricular geometry. This would be anticipated to modify systolic as well as diastolic function, and each could, independent of the other, modify the clinical course of the disease. Traditional risk stratification is nevertheless nearly focused solely on systolic function, in which numerous studies have demonstrated that ejection fraction or other closely related parameters are powerful guides to select therapies and predict the risk of future events [9-11]. To further understand the disease development after AMI, it would appear likely that a more complete study of ventricular function would be useful. One option is to include Doppler echocardiographic estimates of diastolic function. In this line, small studies have indicated that a mitral filling pattern that mimics the filling pattern seen in patients with restrictive cardiomyopathy characterized by shortening of the mitral deceleration time is associated with an adverse outcome in patients with AMI [12-14]. One further option is to devise estimates, which include systolic as well as diastolic function. To do this, Tei *et al.*, [15] studied, in 1995, the ability of a new Doppler index of combined systolic and diastolic function (Tei index) to separate patients with normal ventricular function from patients with heart failure. They showed that the separation between normal individuals and patients with dilated cardiomyopathy, by use of the Tei index, was superior to other available indexes. Furthermore, 2 small studies have indicated a prognostic value of the index after an AMI [16, 17]. Pulsed Doppler echocardiography has become well accepted as a reliable and useful non-invasive method for assessment of LV diastolic function. Mitral and pulmonary venous flow velocities assessed by Doppler are used for the evaluation of LV filling pressure, relaxation, and chamber stiffness in establishing diagnosis and prognosis [18, 19]. The identification of a restrictive LV filling pattern characterised by increased early to late filling ratio, decreased mitral deceleration time, and decreased systolic pulmonary venous flow has been associated with poor outcome in cardiac disease [18, 19].

As of today many studies done in India were conducted on assessing the systolic function in the post myocardial infarction patients only very few had concentrated on the diastolic dysfunction, so the present study was done mainly to assess the diastolic function among the post MI patients.

Aim

To assess the left ventricular diastolic function among post MI patients using echocardiogram.

Methodology

A cross-sectional study was conducted for a period of one year in the medicine department at Dharmapuri medical college hospital. The study was conducted after getting the clearance from the institutional ethical committee. Patients with a history of previous episode of myocardial infarction in the age group of 30 – 55 years were included in the study. Patients with known history of diabetes and hypertension were excluded from the study. A total of 220 patients with the above mentioned inclusion criteria were enrolled for our

study. Informed consent was obtained from all the study subjects before the start of the study.

A detailed socio-demographic profile of the patients, their presenting complaints, past history and the family history was got by using a pilot tested semi-structured questionnaire. All the basic blood and urine examination was conducted to assess their sugar levels, renal functions and the lipid parameters. ECG was taken for all the subjects. Echocardiogram was performed in the following manner for assessing their systolic and diastolic function.

Two-dimensional echocardiography was videotaped by use of the parasternal long-axis view, multiple short-axis views, and apical 2-, 4-, and long-axis views. Systolic LV function was assessed by use of WMI. The left ventricle was divided into 16 segments, 12 and each segment was assigned a score based on myocardial thickening and endocardial excursion (3 _ hyperkinesis, 2 _ normokinesis, 1 _ hypokinesis, 0 _ akinesis, and -1 _ paradoxical motion). WMI was calculated by dividing the sum of scores by the number of segments analyzed. By using this reverse scoring system, a simple transformation from WMI to LV ejection fraction may be done by multiplying the WMI by 0.30, as described by Berning *et al.* [20]. The assessment of WMI was done by expert reviewers. Inter-observer variability of WMI at our institution has previously been determined as 0.02 _ 0.23 and concordance in assessment of WMI _1.2 of 80% to 87%. LV filling was assessed with pulsed wave Doppler echocardiography. Measurements were obtained with the transducer in the apical 4-chamber view and with the Doppler beam aligned as perpendicular as possible to the plane of the mitral annulus. To obtain mitral flow velocities, Doppler sample volume was placed between the tips of the mitral leaflets during diastole. LV outflow was recorded from the apical long-axis view with continuous wave or pulsed wave Doppler, with the sample volume positioned just below the aortic valve. The Tei index was calculated as the sum of isovolumic relaxation and contraction times divided by ejection time, which was measured from mitral inflow and LV outflow recordings. Analyses of videotaped

Doppler recordings were done off-line on a commercial digitizing system (Echo Pac version 6.2, GE Ultrasound, Oslo, Norway). Analyses of Doppler parameters were performed by a single investigator blinded to WMI and other clinical data. Three consecutive beats were measured and averaged for patients in sinus rhythm and 10 beats for patients in atrial fibrillation [21]. Inter-observer variability of assessment of the Tei index at our institution is 0.02 _ 0.07.11 On the basis of recommendations from the European Study, Group on Diastolic Heart Failure [22], we considered, in patients aged 50 years, mitral deceleration time _280 ms and E/A wave velocity ratio _0.5 and, in patients aged 50 years, a mitral deceleration time _220 ms and E/A ratio _1 to be suggestive of abnormal LV relaxation. We considered restrictive filling physiology to be present when mitral deceleration time was _140 ms [22].

Results

Table 1 shows the age and gender wise distribution of the study population. It is seen from the table that majority of the

study subjects were in the age group between 45 – 55 years. Males have outnumbered females with a male: female ratio of 2.54: 1. The mean age of the study subjects was 48.65 years. Among the various site of infarct inferior wall followed by anterior wall MI were found to be more common among the study subjects and in 18% of the patients there was a combination of both anterior and lateral wall and anterior and inferior wall MI (table2). The mean duration of infarct among our study subjects was 3.3 months and it varied from 1 month to 24 month with majority were between 1 – 4 months (table 3).

The various risk factors for MI among our patients were found to be smoking, alcoholism and hypercholesterolemia among which majority of them had hypercholesterolemia (85.9%), with 51.8% had history of smoking and 46.3% had history of both smoking and alcoholism (table 4). The echocardiogram was performed for all the patients and we found the systolic function to be normal for all the patients with ejection fraction of more than 55% and so we did not analysed the parameters for systolic function and similarly the mean values of all the parameters related to diastolic function (IVRT, E wave, A wave and E/A ratio) found to be in the normal range (table 5). In our study among the 220 patients 65 patients showed features of diastolic dysfunction in echocardiogram with a prevalence of 29.5% among which type I dysfunction found to be more common followed by type II and only one patient had type IV diastolic dysfunction (table 6). The multiple logistic regression analysis had proved that age >45 years, smoking, smoking and alcohol, LDL levels of >130mgs/dl, triglycerides >200mgs/dl and total cholesterol of >200mgs/dl are the major risk factors for influencing diastolic dysfunction among our study subjects.

Table 1: Age and sex wise distribution of the study population

Age group	Gender		Total
	Male	Female	
30 – 35	9 (5.6%)	5 (8%)	14 (6.3%)
36 – 40	12 (7.5%)	5 (8%)	17 (7.7%)
41 – 45	35 (22.1%)	8 (12.9%)	43 (19.5%)
46 – 50	81 (51.2%)	38 (61.2%)	119 (54%)
51 – 55	21 (13.2%)	6 (9.6%)	27 (12.2%)
Total	158 (100%)	62 (100%)	220 (100%)
Mean ± SD	49.03 ± 5.36	48.4 ± 4.86	48.65 ± 5.02

Table 2: Distribution of the study subjects based on their site of infarct

Site of infarct	Frequency	Percentage
AWMI	86	39%
IWMI	94	42.7%
AWMI + LWMI	16	7.2%
AWMI + IWMI	24	10.9%
Total	220	100%

Table 3: Distribution of the study subjects based on their duration of infarct

Duration of infarct	Frequency	Percentage
1 – 4 months	90	40.9%
5 – 8 months	48	21.8%
9 – 12 months	36	16.3%
13 – 16 months	42	19%
17 – 20 months	4	1.8%
Total	220	100%
Mean ± SD	3.3 ± 2.8	

Table 4: Distribution of the study subjects based on their risk factors

Risk factors	Frequency	Percentage
Smoking	114	51.8%
Alcoholism	80	36.3%
Smoking and alcoholism	102	46.3%
Hypercholesterolemia	189	85.9%

Table 5: Mean and SD of the echocardiographic parameters for assessing LV diastolic function

Echocardiographic parameters	Mean	SD
IVRT (m/sec)	83.51	14.76
E wave (cm/sec)	60.57	11.69
A wave (cm/sec)	45.34	10.59
E/A ratio	1.44	0.81

Table 6: Distribution of the study population based on their diastolic dysfunction

Diastolic dysfunction	Frequency	Percentage
Normal diastolic function	155	70.4%
Type I Diastolic dysfunction	46	20.9%
Type II Diastolic dysfunction	14	6.3%
Type III Diastolic dysfunction	4	1.8%
Type IV Diastolic dysfunction	1	0.4%

Table 7: Multilogistic regression for the factors influencing diastolic dysfunction among the study subjects

Factors	LV diastolic dysfunction		P value
	Present (n=65)	Absent (n=155)	
Age >45 years (n=102)	53 (81.5%)	49 (31.6%)	<.0001
H/O smoking (n=114)	60 (92.3%)	54 (34.8%)	<.0001
H/O alcohol (n=80)	20 (30.7%)	60 (38.5%)	0.618
H/O smoking and alcohol (n=102)	61 (93.8%)	41 (26.4%)	<.0001
LDL > 130mg/dl (n=189)	65 (100%)	124 (80%)	<.0001
Triglycerides >200mg/dl (n=189)	65 (100%)	124 (80%)	<.0001
Total Cholesterol >200mg/dl (n=189)	65 (100%)	124 (80%)	<.0001

Discussions

The present study had proven that the prevalence of LV diastolic dysfunction among Post MI patients was 29.5%, which was found to be very high as most of us are usually bothered more about the systolic function in terms of ejection

fraction in the post MI patients. As diabetes and hypertension are the most common risk factors for diastolic dysfunction we excluded those patients with a history of diabetes and hypertension.

LV DD develops in several cardiac diseases as well as in

extra-cardiac pathologies involving the heart (accumulation diseases as amyloidosis, thyroid disorders, acromegaly and others) and in myocardial ischemia due to coronary artery stenosis or even to isolated dysfunction of coronary microcirculation^[23, 24]. However, the main cause of DD is arterial hypertension^[25]. Overweight and obesity, often coexisting with the same hypertension, deeply affects LV diastolic function, forcing the left ventricle to a working overload^[26]. In this view, DD represents one of the cardiac consequences of pluri-metabolic syndrome, where arterial hypertension, obesity, glucose intolerance and hypertriglyceridemia cohabit in the same subject, having their common matrix in the insulin resistance. High levels of insulin resistance, often evident in arterial hypertension, are positively associated with the prolongation of isovolumic relaxation time, independent of LV geometric changes and of increased afterload^[27]. The alteration of diastolic isovolumic relaxation is probably due to an increment of intracellular calcium, which has been observed in insulin resistant hypertensives and is induced in its turn by an abnormal re-uptake of calcium by sarcoplasmic reticulum.^[28] Also the hormones produced by adipose tissue, as leptin – involved into the control of body weight throughout food absorption and energy-giving cost – negatively affects LV diastolic function^[29]. The association of arterial hypertension and diabetes mellitus worsens further Doppler indexes of LV diastolic function as shown into the population of the Strong Heart Study^[30].

It is controversial whether LV DD is necessarily accompanied on the development of LVH or rises up independent of it^[31]. It is true that DD is a direct sequence of pressure overload, associated to elevated 24-hour blood pressure and even more to the increment of night-time diastolic blood pressure^[32]. Recent studies point out that the diastolic abnormalities of hypertensive patients are related to inappropriately high levels of LV mass, disproportionate to the hemodynamic load predicted by the individual body size and cardiac load, more than to the values of LV mass which traditionally define LVH. Inappropriately high LV mass is a potent predictor of cardiovascular risk in hypertensive patients, in presence as in absence of clear cut LVH^[33]. The concept of DD onset preceding the appearance of LVH is consistent with the observation that BNP, whose levels grow gradually with the progression of DD grading (from abnormal relaxation until restrictive Doppler patterns), are increased in patients with diastolic HF independent of the magnitude of LV mass^[34].

Signs of diastolic dysfunction have also been reported in many patient groups with coronary artery disease^[35, 36]. The overall prevalence of diastolic abnormalities in presently studied patients with a history of myocardial infarction or ECG evidence of coronary artery disease was 29.5%. It is almost in par with the study done by M Fischer *et al.*,^[37] where he had proven the prevalence of diastolic dysfunction among CAD patients was 25% but compared to few other studies the rate was found to be lower. Of note, however, we excluded individuals with history of diabetes and hypertension whereas those studies had included diabetes and hypertension as risk factors. Moreover, we did not study the effects of exercise that may precipitate diastolic dysfunction specifically in individuals with significant coronary stenosis. Consistent with

some but not all other reports, diastolic abnormalities were noted to be more common in males than in females. Higher prevalence rates of hypertension, LV hypertrophy and coronary artery disease in men may partly account for this difference. Nevertheless, in the multivariate analysis, a gender-related association with diastolic abnormalities was confirmed with significantly higher rates in men than in women. Therefore, gender may be an independent factor in the pathogenesis of diastolic dysfunction, as previously suggested for systolic heart failure and LV hypertrophy^[38].

The criteria used in the present investigation allow, with increasing age, adaptation of the upper limit for the isovolumic relaxation time and the lower limit for the E/A-ratio. Nevertheless, previous as well as the present investigators, based on these criteria, demonstrated a pronounced increase in diastolic abnormalities in the elderly. However, hypertension, LV hypertrophy, coronary artery disease and obesity, i.e. conditions associated with diastolic abnormalities, also display an increasing prevalence with increasing age. In fact, structural or functional adaptations of the heart that impair LV filling appear to integrate the consequences of such risk factors over time^[39].

Conclusion

The prevalence of diastolic dysfunction is much more common than the systolic dysfunction among the coronary artery disease patients and it is increasing among elderly and also patients with history of smoking, alcoholism and with dyslipidemias other than the well known risk factors like diabetes, hypertension and obesity. In the absence of these risk factors, the condition is rare even in those of 50–75 years of age. Our estimates of the population-attributable risks suggest that a large proportion of diastolic heart failure may be effectively prevented by improved implementation of measures directed against these predisposing conditions. Echocardiography being a non-invasive and cost-effective tool compared to angiogram or other radioisotope studies can be used periodically among the post MI patients to identify the diastolic dysfunction at an early stage and plan appropriate interventions.

References

1. Teerlink JR, Goldhabe SZ, Pfeffer MA. An overview of contemporary etiologies of congestive heart failure. *Am. Heart J.* 1991; 121:1852-1853.
2. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. *Circulation.* 1990; 81:1161-1172.
3. Zornoff LAM, Paiva SAR, Duarte DR *et al.* Ventricular remodeling after myocardial infarction: concepts and clinical implications. *Arq Bras Cardiol.* 2009; 92:157-164.
4. Cleland JGF, Torabi A, Khan NK. Epidemiology and management of heart failure and left ventricular systolic dysfunction in the aftermath of a myocardial infarction. *Heart.* 2005; 91:ii7-ii13.
5. Volpi A, De Vita C, Franzosi MG, *et al.* Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis. Results of GISSI-2 data base. *Circulation.* 1993; 88:416-29.

6. Oh JK, Ding ZP, Gersh BJ *et al.* Restrictive LV diastolic filling identifies patients with heart failure after acute myocardial infarction. *J Am Soc Echocardiogr.* 1992; 5:497-503.
7. Poulsen SH, Jensen SE, Gøtzsche O *et al.* Evaluation and prognostic significance of LV diastolic function assessed by Doppler echocardiography in the very early phase of a first myocardial infarction. *Eur Heart J.* 1997; 18:1882-9.
8. Cerisano G, Bolognese L, Carrabba N *et al.* Doppler derived mitral deceleration time. An early strong predictor of LV remodelling after reperfused anterior acute myocardial infarction. *Circulation.* 1999; 99:230-6.
9. White HD, Norris RM, Brown MA, *et al.* Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation.* 1987; 76:44-51.
10. St John SM, Pfeffer MA, Plappert T *et al.* Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after AMI: the protective effects of captopril. *Circulation.* 1994; 89:68-75.
11. Køber L, Torp-Pedersen C, Jørgensen S *et al.* Changes in absolute and relative importance in the prognostic value of left ventricular systolic function and congestive heart failure after acute myocardial infarction. *Am J Cardiol.* 1998; 81:1292-7.
12. Nijland F, Kamp O, Karreman AJ *et al.* Prognostic implications of restrictive left ventricular filling in acute myocardial infarction: a serial Doppler echocardiographic study. *J Am Coll Cardiol.* 1997; 30:1618-24.
13. Poulsen SH, Jensen SE, Egstrup K. Longitudinal changes and prognostic implications of left ventricular diastolic function in first acute myocardial infarction. *Am Heart J.* 1999; 137:910-8.
14. Oh JK, Ding ZP, Gersh BJ *et al.* Restrictive left ventricular diastolic filling identifies patients with heart failure after acute myocardial infarction. *J Am Soc Echocardiogr.* 1992; 5:497-503.
15. Tei C, Ling LH, Hodge DO *et al.* New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function: a study in normals and dilated cardiomyopathy. *J Cardiol.* 1995; 26:357-66.
16. Møller JE, Søndergaard E, Poulsen SH *et al.* Pseudonormal and restrictive filling predicts left ventricular dilation and cardiac death after first myocardial infarction. *J Am Coll Cardiol.* 2000; 36:1841-6.
17. Cerisano G, Bolognese L, Buonamici P *et al.* Prognostic implications of restrictive left ventricular filling in reperfused anterior acute myocardial infarction. *J Am Coll Cardiol.* 2001; 37:793-9.
18. Poulsen SH, Jensen SE, Nielsen JC *et al.* Serial changes and prognostic implications of a Doppler derived index of combined left ventricular systolic and diastolic myocardial performance in acute myocardial infarction. *Am J Cardiol.* 2000; 85:19-25.
19. Møller JE, Søndergaard E, Poulsen SH *et al.* The Doppler echocardiographic myocardial performance index predicts left ventricular dilation and cardiac death after myocardial infarction. *Cardiology.* 2001; 95:105-11.
20. Berning J, Rokkedal NJ, Launbjerg J *et al.* Rapid estimation of left ventricular ejection fraction in acute myocardial infarction by echocardiographic wall motion analysis. *Cardiology.* 1992; 80:257-66.
21. Hurrell DG, Oh JK, Mahoney DW *et al.* Short deceleration time of mitral inflow E velocity: prognostic implication with atrial fibrillation versus sinus rhythm. *J Am Soc Echocardiogr.* 1998; 11:450-7.
22. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure? *Eur Heart J.* 1998; 19:990-1003.
23. Spirito P, Maron BJ. Relation between extent of left ventricular hypertrophy and diastolic filling abnormalities in hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 1990; 15:808-813.
24. Klein AL, Hatle LK, Taliercio CP, Taylor CL, Kyle RA, Bailey KR *et al.* Serial Doppler echocardiographic follow-up of left ventricular diastolic function in cardiac amyloidosis. *J Am Coll Cardiol.* 1990; 16:1135-1141
25. Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A *et al.* Sacca Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab.* 1999; 84:2064-2067.
26. Galderisi M, Cicala S, Caso P, De Simone L, D'Errico A, Petrocelli A *et al.* Coronary flow reserve and myocardial diastolic dysfunction in arterial hypertension. *Am J Cardiol.* 2002; 90:860-864.
27. Mureddu GF, de Simone G, Greco R, Rosato GF, Contaldo F. Left ventricular filling in arterial hypertension. Influence of obesity and hemodynamic and structural confounders. *Hypertension.* 1997; 29:544-550.
28. Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L *et al.* Insulin resistance in essential hypertension. *N Engl J Med.* 1987; 317:350-357.
29. Galderisi M, Paolisso G, Tagliamonte MR, Alfieri A, Petrocelli A, de Divitiis M *et al.* Is insulin action a determinant of left ventricular relaxation in uncomplicated essential hypertension? *J Hypertens.* 1997; 15:745-50.
30. Liu JE, Palmieri V, Roman MJ, Bella JN, Fabsitz R, Howard BV *et al.* The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. *J Am Coll Cardiol.* 2001; 37:1943-1949.
31. White WB, Schulman P, Dey HM, Katz AM. Effects of age and 24-hour ambulatory blood pressure on rapid left ventricular filling. *Am J Cardiol.* 1989; 63:1343-1347.
32. Galderisi M, Petrocelli A, Alfieri A, Garofalo M, de Divitiis O. Impact of ambulatory blood pressure on left ventricular diastolic dysfunction in uncomplicated arterial systemic hypertension. *Am J Cardiol.* 1996; 77:597-601.
33. De Simone G, Verdecchia P, Pede S, Gorini M, Maggioni AP. Prognosis of inappropriate left ventricular mass in hypertension: the MAVI Study. *Hypertension.* 2002; 40:470-476.
34. Yamaguchi H, Yoshida J, Yamamoto K, Sakata Y, Mano T, Akehi N *et al.* Elevation of plasma brain natriuretic

- peptide is a hallmark of diastolic heart failure independent of ventricular hypertrophy. *J Am Coll Cardiol.* 2004; 43:55-60.
35. Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. *Arch Intern Med.*1996; 156:146-157.
 36. Poulsen SH, Jensen SE, Egstrup K. Longitudinal changes and prognostic implications of left ventricular diastolic function in first acute myocardial infarction. *Am Heart J.* 1999; 137:910-918.
 37. Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S *et al.* Prevalence of left ventricular diastolic dysfunction in the community: Results from a Doppler echocardiographic-based survey of a population sample. *European Heart Journal.* 2003, 24(4).
 38. Luchner A, Broeckel U, Muscholl M *et al.* Gender-specific differences of cardiac remodelling in subjects with left ventricular dysfunction: a population-based study. *Cardiovasc Res.* 2002; 53:720-737.
 39. Grossman W. Defining diastolic dysfunction. *Circulation.* 2000; 101:2020-2021.