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ISCHEMIC MITRAL REGURGITATION IN IRAQI PATIENTS: SINGLE CENTER EXPERIENCE

AL-SAFFAR H.[1]*, AL-ZAIDEE M.R.O.[2] AND MUHAMMED S.M.[3]

[1]Department of Medicine, Collage of Medicine, University of Baghdad, Iraq.
[2]Diploma Interventional Cardiology, Al Emam Ali Hospital, Baghdad Iraq.
[3]Human Resources Training & Development Centre, Baghdad, Iraq.
*Corresponding Author: Email- crescent1957@yahoo.com

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Abstract- Mitral regurgitation (MR) is a relatively common finding in coronary heart disease. It increases morbidity and mortality particularly after myocardial infarction (MI). To estimate the prevalence of mitral valve regurgitation, assess its clinical and echocardiographic severity in patients with ischemic heart disease attending a single tertiary cardiac centre in Iraq, this study is conducted.

One hundred fifty three patients, who were referred for cardiac evaluation of ischemic heart disease at Iraqi centre for heart disease in Baghdad between Jun 2011 and Jun 2012, were enrolled. Medical history, cardiac examination, ECG, trans-thoracic echocardiography and coronary angiography were done. Inclusion echocardiographic criteria were: normal mitral leaflets, normal other valves and significant angiographic coronary arteries lesions. Echocardiographic parameters include: ejection fraction and assessment of mitral regurgitation severity (if present) measured by jet area, venna contracta (VC) and proximal isovelocity surface area (PISA). Coronary angiography was done for all patients using standard views and significant CAD was defined as ≥50% diameter in left main stem artery (LMS) and 70% in other vessels, then patients were classified as having single, double and multi-vessels disease.

Mitral regurgitation was detected by echocardiography in 45 patients (29.4%), while cardiac murmur, suggestive of mitral regurgitation, was found in only 9 of them (20%). The incidence of chronic ischemic mitral regurgitation (CIMR) is significantly more prevalent in patients with previous MI 29/73 patients (39.7%) P=0.04, hypertension 33/87 patients (37.9%) P=0.04 and in 41/71 patients with impaired LV systolic function (57.7%) P =0.0001, chronic ischemic mitral regurgitation were found in 28/62 (45.2%) of patients with multi-vessels diseases P=0.001. Chronic ischemic MR is common among patients with IHD referred for coronary angiography; clinically tend to be silent and more prevalent in patients with hypertension, previous MI, LV systolic dysfunction and multi-vessel diseases.

Keywords- Ischemic mitral regurgitation, Ischemic heart diseases

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Introduction

Ischemic mitral regurgitation (IMR) is a common complication of coronary artery disease (CAD) and may develop in the acute or chronic phase. The acute IMR is secondary to papillary muscle infarction and rupture, and patients usually present in cardiogenic shock due to acute volume overload. In chronic IMR, mitral valve (MV) leaks but the leaflets and sub-valvular apparatus appear normal [1].

Chronic ischemic mitral regurgitation (CIMR) remains one of the most complex and unresolved aspects in the management of ischemic heart disease. CIMR is not only common, but it also significantly affects prognosis [2].CIMR occurs in approximately 20-25% of patients followed up after myocardial infarction [3-7] and in 50% of those with post-infarct congestive heart failure (CHF) [8].

CIMR can be defined as MR occurring as a consequence of MI or chronic myocardial ischemia in the absence of any inherent structural damage to the leaflets, chordae or papillary muscles (PMs) [9]. According to Borger et al., CIMR should be defined as MR occurring more than 1 week after MI, with one or more LV segmental wall motion abnormalities, significant coronary artery disease (CAD) in the territory supplying the wall motion abnormality and structurally normal leaflets and chordae [10]. Myocardial ischemia can induce both LV remodeling and mitral annular remodeling [11-12]. As a consequence, remodeling can lead to significant changes in the geometry of the mitral valve apparatus leading to MR. Thus, CIMR is primarily caused by a disease of the LV and not by a disease of

the valve itself [9-10]. It is important to verify that the etiology of MR is in fact ischemic. Some patients with concomitant MR and CAD do not have ischemic MR, but instead have a primary mitral valve condition and co-existing CAD.

Prevalence

The prevalence of CIMR is difficult to assess because of the heterogeneity of MR patients presented in different studies. In addition to the impact of the modality used to identify MR, discrepancies are also related to the timing of imaging [13]. CIMR occurs in approximately 20-25% of patients followed up after MI [3-7], in 50% of patients with post-infarct CHF [8], in 1.6% to 19.4% in angiographic studies for patients with symptomatic CAD [1] and in 28% of patients undergoing CABG [14]. CIMR is more common after inferior MI (38%) than after anterior MI (10%) on echocardiographic follow-up after 24 months [15]. CIMR may appear up to 6 weeks after MI [16]. The delay is attributed to remodeling of the LV [16]. CIMR is a widespread problem and is likely to increase in the next few decades as survival rates for acute MI improve.

Mechanisms

Historically, the mechanism of chronic IMR was attributed to papillary muscle (PM) dysfunction. However, further studies demonstrated that ischemia of papillary muscles themselves fails to produce significant MR without damage of the underlying myocardial wall [1].

CIMR is a complex and multifactorial disease, which starts primarily in the LV wall and leads to secondary valvular changes. The main pathophysiological mechanisms include ischemia-induced LV remodelling with papillary muscle (PM) displacement and leaflet tethering, a reduced leaflet closing force, PM dysfunction and dyssynchrony and annular enlargement [2].

MI leads to LV remodelling and in this process the LV becomes less elliptical and more spherical ,this causes apical and lateral displacement of the papillary muscles and tethering of both leaflets, restricted systolic leaflet motion displaces the coaptation point apically relative to the annular plane, which results in mitral valve tenting and 'incomplete mitral leaflet closure [11].

Patients and Methods

This cross sectional descriptive study has been designed to assess the rate and severity of ischemic MR in patient with IHD. The patients samples enrolled in this study was collected randomly form patients with symptomatic IHD attending Iraqi Centre for Heart Disease for coronary angiography between Jun 2011 and Jun 2012.

Inclusion Criteria were the following:

1. Normal mitral leaflets, 2. Normal other valves and 3.There is significant lesions in coronary arteries. Whereas the exclusion criteria include:

1. Acute IMR as a mechanical complication of MI., 2. History of rheumatic heart disease, 3. Other organic valvular disease, 4. MR associated with aortic valve or congenital heart disease.

Full data of patients enrolled in this study collected including age, gender, risk factors for IHD history of previous MI and the presenting symptoms, then clinical examination was done focusing on presence or absence of cardiac murmur was recorded.

Hypertension (HT) was defined as blood pressure >140/90 mmHg on > 2 occasion or patients already being on anti-hypertensive therapy.

Diabetes mellitus (DM) was defined when patient had symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL), fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or patients already being on anti-diabetic therapy.

Smoking was defined as any patients with active smoking or quit smoking within one year.

Previous MI referred to documented history and ECG finding of MI of more than one month duration then ECG (was classified as normal, NSTEMI, STEMI, ST-T changes), transthoracic echocardiography and coronary angiography were done for all patients.

Echocardiographic Study

All patients underwent transthoracic echocardiography (CX50 Philips echocardiography machine) to assess LV systolic function, regional wall motion and severity of CIMR (if present). LV systolic function were assessed by quantitative measurement of EF percentage by M mode waves through parasternal long axis view and LV systolic function considered as a normal [17] if EF ≥ 55%, mild LV systolic dysfunction if EF 45-55%, moderate if EF 35-45% and sever if EF <35%.

After exclusion of patients with MR of other cause, the severity of CIMR was evaluated semi quantitatively from colour Doppler visually and by measuring jet area, venna contracta (VC) and proximal isovelocity surface area (PISA).

The colour jet profiles can be measured within the LA. Colour jet areas are influenced by jet velocity and direction. Mild MR Jets cover less than 20% of total LA area (or a maximal jet area < 4.0 cm2.) with severe MR jets more than 40% of total LA area (or a maximal jet area > 10 cm2). At least two orthogonal views should be used with the Nyquist limit set at 50-60 cm/s.

The vena contracta is the narrow neck of the MR jet as it traverses the regurgitant orifice. The vena contracta measured from the parasternal long-axis view is best optimized by using a narrow sector scan, optimal colour gain, and Nyquist limit between 40-70 cm/s. The vena contracta appears as the well-defined light blue or light yellow high-velocity core on the red-blue colour Doppler scale. References for VC mild <0.3 cm, moderate 0.3-0.7 cm and sever > 0.7 cm as in [Fig-1].

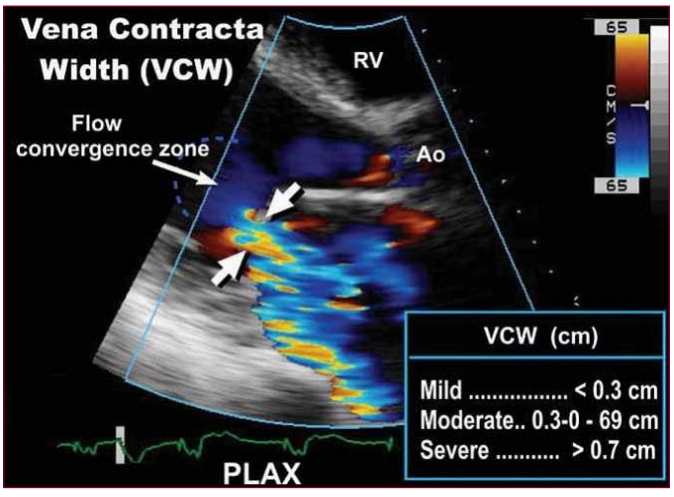

Fig. 1- Vena contracta width measurement.

PISA method can be used for estimating the area of the regurgitant orifice-which is hard to measure directly because actual regurgitant

orifice is dynamic, functional, and 3D. The apical four-chamber view is recommended for optimal visualization of the MR jet PISA measurement. The area of interest is optimized by lowering imaging depth and lowering the Nyquist limit (on the color Doppler scale) to approx 40 cm/s. The velocity at which the blue-red colour shift occurs identifies the PISA shell. The PISA radius (r) is then measured and multiplied by the PISA velocity. References for PISA were mild < 0.4m, moderate 0.4-1m and sever > 1m as in [Fig-2].

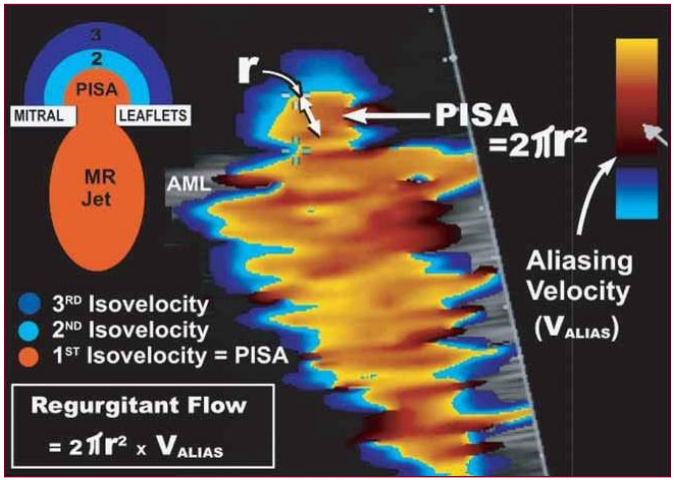

Fig. 2- Proximal iso velocity surface area (PISA).

Coronary Angiography

Diagnostic coronary angiography through right femoral approach was performed using judkins catheter for imaging right and left system using multiple views.

Coronary artery stenosis (if present) assessed visually by multiple orthogonal views to determined its severity. Significant CAD was defined as ≥70% diameter [18]. ALL patients presented with chest pain and coronary angiography show non-significant lesions were excluded from this study. The extent of CAD was classified as single, double and multi-vessels diseases.

Statistical Analysis

All data summaries in No. percentage and mean ± standard deviation between different variables measured by Chi-square test, P≤ 0.05 considered as a level of significance. Software of Statistical Package of Social Signs (SPSS 17) used.

Results

Baseline Characteristics

Age range was 39-73 years mean of 59.06 ± 6.77, 116/153 patients (75.8%) were male and 37/153 (24.2%) were female, diabetes mellitus 61/153patients (39.9%), hypertension 87/153 patients (56.9%) and smoker 79/153 patients (51.6%).

One hundred one patients (66%) presented with chronic stable angina and 52/153 patients (34%) unstable angina and 73 patients (47.7%) of all patients enrolled in this study had history or electrocardiographic evidence of previous myocardial infarction as in [Table-1].

The clinical characteristics indicate that the MR is significantly associated with HTN (33 vs 12) P=0.04 while there was non-significant association with age (58.42±7.63 vs 57.82±7.90) P= 0.660, gender (28.4% vs 32.4%) P= 0.12, DM (37.7% vs 23.9%) P= 1.8 and smoking (27.9% vs 31.1) P= 0.7 [Table-2].

There were only 9 patients (5.9%) had systolic murmur of MR on clinical examination and those represent 20% of patients with MR detected by echocardiography.

Table 1- Demographic Characters

Variable	Number (n=153)
Age (mean ± SD)	59.06± 6.77 years
Male	116 (75.8%)
Female	37 (24.2%)
Diabetic	61 (39.9%)
Hypertensive	87 (56.9%)
Smoker	79 (51.6%)
History of previous MI	73 (47.7%)

Table 2- Demographic Characters and CIMR

Parameter		Total No.	NO MR N (%)	MR N (%)	P value
Age mean ±SD			57.82±7.90	58.42±7.63	0.66
Gender	Male	116(75.8)	83(71.6)	33(28.4)	0.12
	Female	37(24.2)	25(67.6)	12(32.4)	
DM	Yes	61(39.9)	38(62.3)	23(37.7)	1.8
	No	92(60.1)	70(76.1)	22(23.9)	
HTN	Yes	87(56.9)	54(62.1)	33(37.9)	0.04
	No	66(43.1)	58(81.8)	12(18.2)	
Smoking	Yes	79(51.6)	57(72.1)	22(27.9)	0.7
	No	74(48.4)	51(68.9)	23(31.1)	
Previous MI	Yes	73(47.7)	44 (60.3)	29 (39.7)	0.04
	No	80(52.3)	64 (80.0)	16(20.0)	

Echocardiographic Parameters

Mitral regurgitation detected by echocardiography in 45 patients (29.4%), more in patients with past history of MI 29/73(39.7%), those who had no evidence of previous MI 16/80(20.0%) P = 0.04 [Table-2].

There were 17/50(34.0%) patients with anterior MI had CIMR whereas there were 12/23 (52.2%) patients with inferior MI had CIMR P<0.03 [Table-3].

Table 3- Relation between Location of Infarction and MR

Location	Total No.	No MR N (%)	MR N (%)	P value
Anterior MI	50	33(66.0)	17(34.0)	0.03
Inferior MI	23	11 (47.8)	12(52.2)	
	73	44(66.3)	29 (39.7)	

The mean LVEF 50.7± 8.46 (35-70), 82 patients (53.6 %) had normal LV systolic function and (LVEF ≥55) while 71 patients (46.4%) had decrease LV systolic performance [Table-4].

Table 4- Relation between LV Systolic Function and MR

Systolic function	Total No. N (%)	NO MR N (%)	MR N (%)	P value
Normal LVEF ≥55	82(53.6)	78 (95.1)	4 (4.9)	
Depressed LVEF <55	71(46.4)	30(42.5)	41 (57.7)	0.0001
	153	108	45	

There were 39/153 (25.5%) patients had mild LV systolic dysfunction (LVEF 55-45), 23/153 (15.3%) patients had moderate LV systolic dysfunction (LVEF 45-35) whereas only nine (5.8%) patients presented with sever LV systolic dysfunction (LVEF≤35) [Table-5].

The distribution of the severity of CIMR was: 33 patients had mild MR (73.3%), 7 patients had moderate MR (15.5%) and five patients only had sever MR (11.2%) [Table-5].

Table 5- Impaired LV Systolic Function and MR

	Total No. N (%)	NO MR N (%)	MR N (%)	P value
Mild syst. dysfunction EF 55-45	39(25.5)	19 (48.8)	20 (51.2)	
Moderate syst. dysfunction EF 45-35	23(15.3)	9 (39.1)	14 (60.9)	
Sever syst. dysfunction EF ≤35	9(5.8)	2 (22.3)	7 (77.7)	0.004
	71	30	41	

There are only 4 patients with normal LVEF had MR (4.9%) while 41 (57.7%) patients with impaired LV systolic function had CIMR, P <0.0001 [Table-4].

The incidence of MR in correlation with LV systolic dysfunction was as follow: 20 patients (51.2%), 14 patients (60.9%) and seven patients (77.7%) with mild, moderate or severe LV systolic dysfunction had MR respectively, so there is significant association with moderate or severe LV systolic dysfunction and CIMR P=0.004 [Table-5].

Regarding the regional wall motion abnormality, 56/153 (36.6%) patients had normal regional wall motion all of them has no MR and 97/153 (63.4%) patients had regional wall motion abnormalities 45 patients of them (46.4%) were having CIMR, P=0.00001 [Table-6].

Table 6- Regional wall motion and MR

	Total No. N (%)	NO MR N (%)	MR N (%)	P value
No regional wall motion abnormality	56 (36.6)	56 (100)	0	
regional wall motion abnormality	97 (63.4)	35 (43.7)	45 (46.4)	0.00001
	153	108	45	

We found that 31/97 (31.9%) patients had anteroseptal wall motion abnormality, 27/97 (27.9%) patients had inferior wall motion abnormality and 22/97 (22.6%) patients had anteroapical wall motion abnormality while 17/97 (17.5%) patients had combined wall motion abnormalities [Table-7]. The incidence of CIMR was more common in inferior than anterior wall motion abnormalities, P<0.007 [Table-7].

Table 7- Location of Regional Wall Motion and MR

Regional wall motion		NO MR N (%)	MR N (%)	P value
Antero-septal wall motion abnormality	31 (31.9%)	19(61.2)	12(38.8)	
Inferior wall motion abnormality	27 (27.9%)	12(44.5)	15(55.5)	0.007
Antero-apical wall motion abnormality	22 (22.6%)	15(68.2)	7(31.8)	
Combined wall motion abnormality	17(17.5)	6 (35.3)	11(64.7)	0.33

The direction of regurgitation jet was centric in 35 patients and eccentric in 10 patients, 8/10 patients were had inferior wall motion abnormality, while patients with anterior or combined wall motion abnormalities had centric jet direction [Table-8].

Table 8- Location of Regional Wall Motion and MR jet direction

Regional wall motion with MR	N (%)	Eccentric MR jet direction N (%)	Centric MR jet direction N (%)	P value
Antero-septal wall motion abnormality with MR	12(38.8)	1(8.3%)	11(91.7%)	
Inferior wall motion abnormality with MR	15(55.5)	8(53.3%)	7(46.7%)	
Antero-apical wall motion abnormality with MR	7(31.8)	1(14.3%)	6(85.7%)	0.006
Combined wall motion abnormality with MR	11(64.7)	0(0%)	11(100%)	

Coronary Angiographic Finding

The results of coronary angiography in this study show that 41/153 (26.8%) patients had single vessel disease, 50/153(32.7%) patients had two vessels diseases and 62/153(40.5%) patients had multi-vessels diseases, [Table-9].

The correlation of CIMR detected by echocardiography and coronary angiography in this study show that only six patients (14.6%) of those with single vessel disease had CIMR, 11/50(22.0%) patients with two vessels disease were having CIMR and 28/62 (45.2%) patients with multi-vessels diseases were had CIMR P=0.001[Table-9].

Table 9- No. of Vessel with Significant Lesion and MR

No. of vessel with significant lesion	Total No.	NO MR N (%)	MR N (%)	P value
Patients with single vessel diseased	41 (26.8)	35 (85.4)	6 (14.6)	
Patients with two vessels diseases	50 (32.7)	39(78.0)	11(22.0)	0.03
Patients with multi- vessels diseased	62 (40.5)	34(54.8)	28(45.2)	
Total	153	108	45	

Discussion

In this study we found that CIMR is common echocardiographic finding in patients with IHD and is often silent clinically and more in hypertensive patients, those with previous MI and with impaired LV systolic function.

The demographic data in this study show that patients enrolled were younger (mean age 59.06± 6.77 years) than those enrolled in other studies like Grigioni, et al. [4] and de Isla, et al. [19] and this may indicate the earlier presentation of IHD in Iraqi patients may be attributed to stressful conditions, unhealthy dietary habits, and sedentary lifestyle.

The relation between age and CIMR development was inconsistent, in the present study it was not significant factor in CIMR which agrees with Grigioni, et al. [4] study while others disagree like Bursi, et al. [20]. This disconcordance may be attributed to the small number of elderly patient in this study.

Regarding gender, this study found there is no association between gender and CIMR ,opposite to the finding of both de Isla, et al. [19] and Bursi, et al. [20] were they found that CIMR more common in female, and this probably related to small sample of female included in this study.

In comparing the incidence of CIMR and risk factors for CAD, the current study showed that there was a significant association between hypertension and CIMR P = 0.04, this agrees with Francesca Bursi, et al. [20] study. This may be attributed to the fact that hypertension itself may cause MR, so echocardiographic operator should consider this point and should look for other signs of hypertension or use exercise echocardiography to detected the dynamic nature of CIMR. While no significant correlations were found between CIMR and both diabetes mellitus and smoking which agree with result of Grigioni, et al. [4] study.

In the current study we found that cardiac murmur was detected clinically only in 20 % of patients with CIMR detected by echocardiography MR, this clinical observation indicated that the CIMR is often silent and the presence of murmur or its intensity (if present) does not reflect the degree of regurgitation.

Indeed, severe MR may even be silent, this may be due to reduced ventricular function lead to minimizing the atrioventricular gradient, regurgitant flow (in comparison with primary MR), and subsequent murmur, and this agree with that found in Bursi, et al. [20] study, so because CIMR often lacks the typical auscultatory presentation and its detection cannot rely on clinical assessment, thereby requiring imaging studies, most often echocardiography.

The incidence of CIMR in the current study was 29.4%, similar finding by Wierup, et al. [14] which found that the incidence of CIMR is 28%, but lower than that found by Bursi, et al. [20] who found that the incidence was 50%, this discrepancy could be attributed to the fact that all patients in Bursi, et al. [20] study had previous MI, while 47.7% of patients in the current study had evidence of previous MI., but in the current study we found that the incidence of CIMR was high in subgroup who had history or electrocardiographic evidence of previous MI (39.7%) P=0.04.

The incidence of CIMR post infarction depend mainly on the location, size and age of infarct area because development of CIMR related mainly to the degree of LV remodeling. The site of infarction may cause CIMR by tethering effect and displacement of PMs as in CIMR in patients with inferior MI, whereas the size of infarcted zone effect the incidence of CIMR, since larger infarct area lead to more LV remodeling and changing the LV shape form elliptical to more spherical shape and this lead to displacement of both leaflet and more MR.

In the current study we found that CIMR was found in only 20% of patients with no history or electrocardiographic evidence of previous MI, this may attributed to the fact that in patients with chronic stable angina echocardiographic examination may be normal at rest and rate of CIMR may be higher when use exercise echocardiography.

In the current study MR was significantly associated with the inferior location of MI as compared to anterior one (52.2% vs. 34.0%) P= 0.03. This may attributed to localized deformity of the mitral valve complex especially at the PM attachment accompanied by reduced mobility of the posterior leaflet and this lead to apical displacement of posterior PM and cause MR in contrast to the global LV dilatation that occurs in anterior MI, and this agree with Kumanohoso, et al. [15] study whereas disagree with the results of Gahl, et al. [21] study that found no difference in incidence of MR in anterior or inferior MI.

There was a strong association between CIMR and LVEF only 4.9% of patients with normal LVEF had MR while in 57.7 % with depressed LVEF P=0.0001. These results are in concordance with the results of the Francesca Bursi et al [20] and other studies. Many studies as de Isla, et al. [19] and Bursi, et al. [20] study show that existence of CIMR is independent prognostic factor for development of heart failure and cardiac death.

This study showed close correlation between CIMR and the severity of LV systolic dysfunction (46.5% in mild LV systolic dysfunction vs.77.7% in severe dysfunction)), this well correlated with the result of Gahl, et al. [21] and this may be due to segmental dysfunction or LV dilatation, yet these result must be considered with caution because of the small No. of patients with severe LV systolic dysfunction.

There was significant relation between CIMR and the no. of coronary artery involvement so as CIMR was more prevalent in patients with significant multi-vessels coronary artery disease P < 0.03 and this agree with that found de Isla, et al. [19] this may be due to that the multi-vessel disease may associated with more ischemia and multiregional wall motion abnormality.

Limitations

In this study, serial echo assessment was not performed. It would have been useful because functional MR is very variable in its evolution and our echocardiographic findings were observed after occurrence of IHD which do not exclude MR that was present before that.

Conflicts of Interest: None declared.

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