AIM OF THE WORK

The aim of this work was to assess the heart rate response during Dipyridamole stress gated Technetium Tc99m SestaMIBI SPECT study in relation to the severity of the perfusion defect and left ventricular function.

PATIENTS

This study included 40 patients adults, undergoing myocardial perfusion scintigraphy SPECT study associated with dipyridamole stress in the Nuclear Cardiology Lab. Cardiology Department in Alexandria Main University Hospital, after signature of an informed consent in the period from July 2013 for 6 months.

The following patients will be excluded:
1. Patients with contraindications to cardiac stress test.
2. Patients with bronchial asthma.
3. Patients with history of severe valvular heart disease.
4. Patients with history of CABG.
5. Patients with severe heart failure.
6. Pregnant ladies.
7. Patients who did not give their written consent.

METHODS

All patients were subjected to:

A. History taking:

1) **Personal history:** name, age and gender.

2) **Present history**: regarding chest pain and dyspnea.

3) **Past history:** Diabetes Mellitus, hypertension, myocardial infarction and prior revascularization.

4) **Family history:** of coronary heart disease, diabetes mellitus, hypertension and dyslipidemia.

5) **Social history:** smoking and alcohol intake.

6) **Medical history:** especially digitalis, beta blockers, calcium channel blockers and antiarrhythmic drugs.

B. Clinical examination:

Including heart rate, blood pressure and weight.

Chest examination to exclude bronchospasm.

C. Complete resting 12 lead Electrocardiogram:

All electrocardiograms were analyzed for cardiac rhythm, heart rate,

any conduction disturbance, ST segment and T. wave changes.

D. Echocardiography:

To evaluate resting systolic and diastolic left ventricular function.

E. Coronary angiography:

To identify the significant lesions in main coronary arteries and their branches.

F. Gated myocardial perfusion SPECT study:

Stress, rest Tc99m SPECT 2 days protocol to study myocardial perfusion and left ventricular function.

- *Dipyridamole protocol*:

Patients were instructed to withhold smoking, consumption of caffeine or products containing Methylxanthine for 24 hours before testing. Dipyridamole (0.56 mg/kg, to a maximum of 60 mg) was infused over 4 minutes with the patient in the supine position. Complete 12 leads ECG were continuously monitored. HR and BP were recorded at rest and every 1 minute after the onset of dipyridamole infusion for a total of 6 minutes unless there were significant ECG changes or chest pain, monitoring were continued until reversed to the baseline.

20 mCu Tc99m sestaMIBI was injected intravenous 2 min. post dipyridamole.

Significant ST segment depression during dipyridamole stress was defined as ≥1 mm of horizontal or downsloping depression occurring at 80 milliseconds after the J point. Sublingual nitrates and Aminophylline was intravenously given 2 minutes after radiotracer injection at peak stress in a dose of 120 to 240 mg to reverse any adverse effect caused by dipyridamole [79].

- *Myocardial Perfusion Image (MPI) protocol*:

2 day protocol, stress Tc99m sestaMIBI /dipyridamole, rest Tc-99m sestaMIBI. Myocardial perfusion SPECT was performed in all patients. For stress imaging, 20 mCu Tc99m sestaMIBI was injected intravenously, then the patient was instructed to eat fatty meal to decrease hepatic activity during imaging. After 1 hour, imaging acquisition was started. Imaging was in supine position from left anterior oblique to right posterior oblique by Siemens Symbia E Gamma Camera with gated ECG.

In the 2nd day, patients were reinjected by 20 mCu Tc99m sestaMIBI and reimaged after 1 hour with same protocol.

All images were acquired and processed according to the **American Society of Nuclear Cardiology guidelines**. All raw data (2 sets/patient) were reconstructed using standard filtered back projection. Image analysis was performed using a previously validated automated program which determines the extent and severity of LV perfusion defect size and the extent of reversible (ischemia) or fixed (scar) resting hypoperfusion and LVEF [80].

- *Image interpretation*:

We used the grey scale and the colour scale in image interpretation. In the colour scale, 16 colours from black (0% activity) to the white (100% activity) were used.

Semiquantitive visual interpretation of SPECT images was performed with short axis and vertical and horizontal long axis tomography divided into 17 segments (Figure 7). Each segment was scored by consensus of two expert observers using 5-point scale

Normal=0
Mildly reduced=1
Moderately reduced=2
Severely reduced=3
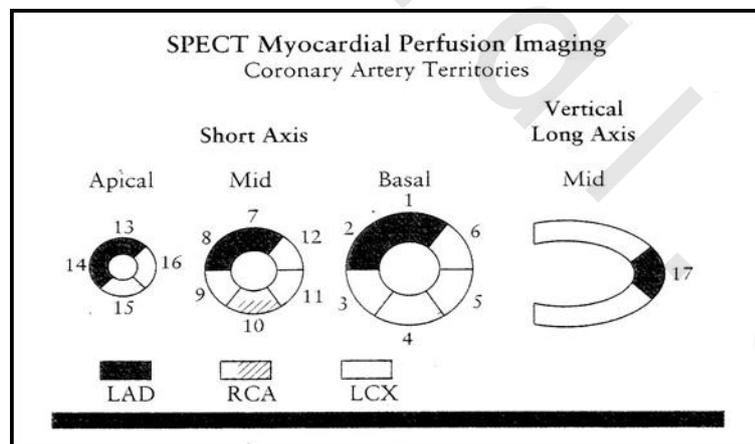Absent uptake=4
The myocardium is divided into 17 segments.

Figure (7): Short and long axis tomography divided into 17 segments[81].

We compared initial and delayed reinjection study and myocardial viability to denote:
- Normal perfusion.

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- Reversible defect i.e. Tc99m sestaMIBI uptake in initial stress image was reduced but increased by at least one grade in reinjection image.
- Fixed defect: fixed mild to moderate reduction of uptake.
- Wall motion abnormalities, thickening, EF during rest and stress.
- SSS, SRS, SDS and TPD.
- Signs of LV dysfunction as LV dilatation and increase lung Tc99m uptake.

The initial summed score, delayed summed score and summed difference score were also determined. The perfusion study was evaluated according to scoring system. Scores for all 17 segments are added to create the summed score. There are two summed scores [82]:

a) Summed stress score (SSS) represents the severity and the extent of stress perfusion abnormality related to ischemia and infarction.

Interpretation of SSS:

4-8 = small defect

9-13 = moderate defect

>13 = large defect

b. Summed rest score (SRS) represent the defect during rest and denote scar.

c. Summed difference score (SDS) is derived by subtracting SRS and SSS represents the extent of stress induced ischemia.

Left ventricular size identified qualitative either:

+ = normal.

T.D = Transient dilatation during stress.

P.D = Permanent dilatation.

Statistical analysis:

All data were expressed as mean ± SD. Statistical analysis was done using Microsoft excel and SPSS software. Qualitative data were described using number and percent. Quantitative data were described using median, minimum and maximum as well as mean and standard deviation. Hemodynamics, perfusion study and EF compared by paired Student's t test or a Fisher's exact test where appropriate. A value of p<0.05 (two-sided) was considered significant. a severity of perfusion defects compared by Z for Mann Whitney test.

1- Arithmetic mean ($\overline{X}$):

Was calculated as follows:

$$\overline{X} = \frac{\sum X}{n}$$

Where: $\overline{X}$ = arithmetic mean
$\sum X$ = Sum of observations
n = number of observations

2- Standard deviation (SD)
Was calculates as follows:

$$SD = \sqrt{\frac{\sum x^2 - \frac{(\sum x)^2}{n}}{n-1}}$$

Where: $\sum x^2$ = sun of squared observations.
$(\sum x)^2$ = square of the sum of observations.
n = number of observations

3- "t" test:

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{S_p^2 \left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

$$S_p^2 = \frac{S_1^2 (n_1 - 1) + S_2^2 (n_2 - 1)}{n_1 + n_2 - 2}$$

Where: S_p^2 = Pooled variance.
S_1^2 = Variance of sample (1).
S_2^2 = Variance of sample (2).
n_1 = Size of sample (1).
n_2 = Size of sample (2).
X_1 = Mean of sample (1).
X_2 = Mean of sample (2).
S_1 = Standard deviation of sample (1).
S_2 = Standard deviation of sample (2).

4- Chi-square (X^2)

For comparison between distribution of patients according to different items of study and use this formula for calculation:

$$X^2 = \sum \frac{(O - E)^2}{E}$$

O = Observed results.
E = Expected results.
$(O - E)^2$ = difference squared.

$$\frac{\text{Total row} \times \text{total column}}{\text{Grand total}}$$

5- F test:

$F = S^2_A / S^2_w$

Where

S^2_A = Mean square among groups.

S^2_w = Mean square within groups.

RESULTS

This is a prospective study including 40 adult patients who were submitted to myocardial perfusion scintigraphy SPECT study associated with dipyridamole stress in the nuclear cardiology lab. Cardiology department in Alexandria Main University Hospital.

Heart rate response to dipyridamole was measured before infusion of dipyridamole, during infusion of the drug and after stopping infusion by 2 minutes for all patients, demographic data, risk factors, clinical presentation, hemodynamics and SPECT parameters collected were subjected to statistical analysis.

1. Classification of the patients as regard heart rate response:

The patients were classified into two groups based on the heart rate response to dipyridamole. Group A consisted of patients with normal heart rate response to dipyridamole (n=13, 32.5%). Group B consisted of patients with blunted or reduced heart rate response (n=27, 67.5%).

Blunted heart rate defined as the ratio of: peak HR/ rest HR is less than 1.2

2. Age and sex:

Age was ranged between 42 – 73 years .The mean age of patients in group A was 58.4±6.9 and the mean age of group B was 58±8.23. As well age had no statistical significance between the 2 groups (table IV).

Regarding the gender there were 25 males (62.5%) and 15 females (37.5%) with no statistical significance (figure 8).

Table (IV): Distribution of studied patients regarding demographic data.

	total population n=40	normal HRR n=13	reduced HRR n=27	test of sig.	P
age (year)	58±7.33	58.4±6.9	58±8.23	t= 0.1	p= 0.9
sex					
male	25(62.5%)	10(76.9%)	15(55.5%)	X^2= 1.7	P= 0.191
female	15(37.5%)	3(23%)	12(44.5%)		
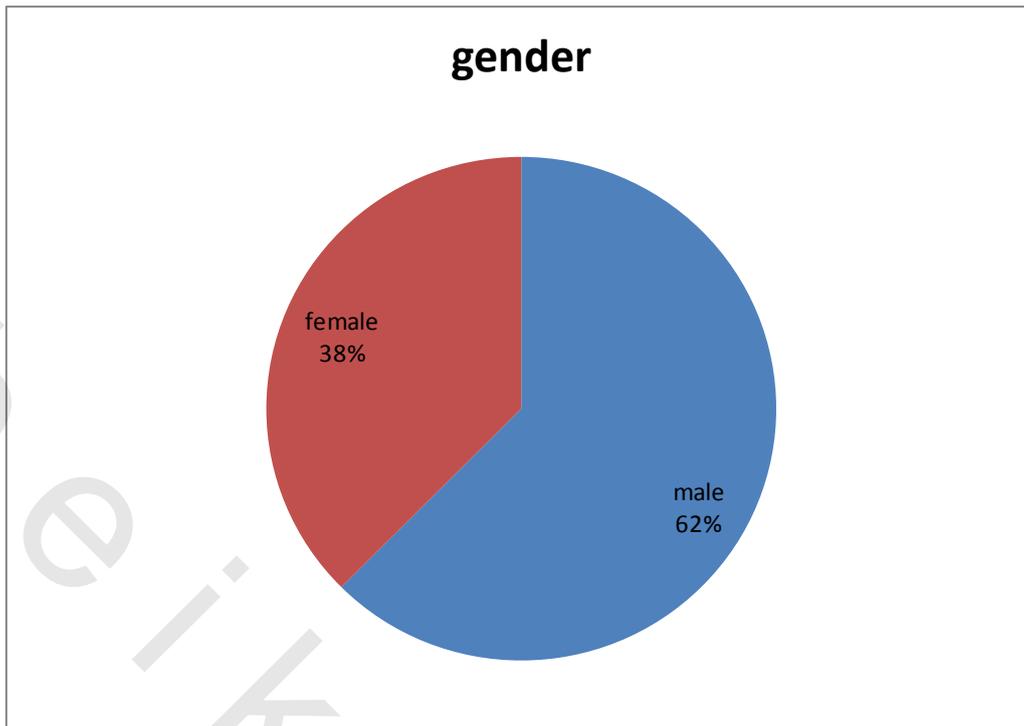
Figure (8): Distribution of studied patients group regarding to the sex.

3. Risk factors:

Are summarized in:

- Six patients (15%) had no risk factor, 10 patients (25%) had single risk factor, 10 (25%) patients had two risk factors and 14 (35%) had more than two risk factors.
- Regarding to the total population we found:
  a. Eleven patients (27.5%) were smokers.
  b. Fifteen patients (37.5%) were diabetics.
  c. Thirteen patients (32.5%) were ischemic.
  d. Twenty-eight patients (70%) were hypertensive.
- In normal heart rate response (HRR) group (group A)we found(figure 9):
  a. Three patients (23%) were smokers.
  b. Two patients (15.3%) were diabetics.
  c. Four patients (30.7%) were ischemic.
  d. Seven patients (53.8%) were hypertensive.

- In blunted heart rate response (group B) group we found (figure 9):
  a. Eight patients (29.6%) were smokers.

b. Thirteen patients (48.1%) were diabetics.
c. Nine patients (33.3%) were ischemic.
d. Twenty-one patients (77.7%) were hypertensive.

- Distribution of these cases according to group A and B is illustrated in (table V)
- DM was the only risk factor that had more represented with blunted HRR group (P=0.04).

Table (V): Distribution of studied patients regarding their risk factors.

	Total pop. N=40		Normal HRR N=13		blunted HRR N=27		Test of sig.	P value
	No.	percent	No.	Percent	No.	percent		
DM	15	37.5%	2	15.3%	13	48.1%	$X^2= 4.01$	P=0.04*
HYPERTENSION	28	70%	7	53.8%	21	77.7%	$X^2= 1.55$	P=0.212
Family history IHD	10	25%	2	15.3%	8	29.6%	$X^2= 0.94$	P=0.32
SMOKING	11	27.5%	3	23%	8	29.6%	$X^2= 0.18$	P=0.66

Figure (9): Distribution of studied patients group regarding their risk factors.
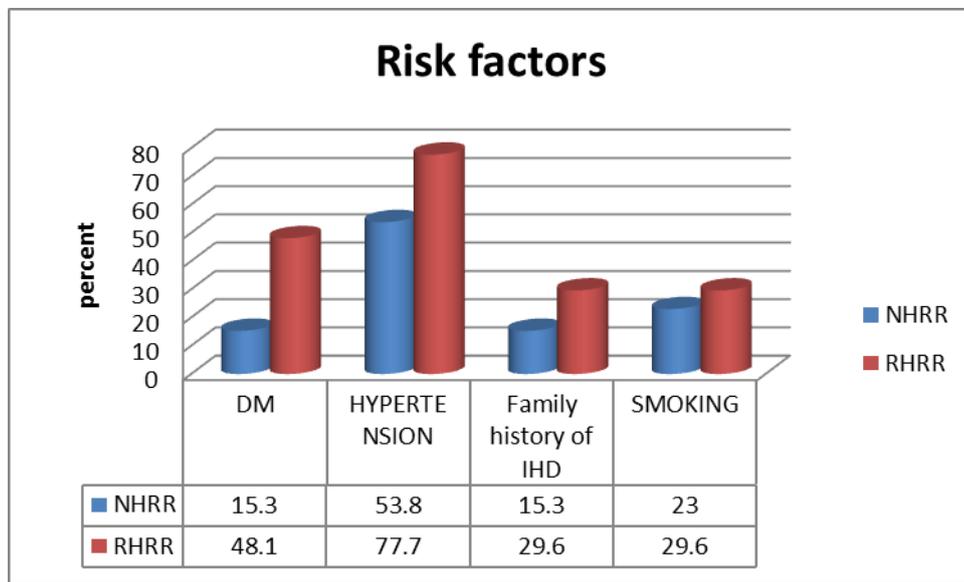
Figure 10: distribution of studied patients group regarding their risk factors

4. Clinical presentation:

Thirty-six patients (90%) complaint of chest pain on exertion. All patients with normal HRR had chest pain on presentation, while 85.1% of patients with blunted HRR complaint of chest pain. 19 patients (47.5%) had dyspnea with 5 of them was in normal HRR group and 14 patients in another group (figure10).
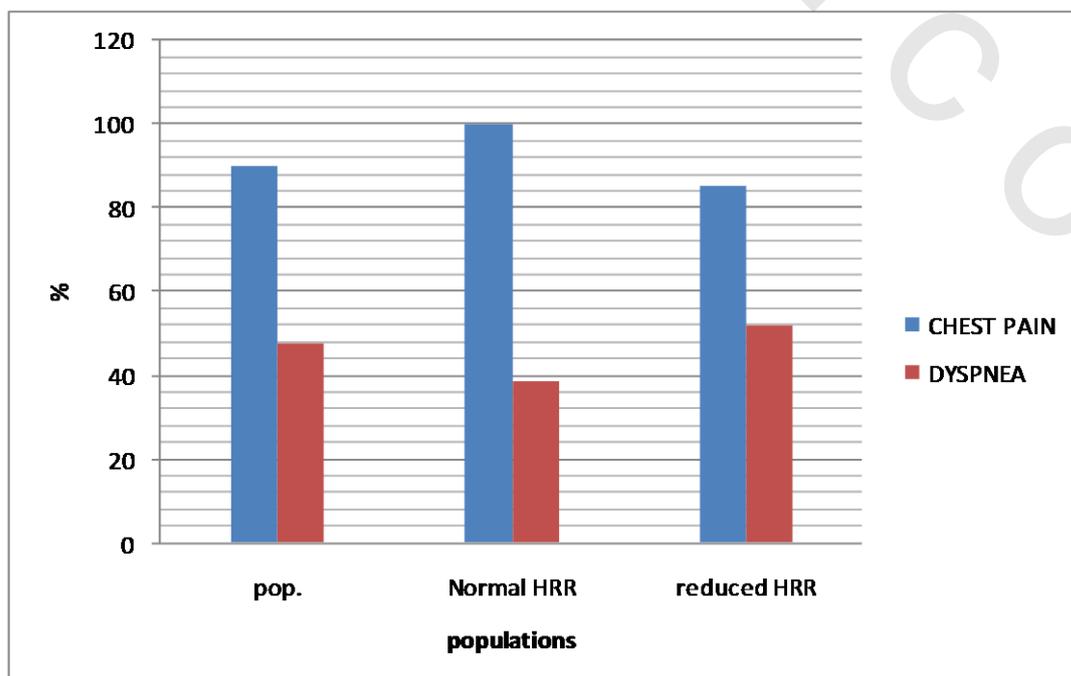

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Figure (11): Distribution of studied patients regarding the clinical presentation.

5. Hemodynamics parameters:
A. Blood pressure:

Blood pressure measured at rest and every minute of dipyridamole infusion and 2 minutes post dipyridamole infusion. Resting systolic blood pressure ranged between 100 -240 mmHg and the peak of systolic blood pressure ranged between 100 - 200mmHg (figure11).

The mean resting systolic blood pressure for group A was 146.1 mmHg and the mean Peak systolic blood pressure was 134.6 mmHg while in group B the mean resting systolic blood pressure was 157.4 mmHg and the mean peak systolic blood pressure was 143.7mmHg.(table VI).

	total population n=40	normal HRR n=13	blunted HRR n=27	test of sig.	p value
heart rate					
resting	75.7±14.8	69.4±13.4	78.7±14.7	t=1.9	p= 0.03*
peak	84.3±13.8	88.3±14	82.41±13.55	t=1.27	p= 0.2
delta HR	8.65±8.81	18.9±5.6	3.7±4.85	t=8.8	p<0.001*
blood pr.					
resting syst.	153±32.2	146.1±33.3	157.4±31.6	t= 1.03	p=0.3
peak syst.	140.75±21.9	134.6±25.3	143.7±19.8	t= 1.23	p=0.22

Table (VI): Distribution of studied patients groups regarding their hemodynamics.

Resting blood pressure as well as peak systolic blood pressure had no significant statistical value regarding to our study groups.
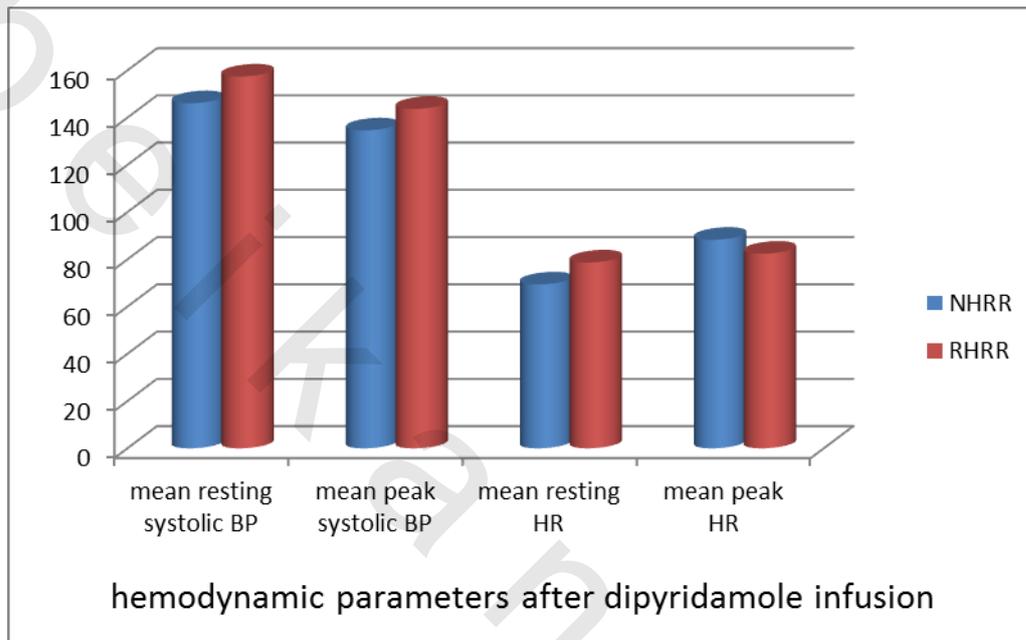

Figure (12): Distribution of studied patients group regarding their hemodynamics.

*NHRR: normal heart rate response

**BHRR: blunted heart rate response

B. Heart rate:

The mean resting heart rate in normal HRR group(A)was 69.4 beat /min. that increased in the peak of stress to 88.3 beat / min. with mean delta HR 18.9 beat / min.

In group (B) blunted HRR group the mean resting HR was 78.7 beat / min. with mean peak heart rate 82.14 beat / min. and delta heart rate had mean 3.7 beat / min.

Resting heart rate and delta heart rate were statistical significant with P value 0.03 to blunted HRR group (table VII).

6. Twelve - lead electrocardiography (ECG):

We performed pharmacologic stress protocol with printing ECG every minute to find any changes in ECG including change in heart rate, ST segment deviations and any type of arrhythmia. Heart rate ranged from 50-107 during rest to 56-122 during stress.

Resting 12- lead ECG revealed sinus rhythm in all patients ,with 15 patients had normal ECG, 4 patients had lateral ischemia, 12 patients had inferior ischemia and 17 patients had anterior ischemia. (figure 12). Only 2 patients complaint of chest pain after pharmacological stress and one patient had non sustained ventricular tachycardia and 3 patients exhibited significant ST depression.

Post stress ECG changes had no significant statistical significance

resting ECG

- ant. 36%
- lat. 8%
- inferior 25%
- non 31%
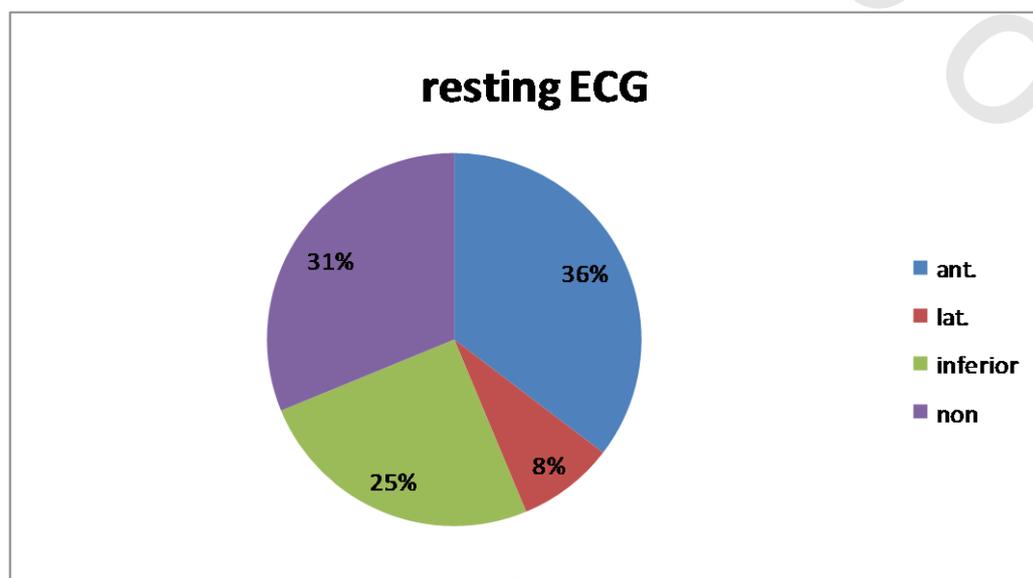
regarding our study groups.

7. Echocardiography:

The left ventricular ejection fraction (LVEF) ranged from 39% to 74% with mean 58±9.9%. 33 patients had EF > 45% and 7 patients had EF< 45% (Figure 13).

In (group A) the LVEF ranged from 50% to 70%. The mean of LVEF was 61.7 % with standard deviation 5.2.

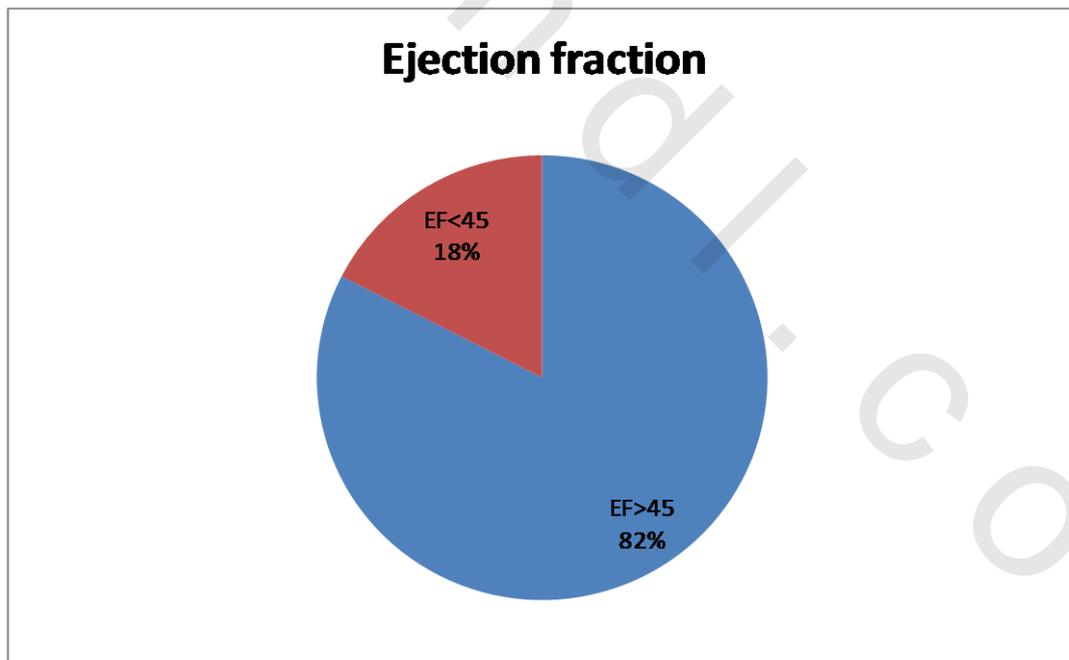In (group B)the LVEF ranged from 39% to 74%. The mean of LVEF was 56.1% with standard deviation 11.5.

Ejection fraction

EF<45
18%

EF>45
82%

Figure 14: Distribution of studied patients regarding left ventricular EF.

8. Coronary angiography:

All patients submitted to coronary angiography with 18 patients had not any significant lesion. Single vessel disease was found in 8 patients (20%%), 9 patients had two-vessel disease (22.5%) and 5 patients had three - vessel disease (12.5%) (figure 15). 13 patients had significant left anterior descending artery (LAD) lesions, 11 patients with right coronary artery (RCA) lesions and 13 patients with left circumflex artery (LCX) lesions. (Figure16).
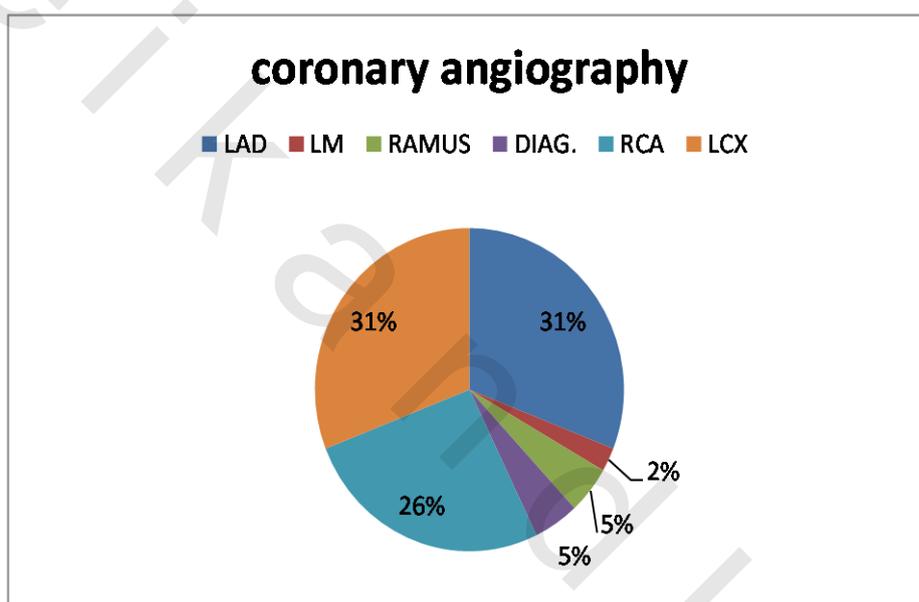

Figure 15: Distribution of studied patients regarding coronary angiography.
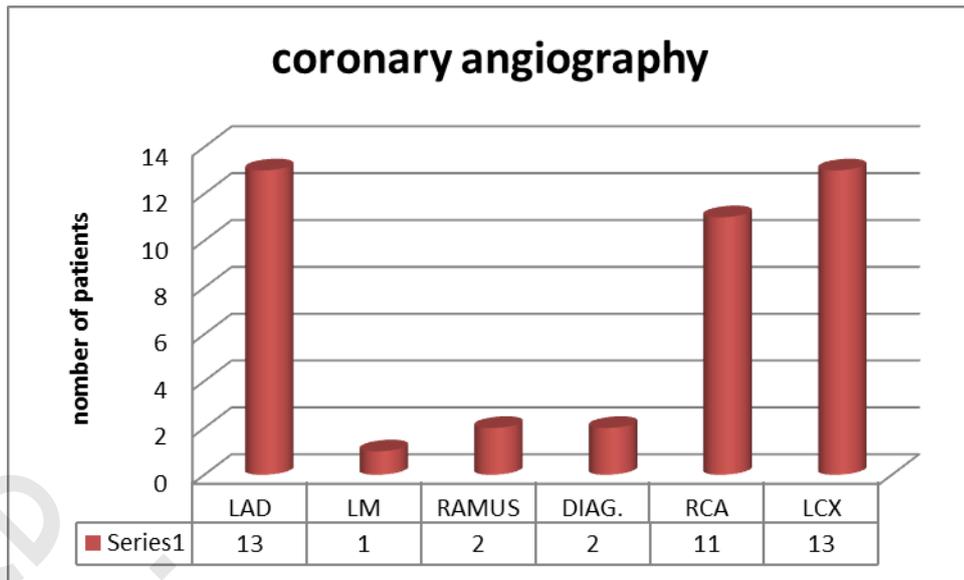
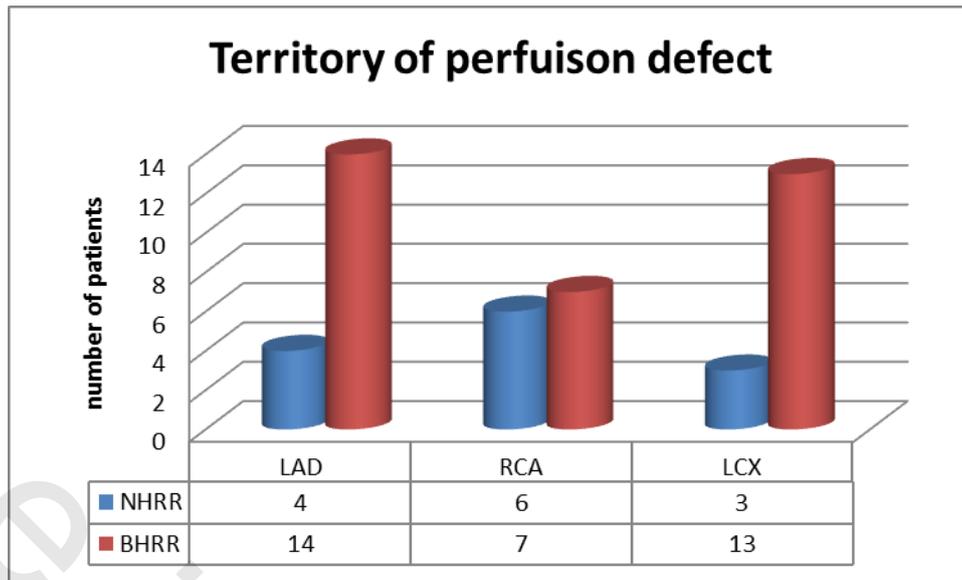**Figure (16):** Distribution of studied patients regarding coronary angiography.

Figure (17): Distribution of studied patients regarding number of vessel disease.
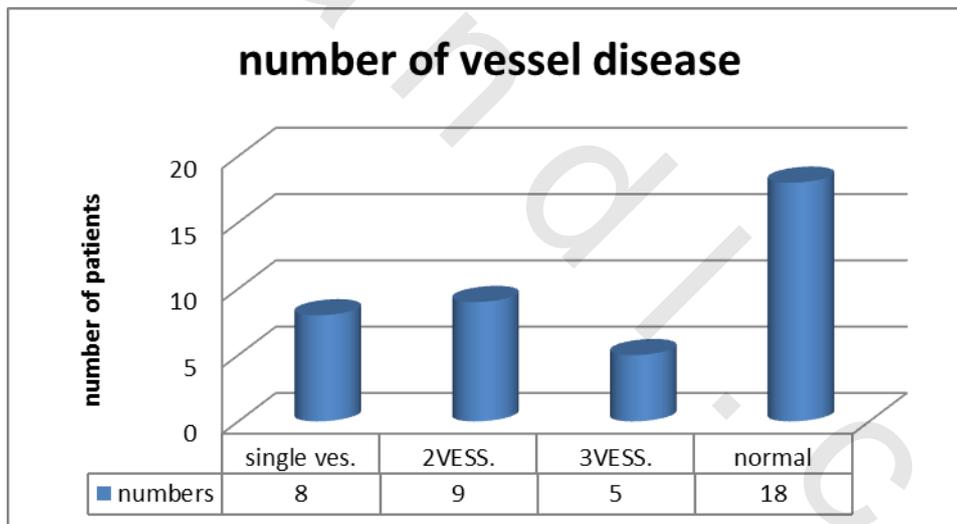

Figure (18): Distribution of studied patients regarding territory of perfusion defects.

NHRR: Normal heart rate response

BHRR: Blunted heart rate response

9. Perfusion study:

We used scoring system for quantitative segmental analysis for Tc-99m sestaMIBI myocardial perfusion gated SPECT study. The summed stress score (SSS) was ranged from 0-15 with mean 3.3±2.9 in group (A) that raised to 0-31 with mean 11.07±9.6 in group B (P=0.005).(table7). Summed rest score (SRS) ranged from 0-5 mean 1.23±1.4 in group (A)but in group (B) SRS ranged from 0-23 with mean 4.8±7(P=0.04). Summed difference score (SDS) changed from 0-10 mean 2.07±2.5 in group (A) to 0-14 mean 6±4.6 in group (B) (P=0.003).

Total perfusion defect (TPD) changed from 0-14% mean 6.38±9.6 % in group (A) to 0-41% with mean 11.9±12.1% in group (B) (P=0.02). L.V dilatation occurred in 3 patients (23%) in group (A) and increased to 8 patients in group (B) with 29.6%. Apical scar and aneurysm didn't occurred in group (A) but there were 5 patients in group (B) had apical scar and aneurysm (18.5%) (P=0.09) (table VIII).

Table (VII): Comparison between normal HRR group and blunted HRR group according to perfusion items**.**

	Normal HRR		Reduced HRR		p
	No.	**%**	**No.**	**%**	
Summed stress score (SSS)					
Range	0-15		0-31		0.005*
Mean	3.3		11.07		
S.D.	2.9		9.6		
Summed resting score (SRS)					
Range	0-5		0 - 23		0.04*
Mean	1.23		4.8		
S.D.	1.4		7		
Summed difference score (SDS)					
Range	0 – 10		0-14		0.003*
Mean	2.07		6		
S.D.	2.5		4.6		
Total perfusion defect (TPD)					
Range	0-14		0-41		0.02*
Mean	6.38		11.9		
S.D.	9.6		12.1		
L.V Dilatation	3	23%	8	29.6%	0.66
Apical scar and aneurysm	0	0%	5	18.5%	0.09

By comparing the territories of perfusion defects and their severity we found 9 patients (22.5%) had normal perfusion study, 14 patients (35%) had mild perfusion defect, 10 patients (25%) had moderate perfusion defect and 7 patients (17.5%) had severe perfusion defect(Figure 18). 18 of them (45%) had a perfusion defect in LAD territory. 13 patients (32.5%) had a perfusion defect in RCA territory and 16 patients (40%) had an LCX territory perfusion defect. (table VIII).

Table (VIII): Distribution of studied patients regarding severity of perfusion defect and its distribution.

	total population		normal HRR		reduced HRR		test of sig.	P value
	No.	percent	No.	percent	No.	percent		
severity of perfusion defect								
normal	9	22.5%	4	30.7%	5	18.5%	Z=-2.02	P=0.04*
mild	14	35%	7	53.8%	7	25.9%		
moderate	10	25%	2	15.3%	8	29.9%		
severe	7	17.5%	0	0.0%	7	25.9%		
distribution of perfusion defect								
LAD	18	45%	4	30.7%	14	51.85%	X2= 1.57	P=0.2
RCA	13	32.5%	6	46.1%	7	25.9%	X2= 1.63	P=0.2
LCX	16	40%	3	23%	13	48.1%	X2= 4.01	P=0.04*
number of vessel diseases								
2 vessel	9	22.5%	4	30.7%	5	18.5%	X2= 0.11	P=0.7
3 vessel	5	12.5%	0	0.0%	5	18.5%	X2=2.7	P=0.09

Blunted HRR group had more severe perfusion defect than normal HRR group with P value 0.04, as well as LCX lesions is more prominent in blunted HRR group with same P value 0.04.
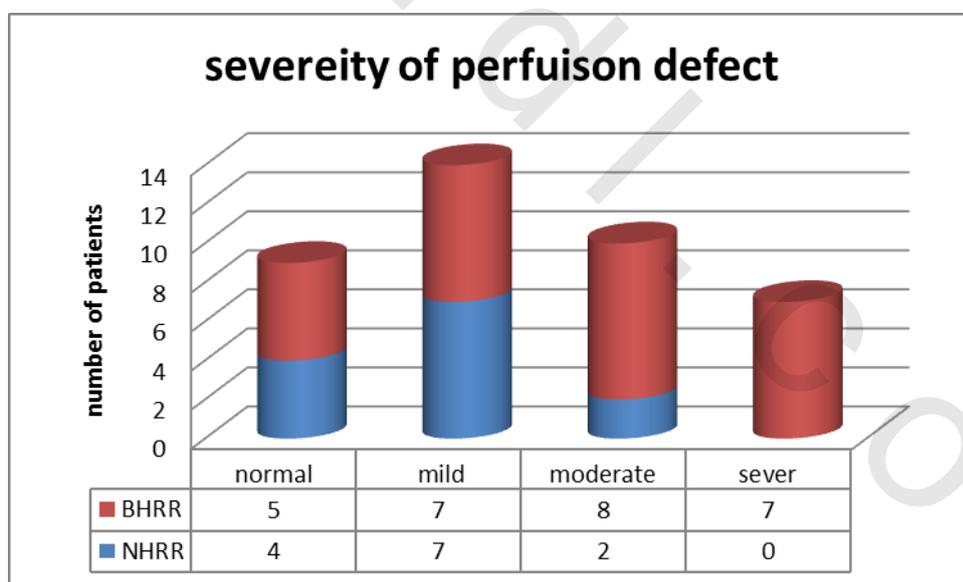

Figure (19): Distribution of studied patients regarding severity of perfusion defect.
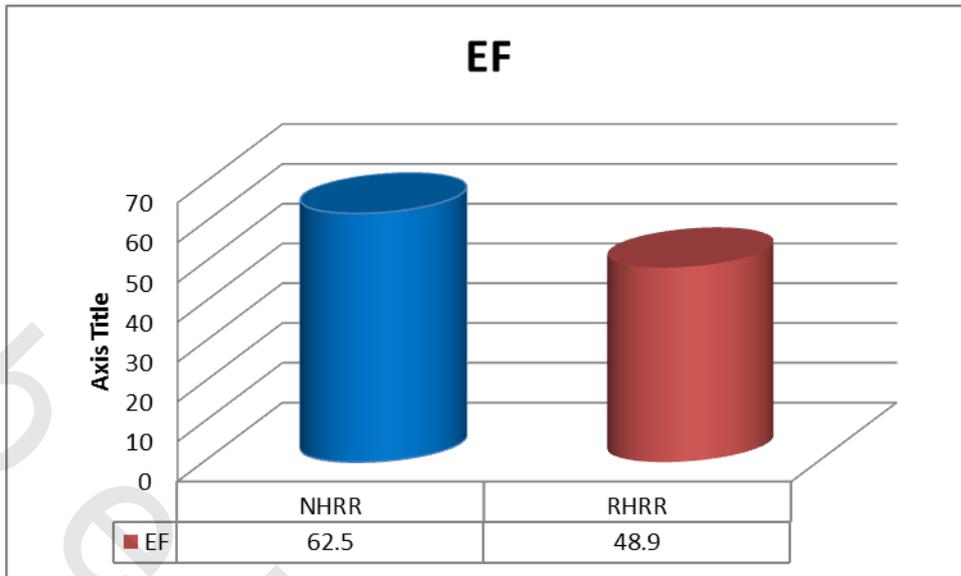
Figure (20): Comparison between normal HRR group to blunted HRR group regarding to EF.

As well as post stress EF scored automated quantitatively that ranged between 20-80%. The mean post stress EF in group (A) was 62.5±9.2 and reduced in group (B) to 48.9±10.7 with significant P value 0.0001. (figure 20).
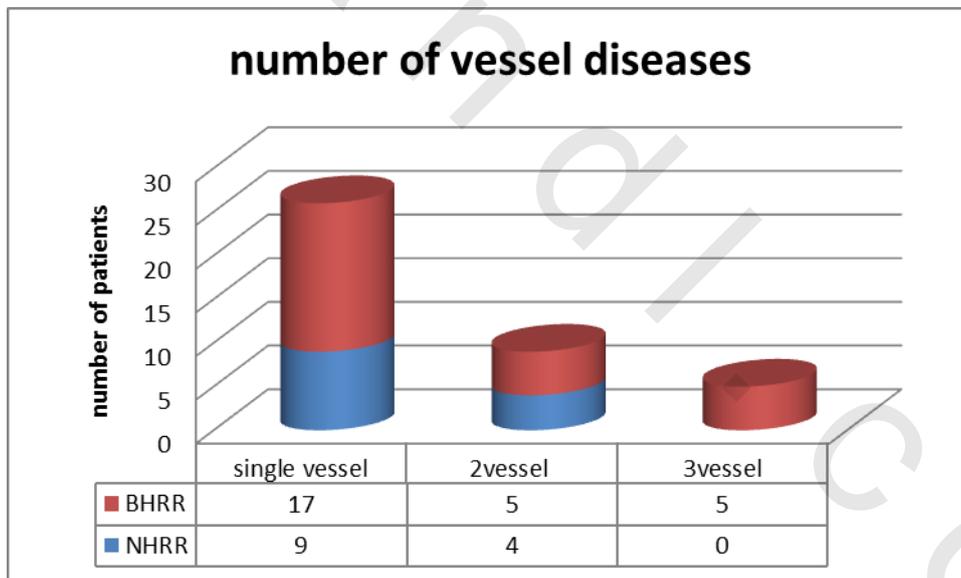

Figure (21): Distribution of studied patients regarding number of vessel disease.
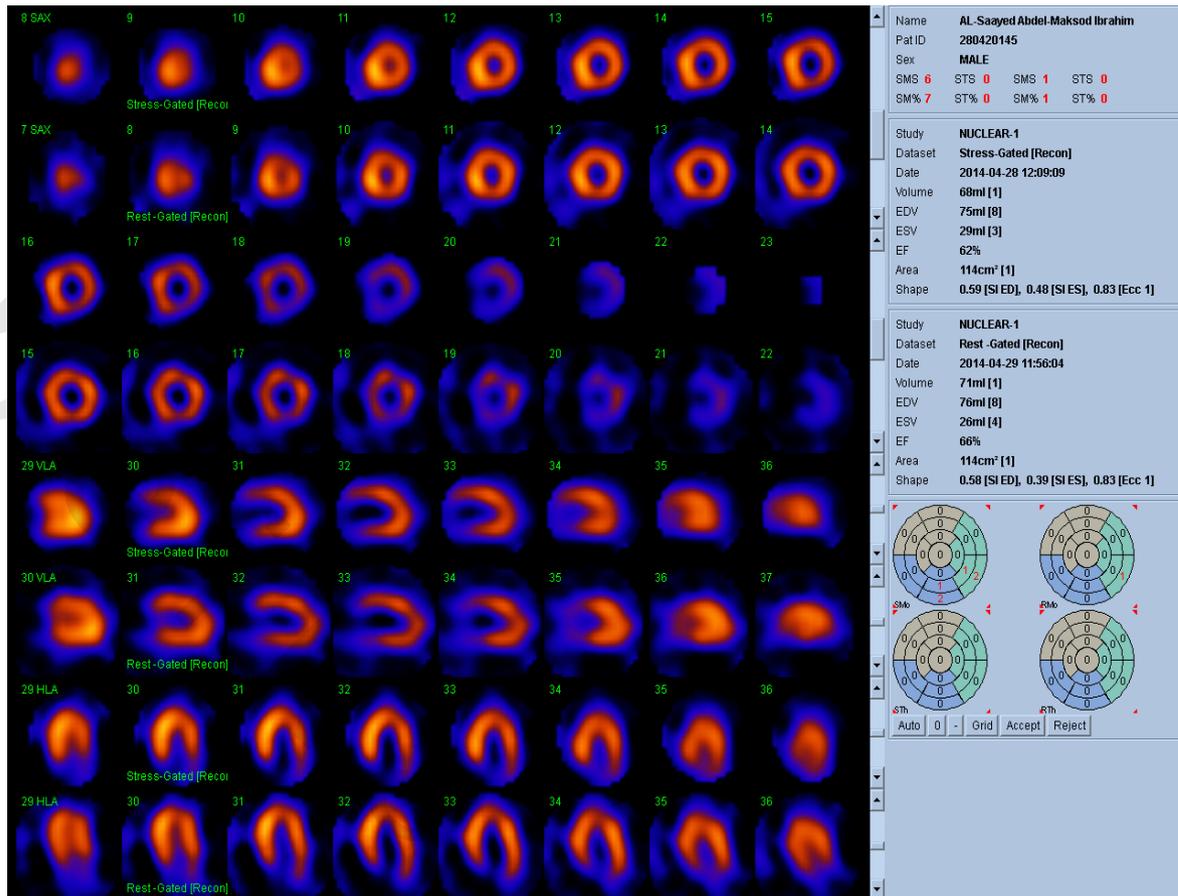
Case 1:

Figure (21): Dipyridamole Tc99m SestaMIBI SPECT study. A 67 years old male patient hypertensive, not diabetic and non-smoker No.30. the patient complaint of atypical chest pain with no dyspnea. During dipyridamole stress, his heart rate ratio >1.2 his study revealed mild ischemia in RCA territory. There was transient ischemic dilatation during stress. TPD during stress=3% and during rest2%. EF during stress and rest was 77%. ECG revel RBBB with no changes after stress.
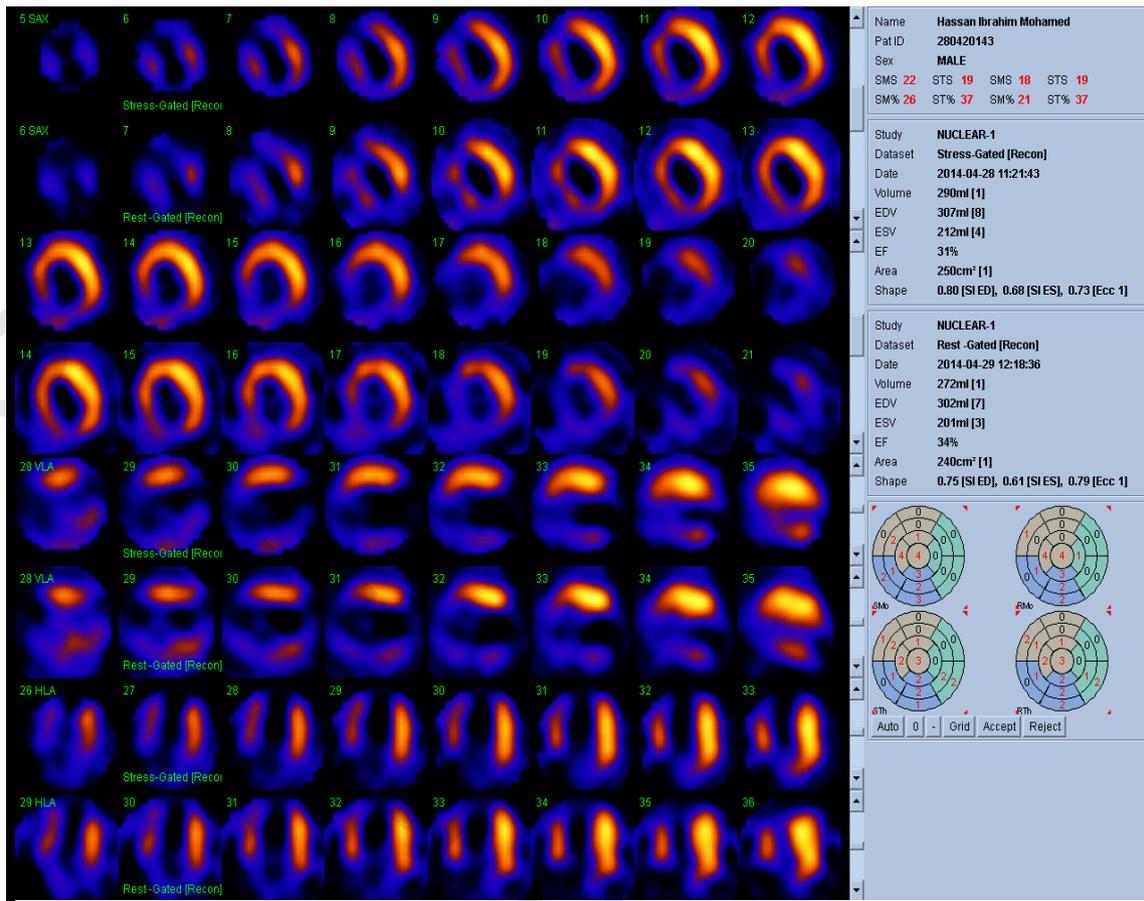
Case 2:

Figure (22): Dipyridamole Tc99m SestaMIBI SPECT study. 56 yaears old male patient No.23 hypertensive, diabetic and ischemic. During dipyridamole stress testing, his heart rate ratio <1.20. the study revealed an extensive perfusion defect involving apex, septum, anteroseptal, inferoseptal and inferior wall from the apex up to the base. There was apical scar and aneurysm. LV was permanent dilated during stress and rest. The delayed resting with reinjection revealed partial reperfusion in the septum, anteroseptal, inferoseptal and inferior wall. TPD during stress 41% and during rest 30%. EF during stress 31% and during rest 34%.