DISCUSSION

Pharmacological stress testing is a commonly used alternative to exercise stress used with both single photon emission tomography (SPECT) and positron emission tomography (PET) myocardial perfusion imaging (MPI). This plays an important role in the diagnosis and risk stratification of patients with coronary artery disease [(83)].

Vasodilators, such as adenosine and dipyridamole, are frequently used in patients who cannot exercise adequately for a variety of reasons [(84)]. The afore-mentioned vasodilators augment coronary myocardial blood flow indirectly via inhibition of deaminase, relaxation of vascular smooth muscles and endothelial release of nitric oxide. This is contrary to the effect seen with exercise where increase in heart rate (HR) and blood pressure (BP) are directly proportional to myocardial oxygen demand [(85)].

When intravenously (i.v.) infused, dipyridamole increases endogenous adenosine by blocking its cellular uptake and by inhibiting its enzymatic degradation by adenosine deaminase [(86)]. Subsequently, adenosine interacts with cardiac and peripheral adrenergic A2a receptors to mediate vasodilatation of coronary and systemic arteries[(87)].

The systemic vasodilatory effects result in a fall in systolic BP (SBP) of at least 10mmHg and a concomitant reflex tachycardia, which increase the heart rate by about 10 beats/min [(87)].

Our study included 40 patients ranged between 42- 73 years old, 15 female patients and 25 male patients. In our study we divided our patients into 2 groups. Normal HRR group to dipyridamole as dipyridamole-induced increase in HR ratio (peak HR/baseline HR) of more than 1.2 and blunted HRR group defined as (peak HR /baseline HR) ratio less than 1.2 . Most patients in BHRR group were hypertensive and about 50% of them were diabetics. BHRR group also had elevated basal heart rate with small delta heart rate. Regarding blood pressure a small decrease in blood pressure less than 10mmHg or even paradoxical increment in SBP in response to dipyridamole were found in BHRR group. Low EF as well as LCX lesions were prominent in BHRR group. Many studies performed on BHRR to dipyridamole and agree with our results that will be discussed later.

Correlation between blunted HRR to dipyridamole and high resting heart rate:

In our study the mean resting heart rate in group (A) 69b/m while in group (B) had mean 78.7b/m with significant P value (0.03). By measuring peak heart rate and delta HR after dipyridamole infusion we found a small increase in delta HR in blunted group 3.7±4.8 b/m but in normal group it increased to 18.9±5.6b/m (P<0.001).

Andrea et al.[88] **(2009)** in a prospective study done on 102 diabetic patients with mean age 64.8±10.4 years evaluated by dual-isotope rest Tl-201/dipyridamole stress Tc-99m tetrofosmin to assess hemodynamics including heart rate response to dipyridamole and LV perfusion and function. They found elevated resting HR in blunted group with mean HR 76±17.1 b/m. while in normal HR group 67.3±10.2 b/m.(X^2=4.7 , P=0.02) and this was matching our results.

Annilina et al.[89] **(2013)** A total of 200 consecutive patients who had a mean age of 57±11years with known or suspected coronary artery disease underwent MPI using a 2 days stress/rest protocol to assess whether there is an association between changes in the heart rate and blood pressure after dipyridamole stress and abnormal scan findings detected with gated technetium-99m methoxyisobutylisonitrile (99mTc-MIBI) myocardial perfusion imaging (MPI). They found BHRR in 85 patients (42.5%) and had statistical significance with abnormal scan finding (P=0.012).

ShishirMathur et al.[90] **(2010)** in retrospective study done on 5,306 patients underwent dipyridamole stress Tc-99m sestaMIBI ECG-gated SPECT MPI in Hartford Hospital over a 10-year period (1/2/1996 through 12/31/2005) with mean age 68.1±12 years to evaluate incremental prognostic value of BHR during pharmacological stress on long-term cardiovascular events and cardiac death. Cardiac death is the primary end point, occurred in 6.8% of patients. Patients with BHR had a significantly lower cardiac death-free survival as compared to NO BHR group in total population (83% vs. 94%; P < .001) as well as in subgroup with normal ejection fraction (89% vs. 96%; P < .001). BHR was an independent predictor of cardiac death. Regarding to the heart rate, mean resting heart rate in blunted group 72.6±13.4b/m while in normal heart rate response group 65.5±10.9b/m.

Also they found peak heart rate had statistical significance, as peak HR in blunted group 78.8±14.2b/m while in normal group 90±18b/m with P value <0.01 and this finding was not matched with ours as no statistical

significance between 2 groups regarding peak HR because peak HR in blunted group 82.4±13.5 b/m and in normal group 88.3±14b/m. with P value 0.2.

In our study we didn't follow up the patients to observe the morbidity and mortality in both groups, but many studies denoted that elevated resting heart rate has been shown to be associated with mortality across several general population studies [91-92] . Resting heart rate is determined by the activity of the autonomic nervous system, levels of circulating hormones and cardiorespiratory fitness [93-94]. Several pathophysiological mechanisms have been proposed to explain the relationship between high resting heart rate and mortality [95]. High heart rate may promote the development of atherosclerosis and plaque rupture through increase in cardiac work, decreased artery compliance and increase in arterial wall stress [96].

Correlation between blunted HRR group and diabetic patients:

In our study we found 13 patients (48%) of blunted HRR group were diabetic and 2 patients (15%) only in normal HRR group were diabetics with X^2=4.01, P=0.04.

Gorur GD et al.[97]**(2012)**201 consecutive patients undergoing dipyridamole stress Tc99m-MIBI or Tl-201 gated myocardial perfusion SPECT were prospectively enrolled demonstrated that Reduced HR response was found in 78 % of patients. Patients with abnormal HR response were more frequently diabetics.

ShishirMathur et al.[90]astudy done on 5,306 patients underwent dipyridamole stress Tc-99m sestaMIBI ECG-gated SPECT MPI found 1247 patients (43%) were diabetics in blunted HRR group while normal HRR group had 459 patients (29%) were diabetics with significant P value <0.01 In this study, they examined the prognostic significance of BHR in diabetes and non-diabetics patients regarding annualized cardiac death rates. They found the diabetic patients with BHR had significantly higher annualized cardiac death rates as compared to nondiabetics with BHR (5.2% vs. 3.3%; P<0.001).

Lee KH et al.[98]**(2001)** 61 non-insulin-dependent diabetes patients without perfusion defects, myocardial infarction nor arrhythmia who underwent thallium 201 SPECT imaging. The control group comprised 28 subjects without diabetes. HR was measured during infusion of dipyridamole. they found that patients with diabetes who had normal

SPECT study, an attenuated HR response observed during stress indicates a high likelihood of cardiac autonomic neuropathy.

Diabetes mellitus is a group of diseases characterized by insufficient production of insulin or by the failure to respond appropriately to insulin, resulting in hyperglycemia. Diabetes typically is classified as either type 2 diabetes, characterized by insulin resistance and relative insulin deficiency, representing greater than 90% of all diabetes cases, or type 1 diabetes, characterized by absolute insulin deficiency [99].

Compared with nondiabetic persons, patients with diabetes have a two- to fourfold increased risk for development of and death from coronary heart diseases(CHD) [100].

Correlation between blunted HRR group and blood pressure response to dipyridamole:

Normal blood pressure response to dipyridamole is reduction in SBP of more than 10mmHg from baseline to peak SBP, whereas a reduction of less than 10mmHg from baseline was considered as an abnormal SBP response.

In our study dipyridamole infusion decreased SBP in normal and blunted HRR groups. High baseline SBP and low delta SBP were found in blunted HRR group compared to those with normal HRR group, although this was not statistically significant.

We found also 28 (70%) patients were hypertensive, with 21patients of them were in blunted HRR group. However hypertension was predominate in blunted group but with no statistical significance in our study. Normal systolic blood pressure (SBP) response as defined before were found in 24 patients 15 of them in blunted group and had no statistical significance.

Abnormal BP response to dipyridamole defined by decreasing in SBP less than 10mmHg or even increment in SBP, This apparent paradox was also demonstrated in our study.

Numerow L et al.(1995)[101] tried to evaluate the etiology and implications of a paradoxical increase in systolic blood pressure (SBP) following dipyridamole infusion (0.56 mg/kg). they examined 341 consecutive patients by dipyridamole stress SPECT study. Most of the patients (n=292) experienced mild hypotensive SBP response (range 0-73 mmHg, average 22 mg Hg). 49 patients experienced hypertensive response to dipyridamole and they divided them to mild, moderate and

severe hypertensive response to dipyridamole. They denoted that no statistical significance between paradoxical hypertensive response to dipyridamole, TPD and territory of perfusion defect. They suggested that moderate and severe paradoxical hypertensive SBP to dipyridamole infusion was more likely related to induced pain symptoms and they explained that by increase catecholamine level.

Andrea et al.[88] demonstrated no relation between resting, peak and delta BP in blunted and normal groups that was matched in our study.

Annilina et al.[89] also agree with our results that there were no statistical significance between the 2 groups regarding blood pressure response to dipyridamole.

ShishirMathur et al.[90] had another opinion about BP as they found Patients with BHRR and NHRR had similar resting systolic BP; however, the peak systolic BP response was significantly lower in BHR as compared to NHRR group that were against our results and of Andre et al. results.

Correlation between blunted HRR group and echocardiography finding:

Echocardiography is one of the best-studied measures in cardiovascular medicine and has proved useful in diagnosis and risk stratification in a variety of cardiovascular diseases [102].

It is used to determine the type of LV dysfunction as EF<35% considered LV systolic dysfunction, 35-50% EF considered mild LV systolic dysfunction, but if EF>50% is more likely with LV diastolic dysfunction [103].

Many studies use EF 45% as appoint below which considered LV dysfunction. In our study we used same point and we found 7 patients had LV dysfunction (EF<45%) in BHRR group while no patient had EF<45% in normal group (P=0.04).

Annilina et al.[89] used EF45% as a point below which considered LV systolic dysfunction. In their study, 200 consecutive with mean age of 57±11 years. Normal myocardial perfusion imaging results were present in 50 patients, with abnormal MPI findings noted in 150 patients. Regarding EF, BHRR group was observed 85 (42.5%) patients for which a statistically significant association with low LVEF was found (P=0.012).

Kim et al.(2006)[104] demonstrated the association between blunted heart rate response to dipyridamole and LV systolic dysfunction. They described a correlation between reduced chronotropic response to dipyridamole and LVEF in postmyocardial infarction patients and found chronotropic incompetence was common with LV dysfunction [105].

Correlation between myocardial perfusion image and blunted HRR group:

The 17-segment model should be used for reference with regard to the nomenclature of such abnormalities (Fig.2). By convention, the 17 segments have been assigned specific vascular distributions so as to standardize interpretation and reporting. In an attempt to describe the severity and extent as a combined value, a variety of scoring systems have been designed, the most popular being the summed stress and summed rest scores. These scores are derived by adding the point value using the range of "0" for normal perfusion to "4" for absent activity for each segment of the 17-segment model. The difference between the summed stress score and the summed rest score is called the summed difference score, a measure of reversibility. Usually, individual segments with a $\leq$ 2-grade improvement on the resting study is felt to represent substantial ischemia [106].

Global left ventricular function may be accurately quantified using various methodologies. When the ejection fraction is >60%, such as occurring in patients with small left ventricular cavities, it is suggested to describe this as "normal" or "hyperdynamic".

Myocardial perfusion images were visually assessed in our study through short, vertical and horizontal long axes tomographic cuts. Abnormal scans findings included reversible defects, fixed defects or both. A polar map of 17 segments was used to assess TC99m uptake in each segment using the following 5-point score scale: 0=normal; 1=mild; 2=moderate, 3=severe and 4=absent uptake. The summed stress score (SSS), which represents the extent and severity of a perfusion abnormalities was obtained by adding the score of the 17 segments representing the stress study. A SSS of less than 4 was interpreted as normal, 4-8 as mild, 9-12 as moderate and more than 12 as severe vascular involvement. The summed difference score (SDS), which reflects the amount of ischemia, when less than 2 was considered as normal, 2-3 as mild, 4-7 as moderate and $\geq$8 as severe ischemia.

Vascular territory involvement of the left anterior descending artery (LAD), the right coronary artery (RCA) and the left circumflex artery (LCx) was recorded.

In our study SSS ranged from 0-31with mean 3.3±2.9 in normal HRR group while in blunted HRR group 11.07±9.6 (P value 0.005). SRS ranged from 0-23 with mean 1.23±1.4 in normal HRR group and 4.8±7 in blunted HRR group (P=0.04). SDS ranged from 0-14 with mean 2.07±2.5 in normal HRR group and 6±4.6 in blunted group (P=0.003). We denoted that SSS, SRS and SDS were statistical significant between the 2 groups.

By measuring TPD and dividing it to mild (TPD <5%), moderate (TPD 5-15%), severe (TPD>15%) we found that mean TPD in normal group 6.38±9.69% that raise into 11.92±12.15% in blunted group(t=2.3, P=0.02). in another ward, an increase in perfusion defect from mild to moderate to severe, more blunting response of heart rate (Z=-2.02, P=0.04).

In our study we tried to find if there was a relation between blunted HRR group and vascular territory and we found LCX territory lesion was more prominent with blunted group as we had 13 LCX lesions in blunted group Vs. 3 lesions only in normal group (P=0.04).But the most lesions found were LAD lesions (18lesions) with no statistical significance (P=0.2). by searching in 2 and 3 vessels lesions we found 5 patients had 3 vessel lesions in blunted group with no patient had same lesions in normal group but no statistical significance (X^2=2.7, P=0.09). As we see; lesions that affect large area in the heart as LAD, LCX and multi-vessel lesions affect HRR to dipyridamole as it affects LV systolic function (physiological lesions) and no relation between anatomical lesions without significant physiological lesions.

Post stress EF calculated automated, in normal HRR group the mean was 62±9.2%, that was dropped significantly to 48.9±10.7% (P=0.002). in another point we found no patient in normal group had EF <45% while in blunted group had 7 patients. That made it statistical significant.

Another point of LV dysfunction was LV dilatation (transient, permanent) found in 8 patients in blunted group Vs. 3 patients only in normal group. And so we can say LV dysfunction component as: increase SSS, increase SRS, increase in SDS, increase TPD, decrease resting and post-stress EF, LV dilatation can be predicted in patients with blunted HRR. As well as , an increase in TPD, an increase in LV dysfunction and subsequent blunted HRR. So, we suggest LCX and LAD territory

perfusion defects are more common with severe perfusion defect and so more LV dysfunction and blunted HRR are found.

Andrea et al.[88] found that SSS was 6.8±7.9 in normal group and raised to 9.7±10.5 in blunted group. SRS was 3.6±5 in normal group and raised to 7.1±10 in blunted group. SDS was 3.3±5.1 in normal group and 3±4.8 in blunted group. However the blunted group had higher score in SSS, SRS and SDS but they found SRS were the only parameter that had statistical significant that were significant in our study. Post-stress EF in normal group had mean 56.8±12.1%that was reduced to 47±16.4% in blunted group (P=0.001).

The association between a low HR response to dipyridamole and left ventricular dysfunction is consistent with the findings of Kim et al. as discussed before [104].

Andrea et al. concluded that blunted heart rate response to dipyridamole was multifactorial, as well as chronic renal failure, high resting HR and low LVEF. But the highest X^2 value found for LVEF, therefor they suggested that LV dysfunction was the strongest predictor of attenuated or blunted HRR to dipyridamole.

ShishirMathur et al.[90]found 43% of blunted group had SSS >3 while in normal group 26% only had SSS >3 with significant P value <0.001. SDS ranged between 23% and 21% in blunted and normal group respectively with no significant value. They matched our significant result of SSS but not in SDS. Regarding mean stress EF in normal group was 60.44±11.1% and in blunted group 54.27±17% (P<0.001). by denoting who had EF below 45% we found 24% of blunted group and 10% in normal group had EF<45%(P<0.001). These results strength ours as we had same one.

As end point to this study was cardiac death they found 9% of blunted group were died and only 2.8% were died in normal group that they try to correlate between blunted HRR, LV dysfunction, DM and cardiac death.

Annilina et al.[89] found 150 patients from 200 patients had abnormal scan finding based on presence of reversible, fixed perfusion defects or both. The majority of their patients 122 (81%) had fixed defects. Post stress LVEF in patients with abnormal MPI results was significantly lower than in patients with normal scan 53±17% vs. 73±9% (P<0.0001).

SUMMARY

The heart rate of an individual reflects an integrated physiological response comprising of autonomic system, central and peripheral reflexes as well as intrinsic cardiac conditions. An abnormal heart rate response to physiological stress may be secondary to multiple metabolic abnormalities such as diabetes or renal failure as well as intrinsic cardiac conditions such as coronary artery disease (CAD) and cardiomyopathy.

The increased risk of death found in patients with a blunted HR response to dipyridamole, even in the presence of normal perfusion, reinforces the importance of the search for the reasons for this phenomenon. Therefore, the aim of this study was to investigate the association demographic, hemodynamic and gated SPECT variables and severity of perfusion defect, ejection fraction and if the blunted heart rate is related to specific territory in patients undergoing myocardial perfusion scintigraphy.

Study population consists of, 40 patients were enrolled in the study (27 male, 13 female, mean ages 58.2±7.33, range 42-73). Hypertension and Diabetes mellitus were prevalent in our study group (70 and 37% respectively). 13 patients (32.5 %) had normal HR response and 27 (67.5 %) patients have reduced HR response to dipyridamole. The prevalence of diabetes mellitus was significantly high in reduced HR response group [48 vs. 15.3 % (p = 0.04)].

By studying the hemodynamics, mean resting HR was higher in blunted HRR group 78.7±14.7 than normal HRR group 69.4±13.4 with statistically significant value (P= 0.03). Mean resting systolic blood pressure in normal group 146.1±33.3 and increase in blunted group to 157.4±31.6 peak systolic blood pressure after stress was not reduced properly in blunted group like normal group but also we found paradoxical increasing in blood pressure.

Perfusion study demonstrated mean TPD 6.38±9.69 in normal group and 11.92±12.15 in blunted group, mean SSS 3.3±2.9 in normal group and 11.07±9.66 in blunted group (P=0.005), mean SRS in normal group 1.23±1.4 and in blunted group 4.81±7.09. Mean SDS 2.07±2.5 in normal group and 6±4.69 in blunted group.

According to the severity of perfusion defect: 9 patients had normal perfusion study 5 of them in blunted group. 14 patients had mild perfusion defect with 7 patients in each group. 10 patients had moderate

perfusion defect with 8 of them in blunted group. 7 patients had severe perfusion defect and all of them in blunted group. In another word, as the severeity of perfusion defect increase, as the blunting heart rate response increase (P=0.04).

According to the territory of perfusion defect, we found 18 patients had LAD lesions with 14 patients had blunted HRR. 13 patients had RCA lesions with 7 of them in blunted group. 16 patients had LCX lesions with 13 of them in blunted group (P=0.04). 5 patients had 3 vessel disease and all of them in blunted group but with no statistical significance (P=0.09).

In our study there were 11 patients had LV dilatation, 8 of them in blunted group but with no statistical significance.

Post stress EF in normal group had mean 62.5±9.2 but it was dropped in blunted group to 48.9±10.7 that signify a strong association between blunted heart rate response and LV dysfunction (P=0.002).

CONCLUSION

From result of this study the flowing could be concluded:

1. Blunted HR response to dipyridamole is independent predictor of the severity of perfusion defect and reduced post stress EF.
2. Blunted HR response group had perfusion defect in LCX territory rather than normal HRR group.