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RESEARCH ARTICLE

PREDICTION OF MYOCARDIAL VIABILITY ON THE BASIS OF SERUMBNP AND HSTROPONIN I LEVELS IN PATIENTS WITH CORONARYARTERY DISEASEWITH LVSYSTOLIC DYSFUNCTION

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Abstract

Introduction: Coronary artery disease (CAD) is the leading cause of heart failure (HF). Only viable dysfunctional myocardium (hibernation) is potentially recoverable with restoration of adequate perfusion. Cardiac imaging modalities have emerged with the ability to differentiate between myocardial scar and viable myocardium and are now often used to direct therapy decisions including revascularization. Decrease in wall motion score (WMS) and improvement in LV ejection fraction (LVEF) during DSE is considered as a surrogate marker for viability of myocardium. It is largely unknown how cardiac specific biomarkers are released in relation the presence and extent of hibernation in patients with ischemic HF. The objectives of this study are to assess the relationship and interaction of the biomarkers BNP and hs TnI with hibernation in patients with chronic ischemic HF.

Materials and methods: It is a single center observational study which is conducted in Department of Cardiology, S.M.S. Medical College, Jaipur. 70 eligible patients with suspected ischemic cardiomyopathy (ICMP) are prospectively recruited into an imaging study using DSE to determine viability of myocardium. The patients also had blood sampling at baseline to determine biomarkers.

Results: Mean age (in yrs) of patients is 63.78 ± 10.69 years. No patient is in NYHA I. 25.7 % of patients are in NYHA II (18 patients); 36 patients (51.4%) are in NYHA III and 16 patients (22.8%) are in NYHA IV. On comparison of baseline characteristics among patients with different NYHA class, there is a progressive increase in level of cardiac biomarkers with increase in NYHA class. Both BNP and hs TnI levels are significantly elevated in patients with Improvement in EF >10% as compared with Improvement in EF <10% There is a continuous relationship between increasing degrees of hibernation and increasing BNP and hs Trop I levels. HsTrop I had predicted a positive 56.6% change in Improvement in LVEF. HsTrop I had predicted a positive 52.5% change in decrease in WMS.

Conclusion: The current study support the novel concept that the extent of LV hibernation are determinant of serum BNP and hs Trop I elevation in patients with ischemic HF and hs Trop I levels in patients with ischemic HF relate to the degree of hibernation.

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Introduction:-

Coronary artery disease (CAD) is the leading cause of heart failure (HF)[1]. Although there isincreased risk, revascularization is often considered in patients with ischemic HF but theselection of patients most likely to benefit remains a challenge[2–4]. In patients with ischemicHF, recurrent myocardial ischemia may lead to scar formation, hibernation or a combinationof both. Although these entities contribute to left ventricular (LV) dysfunction, only viable dysfunctional myocardium (hibernation) is potentially recoverable with rest oration of adequate perfusion[2,5–11].Cardiac imaging modalities have emerged with the ability to differentiate between myocardial scar and viable myocardium and are now often used to direct therapy decisions including revascularization[2,3,5–16].

Stress echocardiography is based on the fundamental causal relationship between stress induced myocardial ischemia and left ventricular regional wall motion abnormalities. The use of dobutamine stress echocardiography (DSE) is based on the observation that viable myocardium will augment in response to β-adrenergic stimulation, where as nonviable myocardium will not. The biphasic response, augmentation at low dose followed by deterioration at higher doses, is most predictive of the capacity for functional recovery after revascularization. Sustained improvement and "no change" are patterns that correlate with lack of improvement after revascularization.

A 17 segment model, endorsed by American society of Echocardiography, is used to analyze wall motion at baseline and during stress. Each of the 17 segments is graded on a scale from1 to 4 in which 1 is considered normal at rest and hyperkinesis during stress, 2 indicates hypokinesis, 3 indicates akinesis and 4 corresponds to dyskinesis. Wall motion score is equal to sum of scores of all 17 segments. Wall motion score is calculated both at rest and during stress test. Maximum decline in wall motion score at any point during stress is taken into account. This decrease in wall motion score (WMS) and improvement in LV ejection fraction (LVEF) during DSE is considered here as a surrogate marker for viability of myocardium. In most series, sensitivity (for predicting functional recovery) of DSE has ranged from 80% to85% with slightly higher specificity (85%-90%).The amount of myocardium identified as viable correlates fairly well with the degree of improvement in global function after revascularization and with long-term out come. When compared with nuclear techniques, DSE provides generally concordant results. However, nuclear techniques will identify significantly more segments (and patients) as viable.

Cardiac PET using 18F-flurodeoxyglucose (FDG) is widely considered a "gold standard" and the most sensitive modality for detecting hibernating viable myocardium[3,6,14]. In most series,sensitivity favors nuclear methods, whereas DSE is consistently more specific. However, the cost of FDG PET scan is much more than that of DSE. So, we are assessing viability of myocardium with help of DSE instead of FDG PET as their positive predictive value is similar.

However, the evidence is conflicting as to whether viability imaging guided strategies alone can yield significant clinical benefit upon revascularization.Some studies do suggest benefits[5–11,13–16], while others suggest no significant role[17,18]. Hence there remains a need to improve approaches to better identify patients with ischemic HF likely to benefit from revascularization.

Cardiac specific biomarkers, such as BNP and hs TnI are excellent prognosticators in patients with HF[19–22]. They may offer an additional approach to compliment current image-guided strategies for patient selection. However, it is largely unknown how cardiac specific biomarkers are released in relation the presence and extent of hibernation in patients with ischemic HF. This relationship may provide additional in sights as to the underlying pathophysiology of biomarker dynamics in ischemic HF. The objectives of this study are to assess the relationship and interaction of the biomarkers BNP and hs TnI with hibernation inpatients with chronic ischemic HF.

Aims and Objectives:-

Primary objective:

To determine the correlation of improvement in LVEF on DSE frombaseline with BNP and hsTroponin I levels in Coronary artery disease with LV systolic dysfunction.

Secondary objective:

To determine the correlation of decrease in wall motion score on DSE from baseline with BNP and hs Troponin I levels in Coronary artery disease with LV systolic dysfunction.

Also prediction of improvement in LVEF and decrease in wall motion score on DSE from baseline on the basis of independent factors (Age, BMI,BNP and hsTroponinI levels).

Materials And Methods:-

The study is conducted in Department of Cardiology, S.M.S. Medical College, Jaipur. It is asingle center observational study. A sample of 70 cases is required at 95% confidence for prediction of improvement in LVEF and decrease in wall motion score on DSE from baselineon the basis of independent factors including BNP & hs Troponin I. Eligible cases included in the study on first come first basis. Duration of study is 18 months from April 2018 to October 2019.

Methodology:-

Patients with suspected ischemic cardiomyopathy (ICMP) are prospectively recruited into an imaging study using DSE to determine viability of myocardium.The patients also had blood sampling at baseline to determine biomarkers.

Patients:

Patients with clinical heart failure or LV systolic dysfunction, who needed further definition of viability, are enrolled[23].Eligible patients are included if they are 18 years of age or older; had known or highly suspected coronary artery disease documented by coronary angiography or by history of previous MI or evidence of ischemia or scar based on prior imaging. Patients were being treated with optimal medical therapy and their LV dysfunction was primarily attributable to ischemic heart disease with EF $\leq$ 45% as documented by echocardiography and NYHA class II to IV symptoms or EF $\leq$30% and NYHA class I to IVsymptoms.

Patients having STEMI within 40 days of presentation and Patients on renal replacement therapy are excluded from this biomarker study.

Blood Biochemistry:

Prior to imaging, blood samples are procured from all patients and sent for BNP and hsTroponin I levels.

Imaging:

Patients underwent routine assessment of LV function with 2D echocardiography to look for regional wall motion abnormalities (RWMA) and baseline LVEF, followed by DSE for improvement in wall motion abnormalities and LVEF. Cardiovascular effects of dobutamine are dose dependent, with augmented contractility occurring at lower doses followed by a progressive chronotropic response at increasing doses. If coronary flow reserve is limited, myocardial oxygen demands will eventually exceed supply and ischemia will develop. A related application has been for the detection of viable myocardium in the setting of either stunned or hibernating myocardium.

DSE Analysis and Interpretation: DSE has been performed as per standard protocol**.** Improvement in LVEF is calculated as difference between maximum LVEF achieved at any stage during DSE showing improvement in wall motion abnormality and LVEF measured by Simpson's method at baseline. Decrease in wall motion score (WMS) is calculated as difference between WMS at baseline and minimum WMS achieved at any stage during DSE.Any improvement in LVEF and decrease in WMS is suggestive of viable myocardium. More improvement in LVEF or decrease in wall motion score is suggestive of more amount of viable myocardium.

Statistical Analysis:

Continuous data are summarized in form of mean ± SD. Difference in more than two means is analyzed using ANOVA. Correlation of two continuous data is done using Pearson correlation coefficient. Prediction of improvement in EF on the basis of independent factors is done by multiple linear regression.Count data is expressed in form of proportions.Difference in proportions is analyzed using Chi Square test. The level of significance is kept 95% for all statistical analysis.

Results:-

70 consecutive eligible patients are included in the study, who underwent DSE and had blood sampling for biomarkers. Baseline characteristics appear in Table 1. Mean age (in yrs) of patients is 63.78 ± 10.69 years. 60% of patients are males. No patient is in NYHA I. 25.7% of patients are in NYHA II (18 patients); 36 patients (51.4%) are in NYHA III and 16 patients (22.8%) are in NYHA IV. Mean NYHA class is 2.97 ± 0.69. Hypertension is found in

23 (32.8%) patients, Diabetes mellitus in 17 (24.3%) patients, Dyslipidemia in 14 (20.0%) patients and 41 (58.6%) patients are found to be smoker. 57 (81.4%) patients had H/o previous MI, 18 (25.7%) patients had H/o revious PCI, 1 patient had previous CABG. The BNP levels ranged from 5.5-4850 pg/mL with a mean of 607.8±1046.58pg/m L. Hs TnI levels ranged from 0.01- 0.48 ng/mL with a mean of 0.104 ± 0.13 ng/mL. Mean baseline LVEF is 31.44 ± 5.29%. Overall on the DSE study, 15 patients had significant improvement in EF >10%, 47 patients had improvement in EF <10% and 8 patients had no improvement in EF. On comparison of baseline characteristics among patients with different NYHA class, there is a progressive increase in level of cardiac biomarkers with increase in NYHA class.

Relationship of Biomarkers to LV Myocardium viability: Both BNP and hs TnI levels are significantly elevated in patients with Improvement in EF >10% (Improvement in EF >10%: mean ± SD: 1526±1448.12pg/mL; vs. Improvement in EF <10%:mean±SD:357.39± 727.67 pg/mL; for BNP; $p<0.05$) and (Improvement in EF >10%: mean ± SD: 0.239 ± 0.133 ng/mL; vs. Improvement in EF <10% : mean ± SD: 0.066 ± 0.098 ng/mL; for hs Tn I; $p<0.01$) (Table 3 & 4). There is a continuous relationship between increasing degrees of hibernation and increasing BNP and hs TnI levels(Figure1, 2, 3 &4).

Hs Trop I had predicted a positive 56.6% change in Improvement in LVEF. Age, BNP, and BMI are not significant predictors. 50.2% of change in improvement in LVEF is contributed by all predictors (adjusted $R^2$is 0.502) (table 5).

Hs TropI had predicted a positive 52.5% change in decrease in WMS.Age, BNP, and BMI are not significant predictors. 43.4% of change in improvement in LVEF is contributed by all predictors (adjusted R^2is0.434) (table 6).

Discussion:-

This study demonstrated that serum levels of BNP and hs TnI were elevated in stable patients with moderate-severe levels of hibernating myocardium and LV dysfunction or HF.The biomarker levels correlated with the extent of hibernation independent of age and BMI in ischemic cardiomyopathy. These data support the novel concept that extent of LV hibernation is determinant of serum BNP and hs TnI elevation in patients with ischemic HF, extending the traditional variables related to EF and the severity of LV dysfunction. Patients with ischemic HF are often considered for revascularization therapy.

Evidence exist that support the notion that revascularization yields clinical benefit in patients with viable myocardium as defined by imaging techniques such as FDG PET[5–9,11,14–16,25]. However, controversy remains as other studies suggest image guided strategies may not yield definitive clinical benefit in this population [2,17,18]. The current study is the step towards understanding the unique information content of BNP and hs TnI in the context of viability imaging and ischemic HF.

Future studies are needed to determine whether BNP and hs TnI levels preceding or in combination with viability imaging, can better predict outcome benefits in ischemic HF patients following revascularization, and thus enable a more precision targeted patient selection process. It is now well established that BNP levels are chronically elevated in patients with ischemic HF [32,37,38].BNP is secreted in response to elevated volume and pressure load in the atria and ventricles, as well as stress and hypoxia[32,39].

One previous study has suggested a correlation between BNP and hibernation as measured with cMRI and dobutamine echocardiography. In this study, the BNP levels were assessed inpatients with recent myocardial infarction, NYHA functional class I-II dyspnea and mild reductions in LVEF (48± 15%)[40].

They observed a moderate correlation between Log BNP levels and indices of viable myocardium and scar. Differences in patient selection (recent MI and mild LV dysfunction) may explain the heterogeneity in results when compared to this study. In contrast, our study included patients with much more significant LV dysfunction (mean 31.44 ± 5.29) and thus greater dynamic range of both biomarkers and extent of hibernation as well as being a potentially more relevant population for defining viability where revascularization decisions are more difficult. Although speculative, it is plausible that hs TnI elevation in patients with hibernation, rather than scar, is due to continued cell death, raising the need for early revascularization in this patient population.

The improved relationship between BNPor hsTnI levels and hibernation severity may bedue to the increased tension and stress on the viable myocardium, inducing further production and release of cardiac stress peptides such as BNP and hs TnI especially from the hibernating myocardium. One may speculate that the ischemic but viable hibernating

myocardium is thus doubly stressed with additional hemodynamic stimulus, thus further increasing the biomarker levels in the circulation. Aktas et al. found decreased BNP levels in patients with large scar (>33%), as evaluated in a relatively homogenous population of patients with ischemic HF with EF <35%.[41] Together these data support the suggestion by Aktas et al that areas with significant scar" may lack the cellular biomachinery required" for this peptide. Further studies are required to support this hypothesis. The release of hs TnI in HF, when acute coronary syndromes have been excluded, has been attributed to supply-demand mismatch, increased myocyte turnover with progressive myocardial dysfunction and/or subendocardial ischemic injury due to wall stress, myocardial apoptosis and oxidative injury[44-48].

Given the proposed mechanism for hibernation as metabolic and functional down-regulation secondary to repeated ischemia, it is logical to surmise that hs TnI release would relate to the degree of hibernation.However, in spite of the known pathophysiological mechanisms for troponin elevations, studies evaluating its relationship to myocardial hibernation have been limited to date. The current study, may represent that hs TnI levels in patients with ischemic HF relate to the degree of hibernation. Regarding natriuretic peptides , recent evidence indicates they are secreted in hypoxic, ischemic and/or hibernating myocardium in addition to known responses to volume and pressure load [20,32,49,50].

Goetze etal.demonstrated that plasma BNP and pro BNP were markedly increased in patients with CAD undergoing revascularization even withoutLV dysfunction and were strongly associated with left ventricle tissue BNP mRNA expression[49]. May et al, using a transgenic model of myocardial hibernation, showed that BNP expression was strongly induced in LVcardiomyocytes coinciding with regions of cellular hypoxemia and hibernation. The authors further demonstrated that reversal of hibernation was accompanied by down regulation of myocardial BNP expression to control levels[50].

Based on this prior research and the current results, one may speculate that the ischemic but viable hibernating myocardium is doubly stressed with additional hemodynamic stimulus,thus further increasing the biomarker levels in the circulation. Further research is required to support this hypothesis and to further understand the mechanisms for BNP and troponin release in patients with hibernating myocardium.

Limitations:
A small sample size precludes its applicability in a large population. Also, in the current study, scarred myocardium was not taken into account, which may affect the level of cardiac biomarkers.

Tables:
Table1:- Baseline characteristics.

TOTAL NO. OF PATIENTS	**70**	
Mean AGE (in yrs)	63.78 yrs±10.69	
SEX	M=42;	M=60%
	F=28	F=40%
NYHA CLASS	I=None	I=0
	II=18;	II=25.7%
	III=36;	III=51.4%
	IV=16	IV=22.8%
	MeanNYHA2.97 ±0.69	
HYPERTENSION	23	32.8%
DIABETES MELLITUS	17	24.3%
DYSLIPIDEMIA	14	20.0%
SMOKER	41	58.6%
FAMILY HISTORY	0	0
COPD	5	7.1%
CVA	0	0
PVD	1	1.5%
CKD	0	0
PREVIOUS MI	57	81.4%
PREVIOUS PCI	18	25.7%

PREVIOUS CABG	1	1.5%
BETA BLOCKER	65	92.85%

ACEI OR ARB	65	92.85%
MRA	62	88.57%
STATINS	67	95.7%
DIGOXIN	7	10%
ANTIPLATELETS	66	94.28%

Mean Height(incm)	167.07 ± 8.85
Mean Weight(inkgs)	70.67 ± 9.82
Mean BSA(m^2)	1.81 ± 0.17
Mean BMI(kg/m^2)	25.22 ± 2.03
Mean BNP(pg/ml)	607.8 ± 1046.58
Mean hs TroponinI(ng/ml)	0.104 ± 0.13
Mean Baseline EF(%)	31.44 ± 5.29
Mean Improvement in EF(%)	8.06 ± 7.24
Mean WMS at rest	28.51 ± 2.12
Mean Decline in WMS at stress	3.04 ± 2.64
Mean Decline in WMSI at stress	0.18 ± 0.15

Table 2:- Comparison of baseline characteristics among patients with different NYHA class.

	NYHAII(N=18)	**NYHAIII(N=36)**	**NYHAIV(N=16))**
AGE (yrs)	63.11±11.86	63.53 ± 10.38	65.12 ± 9.87
SEX	M=14,F=4	M=18,F=18	M=10,F=6
BMI (kg/m^2)	25.13±1.76	25.14 ± 2.26	25.51 ± 1.71
BNP (pg/ml)	97.92±110.56	329.11±585.82	1808.5 ± 1448.2
Hs TroponinI (ng/ml)	0.032±0.04	0.079 ± 0.1	0.24 ± 0.15
Baseline EF(%)	33±5.75	32.64 ± 4.40	27 ± 4.03
Improvement in EF(%)	7.39± 6.85	7.25 ± 7.15	10.63 ± 7.29
WMS at rest	27.89±2.33	28.06 ± 1.79	30.25 ± 1.56
Decline in WMS at stress	2.83± 2.61	2.80 ± 2.64	3.81 ± 2.50
Decline in WMSI at stress	0.17± 0.15	0.17 ± 0.15	0.22 ± 0.15

Table3:- Comparison of independent variables among patients with different degree of improvement in EFon DSE.

Mean values of Independent variables	**Improvement in EF = 0%(8)**	**Improvement in EF1-5%(32)**	**Improvement in EF 6-10%(15)**	**Improvement in EF>10%(15)**
BNP (pg/mL)	33.19	128.81	1017.93	1526
Hs Trop I (ng/mL)	0.011	0.036	0.160	0.239
NYHA	2.75	2.84	3.33	3
Age(yrs)	67	65.625	63	58.93
Sex(males)	50%	56.2%	60%	73.3%
BMI(kg/m^2)	26.06	24.87	25.28	25.47

Table4:- Comparison of independent variables among patients with different degree of decrease in WMS on DSE.

Mean values of independent variables	**Decrease in WMS=0 (8)**	**Decrease inWMS<1-5(51)**	**Decrease inWMS>6(11)**
BNP (pg/mL)	**33.19**	**484.02**	**1599.64**
Hs TropI (ng/mL**)**	**0.011**	**0.083**	**0.266**
NYHA	2.75	3	3
Age (yrs)	67	64	60.45
Sex (males)	50%	61.6%	66.6%
BMI (kg/m^2)	26.06	25.05	25.41

Table5:- Multiple Linear Regression for prediction of improvement of LVEF on the basis of age, BMI, BNP, Hs TropI.

Variable	Standardized'B'	Pvalue
HsTropI	0.566	<0.0001

A significant model was found using enter method ($p<0.0001$, Adjusted $R^2 = 0.502$).

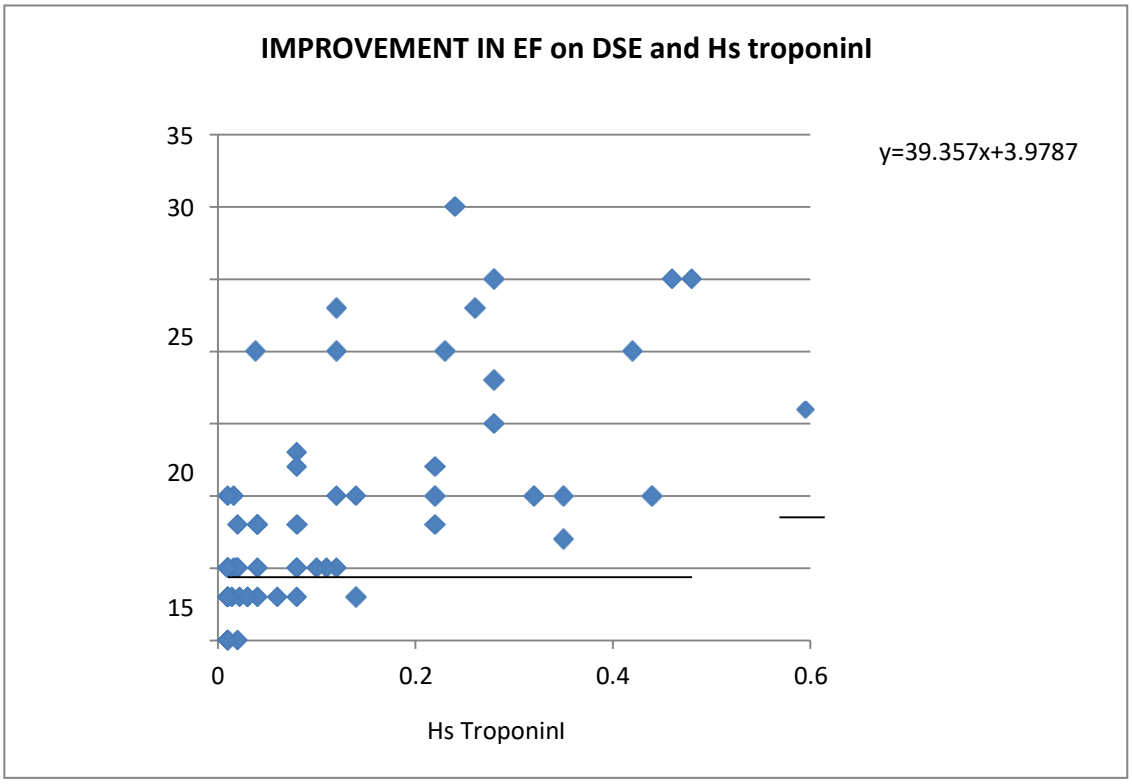
Table6:- Multiple Linear Regression for prediction of decrease in WMS on the basis of age, BMI, BNP, HsTropI.

Variable	Standardized'B'	Pvalue
HsTropI	0.525	<0.0001

A significant model was found using enter method ($p<0.0001$, Adjusted $R^2=0.434$).

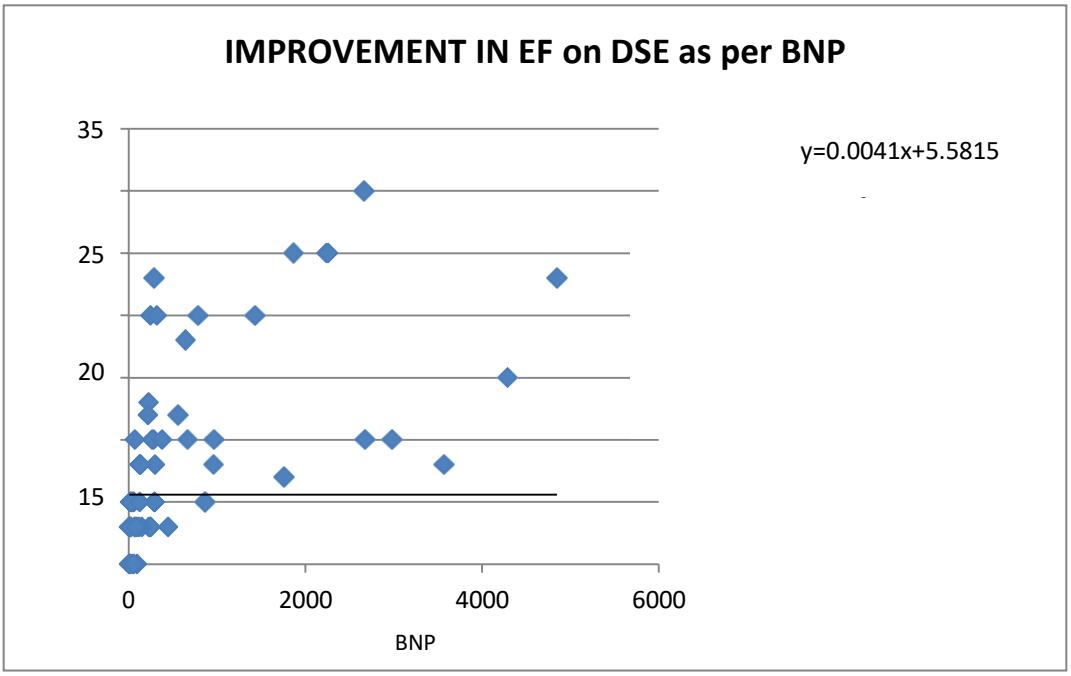
Figures:

Figure1:-Correlation of Increase in LVEF ON DSE and Hs troponin I.



There is a moderate positive correlation between improvement in LVEF and HsTroponin I .The Pearson's correlation coefficient is 0.482. 48% change in improvement in LVEF is attributable to HsTroponinI.

Figure2:-Correlation of increase in LVEF ON DSE and BNP.



There is a moderate positive correlation between improvement in LVEF and BNP. The Pearson's correlation coefficient is 0.346.34% change in improvement in LVEF is attributable to BNP.

Figure 3:- Correlation of Decrease in WMS and Hs troponin I.

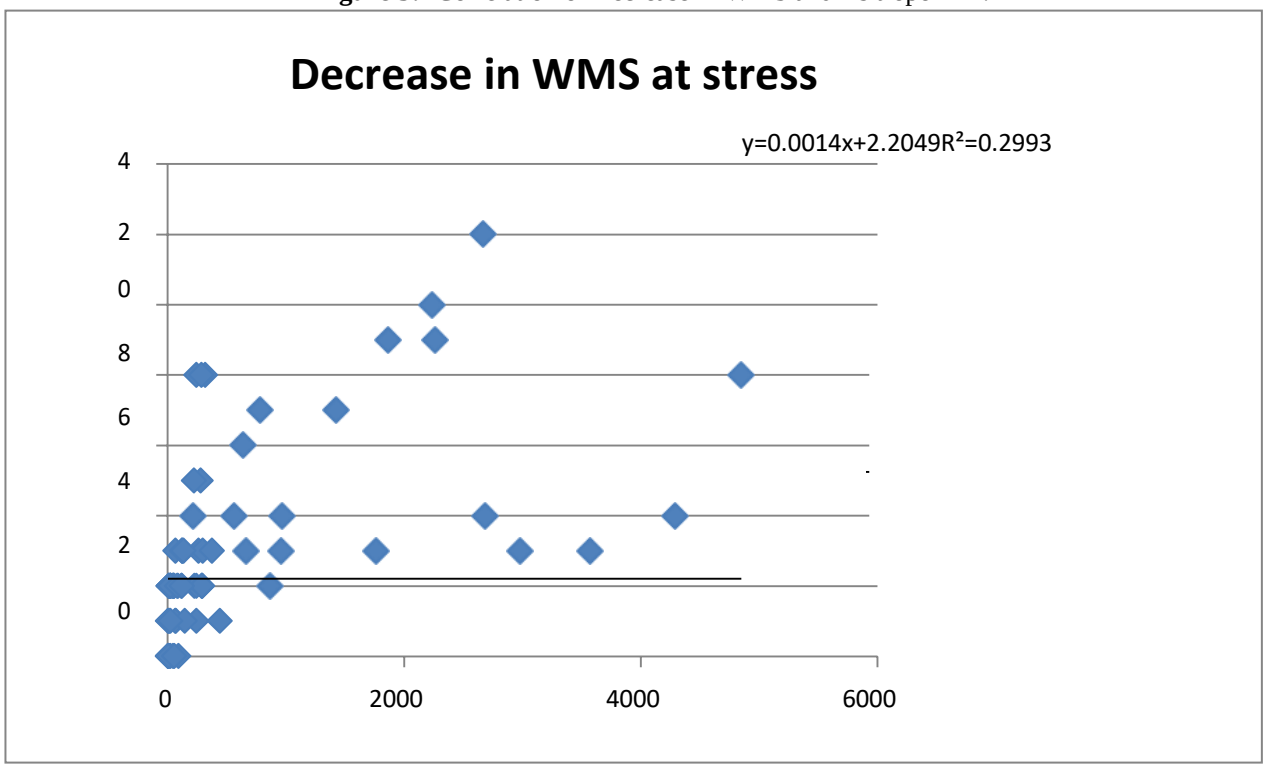
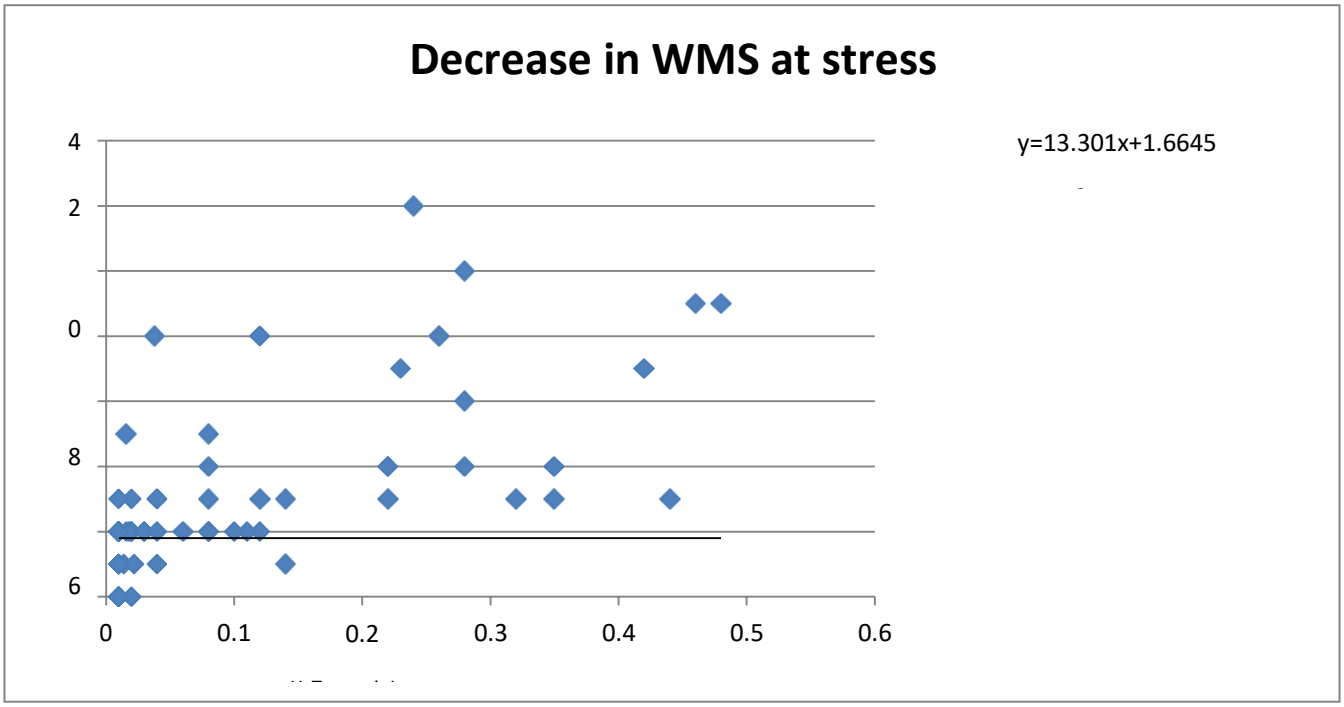


Figure 4:- Correlation of Decrease in WMS on DSE and BNP.



Conclusion:-

The current study support the novel concept that the extent of LV hibernation are determinantof serum BNP and hs TnI elevation in patients with ischemic HF and hs TnI levels in patients with ischemic HF relate to the degree of hibernation.

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