Determination Of Cardiac Dysfunction By T2 * MRI and Tissue Doppler Echocardiography in Patıents With Thalassemia Major

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April 27, 2020

Abstract

Background: Tissue Doppler (TD) measurements give a better information in evaluating the myocardial functions than conventional echocardiography in beta-thalassemia major (β-TM). The aim of this study was to determine cardiac status of thalassemia patients by using both T2*MRI and TD. Methods: The study group included thalassemia patients (n=33) with normal systolic functions defined by conventional echocardiography. The control group (n=37) consisted of age and sex matched healthy individuals. TD measurements from three different regions of myocardium were obtained in both groups. Ferritin was examined in both groups, T2*MRI was performed only patients with thalassemia. Results: Systolic and diastolic functions were found normal by conventional echocardiography in thalassemia patients. However, cardiac functions were significantly impaired when evaluated by TD ($p<0.05$). T2*MRI and TD measurements didn't differ according to serum ferritin levels ($p>0.05$). Twenty-one patients (63.6%) had myocardial iron overload. Both isovolumetric acceleration time of left ventricle and myocardial performance index (MPI-septal) were found significantly impaired in these patients ($p<0.05$). There was negative correlation between MPI-septal and T2*MRI measurements in thalassemia patients (r:-0.343, p=0.050). TD measurements obtained from septum were found similar with the control ($p>0.05$) but, the same measurements from left and right ventricular walls were significantly impaired in iron unloaded group ($p< 0.05$). Coclusion: Iron unloaded patients according to T2*MRI had left and right ventricular dysfunction determined by TD. Therefore, we suggest that combining T2*MRI with TD measurements, for evaluating cardiac status in β-TM, in whose with normal T2*MRI scores, would be better management of cardiac complications.

Determination of Cardiac Dysfunction By T2 * MRI

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Word counts Abstract :247

Text: 2267

References: 26, Tables: 3, Figures:2

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Key Words: Tissue Doppler, Cardiac Dysfunction, Thalassemia Major

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Results: Systolic and diastolic functions were found normal by conventional echocardiography in thalassemia patients. However, cardiac functions were significantly impaired when evaluated by TD ($p<0.05$). T2*MRI and TD measurements didn't differ according to serum ferritin levels ($p>0.05$). Twenty-one patients

(63.6%) had myocardial iron overload. Both isovolumetric acceleration time of left ventricle and myocardial performance index (MPI-septal) were found significantly impaired in these patients ($p<0.05$). There was negative correlation between MPI-septal and T2*MRI measurements in thalassemia patients (r:-0.343, p=0.050). TD measurements obtained from septum were found similar with the control ($p>0.05$) but, the same measurements from left and right ventricular walls were significantly impaired in iron unloaded group ($p< 0.05$).

Conclusion: Iron unloaded patients according to T2*MRI had left and right ventricular dysfunction determined by TD. Therefore, we suggest that combining T2*MRI with TD measurements, for evaluating cardiac status in β-TM, in whose with normal T2*MRI scores, would be better management of cardiac complications.

Introduction:

Beta-thalassemia major (β-TM) is a transfusion dependent hereditary anaemia. Regular transfusion and effective chelator therapy are increased the life expectancy in this group of patients. Iron chelators are used to prevent transfusion related iron overload which is toxic for all the tissues, especially for heart. However, cardiac problems are still the major mortality reason in β-TM.[1-3] Early detection of cardiac iron accumulation helps intensify chelation therapy before heart failure develops. T2* magnetic resonance imaging (MRI) is a non-invasive technic for shows myocardial iron overload.[4,5]

Conventional echocardiography may be insufficient in demonstrating cardiac dysfunction because of diastolic and systolic functions are preserved till the end stage cardiac failure in these patients.[6] Therefore, early detection of myocardial dysfunction and modification of treatment is important for preventing the progression of end stage heart failure and lethal arrhythmias.[7] Tissue Doppler (TD) imaging is an echocardiographic based technic, determines myocardial motion abnormality and its shows regional diastolic and systolic velocities. TD imaging allows additional information to detect early myocardial dysfunction compare to conventional echocardiography.[8,9]

The aim of our study is to compare the TD measurements of our patients with normal conventional echo findings with control group and to investigate the relationship between T2* MRI and TD measurements in patients with thalassemia. Our other aim is to compare TD findings of the patients with no cardiac iron accumulation with the control group.

Methods:

Study Populations:

The study group included 33 β-TM patients (16 girls/17 boys, mean age 18.7±7.7 years) who were transfused every other 3-4 weeks since the early childhood and on regular chelation program. They all had normal systolic functions showed by conventional echocardiography measurements; ejection fraction (EF)>55%, fractional shortening (FS)>30%. None had thyroid, lung, renal and liver dysfunctions. Thirty-seven healthy individuals (18 girls/19 boys, mean age 19.9±8.4 years) were included into the control group.

Serum ferritin measurement: Ferritin ELISA kit (DRG-Germany) were used for serum ferritin measurements. Serum samples were obtained from both groups. The samples from the study group were taken before the transfusion. If there was any signs of infection within one week, sampling was postponed.

T2*MR imaging: T2*MRI was performed by Siemens Magneton-Avento 1.5 tesla MR device. Measurement was made from septum middle segment on short axis by using single cross-section dual echo black blood turbo field echo (TFE) sequences. TFE sequences were taken using electrocardiogram synchronization during late diastolic phase by breath-holding technic These sequence parameters were TR (time to repetition)/TE1 (time echo) /TE2:12/4.6/9.2 milliseconds (msn), flip angel:30, NEX (number of excitations): 3, FOV (field of view): 350-450, slice thickness: 10 mm, TFE factors:6. T2* MRI scan was performed only in the study group within 15-25 minutes and the findings were evaluated by the same radiologist without knowing TD imaging results. T2* MRI and TD surveys were performed on same day. The cut-off level for myocardial overload was accepted as 20 ms.

Echocardiographic evaluation: Conventional echocardiographic and pulsed-wave Doppler studies were performed using General Electric Vivid S6 system with 2.5 or 3.5 MHz transducers. Conventional echocardiographic study included two dimensional, M-mode, pulsed-wave Doppler measurements. Patients' measurements were performed by the same cardiologist without knowing the T2*MRI results within 2 to 5 days following transfusion and on the same day with T2*MRI. Echocardiographic examination was done during normal respiration simultaneously with electrocardiogram tracing in supine or left lateral decubitus position. All patients had sinus rhythm during examination. M-mode traces were recorded at the speed of 50 mm/s and the Doppler signals 100 mm/s. Three consecutive cycles were averaged for every parameter. Left ventricle (LV) diameters, wall thicknesses, EF were measured from M-mode traces recorded from the parasternal long-axis view according to the recommendations of the American Society of Echocardiography.[10] The trans mitral flow velocities were performed in the apical four-chamber view using pulsed Doppler echocardiography with the sample volume sited at the tip of the mitral leaflet. The peak early diastole (E) and late diastole (A) trans mitral flow velocities, deceleration time (DT) were measured.

For the acquisition of TD velocities; LV images were obtained from the apical four-chamber view, and a 5 mm pulsed Doppler sample volume was placed at the level of lateral and septal mitral annuluses. Myocardial velocities of the lateral tricuspid annulus were similarly obtained by placing the sample volume at the junction of the tricuspid valve annulus and the right ventricle free wall. The peak systolic velocity (S_m), early diastolic myocardial peak velocity (E_m), late diastolic myocardial peak velocity (A_m) and isovolumic contraction (IVC) velocity were obtained and the results were given as cm/s. The acceleration rate of isovolumic contraction (IVA) was calculated as the peak IVC velocity divided by the time interval from baseline to peak (Δt). IVA= IVC/ Δt (Figure 1). Ejection time (ET), isovolumic relaxation time (IVRT) and isovolumic contraction time (IVCT) were obtained and the myocardial performance index (MPI) were calculated by the following formulation;

MPI = (IVRT+IVCT)/ET.

The study group was divided into two subgroups according to T2*MRI results (patient with cardiac iron overload <20 ms or non-iron load group [?] 20 ms). The results obtained from TD imaging were compared according to these subgroups.

The Uludag University Ethics Committee gave permission for the study. The written informed consents were also obtained from both patients and controls.

Statistical Analysis:

All statistical analyses were performed with SPSS ver.22.0. Shapiro Wilk test was used to define the normal distribution. Continuous and categorical variables were compared using Student t-test and Pearson's chi-square test, in respectively. Correlations between variables were tested using Pearson correlation coefficients. p-value < 0.05 was considered as significant.

Results:

Distribution of gender and age were similar in both groups ($p>0.05$). Ferritin levels were significantly high in the study group ($p<0.001$). Conventional echocardiographic and pulsed-wave Doppler studies were similar between the two groups (Table I). Systolic and diastolic functions in TD were found significantly more impaired in thalassemia patients compared to the healthy subjects (Table II).

The mean serum ferritin level in the study group was found 2242.3±2174.2 (109-9843) ng/ml. Neither with TD nor T2*MRI measurements were correlated with serum ferritin levels in thalassemia patient.

The mean T2*MRI score was 187.±7.7 (7.3-29.8) ms in the study group. The patients were stratified into two subgroups according to iron load; Group 1: those with iron overload (T2*MRI<20ms) and group 2: those without iron overload (T2*MRI [?]20ms). There were twenty-one (63.6%; 21/33) and twelve (36.4%;12/33) patients in groups 1, and 2, respectively. Serum ferritin levels were similar in both subgroups. Of the TD measurements, only MPI-septal measurement was significantly worsened in myocardial iron overload group

(MPI-septal; 0.47+-0.09 in group 1 versus 0.38+-0.07 in group 2, p<0.01). There was negative correlation between MPI-septal and T2*MRI measurements (r:-0.343, p=0.05, Figure 2). The cut-off level of MPI septal in showing iron overload was found 0.37 ms of which the sensitivity and specificity were found 58.3% and 90.48%, in respectively. The decrease in T2*MRI scores in iron overload group caused longer duration in ET-septal values measured by TD (r:-0.507, p=0,019).

Tissue Doppler measurements in thalassemia patients with no myocardial iron overload were separately compared with the controls. Of the velocity measurements (Am,Em,Sm); only Sm velocity obtained from the left ventricular wall was found significantly different (Sm-LV 10.2+-1.5cm/ms in thalassemia patients versus 12.4+-1.9 cm/ms in the controls, p<0.005, data not shown). Although the time intervals and MPI on the measured interventricular septum were found normal, they were significantly impaired on the lateral wall of left and right ventricles (Table III). Of the septal measurements, only IVA-septal was found more impaired in non-iron overloaded thalassemia patients (p<0.05, Table III).

Discussion:

In the current study, systolic and diastolic dysfunctions determined by echocardiographic parameters were found similar with the healthy subjects. However, TD evaluation showed significant myocardial dysfunction. Although various studies declared that global cardiac functions were reserved and evaluated as normal by conventional echocardiographic findings in thalassemia major, regional wall abnormalities were shown by TD measurements.[8,9,11-13]

When we measured Em, Am and Sm velocities from three different regions of the myocardium, only Sm velocity were found significantly impaired in left ventricular and septal walls compared to the controls. However, these velocity measurements were not different from the controls in the right ventricular wall (p>0.05). This result showed that systolic functions in the left ventricle and septum were impaired in our patients. In addition to that, in the septal region Am velocity was different from controls. Agha et al.[14], Yuksel et al.[15], Balcı et al.[16] and Ragap et al.[17] were found only diastolic dysfunction according to velocities. But the another studies were found both diastolic and systolic dysfunctions.[8,18-20] Interestingly Marci et al.[21] were found Sm abnormalities, and ıt was correlated onset of adverse cardiac event. Mean age was 32 in this study. Although we found normal functions of the right ventricle, according to velocities, abnormalities were detected in the other studies.[13,14,16,19] These studies were not same and there were many differences between them. For example; age groups studied, measured areas and TD parameters evaluated were different. In addition, some studies were correlated the results with BNP, ferritin or T2* MRI. Since the studies are not homogeneous, it is difficult to compare with each other.

In our study, we evaluated not only Em, Am and Sm velocities, but also time intervals such as ET, IVRT and indexes such as MPI and IVA. Limited data was found evaluated time intervals and indexes.[17,20,22] Arı et al.[20] found IVCT abnormality in left ventricle and septum, but ET, MPI and IVRT were normal. Uçar et al.[22] found MPI and ET abnormality three different area, but IVRT was normal in the septum. Ragap et al.[17] found MPI, ET and IVRT abnormality in the septum and lateral wall. These studies' mean ages were under our study. We found MPI abnormality in the all three area, ET was only abnormal in the left ventricle. IVRT abnormality was found in left and right ventricle. We found a negative correlation between MPI-septal and T2*MRI scores (r:-0.343, p=0.05, Figure 2). In the Uçar et al.[22]study, MPI was found correlate BNP, but not was used MRI, and they reported that MPI was important for seeking early impairment. Also Arı et al.[20] found correlation with MPI and T2* MRI result in the iron overload group. We found another positive correlation in the iron overloaded group was ET-septal and MRI results.

In the current data, we calculated IVA index. This parameter was very important in determining myocardial acceleration during isovolumetric contraction (early systolic phase) which was resistant to physiologic load changes.[10] Our study was the second study evaluating IVA in thalassemia patients. Cheung at al.[23] found similar IVA compared with controls in the resting, but during exercises, changes in the IVA was found low from controls. It was showed impaired contractile reserve in this patients. All of them had no cardiac co-morbidities, no Arrhythmias or bundle branch block. Like MPI, we found IVA abnormalities in all region,

and in non iron-loaded patients compared with controls.

In thalassemia patients, the mean T2*MRI scores did not change according to serum ferritin levels ($p>0.05$). Neither TD nor T2*MRI measurements were correlated with serum ferritin level ($p>0.05$). Various studies also supported this finding that serum ferritin levels in thalassemia patients were not a reliable marker in estimating myocardial iron overload.[3,18,22]

We compared with according to T2*MRI result, only MPI-septal measurement was different between iron load or non-load group. There are a limited number of studies to evaluate comparisons. Arı et al.[20], found Sm, Em and Am abnormalities in the left ventricular wall and detected Sm, MPI and IVCT abnormalities in the septal wall between iron load and non-load group. Agha et al.[14] evaluated only velocities from three region and found tricuspid annular A and E/A abnormalities between iron load and non-load group. Vogel et al.[8] was found 87% wall motion abnormalities in patient with T2*MRI<20 ms, versus found 35% wall motion abnormalities in patient with T2*MRI[?]20 ms.

In our study, the septal measurements of Sm, Am and Em velocities, MPI, ET, IVRT were found similar with the controls in thalassemia patients with non-load group (T2*MRI[?]20 ms.). Interestingly, when they were measured from left and right ventricular walls, they were found significantly impaired compared to the controls (Table III). When we searched the literature, only Agha et al.[14] evaluated velocities from three region and found tricuspid annular A´ and E´/A´ abnormalities between non-iron load and control group. But there was no data comparing TD time intervals or indexes between healthy subjects and non-iron overloaded thalassemia patients. This patients who are T2*MRI result is [?]20 ms are usually considered as patients with no cardiac complications. T2* MRI shows myocardial iron load measured from septal region.[4] Iron accumulation and its toxic effect are not evenly distributed in myocardium, regional differences can occur.[24-26] Our data determined that only T2*MRI evaluating was insufficient to cardiac status in this group. Therefore, we strongly suggested to obtain TD measurements from right and left ventricular walls in thalassemia patients with T2*MRI[?]20ms especially elder patients.

Study Limitations:

This is a single-centre study and included limited number of patients.

Conclusion:

The conventional echocardiography was not sufficient to determine the actual myocardial functions in beta-thalassemia major. We showed that systolic and diastolic function was impaired in both myocardial iron loaded (T2*MRI<20ms) and non-loaded (T2*MRI[?]20ms) thalassemia patients when they were evaluated by TD. In our study, TD measurements showed left and right ventricular dysfunction in patients considered as myocardial iron non-load. Normal cardiac T2*MRI in thalassemia patients does not always associated with normal cardiac function. Therefore, we suggest that combining T2*MRI with TD measurements, not only velocities but also time intervals and indexes, especially patients with normal T2*MRI score, could lead to a better management of cardiac complications.

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Table I: Demographic data, serum ferritin level and conventional echocardiographic measurements in the study and control groups

	Study Group (n=33)	Control Group (n=37)	p value
Age (years)	18.7±7.7 years	19.9±8.4 years	>0.05
Gender	16 girls/17 boys	18 girls/19 boys	>0.05
Ferritin (ng/ml)	**2242±2174.2**	**29.2±17.7**	**<0.001**
EF (%)	67.9±5.8	66.5±5.9	>0.05
FS (%)	37.8±4.8	36.8±4.9	>0.05
IVSd (mm)	8.4±1.1	7.9±1.3	>0.05
LVPwd (mm)	8.1±1.2	8±1.2	>0.05
LVIDd (mm)	45.6±7.2	44±4.2	>0.05
LVIDs (mm)	28.2±4.6	27.8±3.3	>0.05
E (cm/sn)	126.8±16.2	119.1±18.7	>0.05
A (cm/sn)	66.5±15.9	64.7±10.3	>0.05
DT (ms)	134.9±20.9	133.1±15.3	>0.05

EF: ejection fraction, **FS** : fractional shortening,**IVSd** : interventricular septal end diastole, **LVPwd:**Left ventricular posterior wall end diastole, **LVIDd:** Left ventricular internal diameter end diastole, **LVIDs:** Left ventricular internal diameter end systole, **E:** early diastole,**A:** late diastole, **DT:** deceleration time of E.

Table II: Tissue Doppler measurements in the study and control groups

	Tissue Doppler measurements	Study Group (n=33)	Control Group (n=37)	p value
Lateral mitral annulus	**Sm-LV (cm/s)**	**10.2±1.8**	**12,4±1,9**	**<0,001**
	Em-LV (cm/s)	20.1±3.9	19.4±4.2	>0.05
	Am-LV (cm/s)	9.1±3.3	9.7±2.2	>0.05
	MPI-LV	**0.46±0.11**	**0.33±0.06**	**<0.001**
	ET-LV (ms)	**268.1±17.9**	**299.7±15.8**	**<0.05**
	IVRT-LV (ms)	**51.1±14.8**	**43.3±9.8**	**<0.005**

	Tissue Doppler measurements	Study Group (n=33)	Control Group (n=37)	p value
	IVA-LV (cm/sn^2)	**2.08±0.9**	**3.2±1.0**	**<0.001**
Septal mitral annulus	**Sm-sep (cm/s)**	**7.3±1.1**	**8.2±1.3**	**<0.05**
	Em-sep(cm/s)	13.7±2.3	14.9±2.7	>0.05
	Am-sep(cm/s)	**6.3±2.3**	**7±0.9**	**<0.05**
	MPI-septal	**0.44±0.09**	**0.36±0.05**	**<0.005**
	ET-septal (ms)	279.2±22.2	283.6±15.1	p>0.05
	IVRT-septal (ms)	53.6±9.1	49.4±11.5	p>0.05
	IVA-sep (cm/sn^2)	**2.1±0.7**	**2.7±0.8**	**<0.05**
Tricuspid valve annulus	Sm-RV (cm/s)	15.8±3.2	15.7±1.8	>0.05
	Em-RV(cm/s)	18.7±3.5	18.5±2.6	>0.05
	Am-RV(cm/s)	14.4±4.5	13.0±2.2	>0.05
	MPI-RV	**0.39±0.13**	**0.47±0.17**	**<0.01**
	ET-RV(ms)	283.6±26.7	278.8±67.1	p>0.05
	IVRT-RV (ms)	**49.6±17.8**	**29.0±12.2**	**<0.001**
	IVA-RV(cm/sn^2)	**2.7±0.8**	**3.9±1.2**	**<0.001**

Em: early diastolic velocity, **Am** : late diastolic velocity, **Sm:** systolic velocity,

MPI: Myocardial performance index, **ET:** Ejection time,**IVRT** : Izovolumetric relaxation time,

IVA: myocardial acceleration during isovolumic contraction

Table III: The data of time intervals and IVA in thalassemia patients without myocardial iron overload and the controls

		Thalassemia patients without iron overload (T2*>20) (n=12)	Control Group (n=37)	p value
Lateral mitral annulus	**MPI-LV**	**0.46±0.09**	**0.33±0.06**	**<0.001**
	ET-LV (ms)	**251±7.3**	**299.7±15.8**	**<0.05**
	IVRT-LV (ms)	**284.1±15.2**	**43.3±9.8**	**<0.005**
	IVA-LV (cm/sn^2)	**2.2±1.1**	**3.2±1.0**	**<0.01**
Septal mitral annulus	MPI-sep	0.38±0.07	0.36±0.05	p>0.05
	ET-sep (ms)	252.9±8.1	283.6±15.1	p>0.05
	IVRT-sep (ms)	289.6±24.4	49.4±11.5	p>0.05
	IVA-sep (cm/sn^2)	**2.0±0.7**	**2.7±0.8**	**<0.05**
Tricuspid valve annulus	**MPI-RV**	**0.40±0.09**	**0.47±0.17**	**<0.005**
	ET-RV (ms)	286.7±26.4	278.8±67.1	p>0.05

		Thalassemia patients without iron overload (T2*>20) (n=12)	Control Group (n=37)	p value
	IVRT-RV (ms)	**54.1±16.9**	**29.0±12.2**	**<0.001**
	IVA-RV (cm/sn^2)	**2.8±0.8**	**3.9±1.2**	**<0.05**

MPI: Myocardial performance index, **ET:** Ejection time,**IVRT** : Izovolumetric relaxation time,

IVA: myocardial acceleration during isovolumic contraction

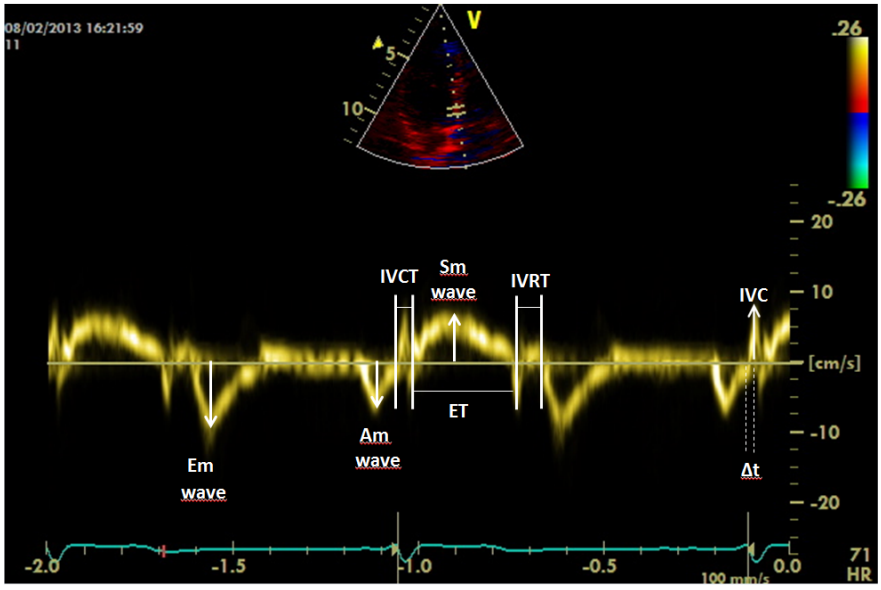

Fig. 1: Tissue Doppler Imaging Measurement

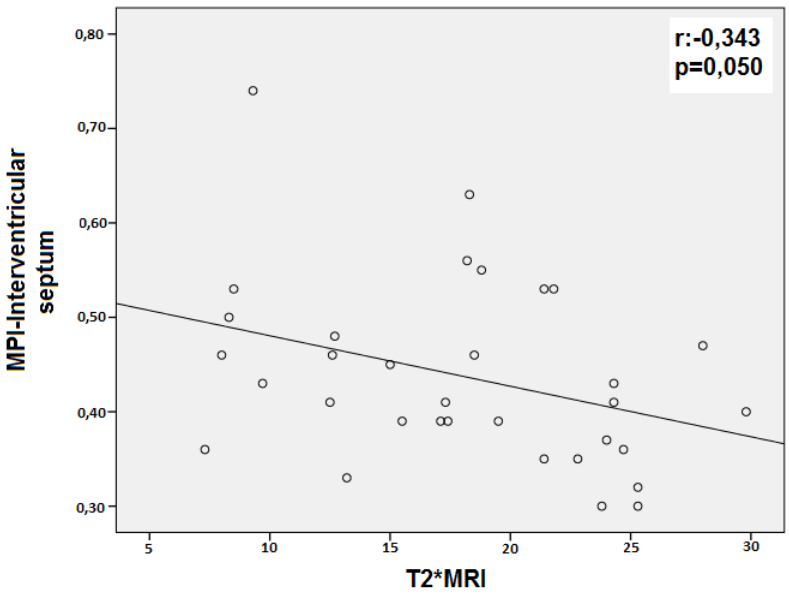

Fig. 2: The correlation between MPI-septal and T2*MRI in all patients