Echocardiographic Evaluation of Cardiac Structural and Functional Changes in Hepatitis C Positive Non-Alcoholic Liver Cirrhosis Patients and Their Plasma NT-ProBNP Levels

Manal Eldeeb[1], Ragai M. F. R. Fouda[1], Mona M.R. Hammady[1] and Laila Rashed[2]

[1]Internal Medicine Department Cairo University, [2]Biochemistry Department Cairo University
monahammady@hotmail.com

Abstract: Background: Cirrhotic cardiomyopathy (CC) refers to cardiac structural, functional, and electrophysiological changes in liver cirrhosis (LC) patients. Emerging role of natruretic peptides in screening LC patients for development of CC was suggested. The aim of this study was to assess structural and functional cardiac changes in hepatitis C positive nonalcoholic (LC) patients and N- terminal pro brain natriuretic peptides (NT-proBNP) blood levels in these patients. **Methods:** Forty hepatitis C positive LC patients classified according to their child - Pugh score underwent transthorathic echocardiographic assessment of cardiac chambers dimensions, and left ventricular functions. Estimation of plasma NT-proBNP levels of these patients and 10 healthy age and gender matched healthy control subjects was done. **Results:** Child-Pugh C LC patients have significantly higher mean left ventricular end diastolic (LVEDD) and end systolic dimensions (LVESD) compared to those of Child- Pugh A and B LC patients. LV systolic function was preserved in the three Child- Pugh groups, while diastolic dysfunction was detected in 78.5% of Child- Pugh C patients. Mean plasma NT-proBNP level was significantly higher in Child-Pugh C patients compared to mean plasma levels in Child- Pugh A and B patients. ProBNP plasma levels correlated significantly with serum albumin, bilirubin, creatinine, international normalized ratio, Child-Pugh score, LVESD, LVEDD, left atrial and right ventricular diameters. **Conclusion:** Child-Pugh C LC patients suffered of cardiac structural changes associated with diastolic dysfunction and raised mean ProBNP plasma level but preserved systolic function. NT-ProBNP levels correlated significantly with echocardiographic changes and Child- Pugh score.
[Manal Eldeeb, Ragai M. F. R. Fouda, Mona M.R. Hammady and Laila Rashed. **Echocardiographic Evaluation of Cardiac Structural and Functional Changes in Hepatitis C Positive Non-Alcoholic Liver Cirrhosis Patients and Their Plasma NT-Probnp Levels.** Life Science Journal 2012; 9(1):786-792]. (ISSN: 1097-8135). http://www.lifesciencesite.com.113

Key words: cirrhosis- cardiomyopathy-echocardiography- NT-proBNP-Hepatitis

1. Introduction:

Cirrhotic cardiomyopathy is a recently recognized condition in cirrhosis [(1)]. This term denotes a chronic cardiac dysfunction, characterized by blunted contractile responsiveness to stress and altered diastolic relaxation with electrophysiological abnormalities, such as prolongation of the QT interval, all occurring in the absence of any other cardiac disease [(2,3)].These changes were previously thought to be related to latent alcoholic cardiomyopathy in alcoholic liver cirrhosis patients but latter clinical and experimental studies showed that these cardiac changes are seen in those with nonalcoholic cirrhosis [(1)].

This cardiac dysfunction may affect the prognosis of the patients and aggravate the course during invasive procedures such as surgery, insertion of a transjugular intrahepatic porto systemic shunts (TIPS), and liver transplantation [(4)].

Many patients chronically infected by hepatitis C virus (HCV) experience symptoms like fatigue, dyspnea and reduced physical activity. However, in many patients, these symptoms are not proportional to the liver involvement and could resemble symptoms of chronic heart failure [(5)]. Several studies have shown increased plasma levels of brain natriuretic peptide (BNP) and NT-proBNP in some patients with cirrhosis, and these findings may suggest cardiac dysfunction [(6)].NT-proBNP has been recently suggested to be an even better indicator of early cardiac dysfunction than BNP because of its stability and longer biological half-life [(7)]. Several studies have shown that plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are reliable diagnostic and prognostic markers for cardiac disease; furthermore, they correlate with symptoms of heart failure and with the severity of systolic and diastolic dysfunction [(8)].

The aim of this study was to evaluate echocardiographic structural and functional changes in non alcoholic HCV positive liver cirrhosis patients and plasma levels of NT-ProBNP in these patients.

2. Subjects and Methods:

The protocol of this study was first approved by the scientific board of Internal Medicine department and Committee of Research Ethics; Faculty of Medicine – Cairo University – Egypt and Informed consents were obtained from all participants.

The study included 40 Hepatitis C positive liver cirrhosis (LC) patients and 10 age and gender matched normal healthy controls. LC diagnosis was based on established clinical, biochemical, and ultrasonography criteria none were proven by biopsy. HCV infection was diagnosed with positive serum HCV - RNA by polymerase chain reaction. Participants were recruited from patients admitted to Internal Medicine departments in Kasr El Eini Hospital- Cairo University during the period between December 2010 and December 2011.Those with history of alcohol consumption, diabetes mellitus, hypertension, cardiac, renal or pulmonary diseases or previous cardiac surgery were excluded. Those suffering from valvular heart disease and those with a poor pericardial window were also excluded.

Patients underwent thorough clinical evaluation, chest X-ray, and electrocardiography (ECG). Blood sampling for hemoglobin, prothrombin time, serum sodium, potassium, urea, creatinine, albumin and bilirubin estimation and abdominal ultrasound imaging were done . Blood samples for analysis of NT-proBNP were centrifuged and plasma stored at −80 °C until analysis. Plasma concentrations of NT-proBNP in LC patients and healthy control subjects were measured by a sandwich immunoassay technique (Roche Diagnostics, Mannheim, Germany).

Patients were classified according to Child-Pugh criteria [serum bilirubin, prothrombin time, serum albumin, ascites, and encephalopathy].Chronic liver disease was classified according to point score into 5-6 points for Child -Pugh A score,7-9 points for child - Pugh B score and 10-15 points for child - PughC score[9].

Two-dimensional and M-mode echocardiography were performed to all patients by physician who was blinded to the results of the plasma NT-ProBNP levels, imaging was performed with Vivid 3N (General electric) equipped with 2.5 MHz and 3.5 MHz phased pulsed array transducers. Two-dimensional imaging examinations were performed in the standard fashion in parasternal long- and short-axis views and apical 4- and 2-chamber views. Cardiac chambers dimensions were measured according to the guidelines of the American Society of Echocardiography using M-mode method [10].

LV systolic and diastolic diameters and volumes , ejection fraction and fraction shortening were derived from biplane apical (2- and 4-chamber) views with a modified Simpson's rule algorithm[11].

Pulsed Doppler spectral recordings were obtained in the apical 4-chamber view from a 4x4-mm sample volume positioned at the tips of the mitral leaflets. The transmitral pulsed Doppler velocity recordings from 3 consecutive cardiac cycles were used to derive measurements as follows: E and A velocities were the peak values reached in early diastole and after atrial contraction, respectively, and deceleration time (DT) was the interval from the E-wave peak to the decline of the velocity to baseline. In those cases in which velocity did not return to baseline, extrapolation of the deceleration signal was performed[12].

LV functions were classified into 3 major categories:[12]

a)Normal LV Function

Normal ventricular function was defined by normal LV end-diastolic (3.5 to 5.5 cm) and end-systolic (2.5 to 3.6 cm) dimensions, no major wall motion abnormalities, an ejection fraction >50%, and no evidence of impaired or restrictive like relaxation abnormalities as described below.

b)LV Systolic Dysfunction

Systolic dysfunction was defined by an ejection fraction <50% .

C)LV Diastolic Dysfunction

Diastolic dysfunction was classified in 3 categories.

Impaired Relaxation

Impaired relaxation was defined as an E/A ratio <1 or DT >240 ms in patients <55 years of age and an E/A ratio <0.8 and DT >240 ms in patients >55 years of age.

Pseudonormal

Pseudonormal was defined as an E/A ratio of 1 to 1.5 and DT >240 ms. Confirmation reversal of the E/A ratio (to <1.0) by **Valsalva** when possible.

Restrictive

Restrictive like filling patterns were defined as DT <160 ms with >1 of the following: left atrial size >5 cm, or E/A >1.5.

Statistical analysis

Statistical Package of Social Science (SPSS) program version 15.0 was used for analysis of data. Data was summarized as mean , SD. T-test was used for analysis of 2 quantitative data, while Non parametric test (Mann Whitney U test) was used when data was not symmetrically distributed. One way ANOVA test was used for analysis of more than 2 quantitative data followed by post HOCC test for detection of significant. Pearson's correlation was also done. r was considered weak if < 0.25, mild if $r \geq 0.25 < 0.5$, moderate if $r \geq 0.5 < 0.75$ and strong if $r \geq 0.75$. P-value was consider significant if ≤ 0.05*.

3. Results:

The clinical and laboratory data of the studied liver cirrhosis patients classified according to their Child- Pugh score into 3 groups (A, B and C). Child- Pugh A group was composed of 9 patients (7men and 2 women) , Child- PughB group was composed of 16 patients(9men and 7 women) and Child- Pugh C patients was composed of 15 patients (10 men and 5 women). Child- Pugh C patients had significantly lower mean haemoglobin and significantly higher mean AST, ALT, INR, bilirubin and NT- proBNP blood levels compared to those of Child- Pugh A and Child- Pugh B patients (table 1).

Table (1) Comparison between laboratory data of patients in relation to child classification

	Child –Pugh A		Child –Pugh B		Child–Pugh C		*P*-value
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	52.90	8.65	57.07	9.96	49.08	5.98	0.06
Hb (g/dl)	10.78[a]	1.36	10.51[a]	0.57	9.32[b]	0.63	0.0001*
AST(IU/L)	60.70[a]	35.74	63.73[a]	19.51	89.47[b]	31.28	0.02*
ALT (IU/L)	58.60[a]	23.45	61.80[a]	23.90	87.53[b]	33.75	0.02*
Urea (mg/dl)	39.90	9.54	39.60	10.81	43.47	12.65	0.6
Creatinine (mg/dl)	0.95[a]	0.21	0.97[a]	0.18	1.12[b]	0.15	0.03*
Total bilirubin (mg/dl)	1.01[a]	0.37	1.95[b]	0.37	3.00[c]	0.78	0.0001*
Albumin (gm/dl)	3.0	0.82	2.8	0.48	2.7	0.8	0.9
INR	1.42[a]	0.28	1.52[a]	0.19	2.00[b]	0.50	0.0001*
NT-proBNP(pg/ml)	59.20[a]	6.08	72.40[a]	15.57	343.13[b]	117.90	0.0001*

Different symbol indicates significant.

The echocardiographic data of the studied liver cirrhosis patients showed that mean left ventricular end systolic diameter (LVESD) and mean left ventricular end diastolic diameter (LVEDD) were significantly higher among Child - Pugh C patients compared to those of Child- Pugh A and Child- Pugh B patients . Mean Child - Pugh C patients left atrial diameter was higher than the mean values of the other Child groups but only mean LA diameter of Child- Pugh B was significantly different from that of Child- Pugh Cpatients. Right ventricle diameter of Child- Pugh C patients was higher than those of Child - Pugh A and Child- Pugh B patients, although that difference did not reach statistical significance (Table 2).

Table 2. Echocardiographic data of liver cirrhosis patients according to child- Pugh classification

	Child A		Child B		Child C		P-value
	Mean	SD	Mean	SD	Mean	SD	
LA(cm)	3.51[ab]	0.70	3.18[a]	0.54	3.80[b]	0.62	0.03*
LVEDd(cm)	4.38[a]	0.51	4.59[a]	0.43	5.27[b]	0.51	0.0001*
LVESd(cm)	2.73[a]	0.50	2.65[b]	0.34	3.14[b]	0.45	0.009*
IVSDd(cm)	1.07	0.22	1.04	0.22	1.06	0.18	0.9
LVPWD(cm)	1.10	0.22	1.08	0.18	1.15	0.22	0.6
EF(%)	68.60	5.89	72.80	6.16	70.73	6.64	0.3
FS(%)	38.50	4.45	42.20	5.40	40.80	5.86	0.3
RVDd(cm)	2.91	0.44	2.70	0.45	3.16	0.59	0.06
E(m/sec)	0.65	0.16	0.70	0.29	0.75	0.16	0.6
A(m/sec)	0.70	0.14	0.82	0.22	0.72	0.13	0.2
E/A	0.95	0.27	.86	0.20	1.06	0.29	0.1
DECT(msec)	190.60	45.46	169.87	18.37	184.86	35.71	0.3

LA: left atrium, LVEDd: left ventricle end diastolic diameter, LVESd: left ventricle end systolic diameter, IVSDd: interventricular septal diameter in diastole, LVPWD:left ventricle posterior wall diameter in diastole,EF:ejection fraction,FS: fractional shortening, RVDd: right ventricle diameter in diastole, E : peak transmitral velocity reached in early diastole, A :peak transmitral velocity after atrial contraction, E/A ratio, ratio of velocity of E wave to velocity of A wave of Doppler mitral valve inflow and DECT: deceleration time. Different symbol indicate significant

Although mean E wave, A wave velocities, E/A values and deceleration time were not statistically different among patients in the 3 Child- Pugh groups (Table2), diastolic function classification according to the previously described echocardiographic classification showed that 50% of Child- Pugh A patients, 66.66% of Child- Pugh B patients and 78.5% of Child- Pugh C patients suffered of diastolic dysfunction (Table 3).

Table 3. Diastolic function of liver cirrhosis patients grouped according to Child classification

	Child- Pugh A	Child - Pugh B	Child- Pugh C
Normal diastolic function	5(50%)	5(33.33%)	3(21.5%)
Impared relaxation	4(40%)	10(66.66%)	8(57.1%)
Pseudonomalization	0(0%)	0(0%)	0(0%)
Restrictive pattern	1(10%)	0(0%)	3(21.4%)

Mean NT-pro BNP blood levels among studied liver cirrhosis patients according to their diastolic function were 140.84±144.14 pg/ml , 176.86±153.13 pg/ml and 231.5± 200.92pg/ml among those with normal diastolic function, impaired relaxation and restrictive pattern respectively (Figure 1).

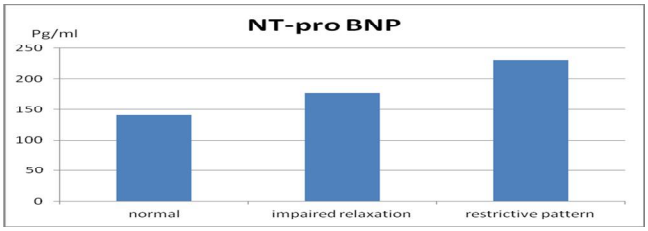

Figure1.NT-proBNP levels in liver cirrhosis according to the diastolic function of liver Cirrhosis patients.

Mean NT-pro BNP blood levels among liver cirrhosis patients in any Child- Pugh group were significantly higher than those of healthy control subjects. Mean NT-proBNP blood levels were significantly higher among Child- Pugh C patients compared to those of Child- Pugh A and Child- Pugh B patients (Figure 2).

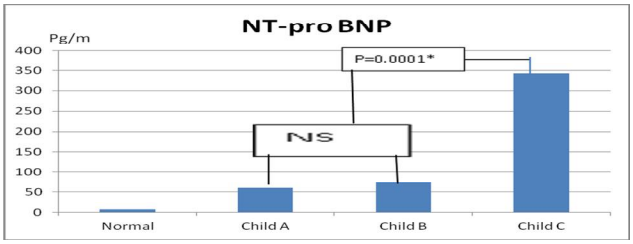

Figure 2. ProBNP levels in healthy control (normal) and liver cirrhosis patients according to Child-Pugh classificatio

There was a significant Correlation between blood NT-ProBNP blood levels and left atrial,LVESD,LVEDD, and right ventricular diameters as well as serum creatinine, bilirubin, albumin, INR and Child- Pugh score(Table 4).

Table4. Pearson Correlation between proBNP blood levels and echocardiographic , laboratory data and child score of liver cirrhosis patients

Variables	Correlation coefficient	proBNP
Left atrium diamater	r	0.3
	P-value	0.04
Left ventricle end diastolic diamater	r	0.7
	P -value	0.0001*
Left ventricle end systolic diamater	r	0.6
	P -value	0.0001*
Right ventricle diamater	r	0.3
	P -value	0.02*
Serum bilirubin	r	0.5
	P -value	0.002*
Serum albumin	r	0.01
	P -value	0.8
International normalized ratio	r	0.5
	P -value	0.0001
Child- Pugh score	r	0.8
	P -value	0.0001*
Creatinine (mg/dl)	r	0.4
	P -value	0.02*

4. Discussion:

In this study cardiac structural and functional changes in nonalcoholic liver cirrhosis patients who were not diabetic or hypertensive, with no history of cardiac disease and no valvular heart disease (that could affect cardiac structure and function) were explored using conventional trans thoracic echocardiography.

The study results showed that Child- Pugh C group of patients suffered of structural cardiac changes, in the form of significantly higher mean LVESD and LVEDD compared to those of Child-Pugh A and Child- Pugh B patients. In addition they have a larger mean right ventricular diameter dimensions compared to those of Child- Pugh A and Child- Pugh B patients but that difference didn't reach statistical significance. Mean left ventricular systolic function parameters (ejection fraction and fractional shortening) were within normal range, among the patients of the three Child groups. Diastolic dysfunction was more prevalent with advancing Child- Pugh score. 50% of Child- Pugh A patients , 66.66% of Child- Pugh B patients and 78.5% of Child- Pugh C patients suffered from diastolic dysfunction.

Similar to our results, Moller and Henriksen in 2002 reported an increase in both systolic and diastolic volumes of the left ventricle in cirrhotic patients, while changes in the right cardiac chambers are less prominent, and mean right ventricle diameters were normal in most studies[13]. Baik *et al.* reported that systolic function is preserved in liver cirrhosis patients with normal or even increased ejection fraction at rest [14].

Finucci et al. reported that cirrhotic patients in addition to increased left ventricular end-diastolic , left atrial , stroke volumes, they showed increased late diastolic flow velocity compared to normal controls; their results indicated an impaired left ventricular relaxation in these patients[15].Raedle, et al. 2008 used tissue Doppler imaging to assess the diastolic function in chronic liver disease patients . Their results showed that left ventricular diastolic dysfunction was found in 25 of 31(80.6%) patients with severe liver fibrosis/cirrhosis versus 2 of 8(25.0%) patients with moderate and 6 of 25(24.0%) patients with mild liver fibrosis. Their results agree with results of the present study regarding prevalence of diastolic dysfunction in patients with advanced liver cirrhosis [16].

In the present study mean NT-proBNP plasma levels were significantly higher in cirrhosis patients compared to healthy controls. In addition mean NT-proBNP plasma levels in Child- Pugh C patients were significantly higher than those of Child- Pugh A and Child- Pugh B patients. PlasmaNT-proBNP levels were positively correlated to Child- Pugh score, bilirubin, INR, serum creatinine, left atrial, right ventricular , LVESd and LVEDd. The previous results are similar to those of Henriksen, et al. in 2003 who showed for the first time that NT-proBNP concentrations are significantly increased in patients with advanced cirrhosis despite no signs of diminished hepatic degradation of NT-proBNP in these patients, in addition they reported that elevated levels of NT-proBNP in these patients are related to markers of advanced liver cirrhosis (Child- Pugh score and coagulation factors) [17].

Results of this study have shown that NT-proBNP blood levels correlates with left atrial, left ventricular, right ventricular dimensions and left ventricular diastolic dysfunction (NT-proBNP) blood levels being highest in those with restrictive filling) .These results are in concordance with results of the following studies.

Lim et al., noticed that BNP and NT-proBNP levels reflect left atrial size, correlating positively with left atrial volume, particularly in the general population and in patients with heart failure with preserved systolic function[18].Daniel and Maisel., reported that BNP and NT-proBNP levels also correlated positively with LV dimensions, volumes, and mass in a variety of settings and populations[19].Mariano-Goulart et al., reported that the right ventricle (RV) contributes to plasma levels of BNP or NT-proBNP, with either normal or impaired LVEF. Levels of both peptides correlate with measures of RV size, increasing with greater dilatation[20].Tschope et al. noticed that narturetic peptides levels increase with greater severity of overall diastolic dysfunction, independent of LVEF, age, sex, body mass index, and renal function, and the highest levels are seen in subjects with restrictive filling patterns[21].

Few studies, like our study was done to assess nonalcoholic hepatitis C liver cirrhosis patients with low cardiovascular risk , no history of cardiac disease and no valvular heart disease which makes data of this study valuable to the medical literature but it got few limitations. First: the limited number of patients included in this study was due to the vast exclusion criteria. Second: the use of conventional transthoracic echo-Doppler instead of tissue Doppler echocardiography might have limited our ability to differentiate normal from pseudonormal diastolic function in this study. Third: although cirrhotic patients with history or documented IHD were excluded from the study and cirrhotic patients in this study were of low cardiovascular risk, a recent study shed light on the fact that end stage liver disease patients have high prevalence of coronary artery disease and that non invasive assessment has limited

diagnostic accuracy in these patients. IHD is a silent disease that can only be accurately excluded invasively, that might be responsible for some of structural and functional changes seen in these patients[22].Fourth limitation is that even in stable subjects, natruretic peptides levels vary with repeat testing as a consequence of assay characteristics and biological variation however relative variation is greater in normal subjects, in whom absolute levels are low, but when absolute levels are higher as seen in our patients, the relative variation is lower [23].

5. Conclusion,

We noticed that the heart is another organ affected in liver cirrhosis. Not only those with alcoholic cirrhosis suffer from cardiac abnormalities, structural and functional changes are seen in advanced hepatitis C positive non-alcoholic liver cirrhosis patients. These changes correlated with increased blood levels of NT-proBNP. These changes were detected in a group of them with low cardiovascular risk, no history or documented previous cardiac disease or valvular heart disease. There is still no consensus regarding the diagnosis of cirrhotic cardiomyopathy , it is an interesting topic that merits further research to reach clear diagnostic criteria , gold standard diagnostic tests and a value of naturetic peptides in screening, diagnosis and prognostic assessment of that condition.

Corresponding author
Mona M.R. Hammady
Internal Medicine Department Faculty of Medicine, Cairo University
monahammady@hotmail.com

References:

1). Florence Wong (2009):Cirrhotic cardiomyopathy. HepatolInt.; 3:294–304.
2).Zambruni A, Trevisani F, Caraceni P, Bernardi M.(2006): Cardiac electrophysiological abnormalities in patients with cirrhosis. J Hepatol.;44:994–1002.
3).Møller S, Henriksen JH. (2008): Cardiovascular complications of cirrhosis. Gut;57:268–278.
4).Rabie RN, Cazzaniga M, Salerno F, Wong F. (2009): The use of E/A ratio as a predictor of outcome in cirrhotic patients treated with transjugular intrahepatic portosystemic shunt. Am J Gastroenterol.;104:2458–2466.
5). Antonelli A, Ferri C, Ferrari SM, Colaci M, Sebastiani M, *et al.* (2010): High levels of circulating N-terminal pro-brain natriuretic peptide in patients with hepatitis C. J Viral Hepat. ;17:851-3.
6).Henriksen JH, Gøtze JP, Fuglsang S, Christensen E,Bendtsen F, *et al.* (2003): Increased circulating pro-brain natriuretic peptide (proBNP) and brain natriuretic peptide (BNP) in patients with cirrhosis: relation to cardiovascular dysfunction and severity of disease. Gut;52:1511-7.
7).Gøtze JP, Kastrup J. (2001): Plasma pro-brain natriuretic peptides are strong biochemical markers in clinical cardiology. Scand J Clin Lab Invest (Suppl);234: 47-51.
8).Doust JA, Glasziou PP, Pietrzak E, Dobson AJ. (2004): A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. Arch Intern Med.; 164: 1978–1984.
9).Pugh RN, *Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R.* (1973): *Transection of the oesophagus for bleeding oesophageal varices.* Br J Surg.;60:646-*649.*
10).Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E,, *et al.* (2005): Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr;18(12):1440-63.
11).Schiller NB, Acquatella H, Ports TA, Drew D, Goerke J, *et al.* (1979): Left ventricular volume from paired biplane two-dimensional echocardiography.Circulation;60:547.
12). Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J *et al.* (2002): Utility of B-Natriuretic Peptide in Detecting Diastolic Dysfunction : Comparison With Doppler Velocity Recordings.Circulation; 105:595-601.
13).Moller S, Henriksen JH. (2002): Cirrhotic cardiomyopathy: a pathpphysiological review of circulatory dysfunction in liver disease. Heart; 87: 9-15.
14). Baik S, Fouad T and Lee S. (2007): Cirrhotic cardiomyopathy. Orphanet Journal of Rare Diseases; **2**:15.
15).Finucci G, Desideri A, Sacerdoti D, Bolongnesi M, Merkel C *et al.* (1996): Left ventricular diastolic function in liver cirrhosis. Scand J Gastroenterol.; 31: 279-84.
16).Raedle Hurst TM, Welsch C, Forestier N, Kronenberger B, Hess G, *et al.*(2008): Validity of N-terminal propeptide of the brain natriuretic peptide in predicting left ventricular diastolic

dysfunction diagnosed by tissue Doppler imaging in patients with chronic liver disease. Eur J Gastroenterol Hepatol.; 20(9):865-73.
17).Henriksen JH, Gotze JP, Fuglsang S, Christensen E, Bendtsen F *et al.* (2003): Increased circulating pro-Brain Natriuretic Peptide (proBNP) and Brain Natriuretic Peptide (BNP) in patients with cirrhosis: Relation to cardiovascular dysfunction and severity of disease. Gut; 52(10):1511-7.
18)Lim TK, Ashrafian H, Dwivedi G, Collinson PO, Senior R. (2006): Increased left atrial volume index is an independent predictor of raised serum natriuretic peptide in patients with suspected heart failure but normal left ventricular ejection fraction: implication for diagnosis of diastolic heart failure. Eur J Heart Fail;8: 38 – 45.
19).Daniels LB, Maisel AS. (2007): Natriuretic peptides. J Am Coll Cardiol.;50: 2357–68.
20).Mariano-Goulart D, Eberle MC, Boudousq V, Hejazi-Moughari A, Piot C, *et al.* (2003): Major increase in brain natriuretic peptide indicates right ventricular systolic dysfunction in patients with heart failure. Eur J Heart Fail;5:481– 8.
21).Tschope C, Kasner M, Westermann D, Gaub R, Poller WC, *et al.* (2005): The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur Heart J.;26:2277– 84.
22).Ehtisham J, Altieri, M, Salame´ E, Saloux E, Ollivier I, *et al*.(2010): Coronary Artery Disease in Orthotopic Liver Transplantation: Pretransplant Assessment and Management. LIVER TRANSPLANTATION; 16:550-557.
23).Ordonez-Llanos J, Collinson PO, Christenson RH. (2008): Amino-terminal pro-B-type natriuretic peptide: analytic considerations. Am J Cardiol.;101:9 –15.

2/21/2012