Increased liver stiffness values in patients with heart failure

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Abstract

Background : **Liver stiffness has been claimed to be increased in patients with heart failure.**

Aims : **To determine the magnitude of this increase in liver stiffness, and to clarify whether it is related to the degree of heart failure or not.**

Methods : **Twenty-six patients were prospectively collected, and divided in groups CHF (those with compensated chronic heart failure) and AHF (those with acute decompensated heart failure). Patients underwent routine blood chemistries, pro-BNP determination, echocardiography and transient elastography during outpatient care (group CHF) or at hospital admission (group AHF). Blood chemistries, pro-BNP and transient elastography were repeated in patients in group AHF before being discharged.**

Results : **Correlation between liver stiffness and pro-BNP levels was statistically significant (Rho = 0.747, p = 0.001). Patients in group CHF had lower values of liver stiffness and pro-BNP when compared with patients in group AHF at admission. Median liver stiffness and pro-BNP values were 6.5 vs 14.4 kPa (p = 0.009) and 1511 vs 3535 pg/ml (p = 0.025) respectively. After clinical compensation, liver stiffness decreased in all patients in group AHF. Liver stiffness was 14.4 kPa at admission and 8.2 kPa at discharge (p = 0.008). Pro-BNP values also decreased from a median of 3535 pg/ml to a median of 1098 pg/ml (p = 0.025).**

Conclusions : **Patients with heart failure have increased liver stiffness, that appears to be related with the severity of heart failure.** (Acta gastroenterol. belg., **2013**, 76, **246-250**).

Key words : liver stiffness, transient elastography, heart failure, brain natriuretic peptide.

Introduction

Transient elastography (Fibroscan®) (TE) is a non-invasive tool that determines hepatic stiffness, and it is a useful mean to estimate liver fibrosis in patients with chronic liver disease (1-3). It has been studied mainly in patients with chronic hepatitis C (4,5), but also in other chronic liver diseases such as hepatitis B (6), alcoholic liver disease (7,8), non-alcoholic fatty liver disease (9,10), autoimmune hepatitis, primary biliary cirrhosis (11,12), primary sclerosing cholangitis (11) and hemochromatosis (2,13-16). However, liver fibrosis is not the only determinant of liver stiffness (LS). Several authors have also reported that LS may be increased in relation to necroinflammatory activity (17-19), cholestasis (20) and infiltrative diseases of the liver (21,22).

Hepatic congestion may also produce liver damage, and chronic hepatic congestion can lead to the development of liver fibrosis. In fact, recently published articles have described the relation between LS and hepatic congestion (23-29). The aims of our study were to determine the magnitude of the increase in LS in patients with heart failure, and to study the relationship of LS with other parameters of heart failure. N-terminal pro brain natriuretic peptide (pro-BNP) was used as a surrogate marker of heart failure, as its levels reflect both systolic and diastolic function (they are released from the heart in response to pressure and volume overload) (30-32) – in fact, authoritative guidelines on the clinical diagnosis and management of both acute and chronic heart failure recommend measuring pro-BNP (33-34).

Patients and methods

A total of 26 patients with advanced heart failure were prospectively collected. None of them had previous history of liver disease, and all of them were treated according to the usual standard of care. The study was approved by the Institutional Review Board of the Universidad de Navarra, and written informed consent was obtained in all cases.

Patients were divided in two groups. Group CHF included 12 patients with compensated chronic heart failure, who attended the outpatient clinic. All of them had left ventricular failure with secondary right heart failure. Etiology included ischemic disease in 5 patients, valvulopathy in 4 patients, dilated cardiomyopathy in 1 patient and both ischemic and valvular disease in 2 patients.

Group AHF included 10 patients with acute decompensated heart failure that were admitted to the hospital. 3 patients had primary right heart failure and 7 left ventricular failure with secondary right heart failure. Etiologies included ischemic disease en 5 patients, valvulopathy in 2 patients, dilated cardiomyopathy in 1 patient and pulmonary hypertension related to advanced lung disease in 2 patients. These patients admitted to hospital had NYHA class 3 – 4, that improved after clinical compensation to a NYHA class ≤ 2 in all cases.

Four subjects were excluded of the analysis. LS could not be determined in 2 patients because no reliable data were obtained due to bad acoustic window. Another

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patient had pericardial disease and the last one had normal pro-BNP values despite severe heart failure, with LS at hospital admission being 75 kPa. No control subjects were included in the study.

Data collection

Patients underwent routine blood chemistries : cell blood count, creatinine, sodium, potassium, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transpeptidase (GGTP), albumin, pro-BNP determination, echocardiography and TE during outpatient care (group CHF) or at hospital admission (group AHF). Patients in group AHF had also blood chemistries, pro-BNP and TE repeated before being discharged.

TE was performed with Fibroscan® (Echosens), that consists of a 5 MHz ultrasound transducer probe mounted in the axis of a vibrator. It generates low amplitude and low frequency vibrations that induce an elastic shear wave that propagates through the underlying liver tissue at a velocity that is directly related to tissue stiffness. Data obtained are expressed in kilopascals (kPa) ; a minimun of 10 determinations, with a success rate of at least 66% and an IQR less than 25% were required to consider the test as reliable. Normal LS values in healthy subjects in different studies range from 4.5 to 5.5 kPa (35-38). Pro-BNP was analyzed by using a commercially available immunoassay (Elecsys proBNP, Roche Diagnostics) and echocardiography was performed with the ultrasound system SONOS 5500 (Philips, Andover, Massachusetts) and an ultrasound transducer probe S3 (1.6 to 3.2 MHz). Right and left ventricular ejection fractions, as well as estimated pulmonary artery systolic pressure, were recorded.

Statistical analysis

Non-parametric methods were used for statistical analysis : Spearman correlation for describing Pro-BNP and LS correlation, Mann-Whitney test for the comparison between groups CHF and AHF, and Wilcoxon test for the comparison between results obtained in patients from group AHF at admission and at discharge. Data are presented as median (range).

Results

Baseline data (Table 1)

Except for the NYHA class there was no difference regarding age and biochemical data, including liver enzymes, between the two groups. Patients in group CHF had lower values of TE and pro-BNP when compared with patients in group AHF at admission : 6.5 (5.0-10.8) and 14.4 (8.3-18.8) kpa ($p = 0.009$), and 1511 (671-1918) and 3535 (1798-6878) pg/ml ($p = 0.025$), respectively. There was no significant difference regarding the hemodynamic data measured by echocardiography in the 2 groups.

Table 1. — **Baseline data of patients included in the two groups of patients**

	normal values	CHF group [1] n = 12	AHF group [1] n = 10	p-value [2]
Age (years)		71.5 (66-82)	78 (68-82)	0.447
NYHA class	*0*	2 (1-2)	3 (3-4)	**< 0.001**
Bilirubin (mg/dL)	*0-1.2*	0.9 (0.6-1.2)	1.1 (0.5-2.5)	0.630
AST (U/L)	*1-25*	14 (10-17)	11 (8-14)	0.201
ALT (U/L)	*1-29*	11 (10-16)	12 (10-21)	0.711
Alkaline phospatase (U/L)	*28-207*	96 (66-131)	101 (63-117)	0.806
GGTP (U/L)	*0-38*	22 (15-50)	47 (34-73)	0.141
Albumin (mg/dL)	*3500-4500*	4385 (3977-4667)	3930 (3360-4270)	0.063
Creatinine (mg/dL)	*0.4-1.1*	1.1 (1.0-1.2)	1.2 (1.0-1.5)	0.379
Sodium (mEq/dL)	*134-146*	141 (139-143)	140 (135-142)	0.286
Potassium (mEq/dL)	*3.5-5.0*	4.4 (4,1-4,8)	4.2 (3.9-4.6)	0.325
Liver stiffness (kPa)	*4.5-5.5*	6.5 (5.0-10.8)	14.4 (8.3-18.8)	**0.009**
Pro-BNP (pg/mL)	*< 200*	1511 (671-1918)	3535 (1798-6878)	**0.025**
Ejection fraction (LV) [3]	*> 0.55*	0.33 (0.25-0.40)	0.42 (0.28-0.50)	0.184
Ejection fraction (RV) [4]	*> 0.55*	0.55 (0.50-0.56)	0.45 (0.40-0.54)	0.072
PSBP (mmHg) [5]	*< 30*	50 (29-60)	57 (51-73)	0.074

[1] Data are presented as median (range).
[2] p-values showing statistical significance are presented in bold.
[3] Ejection fraction (left ventricle). n = 19 (11 of CHF group + 8 of AHF group).
[4] Ejection fraction (right ventricle). n = 19 (11 of CHF group + 8 of AHF group).
[5] Pulmonary systolic blood pressure. n = 19 (11 of CHF group + 8 of AHF group).

Table 2. — **Blood chemistries, liver stiffness and Pro-BNP values in patients included in AHF group at admission and after treatment of acute decompensated heart failure**

	normal values	Admission [1]	Discharge [1,2]	p-value [3]
Bilirubin (mg/dL)	*0-1.2*	1.1 (0.5-2.5)	0.8 (0.5-1.4)	0.116
ASAT (U/L)	*1-25*	11 (8-14)	12 (9-15)	0.752
ALAT (U/L)	*1-29*	12 (10-21)	10 (7-23)	0.750
Alkaline phospatase (U/L)	*28-207*	101 (63-117)	98 (81-120)	0.091
GGTP (U/L)	*0-38*	47 (34-73)	36 (15-101)	0.116
Creatinine (mg/dL)	*0.4-1.1*	1.2 (1.0-1.5)	1.5 (1.0-1.9)	0.443
Sodium (mEq/dL)	*134-146*	140 (135-142)	139 (135-140)	0.635
Potassium (mEq/dL)	*3.5-5.0*	4.2 (3.9-4.6)	4.3 (3.8-5.0)	0.476
Liver stiffness (kPa)	*4.5-5.5*	14.4 (8.3-18.8)	8.2 (5.1-11.2)	**0.008**
Pro-BNP (pg/mL)	*< 200*	3535 (1798-6878)	1098 (652-4972)	**0.025**

[1] Data are presented as median (range).
[2] Discharge after clinical compensation of acute decompensated heart failure.
[3] p-values (Wilcoxon) showing statistical significance are presented in bold.

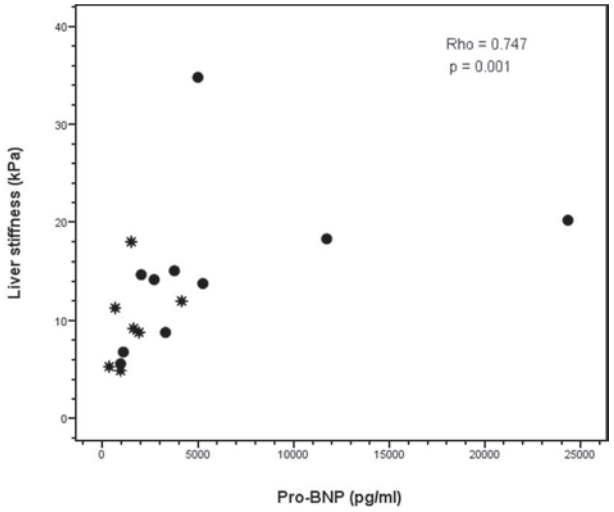

Fig. 1. — Correlation between liver stiffness and pro-BNP.
* Chronic compensated heart failure.
• Acute decompensated heart failure.

Liver stiffness and markers of heart failure

At inclusion in the study, median LS in the whole population (CHF and AHF groups) was 9.0 (5.5-14.8) kPa and median pro-BNP was 2031 (1026-4572) pg/ml. Median ejection fraction (left ventricle) was 0.35 (0.28-0.45) and median estimated pulmonary artery systolic pressure was 55 (36-60) mmHg. Correlation between liver stiffness and pro-BNP levels was statistically significant (Rho = 0.747, p = 0.001), as shown in Figure 1.

Evolution after treatment of acute decompensated heart failure (Table 2)

After clinical compensation, LS decreased in all patients of the AHF group, with a median of 14.7 (8.3-18.8) kPa at admission and 8.2 (5.1-11.2) kPa at discharge (p = 0.008). Absolute changes ranged from 0.1 to 14.4 kPa ; the individual values are shown in Figure 2 (only nine patients are included in the analysis, as one of them had no TE performed before being discharged). Pro-BNP values also decreased in all but one patient, from a median of 3535 (1798-6878) pg/ml to 1098 (652-4972) pg/ml (p = 0.025).

Discussion

Although recent studies have shown that LS is increased in patients with decompensated heart failure (23,25-27), data are scarce and little is known about the magnitude of this change. We also lack information about the relationship between these two phenomena. Our study confirms that patients with heart failure have increased LS, and that the increase in LS appears to be related to the severity of heart failure. Nevertheless, despite providing useful information, our study presents major limitations. Number of patients included is small and some values are lacking in a few patients. In addition, we cannot establish a direct relationship between hepatic venous congestion and increased LS values, as no data regarding caval/hepatic veins or central venous pressure was prospectively recorded.

Millonig *et al*. (25) observed in a recent study, that included 10 patients with advanced decompensated heart failure, high LS values, that decreased after successful cardiac recompensation. Elevated LS values before clinical compensation correlated with the presence of caval vein dilation but no significant correlation was seen with serum BNP levels. Coli *et al*. (26) also published a recent study that showed increased LS in patients with acute decompensated heart failure when compared with a control group. In this second study both LS and pro-BNP improved after treatment of heart failure. Finally, Hopper *et al*. (27) observed elevated LS in all the cardiac dysfunction groups, although changes in volume status did not

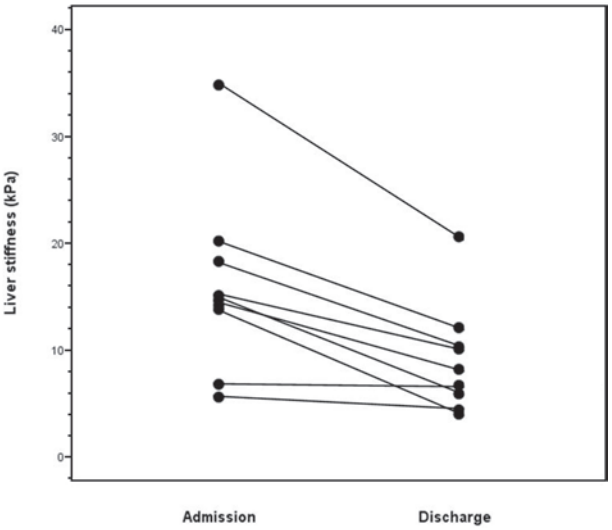

Fig. 2. — Liver stiffness at admission and discharge in patients with acute decompensated heart failure (n = 9).

change the baseline LS in the acute decompensated heart failure group.

In accordance with these previous studies, our data show elevated LS values in patients with heart failure. In fact, they were higher in patients with acute decompensated heart failure requiring admission to hospital than in patients with stable heart failure. No difference in left ventricular ejection fraction, right ventricle ejection fraction and estimated pulmonary systolic arterial pressure was observed between the two groups. However, this may be related to the small number of patients and to the fact that 3 out of 10 patients with decompensated disease had isolated right heart failure (all patients with stable disease had left ventricular heart failure and secondary right heart failure). Contrary to Millonig *et al*. (25), but in accordance with Hopper *et al*. (27), we did observe a significant correlation between LS and pro-BNP values. Differences in the population studied and the low number of subjects in the series may explain this finding. Patients studied by Millonig *et al*. (25) had higher LS values than those collected by Hopper *et al*. (27) and our group, arising the possibility that already established liver fibrosis secondary to chronic hepatic congestion could affect the results.

In our study, LS also decreased after hemodynamic stabilization and clinical improvement in patients with decompensated heart failure. This data are in accordance with those previously reported by Millonig *et al*. (25) and Colli *et al*. (26). However, Hopper *et al*. (27) did not found changes in the baseline LS in patients treated for an acute decompensated heart failure. Again, differences in the population studied, as well as the low number of patients in the series could explain this finding. Nevertheless, data collected support the hypothesis that the increase in LS observed in patients with heart failure could, at least to some extent, be related to hepatic congestion. It remains unclear whether increased LS observed in patients with heart failure without acute decompensation is due to persistence of some degree of hepatic congestion, to development of chronic liver damage secondary to cardiac dysfunction or both.

In conclusion, patients with heart failure have increased LS, that appears to be related with the severity of heart failure. Thus, TE is not valuable for the staging of chronic liver diseases in patients with this associated condition.

References

1. SANDRIN L., FORUQUET B., HASQUENOPH J.M. *et al*. Transient elastography : a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med. Biol*., 2003, **29** : 1705-1713.
2. CASTERA L., FORNS X., ALBERTI A. Non-invasive evaluation of liver fibrosis using transient elastography. *J. Hepatol*., 2008, **48** : 835-847.
3. STEBBING J., FAROUK L., PANOS G. *et al*. A meta-analysis of transient elastography for the detection of hepatic fibrosis. *J. Clin. Gastroenterol*., 2010, **44** : 214-219.
4. CASTÉRA L., VERGNIOL J., FOUCHER J. *et al*. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology*, 2005, **128** : 343-350.
5. ZIOL M., HANDRA-LUCA A., KETTANEH A. *et al*. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology*, 2005, **41** : 48-54.
6. MARCELLIN P., ZIOL M., BEDOSSA P. *et al*. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. *Liver Int*., 2009, **29** : 242-247.
7. NAHON P., KETTANEH A., TENGHER-BARNA I. *et al*. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. *J. Hepatol*., 2008, **49** : 1062-1068.
8. NGYUEN-KHAC E., CHATELAIN D., TRAMIER B. *et al*. Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan : prospective comparison with seven non-invasive laboratory tests. *Aliment. Pharmacol. Ther*., 2008, **15** : 1188-1198.
9. YONEDA M., YONEDA M., MAWATARI H. *et al*. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with non-alcoholic fatty liver disease (NAFLD). *Dig. Liver Dis*., 2008, **40** : 371-378.
10. WONG V.W., VERGNIOL J., WONG G.L. *et al*. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology*, 2010, **51** : 454-462.
11. CORPECHOT C., EL NAGGAR A., POUJOL-ROBERT A. *et al*. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. *Hepatology*, 2006, **43** : 1118-1124.
12. GÓMEZ-DOMÍNGUEZ E., MENDOZA J., GARCÍA-BUEY L. *et al*. Transient elastography to assess hepatic fibrosis in primary biliary cirrhosis. *Aliment. Pharmacol. Ther*., 2008, **27** : 441-447.
13. GANNE-CARRIÉ N., ZIOL M., DE LEDINGHEN V. *et al*. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. *Hepatology*, 2006, **44** : 1511-1517.
14. FOUCHER J., CHANTELOUP E., VERGNIOL J. *et al*. Diagnosis of cirrhosis by transient elastography (FibroScan) : a prospective study. *Gut*, 2006, **55** : 403-408.
15. FRAQUELLI M., RIGAMONTI C., CASAZZA G. *et al*. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. *Gut*, 2007, **56** : 968-973.
16. FRIEDRICH-RUST M., ONG M.F., MARTENS S. *et al*. Performance of transient elastography for the staging of liver fibrosis : a meta-analysis. *Gastroenterology*, 2008, **134** : 960-974.
17. COCO B., OLIVERI F., MAINA A.M. *et al*. Transient elastography : a new surrogate marker of liver fibrosis influenced by major changes of transaminases. *J. Viral. Hepat*., 2007, **14** : 360-369.
18. ARENA U., VIZZUTTI F., CORTI G. *et al*. Acute viral hepatitis increases liver stiffness values measured by transient elastography. *Hepatology*, 2008, **47** : 380-384.
19. SAGIR A., ERHARDT A., SCHMITT M., HÄUSSINGER D. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. *Hepatology*, 2008, **47** : 592-595.
20. MILLONIG G., REIMANN F.M., FRIEDRICH S. *et al*. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. *Hepatology*, 2008, **48**, 1718-1723.

21. LANZI A., GIANSTEFANI A., MIRARCHI M.G., PINI P., CONTI F., BOLONDI L. Liver AL amyloidosis as a possible cause of high liver stiffness values. *Eur. J. Gastroenterol. Hepatol.*, 2010, **22** : 895-897.
22. JANSSENS E., SPAHR L., RUBBIA-BRANDT L., GIOSTRA E., BIHL F. Hepatic amyloidosis increases liver stiffness measured by transient elastography. *Acta Gastroenterol. Belg.*, 2010, **73** : 52-54.
23. LEBRAY P., VARNOUS S., CHARLOTTE F., VARAUT A., POYNARD T., RATZIU V. Liver stiffness is an unreliable marker of liver fibrosis in patients with cardiac insufficiency. *Hepatology*, 2008, **48** : 2089.
24. FRULIO N., LAUMONIER H., BALABAUD C., TRILLAUD H., BIOULAC-SAGE P. Hepatic congestion plays a role in liver stiffness. *Hepatology*, 2009, **50** : 1674-1675.
25. MILLONIG G., FRIEDRICH S., ADOLF S. *et al*. Liver stiffness is directly influenced by central venous pressure. *J. Hepatol.*, 2010, **52** : 206-210.
26. COLLI A., POZZONI P., BERZUINI A. *et al*. Decompensated chronic heart failure : increased liver stiffness measured by means of transient elastography. *Radiology*, 2010, **257** : 872-878.
27. HOPPER I., KEMP W., PORAPAKKHAM P. *et al*. Impact of heart failure and changes to volume status on liver stiffness : non-invasive assessment using transient elastography. *Eur. J. Heart Failure*, 2012 (Epub ahead of print).
28. KOCH A., HORN A., DÜCKERS H. *et al*. Increased liver stiffness denotes hepatic dysfunction and mortality risk in critically ill non-cirrhotic patients at a medical ICU. *Crit. Care*, 2011, **15** : R266.
29. LINDVIG K., MÖSSNER B., PEDERSEN C. *et al*. Liver stiffness and 30-day mortality in a cohort of patients admitted to hospital. *Eur. J. Clin. Invest.*, 2012, **42** : 146-152.
30. YOSHIMURA M., YASUE H., OKUMURA K. *et al*. Different secretion patterns of atrial natriuretic peptide and brain natruiretic peptide in patients with congestive heart failure. *Circulation* 1993, **87** : 464-469.
31. YASUE H., YOSHIMURA M., SUMIDA H. *et al*. Localization and mechanism of secretion of B-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1994, **90** : 195-203.
32. WANG T.J., LARSON M.G., LEVY D. *et al*. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N. Engl. J. Med.*, 2004, **350** : 655-663.
33. JESSUP M., ABRAHAM W.T., CASEY D.E. *et al*. ACCF/AHA guidelines for the diagnosis and management of heart failure in adults : a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*, 2009, **119** : 1977-2016.
34. DICKSTEIN K., COHEN-SOLAL A., FILIPPATOS G. *et al*. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008 : the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC and endorsed by the European Society of Intensive Care Medicine. *Eur. Heart J.*, 2008, **29** : 2388-2442.
35. ROULOT D., CZERNICHOW S., LE CLÉSIAU H., COSTES J.L., VERGNAUD A.C., BEAUGRAND M. Liver stiffness values in apparently healthy subjects : influence of gender and metabolic syndrome. *J. Hepatol.*, 2008, **48** : 606-613.
36. SIRLI R., SPOREA I., TUDORA A., DELEANU A., POPESCU A. Transient elastographic evaluation of subjects without known hepatic pathology : does age change the liver stiffness ? *J. Gastrointestin. Liver Dis.*, 2009, **18** : 57-60.
37. COLOMBO S., BELLOLI L., ZACCANELLI M. *et al*. Normal liver stiffness and its determinants in healthy blood donors. *Dig. Liver Dis.*, 2011, **43** : 231-236.
38. FUNG J., LAI C.L., CHAN S.C. *et al*. Correlation of liver stiffness and histological features in healthy persons and in patients with occult hepatitis B, chronic active heptitis B or hepatitis B cirrhosis. *Am. J. Gastroenterol.*, 2010, **105** : 1116-1122.