Amyloid
The Journal of Protein Folding Disorders

ISSN: 1350-6129 (Print) 1744-2818 (Online) Journal homepage: https://www.tandfonline.com/loi/iamy20

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To cite this article: Véronique Loustaud-Ratti, Anne Cypierre, Annick Rousseau, Fatima Yagoubi, Julie Abraham, Anne-Laure Fauchais, Paul Carrier, Annie Lefebvre, Dominique Bordessoule, Elisabeth Vidal, Denis Sautereau & Arnaud Jaccard (2011) Non-invasive detection of hepatic amyloidosis: FibroScan, a new tool, Amyloid, 18:1, 19-24, DOI: 10.3109/13506129.2010.543443

To link to this article: https://doi.org/10.3109/13506129.2010.543443

Published online: 10 Jan 2011.

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Amyloid, March 2011; 18(1): 19–24

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Non-invasive detection of hepatic amyloidosis: FibroScan, a new tool

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Keywords: *FibroScan, transient elastometry, hepatic amyloidosis, AL amyloidosis*

Abbreviations: *AL = AL amyloidosis; CI = Cardiac involvement; HCV = Hepatitis C virus; LI = liver involvement; LS = liver stiffness*

Abstract

Introduction. FibroScan, a non-invasive tool for measuring liver stiffness (LS), is not specific to liver fibrosis. Other extra-hepatic conditions may modify the LS value.

Objectives. Our aim was to examine whether amyloid deposition in the liver may modify LS.

Methods. LS was measured prospectively in 41 patients with systemic AL amyloidosis (AL) in the French AL Reference Center, comprising: 5 patients with liver involvement (LI) and no cardiac involvement (CI), 11 with CI and no LI, 12 with both LI and CI and 13 with neither (2005 consensus criteria); 26 negative controls, 50 patients infected with Hepatitis C virus (HCV)-infected and 18 AL-free patients with right-sided heart disease ('cardiac controls') were also examined.

Results. Median LS was significantly higher in patients with AL with liver involvement [27.4 (10.3–75) kPa] than in negative controls [4.8 (2.8–11.9) kPa] ($p < 0.0001$), and patients infected with HCV [(6.8 (2.9–69.1) kPa] ($p = 0.001$), and tended to be higher than in the 'cardiac controls' [11 (4.1–75) kPa] ($p = 0.08$). A cut-off value of 17.3 kPa, prioritising specificity, is proposed for routine diagnosis of significant AL liver infiltration.

Conclusion. LS > 17.3 kPa is suggestive of AL hepatic disease in patients with non-fibrotic liver changes, and may have diagnostic value in patients with known AL.

Introduction

Systemic AL amyloidosis (AL) liver involvement is mostly asymptomatic and concerns 70% of cases in autopsy series [1]. Patients with clinical manifestations of liver involvement generally have a poor prognosis, which probably reflects relatively severe disease [2], spontaneous median survival being only 9 months [3]. Liver biopsy with interstitial amyloid deposits is the only definitive diagnostic modality for AL liver involvement [4], however, its safety is controversial [3,5]. As histological diagnosis of amyloid deposition is mandatory, the alternative method of detection is a biopsy of non-hepatic tissue with low risk of bleeding, liver involvement being considered in a patient presenting hepatomegaly or a serum alkaline phosphatase above 1.5 times the upper limit of the institutional normal value [2].

FibroScan is a rapid, non-invasive and reproducible method for measuring liver stiffness (LS) and exploring the degree of liver fibrosis in chronic hepatitis C [6], hepatitis B [7] and cholestatic diseases [8]. Cut-off values have been defined which accurately predict liver cirrhosis independently of the underlying disease, but are highly variable for predicting significant fibrosis [9]. However, LS is not specific for liver fibrosis and may be increased, for

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ISSN 1350-6129 print/ISSN 1744-2818 online © 2011 Informa UK, Ltd.
DOI: 10.3109/13506129.2010.543443

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instance, during alanine aminotransferase flares [10,11], extra-hepatic cholestasis [12] and right-sided heart diseases [13]. As LS is indirectly measured by the propagation velocity of an ultrasound wave within the liver, we hypothesised that the sinusoidal or vascular amyloid liver deposition could enhance LS. A single case report recently comforted this hypothesis [14]. The aims of our study were to evaluate the diagnostic value of FibroScan for AL liver involvement and possibly determine a cut-off value of LS predictive of this diagnosis.

Patients and methods

Forty-one consecutive patients with AL examined at the French National Reference Center for AL amyloidosis between January 2008 and January 2009 were prospectively included. AL was always confirmed histologically [15] on at least one site: kidney ($n=10$), digestive track ($n=9$), accessory salivary gland ($n=9$), subcutaneous abdominal fat ($n=3$), liver ($n=3$), bone marrow ($n=3$) and other varied sites ($n=6$). Eight patients had two or three positive sites. Each biopsy specimen stained positively with Congo red and demonstrated apple-green birefringence under polarised light with immunohistochemical staining of tissues with appropriate light chains antisera [15]. AL liver involvement, defined according to the criteria proposed by the Consensus Opinion from the 10th International Symposium on Amyloid and Amyloidosis [4], was diagnosed in 17 patients with hepatomegaly [total liver span greater than 15 cm on ultrasound study determined on the midhepatic line [16] ($n=12$) or serum alkaline phosphatase 1.5 times the upper limit of our institutional normal value ($n=11$) and amyloid deposits found at another site ($n=12$). Liver amyloidosis was proven with liver biopsy in three patients. As hepatomegaly could also be due to congestive heart disease without amyloid infiltration of the liver, we thoroughly defined AL cardiac involvement. This was implicated in 23 patients with AL who had echocardiographic features of amyloidosis including mean left ventricular wall thickness (septum and posterior wall) greater than 12 mm in the absence of other potential causes of left ventricular hypertrophy. The presence of low voltage on 12-lead electrocardiography was observed in 10 patients; 14 had a diastolic dysfunction and 11 a restrictive cardiopathy. All patients had a compensated cardiac disease. The median N terminal Pro brain natriuretic peptide (NT-proBNP) value of the AL cardiac patients was 604 pg/ml (72–125 283) and their median ejection fraction 67% (30–80). Among the 17 patients with liver involvement, only five had no cardiac involvement (AL liver disease without cardiac involvement). Among the 23 patients with cardiac involvement, 11 had no liver involvement (AL cardiac disease without liver involvement). Twelve patients had both liver and cardiac involvement. Thirteen had none of them.

In all patients, immunofixation electrophoresis of serum and urine demonstrated the presence of a monoclonal light chain (kappa type $n=19$, lambda type $n=22$), and the quantification of free light chains showed an abnormal kappa/lambda ratio.

LS was measured in all patients with AL as described recently in detail by Sandrin et al. [17]. The tip of the probe transducer was placed on the skin between the rib bones and the level of the right lobe of the liver. The measurement depth was between 25 and 65 mm below the skin surface. According to the manufacturer's recommendations, the results were considered as interpretable when 10 measurements were carried out with a success rate of at least 70% and an interquartile range below 30%. The results were expressed in kilopascals (kPa). The median value was chosen as representative.

Simultaneously, LS was measured in 26 negative controls (16 healthy controls plus 10 subjects with multiple myeloma), 50 consecutive Hepatitis C virus HCV-patients considered as 'fibrosis' controls and 18 patients with chronic right-sided heart diseases with clinical signs of passive hepatic congestion and no amyloidosis presenting consecutively in our cardiac unit (cardiac controls).

Ethical considerations

The protocol was approved by the Institutional Review Board and the ethics committee of the CHU of Limoges. All patients gave their informed consent.

Statistical analysis

Statistical analyses were performed using Statview software Version 5 (Abacus Concepts' statistical software). The Mann Whitney U test weighted according to the number of analyses done (Bonferroni correction for multiple comparisons) was used to compare the interpretable LS median values between the different groups. A correlation analysis (by the Spearman-rank correlation method) was performed in the AL liver group to evaluate the relationship between LS values and liver function tests (alkaline phosphatase and bilirubin). Associations between dichotomised or nominal variables were examined using either Pearson χ^2 or Fisher exact test, as appropriate, at 5% significance. The admitted criteria of AL liver involvement (Consensus Opinion on Amyloid and Amyloidosis 2005) were compared to the LS value using the receiver operating characteristic (ROC) curve. [MedCalc

statistical software Version 11 (Medcalc Software, Mariakerke, Belgium)]. ROC curves were constructed to assess the sensitivity and specificity of LS measurement.

Results

The median LS was not statistically different between the healthy and the myeloma controls and both were pooled together as the negative control group. Median stiffness values were 27.4 kPa in the AL liver group (with or without cardiac involvement), 10.4 kPa in the AL cardiac group (with or without liver involvement), 4.8 kPa in the negative controls, 6.8 kPa in the patients with HCV, 11 kPa in the cardiac controls and 6.1 kPa in patients with AL with neither liver nor cardiac involvement (Table I). LS measurements were not interpretable in 35%, 30%, 18%, 20.8%, 25% and 15% of the same groups, respectively.

The LS in the negative controls was significantly lower than in the HCV group ($p = 0.001$), but was not different from the AL group with neither liver nor cardiac involvement. The median LS in the AL liver patients was significantly higher than in the negative controls ($p < 0.0001$) and the HCV group ($p = 0.0008$), and tended to be higher than in the cardiac controls [$p = 0.08$, ($p = 0.01$ before Bonferroni correction)] (Figure 1). Finally, the median LS in patients with AL liver disease with no cardiac involvement or AL cardiac disease with no liver involvement were significantly higher than in the negative controls ($p = 0.005$ and $p = 0.04$, respectively, after Bonferroni correction) (Figure 2). However, the LS of patients with AL cardiac disease and no liver involvement was not different from the LS of the cardiac controls.

Findings of cardiac investigation are presented in Table II. Overall cardiac status was comparable between patients with both AL cardiac and hepatic disease and patients with cardiac disease and no liver involvement. Cardiac parameters included median NT-proBNP value, the presence of a left ventricular wall thickness >12 mm, of low voltage on 12-lead electrocardiography, of an inferior vena cava dilatation >20 mm with no respiration-associated fluctuation in diameter and a right atrium >15 cm^2. This suggested that patients with both liver and cardiac involvement did not suffer from a more advanced cardiac disease than patients without liver involvement.

Finally and interestingly, the serum alkaline phosphatase but not the bilirubin level (expressed as times the upper limit of our institutional normal value) was correlated with the LS value in the AL group with liver involvement ($\rho = 0.67$, $p = 0.0004$).

In differentiating the AL liver group, defined according to the consensus criteria 2005, from a large control group with no amyloidosis including the negative controls, the HCV, and the cardiac controls, an optimal cut-off value of 10.1 kPa was obtained for a sensitivity of 90.9% (95% CI 58.7–99.8), a specificity of 70.9% (95%CI 59.6–80.6) and a ROC AUC of 0.82 ($p = 0.0004$) in patients with evaluable LS (Figure 3). However, in order to diagnose in practice highly significant AL infiltration of the liver, i.e. prioritising the specificity of the FibroScan, a higher cut-off value of 17.3 kPa (Specificity 92.4%, Sensitivity 63.6%) was assessed.

Discussion

Amyloidosis is a complex multisystemic disease with numerous presentations. AL liver involvement is poorly symptomatic (no symptoms or weight loss, fatigue and abdominal pain). A majority of patients have hepatomegaly and the most frequently abnormal test of hepatic function is an elevated serum alkaline phosphatase level (86% of patients) [3]. The final diagnosis of this condition is histological and preferentially made by non-hepatic-tissue biopsies. Indeed most practitioners consider that transparietal liver biopsy is an unacceptably high risk procedure

Table I. Median liver stiffness (LS) values in the different populations.

	Number of patients	Number of patients with evaluable LS	Median LS in kPa (range)
Negative control Group (NCG)	26	21	4.8 (2.8–11.9)
Healthy controls	16	13	4.6 (2.8–6.4)
Myeloma	10	8	5.4 (3.3–11.9)
HCV group	50	46	6.8 (2.9–69.1)
Right-sided heart disease and no amyloidosis (Cardiac control Group)	18	12	11 (4.1–75)
AL patients	41	32	10.4 (4.2–75)
AL Liver disease (with or without cardiac involvement)	17	11	27.4 (10.3–75)
AL liver disease without cardiac involvement	5	5	27.4 (16.3–75)
AL cardiac disease (with or without liver involvement)	23	16	10.4 (4–75)
AL cardiac disease without liver involvement	11	10	9.65 (4–38)
AL with liver and cardiac involvement	12	6	16.3 (10.3–75)
AL without liver and cardiac involvement	13	11	6.1 (4.2–17.5)

with an increased risk of bleeding and/or hepatic rupture, and is not encouraged [3,5]. In the Mayo Clinic cohort, four patients developed bleeding, two of whom required blood transfusions. Several factors may contribute to this increased risk of bleeding, including factor X deficiency, due to binding to amyloid fibrils in the spleen, decreased synthesis of coagulation proteins in patients with advanced liver disease, acquired loss of functional Von Willebrand factor and amyloid infiltration of blood vessel walls [18,19]. As AL liver disease is often associated with multisystemic manifestations of amyloidosis (including nephrotic syndrome, heart failure, peripheral neuropathy, carpal tunnel syndrome ...), the majority of patients (82% in the Mayo Clinic cohort) have amyloid detected in biopsies of non-hepatic tissue [3].

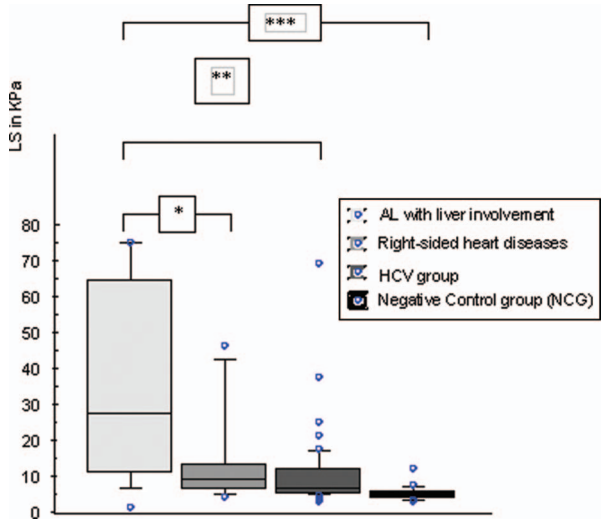


Figure 1. Box plots showing the distribution of LS values (in kPa) in AL with liver involvement (with or without cardiac involvement) ($n = 17$), AL-free patients with right-sided heart disease ('cardiac controls') ($n = 18$), HCV-infected patients ($n = 50$) and negative controls ($n = 26$). The middle lines represent the median value, the upper and lower extremities of the boxes represent the 25th and 75th percentiles, the whiskers represent the 10th and 90th percentiles, and the dots are outliers. *$p = 0.08$ ($p = 0.01$ before Bonferroni correction); **$p = 0.0008$; ***$p < 0.0001$.

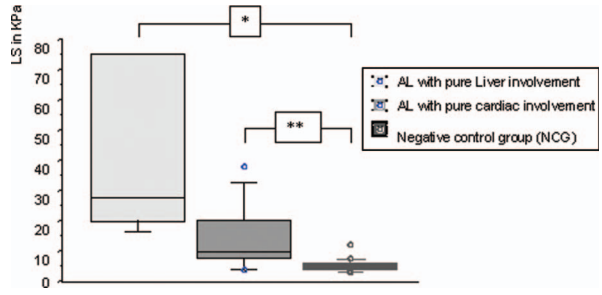


Figure 2. Box plots showing the distribution of liver stiffness (LS) values (in kPa) in AL liver disease without cardiac involvement ('pure liver involvement') ($n = 5$), AL with cardiac disease and without liver involvement ('pure cardiac involvement') ($n = 11$) and negative controls ($n = 26$). *$p = 0.005$; **$p = 0.04$.

In this study, AL liver involvement increased LS in patients without evidence of fibrotic liver disease. LS was elevated to a degree that suggested advanced liver cirrhosis (median value 27.4 kPa) and was much higher than in the negative and the HCV controls, the latter group showing different degrees of fibrosis. Indeed, the three patients who initially revealed their systemic AL with a prevailing liver involvement had a LS of 75 kPa, a rare event even in severe fibrosis. Amyloid deposits probably represent an important obstacle to the propagation velocity of the ultrasound and elastic waves of the FibroScan within the liver. This obstacle seems to be, on average, at least as remarkable as fibrosis and more severe than other previously described causes of increased LS, such as acute hepatitis (mean 12.7 kPa) [10,11] or extrahepatic cholestasis (mean 15.2 kPa) [12]. The ROC curve of 0.82 is fairly consistent with robust diagnostic performance and indicates that FibroScan^{R} has a satisfactory discriminative ability to identify liver involvement in patients with AL.

Moreover, LS values in AL liver disease strongly correlated with the serum alkaline phosphatase level which is the main biological criteria for the diagnosis of liver involvement in AL systemic disease.

Congestive liver disease could be a confusing factor contributing to increased LS, as 12 out of 17 of our AL liver patients also had, even if compensated, cardiac involvement. However, in this study, if the median LS in the cardiac controls was

Table II. Findings of cardiac investigation in the different AL patient groups.

	Left ventricular wall thickness > 12 mm	Low voltage on 12-lead electrocardiography	NT-pBNP value, Median (range)	Inferior vena cava > 20 mm	Right atrium > 15 cm^2	Ejection fraction, Median (range)
AL liver disease with cardiac involvement $n = 12$	$n = 11$	$n = 5$	569 (72–10,000)	$n = 8$	$n = 6$	62% (30–80)
AL liver disease without cardiac involvement $n = 5$	$n = 0$	$n = 0$	97 (36–431)	$n = 0$	$n = 0$	80% (74–80)
AL cardiac disease without liver involvement $n = 11$	$n = 10$	$n = 6$	569 (275–125 283)	$n = 4$	$n = 4$	60% (39–70)
AL without both liver and cardiac involvement $n = 13$	$n = 0$	$n = 1$	145 (20–1206)	$n = 0$	$n = 0$	76% (62–80)

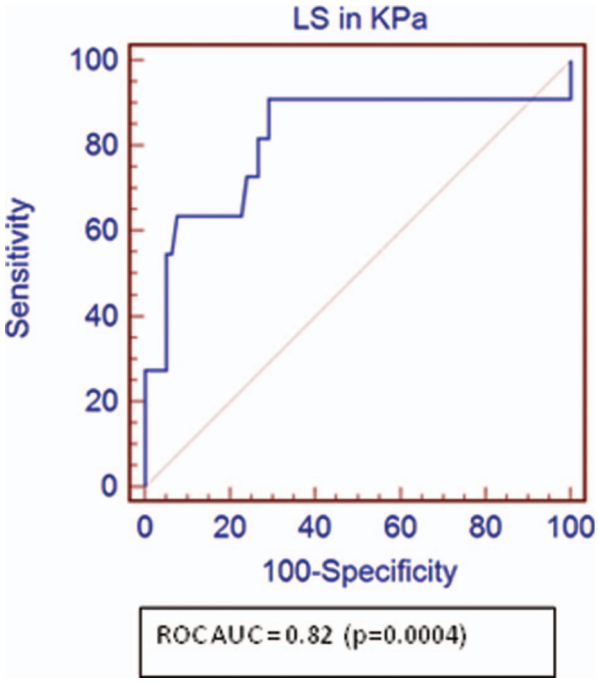


Figure 3. ROC curve comparing the admitted criteria of AL liver involvement (Consensus Opinion on Amyloid and Amyloidosis 2005) and the LS value. Patients with AL amyloidosis were dichotomized as with liver amyloidosis (=1) or without liver amyloidosis (=0) according to the consensus criteria. The AL liver involvement group was differentiated from a large control group with no amyloidosis including the negative controls, HCV-infected patients, and AL-free patients with right-sided heart disease ('cardiac controls').

significantly higher than in the negative controls, it tended to be lower than in the group with AL liver involvement. The mean LS values recently obtained by Millonig et al. in 10 patients with right-sided heart diseases were much higher than ours but were measured during the acute phase of the cardiac disease with median NT-pro-BNP serum levels of 5075 ng/l [13]. Indeed, the right-sided cardiac control group of our study included mostly compensated diseases which could have been a selection bias. However, these controls were better suited to our AL cardiac patients who also presented compensated cardiac diseases.

Finally, strictly respecting the manufacturer's criteria established for liver fibrosis, the high ratio of non-interpretable FibroScan (35%) in comparison with the control groups suggested a technical difficulty in these patients. The median result of LS in the six patients with liver amyloidosis excluded for technical difficulties of the FibroScan was however not far (22.8 kPa, 8.4–75) from that of the interpretable patients. We have no clear explanation for the high incidence of the failure rate of LS measurement in the AL population with liver involvement; indeed the major classical cause of failure due to an increased BMI was excluded here as the mean BMI was of 23 (20–26). However, an interquartile range above 30% was mostly observed in these patients, which shows an important variability among the valid measures. One hypothesis might be the association with AL cardiac disease: in this group with both localisations, the rate of failure was 50%.

In practice, despite the limitations of our study design, mainly due to small sample and technical difficulties exposed above, we suggest that FibroScan may help establish the diagnosis of AL liver involvement, even if it has of course to be confirmed by larger studies. It may have major practical implications in two clinical circumstances. First, in the presence of a known case of AL amyloidosis, the diagnosis of AL liver disease is of prognostic value and reflects a disseminated disease with a median spontaneous survival of 9 months. Second, in routine Hepatology practice, when the presence of viral, autoimmune, genetic, metabolic, fatty liver diseases can be prima facie excluded (and subsequently presumably the reason for development of fibrosis), and in cases presenting with hepatomegaly and raised alkaline phosphatase level with no other suspected liver disease, the finding of significantly increased LS should evoke the possibility of infiltrative process; the presence of a monoclonal gammapathy or detection of free light chains in such cases should suggest the possibility of AL amyloidosis. In order to optimise the decision, notably to avoid a trans-parietal liver biopsy in case of major amyloid infiltration of the liver, we suggested a cut-off value of 17.3 kPa, enhancing the specificity of the Fibroscan. This cut-off value should thus lead to a preference for either the biopsy of extra-hepatic sites or a transjugular biopsy.

We are now carrying out follow-up studies to determine how LS changes following effective anti-plasma cell treatment and therefore if LS value is correlated to the clinical hepatic response [20] These data will indicate whether the LS is evolving in parallel to the intensity of amyloid infiltration and is a useful follow-up tool.

Conclusion

FibroScan should be part of the non-invasive explorations in patients with amyloidosis. A high elastometry value $\geq$17.3 kPa in a patient with an enlarged liver, an asymptomatic cholestasis or an isolated monoclonal gammapathy, and with no evidence of other liver disease, should suggest the diagnosis of liver amyloidosis with a good specificity. FS may also, on a prognostic point of view, warn the physician of the diagnosis of liver involvement in a known case of amyloidosis.

More generally, in chronic liver disease with homogeneous enlarged liver and a LS $\geq$ 17.3 kPa,

physicians should add AL liver disease to their diagnostic shortlist.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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