Real-time elastography (Supersonic), experience of a medical center in Bogotá

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Abstract

Introduction: Real-time two-dimensional shear wave elastography (2D-SWE) (Supersonic Imagine SA), is a non-invasive test used to determine liver elasticity and calculate the degree of liver fibrosis. In Colombia, this test was introduced in 2016 and, to date, no study has tested its behavior in all liver patients, only in healthy and cirrhotic patients. **Objective:** To analyze the experience of real-time elastography implementation in subjects treated at the Centro de Enfermedades Hepáticas y Digestivas in Bogotá, Colombia. **Materials and methods:** This is a retrospective descriptive study of a cohort of subjects treated between March 2016 and July 2017. A complete medical report and a real-time elastography (Supersonic) test were performed. **Results:** 654 subjects were included, with a median age of 55 years (interquartile range [IQR]: 45-64). The median fibrosis values expressed in kilopascals (kPs) were 8.3, with an average of 5 measurements. There was a significant difference in the degree of fibrosis between the age groups and in relation to the final diagnosis, where there was a greater fibrosis in the cholestatic disease group (autoimmune, primary biliary cholangitis [PBC], and overlap). The overall failure rate was less than 1 %. **Conclusions:** This is the first description of this test behavior in the country. Hepatic stiffness values observed in the different stages demonstrate the usefulness of the test to establish the degree of liver fibrosis in patients with multiple diseases.

Keywords

2D-SWE, Real-time elastography, Supersonic, Liver fibrosis, Non-invasive assessment of liver fibrosis.

INTRODUCTION

After having properly diagnosed a patient with chronic liver disease, the specialist is faced with the challenge of establishing the stage of liver fibrosis in order to determine both prognosis and adequate treatment (1, 2). In daily clinical practice, the stage of liver fibrosis is determined by means of liver biopsy, which is the gold standard, using the French METAVIR scoring system, a 5-point scale (from 0 to 4) in which the following stages are used: F0: absent fibrosis; F1: periportal fibrosis; F2: initial portal-portal septa but intact architecture; F3: architectural distortion, but no obvious cirrhosis; and F4: cirrhosis (3). Liver biopsy involves an invasive procedure, and there are inter- and intraobserver errors (4-6). This has encouraged research to focus in recent years on developing noninvasive tests that also allow establishing the stage of liver fibrosis; among these, non-invasive tests based on liver ultrasound that use shear

waves have been developed (7-11). One of such tests was first introduced in Colombia at the beginning of 2016: two-dimensional shear wave elastography (2D-SWE; Supersonic Imagine, Aixplorer®, Aix-en-Provence, France) (12-18), known as Supersonic in our country. However, so far there are no publications describing the experience of using 2D-SWE in all types of patients in Colombia; in fact, only 2 pilot studies that were conducted in Colombian healthy patients and in patients with cirrhosis and sought to validate the respective cut-off points in both population groups have been published (19-20). Bearing this in mind, the aim of this work is to show the experience of our health center in using this test in patients with different diseases.

METHODOLOGY

Retrospective and descriptive study. The study population consisted of the patients who visited the hepatology outpatient service of the Centro de Enfermedades Hepáticas y Digestivas (Center for Liver and Digestive Diseases, CEHYD for its Spanish acronym) in the city of Bogotá. The medical records of all the patients who were assessed between March 2016 and July 2017 and underwent 2D-SWE (inclusion criterion) were reviewed. The test was performed following the protocol recommended by the manufacturer and used in pivotal trials (13-16), which has been previously described in our publications (19-20): Aixplorer ultrasound system (Supersonic Imagine S.A. Aix-en-Provence, France) with a convex broadband probe (SC6-1). The software of the equipment color-codes elasticity data, this creates a two-dimensional tissue stiffness map shown in a box; there, a region of interest (ROI), where liver stiffness is measured, is located; an average 1.5 cm ROI and a 3.5 x 2 cm box are used. First, fasting was required to perform the test in all cases; then, the patient was placed in a supine position with their right arm in maximum abduction, and measurements were made on the right lobe of the liver, through intercostal spaces. Only elastographies with 5 or more adequate measurements were considered. The cut-off points described by Ferraioli et al. in their study conducted in patients with hepatitis C were used in our series, as they are the most frequently used (14).

In accordance with Resolution 8430 of 1993, issued by the Colombian Ministry of Social Protection, this is a risk-free research. In addition, the study was approved by the institution where the patients were treated.

Statistical analysis

Collected data were summarized using descriptive statistics: qualitative variables were expressed using absolute frequencies and quantitative variables, by means of measures of central tendency and measures of dispersion, depending on their normal distribution (Shapiro-Wilk test), and the Mann-Whitney U test and Kruskal-Wallis test.

RESULTS

A cohort of 654 individuals aged 15-90 years were included during the study period (March 2016 to July 2017). Most patients had liver diseases, but there was also a subgroup of healthy individuals. The median age in the entire cohort was 55 years, with an interquartile range (IQR) of 45-64 in women and of 40-63 in men. 62 % of the patients were women. The clinical and laboratory characteristics of the cohort are detailed by sex in **Table 1**.

In relation to the test performance, the median value of liver stiffness, expressed in kilopascals (kPa) and directly related to the stage of liver fibrosis, was 8.3, with an average of 5 measurements; there were no differences by sex. A significant difference in liver stiffness between age groups was found, where a clear trend was observed: the higher the age, the higher the values of liver stiffness.

Regarding final diagnosis, greater stiffness (fibrosis) values were observed in the group of patients with cholestatic liver diseases (autoimmune, primary biliary cholangitis [PBC] and autoimmune disease-PBC overlap syndrome), with a median value of 9.7 kPa, followed by those with liver diseases caused by viral infections (Hepatitis B and C) and those with fatty liver. Minimal liver stiffness, with a median of 4.4 kPa, was reported in 25 patients, suggesting zero fibrosis and, therefore, they were considered healthy individuals. Complete data are shown in **Table 2**. Finally, the performance of the test is depicted in **Figure 1**, where liver stiffness values are expressed as liver fibrosis stages according to the METAVIR scale (using the cut-off points of the pivotal trial by Ferraioli) (14), and a significant difference is observed in terms of the stage classification and the median values of fibrosis (kPa).

Failed procedures were reported in 4 patients during the study period, all of them due to inadequate imaging for measurement as a result of obesity or narrow intercostal spaces. Inability to perform the apnea was not the cause of failure in none of the procedures.

DISCUSSION

As the gold standard, liver biopsy is an incomplete test (5, 6) that requires an adequate interpretation in the individual context of each patient. This has encouraged the research of non-invasive and massive use methods that allow the assessment of liver fibrosis and that can be used routinely in the evaluation of patients with liver disease. As a result of this, there are several guidelines about non-invasive

Table 1. Clinical and laboratory characteristics

Characteristic	Women		Men	
	n	Median (IQR)*	n	Median (IQR)*
Age in years	406	56 (45-64)	248	52 (40-63)
BMI	354	25 (22-28) ±	197	26 (23-28) ±
Leukocytes (cel/mL)	362	5440 (4580-6600)	199	5710 (4900-6800)
Hgb (g/dL)	362	14 (13-15) ±	198	16 (15-17) ±
HCT (%)	362	43 (40-45) ±	199	48 (45-50) ±
Platelets (cel/mm³)	362	250 000 (196 000-303 000) ±	199	210 000 (169 000-254 000) ±
Blood glucose (mg/dL)	355	90 (83-97) ±	195	94 (87-102) ±
AST (IU/dL)	364	40 (24-78)	200	36 (25-59)
ALT (IU/dL)	364	46 (25-92)	200	51 (29-103)
GGT (IU/dL)	351	60 (25-184)	192	62 (34-146)
Alkaline phosphatase (IU/dL)	362	106 (77-184) ±	194	90 (72-121) ±
Total Bilirubin (mg/dL)	355	0.6 (0.4-1.0) ±	189	0.7 (0.6-1.2) ±
Total proteins (g/dL)	340	7.3 (7-7.8)	185	7.3 (7-7.7)
Albumin (g/dL)	348	4.3 (4-4.5) ±	183	4.4 (4.1-4.7) ±

*Normality test (Shapiro-Wilk). ±significant differences between women and men ($p < 0.05$), Mann-Whitney U test. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: gamma-glutamyltransferase; Hgb: Hemoglobin; HCT: Hematocrit; BMI: Body mass index; IQR: Interquartile range (25th and 75th percentile).
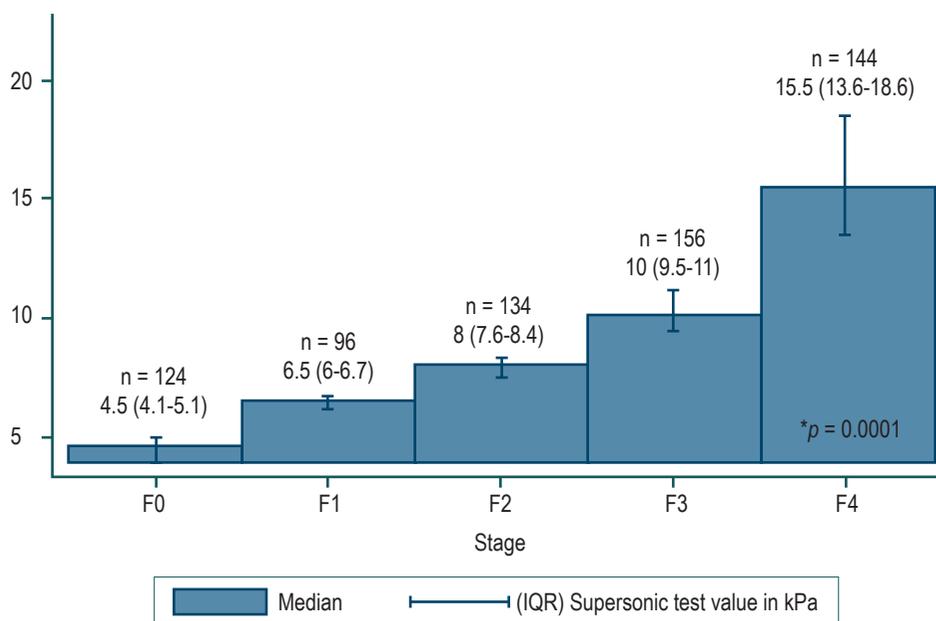

Figure 1. Fibrosis stages obtained using Supersonic test. *Significant differences between the staging groups, Kruskal-Wallis test.

Table 2. Performance of Supersonic test according to sex, age and liver disease

Variable	n (%)	Median (IQR)* values in kPa	Median (IQR)*, number of measurements
Total subjects	654	8.3 (6.4-11.5)	5 (5-6)
Sex			
- Women	406 (62.1)	8.3 (6.3-11.7)	5 (5-6)
- Men	248 (37.9)	8.3 (6.5-11.9)	5 (5-6)
**Age **		**	
- ≤ 20	23 (3.5)	5 (4.4-5)	5 (3-6)
- 21-30	49 (7.5)	5.8 (4.2-8.1)	5 (4-5)
- 31-40	70 (10.7)	7.6 (5.5-8.9)	5 (5-6)
- 41-50	115 (17.6)	7.7 (5.7-10.4)	5 (5-6)
- 51-60	180 (27.5)	8.5 (6.8-11.7)	5 (5-6)
- 61-70	145 (22.2)	9.1 (7.6-12.5)	5 (5-6)
- ≥ 71	72 (11)	10.8 (8.1-14.1)	5 (5-6)
**Final diagnosis of liver disease **		**	**
- Fatty liver	179 (44.8)	8.1 (6.6-10.5)	5 (5-6)
- Cholestatic liver disease	100 (25.0)	9.7 (7.7-13.6)	5 (5-6)
- Viral	82 (20.5)	8.6 (7.4-11.8)	5 (5-7)
- Portal vein thrombosis	4 (1.0)	6.5 (4.4-8.3)	5 (4-5)
- Healthy	35 (8.7)	4.4 (3.8-4.9)	3 (3-5)

*Normality test (Shapiro-Wilk). **$p = 0.0001$, significant differences between groups, Mann-Whitney U test.

methods that even suggest elastography as an alternative method to liver biopsy (21-23).

In Colombia, real-time elastography (2D-SWE), or simply Supersonic, has been available since early 2016. This is an ultrasound-based non-invasive test for measuring liver fibrosis that has been validated in different studies; in fact, although several studies have reported it has a better performance than transient elastography, it is possible to say that at least it has a similar efficacy and offers additional advantages such as the visualization of the liver and the possibility of being performed in patients with ascites (24-34). This is the first paper describing the experience of using this test in Colombian patients, and it was presented as a pos-

ter in the 2017 Congress of ACADI (Spanish acronym for Colombian Associations of the Digestive Tract).

There are several aspects to be highlighted according to our data:

- The older the patient, the greater the fibrosis; there are studies conducted in humans and animal models in which greater fibrosis has been associated with age due to the progressive damage caused by fatty liver; in this regard, almost a third of the patients in our study had fatty liver; another possible reason, and perhaps more important, is that the longer the course of a disease, the greater its progression towards cirrhosis, as its the case of hepatitis C and alcoholic liver disease, diseases in which manifestations occur 20 to 40 years after their onset, ending in cirrhosis (35-38).

- Fibrosis was higher in the group of patients with cholestatic liver diseases (autoimmune, PBC and autoimmune disease-PBC overlap syndrome), followed by those with liver disease associated with viral infections (C and B virus) and those with fatty liver. Similar to our results, in the meta-analysis by Hermann (30), fibrosis was greater in patients with hepatitis C than in those with fatty liver, however little mention of cohorts of patients with cholestatic liver diseases is made in the study by Hermann (30), as well as in other series that were reviewed. This could be explained, on the one hand, by the fact that most studies were conducted during the time hepatitis C was a main topic of research, and, on the other, it seems there were more patients with cholestatic liver diseases in our study (data to be confirmed).

- The proportion of failed procedures in our study was 1 %, and most of them occurred during the first months the equipment was used and were possibly associated with the learning curve. In this regard, Leung (18) reported a failure rate of real-time elastography of 1.1 % vs. a 10.4 % failure rate of transient elastography. Somehow, Ferraioli (14) described a failure rate of 2.5 % in patients with hepatitis B, excluding ascites cases, and similar transient elastography failure rates. Castera (39), in the largest study about transient elastography, found a failure rate of 3.1% in all tests (4% in the first examination, n = 7261), plus unreliable results in an additional 16%; most failures were due to obesity, narrow intercostal spaces and the patients' inability to perform the apnea properly (13, 14, 16). 2D-SWE or Supersonic is also affected by these factors, but to a less extent by obesity, since the additional pressure on the probe reduces the thickness of the fat layer between the probe and the rib cage, and the depth can reach 10-12 cm (27-31). Another factor that can reduce the failure rate is the experience of the operator, as described in some series (40, 41).

- The clear differentiation of our patients into 5 groups according to the stage of fibrosis (adapting them to the METAVIR scoring system), allows determining a prognosis and guiding the treatment accordingly in each group. In our study we used the cut-off points described by Ferraioli et al. in patients with hepatitis C (14), i.e.: F ≥ 2 of 7.1, F ≥ 3 of 8.7, and cirrhosis ≥ 10.4 kPa. Herrmann et al. (30) used similar cut-offs for all patients: F ≥ 2 of 7.1, F ≥ 3 of 9.2, and cirrhosis ≥ 13.4 kPa, which are very similar for patients with fatty liver, but much higher than those in patients with hepatitis B; however, in our study the total number of hepatitis B cases was very low. In addition to the above cut-off points, the cut-off points for cirrhosis were 10.7 kPa and 11.5 kPa in the studies by Cassinotto and Sporea (12, 42), respectively. In recent studies, ≥ 14 kPa has been established as the cut-off point for clinically significant portal hypertension in patients with cirrhosis (43) and a value of 10 kPa can be used to rule out compensated advanced chronic liver disease (cACLD). According to the Baveno VI criteria (44), all these data place a cirrhosis value close to 12-13 kPa, which is the threshold used in daily clinical practice and a value close to the one found in our study in patients with cirrhosis, without differentiating whether it is compensated or decompensated cirrhosis, or its cause (20).

We are aware of the limitations of our case series, such as its retrospective nature and the unavailability of own cut-off points for the different diseases that were considered, but we hope soon to extend the series, compare it with biopsy results, and validate the cut-off points in the patients with fatty liver and cholestatic diseases treated in our health center, as they are important given their prevalence (about 40 % and 10 %, respectively) in our database (unpublished). Nevertheless, this is the first paper describing the experience of using 2D-SWE in our country with a good number of patients and in which the failure rate of the procedure stands out (less than 1 %).

CONCLUSION

This is the first description of the performance of this test nationwide using liver stiffness values reported in pivotal trials. Fibrosis values observed in the different stages prove the usefulness of the test for determining liver fibrosis in patients with different diseases with a very low rate of failure. We expect to conduct further studies in larger sample sizes.

Conflicts of interests

None declared by the authors.

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