Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Cystic fibrosis and noninvasive liver fibrosis assessment methods in children

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BACKGROUND: Noninvasive assessments of liver fibrosis are currently used to evaluate cystic fibrosis (CF)-related liver disease. However, there is scarce data regarding their repeatability and reproducibility, especially in children with CF. The present study aimed to evaluate the repeatability and reproducibility of transient elastography (TE) (FibroScan®) and point shear-wave elastography using virtual touch quantification (pSWE VTQ) in children with CF.
METHODS: TE and pSWE VTQ were performed in 56 children with CF by two different operators. Analysis of repeatability and reproducibility was available in 33 patients for TE and 46 patients for pSWE VTQ. Intra- and interobserver agreement were assessed using the intraclass correlation coefficient (ICC) and their 95% confidence interval (CI), and Bland and Altman graphs.
RESULTS: For TE, ICC was 0.91 (0.83–0.95) for intraobserver agreement and 0.92 (95% CI: 0.86–0.96) for interobserver agreement. For pSWE VTQ, ICC was 0.83 (0.72–0.90) for intraobserver agreement and 0.67 (0.48–0.80) for interobserver agreement.
CONCLUSIONS: Both technics can be proposed in the follow-up of patients, according to their availability in CF centers.

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IMPACT:

- This study shows that TE and pSWE VTQ are reliable methods to evaluate liver fibrosis in children with CF.
- This study shows for the first time that TE and pSWE VTQ are both repeatable and reproducible in children with CF.
- These data indicate that both TE and pSWE VTQ can be proposed for the follow-up of patients with CF, according to their availability in each CF center.

BACKGROUND

Cystic fibrosis (CF) transmembrane conductance regulator (CFTR) is expressed at the level of the apical membrane of cholangiocytes. Defects in the function of this protein lead to defective bile alkalization and dilution, bile duct obstruction, inflammation of the biliary tree, and biliary fibrosis, which may progress towards multilobular cirrhosis. CF-related liver disease (CFLD), the third cause of death in CF after cardiorespiratory diseases and posttransplantation complications, accounts for 2.5% of overall mortality.[1] CFLD appears gradually during the first decade of life, and affects ~40% of subjects at the age of 12 years.[2] Multilobular cirrhosis develops only in a minority of patients, ~10%, during the first decade of life,[3] and exceptionally thereafter.[4] The diagnosis of CFLD usually relies on clinical (hepatomegaly), biological (elevated transaminases), and ultrasonographic abnormalities (heterogeneous and/or nodular parenchyma, signs of portal hypertension).[3] However, CFLD develops slowly and insidiously, and this diagnosis is often difficult to make at an early stage. Clinical, biological, and imaging parameters may remain normal for a long period of time, until obvious signs of cirrhosis become apparent.[3] To date, no tool has shown the required performance to reliably screen children for CFLD.[5] Most CF teams are reluctant to perform liver biopsies in children with CF because this procedure is invasive and may underestimate the degree of fibrosis, which is initially focal. Nonetheless, monitoring of liver involvement is helpful to initiate treatment with ursodeoxycholic acid, predict progression towards cirrhosis, and decide on the optimal time to screen for esophageal varices using endoscopy.

Noninvasive techniques for measuring liver fibrosis such as transient elastography (TE) (FibroScan®) and, more recently, acoustic radiation force impulse imaging (point shear-wave elastography using virtual touch quantification (pSWE VTQ)) have been developed during the past decade. Initially validated in adult patients with chronic hepatitis C, they are now being used for the follow-up of numerous chronic liver diseases[6] including CFLD.[7–13] In contrast to the rapid spread of these techniques, there are very few studies on their reliability, especially in children.

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The aim of the present study was thus to evaluate the intraobserver repeatability and interobserver reproducibility of TE and pSWE VTQ in children with CF.

PATIENTS AND METHODS

Patients

The study was approved by the ethical committee of South West of France (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III, Ref: DC 2012/78) and written informed consent was obtained from the parents and patients when aged 6 years or more.

Between November 2011 and June 2012, consecutive children with CF were asked to participate in the study during their annual follow-up at Bordeaux University Hospital tertiary-care regional reference center for CF. The diagnosis of CF was based on abnormal results of at least two sweat tests and/or on the presence of two mutations in the *CFTR* gene. Patients with a forced expiratory volume in one second <30% were not included in the study.

The annual check-up included clinical examination, ultrasound (US) examination of the abdomen, and blood testing. The following data were collected: sex, age, body mass index, platelet count, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and prothrombin time.

Patients were classified using the phenotyping reportings of CFLD:[3] no signs of liver involvement; signs of liver involvement without cirrhosis: ALT >1.5 upper limit of normal value and/or abnormal GGT, and/or increased echogenicity of liver parenchyma on US, and/or hepatomegaly, and/or portal hypertension (hypersplenism with splenomegaly, esophageal varices); cirrhosis on imaging (heterogeneous and dysmorphic liver parenchyma).

Measurement of liver stiffness

TE was performed using Fibroscan® (Echosens, Paris, France): a probe with an ultrasound transducer (3.5 MHz) and a vibrator generates an elastic shear wave that propagates through the liver tissue.[6] Pediatric probes were used according to the manufacturer's recommendations. The wave propagation velocity is related directly to tissue stiffness; the faster it moves the harder is the tissue. Results are expressed in kilopascal (kPa) and values provided by the Fibroscan® device can vary between 2.5 and 75 kPa. TE explores a cylinder of liver parenchyma 1 cm wide and 4 cm long, between 25 and 65 mm below the skin surface.

Fibroscan® was performed in a fasting patient in the supine position, the right arm under his head to clear the right upper quadrant of the liver. The probe was positioned on the chest wall at the intercostal space beside the right hepatic lobe, on the mid-axillary line. For each series, ten validated measurements were recorded, and the results were considered as representative of liver stiffness when interquartile range (IQR) to median ratio was <30%.[6]

pSWE VTQ was performed using an ultrasound device associated with a 9 MHz probe and pSWE VTQ software (Siemens Acuson S2000® Virtual Touch ultrasound system, Siemens AG, Erlangen, Germany). This procedure was conducted in a fasting patient, lying in the dorsal decubitus position, the right arm placed behind the head to clear the right upper quadrant, during a short apnea at the end of inspiration. The principle is to visualize and quantify the liver stiffness by measuring the velocity of the shear wave following a focused ultrasound pulse source in the right hepatic lobe, through intercostal or subcostal approach. Measurements can be performed at the same time as the morphological study of the liver. Propagation velocity is estimated in a region of interest, which can be selected by the operator and corresponds to a region of $5 \times 6\ mm^2$ to a maximum depth of 5 cm from the skin surface. In case of movement during the acquisition, XXX value was displayed on screen, indicating a wrong measurement; 12 valuable measures were performed, and results, excluding the lower and higher values, were expressed in meters per second (m/s), correspond to the median of ten remaining measurements, and can vary between 0.5 and 4.4 m/s.[14]

TE and pSWE VTQ were performed on the same day. For each procedure (TE and pSWE VTQ), three sets of ten measurements were made by two different operators. For TE, the same operator, a trained junior (A.F.), performed measurements in series 1 and 3, and a different operator, senior hepatologist (V.d.L.) performed series 2. For pSWE VTQ, each participant was evaluated by a different set of two senior radiologists, randomly selected from a large population of four radiologists. Operators were blinded for clinical and laboratory data of patients and for results of previous procedures (TE or pSWE VTQ).

Statistical analysis

Categorical variables were described in terms of numbers and percentages and quantitative variables in terms of numbers, mean ± standard deviation, median (minimum, maximum, and first and third quartile). Comparisons of quantitative variables were performed by the Student's *t* test or Wilcoxon's test as appropriate. Comparisons of qualitative variables were performed by the X^2 test or Fisher's exact test as appropriate.

TE (kPa) and pSWE VTQ (m/s) results were median values of validated measures. Intraobserver reliability (or repeatability) and interobserver reliability (or reproducibility)[15] were analyzed using the intraclass correlation coefficient (ICC) and its 95% bilateral confidence interval (95% CI). The agreement was considered satisfactory if the estimated ICC was >0.7 and the lower limit of the 95% CI was >0.6. We used the ICC (1,1) for pSWE VTQ analysis, and the ICC (1,2) for TE analysis.[16]

The graphic method described by Bland and Altman[17] was used to visually assess the intra- and interobserver agreement for TE and pSWE VTQ. We also represented the upper and lower limits of agreement (mean of difference ± 1.96 × standard deviation of the difference), since 95% of differences will lie between these limits if differences are normally distributed. The maximum acceptable differences between the two measures were expressed as the relative difference of 10 and 20% (i.e., ratios of first measurement to second measurement from 1/0.9 to 1/1.1, and from 1/0.8 to 1/1.2, respectively). The characteristics of participants with discrepancies were compared to those of participants without discrepancies, for both thresholds, using statistical tests described above.

The type 1 error α was set at 5%. A two-sided $p < 0.05$ was considered significant. Statistical analyses were performed with the SAS Statistical package (version 9.2; SAS Institute Inc., Cary, NC).

RESULTS

Fifty-six patients (27 girls (48%) and 29 boys (52%)), aged 1–18 years (mean 10 ± 5 years), were included in the study. According to the phenotypic classification,[3] 41 patients had no evidence of liver involvement, 10 patients had liver involvement, and 5 patients had cirrhosis. Patient characteristics are summarized in Table 1.

Repeatability and reproducibility of TE

TE was performed in 41 children, using the M probe in 14 children and the S probe in 27 children. The success rate was 71–100% (average 96.6%). Eight children (19%) had an IQR >30% of the median for at least one series of measurements and were excluded. In the 33 patients whose measurements were valid, the average duration of TE was 2.9 ± 0.9 min. The median value of hepatic stiffness was 4.3 kPa (range 2.5–11.5). The mean intraobserver difference for TE was −0.137 kPa (95% CI: −0.491; 0.218).

Table 1. Characteristics of CF children included in the study.

	All patients, $n = 56$	TE, $n = 33$[a]	pSWE VTQ, $n = 46$[a]
Boys/girls	29/27	20/13	25/21
Age (years)[b]	10 ± 5	11 + 5	10 + 5
Weight (kg)[b]	33.7 ± 17.4	36.2 ± 18.8	33.8 ± 16.9
Height (m)[b]	1.34 ± 0.27	1.37 ± 0.25	1.34 ± 0.26
BMI (kg/m^2)[b]	17.4 ± 2.8	17.7 ± 3.1	17.5 ± 2.9
ALT (xULN)[b]	1.0 ± 0.2	1.0 ± 0.0	1.1 ± 0.2
GGT (UI/L)[b]	18 ± 13	18 ± 13	19 ± 14
Platelet count (×10^3/μL)[b]	314 ± 94	300 ± 89	312 ± 88
Hepatic ultrasonography (*n*)			
Normal	41	21	33
Diffuse hyperechogenicity	10	8	8
Hyperechogenicity and dysmorphy	5	4	5
without portal hypertension[c]	3	2	3
without portal hypertension[c]	2	2	2
Hepatic involvement			
No liver involvement	41	21	33
Liver involvement	10	8	8
Cirrhosis	5	4	5

TE transient elastography, *ARFI* acoustic radiation force impulse imaging; TE was performed and analyzed in 33 patients and ARFI in 46 patients, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *GGT* gamma-glutamyl transferase, *ULN* upper limit of normal values.
[a]Among the 56 CF children.
[b]Mean ± SD.
[c]Dilation of the portal vein with reversed blood flow and splenomegaly.

The mean interobserver difference for TE was 0.045 kPa (95% CI: −0.278; 0.369).

The ICC for intraobserver agreement was estimated at 0.91 (95% CI: 0.83; 0.95). The Bland and Altman graph for intraobserver agreement is indicated in Fig. 1 (limits of agreement: −2.06; 2.17 kPa).

Thirteen of 33 patients (39.4%) showed an intraobserver discrepancy of liver stiffness measurement >±10% between two measurements. Six of 33 patients (18.2%) demonstrated an intraobserver discrepancy >±20% between two measurements. The maximum intraobserver discrepancy observed (absolute value) was 3.5 kPa. Patients with an intraobserver discrepancy (>±10%) were younger (7.0 vs 13.5 years, $p = 0.01$).

The ICC for interobserver agreement was estimated at 0.91 (95% CI, [0.84; 0.95]). The Bland and Altman graph for interobserver agreement is reported in Fig. 2 (limits of agreement: −1.78; 1.87 kPa). Eighteen of 33 patients (54.5%) showed an interobserver discrepancy of liver stiffness measurement using TE >±10% between two operators. Seven of 33 patients (21.2%) had an interobserver discrepancy >±20% between two measurements. The maximum interobserver discrepancy observed (absolute value) was 3.2 kPa. There was no association between the age of children and interobserver discrepancy.

Repeatability and reproducibility of pSWE VTQ

pSWE VTQ was performed in 49 children. Three children (6%) had an IQR >30% of the median and were excluded. In the remaining 46 patients, median value of liver stiffness was 1.11 m/s (range 0.88–1.52). The mean intraobserver difference for pSWE VTQ was 0.008 m/s (95% CI: −0.016; 0.033). The mean interobserver difference for pSWE VTQ was 0.016 m/s (95% CI: −0.020; 0.052).

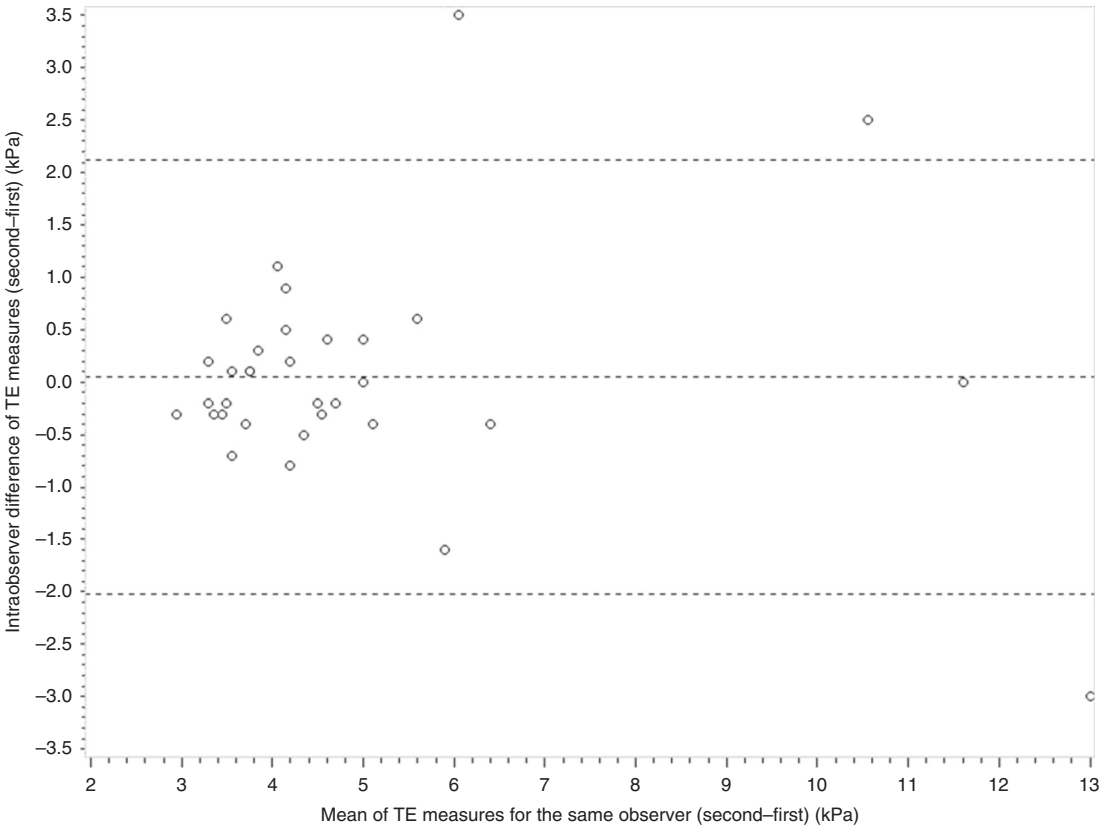

Fig. 1 Bland–Altman plot of intraobserver concordance with FibroScan® (FibroScan® 1 vs FibroScan® 3, $n = 33$). The dashed lines represent the mean of the intraobserver difference of TE measures and the upper and lower limits of agreement (mean ± 1.96 × standard deviation).

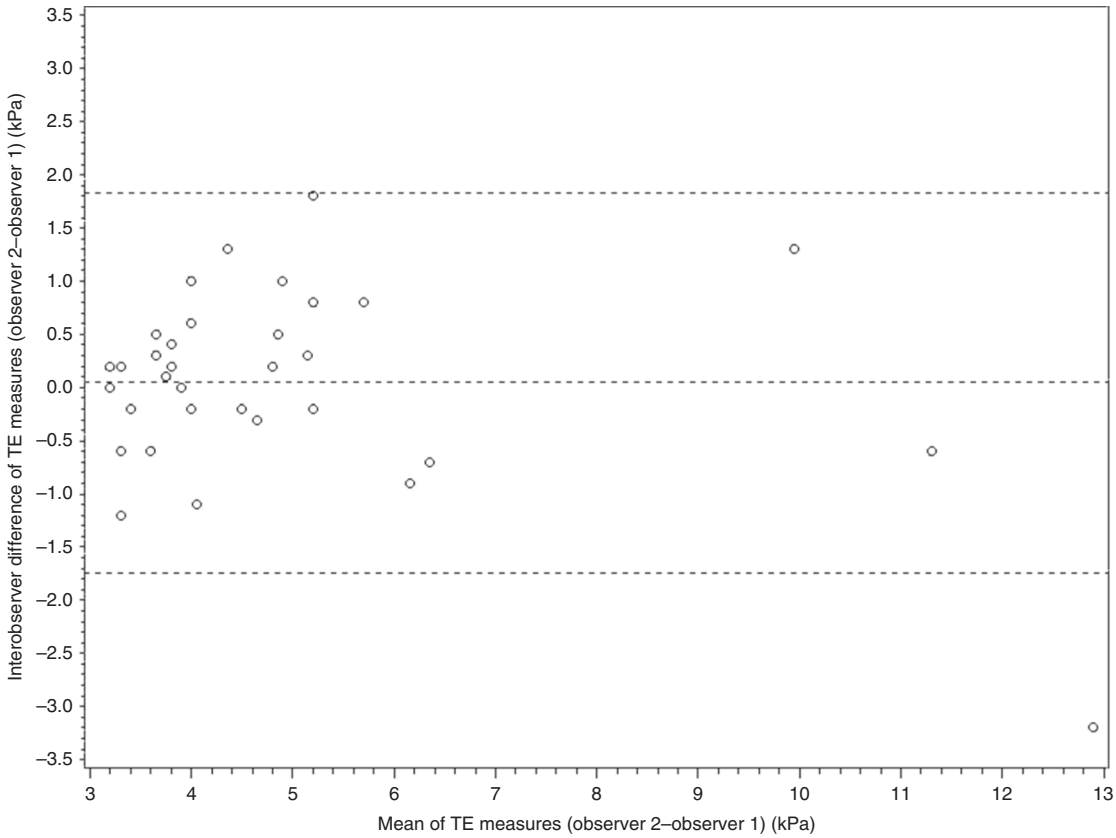

Fig. 2 Bland–Altman plot of interobserver concordance with FibroScan® (FibroScan® 1 vs FibroScan® 2, $n = 33$). The dashed lines represent the mean of the interobserver difference of TE measures and the upper and lower limits of agreement (mean ± 1.96 × standard deviation).

The ICC for intraobserver agreement was estimated at 0.83 (95% CI: 0.72–0.90). The Bland and Altman graph for intraobserver concordance is reported in Fig. 3 (limits of agreement: −0.157; 0.174 m/s). Five of 46 patients (11%) had an intraobserver discrepancy of liver stiffness measurement using pSWE VTQ > ±10% between two measurements. No patient had a discrepancy >±20%. The maximum intraobserver discrepancy observed (absolute value) was 0.230 m/s. There was no association between the age of children and intraobserver discrepancy.

The ICC for interobserver agreement was estimated at 0.67 (95% CI: 0.48–0.80). The Bland and Altman graph for interobserver agreement is reported in Fig. 4 (limits of agreement: −0.229; 0.261 m/s). Twelve of 46 patients (26.1%) had an interobserver discrepancy of liver stiffness measurement using pSWE VTQ > ±10% between two operators. Three of 46 patients (6.5%) had an interobserver discrepancy >±20%. The maximum interobserver discrepancy observed (absolute value) was 0.370 m/s. There was no association between age of children and interobserver discrepancy.

DISCUSSION

Our study shows that TE and pSWE VTQ are two reproducible methods for the assessment of liver fibrosis in the children with CF. Repeatability was good for both TE and pSWE VTQ, with an ICC of 0.91 and 0.83 for intraobserver agreement, and a discrepancy between two measurements >±20% in 18% of cases for TE and none for pSWE VTQ. Reproducibility between two operators was also good for both technics, with an ICC of 0.92 and 0.67 for interobserver agreement, respectively, and a discrepancy >±20% in, respectively, 21% of cases for TE and 6% for pSWE VTQ.

TE is a rapid, noninvasive, and painless tool to assess liver stiffness, exploring a larger volume of hepatic parenchyma than a liver biopsy.[6] In adults, TE has been validated in comparison to liver biopsy and several studies have shown that it has very good reproducibility.[18,19] Pediatric studies have shown that TE is a simple, fast, and feasible method to quantify liver fibrosis even in small children.[20,21] The rate of invalid measurements in the pediatric population, 10–15% according to studies, is slightly higher than in adults (5–11%). Although TE is feasible as early as the age of 2 months,[20] invalid measurements occur more frequently in young children,[10,22] with a rate of 27% in a German study in 0–5 year olds.[22] In the present study, TE was deemed invalid in eight children (19%) due to an IQR/median ratio >30%, explained by the young age of three patients and mental retardation in another. This is in accordance with the 16% rate of invalidated measurements in adults reported by Castéra et al.[23] Different cutoff values for TE have been published in adults to discriminate between different fibrotic stages, depending on the etiology.[6] The accuracy of TE for diagnosing cirrhosis was high but poor for significant fibrosis.[7] Although these data are not available in patients with CF because of the lack of biopsy material, some studies suggest cutoffs to separate groups without CFLD, with CFLD, or with cirrhosis.[8,10,24] Some studies showed a correlation between TE and the severity of ultrasound lesions, but were mainly able to distinguish between patients with and without signs of portal hypertension.[7–10]

Various factors can influence the intra- and interobserver reproducibility of TE. A high BMI (>25 kg/m^2) and subcutaneous fat tissue disturb the wave propagation and increase the risk of measurement failure in adults.[6,18,19] Nevertheless, in their study including 52 children with nonalcoholic steatohepatitis (NASH),

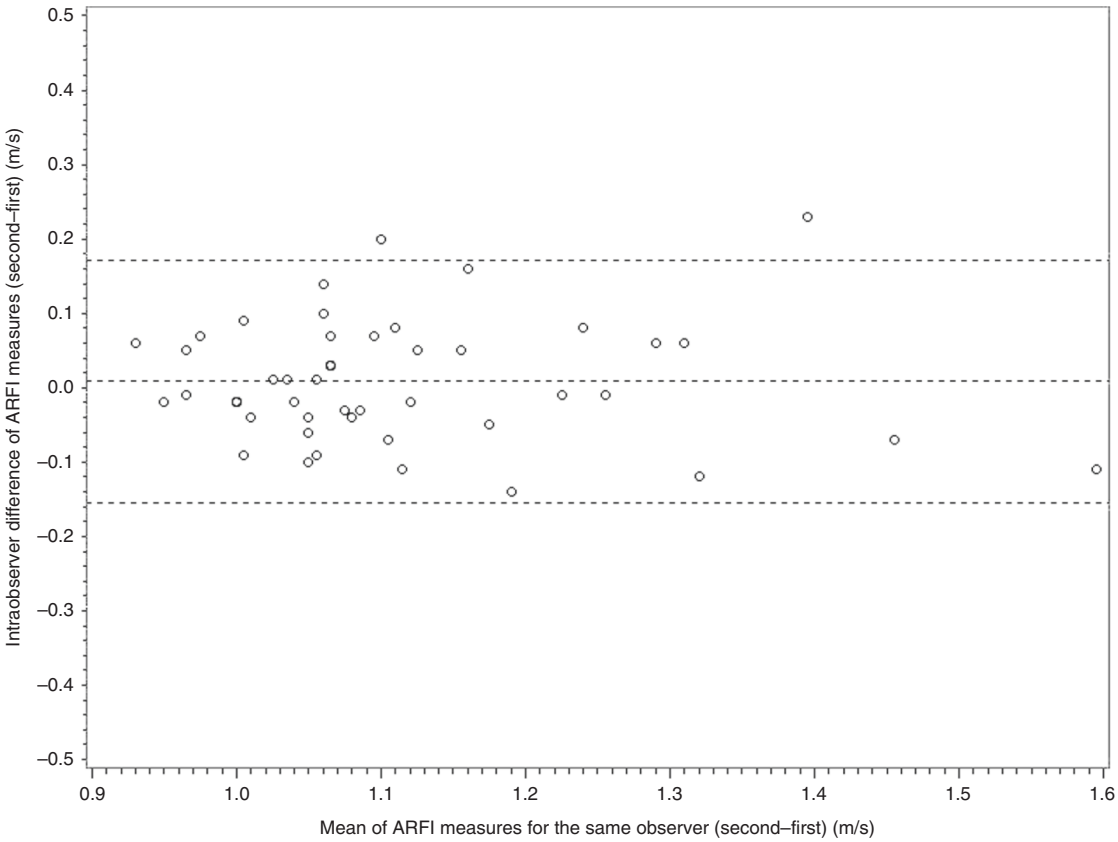

Fig. 3 Bland–Altman plot of intraobserver concordance for the median of ten measures with PSWE VTQ (PSWE VTQ 1 vs PSWE VTQ 3, $n = 46$). The dashed lines represent the mean of the intraobserver difference of PSWE VTQ measures and the upper and lower limits of agreement (mean ± 1.96 × standard deviation).

Nobili et al.[25] found a good interobserver reproducibility (0.96 (90% CI: 0.92–0.97) despite a high BMI for most children. This factor should not be a problem in children with CF as they are rarely overweight. In our study, we found a higher intraobserver discrepancy in younger children. The influence of age on TE reproducibility may be explained by the slow worsening of liver fibrosis with age in CF patients.[26] Young children are more likely to have no or minimal liver fibrosis, and it has been shown that TE reproducibility is decreased when fibrosis is less pronounced.[18,19] Liver steatosis, present in 16% of our patients, has been shown to reduce interobserver agreement when it is >25%.[18] Nevertheless, steatosis does not appear to be a factor of discrepancy in children with NASH.[25] The heterogeneous distribution of fibrotic lesions, which is characteristic of CFLD,[3] could also contribute to reducing the reproducibility of elasticity measurements. As the anatomic site for positioning the probe may also influence the reproducibility, we chose the mid-axillary line that has been shown to give good results.[19]

pSWE VTQ is a more recent noninvasive tool used to study liver stiffness in adults[24] and children,[27,28] showing a good correlation with the fibrosis stage on liver biopsy.[29,30] In CF, pSWE VTQ values increase in parallel to ultrasound liver damage score,[31] and can distinguish between two groups of patients "with cirrhosis" vs "with liver disease without cirrhosis."[24,32] For Behrens et al.[32] pSWE VTQ offers more diagnostic advantages for the detection of early stages of liver disease than conventional ultrasound without pSWE VTQ. Several authors suggest that pSWE VTQ may be useful in CF for the diagnosis and the follow-up of CFLD in adults and children.[12,14,31–33] Matos et al.[27] demonstrated that the site (right vs left lobe) and the depth of measurement could influence pSWE VTQ values. Another study by Hanquinet et al.[28] showed that choosing the right lobe with a depth between 3 and 5 cm enhances the reproducibility of the measurement. In adults, older age, male sex, and higher BMI were found to be associated with the risk of failed pSWE VTQ measurements.[34] Few studies have evaluated the reproducibility of pSWE VTQ. In adult patients with hepatitis B and C, pSWE VTQ was found to be reproducible with a good correlation of intraobserver measurements.[35,36] Consistent with these results, we also found good intraobserver agreement (ICC = 0.83), although the interobserver reproducibility was less satisfactory (ICC = 0.67). In our patients, having three sets of ten measurements, difficulty to keep a short end-inspiration apnea, in relation to chest status, was responsible for a longer examination time, and some weariness during the last set of measurements. pSWE VTQ has been shown to have similar diagnostic accuracy than TE in adults with various liver diseases,[35] and also in adults[24] and children[37] with CF. Sağlam et al.[12] performed several liver pSWE VTQ in children with CF (five measurements in each patient). They found an interobserver reliability of 0.72, considered as good, and did not study the repeatability of pSWE VTQ. In the same way, five measurements of liver elasticity were obtained with pSWE VTQ in the study of Canas et al.,[38] with only one operator, and with standard deviation only given for the entire population.

Another method known as shear-wave (supersonic) elastography, also expressed in kPa, demonstrated accurate assessment of liver fibrosis in children, even in children with early-stage disease,[39] but the choice of the transducer influences liver stiffness values.[40] Calvopina et al.[41] evaluated children with CF using supersonic shear-wave elastography, and confirmed the accuracy of this ultrasound approach, but without details regarding reproducibility. With respect to TE and pSWE, shear-wave elastography benefits from a real-time color mapping of the tissue stiffness in an image superimposed on the standard

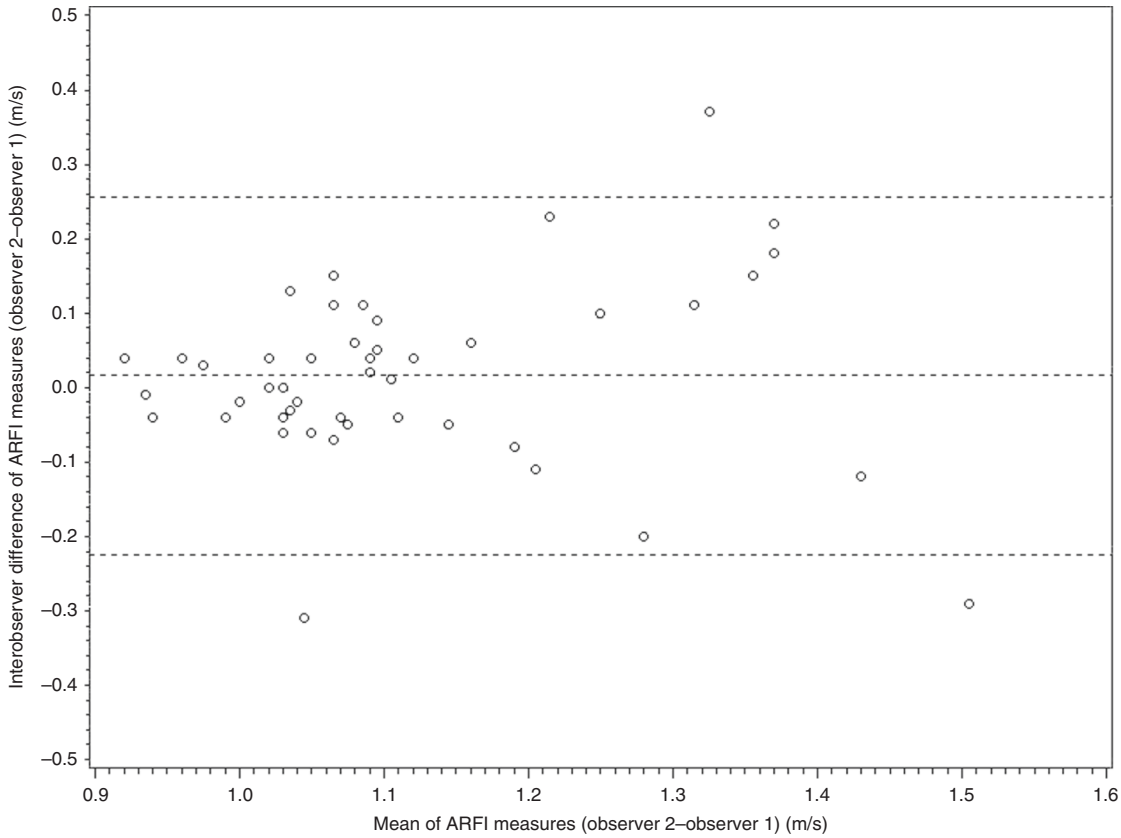

Fig. 4 Bland–Altman plot of interobserver concordance for the median of ten measures with PSWE VTQ (PSWE VTQ 1 vs PSWE VTQ 2, $n = 46$). The dashed lines represent the mean of the interobserver difference of PSWE VTQ measures and the upper and lower limits of agreement (mean ± 1.96 × standard deviation).

ultrasound B-mode,[42] allowing performance of liver stiffness measurement in regions with sufficient acoustic signal and without artifacts.

A limitation of this study is the small number of patients, especially with advanced liver fibrosis. This is due to the low prevalence of cirrhosis, which occurs in <10% of CF children,[2,3] and the less usefulness of liver stiffness measurement when advanced liver disease is clinically obvious. Only one of the two procedures was performed in some of the patients, and more comparable results would have been obtained performing both TE and pSWE VTQ on the strictly same cohort. A comparison with the histological staging of liver fibrosis would have been useful, but liver biopsy is an invasive method rarely performed in these children because histology is not mandatory for the diagnosis of CFLD and because its accuracy for the staging of fibrosis is questionable due to the heterogeneous distribution of histological lesions.

CONCLUSION

This study shows that TE has satisfactory repeatability and reproducibility in children with CF, while pSWE VTQ has satisfactory repeatability but slightly lower reproducibility. Despite possible disagreements, both techniques can be proposed for the follow-up of patients with CF, according to their availability in each CF center.

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AUTHOR CONTRIBUTIONS

R.E.: interpreting data, drafting the manuscript; approved the final draft submitted. E.F.: performing statistical analysis; revising the article critically for important intellectual content; approved the final draft submitted. S.M.: conducting the study (pSWE VTQ measurements); approved the final draft submitted. A.F.: planning and conducting the study (TE measurements); approved the final draft submitted. V.d.L.: collecting and interpreting data; revising the article critically for important intellectual content; approved the final draft submitted. P.P.: performing statistical analysis, interpreting data; approved the final draft submitted. S.B.: collecting data; revising the article critically for important intellectual content; approved the final draft submitted. M.F.: interpreting data; revising the article critically for important intellectual content; approved the final draft submitted. J.-F.C.: interpreting data; revising the article critically for important intellectual content; approved the final draft submitted. T.L.: planning the study, interpreting data, drafting and revising the manuscript critically for important intellectual content; approved the final draft submitted.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Ethics approval: The study was approved by the Ethics committee for the South West of France (Ref.: DC 2012/78) and written informed consent was obtained from the parents and patients when aged 6 years or more.

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