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ORIGINAL ARTICLE

Acoustic radiation force impulse imaging—normal values of liver stiffness in healthy children

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Abstract
Background Acoustic radiation force impulse imaging (ARFI) is a recent ultrasound technique to assess tissue stiffness.
Objective Our aim was to describe the feasibility and to define normal ARFI values in liver in children.
Materials and methods ARFI values were measured in 103 children (ages 2 weeks to 17 years) divided into four age groups, at a minimum depth of 3 cm. In 20 children, measurements were done at 3-, 4- and 5-cm depth in the liver to assess the suitability of measurement location. The impact of age groups and of depth groups was examined using multilevel models. The precision of the measurements was determined using intraclass correlation coefficient (ICC).
Results There was no statistical difference between measurements taken at different ages, with a mean propagation velocity of 1.12 m/s (range: 0.73 to 1.45 m/s). There was no significant difference according to the depth of the regions of interest (up to 5 cm). The ICC was 0.77 (95% CI 0.69–0.83).
Conclusion ARFI is feasible in children at any age with an acceptable reliability. The depth of measurements in the liver seems to have no influence on test results. We set the standard ARFI elastography values for healthy liver in children.

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Introduction

Chronic liver diseases in children have a variety of causes and their evolutions vary as they can sometimes decompensate very quickly. The knowledge of the degree of liver fibrosis is essential in the management of these patients and in the decision for liver transplantation. Although liver biopsy remains the gold standard for detection of fibrosis, it has several drawbacks: it is an invasive procedure with risk of hemorrhage, it requires anesthesia in children and may sometimes lack reliability due to a sampling bias [1]. Noninvasive techniques exist but are poorly developed in children, unlike in adults. The APRI blood test (ASAT to platelet ratio index) is the most commonly used [2], but there is no real standard in children. Other blood tests were studied in children to assess liver fibrosis [3–5]. Few pediatric studies with transient elastography of the liver using Fibroscan (Echosens, Paris, France) [6–9] have been reported. Fibroscan has well-known technical limitations in adults, such as ascites and obesity. On the other hand, the measurements are not guided by a real-time US [10–12]. Recently, a new method based on acoustic radiation force impulse (ARFI) imaging, Virtual Touch™ tissue quantification, has been introduced to evaluate organ stiffness. The ARFI module is included in standard US probes on a conventional US machine (S 2000, Siemens, Erlangen, Germany). Due to the diversity of children and anatomical differences between infants and teenagers, it seemed essential to establish a normal range of liver stiffness measurements in children before analyzing patients with liver disease. There is one paper with pediatric standards, but it is based on 20 healthy children with no details about different age groups or how the measurements were made [13].

Materials and methods

We performed ARFI measurements in 109 children ages 7 days to 17 years after parental consent based on the rules of the ethics committee of our institution. This study was approved by the ethics committee of our hospital under the number 10–248 CER. The ARFI module is installed on a conventional US machine (Acuson S2000; Siemens Medical Solutions, Germany) and the technique is currently available with two types of probes: linear 9 MHz and convex 4 MHz (Fig. 1). The choice of the probe depended on the child's morphology (Fig. 1). Using a high frequency probe in young children allows a better analysis of the liver parenchyma and a better visualization of vessels and bile ducts due to their relatively superficial position.

The 9-MHz probe allows a region of interest (ROI) of 5 × 4 mm and can be placed in up to 5 cm of depth whereas the 4-MHz probe gives an ROI of 5 × 10 mm with a possible depth of up to 8 cm. With the US image in real time, it is possible to set the ROI at a specific location within the liver parenchyma. The measurements were made independently in different patients by two senior radiologists (MA and SH), who worked together for 25 years and had previously agreed on the technique. The ARFI system is based on sending a short high intensity ultrasonic wave in the region of interest. The ultrasonic wave velocity depends on tissue stiffness and is expressed in m/s. We obtained a value representing speed, a quantitative measurement, which increases with the stiffness of the examined tissue.

Our control population had to have an abdominal US for any reason other than liver pathologies. The indications for US were multiple, for example, kidneys (dilated renal cavities, malformation), musculoskeletal (dislocation of the hip, limping), genital (precocious puberty, malformations) or

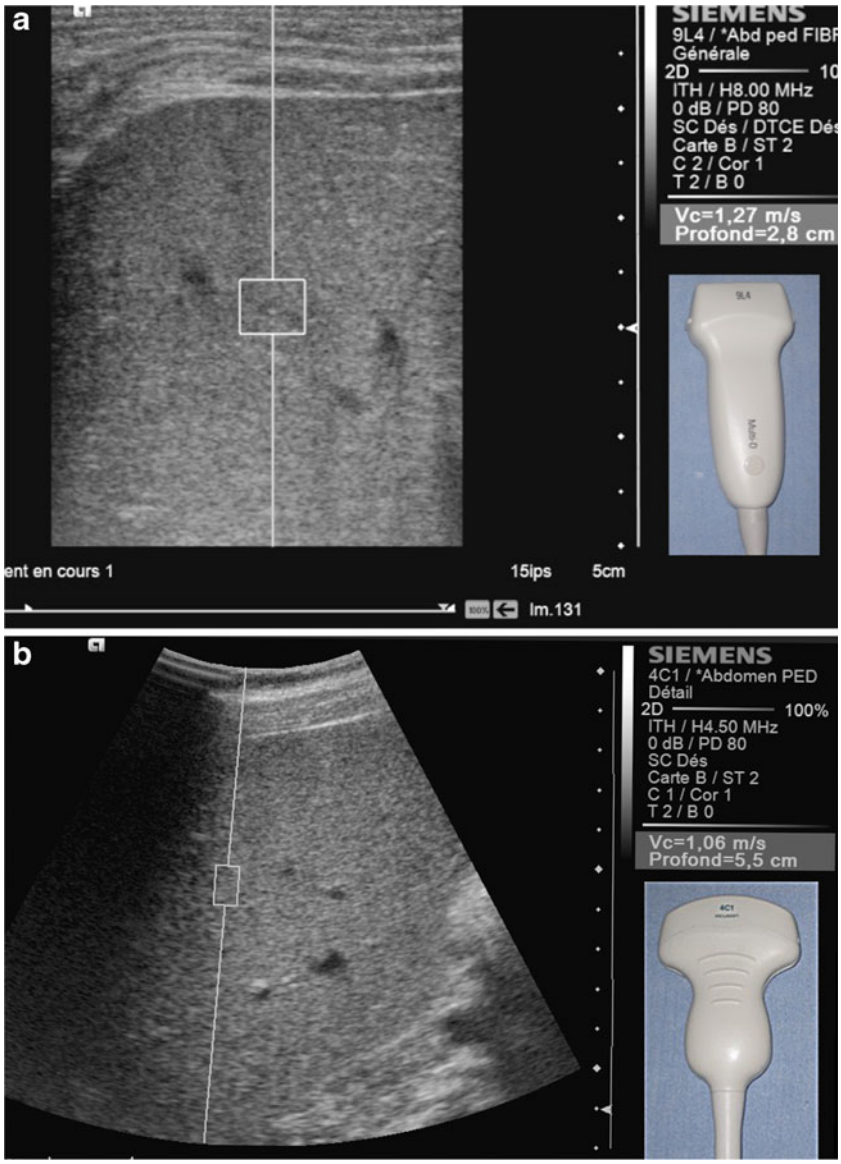

Fig. 1 In liver ultrasound acoustic radiation force impulse (ARFI) measurements, the depth of region of interest (ROI) was adapted according to the liver volume. **a** In a 3-year-old child with a 9-MHz probe, shear wave velocity was 1.27 m/s at 2.8 cm depth. **b** In an 11-year-old boy with a 4-MHz probe, shear wave velocity was 1.06 m/s at 5.5 cm depth

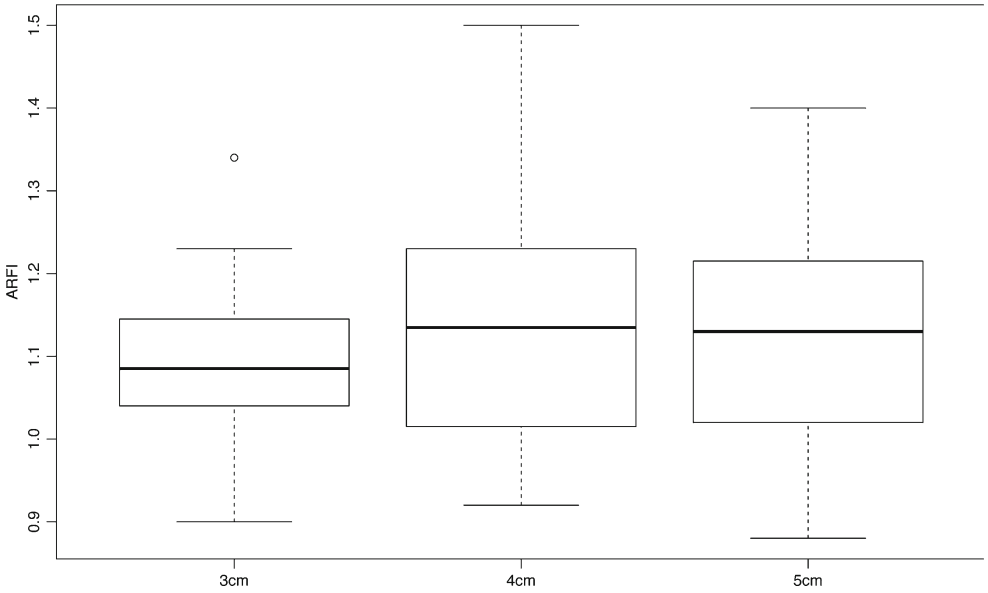

Fig. 2 Shear wave velocities (m/s) in 20 children at different depths. Boxplots of acoustic radiation force impulse (ARFI) values by depth. (*Boxes* represent upper and lower quartiles and *horizontal thick line* through each box represents median value)

brain (macrocrania, malformation). Before ARFI measurements, a US of the liver, gallbladder, pancreas, spleen and the biliary tract was done to exclude an abnormality of this region. Children (or guardians) were asked if the child was under no medication. Inclusion criteria were absence of known liver disease based on history and US findings.

The study was always performed after a minimum fasting of 4 h for young infants (0 to 1 year) and 6 h for the others. Five valid ARFI measurements were performed in each child in the same region of the liver. Only the measurements obtained successfully were selected. The machine that gives default values as "XXXX" immediately rejected invalid measurements.

Measurements were obtained with free breathing or apnea depending on whether the child was able to hold his breath. It was possible to apply an apnea for each measurement from 8 to 9 years depending on the child. Measurements take only a few minutes, about 3 to 4 min maximum, for all five measurements. ARFI measurements were taken at the end of the US study.

Table 1 Characteristics of acoustic radiation force impulse (ARFI) [m/s] values by age group

Age (years)	Minimum-maximum	Mean (SD)	*p*	95% confidence interval	
				Lower bound	Upper bound
< 1	0.73–1.45	1.11 (0.19)	-	1.04	1.19
1–5	0.92–1.45	1.15 (0.13)	0.13	1.10	1.20
5–10	0.91–1.33	1.08 (0.11)	0.36	1.04	1.13
10–17	0.85–1.29	1.14 (0.10)	0.20	1.10	1.17

All measurements were made in the right lobe of the liver with an intercostal or subcostal approach, according to the best hepatic image accessibility. The deliberate choice of the right lobe was based on anatomical characteristics of the left lobe, which is more prone to influence by respiratory fluctuations due to the surrounding diaphragm and pulsations from the aorta. This has also been shown in adult series [14, 15]. Furthermore, liver biopsies are mainly done in the right lobe. The most important element is to fully place the cursor in the liver with the operator careful not to include a blood vessel or a bile duct in the ROI. Depth of the sampling (3, 4 and 5 cm) was systematically varied for the first 20 children. Each child had five measurements at each depth. Depths below 3 cm were avoided to diminish respiratory influence [16]. We deliberately chose depths from 3 to 5 cm to avoid being influenced by respiratory movements and also to be able to cover the entire pediatric population. Taking measurements beyond 5 cm is more difficult in very young children. Since results showed that chosen depths did not impact the measurements, the remaining children were measured only at the most appropriate depth based on the children's age and corpulence as well as on the probe used.

Statistical analysis

The impact of ARFI measurement depth was evaluated using multilevel modeling to account for repeated measurements within the same subject. Multilevel models are statistical models of parameters that vary at more than one level. These models are generalizations of linear models (such as linear regression) and are particularly appropriate for research designs where the data for participants are organized

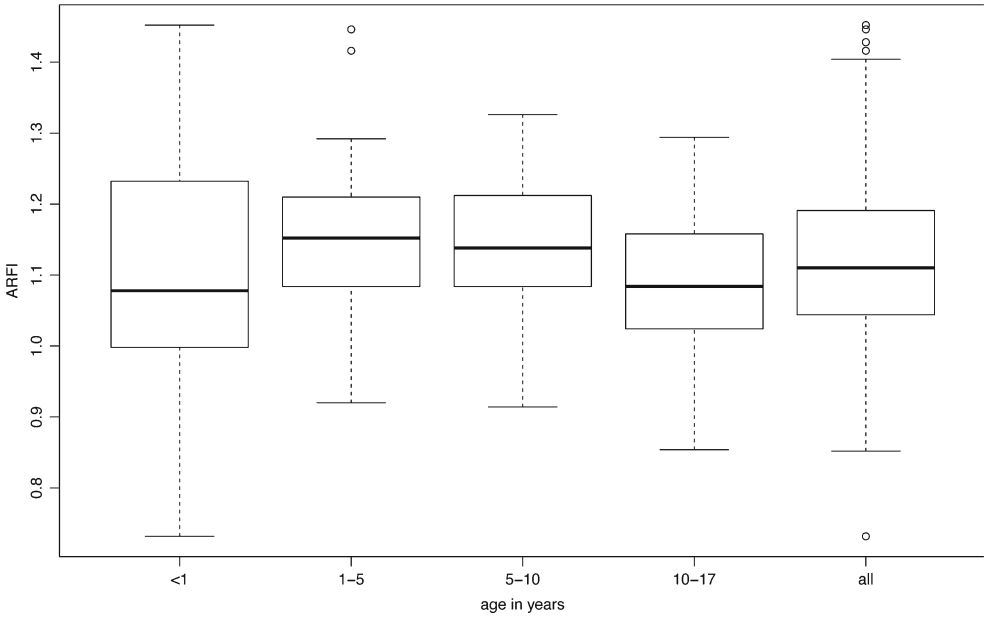

Fig. 3 Shear wave velocities (m/s) in healthy children. Boxplots of the results of acoustic radiation force impulse (ARFI) values by age group. (*Boxes* represent upper and lower quartiles and *horizontal thick line* through each box represents median value)

at more than one level. In this study, the units of analysis are the three measurement depths (at a lower level) nested within children (at a higher level).

Similarly, since each child was measured five times, multilevel models were used to determine the effect of age accounting for similarity of measurements within each child. The precision of the measurements and their variability within a child were determined using intraclass correlation coefficient (ICC); ICC ranges between −1 and +1, with +1 indicating a perfect agreement between measures. All analyses were done using R statistical software (2011) www.r-project.org.

Results

Six of the 109 recruited children (two ages 0–1 year and four ages 1–3 years) who were too agitated or crying too much, and in whom we were not able to obtain five valid measurements, were excluded from this study. With 103 healthy children, a set of 515 measurements were obtained and retained for statistical analysis.

Our population, ages 2 weeks to 17 years (mean age: 75.1 months; SD = 62.3), was divided into four age groups with a balanced number per group: 0–1 year (n = 26), 1–5 years (n = 26), 5–10 years (n = 26), and 10–17 years (n = 25). The mean BMI of this sample was 17.4 (SD = 4.5).

There were 48 girls and 55 boys, mean ARFI values were similar across gender (girls 1.14; boys 1.11; P=0.30).

Of the 103 children, 51 studies were done with the 9-MHz probe and 52 with the 4-MHz probe (between 0 and 5 years, 44 children were examined with the 9-MHz probe and six children with the 4 MHz probe; between 6 and 17 years, 46 children were examined with the 4-MHz probe and seven children with the 9-MHz probe). Mean ARFI values were similar for the two probes (for the 4-MHz probe, 1.13; for the 9 MHz probe, 1.11; P=0.52)

Most ARFI measurements were taken between 3 and 5 cm in all but one child ages 5–10 years (6 cm) and six children ages 10–17 years (two at 6 cm, three at 7 cm, one at 8 cm).

We analyzed different ARFI values among three different depths in 20 children (age range: 1 month to 16 years; mean age: of 92.7 months (SD=53.2); 10 boys, 10 girls). Among these 20 children, 11 were examined with the 4-MHz probe and nine with the 9-MHz probe.

The average value was 1.09 m/s at 3 cm, 1.18 m/s at 4 cm and 1.11 m/s at 5 cm, which was not significantly different either globally (P = 0.18) or within each age group (data not shown). The median and variability of the three depths (3, 4 or 5 cm) in the liver parenchyma were very similar (Fig. 2). Furthermore, ARFI values were also similar for the two probes for each depth (3-cm depth, mean difference =

Table 2 Acoustic radiation force impulse (ARFI) imaging values for liver stiffness in healthy children: centiles by age. References for normal liver elasticity ARFI values (10th, 20th, 30th, 40th, 50th, 60th, 70th, 80th, 90th percentiles) in function of age

Quantile	< 1 year old	1–5 years old	5–10 years old	10–17 years old
10	0.94	1.00	1.00	0.94
20	0.95	1.04	1.07	1.01
30	1.04	1.09	1.09	1.04
40	1.06	1.13	1.11	1.07
50	1.08	1.15	1.14	1.08
60	1.12	1.16	1.17	1.10
70	1.15	1.18	1.20	1.13
80	1.32	1.22	1.22	1.16
90	1.40	1.29	1.24	1.22

0.04, $P = 0.33$; 4-cm depth, mean difference = 0.003, $P = 0.97$; 5-cm depth, mean difference = 0.06, $P = 0.27$).

The means of the age groups were not significantly different (Table 1). Furthermore, the median and variability were very similar (Fig. 3). References for normal liver elasticity ARFI values are given in percentiles in Table 2.

The overall average was 1.12 m/s (range: 0.73 to 1.45 m/s). The ICC was 0.77 (95% CI 0.69–0.83), indicating an acceptable precision.

Discussion

Our study is based on 103 healthy control children. We wanted to establish normal values according to age as our population was evenly distributed between 2 weeks and 17 years. The intra-observer reliability was acceptable (ICC = 0.77). While this ICC is slightly below the threshold of 0.80 that indicates good precision, this result is still very good for a healthy population. Indeed, ICC is based on a ratio of true variance over total variance. In a healthy population, the true variability is low because everyone is healthy. Thus, variability of ARFI measures will be in large part due to imprecision. In children with liver disease, the variability in ARFI measures would have been larger and, by comparison, measurement error would have been smaller. Furthermore, we did not observe significant differences related to the age or sex of the children. This observation is, in fact, also found in adult studies [17–19], and we did not observe significant differences related the depth of measurement (3–5 cm). We did not observe any difference with the type of probe, but it must be remembered that in our study the choice of the probe was based on the age of the child and no child was examined with two probes. This can be considered a limitation to this statement. Thus, ARFI measurements seem to be both reliable and usable for children

ARFI elastography is a noninvasive technique for assessing the stiffness of the liver parenchyma [20]. Studies in adults have shown a good reliability of the technique and its reproducibility in the analysis of liver disease. It has advantages over Fibroscan, as it is not limited by obesity or ascites [12, 21]. The best advantage of the ARFI system is to link the US image with the location of measurements and hence the visibility of the exact position of the sampling.

Currently, only one pediatric study provides normal values based on 20 children (mean age; 7 years; range; 1–16 years). Their value was 1.11 m/s (range; 0.88–1.37 m/s; median; 1.09 m/s). The authors do not specify ARFI values according to age [13]. The average value of ARFI in our pediatric sample was 1.12 m/s (range; 0.73–1.45 m/s). ARFI values in healthy adults showed similar values: 1.1 m/s [22], 1.09 m/s [23], 1.15 m/s [18], 1.19 m/s [17], 1.08 m/s [24], 1, 07 m/s [19]. There is therefore no significant difference between an adult population and children as we could have expected since external factors related to lifestyle (food, alcohol consumption, tobacco) could influence the values, according to some authors [25]. It is interesting to consider that the adult studies have shown no difference between measurements taken by subcostal and intercostal approaches [14], but differences were found between the measurements of the left and right lobes of the liver [15].

With regards to depth, we wanted to ensure the absence of influence of the sampling depth on ARFI values. We tested three different depths (3, 4 and 5 cm) and again our results do not show significant differences up to 5 cm. So the depth of the position of the ROI in the liver does not seem to influence the values of measurements for measurements made deeper, i.e. between 3–5 cm. Also, a child's liver is closer to the skin in contrast to the adult liver where the capsule is likely to be thick and fibrous. Among adult studies, the depth of placement of the ROI is not always specified. Some authors of adult studies consider that the ROI can be placed below 2 cm [16, 18] or 2–3 cm [19]; some authors specify placing the ROI between 20 and 55 mm [14, 26]. In our experience, however, we found that it is best to put the cursor at least 3 cm in order not to interfere with breathing.

Our experience has shown that ARFI is easily performed in children; they do not feel any pain or discomfort during the study since no compression is required. Measurement is fast and only takes a few minutes. On the other hand, it is difficult to obtain accurate measurements in children who move too much or cry. This is a limitation to obtain valid ARFI values in young children.

While the results of this study show that ARFI is a promising tool to estimate liver stiffness in children, four main limitations should be noted. First, the repeated within-child measurements were made by the same operator and thus only intra-observer reliability could be assessed. Further studies are needed to determine if ARFI measurements obtained by different observers are in agreement. Second, we did not formally examine the influence of breathing in children old enough to hold their breath. Our population is very diverse from small infants to adolescents, the majority of studies in children between 0 and 9 years was done with the child breathing while those in many children 9 years and older were done during breathhold. Since our results in different age groups do not show significant differences, we can assume that apnea is not a limiting factor to obtain reliable values. Indeed, if the child is breathing quietly, ARFI values are similar and, therefore, reproducible and strict apnea seems not to be necessary for taking measurements. In a pediatric setting, it is usually very difficult to obtain apnea. An adult study advises performing ARFI measurements in a resting respiratory position, ideally in a breathhold technique only if tolerable for the patient [26]. A third limitation is that we did not test ARFI measurements

between 5 and 8 cm of depth. Since deeper values are difficult to use in young children, we preferred to use depths that were applicable to the whole pediatric population. Finally, a fourth limitation is that six children could not be measured in this study because they were too agitated. For study purposes, this represents a 5.5% failure rate.

Conclusions

In this study, we established normal ARFI values in a pediatric population. Values were similar across age, gender, depth of measurement (3–5 cm) and type of probe. It is also feasible in 95% of children regardless of age. ARFI is a promising tool to assess liver elasticity in chronic liver diseases in children.

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