REVIEWS

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Ultrasound Elastography – Review of Techniques and Its Clinical Applications in Pediatrics – Part 1

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Abstract

Sonoelastography is a novel technique that uses ultrasound waves to assess the elasticity of tissues noninvasively. It provides an ultrasound-based method to detect and display the relative stiffness of tissue. The main principle of sonoelastography is the measurement of tissue distortion in response to external compression. Changes in elasticity and tissue deformation elicited by compression are measured, processed and then shown in real time presentation with color-coded elastograms. One of the most important applications of sonoelastography is the evaluation of liver diseases, mainly liver fibrosis assessment and staging. Although in terms of definite diagnosis the liver biopsy still remains the golden standard, elastography seems to be a very inexpensive, repeatable and noninvasive method to evaluate most of liver conditions. The technique is also applicable in detection and differential diagnosis of focal lesions. It provides better imaging information and therefore more accurate evaluation of the lesions nature, e.g. in liver, lymphatic nodes or thyroid gland. Most of the applications mentioned above are well known and have been described in details in adults. Similarly, most of sonoelastographic studies are based on groups of adults. The purpose of this review article is to bring this technology closer to pediatric clinicians and to summarize some of its current clinical applications that are being pursued. In this part we focus on utility of elastography in liver assessment in pediatric patients (**Adv Clin Exp Med 2015, 24, 3, 537–543**).

Key words: sonoelastography, liver cirrhosis, cystic fibrosis, chronic hepatitis, NAFLD.

Elastography is a recently developed diagnostic method that aims to evaluate tissues stiffness. Its utility is based on the fact that pathological tissues are generally stiffer than surrounding healthy tissues, e.g. breast cancer or prostate cancer which often show up as a hard lesion ("a bump") [1]. What is more, in scientific research, it is generally agreed that no other physical parameter of tissue is changed by pathological or physiological process to as remarkable an extent as the tissue elasticity [2].

The term "elastography" had been used for the first time at the beginning of last decade of 20th century. Since that moment many elastography techniques have been developed [2].

The most popular and widely spread in clinical use method is ultrasound elastography – called sonoelastography. Ultrasound waves can be used in many different ways to estimate the stiffness of the tissue; however, for the sake of simplicity, it is convenient to separate two main groups: static and dynamic elastography [2, 3].

Static elastography (SE), the most common, is based on tissue compression by external mechanical force, e.g. compression applied by the investigator using ultrasound probe or an internal endogenous force, e.g. cardiac motion (displacement about 1–2%) [1, 4]. The device analyses the displacement of the tissue and presents the result as color map overlaid on the B-mode image [1]. Real-Time Elastography (RTE) is an application which allows us to estimate color-coded elastograms in real-time presentation. Repeatability and reliability

of the results are strongly related to the physician performing the examination. For example too strong compression of the tissue or an incorrect angle of transducer compression might lead to misinterpretation [1]. However, the most important limitation of static elastography seems to be its qualitative character. Colors covering "suspected" area are relatively calculated in comparison to surrounding "healthy" tissue [1]. There are some color scales developed that stage the probability of malignancy of lesion respectively to its color pattern, e.g. Tsukuba scale [5]. There were some attempts to solve that problem and the so-called semi-quantitative elastography (SQE) was developed. In this method, two areas within the sonoelastographic image are marked by Region of Interest gate (ROI): healthy tissue and target lesion. The calculated result is called Strain Ratio and it is a simple proportion between relative elasticity in those two ROIs. Currently, there are some attempts to estimate if Strain Ratio values can be considered as a reliable parameter particularly indicating malignancy in different tissues [6] and if yes, how could they do so. In the next couple of years further development of static elastography is expected. Other SQE applications allow us to create histogram or calculate the intensity of color pixels or so called DS score [7].

Dynamic elastography (DE) defines elasticity of the tissue by measuring the velocity of shear wave propagation – the stiffer tissue, the higher value of the velocity measured [8]. Ways of generating shear waves in the tissues and measuring their speed can differ a lot depending on the chosen technique; however, all those methods have an extremely important common feature – they are quantitative elastography [4]. This has an enormous impact while examining diffuse pathologies when a reliable healthy reference area is hard to find, e.g. liver fibrosis. The most popular dynamic elastography applications are Transient Elastography (TE), Acoustic Radiation Force Impulse (ARFI) and Shear Wave Elastography (SWE) [4] (Table 1).

TE is commercially available as Fibroscan. This technique uses both ultrasound (around 5 MHz) and mechanically generated shear waves of low-frequency (50 Hz). The shear wave is produced by an external low frequency vibrator (50 Hz), which strikes the patient's skin. One-dimensional ultrasound system is responsible for measuring its velocity. The result is given in kilopascals (kPa) as an average of ten subsequent measurements. This technique was dedicated to liver fibrosis evaluation and its value has been already well estimated in many studies. However, it has some limitations like low volume of parenchyma explored, absence of ultrasound imaging to guide the measurement or possible measurement difficulties in cases of obesity/presence of ascites [4]. It should be noted that a special probe dedicated to small children and neonates has been recently developed [9].

ARFI generates shear wave by using focused ultrasound beam. This technique allows us to generate a shear wave located precisely in a chosen area [4]. The result of shear wave propagation velocity is given directly in meters per second (m/s) [10]. Nowadays, ARFI is integrated with conventional ultrasound devices and morphological evaluation of investigating area is possible simultaneously [10]. The main limitations of this technique are: relatively small ROI gate which size cannot be modified, lack

Table 1. Most popular or promising elastography techniques

Elastography technique	Semi-quantitative elastography	SWE	ARFI	Transient elastography
Tissue compression necessity	+++	–	–	–
Repeatability of the results	+/++	+++	+++	+++
Quantitative assessment	+/++	+++	++/+++	+++
Color map quality	+++	++	–	++
Independence of the researcher experience	+	+++	+++	+++
Quickness of the examination	++	+++	+++	+++
Other	most common relatively cheap	still small popularity of this method	non-changeable ROI size no information about SD	only for liver fibrosis problems with patients with ascites no US guiding

of information concerning standard deviation (SD) from ROI and a tendency to overheat the probe, especially when deeper tissues are investigated [4].

SWE uses several precisely located radiation forces inducing simultaneously several shear waves, which interfere and give conical shear wave front. Estimation of such wave requires very rapid acquisition of ultrasound probe (from 5000 images/s up to 20000 images/s) [4]. The result of measurements is usually given in kPa; however, color coding of the ROI is also possible. SWE, like ARFI, allows a morphological, simultaneous evaluation of an assessed region. An important benefit of rapid data acquisition is the reduced risk that the patient or physician movements will alter the measurements [4]. However, some studies suggest that SWE is more operator-dependent than it was considered to be at the beginning [8].

Sonoelastography and many clinical applications of this technique are developing very rapidly. Although, recently published guidelines and recommendations concerning ultrasound elastography [2, 11] refer only to adult patients, as most of elastography studies are based on groups of adults as well. It should be noted that pediatric ultrasound examination differs a lot from the adult one. Not only differences concerning size, anatomy and morphology but also a different spectrum of abnormalities can be challenging. The technique of sonoelastography exam seems to make it even more difficult in children than routine US. These facts are probably the main reasons that pediatric elastography can be still considered as "terra incognita", thus a "no man's land" of pediatric radiology.

Liver

Liver elastography is one of the most developed and evaluated elastography applications [2]. Despite the fact that elastography allows us to better discern hepatic focal lesions, its main purpose remains to assess liver fibrosis. Liver biopsy, however, is still the golden standard; nonetheless, some elastography applications are considered useful, safe and repeatable methods to characterize liver condition [12]. About ten years' experience in using TE gave us numerous studies confirming the value of this application. TE was used and validated for evaluation of liver fibrosis in such states like chronic hepatitis C (HCV), chronic hepatitis B (HBV), nonalcoholic steatohepatitis (NASH), human immunodeficiency virus (HIV) with hepatitis C virus (HCV) coinfection, primary biliary cirrhosis or post-transplant patients. Researches where ARFI, SWE and SE were used also showed encouraging results [13]. However, those studies were based mainly on adult patients. Research on children is not numerous and usually based on a small groups of patients. The frequently encountered belief that elasticity values do not depend on age or etiopathogenesis of liver fibrosis is in our opinion at least a delicate overuse. Commonly distinct pathogenesis, different course of progression and specific symptomatology characterizing particular forms of liver fibrosis in children together with distinguishable compensation skills of immature organisms, obligate us conduct deeper studies on the utility of elastography in pediatric liver diseases. What is more, some data is quite equivocal – even in huge studies involving large groups of adult patients [13]. Such an example was given by Tsochatsiz et al. – they revealed in their meta-analysis that cut-off values for different stages of liver fibrosis were visibly different in HCV and HBV patients [14].

De Ledingen et al. proved the usefulness of TE in diagnosing hepatic cirrhosis in children with liver diseases (AUROC 0.88). The limitation of the study was the fact that from 116 patients only 33 had liver biopsy [9].

Distinguishing between significant and nonsignificant liver fibrosis is possible also by using laboratory tests [12] – the real challenge is to define the precise stage of liver fibrosis without a biopsy. This issue is particularly important in the case of viral infections (Fig. 1) and NAFLD due to the necessity of choosing the right therapy [12]. A very

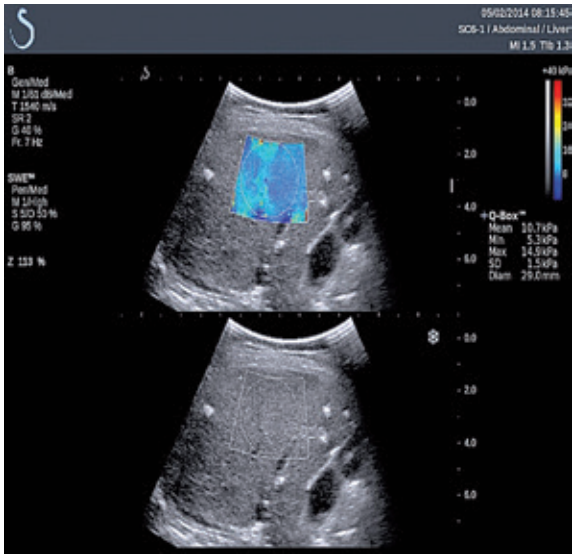

Fig. 1. A 7-year-old boy with chronic hepatitis C (diagnosed at the age of 6) has been admitted to the clinic with clinical and laboratory symptoms of deterioration of liver function: enlarged liver (in US right lobe was 13.7 cm in AP diameter), AST 377 U/L, ALT 402 U/L, alkaline phosphates 155 U/L. SWE revealed following results: 10.7, 10.4, 10.6, 10.9 and 10.9 kPa. Mean result (μ) was 10.7 kPa which was interpreted as F3 in the Metavir scale

interesting study was performed by Hanquinet et al. Liver biopsy was compared to ARFI values in 39 patients with liver disease. Heterogeneity of group is noticeable – 3 patients with biliary atresia with previous Kasai operation, 3 with congenital fibrosis-cholestasis, 3 with Alagille syndrome, 2 with Caroli disease, 1 with choledocal cyst, Wilson disease and mesenterico-caval shunt and 23 after liver biopsy [10]. The main goal was to assess the correlation between ARFI values and METAVIR scale [15] (scoring system developed and validated for HCV--infected adults) and SSS (semi quantitative scoring system). Results were very encouraging – distinguishing between METAVIR score ≤ F2 and > F3 and SSS < 5 and > 5 was 100% sensitive with using 2m/s cutoff. However, specificity was visibly lower and reached 32.1% for METAVIR and 39.1% for SSS – precise differentiation between e.g. F1 and F2 or F3 and F4 is still difficult [10].

HIV

Monpoux et al. examined 21 vertically-infected children by using TE. No HCV co-infection was mentioned. The study showed that HIV infected patients revealed a significantly higher TE results than healthy control children group and the increase in liver stiffness within HIV-infected group was correlated with age in a linear manner. Authors connect this reliance to chronic exposure to antiviral treatment [16].

NAFLD

The prevalence of childhood obesity is still increasing and nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in children in industrialized countries [17]. Progression of NAFLD connected with the presence of hepatocellular damage, inflammation and fibrogenesis is called nonalcoholic steatohepatitis (NASH). Nobili et al. conducted a study of 52 biopsy-proven nonalcoholic steatohepatitis children patients in whom the liver stiffness was measured by using TE technique. Results were very promising – statistical analysis revealed cutoff values of 5, 7 and 9 kPa suggesting the presence of any/significant/advanced fibrosis, respectively [18]. Alkhouri et al. examined 67 children with biopsy-proven NAFLD by using TE. Values were compared to the biopsy-staged fibrosis levels according to the Nonalcoholic Steatohepatitis Clinical Research Network. Statistical analysis confirmed the utility of TE to distinguish significant and non-significant (F < 2) fibrosis with a cutoff value of 8.6 kPa. However, the possible usefulness of TE for more precise staging purposes was not mentioned [17]. Some other research, which assessed in their groups not only patients with NAFLD, seems to confirm the utility of quantitative elastography in the evaluation of liver fibrosis [19, 20]. Fitzpatrick et al. examined 104 children with biopsy-staged liver fibrosis by using TE. Among them were 37 patients with NAFLD. The AUROC for the prediction of ≥ F2, ≥ F3, and F4 was 0.78, 0.79, and 0.96, respectively. However, authors concluded that TE brings the best results while performed in children with autoimmune liver disease (n = 27) and in those posttransplant (n = 16) [20].

CF-Associated Liver Disease

Pathognomonic hepatic manifestations of cystic fibrosis (CF) is biliary cirrhosis which leads to CF-associated liver disease (CFLD) in around one-quarter of patients [21]. Conventional ultrasound examination with B-mode seems to be insufficient in assessing liver condition in patients with CF [22]. Research conducted by Behrens et al. and Menten et al. compares respectively ARFI and TE value to B-mode. In spite of its good results, its value is slightly decreased due to this limitation [21, 23]. Friedrich-Rust et al. used ARFI, TE and biochemical markers of fibrosis on 106 adult patients with fibrosis. Despite the fact that all patients were adult, this study is worth mentioning as the most complete research of elastography in CFLD. As a result authors concluded that TE and ARFI seemed to be valuable method for non-invasive diagnosis of CFLD [24].

Post-Transplantation Liver

Apart from the research by Fitzpatrick et al. mentioned above [20], the study by Pinto et al. seems to be very relevant to the topic. These authors measured ARFI values, aspartate-to-platelet ratio index (APRI) and aspartate aminotransferase/alanine aminotransferase ratio index (AST/ /ALT). Prospectively they assessed liver fibrosis through biopsy. They divided the achieved results into two groups: non-significant fibrosis (F < 2) and significant fibrosis. The conclusion was that ARFI could serve as a potential method for assessing significant fibrosis in pediatric liver transplant patients, particularly in combination with AST/ALT ratio index [25]. Another example is a pilot study performed by Tomita et al. These authors also used ARFI to make 73 measurements in patients after living donor liver transplantation (LDLT). Fifty nine measurements were confronted with the biopsy result. The result showed that ARFI values significantly increased with the rise in portal and

pericellular fibrosis grades. Remarkably, AUROC values for measuring liver stiffness were higher when performed through the intercostal space than the midline (0.849, $p < 0.001$ vs. 0.760, $p = 0.005$). The optimal cutoff values were 1.30 and 1.39 m/s for midline and intercostal values, respectively [26].

Biliary Atresia

Biliary atresia (BA) is a progressive inflammatory disease of unknown pathogenesis, connected with the obliteration of the extrahepatic bile ducts. The obstruction of the biliary tree results in aggravation of cholestasis, hepatic fibrosis, biliary cirrhosis and finally end-stage liver disease leading to death within few years. [35] At present, the treatment of choice for children with BA is hepatoportoenterostomy (the Kasai operation), which can successfully restore bile flow in 60–90% of patients. Even though 75% of them progress to hepatic cirrhosis and ultimately require liver transplantation. [27]

As progressive hepatic fibrosis leading to liver cirrhosis in patients who underwent a Kasai surgery is the main indication for children's liver transplantation, hepatologic evaluation (including assessment of liver fibrosis) is crucial for these patients. Although liver biopsy is the "gold standard" for liver assessment, there is a need to develop none or less traumatic methods [10, 12]. As mentioned above, elastography is one of these noninvasive procedures, being currently in common use in older patients with liver fibrosis due to many pathological conditions e.g. HCV hepatitis [29]. However, the difference between congenital biliary atresia and well-investigated hepatic pathologies (e.g. liver cirrhosis in early age, in necessity of relatively quick post-surgical liver fibrosis assessment), leads to doubts whether the value of quantitative elastography should be confirmed again – specifically for biliary atresia. Thankfully, some available research seems to confirm its usefulness.

S.M. Hahn et al. focused on determining the risk factors to develop liver – related events (LRE) such as ascites, varical bleeding and death in children who underwent a successful Kasai surgery. Multifactorial study involved some laboratory examinations such as AST, ALT, GGT, ALP levels, PT-INR and also liver stiffness measurements by using TE technique. Research concerned 69 BA patients divided in two groups (with and without LRE). It showed that LSM value is the most important independent factor indicating the development of LRE [30]. Chongsrisawat et al. confirm the usefulness of elastography in predicting LRE. In their study, 73 children after portoenterostomy and 50 healthy controls were included. The study revealed that transient elastography may be an equally useful tool for predicting the presence of esophageal/gastric varices as physical examination and biochemical or hematological tests. The sensitivity and specificity of TE in this study were 84% and 74% respectively; however, the sensitivity and specificity of splenomegaly (clinical parameter which was also assessed in this research) were 92% and 85% [28]. The other studies focused on TE were presented by Honsawek et al. The main goal of this research was apparently to distinguish if serum adiponectin, galectin-3, tissue growth factor, osteopontine or soluble receptor for advanced glycation end products (sRAGE) level might be responsible for liver fibrosis. However, not only patients after Kasai operation but also some healthy controls were enrolled (in all researches). Higher kPa values in BA patients than in control groups allowed authors to conclude that TE could be useful tool for monitoring the severity and progression of postoperative BA [27, 31–34].

Shima et al. used ARFI technique to evaluate the stiffness of the liver tissue in a group of eight patients with BA. The results of these measurements were compared to serum hyaluronic acid level, which is one of the serum elastic markers. These findings allowed the researchers to come to the conclusion that the ARFI method may have a significant value for evaluating the severity of liver fibrosis in patients after a hepatoportoenterostomy [35].

Yet, none of this research compared elastography to the mentioned-above diagnostic "golden standard" – liver biopsy. Moreover, in a few cited researches, elastography was used as a reliable method to compare other investigated factors [27, 31–34]. In our opinion more research is required to establish the role of elastography in postoperative monitoring patients with BA.

Other

Some mentioned-above research included also a small group of patients with other relatively rare diseases that affect liver, as Wilson disease, autoimmune hepatitis, alpha-1 antitrypsin deficiency, Allagile syndrome etc. [10, 19]. Kummer et al. suggest value of TE to improve diagnosing of liver fibrosis in children with autosomal-recessive polycystic kidney disease (ARPKD) [36]. Impossible to ignore are also studies by Fontanilla et al. and Lee et al., where normal ARFI values of the children liver were assessed [37, 38]. Moreover, Lee et al. also assessed age-related ARFI values for kidneys and spleen [38]. Normal SWE values of liver stiffness in a group of 91 healthy children (46 from 0 to 10 years old) were measured by Selmi et al. [39]

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