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Impact of probe-induced abdominal compression on two-dimensional shear wave elastography measurement of split liver transplants in children

Der Einfluss der schallkopfinduzierten abdominellen Kompression auf die 2-dimensionale Scherwellen-Elastografie in Kindern mit Split-Leber-Transplantaten

Authors

Michael Groth[1], Lutz Fischer[2], Uta Herden[2], Florian Brinkert[3], Jan Beime[3], Philipp Deindl[4], Gerhard Adam[5], Jochen Herrmann[1]

Affiliations

1 Department of Diagnostic and Interventional Radiology and Nuclear Medicine, Section of Pediatric Radiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2 Hepatobiliary Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
3 Pediatric Gastroenterology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
4 Department of Neonatology and Pediatric Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
5 Department of Diagnostic and Interventional Radiology and Nuclear Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Key words

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Correspondence

PD Dr. med. Jochen Herrmann
Department of Diagnostic and Interventional Radiology and Nuclear Medicine, Section of Pediatric Radiology, University Medical Center Hamburg-Eppendorf, Hamburg, Deutschland
Tel.: +49/40/4 28 03 27 12
jherrmann@uke.de

ABSTRACT

Purpose To evaluate the effect of probe-induced abdominal compression of split liver transplants (SLT) in children on 2D-shear wave elastography (SWE) values.

Materials and Methods Data from 11 children (4.7 ± 4.8 years) who had undergone SLT and SWE were evaluated retrospectively. Elastograms were obtained with probes placed in an epigastric, midline position on the abdominal wall, with no and slight compression, using convex and linear transducers. For each identically positioned probe and condition, 12 serial elastograms were obtained and the SLT diameter was measured. Liver stiffness and degree of SLT compression were compared.

Results Slight probe pressure resulted in SLT compression, with a shorter distance between the cutis and the posterior margin of the liver transplant than in the measurement with no pressure (curved array, 5.0 ± 1.1 vs. 5.9 ± 1.3 cm, mean compression 15 %± 8 %; linear array, 4.7 ± 0.9 vs. 5.3 ± 1.0 cm, mean compression 12 %± 8 %; both $p < 0.0001$). The median liver stiffness was significantly greater with slight pressure than with no pressure (curved transducer, 13.38 ± 3.0 vs. 7.02 ± 1.7 kPa, $p < 0.0001$; linear transducer, 18.53 ± 7.1 vs. 9.03 ± 1.5 kPa, $p = 0.0003$).

Conclusion Slight abdominal compression can significantly increase SWE values in children with left-lateral SLT. To obtain meaningful results and reduce operator dependency in free-hand examinations, probe pressure must be controlled carefully.

Key points:

- Probe-induced compression can increase elastography values in split liver transplants in children
- In free-hand examination, probe pressure must be controlled carefully
- Pressure loading can be determined indirectly by the anteroposterior transplant diameter

Citation Format

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ZUSAMMENFASSUNG

Ziel Evaluation des Effektes der Kompression durch die Ultraschallsonde bei der 2D-Scherwellen-Elastografie (SWE) auf die Elastografiewerte bei Split-Leber-Transplantaten (SLT) in Kindern.

Material und Methoden 11 SWE-Untersuchungen von Kindern (4.7 ± 4.8 Jahre) nach SLT wurden retrospektiv ausgewertet. Elastogramme wurden mit der Konvex- und Linearsonde in einer mittig epigastrischen Position mit nahezu keiner und wenig Kompression angefertigt. Es wurden jeweils 12 Elastogramme erfasst. SLT-Diameter wurden bestimmt. Leber-Steifigkeit und SLT-Kompression wurden verglichen.

Ergebnisse Wenig Sondendruck resultierte, verglichen mit nahezu keinem Druck, in einer SLT-Kompression mit kürzerer Entfernung zwischen Kutis und SLT-Hinterrand (Konvex: 5.0 ± 1.1 vs. 5.9 ± 1.3 cm, mittlere Kompression 15 % ± 8 %; Linear: 4.7 ± 0.9 vs. 5.3 ± 1.0 cm, mittlere Kompression: 12 % ± 8 %; beide p < 0.0001). Die mediane Leber-Steifigkeit war mit leichter Kompression signifikant höher als nahezu ohne (Konvex: 13.38 ± 3.0 vs. 7.02 ± 1.7 kPa, p < 0.0001; Linear: 18.53 ± 7.1 vs. 9.03 ± 1.5 kPa, p = 0.0003).

Schlussfolgerung In Kindern nach SLT kann leichte Kompression SWE-Werte signifikant erhöhen. Um aussagekräftige Ergebnisse zu erhalten und zur Reduzierung der Auswerterabhängigkeit sollte der Sondendruck kontrolliert werden.

Kernaussagen:
- Ultraschallsondendruck kann Elastografiewerte bei Kindern mit Split-Leber-Transplantaten erhöhen
- Der ausgeübte Sondendruck muss beim Untersuchen aufmerksam kontrolliert werden
- Ultraschallsondendruck kann indirekt über den anteroposterioren Transplantatdiameter bestimmt werden

Introduction

Ultrasound elastography is used widely to quantitatively assess liver stiffness, and normal values for adults and children have been published [1–3]. Many centers have included ultrasound elastography in standardized protocols for patient follow-up after liver transplantation [4, 5], as this modality enables the noninvasive determination of the degree of fibrosis and identification of acute allograft damage such as rejection, infection, and hepatic outflow obstruction [5–10].

Available techniques for quantitative ultrasound elastography include transient elastography (TE), point shear wave elastography (pSWE), and two-dimensional shear wave elastography (2D-SWE) [11, 12]. The appropriate method depends on the clinical situation. 2D-SWE is used widely for the evaluation of liver transplantations, including left-lateral split transplantations (LTXs), which account for the majority of pediatric transplants [6, 7, 13], and has been shown to be more accurate than pSWE for the evaluation of liver fibrosis in children [14].

In contrast to the published recommendations for elastography measurement of whole livers, the favored intercostal approach cannot be used in pediatric cases of left-lateral LTX with midline grafting [1]. For a sufficient acoustic window in left lateral splits, the transducer needs to be placed in an epigastric position [13]. Yet, unshielded placement of the probe directly on the transplanted liver raises the concern that pressure loading via transducer compression of the liver could falsely elevate measurements as suggested by the performance of ex-vivo measurements in piglet livers and other superficially localized organs including the breast, thyroid, transplanted kidneys, and skeletal muscle [15–18].

The aim of this study was to evaluate the effect of probe-induced abdominal compression of left split LTXs in children on 2D-SWE values. We hypothesized that variable degrees of transducer compression applied during free-hand clinical examinations of children who had undergone LTX would be a source of unrecognized error.

Materials and Methods

Subjects

This retrospective study was legitimated by the local medical statute (Ethik-Kommission der Ärztekammer Hamburg, WF-71/16), and the requirement for written informed consent was waived. All examinations were conducted according to the Declaration of Helsinki. All pediatric patients who had undergone LTX of segments 2/3 in January and February 2018 at our university hospital and received a standardized ultrasound examination, including 2D-SWE examination with variable degrees of transducer pressure, were included. The evaluated examinations were all clinically indicated. Two different modes of probe placement and respective measurements were performed in the context of clinical introduction of elastography to the pediatric transplantation scenario in the assessed two-month period. The results of both settings were acknowledged in the findings and were considered a means of internal quality control in order to avoid overestimation or false interpretation of the results. After the two-month initiation period, the protocol was changed to “low pressure” examinations only based on the initial data. Therefore, more patients could not be included in this study.

The exclusion criteria were insufficient documentation and incomplete examination. 3 of 14 consecutive patients were excluded, due primarily to incomplete examination caused by agitation during the examination. The final cohort thus included 11 children (3 females and 8 males; mean age ± standard deviation [SD], 4.7 ± 4.8 years; ▶ **Table 1**). The primary diagnoses that led to liver transplantation were biliary atresia (*n* = 5), ornithine transcarbamylase deficiency (n = 2), hepatopathy of unknown etiology (n = 2), arginase deficiency (n = 1), and type 2 progressive familial intrahepatic cholestasis (n = 1).

Of the 11 patients, 7 had no fibrosis proven by biopsy (METAVIR F0) or low-grade fibrosis (METAVIR F1). Of the remaining four patients without available biopsy, three patients had elastography

▶ **Table 1** Curved transducer elastography measurements performed with no and low transducer-induced pressure.
Data are presented as means with standard deviations.
IQR: interquartile range.
Median liver stiffness with no vs. slight transducer pressure, $p < 0.001$; IQR of measurements with no vs. slight transducer pressure, $p = 0.016$; IQR/median with no vs. slight transducer pressure, $p = 0.164$.

▶ **Tab. 1** Konvexschallkopf-Elastografiemesswerte mit wenig und nahezu ohne Ultraschallkopfdruck.
Die Daten werden als Mittelwerte mit Standardabweichung angegeben.
IQR, interquartile range.
Mediane Leber-Stiffness mit vs. nahezu ohne Ultraschallkopfdruck, $p < 0.001$; IQR der Messwerte mit vs. ohne Ultraschallkopfdruck, $p = 0.016$; IQR/Median mit vs. ohne Ultraschallkopfdruck, $p = 0.164$.

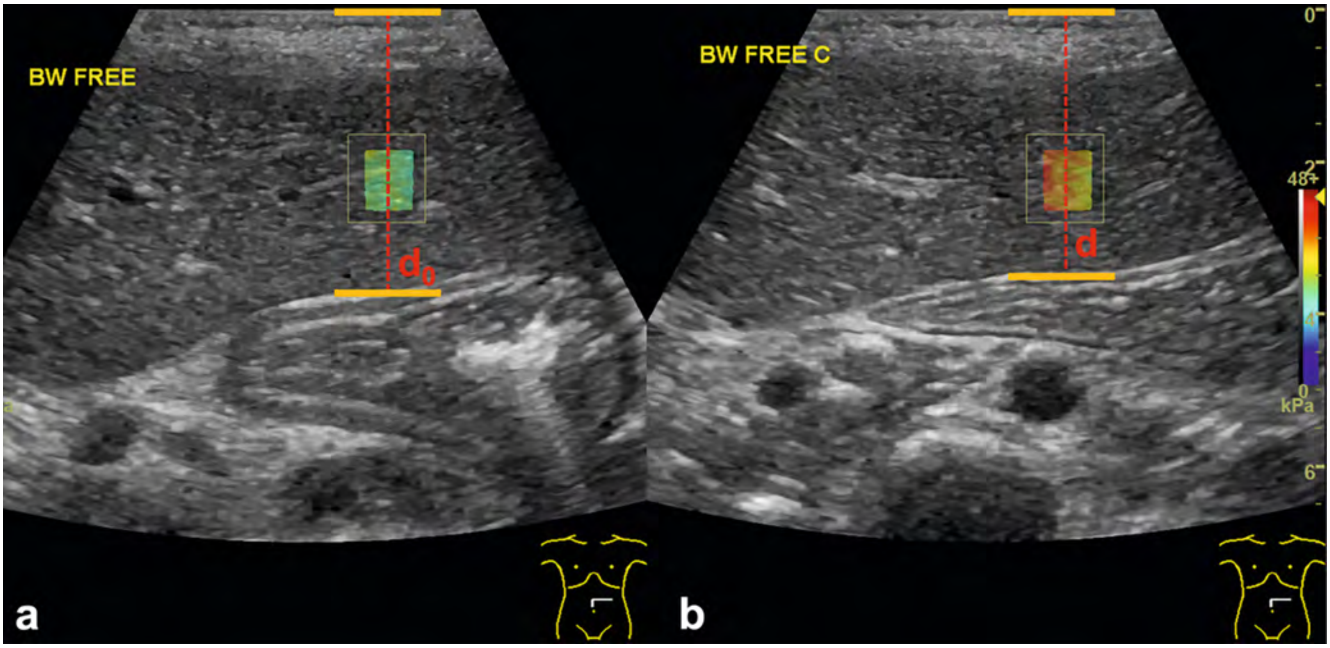
	Median liver stiffness (kPA)		IQR (kPA)		IQR/median	
Patient age (y)/gender	**Transducer pressure**		**Transducer pressure**		**Transducer pressure**	
	No	**Low**	**No**	**Low**	**No**	**Low**
1/8/m	8.8	16.28	1.85	2.15	0.21	0.13
2/0/m	5.46	12.26	0.93	1.43	0.17	0.12
3/0/m	5.94	10.73	0.6	2.80	0.10	0.26
4/3/m	9.87	17.11	0.77	3.68	0.08	0.22
5/16/f	9.04	13.64	1.20	1.37	0.13	0.10
6/3/f	6.42	12.03	0.60	1.49	0.09	0.12
7/3/f	6.6	15.14	0.81	1.97	0.12	0.13
8/6/m	7.7	18.27	1.21	7.94	0.16	0.43
9/0/m	4.52	8.45	0.67	0.71	0.15	0.08
10/8/m	7.39	11.82	1.13	1.16	0.15	0.10
11/5/m	5.47	11.42	0.64	2.00	0.12	0.18
All patients	7.02 ± 1.7	13.38 ± 3.00	0.95 ± 0.38	2.43 ± 2.0	0.13 ± 0.04	0.17 ± 0.1

measurements during their early post-operative course after LTX (day 3–31 after LTX). For this subset of patients, absence of fibrosis can be safely assumed soon after LTX also without histological confirmation.

Ultrasound Examination

A single experienced pediatric radiologist (J. H.) performed the ultrasound examinations using a predefined protocol with prospective documentation and a commercial scanner (GE Logiq E9 ultrasound system; GE Medical Systems, Milwaukee, WI, USA) with a C1–5 MHz curved array transducer and an L9 MHz linear array transducer. The children were examined in a supine position under free breathing after ≥ 2-hour fast. An epigastric abdominal wall approach and two free-hand adjusted probe pressure modes were used. Measurements were performed in the same location with both arrays using the lowest possible probe pressure ("no pressure settings," d_0), and then using slight abdominal wall compression ("low pressure settings," d) to achieve a closer connection. In the "no pressure setting", the probe was placed on the abdominal wall above the liver transplant with the lowest possible pressure to just achieve acoustic coupling with the underlying tissue. With the curved array transducer only acoustic coupling in the center of the window needed to be achieved and coupling at the outer portions of the transducer was omitted as full coupling of the more distant sides of the convex surface would require higher probe pressure. With the low-pressure setting, full acoustic coupling needed to be achieved with slight compression of the underlying tissues. Stronger compression of the underlying liver transplant was not performed. A shear wave color map was positioned in the liver parenchyma ≥ 1–2 cm below the liver capsule. Vessels and focal lesions were omitted. The examinations were stopped when 12 successful elastograms had been recorded.

To semiquantitatively assess the degree of probe-induced compression and its effect on the underlying liver transplants, the methods of Barr et al. and Vachutka et al. were adapted [16, 17]. The distance between the cutis and the posterior margin of the liver transplant was measured at the level of the elastogram, and mean values for each condition and probe type were calculated. The degree of compression was calculated using the formula ($\delta = 1 - d/d_0$) (▶ **Fig. 1**). Two experienced pediatric radiologists (J. H. and M. G.) then performed consensus reading of the measurements on a PACS workstation (Ventricity Universal Viewer GE Healthcare, Milwaukee, WI, USA). Anomalies and artifacts on the



▶ **Fig. 1** 2D-SWE of a lateral LTX (patient 4) measured under low (**a**) and slight (**b**) probe pressure. Indicated are the distances between the cutis and the posterior margin of the liver, obtained with identical probe positioning. The degree of compression was calculated using the formula δ = 1 – d/d0; for patient number 4: 0.07 = 1–4.30 cm/4.64 cm.

▶ **Abb. 1** 2D-SWE eines lateralen LTX (Patient 4) nahezu ohne (**a**) und mit wenig (**b**) Ultraschallsondendruck. Eingezeichnet sind die Abstände zwischen der Kutis und dem posterioren Leberrand mit identischer Sondenposition. Der Kompressionsgrad wurde mit der Formel δ = 1 – d/d0 berechnet. Für Patient 4: 0,07 = 1–4,30 cm/4,64 cm.

B-mode images and embedded elastograms were noted when present.

Statistical Analysis

Elastography measurements obtained under the d_0 and d conditions were compared using Bland-Altman analysis and Student's t test. All liver stiffness values (median liver stiffness, interquartile ranges (IQR), and IQR/median ratio) and the distances between the cutis and lower transplant margin measured under the d_0 and d conditions were compared using Student's t test. Statistical analysis was performed using MedCalc Version 19.4.1 for Windows (MedCalc Software Ltd, Ostend Belgium) and Excel (Microsoft Corporation, Redmond, WA, USA).

Results

In total, 528 single hepatic 2D-SWE measurements on 11 children who had undergone left-lateral LTX were performed and evaluated. Examination quality was good under both conditions, with no anomalies or artifacts noted. All patients tolerated the examination well.

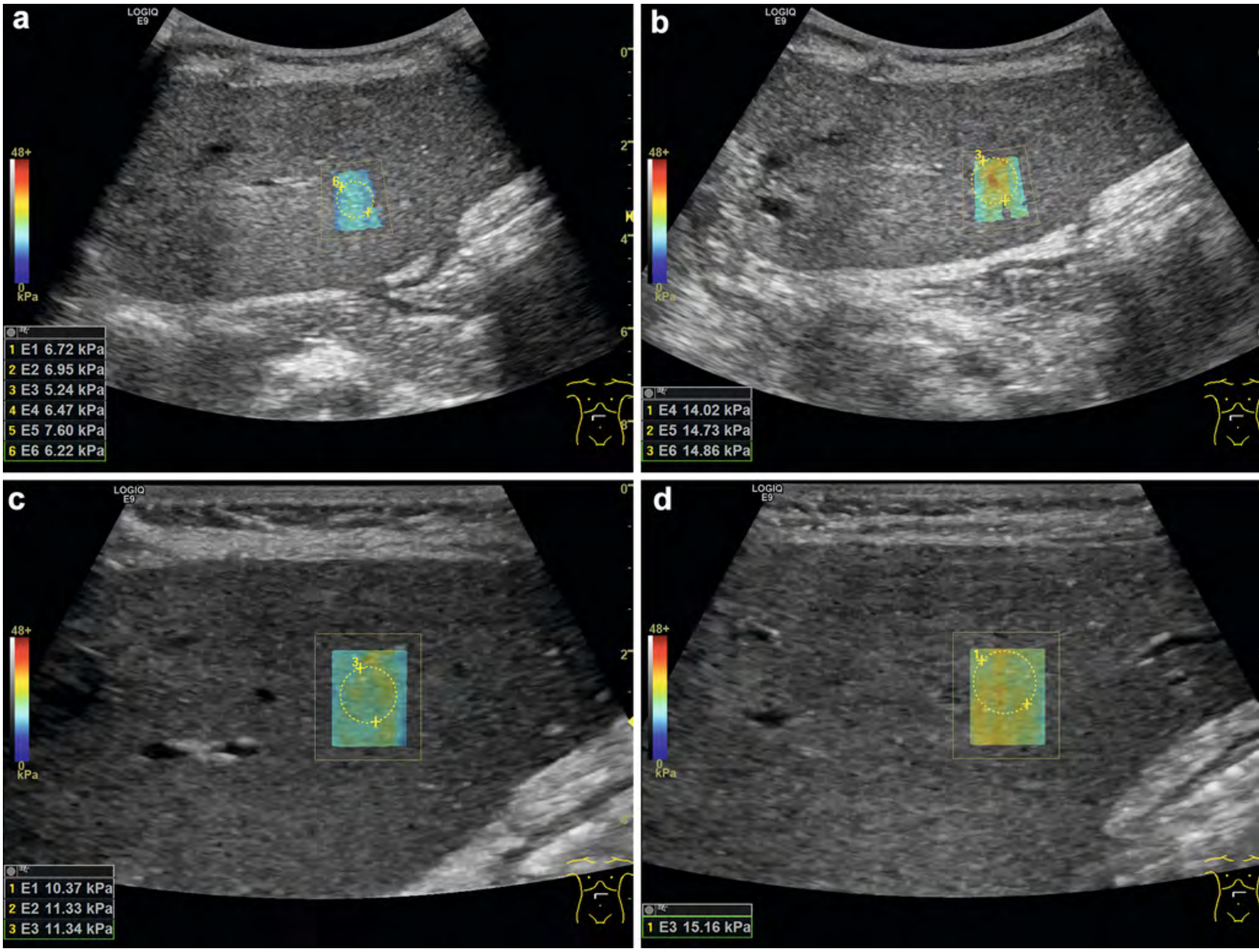
Under the d_0 and d conditions, the mean distances between the cutis and lower LTX margin were 5.9 ± 1.3 and 5.0 ± 1.1 cm ($p < 0.0001$), respectively, for the curved array, and 5.3 ± 1.0 and 4.7 ± 0.9 cm ($p < 0.0001$), respectively, for the linear array. The degrees of abdominal compression under d were 15 % ± 8 % with the curved transducer and 12 % ± 8 % with the linear transducer.

For examinations performed with the curved and linear transducers, the median liver stiffness was significantly greater (by 6.6 and 9.8 kPa, respectively) under d than under d_0 (13.38 ± 3.0 vs. 7.02 ± 1.7 kPa and 18.53 ± 7.1 vs. 9.03 ± 1.5 kPa; $p < 0.0001$ and $p = 0.003$, respectively; ▶ **Fig. 2, 3,** ▶ **Table 1, 2**). The measurement variability was greater under d than under d_0 for examinations performed with both transducers (▶ **Table 1, 2**). No significant difference in the IQR/median ratio was observed.

Discussion

This study evaluated the effect of probe-induced abdominal compression on 2D-SWE values obtained for children who had undergone left-lateral LTX. With epigastric probe positioning, even slight compression of the abdominal wall and underlying liver transplant resulted in the acquisition of significantly higher stiffness values compared to the use of the lowest possible pressure. This finding is in accordance with one experimental ex-vivo study examining the use of 2D-SWE in piglet livers, in which slight tissue compression altered the quantitative elastography results [16]. Similar observations were reported for 2D-SWE in skeletal muscle, thyroid, breast, and transplanted kidneys [15–18].

With ultrasound elastography, the estimation of liver stiffness is based on the measurement of shear wave speed; commercial systems apply simplified equations assuming that tissues are homogeneous, linear, isotropic, and incompressible (Palmeri et al.) [19]. However, in biological tissues and clinical situations,

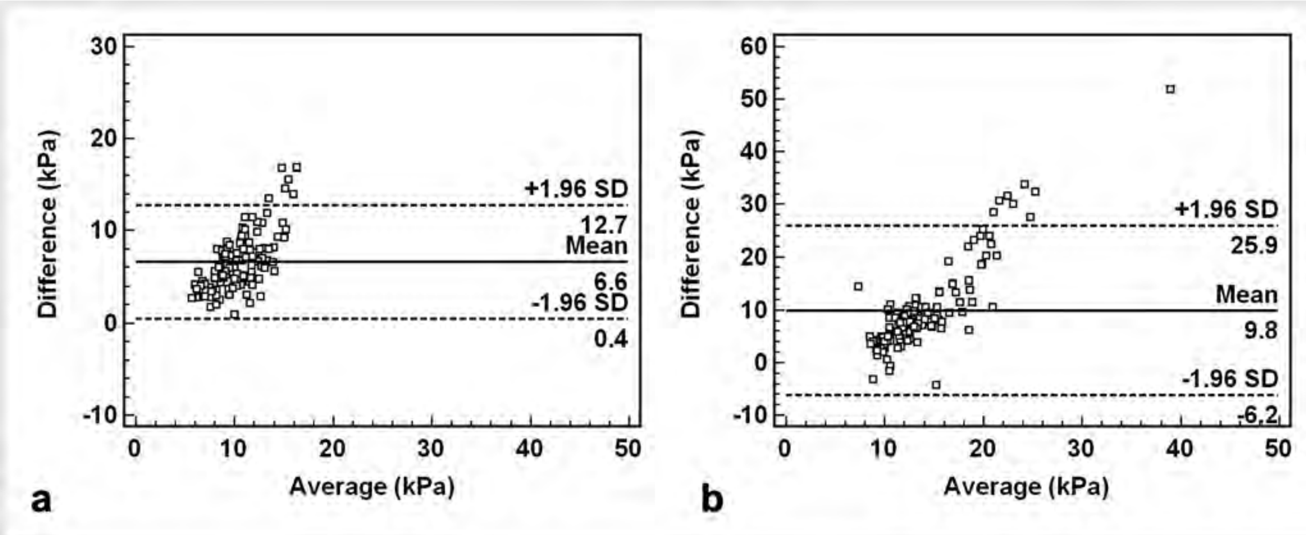


▶ **Fig. 2** 2D-SWE of a 3-year-old boy (patient 4) who underwent LTX of liver segment 2/3, with the probe placed on the abdominal wall directly above the transplant using curved (**a, b**) and linear (**c, d**) transducers with low (**a, c**) and slight (**b, d**) probe pressure.

▶ **Abb. 2** 2D-SWE eines 3-jährigen Jungen (Patient 4) mit Z. n. Lebersegmenttransplantation der Segmente 2/3. Die Ultraschallsonde wurde unter Verwendung des Konvexschallkopfes (**a, b**) und des Linearschallkopfes (**c, d**) direkt über dem Lebertransplantat auf der Bauchdecke positioniert nahezu ohne (**a, c**) und mit wenig (**b, d**) Ultraschallsondendruck.

these assumptions may be violated to various degrees [20]. Probe-induced pressure on the abdominal wall can induce tissue compression, as indicated by the reduced distance between the cutis and the posterior margin of the liver transplant acquired under the *d* condition in this study. SWE measurement with slightly more pressure led to mean increases in elastography results with the curved and linear transducers, respectively. Depending on the clinical context, these increments could lead to misinterpretation of the results. Six of our patients were assessed in the early postoperative period after transplantation (< 1 month after LTX), when elevation of liver stiffness can be a sign of acute rejection, inflammation, or hepatic outflow obstruction [5–10]. Four children prone to chronic changes like post-transplant fibrosis or chronic rejection associated with increased elastography values were evaluated during the later follow-up phase [5–10]. Quantitative longitudinal measurements of liver stiffness are seen as especially useful for monitoring disease activity in a variety of disorders including liver transplantation. However, as the change of liver stiffness over time (delta) can also be a result of measurement variability, a standardized setup for the follow-up of individual patients is important [21].

In adult patients with whole livers, the problem of tissue deformation as a result of transducer compression seems to be less relevant. When performing shielded elastography measurements via the right intercostal space with the right arm elevated as recommended by EFSUMB guidelines [1], even a high transducer pressure can be exerted to reduce the skin-to-capsule distance in obese patients without changing the tests' diagnostic performance [22]. Maximum pre-compression in the cited study led to slightly lower SWE values than normal probe pressure settings (5.02 vs. 5.49 kPa) with the benefit of an improved technical success rate (87.6 % vs. 98 %) [22]. The small opposite effect can be explained by the lower attenuation of the ultrasound waves which can better traverse compressed than non-compressed subcutaneous fatty tissues. Interestingly, another experimental study performed in healthy adult volunteers also found that increased



▶ **Fig. 3** Bland-Altman plots of median liver stiffness (kPa) obtained with slight pressure (x axis) and the least possible pressure with curved (**a**) and linear (**b**) transducers.

▶ **Abb. 3** Bland-Altman-Graph der medianen Leber-Steifigkeit (kPa) mit wenig (X-Achse) und dem geringst möglichen Druck für den Konvex- (**a**) und Linearschallkopf (**b**).

▶ **Table 2** Linear transducer elastography measurements performed with no and low transducer-induced pressure.
Data are presented as means with standard deviations.
IQR: interquartile range.
Median liver stiffness with low vs. slight probe pressure, $p < 0.001$; IQR of measurements with low vs. slight transducer pressure, $p = 0.013$; IQR/median with no vs. slight transducer pressure, $p = 0.374$.

▶ **Tab. 2** Linearschallkopf-Elastografiemesswerte mit wenig und nahezu ohne Ultraschallkopfdruck.
Die Daten werden als Mittelwerte mit Standardabweichung angegeben.
IQR, interquartile range.
Mediane Leber-Stiffness mit vs. nahezu ohne Ultraschallkopfdruck, $p < 0.001$; IQR der Messwerte mit vs. nahezu ohne Ultraschallkopfdruck, $p = 0.013$; IQR/Median mit vs. ohne Ultraschallkopfdruck, $p = 0.374$.

	Median liver stiffness (kPA)		**IQR (kPA)**		**IQR/median**	
Patient no./ age (y)/sex	**Transducer pressure**		**Transducer pressure**		**Transducer pressure**	
	No	**Low**	**No**	**Low**	**No**	**Low**
1/8/m	10.51	25.92	1.02	5.02	0.10	0.19
2/0/m	9.44	15.24	0.91	1.19	0.10	0.08
3/0/m	8.59	16.00	0.51	1.51	0.06	0.09
4/3/m	9.83	19.31	1.28	1.05	0.13	0.05
5/16/f	6.58	15.93	0.94	1.37	0.14	0.09
6/3/f	7.95	11.78	1.38	2.30	0.17	0.20
7/3/f	10.14	17.24	1.63	2.73	0.16	0.16
8/6/m	11.86	22.47	2.92	7.83	0.25	0.35
9/0/m	7.93	10.57	1.07	0.53	0.13	0.05
10/8/m	7.28	35.24	0.95	6.67	0.13	0.19
11/5/m	9.18	14.14	1.86	2.78	0.20	0.20
All patients	9.03 ± 1.55	18.35 ± 7.1	1.32 ± 0.65	3.00 ± 2.4	0.14 ± 0.05	0.15 ± 0.09

transducer force applied on the epigastric abdominal wall slightly reduced ARFI (acoustic radiation force imaging) values measured in the left lobe [23].

The anatomical conditions, however, found in adult patients with whole livers are not fully applicable to the pediatric population. Children have substantially narrower intercostal spaces than adults, and higher technical failure rates have been reported for TE using an intercostal approach (up to 17 % for patients aged < 2 years and up to 10 % for all other ages) [14, 24]. Children with segment 2/3 transplants can generally only be examined in the epigastric position with the graft located in the midline position in the limited space of the abdominal cavity above the spine [13]. Contrary to the situation in adults, the abdominal wall in young children is thin-layered and contains only small amounts of subcutaneous fat and muscle. This explains why even the low transducer pressure applied in our study was relatively directly passed on to the graft, thereby inducing a substantial SWE value increase due to tissue deformation.

Since a variable degree of transducer compression in free-hand examinations can be a significant source of error, the applied transducer force needs to be controlled in comparative as well as in longitudinal studies evaluating disease progression. A semi-quantitative method to indirectly capture the degree of transducer compression during follow-up examinations is to measure the distance from the skin to a lower anatomical landmark beneath the probe [19]. This method is also feasible in children with split liver transplants. For the breast it has been postulated that a transducer pre-compression < 1 % of the respective organ depth will give the most reproducible imaging results [25]. A possible future alternative to free-hand SWE examinations is to technically control the probe pressure with the help of a robotic device. A system has been developed and successfully tested in phantoms and human volunteers under breath-hold conditions [26].

This study has several limitations. First, it was retrospective and involved the comparison of two transducer pressure modes adjusted subjectively by a single sonographer. Due to this clinical situation, inter-rater variability could not be assessed. Second, we did not precisely measure the probe pressure applied to the abdominal wall. To our knowledge, no scale to control for probe pressure in quantitative SWE performed with a commercial system is available. Third, which measurement better reproduces actual liver stiffness remains unclear. We consider the floating probe position with the lowest possible probe pressure to be representative, as the ultrasound system's internal quality control validated the measurements obtained under this condition. In addition, the elastography values were within the range of normal stiffness values reported for liver transplants [13, 27]. Histological confirmation of the absence of clinically significant fibrosis (METAVIR ≤ F1) was available for seven of our patients and can be postulated for three further cases without available biopsy who were evaluated within one month after the transplantation.

In conclusion, SWE measurement of split liver transplants performed via the abdominal wall can be altered by even slight transducer pressure, indicating the need for careful pressure control. Differences in free-hand compression among examiners remains a concern for quantitative SWE, as a proper B-mode image can almost never be obtained without exerting some pressure on the underlying transplant [19]. A technical solution, such as commercial systems' measurement and registry of the probe pressure applied during quantitative SWE, would enhance the accuracy of the examination of split liver transplants and other indications involving direct probe impact.

Conflict of Interest

The authors declare that they have no conflict of interest.

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