의학석사 학위논문

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2016 년 2 월

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A thesis of the Degree of Master of Science in Medicine

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February 2016

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이 논문을 의학석사 학위논문으로 제출함
2016년 2월

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정선지의 의학학사 학위논문을 인준함
2016년 2월

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Abstract

Purpose: To evaluate the reliability and validity of three-dimensional (3D) ultrasound (US) volumetric measurements of the liver in children.

Methods: Sixteen consecutive children (mean age: 5.75 years, range: 1-10 years of age) who underwent both 3D liver US and CT examinations within the same week comprised our study group. 3D US data were acquired by one experienced radiologist using an US machine equipped with a position sensing system. The reference liver volume was calculated from the CT scan using the voxel-count method. Two radiologists who were blinded to the reference CT liver volume measured the liver volume two times from the 3D US data. For evaluation of validity, the mean value of two US liver volume measurements for each patient were compared with the reference CT liver volume. The reliability of the 3D US liver volume measurements was assessed by calculating the intraclass correlation coefficient (ICC) and Spearman's correlation coefficient. Bland-Altman plots were created.

Results: The mean and standard deviation of the liver volumes with 3D US and CT was 658.32 ± 222.92 ml and 665.82 ± 220.49 ml, respectively. The mean absolute volume difference between the

3D US and reference CT liver volumes was −7.5 ml (range, −173.01 ml to 143.63 ml). The ICCs for intraobserver reliability were 0.997 (95% confidence interval, 0.897−0.987) for observer A and 0.997 (95% confidence interval, 0.936−0.992) for observer B. The interobserver ICC was 0.964. Regarding the validity of the 3D US measurement, the ICC between the 3D US and CT was 0.922 (0.792-0.972). The Bland−Altman plots showed good repeatability. For reproducibility, the measured 3D US liver volume by observer A was larger than that obtained by observer B on Bland−Altman plot. The range of limit of agreement on the Bland−Altman plot for validity was −178.3 mL to 163.3 mL

Conclusion: Liver volume measurement in children with the 3D US system showed good repeatability. For clinical applications, an observer consensus and detailed instructions for measurement should be implemented.

Keyword : Liver, Volume, Children, 3D US, Validity, Repeatability, Reproducibility

Student Number : 2014−21139

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LIST OF ABBREVIATIONS

2D = two-dimensional

3D = three-dimensional

US = ultrasound

CT = computed tomography

MRI = magnetic resonance imaging

SD = standard deviation

ICC = intraclass correlation coefficients

LoA = limits of agreement

INTRODUCTION

Accurate measurement of liver size is of clinical value not only in monitoring the progress of disease but also as a unit of reference for quantitative hepatic function tests. Liver volume does not accurately reflect liver function, but it is closely related (1, 2). Hepatomegaly is a well-known manifestation of various diseases involving the liver, such as acute hepatitis, metabolic diseases, or hemato-oncologic diseases (3, 4). Accurate noninvasive assessment of liver volume is used in the clinical treatment of patients with these diseases. Knowledge of liver size is also of clinical relevance when determining graft size for liver transplantation and organ viability after resection. Recently, there have been some reports that liver volume is associated with the outcome of the liver transplantation (5-7). An accurate assessment of liver volume is also important for curative treatment of hepatic malignancy, which frequently requires massive resection of the liver. In these situations, an accurate assessment of hepatic reserve function, including liver volume, is important for the estimation of postoperative functional reserve and appropriate operative management (2, 8).

Physical examination is a basic method for identifying

hepatomegaly in clinical practice. It is simple, but the accuracy and repeatability are low (9). Previously described imaging techniques for measuring liver volume have relied on conventional 2-dimensional (2D) ultrasound (US) and tomographic imaging, including computed tomography (CT) and magnetic resonance imaging (MRI). CT is known to be a reliable and accurate method for assessing the volume of the liver and other intra-abdominal organs. However, the radiation exposure associated with CT is a problem for clinical applications of liver volume measurement in children. MRI may be a good modality for liver assessment, but it is time consuming, expensive, and not readily available. Because of its high accuracy, availability, non-invasiveness, and convenience, conventional 2D US plays an important role in the measurement and assessment of the liver. On 2D US, the liver volume is usually assessed by its length (10). However, due to the complex shape of the liver, 2D US cannot accurately reflect hepatic volume. Recently, three-dimensional (3D) US imaging has become available in clinical practice. It is possible to obtain tomographic imaging and 3D volume data using 3D US. 3D volume data acquisition using a position-tracking method is one of the 3D US techniques (11). It functions similarly to a global positioning system. As the operator sweeps the area with the US probe head, it instantly localizes the position and

orientation of the probe head in relation to the patient's position (11). There have been many studies published about image fusion and needle guidance using the position sensing technique (12, 13). There have been very few reports that assessed the volume of intra-abdominal solid organs in children using 3D US. The purpose of this study is to evaluate the reliability and validity of 3D US volumetric measurements of the liver in children.

MATERIALS AND METHODS

Patients

Our institutional review board approved this study, and the need for informed consent was waived. From November 2014 to February 2015, 16 consecutive children who underwent both 3D abdominal US and CT examinations within the same week comprised our study group. Their mean age was 5.75 years (range: 1–10 years of age). The mean time interval between CT examination and US examination was 2.6 days (range: 0–7 days). Except for two patients, the CT examinations were performed before the US exams. The patient group consisted of eight girls and eight boys. The reasons for CT and US examination were the evaluation of a hematologic malignancy (n = 4), a follow-up study after liver transplantation (n = 3), an evaluation of an extrahepatic solid tumor (n = 2), an evaluation of acute appendicitis (n = 3), and other reasons (n = 4).

3D US data acquisition

The 3D US data were acquired by one experienced pediatric radiologist (Y.H.C) using an US machine equipped with a position sensing system (LOGIQ E9; GE Healthcare, Chalfont St. Giles, UK).

C1-6-D and C2-9-D convex US transducers were used. The radiologist moved the US probe with position sensors over the region of interest, which can cover the whole liver.

CT image acquisition

CT examinations were performed with a SOMATOM Definition system (Siemens Healthcare, Forchheim, Germany). All CT scans were obtained with contrast media injection. Slice thicknesses ranged from 3 mm to 5 mm.

Volume measurement

The liver volume on CT as a standard of reference was calculated manually by one radiologist using the voxel-count method. Two radiologists who were blinded to the reference CT liver volumes measured the liver volume twice from each set of 3D US data, at 1-week intervals. Measurements were performed using US machine software. Two observers were instructed to manipulate the 3D US image. The sagittal axis with a 5-mm interval was used for the measurements. As the observer marked the contour of the liver in each section, the software calculated and summated the volume automatically (Fig. 1). The extrahepatic portal vein and the inferior vena cava were not included in measurements on both CT and US.

Statistical analysis

Reliability was assessed using the repeatability and reproducibility of the measurements. The repeatability was defined as the intraobserver agreement for the two measurements by the same observer for each liver. The reproducibility was defined as the interobserver agreement for the measurements per liver by the two observers. Validity was assessed by the evaluation of agreement between the CT and US-based measurements. To assess the reliability and validity, Spearman's correlation, intraclass correlation coefficients (ICC), and the Bland-Altman method were used. The ICCs ranged from 0 to 1 and were classified as the degree of agreement as is commonly used: <0.75, poor; 0.75-0.9 moderate; and >0.9, high. The averaged values of two measurements per liver by each observer were used for assessing the reproducibility. To assess the agreement between 3D US and CT volumetry, the averaged values of two observers were used. For the presence of heteroscedasticity, which means proportional error to the mean, the Bland-Altman plots were visually inspected (14). If heteroscedasticity was suspected, the Kendall's tau correlation coefficient was calculated to obtain statistical significance using logarithmic transformed absolute differences and

corresponding means. If the line of equality was out of the 95% confidence interval of the mean difference, it was considered to indicate significant mean bias. Statistical analyses were performed with SPSS version 22.0(IBM, Armonk, NY) and Medcalc Software Version 15.11.4 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

The mean and standard deviations of the measured liver volumes with 3D US and CT were 658.32 ± 222.92 ml and 665.82 ± 220.49 ml, respectively. Table 1 summarizes the results. The mean absolute volume difference between the 3D US and reference CT liver volumes was −7.5 ml (range, −173.01 ml to 143.63 ml) and the mean percent volume difference was 0.7% (range, −17% to 24%).

Repeatability

The Spearman's correlation coefficients of the two measurements per liver by observer A and B were 0.979 and 0.991, respectively (Fig. 2 a, c). The ICC (95% CI) for observer A and B were 0.997 (0.936–0.992) and 0.995 (0.986–0.998), respectively (Table 2). Results from the Bland−Altman plots were similar to those from the ICC, with a mean difference (lower, upper LoA) of −0.38 (−91.7, 99.3) for observer A and 5.6 (−37.7, 48.9) for observer B (Fig. 2 b, d). On visual inspection, the Bland−Altman plots of observer A and observer B appeared to exhibit heteroscedasticity. Measurements of observer A showed heteroscedasticity on the Kendall's tau correlation test (τ = 0.450, p = 0.015),

but no significant heteroscedasticity was observed in measurements

of observer B (τ = 0.350 p = 0.059).

Reproducibility

Reproducibility was defined as the interobserver agreement. Spearman's correlation coefficient between the two observers was 0.966 (Fig. 3 a). The ICC was 0.964 (0.924–0.986) (Table 3). The results of the ICC and Spearman's correlation indicate a high correlation between the two observers. The Bland–Altman plots identified a mean difference (lower, upper LoA) of −64.4 (−60.5, 189.2). The 95% confidence interval of the mean difference (95% CI: 30.4237 to 98.2926, $p < 0.0011$) did not included the line of the equality, meaning that the measurements of observer A were significantly larger than those of observer B (Fig. 3b).

Validity

There was a strong correlation (r = 0.932, $p < 0.001$) between the 3D US results and the CT results, according to Spearman's correlation coefficient (Fig. 4 c). The ICC (95% CI) between the 3D US measurements and the CT results was 0.922 (0.792–0.972) using the averaged values of the two observers. The ICC between the 3D US measurements of observer A and the CT volumetry was

0.895 (0.726–0.962). The ICC between the 3D US measurement of observer B and the CT volumetry was 0.931 (0.814, 0.975) (Table 4). The mean difference (lower, upper LoA) between the 3D US measurements and CT volumetry was −7.5 mL (−178.3, 163.3) (Table 4, Fig. 4 d). The Bland–Altman plots comparing the CT volumetry with the 3D US measurements of the two observers separately are shown in Figures 4a and 4b. The mean differences (lower, upper LoA) were 24.7 mL (−176.7, 226) for observer A and −39.7 mL (−199.7, 120.3) for observer B. The distribution on the Bland–Altman plots did not show any proportional errors or signs of heteroscedasticity.

DISCUSSION

3D-US measurements of liver volume showed good repeatability and reproducibility. However, the measurements of observer A showed heteroscedasticity on the Bland-Altman plots and there was a mean bias in the 3D-US measurement of liver volume between the two observers. Validity defined as inter-modality agreement between CT and 3D US was highly correlated on Spearman's correlation test and ICC analysis, but the limit of agreement ranged from -178.3 ml to 163.3 ml. There is no known limit but a smaller range between these two limits means a better agreement (15).

There are many reasons for the limited accuracy of 3D US hepatic volume measurement. The major causes of the error may be associated with characteristics of liver morphology and location. On conventional 2D US examination, accurate measurement of solid organ volume is difficult because of variability in the traditional 2D US examination (16). For example, liver size can be determined by many different methods using 2D US (17). Other intra-abdominal solid organs, such as the kidneys and spleen, have a relatively simple shape. For these organs, formulas are available to calculate volumes using the 2D length (18, 19). However, due to its complex

shape, the liver volume is not easy to estimate.

Many studies have assessed the accuracy and reliability of 3D US volume measurements using phantoms and small-sized organs such as the thyroid, prostate, or ovaries (20-23). The volumes of such organs are usually less than 100 cc (20, 21, 24). The volume of the phantom used in the other studies was usually smaller than the liver volume, less than 20 ml (23). The results of the previous studies show good reliability and validity for small organs, which can be fully examined with a single sweep of the US probe (20-23, 25). However, large and complex shaped organs such as the liver are difficult to cover with a single sweep unless volume measurements using 3D US are applied restrictively to the small size of the liver in pediatric patients or after living donor liver transplantation, where the liver can be covered in a single scan (26).

The data quality and interpretation of the reconstructed 3D data influenced the measurement. Artifacts caused by shadows from interposed lung and ribs, and motion during the examination, were commonly seen in the measurements. These obstacles hide the liver, and therefore, some of the 3D US data were not fully covering the entire liver and the outline of the liver was obscured. In spite of our expectation that measured volume on 3D US could be smaller

than that on CT, our study shows that liver volume measured on 3D US was larger than that on CT. This can be explained by the fact that the perception of liver contour can be variable among observers. The exact placement of the contours around a liver is subject to individual variation, as shown by the small differences between the two observers and the heteroscedasticity of observer A. Usually, the observer draws the segmentation line slightly outside the real surface in the geometric visualization mode, and volume estimations with outer surfaces tend to become larger on 3D US.

The quality of 3D US data acquisition can be improved by repeated 3D US scans. US is the safest method for evaluating children and there is no hazard from repeated examinations. Good quality 3D US data acquisition from repeated scans could improve the validity of 3D US measurement of liver volume. For improvement of interobserver agreement, the two observers gave instructions for the 3D US measurement before the actual measurement. More detailed instructions for the measurement methods will improve the systematic error rate.

Parameters such as the number of slices, the initial and final slice locations, and the axis of the measurement can partially influence

the results. We chose a 5 mm interval for 3D US measurements. Pang et al. reported that when using phantoms less than 15 mL, a lesser number of image planes was practical for 3D US volumetric measurements within a short measurement time and showed similar measurement accuracy (27).

We used the measurement of liver volume on CT as the reference standard. In many studies, the accuracy of CT liver volumetry was assessed by using intraoperative hepatic volume measurement as a reference standard and the deviation from the intraoperative volume ranged from 0% to 30% (7, 28, 29). Partial volume effects are considered as one of the causes of the error (30). CT volumetry as a reference standard has an inherent error. The pediatric liver is smaller than the adult liver and the ratio of slice thickness to liver size in children is relatively larger than in the adult. Therefore, CT volumetry in children can be more highly influenced by the partial volume effect.

In conclusion, in spite of many sources of error that may affect volume measurement of the liver such as limitations of the 3D volume acquisition 2D data set, movement artifacts, and incorrect tracing of contours, the present study showed that the liver volume measurement in children with the 3D US system showed good

repeatability, reproducibility, and validity. For clinical applications, high-quality data acquisition should be performed and a consensus on and detailed instructions for measurements should be implemented.

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Table 1. Data of liver volumetry

Patient no.	A1(ml)	A2(ml)	mean A(ml)	B1(ml)	B2(ml)	mean B(ml)	mAB (ml)	CT(ml)
1	808.72	880.70	844.71	725.79	759.07	742.43	793.57	856.22
2	750.80	713.81	732.31	659.55	632.48	646.02	689.16	657.96
3	1080.80	971.36	1026.08	845.00	802.55	823.78	924.93	781.30
4	416.46	407.70	412.08	390.95	377.79	384.37	398.23	431.28
5	613.64	693.26	653.45	576.00	548.94	562.47	607.96	655.77
6	720.46	638.20	679.33	512.66	515.26	513.96	596.65	698.84
7	348.18	362.90	355.54	354.44	345.89	350.17	352.85	425.05
8	950.59	973.93	962.26	870.20	859.55	864.88	913.57	906.43
9	917.42	926.75	922.09	996.17	982.14	989.16	955.62	1128.63
10	425.06	432.70	428.88	375.42	371.17	373.30	401.09	323.94
11	778.61	801.90	790.26	719.29	739.04	729.17	759.71	806.17
12	346.52	347.87	347.20	289.49	281.19	285.34	316.27	377.71
13	670.14	668.08	669.11	599.53	641.00	620.27	644.69	668.67
14	610.79	626.01	618.40	555.92	557.12	556.52	587.46	499.52
15	992.59	1041.76	1017.18	998.12	972.95	985.54	1001.36	860.40
16	586.64	591.75	589.20	594.31	587.66	590.99	590.09	575.20
mean	688.59	692.42	690.50	628.93	623.36	626.15	658.32	665.82
standard deviation	230.00	227.42	227.41	220.56	217.85	218.93	220.93	220.49

A1, first measurement of observer A; A2, second measurement of observer A; B1, first measurement of observer B; B2, second measurement of observer B; mean A, mean value of first and second measurement by observer A; mean B, mean value of first

and second measurement by observer B; mAB, mean value of measurement by observer A and observer B.

Table 2. Repeatability of liver volume measurement with 3D US

	Mean difference (ml)	Limit of agreement		ICC (95% CI)	
		Lower (ml)	Upper (ml)		
Repeatability					
A1−A2	−3.8	−99.3	91.7	0.977	(0.936−0.992)
B1−B2	5.6	−37.7	48.9	0.995	(0.986−0.998)

LoA, limits of agreement; CI, confidence interval; ICC, interclass correlation coefficient; A1, first measurement of observer A; A2, second measurement of observer A; B1, first measurement of observer B; B2, second measurement of observer B; mAB, mean measurement of observer A and B; mA, mean measurement of observer A; mB, mean measurement of observer B.

Table 3. Reproducibility of liver volume measurement with 3D US

	Mean difference (ml)	Limit of agreement		ICC (95% CI)	
		Lower (ml)	Upper (ml)		
Reproducibility					
mA−mB	64.4	−60.5	189.2	0.964	(0.924−0.986)

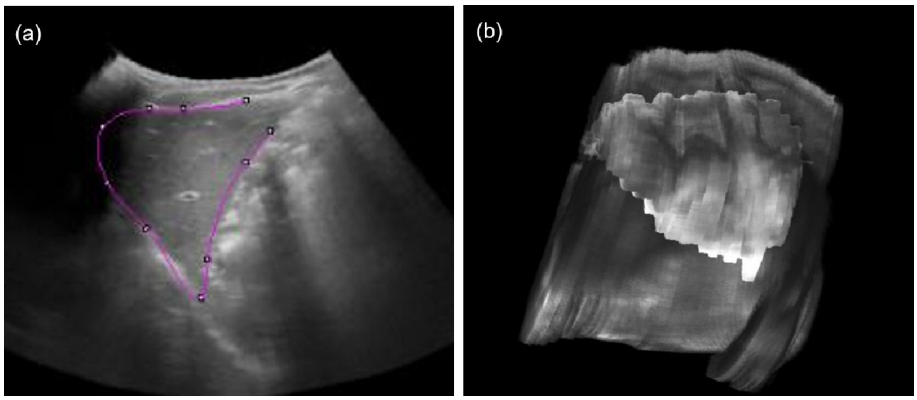
LoA, limits of agreement; CI, confidence interval; ICC, interclass correlation coefficient; A1, first measurement of observer A; A2, second measurement of observer A; B1, first measurement of observer B; B2, second measurement of observer B; mAB, mean measurement of observer A and B; mA, mean measurement of observer A; mB, mean measurement of observer B.

Table 4. Validity of liver volume measurement with 3D US

	Mean difference (ml)	Limit of agreement		ICC (95% CI)	
		Lower (ml)	Upper (ml)		
Validity					
mAB−CT	−7.5	−178.3	163.3	0.922	(0.792−0.972)
mA−CT	24.7	−176.7	226	0.895	(0.726−0.962)
mB−CT	−39.7	−199.7	120.3	0.931	(0.814−0.975)

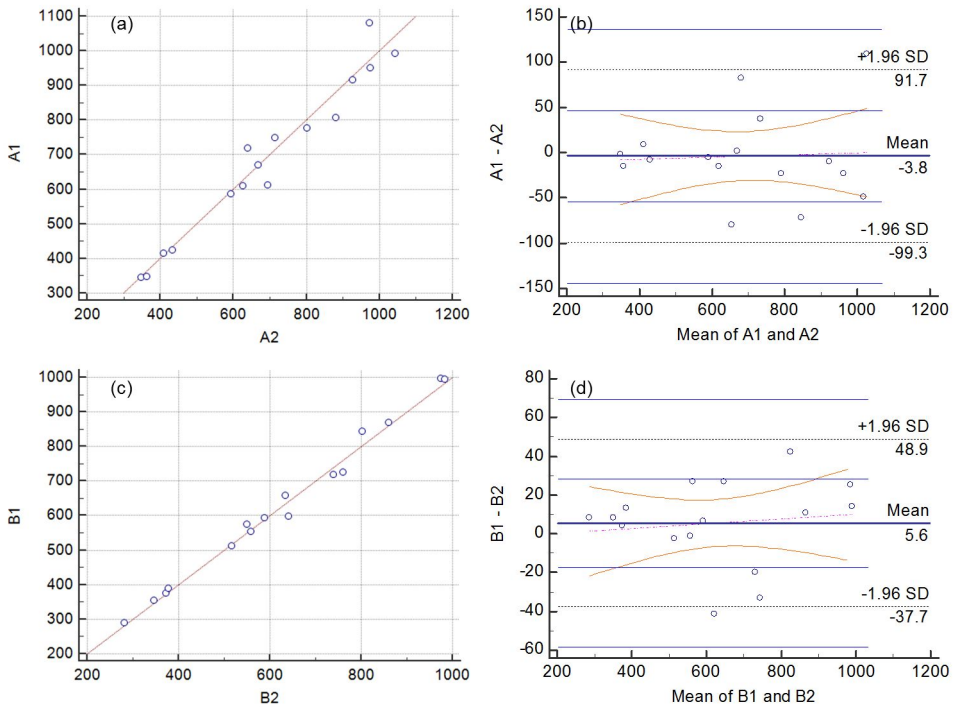
LoA, limits of agreement; CI, confidence interval; ICC, interclass correlation coefficient; A1, first measurement of observer A; A2, second measurement of observer A; B1, first measurement of observer B; B2, second measurement of observer B; mAB, mean measurement of observer A and B; mA, mean measurement of observer A; mB, mean measurement of observer B.

Figure 1. 3D-US measurement of the liver.



(a) As an observer marked the contour of the liver manually in each section every 5mm interval, the software calculates the liver volume automatically and generates the 3-D reconstructed volume image of liver (b, partially reconstructed).

Figure 2. Repeatability of liver volume measurements of 3D US by observers A and B

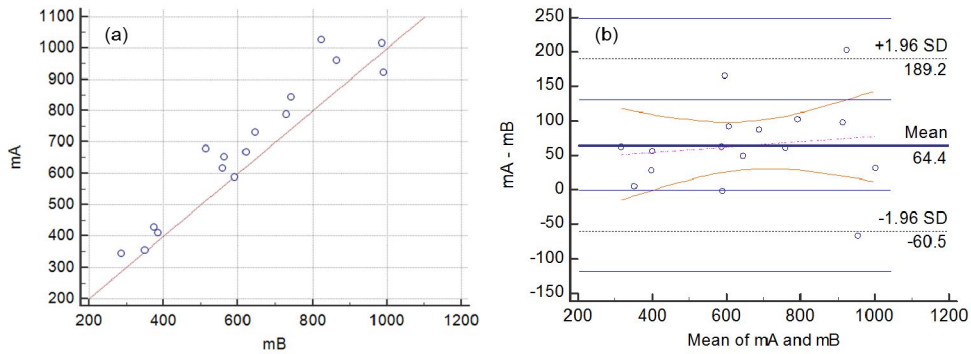


(a, c) Two measures per liver from each of the observers are highly related as shown with Spearman's correlation coefficient of 0.979 for observer A and 0.991 for observer B.

Bland–Altman plots for the average and the difference of intraobservation by observers A (b) and B (d), respectively. The solid line shows the mean difference. The dotted lines show 95% limits of agreement. The difference between the two measurements of each observer seemed not to vary in any systematic way over the range of measurements.

A1, first measurement of observer A; A2, second measurement of observer A; B1, first measurement of observer B; B2, second measurement of observer B; Red dashed line, regression line of differences; blue solid lines, 95% CI of regression line of differences; black dashed lines, 95% CI of limits of agreement.

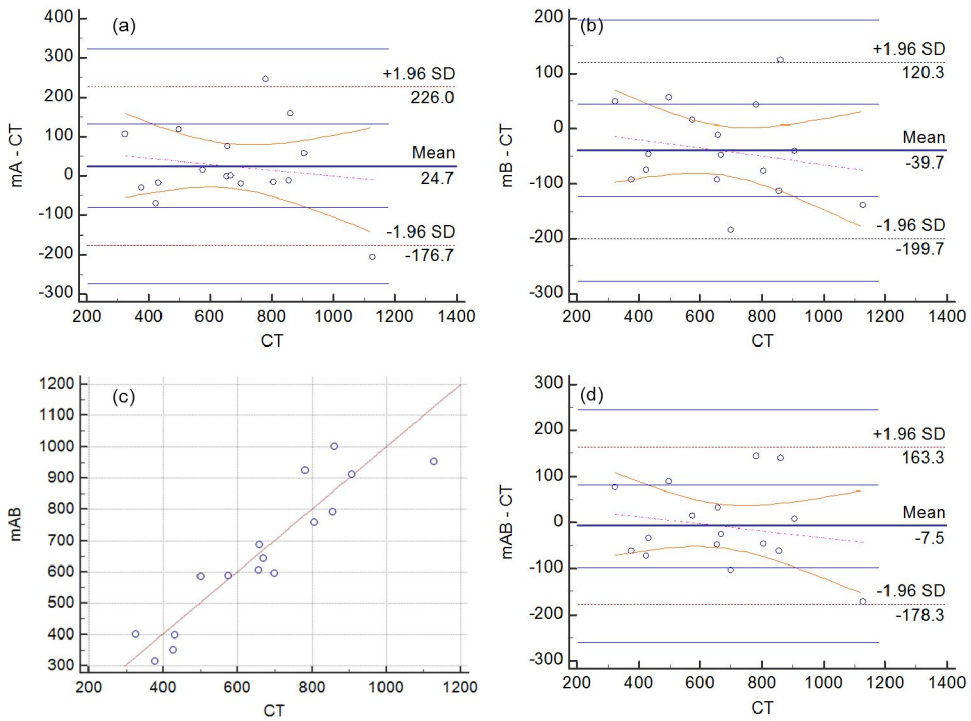
Figure 3. Reproducibility of liver measurements of 3D US between the two observers



(a) There is a high correlation (r = 0.966, $p < 0.001$) with Spearman's correlation coefficient between the two observers. (b) Bland–Altman plot for the average and the difference between the observers. The measurements of observer A are significantly larger than those of observer B (95% CI: 30.4237 to 98.2926, $p < 0.0011$).

mA, mean measurement of observer A; mB, mean measurement of observer B; Red dashed line, regression line of differences; blue solid lines, 95% CI of regression line of differences; black dashed lines, 95% CI of limits of agreement.

Figure 4. Agreement of mean liver measurements with 3D US by two observers and CT volumetry



(a) Bland–Altman Plots for the CT and the difference between the 3D US measurements of observer A and the CT volumetry. (b) Bland–Altman Plots for the CT and the difference between the 3D US measurements of observer B and the CT volumetry. (c) There is a high correlation ($r = 0.932$, $p < 0.001$) with Spearman's correlation coefficient between the 3D US results and the CT. (d) Bland–Altman plots for the average and the difference between 3D US and CT volumetry.

mA, mean measurement of observer A; mB, mean measurement of observer B; mAB, mean measurement of observer A and B; Red dashed line, regression line of differences; blue solid lines, 95% CI of regression line of differences; black dashed lines, 95% CI of limits of agreement.

국문초록

서론: 이 연구의 목적은 소아에서 삼차원 초음파를 이용한 간 용적 측정의 신뢰도 및 타당성을 평가하는 것이다. .

방법: 2014년 11월부터 2015년 2월까지 3D 간 초음파 검사 자료가 있는 환자 중 일주일 내에 시행한 복부 전산화 단층 촬영(CT) 영상이 있는 16명의 소아의 영상을 후향적으로 분석하였다. 3D 간 초음파영상은 경험있는 영상의학과 의사가 위치 감각 체계가 있는 초음파 기계를 사용하여 얻었다. 복셀계산방법을 이용하여 CT영상에서 기준치가 되는 간 용적 값을 구하였다. CT에서 측정한 간 용적의 기준 값을 모르는 두 명의 영상의학과 의사가 각 환자의 3D 초음파 영상 데이터를 이용하여 간 용적을 일주일 간격으로 두 번 측정하였다. 3D 초음파 용적의 타당성 평가를 위하여 CT 용적 값과 비교하였다. 3D 초음파 용적의 신뢰도 평가를 위해 급내 상관계수, Spearman 상관계수를 계산하였고, Bland-Altman 도표를 작성하였다.

결과: 3D 초음파와 CT를 이용하여 측정한 간 용적의 평균값 ± 표준편차는 각각 58.32 ± 222.92ml, 665.82 ± 220.49ml 이었다. 3D 초음파와 CT 절대적인 용적차이는 평균적으로 -7.5 ml(최소값: -173.01ml, 최대값: 143.63ml) 이었다. 관찰자내 급내상관계수는 관찰자 A에서 0.997(95% 신뢰구간, 0.897-0.987), 관찰자 B에서 0.997 (0.936-0.992)이었다. 관찰자간 급내상관계수는 0.964이었다. 타당성 평가를 위한 3D초음파와 CT사이의 급내상관계수는 0.922이었다. Bland-Altman 도표상에서 좋은 반복성을 보여주었다. 재현성에 있어서 관찰자 A가 관찰자 B에 비해서 3D 초음파 상 측정한 간용적 값이 큰 경향을 보였다. 타당성에 있어서는 CT와 3D 초음파간에 limit of agreement는 −178.3 mL에서 163.3 mL 사이였다.

결론: 소아에서 3D 초음파를 이용한 간용적 측정은 신뢰도가 좋은 방법이다. 임상적 적용을 위해서는 측정방법의 세밀한 조정과 일치가 필요할 것으로 보인다.

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주요어 : 간, 용적, 소아, 삼차원 초음파, 신뢰도, 타당성, 반복성, 재현성

학 번 : 2014-21139