Standardize and Compare Contrast-enhanced Ultrasonographic Digital Images Obtained with Different Technologies: How to Overcome the Subjectivity

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Objective: This study was conducted to compare digital images obtained with cadence contrast pulse sequencing (CPS) and coherent contrast imaging (CCI) technologies for contrast-enhanced ultrasonography (CEUS). **Methods:** A CEUS study on 17 focal liver lesions was performed using CPS and CCI technologies with a second-generation contrast media. The lesion/liver ratio and conspicuity index were then calculated and compared with Adobe Photoshop 6.0. **Results:** Lesion/liver ratio and conspicuity index using CCI ranged from 1.3 to 7.1 (mean value, 3) and 19 to 127 (mean value, 58), respectively; by using CPS, we obtained results ranging from 2 to 19.1 (mean value, 8.9) and 57 to 164 (mean value, 109.2). Lesion/liver ratio and the conspicuity index for the lesions using CPS showed significantly ($p < 0.0001$) superior results than those obtained using CCI. **Conclusion:** The computed analysis with standardization allows an objective evaluation of digital images of CEUS. CPS technology resulted in better lesion conspicuity compared to CCI during CEUS study on focal liver lesions.

KEY WORDS: Ultrasound, contrast-enhanced, focal liver lesion, standardization, adobe photoshop

INTRODUCTION

Important advances have been achieved in ultrasonography (US) in contrast agent detection in recent years. As a result, contrast-enhanced ultrasonography (CEUS) with second-generation microbubble (MB) contrast agents is widely used nowadays, increasingly often in clinical practice.¹⁻⁷

Using low mechanical index (MI) contrast-specific US imaging techniques and second-generation contrast agents, optimized for low-MI US imaging

such as SonoVue (Bracco, Milan, Italy), CEUS allows for assessment of tumor microvascularization in real time.⁸⁻¹¹

Cadence coherent contrast imaging (CCI; Siemens-Acuson, Mountain View, CA, USA) is a filtered harmonic imaging technology based on the inversion of the phase of alternate pulses. Summing the resulting echos, the linear signals are cancelled in favor of the (remaining) nonlinear ones.

Cadence contrast pulse sequencing (CPS; Siemens-Acuson) is a new and promising technology among recent technical developments on ultrasound detection of MB contrast agents. This technology takes advantage of the nonlinear fundamental imaging of MB resulting from precise changes in amplitude and phase of the transmitted pulses.¹²

Correct tumor characterization is often related to the imaging demonstration of lesion vascularization, such as hypervascularity for hepatocellular carcinoma. Therefore, high software capability of

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imaging techniques in the detection of contrast agent is always required to correctly image *in vivo* tumor vascularization. The aim of this study was to quantify the advantages of the new CPS technology in comparison to the previously used CCI software. To our knowledge, there is no report in the literature regarding the *in vivo* comparison of these technologies in studying focal liver lesions.

MATERIALS AND METHODS

From February to May 2005, 17 focal liver lesions were studied with CEUS in 17 consecutive patients (M/F = 16:1). The ethical committee did not require specific approval as microbubble contrast agents are commercially available in our country. Declaration of Helsinki principles¹³ were strictly followed, and written, informed consent was obtained from all patients before the examination.

Of the 17 lesions, 10 were hepatocellular carcinomas, 4 were endocrine metastases, 2 were focal nodular hyperplasias, and one was capillary hemangioma. Diagnoses were obtained by histology (seven hepatocellular carcinomas and four endocrine metastases) or by concordance of imaging findings (three hepatocellular carcinomas, two focal nodular hyperplasias, and one capillary hemangioma). The dimension range of the lesions was 1.5–8 cm (mean, 4.7; standard deviation, 1.72).

Imaging Protocol

A Siemens-Acuson Sequoia 512 (version 8) and a 3- to 5-MHz harmonic imaging transducer (4C1-S) were used. A 2.4-mL bolus injection (1 s) of SonoVue (Bracco), followed by a saline flush, was manually intravenously administered. Enhanced dynamic ultrasonographic examination of the lesion was then performed from 0 to 60 s, acquiring a continuous video clip. Lesion perfusion study was obtained twice, each after an injection of 2.4 mL contrast medium, by using different microbubble contrast medium detection softwares and maintaining the same depth and focus on images. For the first nine patients, the enhanced study on the focal liver lesion was performed with CCI and the second with CPS, using the same examination timing and protocol so as to compare the results. For the eight remaining patients CPS was used first. The second dynamic study was always performed more than 30 min after the first dynamic study in order to reach the complete elimination of microbubbles from the liver.

Cadence Coherent Contrast Imaging

The evaluation of enhancement of the examined focal liver lesion was dynamically performed by using the microbubble harmonic-specific, contrast-enhanced imaging CCI (Siemens-Acuson) software with a continuous observation of the perfusion of the lesion.¹⁴ Ultrasound examination parameters

for the enhanced study using CCI were as follows: H 3.0 MHz; MI < 0.2; S2/ + 1/3/3; Delta 3.

Cadence Contrast Pulse Sequencing

Enhancement of the examined focal liver lesion was evaluated dynamically by using the microbubble harmonic-specific, contrast-enhanced imaging CPS (Siemens-Acuson) software with a continuous observation of the perfusion of the lesion.¹⁴ Ultrasound examination parameters for the enhanced study using the CPS software were as follows: P 1.5 MHz; MI < 0.2; S1/0/3/4; Delta 14.

Imaging Analysis

To evaluate and compare the enhancement of the studied focal liver lesion during the early dynamic phase after contrast medium injection, a qualitative and a quantitative analysis were performed.

Qualitative

Enhancement of the studied focal liver lesion was evaluated with a separate and independent review of the recorded examination by two radiologists; any disagreement was solved by means of consensus after discussion. For the evaluation of enhancement, we considered the extralesional liver parenchyma and the intrahepatic arteries during the dynamic study. The focal liver lesions were then classified at CEUS into four groups according to the lesional enhancement in the early contrast-enhanced phase (arterial phase, 15–30 s after bolus injection) in the two dynamic studies performed with the two softwares. The four categories of enhancement were as follows: 1 = hypoechoic lesions almost without enhancement; 2 = isoechoic lesions with enhancement similar to that of the adjacent parenchyma; 3 = slightly hyperechoic lesions with enhancement slightly superior to that of the adjacent parenchyma; 4 = hyperechoic lesions with enhancement similar to that of the intrahepatic arteries. This subjective judgment on liver lesion enhancement was performed to evaluate the differences between the two softwares in everyday clinical practice. The ability of the two softwares to detect enhancement of the studied focal liver lesion was assessed by calculating the correlation coefficient (*R*) between enhancement categories via Spearman's test (Piemer 1.0, McGraw-Hill, Italy).

Quantitative

The video clip of the enhanced dynamic ultrasonographic examination of the lesion, recorded on the ultrasound unit internal hard disk, was exported by using a 230-MB (3.5-in.) magneto-optical disk (Verbatim Corporation, USA, 1994). The video clip was transferred from the MO disk into a computer via an MO disk reader, Dynamo 1300U2 (Fujitsu Limited, 2003), and visualized with ViewPro program (ViewPro Net Beta, Version 2.0, 1996–1998). The time (second) of peak

enhancement (PE) of the studied focal liver lesion was selected on the first enhanced study (CCI), and a single frame was extracted from the two dynamic studies performed with CCI and CPS at that same time (second).

The single images were standardized to obtain a normalization of the gain differences in echogenicity introduced during the examination. The process was performed by using Adobe Photoshop 6.0.1 (Adobe Systems, San Jose, CA, USA, 1984–1998).¹⁵ In particular, on the selected images of PE on CCI and CPS, two reference points (liver contours and unenhanced liver parenchyma) were defined. The grayscale

median (GSM) of these reference points was calculated with the "histogram" facility. The values were then used as input parameters in the "levels" option of the software with fixed output parameters (0 and 255), corresponding respectively to the minimum and the maximum values that the software imposed. In the resultant normalized images, the GSM of the liver contours ranged from 0 to 5 and that of the unenhanced liver parenchyma ranged from 250 to 255. After this operation, the native images (Fig. 1) from contrast-enhanced studies were standardized so as to make them comparable. The quantitative analysis of the enhancement was obtained by calculating the

Fig 1. Native images from contrast enhanced ultrasonographic study of a small hepatocellular carcinoma by using (a) CCI and (b) CPS software technology.

Fig 2. Quantitative analysis of the enhancement of small hepatocellular carcinoma obtained calculating the GSM of an ROI localized in the focal liver lesion studied with (a) CCI and (b) CPS software technology.

GSM (median of the frequency distribution of the gray levels of the pixels) of a region of interest (ROI) localized in the focal liver lesion in the normalized images obtained with CCI and CPS. The ROI was of the same size and in the same position in the two quantitative analyses. The same was carried out for the quantitative analysis of the adjacent liver parenchyma enhancement. Lesion/liver ratio and conspicuity index, obtained by subtracting the enhancement of the adjacent liver parenchyma to that of the lesion, were calculated and compared by using Wilcoxon and comparative descriptive tests [Analyse-it for Microsoft Excel, version 1.68 (May 2003), Analyse-it Software Ltd, 1997–2000].

RESULTS

Comparison between focal liver lesions conspicuity studied with CPS and CCI at qualitative analysis gave statistically significant different results. When we analyzed the concordance between enhancement categories, correlation between CPS and CCI ($R = 0.596$; $p = 0.013$) was not statistically significant. In 6/17 cases the liver lesion was judged as slightly hyperechoic,

with enhancement slightly superior to that of the adjacent parenchyma (category 3). Two of 17 cases were classified as isoechoic, with enhancement similar to that of the adjacent parenchyma (category 2), in CCI; in CPS, the lesions were considered hyperechoic, with enhancement similar to that of the intrahepatic arteries (category 4) (Fig. 2).

At quantitative analysis, lesion/liver ratio and conspicuity index for the lesions using CCI ranged from 1.3 to 7.1 (mean value, 3) and 19 to 127 (mean value 58), respectively (Table 1). Lesion/liver ratio and conspicuity index for the lesions using CPS ranged from 2 to 19.1 (mean value, 8.9) and from 57 to 164 (mean value, 109.2), respectively (Table 2). Using CPS, lesion/liver ratio and the conspicuity index for the lesions yielded significantly superior results ($p < 0.0001$) to those obtained using CCI (Fig. 3).

DISCUSSION

Use of contrast media has been shown to improve the diagnostic performance of the baseline ultrasound study on focal liver lesions.¹⁻⁷

A correct identification of the vascularization of liver lesions is fundamental for the possibilities of lesion characterization. For example, perfusional characterization of hepatocellular carcinoma de-

pends on demonstration of the newly formed vascularization of the lesion, which will therefore be hypervascularized in the dynamic phase at imaging. Consequently, it is essential that the imaging modality be as accurate as possible. Sensitivity of the technique in contrast medium detection is among the factors that can influence accuracy in demonstrating vascularization in the studied lesions.

Subjectivity in evaluating perfusion in focal liver lesions during CEUS can be overcome by a computer-assisted analysis of the enhancement. Then objective quantification of the enhancement can be employed in clinical and technological studies to improve lesional characterization and differential diagnosis or to test equipment performances.

CPS is a new and promising tool among recent technical developments on ultrasound detection of MB contrast agents. However, we found no *in vivo* studies in the literature comparing this new technology with previous ones, in order to quantify the real diagnostic gain from its usage. Our results show the superiority of CPS compared to CCI in demonstrating hypervascularization of focal liver lesions. This outcome was obtained via qualitative and quantitative analysis of the conspicuity of the examined lesions. In 2/17 cases the studied focal liver lesions was judged as isoechoic to the rest of liver parenchyma at CCI, but were considered hyperechoic at CPS. In these cases, a wrong charac-

Table 1. Results on the Enhancement Quantification of the 17 Focal Liver Lesions Studied with CEUS by using CCI Technology

No.	Dimension (cm)	Diagnosis	Arterial phase	ROI Lesion	ROI Liver	Lesion/Liver ratio	Conspicuity index
1	2	HCC	3	62	24	2.6	38
2	2	MET	2	78	59	1.3	19
3	3	HCC	3	92	43	2.1	49
4	1.5	HCC	4	82	34	2.4	48
5	2	MET	3	78	35	2.2	43
6	5	MET	3	44	9	4.8	35
7	2	HCC	4	114	16	7.1	98
8	4	HCC	3	87	45	1.9	42
9	2.5	HCC	2	86	65	1.3	21
10	1	HAE	4	148	41	3.6	127
11	1	MET	4	90	31	2.9	59
12	3	HCC	4	104	24	4.3	80
13	2	HCC	4	134	37	3.6	97
14	2	HCC	3	94	65	1.4	29
15	2	HCC	4	106	49	2.1	57
16	4	FNH	4	139	23	6	116
17	8	FNH	4	37	5	1.4	32

Table 2. Results on the Enhancement Quantification of the 17 Focal Liver Lesions Studied with CEUS by using CPS Technology

No.	Dimension (cm)	Diagnosis	Arterial phase	ROI Lesion	ROI Liver	Lesion/Liver ratio	Conspicuity index
1	2	HCC	4	172	82	2	90
2	2	MET	4	99	10	9.9	89
3	3	HCC	4	65	5	13	60
4	1.5	HCC	4	164	19	8.6	145
5	2	MET	4	108	22	4.9	86
6	5	MET	4	150	13	11.5	137
7	2	HCC	4	126	17	7.4	109
8	4	HCC	4	98	41	2.3	57
9	2.5	HCC	4	147	23	6.3	124
10	1	HAE	4	151	13	11.6	138
11	1	MET	4	81	14	5.7	67
12	3	HCC	4	138	24	5.7	114
13	2	HCC	4	148	35	4.2	113
14	2	HCC	4	143	27	5.2	116
15	2	HCC	4	115	6	19.1	109
16	4	FNH	4	175	11	15.9	164
17	8	FNH	4	147	8	18.3	139

terization with CCI was therefore corrected by the use of CPS. In 6/17 cases, liver lesion was judged as slightly hyperechoic at CCI, but was classified as hyperechoic at CPS. In these cases, focal liver characterization with CCI was improved by the use of CPS.

The results of this new technology are a consequence of the better, more selective, cancellation of background tissue in the dynamic phase, together with the high signal intensity from nonlinear

fundamental imaging of microbubbles. The high sensitivity for contrast medium clearly improves perfusional study of liver lesions, but also of liver parenchyma. Nonetheless, the high capability of identifying microbubbles in the US scan leads to a demonstration of arterial vascularization in liver lesions, which is nearly “pure”—i.e., without venous perfusion. Therefore, contrast medium accumulation is less necessary for lesion conspicuity to reach a level that would be enough for lesion

Fig 3. Graphic representation of the values of lesion/liver ratio and lesion conspicuity index of 17 focal liver lesions studied with (a) CCI and (b) CPS software technology.

detection. Thanks to the high sensitivity in contrast medium detection, hypervascularized lesions are therefore detectable against a "black" background during purely arterial perfusion of the liver, with a consequently useful increment in lesion conspicuity. Characterization of focal liver lesions is improved, even if there are limitations in this study relating to the fact that inter- and intraobserver variability were not considered.

CONCLUSION

Computed analysis with standardization allows an objective evaluation of digital images of CEUS. CPS technology resulted in better lesion conspicuity compared to CCI during the CEUS study of focal liver lesions. CPS technology for CEUS is superior to CCI software in demonstrating perfusion of focal liver lesions.

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