Value of time-intensity-based quantification of focal liver lesions on contrast enhanced ultrasound

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Purpose

The recent Consensus Conference on Contrast Ultrasound in Rotterdam (1) emphasized the role of contrast enhanced ultrasound in the detection and characterization of focal liver lesions, especially for those where a definite diagnosis cannot be achieved on B-mode sonography. The introduction of microbubble contrast agents has enabled functional studies that go beyond what was previously achievable with Doppler. Intravenous bolus administration of a contrast agent such as Sonovue® (Bracco, Milan), tracking its passage through an organ, focal lesion, or blood vessels, can provide useful hemodynamic data by analysing the wash-in and wash-out curves. The clinical value of contrast-enhanced US has been previously demonstrated in the setting of cirrhosis and liver metastases detection, both for morphological assessment and functional data retrieval concerning intra-hepatic vascular transit times (2-6).

The time course of a microbubble (MB) injection can be assessed using nonlinear imaging modes such as contrast pulse sequencing (CPS, Siemens), and monitored by user-defined regions-of-interest (ROI) as a function of time. The enhancement profile can be displayed by a time-intensity curve (TIC) where the average signal from selected ROI's are plotted as a function of time or an entire colour-coded functional image generated. Other parameters such as the time from injection to the peak signal (time-to-peak) or the arrival time can also be extracted.

The recent development of specific evaluation software, made possible to record a sequence of contrast-enhanced US over a time period, creating a tool for objective perfusion analysis. The purpose of the present study was to evaluate the diagnostic value of time-intensity-based quantification of solid focal liver lesions perfusion (FLL) using contrast-enhanced ultrasound.

The purpose of this study was to evaluate the diagnostic value of time-intensity-based quantification of solid focal liver lesions (FLL) on contrast-enhanced ultrasound (CEUS).
Methods and Materials

From January to September 2010, 27 patients (17 female, 10 male, mean age = 49 years) with a previously known focal liver lesion were prospectively recruited to enter the study. Inclusion criteria were the presence of a detectable FLL on a B-mode abdominal survey at least with 1cm in diameter, regardless of the clinical context. Exclusion criteria were previous allergic history to Sonovue®, cardiac insufficiency, vascular thrombosis of hepatic vessels or presence of a portal cavernoma. Only one FLL was enrolled per patient and in case of multiple lesions only the one considered the most representative (homogeneously solid, without obvious cystic areas on B-mode examination) was chosen. There were 4 HCC (13.8%), 3 hypovascular metastasis (10.3%) from colorectal cancer, 2 adenomas (6.9%), 6 FNH (20.7%), and 12 haemangiomas (41.4%). The gold standard was percutaneous biopsy in 2 cases (HCC) and confirmation by MR and serial follow-up at least during 12 months for the remainder.

Examinations were performed with a Siemens Antares (Siemens Medical Systems, Erlangen, Germany) equipped with specific contrast software evaluation (CPS). The CPS technology employs multipulse sequences per image line with precise changes in transmitted interpulse amplitudes and phases. With selective scaling of each received echo and subsequent addition of all echoes, linear fundamental tissue signals are rejected and nonlinear signals from MBs are retained. This achieves unique signal separation. Tissue signals are rejected and strong nonlinear fundamental signals are detected with precise control of amplitude and phase sequences.

Before injection of the ultrasound contrast agent, all patients underwent conventional sonography using tissue harmonic imaging in longitudinal and transverse sections for determination of the best scanning plane for tumor display. A bolus injection of 2.4ml of Sonovue® (Bracco, Milan) into an antecubital vein was performed, followed by a 10-ml saline chaser bolus. The study was conducted during quite breathing over 60 seconds.

Cine-loop was stored in the hard disk, and a video display in DICOM format was retrieved for image analysis using a dedicated software program (Visilog, Noesis, France®- fig 1,2,3). Three regions of interest (ROI) were created, one at normal parenchyma (NP), and 2 at the FLL encompassing its central area (NC), and periphery (Nper). ROIs were manually repositioned between video frames to correct for respiratory motion displacements. A time intensity curve (TIC) was generated for each ROI with individual intensity values (displayed as dB units) also available in an Excel sheet format. Regarding the enhancement properties, the following parameters were evaluated: maximum signal intensity (SImax) considered to represent the maximum value of enhancement; mean signal intensity (SImean); time to peak, considered as the time elapsed to achieve peak enhancement (Tmax); time to enhancement, considered as the time elapsed to achieve an increase in signal intensity over 2dB (Te) and washout velocity, considered to represent the percentage of loss of the maximum enhancement (Wv). A blinded reading
of all the videos was also performed by two radiologists adopting a consensus reading regarding tumor categorization. Assignment of different tumor categories was based on the visual inspection of the B-mode static images and contrast-enhanced cine-loop display using previously accepted criteria for tumor differentiation. The gold standard was percutaneous biopsy in HCC and metastasis cases, and confirmation by MR and serial follow-up at least during 12 months (from 12 to 24 months).

Statistical analysis was performed using the Friedman, Kruskal-Wallis, and Mann-Whitney test with p value <.05 considered statistically significative.
Images for this section:

Fig. 1: Visilog Software for curve analysis

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Fig. 2: Time-intensity curve

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Fig. 3: Excel sheet with all the quantitative values in Db for each second

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Results

Enhancement curves for the different types of FLL compared to the enhancement curve observed at the normal liver revealed for HCC an earlier \( T_{\text{max}} \) (21s versus 33.5s), both at the tumor center and periphery (fig 4), a higher \( S_{\text{max}} \) (mean dB=43.3dB versus 25.4dB) and a lower signal intensity 60s after injection (mean dB=12.5 versus 21.3dB). This decrease of enhancement was observed both in the center and periphery of the tumor and was of higher magnitude than that observed for the normal liver (0.8 and 0.7% respectively, versus 0.15%). \( T_{\text{e}} \) was also lower in the nodule center and periphery, comparing to normal parenchyma (\( T_{\text{e}} \) in the center of 13.5s comparing to 16s). For metastases (fig 5) the \( S_{\text{max}} \) at the tumor center was significantly lower than that of normal parenchyma (11dB versus 23.6dB); for liver adenomas enhancement curves in the center and periphery of the tumor were similar (fig 6). Despite a higher dB value observed for tumor enhancement compared to normal parenchyma (24dB in the nodule center versus 21.6dB in the normal parenchyma), the difference was not statistically significant. FNH had similar enhancement curves (fig 7) in the center and periphery of the nodule with earlier \( T_{\text{max}} \) comparatively to normal parenchyma (23.3s versus 42s), higher \( S_{\text{mean}} \) (mean dB= 20.4 versus 15.3dB) and shorter \( T_{\text{e}} \) (8.9s versus 13s). \( S_{\text{max}} \) of hemangiomas (fig 8) was significantly higher at the periphery of the tumor when compared to normal parenchyma (37.6 dB versus 26.6dB) and significantly lower at the center of the nodule (13.6 dB versus 26.6dB). Also the measured \( T_{\text{e}} \) at the center of the hemangioma was longer (22.1s versus 15.2s).

For tumor categorization, the enhancement pattern observed at the tumor center (fig 9) was the most important discriminator regarding the functional parameters \( S_{\text{mean}} \), \( S_{\text{max}} \), and \( T_{\text{max}} \). Performance of an in-depth analysis of the enhancement pattern at the tumor center showed that HCC and FNH possess the highest \( S_{\text{max}} \) among all nodules (43.28dB) and metastases and hemangiomas the lowest (11.08dB and 13.66dB, respectively); \( T_{\text{e}} \) tends to be higher in hemangiomas (22.17s) and metastases and haemangiomas had the lowest \( S_{\text{mean}} \) (4.43 dB and 6.69 dB, respectively). The full range of statistical data is shown on table 2 (fig 10).

Considering the most relevant quantitative parameters for tumor differentiation HCC showed a higher \( S_{\text{max}} \) (>25.5dB) and washout velocity (> 0.08); metastasis a lower \( S_{\text{max}} \) at the tumor periphery (<28dB) and slow washout velocity enhancement (< 0.21dB); adenomas the lowest \( T_{\text{max}} \) both in the centre and periphery of the tumor (<17.5dB and <15dB, respectively); FNH a high \( S_{\text{mean}} \) (>13.75dB) and \( S_{\text{max}} \) (>24.91dB) with slow \( T_{\text{e}} \) (<12.31s) at the tumor center; hemangiomas the lowest \( S_{\text{mean}} \) (<8.1dB) and \( S_{\text{max}} \) (<20dB). Taking in consideration the statistical significance of the data collected in order to assign a specific tumor category, quantitative evaluation would allowed the diagnosis of 3 out of 4 HCC, 3 out of 6 FNH, 6 out of 12 haemangioma, 2 out of 3 metastasis, and 1 adenoma.
The **qualitative analysis** correctly diagnosed 3 of the 4 HCC, 4 of the 6 cases of FNH, 9 out of the 12 hemangiomas, and all cases of metastasis. These results yielded a sensitivity and specificity of 75% and 88% for HCC; 100% for metastasis; 66.7% and 91.3% for FNH; and 75% and 88.2% for hemangiomas. Combining the quantitative and qualitative analysis, all HCC cases, 5 of the 6 FNH and 11 of the 12 haemangiomas would have been correctly assigned (fig 11). Some of the discordant cases are shown through images 12 to 15.

In clinical practice, liver ultrasound is usually the first imaging modality in upper abdomen work-up imaging studies. Regarding focal liver lesion detection and/or characterization many authors tried to improve the diagnostic accuracy by using the color Doppler Mode or the Power-Mode to depict and characterise the vascular pattern and so to better assess lesion's nature (9 - 12). Despite recent improvements, Doppler is still limited by its lack of sensitivity in the detection of flow in intranodular micro vessels or flow in deeply located liver lesions being also limited by motion artefacts. Doppler imaging led to the development of ultrasound contrast agents based on gas-filled microbubbles such as albumin-encapsulated micro spheres, saccharide micro particle suspensions and perfluorcarbons (13, 14, and 15). Basic and clinical research carried out in the field of ultrasound contrast media has developed products which ameliorate the diagnostic capabilities of ultrasound techniques through an increase of signal intensity in B mode and/or in Doppler studies. Furthermore, it has also opened new perspectives in functional evaluation of the different organs through development of new, "non conventional" examination techniques. A more promising approach is the quantitative analysis carried out by using dedicated evaluation software. The possibility of a quantitative evaluation of post contrast enhancement of ultrasound signals is based on the linear relationship between the relative blood concentration of contrast medium and Doppler signal intensity. This linear relationship has been well demonstrated in both in vitro and in vivo studies (16 - 19). Measurements can be obtained off-line, through a dedicated software (20), or directly from the ultrasound equipment (21, 22, and 23). Some equipments are capable of providing direct measurements through specific analysis of the raw Doppler data, while others analyse video images after post-processing to eliminate the effects of nonlinear power Doppler maps.

Our results show that center TIC is the most important to distinguish between the different types of hepatic lesion. HCC showed the highest washout velocities, and the highest signal intensity (43.2dB) values in the center region. These nodules also have the lowest $T_{max}$ (21.2sec), comparing to the other nodules. These features quantify the qualitative analysis that is usually made in the interpretation of contrast enhanced US, CT and MRI. After intravenous administration of an US contrast agent, HCC typically shows strong intra-tumoral enhancement in the arterial phase followed by an isoechoic or hypoechoic appearance in the portal venous and delayed phases. Metastasis displayed the lowest center signal intensity (11dB). Comparing to the other nodules metastasis also displayed the lowest $S_{max}$ in the periphery ($p=0.029$), and maintained these values throughout
the entire 60 seconds. Despite a higher dB value observed for tumor enhancement compared to normal parenchyma (24dB in the nodule center versus 21.6dB in the normal parenchyma), the difference was not statistically significant for adenomas. Comparing to other nodules adenomas presented the lowest $T_{\text{max}}$ both in the centre and periphery ($T_{\text{max}}$ center <17.5dB; sensibility of 100% and specificity of 92.6%. $T_{\text{max}}$ periphery <15dB; sensibility of 100% and specificity of 96%). FNHs displayed higher $S\text{I}_{\text{mean}}$ and $S\text{I}_{\text{max}}$ in the center (20.4dB, p=0.008; 34.8dB, p=0.041), comparing to the normal parenchyma. This data is consistent with the qualitative contrast enhanced imaging, in which FNH shows a homogeneous strong enhancement during arterial phase: the degree of enhancement reflects the arterial hipervascularity, and the homogeneous distribution is related to the uniform internal architecture of the tumour.

Our data showed a quite low number of false negatives when we used the quantitative evaluation. However, there are a high number of false positive cases. This limitation can easily be overcome by associating the qualitative analysis. In fact, this analysis showed higher values of specificity. Therefore, the quantitative analysis must be done together with the qualitative analysis.

Using these imaging modalities, a more precise characterization of liver lesions is possible by the assessment of morphology, contrast uptake, and time-intensity cirves analysis.

This study has some limitations: only hypervascular HCC and hypovascular metastases entered the study; the small number of cases do not allow to derive definite conclusions; reproducibility of the results for the same patient was not verified; signal intensity measurements were not normalised to the normal hepatic parenchyma.
Fig. 4: Time-intensity curves in the nodule center, periphery and normal parenchyma for hepatocellular carcinoma. Earlier time to enhancement (Te) and peak enhancement (Tmax), both at the center and periphery. Increased enhancement (Slmax) both center and periphery. Lower center and periphery enhancement 60 seconds after injection (washout effect).

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**Fig. 7:** Time-intensity curves in the nodule center, periphery and normal parenchyma for focal nodular hyperplasia. FNH showed similar curve profile in the center and periphery. Comparing to normal parenchyma Te and Tmax are significantly lower. Center and periphery curves also show higher SImean comparing to normal parenchyma.

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**Fig. 6:** Time-intensity curves in the nodule center, periphery and normal parenchyma for adenoma. The curves in center and periphery are very similar.

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![Enhancement curves (Hemangioma)](image)

**Fig. 8:** Time-intensity curves in the nodule center, periphery and normal parenchyma for hemangioma. Three curves are similar with respect to the maintenance of the signal intensity after the peak is reached. Nodule center is the region with the lowest signal intensity (SI_{mean}, SI_{max}). Nodule center has the highest Te, and time to peak. Nodule periphery has the lowest Te and highest SI_{max}.

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<table>
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**Fig. 9:** For tumor categorization, the enhancement pattern observed at the tumor center was the most important discriminator regarding the functional parameters SI\text{mean}, SI\text{max}, and T\text{max}

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<table>
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<td>6/12</td>
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<tr>
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**Fig. 11:** Combined qualitative and quantitative analysis

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**Fig. 5:** Time-intensity curves in the nodule center, periphery and normal parenchyma for metastasis. The signal intensity was lower in the center of the nodule comparing to the nodule periphery and the normal parenchyma.
<table>
<thead>
<tr>
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<th>Aden</th>
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<tr>
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<td>T enhanc &gt;</td>
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<td></td>
<td></td>
<td>22.17s</td>
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**Fig. 10:** Comparison of the quantitative evaluation for each tumour using the enhancement curves in the nodule center (quantitative values)
Fig. 12: Cirrhotic liver with an hyper vascular nodule diagnosed as a hepatocellular carcinoma in the qualitative evaluation.

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**Fig. 13:** Time intensity curves for the nodule in fig 12 yielded Slmax at the center of 22.84dB, and the expected was over than 48dB. However, we could see that the center as well as the periphery showed washout comparing to the normal parenchyma.

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Fig. 14: This case was diagnosed as a FNH. The nodule was hipervascular in arterial phase.

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**Fig. 15:** However, quantitative analysis for the nodule of fig 14, showed SImax greater than 48dB and the curve profile showed a washout of both the central and periphery in portal venous phase, comparing to the normal parenchyma, allowing the correct diagnosis of an HCC.

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Conclusion

This simple method of time-intensity curves analysis of two ROIs positioned in the nodule center and periphery may in fact provide an additional tool for the correct diagnosis of a solid focal liver lesion by ultrasound. We demonstrated some quantitative values that are associated and can discriminate some specific nodules. If combined with the qualitative analysis, which is always done during the exam, the results can be improved as also as the degree of confidence in the correct diagnosis.

Quantification techniques complement the skilled observations of Radiologists of the hepatic tumours usual enhancement patterns and further fuel new imaging techniques and clinical applications.
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