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Full Length Research Paper

Pulse Harmonic Inversion Imaging and Contrast Transition Time Value in the Detection of Liver Metastases

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The aim **of this study was to detect of liver metastasis by contrast enhanced Doppler ultrasound with measuring the contrast transitions times.** ***Material and methods:*** **We estimate 60 patients with colorectal carcinoma with or without liver metastasis and 60 healthy subjects.** ***Results:*** **The mean value of HATVTT in control group was 32±1,8sec. The HATVTT results in group with or without liver metastasis were: 25±2,1; 24±1,9; 23±2,0; 21±2,4 and 19±1,8sec versa 32±1,6; 32±1,0; 31±1,4; 29±1,9; and 26±1,5sec respectively. The percents of liver metastasis were: 6,6%, 15%, 20,0%, 28,3% and 36,6% inside in subgroups. There were no cases with normal HATVTT and liver metastasis.** ***Conclusion:*** **We can constitute that the contrast transition time has a significant impact on the detection of metastases, in particular the very small dimensions, which meaning is significantly longer than classical B-mode ultrasonography.**

Keywords: Liver metastases, Doppler, Contrast Enhanced Ultrasonography, Pulse Harmonic Imaging, Transition time.

INTRODUCTION

Liver hemodynamics

The liver is the second most commonly involved organ by metastatic disease, after the lymph nodes. The liver provides a fertile soil in which metastases may become established, not only because of its rich, dual blood supply but also because of humoral factors that promote cell growth. Most metastases are hypovascular, but some primary tumors characteristically have hypervascular metastases (neuroendocrine tumors, renal carcinomas,thyroid carcinomas...). Large metastases tend to displace the surrounding vessels, and they may compress or occlude the portal venous branches. However, neovascularity, vascular encasement, and arteriovenous shunting are rare. The patterns of blood supply of liver metastases are of considerable clinical importance because a number of diagnostic and therapeutic approaches depend on the degree of neovascularity and the source and type of the blood supply. A humoral mediator-induced portal venous flow reduction causes perfusion changes in liver metastases. The portal vein contributes little to the blood supply of established liver metastases in the presence of a patent hepatic artery. However, its role in the perfusion of early metastatic liver disease remains controversial. Injection via the portal vein showed that more than 50% of liver metastases had a distinct portal blood supply to the tumor periphery (Bernatik et al. 2004). In approximately one-third of cases, the portal blood supply extended centrally.

Imaging Techniques

Conventional imaging techniques such as computed tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), and scintigraphy are capable of diagnosing overt hepatic metastases, although they are unable to detect small metastases. This is because they are base on tissue tumor contrast and there is a

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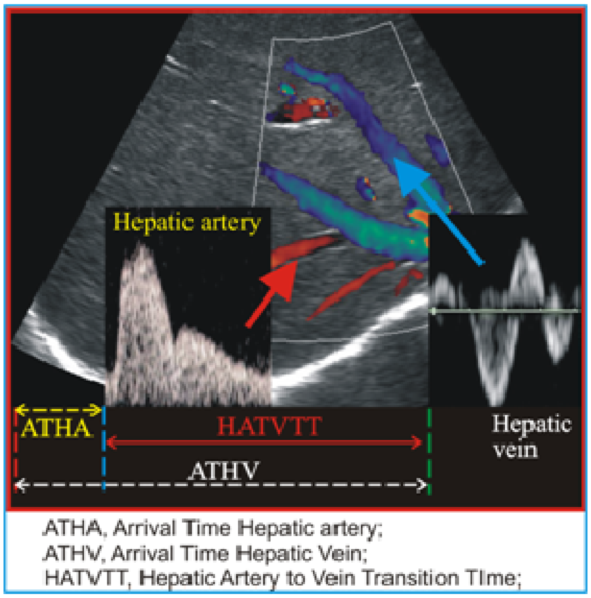

Figure 1. Signal-timing diagram of liver vascular arrival and transition times.

threshold size below which they are unable to discriminate between normal and abnormal tissues.

Pulse harmonic inversion imaging

Is a non-linear method specifically made for enhanced detection of micro bubble ultrasound contrast media. As opposed to conventional B-mode or harmonic imaging where only one ultrasound pulse is transmitted along each scan line, here two consecutive ultrasound pulses are transmitted, the second pulse being an inverted copy of the first one. The resulting echoes were added at reception, and these echoes will therefore cancel out when added. In harmonic imaging, the frequency range of the transmitted pulse and the received signal should not overlap, but this restriction is less in pulse inversion imaging since the transmit frequencies are not filtered out, but rather subtracted.

Transition time

The use of micro bubble contrast agents in ultrasonography has improved detection and characterization of focal liver lesions. These echo enhancers have also been use as tracers, and studies have shown that transit time through the liver is shorten in patients with liver metastases compared with that in control subjects.

Liver metastasis are known to be associated with both arterialization of the liver blood supply and the presence of vascular shunts. Thus, for both reasons, metastatic disease should be associated with a left shift of the timeintensity

profile, with much more of the enhancement occurring during the antenial

phase (Quaia et al. 2003). It so normally, that the arrival time of contrast in hepatic vein is shorter across shunting vessels of metastasis. Measuring of that arrival time is derive for evaluation of vessels configuration and vessel impedance in focal liver parenchymatous lesion.

MATERIAL AND METHODS

The aim of this study was to evaluate the use of duplex/color Doppler ultrasound in the detection of hepatic metastases by measuring the transitions times in vascular structures during contrast enhanced ultrasound tomography for liver metastasis detection in early stadium. We used Doppler ultrasonography machine GE Logiq 5 pro, manufacturer: General Electric, GE Healtcare, Waukesha, Wi, U.S.A. and convex multifrequency abdominal probe 2 – 5MHz.

1. We measure the arrival time of hepatic artery (ATHA).
2. We measure the arrival time of hepatic vein (ATHV).
3. We calculate the subtraction arrival times of ATHA and ATHV, expressed as Hepatic Artery to Vein Transition Time (HATVTT).

$$HATVTT = ATHA - ATHV = (-ATHA) - (-ATHV) =$$
$$-ATHA + ATHV = ATHV - ATHA$$

The minus sign before value is because a reverse of flow direction signal appearing. The arrival and transition time are expressed in **figure 1**.

Table 1: HATVTT duration according metastasis appearing during four quartiles.

			Control group	Preoperative		1 trimester		2 trimester		3 trimester		4 trimester	
				Metastasis		Metastasis		Metastasis		Metastasis		Metastasis	
				Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
HATVTT (mean ± SD)	Shortened	[s]		25 ± 2,1		24 ± 1,9		23 ± 2,0		21 ± 2,4		19 ± 1,8	
	Normal		32 ± 1,8		32 ± 1,6		32 ± 1,0		31 ± 1,4		29 ± 1,9		26 ± 1,5
No. of patients	Shortened	[s]		4		9		12		17		22	
	Normal		60		56		51		48		43		38
Percent of ms [%]				6,6		15		20,0		28,3		36,6	

ms, metastasis; HATVTT, Hepatic Artery to Vein Transition Time;

4. We approve new appears of metastasis by ultrasound, by biopsy (intraoperative) and/or MRI (Siemens, Magnetom Essenza 1.5T, Siemens AG, Healthcare Sector Henkestr. 127 91052 Erlangen Germany) as adjuvant relevant imaging technique in groups with or without transitions times changes during one year following.

Local ethics committees approved the study design, and patients gave written informed consent before entering the study. The study was approved by Medical University scientific board and this study was a part (with unpublished results) of MD thesis/dissertation defended of December 2008.

We estimate 60 patients (37 male and 23 female, from 43 to 82 ages old, 54 ± 13) with colorectal carcinoma included in study randomized with first US examination, diagnosed before by optical electronic colonoscopy (Olympus CV-100, Sunrise Co. L.T.D, Japan).

We divide the patents in two groups on the first preoperative control ultrasound examination:

Group A - patients with ultrasound and biopsy verified liver metastasis.

Group B - patients without liver metastasis.

The control group is composed of 60 healthy subjects (34 male and 26 female, from 45 to 80 ages old, 53 ± 11). Excluded criteria were fatty liver, hepatitis, cirrhosis and malignant neoplasm. The age and sex distribution of the control group was similar like homogenous of the examined group.

The baseline was preoperative US examination, not more two weeks before surgeon intervention. The next US surveys were making in the every three moths during following year. The patients with new detections of metastasis, diagnosed by intra operative ultrasound and biopsy were regrouping in the group A.

We start the study with measuring the arrivals times (AT) of HA and HV in control group with purpose to estimate the reference value of the (HATVTT).

All patients fasted overnight or for a minimum of 8 hours before US examination to reduce variations in splanchnic flow that could be attributed to digestion.

Continuous spectral Doppler tracing of a hepatic vein was performing with the patient in quiet respiration by using the GE Logiq Pro 5 machine.

A bolus of contrast agent (2,5g Levovist®, Schering AG, Berlin, Germany) was injected into an antecubital vein and spectral Doppler signals were recorded from both the right and middle hepatic veins for analysis. We measure time interval between injection of contrast bolus and the signal appearing of hepatic vein and hepatic artery, separately: we detected the hepatic artery signal first, and after dozen second, we detected the hepatic vein flow.

ATHA and ATHV were calculated as the time from injection to a sustained rise in Doppler signal >10% above baseline in hepatic artery flow signal and in hepatic vein flow signal, respectively.

After transition time measuring, we made two subgroups: group with normal HATVTT and group with shortened HATVTT.

Statistical analysis

The data were analyzed using SPSS 16.0 for Windows. Parametric variables was expressed by mean±SD. We used independent t-test to detect statistical significance between normal and shortened HATVTT between gropus and subgroups. A value of $p<0.05$ was considered significant statistically.

RESULTS

The mean duration time and standard deviation of HATVTT results in group with or without liver metastasis are shown in Table 1.

The mean value and standard deviation of HATVTT in control group is 32 ± 1,8 sec, measured on 60 control objects.

The trend of HATVTT results in group with liver metastasis are: 25 ± 2,1 sec, 24 ± 1,9 sec, 23 ± 2,0 sec, 21 ± 2,4 sec and 19 ± 1,8 sec looking from preoperative to 4 trimester. The trend of HATVTT results in group without liver metastasis are: 32 ± 1,6 sec, 32 ± 1,0 sec, 31 ± 1,4 sec, 29 ± 1,9 sec and 26 ± 1,5 sec looking from preoperative to 4 trimester.

The numbers of cases with liver metastasis and shorter

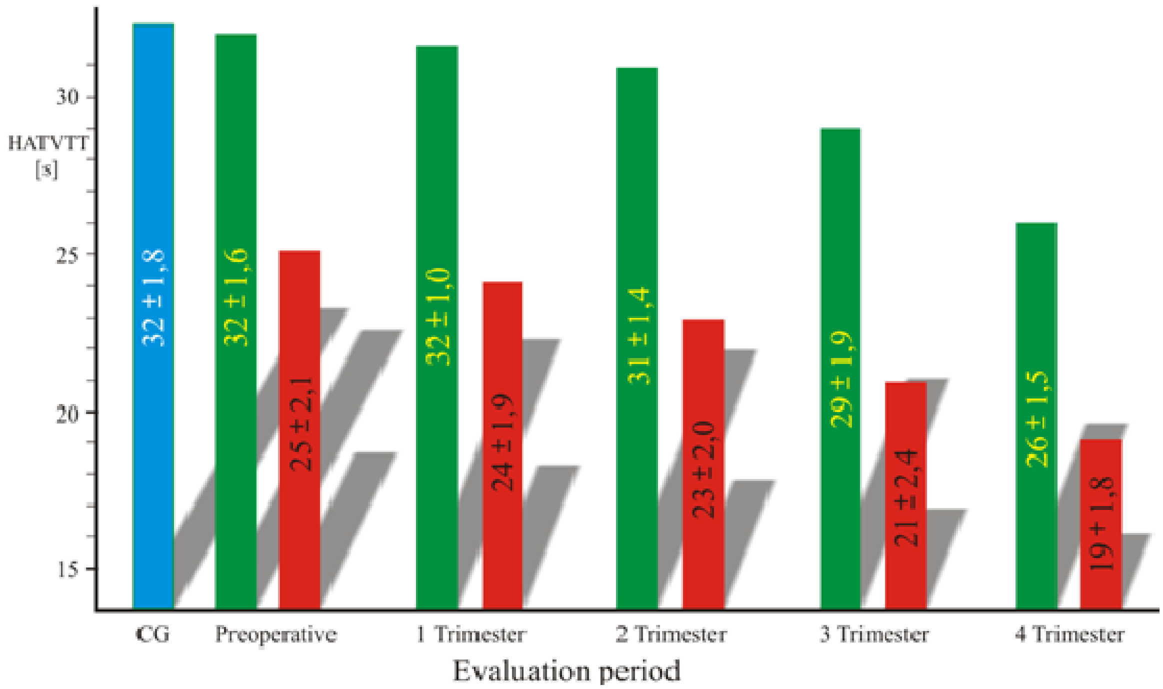

Figure 2: Comparison of mean HATVTT between patient with or without liver metastasis and control group during four quartiles.

HATVTT duration are: 4, 9, 12, 17 and 22, but the percents of liver metastasis are: 6,6%, 15%, 20,0%, 28,3% and 36,6% inside in subgroups, according same evaluation period . There no cases with normal HATVTT and liver metastasis.

Normal HATVTT have 56, 51, 48, 43 and 38 patients without liver metastasis in the same period. There no cases with shorter HATVTT and no liver metastasis.

Visual comparison of mean HATVTT values between control group and metastatic or no metastatic group, during five evaluations time, are shown with column diagram in the following figure 2:

In our investigation by Pulse Harmonic Imaging (PIHI), we detect 3 from real 4 case (3/4) with liver metastasis and only 1 (1/4) identical case with conventional B-mode ultrasound (cUS) in the preoperative period. In the next four trimester of examination, we detect by PIHI: 8/9, 11/12, 17/17 and 22/22 case of liver metastasis across the number of real case of liver metastasis. In the same period, we detect by cUS: 3/9, 7/12, 12/17 and 18/22.

We detected by PIHI: 75% from real number of metastatic liver case in the preoperative period. In the next four evaluations periods we detect 88,9% for the first, 91,7% for the second, 100% for the third and fourth trimester, from real number of metastatic liver disease.

We detected by cUS: 25% from real number of metastatic liver case in the preoperative period. In the next four evaluations periods we detect 33,3%, 58,3%, 70,6% and 81,8%, respectively in the first, second, third and last fourth trimester, from real number of metastatic liver disease too.

We can se these results in Table 2.

Sensitivity of PIHI imaging is 3 times more then cUS sensitivity in preoperative period. The sensitivity PIHI/cUS ratio decrease in the next first to fourth trimester: 2,67 times, 1,57 times, 1,41 times and 1,22 times.

DISCUSSION

Undisputed fact is that MRI is a highly sensitive method of pre-operative imaging of colorectal liver metastases and should be considered the "gold standard" for this purpose, accepting that experienced interpretation is a pivotal factor in achieving such a high degree of sensitivity. A step down with his sensitivity near this imaging technique is PIHI. The PIHI is more sensitive then conventional B-Mode ultrasound. As the metastasis dimension is less, so the higher is PIHI sensitivity (Albrecht et al. 2003). These make the PIHI to the method of choice in early preoperative stage of colorectal carcinomas. PIH/cUS sensitivity ratio decrease with passing time during postoperative period (Tranquart F et al. 2004). After fourth trimester the both of sensitivities are approaching.

Data that significantly increases sensitivity of PIHI in metastasis detection is application of measuring the

Table 2: Compative of metastasis detection by conventional and contrast enhanced US imaging.

		Control group	Preoperative		1 trimester		2 trimester		3 trimester		4 trimester	
			Metastasis		Metastasis		Metastasis		Metastasis		Metastasis	
			Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Real	No. of patients	60	**4**	56	**9**	51	**12**	48	**17**	43	**22**	38
PIHI	No. of patients	60	**3** +1?	56	**8** +1?	51	**11** +1?	48	**17**	43	**22**	38
cUS	No. of patients	60	**1** +3?	56	**3** +6?	51	**7** +5?	48	**12** +5?	43	**18** +4?	38
Detected by PIHI [%]			75		88,9		91,7		100		100	
Detected by cUS [%]			25		33,3		58,3		70,6		81,8	
PIH/cUS sensitivity ratio			3		2,67		1,57		1,41		1,22	

ms, metastasis; PIHI, Pulse Inversion Harmonic Imaging; cUS, conventional B-mode Ultrasound;

contrast transition time. Thus this method becomes similar to late phase KTM and EMR (Chiara et al. 2003).

Applying this method of investigation, we observed that the transition time is significantly reduced, looking at the preoperative period to the next quarter. This is the reason for the increase of neovascular blood vessels in metastasis, that shunting hepatic blood flow and shorter the hepatic to vein transition time (HTVTT). Parallel with the increasing percentage of the metastasis from preoperative to fourth quarter of evaluation, decrease the mean value of HTVTT, because of reduced vascular resistance as a result of more number of drifts and shunts (Zhou et al. 2008).

Early arrival of the contrast agent in the liver veins could be seen in patients with cirrhosis and in patients with liver metastases only (Blomley et al. 2002). Several minute recording could assess arrival time during contrast transit or the transit time can be assessed much more easily using the pulse inversion imaging technique. The major advantage of this pulse inversion technique is that arrival of the contrast agent in the hepatic veins can be directly seen within a minute after contrast agent is injected and does not need subsequent computer analysis (Bang N et al. 2001). Furthermore, movement caused by the patient breathing is not a significant problem with PIHI. There is no need to kept the Doppler gate constantly in the vein, because the vein signal from an inversed pulse scanning will be dominated by the reflections from the contrast agent in which the contrast agent appears as white bright reflections (Bleuzen et al. 2006).

The transit times found in our study were in accordance with those obtained by others: Blomley et al found values less than 25s, and median transit time 31 s in control subjects, while Albrecht et al found a mean arrival time at 49.8 s for normal subjects, all values being at least 24 s.

The current results demonstrate that a short transit time may indicate some kind of hepatic pathology with shunting vascularisation: cirrhosis or metastasis (Tranquart et al. 2003). The PIHI do not determine whether the shunting takes place within the liver or outside the liver, but the difference in transit times, shorter in cirrhosis then in metastasis and differences in B-mode us appearing, can suggests that least part of the shunting is inside the liver. As transit time assessment is completed within 1 min from the bolus injection, it is possible to use the injected contrast agent for late phase imaging of the liver parenchyma.

As conclusion, we can constitute that PIHI with measuring of the contrast transition time has a significant impact on the detection of metastases, in particular the very small dimensions, which meaning is significantly longer than classical B-mode ultrasonography.

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