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Review Article

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Improved Diagnosis of Liver Medical Conditions by Use Contrast Enhanced Ultrasound

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Abstract

The aim of this systemic review was to provide a complete overview of existing publication on the rule of CEUS in assessment of liver disease and evaluating post-interventional success in liver Contrast-Enhanced Ultrasound (CEUS) or Contrast-Enhanced Computed Tomography (CECT) and general solution of the evaluation of post-liver transplant vasculature.

Method

An analysis of 11 sources include use video podcast evaluating the diagnostic performance and comparing studies and textbooks.

Results

CEUS with color- coded perfusion imaging is a valuable supporting tool for post-interventional success control following TACE of liver lesions. The diagnostic performance of CEUS was superior to CECT for detecting residual tumour after TACE. In clinical, CEUS should be recommended as an optional procedure for assessing the tumour response to TACE.

The study demonstrated that the enhancement pattern of HCC on CEUS was consistent with that on CECT, although CEUS has the advantages of easy performance, real-time scanning, and availability, but it lacks panoramic exploration and capability in studying multiple hyper vascular.

CEUS is particularly helpful in evaluating complications of smaller vessels such, as the HA, and can be useful in evaluating portal and hepatic venous complications as demonstrated.

Ultrasound is the first-line imaging technique after liver transplant because it is portable, non-invasive and cost effective

Conclusion

The liver disease is continue to increase although ultrasound scanning of liver with Doppler capability is noninvasive but it has some limitation in case of slow flow especially small vessel after liver transplant. the use of contrast enhance ultrasound CEUS can solve this problem and the literature review in this report defining the overall problem and offer some solution.

However, further research is needed to more clearly categorize the difficulties of use CEUS and effective training program for sonographer for use this facility in future. And conclude that CEUS is very significance in assessing the liver and needed for today and tomorrow examination.

Keywords

Contrast-enhanced ultrasound; Liver medical conditions; Liver transplant; Diagnostic

Introduction

Conventional ultrasound (US) is the first-line noninvasive imaging modality for diagnosis of liver. However, characterization of liver lesions using conventional gray-scale US is limited because only visualization of tumor morphology can be achieved. Moreover conventional Doppler imaging is insensitive to slow flow and deep-located flow, moreover it suffers from the motion artifacts due to respiratory or cardiac activity [1,2]. Today, increased use of CEUS has provided safe and rapid diagnosis of many medical conditions but it still not common in many countries although it has many features over the other tools thus representing a major healthcare problem. Contrast-enhanced US (CEUS) provides us a noninvasive modality to detect and characterize liver lesions more reliably.

Various published guidelines agree on a study the importance of CEUS in liver scan [2].

Many pharmaceutical companies developed and continue to be refined intravenous contrast agents based on Micro bubble. Different encapsulating agents and gases are utilized to vary the durability, size, and metabolism of the bubbles. In general, they all small enough to pass through the pulmonary and systemic circulation and being durable enough to recirculate for several minutes. This bubbles increase the strength of the backscattered signal from blood by several orders of magnitude. Considerably easier to detect the Doppler signal from flowing blood after administration of intravenous contrast agents. This allows exam where vessels may be difficult to see (such as the renal arteries), where the flow may be slow (such as the portal vein), or where the signal may be attenuated by overlying structures (such as transcranial Doppler) [3].

When ultrasound waves propagate the Microbubbles make it oscillate generating harmonic signals that are stronger than the harmonic signals generated by soft tissues. Therefore, post contrast harmonic imaging allows for visualization of blood flow and enhanced soft tissues in the gray-scale mode. This has significant advantages over color and power Doppler because the frame rates are higher in gray-scale imaging and the resolution is better. In addition, the blooming artifacts that occur with post contrast color and power Doppler are not present in gray-scale harmonic imaging. Technique that has been developed to take advantage of unique properties of contrast agents is Pulse inversion imaging. A pulse is transmitted and the returning signals are digitally stored. A second pulse that is the inverse of the first is then transmitted and the returning signal is again digitally stored.

The system then sums the two signals together. Because the fundamental soft-tissue signals are inverted, they cancel each other out. Because the harmonic signal from contrast is nonlinear, the summation process does not cancel it out, and the image shows

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contrast to a much greater degree than soft tissue. This maintains the superior resolution attained with gray-scale imaging, reduces clutter from back- ground tissues, and further enhances signals from contrast.

The aforementioned techniques can be used in two modes to emphasize different facets of contrast distribution. Continuous imaging at low-output powers will display flowing contrast in larger vessels. If the scanning is stopped for a certain period, contrast will accumulate in the microvasculature. After a delay, resumption of scanning at high-output levels will cause bubble destruction (proceeding from the near field to the far field) and an even stronger signal from contrast. The resulting image gives additional information about the vascular volume of normal and abnormal tissues [3].

Contrast Injected into the body to enhance anatomic structures. Types of Contrast include encapsulated gas bubbles, free gas bubbles, colloidal suspensions, emulsions, and aqueous solutions. Reflectivity of small particles is dependent on the frequency. Microbubbles increase scatter and emit sound waves at harmonic frequencies. Contrast agents improve lesion detection when lesion echogenicity is similar to surrounding tissue, lesions demonstrating arterial and portal phases, and weak Doppler signals. Contrast agents approved in the United States include Definity (perflutren lipid microsphere), Imagent (perflexane lipid microsphere), and Optison (perflutren protein-type A microsphere). Contrast agents approved in Canada, Europe, and Japan include Echovist, Levovist, and SonoVue [4].

Contrast-enhanced ultrasound (CEUS) has become progressively available in recent years and has been used widely in various hepatic and non-hepatic investigations [5].

Review

The following review of literature confirm that CEUS is very important in diagnosis liver disease and evaluating post-interventional success in liver and discus specifically the problem of gray scale and Doppler in assessing slow flow in liver and comparing contrast-enhanced ultrasound (CEUS) or contrast-enhanced computed tomography (CECT) in hepatic scanning and general solution of the evaluation of post-liver transplant vasculature and conclude that CEUS are needed for today and tomorrow examination.

Janine Rennert et al., said in their study to evaluate CEUS for the post-interventional success control following TACE in patients with HCC. CEUS with color- coded perfusion imaging is a valuable supporting tool for post-interventional success control following TACE of liver lesions. Peak enhancement seems to be the most valuable parameter Rennert et al. [6]. They aim to Evaluation of anexternal color coded perfusion quantification software with CEUS for the post -interventional success control following TACE in patients with HCC.

The researcher examine 31 patients (5 females, 26 males, age range 34–82 years, mean 66.8 years) with 59 HCC lesions underwent super selective TACE using DSM Beads between 01/2015 and 06/2018. All patients underwent CEUS by an experienced examiner using a convex multifrequency probe (1–6 MHz) within 24 hours following TACE to detect residual tumor tissue. Retrospective evaluation using a perfusion quantification software regarding pE, TTP, mTT, Ri and WiAUC in the center of the lesion, the margin and surrounding liver. They found In all lesions, a post-interventional visual reduction of the tumor micro vascularization was observed. Significant differences between center of the lesion vs. margin and surrounding liver were found regarding peak enhancement (867.8 ± 2416 center vs 2028 ± 3954 margin $p<0.005$) and center 867.8 ± 2416 vs 2824 ± 4290 surrounding liver, $p<0.0001$)). However, no significant differences were found concerning Ri, WiAuC, mTT and TTP. And conclude that CEUS with color- coded perfusion imaging is a valuable supporting tool for post-interventional success control following TACE of liver lesions. Peak enhancement seems to be the most valuable parameter [6].

Ming Liu & Man-xia Lin aimed to compare contrast-enhanced ultrasound (CEUS) with Contrast-Enhanced Computed Tomography (CECT) for evaluating the treatment response to Trans Catheter Arterial Chemoembolization (TACE) of Hepatocellular Carcinoma (HCC).

They examine the Treatment responses of 130 patients who underwent TACE were evaluated by CEUS and CECT. We initially compared the abilities of CEUS and CECT to detect residual tumour, which were confirmed by histology or angiography. Then, we compared the tumour response to TACE assessed by CEUS and CECT, according to Modified Response Evaluation Criteria in Solid Tumours (mRECIST) [7]. The article Results that the sensitivity and accuracy of detecting residual tumour by CEUS vs. CECT were 95.9% vs. 76.2 % ($p<0.001$) and 96.2 % vs. 77.7 % ($p<0.001$), respectively. For target lesions, 13 patients were observed as complete response (CR) by CEUS, compared to 36 by CECT ($p<0.001$). For nontarget lesions, 12 patients were observed as CR by CEUS, compared to 22 by CECT ($p=0.006$). For overall response, eight patients were observed as CR by CEUS, compared to 31 by CECT ($p<0.001$). In conclusion of their research the diagnostic performance of CEUS was superior to CECT for detecting residual tumour after TACE. In clinical, CEUS should be recommended as an optional procedure for assessing the tumour response to TACE [7].

Guang-Jian Liua, and Hui-Xiong Xua, also compared the enhancement pattern on contrast-enhanced ultrasound (CEUS) and contrast-enhanced computed tomography (CECT) of 98 hepatocellular carcinoma nodules in 92 patients Contrast-enhanced ultrasound was performed with SonoVue and a low mechanical index method. In arterial phase, 98 nodules were hyper enhancing on CEUS and 94 on CECT. In portal phase, 82 nodules were hypo enhancing on CEUS and 83 on CECT. Peripheral thin-rim-like enhancement was exhibited in 30 nodules on CEUS and 31 on CECT. Intra-tumoral vessels were visualized in 94 nodules on CEUS and 36 on CECT [8].

Results

The Results that in arterial phase, all 98 lesions showed enhancement on both CEUS and CECT. Compared with the surrounding liver parenchyma, 98 (100%) lesions showed hyper enhancing on CEUS, whereas 94 (95.9%) lesions showed hyper enhancing and 4 (4.1%) lesions showed isoenhancing on CECT (McNemar test, PN1.000) (Table 1, Figure 1). In arterial phase of CEUS, 50 (51.0%) lesions (mean size, 3.3F2.0 cm; range, 1.2~9.9 cm) showed homogenous enhancement and 48 (49.0%) lesions (mean size, 7.7F3.7 cm; range, 1.8~16.9 cm) showed heterogeneous enhancement. On CECT, 40 (40.8%) lesions (mean size, 2.8F2.0 cm; range, 1.2~5.9 cm) showed homogeneous enhancement and 58 (59.2%) lesions (mean size, 7.3F3.4 cm; range, 2.0~16.9 cm) showed heterogeneous enhancement. The study demonstrated that the enhancement pattern of HCC on

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CEUS was consistent with that on CECT, although CEUS has the advantages of easy performance, real-time scanning, and availability, but it lacks panoramic exploration and capability in studying multiple hyper vascular lesions simultaneously [8].

CECT					
	CR	**PR**	**SD**	**PD**	**TOTAL**
CR	9	2	2	0	13
PR	23	34	3	1	61
SD	2	10	35	0	47
PD	2	0	1	6	9
TOTAL	36	46	41	7	130

p<0.001, =0.486, 95 % CI: 0.427–0.545

Abbreviations: CECT: Contrast-Enhanced Computed Tomography; CEUS: Contrast-Enhanced Ultrasound; CR: Complete Response; IR: Incomplete Response; SD: Stable Disease; PD: Progressive Disease

Table 1: Target lesion response.

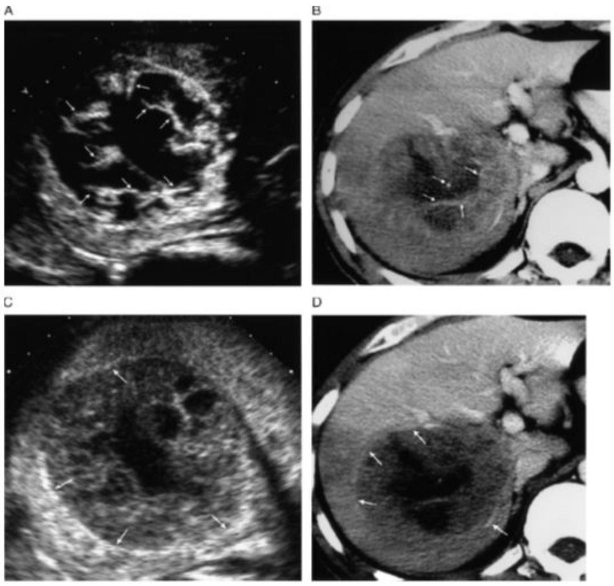

Figure 1: A 37-year-old man with HCC 4.4 cm in maximum diameter located at segment VI. (A) Contrast-enhanced ultrasound of the tumor at 18 s after injection of SonoVue. The tumor is heterogeneously enhanced with central necrosis. Arrowhead points to the margin of the tumor. (B) Contrast-enhanced computed tomography of the tumor in arterial phase. The tumor is heterogeneously enhanced with central necrosis. (C) Contrast-enhanced ultrasound of the tumor at 90 s after the injection of SonoVue. The tumor is hypo echogenic. (D) Contrast-enhanced computed tomography of the tumor in portal phase. The tumor is hypo attenuated.

Goh et al., [9] in their Pictorial Review of Role of contrast-enhanced ultrasound in the evaluation of post-liver transplant vasculature says Liver transplantation is a frequently used treatment for patients with end-stage liver disease and ultrasound is often the first-line imaging technique for detection of vascular complications after liver transplant. Although colour Doppler ultrasound is a good screening method for evaluation of post-liver transplant vasculature, it has limitations in evaluating small-calibre vessels and vessels in close proximity. Contrast-enhanced ultrasound (CEUS) has been proposed to overcome these limitations by improving visualization of post-liver transplant vasculature and reducing the number of false-positive cases, which necessitate unnecessary additional investigations such as computed tomography or angiography. Liver transplant anatomy and the wide array of post-transplant imaging findings on colour Doppler have already been well described but literature on the use of CEUS and its image interpretation remain scarce. This review aims to discuss the indications for CEUS after liver transplant, to demonstrate CEUS technique and familiarise readers with the imaging appearances of post-transplant vascular complications on CEUS [9]. In inconclusive Doppler cases, the use of CEUS could potentially reduce false-positive rates. This would reduce unnecessary ionizing radiation in further investigations, such as CT, while improving dynamic visualization (Figure 2).

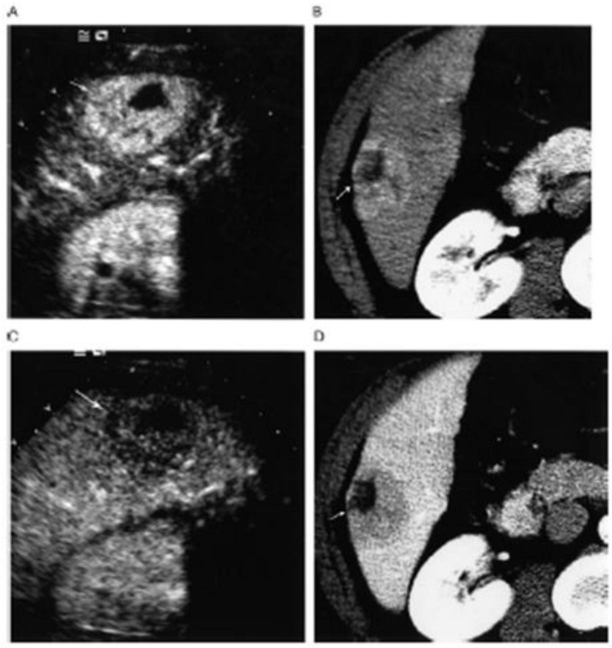

Figure 2: A 42-year-old man with HCC 7.9 cm in maximum diameter located at segments VI and VII. (A) Contrast-enhanced ultrasound of the tumor in arterial phase. Arrowheads point to the tortuous intra tumoral vessels. (B) Contrast-enhanced computed tomography of the tumor in arterial phase. Arrowheads point to the tortuous intra tumoral vessels that are much less than that in CEUS imaging. (C) Contrast-enhanced ultrasound of the tumor in portal phase. Arrowheads point to the enhanced tumor capsule. (D) Contrast-enhanced computed tomography of the tumor in portal phase. The tumor capsule is enhanced similarly with CEUS imaging.

CEUS is particularly helpful in evaluating complications of smaller vessels such, as the HA, and can be useful in evaluating portal and hepatic venous complications as demonstrated.

Techniques

In the immediate postoperative stage, the patient is located in the ICU and ultrasound is performed at the bedside. Finding an optimal acoustic window is often challenging due to overlying surgical bandages and tubes/ lines from ICU equipment. The curvilinear transducer (5 MHz) is the preferred transducer and is often placed at the intercostal window for evaluation of the adult patient (i.e., whole-liver or right lobe grafts). A subcostal approach from the epigastrium may also be performed in absence of overlying surgical bandages. For the pediatric patient (i.e., left lobe graft), the neonatal curvilinear transducer (5 MHz) is used and is usually placed at the epigastrium

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due to the central location of the liver graft. At National University Hospital, CEUS is performed using an iU22 x MATRIX (Philips) at a low mechanical index of 0.15e 0.20. There are no clear published guidelines on the acceptable range of mechanical index values as the image quality differs between vendors with reported values in literature ranging from 0.06 e 0.38 across different machines. 2,4,5,7 Sonovue (sulfur hexafluoride gas with a phospholipid shell; Bracco, Milan, Italy) is injected intravenously into patients via a three-way intravenous cannula in the peripheral veins followed by a flush using 5 ml sodium chloride 9 mg/ml (0.9%) solution. As mentioned earlier, there are few data on the intravenous use of Sonovue in children, but it has been considered to be safe at doses adjusted according to age (i.e., 0.1 ml/year of age) or body weight (0.03 ml/kg).16 In our institution, we use a recommended dose of 1.5 ml for adult patients and 0.03 ml/kg for children (Figure 3).

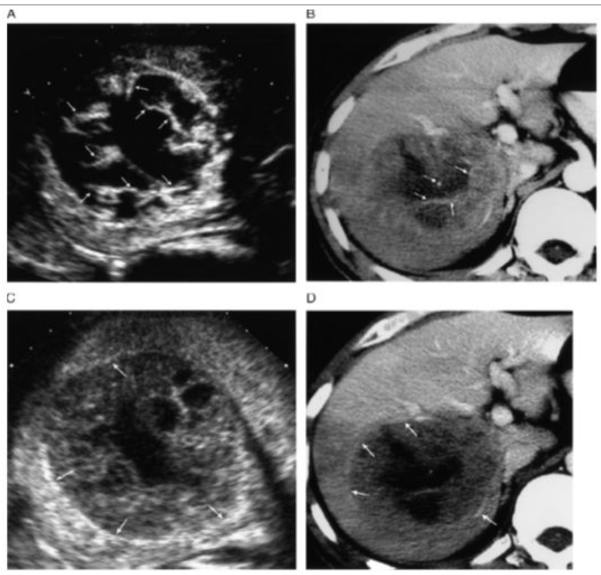

Figure 3: A 48-year-old man with HCC 2.1 cm in maximum diameter located at segment VI. (A) The lesion is hypoechoic on gray-scale US imaging. Arrowhead points to the margin of the tumor. (B) Contrast-enhanced ultrasound of the tumor at 23 s after injection of SonoVue. The tumor is homogeneously hyper enhanced. (C) Contrast-enhanced ultrasound of the tumor at 87 s after the injection of SonoVue. The tumor is hypo enhanced. (D) The lesion is hypo attenuated on baseline CT imaging. Arrowhead points to the margin of the tumor. (E) Contrast-enhanced computed tomography of the tumor in arterial phase. The tumor is isoenhanced. (F) Contrast-enhanced computed tomography of the tumor in portal phase. The tumor is hypo attenuated.

A dual-screen display with low mechanical grey-scale image and contrast images side-by-side is used and images are interpreted real-time. The field-of-view is placed at the hepatic hilum where the PV and HA enters the liver. The HA and its intrahepatic branches are evaluated in the arterial phase followed by evaluation of the PV and hepatic parenchyma perfusion in the portal venous phase (Table 2 and 3). The contrast arrival time for both HA and PV are measured. The hepatic veins enhance at a later stage and are evaluated. Repeated boluses of Sonovue can be injected for further evaluation if required and can be performed up to a maximum of three times [9]. Ultrasound is the first-line imaging technique after liver transplant because it is portable, non-invasive and cost effective [10].

		CECT			
		CR	**IR/SD**	**PD**	**Total**
CEUS	CR	11	1	0	12
	IR/SD	14	40	1	55
	PD	0	0	1	1
	Total	25	41	2	68
p=0.003, =0.474, 95 % CI: 0.371–0.577					
Abbreviations: CECT, Contrast-Enhanced Computed Tomography; CEUS: Contrast-Enhanced Ultrasound; CR: Complete Response; IR: Incomplete Response; SD: Stable Disease; PD: Progressive Disease					

Table 2: No target lesion response.

		CECT				
		CR	**PR**	**SD**	**PD**	**TOTAL**
CEUS	CR	5	1	1	1	8
	PR	22	26	2	3	53
	SD	1	9	27	0	37
	PD	3	1	1	27	32
	TOTAL	31	37	31	31	130
p<0.001, =0.534, 95 % CI: 0.480–0.588						
Abbreviations: CECT: Contrast Enhanced Computed Tomography; CEUS: Contrast-Enhanced Ultrasound; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease						

Table 3: Overall response.

Early detection of post-liver transplant vascular complications, such as hepatic artery (HA) thrombosis (HAT), is crucial in preventing graft failure; however, making an accurate diagnosis can be challenging at times due to the inherent limitations of ultrasound. It is particularly testing to demonstrate vascular patency in pediatric liver transplants (i.e., small calibre vessels) and in transplant cases where hepatic vessels are in close proximity. In addition, there is also a wide spectrum of imaging findings post-liver transplant of which some may appear worrisome and mimic post-transplant vascular complications. Hence, potential misinterpretation of results is common and often lead to false positives and unnecessary further investigations [10,11].

Conclusion

The liver disease continues to increase although ultrasound scanning of the liver with Doppler capability is noninvasive but it has some limitations in case of slow flow especially small vessels after liver transplant. the use of contrast-enhanced ultrasound CEUS can solve this problem and the literature review in this report defining the overall problem and offer some solution.

However, further research is needed to more clearly categorize the difficulties of using CEUS and effective training programs for sonographers to use this facility in the future. And conclude that CEUS is very significant in assessing the liver and needed for today and tomorrow's examination.

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