World Journal of Radiology

Online Submissions: http://www.wjgnet.com/1949-8470office
wjr@wjgnet.com
doi:10.4329/wjr.v3.i5.141

World J Radiol 2011 May 28; 3(5): 141-146
ISSN 1949-8470 (online)

AUTOBIOGRAPHY OF EDITORIAL BOARD MEMBERS

Era of diagnostic and interventional ultrasound

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Author contributions: Xu HX solely contributed to this article.
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Received: March 2, 2011 Revised: March 19, 2011
Accepted: March 25, 2011
Published online: May 28, 2011

Abstract

It is an era of diagnostic and interventional ultrasound (US). Various new techniques such as three-dimensional US (3D US), interventional US, and contrast-enhanced US (CEUS) have been introduced into clinical practice. Dr. Xu and his colleagues have taken advantage of these techniques and carried out a series of relevant studies. Their use of 3D US in the liver, gallbladder, liver tumor volumetry, guidance for ablation, and 3D CEUS has widened the application of 3D US in the clinic. They found that prognosis in patients with hepatocellular carcinoma (HCC) after thermal ablation with curative intent was determined by treatment response to ablation, pretreatment serum AFP, and liver function reserve. Tumor response to treatment was the most predictive factor for long-term survival. They compared the use of percutaneous microwave ablation and radiofrequency ablation for the treatment of HCC and found that both are effective methods in treating HCCs. The local tumor control, complications related to treatment, and long-term survival were equivalent for the two modalities. They first compared the enhancement patterns of HCC and intrahepatic cholangiocarcinoma (ICC) and proposed the diagnostic clues for ICC, liver angiomyolipoma (AML), gallbladder cancer, renal carcinoma, and renal AML, which have greatly enhanced the role of CEUS in the clinic. They also evaluated the diagnostic performance of CEUS in characterizing complex cystic focal liver lesions and the agreement between two investigators with different experience levels; and found that CEUS is especially useful for the young investigator. They assessed the effect of anti-angiogenic gene therapy for HCC treated by microbubble-enhanced US exposure and concluded that gene therapy mediated by US exposure enhanced by a microbubble contrast agent may become a new treatment option for HCC.

Key words: Ablation; Cancer; Contrast-enhanced ultrasound; Interventional ultrasound; Liver; Three-dimensional ultrasound

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Xu HX. Era of diagnostic and interventional ultrasound. *World J Radiol* 2011; 3(5): 141-146 Available from: URL: http://www.wjgnet.com/1949-8470/full/v3/i5/141.htm DOI: http://dx.doi.org/10.4329/wjr.v3.i5.141

INTRODUCTION AND EDUCATIONAL EXPERIENCE

Professor Dr. Hui-Xiong Xu is the Chair of the Department of Medical Ultrasound and the Vice-Chair of the Medical Imaging Center, Shanghai Tenth People's Hospital and the Tenth People's Hospital of Tongji University, Shanghai, China. He was enrolled in Tongji Medical University, Wuhan, China, in 1989 and obtained his M.D. degree in 1994. After graduation, he became a resident in the Department of Ultrasound, Tongji Hospital, Tongji Medical University and from then on he has devoted his career to the research and application of ultrasound (US) in medicine. In 1996, he became a doctoral student of Professor Qing-Ping Zhang, a famous pioneer in Diagnostic Ultrasound. He learned a lot from Professor Zhang, not only the knowledge of specialty, but also how to be a righteous person. In 2000, his article entitled "3D Ultrasound of Abdominal Structures" was awarded The Grand Prix of The First 3D Clinical Contest, which was sponsored by the 3D Ultrasound Research Foundation in Korea. After 5-year doctoral course, he finished his thesis on Three-dimensional Ultrasound in Abdomen and obtained a PhD degree in Medical Imaging from Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. To further strengthen his academic background, he continued to seek strict scientific training and found a postdoctoral position in The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China, under the instruction of Professor Ming-De Lu. In 2003, he became an Associate Professor and in 2006 a Professor of Sun Yat-Sen University through a non-routine promotion due to his significant academic achievements. In 2005, he visited the Department of Gastroenterology and Hepatology of Tokyo Medical University Hospital, Tokyo, Japan. He stayed there for 1 year to carry out research on contrast-enhanced US (CEUS) under the instruction of Professor Moriyasu as a Visiting Research Fellow. In 2011, he transferred to his current position. His academic positions are as follows: Supervisor of PhD candidates; Vice-president, Youth Committee of Ultrasound Branch, Chinese Medical Association (CMA); Member of Abdominal Group, Ultrasound Branch of CMA; Council Member of Abdominal Branch, Chinese Association of Ultrasound and Medical Engineering (CAUME); Member of Standing Council, Interventional Ultrasound Committee, Chinese Association of Medical Imaging Technique; Secretary-General, Member of Standing Committee of Ultrasound Branch, Guangdong Medical Doctor Association; Member of Standing Committee of Ultrasound Branch, Guangdong Association of Liver Diseases; Corresponding Member, European Society of Radiology; Member, International Contrast Ultrasound Society. He is the expert panel member for the new international liver CEUS guideline sponsored by the World Federation of Ultrasound in Medicine and Biology (WFUMB) and the American Institute of Ultrasound in Medicine, which will be released in August 2011 in Vienna, Austria. He serves as an editorial board member of a number of journals including the *Chinese Journal of Cancer*, *Chinese Journal of Medical Imaging Technique*, *Journal of US-China Medical Science*, and he is proud to be the Vice Editor-in-Chief of *World Journal of Radiology*. He is also a peer reviewer for journals such as *European Radiology* and *Journal of Ultrasound in Medicine*. In recent years, he has published approximately 30 articles in international journals as the first or corresponding author in the field of diagnostic and interventional US. Because of his outstanding achievements, he was named as the New Century Excellent Talent sponsored by the Chinese Ministry of Education and Distinguished Scholar by CAUME.

ACADEMIC STRATEGIES AND GOALS

In recent years, Dr. Xu's research areas focused on three-dimensional US (3D US), CEUS, and interventional US. Besides the use of 3D US in prenatal diagnosis, he also utilized 3D US to visualize the liver and gallbladder, guide interventional procedures, and evaluate treatment response after local therapies. Since the introduction of CEUS in China in 2004, he has carried out a number of studies to evaluate its usefulness in clinical practice. He first reported the use of CEUS in small focal liver lesions by using the new generation contrast agent SonoVue and novel low mechanical index contrast specific techniques, as well as the enhancement pattern of intrahepatic cholangiocarcinoma (ICC). Due to his contribution concerning the use of CEUS in liver, he was invited by Professor Claudon, the Chairman of WFUMB, to compile the new version of the International CEUS Guideline for Liver. His career goal is to utilize up-to-date US techniques to improve the diagnosis and treatment of various diseases.

ACADEMIC ACHIEVEMENTS

Dr. Xu's activities in diagnostic and interventional US and his contributions are as follows:

3D US

Xu *et al*[1] assessed the differences between 2D and 3D US in evaluating fetal malformations. The results showed that in comparison with 2D US, 3D US improves the diagnostic capability by offering more diagnostic information in evaluating fetal malformations, particularly in displaying malformations of the cranium and face, spine and extremities, and body surface. 3D US is a valuable adjunct to 2D US in prenatal diagnosis. They investigated the potential clinical usefulness of 3D gray scale volume rendering in the liver. That is a challenging task since few investigators had previously evaluated this. They found that in patients with ascites, 3D US was superior to 2D US in terms of surface features, edges, overall 3D impression, image clarity, and structural relationships. In patients without ascites, 3D US was superior to 2D US with respect to the continuity of intrahepatic vessels, overall 3D impression of the vessels, image clarity, and the relationship between lesions and neighboring vessels[2]. They first evaluated the accuracy and reproducibility of a commercially-available 3D US volume measurement system based on automatic border detection technique, VOCAL™ (virtual organ computer-aided analysis) in the volumetry of liver tumors. They confirmed that the new system can greatly reduce the time taken and manual labor needed for volume measurement with high accuracy and reproducibility. 3D US volumetry using the new system is more acceptable and valuable in clinical practice and is expected to be useful for evaluation of the efficacy of tumor therapy *in situ* in patients with hepatic tumors[3]. They also found that a 3D power Doppler projection image gives a better overall picture of vascular distribution than a 2D slice and significantly correlates with angiography for delineating vascularity in hepatocellular carcinoma (HCC)[4]. The gallbladder is an idea organ for 3D US, Xu *et al*[5] compared 3D US with 2D US for the diagnosis of gallbladder diseases. It was found that 3D US adds no advantages for the diagnosis of gallstones compared with 2D US, but it is better than 2D US for differential diagnosis of gallbladder polyps and may improve the localization and staging for gallbladder carcinoma. Their efforts have widened the utility of 3D US in clinical practice.

Interventional US

US-guided ablation therapy for HCC has gained increased attention as a curative option for early HCC. Xu *et al*[6] investigated the therapeutic efficacy of thermal ablation for the treatment of HCC using microwave and radiofrequency (RF) energy application. Complete ablation was obtained in 92.6% (176/190) nodules and local recurrence was found in 9.5% nodules in the follow-up. 1, 2 and 3-year cumulative survival was 75.6, 58.5, and 50.0%, respectively. The relatively low survival rates were partly due to the fact that recurrent HCC accounted for the majority of the cases. They also tried to identify prognostic factors for long-term outcome in patients with HCC after percutaneous microwave or radiofrequency ablation[7]. Prognosis for patients with HCC after thermal ablation with curative intent was determined by treatment response to ablation, pretreatment serum AFP, and liver function reserve. Tumor response to treatment was the most predictive factor for long-term survival and was related to tumor size, thus careful selection of patients for ablation therapy is recommended. They compared the use of percutaneous microwave ablation and radiofrequency ablation for the treatment of HCC and found that percutaneous microwave ablation and radiofrequency ablation are both effective methods in treating HCCs. The local tumor control, complications related to treatment, and long-term survival were equivalent for the two modalities[8,9]. To improve the targeting and monitoring of ablation, they applied 3D US in the guidance. Their results showed that 3D US was useful in delineation of expandable RF electrodes, improvement of operator confidence level, determination of applicator placement, and visualization of the position relationship between the applicator and adjacent critical structures during procedures of liver cancer ablation under image guidance[10]. Tumor location close to the diaphragm or gastrointestinal tract was regarded as a treatment contraindication due to poor visibility of the tumor or increased risk of thermal injury to the adjacent organs. To solve this problem, Xu *et al*[11] utilized artificial pleural effusion or ascites to improve visualization of the tumor and isolation from adjacent critical structures. The technical success rates were 95% for artificial pleural effusion and 100% for artificial ascites. These techniques are safe and effective, which provide treatment opportunities for complicated cases. To improve the treatment response evaluation after ablation therapy, Xu *et al*[12] investigated the potential usefulness of 3D CEUS for this purpose. They found that 3D CEUS enhances the diagnostic confidence in the majority of patients and even changes the management in some patients. 3D CEUS has potential usefulness in evaluating treatment response in liver cancer after local therapies.

CEUS

Low mechanical index CEUS has greatly changed the status of US techniques since its introduction into clinic practice.

Liver: Xu *et al*[13] evaluated its performance in diagnosing focal liver lesions. Their results showed that the sensitivity, specificity, and positive predictive value, respectively, were 88.8%, 89.2%, and 91.3% for HCC; 81%, 100%, and 100% for liver metastasis; 57.1%, 100%, and 100% for ICC; 94.6%, 100%, and 100% for liver hemangioma; and 90.9%, 97.8%, and 71.4% for focal nodular hyperplasia. Xu *et al*[14] further assessed the diagnostic performance of CEUS characterization of small focal liver lesions (FLLs; ≤ 3.0 cm in diameter). Their results showed that after review of CEUS, ROC analysis revealed a significant improvement in differentiating between malignant and benign small FLLs, where the areas under the ROC curve were 0.856 at baseline US *vs* 0.954 at CEUS ($P < 0.001$) and 0.857 *vs* 0.954 for reader 2 ($P = 0.003$). The sensitivity, negative predictive value, and accuracy for both readers also improved significantly after contrast agent administration (all $P < 0.001$). A better result of specific diagnosis was obtained [38.5% (77/200) at baseline US *vs* 80.5% (161/200) at CEUS for reader 1 and 34.5% (69/200) *vs* 80.5% (161/200) for reader 2; both $P < 0.001$] after contrast agent administration, and a better interobserver agreement was achieved ($\kappa = 0.425$ at baseline US *vs* 0.716 at CEUS). Thus, CEUS improves the diagnostic performance in small FLLs compared with baseline US. For smaller FLLs (≤ 2 cm), similar results were obtained although the sensitivity for HCC was relatively low[15].

ICC is a malignant tumor originating from the bile duct epithelium of the interlobular biliary duct. US findings are nonspecific for ICC. Xu *et al*[16] and Chen *et al*[17,18] evaluated the use of CEUS in characterization of ICC. They first reported that four enhancement patterns exist in the arterial phase for ICC, which were (1) peripheral irregular rim-like hyperenhancement; (2) diffuse heterogeneous hyperenhancement; (3) diffuse homogeneous hyperenhancement; and (4) diffuse heterogeneous hypoenhancement, which accounts for 47.5%, 22.5%, 12.5% and 17.5%, respectively, for ICC[17]. The enhancement patterns of ICC on CEUS were consistent with those on contrast-enhanced CT (CECT) in the arterial phase, whereas in the portal phase ICC faded out more obviously on CEUS than on CECT. CEUS had the same accuracy as CECT in diagnosing ICCs, and so can be used as a new modality for the characterization of ICC. Concerning the differentiation between ICC and HCC, the sensitivity (28%-44% *vs* 82%-90%) and accuracy

(64%-71% *vs* 90%) improved significantly after CEUS (all $P < 0.05$). The interobserver agreement increased from $\kappa = 0.575$ at BUS to $\kappa = 0.720$ after CEUS[18]. Thus CEUS significantly improves the diagnostic performance in the differentiation between ICC and HCC.

Complex cystic FLLs are those containing large fluid-filled areas within the lesions; they are increasingly common in clinical practice as a result of the increasing use of hepatic imaging. Lin *et al*[19] evaluated the diagnostic performance of CEUS in characterizing complex cystic FLLs. The US and CEUS images were reviewed by a resident radiologist and a staff radiologist independently. After ROC analysis, the areas (Az) under the ROC curve were 0.774 at US *vs* 0.922 at CEUS ($P = 0.047$) by the resident radiologist, and 0.917 *vs* 0.935 ($P = 0.38$) by the staff radiologist. A significant difference in Az between the resident and the staff radiologist was found for US (0.774 *vs* 0.917, $P = 0.044$), but not for CEUS (0.922 *vs* 0.935, $P = 0.42$). Interobserver agreement was improved after CEUS ($\kappa = 0.325$ at US *vs* $\kappa = 0.774$ at CEUS). Real-time CEUS improves the capability of discriminating between benign and malignant complex cystic FLLs, especially for the resident radiologist.

Hepatic angiomyolipoma (AML) is generally considered a rare benign mesenchymal tumor of the liver. With the increasing clinical application of imaging, more and more hepatic AMLs are being detected. Wang *et al*[20] found that arterial hyperenhancement and subsequent sustained enhancement on CEUS were found in the majority of hepatic AMLs. The combination of BUS and CEUS leads to the correct diagnosis in the majority of hepatic AMLs, and is higher than the success rate achieved by BUS alone. For those unusual benign FLLs, Xu *et al*[21] found that CEUS was beneficial in leading to a benign diagnosis for some lesions showing hyperenhancement during the arterial phase and sustained enhancement during the portal or late phase, such as liver AML and lipoma. The benign nature of other lesions showing no enhancement during all phases, such as solitary necrotic nodules and focal fibrosis, was also observable. On the other hand, for those lesions showing hyperenhancement, isoenhancement, or hypoenhancement during the arterial phase and hypoenhancement during the late phase, including intrahepatic biliary cystadenoma, biliary epithelial dysplasia, infected liver diseases, inflammatory pseudotumor, sarcoidosis, and peliosis hepatis, the differential diagnosis between benignity and malignancy was difficult, and pathologic tests were mandatory.

The feasibility of 3D CEUS in liver imaging was evaluated by Xu *et al*[22]. The patients were classified into two groups: those for characterization and those for local treatment response evaluation. The investigators found that 3D CEUS results in better image quality and leads to higher diagnostic confidence in those for treatment response evaluation, and perhaps is more useful in this aspect in future clinical setting.

Gallbladder and bile duct: Conventional gray-scale US is the first-line imaging investigation for diagnosis of gallbladder diseases, but can result in difficulty in determining the nature of the gallbladder lesions in some cases, especially in differentiating chronic cholecystitis with thickened wall from gallbladder carcinoma with thickened wall or in differentiating motionless sludge from gallbladder cancer[23,24]. Xie *et al*[23] evaluated the usefulness of CEUS in diagnosing gallbladder diseases. They found that characters such as hyperenhancement or isoenhancement in the early phase and then fading out to hypoenhancement, as well as destruction of the gallbladder wall intactness, are more frequent in malignancy. Conventional US resulted in correct original diagnoses in 68.8% patients, and CEUS in 96.3%. Thus, CEUS is useful in the differential diagnosis between malignant and benign gallbladder diseases.

Xu *et al*[25] compared the enhancement pattern of hilar cholangiocarcinoma on CEUS with that on CECT. They found that the enhancement pattern of hilar cholangiocarcinoma on CEUS was similar with that on CECT in the arterial phase, whereas in the portal phase, hilar cholangiocarcinoma shows hypoenhancement on CEUS. CEUS and CECT lead to similar results in evaluating portal vein infiltration and diagnosis of this entity.

Xu *et al*[26] first reported the experience of CEUS in villous adenoma of the extrahepatic bile duct. In this disease, CEUS showed hyperenhancement during the arterial phase and subsequent washout, suggesting it was a hypervascular lesion and excluded the diagnosis of sludge, nonshadowing stones, and blood clots. Because the lesion exhibited homogeneous echogenicity, the bile duct wall was intact, and invasive signs were absent on a BUS, the diagnosis of a benign tumor such as an adenoma was suggested.

Kidney: Renal cell cancer (RCC) is the most common malignant tumor of kidney, which accounts for 80% to 90% of renal tumors. Xu *et al*[27] observed the CEUS features of RCC and found that hyper- or iso-enhancement during the cortical phase, subsequent washout in the late phase, inhomogeneous enhancement, and perilesional rim-like enhancement are clues for RCCs, which might be useful for characterization of RCCs. They[28] further evaluated the usefulness of CEUS in differentiating RCC from renal AML (RAML). They found that the CEUS features of early wash-out, heterogeneous enhancement, and an enhanced peritumoral rim are highly suggestive of RCC, whereas homogeneous enhancement and prolonged enhancement are characteristic manifestations of RAML. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CEUS in differentiation were 88.2%, 97.0%, 98.8%, 74.4%, and 90.5%, respectively. Thus, CEUS is valuable in differentiating RCC from RAML.

Experimental study: Nie *et al*[29] explored the effects of US exposure combined with microbubble contrast agent (SonoVue) on the permeability of the cellular membrane and on the expression of plasmid DNA encoding enhanced green fluorescent protein (pEGFP) transfer into human umbilical vein endothelial cells (HUVECs). They found that the percentage of FD500-positive HUVECs in the group of US exposure combined with SonoVue was significantly higher than that of the group of US exposure alone (66.6% ± 4.1% *vs* 24.0% ± 5.5%, $P < 0.001$). Compared with the group of US exposure alone, the transfection expression rate of pEGFP in HUVECs was markedly increased with the addition of SonoVue (1.5% ± 0.2% *vs* 16.1% ± 1.9%, $P < 0.001$). No statistically significant difference was observed in the survival rates of the HUVECs between the US group with and without the addition of SonoVue (94.1% ± 2.3% *vs* 91.1% ± 4.1%). The cell membrane permeability of HUVECs and the transfection efficiency of pEGFP into HUVECs exposed to US are significantly increased after addition of an US contrast agent without obvious damage to the survival of HUVECs. This noninvasive gene transfer method may be a useful tool for clinical gene therapy.

They further assessed the effect of anti-angiogenic gene therapy for HCC treated by microbubble-enhanced US exposure[30]. Compared with the group treated by US alone, KDR-tk gene treatment by US combined with SonoVue inhibited tumor growth and increased survival time of tumor-bearing mice; microvessel density in the US and SonoVue group was significantly lower than that in the US alone group (12.3 ± 1.4 *vs* 27.4 ± 3.2, $P < 0.05$). An apoptosis index increased in the group treated with US and SonoVue compared with the group treated with US alone (25 ± 3.6 *vs* 36 ± 3.8, $P < 0.05$), whereas there was no significant difference between the SonoVue alone group and the phosphate-buffered saline alone group (17 ± 1.8 *vs* 14 ± 1.2, $P > 0.05$). The authors concluded that gene therapy mediated by US exposure enhanced by a microbubble contrast agent may become a new treatment option for persistent HCC.

CONCLUSION

Due to the rapid progress in image processing and transducer design, US has gained increasing attention in clinical practice in recent years. It is now an era of diagnostic and interventional US[31-33]. Dr. Xu's studies in the fields of 3D US, interventional US, and CEUS has greatly enriched the use of US in diagnosis and treatment.

ACKNOWLEDGMENTS

I am grateful to Professor Qing-Ping Zhang for bringing me to the world of US, to Professor Ming-De Lu for giving me numerous chances to learn and practice, and to Prof. Moriyasu F for opening a new window of US to me. I would also express my gratitude to my colleagues worldwide for their kind collaboration.

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