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# Application of ultrasound contrast in identification and diagnosis of ocular spaceoccupying lesions

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Received:2011-04-20 Accepted:2011-06-18

## Abstract

• AIM: To analyze the application significance of ultrasound contrast agent in identification and diagnosis of ocular spaceoccupying lesions, and mainly analyze its advantages and problems.

• METHODS: Thirty-two representative literatures about the application of ultrasound contrast agent in diagnosis of spaceoccupying lesions at home and abroad were collected after focused on sorting the literature reporting the application of ultrasound contrast diagnostic technology in the diagnosis and identification of ocular spaceoccupying lesions in recent years. Its advantages and problems were retrospectively analyzed, and reasonable assessment on existing problems was made and possible solutions to the problems were proposed.

• RESULTS: As a new imaging diagnostic technique, the contrast-enhanced ultrasound, which can enhance the display of tumor microcirculation vessels and improve the tumor's ultrasound diagnostic capability, was analyzed. Through sorting and comprehensively analyzing the collected literatures, the positive rate of ocular spaceoccupying lesion diagnosis could be significantly improved with ultrasound contrast technology. Thus, the vascular perfusion in normal tissues and lesions was reflected objectively. According to the lesion's perfusion characteristics of the contrast agent plus with the performance features of two-dimensional ultrasound, the ocular spaceoccupying lesions can be accurately diagnosed, and this could provide clinicians with reliable research basis in this field.

• CONCLUSION: Ultrasound contrast examination is a new testing method, and ultrasound contrast agent can significantly enhance the ultrasonic detection signal, clearly show the blood perfusion in vessels and tissues, increase the image contrast resolution, and improve the lesion's detection capability in the microcirculation perfusion level, especially its important value in the diagnosis of ocular tumor.

• KEYWORDS: ultrasound contrast; ocular spaceoccupying lesion; differential diagnosis; new microbubble contrast agent
DOI:10.3980/j.issn.2222-3959.2011.04.02

Yuan JY, Zhang JH, Tang C, Zhao JZ, Pang C, Ren XC, Zhu H, Zhang YT. Application of ultrasound contrast in identification and diagnosis of ocular spaceoccupying lesions. *Int J Ophthalmol* 2011;4(4):337-342

## INTRODUCTION

The emergence of ultrasound examination, especially the emergence of color Doppler ultrasound examination, provides a new testing way for diagnosing ocular spaceoccupying lesions, which can not only observe the morphological features of lesions, but simultaneously provide the blood flow characteristics. However, affected by the blood flow and the equipment's poor sensitivity to low-velocity blood flow, the assessment of blood flow of some lesions may be false negative. The emergence of ultrasound contrast has greatly improved the ultrasonic diagnostic device's capability of displaying the blood flow in the lesions, thereby providing a new approach for diagnosing ocular spaceoccupying lesions[1,2].

Ultrasonic contrast is a hot research direction in current ultrasonic diagnosis. It improves the contrast differences between tissues through enhancing the strength of reflection signals, and in particular, it can improve the detectable rate

of the microvascular, low-velocity and low-flow blood signals, and can display the blood perfusion features in tissues. The application of new microbubble contrast agents has greatly improved the resolution of ultrasound contrast, and the ultrasound contrast has important value for the diagnosis of ocular diseases, especially that of ocular tumors.

## MATERIALS AND METHODS

**Materials** The ultrasound contrast needs corresponding ultrasound equipment and signal post-processing software, and conventional ultrasound can be used for ultrasound contrast, but due to the probe frequency, the output sound power and post-processing and other factors, it is difficult to obtain good contrast results. At present, there have already been dozens of ultrasound contrast imaging technologies used in clinic, such as second harmonic imaging, pulse inversion harmonic imaging, acoustic stimulation imaging, harmonic imaging, microvascular imaging and so on. In addition, there are still many new technologies being developed.

Ultrasound contrast examination is a new testing method, and the ultrasound contrast agent (UCA) can significantly enhance the ultrasonic detection signal, clearly show the blood perfusion in vessels and tissues, increase the image contrast resolution, and improve the lesion's detection capability in the microcirculation perfusion level, so it is another milestone in the medical development history of ultrasound [3]. The application of contrast agent in the ultrasound examination began in 1968, but due to unstable bubble used, short duration, disability to pass through the pulmonary circulation and other factors, its clinical application is limited. The new generation of vascular pool contrast agent Sono Vue is composed of tiny bubbles and stable shell, and the bubble with a diameter of about 1-10μm has good stability and can pass the pulmonary circulation. It can meet the needs of cardiac contrast, and has widely used in the diagnosis of diseases in the abdomen and other organs. To use the ultrasound contrast examination in the eye is a pilot study based on its safe and effective application in other organs. In recent years, researchers[4] firstly carried out the relevant animal experiments, confirming that the application in the eye did not cause ocular and systemic side effects, and that it would not significantly affect the retinal function and structure, and this did not have obvious differences with the changes in the ocular tissues of animals that were given contrast agent in other organs.

### Diagnosis of Ocular Spaceoccupying Lesions

**Literatures at abroad** Coppola *et al* [5] found that while using Levovist color Doppler ultrasound contrast to study patients with intraocular tumor or orbital tumors, the color Doppler signals were indeed enhanced after the use of contrast agent, of which the signal to noise ratio (SNR) of 70% cases improved, and this was conducive to identifying the tumor's blood vessel patterns and also improved the accuracy of measuring the blood flow velocity. There was no significant correlation between the signal enhancement and the lesion's histological type or the lesion site; and also that the enhanced vascular signal sites after contrast sometimes would become the noise affecting the results of ultrasound examination. Lemke *et al* [6] found while examining patients with uveal melanoma that Levovist color Doppler ultrasound contrast could slightly improve the detectable rate of uveal melanoma and orbital small blood vessels, but could not discriminate the normal blood vessels and tumor vessels; meanwhile, it was also found that it was helpful for differentiating orbital solid tumors and retinal hematoma or hemorrhage.

The results of Fore *et al* [7] showed that the ultrasound contrast could effectively observe the pattern of tumor microcirculation and found the tumor's internal vitreous planting, and the authors also found that the microcirculation pattern of the choroidal malignant melanoma was an important factor for assessing the tumor prognosis, and the ring or reticular pattern showed a poor prognosis, while the band pattern showed a better prognosis. Sehlottmann *et al* [8] found that Sono Vue low mechanical index harmonic ultrasound contrast is completely feasible, and that the Doppler examination of some post-radiotherapy eutic energy no longer had the choroidal melanoma with unusual signals, while it could be found a lot of perfusion imaging after using microbubble contrast, but this research still had no data to indicate that these patients would see local melanoma recurrence; and no retinal hemorrhage or other complications were found in the follow-up survey during and after the examination. The researchers also believed that the low mechanical index harmonic ultrasound contrast was the most sensitive method for diagnosing choroidal tumors at present, and was also a powerful tool for assessing the radiotherapy eutic effect of ocular melanoma. If the melanoma microbubble signals were strongly positive after radiotherapy, then it showed that the radiotherapy was insufficient.

**Literatures at home** The real-time ultrasound contrast technology is another milestone in the history of medical imaging development, and is the third revolution following the real-time two-dimensional imaging as well as Doppler and color flow imaging. Contrast-enhanced ultrasound has

been widely applied in liver, heart and other organs, and has obtained satisfactory results in the diagnosis and treatment of diseases. Yang *et al* [9] proved in their experiments that contrast-enhanced ultrasound also could enhance the display capability of eyeball blood vessel, and that it had its own advantages and prospects in discovering small lesions and treating diseases. Meanwhile, Sono Vue real-time ultrasound contrast would not have significant negative effects on the choroidal retinal function and structure. However, the research reports on the application of contrast-enhanced ultrasound in ophthalmology are very few, and its application effect and security still need further verification.

Li *et al* [10] studied the application value of contrast-enhanced ultrasound in the diagnosis of ocular spaceoccupying diseases, proposed that the contrast-enhanced ultrasound could provide important differential diagnostic information for the diagnosis of ocular spaceoccupying diseases, thus to help for more accurately diagnosing the ocular spaceoccupying lesions. Zhang *et al* [11] used contrast-enhanced ultrasound to diagnose and differentially diagnose intraocular tumors. They found that the contrast agent's time-concentration curves had their own characteristics. The contrast agent's concentration gradually increased with the time in normal ocular tissues, and then gradually decreased after reaching the peak. In the choroidal melanoma, it showed as the parabolic curve-alike shape which immediately reached the peak with time and then sharply decreased, and it was the typical curve of fast in and out for malignant tumor. In the choroidal hemangioma tumors, it showed a curve similar to the normal tissues, but the contrast agent's concentration and duration in tumor were both stronger than normal tissues, showing the typical curve of fast-in and slow-out. There were no contrast agents filled in the subretinal hemorrhage lesions, and the time-concentration curves were close to be flat.

The orbital cavernous hemangioma has package outside, and is composed of a large number of vessel cavities covered by endothelial inside, belonging to the deformity hamartoma at the low-flow artery side in histology and hemodynamics. The tumor has direct and relatively small arterial input and output, and is composed of interlocked and connected vascular channels, with slow filling of internal blood flow, and the ultrasound contrast technology is considered to be the new technology that can dynamically and directly observe the tissue's microperfusion process. The study of Ren *et al* [12] showed that the orbital cavernous hemangioma's contrast-enhanced ultrasound mostly showed as typical dynamic enhancement pattern as the sign of "rolling a snowball", and such enhancement pattern was not found in the observation of other types of orbital tumors. The noninvasive ultrasound contrast technology is of simple operation and low price, and can directly observe the tumor's perfusion process, so it may be more suitable for clinical needs, and is worth further studying. Lu *et al* [13] discussed the diagnostic value of orbital cavernous hemangioma's contrast-enhanced ultrasound and magnetic resonance enhancement, and compared the advantages and disadvantages of the two methods. The results showed that the orbital contrast-enhanced ultrasound and MRI enhancement both had the significance of qualitative diagnosis for the orbital cavernous hemangioma, and the accuracy of orbital MRI enhancement was higher than that of the orbital contrast-enhanced ultrasound, while the contrast-enhanced ultrasound had the suggestive role for the size of sinus in the orbital cavernous hemangioma.

Confirmed by the above literatures, the intraocular solid lesions are filled with contrast agents that mainly showed as rapid increase, and the dissipation speed of the contrast agent is faster than that of normal tissues, indicating that the contrast agent has a short duration in the lesions, being a typical type of fast-in and fast-out. The contrast agent in benign tumors generally simultaneously enhances with the contrast agent in normal tissues, but the intensity of contrast agent in lesions is higher than that in normal tissues, and the dissipation speed is also slower than that in normal tissues, which indicates that the contrast agent has a long duration in lesions, being the typical type of slow in and slow out.

**Security issue** The contrast agent enters into the artery and vein and capillary through peripheral vein and through the systemic circulation, and under the acoustic force, the microbubbles begin to oscillate in their resonant frequency. When the acoustic pressure is very heavy, the microbubbles' oscillation becomes very intense, so their membrane ruptures and the microbubbles disappear ultimately. Sono Vue's advantage of lively shell makes such oscillation begin under very low acoustic force, much lower than its rupture threshold, *i.e.* the microbubbles can continue to oscillate but not rupture under a wide range of acoustic pressure. The existence of microbubbles significantly increases the blood signal enhancement, but also greatly reduces the cavitation. The cavitation effect is one of the important effects of ultrasonic biology, and it can cause the damage and destruction role of the body, cells and microorganisms. High intensity of ultrasound wave can not only damage blood cells and tissues, but also promote the formation of cavities and bubbles, and may enhance the cavitation effect. It is reported

that the microbubble cavitation can produce hemolysis, bleeding and DNA fragment breaking and other biological effects.

It is confirmed by a large number of clinical studies that Sono Vue is a good and safe ultrasound contrast agent. Moerl *et al* [14] studied the Sono Vue's hemodynamics, safety and mechanical tolerance, and found that its hemodynamics was not dependent on dose, and it was discharged soon *via* the lung after entering into the body. Bokor *et al* [15] investigated the patients with chronic obstructive pulmonary diseases, and they found that Sono Vue injection had no serious adverse reactions occurred, and that the results between the chronic obstructive pulmonary disease group and the control group had no significant differences. The literature reported the safety of Sono Vue in patients with severe left ventricular dysfunction and pulmonary hypertension, which indicated that even if large doses of Sono Vue would not cause significant clinical symptoms of patients, and would not make the left ventricular dysfunction severer and not affect the lung function[16].

**Methods** With the extensive research on the application of ultrasound contrast agent in liver, heart and tumor diagnosis, many scholars also introduced it into the ophthalmology and conducted a preliminary exploration. At present, the researches on the ocular spaceoccupying lesions have successively reported and conducted comparative studies on the advantages and disadvantages of using ultrasound contrast agent in the ocular spaceoccupying lesions, thereby studying appropriate ultrasonic irradiation safety parameters to add new effective methods to the diagnosis of ocular spaceoccupying lesions.

In recent years, 32 literatures were collected about the role of ultrasound contrast agent in the diagnosis of ocular spaceoccupying lesions at home and abroad, including 18 domestic ones (accounting for 56.3%) and 14 foreign ones (accounting for 43.7% ), and a retrospective analysis was made on the above references in the condition of multi-parameters, with the respect of the application effect and safety of the ultrasound contrast agent in the diagnosis of ocular spaceoccupying lesions and other aspects. From the above literatures, the differences of the ultrasound contrast agent were analyzed in the diagnosis of ocular spaceoccupying lesions with other imaging diagnostic techniques as well as its characteristics. Whether there were disagreements on the application of ultrasound contrast technology in the diagnosis of ocular spaceoccupying lesions between China and foreign countries as well as their existing basis was also reviewer. The predictive analysis was focused on the specificity and effect of the ultrasound contrast agent in the diagnosis of ocular spaceoccupying lesions, and meanwhile, a full range of analysis of the problems was also reviewer in related researches, thus to provide a theoretical basis for the application of ultrasound contrast agent in the diagnosis of ocular spaceoccupying lesions.

As orbital lesions are of many kinds, there is still lack of detailed researches on the characteristics of ultrasound contrast examination currently. According to the pathophysiological basis for tumor formation, there are a large number of invasive capillaries generating at the peripheral and internal malignant tumors, so as to diffuse and penetrate oxygen and nutrients from the surrounding tissues to maintain their proliferation, progression and metastasis. There are fewer capillaries generating in benign tumors. Based on the above theoretical basis, the application of ultrasound contrast technology in the diagnosis of ocular spaceoccupying lesions was also studied. The ocular benign, malignant tumors and vascular tumors were analyzed. At the meantime, targeting analysis was made on each aspect's research findings involving the application of ultrasound contrast technology in the diagnosis of ocular spaceoccupying lesions, thus to further obtain comprehensive empirical experimental basis.

**RESULTS**

In recent years, the research and development of ultrasound contrast agent have made significant progress. Through sorting and comprehensively analyzing the collected literatures, clinical practical information was obtained on the application of ultrasound contrast technology in the diagnosis of ocular spaceoccupying lesions, and this could also provide reliable research basis for clinicians in this field. As a new imaging diagnostic technique, the contrast-enhanced ultrasound can enhance the display of tumor microcirculation vessels and improve the tumor's ultrasound diagnostic capability. The ultrasound contrast features of different tumors are summarized according to the density of angiogenesis in the lesions, the vascular diameter, the degree of vascular tortuosity, the arteriovenous shunt and the lymphatic network and other relevant factors. Many studies at home and abroad have confirmed that the advantages of ultrasound contrast diagnostic technology were as follows. In contrast with normal tissues, the slowly increased lesions had low supporting vascular density and small vascular diameter; the lesions synchronously increased with normal tissues, indicating that its supporting vascular density was close to the normal tissues. If the lesions increased faster than normal tissues, then its supporting

vascular density was much higher and the vascular diameter was larger. The long enhancement time of the contrast agent indicated the vascular tortuosity, small venous lumen and low density in the lesions. If there were a large number of thrombi in the malignant tumors, it would lead to the retention of the contrast agent in the vascular bed and prolonged duration. The short enhancement time of the contrast agent suggested the venous patency, large density of venous blood vessels and large vascular diameter in the lesions, which was also related with the presence of arteriovenous shunt in the lesions. The differences in the degree of contrast agent enhancement might be related to the degree of angiogenesis in the lesions.

In the case of very few bursts containing $SF_6$ phospholipid microbubbles, the ultrasound contrast agent Sono Vue combined with low mechanical index contrast technology displayed in real time the dynamic distribution of contrast agent microbubbles in the eye and lesions, which not only improved the color Doppler blood's detection capability for the blood flow within the lesions, but also dynamically observe the enhancement processes of the contrast agent in normal ocular tissues and the lesions, thereby improving the accuracy of ultrasonic diagnosis. The ultrasonic diagnosis technology has an irreplaceable important role in the ophthalmic clinical auxiliary examination, and to fully understand each examination technology's application scope, advantages and limitations, and solidly grasp the operating methods of each technical examination, and comprehensively and reasonably use various ultrasound examination means can improve the accuracy of ultrasonic diagnosis.

The positive rate of ocular spaceoccupying lesion diagnosis could be significantly improved with ultrasound contrast technology, thus to objectively reflect the vascular perfusion in normal tissues and lesions, and according to the lesion's perfusion characteristics of the contrast agent plus with the performance features of two-dimensional ultrasound, the ocular spaceoccupying lesions cam be accurately diagnosed. Compared with the color ultrasound Doppler examination, the ultrasound contrast technology had no angular dependence on the display of blood vessels and no color overflow and other artifacts, so the test results of blood flow were more reliable. As the application of this technology remains at the initial stage, it will become one of the methods of ultrasonic diagnosis for ocular diseases with the accumulation of cases and the improvement of examination techniques.

## DISCUSSION

The ultrasound contrast technology is also known as acoustic contrast, and it uses contrast agent to enhance the backscatter echo, so as to significantly improve the resolution, sensitivity and specificity of the ultrasonic diagnosis [17-19]. With the improvement of instrument performance and the emergence of new acoustic contrast agents, the contrast-enhanced ultrasound has been able to effectively enhance the two-dimensional ultrasound imaging of the myocardium, liver, kidney, brain and other substantial organs. The Doppler signals in the blood flow reflect the blood perfusion in vessels and tissues, which becomes an important development direction for ultrasonic diagnosis. It is the third revolution after the two-dimensional imaging as well as Doppler and color flow imaging[11].

To apply the ultrasound contrast examination in the ophthalmology turns on a new chapter for the ultrasonic diagnosis technology, and the perfusion states of ocular tissues are observed using the harmless sulfur hexafluoride microbubble contrast agent, as the microbubbles have three important characteristics which are good scattering, able to produce rich harmonics and having the rupture effect under the acoustic pressure. As mentioned earlier, the size of the ultrasonic transmission power will affect the CDFI displaying the blood flow signals in the lesions, so the retinal hemorrhage and ocular spaceoccupying lesions difficult to distinguish each other are easily been missed diagnosis or misdiagnosed, while in the contrast-enhanced ultrasound, it can be determined that there is arterial blood supply at the sites filled with microbubbles, and it won't make the above errors. The time-contrast agent concentration curve is obtained through software analysis, the perfusion states of the lesion and the surrounding normal tissues are compared and analyzed, and the nature of the spaceoccupying lesion is preliminarily determined, and this is of important significance to the clinical diagnosis and the development of treatment program. Currently, in addition to the rapid development of the acoustic contrast agents used for tissue imaging, the targeted acoustic contrast agents that have dual role of diagnosis and treatment are also being studied.

To sum up, the positive rate of ocular spaceoccupying lesion diagnosis could be significantly improved with ultrasound contrast technology[10], thus to objectively reflect the vascular perfusion in normal tissues and lesions, and according to the lesion's perfusion characteristics of the contrast agent plus with the performance features of two-dimensional ultrasound, the ocular spaceoccupying lesions can be accurately diagnosed. Compared with the color ultrasound

Doppler examination, the ultrasound contrast technology has no angular dependence on the display of blood vessels and no color overflow and other artifacts, so its test results of blood flow are more reliable [20]. As the application of this technology remains at the initial stage, it will become one of the methods of ultrasonic diagnosis for ocular diseases with the accumulation of cases and the improvement of examination techniques.

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