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CEUS

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CEUS is an enhanced form of ultrasound scan using intravenous administration of a microbubble contrast agent. The contrast agent is an intraluminal tracer and can be used to obtain angiography-like images of the carotid arteries. Ultrasound scan contrast agents were introduced into clinical practice in the early 1990s. The currently approved and used agents include SonoVue (Bracco SpA, Milan, Italy), Optison (GE Healthcare, Princeton, NJ), Definity (Lantheus Medical Imaging, N. Billerica, Mass), and Levovist (Schering AG, Berlin, Germany). The contrast agents consist of microbubbles (approximately 1–8 μm), generally filled with a perfluorinated gas that has a low solubility, and stabilised with a phospholipid or protein shell to improve circulation time. Microbubble contrast agents are intravascular tracers that, because of their size, cannot leave the intravascular compartment. The microbubble shell is eliminated from the body through the reticulo-endothelial system when the gas is exhaled. Contraindications for microbubble contrast agents are unstable angina, acute cardiac failure, acute endocarditis, known right-to-left shunts, and known allergy for microbubble contrast agents. Microbubble contrast agents have been administrated in millions of patients and are safe; side effects are extremely rare [1]. In fact the use of contrast agents in clinical cardiology have been present for at least a decade, both in Europe and the USA. The study of ultrasound contrast agents in clinical practice have stimulated ultrasound machine companies to improve the clinical images based on the new physical properties of the agents. One example is the introduction of harmonic imaging. This concept was based on the non-linear reflections after ultrasound scanning of the microbubbles. For clinical applications, microbubble contrast agents have been registered for tissue perfusion imaging and cardiac chamber border enhancement. None of the contrast agents have been registered for imaging of carotid intraplaque neovascularisation. However, the 2011 updated guideline on non-hepatic applications of CEUS by the European Federation of Societies for Ultrasound in Medicine and Biology, recommends the use of CEUS for the differentiation between total carotid occlusion and residual flow in tight stenosis, the improvement of lumen delineation in technically difficult carotid arteries, and for the evaluation of carotid plaque neovascularisation [2]. Previous studies have demonstrated that CEUS has a high diagnostic accuracy for the detection of carotid artery occlusion and assessment of carotid artery stenosis. These studies have demonstrated that CEUS findings were in good agreement with the results from digital subtraction angiography and/or surgery, and also in patients with poor non-enhanced examination conditions. Most commercially available ultrasound systems provide specific pulse sequences (e.g., amplitude modulation or pulse inversion) that retrieve non-linearities at low acoustic power, which are only exhibited by microbubbles. These techniques enable the suppression of tissue in the image and allow the specific identification of individual microbubbles. Microbubble contrast agents enhance the arterial lumen, improving the delineation of the lumen, and consequently the detection of atherosclerotic plaques and vessel wall irregularities (fig. 1 of Kaspar). The capability of ultrasound scans to detect individual microbubbles passing though the capillary system allows direct visualisation of intraplaque neovascularisation. As the microbubbles are strict intravascular tracers, their presence in plaque represents the presence of an intraplaque neovessel (fig. 2 of Kaspar). The identification of individual neovessels cannot be matched by any of the currently available imaging modalities (e.g., magnetic resonance imaging is capable of making estimations about the amount of intraplaque vascularisation based on contrast diffusion). This has been supported by *in vivo* studies in animal models of atherosclerosis, showing an increase in plaque echogeneity after contrast infusion and confirming the presence of neovascularisation with histology [3].

Also the authors of the present article have previously shown the association between CEUS findings and cardiovascular disease [4]. The presence of intraplaque neovascularisation was associated with a history of cardiovascular events.

The assessment of intraplaque neovascularisation with CEUS has also been reported in a meta-analysis [5]. It was shown that the presence and degree of neovascularisation was correlated with contrast enhancement.

The authors of the present review [6] have to be congratulated for their observations and description of this new methodology.

Newer applications of ultrasound microbubbles are under investigation, such as its use for molecular imaging and its use for gene and drug delivery. Although these studies are

still in an experimental state and based on animal experiments, expectations of its clinical use are positive.
It is expected that CEUS for intraplaque neovascularisation may be a new tool in the diagnosis and follow up of new treatment methodologies in vascular disease.

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