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Recent advances in molecular, multimodal and theranostic ultrasound imaging☆

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ABSTRACT

Ultrasound (US) imaging is an exquisite tool for the non-invasive and real-time diagnosis of many different diseases. In this context, US contrast agents can improve lesion delineation, characterization and therapy response evaluation. US contrast agents are usually micrometer-sized gas bubbles, stabilized with soft or hard shells. By conjugating antibodies to the microbubble (MB) surface, and by incorporating diagnostic agents, drugs or nucleic acids into or onto the MB shell, molecular, multimodal and theranostic MBs can be generated. We here summarize recent advances in molecular, multimodal and theranostic US imaging, and introduce concepts how such advanced MB can be generated, applied and imaged. Examples are given for their use to image and treat oncological, cardiovascular and neurological diseases. Furthermore, we discuss for which therapeutic entities incorporation into (or conjugation to) MB is meaningful, and how US-mediated MB destruction can increase their extravasation, penetration, internalization and efficacy.

Contents

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1. Introduction

1.1. Current indications for using ultrasound imaging

Due to its non-invasive nature, low cost, broad diagnostic applicability and easy handling, ultrasound (US) imaging is the second-most used imaging modality in clinical practice after conventional x-ray radiography [1]. It is used by medical doctors from various different disciplines, including radiologists, gynecologists, cardiologists, gastroenterologists, surgeons and many more as an initial screening tool, as well as for fast-look follow-up examinations. Its ability to visualize blood flow, blood velocity and blood vessels by Power and Color Doppler further recommends US imaging for vascular diagnosis, e.g. for measuring the degree of stenosis in carotid arteries [2], and for looking at the perfusion of tumors [3] and organs after transplantation [4].

Besides these diagnostic applications, High-Intensity Focused US (HIFU) has been attracting ever more attention as a valuable therapeutic option to destroy ureteric stones [5], and to ablate benign uterus myomas and other benign and malignant tumors [6]. In this context, the acoustic energy focused to one defined spot is moved over the pathological tissue. Due to absorption of the acoustic energy and the resulting local temperature increase, the pathological tissue is destroyed. Recently, the first commercial HIFU-systems that can be used inside clinical MR scanners have been introduced which enable highly personalized and well-controlled tissue ablation by getting anatomical information about the pathology and the local temperature rise from MR imaging.

However, the diagnostic and therapeutic potential of US imaging has not yet been fully explored and translated to clinic. In this regard, US contrast agents, which are gas-filled microbubbles (MBs) stabilized by a shell made of lipids, proteins or polymers can enormously improve US imaging. In particular, the use of MB significantly expands the diagnostic potential of US for characterizing pathologies based on functional and molecular vascular characteristics. Furthermore, the use of MB-based contrast agents in US imaging offers possibilities for image-guided (theranostic) interventions. In the present manuscript, recent developments in this emerging and interdisciplinary field are summarized and discussed.

1.2. Impact of contrast-enhanced US imaging on routine clinical practice

US contrast agents in combination with contrast agent-specific US imaging techniques are increasingly accepted in routine clinical practice for diagnostic imaging of several organs and pathologies. Particular interest is given to examinations of the liver, because of the significant improvement over conventional US in both, the detection and characterization of focal liver lesions. Recent studies even show that the diagnostic performance of contrast-enhanced ultrasound (CEUS) can reach that of contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) (Fig. 1) [7–9]. The high diagnostic accuracy of CEUS in liver imaging is based on two characteristics:

1. the detection and early enhancement of a malignant liver lesion during the arterial phase
2. the rapid wash-out of the contrast agent in malignant liver lesions.

A further benefit of US contrast agents in the clinical routine is their good safety profile, which enables the administration of contrast agents to patients who have contra-indications for contrast-enhanced CT or MRI (e.g. patients with severe renal dysfunction). As a consequence, focal liver diseases have evolved into the single most important

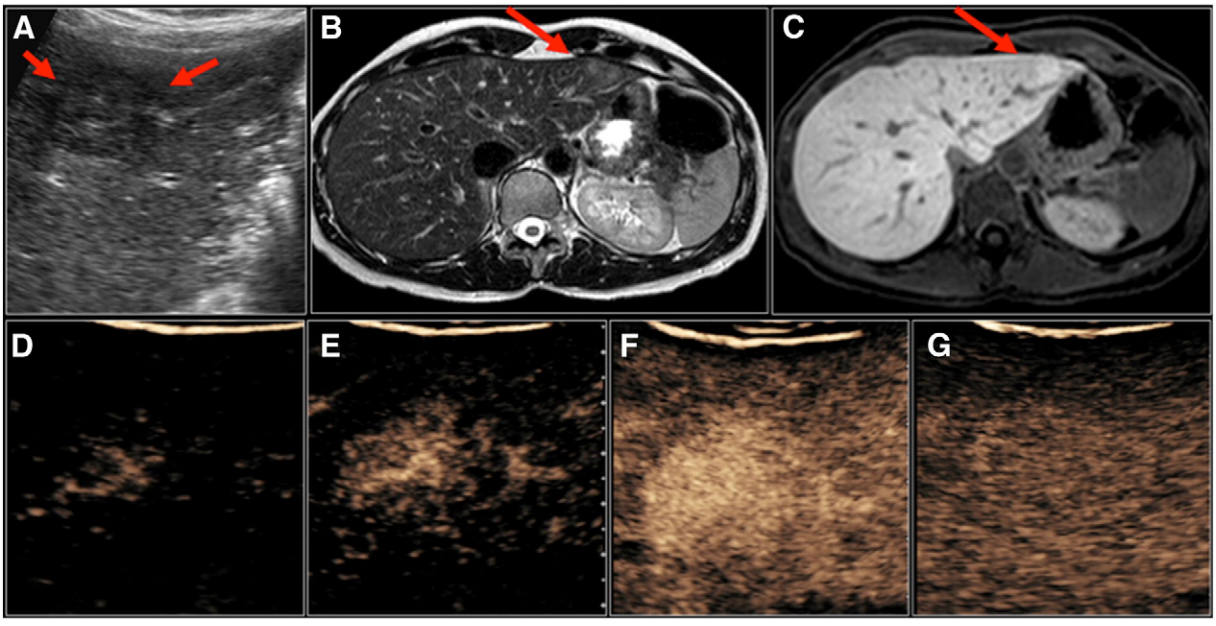

Fig. 1. Examples for the use of CEUS in clinical liver imaging in comparison with MRI. A + B: In B-mode US and in T_2-weighted MRI, a benign liver tumor (fibronodular hyperplasia, FNH) can be delineated. C: Twenty minutes after the administration of the hepatocyte-specific MR contrast agent Gd-EOB-DTPA, the lesion and the surrounding tissue provide comparable contrast enhancement, which is typical for a FNH. D–F: In contrast-specific US mode, one can depict the rapid centrifugal ("spoke-wheel") enhancement of the lesions. In the late phase (G; i.e. 180 s after injection), the lesion provides no wash-out pattern. Knowledge on the microbubble (MB) kinetics in the late phase enables the exclusion a malignant tumor. The enhancement pattern in the arterial phase further supports the diagnosis of a FNH.