Contrast ultrasound molecular imaging: harnessing the power of bubbles

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Over the past decade, there has been an escalating effort by researchers in academic institutions and industry to develop novel, non-invasive medical imaging approaches for evaluating tissue phenotype. These emerging techniques are designed to detect the cellular or molecular mediators of disease rather than structural or functional consequences of disease. The clinical justification for this trend is that molecular imaging provides unique information that could potentially be used to diagnose disease at a very early stage, to make a more definitive diagnosis, or to guide therapeutic decisions based on molecular profile. This technology is already used by oncologists to diagnose certain types of cancers, such as thyroid cancer, neuroendocrine tumours, and non-Hodgkins lymphoma, and to select the most appropriate anti-neoplastic therapy. It is likely that molecular imaging will have a similar role in cardiovascular disease. One could even argue that myocardial viability imaging with 18F-fluorodeoxyglucose positron-emission tomography is a form of molecular imaging that is already routinely used in clinical practice. It should be mentioned that molecular imaging technology will also be an important research asset. It is able to characterize pathophysiology without the need for pathology specimens and, under certain circumstances, can be a surrogate endpoint to test therapies aimed at a specific molecular pathway.

A series of six reviews in the current and subsequent issues of Cardiovascular Research focus on non-invasive molecular imaging in cardiovascular disease. These review articles address the specific topic of molecular imaging with targeted contrast ultrasound. The overview article by Saraste et al. provides a foundation where the relative strengths and drawbacks of the different imaging techniques and tracers are highlighted. Some of the unique properties of ultrasound are the widespread availability and rapid nature of the molecular imaging protocols. Accordingly, a common thread through many of the accompanying review articles is that ultrasound molecular imaging techniques are being targeted to applications where urgent information is needed, where the portability of the technique can be exploited, or where cost and speed are of the utmost importance. For example, the articles provided by Kaufmann on atherosclerosis imaging and by myself on imaging inflammation describe progress made in the development of ultrasound probes that are able to be used to screen for high-risk plaque phenotype or for the rapid bedside diagnosis of myocardial infarction or transplant rejection. The fact that an ultrasound-based approach can provide information to the clinician almost immediately and does not require an expensive infrastructure to perform makes this approach quite feasible.

Many of the review articles also highlight the potential research applications of the technique. The ability to spatially and temporally assess molecular mediators of disease may provide a unique opportunity to study the complex pathophysiology or response to treatment in animal models of disease or in humans. Nowhere is this more apparent than in the article by Leong-Poi, which describes how contrast ultrasound molecular imaging can be used to better understand the complex processes that coordinate remodelling of the vascular network in ischaemic tissues or in tumours, and how these processes can be manipulated. However, implicit in the introductory article is that imaging of important molecular mediators that reside outside of the vascular space are best left to other imaging approaches that utilize smaller diffusible probes.

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Contrast-enhanced ultrasound is one of the few imaging approaches that rely on a structural change of the tracer for signal production. The generation of an acoustic signal from microbubbles is complex. Briefly, microbubble or nanoparticle ultrasound contrast agents emit high enough signal relative to noise to be detected in tissue by clinical scanners when they oscillate non-linearly in the acoustic field, or when they are disrupted and form rapidly collapsing free gas bubbles.\(^6,7\) There are a host of different bioeffects (pressure, thermal, ballistic, etc.) that can alter the biologic microenvironment or cellular function around the cavitation event. The articles by Porter\(^8\) and Laing and McPherson\(^9\) illustrate some of the potential therapeutic opportunities presented by these bioeffects. Ultrasound destruction of microbubble or nanoparticle agents can be used not only to target delivery of therapeutic agents to a specific tissue of interest, but at the same time can produce bioeffects that enhance vascular permeability for drug/gene delivery or enhance thrombolysis. The ability to entrain bioeffects and target them using focused ultrasound make the therapeutic applications for targeted contrast ultrasound as exciting as the potential diagnostic applications.

This series of articles from leaders in the field of molecular imaging provides a superb overview of the potential role of ultrasound in research and medicine. The transition of these innovations to routine clinical practice will hinge on whether they provide sufficient incremental value to alter patient outcomes. Many of these techniques have reached a stage, however, where they can be incorporated into research programs in order to probe pathophysiology non-invasively or to enhance gene delivery.

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**References**