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EDITORIAL COMMENT

Albumin-Binding MR Probe Detects High-Risk Coronary Plaques in Patients*

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In patients with atherosclerosis, timely detection of high-risk thin-cap atheromata in the coronary or carotid arteries could prevent thromboembolic events such as acute myocardial infarction and stroke. Scenarios of risk assessment and patient selection, where measurement of circulating biomarkers and noninvasive imaging go hand-in-hand, have been discussed for more than a decade as the holy grail of prevention and have motivated a growing field of preclinical molecular imaging of vascular targets. Based on the pathological features of culprit plaques, a number of imaging targets have been explored, including adhesion molecules, chemokines and their receptors, inflammatory cells, and proteases (1). However, to date most of the work has remained in the preclinical stage, and few clinical studies have attempted to reach this goal in patients. The study by Engel et al. (2) in this issue of *iJACC* is among the first to attempt detection of thin-cap vulnerable coronary plaques by cardiac magnetic resonance (CMR) in patients.

The authors evaluated the diagnostic value of noninvasive CMR imaging by using an albumin-binding CMR probe, gadofosveset. The concept relies on the pathological leakiness of endothelium that lines inflamed atherosclerotic plaques. Binding of gadofosveset to albumin, the most prevalent protein of blood plasma, creates a large paramagnetic complex with a long blood half-life and high relaxation. Thus, gadofosveset-labeled albumin primarily acts as a blood pool agent and was initially developed for that purpose. Albumin is too large to extravasate from normal vasculature, unless the endothelium is leaky. Leakage of albumin into high-risk plaques arises most likely from a combination of neovascularization within the plaque, damaged endothelium with widening gaps between endothelial cells, and a discontinued basement membrane (3,4).

In atherogenesis, inflammatory processes and turbulent blood flow activate the arterial endothelium, propelling a cascade of events in which the endothelium generates reactive oxygen species and expresses inflammatory adhesion proteins (5,6). Growth factors, cytokines, and vasoregulatory molecules such as nitric oxide participate in local inflammatory processes that aggravate endothelial damage during subendothelial accumulation of lipids and leukocytes (3,7). Neovascularization associates with thin-cap atheroma, macrophage infiltration, and large necrotic cores leading to intralesional hemorrhage (8). In high-risk patients, an exuberant inflammatory response damages the endothelium lining 1 or more plaques (9).

Several preclinical studies reported albumin leakage into the inflamed arterial wall (10,11). Gadofosveset enhancement detected by CMR correlates with plaque microvessel density (11,12). During angiogenesis, the vascular wall is breached, leading to leakage of high-molecular-weight serum proteins such as albumin (13). Endothelial damage adjacent to inflammatory foci facilitates extravasation of gadofosveset in preclinical studies. Transmission electron microscopy of gadofosveset-enhanced plaques revealed endothelial cell death, vascular denudation, and widening of the tight junctions in those lesions (4,11).

In the current study, Engle et al. (2) elegantly combine 3 imaging modalities to elucidate the value of gadofosveset-enhanced CMR for defining coronary plaque characteristics. In addition to CMR, patients underwent x-ray coronary angiography to detect luminal stenosis and optical coherence

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tomography (OCT), which delivers high-resolution data for plaque composition, especially with respect to thickness of the fibrous cap (14,15). Such multimodal integration enabled assessing the added value of noninvasive CMR in 25 patients who underwent all 3 imaging procedures within 24 h. The patient cohort consisted of cases with stable coronary artery disease and acute coronary syndromes, which provided a necessary variety in pathologies. OCT served as the gold standard, contributing "in vivo histology" data for coronary segments that were identified as culprit lesions and classified as thin-cap fibroatheroma with lipid-rich cores. Gadofosveset-enhanced CMR returned robustly increased signal intensities in the 11 culprit lesions detected by OCT, with a sensitivity of 82% and a specificity of 83%. The imaging approach could categorize low-risk (i.e., fibrotic lesions), intermediate-risk (i.e., fibroatheroma), and high-risk coronary plaques (i.e., thin-cap fibroatheroma). In patients with acute coronary syndrome, CMR signal intensities were particularly high.

What is the value of such an imaging technology, and which patients could benefit from it? These questions are currently unanswered and will be addressed in follow-up studies, if gadofosveset remains available to pursue large-scale studies. Motivated by the current data, we should next evaluate if and how gadofosveset-enhanced CMR improves patient management and outcomes while being cost effective. The technique could be useful in stepwise risk stratification, in which clinical data and circulating biomarkers, including those for inflammation, select a very high-risk group of patients with an imminent ischemic event. In such a cohort, a sensitive and specific imaging readout could answer the question of whether future culprit lesions reside in vascular territories that could threaten the patient's life. For example, an inflamed plaque may be located either in a coronary artery or in the aorta, where it is perhaps less dangerous. If plaque vulnerability and location predict an ischemic event in the near future, a patient may undergo regional or systemic preventive measures, for example, a prophylactic stent placement or immunotherapy. Any such scenario will need to be evaluated in a prospective trial and is currently highly speculative. From a pathophysiological perspective, the technique may also report the natural course of vulnerable plaques. For instance, it is being debated whether several such plaques occur simultaneously and if vulnerable plaques "cool down" spontaneously when systemic inflammatory stimuli discontinue.

Likely, gadofosveset-enhanced CMR will compete with other emerging noninvasive imaging tools in development, some of which target different biological processes in inflamed plaque by using labeled small-molecule probes, nanoparticles, and immuno-positron emission tomography (PET) (1). Another competitor closer to clinical use is fluorine-18-labeled fluorodeoxyglucose ([^{18}F]FDG) PET, although coronary PET imaging remains technically challenging. Ultimately, there will be conversion on the most sensitive and specific biological target or a combination of such targets, especially if any 1 or more of these approaches proves its value in managing patients. An imaging approach such as gadofosveset-enhanced CMR has the potential to report on the locations of high risk arterial lesions and become a tool to prevent myocardial infarction and stroke.

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