EDITORIAL COMMENT

PET Imaging: Hot on the Trail of the HDL Particle*

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Molecular imaging is a rapidly evolving field that allows us to investigate the activity of specific physiological and pathological processes in vivo. However, this approach will only be as good as the imaging tracers that can be developed, and at present these are somewhat limited, at least for cardiovascular imaging. Ideally, novel tracers should not only be specific for a disease process of biological interest but also should inform about its activity in a safe, high-resolution, and non-obtrusive manner. The description by Pérez-Medina et al. (1), in this issue of JACC, outlining the effective labeling of the high-density lipoprotein (HDL) particle with a positron-emitting radiotracer is therefore of major interest, providing us with a new tool with which to study the biological features of reverse cholesterol transport and to identify high-risk atheroma. In fact, the authors (1) have already labeled the HDL particle using magnetic resonance (MR)-based contrast agents (2). However positron emission tomography (PET) offers major advantages principally related to its exquisite sensitivity, which allows detection of even nanomolar concentrations of a radiotracer. The tracking of labeled particles at concentrations low enough not to influence the underlying disease process has therefore become feasible.

Although the objective of this paper is in many ways simple—to label and track the HDL particle using PET—the methodology used is both innovative and comprehensive. In-depth investigation of the behavior and biodistribution of the zirconium-89 (\(^{89}\text{Zr}\))-labeled HDL particle is provided in 3 different species (mouse, rabbit, and pig) using a combination of in vivo molecular imaging (micro-PET/computed tomography [CT], PET/MR, and PET/CT) and ex vivo validation with assessment of tissue radioactivity, autoradiography, and near-infrared fluorescence imaging.

In fact, Pérez-Medina et al. (1) compared 2 approaches, using \(^{89}\text{Zr}\) to label either the phospholipid or apolipoprotein A1 components of the HDL particle with similar results. In the ApoE\(^{-/-}\) mouse model, autoradiography and near-infrared fluorescence imaging demonstrated migration of both particles to regions of aortic atherosclerosis, whereas flow cytometry confirmed preferential binding of these \(^{89}\text{Zr}\)-labeled HDL particles to plaque macrophages.

The migration of these \(^{89}\text{Zr}\)-labeled HDL particles to atherosclerotic plaques was then confirmed in 2 further species. In the rabbit model, increased PET activity was observed in aortic atheroma by day 5 using both PET/CT and PET/MR and confirmed on ex vivo analysis. The close agreement between both imaging modalities suggests that PET/MR is capable of accurate PET quantification in this animal model and may ultimately be preferable because of reduced radiation exposure. In the pig (the closest available animal model to humans), an increased PET signal was again clearly observed at sites of iliofemoral atheroma on noninvasive imaging.

In summary, what have Pérez-Medina et al. (1) shown? They have demonstrated that PET labeling of the HDL particle is feasible and that these \(^{89}\text{Zr}\)-labeled particles behave like regular HDL, migrating to regions of aortic atheroma in 3 atherosclerotic animal models and preferentially targeting macrophages. The labeling process would therefore appear to have left the natural activity of these HDL particles unchanged, in contrast to the oxidized HDL particles generated in this study.

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The potential of these tracers in pre-clinical models is exciting and wide ranging. The long half-life of $^{89}$Zr should allow these particles to be tracked longitudinally after a single injection, providing insight into how they traffic between different tissue systems and how their behavior might be manipulated. For example, PET could be used to assess the effect on the HDL pathway of cholesterol ester transfer protein inhibitors and other agents. There have been 2 high profile studies of cholesterol ester transfer protein inhibitors which either did not affect outcome (3,4) or caused harm (5) despite effectively increasing HDL levels. Clearly understanding the trafficking and flux of HDL and cholesterol is central to our understanding of novel inhibitors and the consequence for atherogenesis. This approach may also be of interest beyond pharmacological manipulation. For example, the importance of macrophages to HDL plaque binding could be explored using macrophage-depletion experiments.

This technique may be important in other settings, not just tracking HDL metabolism. The natural migration of the HDL particle to inflamed lipid-laden plaques means that such particles have the ability to identify regions of high-risk atheroma. Moreover, the HDL particle holds promise not only as an imaging particle but also as a drug delivery system, transporting medication housed in its core directly to those plaques requiring therapy. Although $^{89}$Zr-labeled particles are unlikely to be of use in humans because of $^{89}$Zr’s long half-life and consequent radiation exposure, the development of these particles may accelerate the translation of HDL particle technology through the pre-clinical stages and help us to better understand the effect of drug interventions on HDL particle trafficking and flux.

Although further proof-of-concept validation is needed, this extensive and comprehensive imaging characterization is a first major step on a new trail allowing us to track fundamental atherosclerotic processes—an exciting and enticing prospect for those in the field.

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