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CORRESPONDENCE

Letters to the Editor

Simvastatin and Plaque Inflammation

We read with great interest the study by Tahara et al. (1) published recently in the *Journal* and concerned with tracking statin-induced inflammation reduction in atherosclerotic plaques using fluorodeoxyglucose positron emission tomography (FDG-PET).

Although this study highlights the very real potential of FDG-PET imaging of atherosclerosis for the detection and monitoring of plaque inflammation, we would like to comment on several aspects of the study's methodology that may have impacted the results seen by the investigators.

First, we believe that the time between injection of FDG and PET image acquisition was too short at 1 h. Previous studies have shown that a circulation time for FDG in excess of 2 h gives a much higher target (plaque)-to-background (blood) ratio (2–4). A high target-to-blood ratio is crucial to ensuring proper region-of-interest placement and thus accurate quantification of plaque FDG uptake.

Second, especially given their choice of early imaging time point, the researchers should have attempted to correct the plaque FDG uptake for blood activity. This is typically achieved by measurement of the mean of several blood values from a large vein. This value is then divided into the plaque standardized uptake value to yield a tissue-to-blood ratio of FDG uptake. This is the method adopted in previous studies, and in the elegant study by Tawakol et al. (2) which appears in the same issue of the *Journal.* Although Tahara et al. (1) defend their decision not to do this, we do not believe the reasons they give justify the absence of a correction. The investigators suggest that the patchy uptake of vascular FDG and the nonvisualization of veins means that the blood-pool signal is likely insignificant. More likely is the fact that atherosclerosis is a diffuse condition, taking up FDG variably along the length of the vessel. Additionally, we believe that blood-pool activity would still be significant at such an early imaging time point, with a standardized uptake value well above other background structures.

Additionally, we suggest the use of a combined PET/computed tomography scanner may have made accurate anatomical coregistration easier. This will be particularly important when extending this kind of study into the aorta and other vascular beds.

Finally, we contend that the investigators might have chosen a more potent anti-inflammatory drug than low-dose simvastatin for testing their hypothesis that FDG-PET imaging could track inflammatory change within plaque. Although their study yielded positive results, the magnitude of the effect would surely have been greater with a higher dose of a more powerful statin, and this might have answered some of the questions with which the researchers were left at the end of their study, such as why the FDG reduction induced by statin treatment correlated more closely with the high-density lipoprotein increase than with low-density lipoprotein decrease.

Tahara et al. (1) should be congratulated on completing such an exciting piece of work, but we suggest that for future studies in this area a longer FDG circulation time with appropriate blood activity correction should be used. If these ideas had been adopted by the investigators in their current study, we believe they would have shown an even greater positive impact of the statin upon plaque inflammation as assessed by FDG-PET.

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Reply

We thank Drs. Rudd, Machac, and Fayad for having interest in our recent study (1). There is a growing body of evidence that fluorodeoxyglucose positron emission tomography (FDG-PET) imaging has a great potential for noninvasively detecting and quantifying plaque inflammation in humans. Anecdotal studies have reported increased FDG uptake in the regions of the aorta and large arteries in patients who had undergone FDG-PET imaging for cancer diagnosis and staging (2,3). Recently, we and others have validated FDG uptake in the arterial wall (i.e., plaques) by coregistering FDG-PET imaging with structural imaging, such as computed tomography and magnetic resonance imaging (1,4–7). More importantly, histological examination of the end-arterectomized specimen obtained from the FDG uptake-documented carotid arteries has provided solid evidence that the vascular FDG uptake is associated with macrophage accumulation,

namely plaque inflammation, not only in symptomatic but also asymptomatic carotid plaques, irrespective of the severity of the luminal stenosis (5–7). In addition, our recent study has revealed that FDG-PET imaging is a practical tool to monitor the effectiveness of anti-inflammation therapy for atherosclerotic diseases (1).

Because of limited time available for PET imaging for patients in our institution, PET imaging was performed 1 h after FDG injection. We agree that longer time may provide clearer PET imaging. Standardized uptake value (SUV) of the juglar vein (blood uptake) was low and almost constant in our study. Thus, we did not normalize SUV of the plaque by blood SUV. However, we agree that normalization may give more accurate identification of inflamed plaques. The dose of FDG administered, the duration between FDG injection and PET image acquisition, and the method of quantification of FDG uptake should be standardized before this modality is widely applied for clinical practice, especially for plaque inflammation imaging. The use of a combined PET/computed tomographic scanner will improve the accuracy of the anatomical diagnosis of plaque FDG uptake. Also, more macrophage-specific PET tracer is desirable to image plaques in metabolically active tissues such as the heart and brain.

Considering the future direction, it would be interesting to study 1) the prevalence of inflammation of the documented plaques, 2) risk factors contributing to plaque inflammation, and 3) whether more powerful statins would show greater reduction in plaque inflammation or whether other potentially anti-inflammatory drugs, such as angiotensin receptor blockers, would decrease FDG uptake in inflamed plaques. A prospective study with a large number of patients is warranted to elucidate whether vascular FDG uptake can be a predictor of cardiovascular events. Finally, the comments made by Rudd et al. will be very helpful in making FDG-PET imaging clinically more useful in future studies.

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