Is ^{18}F-FDG PET really a promising marker for clinically relevant atherosclerosis?

To the Editor: Bural et al (2013) [1], retrospectively investigated 143 subjects who received whole body fluorine-18-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG PET) imaging for the assessment of non-cardiovascular diseases. They reported an increase of ^{18}F-FDG-positive lesions in various aortic segments, which increased with age, and were more pronounced in subjects being aged below 50 years as compared to those above 50. Bural et al [1] also found the highest segmental ^{18}F-FDG-uptake in the descending thoracic aorta, but not in the abdominal aorta, where the majority of the most severe atherosclerotic lesions essentially appear. In addition, they did not appreciate any significant gender difference. Despite the severe limitation that no correlation to vascular disease, risk factors, or any clinical parameter was available, this report again raises the question as to what positive ^{18}F-FDG imaging really reflects and whether it will ever reach the great expectations.

Conventional radiotracers revealed an excellent experimental correlation [2], as well as morphology [3]. Uptake ratios of symptomatic lesion vs. contralateral unaffected side were comparable between ^{111}In-platelets, ^{123}I-LDL [4] and ^{18}F-FDG [5]. There was also a mass strategic correlation [6], but no individual prediction of events at all [7]. Due to better statistics, image quality and solution PET imaging of atherosclerosis holds great promise. However, correlations between various tracers and vascular wall characteristics (and staining methodologies) in 1% cholesterol fed rabbits reveal that ^{18}F-FDG is not always the best tracer (Table 1). Vascular foam cell content is reflected by ^{111}In-HIG > ^{125}I-oxLp(a) > ^{18}F-FDG > ^{125}I-LDL (Brammen L, Palumbo B, Lupattelli G et al. Unpublished data). A close correlation to Framingham risk score [8] is for example not helpful, as this score has a low predictive value of only 0.6 [9].

The available clinical correlations between ^{18}F-FDG-uptake and arterial wall characteristics are poor. For example, Lederman RJ et al (2001) [10] reported a correlation between ^{18}F-FDG uptake with intima/media ratio, whereas no correlation was established in a paper by Ogawa M et al (2004) [11]. On the other hand, Laitinen I et al (2006) [12] described a correlation between ^{18}F-FDG-uptake and calcifications, however, Tatsumi M et al (2003) [13] did not observe this in his paper. The claim that inflammation and macrophage uptake of ^{18}F-FDG may be able to characterize and identify early atherosclerotic lesions [14, 15] has never been substantiated. Earlier studies reveal a negative correlation between ^{18}F-FDG uptake and smooth muscle cells [16], but a positive one with macrophages [11]. The extent of uptake by different vascular wall cells (e.g. endothelial cells, smooth muscle cells, macrophages) in different atherosclerotic lesion types under various biochemical conditions has thus far not been extensively studied, neither in vitro nor in experimental or clinical work. Only one recent report does deal with this issue [17]. Our preliminary studies show that the cellular uptake extremely varies depending on the local metabolic condition. For example, smooth muscle and endothelial cells, when exposed to pro-inflammatory cytokines, exhibit an extremely enhanced ^{18}F-FDG uptake while local hypoxia results in an opposite behavior. This is not observed in macrophages. Furthermore, when cultured cells were studied, uptake was severely dependent on the duration of incubation and the type of stimulation. This data indicates that ^{18}F-FDG uptake is enhanced in early foam cell formation, as well as in activated smooth muscle cells that eventually reach, under certain conditions, a comparable uptake. In addition, there is a lack of standardization and of prospective studies preventing reliable clinical interpretation [18].

There seems to be only one consensus. There is no abnormal uptake of ^{18}F-FDG as well as of conventional tracers in the intact vascular wall and intra individual therapeutic intervention is truly reflected. The goal of non-invasive imaging in humans is to identify plaques at risk, an active lesion or the extent of the disease. As long as no prospective controlled data with other imaging modalities identifying vascular alterations defined per lesion and not per segment are available, it seems very unlikely that ^{18}F-FDG may significantly succeed in this particular indication.

The authors declare that they have no conflicts of interest.

Bibliography

1. Bural GG, Torigian DA, Basu S et al. Atherosclerotic inflammatory activity in the aorta and its correlation with aging and gender as assessed by ^{18}F-FDG-PET. *Hell J Nucl Med* 2013; 16: 164-8.
2. Prat L, Torres G, Carrió I et al. Polyclonal ^{111}In-IgG, ^{125}I-LDL and ^{125}I-endothelin-1 accumulation in experimental arterial wall injury. *Eur J Nucl Med* 1993; 20: 1141-5.
3. Virgolini I, Angelberger P, O´Grady J et al. Low-density lipoprotein labeling characterizes experimentally induced atherosclerotic lesions in rabbits in vivo as to presence of foam cells and endothelial coverage. *Eur J Nucl Med* 1991; 18: 944-7.
4. Virgolini I, O´Grady, J, Lupattelli G et al. In vivo quantification of

Table 1. *Functional morphology vs. tracer uptake*

Characteristic \ Tracer	^{18}F-FDG	^{125}I-LDL	^{125}I-Lp(a)	^{111}In-HIG
Mononuclear cells	0.8612	0.8380	0.8544	**0.9133**
Sudan III	0.7217	**0.8623**	**0.8914**	0.8512
Oil Red O	0.7016	0.8433	0.8563	**0.8617**

allp < 0.001 (total); n = 8 each (rabbits)

cholesterol content in human carotid arteries by quantitative gamma-camera imaging after injection of autologous low density lipoproteins (LDL). *Int J Rad ApplInstrum* B 1992; 19: 245-50.
5. Rudd JHF, Warburton EA, Fryer TD et al. Imaging atherosclerotic plaque inflammation with ^{18}F-Fluorodeoxyglucose positron emission tomography. *Circulation* 2002; 105: 2708-11.
6. Pramsohler B, Lupattelli G, Scholz H et al. Platelet scintigraphy and survival in juvenile stroke patients. in: H. Sinzinger, M.L.Thakur (Eds). *Proc. Radiolabelled Cellular Blood Elements.* Wiley-Liss Inc., New York, 1990; 71-80.
7. Sinzinger H, Virgolini I. Nuclear Medicine and atherosclerosis. *Eur J Nucl Med* 1990; 17: 160-78
8. Kim TN, Kim S, Yang SJ et al. Vascular inflammation in patients with impaired glucose tolerance and type 2 diabetes: analysis with ^{18}F-fluorodeoxyglucose positron emission tomography. *Circ Cardiovasc Imaging* 2010; 3: 142-8.
9. Sinzinger H, Derfler K, Leimer H et al. Risk charts - very popular but useless? *VASA* 39; 2010: 287-9.
10. Lederman RJ, Raylman RR, Fisher SJ et al. Detection of atherosclerosis using a novel positron-sensitive probe and 18-fluorodeoxyglucose. *Nucl Med Commun* 2001; 22: 747-53.
11. Ogawa M, Ishino S, Mukai T et al. ^{18}F-FDG accumulation in atherosclerotic plaques: immunohistochemical and PET imaging study. *J Nucl Med* 2004; 45: 1245-50.
12. Laitinen I, Marjamaki P, Haaparanta M et al. Non-specific binding of ^{18}F-FDG to calcifications in atherosclerotic plaques: experimental study of mouse and human arteries. *Eur J Nucl Med Mol Imaging* 2006; 33: 1461-7.
13. Tatsumi M, Cohade C, Nakamoto Y et al. Fluorodeoxyglucose uptake in the aortic wall at PET/CT: possible finding for active atherosclerosis. *Radiology* 2003; 229: 831-7.
14. Bural GG, Torigian DA, Chamroonrat W et al. FDG-PET is an effective imaging modality to detect and quantify age-related atherosclerosis in large arteries. *Eur J Nucl Med Mol Imaging* 2008; 35: 562-9.
15. Ben-Haim S, Kupzov E, Tamir A et al. Evaluation of ^{18}F-FDG uptake and arterial wall calcifications using ^{18}F-FDG PET/CT. *J Nucl Med* 2004; 45: 1816-21.
16. Tawakol A, Migrino RQ, Hoffmann U et al. Noninvasive in vivo measurement of vascular inflammation with F-18 fluorodeoxyglucose positron emission tomography. *J Nucl Cardiol* 2005; 12: 294-301.
17. Ogawa M, Nakamura S, Saito Y et al. What can be seen by ^{18}F-FDG PET in atherosclerosis imaging? The effect of foam cell formation on ^{18}F-FDG uptake to macrophages. *J Nucl Med* 2012; 53: 55-8.
18. Rosenbaum D, Millon A, Fayad ZA. Molecular imaging in atherosclerosis: FDG PET. *Curr Atheroscler Rep* 2012; 14: 429-37.

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Authors' reply:

We wish to thank Prof. Sinzinger for his thoughtful letter to the Editor, raising some concerns about the role of ^{18}F-FDG-PET imaging in assessing atherosclerosis in normal aging and disease states. We agree with him about the issues that he has brought up in his communication with the journal about the role of this methodology as a routine test in the daily practice of medicine. We believe that the basic assumptions and concepts with regard to the nature of localization of ^{18}F-FDG in the plaques are sound but not completely proven at this time. In fact, the observation made by our group [1, 2] was entitled, "F-18 FDG uptake in the large arteries: a new observation," indicating that we were unsure about the exact location of ^{18}F-FDG uptake in the major arteries. However, the evidence is becoming increasingly strong for a significant association between positive ^{18}F-FDG lesions and presence of atherosclerosis in either animals or human beings. Nevertheless, more work needs to be performed in a prospective manner to definitively validate about the role of this technique in detecting and characterizing atherosclerotic plaques. I wish to point out that the efficacy of a technique such as ^{18}F-FDG PET should be considered by taking into account the settings in which these small lesions are located. Partial volume effect (PVE) and corrections for its impact in accurate quantification of these thin structures is becoming clear as we have explained in this very important domain [3, 4]. As such, we may resort to assessing larger segments of vessels for accurate quantification of disease activity. We wish to point out that global assessment may prove to be superior to regional values generated by standard approaches that have been employed in past analysis of plaques [5]. Also, delayed imaging (at least 2 or preferably 3h) after injection of ^{18}F-FDG may prove to be essential for optimal visualization of atherosclerotic lesions [6]. Up until now, most studies have been carried out with early imaging, and therefore, further work is needed to determine the optimal timing for such studies.

Bibliography

1. Yun M, Yeh D, Araujo LI et al. F-18 FDG uptake in the large arteries: a new observation. *Clin Nucl Med* 2001; 26(4): 314-9.
2. Yun M, Jang S, Cucchiara A et al. ^{18}F FDG uptake in the large arteries: a correlation study with the atherogenic risk factors. *Seminars in nuclear medicine* 2002; 32(1): 70-6.
3. Bural GG, Torigian DA, Chamroonrat W et al. Quantitative assessment of the atherosclerotic burden of the aorta by combined FDG-PET and CT image analysis: a new concept. *Nucl Med Biol* 2006; 33(8): 1037-43.
4. Hickeson M, Yun M, Matthies A et al. Use of a corrected standardized uptake value based on the lesion size on CT permits accurate characterization of lung nodules on FDG-PET. *Eur J Nucl Med Mol Imaging* 2002; 29(12): 1639-47.
5. Basu S, Zaidi H, Houseni M et al. Novel quantitative techniques for assessing regional and global function and structure based on modern imaging modalities: implications for normal variation, aging and diseased states. *Seminars in nuclear medicine* 2007; 37(3): 223-39.
6. Blomberg BA, Akers SR, Saboury B et al. Delayed time-point ^{18}F-FDG PET CT imaging enhances assessment of atherosclerotic plaque inflammation. *Nucl Med Commun* 2013; 34(9): 860-7.

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