In Vivo Imaging of Hypoxia in Atherosclerotic Plaques in Humans

JACC: CARDIOVASCULAR IMAGING
VOL. 8, NO. 11, 2015

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.

iMAIL

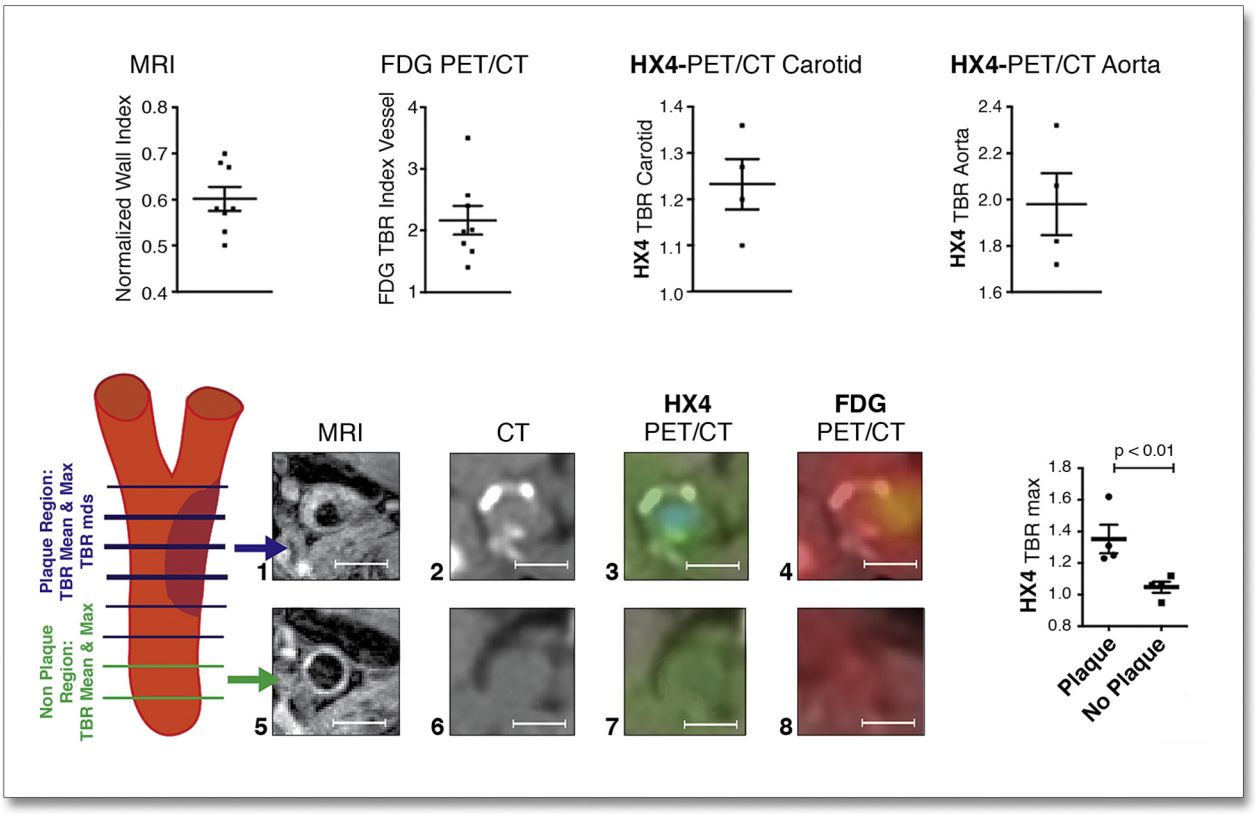
LETTERS TO THE EDITOR

In Vivo Imaging of Hypoxia in Atherosclerotic Plaques in Humans

In recognition of hypoxia's involvement in atherogenesis, it has been suggested that plaque hypoxia be used as a target for molecular imaging to identify high-risk patients, anticipate acute cardiovascular events, and monitor atheroma therapies (1). We demonstrate the potential of hypoxia imaging in humans using a highly selective hypoxia marker, ^{18}F-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol (HX4), for positron emission tomography/computed tomography (PET/CT) (2).

In 8 patients with carotid artery stenosis, we performed multimodal imaging within 3 weeks, consisting of: 1) magnetic resonance imaging (MRI) with a 3.0-T whole-body scanner (Intera, Philips, Best, the Netherlands) to calculate the normalized wall index (mean wall area/outer wall area) (3); 2) ^{18}F-fluorodeoxyglucose (FDG)-PET/CT (100 MBq); and 3) HX4-PET/CT (100 MBq) imaging on a dedicated scanner (Gemini, Philips) 90 min after tracer infusion. FDG and HX4 uptake was quantified in the carotid

FIGURE 1 Hypoxia Imaging in Atherosclerosis



Patients included in this study were characterized by advanced atherosclerosis, as detected by the elevated normalized wall index (NWI) on magnetic resonance imaging (MRI) and elevated 18F-fluorodeoxyglucose (FDG) uptake in the arterial wall, expressed as the target-to-background ratio (TBR) in the index vessel measured with positron emission tomography/computed tomography (PET/CT). As a marker of hypoxia, 18F-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol (HX4) uptake was enhanced in both the carotid arteries as the aorta, quantified as HX4 TBR using PET/CT (scale bars indicate 2 cm). A schematic of the analyzed segments with the corresponding MRI, CT, HX4-PET/CT, and FDG-PET/CT images in the most diseased area of the plaque compared to nonplaque regions underscore plaque-specific HX4 uptake in patients (scale bars indicate 1 cm).

arteries and aorta in regions with and without plaque, providing a target-to-background ratio (TBR) as the ratio of maximal/mean arterial wall standardized uptake values and mean venous blood activity (3).

The included patients (4 men and 4 women; mean age 68 ± 6 years) had a history (>6 months) of transient ischemic attack (n = 5), ischemic stroke (n = 3), and/or myocardial infarction (n = 3). Patients had an increased carotid wall thickness as shown by MRI, providing a mean normalized wall index of 0.60 ± 0.07 (**Figure 1**). In addition, patients exhibited enhanced FDG uptake at the level of both the carotid arteries and aorta as assessed with PET/CT, as shown by the increased maximal target-to-background ratio for ^{18}F-fluorodeoxyglucose (^{FDG}TBRmax) for the carotid arteries (1.72 ± 0.25) and aorta (2.61 ± 0.64) (**Figure 1**).

Subsequently, HX4 uptake was assessed at the level of the carotid arteries in 4 patients and at the level of the aorta in the other 4 patients (**Figure 1**). When quantified, ^{HX4}TBRmax of the carotid arteries was 1.27 ± 0.13 and 1.98 ± 0.27 for the aorta (**Figure 1**). HX4 uptake was specific to plaque regions —^{HX4}TBRmax was 1.32 ± 0.16 in the most diseased segment compared with 1.15 ± 0.20 in the nonplaque region ($p < 0.01$) (**Figure 1**). Following the relationship between plaque burden and hypoxia, we observed a strong correlation between atherosclerotic HX4 uptake and carotid arterial wall dimensions ($r = 0.97$; $p = 0.04$). In addition, we showed a correlation with HX4 uptake and FDG uptake in the plaque ($r = 0.75$; $p = 0.03$).

Taken together, we showed increased HX4 uptake in plaque regions that correlated to arterial wall dimensions and metabolic activity. Recently, a preclinical PET study in atherosclerotic rabbits showed positive correlations of the hypoxia tracer ^{18}F-fluoromisonidazole to plaque burden and macrophage content, but not to FDG uptake, which might reflect distinct differences in rabbit and human plaque composition (4). In support, previous work in human carotid artery specimens showed in situ correlations between a nonradioactive structural analogue of HX4, pimonidazole, and features of plaque vulnerability (5). Nonetheless, additional studies are warranted to assess HX4's relationship with FDG and its direct link to hypoxia-associated molecules in human plaques. Future studies are aimed at: 1) using additional MRI imaging sequences or MRI-traceable HX4 to overcome the low spatial resolution of PET and provide greater insight in HX4 uptake in different plaque components; and 2) addressing the relationship between HX4, hypoxia, and plaque vulnerability in vivo.

In conclusion, we present a noninvasive imaging approach to visualize hypoxia in advanced atherosclerotic lesions in humans in vivo. Current data support efforts to develop and implement imaging modalities to quantify hypoxia in patients at risk for cardiovascular disease.

Fleur M. van der Valk, MD
Judith C. Sluimer, MD, PhD
Stefan A. Vöö, MD
Hein J. Verberne, MD, PhD
Aart J. Nederveen, PhD
Albert D. Windhorst, MD, PhD
Erik S.G. Stroes, MD, PhD
Philippe Lambin, MD, PhD
Mat J.A.P. Daemen, MD, PhD*
*Academic Medical Center
Department of Pathology, Room M2-206
PO Box 22660
1100 DD, Amsterdam
the Netherlands
E-mail: m.j.daemen@amc.nl

http://dx.doi.org/10.1016/j.jcmg.2014.12.015

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Carlin S, Humm JL. PET of hypoxia: current and future perspectives. J Nucl Med 2012;53:1171–4.

2. Chen L, Zhang Z, Kolb HC, et al. ^{18}F-HX4 hypoxia imaging with PET/CT in cancer: comparison with ^{18}F-FMISO. Nucl Med Commun 2012;33:1096–102.

3. Fayad ZA, Mani V, Woodward M, et al. Rationale and design of dal-PLAQUE. Am Heart J 2011;162:214–21.e2.

4. Mateo J, Izquierdo-Garcia D, Badimon JJ, et al. Noninvasive assessment of hypoxia in rabbit advanced atherosclerosis using ^{18}F-fluoromisonidazole positron emission tomographic imaging. Circ Cardiovasc Imaging 2014;7:312–20.

5. Sluimer JC, Gasc JM, van Wanroij JL, et al. Hypoxia, hypoxia-inducible transcription factor, and macrophages in human atherosclerotic plaques are correlated with intraplaque angiogenesis. J Am Coll Cardiol 2008;51:1258–65.

Serial Multimodality Evaluation of Aortocoronary Bypass Grafts During the First Year After CABG Surgery

The CABG-PRO (Cardiac Catheterization for Bypass Graft Patency Rate Optimization) trial (NCT01063491), was a randomized, controlled, double-blind, parallel-group study of early versus no early graft angiography in patients undergoing coronary artery bypass graft (CABG) surgery. Enrollment in the CABG-PRO trial was stopped early because of low rates of saphenous vein graft (SVG) percutaneous coronary intervention among patients undergoing early coronary angiography (1 of 21 patients). Of those 21 patients, matched