Am J Nucl Med Mol Imaging 2013;3(5):393-396
www.ajnmmi.us /ISSN:2160-8407/ajnmmi1307003

Invited Perspective

PET/MR imaging of atherosclerosis: initial experience and outlook

Christoph Rischpler, Stephan G Nekolla, Ambros J Beer

Department of Nuclear Medicine, Technische Universität München, Klinikum rechts der Isar, Munich, Germany

Received July 25, 2013; Accepted August 9, 2013; Epub September 19, 2013; Published September 30, 2013

Abstract: Hybrid scanners such as PET/CT have in the past emerged as a valuable modality in clinical routine as well as an important research tool. Recently, the newly developed fully integrated PET/MR scanners were introduced to the market, raising high expectations especially due to the excellent soft tissue contrast and functional imaging capabilities of MRI. In this issue of the American Journal of Nuclear Medicine and Molecular Imaging, initial experiences using a hybrid PET/MR scanner for carotid artery imaging in a group of patients with increased risk for atherosclerosis are described. This represents a proof-of-principle study, which could stimulate future applications of this powerful modality in atherosclerotic plaque imaging.

Keywords: PET/MR, PET/CT, hybrid imaging, atherosclerosis, FDG

Hybrid imaging with combined nuclear medicine/radiological techniques is of increasing relevance in the field of molecular imaging. The combination of positron emission tomography (PET) and computed tomography (CT) in a single scanner (PET/CT) has entered the market in 2000 and rapidly replaced standalone PET nearly completely, as it proved to be an extremely powerful modality in clinical routine as well as for research applications. The next logical step was the combination of PET and magnetic resonance imaging (MRI), as MRI is superior to CT in many aspects and does not expose the patient to ionizing radiation. With the introduction of the recently available fully integrated PET/MR scanners for clinical use, imaging experts are now evaluating the general technical feasibility and potential of those new hybrid scanners for a variety of indications and disease entities and are comparing them to the conventional PET/CT. Furthermore, the imaging community is looking for distinct applications of hybrid PET/MR, which yield an incremental diagnostic value both over standalone PET and MR scanners as well as over hybrid PET/CT scanners. As PET/MR has the advantage of a lower radiation exposure of the patients compared to PET/CT [1], it might be of special interest in non-oncological applications, like cardiovascular imaging. In this respect, imaging of atherosclerosis might benefit from hybrid PET/MR, as delineation of the vessel wall and atherosclerotic plaques is in general superior in MRI compared to CT [2].

In the 2013 4th issue of the American Journal of Nuclear Medicine and Molecular Imaging, Ripa et al. evaluated the feasibility of a fully integrated hybrid PET/MR system for imaging the carotid arteries in a small group of HIV positive patients with the radiotracer ^{18}F-fluorodeoxyglucose (^{18}F-FDG) [3]. Additionally, these patients were scanned on a PET/CT scanner and the obtained standardized uptake values (SUV) of both modalities were compared. With PET/MR it was feasible to image the carotid arteries with PET and MRI simultaneously in all patients. The SUVs obtained by PET/MR and PET/CT showed a good correlation, however, PET/MR demonstrated slightly but significantly lower SUVs. The authors concluded that simultaneous PET/MR can be used to image the carotid artery in patients without large atherosclerotic plaques and that ^{18}F-FDG quantification by PET/MR is comparable to PET/CT.

The present publication by Ripa et al. nicely illustrates the technical capabilities and the initial experiences using the newly available inte-

grated PET/MR scanners to image the carotid arteries in patients with increased risk of atherosclerosis [3]. As the authors stated, PET/MR is – also based on our own experience – feasible in a clinical setting for this indication meaning that high-quality images comparable to conventional PET/CT can be acquired [4] although the limits of PET's spatial resolution might be reached. As published before – e.g. in the field of oncology - the obtained SUVs show a good correlation within tracer kinetic limits between PET/MR and PET/CT [5]. Corresponding to data reported from other groups, the SUVs derived from PET/MR were slightly lower compared to PET/CT [6, 7]. Due to the higher soft tissue contrast of MR this technique facilitates to differentiate between the carotid artery wall and the lumen and thus allows for an even more detailed analyses as compared to PET/CT. This publication should be seen as stimulus for further, more elaborate work-up of patients with overt atherosclerosis using PET/MR.

While the present work focused on the evaluation of the general feasibility of PET/MR for carotid imaging in patients with no overt atherosclerosis, one might speculate whether PET/MR has the capability to characterize present atherosclerotic lesions and differentiate culprit from non-culprit lesions. PET/MR seems to be very promising for this application due to several reasons. While PET imaging might be used for initial detailed characterization of the functional status of the plaque, MR imaging is useful for repetitive morphological follow-up as it does not use ionizing radiation and as it allows to image both the lumen and the wall of the artery. This would enable a non-invasive evaluation of new drugs in clinical trials or the monitoring of individual therapies for specific lesions. In patients with overt atherosclerosis MR does not only allow for diagnosing luminal stenoses or ruptured plaques, also a detailed analysis of precursors of plaque rupture is possible. Based on a recent publication by several experts in this field, the luminal stenosis alone is not sufficient to characterize plaque vulnerability [8, 9]. In these publications 5 minor and 5 major characteristics for the vulnerability of a plaque were defined. The major criteria include - besides severe stenosis - a thin cap with a large lipid core, endothelial denudation with superficial platelet aggregation, fissured/injured plaque and active inflammation. Interestingly, PET/MR seems to represent the ideal modality to image these characteristics with sufficient accuracy [10-12]. On the one hand, the described morphological features of plaque vulnerability can be nicely imaged by MRI [12]. On the other hand biological features of plaque vulnerability can be visualized by PET, as e.g. inflamed plaques are known to show an increased uptake of ^{18}F-FDG which is thought to be predominantly related to macrophage infiltration [10, 13]. Thus PET/MR allows for a multiparametric characterization of plaque morphology and biology in a one-stop-shop approach and should facilitate the identification of high-risk plaques in patients with atherosclerotic disease.

Other potential tracers for the identification of plaque inflammation/vulnerability are tracers that target somatostatin receptors (such as ^{68}Ga-DOTATATE), especially those targeting the subtype 2 which is known to be overexpressed on activated macrophages [14]. In a pilot study by Li et al. there was a stronger association of ^{68}Ga-DOTATATE uptake with cardiovascular risk factors when compared to ^{18}F-FDG uptake [15]. Furthermore, there are more promising agents under investigation in preclinical models [16, 17], which might add important information in the characterization of plaques such as agents targeting the integrin $\alpha_V\beta_3$ [18-20]. These tracers are thought to target both inflammation and neoangiogenesis in atherosclerotic lesions [21]. In a study from our institution, it was shown that a lipid-lowering diet intervention caused a significant reduction of ^{18}F-galacto-RGD uptake in atherosclerotic lesions in hypercholesterolemic LDLR$^{-/-}$ ApoB$^{100/100}$ mice indicating that this tracer might not only be valuable for inflammation imaging but also for therapy monitoring and investigation of new drugs [18].

These studies and the present study by Ripa et al. show that now further clinical studies with PET/MR on imaging of atherosclerosis – especially in patients with known plaques – are justified and warranted. The newly available hybrid PET/MR scanners might prove to be extremely valuable for this research field, as they allow for multiparametric profiling of plaque morphology and biology and thus potentially vulnerability in one imaging session. As a perspective, this new combined imaging modality might pave the way for a more widespread use of hybrid imaging of plaque vulnerability and translation from experimental application to clinical routine.

Address correspondence to: Dr. Ambros J Beer, Department of Nuclear Medicine, Technische Universität München, Klinikum rechts der Isar, Ismaningerstrasse 22, 81675 Munich, Germany. Tel: +49 89 4140 6085; Fax: +49 89 4140 7431; E-mail: ambros.beer@tum.de

References

[1] Balyasnikova S, Lofgren J, de Nijs R, Zamogilnaya Y, Hojgaard L and Fischer BM. PET/MR in oncology: an introduction with focus on MR and future perspectives for hybrid imaging. Am J Nucl Med Mol Imaging 2012; 2: 458-74.

[2] Yuan C, Mitsumori LM, Beach KW and Maravilla KR. Carotid atherosclerotic plaque: noninvasive MR characterization and identification of vulnerable lesions. Radiology 2001; 221: 285-99.

[3] Ripa RS, Knudsen A, Hag AM, Lebech AM, Loft A, Keller SH, Hansen AE, von Benzon E, Højgaard L and Kjær A. Feasibility of simultaneous PET/MR of the carotid artery: first clinical experience and comparison to PET/CT. Am J Nucl Med Mol Imaging 2013; 3: 361-71.

[4] Rischpler C, Nekolla S and Schwaiger M. PET and SPECT in heart failure. Curr Cardiol Rep 2013; 15: 337.

[5] Drzezga A, Souvatzoglou M, Eiber M, Beer AJ, Fürst S, Martinez-Möller A, Nekolla SG, Ziegler S, Ganter C, Rummeny EJ and Schwaiger M. First clinical experience with integrated whole-body PET/MR: comparison to PET/CT in patients with oncologic diagnoses. J Nucl Med 2012; 53: 845-55.

[6] Souvatzoglou M, Eiber M, Takei T, Fürst S, Maurer T, Gaertner F, Geinitz H, Drzezga A, Ziegler S, Nekolla SG, Rummeny EJ, Schwaiger M and Beer AJ. Comparison of integrated whole-body [C]choline PET/MR with PET/CT in patients with prostate cancer. Eur J Nucl Med Mol Imaging 2013; [Epub ahead of print].

[7] Gaertner FC, Beer AJ, Souvatzoglou M, Eiber M, Fürst S, Ziegler SI, Brohl F, Schwaiger M and Scheidhauer K. Evaluation of feasibility and image quality of 68Ga-DOTATOC positron emission tomography/magnetic resonance in comparison with positron emission tomography/computed tomography in patients with neuroendocrine tumors. Invest Radiol 2013; 48: 263-72.

[8] Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Juhani Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK and Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 2003; 108: 1664-72.

[9] Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK and Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation 2003; 108: 1772-8.

[10] Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N, Johnström P, Davenport AP, Kirkpatrick PJ, Arch BN, Pickard JD and Weissberg PL. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. Circulation 2002; 105: 2708-11.

[11] Davies JR, Rudd JH, Weissberg PL and Narula J. Radionuclide imaging for the detection of inflammation in vulnerable plaques. J Am Coll Cardiol 2006; 47: C57-68.

[12] Saam T, Hatsukami TS, Takaya N, Chu B, Underhill H, Kerwin WS, Cai J, Ferguson MS and Yuan C. The vulnerable, or high-risk, atherosclerotic plaque: noninvasive MR imaging for characterization and assessment. Radiology 2007; 244: 64-77.

[13] Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999; 340: 115-26.

[14] Temma T and Saji H. Radiolabelled probes for imaging of atherosclerotic plaques. Am J Nucl Med Mol Imaging 2012; 2: 432-47.

[15] Li X, Samnick S, Lapa C, Israel I, Buck AK, Kreissl MC and Bauer W. 68Ga-DOTATATE PET/CT for the detection of inflammation of large arteries: correlation with18F-FDG, calcium burden and risk factors. EJNMMI Res 2012; 2: 52.

[16] Alauddin MM. Positron emission tomography (PET) imaging with ^{18}F-based radiotracers. Am J Nucl Med Mol Imaging 2012; 2: 55-76.

[17] Nolting DD, Nickels ML, Guo N and Pham W. Molecular imaging probe development: a

chemistry perspective. Am J Nucl Med Mol Imaging 2012; 2: 273-306.
[18] Saraste A, Laitinen I, Weidl E, Wildgruber M, Weber AW, Nekolla SG, Hölzlwimmer G, Esposito I, Walch A, Leppänen P, Lisinen I, Luppa PB, Yla-Herttuala S, Wester HJ, Knuuti J and Schwaiger M. Diet intervention reduces uptake of alphavbeta3 integrin-targeted PET tracer 18F-galacto-RGD in mouse atherosclerotic plaques. J Nucl Cardiol 2012; 19: 775-84.
[19] Laitinen I, Saraste A, Weidl E, Poethko T, Weber AW, Nekolla SG, Leppänen P, Ylä-Herttuala S, Hölzlwimmer G, Walch A, Esposito I, Wester HJ, Knuuti J and Schwaiger M. Evaluation of alphavbeta3 integrin-targeted positron emission tomography tracer 18F-galacto-RGD for imaging of vascular inflammation in atherosclerotic mice. Circ Cardiovasc Imaging 2009; 2: 331-8.
[20] Liu S, Park R, Conti PS and Li Z. "Kit like" (18)F labeling method for synthesis of RGD peptide-based PET probes. Am J Nucl Med Mol Imaging 2013; 3: 97-101.
[21] Haukkala J, Laitinen I, Luoto P, Iveson P, Wilson I, Karlsen H, Cuthbertson A, Laine J, Leppänen P, Ylä-Herttula S, Knuuti J and Roivainen A. 68Ga-DOTA-RGD peptide: biodistribution and binding into atherosclerotic plaques in mice. Eur J Nucl Med Mol Imaging 2009; 36: 2058-67.