What did we learn from PET/MR?

Markus Schwaiger, MD,[a] and Stephan G. Nekolla, PhD[b,c]

[a] Technical University of Munich, Munich, Germany
[b] Department of Nuclear Medicine, Technical University of Munich, Munich, Germany
[c] DZHK (Deutsches, Zentrum für Herz-Kreislauf-Forschung e.V.), partner site Munich Heart Alliance, Munich, Germany

Received May 23, 2019; accepted May 23, 2019
doi:10.1007/s12350-019-01815-8

See related article, pp. 891–898

^{68}Ga-DOTA chelate, a novel imaging agent for assessment of myocardial perfusion and infarction detection in a rodent model

by Anu Autio,

Turku PET Centre, University of Turku

Heart Center, Turku University Hospital and University of Turku

Turku Center for Disease Modeling, University of Turku

In this JNC issue, Dr. Autio and his colleagues introduce ^{68}Ga-DOTA chelate as new tracer for the delineation of myocardial perfusion as well as extracellular space in a rodent infarct model. This application has most likely been triggered by the fact that gadolinium chelates are widely being used as contrast agent in magnetic resonance imaging (MRI). In cardiac MRI (CMRI), the use of Gd-chelates represents an established technology for the work-up of patients with coronary artery disease. Quite interestingly, this class of MR contrast agents was modeled in the 1980s after a tracer principle in nuclear medicine—^{99m}Tc-DTPA.[1]

The advantages of MRI in terms of high spatial resolution and lack of ionizing radiation have supported the clinical application of Gd-chelates for the imaging of myocardial perfusion, the delineation of myocardial scar as well as—in more general terms—for the detection of alterations in extracellular volume.[2-4] However, there have been questions about the possible toxicity of these contrast agents as gadolinium deposits were found in brain tissue.[5] Nevertheless, the technology remains a standard procedure in many cardiovascular imaging centers. Based on this positive experience, it is not surprising that using ^{68}Ga-labelled chelates in combination with dynamic PET acquisition allows a replication of data established in the MR community. The sophisticated first-pass analysis established at the laboratory of the Turku investigators, mainly using ^{15}O-water as the PET tracer, allows an almost automatic quantitative analysis yielding absolute measurements of myocardial perfusion as shown in many publications.[6] The group at the University of Turku has already demonstrated that PET ^{15}O-water studies in the normal flow range correlate with the perfusion results obtained after the intravenous bolus injection of ^{68}Ga-DOTA.[7]

The paper by Dr. Autio et al raises an important question: What are the relative advantages of PET vs MR imaging for extracting biological information such as myocardial perfusion, extracellular space and myocardial infarct extension? For the clinical work-up of patients with suspected coronary artery disease the need for an accurate and robust assessment of myocardial perfusion and coronary flow reserve has been recognized for decades.[8] Currently, the most commonly used PET tracer is rubidium-82 (^{82}Rb) because it is generator-used and allows rapid evaluation of rest and stress perfusion due to its short physical half-life of 76 seconds.[9] In the scientific community, ^{13}N-ammonia has gained acceptance since it has a high myocardial extraction coupled with a suitable physical half-life of 10 minutes to provide excellent image quality due to the high-tracer retention.[10] The drawback of ^{13}N-ammonia is the need of an onsite cyclotron, which limits the use to primarily academic institutions. The same applies to ^{15}O-water, which represents a freely diffusible used for cerebral and myocardial perfusion measurements.

Many publications have indicated that with both ^{15}O-water and ^{13}N-ammonia global as well as regional

Reprint requests: Markus Schwaiger, MD, Technical University of Munich, Munich, Germany; *markus.schwaiger@tum.de*
J Nucl Cardiol 2020;27:899–902.
1071-3581/$34.00

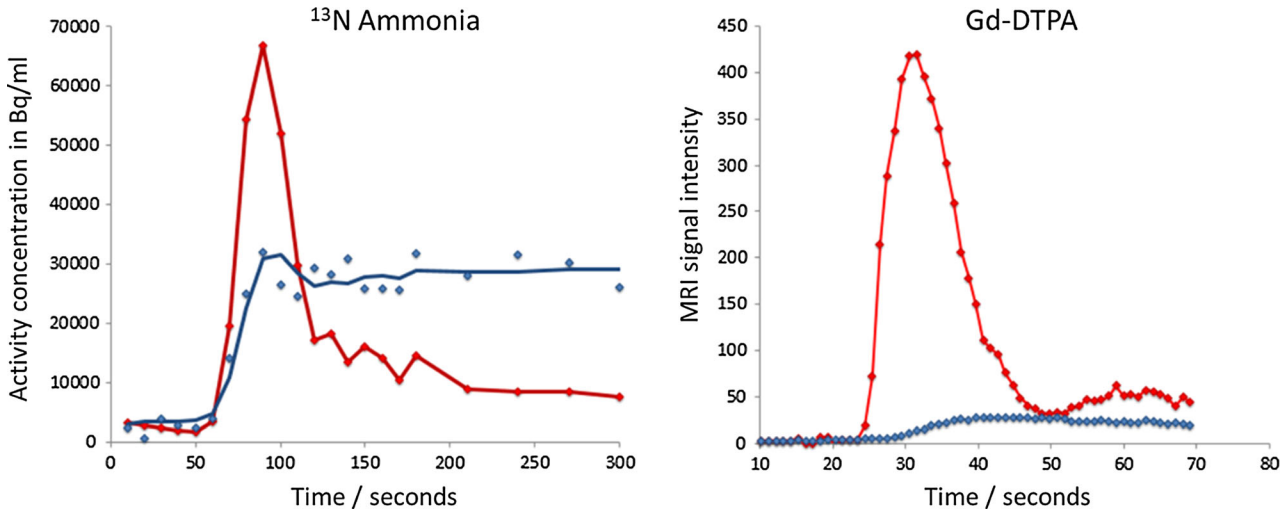

Figure 1. Time and signal activity curves from a near simultaneous tracer and contrast media injection in a human using a PET/MR system. The red dots and lines represent the arterial input function from a volume of interest (VOI) in the left ventricle, the blue dots and lines are generates from VOIs in the LV myocardium. Note the drastic difference in the tissue curves which reflects the differences in the volume of distribution. Whereas NH3 can distribute to the cell, Gd-chelates are limited to the plasma volume and interstitial space.

myocardial blood flow can be well quantified. The non-invasive delineation of coronary reserve has been advocated not only as diagnostic but also prognostic tool.[11,12] With the advance of multimodal imaging using PET/CT systems, the combination of both tracers with coronary angiography provides a very attractive but costly tool for the functional and anatomic assessment of regional coronary artery disease.[13,14]

^{68}Ga DOTA is introduced as tracer for both perfusion and ECV. To apply one tracer providing not only information on perfusion but also on tissue characterization is a promising approach. The authors used ^{11}C-acetate as reference tracer for the estimation of perfusion. ^{11}C-acetate is well extracted by the myocardium but rapidly metabolized by TCA cycle as a function of myocardial oxygen consumption.[15] The relatively high first-pass extraction of ^{11}C-acetate allows flow estimates, while fitting of myocardial time activity curves yields estimates of oxidative metabolism.[16,17] Nevertheless, such combination provides an attractive research tool to define the integrity of myocardial perfusion and metabolic performance. Together with hemodynamic estimates of cardiac work, several studies have attempted to delineate the cardiac efficiency as marker of overall cardiac performance.[18] However, this sophisticated imaging approach has never gained wide clinical acceptance in the management of patients with heart failure primarily due to the challenging imaging technology required for clinical work-up of such patients.[19] ^{68}Ga DOTA does not provide metabolic data, but myocardial tracer retention reflects extracellular space (ECV). This differential tracer kinetics can be exploited to quantitatively assess ECV in similar fashion as done with Gd-chelates by MRI. ECV estimates provide information on infarct extension (late enchancement) and myocardial fibrosis.[20] No direct comparison to MR data in the rodent model is provided in the paper by Dr. Autio et al. As shown in their Figure 2a, the time activity curves indicate very little differences in retention, which may limit the infarct extension measurements with ^{68}Ga DOTA in the clinical setting.

The introduction of PET/MR made it possible to compare both imaging modalities in the same patients under identical physiologic conditions.[21] Expanding on earlier work, our group indicated recently that myocardial blood flow measurements provided by ^{13}N-ammonia PET and Gd-chelate MR correlate very closely when using a suitable modelling approach.[21,22] However, there are distinct differences in the imaging characteristics of both methodologies. PET excels by its high sensitivity but limited spatial resolution as compared to MRI. In addition, the direct comparison of ^{13}N-ammonia kinetics and gadolinium chelate kinetics also demonstrate the difference in contrast kinetics: With the high first-pass extraction of ^{13}N-ammonia myocardial cells and the high sensitivity of PET, excellent imaging quality can be achieved with a relatively small amount of injected tracer activity. A number of tracer kinetic models have been validated indicating that this technology provides robust qualitative, semi-quantitative

and quantitative information in many settings of clinical cardiology.[23] The kinetics measured simultaneously for Gd-DTPA as shown in Figure 1 indicates that the basic behavior of ^{13}N-ammonia and Gd-chelates are quite different because gadolinium chelates never enter a myocardial cell but are restricted to the plasma volume and the interstitial space. Therefore, the imaging signal is very transient and requires challenging modelling with relatively low signal to noise ratio to extract quantitative information. However, several groups have demonstrated that robust, global and regional blood flow measurements can be obtained in normal volunteers as well as in patients with coronary artery disease.[24] The direct comparison of PET and MR highlights the relative strength of each modality. The robust flow visualization and semi-quantitative assessment favors PET as useful tool for ''staging'' CAD, especially by PET/CTA.[14] The high spatial resolution and accurate estimate of infarct size supports the use of MRI. The drawback of MR technology for cardiac imaging currently is the lack of robust and diagnostic coronary angiography.[25]

Based on the existing data, there seems to be little need for adding a new PET tracer approach based on the positive experience with Gd-DTPA in the MR community. ^{68}Ga DOTA offers inferior tracer kinetics in the myocardium as compared to the available PET approaches. In addition, there is a number of imaging approaches characterizing infarcted myocardium.[26] Since tissue viability has been an issue in patients with recent infarction, the advantage of metabolic tracers as compared to delineation of scar tissue has been addressed by several studies.[27] More recently, the emphasis of PET imaging has focused on the identification of inflammation associated with acute ischemic injury.[28] With the adjunct of new molecular imaging probes not only the extent of scar but also the ''healing'' of acutely infarcted myocardium can be followed by a variety of interesting new tracer approaches. However, these exciting new signals have to prove the clinical value in the future.[29] It is foreseen that some of these new molecular tracers will be able to target the inflammatory reaction to myocardial infarction and thus provide guidance in possible therapeutic interventions to limit the inflammatory process and, therefore, improve the healing process of the ischemic injury.

In summary, this paper demonstrates that ^{68}Ga DOTA can indeed be used as a radiotracer in a similar fashion as Gd-chelates in cardiac MR imaging. However, in difference to CMRI where it is the only valid option, there seems to be no urgent clinical need for the nuclear cardiology community to translate and validate this tracer approach in nuclear cardiology. The relative strength of PET vs MR favors the use of tracers targeting biological processes associated with ischemic injury, which, however, need further validation as important tools for managing patients with CAD.

Disclosure

Markus Schwaiger reports consultancy for GE Healthcare. Stephan G. Nekolla has nothing to declare.

References

1. Laniado M, Weinmann HJ, Schorner W, Felix R, Speck U. First use of GdDTPA/dimeglumine in man. Physiol Chem Phys Med NMR. 1984;16(2):157-65.
2. Wilke N, Simm C, Zhang J, Ellermann J, Ya X, Merkle H, et al. Contrast-enhanced first pass myocardial perfusion imaging: correlation between myocardial blood flow in dogs at rest and during hyperemia. Magn Reson Med. 1993;29(4):485-97.
3. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999;100(19):1992-2002.
4. Kunze KP, Rischpler C, Hayes C, Ibrahim T, Laugwitz KL, Haase A, et al. Measurement of extracellular volume and transit time heterogeneity using contrast-enhanced myocardial perfusion MRI in patients after acute myocardial infarction. Magn Reson Med. 2017;77(6):2320-30.
5. Gulani V, Calamante F, Shellock FG, Kanal E, Reeder SB, International Society for Magnetic Resonance in Medicine. Gadolinium deposition in the brain: summary of evidence and recommendations. Lancet Neurol. 2017;16(7):564-70.
6. Nesterov SV, Han C, Maki M, Kajander S, Naum AG, Helenius H, et al. Myocardial perfusion quantitation with 15O-labelled water PET: high reproducibility of the new cardiac analysis software (Carimas). Eur J Nucl Med Mol Imaging. 2009;36(10):1594-602.
7. Autio A, Saraste A, Kudomi N, Saanijoki T, Johansson J, Liljenback H, et al. Assessment of blood flow with (68)Ga-DOTA PET in experimental inflammation: a validation study using (15)O-water. Am J Nucl Med Mol Imaging. 2014;4(6):571-9.
8. Johnson NP, Gould KL, Di Carli MF, Taqueti VR. Invasive FFR and Noninvasive CFR in the Evaluation of Ischemia: What Is the Future? J Am Coll Cardiol. 2016;67(23):2772-88.
9. Sampson UK, Dorbala S, Limaye A, Kwong R, Di Carli MF. Diagnostic accuracy of rubidium-82 myocardial perfusion imaging with hybrid positron emission tomography/computed tomography in the detection of coronary artery disease. J Am Coll Cardiol. 2007;49(10):1052-8.
10. Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE. Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. J Am Coll Cardiol. 1990;15(5):1032-42.
11. Murthy VL, Di Carli MF. Non-invasive quantification of coronary vascular dysfunction for diagnosis and management of coronary artery disease. J Nucl Cardiol. 2012;19(5):1060-72; quiz 75.
12. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, Bober R, et al. Anatomic versus physiologic assessment of coronary artery disease: Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol. 2013;62(18):1639-53.

13. Neglia D, Rovai D, Caselli C, Pietila M, Teresinska A, Aguade-Bruix S, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging. 2015;8(3):e002179.
14. Driessen RS, Danad I, Stuijfzand WJ, Raijmakers PG, Schumacher SP, van Diemen PA, et al. Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis. J Am Coll Cardiol. 2019;73(2):161-73.
15. Buxton DB, Schwaiger M, Nguyen A, Phelps ME, Schelbert HR. Radiolabeled acetate as a tracer of myocardial tricarboxylic acid cycle flux. Circ Res. 1988;63(3):628-34.
16. Buck A, Wolpers HG, Hutchins GD, Savas V, Mangner TJ, Nguyen N, et al. Effect of carbon-11-acetate recirculation on estimates of myocardial oxygen consumption by PET. J Nucl Med. 1991;32(10):1950-7.
17. Sun KT, Yeatman LA, Buxton DB, Chen K, Johnson JA, Huang SC, et al. Simultaneous measurement of myocardial oxygen consumption and blood flow using [1-carbon-11]acetate. J Nucl Med. 1998;39(2):272-80.
18. Wolpers HG, Buck A, Nguyen N, Marcowitz PA, Armstrong WF, Starling MR, et al. An approach to ventricular efficiency by use of carbon 11-labeled acetate and positron emission tomography. J Nucl Cardiol. 1994;1(3):262-9.
19. Beanlands RS, Armstrong WF, Hicks RJ, Nicklas J, Moore C, Hutchins GD, et al. The effects of afterload reduction on myocardial carbon 11-labeled acetate kinetics and noninvasively estimated mechanical efficiency in patients with dilated cardiomyopathy. J Nucl Cardiol. 1994;1(1):3-16.
20. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson. 2017;19(1):75.
21. Kunze KP, Nekolla SG, Rischpler C, Zhang SH, Hayes C, Langwieser N, et al. Myocardial perfusion quantification using simultaneously acquired (13) NH3 -ammonia PET and dynamic contrast-enhanced MRI in patients at rest and stress. Magn Reson Med. 2018;80(6):2641-54.
22. Ibrahim T, Nekolla SG, Schreiber K, Odaka K, Volz S, Mehilli J, et al. Assessment of coronary flow reserve: comparison between contrast-enhanced magnetic resonance imaging and positron emission tomography. J Am Coll Cardiol. 2002;39(5):864-70.
23. Murthy VL, Bateman TM, Beanlands RS, Berman DS, Borges-Neto S, Chareonthaitawee P, et al. Clinical Quantification of Myocardial Blood Flow Using PET: Joint Position Paper of the SNMMI Cardiovascular Council and the ASNC. J Nucl Cardiol. 2018;25(1):269-97.
24. Morton G, Chiribiri A, Ishida M, Hussain ST, Schuster A, Indermuehle A, et al. Quantification of absolute myocardial perfusion in patients with coronary artery disease: comparison between cardiovascular magnetic resonance and positron emission tomography. J Am Coll Cardiol. 2012;60(16):1546-55.
25. Di Leo G, Fisci E, Secchi F, Ali M, Ambrogi F, Sconfienza LM, et al. Diagnostic accuracy of magnetic resonance angiography for detection of coronary artery disease: a systematic review and meta-analysis. Eur Radiol. 2016;26(10):3706-18.
26. Klein C, Nekolla SG, Bengel FM, Momose M, Sammer A, Haas F, et al. Assessment of myocardial viability with contrast-enhanced magnetic resonance imaging: comparison with positron emission tomography. Circulation. 2002;105(2):162-7.
27. Rischpler C, Langwieser N, Souvatzoglou M, Batrice A, van Marwick S, Snajberk J, et al. PET/MRI early after myocardial infarction: evaluation of viability with late gadolinium enhancement transmurality vs. 18F-FDG uptake. Eur Heart J Cardiovasc Imaging. 2015;16(6):661-9.
28. Rischpler C, Dirschinger RJ, Nekolla SG, Kossmann H, Nicolosi S, Hanus F, et al. Prospective Evaluation of 18F-Fluorodeoxyglucose Uptake in Postischemic Myocardium by Simultaneous Positron Emission Tomography/Magnetic Resonance Imaging as a Prognostic Marker of Functional Outcome. Circ Cardiovasc Imaging. 2016;9(4):e004316.
29. Rischpler C, Nekolla SG, Kossmann H, Dirschinger RJ, Schottelius M, Hyafil F, et al. Upregulated myocardial CXCR29-expression after myocardial infarction assessed by simultaneous GA-68 pentixafor PET/MRI. J Nucl Cardiol. 2016;23(1):131-3.