# EDITORIAL

# Myocardial blood flow quantification with SPECT and conventional tracers: a critical appraisal

Stephan G. Nekolla, PhD, FESC,[a] Christoph Rischpler, MD,[a] and Kenichi Nakajima, MD, PhD[b]

[a] Nuklearmedizinische Klinik und Poliklinik, Klinikum rechts der Isar, Technischen Universität München, Munich, Germany
[b] Department of Nuclear Medicine, Institute of Medical, Pharmacological and Health Sciences, Kanazawa University, Kanazawa, Japan

Received Sep 3, 2014; accepted Sep 3, 2014
doi:10.1007/s12350-014-9996-z

Quantification of absolute myocardial blood flow (MBF) and flow reserve (MFR) from rest and stress studies is a valuable technique in cardiac PET since well over two decades using short- and medium-lived tracers such as $^{15}$O-water, $^{82}$Rb-rubidium, $^{13}$N-ammonia or, more recently, $^{18}$F-labeled compounds such as $^{18}$F-Flurpiridaz. However, due to complex logistics, their clinical use is limited as compared to the widely used single-photon imaging tracers $^{99m}$Tc-labeled or $^{201}$Tl reaching annual world wide examination numbers in the two-digit million range. Actually, as one can see from these sheer numbers, the lack of non-invasive, absolute quantification of MBF did not stop the success of these agents at all. So, why bother with dynamic imaging and kinetic modeling at all? In general, the authors firmly believe that it represents the step from the assessment of a relative distribution of tracer uptake in an image to the physiologically relevant value of absolute myocardial blood flow and flow reserve. Independent of this conviction, other modalities such as MRI[2] and CT[3] try to duplicate this since many years. Finally, even invasive imaging in the cath lab found this to be a powerful method to assess in absolute rather than relative terms the hemodynamic relevance of a stenosis.[4,5] But also in more subtle alterations of myocardial perfusion, sophisticated quantification allows a more truthful characterization of the functional capabilities of myocardial tissue (diabetes, chronic kidney disease, etc.). So, why did absolute myocardial perfusion assessment with PET did not bypass SPECT already? The answer is rather simple: PET cameras are more complex to design, produce, and operate than SPECT systems, and the same holds true for the production and distribution of the short-lived radiopharmaceuticals. Thus, blood flow quantification with SPECT would be a very welcomed addition to the armamentarium of nuclear cardiology.

Unfortunately, due to the rapid kinetics of perfusion agents and the limited temporal resolution of SPECT cameras—which can lead to inconsistent projection data as the tracer distribution changes during the rotation of the heads[6]—the technological hurdle is high. However, early feasibility studies using conventional photo-multiplier-based SPECT systems[7–9] and recently a new generation of SPECT cameras using solid-state photon detectors[10] showed potential to expand quantification of absolute blood flow and flow reserve also into the single-photon domain.

It is worthwhile remembering that myocardial blood flow and flow reserve is a complex issue as illustrated by Johnson and Gould in a recent publication where they suggested a segmentation scheme for a scatter diagram if regional stress flow values are plotted against the flow reserve values.[11] Such a diagram would allow the identification of different tissue types such as ''definitive ischemia'' or ''moderately ischemia'' indicating that a binary (''black and white'') answer does not give a proper picture of the state of the myocardium under investigation. Although such a sophisticated approach is

**See related article, pp. 1075–1088**

We took the words ''critical appraisal'' from a recent review by Wolfgang A. Weber on the use of PET/MR on oncological imaging as we see some parallel aspects.[1]

This is an editorial for the Journal of Nuclear Cardiology on: Ran Klein et al: Feasibility and operator variability of myocardial blood flow and reserve measurements with 99mTc-sestamibi quantitative dynamic SPECT/CT imaging.

This is an editorial to the article available in doi:10.1007/s12350-014-9971-8.Reprint requests: Stephan G. Nekolla, PhD, FESC, Nuklearmedizinische Klinik und Poliklinik, Klinikum rechts der Isar, Technischen Universität München, Ismaninger Str. 22, 81675, Munich, Germany; *stephan.nekolla@tum.de*

J Nucl Cardiol 2014;21:1289–91.
1071-3581/$34.00

not yet used widely in PET, it points in the right direction, namely the translation of quantitative, even absolute numerical values into something even more meaningful from a physiological point of view. However, there is a certain precision required to make this work. This precision is (at least) necessary in two sequential steps: the first is the kinetic modeling of the data, and the second is the conversion of the derived parameters into myocardial blood flow (the generation of the underlying activity curves in units of Bq/ml is another complex issue which should be ignored here).

Kinetic modeling, simply put, segments the myocardium into two or more compartments (in the simplest case, blood and tissue) and describes the exchange between the two with rate constants (here: blood → tissue: K1 and tissue → blood: k2). From a plain computational point of view, this leads to a set of differential equations which are solved by numerical algorithms that look for such a solution of K1 and k2 which fits the measured tissue data best—preferably with noise-free data. Another tricky, second part is the transition from K1 to the parameter, which is of interest here: myocardial blood flow in order to correct for the flow-dependent extraction from blood into the myocyte (with the notable exception of $^{15}$O-labeled water which is freely diffusible)—which leads to a key problem with commercially available SPECT agents: $^{99m}$Tc-labeled compounds such as sestamibi and tetrofosmin were introduced 2-3 decades ago and already early, a ''roll-off'' was recognized: this is a slightly downplaying term indicating the reduced extraction fraction at higher blood flows.[12,13] Whereas in static imaging this does not really matter in daily routine, it hampers blood flow quantification. Thus, for the second element, its precision is directly related as a numerical function connects the measured K1 values and flow. In cardiac PET with $^{15}$O-water, $^{13}$N-ammonia, and $^{18}$F-Flurpiridaz, the corrections in the physiological flow range can almost be neglected, and for other tracers, this is unfortunately not the case. Such a function is typically derived from validation studies either using microspheres in animal models[14–16] or using a correlation derived from sequential examinations in humans.[17] In other words, the more any algorithm has to amplify patient-derived K1 values with an animal or population-based function to correct for such a reduced extraction fraction, the more variable will be the flow values (Figure 1). This holds especially true for tracers with low extraction fractions such as $^{82}$Rb and to an even higher degree with $^{99m}$Tc-labeled compounds (e.g., sestamibi[12] or tetrofosmin.[13]) In the publication by Klein and colleagues, this fact can be appreciated in the increased scatter of the intra-operator curves for the stress examination (Fig. 7) and the comparison of the ratios of measured K1 values

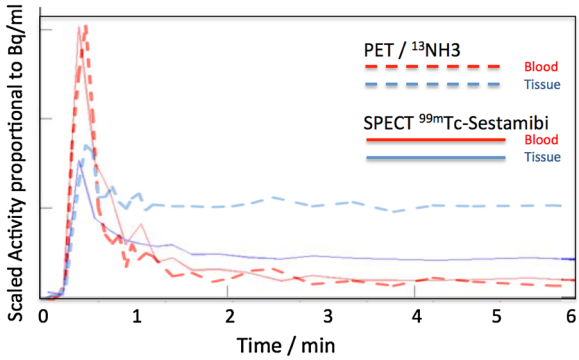


**Fig. 1.** Using the blood (*red*) and tissue (*blue*) time activity from the rest scan in Fig. 4 (*solid lines*), the corresponding curves from a rest scan with $^{13}$N-ammonia (*dashed lines*) are shown to demonstrate the difference in tracer extraction even at resting flow levels between $^{99m}$Tc-Sestamibi and $^{13}$N-ammonia. The $^{13}$N-ammonia data are from a typical patient and are scaled to achieve matching input function for comparison.

(1.25) and the corrected MFR-no-RPP (1.73) and MFR-RPP (2.45) in Table 3.

Are there tracers available, which do not suffer from the described ''roll-off'' phenomenon at higher flow? Actually, there are. $^{201}$Thallium has very good kinetic properties and is inexpensive, but suffers from a reduced image quality due to the relatively low energy of the emitted photon ($\approx$70 keV)—this effectively results in a very high exposure to ionizing radiation which already stopped its use in some countries. Using quantitative dynamic SPECT with iterative reconstruction and optimal correction for attenuation and scatter, however, MBF can be successfully measured using a three-compartment model.[18] Another option would be Teboroxime.[19–21] Known since more than two decades, it showed reasonable dosimetry data and very good extraction even at higher flows comparable and potentially better than $^{201}$Tl and clearly showing superiority to $^{96}$Tc-sestamibi as shown in a rodent model.[22] Unfortunately, it shows a rather rapid washout from the myocardium, which could limit the quality of the static images. In addition, the optimal time window for imaging is clearly earlier than with the tracers used today. However, such a situation can be handled clinically as $^{82}$Rb-PET shows.

So, what is the immediate message one can derive from the paper by Klein et al? On the negative side, it is a confirmation that conventional SPECT agents are no ideal candidates for kinetic modeling and thus quantification of myocardial blood flow and flow reserve in absolute terms. On the positive side, however, the authors show that even conventional cameras with suitable collimators, well-validated attenuation and scatter correction, and optimized image reconstruction

capabilities have the potential to acquire dynamic data which—at least—are the prerequisites to become truly quantitative.

Now, throw in a suitable SPECT perfusion tracer, and nuclear cardiology is good to go another two decades—at least!

## References

1. Weber WA. PET/MR imaging: a critical appraisal. J Nucl Med. 2014;55:56S–8S.
2. Morton G, Chiribiri A, Ishida M, 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;60:1546–55.
3. George RT, Jerosch-Herold M, Silva C, et al. Quantification of myocardial perfusion using dynamic 64-detector computed tomography. Invest Radiol. 2007;42:815–22.
4. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360:213–24.
5. Fearon WF, Shilane D, Pijls NH, et al. Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. Circulation. 2013;128:1335–40.
6. Nakajima K, Shuke N, Taki J, et al. A simulation of dynamic SPECT using radiopharmaceuticals with rapid clearance. J Nucl Med. 1992;33:1200–6.
7. Nakajima K, Taki J, Bunko H, et al. Dynamic acquisition with a three-headed SPECT system: application to technetium 99 m-SQ30217 myocardial imaging. J Nucl Med. 1991;32:1273–7.
8. Smith AM, Gullberg GT, Christian PE, Datz FL. Kinetic modeling of teboroxime using dynamic SPECT imaging of a canine model. J Nucl Med. 1994;35:484–95.
9. Khare HS, Dibella EV, Kadrmas DJ, Christian PE, Gullberg GT. Comparison of static and dynamic cardiac perfusion thallium-201 SPECT. IEEE Trans Nucl Sci. 2001;48:774.
10. Ben-Haim S, Murthy VL, Breault C, et al. Quantification of myocardial perfusion reserve using dynamic SPECT imaging in humans: a feasibility study. J Nucl Med. 2013;54:873–9.
11. Johnson NP, Gould KL. Integrating Noninvasive Absolute Flow, Coronary Flow Reserve, and Ischemic Thresholds Into A Comprehensive Map Of Physiological Severity. JACC Cardiovasc Imaging. 2012;5:430–40.
12. Leppo JA, Meerdink DJ. Comparison of the myocardial uptake of a technetium-labeled isonitrile analogue and thallium. Circ Res. 1989;65:632–9.
13. Glover DK, Ruiz M, Yang JY, Smith WH, Watson DD, Beller GA. Myocardial 99mTc-tetrofosmin uptake during adenosine-induced vasodilatation with either a critical or mild coronary stenosis: comparison with 201Tl and regional myocardial blood flow. Circulation. 1997;96:2332–8.
14. Muzik O, Beanlands RS, Hutchins GD, Mangner TJ, Nguyen N, Schwaiger M. Validation of nitrogen-13-ammonia tracer kinetic model for quantification of myocardial blood flow using PET. J Nuclear Medicine. 1993;34:83–91.
15. Nekolla SG, Reder S, Saraste A, et al. Evaluation of the novel myocardial perfusion positron-emission tomography tracer 18F-BMS-747158-02: comparison to 13N-ammonia and validation with microspheres in a pig model. Circulation. 2009;119:2333–42.
16. Lautamaki R, George RT, Kitagawa K, et al. Rubidium-82 PET-CT for quantitative assessment of myocardial blood flow: validation in a canine model of coronary artery stenosis. Eur J Nucl Med Mol Imaging. 2009;36:576–86.
17. Lortie M, Beanlands RS, Yoshinaga K, Klein R, Dasilva JN, DeKemp RA. Quantification of myocardial blood flow with 82Rb dynamic PET imaging. Eur J Nucl Med Mol Imaging. 2007;34:1765–74.
18. Iida H, Eberl S. Quantitative assessment of regional myocardial blood flow with thallium-201 and SPECT. J Nucl Cardiol. 1998;5:313–31.
19. Bontemps L, Geronicola-Trapali X, Sayegh Y, Delmas O, Itti R, Andre-Fouet X. Technetium-99m teboroxime scintigraphy. Clinical experience in patients referred for myocardial perfusion evaluation. Eur J Nucl Med. 1991;18:732–9.
20. Smith AM, Gullberg GT, Christian PE. Experimental verification of technetium 99m-labeled teboroxime kinetic parameters in the myocardium with dynamic single-photon emission computed tomography: reproducibility, correlation to flow, and susceptibility to extravascular contamination. J Nucl Cardiol. 1996;3:130–42.
21. Di Bella EV, Ross SG, Kadrmas DJ, et al. Compartmental modeling of technetium-99m-labeled teboroxime with dynamic single-photon emission computed tomography: comparison with static thallium-201 in a canine model. Invest Radiol. 2001;36:178–85.
22. Di Rocco RJ, Rumsey WL, Kuczynski BL, et al. Measurement of myocardial blood flow using a co-injection technique for technetium-99m-teboroxime, technetium-96-sestamibi and thallium-201. J Nucl Med. 1992;33:1152–9.