University of Groningen

Preclinical Models of Cancer Therapy-Associated Cardiovascular Toxicity

Amer Heart Assoc Council Basic Car; Council Genomic Precision Med; Council Clinical Cardiology; Council Peripheral Vasc Dis; Council Arteriosclerosis Thrombosi; Asnani, Aarti; Moslehi, Javid J.; Adhikari, Bishow B.; Baik, Alan H.; Beyer, Andreas M.

[Link to publication in University of Groningen/UMCG research database](#)

EDITORIAL

Accurate quantification of myocardial perfusion

Adriaan A. Lammertsma, PhD[a,b]

[a] Medical Imaging Center, Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[b] Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands

---

See related article, https://doi.org/10.1007/s12350-021-02631-9.

''In Myocardial Perfusion Imaging (MPI) with Positron Emission Tomography/Computed Tomography (PET/CT) systems, accurate quantification is essential'' reads the first sentence of the abstract of an article by Siekkinen et al[1] in which they describe a phantom study to assess the accuracy of myocardial blood flow (MBF) measurements using two different (types of) scanners. Within the context of a phantom study, the clinical value of this opening statement could easily be overlooked, given that quantification often is ignored in clinical practice, where decisions can be based on the spatial distribution of a perfusion tracer (visual or semi-quantitative assessment). Therefore it is important to reiterate the value of quantitative MBF measurements.

There are many situations where quantification is indeed essential, such as identification of three-vessel disease, assessment of cardiotoxicity after chemotherapy, and other conditions that lead to a global change in myocardial perfusion. Clearly, there are also many cases where a relative assessment would be sufficient, but at the same time it is strange that the scanning protocol used will depend on the (potentially erroneous) expected outcome of the scan. In addition, in a prospective study it was shown that quantitative $[^{15}O]H_2O$ PET studies were superior over semi-quantitative SPECT studies in selecting patients for the cath lab.[2]

$[^{15}O]H_2O$ PET is the ''gold standard'' method for absolute measurement of MBF. This is based on first principles, as water is freely diffusible and has no (molecular) interactions in tissue (i.e. also no labeled metabolites). In addition, already in the early days of PET, $[^{15}O]H_2O$ PET perfusion measurements were validated against labeled microspheres.[3] Other advantages of $[^{15}O]H_2O$ PET are the short overall study duration (rest-stress perfusion measurements can be performed well within half an hour) and the intrinsic ability to distinguish between viable and non-viable myocardial tissue, making it possible to distinguish between ischemic and infarcted tissue. Finally, software packages are available to perform data analysis in a semi-automated manner.[4,5] To advance the field, it is now time for cyclotron manufacturers to produce small and cheap mini-cyclotrons for the production of oxygen-15 that can be operated by a nuclear medicine technician, enabling hospitals with a PET scanner, but without a (larger) cyclotron and radiochemistry facilities, to perform myocardial perfusion (and viability) measurements. In addition, such a mini-cyclotron could also be used for perfusion measurements in brain and tumors.

Once a quantitative method, such as $[^{15}O]H_2O$ PET, has been validated in carefully conducted research studies, its correct application in routine clinical studies also needs to be guaranteed. Absolute quantification implies attention to detail with respect to a series of steps that are involved in generating quantitative parametric maps.[6] In case of measuring myocardial perfusion using $[^{15}O]H_2O$ (and most other perfusion tracers), the following steps need to be taken into account:

1. Accurate normalization of the PET scanner with accurate corrections for decay, dead time, attenuation, and random and scattered coincidences.
2. An appropriate scanning protocol. To obtain accurate results, not only the scanner needs to be tuned optimally, but also a scan protocol is required that is

able to catch the kinetics of the tracer. To properly define the arterial input function (image derived input function), this requires frame durations of about 5 seconds during the early part of the curve.

3. An injected dose that falls within the range that can be properly managed by the scanner, in practice setting a maximum to the injected dose depending on the performance of the scanner.

4. Close observation of the patient during scanning. Any patient motion should be corrected immediately, if possible. Otherwise, motion correction should be carried out retrospectively using either data from an on-line monitoring system or by realigning successive frames to each other.

5. Use of a reconstruction algorithm that provides the highest possible spatial resolution (given the thickness of the myocardium) without producing excessive noise levels. In general, an iterative reconstruction algorithm will be used. In that case it is important to check that convergence in reconstructed blood and tissue concentrations is reached, especially during the first part of a dynamic scan (high activity in the left ventricle, low activity in myocardium).

6. Correction for partial volume effects. This is not needed for $[^{15}O]H_2O$, as the tracer kinetic model for $[^{15}O]H_2O$ has a built-in correction for partial volume effects.[7] For other flow tracers, however, such a correction needs to be applied to the reconstructed data.

7. Extraction of the arterial input function. For $[^{15}O]H_2O$ and several other flow tracers an image derived input function can be used. Software packages exist that allow for semi-automated extraction of the arterial input function.[5] Nevertheless, a quality control procedure is needed to exclude artefacts and guarantee accurate results.

8. An appropriate tracer kinetic model, ideally as part of a user friendly software package. The good news is that such packages do exist and that different packages provide essentially identical results.[8]

Most of the items listed above need to be addressed only once, and others can be found in the literature (optimal tracer kinetic model, optimal scanning protocol, etc.). As mentioned above, MBF measurements using $[^{15}O]H_2O$ PET have already been validated by comparison with radiolabeled microspheres.[3] Nevertheless, once the method is implemented in a new institute or on a new scanner, some sort of evidence needs to be gathered to demonstrate that obtained results are as correct as they can be. Clearly, it would be overkill to repeat validation against microspheres. The standard way of demonstrating appropriate performance is by

carrying out phantom studies. Phantom measurements provide an overview of the overall accuracy, provided that the phantom can give a fair representation of the clinical process being measured. In addition, phantom measurements are of the utmost importance for harmonizing different scanners in a multicentre trial.

In general phantom measurements carried out to characterize scanner performance make use of static scans of non-moving phantoms. The beauty and novelty of the study by Siekkinen et al[1] is that they used dynamic scans together with a flow phantom. By doing so, they were able to check quantification of the entire (dynamic) process involved in MBF measurements by comparing obtained results with the known ground truth. Measured errors in myocardial perfusion for two state-of-the-art scanners (digital and analogue) were smaller than 12% for administered activities ranging from ∼ 350 to ∼ 1250 MBq. The authors recommend that in future studies higher administered activities should be investigated and, based on the data presented, it is likely that errors will increase somewhat. This will primarily affect ^{82}Rb studies, where higher administered doses are used. For $[^{15}O]H_2O$, however, an administered dose of ∼ 500 MBq is sufficient, even for analogue state-of-the-art PET scanners. For the latter dose, errors will be closer to a very acceptable 5%, which will clearly be an advantage of $[^{15}O]H_2O$ over ^{82}Rb MBF measurements.

The main purpose of the study by Siekkinen et al[1] was to assess the effects of administered dose on accuracy of myocardial perfusion measurements. This is a valid question as, immediately after injection, the total dose is within the field of view of the scanner, potentially resulting in count rate limitations. It is reassuring to note that such limitations were not observed. Siekkinen et al[1] claim that their phantom protocol could be used ''for MPI harmonization studies for several PET/CT systems, according to their count-rate performance and reconstruction methods'', i.e. for harmonising scanners in a multicentre study. Unfortunately, this aspect was not further investigated, as only standard scanning and reconstruction protocols (as used locally) were used. Therefore, in future studies, it would be of interest to assess the effects of fine-tuning reconstruction (and smoothing) settings to harmonize final images even further, i.e. to make sure they are comparable in terms of both spatial resolution and noise level.

References

1. Siekkinen R, Kirjavainen AK, Koskensalo K et al. Assessment of a digital and an analog PET/CT system for accurate myocardial perfusion imaging with a flow phantom. J Nucl Cardiol. 2021. https://doi.org/10.1007/s12350-021-02631-9

2. Danad I, Raijmakers PG, Driessen RS et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. JAMA Cardiol 2017; 2:1100-07

3. Araujo LI, Lammertsma AA, Rhodes CG et al. Noninvasive quantification of regional myocardial blood flow in coronary artery disease with oxygen-15-labeled carbon dioxide inhalation and positron emission tomography. Circulation 1991; 83:875-85

4. Nesterov SV, Han C, Maki M et al. Myocardial perfusion quantitation with ^{15}O-labelled water PET: High reproducibility of the new cardiac analysis software (Carimas). Eur J Nucl Med Mol Imaging 2009; 36:1594-02

5. Harms HJ, Knaapen P, de Haan S et al. Automatic generation of absolute myocardial blood flow images using [^{15}O]H$_2$O and a clinical PET/CT scanner. Eur J Nucl Med Mol Imaging 2011; 38:930-39

6. Lammertsma AA. Essentials of quantitative imaging with PET. In: Volterrani D, Erba PA, Carrió I, Strauss HW, Mariani G (eds) Nuclear medicine textbook: methodology and clinical applications, vol I. Springer Nature, Cham, 2019; pp 219-33

7. Lida H, Kanno I, Takahashi A et al. Measurement of absolute myocardial blood flow with H$_2$^{15}0 and dynamic positron-emission tomography: Strategy for quantification in relation to the partial volume effect. Circulation 1988; 78:104-15

8. Harms HJ, Nesterov SV, Han C et al. Comparison of clinical non-commercial tools for automated quantification of myocardial blood flow using oxygen-15-labelled water PET/CT. Eur Heart J Cardio-vasc Imaging 2014; 15:431-41