Cardiac ^{15}O -water PET: Does mismatched attenuation correction not matter?

Benjamin C. Lee, PhD^a

^a Dalio Institute of Cardiovascular Imaging, Weill Cornell Medicine/NewYork-Presbyterian, New York, NY

Received Feb 8, 2021; accepted Feb 8, 2021
doi:10.1007/s12350-021-02573-2

See related article, pp. 1119–1128

^{15}O -water positron emission tomography (PET) is considered the reference standard for non-invasive measurement of myocardial blood flow (MBF).^{1,2} However ^{15}O -water PET has no FDA approval and is not widely used clinically in Europe due to several factors including needing an onsite cyclotron access and requiring advanced image processing software. Specifically, ^{15}O -water is not retained in the myocardium and an equilibrium between the blood and tissue prevents direct generation of static uptake images.³ Visual interpretable images, however, can be generated either by digital subtraction of the blood pool from the tissue images or by voxel-wise parametric imaging of MBF.⁴ For this latter approach, a 1-tissue compartment model based on the clearance or wash-out rate that is proportional to MBF is employed.³

Attenuation correction (AC) recovers signals in soft tissue surrounded by dense structures and can increase diagnostic yield. Yet AC relies on proper coregistration of the computed tomography (CT) image to the PET image and if they are misaligned then quantification accuracy suffers. A CT image is often acquired as a snapshot prior to a respiration-averaged and post-stress PET acquisition, where these differences can introduce AC errors during image reconstruction.⁵ Attempts to correct respiratory motion errors have been made with external motion tracking devices and data-driven algorithms but many of these methods are too complicated to

be practical.⁴ Surprisingly, however, earlier work by Lubberink et al. showed that computation of MBF is possible without the need for attenuation correction for ^{15}O -water PET, owing to the fact that AC affects the overall amplitudes or scale of the time-activity curves and not their time-varying changes in amplitude or shape.⁶ This is because ^{15}O -water MBF quantification models the wash-in and wash-out rates and not the relative uptake in the myocardium.⁷ AC may not be essential for ^{15}O -water PET quantification of MBF, but no study to date has analyzed the effects of ^{15}O -water PET-CT misalignment on MBF when AC is applied. While AC errors have been studied in other PET tracers,^{8,9} the study reviewed here seeks to evaluate if the effects are the same for less used ^{15}O -water PET.

In the current issue of the Journal of Nuclear Cardiology, Nordström et al. investigated how CT attenuation map misalignment due to respiratory and patient body motion affects accuracy of flow characteristics in the myocardium using ^{15}O -water PET.¹⁰ Stress scans without PET-CT misalignment from 10 patients who were referred for ischemic evaluation were selected. Various motion directions (cranio-caudal, anterior, and lateral) and magnitudes (10 or 20 mm) were simulated and imposed uniformly across the dynamic sequence. Changes in global flow and flow in each of the LAD, LCX, and RCA vascular territories, compared to flows from aligned images, were observed. The clearance-based MBF was minimally affected with average global changes of 2% and average changes up to 6% in the vascular territories. These results of minimal impact on MBF from misaligned AC were concordant with prior results of not applying AC.⁶

However, these results differed in another measure of flow that Nordström et al. refer to as uptake-based transmural MBF (MBFt), which are comparable to the uptake rates measured by other PET tracers. The earlier clearance-based MBF using ^{15}O -water PET only reflected flow in perfusable tissue. To incorporate flow

Reprint requests: Benjamin C. Lee, PhD, Dalio Institute of Cardiovascular Imaging, Weill Cornell Medicine/NewYork-Presbyterian, New York, NY; bcl2004@med.cornell.edu

J Nucl Cardiol 2022;29:1129–31.

1071-3581/\$34.00

Copyright © 2021 American Society of Nuclear Cardiology.

in non-perfusible tissue like scar tissue, a perfusable tissue fraction (PTF) was calculated as a partial volume correction factor. Then the uptake-based MBFt was calculated as a product of the MBF and PTF normalized by the spillover coefficients of the LV and RV blood pools.² The advantage of using ^{15}O -water PET to compute both clearance-based MBF and uptake-based MBFt was the ability to measure both perfusion and viability with a single tracer. The uptake-based MBFt had greater changes with an average change of 5% globally and average changes up to 20% in the vascular territories, with the greatest changes in the LCX and LAD territories. The authors' rationale that the LAD and the LCX were affected more by being near the lung field versus the RCA was reasonable. It was noted that prior work showed ^{82}Rb PET-CT misalignment reported stress MBFt changes of 10% globally and up to 39% in 5-segment regions from 10 mm shifts in one study⁸ and up to 500% MBFt errors in 5-segment regions from 20 mm shifts in a different simulation study.⁹ While it may be surprising that clearance-based MBF was minimally affected by PET-CT misalignment compared to the uptake-based MBFt, the explanation was similar to not applying attenuation correction at all. Clearance-based MBF was not affected by the misalignment because it models the wash-in and wash-out rates rather than the relative myocardial uptake. This was found not to be the case for the uptake-based MBFt since the PTF used to calculate MBFt was more sensitive to AC errors.^{11,12}

The originality of this investigation was in the manner which the authors simulated movement. In future investigations, other methods of simulating movement may be considered in particular dynamic patient motion. Patient body motion occurs not only before the start of PET acquisition but also over the entire dynamic sequence. Due to myocardial creep and stressing-agent induced motion, particularly with adenosine as used in this study,^{13,14} the greatest motion occurs in the early frames within the first minute.¹⁵ A more clinically realistic PET-CT misalignment would be a time-varying misalignment occurring within the first minute of the dynamic sequence. Breaking the assumption of a constant misalignment, dynamic patient body movement would affect the shape of the time activity curves and thus flow estimates. Recent ^{82}Rb PET-CT misalignment studies showed frame-by-frame adjustment of attenuation maps were not necessary for accurate uptake-based MBFt quantification.^{16,17} While a prior ^{15}O -water study showed that inter-frame dynamic patient motion correction in fact had a significant change in clearance-based MBF,¹² it is an open question if frame-by-frame adjustment of attenuation maps are necessary for ^{15}O -water clearance-based MBF and uptake-based MBFt. In summary, an attractive aspect of

this other motion simulation is that it reflects what is often realistically observed in clinical scans.

Effects of PET-CT misalignment on myocardial flow reserve (MFR), the ratio of stress and rest MBF, were not studied due to the availability stress scans only as noted by Nordström et al. and also for reasons that stress MBF has been shown to be more accurate at detecting coronary artery disease than MFR for ^{15}O -water.^{18,19} Prior studies have shown that ^{15}O -water MFR estimates were unaffected by applying attenuation correction,^{6,7} yet the effect of attenuation map misalignment on MFR remain unexplored especially if calculating based on the uptake-based MBFt.

The authors have presented an interesting take on this technical issue of the unique effects of ^{15}O -water PET-CT misalignment on myocardial flow. So does this mean a mismatched attenuation correction does not matter for cardiac ^{15}O -water PET? For clearance-based MBF it seems to be that way. However, certainly more work is needed to better understand the uptake-based flow characteristics between ^{15}O -water and more commonly used tracers, particularly as it relates to AC. Though if the field continues to demonstrate ^{15}O -water imaging does not need further processing like AC, we may realize wider-spread use of ^{15}O -water.

References

1. Bergmann S, Fox K, Rand A, McElvany K, Welch M, Markham J, et al. Quantification of regional myocardial blood flow in vivo with H215O. *Circulation*. 1984;70:724-33. <https://doi.org/10.1161/01.CIR.70.4.724>.
2. Bol A, Melin JA, Vanoverschelde JL, Baudhuin T, Vogelaers D, De Pauw M, et al. Direct comparison of [^{13}N]ammonia and [^{15}O]water estimates of perfusion with quantification of regional myocardial blood flow by microspheres. *Circulation*. 1993;87:512-25. <https://doi.org/10.1161/01.CIR.87.2.512>.
3. Iida H, Kanno I, Takahashi A, Miura S, Murakami M, Takahashi K, et al. Measurement of absolute myocardial blood flow with H215O and dynamic positron-emission tomography. Strategy for quantification in relation to the partial-volume effect. *Circulation*. 1988;78:104-15. <https://doi.org/10.1161/01.CIR.78.1.104>.
4. Sciarra R, Lubberink M, Hyafil F, Saraste A, Slart RHJA, Agostini D, et al. EANM procedural guidelines for PET/CT quantitative myocardial perfusion imaging. *Eur J Nucl Med Mol Imaging*. 2020. <https://doi.org/10.1007/s00259-020-05046-9>.
5. Souvatzoglou M, Bengel F, Busch R, Kruschke C, Fernolendt H, Lee D, et al. Attenuation correction in cardiac PET/CT with three different CT protocols: A comparison with conventional PET. *Eur J Nucl Med Mol Imaging*. 2007;34:1991-2000. <https://doi.org/10.1007/s00259-007-0492-4>.
6. Lubberink M, Harms HJ, Halbmeijer R, de Haan S, Knaapen P, Lammertsma AA, et al. Low-dose quantitative myocardial blood flow imaging using ^{15}O -water and PET without attenuation correction. *J Nucl Med*. 2010;51:575-80. <https://doi.org/10.2967/jnumed.109.070748>.
7. Tuffier S, Legallois D, Belin A, Joubert M, Bailliez A, Redonnet M, et al. Assessment of endothelial function and myocardial flow

- reserve using ¹⁵O-water PET without attenuation correction. *Eur J Nucl Med Mol Imaging*. 2016;43:288-95. <https://doi.org/10.1007/s00259-015-3163-x>.
8. Rajaram M, Tahari AK, Lee AH, Lodge MA, Tsui B, Nekolla S, et al. Cardiac PET/CT misregistration causes significant changes in estimated myocardial blood flow. *J Nucl Med*. 2013;54:50-4. <https://doi.org/10.2967/jnumed.112.108183>.
 9. Hunter CRRN, Klein R, Beanlands RS, deKemp RA. Patient motion effects on the quantification of regional myocardial blood flow with dynamic PET imaging: Patient motion effects on regional myocardial blood flow. *Med Phys*. 2016;43:1829-40. <https://doi.org/10.1118/1.4943565>.
 10. Nordström J, Harms HJ, Kero T, Ebrahimi M, Sörensen J, Lubberink M, et al. Effect of PET-CT misalignment on the quantitative accuracy of cardiac ¹⁵O-water PET. *J Nucl Cardiol*. 2020. <https://doi.org/10.1007/s12350-020-02408-6>.
 11. Hirano Y, Koshino K, Watabe H, Fukushima K, Iida H. Monte Carlo estimation of scatter effects on quantitative myocardial blood flow and perfusable tissue fraction using 3D-PET and ¹⁵O-water. *Phys Med Biol*. 2012;57:7481-92. <https://doi.org/10.1088/0031-9155/57/22/7481>.
 12. Koshino K, Watabe H, Enmi J, Hirano Y, Zeniya T, Hasegawa S, et al. Effects of patient movement on measurements of myocardial blood flow and viability in resting ¹⁵O-water PET studies. *J Nucl Cardiol*. 2012;19:524-33. <https://doi.org/10.1007/s12350-012-9522-0>.
 13. Naum A, Laaksonen MS, Tuunanen H, Oikonen V, Teräs M, Kemppainen J, et al. Motion detection and correction for dynamic ¹⁵O-water myocardial perfusion PET studies. *Eur J Nucl Med Mol Imaging*. 2005;32:1378-83. <https://doi.org/10.1007/s00259-005-1846-4>.
 14. Memmott MJ, Tonge CM, Saint KJ, Arumugam P. Impact of pharmacological stress agent on patient motion during rubidium-82 myocardial perfusion PET/CT. *J Nucl Cardiol*. 2017. <https://doi.org/10.1007/s12350-016-0767-x>.
 15. Lee BC, Moody JB, Poitrasson-Rivière A, Melvin AC, Weinberg RL, Corbett JR, et al. Blood pool and tissue phase patient motion effects on ⁸²rubidium PET myocardial blood flow quantification. *J Nucl Cardiol*. 2018. <https://doi.org/10.1007/s12350-018-1256-1>.
 16. van Dijk JD, Jager PL, Ottervanger JP, Slump CH, van Dalen JA. No need for frame-wise attenuation correction in dynamic Rubidium-82 PET for myocardial blood flow quantification. *J Nucl Cardiol*. 2019;26:738-45. <https://doi.org/10.1007/s12350-019-01654-7>.
 17. Armstrong IS, Memmott MJ, Saint KJ, Saillant A, Hayden C, Arumugam P. Assessment of motion correction in dynamic rubidium-82 cardiac PET with and without frame-by-frame adjustment of attenuation maps for calculation of myocardial blood flow. *J Nucl Cardiol*. 2019. <https://doi.org/10.1007/s12350-019-01834-5>.
 18. Kajander S, Joutsiniemi E, Saraste M, Pietilä M, Ukkonen H, Saraste A, et al. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. *Circulation*. 2010;122:603-13. <https://doi.org/10.1161/CIRCULATIONAHA.109.915009>.
 19. Danad I, Raijmakers PG, Appelman YE, Harms HJ, de Haan S, van den Oever MLP, et al. Hybrid imaging using quantitative ¹⁵O PET and CT-based coronary angiography for the detection of coronary artery disease. *J Nucl Med*. 2013;54:55-63. <https://doi.org/10.2967/jnumed.112.104687>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.