Simplified quantification of PET myocardial blood flow: The need for technical standardization

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Noninvasive estimation of absolute myocardial blood flow (MBF) by positron emission tomography (PET) has a long history in clinical imaging.^{1–3} Many different flow models have been developed over the years,^{4–10} which have prompted numerous model comparison studies.^{11–13} In recent years, several of these validated flow models have now been implemented in a new generation of software applications.^{14–18} Thus, the focus has gradually shifted from development and validation of flow models to implementation and wider dissemination of clinical tools for MBF estimation in routine patient care. This new focus has emphasized the pressing need for technical standardization.

In this issue, the study of Chang et al¹⁹ continues this trend. The authors compared ¹³N-ammonia MBF quantification using two previously validated MBF models provided by two FDA-approved commercial software packages: the simplified retention model⁸ implemented in *HeartSee* (University of Texas, Houston), and compartmental modeling with the two-tissue model⁵ implemented in *syngoMBF* (Siemens Healthineers). The authors' aims were to validate the retention

model for ¹³N-ammonia cardiac PET/CT with the compartmental modeling serving as a reference standard, and to establish normal MBF reference values using the shorter retention model PET protocol.

The HeartSee software used in this study was developed at Dr K.L. Gould's lab at the University of Texas, which may be considered the reference implementation of the simplified retention model.^{8,14} The retention model has also been implemented in other academic and commercial software packages, including *FlowQuant* (Ottawa Heart), *ImagenQ* (CVIT), *MunichHeart* (Technical University of Munich), and *4DM* (INVIA). Since the 1990s, several research groups have performed detailed validation studies of the retention model for both ¹³N-ammonia^{6–8} and ⁸²Rb.^{8,20} The major advantage of the retention model for clinical measurement of MBF is the simplified PET protocol and greatly reduced computing demands for image reconstruction and processing compared with compartmental modeling. The retention model trades flexibility for simplicity and efficiency, which, for earlier generations of clinical PET scanners, addressed the inherent technological limitations that made dynamic PET and full compartmental modeling impractical for routine use.^{8,21} Another important potential advantage of the retention model is reduced variability of the MBF estimates^{22,23} at the expense of increased bias due to the use of approximations and fixed correction factors.⁸ In routine clinical applications, utility is very often determined by physiological and methodological variability rather than systematic error (bias).

There are three primary limitations of the retention model. First, the model assumes that tracer taken up by the myocardium is irreversibly trapped and does not subsequently wash out.⁸ This approximation is

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sufficiently accurate for normally perfused, viable myocytes, but in practice, tracer washout may occur in the presence of severe ischemia or non-transmural scar.^{8,24} Our own recent work has demonstrated that ⁸²Rb washout can in fact be used to reliably assess myocardial viability in ischemic cardiomyopathy patients.²⁵

Second, the retention model assumes that the entire integrated arterial input function can be captured during the initial fixed two-minute blood pool image, which may be inaccurate in cases with low cardiac function, or when physiological delay of the initial tracer bolus is exacerbated by the lack of a saline flush in the infusion system.²⁶ A hybrid approach²⁷ which largely overcomes this limitation (when list-mode acquisition is available on the PET scanner) consists in performing preliminary image reconstructions of short dynamic frames during the blood pool phase to determine the time course of activity in the left ventricle, and then summing the appropriate dynamic images to generate the integrated arterial input image. Although this procedure undermines the simplicity of the retention model, it can largely be automated, and additionally provides the opportunity to perform motion correction between dynamic frames during this crucial period of the PET acquisition.²⁸

Finally, the retention model requires partial volume-correction factors which must generally be determined locally by phantom scans for each PET scanner and radionuclide.⁸ Previous determinations have been described for ⁸²Rb and ¹³N-ammonia for the University of Texas cesium-fluoride PET scanner,⁸ and for ⁸²Rb and ¹⁸F for the BGO-based GE Discovery ST PET/CT scanner.²⁹ In the present study,¹⁹ although the manufacturer was noted (GE Healthcare), the PET scanner model was not reported, and the authors did not report the determination of partial volume-correction factors appropriate for their PET scanner or for ¹³N-ammonia, although partial volume corrections were performed by the HeartSee software.¹⁹ It is common that the same fixed partial volume-correction factors are used for all patients, assuming a mean diastolic wall thickness of 1 cm, which may become inaccurate at the extremes of very thin or very thick myocardial walls. This could be improved by utilizing patient-specific correction factors,²⁹ but again this may reduce the simplicity and appeal of the retention model.

Does the retention model continue to offer advantages today? The retention model was primarily developed and utilized on 2D PET scanners,^{6,7,14,20} and may still be preferred or necessary in the case of older BGO-based PET-only and PET/CT scanners without list-mode capabilities. Some remanufactured 2D systems have now added list-mode features, and for such systems, the retention model with modifications

mentioned above may offer some advantages over full compartmental modeling. However, all contemporary 3D PET/CT scanners have list-mode capabilities, and newer tracer delivery systems and clinical software have largely mitigated the technical challenges that previously limited the role of routine compartmental modeling and MBF estimation in the clinic.

Finally, did Chang et al¹⁹ achieve their stated aims in this study? The mean flows are consistent with values from the literature (see Ref. ³⁰ online appendix). However, it is necessary to consider the methodological variability of each approach to determine whether the MBF estimates from the two models are “close enough.” The short-term repeatability (within minutes) of the retention model (in terms of the 95% repeatability coefficient, RPC) has only been reported for Rb-82 (15–20%),^{22,23} while the 95% RPC of compartmental modeling is 20% for ¹³N-ammonia.³¹ Considering the global flow estimates in Figure 1 of Ref. ¹⁹, and using 95% RPC limits of $\pm 20\%$, we find that 27% of rest scans and 32% of stress scans were beyond these limits (Figure 1), suggesting a notable lack of agreement in as many as one-third of patients studied. Possible reasons for this disagreement might be the possible use of incorrect partial volume-correction factors in the retention model, or that metabolite correction was performed for the retention model but not for the compartmental model, which could lead to MBF underestimation by 5–10%.^{5,32} Moreover, regarding clinical efficiency, it is noteworthy that validation^{5,33} of the compartmental model used by Chang et al¹⁹ was originally demonstrated with PET

Figure 1. Bland-Altman global left ventricular flow data from Figure 1b of reference,¹⁹ replotted with 95% repeatability limits (RPC $\pm 20\%$, dashed lines).^{22,23,31} R-flow Simplified retention model, C-flow compartment model. 27% of rest scans and 32% of stress scans were outside the 95% repeatability limits.

scan durations of only 10 min (rather than the 16 min used here), and there are other validated compartmental models available for ^{13}N -ammonia that require even shorter durations.^{12,13}

If the underlying goal is local implementation of reliable, routine clinical MBF measurement, Chang et al may be on the right track, but we must conclude that additional protocol optimization may be necessary. The difficulty is not a lack of tools, but a lack of technical standardization. The implementation process could be made truly simpler if all stakeholders engaged collaboratively to develop technical standards for MBF quantification that will ultimately bring quantifiable clinical value and tangible benefits for patient care.

Disclosure

J.B. Moody is an employee of INVIA. E.P. Ficaro is a stockholder of INVIA, which produces 4DM, a clinical software package for cardiac PET analysis. V.L. Murthy owns stock in General Electric and Cardinal Health and stock options in Ionetix. He has received consulting fees from Ionetix and Jubilant DraxImage. He has received grant funding from Siemens Medical Imaging. He has further received funding under #Grant R01HL136685 from the National Heart, Lung, and Blood Institute; and Grant #R01AG059729 from the National Institute on Aging.

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