EDITORIAL

Accounting for residual activity in the estimate of myocardial blood flow with PET

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Estimation of myocardial blood flow (MBF) has many positives for patient care but the data collection and computation of flow are difficult to do well. The technical challenges of dynamic PET imaging for flow are many and may depend on the radiotracer employed,[1] administration method,[2] stress protocol,[3] settings of the imaging system,[4] motion management,[5] and choice of kinetic model.[6] The ideal radiotracer should have a high first-pass extraction that is not dependent on flow. A non-linear dependence leading to a roll-off in extraction at high flows, particularly for [Rb-82] chloride, puts further pressure on the user to ensure technical factors and corrections are accurate to avoid unintentionally amplifying measurement bias. Secondly, the radioactive label must have a sufficiently long half-life such that the radiotracer equilibrates or is trapped in the myocardium with sufficient counts to achieve good image quality and contrast compared with blood pool. Historically, clinical determination of MBF with PET has been limited to two radiotracers with markedly different extraction fractions and half-lives as well as their own logistical challenges in obtaining the agents.

[Rb-82] chloride has the shortest half-life with the convenience of being on-demand from a generator. These two advantages permit a rest/stress exam to be conducted in rapid succession. At the end of the rest study, nearly all activity from the administration has decayed leaving a ''clean'' patient state for the stress administration. However, other challenges remain such as the need to administer relatively high amounts of radioactivity such that sufficient counts are collected following blood pool clearance.[7] [N-13] Ammonia has a higher extraction than [Rb-82] chloride, particularly at high flows, and a longer half-life resulting in improved count statistics. The major barrier with [N-13] ammonia is the need for a cyclotron to be within a reasonable distance to produce individual or bulk doses sufficient for a rest and stress exam. [N-13] ammonia may also be conducted in short succession although the logistics of timing the delivery of [N-13] ammonia tends to introduce delays, particularly if individual doses are arriving between rest and stress studies. This may be overcome in part with a dedicated N-13 production system[8] but with the caveat that when the delay between rest and stress administrations shortens, radioactivity may be present in the heart from the previous administration. Finally, the initial reporting of [F-18] flurpiridaz has been encouraging given its high extraction at high flows and long half-life that effectively de-couples the user from the costs and management of the radioisotope production pipeline and permits the shipment of single doses. Although this could be a benefit to wider clinical use of MBF, the consequence is that meaningful amounts of radioactivity from the rest administration will be remaining in the myocardium during the stress administration. Thankfully, quantifying repeated administration of long-lived perfusion radiotracers has a breadth of literature support and techniques developed for 1-day [Tc-99m] sestamibi have been adopted in the processing of same-day [F-18] flurpiridaz.[9,10] What remains to be answered is how a same-day protocol, where residual radioactivity remains in the myocardium, impacts the calculation of myocardial blood flow?

To address this question, we can start with reviewing the kinetic model assumptions. Of the numerous approaches available to estimate MBF, all fall

into two primary categories: (1) a first-pass model that includes a reversible compartment and (2) a retention model (e.g., microsphere analog). The latter is the most simplistic in implementation and has been proposed for [F-18] flurpiridaz[11] while the former is typically employed for [Rb-82] chloride and [N-13] ammonia[12,13] but not in all cases.[14,15] What's important to note is that all model approaches share one common assumption, there is no radioactivity in the system at the time of radiotracer administration. In the cases described above for successive administration of [N-13] ammonia or [F-18] flurpiridaz, blood pool radioactivity concentrations are typically negligible at the time of second administration; however, substantial radioactivity may remain in the myocardium.[16,17]

To understand the magnitude of residual activity on MBF, we propose a simple simulation consisting of two successive radiotracer administrations of the same amount. Figure. 1A displays a decay-corrected flow curve from the first administration with no prior radioactivity in the system and the computed flow values using a first pass and a retention model. In Figure 1B, 20% of the radioactivity that perfused the heart in the first administration remains in the myocardium at the time of the second administration and the flow values are recomputed. When comparing the scenarios in Figure 1A and B we find that there is roughly a 19-21% increase in MBF for the second administration. Therefore, when residual activity is on-board in the myocardium, the calculation of MBF will be biased high and this result is a consequence of the modeling assumption that the system's initial state has no activity, which is violated in Figure 1B.

The experimental support to the hypothesis that residual radioactivity in the myocardium biases MBF is presented by Poitrasson-Riviere et al.[18] for the two flow agents, [N-13] ammonia, and [F-18] flurpiridaz. Their team expertly demonstrate that residual radioactivity in the myocardium leads to an upward bias in the calculation of MBF and this bias increases with higher residual radioactivity on-board (see Figure 2a and b in Ref. 18). Their proposed solution is to measure the residual activity in the heart by collecting data a few minutes prior to the second radiotracer administration. The residual radioactivity is then subtracted from the myocardial tissue regions of interest prior to the post-processing of the second scan. This practical approach adds negligible complexity to the dynamic PET protocol and preserves the assumptions of the kinetic model. Furthermore, Poitrasson-Riviere and colleagues provide Figure 1B to assist the reader in design of their protocol that includes (1) how the time delay between the rest and stress administrations relates to overestimation of MBF and (2) how increasing the amount of activity administered at stress compared to rest can reduce overestimation in MBF.

Given the large number of challenges to estimating MBF with PET, Poitrasson-Riviere et al.[18] have provided a straightforward approach to manage the problem of residual radioactivity. With the anticipation of [F-18] flurpiridaz entering the clinic, this agent along with centers implementing [N-13] ammonia imaging with short delays should carefully scrutinize their image processing tools and software purchases for features that account for residual activity. As demonstrated by the authors, it will be important how the administration
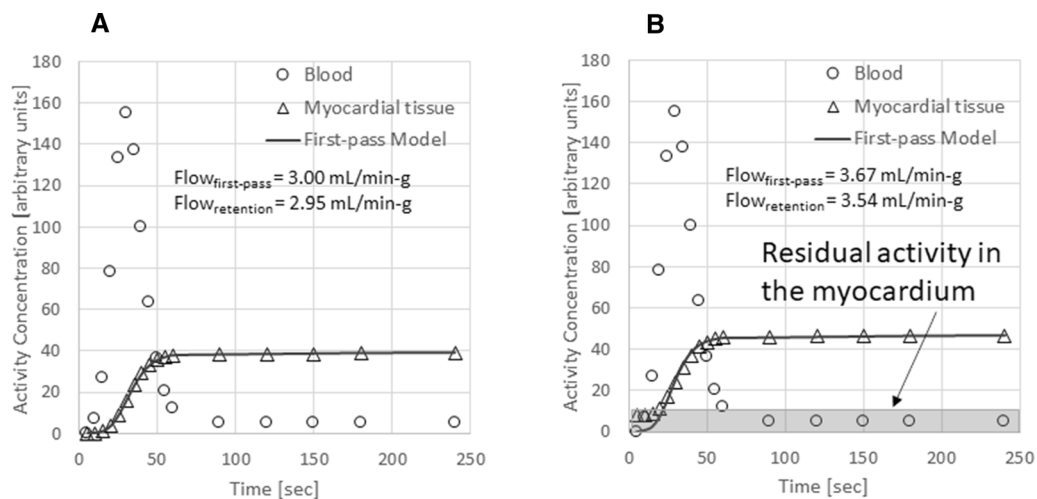
Figure 1. A simulation of flow with (**A**) no residual activity on-board and (**B**) 20% residual activity in the myocardium as indicated by the shaded area. The calculated flow values for each case are presented for first pass and retention models.

protocol is setup and how residual activity is addressed in post-processing to ensure the best accuracy and precision in calculation of MBF.

Disclosures

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