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EDITORIAL COMMENT

How Close Is Close Enough?*

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In this issue of *iJACC*, Nesterov et al. (1) report on a multicenter clinical trial (RUBY-10) designed to determine the extent to which 10 different "software packages" (SPs) agreed in measurements of absolute values of rest and adenosine stress myocardial blood flow (MBF) and flow reserve (MFR). The SPs were applied to a common set of positron emission tomography (PET) rubidium 82 (^{82}Rb) data. Each of 10 sites used its own SP for MBF determinations. PET data were acquired at University Hospital, Lausanne, which performed image reconstruction. The study population consisted of 48 patients with known (~50%) or suspected coronary artery disease.

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Output of the SPs agreed "if they simultaneously had an intraclass correlation coefficient (ICC) >0.75 and a difference <20% of the median across all programs." The number of pairwise and other relevant comparisons is enormous, and the authors are to be commended for development of Figures 1 and 2, which provided an excellent visual representation of a very complex data analysis (1). Although it is readily apparent from Figure 1 that wide differences both in rest and stress MBF (and hence MFR) resulted from different SPs applied to the same dataset, the authors focus on Figure 2 which shows results from 8 SPs that used a single-tissue compartment tracer model (1-TCM) (Lortie et al. [2]). The results from 1 SP (retention model of Yoshida et al. [3]) were judged outliers, and those of the other 7 satisfied the prespecified conditions for agreement. Accordingly, the authors conclude any of the 7 SP implementations of the 1-TCM may be used "interchangeably to process data acquired with a common imaging protocol."

Another goal was to "analyze the current situation in ^{82}Rb PET quantification to help establish common and robust methods to support collaborative multicenter clinical trials." Such trials, of course, would send PET data to a core laboratory for processing and analysis. The present study, although exploratory, did exactly the opposite. Given the differing modeling approaches that each "black box" used for determining crucial factors such as arterial input function, spill over, and partial volume corrections and dependence of ^{82}Rb myocardial uptake on MBF, it is unsurprising that MBF values differed, in some comparisons considerably. Thus, the reader may ask: 1) how great a difference between SP results is acceptable; and 2) if SP output differs, which (if either or among many) is correct?

The authors address the first question by noting that test-retest reproducibility is ±20% (4). However, Efseaff et al. (4) considered only rest MBF and tested multiple methods for image reconstruction, each of which provided different values of MBF and reproducibility. Ultimately, an OSEM method was used and rest MBF data normalized to rate-pressure product (not done in the present study) to obtain the ±20% result. Whether the OSEM parameters and other methods used to acquire and reconstruct the images at Lausanne (1) were exactly the same as those used in Ottawa (4) is not stated but obviously matters. Then, too, there is the physiology and what acceptance of ±20% means regarding both rest but more importantly stress MBF. Figure 2 (present study [1]) shows for each major coronary vascular territory the green zone (±20%) for stress MBF encompasses ±0.40 ml/min/g and similar spread for MFR (unit less). Further, any given SP may have data points on both sides of the zero difference point. Thus, the full range of observed variation for a given program was as much 0.8 ml/min/g for stress MBF and MFR. Given that an ischemia threshold of just 0.91 ml/min/g has been demonstrated for ^{82}Rb PET and dipyridamole stress (5,6), "agreement" among SPs that may vary by nearly 50% of that level is unacceptably high and carries the risk of misclassifying a great many patients.

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The authors address the second question by acknowledging the most important limitation of their study—the absence of a gold standard by which to judge the accuracy of each SP. It is entirely possible that one of the outlier SPs was most accurate. Thus, the tissue retention model of Yoshida et al. (3), incorporated in a version employed by the Cardiovascular Imaging Technologies (CVIT) group and in part in the 1-TCM model of El Fakhri et al. (7), was found to differ notably (CVIT group greater than that of El Fakhri et al. [7]) from the 7 SPs using some version of Lortie 1-TCM (2). The retention model of Lautamaki et al. (8) that was used by the Munich group was virtually identical to that of Yoshida et al. (3) and also was an outlier. Although all 3 models have objective data to support them, the study of Lortie et al. (2) was validated in human subjects with ^{13}N-ammonia as the gold standard. In contrast, Yoshida et al. (3) and Lautamaki et al. (8) both made direct measurements in closed chest canine models either by comparing PET ^{82}Rb coronary flow reserve with that of coronary flow reserve by electromagnetic flow meter (3) or with microspheres values of MBF (8). Accordingly, the retention models may provide more accurate measurements of absolute MBF than that of 1-TCM. The Yoshida et al. (3) model also is the only one for which quantitative measurements of absolute MBF with PET ^{82}Rb and dipyridamole stress and objective indicators of ischemia (not percent of stenosis or fractional flow reserve) has been used to define a level of MBF (0.91 ml/min/g) below which actual ischemia is likely to occur (5,6). Thus, the importance of getting the absolute value of stress MBF correct is underscored not only by the data of Johnson and Gould (5,6) but also by the fact that the level of the ischemic threshold for exercise stress likely is higher, because 40% of those with "definite ischemia" reported by Johnson and Gould exhibited coronary steal with dipyridamole (5), and data from several experiments in which increased myocardial oxygen demand is involved indicate the ischemia threshold more likely is in the range of 2 to 3 ml/min/g (9–11).

Accordingly, take-away points for those using PET ^{82}Rb for quantitative measurements of absolute MBF are as follows. First, caveat emptor, the SP used to obtain absolute MBF matters and ±20% especially for the stress study translates into differences in absolute MBF that are too large to accept as "interchangeable." A core laboratory for a clinical trial naturally would use only 1 SP, but readers will want to know which one, an important contribution of the paper.

Second, which SP(s) provides accurate absolute values of MBF obviously matters. Although 1-TCM's and retention models have validation data, animal experiments (3,8) associated with retention SPs are more robust and may be more accurate. In any case, absolute values of MBF obtained with reported SPs (including that of 1-TCM) are neither necessarily equivalent nor "interchangeable" from a physiological standpoint, another very valuable contribution of the current paper.

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