Motion correction to enhance absolute myocardial blood flow quantitation by PET

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In this issue of the *Journal of Nuclear Cardiology,* Poitrasson-Rivière et al propose that automated motion correction followed by technologist manual adjustment reduces inter-user variability in the assessment of positron-emission tomography (PET)-derived absolute myocardial blood flow (MBF) and myocardial flow reserve (MFR).[1] We will highlight the importance of PET MFR assessment, provide an overview of issues related to motion and suggested corrections, discuss essential features of the article, and propose future directions.

Coronary vasodilator function in patients with or without epicardial coronary artery disease (CAD) has been demonstrated to carry significant incremental and independent prognostic significance,[2] with correct reclassification of ~ 1/3 of intermediate-risk patients into low- and high-risk cardiovascular mortality groups.[3] A similar strong improvement in prognosis has been determined in key subgroup analyses. For example, among diabetic patients without significant epicardial CAD, impaired MFR was associated with mortality rates comparable to those with prior CAD.[4] Conversely, diabetics with preserved MFR have event rates comparable to those of nondiabetics.[4] Similar observations highlighting the importance of PET-derived MFR were made in end-stage renal disease patients who are dialysis-dependent.[5] Importantly, increased risk of cardiovascular death and non-fatal myocardial infarction in women is independently associated with impaired MFR, representing a physiological risk less amenable to revascularization.[6] In addition to its prognostic utility, impaired MFR in symptomatic patients without overt coronary artery disease has been associated with diastolic dysfunction and heart failure hospitalization.[7] Beyond prognostic risk stratification, initial retrospective work suggests that patients with a low MFR may benefit from early revascularization.[8,9] Moreover, among obese patients, MFR may identify higher-risk patients more likely to benefit from bariatric surgery than lower-risk patients.[10] In aggregate, impaired MFR, particularly absent severely obstructive CAD, is of recognized clinical value and may represent a novel target for cardiovascular disease risk reduction. However, prospective validation of these observations is critically needed.

Societal guidelines by the American Society of Nuclear Cardiology (ASNC)[11] and the Society of Nuclear Medicine and Molecular Imaging (SNMMI)[12] on the quantitation of MBF by PET underscore the importance of motion detection to decrease the occurrence of significant artifacts. Motion can be due to frank patient motion, cardiac motion, and/or respiratory motion, necessitating rigorous quality control of the time-activity curves prior to data analysis and interpretation.[13] Indeed, motion artifacts are recognized as significant contributors to MBF and MFR inaccuracy.[13] Gross patient motion will result in misregistration of transmission and emission data, leading to inaccurate time-activity curves and MBF quantitation.[13,14] The patient's position should be maintained between the

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transmission and emission scans, particularly during hyperemic stress, to decrease errors in MBF quantitation.[14,15] Although 'upward creep' was originally used to describe artifacts resulting from the upward movement of the heart seen in SPECT studies during recovery from exhaustive physical exercise,[16] we have observed movement of the heart in other directions as well.[17] We have described this occurrence as 'myocardial creep' to refer to the heart drift which is common during pharmacological stress[17] and may occur in ~ 50% of cases.[18] 'Myocardial creep' is most likely due to diaphragmatic/breathing changes occurring as a side effect of pharmacological vasodilation and represents an additional source of motion-based artifact.[17] In addition to patient and/or cardiac motion correction, further enhancement of cardiac PET imaging may be achieved by respiratory motion correction.[19,20] Application of a continuous motion correction algorithm in dynamic studies has been proposed to decrease artifacts ensuing from respiratory motion.[21]

Motion-degraded images are not simply accurate images that have shifted to another position. At the very least the resolution will be degraded. Moreover, there could be multiple images, as well as induced artifacts from mismatched attenuation data as described above. We also believe that most patient-technologist teams recognize these complications and work together to have the highest quality images. Hence, most motion is likely not frank patient motion, but myocardial creep induced by the pharmacologic stressor. Evidence supporting this is the far greater fraction of stress studies containing motion than rest studies.[22,23] Proper reconstruction of images when the heart has shifted with respect to the attenuating organs is non-trivial.

Current efforts are aimed toward aligning the reconstructed images as well as possible in the hope that this will lead to more accurate MBF estimates, even if the images contain artifacts due to movement. It is important to note that although motion detection can be corrected manually, it is subject to operator bias.[24] In this setting, automated motion correction algorithms have been proposed. Automated patient motion correction of dynamic PET frames using an image-based registration scheme was proposed to improve quantitation of MBF.[25] Previously, Poitrasson-Rivière et al introduced an automated algorithm localizing the left and right ventricular blood pools in 4-D, with registration of each frame to a tissue reference image volume using normalized gradient fields.[22] This image-based, automated motion correction algorithm using normalized gradient fields applied to dynamic PET sequences matched the results of manual motion correction, reducing bias and variance in MBF and MFR.[22]

It is also important to realize that motion correction must be practical in the clinical setting. Manual correction consists of separately aligning up to 15 frames to a standard frame. Typically, the user translates and rotates a nonstandard frame with mouse movements or arrow presses until the two frames are judged to be in alignment. The correction usually needs a 3D adjustment, and determining when two images are aligned is difficult. It can only be done by evaluation from several points of view. The process is time consuming even for well-trained and experienced technologists. We thus agree with the investigators that an automated solution is required for adoption into clinical practice. Future work will attempt to reconstruct with proper attenuation correction and remove any blur from motion contaminated images.

The authors performed a trial to evaluate whether automatic motion correction reduces inter-user variability in quantification of MBF. We underscore that if the technologists did nothing after the automatic motion correction, then their results (Figs. 1c and 2c) would show a perfect correlation. On the other hand, if the human experts are the gold standard, then the initial alignments of the images should not matter—the users will just make alternate adjustments to arrive at the same solution. But this did not happen, manual alignment after automatic alignment resulted in reduced variability (compare Fig. 1a–c). The authors' results imply that the technologists' judgement of a good alignment is influenced by the initial alignment of the images. In this minimization protocol, it appears that the human users can get trapped in local minima.

The scientific question that remains unanswered is the appropriate validation tool, or reference standard, to establish the clinical value of motion correction algorithms. A gold standard for human MBF studies does not exist. Percent stenosis by invasive coronary angiography is known to be an inadequate reference standard for the physiological assessment of CAD by PET MFR.[26] Fractional flow reserve, although used in routine clinical practice, has a non-linear, triangle-shaped relationship with PET MFR.[27] Further, whereas coronary flow reserve using intravascular Doppler correlates with PET findings,[28] this technique is subject to variability[29] and no longer favored in the catheterization laboratory. The ideal validation would be a large clinical study where risk stratification according to major adverse cardiovascular events such as death or myocardial infarction—with and without automated alignment correction of PET MFR—is compared. Short of that, what intermediate steps can be taken? We recognize that this is an evolving discipline. We propose the field adopts a test-retest strategy, ideally obtaining PET MBF studies on successive days,[30–32] to assess the reproducibility of

MBF and the potential benefit of motion correction algorithms. Automated alignment and correction algorithms that reduce the test-retest variability the most would be excellent candidates for further evaluation. We urge the field as a whole to collaboratively produce an open-source database of test-retest PET MBF studies that different research groups can use to develop their methods and test their approaches.

Disclosures

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