Supplemental Data

Abbreviations:

AC – attenuation correction

AI – artificial intelligence

CA – cardiac amyloidosis

CAD – coronary artery disease

CCTA – coronary computed tomography angiography

CFR – coronary flow reserve

CRT – cardiac resynchronization therapy

CS – cardiac sarcoidosis

DL – deep learning

EDV – end-diastolic volume

ESV – end-systolic volume

ERNA – equilibrium radionuclide angiography

FPRNA – First pass radionuclide angiography

LV – left ventricle

MBF – myocardial blood flow

ML – machine learning

MFR – myocardial flow reserve

MPI – myocardial perfusion imaging

OMC – onset of mechanical contraction

OMR – onset of mechanical relaxation

PET – positron emission tomography

RFR – relative myocardial flow reserve

ROI – region of interest

RNA – radionuclide angiography

RV – right ventricle

SD – standard deviation

SPECT – single photon emission computed tomography

TAC – time-activity curve

Motion-corrected quantification of relative perfusion

Cardiac gating during SPECT MPI acquisition was initially implemented to facilitate assessment of cardiac function. Perfusion quantitation was originally performed with ungated data, but assessment of gated images may be useful in specific situations. Visual interpretation of end-diastolic images may improve detection of CAD in patients with small end-systolic volume, identifying more ischemic defects compared to summed images, as shown in a prospective study of 53 female patients (*1*). Quantitative analysis of perfusion in patients with left bundle branch block is characterized by lower radiotracer counts in the septum compared to the lateral wall in end-systolic, but not end-diastolic images (*2*). This suggests that left bundle branch block perfusion defects are at least partially related to decreased wall thickening. A cardiac “motion-frozen” quantification technique, can be implemented to automatically generate images similar to end-diastolic images, but utilizing several gated frames in order to decrease image noise (*3*). This technique is accomplished through motion tracking of the LV endocardial and epicardial borders, applying non-linear image warping in each phase to match the position of the end-diastolic phase. Suzuki et al. demonstrated improved prediction of obstructive disease in obese patients with this technique compared to summed images (AUC 0.93 vs 0.88) (*4*).

In addition to cardiac motion, respiratory and patient motion can negatively impact MPI quantification. Respiratory gating of MPI improves assessment of LV function, demonstrating higher correlation with echocardiography after respiratory motion correction (*5*). Respiratory gating also leads to significant differences in assessment of LV volumes and regional wall motion (*6*). A method for dual "motion-frozen" imaging, including both respiratory and cardiac motion correction, significantly improves image quality compared to cardiac or respiratory corrections in isolation (*7,8*). While robust motion correction improves quality, it remains to be shown that it significantly diagnostic accuracy or risk stratification in routine clinical use.

Dynamic motion correction for MBF quantification

Similar to perfusion quantification, cardiac, respiratory, and gross patient motion can be a significant source of MBF error(*9*). Two types of motion correction have been applied to dynamic imaging: 1) reconstruction-based, which uses sinograms or list-mode events to correct periodic motion (respiratory and/or cardiac) during image reconstruction(*10*); and 2) image-based, which corrects frame-to-frame gross patient (and, to a limited extent, respiratory) motion by registering each frame relative to a reference frame, typically a summed static uptake image after tracer clearance from blood (*9*). For image-based correction, it is particularly important to apply the correction over the entire dynamic sequence, including the blood pool phase(*9*), as localization of the LV myocardium and blood pool TACs from the early frames is key for MBF accuracy(*11*,*12,13*,*14*). Such a method for automated motion correction was recently

introduced (*14*) which was shown to decrease MBF variability while substantially improving dynamic PET processing efficiency (*15*). Frame-to-frame correction of the corresponding shifts in the underlying attenuation maps however does not appear to be necessary (*16*).

Phase analysis to measure left ventricular diastolic dyssynchrony

In addition to systolic dyssynchrony, LV *diastolic* dyssynchrony can also be quantified from gated myocardial studies. In this case, regional time delays in the onset of mechanical relaxation (OMR) over the LV myocardium are measured (*17*). Phase analysis to measure OMR uses the same principles as those used to measure OMC except that the first three Fourier harmonic functions are used to more accurately approximate the discrete sample points into a continuous wall-thickening curve. For each region, the wall-thickening curve provides a phase angle that represents the OMR of the particular region. Once the OMR phase angles of all LV segments are obtained, a phase distribution is generated and displayed in a polar map and histogram. The quantitative parameters for LV diastolic dyssynchrony derived from the phase histogram are measured using the same method as for OMC and include the diastolic phase SD and diastolic histogram bandwidth. Although these OMR measurements have not been as extensively validated as those for OMC, they have good correlations with tissue Doppler imaging, and are useful in assessing patients with end stage renal disease (*17)*.

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