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Routine Clinical Quantitative Rest Stress Myocardial Perfusion for Managing Coronary Artery Disease

Clinical Relevance of Test-Retest Variability

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ABSTRACT

OBJECTIVES Positron emission tomography (PET) quantifies stress myocardial perfusion (in cc/min/g) and coronary flow reserve to guide noninvasively the management of coronary artery disease. This study determined their test-retest precision within minutes and daily biological variability essential for bounding clinical decision-making or risk stratification based on low flow ischemic thresholds or follow-up changes.

BACKGROUND Randomized trials of fractional flow reserve–guided percutaneous coronary interventions established an objective, quantitative, outcomes-driven standard of physiological stenosis severity. However, pressure-derived fractional flow reserve requires invasive coronary angiogram and was originally validated by comparison to noninvasive PET.

METHODS The time course and test-retest precision of serial quantitative rest-rest and stress-stress global myocardial perfusion by PET within minutes and days apart in the same patient were compared in 120 volunteers undergoing serial 708 quantitative PET perfusion scans using rubidium 82 (Rb-82) and dipyridamole stress with a 2-dimensional PET-computed tomography scanner (GE DST 16) and University of Texas HeartSee software with our validated perfusion model.

RESULTS Test-retest methodological precision (coefficient of variance) for serial quantitative global myocardial perfusion minutes apart is ±10% (mean ΔSD at rest ±0.09, at stress ±0.23 cc/min/g) and for days apart is ±21% (mean ΔSD at rest ±0.2, at stress ±0.46 cc/min/g) reflecting added biological variability. Global myocardial perfusion at 8 minutes after 4-min dipyridamole infusion is 10% higher than at standard 4 min after dipyridamole.

CONCLUSIONS Test-retest methodological precision of global PET myocardial perfusion by serial rest or stress PET minutes apart is ±10%. Day-to-different-day biological plus methodological variability is ±21%, thereby establishing boundaries of variability on physiological severity to guide or follow coronary artery disease management. Maximum stress increases perfusion and coronary flow reserve, thereby reducing potentially falsely low values mimicking ischemia. (J Am Coll Cardiol Img 2017;■:■–■) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ANOVA = analysis of variance
CAD = coronary artery disease
CFR = coronary flow reserve
COV = coefficient of variance
ECG = electrocardiography
KS = Kolmogorov-Smirnov
LV = left ventricle
PET = positron emission tomography
PRP = pressure rate product
RCA = right coronary artery

Positron emission tomography (PET) quantifies stress myocardial perfusion in units of cc/min/g and coronary flow reserve (CFR) (1-3) as noninvasive guides to management of coronary artery disease (CAD) paralleling indirect relative flow reserve of invasive pressure-derived fractional flow reserve (4,5) originally validated by comparison to PET (6). Therefore, their test-retest precision and daily biological variability are essential for clinical decision-making based on thresholds of low myocardial perfusion causing ischemia.

Despite the long history of dipyridamole stress originated by Gould et al. (7,8), we critically examined our technology and biological variability of stress perfusion and CFR to determine whether methodology variability needed technical improvement or day-to-day biological variability were limitations to guiding or following management of CAD as recently reported for regadenoson (9). Therefore, this study aimed to establish the essential link between comprehensive quantification of perfusion measurements and their variability that sets bounds for clinical decision-making or risk stratification.

METHODS

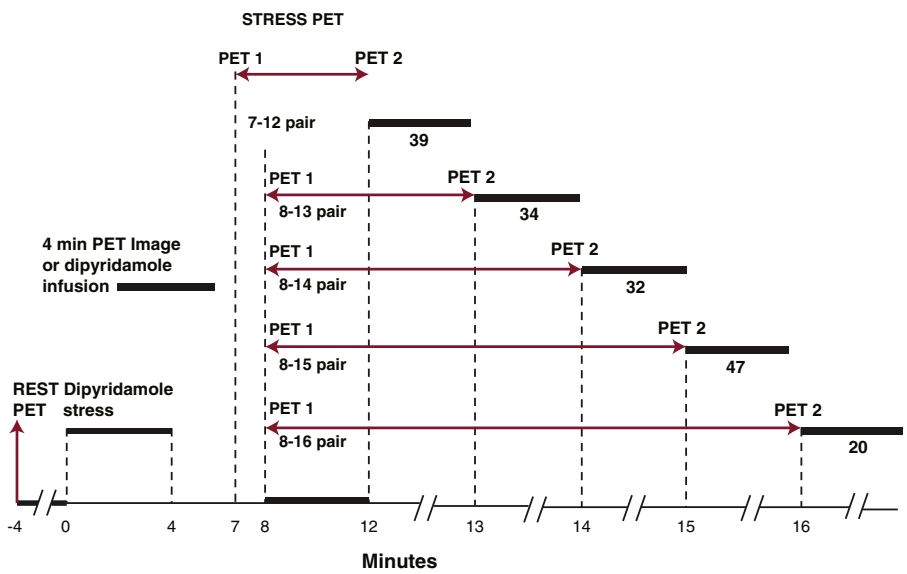
From November 2014 to August 2015, subjects 40 years or older were recruited at Weatherhead PET Center for Preventing and Reversing Atherosclerosis of University of Texas Medical School. Written informed consent was obtained from volunteers (commonly with risk factors), patients referred for clinical PET who did not have insurance coverage, or clinic patients who desired PET follow-up.

Exclusion criteria included contraindication to dipyridamole, pregnancy, active breastfeeding, clinical instability, and inability to undergo 2 PET protocols (**Figure 1**) within 2 days to 3 weeks apart in which early-late sequences within minutes were randomized before the first PET scan.

CARDIAC PET ACQUISITION AND ANALYSIS. Subjects were instructed to fast for 4 h and to abstain from caffeine, theophylline, and cigarettes for at least 24 h. Cardiac PET used the Discovery ST 16-slice PET-computed tomography scanner (GE Healthcare, Waukesha, Wisconsin) in 2-dimensional mode as previously reported (2,3,7-12).

Emission images were obtained over 4 min at starting intravenous injection of 30 to 50 mCi of

FIGURE 1 Protocols for Quantitative Myocardial Perfusion Imaging by PET Using Rb-82



Solid heavy horizontal bars indicate 4 min of dipyridamole infusion. Numbers under each solid bar are the number of paired positron emission tomography (PET) scans for timing protocols. **Small parallel lines** indicate a time break in x-axis for different paired protocols.
CFR = coronary flow reserve.