Optimizing diagnosis and risk stratification of ischemic heart disease by myocardial perfusion imaging: The incremental values of non-perfusion variables during vasodilator stress

Guang-Uei Hung, MD^a

^a Department of Nuclear Medicine, Chang Bing Show Chwan Memorial Hospital, Changhua, Taiwan

Received Jun 21, 2021; accepted Jun 22, 2021
doi:10.1007/s12350-021-02725-4

See related article, pp. 921–933

In this issue of Journal of Nuclear Cardiology, Frey et al. retrospectively enrolled a very large-scale population of 2496 patients to study the stress-induced effects of two vasodilator agents (adenosine and regadenoson) by ECG-gated myocardial perfusion imaging (MPI) with Rb-82 PET/CT on functional variables including stress left ventricular ejection fraction (LVEF), rest LVEF, LVEF reserve, stress myocardial blood flow (MBF), rest MBF, MBF reserve and hemodynamic variables in patients with or without prior history of coronary artery disease (CAD) and normal or abnormal scan results (summed stress score [SSS] < 4 or SSS ≥ 4).¹ Although similar studies on comparing different vasodilator agents had been reported, this study was likely the largest single center study of Rb-82 PET data. The main findings concluded by the authors were: (1) rest and stress LVEF, LVEF reserve as well as MBF values are considerably lower in patients with abnormal PET compared to patients with normal PET regardless of prior CAD history; (2) adenosine and regadenoson vasodilator stress seem to result in similar stress LVEF and MBF responses; (3) a stress LVEF ≥ 70% or LVEF reserve ≥ 5% had a high negative predictive value to

exclude “relevant ischemia” (summed difference score [SDS] ≥ 7 or %ischemic myocardium ≥ 10%) as shown on MPI with Rb-82 PET.

The clinical significance of non-perfusion variables obtained from vasodilator-stress gated MPI with SPECT or PET, such as LVEF, LVEF reserve, wall motion, transient LV ischemic dilation (TID), and dyssynchrony had been widely studied and shown to have incremental values on the diagnosis and risk stratification of patients with ischemic heart disease.^{2–9} As the example shown in Figure 1, the non-perfusion variables are especially useful for the patients whose perfusion abnormality was underestimated or falsely negative due to “balanced ischemia”. The underlying pathophysiological mechanisms for the development of these high-risk patterns on MPI were complex. Although the “ischemia” shown on perfusion images of MPI were actually indicative of perfusion gradients between the individual myocardial territories secondary to hyperemic effect of vasodilator agents, “real myocardial ischemia” sometimes did occur due to the synergy of increased oxygen demand by enhanced sympathetic activity and flow steal among vascular territories during vasodilator stress.^{10,11} Therefore, patients who encountered real myocardial ischemia might have variable degrees of transiently suppressed LV function (so-called stunning) and then express worsening stress wall motion,⁴ reduced LVEF reserve,⁶ and worsening stress LV dyssynchrony,⁹ depending on the severity of ischemia. On the other hand, the patients who did not experience ischemia during vasodilator-stress might have improved stress wall motion, increased LVEF reserve, smaller stress LV volume and/or improved stress LV dyssynchrony,¹²

Reprint requests: Guang-Uei Hung, MD, Department of Nuclear Medicine, Chang Bing Show Chwan Memorial Hospital, Changhua, Taiwan; 106143@gmail.com

J Nucl Cardiol 2022;29:934–7.

1071-3581/\$34.00

Copyright © 2021 American Society of Nuclear Cardiology.

Figure 1. A 79-year-old male patient suspected of ischemic heart disease was referred for myocardial perfusion imaging for diagnosis and risk stratification. Dipyridamole was infused at a rate of 0.56 mg/kg for 4 minutes, then 3mCi of Tl-201 was injected 3 minutes after the end of dipyridamole infusion. ECG-gating SPECT was performed 5 minutes and 4 hours later, respectively. Chest tightness and dyspnea developed during dipyridamole infusion and O₂ was given first. After injection of Tl-201, 62.5 mg of aminophylline was slowly infused and the discomfort quickly resolved. The perfusion images showed only mildly reversible perfusion abnormality involving apical anterior wall, indicative of flow limiting stenosis at the middle or distal region of left anterior descending coronary artery. This patient might be considered as low-risk based on perfusion abnormality alone; however, significant transient ischemic dilation was also demonstrated. In addition, left ventricular (LV) functional analysis showed worsening stress wall motion and severely reduced stress LVEF, indicative of the high-risk probability. Invasive coronary angiography was performed on the next day and revealed 60% stenosis in the left main coronary artery, 95% stenosis in proximal left anterior descending coronary artery and 70% stenosis in the right coronary artery.

depending on the degree of stress-induced enhancement of LV function.

It should also be noted that perfusion images reflect the real-time information at the moment of radiotracer injection; however, non-perfusion variables reflect the average information during image acquisitions. Therefore, the major determinants of vasodilator-induced ischemic stunning detected by non-perfusion variables would include (1) the duration of patient under the effect of a vasodilator, (2) the starting time of image acquisition, (3) the elapsed time of image acquisition, and (4) the duration of ischemic stunning.^{13,14} Figure 2 demonstrates the estimated duration of patient under the effect of a vasodilator and the starting and elapsed time of image acquisition for common MPI protocols. Regarding the duration of ischemic stunning, it had been

reported that stress-induced myocardial stunning might persist for 30 to 240 minutes¹⁵ or even more than 24 hours¹⁶ after stress, but most of it resolved during the first 30 to 60 minutes.¹⁵ Rb-82 PET seems to have the highest chance to detect ischemic stunning, followed by N-13 NH₃ PET, Tl-201 SPECT and SPECT with Tc-99m agents. Compared to MPI with SPECT, PET imaging has the additional advantages of faster acquisition, better image quality, less attenuation artifact, lower radiation burden and more accurate quantitation of MBF and MFR. Therefore, MPI with Rb-82 PET could be an ideal tool for the diagnosis and risk stratification in patients with ischemic heart disease.

In the study by Frey et al.,¹ the definition of abnormal scan was SSS $\geq$ 4, similar to most of the previous studies. Since SSS is a mixed marker of

Figure 2. The estimated duration of patient under the effect of three major clinically used vasodilators and the starting and elapsed time of image acquisition for the commonly used MPI protocols.

ischemia and infarction, it is easy to understand that the mean values of rest and stress LVEF as well as LVEF reserve are lower in patients with an abnormal than a normal scan. In addition, the authors defined “relevant ischemia” as $\text{SDS} \geq 7$ (or %ischemic myocardium $\geq 10\%$), which had been validated as a high-risk indicator and as a threshold that patients might benefit from revascularization over medical treatment.¹⁷ This was an even more important finding that stress LVEF $\geq 70\%$ and LVEF reserve $\geq 5\%$ were powerful indicators to exclude “relevant ischemia” so that the physicians could be comfortable to manage the patients with medical therapy. However, it should be noticed that the “ischemia” shown on MPI ($\text{SDS} > 0$) in fact is “perfusion gradient” between different vascular territories. Certain percentages of those with a positive SDS do experience “real ischemia” during vasodilator stress and express ischemic stunning (low stress LVEF or negative LVEF reserve), but others may not have ischemic stunning and express high stress LVEF or positive LVEF reserve even though SDS was high (high-risk perfusion pattern) as shown in Figure 2 of Frey et al.¹ On the other hand, some patients with a zero or low SDS (low-risk perfusion pattern) had low stress LVEF or negative LVEF reserve (high-risk function pattern). Such patients needed special cautions for severe and extensive CAD with balanced ischemia on perfusion images. In the Rb-82 PET/CT studies by Dorbala et al.,^{6,7} in the cohort of the patients with left main/3-vessel CAD, no one showed defect in 3-vessel pattern, only 50% 2-vessel pattern, 43% 1-vessel pattern and 7% no defect. When combining perfusion and abnormal LVEF reserve (less than $+5\%$), 79% of patients with left main/3-vessel CAD were correctly diagnosed as having multivessel CAD. In addition, an LVEF reserve of equal to or more than -14% had a 100% of positive predictive value on diagnosing left main/3-vessel CAD in spite of only 25% sensitivity. Furthermore, those with a LVEF reserve $< 0\%$ had

significantly more cardiac events (5.3% vs. 2.1%, $P < 0.001$) and all-cause death (4.3% vs. 9.2%, $P < 0.001$) than those with a LVEF $\geq 0\%$; and LVEF reverse provided significant independent and incremental value to MPI for predicting the risk of future adverse events. Therefore, it would be interesting to see the angiographic and prognostic data from the future study of Frey et al.

Another issue should be discussed is that the methodology of the current study used for comparing the effect of regadenoson and adenosine was not a “paired design” (one patient receiving two PETs with regadenoson and adenosine as stressors for comparison) and this may cause bias on comparison results. Johnson NP et al conducted a paired study comparing regadenoson to dipyridamole by Rb-82 PET and found that regadenoson with the standard timing protocol from the package insert achieved approximately 80% of absolute stress flow and CFR of dipyridamole.¹⁸ A non-standard protocol using a more delayed radionuclide injection after the regadenoson bolus improved its effect to 90% of dipyridamole hyperemia. Therefore, it should be the case that the effect of regadenoson and adenosine may be “similar” but may not be “the same”.

Myocardial perfusion imaging has been clinically utilized as a gatekeeper for invasive management with percutaneous coronary intervention (PCI) worldwide because of the long-time accumulated abundant and solid evidence.¹⁹ According to our recent investigation, MPI was the most commonly used stress test within 90 days prior to elective PCI and accounted for 79.1% of the totally investigated 3,163 patients, followed by treadmill exercise test (66.4%) and stress echocardiography (only 0.05%).²⁰ However, high-risk patients with balanced ischemia might be inappropriately considered as low-risk and put on conservative management due to underestimated perfusion defects or even falsely normal perfusion. Careful inspections on the non-perfusion variables would be very helpful for avoiding the pitfalls

for optimizing the diagnosis and risk stratification for patients with ischemic heart disease.

Disclosure

The author declare that he has no conflict of interest.

References

1. Frey SM, Honegger U, Clerc OF, Caobelli F, Haaf P, Zellweger MJ. Left ventricular ejection fraction, myocardial blood flow and hemodynamic variables in adenosine and regadenoson vasodilator 82-Rubidium PET. *J Nucl Cardiol.* <https://doi.org/10.1007/s12350-021-02729-0>.
2. Sharir T, Germano G, Kavanagh PB, Lai S, Cohen I, Lewin HC, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. *Circulation.* 1999;100:1035-42.
3. Abidov A, Bax JJ, Hayes SW, Cohen I, Nishina H, Yoda S, et al. Integration of automatically measured transient ischemic dilation ratio into interpretation of adenosine stress myocardial perfusion SPECT for detection of severe and extensive CAD. *J Nucl Med.* 2004;45:1999-2007.
4. Hung GU, Lee KW, Chen CP, Yang KT, Lin WY. Worsening of left ventricular ejection fraction induced by dipyridamole on TI-201 gated myocardial perfusion imaging predicts significant coronary artery disease. *J Nucl Cardiol.* 2006;13:225-32.
5. Petix NR, Sestini S, Marcucci G, Coppola A, Arena A, Nassi F, et al. Can the reversible regional wall motion abnormalities on stress gated Tc-99m sestamibi SPECT predict a future cardiac event? *J Nucl Cardiol.* 2005;12:20-31.
6. Dorbala S, Vangala D, Sampson U, Limaye A, Kwong R, Di Carli MF. Value of vasodilator left ventricular ejection fraction reserve in evaluating the magnitude of myocardium at risk and the extent of angiographic coronary artery disease: A 82Rb PET/CT study. *J Nucl Med.* 2007;48:349-58.
7. Dorbala S, Hachamovitch R, Curillova Z. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. *JACC Cardiovasc Imaging.* 2009;2:846-54.
8. Shen TY, Chang MC, Hung GU, Kao CH, Hsu BL. Prognostic value of functional variables as assessed by gated TI-201 myocardial perfusion SPECT for major adverse cardiac events in patients with coronary artery disease. *Acta Cardiol Sinica.* 2013;29:243-50.
9. Huang WS, Huang CH, Lee CL, Chen CP, Hung GU. Relation of early post-stress left ventricular dyssynchrony and the extent of angiographic coronary artery disease. *J Nucl Cardiol.* 2014;21:1048-56.
10. Akinboboye OO, Idris O, Chou RL, Sciacca RR, Cannon PJ, Bergmann SR. Absolute quantitation of coronary steal induced by intravenous dipyridamole. *J Am Coll Cardiol.* 2001;37:109-16.
11. Van Tosh A, Votaw JR, Reichek N, Palestro CJ, Nichols KJ. The relationship between ischemia-induced left ventricular dysfunction, coronary flow reserve, and coronary steal on regadenoson stress-gated (82)Rb pet myocardial perfusion imaging. *J Nucl Cardiol.* 2013;20:1060-8.
12. Chen CC, Shen TY, Chang MC, Hung GU, Chen WC, Kao CH, et al. Stress-induced myocardial ischemia is associated with early post-stress left ventricular mechanical dyssynchrony as assessed by phase analysis of 201Tl gated SPECT myocardial perfusion imaging. *Eur J Nucl Med Mol Imaging.* 2012;39:1904-9.
13. Dilsizian V, Bacharach SL, Beanlands RS, Bergmann SR, Delbeke D, Dorbala S, et al. ASNC imaging guidelines/SNMMI procedure standard for positron emission tomography (PET) nuclear cardiology procedures. *J Nucl Cardiol.* 2016;23:1187-226.
14. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. *J Nucl Cardiol.* 2016;23:606-39.
15. Ambrosio G, Betocchi S, Pace L, Losi MA, Perrone-Filardi P, Soricelli A, et al. Prolonged impairment of regional contractile function after resolution of exercise-induced angina. Evidence of myocardial stunning in patients with coronary artery disease. *Circulation.* 1996;94:2455-64.
16. Lee DS, Yeo JS, Chung JK, Lee MM, Lee MC. Transient prolonged stunning induced by dipyridamole and shown on 1- and 24-hour poststress 99mTc-MIBI gated SPECT. *J Nucl Med.* 2000;41:27-35.
17. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation.* 2003;107:2900-7.
18. Johnson NP, Gould KL. Regadenoson versus dipyridamole hyperemia for cardiac PET imaging. *J Am Coll Cardiol Img.* 2015;8:438-47.
19. Hung GU, Ko KY, Lin CL, Yen RF, Kao CH. Impact of initial myocardial perfusion imaging versus invasive coronary angiography on outcomes in coronary artery disease: A nationwide cohort study. *Eur J Nucl Med Mol Imaging.* 2018;45:567-74.
20. Yang HP, Hung GU, Lin CL, Shen TY, Chen CC, Niu YL, et al. The utilization of stress tests prior to percutaneous coronary intervention for stable coronary artery disease in Taiwan. *Acta Cardiol Sin.* 2019;35:111-7.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.