Revival of an old stressor: Dobutamine-stimulation for PET myocardial perfusion imaging in patients with end-stage liver disease?

Thomas H. Schindler, MD, PhD,^a and Thorsten Leucker, MD^b

^a Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO

^b Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, MD

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In patients with end-stage liver disease (ESLD), the exclusion of hemodynamically obstructive coronary artery disease (CAD) and normal left ventricular function with e.g., stress-rest scintigraphic myocardial perfusion imaging (MPI) commonly constitutes a pre-requisite to be listed for liver transplantation.^{1,2} An indeed, perioperative risk and clinical outcome may be affected by the CAD process in liver transplant recipients.² Most ESLD patients may not be able to sufficiently exercise on the treadmill to reach 85% of predicted maximal heart rate and/or more than 5 METS for a sufficient diagnostic yield with MPI.^{3,4} In such patients, pharmacologic stress testing with either vasodilator stress such as with regadenoson, dipyridamole, or adenosine, or with β 1-stimulated increase in heart rate and contractility by dobutamine remain viable options to induce hyperemic myocardial blood flow (MBF) increases.⁵ The mechanism of these pharmacologic agents to stimulate hyperemic MBFs are distinct different. For example, pharmacologic vasodilation of the coronary arteriolar resistance vessels with regadenoson will lead to sub-maximal or maximal hyperemic flow increases uncoupled from the metabolic demand of the left ventricle.⁶ In the presence of flow-limiting CAD lesions, relative

differences in radiotracer uptake or perfusion heterogeneity can be noted as the hyperemic MBF increases in the myocardial region subtended by an obstructive CAD lesion will be less than in the remote myocardial region without significant coronary obstruction.^{7,8} Such observed differences in regional radiotracer uptake is a sensitive approach for the identification of flow-limiting CAD burden but it may not necessarily cause classical ischemia as evidenced by corresponding wall motion abnormalities.⁹ Conversely, dobutamine-stimulation with increases in heart rate and contractility increase MBFs indirectly by elevations in myocardial metabolic and thus oxygen demand leading to a metabolically mediated vasodilation of the coronary microcirculation. Consequently, impaired coronary flow increases in response to dobutamine-stimulation due to a flow-limiting epicardial lesion is more likely to cause a perfusion deficit associated with classical ischemia induced wall motion abnormality or myocardial stunning due to a mismatch between increased metabolic demand and insufficient oxygen supply. Given these mechanistic differences in pharmacologic induced hyperemic MBF increases among vasodilator—and dobutamine stressors, cardiac PET flow studies revealed distinct higher hyperemic MBF values with pharmacologic vasodilation of the coronary arteriolar vessels than with dobutamine-stimulation.^{10–12} For example, Jagathesan et al.⁵ reported of hyperemic MBF increases and MFR in the normal range, as determined with ¹⁵O-water PET, but significantly higher for flow increase stimulation with the vasodilator adenosine than with dobutamine (hyperemic MBFs: 4.04 ± 0.51 vs 3.18 ± 0.96 ml/g/min and MFR: 3.36 ± 0.48 vs 2.62 ± 0.57 ; $P < 0.05$, respectively). Such observations may provide a rationale for the commonly observed higher sensitivities of pharmacologic

Reprint requests: Thomas H. Schindler, MD, PhD, Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University School of Medicine, 1510 S. Kingshighway, St. Louis, MO 63110; thomas.h.schindler@gmail.com

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vasodilator versus dobutamine stress scintigraphic MPI, while dobutamine stress stimulation afforded a higher specificity in CAD detection and characterization.^{13,14}

In this issue of the Journal of Nuclear Cardiology, Abele et al.¹⁵ report of hyperemic MBF and myocardial flow reserve (MFR = hyperemic MBF/rest MBF) value, as determined with ⁸²Rubidium-PET/CT, in patients with and without ESDL undergoing either pharmacological vasodilation with dipyridamole or dobutamine-stimulation. Patients were grouped into ESDL group undergoing ⁸²Rubidium-PET/CT with dipyridamole-stress (n = 27) or dobutamine-stimulation (n = 26), while twenty low-risk individuals without evidence of coronary calcifications served as control group with dipyridamole-stress. As it was observed, ESDL group with dipyridamole-stress had a lower myocardial flow reserve (MFR) than the control group (1.89 ± 0.79 vs. 2.79 ± 0.96 ; $P < 0.05$), while the ESDL group with dobutamine-stimulation demonstrated significantly higher MFR values than both of these groups (3.69 ± 1.49). Further, there was a moderate negative correlation between clinical model for end-stage liver disease (MELD) score and left ventricular MFR among the ESDL dipyridamole-stress group ($r = 0.47$, $P < 0.05$), not observed for the ESDL dobutamine-stimulation group ($r = 0.25$, $P = 0.21$). Albeit that this inverses relationship is modest and based on low numbers, it signifies a progressive decrease in MFR with an increasing stage of ESDL. Such inverse relationship may outline yet unknown substances, released from the liver, to affect the MBF response to dipyridamole-stress. This contention is emphasized by the “paradoxical” higher increase in hyperemic MBFs and MFR during dobutamine-stimulation than during dipyridamole-stress. Further, the striking difference between hyperemic MBFs is between ESDL with dipyridamole-stress (about 1.8 ml/g/minute) versus dobutamine-stimulation (about 2.8 ml/g/minute). This contrasts previous observations⁵ comparing the hyperemic MBF response of direct vasodilators such as adenosine or dipyridamole versus dobutamine-stimulation. Such observations raise indeed some concern about the use of vasodilator agents as appropriate stressor to induce hyperemic flow increases in ESDL patients. Someone could indeed argue that the difference in radiotracer uptake during hyperemic flows between regions subtended to obstructive, flow-limiting CAD lesions and remote regions may be relatively low or minimal to bring out meaningful perfusion deficits during dipyridamole-stress.¹⁶ This could then indeed result in a lower sensitivity and diagnostic accuracy in CAD detection in patients with ESDL than in those without. While such considerations may be intuitively correct, further head-

to-head PET perfusion-flow studies between dipyridamole-stress and dobutamine-stimulation in the detection of obstructive CAD are needed before more definite recommendations can be stated. Of further interest, the hyperemic MBF increase in the control group with dipyridamole-stress to increase hyperemic MBF was virtually the same as in the ESDL with the same stressor. The reason for this finding remains uncertain but likely is related to adverse effects of cardiovascular risk factors and yet unknown factors on microvascular function in the low-risk control group.¹⁷ Unfortunately, more detailed information of ⁸²Rb-PET/CT-determined MBFs during dipyridamole-stress or dobutamine-stimulation in healthy controls without known cardiovascular risk factors is missing, which would have provided an important framework of reference MBF values for the range of normal hyperemic MBFs and MFR. Taken together, the findings of the current investigation reported by Abele et al.¹⁵ are unique because they raise an important clinical issue in the value of dipyridamole-stress with MPI for CAD detection and prognostication in ESDL patients. It may be indeed possible that in such patients dobutamine-stimulation of hyperemic MBFs may indeed reflect a better pharmacologic stressor for the provocation of regional perfusion deficits and, thus, for CAD detection than dipyridamole-stress that, however, awaits further clinical testing.

Disclosure

The authors declare that they have no conflict of interest.

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