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Perfusion Imaging With Vasodilator Stress Echocardiography:

A Physiologically Sound Approach to Coronary Disease?

Jonathan R. Lindner, MD
Division of Cardiovascular Medicine and Department of Biomedical Engineering, Oregon Health & Science University, Portland, OR

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Cardiac stress testing with noninvasive imaging is increasingly used not only to detect the presence of coronary artery disease (CAD), but also to help to select appropriate therapy according to the extent and severity of disease. To that end, there have been continuous efforts to improve the performance of all forms of stress testing. For example, recent advances in stress radionuclide imaging, such as gated acquisition for regional function, iterative reconstruction processing, and the development of new tracers, have occurred with the goals of improving sensitivity, reducing artifacts, and reducing ionizing radiation dose. For stress echocardiography, the use of strain imaging derived from tissue Doppler echocardiography or speckle-tracking algorithms are being applied to improve the detection of subtle myocardial dysfunction during exercise or inotropic stress.[1] In this issue of *Circulation: Cardiovascular Imaging*, Porter and colleagues[2] evaluate the diagnostic accuracy of an approach that combines two advances in stress imaging that have not been paired previously: (1) myocardial perfusion imaging with myocardial contrast echocardiography (MCE) and (2) vasodilator stress with the adenosine A_{2a}-receptor agonist regadenoson.

The use of MCE during stress to enhance detection of CAD is not a new concept. Based on several decades of clinical studies, we know that conventional exercise or dobutamine echocardiography will miss the presence of CAD in ≈ 1 of 5 patients, although this exact figure can be argued because trials vary according to the population studied (eg, pretest probability of disease, prevalence of multivessel disease) and the definition of disease (eg, >50% or >70% stenosis).[3,4] The subjective nature by which wall thickening is interpreted has taken blame for the sensitivity of stress echocardiography being lower than perhaps desired. An equally important issue is that the relation between hyperemic myocardial blood flow and radial thickening during stress is not linear. Canine studies have clearly demonstrated that wall thickening during dobutamine stress can be normal or near normal in myocar-dial regions where stenosis produces mild or even moderate reductions in hyperemic flow measured by microsphere technique.[5] The logical response has been to try to directly assess hyperemic flow using MCE to improve diagnostic performance. Clinical studies

Correspondence to Jonathan R. Lindner, MD, Cardiovascular Division, UHN-62, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239. linderj@ohsu.edu.

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using dobutamine or exercise have shown consistently that the addition of MCE perfusion information to wall motion assessment significantly increases the sensitivity of detecting stenosis, particularly for moderate rather than severe stenosis, and provides additional prognostic information.[6–8]

Accurate detection of CAD with MCE has also been established using vasodilator rather than inotropic stress.[9–11] MCE evaluates perfusion at the capillary level. At this level, vasodilators manifest their effect more through an increase in erythrocyte flux rate than through the relatively smaller expansion of capillary blood volume.[12,13] Accordingly, detection of stenosis with adenosine or dipyridamole MCE has relied primarily on detecting abnormal microvascular blood flux rate from microbubble destruction-replenishment kinetics. In the study by Porter et al,[2] qualitative assessment of refill kinetics formed the criteria for defining normal versus abnormal. Although not performed in this study, numeric quantification of flux rate (β-value) is possible with MCE,[10,15] and when performed in patients with CAD, the relationship between stenosis severity and β-reserve bears a striking resemblance to the relation between stenosis severity and hyperemic blood flow reserve described by Gould and colleagues[14] 35 years ago, which provided the basis for using stress perfusion imaging.

The novelty of the study resides almost exclusively in the permutation of using an A_{2a}-receptor-specific vasodilator in conjunction with MCE. Regadenoson and other adenosine A_{2a}-receptor-specific agonists originally were developed with the intent of producing coronary arteriolar vasodilation while minimizing some of the undesirable negative chronotropic effects and other side effects (dyspnea, flushing, chest pain, headache) of A_1-, A_{2b}-, and A_3-receptor activation. According to clinical studies, however, regadenoson does not substantially reduce the incidence of side effects compared with adenosine.[16] Rather, it decreases the severity of these symptoms and may offer a safer alternative in patients with lung disease that may have a reactive component.[16,17]

It is commonly believed that in the presence of a stenosis that is not flow limiting at rest, vasodilator stress does not produce ischemia but, instead, simply results in flow heterogeneity between territories that can be detected by perfusion imaging. It would then seem that the comparison of perfusion to wall motion in this study was an effort to erect a “straw man” to highlight the superior performance of MCE perfusion to wall motion. However, some have advocated the use of vasodilator wall motion assessment on the basis of trials that suggested that sensitivity for detecting CAD is acceptable with this approach.[18] Mechanisms by which vasodilators can potentially produce flow-demand disparity include (1) critical reduction in perfusion pressure distal to a stenosis, which tends to be greater for vasodilator than for inotropic stress despite similar epicardial flows[19] and (2) an increase in heart rate that is either reflexive or due to direct sympathetic stimulation by adenosine receptor activation, which increases myocardial oxygen demand.[13,20] Animal models of chronic CAD have demonstrated that contractile response to adenosine stress directly correlates with the degree of endocardial flow reserve.[19] An increase in wall thickening tends to occur when endocardial flow reserve is >2.5, and a reduction in wall thickening occurs when flow reserve is <1.5.[19] Hence, the finding by Porter and colleagues[2] that MCE perfusion imaging is far more sensitive than wall motion assessment is both “fair game” and pertinent.

The diagnostic accuracy for identifying CAD on a per-patient basis reported by Porter et al[2] is comparable to previous studies pairing MCE with vasodilator stress in a relatively high pretest probability group of patients.[9–11] There are several other comforting observations. First, the specificity was not as low as that reported in some earlier studies,[9,11] indicating that our ability to recognize attenuation artifacts continues to improve. Second, fixed

perfusion defects were appropriately found in all segments with resting wall motion abnormalities, although it is unclear whether interpretation of wall motion and perfusion were made blinded to each other. Third, MCE perfusion imaging could be performed very rapidly after regadenoson administration, which would simplify protocols by allowing the operator to obtain rest and stress images after initiating a single, uninterrupted, continuous infusion of contrast.

A rather striking finding of the study was the sensitivity of MCE for detecting disease on a per-territory basis (≈50%), which was substantially lower than what has been described previously.[9–11] The explanation for this finding is not immediately clear. Multivessel disease was present in many patients in whom there was a false-negative territory by MCE. Although multivessel disease can affect regional sensitivity when *relative* contrast enhancement is used, this study applied semiquantitative evaluation of reperfusion kinetics. In this case, diagnostic sensitivity would actually be enhanced because of a lower likelihood of collateral supply between territories. The higher sensitivity on a per-patient rather than a segmental basis was either because the high prevalence of multivessel disease permitted detection of disease in another territory or because perfusion imaging has the ability to detect microvascular functional abnormalities that can occur in remote territories where stenosis severity is <50%. Either way, it is a bit concerning that the true extent of disease may be underestimated. There are data that suggest that the study results would have fared better if quantitation of MCE data was performed.[10]

In summary, the central message of the study by Porter et al[2] that MCE perfusion imaging in conjunction with regadenoson vasodilator stress can be used to detect the presence of CAD in patients and is superior to vasodilator wall motion is correct. However, the study raises some issues on the ability of this approach to accurately characterize the territorial extent of epicardial disease, which seems to be a departure from previous studies.

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