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EDITORIAL COMMENT

More May Not Always Be Better*

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The study by Gaibazzi et al. (1) in this issue of *iJACC* sought to determine whether there is sufficient additional prognostic information provided by adding Doppler coronary flow reserve in the left anterior descending coronary artery (CFR-LAD) and myocardial perfusion imaging (MP) to standard wall motion analysis (WM) and clinical parameters (PARA) during vasodilator stress echocardiography to justify the additional complexity of the combined tests. The investigators studied 752 patients undergoing contrast high-dose dipyridamole stress echocardiography (SE) with suspected or known coronary artery disease (one-third). The cohort was followed for a median of 16.5

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months post-testing and the ability of individual and combined measures to predict risk of cardiac events (death, nonfatal myocardial infarction, or acute coronary syndromes) was studied using multivariate models and risk reclassification. The study found that reversible WM abnormalities were present in 18% of patients compared with 27% with inducible myocardial perfusion defects (MPD) and 38% with reduced CFR-LAD. Presence of any SE abnormality had a higher event rate than did normal SE (10.8% vs. 2.1%, $p < 0.001$). Multivariate analysis showed that when combined with clinical risk parameters, the sequential addition of WM, WM + CFR <2, MPD alone, and WM + CFR <2+ MPD progressively improved risk stratification. The study is of interest because of the large number of patients analyzed and the investigators' prior experience with these techniques, particularly CFR-LAD and dipyridamole SE. However, as in most studies, the nature of the experimental model and complexity of the protocol chosen affect a number of results reported and thus are worthy of further examination.

The first relates to the type of echocardiographic stress testing performed. Most clinical laboratories prefer to use exercise stress where possible for a number of reasons including: 1) physiological correlation of ischemia with exercise and its significance at varying workloads; 2) the established value of exercise as a prognostic determinant; 3) the greater potency of exercise versus pharmacological stressors; 4) the complementary information derived from electrocardiogram changes consistent with ischemia and the detection of arrhythmias occurring during exercise; and 5) the ability to relate the presence and nature of symptoms or lack thereof during exercise to the patient's pre-test complaints. The investigators acknowledge that exercise might have been considered the best protocol in their patients who could exercise, but they selected pharmacological stress presumably due to the extreme difficulty in recording coronary flow by Doppler in the exercising patient. In patients who are unable to exercise, pharmacological stress testing is appropriate with dobutamine employed most commonly in laboratories in the United States, whereas dipyridamole (as in this study) or adenosine is often used in Europe. Because these agents have different mechanisms of action, their appropriateness for different types of testing varies. Dobutamine, by increasing heart rate, blood pressure, and contractility, increases demand in the face of limited supply with resulting ischemia, whereas dipyridamole and adenosine create relative differences in flow between

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regions supplied by normal and stenotic vessels (MP) or between resting and vasodilator flow in the region of a coronary artery distal to a stenosis (CFR). Production of ischemia in the latter case then depends on the presence of either vertical or horizontal steal phenomena that are more difficult to predict (2). In theory, the former method would appear to be preferable for WM analysis, and the latter would be better suited to demonstrate flow abnormalities; indeed, experimental and clinical studies support this concept. Experimental studies comparing dobutamine and dipyridamole have shown that dipyridamole produces segmental dysfunction less often and, when present, the degree of dysfunction is less (3,4). In a clinical study of 97 patients undergoing coronary angiography without prior infarcts, Marwick et al. (5) reported a sensitivity of 59% for adenosine SE compared with 86% for dobutamine SE for the detection of WM abnormalities in the same patients. The percentage of nondiagnostic studies was also higher for the adenosine stress studies (5). In addition to the stressor, the nature of image acquisition may also adversely affect the WM analysis. It is standard practice that the minimum views required for an adequate SE include parasternal long- and short-axis views (papillary muscle level) with additional short-axis views being desirable in addition to apical recordings (6). In this study, only apical views were recorded as these are more appropriate for the perfusion and coronary flow studies, but unfortunately, they select against the WM analysis. Although the addition of contrast should have improved endocardial definition, this can create its own problems when only apical views are used. Finally, as the investigators point out, censoring of patients undergoing early revascularization may have also led to a more pronounced underestimation of WM abnormalities, because their presence and extent are used as an indication for revascularization. Thus, although WM performed least well in this study, the study was designed to facilitate coronary and perfusion analysis at the expense of WM; hence, the value of this parameter in a more appropriate setting is likely understated.

Second, in this study, CFR-LAD detected abnormal flow more often than MP. This is surprising because CFR looks only at flow in a distal segment of the LAD, which is not involved in all patients with coronary artery disease (72% to 84%) (7,8), whereas MP looks at the entire ventricle. Because there is no gold standard, one can only speculate that this may also relate to the production of ischemia as it is likely more difficult to distinguish normal from increased flow (due to signal saturation) than from reduced flow by visual assessment of contrast. Alternatively, as the investigators note, 140 patients had abnormal WM or CFR with normal MP, mostly because of reduced CFR-LAD with normal WM that was presumed due to errors in the CFR measurements or microvascular disease. Because 83 of the 129 patients with WMA had WMA and abnormal CFR-LAD, at least 94 patients (140 minus 46) must have had abnormal CFR with normal WM and MP or 27% of the positive studies. As the authors point out, the majority of these abnormalities resulted from borderline values, however, they are still classified as abnormal, which affects the risk assessment. Further, by employing 3 tests, one increases the probability of discrepant results, and the physician must then decide whether to rely on the approach felt to be most accurate or the majority.

Third, while univariate analysis demonstrated that multiple clinical (hypercholesterolemia, diabetes, known CAD, and aspirin therapy) and SE (WM, CFR, and MP) parameters along with reduced resting LVEF were predictive of risk, on multivariate analysis of SE parameters WM was no longer independently predictive. Although both CFR and MP remained independent predictors the latter was clearly the stronger of the two (HR 2.25 vs. 5.97). The authors then look at the sequential addition of WM, WM/CFR, MP alone, and WM/CFR+MP to clinical parameters in the prediction model and show that there is incremental improvement, however, in the end there is no significant difference between the combined model (PARA+WM/CFR+MP) and clinical parameters and MP alone. Thus, while the authors argue that in this model it is important to add either CFR or MP to wall motion analysis, which the data supports, it is not clear that adding CFR and WM is better than simply analyzing MP alone and avoiding the added complexity of the CFR study.

Finally, given the complexity of this protocol one might ask whether this approach is equivalent or superior to exercise or dobutamine stress echo for routine clinical use. Although this question was not addressed in this study, the answer in all likelihood relates to the difference between feasibility and practicality. Although clearly not perfect, the feasibility and practicality of exercise and dobutamine stress echocardiography are well established and standard practice in most laboratories. In contrast, despite numerous reports describing the diagnostic

accuracy and prognostic value of MP and CFR, they have not been widely employed beyond dedicated research laboratories. For CFR, the ability to record a small vessel moving in space was hard in the beginning and, despite the use of color flow and contrast, is technically demanding now. For Doppler studies, this is further complicated by the need to maintain the sample volume within the small, moving vessel, the varying intensity of the contrast following bolus injection that will affect the measured velocity, and the difficulty in aligning the beam to optimally report flow velocity. Whereas the advantage of this technique is that it provides a quantitative measure, the need to average the 3 "best" flow profiles adds a subjective component and as the investigators note, ratios can vary across the threshold of 2 in the same patient. Feasibility has also been a problem for MP. Although the investigators state that the test was deemed uninterpretable for at least 1 of the 3 tested parameters in only 4% of patients, the group does not appear to have been consecutive; the number excluded for poor echocardiographic window was unstated; and the number of left ventricular segments excluded from MP interpretation if they were not clearly visualized, due to shadowing artifacts or low ultrasound penetration, is unclear. Again, as the investigators point out, perfusion imaging is limited by technical complexity and subjectivity in its interpretation. Furthermore, there has been a failure to agree on a standardized technique or protocol for test performance among different groups with resulting variations in contrast delivery (e.g., bolus vs. infusion), contrast agents, instrument settings, and image capture and display formats. Interobserver variability has also been a problem. As noted, the interobserver agreement in this study for MP was 80% versus 95% for WM. Although the investigators clearly acknowledge these limitations in the aggregate, they represent the difference between techniques that, at present, are feasible when performed by experts and those that are practical for routine clinical application. Whether this will change with better standardization of methods, broader clinical experience, and studies comparing both methods in the same patients remains to be seen.

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Key Words: contrast echocardiography ■ coronary artery disease ■ coronary flow reserve ■ dipyridamole ■ myocardial perfusion ■ prognosis ■ stress echocardiography.