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EDITORIAL COMMENT

Myocardial Perfusion Imaging and Multidetector Computed Tomographic Coronary Angiography

Appropriate for All Patients With Suspected Coronary Artery Disease?*

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Over the last 5 years, we have witnessed an impressive introduction of new imaging technology for the evaluation of patients with known or suspected coronary artery disease (CAD). The introduction of multidetector computed tomographic (CT) scanners with submillimeter spatial resolution and subsecond gantry rotations has revolutionized the field of cardiac imaging by making "direct" noninvasive imaging of the coronary arteries possible. The application of this technology in the form of CT coronary angiography (CTA) results in an accurate test for excluding coronary atherosclerosis with a very high negative predictive value (>95%), especially when using 16- or 64-slice CT (1). The

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use of CTA also provides excellent diagnostic sensitivity for identifying stenoses in the proximal and middle segments (>1.5 mm in diameter) of the main coronary arteries. Unlike invasive coronary angiography, CTA not only assesses disease within the coronary lumen but also provides direct qualitative and quantitative information about nonobstructive atherosclerotic plaque burden and its composition. Thus, it is possible that CTA-based patient evaluation may provide more clinically relevant information upon which to base risk assessments compared with conventional "lumenography."

Consequently, CTA is without a doubt a powerful noninvasive modality for evaluating and excluding CAD—with respect to both obstructive stenoses and atherosclerosis—and it will likely play an important role in the diagnosis of CAD. Before the widespread clinical application of CTA to daily practice, however, major questions must be answered. For example, where in a testing algorithm will this test fit? Does it replace exercise treadmill testing, stress myocardial perfusion imaging (MPI), both, or neither? Who are appropriate candidates for CTA? To this end, defining the role of CTA in a patient testing algorithm awaits the results of investigations defining the relative roles and capabilities of CTA compared with conventional noninvasive testing.

COMPARING CTA AND STRESS SPECT

In this issue of the *Journal*, Schuijf et al. (2) evaluate the relationship between CTA and single-photon emission computed tomography (SPECT) MPI in a cohort of 114 patients with predominantly intermediate pretest likelihood of CAD undergoing both tests within 30 days of each other. The 2 noninvasive imaging approaches were also compared with respect to their accuracy in identifying coronary anatomy as defined by invasive coronary angiography in a subgroup of 58 patients. The CTA was performed using 16- and 64-slice CT in 28 and 86 patients, respectively. The MPI was performed using either bicycle exercise, dobutamine, persantine, or adenosine stress combined with a technetium-99m imaging agent.

CTA versus invasive coronary angiography. Overall, only 36% of patients (46% of coronary vessels) in this study showed normal coronary arteries on CTA. Confirming previous studies, the agreement between CTA and invasive coronary angiography was excellent, with 52 of 58 patients being correctly diagnosed as either no CAD (9 of 9), nonobstructive CAD (stenosis <50%, 16 of 16), or obstructive CAD (stenosis ≥50%, 27 of 33). Six patients (10%) showed obstructive CAD on CTA but only mild disease on invasive coronary angiography.

CTA versus MPI. There was greater discordance between CTA and MPI results. On the one hand, most patients with normal CTA also showed normal myocardial perfusion (n = 37; 90%). However, only 45% (33 of 73) patients with abnormal CTA showed corresponding perfusion abnormalities on stress SPECT; that is, 20 of 40 patients (50%) with obstructive CAD on CTA, and 13 of 33 patients (39%) with nonobstructive CAD had MPI abnormalities. These findings also confirm earlier studies (3–5).

The low frequency (59%) of perfusion defects in the group with obstructive CAD on invasive angiography may be attributed to a balanced reduction in myocardial perfusion. This approach often underestimates the extent of underlying anatomic CAD owing to the compromised coronary vasodilator reserve in patients with CAD even in territories supplied by noncritical angiographic stenoses (6), thereby reducing the heterogeneity of flow between "normal" and "abnormal" zones. However, on a per-patient basis, the test has an excellent sensitivity to detect obstructive CAD (7), and only rarely is severe CAD missed by stress SPECT (7). The excellent prognostic value associated with a normal stress SPECT further supports the low frequency of such a phenomenon (7). The relatively high

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frequency (18%; 2 of 11 patients) of normal stress SPECT in patients with 3-vessel CAD in the present study likely reflects the small numbers of patients and/or selective referral to angiography of patients with ongoing symptoms.

The authors conclude that CTA and MPI appear to provide complementary information, the former regarding atherosclerosis and the latter regarding ischemia. These results also extend previous findings of CTA's discrimination for anatomic end points to an intermediate likelihood cohort.

WHY THE DISCORDANCE BETWEEN CTA AND STRESS PERFUSION IMAGING?

Historically, numerous investigators have shown that anatomic measures of CAD have well-described limitations with respect to delineating the physiologic implications of epicardial coronary stenoses (8). First, percentage diameter stenosis is only a modest descriptor of coronary resistance that does not incorporate other lesion characteristics (e.g., length, shape, eccentricity) or stenoses in series that may greatly affect the impedance to blood flow. Second, vasomotor tone and coronary collateral flow, both of which are known to affect myocardial perfusion, are not assessed by simple measures of stenosis severity. In contrast, MPI provides a simple and accurate integrated measure of the effect of all these parameters on coronary resistance and tissue perfusion. It follows, as shown by numerous studies over the last 3 decades, that physiologic approaches to defining CAD risk—whether stress electrocardiography, stress perfusion, or direct invasive measures of coronary flow reserve—are superior to anatomic measures with respect to clinical and cost-effectiveness end points (7,9–11).

In addition to the intrinsic limitations associated with anatomic measures, there are additional limitations to the CTA technique that introduce further error into the estimation of coronary anatomy by this technique. Recent evidence obtained with 64-slice CT indicates that quantitative estimates of stenosis severity (as a surrogate for physiologic significance) by CT correlate only modestly with quantitative coronary angiography, the former explaining only 29% of variability in the later (12). Image degradation by motion, calcium, and metal implants may all contribute to under- and overestimation of luminal narrowing by CTA. These factors may explain the significant discrepancies observed between the frequency of anatomic CAD by CTA and functionally significant stenoses by stress perfusion imaging, as evidenced by increasing evidence that anatomic-based predictions of physiologic significance by CTA differ substantially from direct measures of inducible myocardial ischemia (3–5). Finally, the referral biases inherent in many studies, including the present report, comparing these modalities (especially with respect to why a patient would have been sent to CTA versus MPI as an initial test, recruitment rates from CTA vs. MPI, and so on) further obfuscate these results. Thus, the enthusiasm for CTA as a potential noninvasive tool for guiding patient management decisions is tempered for many clinicians by a growing awareness that CTA may be limited in defining physiologic significance of coronary stenoses and, therefore, defining which patients may potentially benefit from a revascularization strategy.

SELECTING IMAGING TESTS FOR CAD

In patients with a low to intermediate (15% to 50%) pre-test likelihood of CAD the performance characteristics of conventional tests such as exercise treadmill testing or nuclear perfusion imaging limit definitive exclusion of CAD. In contrast, the expected frequency of normal CTA is high, and its use as an initial test may decrease downstream resource use and aid patient management in symptomatic subjects. In asymptomatic subjects, the dye load and radiation burden may limit the use of CTA for diagnostic purposes, but a calcium score may be helpful to guide aggressiveness of medical management.

However, this approach may not be applicable to patients with an intermediate to high (50% to 85%) pre-test likelihood of CAD. Whether CTA will be a cost-effective first step depends on its relative cost, the prevalence of abnormal CTA in the cohort to be examined, and the number of patients that can be identified as not needing further evaluation. If the prevalence of abnormal CTA is sufficiently high, or insufficient numbers of patients are spared further testing, MPI would be a superior first step. The present study and an earlier study (3) suggest that the frequency of obstructive CAD on a CTA study is ~33% (range 31% to 35%) in patients with low to intermediate or intermediate likelihood of CAD. This frequency in a higher-likelihood cohort has not been described. In this cohort, MPI in conjunction with or after CTA would also be justified. Approximately 50% of patients (3) and one-third of the coronary vessels with obstructive disease on CTA (2–5) may

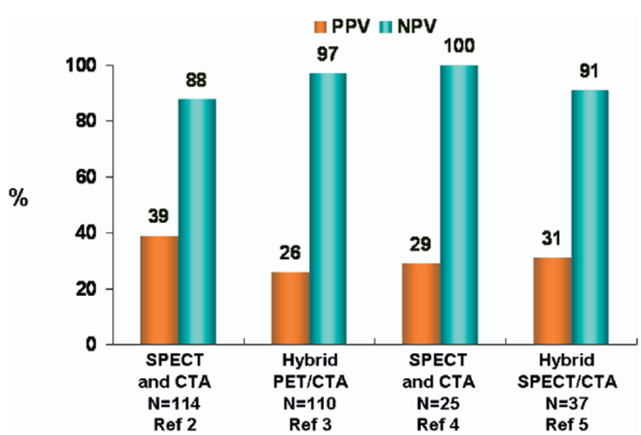

Figure 1. Value of multidetector computed tomographic coronary angiography (CTA) for predicting ischemia on myocardial perfusion imaging (per-vessel basis). NPV = negative predictive value; PET = positron emission tomography; SPECT = single-photon emission computed tomography; PPV = positive predictive value. Data adapted from Schuijf et al. (2), Di Carli et al. (3), Hacker et al. (4), and Rispler et al. (5).

show no evidence of ischemia (Fig 1). Therefore, MPI would be necessary to identify appropriate candidates for catheterization and revascularization, because this approach would not yield a benefit in patients without objective evidence of ischemia or with only small amounts of ischemic myocardium (9,11). Also, in patients with stable angina, a strategy of invasive therapy as guided by SPECT MPI was shown to be cost-effective with no increase in adverse outcomes, compared with a direct invasive approach at all levels of pre-test clinical risk. Indeed, the increased costs in the direct invasive arm was related not only to the upfront costs of a coronary angiogram but also to follow-up costs related to revascularization and other downstream costs (10). Because CTA has limited ability to define myocardium jeopardized by ischemia, its potential for predicting benefit from revascularization is limited. Therefore, evaluation of ischemic burden by MPI as an initial test, with CTA reserved for discordant test results, may be the optimal strategy for patients with intermediate to high pre-test likelihood of CAD.

In patients with a high pre-test likelihood of CAD (>85%), a negative MPI study does not exclude the diagnosis of atherosclerosis, whereas CTA is unlikely to miss severe or extensive CAD. Except in patients with high-risk scan features, combined testing with SPECT and CTA may be an effective strategy to both diagnose extent of CAD and guide management to the appropriate vessel. Patients with high-risk features on MPI are best managed by an invasive coronary angiogram with intent of revascularization. Of course, the substantial radiation burden from combined evaluation with multidetector CT (~7 to 12 mSv, chest dose) and MPI (~15 mSv, whole-body dose) needs to be balanced against the potential risks of invasive coronary angiography on a patient-by-patient basis.

The study by Schuijf et al. (2) demonstrates interesting, although expected, differences between anatomic and physiologic measures of atherosclerosis in diagnosis of CAD. These differences should be interpreted in the context of the patient cohort studied and the potential selection bias in recruiting patients with 1 abnormal test or high clinical suspicion for underlying obstructive CAD. Further, these results lead to more questions. Do the combined tests provide incremental clinical value over conventional tests? Are they cost-effective? Are both tests necessary (CTA and SPECT or positron emission tomography [PET], or hybrid PET/CT or SPECT/CT), or in what sequence (CTA first or SPECT first), and in which patient cohort (low, intermediate, or high pre-test likelihood of CAD)? The Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in CAD (SPARC) is a large prospective study registry recruiting 4,000 patients with known CAD or intermediate to high likelihood of CAD at over 40 medical centers in the U.S. This study will evaluate the impact of SPECT, PET, CTA, and PET/CT on outcomes, post-test resource use, and cost. We hope that the results will provide us with answers to many of these questions.

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