Hybrid PET/CT is greater than the sum of its parts

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The integration of radionuclide imaging of myocardial perfusion with multidetector computed tomography (CT) scanners (eg, positron emission tomography [PET]-CT and single-photon emission computed tomography [SPECT]-CT) provides a unique opportunity to delineate cardiac and vascular anatomic abnormalities, and their physiologic consequences, in a single sitting. For the evaluation of a patient with known or suspected coronary artery disease (CAD), hybrid imaging introduces a multifaceted approach to cardiovascular assessment. This approach includes the detection and quantification of the extent of calcified and noncalcified plaques via coronary artery calcium and coronary angiography, as well as the quantification of vascular reactivity and endothelial health, the identification of flow-limiting coronary stenoses, and the assessment of myocardial viability by means of PET. Consequently, by revealing the burden of anatomic CAD and its physiologic significance, hybrid imaging can provide unique information that may improve the noninvasive diagnosis, risk assessment, and management of CAD. In addition, by integrating detailed anatomic information from CT with the high sensitivity of radionuclide imaging to evaluate targeted molecular and cellular abnormalities, hybrid imaging may play a key role in shaping the future of molecular diagnostics and therapeutics. Our discussion in support of hybrid imaging will follow three key assumptions: (1) there are important limitations to both PET and computed tomographic angiography (CTA) alone for evaluating suspected CAD, (2) there is added value and complementary information in the integrated approach, and (3) hybrid imaging is the only way forward for molecular imaging.

THERE ARE IMPORTANT LIMITATIONS TO PET AND CTA ALONE

It is important to reexamine the strengths and limitations of both PET and CTA for evaluating patients with suspected CAD.

CT coronary angiography

Using state-of-the-art technology in carefully selected patients, CTA can provide high-quality images of coronary arteries noninvasively. The available evidence, mostly from single-center studies, suggests that on a per-patient basis, the average weighted sensitivity for detecting at least one coronary artery with >50% stenosis is 94% (range, 75% to 100%), whereas the average specificity is 77% (range, 49% to 100%). The corresponding average positive predictive value (PPV) and negative predictive value (NPV) are 84% (range, 50% to 100%) and 87% (range, 35% to 100%), respectively, and the overall diagnostic accuracy is 89% (range, 68% to 100%). On a per-segment basis, the average weighted sensitivity for detecting at least one coronary artery with >50% stenosis is 83% (range, 30% to 99%), whereas the average specificity is 92% (range, 64% to 98%). The corresponding average PPV and NPV are 67% (range, 14% to 91%) and 97% (range, 83% to 99%), respectively, and the overall diagnostic accuracy is 92% (range, 66% to 98%).

Data from the Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography (CorE 64) Trial, the first multicenter evaluation of the diagnostic performance of 64-slice CTA for the detection of CAD, provide further evidence that seems to temper the initial, optimistic results from single-center studies. This prospective trial enrolled patients with suspected CAD already referred for diagnostic coronary angiography at nine centers across seven different countries, using the same scanner technology. Invasive and noninvasive angiography analyzed the entire coronary tree and all nonstented segments >1.5 mm; any lesion with stenosis >50% was considered “significant.”

Of 405 patients initially recruited, the investigators selected a subset of 291 men and women aged >40 years (median age, 59 years; 74% male; median body mass index, 27; prevalence of disease on catheterization, 56%) for inclusion in the data analysis. The elimination of 48% of the recruited patients was based on several important limitations to PET and CTA alone.

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exclusion criteria, including coronary artery calcium (CAC) >600 (89 patients) and technically limited CTA or angiographic data (25 patients). Importantly, the prevalence of CAD (56%) was similar to that in previous single-center studies.

The results confirmed the robustness of 64-slice CTA for complete visualization of the coronary tree: 95% of segments and 98% of vessels were evaluable, and all coronary segments were evaluable in 97% of patients. On a per-patient basis, the sensitivity for detecting at least one coronary artery with >50% stenosis was 85% (95% confidence interval [CI], 79% to 90%), lower than in single-center studies using similar technology, whereas the specificity was 90% (95% CI, 83% to 94%). The corresponding average PPV and NPV were 91% (95% CI, 86% to 95%) and 83% (95% CI, 75% to 89%), respectively. On a per-vessel basis, the reported sensitivity for detecting coronary arteries with >50% stenosis was 76%, whereas the specificity was 93%. The corresponding PPV and NPV were 82% and 89%, respectively.

Despite widespread praise for this trial, and claims that its data support the use of 64-slice CTA as an alternative to invasive catheterization, a number of limitations must be acknowledged. First, this trial, as with previous reports on the accuracy of CTA, should be interpreted in light of the relatively narrow range for the likelihood of CAD in the patients examined (ie, intermediate-high or high), as evidenced by the high prevalence of obstructive CAD in these series (range, 56% to 62%).

Extrapolation of these results to cohorts with a lower prevalence of CAD, a population in which CTA is more likely to be used, results in a further increase of NPV (>90%), but a significant lowering of PPV (<60%).

Further, results are generally limited to relatively large vessel sizes (≥1.5 mm), excluding the results of smaller or uninterpretable vessels (generally distal vessels and side branches), the inclusion of which lowers sensitivity. An ongoing problem with CT is that high-density, calcified coronary plaques limit its ability to delineate accurately the degree of coronary luminal narrowing, which generally results in an overestimation of stenosis severity and an overall reduction in test specificity and PPV. Indeed, Core 64 excluded patients with a CAC >600. From a clinical perspective, a normal CTA is helpful because it effectively excludes the presence of obstructive CAD and the need for further testing, defines a low clinical risk, and makes management decisions straightforward. Because of its limited accuracy in defining severity of stenosis and in predicting flow-limiting disease, however, abnormal CTA results are more problematic to interpret and use as a basis for defining the potential need for invasive coronary angiography and myocardial revascularization.

A number of studies examined the accuracy of CTA in identifying myocardial perfusion-defined ischemia. In these studies, patients underwent both tests within a limited timeframe, and the myocardial perfusion imaging (MPI) results were considered the “gold standard” in the analysis. Whether using PET-defined or SPECT-defined ischemia, and 16-slice or 64-slice CTA, CTA is consistently associated with outstanding NPVs (usually >90%), but with mediocre PPVs (range, 29% to 44%).

These findings are consistent with previous studies suggesting this test’s value in excluding CAD, but of limited value to identify functionally significant CAD.

**Positron emission tomography**

Positron emission tomography imaging represents a robust approach to diagnosing obstructive CAD, quantifying the magnitude of jeopardized myocardium, and assessing the extent of myocardial viability. The published literature suggests that its average sensitivity for detecting >50% angiographic stenosis is 91% (range, 83% to 100%), whereas the average specificity is 89% (range, 73% to 100%). The corresponding average PPV and NPV are 94% (range, 80% to 100%) and 73% (range, 36% to 100%), respectively, and the overall diagnostic accuracy is 90% (range, 84% to 98%).

Although the relative assessment of myocardial perfusion with radionuclide imaging remains a sensitive means for diagnosing obstructive CAD, this approach often uncovers only that territory supplied by the most severe stenosis. This is based on the fact that in patients with CAD, coronary vasodilator reserve is often abnormal, even in territories supplied by noncritical angiographic stenoses, thereby reducing the heterogeneity of flow between “normal” and “abnormal” zones, and limiting the ability to delineate the presence of multivessel CAD. This is true for both PET and SPECT myocardial perfusion imaging. One advantage of PET over SPECT is its unique ability to assess left-ventricular function at rest and during peak stress (as opposed to post-stress with SPECT). It was recently shown that changes in left ventricular ejection fraction (LVEF) from rest to peak vasodilator stress are fundamentally different in patients with normal perfusion (increase in ejection fraction [EF]) compared with those who manifest underlying multivessel disease (decrease in EF). Consequently, by integrating myocardial perfusion results with changes in LVEF, it is possible to improve the diagnostic sensitivity of gated PET from 50% to 79% for correctly ascertaining the presence of multivessel disease. Although absolute measurements of myocardial blood flow (in mL/min/g) and coronary vasodilator reserve could also help improve the detection of multivessel CAD or characterize endothelial function, especially in the co-