Anatomic and Functional Assessment of Coronary Artery Disease
Convergence of 2 Aims in a Single Setting

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Between two worlds life hovers like a star, twixt night and morn, upon the horizon’s verge.
—Lord Byron

C
onventional noninvasive methods of evaluation of individuals with suspected coronary artery disease (CAD) have relied on functional testing by an array of modalities, including exercise treadmill testing, stress echocardiography and myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT).1 or positron-emission tomography (PET).2 In their most commonly used applications, these modalities are useful for assessing myocardial perfusion and function at rest and in response to exercise or pharmacological intervention, providing valuable information regarding the presence or absence of obstructive CAD, future cardiac events, and predicting benefit from appropriate therapies.

Among the wide range of functional imaging tests, SPECT-MPI has emerged as the most commonly used modality—accounting for nearly 90% of imaging stress tests performed in the United States each year.3 Early studies examining SPECT indicate that myocardial perfusion is reduced in the presence of a ≥70% intraluminal epicardial stenosis.4 Beyond its diagnostic potential, the widespread use of SPECT-MPI stems from its robust ability for prognostic risk stratification, such that individuals with normal SPECT have very low rates of near- and intermediate-term adverse CAD events, whereas those with severely abnormal SPECT-MPI have high rates of adverse CAD events.5 Further, SPECT may identify patients who may most benefit from invasive coronary angiography (ICA) and coronary revascularization in addition to medical therapy versus those who would benefit from medical therapy alone.6,7

Given its ability for high count-rate dynamic studies, PET promises a noninvasive assessment of coronary flow reserve and absolute coronary flow.11 Although SPECT and PET function-based evaluations for flow-limiting CAD lesions have become the standard, these approaches are costly. Additionally, SPECT misclassifies a significant proportion of patients as low risk12,13 and has a false-positive rate such that the proportion of patients undergoing ICA after SPECT, in whom no obstructive CAD is identified, remains substantial. Recent estimates indicate that >50% of individuals referred for elective ICA do not have obstructive CAD; patients with equivocal or positive SPECT studies constitute a large proportion of these patients.14

Recently, coronary computed tomography angiography (CCTA) has emerged as an accurate anatomic method for detection of CAD.15,16,17 Particularly for individuals without known CAD, the sensitivity to detect as well as the negative predictive value to exclude obstructive CAD at both the 50% and 70% intraluminal stenosis thresholds approaches 100%. However, specificity and positive predictive value of current-generation CCTA interpretation have been less robust, reflecting a higher than desirable rate of false-positives. In this regard, prior reports have suggested that interpretation of CCTA is commonly associated with a general overestimation of CAD stenosis severity, and recent data suggest an inability to differentiate between slight differences in stenosis severity (eg, 50% to 69% versus ≥70%).18 Because anatomic definitions of CAD significance are generally defined at the 70% stenosis threshold, some have contended that the use of CCTA may simply increase rates of unnecessary ICA and coronary revascularization.19 Furthermore, dense coronary calcification often makes it impossible to evaluate luminal stenosis in patients with CAD. Thus, there is concern that CCTA will also result in an increase in the rate of unnecessary ICA.

Thus, there are strengths and limitations of both the SPECT and PET functional approaches and the anatomic approach of CCTA. It has become common practice to begin an evaluation with one of these modalities and to perform imaging with the complementary modality when the results of the first test are in question.20 Alternatively, several recent studies have evaluated the feasibility of hybrid imaging by SPECT-CT or PET-CT, with aims to maximize the advantages of both.

After early validation as a sensitive method for assessing reduction in coronary flow reserve,8 PET-MPI has also become a clinically useful method for the same applications as SPECT-MPI, adding higher resolution imaging and the ability to image ventricular function during peak stress.9,10 Given its ability for high count-rate dynamic studies, PET promises a noninvasive assessment of coronary flow reserve and absolute coronary flow.11

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163
functional and anatomic imaging methods. These early studies suggest enhanced diagnostic test performance by hybrid imaging, as compared with functional or anatomic imaging alone, for the detection of “functionally significant” stenoses. It is very difficult, however, to know a priori that a patient will need both the PET or SPECT and CCTA, and performance of both tests increases radiation burden and costs. Thus, an active area of scientific pursuit has been to identify a “1-stop shop” that is capable of concurrently evaluating coronary artery stenosis presence and severity and myocardial perfusion by a single modality during a single examination.

In this issue of Circulation: Cardiovascular Imaging, George et al examine single-modality imaging by CCTA for assessment of both anatomic coronary artery stenosis severity and functional myocardial perfusion. In this pilot study of 40 patients with abnormal SPECT undergoing rest and adenosine stress CCTA by either 64- or 256-detector-row CCTA, diagnostic performance of CCTA and CT perfusion (CTP) (CCTA/CTP) was compared for 27 individuals undergoing ICA, using the combination of quantitative coronary angiography (QCA) and SPECT-MPI (QCA/SPECT) as a reference standard. Per-patient diagnostic sensitivity, specificity, positive predictive value, and negative predictive value were measured from a canine model from the same group, in which the transmural perfusion ratio (TPR) of subendocardial to subepicardial attenuation density correlated with myocardial blood flow as measured by microspheres.

This study represents a large step forward for the field of CCTA, demonstrating the potential feasibility of myocardial perfusion imaging by CCTA using the TPR. Nevertheless, this study is not unlike many early “proof of principle” studies, which tend to raise as many questions as they seek to answer.

In the present analysis, the study cohort represented a selective population of individuals prechosen because of an abnormal SPECT. This criterion alone probably contributed to the escalation of the diagnostic performance of CCTA/CTP caused by referral bias. Further, the overall study population was small. Indeed, only 43 patients underwent CCTA/CTP, and, among these, less than two thirds of patients eventually underwent ICA for diagnostic confirmation. Diagnostic performance of the CCTA/CTP technique was based solely on patients undergoing ICA, thus further exacerbating referral bias. Compounding these biases was a heterogeneous mixture of individuals both with and without known CAD.

In the study, the definition of a normal TPR was based on 14 patients who underwent CCTA/CTP who did not exhibit >30% stenosis by CCTA. This ratio in “normal” individuals was 1.12, and an abnormal TPR was then designated as <0.99, which represented only 1 standard deviation below that considered normal. A number of potential limitations arise from these definitions, including a lack of a validation cohort for the derived normal patients, inclusion of the 14 normal patients into the overall cohort, and the classification of a sizable proportion of patients within 2 standard deviations from the mean 1.12 ratio as abnormal.

Although the TPR may theoretically enhance detection of subendocardial ischemia, it is unclear how it would perform for transmural ischemia. In this scenario, a subendocardial to subepicardial ratio may be decreased, which may result in a falsely elevated TPR. It is this issue of per–myocardial segment balanced reduction of perfusion that may result in discordance between CCTA/CTP and QCA/SPECT.

The issue of balanced reduction of perfusion that has been described with SPECT was addressed by the authors, but only as it related to SPECT. For patients with QCA-confirmed 3-vessel or left main disease, perfusion deficits identified by the CCTA/CTP strategy were considered true-positives—even if SPECT perfusion was normal—in an attempt to avoid “penalizing” CCTA/CTP for SPECT misdiagnosis of balanced ischemia. This type of analysis is problematic because QCA/SPECT had been defined a priori as the reference standard and probably serves to falsely elevate the diagnostic performance of CCTA/CTP. Just as artifactual perfusion defects. CTP performed during adenosine infusion increases heart rate and thus the likelihood of artifactual reductions in CT attenuation densities caused by heart motion, partial volume effects, and beam-hardening artifacts. The authors used a beam-hardening correction software, although the performance of CCTA/CTP with and without the software was not discussed in the study results.

A potentially interesting analysis would have been a comparison of the results of CCTA/CTP versus QCA/SPECT for both 64- and 256-detector-row CT. The wide-area 256-detector CT permits single axial image acquisition of the heart in less than a single heartbeat. Whether simultaneous imaging of all myocardial segments renders different diagnostic performance as compared with sequential imaging of the heart in 4 to 7 heartbeats, as is required by 64-detector-row CT, remains unknown because this analysis was not performed (probably because of the small number of patients). Finally, in keeping with prior studies, it would have been valuable to determine the incremental value of CTP to CCTA alone for the diagnosis of QCA/SPECT-defined obstructive CAD.

Despite its limitations, this study represents a significant advance for the field of CCTA. Criticisms of CCTA have focused on the inability of CCTA to assess the “functional” significance of an identified stenosis. In their pilot study, George et al demonstrated that this assessment can be accomplished without additional testing modalities. Clearly, a great deal of work in refining and validating the approach is needed before this approach becomes a clinical reality. Nonetheless, this pilot study provides important early evidence that CCTA may hold the potential to serve as a single modality for the concurrent assessment of both anatomic coronary stenoses and their functional physiological significance.

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References


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