



Functional and Anatomical Imaging in Patients with Ischemic Symptoms and Known Coronary Artery Disease

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Abstract

Purpose of Review This review is aimed at summarizing recent advances in functional, anatomical, and hybrid imaging techniques used in the assessment of ischemic complaints in patients with known coronary artery disease (CAD).

Recent Findings Cardiovascular imaging has seen significant growth over the last decade in the fields of coronary computed tomography angiography (CCTA), FFR derived from CCTA, cardiac magnetic resonance, radionuclide myocardial perfusion imaging, and hybrid imaging for the purposes of evaluating symptoms concerning for ischemia. This growth stems from refinement of imaging techniques and hardware and software advances that have made current techniques more accurate with less acquisition time. However, every anatomic and functional imaging modality has important technical and patient-specific limitations. This review assesses these issues, guides a patient-centered imaging approach, and identifies important research questions to resolve.

Summary Recent advances in non-invasive cardiovascular imaging can provide important information in patients with known CAD beyond traditional imaging techniques; the use of these novel tools refines the clinical management of complex patients with ischemic symptoms and known CAD.

Keywords Functional imaging · Anatomical imaging · Coronary artery disease · Coronary computed tomography angiography · Radionuclide myocardial perfusion imaging · Cardiac magnetic resonance

Introduction

A growing and challenging aspect of managing patients with ischemic chest pain is assessing these symptoms in the context of known coronary artery disease (CAD). The population with known CAD is expanding; the American Heart Association 2016 Heart Disease and Stroke Statistics update predicts an increase from 6.2% of US adults to 18.0% by 2030 [1]. The

presence of extensive known CAD complicates imaging. In addition, those with known CAD also have high rates of comorbidities such as heart failure, atrial fibrillation, valvular heart disease, chronic kidney disease (CKD), and diabetes mellitus. These concomitant conditions lead to symptoms that can be difficult to differentiate from those caused by myocardial ischemia and can also serve as relative or absolute contraindications to certain imaging techniques. Finally, coronary revascularization with coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI) creates unique challenges and considerations.

Imaging techniques have been developed to help address considerations in the known CAD population such as differentiating the presence, degree, and location of myocardial ischemia when multiple obstructive lesions are present, assessing incomplete revascularization, identifying graft/stent restenosis, evaluating de novo stenoses in the native coronary vasculature, and quantifying the presence and degree of myocardial viability. Identifying risk and optimal treatment strategies in these patients is essential given the expanding revascularization options now available, including high-risk

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and complicated PCI, PCI for chronic total occlusion (CTO), mechanically supported PCI in heart failure, and CABG. Advanced functional testing can identify coronary microvascular dysfunction (CMD), which increases the rates of major adverse cardiovascular events (MACE) both in those with epicardial CAD and in the up to 44.5% of patients referred for invasive coronary angiography (ICA) who are found to have normal or non-obstructive CAD [2•, 3, 4, 5•].

To meet the demand of assessing ischemic symptoms in patients with known CAD, there have been significant advancements in anatomical and functional imaging processes. These improvements stem from breakthroughs in imaging techniques, hardware, and software. These advancements now allow for generation of valuable diagnostic information beyond the presence of myocardial ischemia. Modern non-invasive techniques can now better visualize coronary anatomy, precisely quantify myocardial ischemia, diagnose CMD, and assess myocardial viability with better accuracy than historical processes. Moreover, a comprehensive anatomic and functional evaluation can be performed through hybrid single-photon emission computed tomography (SPECT)-CT or PET-CT imaging, and there is an early progress in the use of hybrid PET-MR imaging. The presence of known CAD increases the pretest risk and creates specific challenges. Nevertheless, these techniques can be applied selectively to take advantage of each modality's benefits, minimize specific limitations, and optimize patient-centered imaging. In this review, we will summarize the recent advances and compare and contrast the advantages and weaknesses of different anatomical, functional, and hybrid imaging techniques for the evaluation of ischemic symptoms in patients with existing known CAD.

Anatomical Imaging

Anatomical imaging to directly visualize coronary artery obstruction can be used in patients with ischemic symptoms and known CAD. Several techniques exist for this purpose, ranging from an invasive approach with ICA (the most commonly used technique) to non-invasive anatomic modalities, including computed tomography (CT) coronary angiography alone or with concomitant non-invasive fractional flow reserve (FFR_{CT}) assessment and coronary magnetic resonance angiography (MRA).

ICA was the first anatomic imaging modality to be developed and has served as the “gold standard” for imaging coronary arteries for the last 50 years. The primary indication for ICA in symptomatic patients with known CAD is to confirm the diagnosis and guide revascularization in the setting of a stress test demonstrating significant inducible ischemia (≥ 10 –12.5% of the left ventricle). ICA is appropriate without stress testing in the immediate hours or days following CABG to assess for anastomotic failure or graft occlusion/thrombosis or

following PCI for acute stent thrombosis or deployment complications. The role of ICA without prior stress is limited after that time period as stress testing has advantages such as quantification of the extent, location, and severity of new or remaining ischemia and non-invasive evaluation of atypical symptoms. Current guidelines recommend stress testing prior to ICA in patients who develop ischemic symptoms weeks to months following revascularization [6•]. Therefore, in the absence of an acute coronary syndrome, most patients with known CAD do not need to be sent directly to ICA without a non-invasive functional or anatomic assessment.

Non-invasive anatomic imaging has expanded to provide information beyond the simple luminal obstruction information assessed by ICA, including coronary artery calcification (CAC) scoring, vessel wall visualization, and approximation of functional impact (with FFR_{CT}). CAC scoring has a very limited role in patients with known CAD and is not appropriate as the sole assessment of new ischemic complaints due to the moderate prevalence of non-calcified coronary obstruction in symptomatic patients [6•, 7]. CCTA has undergone technical improvements and concomitant reductions in radiation dose over the last 20 years that have increased its utility to assess for the presence or absence of epicardial CAD [6•, 8•, 9]. CCTA can accurately exclude the presence of CAD in patients with ischemic symptoms and no known CAD due to its high negative predictive value (NPV) [10–12]. Thus, CCTA is listed in several Appropriate Use Criteria (AUC) guidelines as a reasonable initial diagnostic test to assess for CAD in patients at low or intermediate pretest probability of CAD who have an uninterpretable ECG or inability to exercise [6•, 8•, 9]. However, its role in patients with known CAD is much more limited. CCTA overestimates the degree of stenosis and functional impact of coronary lesions, with multiple studies showing a positive predictive value (PPV) of $< 50\%$ for ischemia in lesions read as $\geq 50\%$, particularly in those with heavy calcification [13–15]. The number and severity of these lesions are increased in patients with known CAD. Thus, CCTA's well-established role in diagnosing CAD must be distinguished from its ability to assess patients with known CAD, particularly in those who have complex multivessel disease or who are status post-coronary revascularization. Current AUC guidelines give CCTA a class III recommendation for patients with known moderate to severe native coronary artery calcification, a finding common in patients with advanced known CAD [8•]. Coronary anatomy in regions with prior coronary revascularization can be assessed with CCTA; however, additional diagnostic challenges must be taken into consideration.

For patients with coronary artery bypass grafts, the origin and proximal portions of the venous and arterial conduits can be easily imaged by CCTA given that the grafts are relatively static in this region adjacent to the aorta and subclavian arteries. In contrast, the distal graft segments and anastomotic site move

more freely, leading to increased motion artifact. Furthermore, the anastomotic site is narrower, typically < 2 mm in diameter. Despite these challenges, CCTA shows excellent concordance with ICA for graft obstruction [16–18]. Additionally, Ropers and colleagues demonstrated high sensitivity and specificity in assessing both native vessels and grafts compared with ICA [18]. These findings have been confirmed by a 2016 meta-analysis by Barbero et al. [19]. This performance is important given that patients with CABG anatomy may have new or worsening ischemia from obstruction in either their grafts or native vessels. Moreover, these studies also demonstrated the high diagnostic accuracy of CCTA to detect venous graft occlusion [16–18]. Identifying occluded grafts can minimize issues from attempted engagement with diagnostic catheters and reduce radiation exposure, contrast load, aortic injury, and other risks. Although CCTA post-CABG evaluation has improved, patients with prior CABG and new ischemic symptoms typically receive a functional imaging assessment.

In contrast to post-CABG evaluation, there have been limited studies using CCTA to assess stent patency in patients with ischemic symptoms. The primary limitation of CCTA in patients with prior PCI is that metallic stents can cause blooming artifacts, making stent evaluation challenging and lowering the positive predictive value. Two meta-analyses have shown high sensitivity (> 86%) and specificity (> 91%) for in-stent restenosis detection using CCTA compared with ICA as a gold standard [20, 21]. However, it is important to note that several studies included in these analyses excluded or had small numbers of patients with stents < 3 mm, a substantial proportion of those with prior revascularization. To date, the use of CCTA in coronary stent evaluation has traditionally been limited to coronary stents > 3 mm. However, a small but encouraging study by Li and colleagues has demonstrated preserved sensitivity and reduced specificity (84.2%) for assessing in-stent restenosis in coronary stents < 3 mm with the introduction of third-generation dual-source CT [22•]. The 2014 American College of Cardiology/American Heart Association (ACC/AHA) Stable Ischemic Heart Disease guideline gives CCTA a class IIb recommendation to assess CABG or coronary stent patency regardless of graft diameter and in the absence of severe coronary calcification [8•]. The most recent AUC guideline states that CCTA “may be appropriate” in these patients [6•]. It is important to note that moderate to severe coronary calcification is typically present in patients with known CAD, especially in those with CABG or multiple prior stents. These recommendations will need re-examination as imaging techniques improve. However, given these current limitations with CCTA, functional imaging is preferred in patients with known CAD and particularly in those post-revascularization.

While CCTA detection of obstruction remains challenging in patients with known CAD, there is significant benefit in one application. In patients with coronary CTO, CCTA is being

used to assist the planning of complex recanalization interventions. CTO interventions require careful scrutiny of the course of the coronary artery planned for intervention. ICA typically provides incomplete data in this situation because contrast is unable to fill the coronary distal to the complete obstruction. CCTA can visualize the path of the coronary in the absence of contrast and can thus help guide recanalization [23, 24•]. The use of CCTA has been shown to improve success rates in complex CTO interventions compared with ICA alone [25]. Furthermore, the additional information provided by CCTA may help predict the likelihood of success and of complications of a CTO intervention prior to the procedure, which can greatly aid in planning and inform the decision of whether to proceed with the intervention [26, 27]. In addition to the challenges created by known CAD and its revascularization, there are additional patient-specific limitations that have increased the prevalence in patients with known CAD and may pose a barrier. For instance, CCTA is ideally performed in patients in a sinus rhythm with heart rate < 70 beats/min. This can be a limiting factor for patients with atrial fibrillation or those with high ventricular or atrial ectopy, which are rhythms with higher incidence in those with known CAD. Moreover, CCTA requires the use of iodinated contrast, which needs to be given cautiously in all patients with CKD and should be avoided entirely in patients with severe CKD.

The greatest diagnostic limitation of CCTA is its inability to directly assess the physiologic significance of stenotic lesions. To address this shortcoming, FFR_{CT} has been developed and is an important developing technique. FFR derived invasively is considered the “invasive gold standard” for determining the functional significance of coronary stenosis without concomitant use of functional imaging [28]. FFR_{CT} allows functional significance to be estimated non-invasively, utilizing CCTA anatomical imaging information and computational fluid dynamics to provide an estimated FFR. This technique was developed by Taylor et al. and has seen significant growth over the last several years [29]. In the NXT trial, FFR_{CT} provided improved diagnostic accuracy and performance for the diagnosis of hemodynamically significant coronary lesions compared with traditional CCTA when invasive FFR was used as the reference standard [30]. By incorporating this and other similar studies, a meta-analysis confirmed the preserved sensitivity but improved specificity of FFR_{CT} over CCTA alone for hemodynamically significant coronary lesions [31]. Nørgaard and colleagues recently retrospectively analyzed 3674 patients with ischemic chest pain evaluated by CCTA and FFR_{CT} to assess performance with regard to outcomes in intermediate coronary stenosis (30–70%). Those patients with a FFR_{CT} > 0.8 had similar 3-year MACE outcomes as patients with coronary lesions < 30% (3.9% vs. 2.8%, *p* = 0.68) [32••]. This is promising data, with regard to the assessment of patients with known CAD, as coronary lesions identified with FFR measurements > 0.80 can likely be safely

monitored with FFR_{CT} . Furthermore, FFR_{CT} can likely exonerate individual lesions as the culprit lesion causing ischemic symptoms. Further similar studies studying patients with known CAD are indicated to assess FFR_{CT} 's role in this population.

FFR_{CT} has limitations, however, in patients with known CAD and particularly in those with prior coronary revascularization. As with CCTA, FFR_{CT} use is limited in scans with blooming and motion artifacts. Additionally, FFR_{CT} cannot be used to assess vein grafts, nor can it be used to assess lesions with coronary stents. To date, FFR_{CT} is not included in AUC guidelines [6•, 8•]. In fact, the 2018 European Society of Cardiology Guidelines on Myocardial Revascularization specifically state that clinical trial data with FFR_{CT} are currently insufficient to make a recommendation for its use in clinical practice [33•]. Despite these caveats, we anticipate that FFR_{CT} will be added in subsequent iterations of CAD guidelines for appropriate patients. Of note, FFR_{CT} is currently limited by institutional access as the technique is a proprietary technology of HeartFlow (Redwood City, CA, USA). At this time, we believe there is insufficient data to warrant FFR_{CT} 's widespread use in patients with ischemic complaints and known CAD, particularly in patients who are status post-revascularization.

In contrast to the growth of CCTA, magnetic resonance angiography (MRA) has remained an infrequently utilized anatomic coronary imaging technique. Coronary MRA has the potential to detect high-risk plaque characteristics and plaque burden without exposure to radiation. Moreover, it is not limited by coronary calcium to the same degree as CCTA [34]. While MRA has been recommended for identifying anomalous coronary artery origins and coronary artery aneurysms [35], current AUC guidelines do not otherwise endorse its use for the detection of significant coronary artery stenosis in patients with ischemic symptoms [6•]. The only application of coronary MRA studied in known CAD is for the assessment of bypass graft patency. However, this technique is limited by sternal wires, metallic vascular clips, graft markers, and other implanted prosthetic material [35]. Given this limitation and the otherwise lack of data in patients with known CAD, coronary MRA plays a limited role in this population and we expect future AUC documents to refrain from recommending coronary MRA in patients with known CAD.

Functional Imaging

The fundamental purpose of functional imaging is to detect the presence and degree of myocardial ischemia, which is the hemodynamic consequence of epicardial coronary stenosis or CMD. If ischemia is present and significant, revascularization may be warranted. Functional imaging also provides helpful prognostic information. Traditional functional techniques

have included exercise electrocardiography (ExECG), exercise echocardiography (ExEcho), dobutamine stress echocardiography (DSE), and exercise and pharmacologic myocardial perfusion imaging (MPI) utilizing single-photon emission computed tomography (SPECT). However, functional imaging has seen significant growth over the last 20 years in the fields of positron emission tomography (PET) and cardiac magnetic resonance (CMR); these advanced imaging modalities can provide additional diagnostic information beyond traditional functional techniques, assessing myocardial scar burden, CMD, and myocardial viability in addition to perfusion. Given these advancements, functional imaging can be divided into epicardial and microvascular perfusion and metabolic and hybrid imaging.

Functional Imaging in Epicardial Coronary Artery Disease

ExECG has been used for decades to establish a diagnosis of CAD. ExECG is considered an appropriate initial test in patients presenting with ischemic symptoms without known CAD who have an interpretable ECG and are able to exercise [8•]. In patients with known CAD and in those who are post-revascularization, ExECG is considered “maybe appropriate” by current AUC guidelines rather than “appropriate” [6•], as it cannot reliably demonstrate the extent of myocardial ischemia nor localize which coronary vessels are inducing ischemia outside of ST elevation without Q waves [36]. However, regardless of revascularization status, ExECG provides exercise capacity, the most powerful stress predictor of mortality [37]. For example, patients with and without known CAD who achieve ≥ 10 METS on ExECG without ischemic electrocardiographic changes have a very low prevalence of significant ischemia on MPI and subsequent cardiac events [38, 39]. This may reduce the importance of adding imaging to ExECG in some patients able to achieve a high workload. Novel enhancements to traditional ExECG, such as high-frequency QRS analysis (HF-QRS), can improve diagnostic accuracy over conventional ST segment analysis. Future studies of this technique in patients with known CAD are warranted to identify lower-risk patients without significant ischemia in whom MPI or echocardiographic imaging may not be necessary [40•].

ExEcho/DSE and SPECT MPI are the most commonly used techniques in functional imaging. A meta-analysis from 2007 showed impressive negative predictive values ($> 98.4\%$) for both of these techniques in patients with and without CAD up to 33 months following testing [41]. One study of 266 patients with known CAD followed for 12 years found an annualized cardiac mortality rate of 0.9% following a normal SPECT MPI [42]. Current guidelines state that ExEcho/DSE and MPI (SPECT or PET) are “appropriate” first-line studies

to assess for ischemic symptoms in patients with known CAD with and without prior revascularization [6•, 8•]. However, patients with known CAD have substantial rates of issues known to limit ExEcho/DSE accuracy, including poor sonographic windows, underlying wall motion abnormalities (WMAs), ventricular pacing, and bundle branch blocks [43]. Furthermore, it is more challenging to quantify ischemia using ExEcho/DSE compared with MPI. Visual separation of affected myocardial segments into dichotomous hypokinetic or normal wall motion provides less precision than the grading and quantitative scoring possible with nuclear MPI. The degree of ischemia on MPI can predict benefit with coronary revascularization in all patients [44], specifically in diabetics and the elderly [45, 46].

In contrast to the limitations of other anatomic and functional modalities, SPECT MPI is not limited by heart failure, resting WMA, ventricular pacing, atrial fibrillation, bundle branch blocks, or CKD and is generally reproducible between different institutions and laboratories. Thus, SPECT MPI can be used to assess ischemic symptoms in more patients with known CAD compared with ExEcho/DSE and other techniques. However, MPI does require radiation and more time to perform compared with ExEcho/DSE. However, high-efficiency imaging SPECT cameras incorporating solid-state cadmium-zinc telluride (CZT) detectors and new iterative reconstruction methods have been developed and enable faster MPI with less radiation, increased count sensitivity, and higher resolution [47]. For example, Einstein and colleagues showed that very low-dose rest imaging with high-efficiency CZT cameras led to superior image quality and similar perfusion assessments versus usual-dose conventional SPECT Anger camera imaging despite a lower radiation dose [48]. The prevalence of prior MI in this population was 45.5%, making this technique applicable to patients with known CAD. Other protocols to limit radiation have also been reported, particularly with stress-only imaging, which has also been shown to be safe and effective. Chang et al. showed lower mortality (2.57% vs. 2.92%, $p = 0.02$) with normal stress-only SPECT compared with rest/stress imaging in 16,854 patients [49]. Of note, 4652 (27.1%) of the patients in this study had prior known CAD. While these improved SPECT imaging techniques are promising, however, PET MPI has several advantages over SPECT MPI.

The use of PET MPI in functional imaging has grown significantly over the last 15 years due to multiple factors. PET MPI has improved spatial resolution, higher count sensitivity, and more accurate soft issue attenuation correction compared with SPECT, allowing better imaging quality regardless of body habitus. Furthermore, PET MPI has superior diagnostic accuracy compared with SPECT MPI as shown in two meta-analyses published in 2012. These studies demonstrated sensitivities of 90–92.6% and 85–88.3% and specificities of 81.3–88% and 75.8–85% for PET and SPECT,

respectively, when compared with ICA [50, 51]. Both of these studies included patients with known CAD. Ischemic burden on PET MPI predicts all-cause mortality as with SPECT, but there are additional diagnostic and prognostic measures with PET [52]. PET MPI provides a true stress left ventricular ejection fraction (LVEF), and the LVEF reserve (difference between stress and rest) predicts the extent of obstructive disease and MACE [53]. PET MPI also allows for quantification of regional and global absolute myocardial blood flow (in mL/g/min) and the ratio of stress to rest flow and the myocardial perfusion reserve (MPR). These measures can improve diagnostic accuracy and are prognostically significant in patients with known CAD [54–56]. This analysis requires no additional imaging time or radiation exposure. PET radiotracers also have superior characteristics; ^{13}N -ammonia and ^{82}Rb rubidium have improved myocardial uptake across coronary flow rates compared with typical SPECT radiotracers. However, the cost and production challenges with PET MPI radiotracers have limited the growth of PET MPI, and it remains 20 times less utilized than SPECT despite its advantages [57]. Limitations to this technique are improving. PET radiotracers are becoming easier to procure with the advent of onsite compact cyclotrons for ^{13}N -ammonia and onsite generators for ^{82}Rb rubidium. This will improve the accessibility to PET MPI in the future. Given the significant benefits of PET MPI over SPECT MPI, the American Society of Nuclear Cardiology and Society of Nuclear Medicine and Molecular Imaging recently released a position statement stating that PET MPI is the preferred modality over SPECT MPI in patients requiring pharmacologic stress [58••]. Accessibility will also improve with the development of new potential radiotracers such as ^{18}F -flurpiridaz, which is undergoing a phase 3 study [59••]. The 110-min half-life of this agent allows production remote to the imaging location.

The other advanced stress imaging modality, stress CMR, has several important applications within functional imaging for CAD. CMR allows for a comprehensive evaluation of myocardial structure, ventricular function and volume, myocardial perfusion, absolute myocardial blood flow, and detailed scar mapping, which also provides information on myocardial viability [60]. All of this information can be gleaned without exposure to ionizing radiation. CMR MPI is not limited by attenuation artifacts, yielding improved spatial resolution that better identifies myocardial scar compared with SPECT. For the purposes of evaluating possible obstructive epicardial CAD, CMR MPI has improved diagnostic accuracy over SPECT [61]. For patients with ischemic complaints and known CAD with an uninterpretable ECG or inability to exercise, stress CMR is considered “reasonable” by current guidelines [6•]. It is also a reasonable technique to ascertain the functional significance of coronary artery stenosis identified by ICA or CCTA [6•].

It is important to note that CMR has substantial patient-specific limitations, including contraindications to all MRI scanning such as with certain pacemakers/cardioverter-defibrillators and patient intolerance due to claustrophobia and inability to follow breath-hold instructions. CMR's greatest limitation is the use of gadolinium, which is contraindicated in patients with acute renal insufficiency or eGFR less than 30 mL/min/1.73 m² [2••], both of which may limit CMR use in patients with known CAD. However, it is important to note that coronary stents, mechanical heart valves, valvular annuloplasty rings, and sternal wires are not limitations for CMR.

The most intriguing recent development in CMR MPI has been the ability to quantitate absolute stress perfusion. CMR quantitative perfusion utilizes deconvolution techniques to measure absolute myocardial blood flow. Mordini and colleagues demonstrated a sensitivity of 87% and a specificity of 93% compared with ICA in a population with 25% prevalence of known CAD status post-PCI [62]. Absolute myocardial blood flow is helpful in assessing CMD in patients with CAD. This technique has also been shown to be effective in diagnosing CMD in at-risk patients with angina and non-obstructive CAD on ICA [63••]. A recent study performed by Liu and colleagues validated the diagnostic accuracy of assessing both epicardial CAD and CMD. They measured the index of microcirculatory resistance (IMR) during ICA in patients with reduced myocardial perfusion reserve index (MPRI) and found that MPRI correlated significantly (inversely proportional) with IMR ($\rho = -0.67, p < 0.001$) [64].

Functional Imaging in Coronary Microvascular Disease

CMD has been traditionally defined as the presence of poor coronary microvascular perfusion, which may be severe enough to cause myocardial ischemia. This can occur in the presence or absence of epicardial CAD. Patients with ischemic complaints and no obstructive epicardial CAD appreciated on ICA who have reduced CFR measurements derived during PET MPI or CMR likely have microvascular angina (MVA) secondary to CMD. Conversely, normal coronary flow reserve (CFR) in these patients may help eliminate CAD or MVA as the etiology of chest pain. Thus, these measurements are essential in patients with known CAD to help determine symptom etiology. Knowing the presence of CMD is also important prognostically. Patients with CMD with and without known epicardial CAD have higher rates of MACE [3, 4]. These adverse outcomes are independent of gender, as the prevalence of CMD is similar among both men and women [65]. It is important to note that women have been shown to have less obstructive epicardial disease than men

in the presence of impaired CFR, but are not protected from MACE [66].

Taqueti and colleagues demonstrated that patients with low CFR undergoing early revascularization with CABG experienced similar event rates compared with those with preserved CFR. They also showed that patients with low CFR experienced rates of MACE similar to those of subjects with advanced epicardial disease as evident in high angiographic scores [56]. This study and others suggest that CFR may have the potential to risk stratify patients with ischemia who may benefit from early revascularization. However, future studies utilizing CFR in patients with CAD with and without prior revascularization are needed. Furthermore, prospective clinical trials are needed to determine optimal treatment therapies for patients with CMD and MVA as there is little evidence to support therapies offered at this time [5•, 67].

Myocardial Metabolic and Viability Imaging

Revascularization decisions in patients with known obstructive CAD and ischemic heart failure are challenging because improvement in function and MACE events is variable and this cohort has elevated surgical risk. The question of whether revascularization will improve myocardial function and/or MACE becomes the key. Classically, it has been thought that the myocardium that is “stunned” or “hibernating” may have some function restored following revascularization in contrast to myocardial tissue that has undergone necrosis and remodeling [68]. Techniques have been developed over the past 30 years to assess myocardial viability, each modality assessing a different physiologic aspect: DSE examines contractile reserve, SPECT reveals cellular integrity, F18-FDG PET assesses myocardial cellular metabolism, and CMR imaging with late gadolinium enhancement (LGE) identifies the presence or absence of myocardial scar. A frequently cited meta-analysis by Allman and colleagues demonstrated a strong association between myocardial viability on non-invasive testing and improved survival after revascularization in patients with chronic CAD and LV dysfunction [69]. When this analysis was redone with more restrictive evidence-based inclusion criteria, the magnitude of benefit was lower but still present [70]. The 2013 ACCF/ACR/AHA/ASNC/SCCT/SCMR Appropriate Utilization of Cardiovascular Imaging in Heart Failure guideline states that viability testing (with rest and stress imaging) is appropriate in patients with reduced left ventricular function with and without angina who are known to have anatomy amenable to revascularization [71•]. Furthermore, revascularization is given a class I recommendation in patients

with heart failure with a large area of the viable myocardium and high-risk criteria on non-invasive testing [71•].

It is important to note that a non-randomized subgroup of the STICH trial showed no differential survival benefit with a strategy of CABG-based revascularization guided by viability testing versus optimal medical therapy [72•]. However, this study had significant patient selection bias and was primarily limited to SPECT and DSE testing. In part due to the results of this analysis, advanced imaging techniques utilizing FDG PET and LGE on CMR are becoming the preferred techniques for viability imaging. Another important randomized trial comparing the use of FDG PET in the evaluation of revascularization in patients with heart failures did not show a difference in MACE. MACE was seen in 30% of patients when FDG PET was included versus 35% when FDG PET was not included; however, this was not statistically different. In patients in whom the revascularization decision followed the recommendation of the FDG PET study compared with the group with no FDG, there was a statistically significant benefit (HR 0.62, 95% CI 0.42–0.93, $p=0.019$) [73]. Given these findings, the 2013 ACC/AHA Guideline for the Management of Heart Failure gave viability testing a class IIa recommendation for the purposes of planning revascularization [74•]. Randomized trials with modern imaging and revascularization techniques are warranted to examine this area further. In the meantime, it is our opinion that viability testing is reasonable when planning revascularization in patients at high surgical/interventional risk in whom revascularization in the setting of limited myocardial viability should likely be avoided. Low-risk patients likely would not benefit from viability testing.

Hybrid Imaging

Hybrid imaging techniques combine SPECT or PET with CCTA or CMR to produce synergistic anatomic and functional information. In essence, all of the benefits of each technique can be used to complement each other when acquired together (often in one session) to ascertain the presence of coronary artery stenosis/plaque characteristics and the physiological/metabolic significance of obstruction. The benefit of these techniques is best highlighted in patients who have equivocal results on CCTA (moderate coronary stenosis, lesions complicated by coronary calcium, etc.) to determine their physiological significance and in patients with multiple stenoses to determine which are physiologically significant. A recent meta-analysis of 12 studies comparing CCTA with hybrid imaging techniques showed unchanged sensitivity but improved specificity (93% vs. 66%, $p<0.001$) for hybrid imaging over CCTA alone in a per-patient analysis [75•]. Several of the studies in this meta-analysis included patients with known CAD. However, a recent prospective study compared SPECT MPI, PET MPI, CCTA, SPECT-CT, and PET-CT with ICA with FFR in 208 patients with suspected CAD. Each patient received SPECT MPI, PET MPI, and CCTA; to generate hybrid images, fusion images were created with CCTA and SPECT or PET. They found PET MPI to have the highest diagnostic accuracy with no improved accuracy with hybrid SPECT/CT or PET/CT [76•]. Similar prospective studies are warranted in patients with known CAD presenting with ischemic complaints to assess its usefulness in terms of MACE.

To date, hybrid techniques are not listed in multimodality imaging guidelines for the initial evaluation of patients with ischemic symptoms and known CAD; however, these

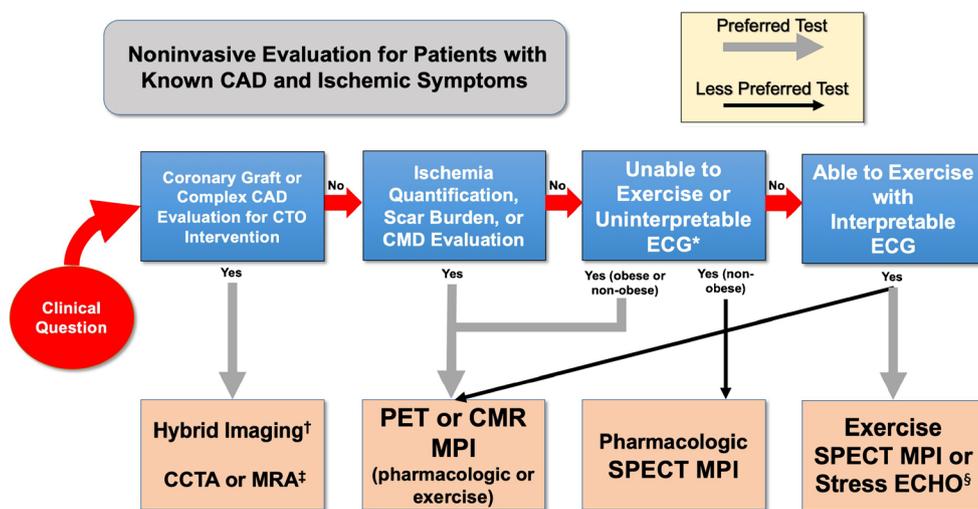


Fig. 1 Proposed algorithm for the use of different non-invasive imaging modalities to aid in the evaluation of patients with ischemic symptoms with known coronary artery disease. *PET or CMR MPI is strongly preferred in patients who are unable to exercise or have an uninterpretable ECG (regardless of body habitus). Patients who are non-obese can undergo SPECT MPI; however, this is less preferred.

†Hybrid imaging is preferred when both coronary anatomy and myocardial perfusion data are needed. ‡CCTA or MRA may be used to assess coronary artery graft patency. CCTA can also be used for CTO intervention planning. §Stress echocardiography is reasonable in patients with normal left ventricular systolic function and no resting regional wall motion abnormalities

guidelines do state that functional imaging is appropriate in patients with obstructive CAD seen on recent CCTA/ICA [6•]. At this time, compared with SPECT/PET/CCTA alone, hybrid imaging techniques require increased radiation exposure and are more expensive. Hybrid techniques should be limited to patients for whom both anatomical and functional information will alter the clinical management of a patient. However, given the growth of complicated PCI in higher-risk patients, hybrid imaging may serve an important role in determining which patients would benefit from intervention and which coronary artery obstruction should be targeted.

Conclusion and Our Approach

For patients with known CAD presenting with ischemic symptoms, we recommended analysis of all available patient data (prior echocardiograms, catheterization reports, stress tests, etc.) to help dictate additional testing. If additional testing is deemed necessary, our approach is summarized in Fig. 1. We favor SPECT or PET MPI for most patients with known CAD. In patients without a known resting WMA and without heart failure, ExEcho/DSE or SPECT/PET MPI is reasonable based on local availability, cost, and local expertise with each modality. If resting WMAs are present, we strongly favor SPECT, PET, or CMR MPI as an initial test given the ability to quantify ischemia/scar burden. If additional information is needed beyond myocardial perfusion (including CMD, coronary anatomy, myocardial viability, or myocardial scar burden), referral to a center capable of performing PET MPI, CMR, CCTA, or FFR_{CT} is advised.

Compliance with Ethical Standards

Conflict of Interest Christopher A. Hanson declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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