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CARDIAC PET, CT, AND MRI (S ACHENBACH, SECTION EDITOR)

Cardiac PET, CT, and MR: What Are the Advantages of Hybrid Imaging?

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Abstract Cardiac hybrid imaging combines different imaging modalities in a way where both modalities equally contribute to image information. Hybrid positron emission tomography-computed tomography (PET-CT) imaging is a promising tool for evaluation of coronary artery disease (CAD) because it enables detection of coronary atherosclerotic lesions by CT angiography and their consequences on myocardial blood flow by PET perfusion in a single study. This appears to offer superior diagnostic accuracy in patients with intermediate risk for CAD compared with stand-alone imaging. Novel, commercially available hybrid scanners containing PET and magnetic resonance as well as development of targeted probes to evaluate molecular and cellular disease mechanisms are expected to provide many new applications for cardiac hybrid imaging. This article focuses on the advantages of cardiac hybrid imaging in the detection of CAD in light of currently available clinical data and discusses the potential future applications.

Keywords Coronary artery disease · Hybrid imaging · PET · CT · CT angiography · MR

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Clinical Trial Acronyms

ACCURACY	Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography
CORE-64	Coronary Evaluation Using Multi-Detector Spiral Computed Tomography Angiography Using 64 Detectors
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
EVINCI	Evaluation of Integrated Cardiac Imaging in Ischemic Heart Disease
FAME	Fractional Flow Reserve Versus Angiography for Guiding PCI in Patients with Multivessel Evaluation
SPARC	The study of myocardial perfusion and coronary anatomy imaging roles in CAD

Introduction

Cardiac hybrid imaging combines different imaging modalities in a way that both modalities equally contribute to image information [1]. The added value of hybrid imaging originates from the spatial correlation of structural and functional information into one fused image. This should provide incremental information beyond that offered by attenuation correction or side-by-side interpretation of the data sets [1, 2]. Hybrid scanners combining positron emission tomography (PET) with high-resolution multi-detector computed tomography (CT) are becoming the standard for almost all commercially available systems. The newest generation of hybrid scanners offers combination of PET with magnetic resonance (MR) imaging. Co-registration of images is immediate and reliable with integrated scanners due to capability to perform PET and either CT or MR image acquisition almost simultaneously with the patient's position fixed. However, software-based co-registration of image data sets from stand-alone scanners is also reliable and feasible. Dedicated cardiac fusion software packages are now commercially available, allowing hybrid imaging with an excellent interobserver reproducibility and short processing durations. Furthermore, image transfer processes to workstations performing co-registration are currently simple and fast.

The main clinical application of cardiac hybrid imaging is anatomical and functional evaluation of coronary lesions in patients with suspected or documented coronary artery disease (CAD). Multidetector CT can now provide an angiographic visualization of the coronary arteries with high temporal and spatial resolution, offering an acceptable and attractive noninvasive alternative to invasive coronary angiography [3]. However, anatomical imaging, noninvasive or invasive, does not accurately indicate whether the detected coronary narrowing causes ischemia, which is the cause of symptoms of the patients and the target of the revascularization therapy. Prior to elective invasive coronary angiography, a test for ischemia is strongly recommended by professional practice guidelines [4]. Both earlier observational studies and recent randomized trials indicate that revascularization procedures performed in patients with documented ischemia reduce total mortality through reduction of ischemia [4–7]. The prospective nuclear substudy of the COURAGE trial showed that percutaneous coronary interventions were more effective in reducing myocardial ischemia than optimal medical treatment alone, and that the extent of reduction was associated with the prognosis of the patient [6]. In the randomized prospective FAME trial, measurement of fractional flow reserve (FFR) that detects hemodynamic significance of stenosis based on intracoronary pressure gradient, prior to percutaneous coronary intervention, resulted in a significant 35% reduction in overall mortality and rate of myocardial infarction compared with anatomic evaluation of stenosis alone [7]. Because discrepancies between the apparent anatomical severity of a lesion and its hemodynamic significance are common, especially in stable CAD [8], functional evaluation of intermediate stenosis is essential for therapeutic decisions.

Hybrid imaging combining PET and multidetector CT angiography (CTA) allow combining morphologic information about coronary artery stenosis location and degree with functional information on pathophysiologic lesion severity. The new PET/MR scanners offer attractive possibilities for combining measures of ventricular function, perfusion, viability, and infarct scar for evaluation of ischemic heart disease. There are also other promising future applications that involve molecular imaging of cardiac targets, and these may further enhance the clinical utility of hybrid imaging using PET/CT or PET/MR. This article presents the benefits of hybrid imaging in light of currently available clinical data and discusses future possibilities.

Features of Stand-Alone Imaging Modalities in Detection of CAD

Coronary CTA

Coronary CTA has become an established noninvasive method for anatomic detection of coronary atherosclerotic plaques and luminal stenosis. Current multislice devices coupled with up-to-date acquisition protocols allow robust and reproducible assessment of coronary atherosclerosis with high temporal and spatial resolution as well as acceptable radiation dose [3]. Multiple single-center studies [3] as well as multicenter studies [9–11] have demonstrated high diagnostic accuracy of CTA for the identification of coronary artery stenosis that is greater than 50% by invasive angiography. In the ACCURACY trial, 230 patients underwent CTA and invasive coronary angiography. On a patient-based analysis, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 95%, 83%, 64%, and 99%, respectively, to detect ≥50% stenosis [11]. With the exception of the CORE-64 trial, the studies have consistently shown that CTA has a particularly high NPV close to 100%. This makes CTA an excellent tool for exclusion of CAD in patients with low-to-intermediate pretest likelihood of disease [3, 4, 9, 11].

The assessment of the severity of coronary artery stenosis can be challenging by coronary CTA. Typically, it tends to overestimate the degree of intermediate stenosis, especially in the presence of dense calcified plaques (blooming artifact) resulting in lower PPV [3]. Furthermore, evaluation of stenosis in vessels with small diameter and in the presence of image artifacts caused by irregular or fast heart rate is challenging [3]. Studies comparing coronary CTA and single photon emission computed tomography (SPECT) perfusion imaging have indicated that only 40% to 65% of the stenoses classified as significant by coronary CTA are associated with myocardial ischemia [12–15]. Similarly, the correlation comparing the stenosis severity by coronary CTA and invasive quantitative coronary angiography has been only modest [16, 17].

PET Perfusion Imaging

Myocardial perfusion imaging is an extensively validated noninvasive method for the detection of myocardial ischemia [18]. Myocardial ischemia is depicted by reduced uptake of the perfusion tracer during exercise or pharmacological stress. Myocardial perfusion imaging has high diagnostic accuracy for the detection of angiographically significant CAD. Data from a large number of studies using either SPECT or PET perfusion imaging indicate that normal myocardial perfusion in patients with intermediate to high likelihood of CAD predicts a very low rate of cardiac death or nonfatal myocardial infarction (1%/year) [19, 20]. Moreover, patients with less reversible ischemia on perfusion imaging have a survival advantage with medical therapy rather than revascularization, whereas those with more extensive ischemia are more likely to benefit from invasive procedures [5, 6]. These features make myocardial perfusion imaging a strong technique to guide selection of candidates for cardiac catheterization and possible revascularization.

Myocardial perfusion PET offers certain advantages compared with SPECT. PET can measure myocardial radioactivity concentrations with better spatial and contrast resolutions and it has accurate, well-validated attenuation correction. As a result, image artifacts caused by soft tissue attenuation are rare and perfusion images of the myocardium are of high quality. The diagnostic accuracy of perfusion PET for the detection of angiographically significant anatomical CAD is very high (both sensitivity and specificity ≥90%) [20]. A unique feature of PET is that myocardial blood flow can be quantified in mL/min/g at rest and during pharmacologically induced hyperemia using PET [20–23]. The clinical benefits of measuring myocardial perfusion in absolute terms have been highlighted in a recent clinical study comparing diagnostic accuracy of quantitative and relative analysis of ^{15}O-water PET perfusion imaging in patients with suspected CAD [24] as well as in earlier studies [25, 26]. The studies have shown that quantitative analysis of myocardial blood flow by PET is particularly helpful for revealing the true extent of CAD in patients with multivessel disease and for detection of balanced multivessel disease [23–26]. Compared with SPECT, the use of myocardial perfusion PET imaging is low. However, due to increase in the number of PET scanners and development of techniques and perfusion tracers that do not require on-site cyclotron its use is expected to increase [20, 27].

A challenge for interpretation of PET perfusion imaging is caused by the lack of anatomical information of the coronary tree in the images. Thus, perfusion imaging alone is unable to differentiate microvascular dysfunction from epicardial stenosis as a cause of abnormally low perfusion. The knowledge on individual coronary anatomy would also help assignment of perfusion defects to certain coronary lesions, because the standard distribution of myocardial perfusion territories does not correspond to the true coronary anatomy in a large number of patients, particularly in the vascular territories of the left circumflex and right coronary artery [27, 28]. In a recent study, disagreement between the standard myocardial vascular territories and the individual obtained using hybrid perfusion and CTA was found in 9% of all segments. Finally, a limitation of myocardial perfusion PET is that it reveals coronary lesions that induce perfusion defects, but do not exclude the presence of subclinical nonobstructive coronary atherosclerosis that may also have prognostic significance [29].

Cardiac MRI

Cardiac MR has become an important tool for investigating the morphology and function of the cardiovascular system [30]. The strengths of MRI are that it provides high resolution images of the myocardium with high blood-tissue contrast that enables accurate measurement of ventricular volumes without the need for using geometrical models. Detection of CAD by MR is based on evaluation of reversible wall motion abnormalities during dobutamine stress, but more recently also on visualization of myocardial perfusion by T1-weighted imaging after gadolinium contrast injection. A unique feature offered by MR is the detection of myocardial tissue abnormalities, particularly necrosis or scar, using the late gadolinium enhancement imaging technique [30, 31].

Hybrid imaging combining MR with PET or CT is potentially desirable for many reasons, including lack of additional ionizing radiation, good tissue characterization properties of MR, possibility to detect myocardial infarct scar with MR in parallel to viable tissue with fluorodeoxyglucose PET, and possibility to do simultaneous (isochronic) acquisition with MRI and PET. Hybrid scanners containing MR and PET scanners have been available for short period of time and there are still technical issues to be resolved before their potential in cardiac applications can be fully explored [32•, 33]. However, there are clinical examples that novel fast-perfusion sequences (kt-SENSE) allow the ability to obtain full-coverage volumetric perfusion data of the left ventricle, which permits simple fusion with three-dimensional volume-rendered CTA into hybrid images [34].

Advantages of Hybrid Imaging in the Detection of CAD

Clinical Data on Hybrid Imaging

The clinical feasibility of integrated hybrid imaging of CTA and myocardial perfusion was first documented in 2005 with the use of ^{13}N-NH_3 PET and 4-slice CT scanner [35]. This and subsequent studies have confirmed the complementary role of both techniques in the evaluation of patients with suspected CAD, resulting in improved specificity and PPV in the detection of angiographically significant stenosis [35–37, 38••, 39]. The largest of these studies using integrated PET and 64-detector CT prospectively enrolled 107 patients with chest pain with intermediate likelihood of CAD and compared hybrid $^{15}O\text{-}H_2O$ PET and CTA versus CTA alone in the detection of hemodynamically significant coronary stenosis [38••]. Hybrid imaging was technically feasible and scan time remained short, because single 6-min PET scan during adenosine stress was used. The hemodynamic significance of stenoses was defined by quantitative coronary angiography including FFR measurement of intracoronary pressure gradient when feasible. Although both PET and CTA alone demonstrated high (97%) NPV, CTA alone was suboptimal in assessing the severity of stenosis (PPV 76%) and perfusion imaging alone could not separate microvascular disease from epicardial stenoses (PPV 77%) in all patients. The use of PET-CTA significantly improved diagnostic accuracy to 98%. Sensitivity, specificity, PPV, and NPV were 93%, 99%, 96%, and 99%, respectively. This indicates that noninvasive hybrid PET-CTA imaging is a highly accurate diagnostic method for the detection of hemodynamically significant CAD compared with PET or CTA alone. The promising results of hybrid PET-CT imaging in the detection of CAD need to be confirmed in prospective, multicenter studies involving different tracers and scanner types.

The incremental value of co-registration and fusion of stand-alone acquired CTA and myocardial perfusion images compared with the side-by-side analysis for the diagnosis of obstructive CAD has been addressed in several studies [40–42]. The results indicate that fusion of perfusion and CTA added diagnostic information in approximately one third of patients resulting in improved diagnostic performance compared with the side-by-side analysis [40–42]. In one study, the number of lesions with equivocal hemodynamic relevance was reduced especially in patients with multivessel disease, intermediate severity stenoses, and diseased side branches [40]. Another study pointed to improved sensitivity in patients with multivessel disease [41]. A recent study implemented automated CTA-guided SPECT contour and territory adjustments found that hybrid imaging particularly improved diagnostic accuracy in the left circumflex and right coronary artery territories [42].

The prognostic value of CTA combined with perfusion imaging over myocardial perfusion imaging alone was demonstrated in a trial including 541 patients at intermediate risk of CAD [43••]. After adjusting for clinical risk factors, obstructive plaque visualized by CTA and abnormal myocardial perfusion scan were independent predictors of late events, with significant incremental improved prediction of risk by the combination of the two modalities compared with either modality alone. An annual event rate of 1% was found in those with concordantly normal CTA and perfusion, and conversely those with concordantly abnormal CTA and perfusion had an event rate of 9%. The findings were confirmed in another, more recent study using SPECT-CT hybrid imaging [44]. The prognostic value of combining quantitative analysis of myocardial perfusion by PET with CTA will be interesting topic for future studies.

In addition to luminal stenosis, CT allows visualization of the coronary vessel wall, thereby providing information on the presence and composition of eccentric nonobstructive plaques. Although the clinical significance of atherosclerotic plaque characterization by CT is still investigational, evidence is accumulating that some features, such as plaque size, low attenuation, spotty calcifications, and eccentric vascular remodeling, can provide prognostic information on the risk of future cardiac events in stable CAD patients [43••, 45, 46].

Clinical Impact of Hybrid Imaging

Challenges in the detection of CAD and the advantages provided by hybrid imaging with PET/CT are summarized in Table 1. Currently it remains largely unknown what kind of patients should undergo such integrated examinations for clinical effectiveness and minimization of costs and radiation dose [2]. One of the strengths of hybrid imaging is that it can guide selection of the most appropriate treatment strategy (medical conservative vs percutaneous vs surgical revascularization). Therefore, it can be anticipated that the patients with multivessel disease are most likely to benefit from hybrid imaging that can be helpful for the evaluation of the extent of disease and localize the culprit flow-limiting lesions as shown in Fig. 1. Thus, the proportion of patients needing dual scanning depends on the characteristics of the patient population, especially the pretest likelihood of CAD. An observational study indicated that the finding of flow-limiting coronary stenosis by noninvasive hybrid imaging

Table 1 The challenges in evaluation of severity of CAD and advantages of hybrid PET/CT imaging

Challenge	Solution
Microvascular disease	Imaging of anatomy in patient with global perfusion reduction
Nonobstructive lesions	Imaging of vessel wall anatomy when perfusion is normal
Left main disease	Identification of left main stenosis corresponding to large anterior perfusion defect
Balanced three-vessel disease	Imaging of stenosis and quantification of perfusion
Multivessel disease	Imaging of stenosis and abnormal quantitative perfusion in corresponding vascular region
Identification of culprit lesion	Imaging of stenosis and corresponding perfusion defect
Calcified lesions in CT	Imaging of perfusion in corresponding vascular region

CAD coronary artery disease; *CT* computed tomography; *PET* positron emission tomography.

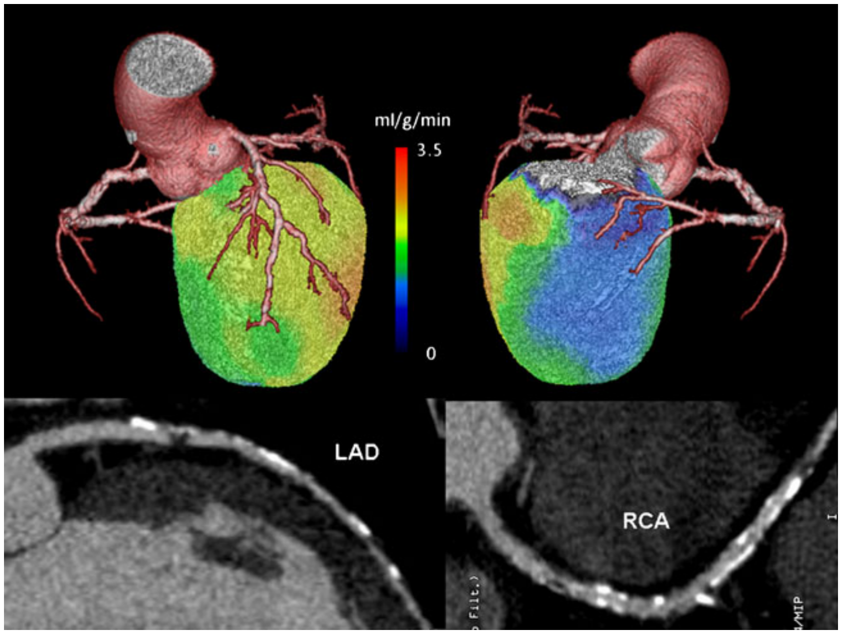

Fig. 1 Detection of culprit lesion by hybrid positron emission tomography/computed tomography (PET/CT) angiography imaging in a patient with multivessel coronary artery disease (CAD). A 58-year-old lady with multiple risk factors of CAD (hypercholesterolemia, hypertension, and previous smoking), atypical chest pain, and asymptomatic ST-depression in exercise test. Multiplanar reconstructions of CT angiography images of the right coronary artery (RCA) and the left anterior descending coronary artery (LAD) show multiple atherosclerotic lesions associated with luminal narrowing. Hybrid volume-rendered images of CT angiography and myocardial perfusion during adenosine stress as assessed by ^{15}O-labeled water PET show normal (> 2.5 mL/g/min) or mildly reduced (2.0–2.5 mL/g/min) perfusion as seen in *yellow* and *green* colors, respectively, in the LAD territory (*left image*). Stress myocardial perfusion was severely reduced as seen in *blue* color (< 1.5 mL/g/min) in the areas supplied by the RCA (*right image*). Invasive coronary angiography showed three-vessel disease, but the most severe stenosis was in the distal RCA corresponding with the noninvasive findings. After percutaneous coronary intervention of the single stenosis patient became asymptomatic

had impact on the frequency of subsequent revascularization [47]. However, further studies are needed to evaluate whether imaging-guided use of interventions will also influence clinical outcome of patients.

In clinical practice, a sequential diagnostic approach is often applied, with additional scans performed only if the results of the initial modality are equivocal. For example, the hemodynamic severity of intermediate stenosis in CTA can be confirmed by immediate perfusion imaging or the culprit lesion responsible for perfusion defect can be localized by CTA. In sequential approach, the order of the scans can vary depending on the pretest likelihood. Because of the very high NPV of CTA, patients with low to moderate pretest likelihood of CAD could undergo CTA as the first-line examination followed by confirmation of ischemia by perfusion imaging only in those patients with suspicion of obstructive CAD. Conversely, in the presence of higher likelihood of CAD, the fraction of patients with obstructive disease is high and, therefore, perfusion as the first-line examination would make sense. CTA would be needed only if anatomical information is needed over positive perfusion result. Naturally, both of these approaches have limitations. In the first option, knowledge of coronary function or microvascular disease is missed. In the second option, preclinical atherosclerotic disease is not detected.

Radiation Exposure

In addition to costs, an obvious concern related to hybrid imaging is patient radiation dose that requires careful consideration of the needs and benefits of imaging [48]. It is currently assumed that there is a linear relationship between radiation dose and the risk of cancer. The effective patient radiation dose from cardiac CT varies widely depending on the protocol, instrumentation, and patient size [48, 49]. Due to improvements in image acquisition protocols (eg, the introduction of electrocardiogram (ECG)-dependent tube current modulation, body mass index–adapted tube voltage modulation, and prospective ECG-triggered sequential scanning), the radiation exposure from CTA has diminished considerably in the clinical practice [49–51]. It has been reported that the use of new iterative reconstruction enables further reduction of the radiation dose by 30% to 50% [52]. An advantage of the short half-life of PET perfusion tracers is that the radiation exposure is much lower than that related to SPECT perfusion imaging [38••]. The radiation doses from PET perfusion imaging are ranging from 1 to 2 mSv [38••, 48]. Recent developments in detector technology as well as the omission of rest study in the presence of normal stress study may allow further reduced radiation exposure.

An advantage of MR over CT and PET imaging is that it does not cause exposure to ionizing radiation.

Novel Applications of Hybrid Imaging

Molecular Imaging

Although traditional imaging is based on detection of changes in the anatomy and physiologic features, such as blood flow or contractile function, cardiovascular molecular imaging aims at visualization and measurement of biological processes at the molecular and cellular levels. Molecular imaging has provided techniques and new targeted probes to better understand the pathophysiologic mechanism underlying cardiovascular diseases [53, 54]. Examples of clinical problems that might benefit from molecular imaging include the identification of vulnerable atherosclerotic plaques before rupture and subsequent myocardial infarction [55, 56], detection of biomechanisms that precede left ventricular remodeling and development of heart failure [57, 58], and the assessment of risk of ventricular arrhythmias by neuronal imaging [59]. Additionally, molecular imaging has great potential to facilitate the discovery and development of novel therapies through improved target identification and implementation of more efficient end points. Owing to high sensitivity and availability of tracers with low risk of toxicity, PET is the leading imaging technique to proceed with translation of molecular imaging into clinical trials [53, 60]. Molecular imaging depends on hybrid imaging approaches, where the nuclear imaging component is used for molecular targeting seen as a “hot spot” and the CT or other anatomical imaging modality is used for localization of the molecular signal. For example, hybrid PET and CT or MR scanners offer the possibility to integrate targeted PET images with high-resolution morphologic images provided by CT or MR to obtain an anatomic distribution of the probe and account for partial volume errors that would cause underestimation of the true regional radiotracer activity.

Conclusions

Cardiac hybrid imaging has rapidly developed into a useful technique for the clinician. The combination of morphologic imaging of coronary arteries using multidetector CTA and functional imaging of myocardial perfusion using PET, SPECT, and also recently cardiac MR is very powerful noninvasive imaging method that provides comprehensive information both for diagnosis and decision making for treatment of CAD. Hybrid imaging appears to offer superior diagnostic information in patients with intermediate risk for disease compared with stand-alone imaging. However, further studies are needed to confirm the clinical impact and cost effectiveness of this technique. Ongoing multicenter trials, such as SPARC and EVINCI, are expected to provide important information on these issues in the near future. The new PET/MR scanners and targeted molecular probes have provided interesting possibilities for hybrid imaging that are developing toward clinical application.

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- •• Of major importance

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