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Cardiac hybrid imaging

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Cardiac hybrid imaging combines different imaging modalities in a way where both modalities equally contribute to image information. The most common and best-studied approach is to combine computed tomography coronary angiography (CTCA) and myocardial perfusion imaging either with single-photon emission computed tomography or with positron emission tomography (PET). This combination is a promising tool for evaluation of coronary artery disease since it allows visualization of coronary atherosclerotic lesions and their haemodynamic consequences in a single study and it appears to offer superior diagnostic accuracy when compared with stand-alone imaging. More recent applications are a combination of CTCA and cardiac magnetic resonance imaging by using software image fusion and utilization of commercially available hybrid PET/MRI scanners for cardiac applications. Currently, these methods have been reported only as case reports, but several potential applications also in cardiology can be anticipated. The development of new molecular imaging probes will also open completely new possibilities for guidance and monitoring of advanced therapies. This review will focus on the concepts and currently available clinical experiences from cardiac hybrid imaging as well as discuss the potential future applications.

Keywords Hybrid imaging • Coronary artery disease • PET • MRI • SPECT

Background

A number of landmark studies using intraoperative Doppler ultrasound, positron emission tomography (PET), or fractional flow reserve (FFR) have consistently demonstrated that the angiographic severity of coronary lesions is a poor predictor of its haemodynamic relevance.[1–4] Similarly, comparative studies of computed tomography coronary angiography (CTCA) and myocardial perfusion imaging (MPI) show that only 30–50% of stenoses with more than 50% luminal narrowing are associated with reversible perfusion defects on MPI, and conversely, many patients with completely normal myocardial perfusion may harbour subclinical coronary artery disease (CAD).[5–8]

Large randomized clinical trials have failed to demonstrate superiority of revascularization over modern medical treatment in terms of long-term cardiovascular events if patients are not stratified by prior ischaemia testing.[9,10] In the presence of significant myocardial ischaemia, however, revascularization seems to improve the outcome by reducing the ischaemic burden on the left ventricular myocardium.[11,12] The pivotal role of ischaemia-targeted revascularization in stable CAD patients has further been highlighted in the randomized FAME trial.[13,14] Consequently, the role of testing for myocardial ischaemia has been incorporated in revascularization guidelines.[15] These data emphasize the importance of interrogating both morphology and function in patients with stable CAD in order to offer the most appropriate treatment strategy.

The tremendous developments in non-invasive imaging technology over the last decades coupled with improved and faster dedicated software products for image processing and analysis have facilitated the rapid clinical introduction of cardiac hybrid imaging.[16] A great leap forward came with the introduction of high-end multidetector CT scanners with the ability to depict the small coronary arteries with a resolution and accuracy that was robust enough for clinical practice. Additionally, cardiac hybrid imaging was spurred by the tremendous success of hybrid whole-body PET/CT in oncology which allowed for the first time to merge high-resolution anatomy with a functional tumour-seeking agent. Initially, thoracic CT data were used only for attenuation correction of MPI images,[17] and several technical issues had to be resolved prior to wide clinical dissemination: spatial shifts and intrinsic mismatch between the electrocardiogram-gated CTCA and non-gated perfusion study had to be compensated. In addition, the correlation of the perfusion information with the coronary anatomy could not be properly appreciated on a

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slice-by-slice display. Thus, three-dimensional (3D) volume-rendering techniques are crucial to exploit the full potential of the technique.[18]

The historical use of CTCA in combination with MPI has also generated confusion as to the exact definition of cardiac hybrid imaging. Some have referred to CT-based attenuation correction of MPI as hybrid imaging; others have called the mere side-by-side reading of CTCA and MPI 'hybrid imaging'. We refer to the term 'hybrid imaging' in a more stringent way as the combined or fused imaging of two data sets where both modalities equally contribute to image information.[19] Thus, neither CT-based attenuation correction nor mental integration of side-by-side modalities are considered or discussed in this manuscript.

Strengths and weaknesses of separate techniques

Computed tomography coronary angiography

Computed tomography coronary angiography has become an established non-invasive method for anatomic detection of coronary atherosclerotic plaques and luminal stenosis. The 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.[20] Multiple single-centre studies[20] as well as multicentre studies[21–23] have demonstrated the high diagnostic accuracy of CTCA for the identification of >50% coronary artery stenosis and very low rates of non-evaluable scans. In the ACCURACY trial, 230 patients underwent CTCA and invasive coronary angiography (ICA). 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.[23] With the exception of the CORE 64 trial, the studies have consistently shown that CTCA has a particularly high NPV close to 100% that makes CTCA an excellent tool for exclusion of CAD in patients with low-to-intermediate pre-test likelihood of disease.[15]

Computed tomography coronary angiography has only limited capability to assess comprehensively the severity of coronary artery stenosis. As previously explained, the angiographic severity of coronary lesions is a poor predictor of its haemodynamic relevance and only a proportion of stenoses in CTCA are associated with myocardial ischaemia. There is a tendency to overestimate the degree of stenosis, especially in the presence of dense calcified plaques (blooming artefact) resulting in lower PPV.[20] Furthermore, evaluation of stenosis in vessels with small diameter and in the presence of image artefacts caused by irregular or fast heart rate is challenging.[20] Thus, a combination of CTA with functional assessment would be important for evaluation of intermediate stenoses to identify those patients who may benefit from revascularization.

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) has become an important tool for investigating the morphology and function of the cardiovascular system.[24] CMR can provide high-resolution images of the myocardium with high blood-to-tissue contrast that enables accurate measurement of ventricular volumes without need for using geometrical models. Detection of CAD by CMR is based on either evaluation of reversible wall motion abnormalities during dobutamine stress, but more recently also on visualization of myocardial perfusion by T1-weighed imaging after gadolinium contrast injection. A unique feature offered by CMR is the visualization of myocardial tissue abnormalities, particularly necrosis or scar, using the late gadolinium enhancement imaging technique.[24,25] Routine coronary angiography is not feasible with the current CMR techniques.

Combining CMR with PET or CT is potentially desirable for many reasons, including lack of additional ionizing radiation, good tissue characterization properties of CMR, possibility to detect myocardial infarct scar with CMR in parallel to viable tissue with fluorodeoxyglucose PET, and possibility to do simultaneous (isochronic) acquisition with CMR and PET. Hybrid scanners containing CMR and PET 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.[26,27]

Myocardial perfusion single-photon emission computed tomography and positron emission tomography

Myocardial perfusion single-photon emission computed tomography (SPECT) is a widely available and extensively validated non-invasive method for the detection of myocardial ischaemia. SPECT perfusion scintigraphy is performed to produce images of regional tracer uptake that reflect relative regional myocardial blood flow. Without correction for referral bias, the reported sensitivity of exercise SPECT for the detection of angiographically significant CAD is high (87–89%).[28,29] The normalcy rate corrects for referral bias that has impact on specificity, and it is estimated at 89%.[29] In addition to detection, myocardial perfusion SPECT can also reveal the extent of ischaemic myocardium and viability. Normal perfusion SPECT in patients with intermediate-to-high likelihood of CAD predicts a very low rate of cardiac death or non-fatal myocardial infarction (MI) (≤1%/year).[30] Moreover, it has been shown that patients with less reversible ischaemia on SPECT have a survival advantage with medical therapy rather than revascularization, while those with more severe ischaemia are more likely to benefit from invasive procedures.[11,12] These features make myocardial perfusion scintigraphy a strong technique to guide selection of candidates for cardiac catheterization and possible revascularization.

Compared with SPECT, PET MPI offers certain advantages. PET can measure myocardial radioactivity concentrations with better spatial and contrast resolutions and it has accurate, well-validated attenuation correction. As a result, image artefacts caused by soft tissue attenuation are rare and perfusion images of the myocardium are of high quality. A large number of studies have shown that PET is an accurate method for detecting obstructive coronary artery disease (sensitivity and specificity ≥90%).[31] A unique feature of PET is that myocardial blood flow can be quantified in mL/min/g at rest and during pharmacologically induced hyperaemia.[31–34] The clinical benefits of measuring myocardial

perfusion in absolute terms have been highlighted in a recent clinical study comparing the diagnostic accuracy of quantitative and relative analysis of ^{15}O-water PET perfusion imaging in patients with suspected CAD[35] as well as in earlier studies.[36,37] The studies have shown that quantitative analysis of myocardial blood flow by PET improves the diagnostic accuracy of detecting CAD and is particularly helpful for revealing the true extent of CAD in patients with multivessel disease and for detection of balanced multivessel disease.[35–37]

Diagnostic problems for MPI techniques are presented by increasing number of patients who are presenting with obesity as well as extensive, multivessel CAD or endothelial dysfunction.[31,32] Particularly, in obese subjects, SPECT is prone to false-positive results due to non-uniform photon attenuation. In patients with multivessel CAD, SPECT underestimates the true extent of disease, since the technique emphasizes the territory supplied by the most severe stenosis.[31,32] Balanced reduction in myocardial hyperaemic blood flow is probably rather rare but it may explain the paradoxical underestimation of clinical risk in some high-risk cohorts with a normal or near-normal SPECT.[31,32,35] Although quantification of myocardial blood flow by PET can pertly overcome these problems, differentiation of microvascular dysfunction from epicardial stenosis as a cause of abnormally low perfusion as well as assignment of perfusion defects to certain coronary lesions remains a problem in the absence of information on individual coronary anatomy. Another limitation of myocardial perfusion SPECT or PET is that they reveal coronary lesions that induce perfusion defects, but do not exclude the presence of subclinical non-obstructive coronary atherosclerosis that is also of prognostic value.[38]

Hybrid imaging: clinical data

Traditionally, integration of coronary morphology and functional information from imaging studies is performed by mental coregistration using standardized myocardial segmentation models which allocate each myocardial segment to one of the three main coronary arteries.[39] However, coronary artery anatomy varies considerably among individuals and may disagree with standardized vascular territories in up to 72% of patients referred to MPI.[40] This applies particularly to the inferior and inferolateral wall, which are traditionally those territories with the largest variability in coronary anatomy. Hence, the incremental value of hybrid cardiac imaging resides in the accurate spatial co-localization of myocardial perfusion defects and subtending coronary arteries (*Figures 1* and *2*).

The majority of clinical data on hybrid imaging has accrued from rather small diagnostic single-centre studies. One group of studies has compared the diagnostic accuracy of hybrid imaging with the single techniques (i.e. either CTCA alone or MPI alone) using invasive coronary angiography as the gold standard (*Table 1*), while another group of studies has focused on the incremental clinical value of hybrid imaging over the side-by-side analysis of CTCA and MPI (*Table 2*). The feasibility and clinical robustness of non-invasive hybrid imaging was first documented by Namdar *et al.*[41] in a clinical study involving fusion of ^{13}N-NH_3 PET with four-slice CTCA in 25 patients with CAD. Using ICA combined with PET as the reference standard, the hybrid PET/CTCA approach allowed to detect flow-limiting coronary lesions which required a revascularization procedure with a sensitivity, specificity, PPV, and NPV of 90, 98, 82, and 99%, respectively. These encouraging results were confirmed by a similar study with SPECT and CTCA, showing that the hybrid approach resulted in a significant improvement in specificity (from 63 to 95%) and PPV (from 31 to 77%) compared with CTA alone for detecting flow-limiting coronary stenoses.[42] A similar diagnostic performance was reported by Groves *et al.*[43] using a ^{82}Rb PET/CT hybrid system. Sato *et al.*[44] showed that adding SPECT information in non-evaluable arteries on CTCA improved particularly specificity and PPV of the latter techniques significantly (from 80 to 92%, and from 69 to 85%, respectively). One of the largest, recently published studies included 107 patients undergoing hybrid ^{15}O-H_2O PET/64-slice CTCA.[45] In this study, haemodynamic significance of ICA stenoses was confirmed in 40 patients with FFR providing a more comprehensive gold standard. Consequently, the use of PET/CTCA increased the PPV significantly from 76 to 96% compared with CTCA alone. Despite these promising early results, it should be noted that the aforementioned studies included limited number of patients, a variety of hybrid systems were used, and no uniform gold standard was used. Thus, larger multicentric trials will be needed to confirm these early results.

While the latter reports document the high diagnostic accuracy of hybrid imaging, another set of studies documents that its clinical value is rather synergistic than just additive (*Table 2*). In an early report of 38 patients with perfusion defects on SPECT, the number of lesions with equivocal haemodynamic relevance was significantly reduced using SPECT/CTCA fusion compared with the side-by-side analysis.[46] Among these equivocal lesions, the hybrid approach confirmed haemodynamic significance in 35% and excluded it in 25%. This added important clinical information in 29% of all patients and was particularly useful in patients with multivessel disease and intermediate severity stenoses or in patients with diseased side branches. Santana *et al.*[47] demonstrated a significantly higher diagnostic performance of fused SPECT/CTCA imaging compared with SPECT alone ($P < 0.001$) and to the side-by-side analysis of SPECT and CTCA ($P = 0.007$). Interestingly, this improved diagnostic performance was mainly a result of a higher sensitivity in patients with multivessel disease. A recent study implementing motion-frozen SPECT data and CTA-guided SPECT contour and territory adjustments found that the improved diagnostic value of hybrid imaging was driven by higher accuracy in left circumflex coronary artery and right coronary artery territories.[48]

Hence, through spatial coregistration of anatomical and functional information, hybrid imaging may not only improve the diagnostic accuracy of non-invasive CAD assessment, but also provide vessel-specific functional information to allow targeted revascularization strategies.[14] The independent prognostic value of morphological and functional coronary information was demonstrated in a multicentre follow-up study in more than 500 patients supporting the notion that both parameters need to be investigated in patients with CAD.[49] Moreover, a recent prospective follow-up trial assessed the incremental prognostic value of hybrid imaging over the side-by-side findings from both techniques.[50] In this study, 324 consecutive patients undergoing hybrid SPECT/CTCA were

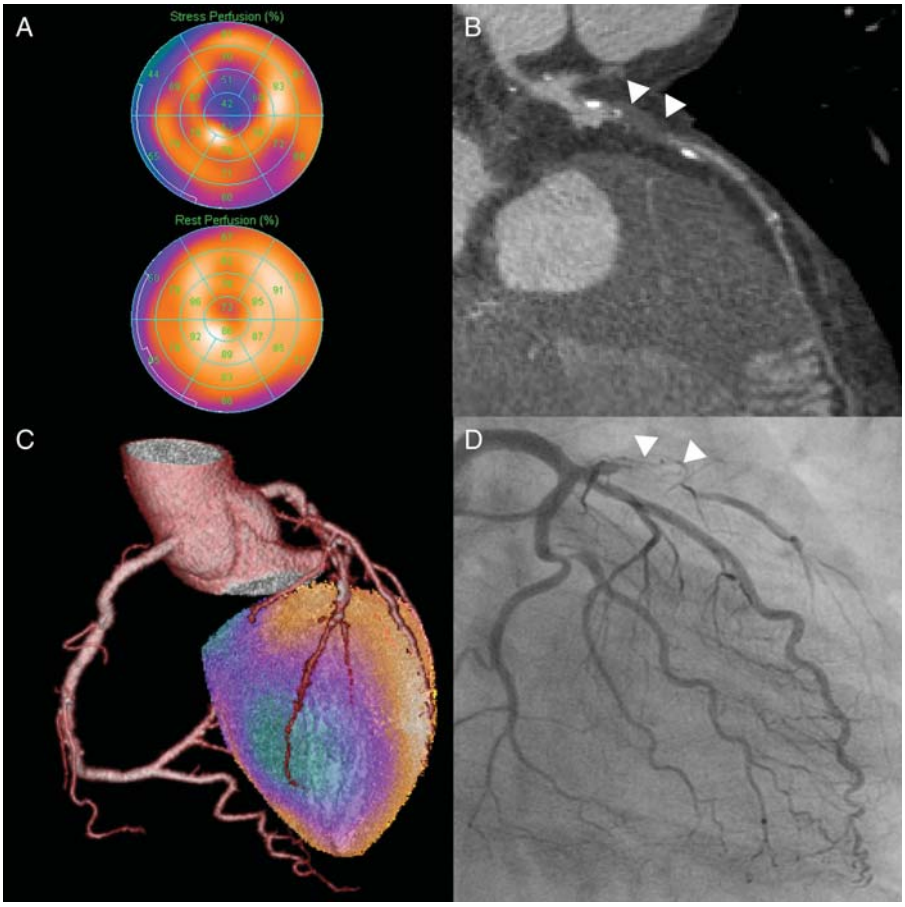

Figure 1 Example of a 47-year-old patient with typical angina. His stress and rest myocardial perfusion single-photon emission computed tomography (*A*) show a reversible anteroapical perfusion defect. On computed tomography angiography, a complete occlusion of the proximal left anterior descending artery can be observed (arrowheads in B) with distal vessel opacification suggesting collateralization. The hybrid volume-rendered single-photon emission computed tomography/computed tomography images (*C*) demonstrate that the anteroapical ischaemic territory is supplied by the occluded left anterior descending artery. The invasive angiogram confirms the total occlusion of the proximal left anterior descending artery (*D*, arrowheads).

subdivided into three groups: (i) stenosis by CTCA and matching reversible SPECT defect (i.e. the perfusions defects were superimposed on the stenotic coronary artery on the hybrid 3D display); (ii) unmatched CTCA and SPECT findings; and (iii) normal finding by CTCA and SPECT. On follow-up (median 2.8 years), a corresponding matched hybrid finding was associated with a significantly higher event rate (death or MI) and proved to be an independent predictor for major adverse cardiac events. The annual death/MI rate was 6.0, 2.8, and 1.3% for patients with matched, unmatched, and normal findings (*Figure 3*). Revascularization rates within 60 days were 41, 11, and 0% for matched, unmatched, and normal findings, respectively ($P < 0.001$), indicating that hybrid imaging findings had a significant impact on patient management.[51] However, larger prospective studies are needed to confirm these results and to assess whether changes in treatment based on hybrid imaging may have an impact on the patients' prognosis. Results of ongoing prospective multicentre trials such as SPARC, EVINCI, and PROMISE are therefore eagerly awaited and will hopefully shed more light into the future of cardiac hybrid imaging.[52,53]

Clinical implications: how to implement cardiac hybrid imaging into current algorithms

Currently, it remains unknown what kind of patients should undergo integrated examinations for clinical effectiveness and minimization of costs and radiation dose. There are several situations in which hybrid imaging can obviously provide clinically beneficial information. Patients with multivessel disease are most likely to benefit from hybrid imaging. For example, it is possible to localize the culprit flow-limiting lesion as shown in *Figures 1* and *2*. It can also be expected that the proportion of patients needing dual scanning depend on the characteristics of the patient population, especially the pre-test likelihood of CAD.

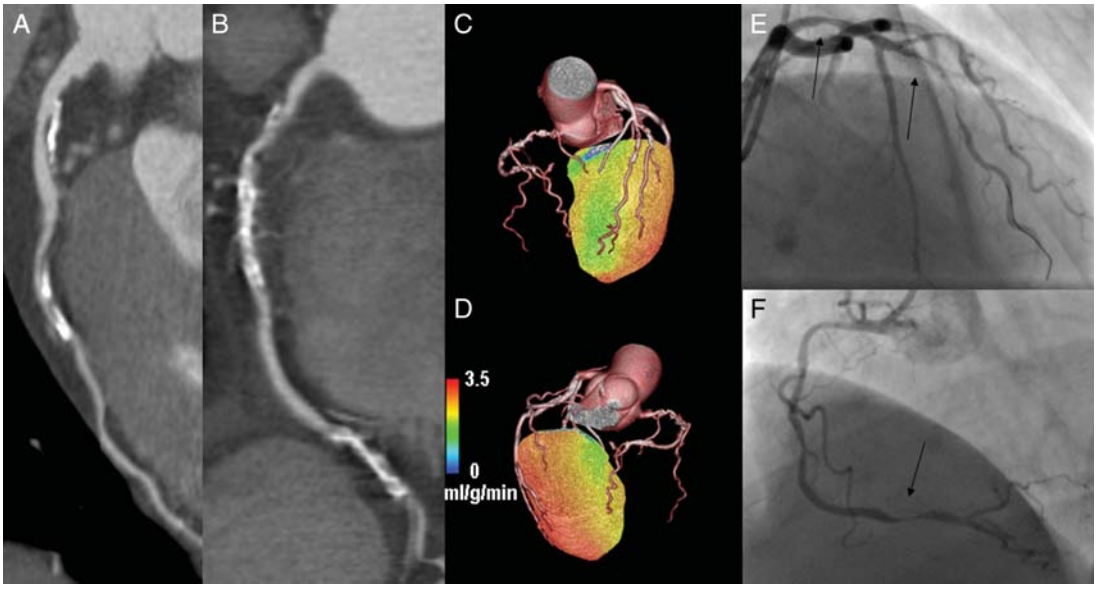

Figure 2 Detection of culprit lesion by hybrid positron emission tomography/computed tomography angiography imaging in a patient with two-vessel coronary artery disease. A 49-year-old man with multiple risk factors of coronary artery disease (hypercholesterolaemia, hypertension, family history, and diabetes) and atypical chest pain. Exercise test was not feasible due to severe polyneuropathy. Multiplanar reconstructions of computed tomography angiography images of the left anterior descending coronary artery (*A*) and the right coronary artery (*B*) calcified atherosclerotic plaque and luminal narrowing in the proximal and mid-left anterior descending artery as well as in the proximal and distal right coronary artery. Hybrid volume-rendered images of computed tomography angiography and myocardial perfusion during adenosine stress as assessed by ^{15}O-labelled water positron emission tomography show area of mildly reduced (2.0–2.5 mL/g/min) perfusion as seen in green and yellow colours in the left anterior descending artery territory (*C*). Stress myocardial perfusion was moderately reduced (2.0 mL/g/min) as seen in green colour in the area supplied by the right coronary artery (*D*). Perfusion is normal (>2.5 mL/g/min) as seen in red colour in the area subtended by the left circumflex coronary artery that did not contain atherosclerosis (*C* and *D*). Consistent with the non-invasive findings, invasive coronary angiography showed significant stenosis in the distal left anterior descending artery (fractional flow reserve 0.54, *E*). After percutaneous coronary intervention of the distal stenosis, fractional flow reserve normalized being 0.85. Moreover, invasive angiography showed significant stenosis in the distal right coronary artery (fractional flow reserve 0.63, *F*) that was also treated by percutaneous coronary intervention.

Table 1 Added diagnostic accuracy of cardiac hybrid imaging (single-photon emission computed tomography/computed tomography coronary angiography and positron emission tomography/computed tomography coronary angiography) (vessel-based analysis)

Author	Hybrid system	*n*	Gold standard (definition of significant CAD)	Sens	Spec	PPV	NPV
Namdar *et al.*[41]	^{13}N-NH_3 PET/4-slice CTCA	25	Flow-limiting coronary stenoses requiring revascularization (ICA + PET)	90	98	82	99
Rispler *et al.*[42]	SPECT/16-slice CTCA	56	Flow-limiting coronary stenoses (>50% stenosis on ICA + SPECT pos.)	96	95	77	99
Groves *et al.*[43]	^{82}Rb PET/64-slice CTCA	33	>50% stenosis on ICA	88	100	97	99
Sato *et al.*[44]	SPECT/64-slice CTCA[a]	130	>50% stenosis on ICA	94	92	85	97
Kajander *et al.*[45]	^{15}O-H_2O PET/64-slice CTCA	107	Flow-limiting coronary stenosis (>50% stenosis of ICA + FFR)	93	99	96	99

n denotes the number of patients in each study. SPECT, single photon emission computed tomography; CTCA, CT coronary angiography; PET, positron emission tomography; CAD, coronary artery disease; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; ICA invasive coronary angiography; FFR, fractional flow reserve.

[a]Hybrid SPECT/CTCA only applied for non-evaluable arteries on CTCA (14%).

Table 2 Synergistic clinical value of fused hybrid imaging compared with the side-by-side analysis

Author	Hybrid system	Patient population	Incremental value of fused hybrid imaging
Gaemperli *et al.*[46]	SPECT/64-slice CTCA and 3D image fusion	38 patients with ≥1 SPECT defects	Modification of initial interpretation in 29% of patients In equivocal lesions, hemodynamic relevance could be confirmed in 35% and excluded in 25%
Santana *et al.*[47]	16- and 64-slice CTCA and MPI (SPECT or ^{82}Rb PET)	50 patients with suspected CAD	Modification of initial interpretation in 28% of patients Trend towards increased sensitivity (by 17%) in patients with multivessel disease
Slomka *et al.*[48]	Motion-frozen SPECT/64-slice CTCA (automatic coregistration)	35 patients with suspected CAD	Improved diagnostic performance in RCA and LCX territories

SPECT, single-photon emission computed tomography; CTCA, CT coronary angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; CAD, coronary artery disease.

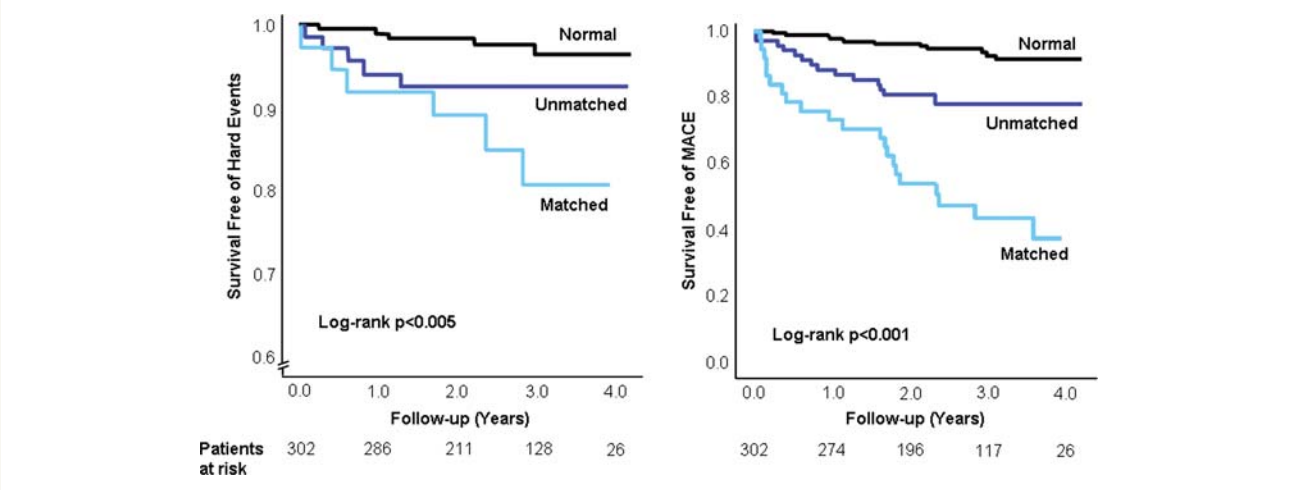

Figure 3 The Kaplan–Meier survival curves showing the prognostic value of cardiac hybrid imaging. Cardiac hybrid findings predict (*A*) all-cause death or non-fatal myocardial infarction and (*B*) major adverse cardiac events (death, myocardial infarction, unstable angina requiring hospitalization, and coronary revascularization). Event rates are higher in the presence of matched findings (i.e. spatial superposition of perfusion defect and stenotic coronary arteries) compared with unmatched or normal findings. Reproduced with permission of Oxford University Press from Pazhenkottil *et al.*[50]

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 haemodynamic severity of intermediate stenosis in CT angiography can be confirmed by immediate perfusion imaging or the culprit lesion responsible for perfusion defect can be localized by CT angiography. If a sequential approach is used, the order of the scans depends also on the pre-test likelihood. It is rational to suggest that patients with low-to-moderate pre-test likelihood of CAD should start with CTCA and MPI would be performed only in those patients with obstructive CAD in CTCA. This can be justified by very high NPV of CTCA. On the other hand, if the likelihood of CAD is higher, larger fraction of the patients will have obstructive disease and starting with perfusion imaging would make sense. CTCA would be needed only if anatomical information is needed over a positive perfusion result. Naturally, both of these approaches have specific limitations. In the first option, knowledge of coronary function or microvascular disease is missed. In the second option, preclinical atherosclerotic disease is not detected.

One of the major strengths of hybrid imaging is that it powerfully guides the selection of the most appropriate treatment strategy (medical conservative vs. percutaneous vs. surgical revascularization). An observational study indicated that indeed, the finding of flow-limiting coronary stenosis by non-invasive hybrid imaging had impact on the frequency of subsequent revascularization.[51] However, further studies are needed to evaluate whether the imaging-guided use of interventions will also influence clinical outcome of patients.

Critical issues of hybrid imaging

It is obvious that putting together two modalities instead of single one creates specific challenges. The increased costs and potentially

radiation exposure from hybrid imaging procedures have also raised concerns on the appropriate use of hybrid imaging. It is currently assumed that a linear relationship exists between radiation dose and radiation-induced cancer risk. Obviously, all efforts should be made to reduce individual exposure to the lowest acceptable level.[54] Thus, over the last years, devices and acquisition protocols for CTCA and MPI have undergone significant modifications in order to comply with this principle.

Myocardial perfusion SPECT using ^{99m}Technetium-based perfusion tracers allows to perform a full 1-day stress/rest study with a radiation dose of approximately 11.3 mSv, which is considerably lower than with ^{201}Thallium. However, introduction of novel dedicated small footprint cardiac scanners equipped with solid-state detectors based on the cadmium–zinc–telluride alloy that provides higher count statistics and improved energy resolution may allow further reductions in radiation exposure.[55] Duvall *et al.* have documented the feasibility and high diagnostic quality of half-dose 1-day stress/rest SPECT MPI with a total radiation dose of 5.8 mSv.[56] In addition, the linear count rate response of semiconductor detectors may allow low-dose-low-dose 1-day SPECT studies using count subtraction from sequential scanning.[57] Moreover, some of the currently used cyclotron-dependent perfusion tracers for PET imaging (i.e. ^{15}O-H_2O and ^{13}N-NH_3) are associated with even lower radiation doses and therefore may be particularly suitable for hybrid imaging (*Table 3*).[41,45]

The last years have witnessed tremendous reductions in radiation dose from CTCA through improvements in image acquisition protocols, particularly the introduction of electrocardiogram (ECG)-driven tube current modulation, body mass index-adapted tube voltage modulation, and prospective ECG-triggered sequential scanning.[58,59] The most recent high-pitch scanning protocols using dual-source CT scanners have lowered doses even further into the sub-milli-Sievert range (*Table 3*).[60]

The use of lower radiation protocols may promote the clinical use of cardiac hybrid imaging. In fact, a recent hybrid study reported a cumulative radiation exposure of 5.4 mSv for a hybrid stress-only SPECT/CTCA study which is well within the range of invasive diagnostic angiography (*Table 3*).[61]

Table 3 Estimated effective radiation dose from cardiac diagnostic imaging

Protocol	Injected activity (MBq)[a]	Effective dose (mSv)
^{201}Tl stress/redistribution	130	22.0
^{99m}Tc sestamibi 1-day stress/rest	350/1000	11.3
^{99m}Tc sestamibi half-dose CZT 1-day rest/stress[56]	185/555	5.8
^{82}Rb stress/rest[71]	1850/1850	4.6
^{13}N-NH_3 stress/rest	550/550	2.4
^{15}O-H_2O stress/rest	1100/1100	2.5
^{18}F-fluorodeoxyglucose (viability)	350	7.0
64-slice CTCA (without tube current modulation)		8.0–21.4
64-slice CTCA (with tube current modulation)		7.0–14.0
64-slice CTCA (prospective ECG-triggering)[59]		2.1
320-slice CTCA (prospective ECG-triggering)[72]		6.8
2 × 128-slice (dual source), high-pitch spiral-CTCA[60]		0.9
Diagnostic coronary angiography		2.3–22.7

Adapted from Einstein *et al.*[73] CZT, cadnium-zinc-telluride; CTCA, CT coronary angiography; ECG, electrocardiogram.
[a]Effective radiation doses are estimated using ICRP publication 60 tissue weighting factors.[74]

Future perspectives

In the last 10 years, cardiac hybrid imaging has advanced from a curiosity created by a group of 'image tinkerers' to a useful tool that is finding increasing clinical acceptance. The success of combining nuclear techniques (i.e. myocardial perfusion PET and SPECT) with CTCA was built on the impressive example that whole-body PET/CT has set in oncology. Nevertheless, other techniques such as CMR are accessible for hybrid imaging and may have distinct advantages. While CMR has been envisaged as a partner modality of hybrid imaging due to the lack of ionizing radiation, one important impediment was the fact that perfusion data could only be obtained in three cross-section of the left ventricle, which is insufficient to extrapolate onto a 3D volume. However, novel fast perfusion sequences (*kt*-SENSE) are now available that allow to obtain full-coverage volumetric perfusion data of the left ventricle and permit simple fusion with 3D volume-rendered CTCA into hybrid images (*Figure 4*).[62] Another possibility available already today is the combined systems with CMR and PET. Since CMR does not currently allow robust coronary angiography, the applications are likely elsewhere than in CAD. The experience is currently limited only to case reports, but based on the knowledge about the stand-alone techniques, one could expect that this combination would be very powerful in viability imaging and in various inflammatory cardiac diseases such as cardiac sarcoidosis and potentially in heart failure where PET and CMR can provide complementary information.

One interesting approach consists of the fusion of morphological information from CTCA with colour-coded CTCA-derived FFR (FFR_{CT}) values. The method calculates FFR from patient-specific CCTA data using computational fluid dynamics during rest and simulated maximal coronary hyperaemia.[63] Preliminary results in patients suggest that non-invasive FFR_{CT} may be useful to assess the haemodynamic significance of coronary lesions. These findings need to be confirmed in larger trials. Naturally, if CT could be used to image myocardial perfusion accurately, the obvious 'hybrid' imaging of choice would be combining CTCA and CT perfusion.

While traditional imaging is based on the detection of changes in the anatomy and physiological 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 pathophysiological mechanism underlying cardiovascular diseases.[64,65] Examples of clinical

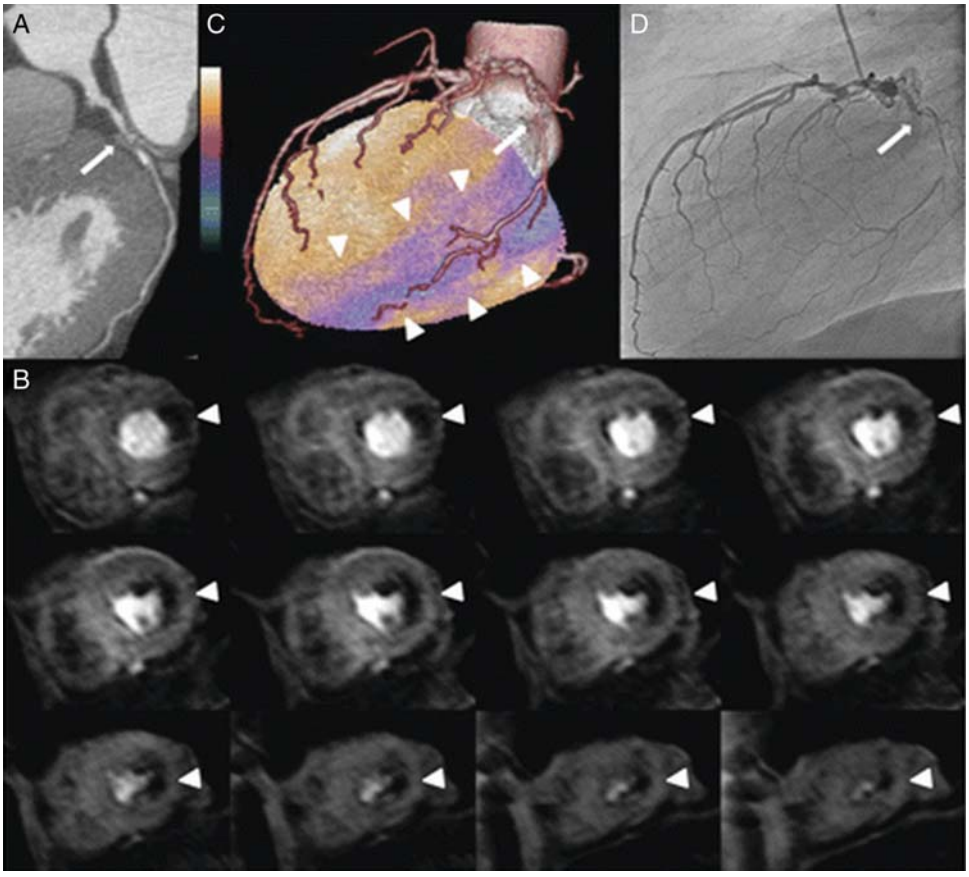

Figure 4 The hybrid images can also be created by fusion of images from coronary computed tomographic angiography and cardiac magnetic resonance. A 65-year-old male patient with typical chest pain underwent low-dose coronary computed tomographic angiography for evaluation of coronary artery disease. (*A*) On CT angiography a high grade stenosis of the first large obtuse marginal branch (OM1) could be seen. Subsequently, a stress cardiac magnetic resonance perfusion imaging (adenosine 140 μg/kg/min, 0.1 mmol/kg Gadobutrolum, kt-SENSE) was performed with a new sequence allowing three-dimensional perfusion assessment. This revealed a lateral perfusion defect, involving 13% of the left ventricular myocardium (*B*, white arrowheads). The three-dimensional hybrid images showed a perfect match of the perfusion defect (white arrowheads) and the culprit lesion (white arrow) (*C*), documenting a prognostically important finding requiring revascularization. A 50% stenosis of the proximal left anterior descending artery was not associated with any perfusion defect on three-dimensional hybrid. Finally, the patient underwent invasive coronary angiography confirming a subtotal occlusion of the OM1 (*D*, white arrow) which was successfully revascularized. On clinical follow-up, the patient was well and reported no further anginal episodes (adapted with permission from Manka *et al.*[62]).

problems that might benefit from molecular imaging include the identification of vulnerable atherosclerotic plaques before rupture and subsequent MI,[66,67] detection of biomechanisms that precede left ventricular remodelling and development of heart failure,[68] and the assessment of risk of ventricular arrhythmias by neuronal imaging.[69] Additionally, molecular imaging has great potential to facilitate the discovery and development of novel therapies through improved target identification and implementation of more efficient endpoints. 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.[64,70] Molecular imaging depends on hybrid imaging approaches, where the nuclear imaging component is used for molecular targeting seen as '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 morphological 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 is entering into routine clinical use. The combination of morphological imaging of coronary arteries using multidetector CT angiography and functional imaging of myocardial perfusion using PET, SPECT, and recently also CMR is a very powerful non-invasive imaging method that provides

comprehensive information both for diagnosis and decision-making for the treatment of CAD. While the performance of hybrid imaging appears to outweigh stand-alone methods, more studies are warranted to demonstrate the cost effectiveness of this technique. The new PET/CMR systems and specific molecular imaging probes provide novel applications which are also likely to enter into clinical cardiology during the following years.

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