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Multimodality imaging in coronary artery disease – "The more the better?"

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SOUHRN

Termínem multimodální zobrazování u ischemické choroby srdeční (ICHS) se označuje použití kombinací zobrazovacích metod k získávání informací. Mezi tyto kombinace, používané v režimech „side-by-side" nebo „fusion", patří výpočetní tomografie (computed tomography, CT) a jednofotonová emisní výpočetní tomografie (single photon emission computed tomography, SPECT), pozitronová emisní tomografie (positron emission tomography, PET) a CT a PET s magnetickou rezonancí (MR). Tímto způsobem získané údaje umožňují souhrnné (sumární) nebo synergistické získávání informací. Například morfologii (koronární pláty/stenózy) lze zobrazovat koronární CT angiografií, zatímco funkční aspekty ICHS jako abnormality perfuze myokardu nebo jeho metabolismus lze hodnotit vzájemně se doplňujícími metodami, aby bylo možno odlišit hemodynamicky významné stenózy od hemodynamicky nevýznamných stenóz. Rozlišení těchto dvou entit významně ovlivňuje léčbu pacienta. Kromě diagnostického přínosu mají tyto kombinace různých metod zobrazování využití i v prognostice. V tomto článku se zabýváme různými možnostmi multimodálního zobrazování (CT/SPECT, PET/CT a PET/MR) při vyšetřování pacientů s podezřením na ICHS, případně s potvrzenou ICHS, a uvádíme je do kontextu současných poznatků.

Keywords:
Computed tomography
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Magnetic resonance imaging
Multimodality imaging
Positron emission tomography
Single photon emission computed tomography

ABSTRACT

Multimodality imaging in coronary artery disease (CAD) comprises a combination of information from more than one imaging technique. These combinations, performed in a side-by-side or fusion mode, include computed tomography (CT) and single photon emission computed tomography (SPECT), positron emission tomography (PET) and CT, and PET with magnetic resonance imaging (MRI). Data thus obtained lead to either a summative or synergistic gain of information. For instance, morphology (coronary plaques/stenosis) can be depicted by coronary CT angiography, whereas functional aspects of CAD such as myocardial perfusion abnormalities or myocardial metabolism can be evaluated by the complementary technique in order to separate a hemodynamic significant coronary stenosis from a hemodynamic non-significant stenosis. Distinguishing these two entities has an important impact on patient management. Beyond the diagnostic yield, some of these combinations in multimodality imaging also have prognostic implications. In this article, we will describe different multimodality imaging approaches (CT/SPECT, PET/CT and PET/MRI) for evaluation of CAD in patients with suspected or known CAD and put them into the context of current knowledge.

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Introduction

Strictly defined multimodality (hybrid) cardiovascular imaging comprises a combination of at least two out of the four following cardiovascular imaging techniques: CT, SPECT, PET, MRI. More general, multimodality cardiovascular imaging is frequently used for any combination of imaging techniques employed to study the diagnosis or functional implications of cardiovascular disease. In this article, we will focus on multimodality cardiovascular imaging using the stricter definition.

Non-invasive methods of cardiac imaging have developed rapidly during the last ten years [1]. This is most obvious in the field of suspected or known coronary artery disease, where non-invasive imaging techniques are employed for the evaluation of diagnosis, prognosis and risk stratification. Beside morphology of the coronary vessels, functional alterations on myocardial perfusion and metabolism due to coronary stenosis are of high clinical interest, since only patients with both anatomically and functionally relevant stenosis benefit from revascularization [2]. The primary aim of a multimodality imaging approach should be providing synergistic rather than summative diagnostic and prognostic information, guiding the clinician in his further treatment options. By the use of multimodality imaging, the clinician should be capable of dividing patients with suspected or known CAD in a conservative, optimal medical therapy group vs. a group who might benefit with reasonable probability from interventional therapies. Despite all improvements and refinements in non-invasive imaging, a patient-tailored approach, which is additionally based on clinical judgment, remains mandatory to find the best practice for the individual patient. This article summarizes commonly used imaging techniques (except echocardiography) and their combinations for the non-invasive evaluation of patients with suspected or known CAD.

Commonly used combinations of cardiac imaging modalities

CT/SPECT

Coronary artery calcium score (CACS) detected by CT has wide implications not only for detection of CAD, but also for patient prognosis. A recent report including 351 patients with symptoms suggestive of CAD could demonstrate that sensitivity for CAD detection by CACS alone was very high (99.2%), whereas specificity was very low (30.3%), with an excellent negative predictive value of 98.5%. Adding SPECT to CACS in patients with CACS >0 yielded to increased specificity (80.9%) with only a slight decrease of sensitivity (87.9%). The authors stated that SPECT perfusion imaging in addition to CACS alone in patients with a CACS >0 increases the diagnostic accuracy for detection of relevant CAD and lowers the number of patients referred for coronary angiography [3]. On the other hand, in asymptomatic patients without previous CAD who have a normal SPECT CACS adds incremental prognostic information, with a 3.6-fold relative increase for any cardiac event (2.8-fold for death/myocardial infarction) when CACS is high (>400) vs. minimal (≤10) [4].

Coronary CT angiography (CTA) is the most promising non-invasive technique to depict both non-calcified and calcified plaques and to estimate luminal narrowing of the coronary arteries. Its negative predictive value is excellent in cohorts of patients with low pre-test probability, sparing the patient further examinations. However, if the pre-test probability is higher, the negative predictive value of coronary CT angiography is not that impressive [5]. A positive coronary CT angiogram has both good diagnostic performance for detecting and ruling out coronary stenoses >50% compared to invasive coronary angiography at least in patients with suspected CAD who have a low to intermediate pre-test probability of stenosis as defined by current data by Genders et al. [6]. The main limitation of coronary CTA is in patients who have densely calcified plaques, which can cause "blooming artifacts", resulting in non-interpretable images and lower diagnostic accuracy. Moreover, patients presenting with arrhythmia/tachycardia cannot be studied using low radiation protocols, since diagnostic quality might be severely impaired due to gating problems. Hence, a combination with other imaging techniques providing information about functional parameters, e.g. single photon emission tomography (SPECT), is mandatory in patients who show stenoses by coronary CTA, especially if these stenoses are severely calcified, to increase diagnostic accuracy [7], also see Fig. 1.

SPECT imaging studies also provide good diagnostic accuracy for detecting significant CAD compared to x-ray coronary angiography [8]. Patients with a normal SPECT perfusion have a favorable prognosis, with an annualized event rate of 0.6% which is similar to the event risk in the general population [9]. Conversely, patients with ischemic regions more than ≥10% of the left ventricle (LV) may benefit from revascularization procedures [10].

As SPECT provides 3D-datasets, these can be combined with CT images using dedicated software, permitting correction of misalignment between data sets. Combining these two modalities in patients at higher pre-test probabilities may increase the low specificity of coronary CTA from 63% to 95% and the positive predictive value (PPV) from 31% to 77% [11]. Furthermore, Sato and colleagues demonstrated that of 390 arteries in 130 symptomatic patients with suspected CAD, 54 (14%) were non-evaluable by coronary CTA due to severe calcifications, motion artifacts, and/or poor opacification. All non-evaluable arteries by coronary CTA were considered stenosis-positive leading to a reduced specificity and PPV. The combination with SPECT improved specificity and PPV significantly (from 80% to 92% and from 69% to 85%, respectively) [12]. In the subgroup of patients with chronic kidney disease, coronary CTA has a high sensitivity (93%) for detecting high-grade stenoses as defined by quantitative invasive coronary angiography (prevalence of high-grade stenoses 22%). However, the downside of coronary CTA is the low specificity of only 63% in this patient population [13]. SPECT perfusion imaging has the contrary problem: sensitivity is rather low at only 53% but specificity is good (82%). Combining coronary CTA with SPECT yields a sensitivity of 67% at a specificity of 86% [13].

Fusion images from coronary CTA and SPECT datasets may provide better sensitivity than SPECT alone and even

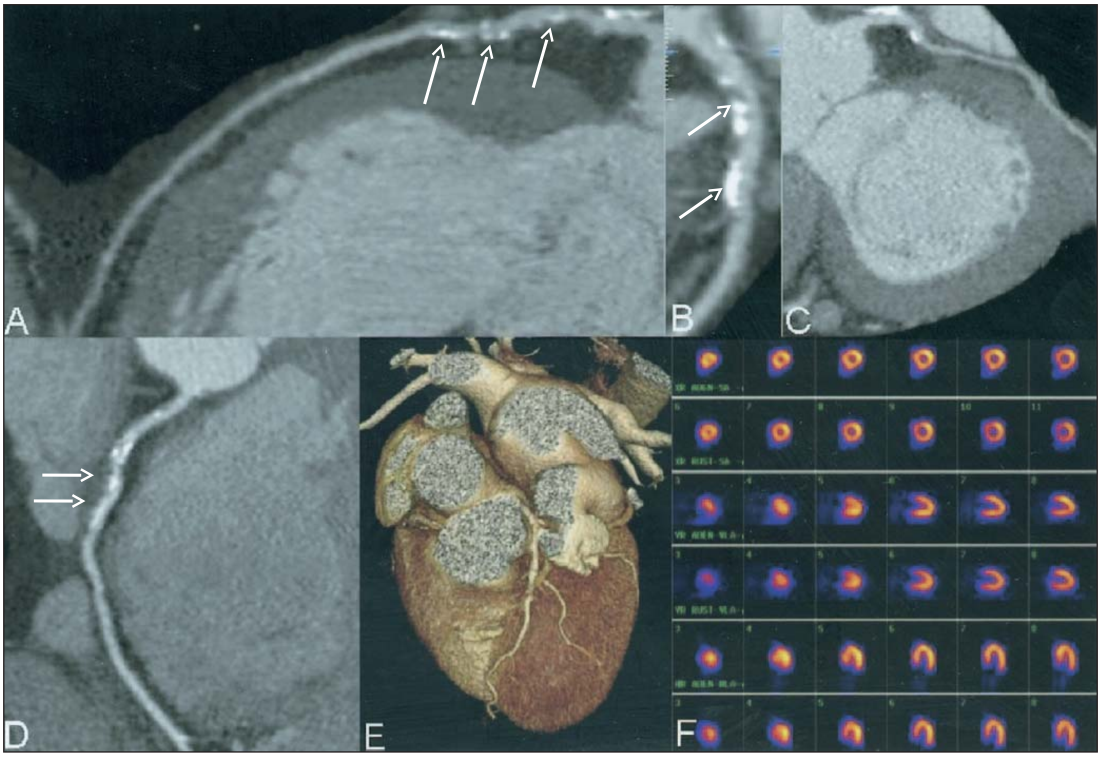

Fig. 1 – 69-year old patient with stenotic lesions on coronary CTA but normal perfusion by SPECT: (A), (C) and (D) display curved multiplanar CT reconstruction of the left anterior descending artery (LAD, =[A]), the left circumflex coronary artery (RCX, =[C]), and the right coronary artery (RCA, =[D]). LAD and RCA seem to have significant stenoses (see arrows). (B) shows an enlarged projection of the LAD perpendicular to (A) (see arrows), whereas (E) displays a 3-dimensional volume rendered reconstruction. On SPECT images (F) no perfusion abnormalities were detected (stress images first, third, fifth rows; rest images second, fourth, and sixth rows). Adapted from [7] with permission.

side-by-side analysis of SPECT and coronary CTA images in patients with multivessel disease [14]. Similar observations were made in patients with stenoses of smaller vessels and side branches such as diagonal branches CAD [15]. In summary, coronary CTA/SPECT multimodality imaging reduces the number of false positive examinations by coronary CTA alone thus avoiding unnecessary invasive coronary angiographies and improves the sensitivity of SPECT alone. Thus, the 2013 ESC guidelines on the management of patients with stable coronary artery disease [16] recommend explicitly an additional functional test in patients who have an unclear coronary CTA examination before sending the patient to invasive coronary angiography. In this guideline, unclear coronary CTA examinations are defined as those that have severe focal or diffuse calcifications.

Combining anatomic and functional information in patients with suspected coronary artery disease also has superior prognostic value. In a study comprising more than 500 patients the combination of coronary CTA and SPECT yielded improved prediction of events (all cause death, nonfatal infarction, unstable angina requiring revascularization) as compared to the single modalities [17]. Patients with a stenosis ≥50% on coronary CTA who showed a matched perfusion defect on SPECT had the highest annualized event rate of 9.0% (during a follow-up of almost 2 years). Patients with normal findings by both modalities had a low annualized event rate of 1.0% whereas those with a normal coronary CTA but an abnormal SPECT had a higher event rate of 3.7% which did not differ from those with an abnormal coronary CTA but a normal SPECT (3.8%). Another recent study consisting of 324 patients [18] confirmed these results using fused cardiac hybrid images. Annual death/MI rates were 6.0, 2.8, and 1.3% for patients with matched, unmatched, and normal findings (p<0.005). The same group reported that revascularization rates within 60 days were 41, 11 and 0% for matched, unmatched and normal findings in both techniques, respectively (p>0.001) [19]. Thus, coronary CTA/SPECT multimodality imaging is able to identify patients who – due to the high event rate in patients with matched findings – are good candidates for invasive coronary angiography and revascularization [16,20].

PET/CT

In contrast to SPECT, positron emission tomography (PET) allows quantification of myocardial blood flow (MBF) in absolute terms. The robust attenuation correction decreases the number of false positive findings as compared to SPECT perfusion imaging. Furthermore, PET shows both a higher spatial resolution and contrast resolution than SPECT [21], resulting in improved detection of even small perfusion deficits, decreasing the number of false negative reports. A meta-analysis reported high sensitivity (92%) and specificity (85%) by PET for detection of CAD (≥50% diameter stenosis by invasive coronary angiography) [22]. Coronary CTA and PET both perform well in excluding CAD; both techniques have a high NPV of 97%

for exclusion of CAD. In contrast, both techniques have limitations in the interpretation of a positive result. In a study from Kajander et al. [23], n=107 patients with an intermediate pretest likelihood of CAD underwent multimodality imaging (^{15}O-H_2O PET/64 slice coronary CTA). Results were compared to invasive angiography, including measurement of fractional flow reserve (FFR) when appropriate. As expected, coronary CTA overestimated the degree of stenosis in some patients (PPV 81%), whereas PET could not always separate microvascular disease from epicardial stenosis (PPV 86%). However, combining these two techniques to a multimodality imaging approach by using information about both anatomy (CTCA) and perfusion (PET) led to an almost perfect accuracy of 98% for detection of ≥50% diameter stenosis on a per patient and on a per vessel analysis. The unique advantage of such an approach is that severe microvascular disease resulting in a diffuse reduction of myocardial blood flow with PET adenosine stress can be easily differentiated from severe triple vessel disease by examining the coronary CTA images (Fig. 2). On the other hand, when coronary CTA shows calcified coronary plaques, PET is able to confirm or rule out hemodynamic stenosis by presence or absence of a perfusion defect [23].

These excellent results were confirmed in a smaller study, which compared the diagnostic accuracy of a combined approach (coronary CTA *and* ^{15}O-water PET) vs. single approach (coronary CTA *or* PET, respectively) in 44 outpatients scheduled for x-ray coronary angiography with an intermediate pretest likelihood of CAD. On a per-patient basis, the positive predictive values (PPV) were 71% for coronary CTA, 87% for PET and 100% for PET/CTA. Similarly, on a per-vessel basis the PPVs were 53% for coronary CTA, 53% for PET and 85% for PET/coronary CTA. In six patients, coronary CTA analysis was impaired by the presence of severe calcifications. However, with consideration of the PET data, all six patients were correctly diagnosed [24].

The results of PET/coronary CTA hybrid imaging also have important implications for patient selection for invasive coronary angiography. This was demonstrated in a recent study of 375 patients with suspected CAD [25]. Twenty-one percent of patients had an unequivocal result by coronary CTA (equivocal lesion or unable to grade stenosis severity due to artifacts). Of these patients, 70% showed regular perfusion by PET. Referral for invasive coronary angiography was 18% for those with regular perfusion but 71% for those with abnormal perfusion, respectively. Revascularization was performed in 59% of the patients with abnormal perfusion but in no one with regular perfusion. Another 30% of patients had obstructive CAD (stenosis ≥50%) by coronary CTA. Of these, 52% showed abnormal myocardial perfusion imaging by PET, resulting in a referral for invasive coronary angiography in 88% and revascularization in 72% of the cases, respectively. Thus, hybrid imaging with PET/coronary CTA – just as the combination of SPECT and coronary CTA – is excellent for pre-selecting patients who might benefit from invasive coronary angiography and subsequent revascularization.

Hybrid imaging by PET/CT has also gained much attention in the field of chronic total occlusions (CTO). Percutaneous coronary interventions (PCI) in these patients are still associated with higher complication rates and higher application of radiation and contrast media compared to patients with non-CTO PCI [26]. Prerequisites for attempting recanalization of a CTO are 1) the presence of symptoms and 2) evidence of ischemia and myocardial viability which can be provided by cardiac imaging [16]. Furthermore, detailed information about the occluded vessels anatomy (e.g. by coronary CTA) is helpful for increasing

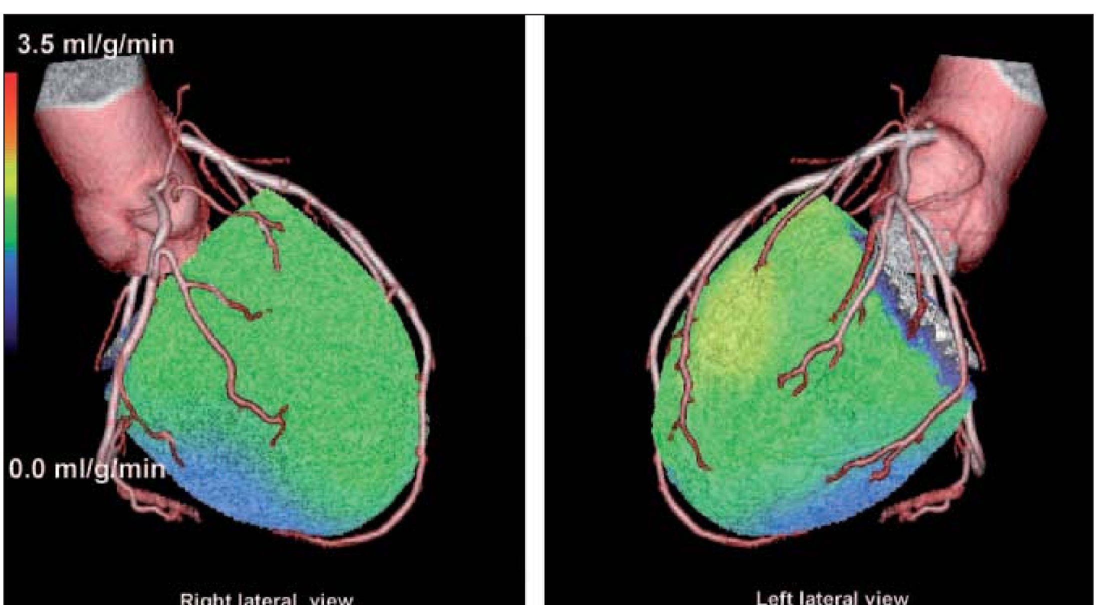

Fig. 2 – A 63-year old male with positive family history who suffers from atypical angina and has 2mm ST-segment depression in the stress ECG. In hybrid images (PET/CT), stress myocardial perfusion is diminished in most areas (green and blue). However, coronary CT (and subsequent invasive coronary angiography) reveals absence of coronary stenoses, suggesting microvascular disease as the cause of symptoms and ischemia in the stress ECG. Adapted from [23] with permission.

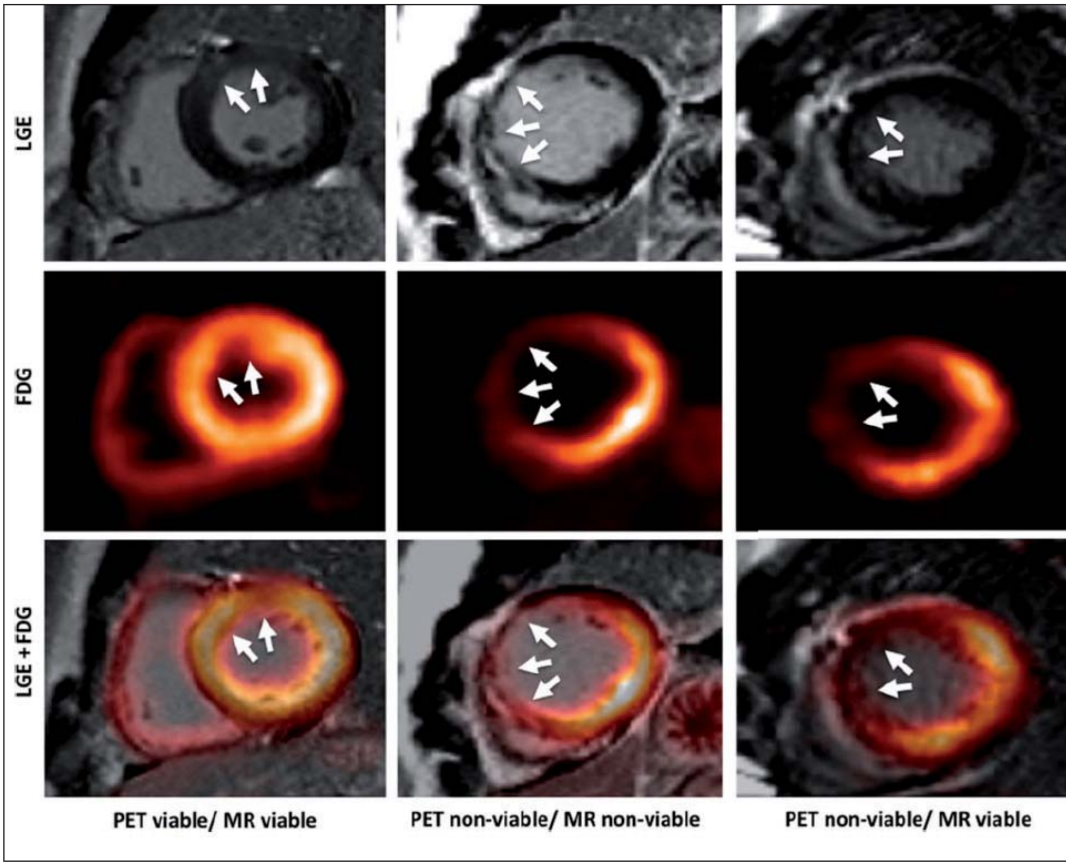

Fig. 3 – Images illustrating different combinations of FDG uptake (PET) and LGE transmurality (MRI). Left column: FDG ≥50%/LGE non-transmural ("PET viable/MRI viable"); middle column: FDG <50%/LGE transmural ("PET non-viable/MRI non-viable"); right column: FDG <50%/LGE non-transmural ("PET non-viable/MRI viable"). White arrows indicate areas of scar (LGE), and areas of ischemia (reduced tracer uptake), respectively. Adapted from [34] with permission.

success rates of the subsequent revascularization procedure [27,28]. CTA displays the amount of calcification, tortuosity and actual length of the occluded segment. Moreover, 3-dimensional reconstruction of the coronary anatomy may give assistance to identify the best angiographic projection [28]. Coronary CTA may be useful as an add-on to ischemia/viability imaging done by another imaging technique for predicting successful revascularization in patients with CTOs.

Luo and colleagues [29] examined patients with at least 1 CTO who underwent coronary CTA and coronary angiography. CT images and fluoroscopic images were placed side by side before or during PCI. Overall success rate was higher in this group as compared to a group without pre-interventional coronary CTA (87% vs 76.4%, p=0.016). Antegrade PCI failed more frequently at a lesion length of >31.89mm on coronary CTA (odds ratio 7.04). Another recent registry [30] comprising 240 CTO lesions in 229 patients analyzed the data of pre-procedural coronary CTA to predict time-efficient successful guidewire crossing ≤30 min. Multivariate analysis provided several CT based morphologic adverse predictors such as multiple occlusions, blunt stump within CTO, calcification ≥50% within CTO and bending ≥45% within CTO and two clinical adverse predictors namely previous attempt of PCI at CTO and occlusion duration ≥12 months or unknown. Every predictor gets one point and the score is calculated as sum of all points. The higher the score, the higher the risk of failed CTO.

Thus, multimodality imaging demonstrating ischemia/viability and morphology of the occluded vessel(s) seems promising for identifying patients in whom an attempt of CTO recanalization is indicated and for identifying a recanalization strategy with the highest chance of success at minimum procedural time.

PET/MRI

PET/MRI is a novel multimodality imaging technique which combines the high sensitivity of PET tracers with the excellent soft-tissue characterization by MRI. ^{18}F-fluorodeoxyglucose (FDG) PET imaging remains the gold standard to differentiate reversible and irreversible myocardial dysfunction [31]. Metabolically active myocardial cells can be detected by increased glucose uptake due to the up-regulation of glucose transporters in conditions of hypoxia and ischemia [32]. A drawback of PET is that only information about perfusion and glucose metabolism is gained rather than information about anatomy and function. MRI is a technique, which offers detailed information about anatomy, function and even perfusion in a single method. While late gadolinium enhancement (LGE) typically reveals areas of irreversible damage, such as acute necrosis and chronic fibrosis, the uptake of

FDG by PET represents a true metabolic signal of viable cells. Combining the strengths of PET and MRI to separate non-viable tissue from remote myocardium could be a promising approach for identifying a maximum of viable myocardial segments in theory, but today the role and potential of PET/MRI in ischemic cardiomyopathy is not clearly defined, and most studies rather suggest a summative than a synergistic effect of combining these two imaging modalities.

Nensa et al. [33] showed the feasibility of hybrid imaging with F-18 fluorodeoxyglucose (FDG) on an integrated 3-T PET/MR imaging system. Twenty patients with acute and chronic myocardial infarction were included. LGE images showed a close correlation to FDG PET images with respect to myocardial viability and infarct quantification. Overall, 306 segments were analyzed, 32% were diagnosed as infarcted on PET, whereas 30% of LGE images were reported as infarcted by MRI imaging. Rischpler et al. [34] extended this information by further studying whether additional information could be gained by this approach. They included 28 patients with primary acute myocardial infarction who underwent simultaneous PET/MRI for assessment of regional FDG uptake and degree of LGE transmurality. "PET viable" was defined as threshold ≥50% FDG uptake in comparison to remote myocardium, whereas "MRI viable" was defined as LGE transmurality ≤50%. Regional wall motion was assessed at baseline and 6 months later by MRI. "PET viable" and "MRI viable" segments demonstrated a lower wall motion abnormality score and a better regional wall motion improvement after 6 months compared with "PET non-viable" or "MRI non-viable" segments, respectively. In discrepant findings, FDG uptake turned out to be a better predictor for functional recovery (Fig. 3) [34].

Hence, for identification of viability alone FDG-PET seems to be superior to MRI. However, as MRI provides more information than PET in terms of function and anatomy it should remain the first line technique to evaluate viability. PET should be employed in those patients where identification of additional regions of viability would turn a clinical decision more towards revascularization.

Does every patient need multimodality imaging?

In most patients who are referred for work-up of suspected or known CAD by non-invasive cardiac imaging, one single imaging technique is often sufficient. MRI in particular is able to provide information about morphology, myocardial function and perfusion in a single "one-stop-shop" technique. Except for MRI and echocardiography, other imaging techniques (CT, SPECT, PET) are associated with some radiation exposure. Furthermore, one has to keep in mind that additional imaging will result in higher costs. Nevertheless, there are some conditions which may justify a multimodality imaging approach: 1) Patients with intermediate pretest likelihood for CAD, in whom the initial imaging test (often coronary CTA) gives an inconclusive result, additional ischemia imaging is a guideline-supported option for obtaining a definite diagnosis [16]. 2) Chronic total occlusions (CTO). Beside the evidence of ischemia associated by an occluded vessel, detailed anatomical information about the occluded vessel is helpful prior to revascularization attempts [35].

Simultaneous acquisition of coronary CTA and stress nuclear perfusion techniques (SPECT; PET) as a hybrid approach in patients with suspected CAD poses difficult questions regarding the use of beta-blockers. They are often requested for coronary CTA to lower heart rate yielding better diagnostic images, whereas use of beta-blockers could reduce the sensitivity of perfusion imaging. Furthermore, routinely combining two imaging techniques using dedicated hybrid machines, which are based on radiation exposure, will inevitably increase the radiation dose, even though recent technical progress has resulted in lower radiation doses both for coronary CTA and for SPECT. Moreover, some of the imaging techniques are still not widely available yet (e.g. PET), restricting its use to highly specialized medical centers. Further technological improvements of each imaging technique (e.g. higher resolution, lower radiation) and ongoing development of dedicated image fusion software might facilitate a more widespread clinical use of multimodality imaging in the clinical setting. Future guidelines should include recommendations for the use of multimodality imaging assisting the clinician in choosing the right combination of imaging modalities for the right patient.

Conclusion

In summary, a multimodality imaging approach is able to provide detailed information about patients with suspected or known CAD in terms of anatomy (plaques, stenosis) and function (perfusion, metabolism). This is of importance, since there is a variable relationship between the anatomic degree of a stenosis and the occurrence of myocardial ischemia. Results will influence diagnosis, risk stratification, potential treatment strategies and even prognosis of the patients. However, major drawbacks of multimodality (hybrid) imaging are increased radiation exposure and higher costs in comparison to a single imaging approach. Further prospective multicenter studies are needed to clarify the future role of its clinical utility, including data about prognosis and cost-effectiveness.

Conflict of interest
No conflict of interest.

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Ethical statement
This article does not contain any studies with human or animal subjects performed by any of the authors.

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