Coronary artery disease imaging

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Cardiovascular disease represents the leading cause of death worldwide. Different imaging methods are available to aide in both the diagnosis of coronary artery disease and monitoring of the disease processes, including ultrasound/echocardiography, nuclear imaging, hybrid imaging, molecular imaging, and invasive imaging. Over the last few years, developments have been made not only from a technical, but also from a medical viewpoint, and these developments have been significant for the management of coronary artery disease. This review will briefly discuss the main cardiac imaging techniques for the assessment of coronary artery disease by focusing on three main areas: (i) coronary artery anatomy, lumen size, and atherosclerotic plaques; (ii) myocardial perfusion; and (iii) myocardial viability. The advancements in imaging technology have expanded the use of imaging for coronary artery disease, and it is now considered an important tool for the prevention and diagnosis of coronary artery disease and the monitoring of the different therapeutic strategies. Cardiovascular imaging has been included in the current international guidelines, demonstrating its appropriateness for the management of patients with suspected or known coronary artery disease.

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Cardiovascular disease represents the leading cause of death worldwide with ischemic heart disease being the number one cardiovascular disease in most countries. An increasing amount of evidence has emerged on the added value of currently available imaging methodologies for the diagnosis of and monitoring of the disease processes.[1,2] Additionally, they may play a significant role in the early detection of disease and prevention. These different imaging methods include: (i) ultrasound/echocardiography and their various modalities; (ii) nuclear imaging (eg, single-photon emission computed tomography [SPECT], positron emission tomography [PET], cardiac computed tomography [CT], magnetic resonance imaging [MRI], cardiac magnetic resonance [CMR]); (iii) hybrid imaging; (iv) molecular imaging; and (v) invasive imaging (eg, conventional angiography, intravascular ultrasound [IVUS], and optical coherence tomography [OCT]). Over the last few years, enormous and exciting developments have not only occurred from a technical, but also from a medical viewpoint,[3-9] and these developments have been significant for the management of coronary artery disease (CAD).

SELECTED ABBREVIATIONS AND ACRONYMS

CAC	coronary artery calcium
CAD	coronary artery disease
CMR	cardiac magnetic resonance
CT	computed tomography
DE-CMR	delayed contrast enhancement CMR
DSE	dobutamine stress echocardiogram
IVUS	intravascular ultrasound
MPI	myocardial perfusion imaging
MRI	magnetic resonance imaging
MSCT	multislice computed tomography
OCT	optical coherence tomography
PET	positron emission tomography
SPECT	single-photon emission computed tomography

Whether the economic impact of these emerging technologies is sustainable is a question the cardiology community will have to answer in the near future when considering the cost-benefit ratio of the selected diagnostic tool.[10,11] The main cardiac imaging modalities for the assessment of CAD will be briefly discussed in this review with a focus on the three main areas where imaging plays a central role: (i) assessment of the coronary artery anatomy, lumen size, and atherosclerotic plaques; (ii) assessment of myocardial perfusion; and (iii) assessment of myocardial viability.

CORONARY ANATOMY ASSESSMENT

In patients with an excellent acoustic window, it may be possible to visualize the origin and proximal coronary arteries with two-dimensional echocardiography (2DE), which is especially significant for cases involving giant coronary aneurysms or for children to screen for the coronary involvement of Kawasaki disease.[12] However, transthoracic echocardiography is insufficient to delineate the anatomical course or lumen size of coronary arteries, and it does not visualize atherosclerotic plaques. Catheter coronary angiography is the gold standard imaging modality to assess coronary artery anatomy. Catheter coronary angiography provides excellent visualization of the coronary artery lumen, and it has a spatial resolution of 0.25 mm and a temporal resolution of 6 ms. It is a technique that requires exposing the patient to ionizing radiation (3 mSv on average), and it is an invasive procedure that has very rare, but potentially serious complications. However, it allows for the diagnosis and, if necessary, treatment of the disease in the same session. It does not assess the coronary vascular wall properties, but this assessment is usually done by complementing catheter coronary angiography with intracoronary ultrasound imaging.

Noninvasive coronary artery imaging is very challenging, and the following factors must be considered when assessing the coronary anatomy: (i) high spatial resolution is needed to assess small and tortuous ves-

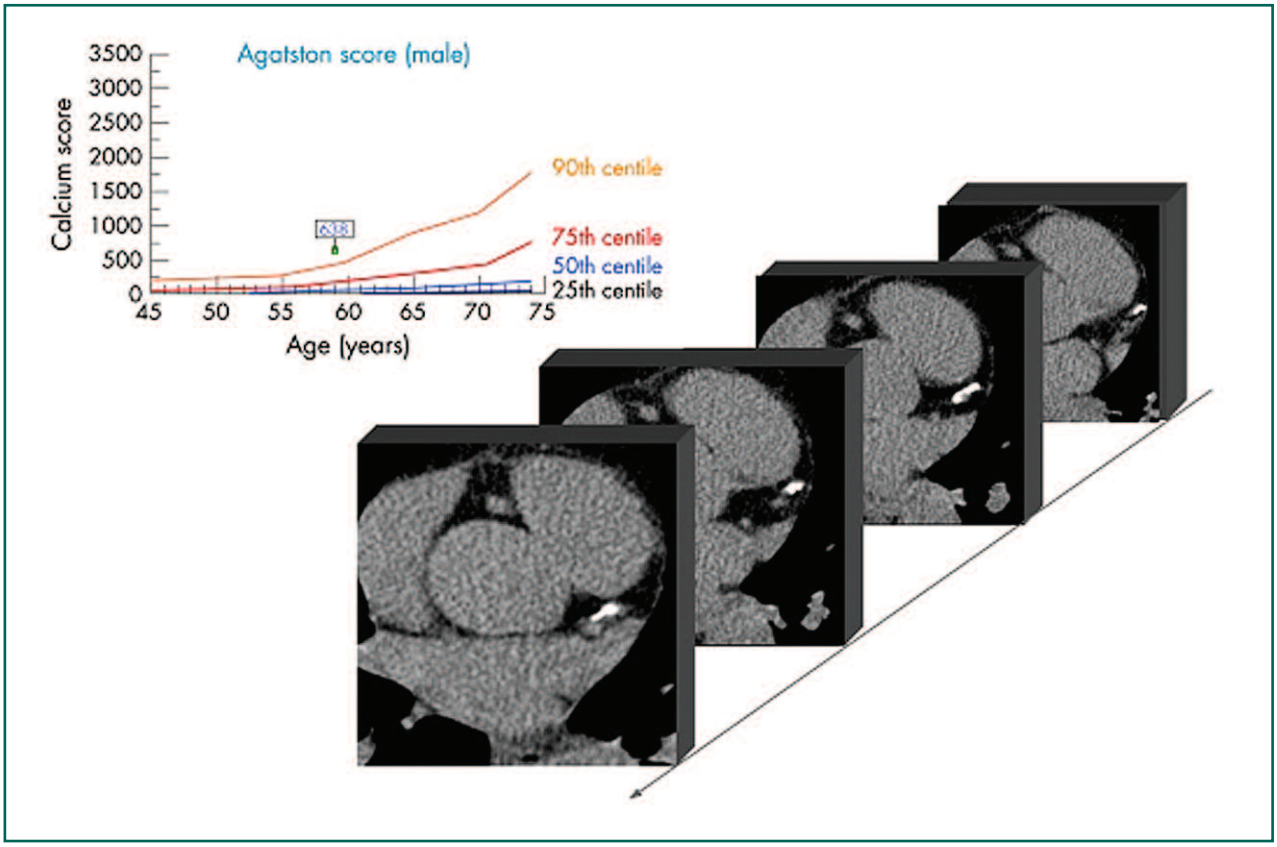

Figure 1. Electron beam computed tomographic images.

The images, which were taken at different scan planes, illustrate extended coronary calcification (Agatston score 638) in a man who, since his youth, was an active sportsman. The percentile distribution (25th, 50th, 75th, 90th centile) in men between 45 and 75 years, which is based on the results of the Heinz Nixdorf Recall study, is presented in Kruk et al[21] and Tornvall et al.[22]

From reference 16: *Erbel et al.* Heart. *2007;93:1620-1629. © 2007, BMJ Publishing Group Ltd.*

sels; (ii) high temporal resolution is required because the coronary arteries undergo substantial motion throughout the cardiac cycle with superimposed respiratory movements; and (iii) high tissue detail and blood-tissue contrast is necessary to delineate the lumen size throughout the coronary system, to identify calcified and noncalcified coronary plaques, and to distinguish epicardial coronary arteries from surrounding epicardial fat and the parallel running veins.

Computed tomography coronary angiography

CT coronary angiography can obtain a quantitative measure of coronary calcium, and it provides information related to coronary tree anatomy, including anatomical course, lumen size, and artery wall status. Furthermore, it has the potential to detect both calcified and noncalcified atherosclerotic plaques.

The detection of coronary artery calcium (CAC) by electron-beam CT or multidetector CT has gained some relevance due to the documented association between CAC scores and the risk of cardiovascular events.[13,14] An increase in CAC scores over time (CAC progression) improves the prediction of coronary heart disease events. In a 2012 study, Okwuosa et al[15] determined whether novel markers that do not involve ionizing radiation could predict CAC progression in a population of 2620 individuals who were at a low risk for coronary heart disease events (Framingham risk score <10%) and who had a follow-up CAC measurement. The authors concluded that in individuals at a low predicted risk according to the Framingham risk score, traditional risk factors predicted CAC progression in the short term with good discrimination and calibration. In addition, prediction improved minimally when various novel markers were added to the model *(Figure 1).*[16-22]

In an extensive document, Waugh et al[20] assessed the clinical and cost-effectiveness of CT screening for asymptomatic CAD. In addition, Waugh et al wanted to establish whether CAC scores predict coronary events and add anything to the risk factor scores and whether measuring CAC changes the patient's treatment. However, no randomized control trials (RCTs) have assessed the value of CT screening in reducing cardiac events. Seven studies were identified that assessed the association between CAC scores on CT and cardiac outcomes in asymptomatic people (n=30 599 people). As the CAC score increased, so did the risk of cardiac events. The correlation between CAC and cardiac risk was consistent across the studies. There was evidence that CAC scores varied among people with the same Framingham risk factor scores and that within the same Framingham bands, individuals with higher CAC scores had significantly higher cardiac event rates. This finding applied mainly when the CAC scores exceeded 300. Information is still needed regarding: (i) the distribution of risk factor scores and CAC scores in asympto-

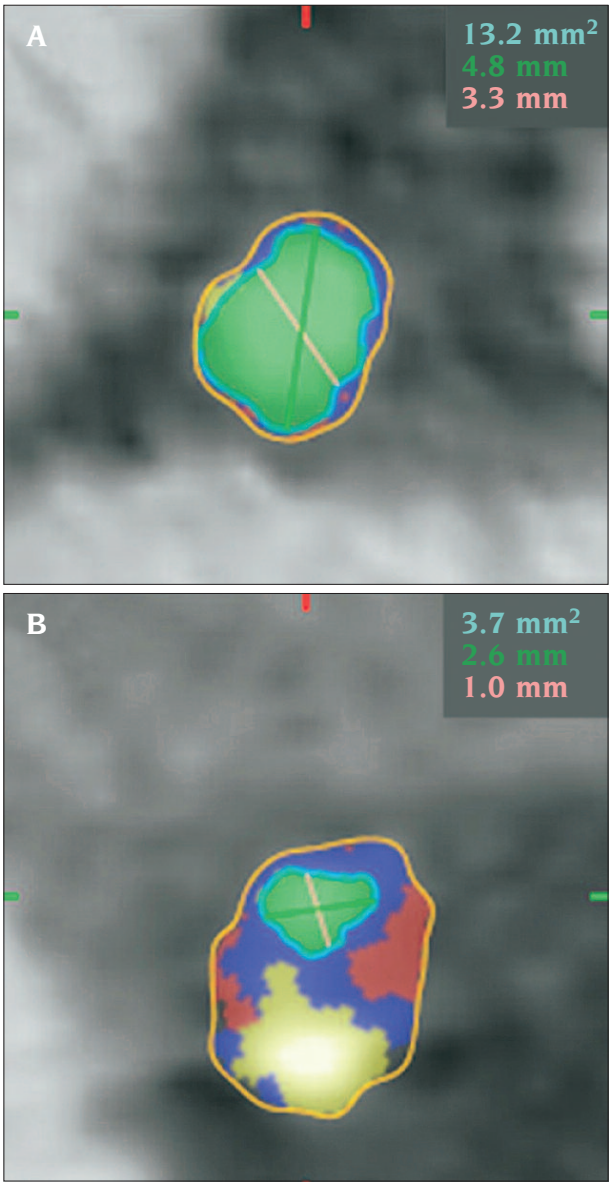

Figure 2. Contrast-enhanced computed tomography coronary angiography for the detection of plaque, minimal lumen area of the plaque, and percent atheroma volume.

The imaging compares a normal coronary arterial segment ***(Panel A)*** *with abnormal arterial segments* ***(Panel B).*** *The green area represents the lumen, and the yellow, blue, and red areas depict components of the plaque.* ***From reference 23:*** *Akram et al.* J Nucl Cardiol. *2008;15:818-829.* *© 2003, American Society of Nuclear Cardiology.*

matic people; (ii) the level of concordance between risk factor scores and CAC scores; (iii) the risk of cardiac events per annum according to CAC score and risk factor scores; (iv) information on the acceptability of CT screening after information about the radiation dose; and (v) an RCT to study the addition of CT screening to current risk factor–based practice.[20]

Multislice computed tomography (MSCT) and dual-scan MSCT have improved the spatial and temporal resolution of acquired images, making it possible to use cardiac CT for noninvasive coronary angiography. In fact, cardiac CT is the best noninvasive modality for visualizing the coronary anatomy. ECG gating should be utilized when coronary artery visualization is required to improve coronary delineation and image quality. Recent studies[23] demonstrated that MSCT is able to visualize both the vessel lumen and wall to detect and characterize the atherosclerotic plaque *(Figure 2, page 251).*

Cardiac CT easily identifies calcified plaques, but it also has a moderate accuracy to detect noncalcified (lipid-rich) and mixed plaques. In patients with chest pain, the extent of noncalcified atherosclerosis as assessed by MSCT was correlated with mortality. Prospective clinical studies are required to clarify the prognostic value of cardiac CT in this context. Plaque characterization promises to help in the detection of vulnerable plaques. However, it is not currently possible or recommended to use cardiac CT in routine clinical practice. Single- and multicenter studies demonstrated that CT coronary angiography has a high negative predictive value (ruling out significant disease), but a low positive predictive value (plaque calcification frequently precludes accurate visualization of the lumen leading to overestimation of luminal stenosis). Thus, from a clinical perspective, the most important advantage of MSCT is the possibility of ruling out significant CAD convincingly.

Current clinical applications of CT coronary angiography

- Noninvasive exclusion of CAD in patients at an intermediate risk who have undergone one or more inconclusive stress tests, including patients with atypical angina pectoris and ambiguous results of previous stress tests.
- Evaluation of the origin and course of anomalous coronary arteries to provide a better characterization than CMR, but special efforts to reduce the radiation exposure should be undertaken since these patients are often young.
- Assessment of the patency of coronary grafts and detection of stenosis within the bypass or at the connection with the primitive coronary tree *(Figure 3).*[9]

CT coronary angiography is not recommended in high-risk patients, such as individuals with typical angina or positive stress tests, in whom the prognosis is more related to functional parameters, such as ischemia and left ventricular dysfunction than to anatomical plaque measurement. CT coronary angiography is not appropriate as a screening examination in asymptomatic individuals or patients at low risk because of its associated radiation exposure, contrast administration, and risk of false positives. New developments in the field will open the way for new potential uses of this technique.[21,24]

Magnetic resonance coronary angiography

Advances in the CMR technique, including the use of parallel image acquisition, fat suppression (T2 preparation), ECG-gating algorithms, and diaphragmatic monitoring with navigator echoes, improved the spatial and temporal resolution, making it possible to visualize the coronary arteries.[10,22,25,26] The anatomical evaluation of the entire coronary tree and lumen size are still tough to visualize, partially because the spatial resolution of CMR is still lower than cardiac CT (0.8 to 1.1 mm vs 0.4 to 0.5 mm).

CMR coronary angiography is not ready for the reliable determination of the location and extent of CAD in routine clinical practice. However, CMR coronary angiography has proven clinically valuable to assess the proximal portions of the coronary system and coronary grafts. The technique can evaluate the origin and course of the proximal coronary artery and detect anomalous coronary artery origins and coronary fistulas.

It can also be used for the detection and follow-up of coronary aneurysms caused by Kawasaki disease. Lastly, CMR coronary angiography can assess the patency of coronary artery bypass grafts, although difficulty remains for the visualization of the connection with the native coronary circulation where stenoses are often located.

Further technological advances, with acquisitions by whole-heart sequences, higher field magnets, higher multiple receiver channel coils, and new intravascular paramagnetic agents, promise to improve the quality of coronary CMR images.[27-30]

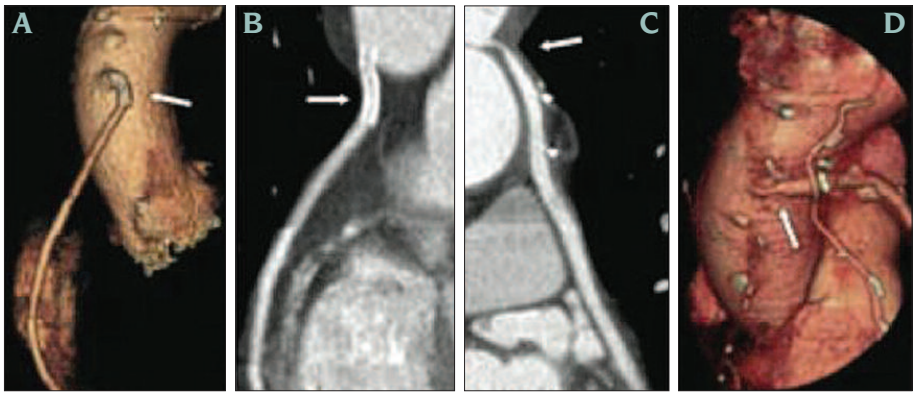

Figure 3. Noninvasive assessment of coronary bypass grafts.

Panels A and B. *3D rendering and multiplanar reconstruction of a coronary artery bypass graft of the right coronary artery after stent implantation in the proximal part.* ***Panels C and D.*** *Stenosis of a proximal coronary artery bypass graft to the right coronary artery in another patient. A left mammarian bypass to the left anterior is crossing the coronary artery bypass graft.*

From reference 9: *Cortez Dias N, Almeida A, Pinto F. Multimodality imaging: When echo is not enough. In Gillam LD, Otto CM, eds.* Advanced Approaches in Echocardiography. *1st ed. Philadelphia, PA: Saunders, an imprint of Elsevier Inc; 2011:199-246.*

ASSESSMENT OF MYOCARDIAL PERFUSION AND ISCHEMIA

Currently, there are many noninvasive techniques to assess myocardial perfusion and ischemia, including stress echocardiography, SPECT-myocardial perfusion imaging (MPI), PET, CMR, and cardiac CT. All of these techniques use either exercise or pharmacologic stress to produce heterogeneity of blood flow between myocardial regions supplied by normal arteries and those regions perfused by stenotic vessels to induce ischemia.

Pharmacological stress can be generated by infusion of vasodilators (dipyridamole or adenosine) or inotropic agents (dobutamine stress). Despite acting by different mechanisms, all methods administered with the appropriate doses have similar ischemic potency. Dobutamine increases contractility and myocardial oxygen demand, resulting in ischemia in regions supplied by stenotic arteries. Dipyridamole inhibits adenosine uptake, which induces adenosine accumulation. The stimulation of adenosine receptors induces potent vasodilatation, which is less pronounced in those areas supplied by stenotic coronary arteries. Thus, flow is diverted away (coronary steal) and the blood flow misdistribution produces ischemia.

Stress echocardiography

Standard stress echocardiography detects stress-induced myocardial ischemia efficiently, but it is unable to assess myocardial perfusion directly,[7,31-33] which reduces its sensitivity since regional wall motion abnormalities do not become apparent until the disease becomes moderate to severe. The major advantages of stress echocardiography include higher specificity, wider availability, bedside examinations, lower costs, its radiation-free nature, and higher temporal/spatial resolution.

Myocardial contrast echocardiography is a technique that uses microbubbles to assess myocardial perfusion. Microbubbles remain within the intravascular space; thus, steady-state myocardial contrast intensity reflects the capillary blood volume. Delivering a high-energy ultrasound destroys microbubbles within the myocardial capillaries. The subsequent rate of contrast replenishment reflects myocardial blood flow in the tissues. Combining myocardial contrast echocardiography with pharmacological stress provides an incremental value for the assessment of CAD.

Stress echocardiography has several limitations that justify the permanent search for alternatives, including the high dependence on operator skills, high inter- and intraobserver variability, and the reliance on the acoustic window quality. The SPECT-MPI imaging stress test is the most widely used to assess myocardial perfusion, but the use of CMR and PET continues to increase.

Single-photon emission computed tomography

SPECT-MPI performed at rest and during stress is a robust, well-validated, and widely available technique to assess regional myocardial perfusion.[32,34] SPECT is based on the detection of the heterogeneous uptake of radiotracers during stress, which is caused by the inability to increase myocardial perfusion within the territory of stenotic arteries *(Figure 4, page 254).*[9]

The major advantages of SPECT in comparison with stress echocardiography include: (i) higher feasibility and lower operator dependency; (ii) higher sensitivity (≈86%), especially for a single-vessel disease involving the left circumflex; (iii) higher accuracy in the presence

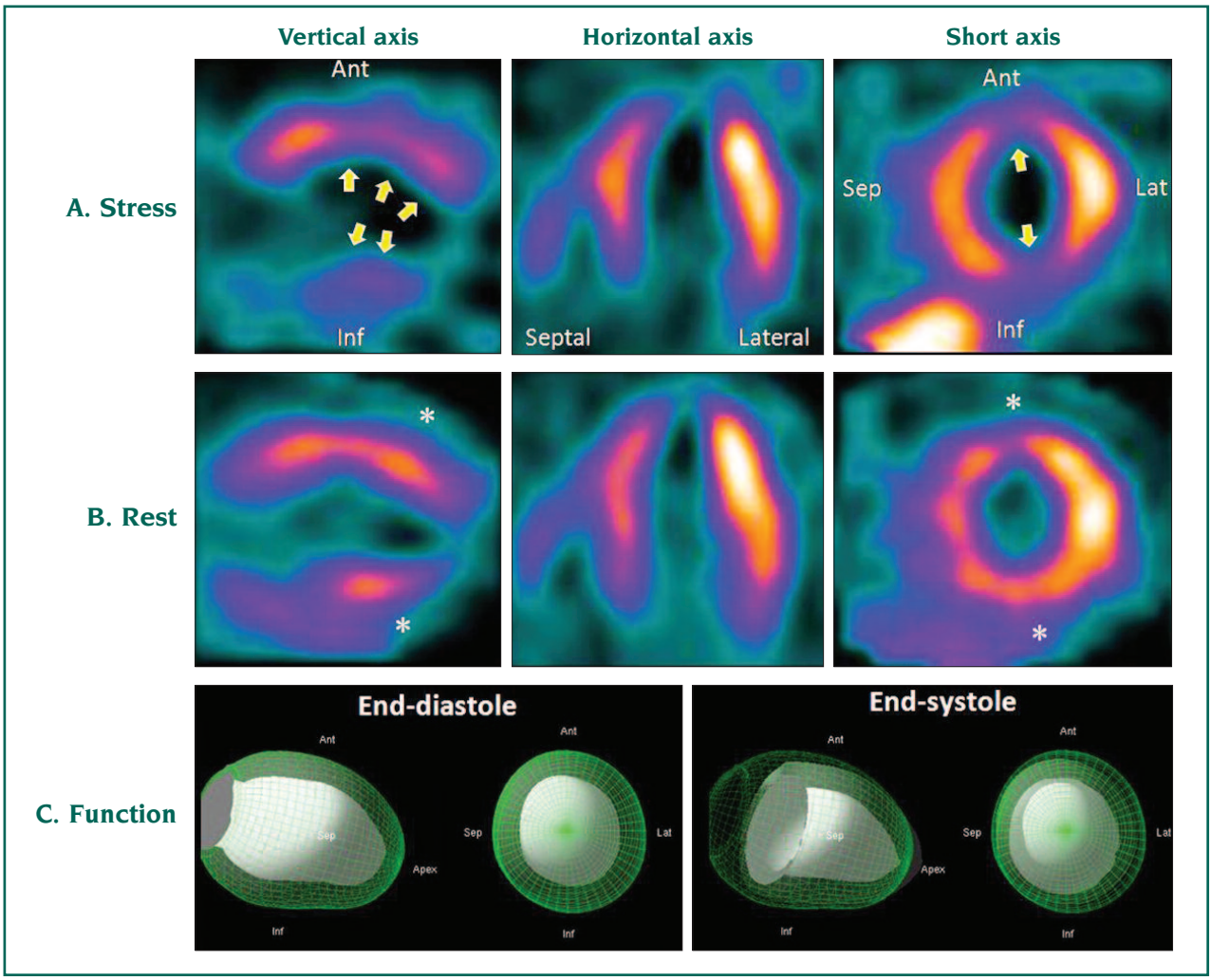

Figure 4. Exercise and rest Tc-99m tetrofosmin SPECT images in a patient with 3-vessel CAD and severe LV systolic dysfunction.

Panel A. *On images obtained after stress, uptake is absent at the apex and it is severely reduced at the inferior and anterior walls (arrows).* ***Panel B.*** *At rest, there is significant improvement in the mid-apical parts of the anterior and inferior walls (asterisk). However, there is no change at the apex.* ***Panel C.*** *ECG gating of the resting tomograms showing the endocardial border at end systole and end diastole. There is akinesia of the apical parts of the anterior and inferior walls. As the latter two regions are ischemic, viable, and akinetic, they fulfill the criteria for myocardial hibernation and are likely to recover function after revascularization. In contrast, there is akinesia of the apex, which, when combined with the lack of viability and ischemia, suggests myo-cardial infarction.*
Abbreviations: *CAD, coronary artery disease; LV, left ventricular; SPECT, single-photon emission computed tomography.*
From reference 9: *Cortez Dias N, Almeida A, Pinto F. Multimodality imaging: When echo is not enough. In Gillam LD, Otto CM, eds.* Advanced Approaches in Echocardiography. *1st ed. Philadelphia, PA: Saunders, an imprint of Elsevier Inc; 2011:199-246.*

of extensive resting wall motion abnormalities; and (iv) it is the most cost-effective technique for patients with an intermediate risk of coronary events.

SPECT is unable to provide absolute quantification of blood flow. In fact, only relative differences in perfusion are assessed from one region of the myocardium to the region with the highest myocardial counts, which frequently results in an underestimation of the extent of CAD in patients with 3-vessel and/or left main CAD, particularly if balanced ischemia occurs during stress. The three available perfusion tracers (thallium-201, ^{99m}Tc-labeled sestamibi, and tetrofosmin) provide similar accuracy in the identification of CAD. Although SPECT is very sensitive for detecting CAD (the absence of reversible perfusion defects has a negative predictive value of 95%), it is only moderately specific (≈74%). The specificity of SPECT-MPI is diminished when artifacts caused by soft-tissue attenuation are interpreted as perfusion defects. Dedicated hardware and software enable image reconstruction for different types of attenuation, reducing artifacts originating from the diaphragm, breast tissue, or adipose tissue in obese patients. In addition to assessing myocardial perfusion,

ECG-gated SPECT evaluates the regional and global LV contractility and wall thickening. ECG-gated SPECT is only possible with the use of ^{99m}Tc-labeled tracers.

The use of ECG gating with the simultaneous evaluation of perfusion and myocardial function improves the differentiation of scars from attenuation artifacts and provides important prognostic information. The extent and severity of inducible perfusion defects have a diagnostic value, which can be used to identify patients who are likely to benefit from revascularization procedures and to provide prognostic stratification (correlates with the risk of coronary events and sudden death). The absence of perfusion defects almost excludes the existence of flow-limiting coronary stenosis, and it is associated with a low risk (<1%) of future coronary events. The prognostic accuracy of gated SPECT derives from the simultaneous assessment of the most important prognostic factors, which includes the following: (i) extension of necrotic myocardial tissue; (ii) extension and severity of inducible ischemia, which is the best predictor of nonfatal myocardial infarction; and (iii) left ventricular volume and systolic function—the post-stress ejection fraction is the best predictor of cardiac death.

Positron emission tomography

PET is the gold-standard assessment of myocardial perfusion because it is the only technique that allows for the absolute quantification of coronary blood flow at rest and coronary reserve during hyperemia.[35,36] Quantification of myocardial blood flow improves the assessment accuracy in patients with multivessel disease and balanced myocardial ischemia in whom the absence of a normal reference segment may produce a false negative with SPECT-MPI *(Figure 5).*[35,37]

The most commonly used tracers for assessing myocardial perfusion with PET are ^{13}N-ammonia, rubidium-82 (^{82}Rb), and ^{15}O-labelled water. These tracers have a high-energy emission, meaning that they are particularly indicated for obese subjects, and they have a short half-life, which guarantees that the tissues are only

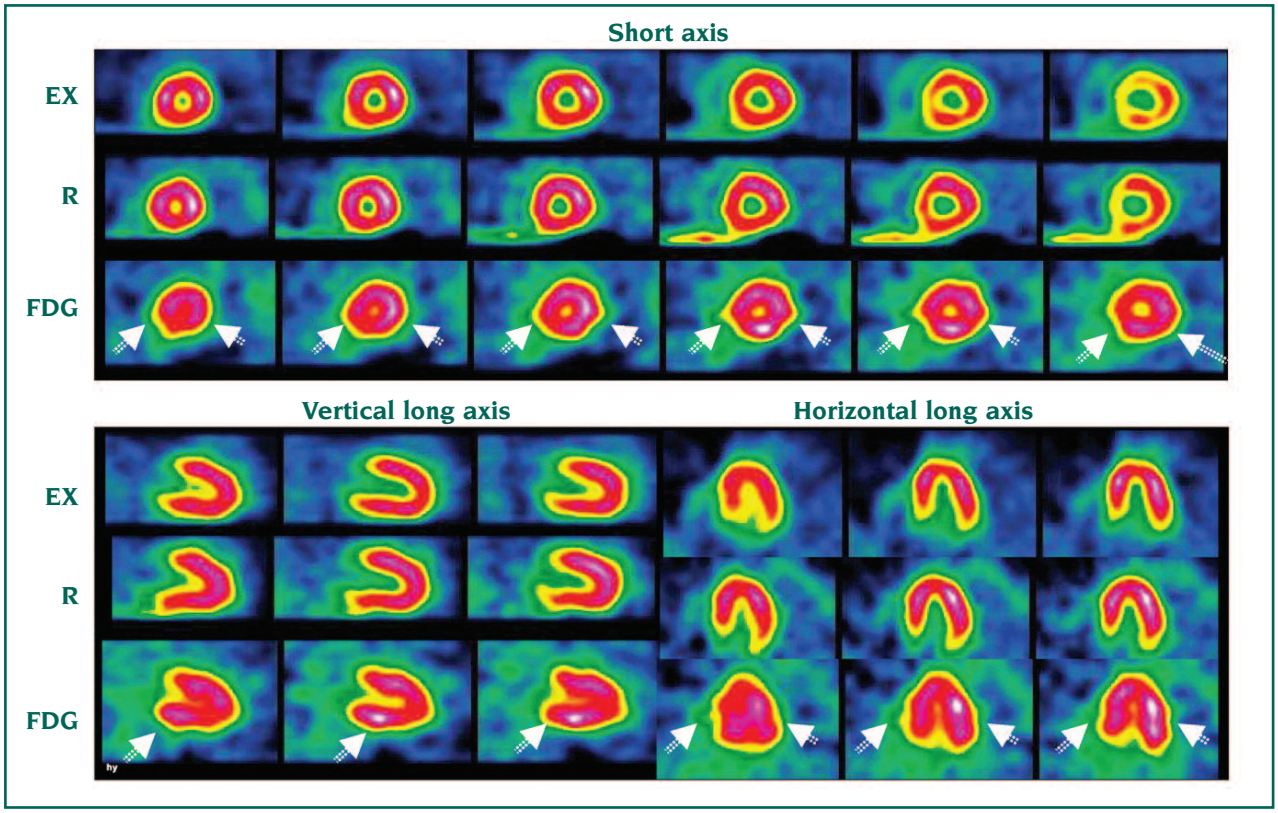

Figure 5. Exercise (Ex) and rest (R) Tc-99m sestamibi and exercise F-18-FDG images in a patient with 3-vessel CAD.

The perfusion images show no focal defects since balanced ischemia was present. However, the F-18-FDG images show intense and abnormally increased global uptake in all three vascular territories.

Abbreviations: *CAD, coronary artery disease; FDG, fluorine-18-2-deoxygluclose.*

From reference 37: *He et al.* Circulation. *2003;108:1208-1213. © 2003, Wolters Kluwer Health, Inc.*

exposed to radiation for a short time. If a cyclotron is available, ^{13}N-ammonia is the preferred tracer for myocardial perfusion because it provides high-quality images due to its high single-pass extraction, prolonged retention in the myocardium, and rapid blood-pool clearance. ^{82}Rb has the advantage of being readily produced without the need for a cyclotron.

Additionally, with ECG gating, PET can assess the regional and global left ventricular systolic function. PET offers many advantages, including higher spatial and contrast resolution, improved image quality, accurate attenuation correction, higher diagnostic accuracy, and excellent risk stratification. However, the cost and availability of PET tracers are significant limitations that hamper their widespread use in clinical practice.

Cardiac magnetic resonance

The presence and extent of myocardial ischemia can be evaluated with dobutamine stress CMR and first-pass stress perfusion CMR.[38] The major advantages of CMR in the assessment of myocardial ischemia include a higher resolution, no radiation, and no attenuation related to the breast tissue, diaphragmatic elevation, or obesity.

Dobutamine stress cardiac magnetic resonance

Dobutamine stress CMR is based on the detection of stress-induced wall motion abnormalities without a direct assessment of myocardial perfusion. Dobutamine is the preferential pharmacological stressor for CMR studies. Similar to echocardiography, CMR visualizes regional wall motion and systolic wall thickening, but it is characterized by superior endocardial border definition. The regional function is qualitatively assessed as normal, hypokinetic, akinetic, or dyskinetic. Several methods for quantification of wall thickening and myocardial deformation have been investigated. Small clinical studies suggest that the quantification of myocardial strain by tagging analysis may reduce the observer variability and increase the sensitivity of stress CMR. The diagnostic performance of dobutamine stress CMR is comparable with stress echocardiography in patients with a good acoustic window, and it is clearly superior in patients with a poor acoustic window. Thus, CMR is an excellent option when stress echocardiography is inconclusive or not feasible.

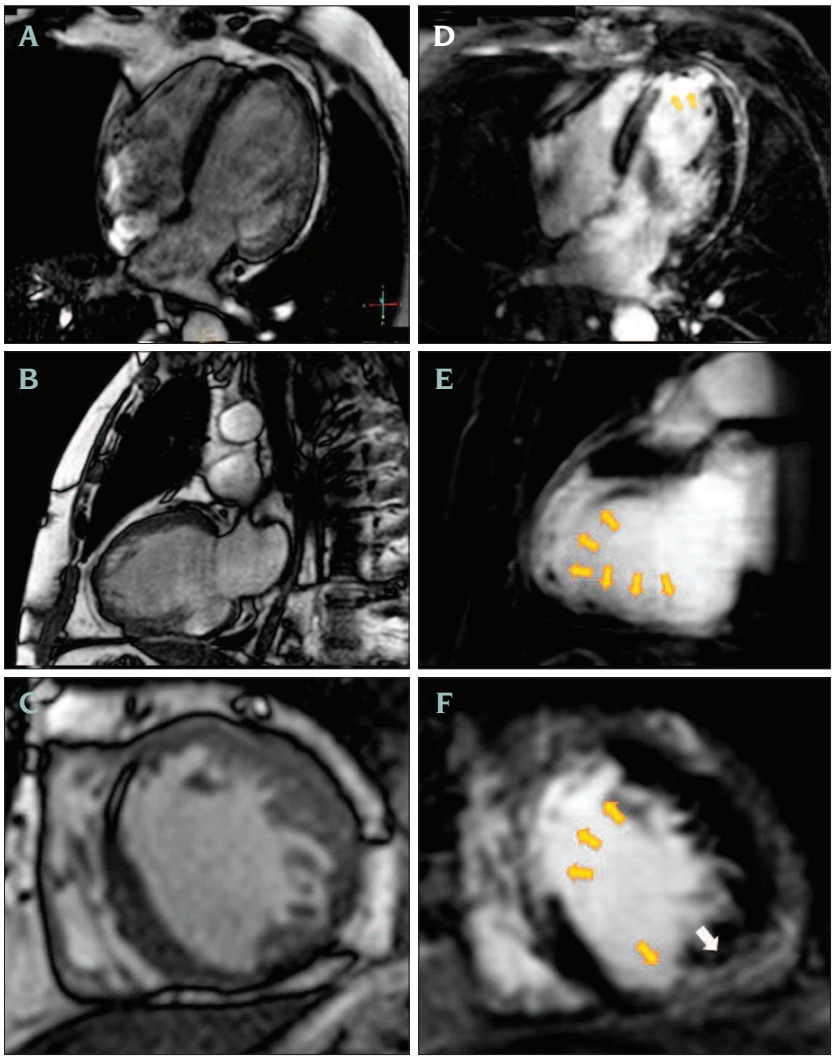

Figure 6. Assessment of myocardial scarring in a responder with ischemic cardiomyopathy (3-vessel CAD) prior to cardiac resynchronization therapy.

Panels A-C. *SSFP cine-CMR demonstrating severe LV systolic dysfunction, with akinesia and severe thinning at the apex, mid-apical anterior and septal walls, and mid-basal segments of the inferior wall.* ***Panels D-F.*** *Delayed contrast enhancement CMR demonstrating transmural myocardial scarring in the same areas as in panels A-C (yellow arrows) and nontransmural hyperenhancement in the basal posterior wall (white arrow). The absence of transmural scar tissue in the mid posterolateral wall, where the LV lead is usually positioned, suggests that effective pacing is possible.*

Abbreviations: *CAD, coronary artery disease; CMR, cardiac magnetic resonance; LV, left ventricular; SSFP, steady-state free precession.*

From reference 9: *Cortez Dias N, Almeida A, Pinto F. Multimodality imaging: When echo is not enough. In Gillam LD, Otto CM, eds.* Advanced Approaches in Echocardiography. *1st ed. Philadelphia, PA: Saunders, an imprint of Elsevier Inc; 2011:199-246. Courtesy of Ana G. Almeida.*

Stress perfusion cardiac magnetic resonance

Myocardial perfusion is analyzed at rest and during infusion of adenosine by measuring the changes in the first-pass signal in the myocardium after a fast intravenous injection of paramagnetic contrast. The myocardial concentration of the contrast agent at rest and during stress directly reflects blood flow. Thus, as for PET, regional myocardial perfusion and perfusion reserve can be measured. Myocardial areas supplied by coronary vessels with high-grade stenosis receive less contrast than adjacent normally perfused regions, and it will appear relatively hypointense.

The excellent spatial resolution of CMR detects perfusion defects limited to the subendocardium, which is impossible for all other imaging modalities, and it evaluates the ischemia transmurality. In routine clinical practice, myocardial perfusion is either qualitatively scored or semiquantitatively analyzed (using the upslope method). Recent advances made it possible to quantify myocardial perfusion using a deconvolution methodology, which promises to improve the diagnostic accuracy and identify collateral perfusion–dependent myocardium. Further advances in perfusion analysis software should make the process less time-consuming and more clinically applicable.

In stress perfusion CMR, regional wall motion and thickening at rest and during stress are also compared, which provides critical information regarding the functional significance of perfusion defects. Late gadolinium enhancement images are also acquired, yielding additional information about infarction/scar and the differentiation of peri-infarct ischemia *(Figure 6).*[10]

First-pass perfusion cardiac computed tomography

Myocardial perfusion assessment with MSCT may be done dynamically or as a first-pass perfusion.[39] Three-dimensional MSCT data sets may be analyzed with precise volumetric quantification of myocardial perfusion. Cardiac CT may provide a comprehensive assessment with anatomical evaluation of the coronary tree using CT coronary angiography, assessment of myocardial perfusion with first-pass perfusion cardiac CT, and detection of delayed hyperenhancement (to evaluate infarction and necrosis). The total radiation dose required to acquire the complete data set is comparable with the exposure in a standard SPECT study. Despite recent advances, the prognostic value and diagnostic accuracy of cardiac CT for assessing myocardial perfusion remain unclear.

Hybrid imaging: SPECT-CT and PET-CT

Hybrid nuclear CT scanners and software fusion of data sets obtained from stand-alone scanners allow image fusion of CT coronary angiography and nuclear imaging.[40-43] The major advantage of hybrid imaging is the integration of information regarding coronary calcium and coronary anatomy obtained by CT, with functional information on cardiac perfusion and/or metabolism obtained with SPECT or PET *(Figure 7).*[40] The potential of such a comprehensive and noninvasive evaluation seems high, especially since the visualization of coronary stenosis complemented by the simultaneous assessment of its hemodynamic significance can theoretically improve specificity without compromising sen-

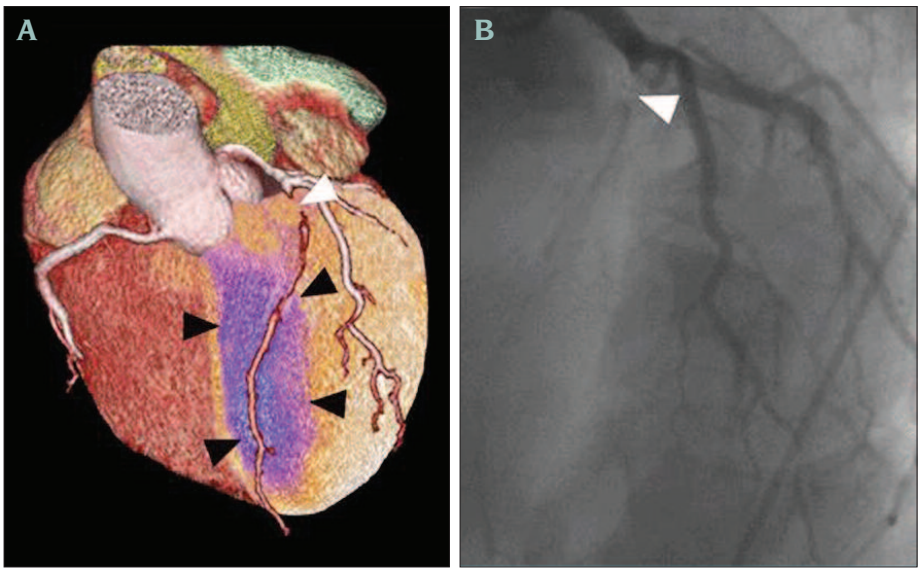

Figure 7. Image fusion of a low-dose gated adenosine stress SPECT-MPI with 13 MBq ^{99m}Tc-tetrofosmin and CTCA using prospective ECG-triggering.

Panel A. *Fused SPECT-CT demonstrated a perfusion defect at stress in the anterior myocardium (black arrows) that corresponds to the total occlusion (white arrow) in the proximal LAD.* ***Panel B.*** *Occlusion of the LAD was confirmed by invasive coronary angiography.*
Abbreviations: *CT, computed tomography; CTCA, computed tomography coronary angiography; LAD, left anterior descending coronary artery; MPI, myocardial perfusion imaging; SPECT, single-photon emission computed tomography.*
From reference 40: *Herzog et al.* Eur Heart J. *2009;30:644. © 2009, Oxford University Press.*

sitivity. With multimodality imaging, maximum diagnostic and prognostic information can be potentially obtained, including information on subclinical coronary atherosclerosis, which would not be detected with nuclear imaging alone. These new multimodality imaging systems carry enormous potential for rapid and efficient diagnosis, but their clinical impact and cost-effectiveness still needs to be evaluated in large clinical trials.

ASSESSMENT OF MYOCARDIAL VIABILITY

Systolic left ventricular dysfunction due to CAD is the complex result of necrosis and scarring, but also of functional and morphological adaptive abnormalities of the viable myocardium.[44-53] Although the viable myocardium encompasses normally contracting and hypocontractile tissue; the term usually refers to the downregulation of contractile function in the surviving myocardium as a response to a periodic or sustained reduction in coronary blood flow. The main goal of assessing myocardial viability is to detect dysfunctional myocardium that can potentially improve contractile function if a normal blood supply is restored with coronary revascularization (either surgical or percutaneous). In patients with extensive areas of viable myocardium, revascularization may improve symptoms, ventricular function, and survival (5-fold lower annual mortality rate when compared with medical treatment alone). For patients with a nonviable myocardium, revascularization seems to have no survival benefit over medical therapy.

Several noninvasive imaging modalities evaluate myocardial viability, including dobutamine stress echocardiogram (DSE), myocardial contrast echocardiography, SPECT, PET, CMR, and hybrid imaging modalities. These imaging modalities have various advantages and limitations when assessing distinct characteristics of the viable, but dysfunctional, myocardium. Large-scale prospective head-to-head comparisons are needed to determine their accuracy in detecting viable myocardium and predicting a patient's response to therapy. Since the use of a single viability test may not be optimal, the value of sequential multimodality imaging should be considered. The assessment of myocardial viability should start with a resting echocardiographic study, evaluating the acoustic window, endocardial borders, and wall thickening in all segments, the severity of wall motion abnormalities, and left ventricular ejection fraction. Resting echocardiograms provide valuable information to help choose the most appropriate viability test for an individual patient.

Patients with adequate acoustic windows and without severe left ventricular dysfunction at rest are particularly suitable for DSE. Patients with severe left ventricular dysfunction are a subgroup in which DSE is less accurate; therefore, SPECT, PET, CMR, and delayed contrast enhancement CMR (DE-CMR) are better in this patient group. SPECT, PET, CMR, and DE-CMR also provide a better assessment of patients with poor acoustic windows *(Figure 7).* The choice of diagnostic imaging modality relies heavily on the expertise of the medical center. Recent advances in fusion imaging in which the PET perfusion and ^{18}F-fluorodeoxyglucose (FDG) uptake patterns are superimposed on CMR images shows the extent of myocardial scar simultaneously with the extent of both hibernating and nonhibernating viable myocardium. The clinical value of multimodality imaging needs to be determined in future clinical research studies.

Single-photon emission computed tomography

Among the radionuclide imaging techniques available to assess myocardial viability, the most commonly used is SPECT with either thallium-201 or ^{99m}Tc-labeled sestamibi *(Figure 4).* Thallium is a perfusion agent and a tracer of myocardial viability because its redistribution is mainly due to active uptake by intact cardiomyocytes. Technetium tracers do not redistribute, and they cannot provide an independent distinction between perfusion and viability. The main advantage of using technetium tracers is their ability to perform ECG gating to assess ventricular function. Several SPECT protocols to evaluate myocardial viability are used under stress and/or rest, including imaging from 8 to 72 hours after stress injection, reinjection of the tracer at rest on the same day as the stress injection, or a resting injection on a separate day. Sublingual nitrates improve resting perfusion and thus the detection of viability when ^{99m}Tc-labelled tracers are used. SPECT is more sensitive, but less specific than DSE for predicting functional improvement after revascularization. It is speculated that the small amounts of viable tissue additionally recognized by SPECT may be unable to contribute to the recovery of left ventricular function. The threshold of maximal myocardial uptake currently used to identify viability is ≥50%, although the best threshold would probably be higher.

Positron emission tomography

PET evaluates myocardial viability by qualitative and quantitative assessment of myocardial function, per-

fusion, and metabolism. The viable tissue is metabolically active, whereas dysfunctional myocardial cells obtain energy by using glucose instead of fatty acid metabolism *(Figure 5).* The detection of myocardial hibernation with PET is based on the combination of one tracer that assesses perfusion (usually ^{13}N-ammonia or ^{82}Ru) with the glucose analog FDG, which evaluates metabolism. Normal tissue has a normal function, perfusion, and metabolism; stunned myocardium has a diminished function, but a normal or an almost normal perfusion and variable glucose metabolism; hibernating myocardium has diminished function and perfusion, but a preserved or increased glucose metabolism (metabolism-perfusion mismatch); and scar tissue has reduced function, perfusion, and metabolism (metabolism-perfusion match).

Several nonrandomized retrospective studies showed that FDG-PET predicts the recovery of regional function after revascularization with high sensitivity (71% to 100%), but a relatively low specificity (33% to 91%). The major disadvantages of PET for assessing myocardial viability are its limited availability, high cost, and significant exposure to radiation without any relevant additional benefit (when compared with radiation-free alternatives).

Cardiac magnetic resonance

The two most important CMR techniques to assess myocardial viability are DE-CMR and dobutamine CMR. Both are excellent options when stress echocardiography is inconclusive or not feasible, particularly in patients with poor acoustic windows. DE-CMR is the technique most commonly used, and it will probably become the routine procedure for CMR assessment of myocardial viability.

Delayed contrast enhancement cardiac magnetic resonance

DE-CMR is a newly established technique to detect acute or chronic infarct areas, which appear as bright regions in inversion recovery images that are acquired 5 to 20 min after the intravenous injection of paramagnetic contrast. Assessment of viability is based on anatomical myocardial tissue characterization, and it does not require pharmacological tests. Viable myocardium (normal, stunned, or hibernating) has a normal distribution volume of the contrast medium and does not have hyperenhancement. Acutely infarcted myocardium shows hyperenhanced areas due to the passive diffusion of contrast into the intracellular space of necrotic cells. Chronic infarcts (fibrotic tissue) appear as hyperenhanced areas due to the increased interstitial space between collagen fibers and delayed washout due to reduced capillary density.

Due to its superior spatial resolution, DE-CMR is effective in identifying the presence, location, and transmural extent of the nonviable myocardium. It can detect small regions of subendocardial infarct with higher sensitivity than all other imaging modalities. The extent of contrast enhancement on a segmental basis is useful to predict contractile recovery after revascularization. Wall motion improvement can be expected in dysfunctional segments if the hyperenhancing portion does not exceed 50% of the wall thickness. An improvement in left ventricular ejection fraction after revascularization correlates with the amount of poorly functioning, but not hyperenhanced myocardium. Unlike stress tests (either DSE or dobutamine CMR), which have a lower accuracy if severe rest dysfunction is present, DE-CMR seems to perform better in these patients.

Historical studies suggest that DE-CMR has a higher sensitivity (≈90%), but a lower specificity (≈50%) than DSE, which is mainly due to the variable functional recovery in myocardial segments with a 25% to 75% hyperenhancement. In patients who have multiple segments with intermediate transmurality (25% to 75%), complementary use of DE-CMR and dobutamine CMR may be the optimal CMR strategy for predicting functional recovery after revascularization, but no comparative studies have been performed yet.

Dobutamine stress cardiac magnetic resonance

Dobutamine CMR assesses contractile reserve during low-dose dobutamine stress testing. The improvement in contractile function with low-dose dobutamine is indicative of myocardial viability. Similar to echocardiography, CMR visualizes regional wall motion and systolic wall thickening, but it is characterized by superior endocardial border definition. The diagnostic performance of dobutamine CMR to predict regional recovery after revascularization is comparable with DSE in patients with good acoustic windows, but it is superior in all other patients.

Cardiac computed tomography

Similar to DE-CMR, the assessment of myocardial viability using cardiac CT is based on the detection of myocardial retention of contrast within areas of nonviable tissue. On delayed enhanced cardiac CT, myocardial infarction shows increased attenuation values

due to a combination of delayed wash-in and washout kinetics and an increased distribution volume within the expanded interstitial compartment. Although preliminary studies proved the reliability of delayed enhanced cardiac CT to detect and characterize scars, it currently cannot be recommended as a tool for routine assessment of myocardial viability. The most important limitations of delayed enhanced cardiac CT that preclude its clinical application include the radiation exposure and the absence of trials proving its usefulness for predicting the recovery of contractile function after revascularization.

Hybrid fusion imaging: SPECT-CMR and PET-CMR

Fusion imaging merges two disparate image datasets into one functional image, enhancing the ability of determining functional consequences of anatomical pathology. Recent software advances have provided the capability to merge CMR and nuclear imaging (SPECT-PET) datasets. This multimodality assessment promises to improve the detection and characterization of both viable and nonviable myocardium.

The anatomical characterization of nonviable tissue by DE-CMR and the functional evaluation of viable myocardium by nuclear imaging modalities are obviously complementary. Regions of chronic myocardial infarction typically exhibit wall thinning. However, chronically hypoperfused myocardium may also be thinned and yet contain substantial amounts of viable myocardium.

- SPECT or PET are often unable to detect viable myocardium within thinned segments due to partial volume effect and because the amount of FDG seen may not appear high enough to display the mismatch pattern.
- Complimentary assessment with DE-CMR makes the absence of substantial scarring within that segment evident and thus suggests that the myocardium is viable.
- DE-CMR cannot distinguish hibernating myocardium from normally perfused myocardium in regions of nontransmural hyperenhancement (the area contiguous with subendocardial hyperenhancement merely shows an absence of scarring).
- Complimentary assessment of perfusion can be beneficial since contractile recovery will likely occur if the region is perfused by an artery with severe stenosis so that a portion of dyssynergy could be attributed to resting hypoperfusion.

The clinical impact of this new imaging technique on treatment strategy and patient outcomes still needs to be determined.

CONCLUSION

Cardiovascular imaging has improved over the last few years, mostly due to the important technological developments that expanded the potential clinical applications. For CAD, the use of imaging has expanded significantly, and it is now considered an important tool for the prevention and diagnosis of CAD and the monitoring of the various therapeutic strategies. Its inclusion in the current international guidelines is proof that the appropriate use of cardiovascular imaging is currently necessary for the management of patients with suspected or known CAD. Future developments are around the corner, including molecular imaging, fusion imaging, etc. These developments will make it possible to be even more precise in the understanding of the pathophysiology of CAD, establishing an earlier diagnosis (detection of subclinical disease), and monitoring the individual patient.[40,41,54]

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