# Coronary Artery Disease Imaging

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Editorial

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CORONARY ARTERY DISEASE IMAGING

Things have changed so much since I obtained my medical degree—fortunately mostly for the better—that I sometimes feel as if I should return to university to resit the same degree. I am sure that this is the case for all fields of medicine and not just for cardiology. In only a few years, the technological innovations and the close, fruitful relationship between industry and academia have created a revolution in cardiology. Cardiologists no longer require only a stethoscope to listen to the heart. Today, we can see the heart and its coronary arteries, and we can witness the heart’s movements and functions with a precision that was unthinkable a few years ago.

The first ECG waves were recorded by Willem Einthoven in 1903, thus developing the first electrocardiogram. This development led to “cardiology” becoming a medical specialty, and those doctors who knew how to use an electrocardiogram were called “cardiovascular specialists.” In 1953, a physician named Inge Gudmar Edler and an engineer named Carl Hellmuth Hertz borrowed a shipyard sonar machine to conduct the first human echocardiogram, which led to echocardiography becoming a widely accepted method for cardiovascular research in the 1960s. And today, after many advancements, we have three-dimensional imaging possibilities.

But we can do so much more. We can enter a small submarine and navigate inside the coronary arteries, discovering all of the abnormalities along the route. Nowadays, thanks to intracoronary imaging, it is also possible to discover the composition of the coronary plaque, assess the kind of stent that would be more suitable for the particular lesion identified, and determine whether the stent is inserted correctly. Francesco Prati, Laura Gatto, and Vito Ramazzotti describe the specific advantages and limitations of the most important imaging techniques used today—optical coherence tomography, intravascular ultrasound, and near-infrared spectroscopy.

If you do not fancy entering a submarine and prefer a more real picture, then you have two additional imaging tools—computer magnetic resonance and coronary computed tomography angiography. Amardeep G. Dastidar and Chiara Bucciarelli-Ducci demon-
strate that, due to its high spatial resolution, computer magnetic resonance plays an amazing role in the diagnosis of patients, and it plays an even more important role in risk stratification. Computer magnetic resonance allows us to determine, with a high degree of precision, the extent of the scar and ischemic tissue. When computer magnetic resonance is combined with late gadolinium enhancement to scrutinize myocyte viability and first-pass perfusion with a vasodilator, you obtain all of the information you need to make a suitable diagnosis and determine the appropriate treatment choice.

**Udo Sechtem** reviews all of the improvements that have made coronary computed tomography angiography safer by reducing the radiation exposure and, at the same time, more accurate by improving the spatial resolution to provide extremely clear pictures of the coronary arteries. These achievements are contributing to the ever-increasing role of coronary computed tomography angiography in preventive medicine, stable coronary artery disease, and coronary artery bypass vasodilation.

As always, you need an overview of the pros and cons, especially when dealing with technology; these are detailed for coronary artery disease imaging in the excellent lead article by **Fausto Pinto, Inês Z. Cabrita,** and **Nuno Cortez Dias.** From a clinical perspective, the authors delineate the roles played by ultrasound, echocardiography, single-photon emission computed tomography, positron emission tomography, and molecular imaging.

The enormous availability of imaging techniques available for cardiologists is such that we now need a new profession – an “imaging doctor.” An imaging doctor would be someone who can decide which is the best imaging tool to answer a given question. This diagnosis will reduce the number of unnecessary examinations, and this will consequently save money. Fausto Pinto and others also address the question concerning whether or not the economic impact of these emerging technologies is sustainable. Cardiology will soon be confronted with the issue of the cost-benefit ratio of each technique. There is no doubt that imaging will take a central role in the correct diagnosis and treatment of patients, but only if used in a manner that is timely, appropriate, and tailored for each patient. These advancements in technology will save lives, and life does not have a price.
Coronary artery disease imaging

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Cardiovascular disease represents the leading cause of death worldwide. Different imaging methods are available to aid 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.

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. 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. 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 and Tornvall et al.

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. An increase in CAC scores over time (CAC progression) improves the prediction of coronary heart disease events. In a 2012 study, Okwuosa et al 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).

In an extensive document, Waugh et al 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 asymptomatic people; (ii) the clinical role of CAC in determining the need for further testing or intervention; and (iii) the cost-effectiveness of CAC screening in asymptomatic people.

![Image](https://example.com/image.png)

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

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). 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
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 normal 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, 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.

ASSESSMENT OF MYOCARDIAL PERFUSION AND ISCHEMIA

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. 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.
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, 99mTc-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 99mTc-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. 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).

The most commonly used tracers for assessing myocardial perfusion with PET are 13N-ammonia, rubidium-82 (82Rb), and 15O-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

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**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-deoxyglucose.

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. 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.
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).

First-pass perfusion cardiac computed tomography

Myocardial perfusion assessment with MSCT may be done dynamically or as a first-pass perfusion. 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. 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). 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-
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. Although the viable myocardium encompasses normally contracting and hypococontractile 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 18F-fluorodeoxyglucose (FDG) uptake patterns are superimposed on CMR images show the extent of myocardial scar simultaneously with the extent of both hibernating and non-hibernating 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 99mTc-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 99mTc-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-
fusio,n 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 ($\approx 90$%), but a lower specificity ($\approx 50$%) 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 anatomic 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.

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Echocardiographic and fluoroscopic fusion imaging for procedural guidance: an overview and early clinical experience.

Coronary Artery Disease Imaging

Expert Answers to Three Key Questions

1

Coronary artery disease imaging: what is the role of magnetic resonance imaging?

_A. G. Dastidar, C. Bucciarelli-Ducci_

2

Coronary artery disease imaging: what is the role of coronary computed tomography angiography?

_U. Sechtem_

3

What is the role of intracoronary imaging?

_F. Prati, L. Gatto, V. Ramazzotti_
Coronary artery disease imaging: what is the role of magnetic resonance imaging?

Amardeep G. Dastidar, MBBS, MRCP; Chiara Bucciarelli-Duca, MD, PhD, FESC, FRCP
Bristol Heart Institute - NIHR Bristol Cardiovascular Biomedical Research Unit - Bristol - UK

Ischemic heart disease (IHD) is a global burden, and it remains the leading cause of death worldwide. Accurate assessment of the presence and extent of IHD is a crucial step in the management of this condition. Noninvasive imaging plays a vital role in the diagnosis and risk stratification of patients. Over the last decade, cardiac magnetic resonance (CMR) imaging has emerged as a very promising noninvasive imaging modality in the assessment of IHD due to its multiparametric nature, high spatial resolution, high reproducibility, and superior tissue characterization properties, all of which are reflected in a large body of evidence in the literature. CMR provides comprehensive information in the assessment of IHD, which guides the detection and differential diagnosis, assists in the clinical decision-making process, and improves risk stratification.

Keywords: cardiovascular magnetic resonance; ischemic heart disease

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SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<td>CE-MARC</td>
<td>Clinical Evaluation of MAGnetic resonance imaging in Coronary heart disease</td>
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<tr>
<td>CMR</td>
<td>cardiac magnetic resonance</td>
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<tr>
<td>EDWT</td>
<td>end-diastolic wall thickness</td>
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<tr>
<td>FAME</td>
<td>Fractional flow reserve versus Angiography for Multivessel Evaluation</td>
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<tr>
<td>FFR</td>
<td>fractional flow reserve</td>
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<td>IHD</td>
<td>ischemic heart disease</td>
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<td>LGE</td>
<td>late gadolinium enhancement</td>
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<td>MR-INFORM</td>
<td>MR perfusion Imaging and Fractional flow Reserve to guide Management of patients with stable coronary artery disease [study]</td>
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<tr>
<td>PET</td>
<td>positron emission tomography</td>
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<td>RWMA</td>
<td>regional wall motion abnormality</td>
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<td>SPECT</td>
<td>single-photon emission computed tomography</td>
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VIABILITY ASSESSMENT

Rationale

In the context of ischemic cardiomyopathy, dysfunctional myocardium can recover systolic function following surgical revascularization. The patients with the most severe left ventricular (LV) systolic dysfunction carry the highest operative risk; but they potentially benefit the most from coronary artery bypass grafting (CABG) in terms of long-term survival. However, not every patient who has ischemic cardiomyopathy with severe LV dysfunction regains meaningful systolic function following revascularization.

Thus, in the context of coronary artery disease, dysfunctional myocardium can be the expression of either nonviable (necrotic) myocardium or viable, but “hibernating,” myocardium, which is in a down-regulated functional state due to chronic ischemia, but the myocardium maintains the possibility of regaining function if the coronary blood flow is restored.

Establishing the presence and extent of myocardial viability in the dysfunctional ischemic myocardium is clinically important to guide surgical revascularization. This concept is supported by pooled data from 3088 patients included in a meta-analysis of 24 studies. This meta-analysis demonstrated a significant survival benefit from revascularizing ischemic cardiomyopathy patients with a viable dysfunctional myocardium vs medical management, but no significant difference was observed between the two treatments in patients with a nonviable myocardium. Furthermore, the role of imaging in assessing myocardial viability to guide the management of patients with chronic ischemic systolic LV dysfunction is recognized in the 2014 ESC/EACTS guidelines on myocardial revascularization. In particular, the interaction between hibernating myocardium and early revascularization was compared with medical therapy, which showed improved survival with revascularization, especially when the extent of viability exceeded 10% of the myocardium.

Several CMR parameters can be used to assess myocardial viability, including LGE, end-diastolic wall thickness (EDWT), and regional wall motion abnormality (RWMA) and contractile reserve.

Late gadolinium enhancement

There are multiple imaging modalities available to assess viability, such as dobutamine stress echocardiography, single-photon emission computed tomography (SPECT), and positron emission tomography (PET). However, the ESC/EACTS guidelines on myocardial revascularization recognize the high diagnostic accuracy for assessing the transmurality of myocardial scar by CMR combined with its ability to assess contractile reserve. CMR provides the highest spatial resolution compared with other established techniques, which enables CMR to detect as little as an estimated 1 g of infarcted myocardium compared with the approximate 10-g lower limit of SPECT. In addition, the reproducibility of the CMR assessment of a chronic infarct is excellent. However, the guidelines also concede that the overall differences in performance between modalities are small, and that local experience and availability are likely the major determinants of which technique should be used.

LGE imaging forms an integral part of the viability assessment by CMR. The principles underpinning CMR viability imaging are different from those with stress echocardiography or nuclear imaging. Briefly, viability imaging by CMR is based on the intravenous administration of a gadolinium-based contrast agent that is metabolically administered, but promptly diffuses from the intravascular pool into the extracellular tissue compartment to reduce the myocardial T1 relaxation times (and to a lesser degree, the T2 relaxation times). Therefore, the contrast agent accumulates in areas of increased extracellular space, which is normally caused by a pathological (ischemic or nonischemic) process. This results in an increased signal return from the tissue containing contrast accumulation. In fact, in normal myocardium, the contrast promptly washes out of the tissue, whereas in nonischemic and ischemic heart disease (indeed in both acute and chronic myocardial infarction), the contrast will accumulate with a much longer contrast washout.

The optimal time for infarct imaging is between 10 to 20 minutes after administering the contrast agent. The accumulation process is likely due to an expanded volume of distribution in both acute and chronic infarction, but via different mechanisms. In acute myocardial infarction, the accumulation results from increased intracellular uptake due to disrupted cell membranes in acute infarction; whereas, in chronic myocardial infarction, it is due to increased extracellular trapping within the increased extracellular space between the collagen fibers of the chronically scarred myocardium. An inversion-recovery sequence is invariably used to exaggerate the difference in signal return from normal and infarcted tissue following the administration of a contrast agent. This inversion signal effectively nulls any T1 signal from normal myocardium, which appears black (hypointense) on the subsequent image, whereas the infarcted tissue
still containing contrast will appear approximately 10-fold brighter (hyperintense) compared with standard T1-weighted sequences. 10

The first step in the LGE assessment is simply to determine the presence or absence of any LGE, which has prognostic implications. Kwong et al.11 demonstrated that the presence of any degree of LGE in chronic myocardial infarction patients led to a 6-fold increase in the risk of major adverse cardiac events. The number of segments demonstrating LGE is also important. In a multicenter, internal study of 1560 patients, a multivariate analysis demonstrated that the number of segments with LGE was an independent predictor of mortality over a 2.4-year follow-up period.12 The presence of LGE may be a better prognostic marker in patients with chronic coronary artery disease than the traditional measurement of ejection fraction.12,13 In a recent study, myocardial scar by LGE was associated with markedly poorer outcomes in patients with diabetes mellitus, while the presence of inducible myocardial ischemia was found to be predictive both in patients with and without diabetes mellitus. Both markers surpassed the predictive value of conventional atherogenic risk factors both in patients with and without diabetes mellitus.14

Owing to its spatial resolution, CMR can move beyond the binary assessment of whether LGE is present or absent and quantify the percentage of the LV wall that is affected by LGE.7 Several methods exist to quantify transmurality, including semiautomated objective techniques.15 However, subjective visual assessment is the most commonly employed technique in clinical settings.16

The importance of LGE transmurality in assessing viability in chronic coronary artery disease was highlighted in the landmark paper by Kim et al.17 which demonstrated that the lack of LGE prior to treatment in patients with ischemic LV dysfunction undergoing revascularization by either CABG or angioplasty corresponded to a 78% chance of segmental functional recovery on CMR at 3 months postintervention. In comparison, when 51% to 75% of the myocardium demonstrated LGE before the intervention, only 10% of the segments functionally recovered, falling to 2% with a transmural LGE >75% (Figure 1). However, when 1% to 50% of LGE was present, the likelihood of functional recovery was indeterminate (=50%). Further quantification is required to guide the decision regarding viability in such intermediate myocardial segments. Selvana-yagam et al.18 produced similar results in patients undergoing surgical revascularization with a longer CMR follow-up interval of 6 months. Moreover, in patients with ischemic LV dysfunction who are treated medically, the presence of dysfunction, but viable, myocardium delineated by CMR was an independent predictor of mortality, suggesting that such patients would benefit instead from revascularization.19

Figure 1. Late gadolinium enhancement transmurality in assessing viability in chronic coronary artery disease.
Panel A. Subendocardial enhancement (white arrow) due to myocardial infarction in the left circumflex artery territory with preserved myocardial viability. Panel B. Transmural enhancement (white arrow) due to myocardial infarction in the left anterior descending territory with nonviable myocardium and thrombus (black arrow).
The STICH trial (Surgical Treatment for Ischemic Heart failure) recently questioned the role of viability, showing that the assessment of myocardial viability in patients with coronary artery disease and LV dysfunction did not identify patients with a differential survival benefit from CABG vs medical therapy alone. However, there were many pitfalls around the viability imaging in the study (eg, viability imaging was not randomized, but offered at the physician’s discretion, multiple viability modalities and no CMR; change in the definition of viability). Further studies are underway to clarify the role of viability imaging in patients with LV dysfunction.

**End-diastolic wall thickness**

The degree of myocardial thinning is related to previous infarct transmurality. An EDWT <6 mm has a low probability of functional recovery after revascularization. However, the clinical utility of this parameter is limited by the fact that a thinned myocardium can also represent extreme hibernation, with the potential for an increase in wall thickening and functional recovery after revascularization.

**RWMA and contractile reserve**

RWMA may be systematically identified only when the degree of transmural infarct is >50%. In isolation, these parameters will underestimate infarct size and they will not help distinguish the patients with no infarct from those with a transmural infarct between 1% and 50%. The poor performance of RWMA in assessing infarct size may be the result of through-plane myocardial motion during systole, falsely creating the impression of myocardial shortening on the short axis cines. Furthermore, normally contracting myocardium adjacent to an infarct can “pull” the infarcted tissue during systole, simulating contractile function. However, RWMA assessment has a role in determining the viability in patients with intermediate LGE of 1% to 50% transmurality when combined with a stressor agent. Kaandorp et al demonstrated contractile reserve, as confirmed by the return of regional contractility in response to low-dose dobutamine stress, in 61% of segments with indeterminate LGE in 48 ischemic cardiomyopathy patients, which implied viability in these segments. Objective quantification of myocardial strain in response to low-dose dobutamine can be achieved with myocardial tagging, which requires tag lines to be imposed on the cine images at the time of image acquisition, or by using a novel postprocessing feature tracking software that can be applied to standard cine images. Romero et al demonstrated the importance of integrating CMR parameters for viability assessment in the meta-analysis of 24 studies that included 698 patients. This analysis showed that LGE provided the highest sensitivity (95%) and negative predictive value (90%), whereas low-dose dobutamine offered the best specificity (91%) and positive predictive value (93%).

**ISCHEMIA ASSESSMENT**

**Rationale**

According to the FAME study (Fractional flow reserve versus Angiography for Multivessel Evaluation), revascularization of patients with symptomatic, but stable, coronary artery disease should be guided by the presence of significant myocardial ischemia as quantified by fractional flow reserve (FFR) at angiography to achieve prognostic benefit in terms of reduced mortality, rates of nonfatal infarction, and repeat revascularization. Furthermore, a meta-analysis of 11 636 patients with suspected coronary artery disease with a mean follow-up of 32 months demonstrated that confirming the absence of ischemia confers prognostic benefit with very low annual event rates for cardiovascular death (0.3%) and myocardial infarction (0.4%). When considering CMR in IHD, the importance of assessing ischemia in addition to viability is unclear at the present, and a prospective outcome study to address this question is still awaited. The ongoing MR-INFORM study (MR perfusion Imaging and Fractional fOW Reserve to guide Management of patients with stable coronary artery disease) is assessing whether a CMR stress perfusion strategy is noninferior to FFR in stable coronary artery disease. The ongoing ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) will demonstrate whether patients with moderate to severe ischemia on stress imaging (SPECT, CMR, stress echo) will benefit from coronary angiography and revascularization. Ischemia assessment by CMR can be performed by either stress perfusion imaging or stress functional imaging, although perfusion may also be included with the latter.

**Stress first-pass myocardial perfusion for inducible perfusion defects**

First-pass myocardial perfusion CMR was first described by Atkinson et al using inversion-recovery gradient-echo imaging after injecting a bolus of a T1-shortening contrast agent to observe contrast agent transit through the cardiac chambers and myocardium. Subsequently, the technique has undergone several developments, including improved spatial resolution, speed of acquisition, myocardial coverage, and improved signal-to-noise ratio, thereby increasing the overall accu-
Myocardial perfusion imaging is usually carried out at peak stress with intravenous vasodilator stress (most commonly with adenosine) and at rest. At peak stress, the images can demonstrate areas of hypoperfusion, which is a surrogate for myocardial ischemia. Due to its high spatial resolution (up to 2 to 3 mm), CMR myocardial perfusion imaging is superior to other imaging modalities in reliably identifying subendocardial ischemia. Recent developments have reduced the spatial resolution to ≈1 mm. Moreover, higher performing scanners with high magnetic fields (3T) can improve the signal-to-noise ratio, thus improving the diagnostic yield of the technique by identifying even smaller perfusion defects and increasing the ability to rule out artifacts.

In perfusion CMR, the stressor is often a vasodilator agent, most commonly adenosine, which results in coronary artery dilatation. Coronary arteries with significant stenosis will dilate less than unobstructed vessels, effectively resulting in a “steal” phenomenon with relative hypoperfusion of the myocardium subtended by the stenosed coronary artery (Figure 2). Consequently, vasodilator stress CMR is an inappropriate modality to assess ischemic burden associated with myocardial bridging of coronary arteries or a malignant coronary course where the coronary obstruction is dynamic and worsens with increased cardiac workload. Therefore, chronotropic and inotropic stressors are recommended instead (exercise or dobutamine). Ischemia is demonstrated as a myocardial perfusion defect on first-pass imaging with an intravenous gadolinium-chelate contrast agent. First-pass imaging is usually performed at both peak stress and at rest (20 min after stress). Inducible perfusion defects appear as a hypo-intense area (dark area, ie, no perfusion or delayed-contrast perfusion due to coronary stenosis), but unfortunately, artifacts could mimic inducible perfusion defects and tend to appear in conjunction with contrast arrival in the LV cavity.

Therefore, the acquisition of both sets of images (at stress and at rest) is useful to distinguish a true perfusion defect from artifact. Hypointensity that is only present in the stress images is suggestive of an inducible perfusion defect, whereas hypoperfusion present in both stress and rest images is suggestive of an artifact.

Dipyridamole and regadenoson are alternative vasodilator stress agents. Dipyridamole inhibits the cellular uptake and metabolism of adenosine, which causes an increase in the interstitial adenosine concentration. Regadenoson is an adenosine receptor agonist. These agents give rise to a super physiologic increase in vascular flow as opposed to the approximate 2-fold increase in vascular flow seen with dobutamine or exercise. In contrast to adenosine or dipyridamole stress protocols involving continuous infusion for 3 to 5 minutes, the regadenoson stress protocol uses a single-bolus injection to obviate the need for a second intravenous line. The contraindications for adenosine or adenosine agonists include high-degree atrioventricular block, obstructive airway disease, and concomitant administration of dipyridamole or carbamazepine. These contraindications are infrequent, but of important general knowledge for any clinician referring patients for stress CMR. Caffeinated food and drink should be avoided before the test as it reduces the efficacy of the stressor.

In clinical practice, the perfusion images are reported qualitatively, and they are based on the assessment of the presence and extent of myocardial hypoperfusion (transmurality and number of segments) and the correspondence with the coronary artery territories. Quantitative assessment of myocardial perfusion is predominantly confined to the research domain. Semi-quantitative assessment of first-pass...
perfusion by measuring changes in myocardial signal intensity over time provides information on relative perfusion; in addition, there is also research on the quantification of absolute myocardial blood flow with CMR. 38

There are several challenges for stress perfusion imaging. A commonly encountered imaging artifact is the dark-rim artifact, which appears at the interface of the blood pool and the subendocardium, which may mimic a perfusion defect. The physics behind its etiology is incompletely understood, but it can be distinguished from pathology because it appears as soon as the contrast arrives in the LV cavity, it rapidly fades away (but may recur during the second pass of contrast), and it is usually darker than a true perfusion defect. This artifact may compound the challenges presented by assessing severe triple-vessel coronary artery disease by stress perfusion CMR. The lack of a region of normal perfusion to act as a reference standard makes assessment difficult in this condition.

However, in these cases, endo-epicardial perfusion gradients may serve as a marker of ischemia. 39

Equally, the assessment of microvascular obstruction (ie, cardiac syndrome X) can be challenging in the context of a dark-rim artifact, particularly because subendocardial perfusion defects crossing anticipated coronary artery territory boundaries are recognized imaging features on stress perfusion CMR in these patients. 40

Vasodilator stress CMR correlates well with FFR, which is the current in-vivo gold standard assessment of hemodynamically significant coronary stenosis. 41 Other modalities exist to assess ischemia, but in a recent meta-analysis of 166 articles assessing SPECT, PET, and CMR for the detection of angiographic coronary artery disease, 42 the CMR diagnostic accuracy was similar to PET (pooled sensitivity, 89%, 95% confidence interval [CI], 88% to 91% and pooled specificity, 76%, 95% CI, 73% to 78%), and CMR achieved the highest diagnostic performance, but without exposure to ionizing radiation. Stress CMR also performs favorably in cost-effective analyses assessing diagnostic pathways for the work-up of suspected coronary artery disease.

MR-IMPACT (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial), the first multicenter, multi-vendor, randomized trial, suggested perfusion CMR as a valuable alternative to SPECT. 44 The subsequent MR-IMPACT II trial showed that perfusion CMR was superior to SPECT, while its specificity was inferior to SPECT. 45 The large, prospective CE-MARC study (Clinical Evaluation of MAGnetic resonance imaging in Coronary heart disease) established CMR’s high diagnostic accuracy in IHD and its superiority over SPECT. 46 In both sexes, CMR has a greater sensitivity than SPECT with no intersex differences. Stress CMR also performs favorably in cost-effective analyses assessing diagnostic pathways for the workup of suspected coronary artery disease. 43 The recently published 5-year follow-up study of CE-MARC indicates that compared with SPECT, CMR is a stronger predictor of risk for major adverse cardiovascular events (MACEs), which is independent of cardiovascular risk factors, angiography result, or initial patient treatment. 48 This further supports the role of CMR as a slightly superior alternative to SPECT for the diagnosis and management of patients with suspected coronary heart disease.

In a small group of patients showing CMR evidence of a significant myocardial-inducible perfusion defect and viability, chronic total occlusion recanalization was shown to reduce ischemic burden, which favors reverse remodeling and ameliorates quality of life. 49

**Stress functional imaging for inducible RWMA**

Ischemia assessment via functional stress imaging is performed by comparing the ventricular function at rest with peak stress. Regional ventricular function can be assessed visually 50 or by measuring wall motion, thickening, and strain. 51 Although there is some initial experience showing that physical exercise can be performed in the CMR scanner with a compatible supine ergometer, 52 stress CMR functional imaging is commonly achieved with dobutamine.

As a β-agonist, dobutamine stimulates myocardial β-receptors, resulting in increased myocardial contractility, heart rate, and stroke volume. The principle of dobutamine stress CMR is that the agent is administered at increasing doses with interval imaging until the target heart rate (which may require the administration of atropine) is achieved or angina symptoms are experienced. Abnormal blood pressure response and development of severe arrhythmia should prompt cessation of the test. When the coronary vasculature is normal, myocardial contractility will progressively increase with an increasing dobutamine dose. In the presence of a flow-limiting coronary stenosis, the myocardium will become increasingly ischemic with an increasing dobutamine dose, and the resultant systolic dysfunction will be manifest as a new RWMA that is relative to the baseline images at lower doses. The regain of function
Quantifying RWMA by myocardial tagging in this context increases diagnostic accuracy. Furthermore, employing an objective strain analysis technique may enable detection of ischemic myocardium below conventional levels of peak stress, potentially reducing the requirement for higher-dose protocols.

Finally, the role of combining stress perfusion and stress functional imaging for ischemia has been investigated. In a study on 455 patients, this approach showed an increased sensitivity, but a reduced specificity, with no overall change in accuracy. However, this approach might be particularly beneficial in patients with concentric hypertrophy and remodeling because RWMA can be more difficult in this patient subset.

**ASSESSMENT OF CHRONIC COMPLICATIONS FROM MYOCARDIAL INFARCTION**

CMR also has a role in assessing chronic complications following a myocardial infarction. CMR is superior to echocardiography for the identification of ventricular thrombi, which appear as dark-filling defects on early gadolinium enhancement or LGE imaging, typically on the endocardial surface of infarcts (Figure 1). CMR is also able to detect other chronic complications of a myocardial infarction, including ventricular aneurysm, pseudoaneurysms, and mitral regurgitation. Furthermore, the high spatial resolution of CMR can assess the involvement of the right ventricle in a myocardial infarction when compared with echocardiography.

**FUTURE PERSPECTIVE**

Quantitative myocardial perfusion reserve assessment by CMR is a promising new dimension. In an animal model, CMR-derived quantitative blood flow estimates have been correlated with true myocardial blood flow. Perfusion CMR is, in theory, more related to coronary flow reserve (CFR) than FFR, although it has been validated against both CFR and FFR. Recently, exercise stress CMR has been investigated in healthy volunteers, showing that peak exercise wall motion as assessed by cine CMR is feasible, and it can be performed as rapidly as stress echocardiography.

The evidence on assessing IHD with an advanced T1 relaxometry technique seems promising. A recent study has shown that T1 mapping at rest and during adenosine stress can differentiate between normal, infarcted, ischemic, and remote myocardium with distinctive T1 profiles. The results of ischemia detection by noncontrast stress/rest T1 mapping were also encouraging.

**CONCLUSION**

CMR is a well-established, comprehensive, and increasingly used noninvasive imaging modality for the assessment of patients with IHD. CMR can assess cardiac anatomy, function, myocardial perfusion, and tissue characterization, without exposure to ionizing radiation, and it can be done in less than 1 hour. Its use in IHD is supported by robust and rapidly expanding evidence.

The challenge is to delineate how CMR can improve patient management and improve clinical outcomes in a cost-effective manner.

Acknowledgments. This work was supported by the Bristol NIHR Cardiovascular Biomedical Research Unit at the Bristol Heart Institute. The views expressed are those of the authors and not necessarily those of the UK National Health Service, National Institute for Health Research, or Department of Health.
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Coronary artery disease imaging: what is the role of coronary computed tomography angiography?

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Coronary artery disease imaging: what is the role of coronary computed tomography angiography (CCTA), have been instrumental for the advancements in our understanding of coronary artery disease. The advent of CCTA will significantly change the treatment approach for three types of patients. For asymptomatic, but high-risk patients, CCTA can identify the presence, extent, and content of plaque formation quickly and precisely to determine the best option for medical therapy. For patients with stable coronary artery disease, CCTA can reliably exclude epicardial stenosis to minimize the number of patients who will need to undergo invasive coronary angiography. Finally, for patients with low-risk acute coronary syndromes, the combination of high-sensitivity troponins and CCTA will safely reduce the number of subsequent outpatient procedures, which will lessen the burden on often-underfinanced health care systems.

Techniques, such as coronary computed tomography angiography (CCTA), have been instrumental for the advancements in our understanding of coronary artery disease. The advent of CCTA will significantly change the treatment approach for three types of patients. For asymptomatic, but high-risk patients, CCTA can identify the presence, extent, and content of plaque formation quickly and precisely to determine the best option for medical therapy. For patients with stable coronary artery disease, CCTA can reliably exclude epicardial stenosis to minimize the number of patients who will need to undergo invasive coronary angiography. Finally, for patients with low-risk acute coronary syndromes, the combination of high-sensitivity troponins and CCTA will safely reduce the number of subsequent outpatient procedures, which will lessen the burden on often-underfinanced health care systems.

Coronary artery computed tomography angiography (CCTA) has opened a new road to the understanding of coronary artery disease (CAD). Since the early beginnings of CCTA, the use of electron-beam computed tomography (CT) to depict coronary arteries has significantly progressed and has achieved superb spatial resolution with ever-declining radiation requirements. This article will review the use of CCTA in preventive medicine, in patients with stable CAD, and in patients with acute coronary syndromes.

**TECHNIQUE**

Coronary artery imaging requires high temporal and spatial resolution to capture the fast moving small structures accurately. State-of-the-art CT machines achieve temporal resolutions down to 66 ms with spatial resolutions ranging from 0.5 to 0.625 mm. By employing a combination of high-pitch spiral acquisitions at a low kV and raw data-based iterative reconstruction, CCTA can now be performed at a radiation dose as low as 0.06 mSv with sufficient image quality in selected patients. The dose of radiation increases and the image quality decreases with an increasing heart rate. Thus, it is recommended to give β-blockers to patients with a resting heart rate > 65 bpm. Only the patients with adequate breath holding capabilities, without severe obesity, with a favorable calcium score (eg, Agatston score < 400) and distribution, in sinus rhythm, and with a heart rate ≤ 65 bpm should be considered for CCTA.

If a calcium score is not obtained and calcifications are only seen on the completed coronary CT angiogram, it may be prudent to refrain from stenosis quantification in areas of extensive calcifications. Even in segments without severe calcifications, CCTA tends to underestimate the coronary lumen and hence the coronary stenosis severity. When compared with the cross-sectional areas of the lumen measured by intravascular ultrasound, CT values tend to be smaller with higher inter-observer variability. CCTA requires the application of contrast media, which limits its use in patients with chronic kidney disease.

**SELECTED ABBREVIATIONS AND ACRONYMS**

- CAC: coronary artery calcium
- CAD: coronary artery disease
- CCTA: coronary computed tomography angiography
- FFR: fractional flow reserve
- MESA: Multi-Ethnic Study of Atherosclerosis
- SPECT: single-photon emission computed tomography
- TAG: transluminal attenuation gradient
PREVENTIVE MEDICINE

In asymptomatic subjects with atherosclerotic risk factors, screening for coronary artery calcium (CAC) is a powerful tool to determine prognosis with a predictive power beyond that of customary risk scores, such as the Framingham score or the ESC SCORE (European Society of Cardiology Systematic COronary Risk Evaluation). Usually, the amount of coronary calcification is expressed using the Agatston score, which weighs both the density and the extent of the calcifications. Technically, CAC scoring is performed without using contrast media, and the radiation burden is <1 mSv.

Prognostic studies confirm the superior predictive benefit of CAC. For instance, Silverman et al reported the CAC scores for 6698 individuals from the MESA study (Multi-Ethnic Study of Atherosclerosis), and the results confirm that the prevalence of intense calcifications (CAC >300) increased with an increasing number of conventional risk factors. Nevertheless, one-third of the patients with ≥3 risk factors had a CAC score of 0. Among patients with zero risk factors, 5% had a CAC score >300. Interestingly, patients with zero risk factors and a CAC score >300 had an event rate 3.5-times higher than individuals with ≥3 risk factors and a CAC score of 0 (10.9/1000 vs 3.1/1000 person-years). Consequently, the 2016 European guidelines on cardiovascular disease prevention in clinical practice consider the CT CAC score to be a risk modifier with reclassification potential vs conventional risk scores.

CAC scoring is increasingly employed in patients with symptoms compatible with stable CAD to diagnose or exclude obstructive and nonobstructive plaque formation in the coronary arteries. CCTA has opened a new window to the heart, providing, for the first time, the opportunity to view the walls of the coronary arteries directly without introducing catheters. Over the past several years, a wealth of information based on CCTA has accumulated, which has changed our view on what may be important in the management of patients with CAD. At a time when symptomatic patients who are undergoing tests to detect myocardial ischemia only have an approximate detection rate of 5%, it may be prudent to use CCTA alternatively to exclude the presence of significant coronary artery stenoses quickly and reliably. Such a strategy may be able to guide patient management in a more efficient and less costly way, especially when initiating secondary prevention medications, such as statins and acetylsalicylic acid.

Another recent study by Dedic et al pointed in the same direction. They found an additional prognostic benefit provided by CCTA in asymptomatic high-risk patients (diabetes mellitus, familial hypercholesterolemia, peripheral artery disease, or severe hypertension) beyond the information given by age, sex, and CAC scoring.

Thus, it is not yet clear whether CCTA is useful in asymptomatic individuals, although there is evidence indicating that it may be helpful beyond CAC scoring in high-risk individuals.

STABLE CAD

Diagnostic performance of CCTA

CCTA is increasingly employed in patients with symptoms compatible with stable CAD to diagnose or exclude obstructive and nonobstructive plaque formation in the coronary arteries. CCTA has opened a new window to the heart, providing, for the first time, the opportunity to view the walls of the coronary arteries directly without introducing catheters. Over the past several years, a wealth of information based on CCTA has accumulated, which has changed our view on what may be important in the management of patients with CAD. At a time when symptomatic patients who are undergoing tests to detect myocardial ischemia only have an approximate detection rate of 5%, it may be prudent to use CCTA alternatively to exclude the presence of significant coronary artery stenoses quickly and reliably. Such a strategy may be able to guide patient management in a more efficient and less costly way, especially when initiating secondary prevention medications, such as statins and acetylsalicylic acid.

Like all other tests, the performance of CCTA depends on the patient population studied, the equipment, the type of patient preparation used, and other variables. Data are surprisingly coherent concerning the high sensitivity of the technique, but specificity falls steeply with increasing amounts of calcium, increasing pretest probability for the presence of obstructive coronary
CAD and coronary computed tomography angiography - Sechtem

What do current guidelines recommend for CCTA?

The 2013 European guidelines on the management of patients with stable CAD\(^4\) recommend CCTA for patients with a pretest probability between 15% and 50% (Figure 1) because the specificity is suboptimal at higher pretest probabilities, as discussed above. However, in the patients within the lower range of intermediate pretest probabilities, CCTA is highly reliable in ruling out relevant CAD. There are two other clinical scenarios for which the guidelines recommend performing CCTA: (i) in patients within the lower range of the intermediate pretest probability for stable CAD after a nonconclusive exercise ECG or stress imaging test; and (ii) in patients who have contraindications to stress testing, which can help avoid an otherwise necessary invasive coronary angiography. However, this only applies to patients in whom full diagnostic image quality of coronary CT images can be expected.

In contrast with the ESC guidelines, the 2012 US guidelines\(^16\) recommend a more restricted use of CCTA (Figure 2, page 280). CCTA plays a role both in patients who have contraindications to stress testing and in patients who are not able to exercise and have an intermediate to high pretest probability of CAD. In the latter group of patients, CCTA...
is competing with pharmacological stress testing using scintigraphy, echocardiography, or cardiac magnetic resonance imaging. The focus on patients within the range of higher pretest probabilities is surprising because intermediate pretest probability is defined in the US guidelines as 20% to 70%, whereas high pretest probability is defined as 71% to 95%. This definition means that in the opinion of the US guidelines, CCTA should be used in a group of patients in whom the likelihood of severe calcification is rather high, and suboptimal imaging results are expected.

The 2010 NICE guidelines were the first to give a broader role to CCTA (Figure 3). In patients with an estimated pretest probability between 10% and 29%, the algorithm begins with CT calcium scoring. If the calcium score is zero, the guidelines recommend looking for other causes of chest pain, especially functional CAD, such as epicardial coronary vasospasm or microvascular coronary disease. If the calcium score is >400, invasive coronary angiography is recommended for diagnostic purposes. CCTA is recommended for patients with a score between 1

**Consider investigating other causes of angina, such as hypertrophic cardiomyopathy or syndrome X in people with typical angina-like chest pain if investigation excludes flow-limiting disease in the epicardial coronary arteries.**
and 400. If significant coronary artery stenosis is observed (>400), then the diagnosis of “stable angina” should be made and patients should be treated accordingly. Patients who have no stenosis should be evaluated further for the presence of functional CAD or other causes of chest pain. Patients with inconclusive results after CCTA (i.e., whether a stenosis is present and not) are recommended to undergo appropriate functional testing.

This brief overview shows that the three main current guidelines differ substantially in their recommendations for when CCTA makes sense as a diagnostic tool. However, the recommendations of the 2012 US guidelines were somewhat revised in the 2014 focused update, where the guidelines now give a similar recommendation as the ESC guidelines, namely to use CCTA for patients in whom the diagnosis of stable CAD is still inconclusive after noninvasive stress testing. In such patients, the US guidelines now recommend CCTA as an alternative to invasive coronary angiography. For indications and contraindications to CCTA, the 2014 update refers to the 2010 expert consensus document and the 2010 appropriate use criteria for cardiac CT. However, the somewhat surprising recommendation to use CCTA in patients with a high pretest likelihood of CAD was not revised.

The 2016 NICE guidelines on the assessment and diagnosis of recent-onset chest pain are publicly being discussed, and they should be available in November. These new guidelines propose abandoning pretest probabilities for selecting appropriate patient management, and they recommend going straight to CCTA in patients in whom stable angina cannot be diagnosed or excluded by clinical assessment alone.

More recent work by Park et al, a useful adjunct to stenosis assessment based on anatomy. In a recent study, Park et al looked at plaque features associated with invasive fractional flow reserve (FFR)-defined myocardial ischemia in 252 patients who had a CCTA assessment. Ischemia was present in 151 of 407 coronary lesions (37%). Aggregate plaque volume was associated with a 50% increased risk of ischemia per 5% additional aggregate plaque volume. Ischemic lesions had a 3-to 5-times higher prevalence than nonischemic lesions when there were low attenuation and spotty calcification within the plaque and positive remodeling. Thus, when in doubt, plaque characteristics should be considered in the diagnostic process to identify ischemia-causing lesions, but this tool is currently not precise enough, and it is too complex to be clinically useful.

Another way of using the information from standard CCTA datasets is by applying computational fluid dynamics for the derivation of noninvasive FFR. A recent publication summarized the three main studies that compared the FFR-CT method with invasive FFR. The main benefit of FFR-CT seems to be to increase the unusually poor specificity of CCTA (25% to 42%) to somewhat better values (54% to 79%). Calculation of FFR-CT is currently expensive and takes time, the number of patients studied is small, and the positive predictive value of FFR-CT (65%) is not high enough to preclude the need for confirmation by invasive FFR.

There have also been attempts to use the attenuation of contrast distal to a stenosis to characterize stenosis severity. In some studies, the transluminal attenuation gradient (TAG), which is computed as the linear regression coefficient between the luminal contrast attenuation in Hounsfield units and the length from the ostium of the coronary vessel, was a useful adjunct to stenosis assessment based on anatomy. Although there is no commonly accepted cut-off value associated with the functional relevance of a coronary lesion, TAG is consistently lower distal to a high-grade stenosis, which may help interpret the CT angiogram correctly, especially if coronary calcification is present.
However, when comparing TAG with invasive FFR for determining the significance of a coronary stenosis, Stuijfzand et al did not find an incremental diagnostic benefit of TAG vs 256-slice CCTA alone. This negative result is not unexpected because there are several technical and flow-related factors beyond stenosis severity that influence distal contrast attenuation.

Finally, CT myocardial perfusion imaging under pharmacological stress has been developed to determine the hemodynamic significance of a stenosis. Static acquisitions use a single dataset obtained during first-pass enhancement to measure attenuation levels in ischemic and nonischemic areas. In contrast, dynamic CT perfusion imaging acquires a sequential dataset during the passage of contrast media, making it possible to construct a time-signal intensity curve from which myocardial blood flow can be calculated. The disadvantage of the dynamics strategy is the approximate 10 mSv increase in radiation exposure. However, acquisition of static myocardial perfusion images also requires an additional CT scan, which results in an additional radiation exposure of approximately 2.5 mSv. Many studies have shown a good agreement between CT myocardial perfusion imaging and single-photon emission computed tomography (SPECT), invasive coronary angiography, and perfusion cardiac magnetic resonance. These studies are nicely summarized in a recent 2015 review by Goncalves et al.

Most of these studies showed that the addition of stress CT myocardial perfusion imaging increases the accuracy of CCTA for detecting reversible myocardial ischemia. Again, it is mainly related to the specificity of CCTA, which is increased by also considering CT myocardial perfusion imaging (Figure 4). In a recent study where stress CT myocardial perfusion imaging was compared with FFR, Ko et al showed that the specificity and the positive predictive value increased from 84% to 98% and from 82% to 97%, respectively, when CCTA was included. The main issue with using CT myocardial perfusion imaging clinically is the radiation issue because cardiac magnetic resonance and echocardiography provide similar information without radiation exposure. Thus, myocardial perfusion imaging using CT currently remains a research tool, but this may change with further improvements in CT technology. In summary, all of the currently investigated approaches for using cardiac CT to diagnose myocardial ischemia are not yet clinically established.

Prognosis

Furthermore, CCTA also has a proven track record of providing stable and reliable prognostic information, especially in stable symptomatic patients who have no atherosclerosis. Revascularization of patients identified by CCTA to harbor significant obstructive CAD may improve prognosis, just as it worsens prognosis in those shown by CCTA to have only a mild disease. Patients with diffuse severe coronary atherosclerosis without epicardial stenosis may indicate myocardial ischemia both by FFR or perfusion imaging and these patients also have a significantly worse prognosis. In fact, diffuse severe coronary atherosclerosis is associated with higher rates of all-cause death, cardiac death, and myocardial infarction than a more focal atherosclerosis or the complete absence of plaque.
The unfavorable outcomes in these patients are similar to that of patients with multivessel obstructive disease.\(^{37}\) This observation may appear initially paradoxical, but it may be explained by the known risk for acute complications associated with nonobstructive plaque\(^{38}\) and the risk of associated microvascular disease and microvascular ischemia, which frequently accompanies epicardial plaque formation.

In a recent trial, 10,000 symptomatic stable patients were randomized to either a strategy of initial anatomic testing using CCTA or an approach using functional testing. The results showed similar outcomes for both strategies,\(^{39}\) and the rates of hard coronary events were low in both arms. More patients in the CT group underwent invasive catheterization (12.2% vs 8.1%), but the CT strategy led to fewer catheterizations showing no obstructive CAD than functional testing (3.4% vs 4.3%). More patients in the CT group underwent revascularization (6.2% vs 3.2%), but this did not lead to differences in the outcomes; however, the study was underpowered to detect such differences.

**ACUTE CORONARY SYNDROME**

CCTA is also a promising tool to be used in patients with acute coronary syndromes. These patients often have low-risk features, such as absent or stable troponin at low levels and a normal ECG or an ECG without significant changes during the time in the emergency department. It is in this group of patients that quick and reliable ruling out of coronary stenosis and plaque formation is desirable. Several randomized studies\(^{40-42}\) reported very low event rates secondary to a normal CCTA during follow-up after patients were discharged from the emergency department. Based on the data, it is clear that patients fulfilling the criteria listed above can be safely sent home. One can argue that many of these patients probably had no acute coronary syndrome, but just acute chest pain and were at a very low risk of developing a myocardial injury. Therefore, the availability of CCTA in the emergency room might lead to unnecessary and unjustified testing and application of radiation. However, current demand by patients and lawyers for diagnostic certainty may render such clinical management unavoidable.

More recently, a multicenter study from the Netherlands randomized patients with acute chest pain or symptoms suggestive of ACS to either CCTA or standard care accord-
ing to current guidelines, and each group had 243 patients. This study included patients in whom serum troponin levels were up to 3 times the upper limit of the 99th percentile. Exclusion criteria included symptoms that clearly had a non-cardiac origin, history of CAD, a clinical need for urgent invasive coronary angiography, clinical instability, impaired renal function, severe arrhythmias, and a body mass index >40 kg/m². The primary outcome (ie, the number of patients requiring revascularization within 30 days) was similar (9% with CT vs 7% with standard care) in the two groups. Similar results were also reported for the frequency of undetected ACS (0.5% with CT vs 1% with standard care). The number of patients who could be discharged immediately from the emergency department was similar between the two groups, which was also true for the median length of stay. The number of outpatient tests was lower in the CT group (4% vs 11%, P<0.01) and the direct medical costs after 30 days were lower in the CT group (€377 vs €511; P<0.01).

The Netherlands study differs somewhat from the other randomized trials as the early performance of CCTA did not shorten the length of stay or reduce the number of hospital admissions (Figure 5, page 283). This result may have been due to the use of high sensitivity troponins that had not been available in the previous studies. The positive role of high-sensitivity troponins is also reflected in the large number of patients who could be directly discharged from the emergency department in the study.

Their number was 2- to 4-times higher than reported in previous randomized trials (Figure 5). However, another important difference between this study and the previous US trials was the different health care system in the Netherlands, which gives different incentives to patient care. The results of this study may be transferable to other European emergency systems, and it may help make the emergency room workup of patients suspected to have acute coronary syndromes cheaper without compromising safety.

CONCLUSIONS

The advent of CCTA will significantly alter our approach to asymptomatic high-risk patients, patients with stable coronary artery disease, and patients with low-risk acute coronary syndromes. In the first group of patients, we will be able to quickly and precisely identify the presence, extent, and content of plaque formation to help us allocate medical therapy better to those who will profit the most. The second group will have the benefit of a reliable exclusion of epicardial stenosis without having to undergo invasive coronary angiography, which is still used in too many of these patients. Finally, in the third group of patients, the combination of high-sensitivity troponins and CCTA will safely reduce the number of subsequent outpatient procedures and save considerable amounts of money for our often-underfinanced health care systems.

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What is the role of intracoronary imaging?

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Intravascular imaging modalities are used by interventional cardiologists to assess atherosclerotic plaque features and stent deployment results, overcoming some limits of coronary angiography. Optical coherence tomography, intravascular ultrasound, and near-infrared spectroscopy are the most commonly used intravascular techniques. Each technique has specific advantages and limitations that make each one appropriate for specific purposes. In the last years, offline analysis software has been developed to diagnose plaque tissue components, such as macrophages, better and improve coronary stent assessment, even in a three-dimensional view (carpet view). Although optical coherence tomography and intravascular ultrasound have been principally used for research purposes, recent evidence supports a clinical role for intracoronary imaging techniques in guiding percutaneous coronary interventions, mainly for complex procedures.

Keywords: atherosclerosis; coronary angiography; intravascular ultrasound; near-infrared spectroscopy; optical coherence tomography; vulnerable plaque

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IMAGING MODALITIES FOR ASSESSING CORONARY ATHEROSCLEROSIS

Angiography is a road mapping technique that can address lumen narrowing due to coronary atherosclerosis. Since its introduction over 50 years ago, angiography is still the gold standard for assessing atherosclerotic impairment of coronary arteries and for providing guidance during percutaneous coronary interventions (PCI). However, angiography only depicts the luminal narrowing caused by coronary plaques; therefore, it is unable to study atherosclerotic lesions with accuracy. Apart from extensive calcifications, which can be revealed with angiography, lipid and fibrous components cannot be identified. In some cases, complicated plaques can also be identified. In fact, intracoronary thrombi typically cause angiographic haziness, whereas plaque ulceration can be visualized when the plaque crater is connected to the lumen. Angiography is certainly an inappropriate technique to study plaque vulnerability. However, even with its inherent limitation of simply offering a luminal view, angiography can be utilized to quantify atherosclerosis extension. For this specific task, a dedicated scoring system has been developed.12

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<td>ADAPT-DES</td>
<td>Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents [trial]</td>
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<td>CLI-OPCI</td>
<td>Centro per la Lotta contro l’Infarto-Optimisation of Percutaneous Coronary Intervention [study]</td>
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<td>IB-IVUS</td>
<td>integrated backscatter intravascular ultrasound</td>
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<td>IVUS</td>
<td>intravascular ultrasound</td>
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<td>MACE</td>
<td>major adverse cardiac event</td>
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<td>NIRS</td>
<td>near-infrared spectroscopy</td>
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<td>OCT</td>
<td>optical coherence tomography</td>
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<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<tr>
<td>PROSPECT</td>
<td>Providing Regional Observations to Study Predictors of Events in the Coronary Tree [trial]</td>
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<tr>
<td>TCFA</td>
<td>thin-cap fibroatheroma</td>
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<td>VH-IVUS</td>
<td>virtual histology intravascular ultrasound</td>
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<td>VIVA</td>
<td>VH-IVUS in Vulnerable Atherosclerosis [study]</td>
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Angiography is a reliable and validated technique to assess lesion severity, however, some anatomical issues can be an obstacle to the assessment. In fact, reference vessel disease, lesion foreshortening, an-gulations, calcifications, and vessel overlap make the angiographic assessment of lesion severity a difficult task. Intravascular imaging modalities are currently adopted to circumvent these angiographic limitations. Intravascular imaging modalities have increased over the past 20 years; some have failed to enter the clinical arena for different reasons, such as being too complex or not being accurate enough. Currently, the most frequently used intravascular imaging techniques are intravascular ultrasound (IVUS), optical coherence tomography (OCT), and near-infrared spectroscopy (NIRS) (Table I).

**OCT**

Frequency-domain (FD) OCT is an imaging modality that uses infrared lights and is capable of studying atherosclerotic plaques and stented segments with high accuracy. The resolution of OCT is around 10 to 20 µm, which is about ten times greater than that of IVUS, which employs ultrasound wave sounds and has a resolution of 100 to 150 µm with the 20 MHz IVUS transducer. This resolution occurs at the expense of penetration depth, which is only 1 to 3 mm vs IVUS, which is 4 to 10 mm. Accordingly, OCT offers a very precise picture of the superficial features of coronary plaque. OCT can address plaque components and distinguish among calcium, lipid and fibrous tissues. However, based on recent findings, quantification of superficial lipid pools can be hampered by superficial inflammatory cells, causing a signal drop off similar to that of the fibrous cap.

OCT may potentially be used to study vulnerable plaques because it can measure the lumen area, fibrous cap thickness, and local inflammation. Calcified nodules, which have been considered responsible for about 8% of acute coronary syndromes (ACS), are easily imaged with OCT. In addition to the ability to identify vulnerable plaques, OCT can identify complicated plaques that previously underwent uneventful ulcerations. Lastly, OCT is the only technique able to study ACS because it addresses the composition of the thrombus (red vs white) and it differentiates between acute thrombosis due to erosions and those caused by ulceration.

**Intravascular ultrasound**

IVUS provides real-time, high-resolution, tomographic images of both the lumen and the atherosclerotic changes to the coronary vessel wall. This imaging technique requires a selective examination of the vessel with an imaging catheter that includes a transducer emitting high-frequency ultrasound waves (20-45 MHz). Detection of the contours of the lumen and the media-adventitia interface allow for direct measurements of the lumen and total vessel cross-sectional areas to be made, and therefore, calculations of absolute and percent plaque area. In addition, morphology, severity, and composition of coronary atherosclerotic plaques can be determined.

Atheromas, calcified plaques that are deposited on blood vessel walls and are composed of lipids and fibrous tissue, have been classified into the following four categories by gray-scale IVUS: (i) soft plaque (lesion echogenicity less than the surrounding adventitia); (ii) fibrous plaque (intermediate echogenicity between soft atheromas and highly echogenic calcified plaques); (iii) calcified plaque (echogenicity higher than the adventitia with acoustic shadowing); and (iv) mixed plaques (no single acoustical subtype, represents >80% of the plaques).

Importantly, IVUS can identify calcified plaques and vessel remodeling due to its capability of imaging both internal and external elastic membranes.

**IVUS-NIRS**

IVUS-NIRS is a novel catheter-based technique that determines the chemical composition of the coronary artery wall. This determination is accomplished by measuring the proportion of near-infrared light that is diffusely reflected by the arterial wall after scattering and absorption.

In particular, NIRS represents the best intracoronary imaging technique to identify lipid core plaques.
A lipid core plaque is defined as a fibroatheroma containing a necrotic core that is at least 200 µm thick, with a circumferential span of at least 60 degrees on cross-section. NIRS cannot distinguish between a superficial and a deep lipid core plaque; for this reason, it needs to be combined with an additional technique, such as IVUS, to locate the lipid pool across the vessel layers.11

Postprocessing of OCT and IVUS images

A postprocessing analysis of both OCT and IVUS images can be carried out using dedicated software. Grayscale IVUS is not capable of distinguishing plaque types; as a result, both virtual histology (VH) IVUS and integrated backscatter (IB) IVUS have been used to elaborate the backscattered IVUS signal further to enhance differentiation of the major plaque components. VH-IVUS uses an autoregression model to generate multiple spectral parameters of the backscattered ultrasound signal to produce a tissue map of the plaque components: fibrous (dark green), fibro-fatty (yellow-green), necrotic core (red), and dense calcium (white).

The PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) was the first prospective natural history study of vulnerable plaque.12 PROSPECT linked VH-IVUS-derived thin-cap fibroatheroma (TCFA), defined as a necrotic core–rich plaque (>10%) without evident overlying fibrous tissue and with a percent plaque volume of 40%, with clinical events.

The IB-IVUS technique uses mathematical manipulation of the ultrasound backscatter signal to improve the ability of IVUS to detect vulnerable plaques. IB values for the various plaque components can then be calculated to construct color-coded IB-IVUS maps that can be categorized into one of five groups: thrombus, intimal hyperplasia/lipid core, fibrous, mixed, and calcified tissues.

OCT images can be postprocessed using new software called “Carpet View,” which unfolds the vessel, reconstructs it as an open structure, and displays it as a three-dimensional reconstruction. The software can improve the offline serial comparisons of both coronary plaque and stented segments, enabling the matching of the imaged cross-section at different time points.13 Dedicated software capable of quantifying macrophages using OCT images has also been developed. Macrophages are inflammatory cells that play a central role in plaque destabilization by releasing proteolytic enzymes and other proinflammatory mediators that in turn, can lead to fibrous cap rupture and subsequent plaque thrombosis. The Tearney Lab (Boston, MA, USA) developed software that measures OCT signal variance (ie, named normalized standard deviation), a parameter that tends to increase in the presence of a significant macrophage content.14 However, a normalized standard deviation may overestimate macrophage presence due to artifacts. Thus, other tissue property indexes have been proposed to characterize macrophage presence further.

The average size of macrophages is usually 20 to 50 µm, although they may eventually generate larger cells called foam cells, which can be identified using granulometry. A two-step algorithm can identify a significant macrophage presence with high accuracy; the normalized standard deviation should be applied first, followed by granulometry.7

Improving the reproducibility of OCT measurements of metrics of plaque vulnerability is a major task to augment the ability of OCT to detect vulnerable lesions and identify the progression-regression of plaque components in response to specific treatments. The conventional manual analysis is obtained by selecting the cross-section with the thinnest part of the fibrous cap. This approach is subject to interobserver variability and does not capture the three-dimensional morphology of the fibrous cap. For this reason, a computer-aided method that provides a volumetric analysis of the fibrous cap and the relevant thickness at every point in the fibrous cap boundary has been validated.15

CLINICAL RELEVANCE OF IMAGING FINDINGS

OCT can identify fresh coronary thrombi that may be missed by angiography. In a substantial number of patients with ACS, typically non–ST-segment elevation myocardial infarction (NSTEMI), angiography does not show significant lesions or clear signs of acute thrombosis. A coronary thrombus, which is the ultimate event of ACS, can be well depicted by OCT because of its optimal resolution. Therefore, OCT has a vital role in diagnosing culprit lesions of ACS when there is uncertainty with the angiography assessment. Furthermore, OCT can depict the pathophysiology of ACS by differentiating between plaque erosion and ulceration. The latter aspect was related to a worse outcome, which serves as a marker of a more aggressive clinical condition.16

In a serial study carried out on patients with ST-segment elevation myocardial infarction (STEMI), Souteyrand et al showed that the morphology of a ruptured plaque remains almost unchanged over
time, while a thrombosis due to erosion has a smooth plaque surface during follow-up. It is reasonable to defer any coronary intervention when there is plaque ulceration detected at IVUS or OCT unless a significant luminal narrowing or a fresh thrombus is present. In fact, ulcerations tend to remain stable without causing cardiac events. In the presence of superficial macrophage clusters, lipid pools may not be easily detected. Macrophages can scatter the OCT signal in the same manner as lipid pools, leading to an overestimation of lipid pool extension.

The recent combination of NIRS with gray-scale IVUS in a single imaging catheter allows simultaneous assessment of plaque composition in terms of both chemical (NIRS) and morphologic (IVUS) characteristics. Specifically, NIRS can be used to quantify plaque lipid content. Yonetsu et al compared NIRS-IVUS with OCT for the detection of lipids in nontarget lesions in a cohort of ACS and stable angina patients. They showed a poor overall agreement between NIRS and OCT for the detection of lipids. In particular, in the presence of superficial calcification, the OCT analysis of nontarget lesions leads to a misinterpretation of the lipid content. In addition, histopathological studies have shown that an accumulation of foamy macrophages on the luminal surface of the vessel wall, which is identified by OCT with a typical appearance of a thick bright line with trailing shadows, may mimic lipid materials, thereby affecting the accurate tissue analysis of deeper structures.

PLAQUE VULNERABILITY

Muller et al described “vulnerable plaques” as nonculprit lesions that potentially lead to cardiac events. Such lesions are characterized by a large lipid pool, a thin fibrous cap, a relatively small lumen area, and macrophage-dense inflammation on or beneath the surface. A recent histopathological study carried out by Narula et al, quantified the features related to plaque vulnerability better. Lesions causing sudden death were compared with other vulnerable plaques that did not cause events. Such lesions had a fibrous cap thickness <84 µm, a large lipid pool, a minimal lumen area <4.0 mm², and the presence of local inflammation.

PROSPECT evaluated the natural history of atherosclerosis by studying 697 ACS patients treated with PCI on the culprit lesion plus optimal medical therapy. All patients had three-vessel imaging with grayscale and VH-IVUS. The study showed that both culprit and nonculprit lesions were equally responsible for major adverse cardiac events (MACE) over 3 years. Most nonculprit lesions causing follow-up events had a mild angiographic narrowing at baseline. A multivariate analysis carried out with IVUS data identified three independent predictors of MACE: plaque burden ≥70%, minimal lumen area ≤4.0 mm², and TCFA at VH-IVUS, identified as a lipid-rich atheroma with only a thin fibrous layer of intimal tissue covering the necrotic core.

Likewise, in the VIVA study (VH-IVUS in Vulnerable Atherosclerosis), three-vessel VH-IVUS was performed in 170 patients with stable angina or ACS before and after PCI. During 1.7 years of follow-up, 19 lesions (13 nonculprit and 6 culprit lesions) resulted in MACE (death, myocardial infarction, unplanned revascularization). Nonculprit lesion factors responsible for total MACE included plaque burden >70% and minimal lumen area <4 mm², while VH-IVUS TCFA and plaque burden >70% were associated with nonstenotic MACE. This evidence suggests that VH-IVUS can identify vulnerable plaques with a greater risk of MACE during follow-up.

The Italian multicenter CLIMA Registry has been conceived to relate the OCT morphology of atherosclerotic lesions located in the left anterior descending artery with clinical outcomes at follow-up. During follow-up, MACE was defined as the presence of cardiac death or anterior ACS (including STEMI or NSTEMI). In the patient group with MACE at follow-up (mean 2.7 years), vulnerable plaques occurred more often (11.4% vs 0.3%, P<0.00001) with the following features of vulnerability: lumen area <4.0 mm², thin fibrous cap (<70 µm), circumferential extension of the lipid pool of at least 2 quadrants, and local inflammation (unpublished data).

OCT-GUIDED PCI

In 2012, our group published the CLI-OPCI study (Centro per la Lotta contro l’Infarto-Optimisation of Percutaneous Coronary Intervention), which analyzed the clinical impact of OCT findings on improving the outcomes of patients undergoing PCI. This multicenter study addressed the role of OCT guidance, and by using a propensity score adjustment, the study compared the clinical outcome of 335 patients receiving OCT-guided intervention with patients in the control group. OCT guidance improved the 1-year composite event of cardiac death or nonfatal myocardial infarction after PCI in a real-world population. The study also addressed the issue of how to treat OCT findings that are indicative of suboptimal stent deployment. In 34% of the stented segments, according to the OCT results, a further intervention with
either balloon dilation (22.3%) or additional stenting (12.4%) was needed. The study concluded that specific quantitative OCT thresholds are required to improve the clinical outcomes of patients undergoing PCI.

OCT studies in patients with ACS have shown that in-stent tissue protrusion due to the presence of a residual thrombus is common. Recent data revealed that a residual intrastent thrombus is related to a periprocedural myocardial infarction if left untreated.

Preliminary data showed that additional OCT-driven in-stent balloon dilatation could significantly reduce the in-stent thrombus area percentage without worsening the microcirculatory indexes. As another crucial application, OCT can clarify the mechanisms of restenosis and thrombosis early or late after the index procedure, guiding repeat revascularization, thus minimizing the risk of additional adverse events.

Assessment of stent underexpansion by OCT can be obtained by comparing the minimal stent area with the reference lumen area. Additionally, a threshold of an absolute minimum lumen cross-sectional area within the stent could be applied; previously, the target minimum stent area advocated to prevent failure was an area of at least 5.0 to 5.5 mm².

In the 2015 CLI-THRO study, our group addressed the incidence of suboptimal OCT results in 21 consecutive patients exhibiting subacute thrombosis. The patients were matched 1:2 with a control group of 42 patients from the Rome Heart Research core lab database. OCT showed that the minimum lumen area and the minimum stent area measurements were significantly smaller in the stent thrombosis group; in addition, there was a higher frequency of stent underexpansion, edge dissection, and reference lumen narrowing.

**IVUS-GUIDED PCI**

Randomized studies conducted in the 1990s evaluated the usefulness of an IVUS-guided approach of bare-metal stent expansion to reduce restenosis. Most of these studies were underpowered and restricted to noncomplex lesions.

After the introduction of drug-eluting stents, the benefits of IVUS was questioned given the improved outcomes with drug-eluting stents vs bare-metal stents.

A recent substudy of the ADAPT-DES trial (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents) compared IVUS and angiography-guided PCI in terms of 1-year outcomes in 8583 consecutive patients. IVUS was utilized in 39% of the patients, while angiography alone was utilized in 61%. Interestingly, in the IVUS-guided arm, interventional cardiologists changed the PCI strategy in 74% of patients, mainly employing a larger stent or balloon. The overall 1-year rate of adjudicated MACE, defined as cardiac death, definite/probable stent thrombosis, or myocardial infarction, was significantly lower in the IVUS-guided group compared with the angiography-guided group (3.1% vs 4.7%; HR, 0.67; 95% CI, 0.53-0.84; P=0.0006). However, the difference was mainly due to a reduced incidence of definite/probable stent thrombosis together with a lower rate of spontaneous and target vessel-related myocardial infarction. The benefits of IVUS were especially evident in patients with ACS and complex lesions, although significant reductions in MACE occurred in all patient subgroups, including those with stable angina and single-vessel disease.

**CONCLUSION**

Intravascular imaging techniques have been broadly used for research purposes to study coronary atherosclerosis and to understand the pathophysiology of acute coronary events better. IVUS guidance of PCIs has an established role, and there is preliminary evidence for a clinical impact of OCT.

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Coronary Artery Disease Imaging

Summaries of Ten Seminal Papers

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1. Multimodality cardiovascular molecular imaging, part II
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   Circ Cardiovasc Imaging. 2009

2. Appropriateness criteria for cardiovascular imaging use in clinical practice: a position statement of the ESC/EACVI taskforce
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4. Cardiovascular imaging practice in Europe: a report from the European Association of Cardiovascular Imaging
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5. Echocardiographic chamber quantification in the era of multimodality imaging: beware of unintended consequences
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6. Low-dose CT coronary angiography with a novel IntraCycle motion-correction algorithm…
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7. Prognostic value of coronary artery calcium scoring in addition to single-photon emission computed tomographic myocardial perfusion…
   E. M. Engbers and others.

8. Workstation-based calculation of CTA-based FFR for intermediate stenosis
   M. Kruk and others.

9. Echocardiographic and fluoroscopic fusion imaging for procedural guidance: an overview and early clinical experience
   J. J. Thaden and others.

10. Diagnostic performance of the 3D bull’s eye display of SPECT and coronary CTA fusion
    T. Nakahara and others.

Selection of seminal papers by Fausto J. Pinto, MD, PhD
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Highlights of the years by Sherri Smith, PhD
Publications office
Molecular imaging has the potential to impact cardiovascular medicine in several ways, including risk assessment, early disease detection, development of personalized and targeted therapeutic regimens, and monitoring of therapeutic efficacy and outcome. In addition to these direct implications, molecular imaging will affect clinical care indirectly by facilitating a more rapid development of novel pharmaceutics and improving the basic understanding of cardiovascular pathophysiology.

Nahrendorf et al summarized the available targeted imaging probes and the specific future applications of molecular imaging for the identification and evaluation of critical pathophysiological processes of the cardiovascular system. Novel imaging strategies for the evaluation of inflammation, thrombosis, apoptosis, necrosis, vascular remodeling, and angiogenesis were also included in the review. Nahrendorf et al also examined the role of targeted imaging for some cardiovascular diseases, such as atherosclerosis, ischemic injury, postinfarction remodeling, and heart failure, and the emerging fields of regenerative, genetic, and cell-based therapies.

Particular emphasis is placed on multimodal imaging, as these hybrid techniques promise to advance the field by combining approaches with complementary strengths and offsetting limitations. The routine application of molecular imaging in the management of patients with cardiovascular disease is likely very close to being achieved. Molecular imaging should develop further with appropriate education of the cardiovascular community and the increased availability of various hybrid-imaging systems (i.e., single-photon emission computed tomography [SPECT]/computed tomography [CT], positron emission tomography [PET]-CT, PET-magnetic resonance imaging [MRI]) that will facilitate quantification of molecular imaging agents. A number of challenges, however, stand in the way of realizing these promises. Current imaging systems have not been optimized for cardiac applications due to the inadequate correction for cardiac and respiratory motion and a lack of quantitative software for targeted agents. The full realization of the promise of cardiovascular molecular imaging will thus require an ongoing and concerted collaboration between industry and both the basic science and imaging communities.

“Smart” amplification strategies, comparative head-to-head analysis of markers, improved reporter performance, and improved hardware will enable the detection of minuscule or trace amounts of novel targets. These noninvasive and targeted approaches will need to be tested for their prognostic value, cost effectiveness, and potential long-term toxicity to translate these technological advances into improved patient care.

2009

The longest-lasting total solar eclipse of the 21st century occurs; the search for exoplanets begins with the launch of the Kepler space observatory; and army ant specialist Carl Rettenmeyer dies at age 78
Interest from the scientific community is growing regarding the appropriate use of cardiovascular imaging techniques for diagnosis and decision making in Europe. A dedicated taskforce has been appointed by the European Society of Cardiology (ESC) and the European Association of Cardiovascular Imaging (EACVI) to develop appropriateness criteria for cardiovascular imaging use in clinical practice in Europe. Cardiovascular imaging is characterized by continuously evolving technology developments in all modalities. Therefore, assistance with the decision-making process regarding both the choice of imaging modality in a certain clinical scenario and the future development of availability at local, national, and European levels becomes crucial.

The appropriateness criteria involve the evidence, guideline-based criteria, and best practice–based criteria for the appropriate use of cardiovascular imaging modalities in clinical practice, which are meant to assist in the decision-making process. These appropriateness criteria will be developed to ensure the best use of diagnostic cardiovascular imaging resources for a given individual, the rational use of cardiovascular imaging resources for all individuals in need of diagnosis, the most efficient use of available funds for society, and the judicious implementation of evolving technology and evidence in clinical practice.

The determination of appropriateness criteria, updated at regular 3-year intervals, will start with the appointment of a panel of reviewers consisting of experts in each cardiovascular imaging modality and a voting panel. The panel will make a selection of clinical scenarios; review the evidence, guidelines, position papers, etc; define indications; and assign an appropriateness score. For more information on the development process, please see Figure 1 from the paper by Garbi et al.

The appropriateness criteria, statement papers, educational material, supporting clinical implementation, and all related documents will be made available online and distributed actively to different entities (eg, European Commission, the European National Societies, Working Groups, and Associations). Additionally, web-based tools and applications will be developed to assist with the clinical decision-making process and the selection of an appropriate imaging test for a particular indication.

The appropriateness criteria will be patient-centered, facilitating the best use of cardiovascular imaging resources for an individual who needs a test, while encouraging the best use of material resources for the entire society, structured development of resources, efficient financial expenditure, and homogenization of care across Europe.

Eyesight has been restored in six patients using a new gene therapy technique; the tsetse fly genome sequencing project is complete after a 10-year multimillion dollar effort; and the length of a day for an exoplanet is measured for the first time.
Patients who have symptoms suggestive of coronary artery disease are often evaluated with the use of diagnostic testing, although limited data are available from randomized trials to guide care. The coronary computed tomography angiography (CCTA) technique is one possible tool that may reduce unnecessary invasive testing and improve patient outcomes. However, the impact of data from noninvasive vs invasive testing on the management of the disease and clinical outcomes is unknown. The PROMISE trial (PROspec-tive Multicenter Imaging Study for Evaluation of chest pain) was designed to compare health-related outcomes between CCTA and functional testing in patients presenting with symptoms of coronary artery disease that required further evaluation.

Douglas et al randomly assigned 10,003 symptomatic patients to a strategy of initial anatomical testing with the use of either CCTA or functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography). The composite primary end point was death, myocardial infarction, hospitalization for unstable angina, or major procedural complications. Secondary end points included radiation exposure and invasive cardiac catheterization that did not show obstructive coronary artery disease.

The mean age of the patients was 60.8±8.3 years, 52.7% were women, and 87.7% had chest pain or dyspnea on exertion. The mean pretest likelihood of obstructive coronary artery disease was 53.3±21.4%. Over a median follow-up period of 25 months, a primary end point event occurred in 164 of 4996 patients in the CCTA group (3.3%) and in 151 of 5007 (3.0%) in the functional testing group (adjusted hazard ratio, 1.04; 95% confidence interval, 0.83 to 1.29; \( P=0.75 \)). CCTA was associated with fewer catheterizations showing no obstructive coronary artery disease than functional testing (3.4% vs 4.3%, \( P=0.02 \)), although more patients in the CCTA group underwent catheterization within 90 days after randomization (12.2% vs 8.1%). The median cumulative radiation exposure per patient was lower in the CCTA group than in the functional testing group (10.0 mSv vs 11.3 mSv), but 52.6% of the patients in the functional testing group had no exposure, so the overall exposure was higher in the CCTA group (mean, 12.0 mSv vs 10.1 mSv; \( P<0.001 \)).

In conclusion, in symptomatic patients with suspected coronary artery disease who required noninvasive testing, an initial strategy of CCTA was not associated with better clinical outcomes than functional testing over a median follow-up of 2 years.

Biodegradable nanoparticles are used to kill brain cancer cells in animals; two lost cities in the Honduras jungle are discovered; and an almost completely intact skeleton of a terror bird is found in Argentina.
Cardiovascular imaging practice in Europe: a report from the European Association of Cardiovascular Imaging


Eur Heart J. 2015;16:697-702

Epidemiology changes in cardiovascular disease and an aging population are expected to result in an increased need for cardiovascular imaging (CVI). However, reliable statistics on the use of CVI in Europe are lacking. The European Association of Cardiovascular Imaging (EACI) and the European Society of Cardiology (ESC) Taskforce on CVI established the status of CVI use across Europe. In 2013, a survey with relevant information regarding CVI was sent to every national imaging/echocardiography society and working group. The survey was designed to assess existing education, training, certification and national accreditation programs, health care organizations, and reimbursement systems.

The percentage of countries with a national certification in CVI for cardiologists was different between imaging modalities. Transthoracic and transesophageal echocardiography were commonly certified techniques, and about one-third of the countries had a certification program for the other imaging modalities. The majority of national societies recommended the Imaging Taskforce of the EACI (EACVI) certification, but one-fifth of the societies had their national certification system. Irrespective of the CVI modality, a national accreditation for centers/laboratories was not required for practice in most countries.

Overall, there were diverse country-specific regulations for performing CVI and a widespread lack of national certification/accreditation. However, the majority of countries recommended the EACVI certification and one-fifth of the countries applied it as a national certification. Cardiologists commonly performed echocardiography, but not computed tomography (CT), cardiovascular magnetic resonance imaging (CMR), or nuclear imaging. However, in most countries, medical imaging performance requires a specialist license (eg, cardiologist, radiologist, and a nuclear imaging specialist). Unexpectedly, a predefined period of training in CVI during specialization was absent in one-third of the countries. In addition, only a few countries offered official national certification guidelines to perform CVI examinations. Interestingly, the adherence to ESC/EACVI guidelines in CVI was reported in a high number of European countries.

Finally, the access to CVI examinations in the public health care system was marked by a long waiting period in some countries.

The current mapping of the practice of CVI techniques across Europe represents the first comprehensive project of the ESC/EACVI Taskforce on CVI. The report symbolizes a preliminary step for further data collection and networking with national imaging societies and working groups. In the future, direct comparisons among the different ESC countries should help standardize health care resources by promoting knowledge of their status and by bringing this information to the attention of all public authorities. It is the hope that such data collection will contribute to improved quality of care through a better use of resources (avoid unnecessary procedures and expenses) and a consequent reduction in the waiting time, thus increasing the availability of CVI.

The Japanese L0 Series maglev becomes the first train to operate at a speed of 600 km/hour; NASA's MESSENGER spacecraft concludes its 4-year orbital mission over Mercury; and the opah is confirmed as the first warm-blooded fish.
The primary purpose of the recently published upgrade to the guideline document for echocardiographic chamber quantification is to set standard measurements, labels, and orientations to improve the communication and standardization among all echocardiography laboratories both in the United States and in Europe. Another aim of upgrading the document was to integrate echocardiographic chamber quantification with other cardiovascular imaging modality categories, with a notorious effort to recognize echocardiography as part of the noninvasive cardiovascular imaging modalities. In this paper, Feigenbaum clearly emphasizes that as with all changes or “advances,” there are likely to be unexpected or unintended consequences, which has been the case for this modality.

An early effort to improve the communication and coherence between echocardiography and nuclear cardiology was to change echocardiography’s standard 16-segment wall motion scoring system by adding a 17th segment at the apex. Echocardiography representatives agreed to make the change so that the scoring would be compatible with the nuclear apical perfusion and multiple-gated acquisition scan for apical motion. However, it was later decided that due to recording specifications in echocardiography when using the 17-segment model to assess wall motion or regional strain, the 17th segment (the apical cap) should not be included.

Another effort was made to obtain standard echocardiographic segmentation labels and orientation so that they would be similar to those used in nuclear perfusion. Unfortunately, this was not possible, for example, it was not possible to standardize the labels for the right ventricle and the papillary muscle. Importantly, the back wall of the left ventricle, which had been labeled “posterior,” is now being labeled “inferior lateral” to make it compatible with nuclear cardiology. This change has caused some comprehensible controversy. Besides the desire to set standard measurements, labels, and orientation, there are likely to be significant differences between echocardiography and cardiac computed tomography and magnetic resonance.

Care must be taken with the concept of integrated and “consensus” multimodality imaging applications in the clinical setting.

Lokiarchaeota, a transitional form between Archaea and Eukaryotes, is discovered; the US Fish and Wildlife Service declares that the eastern cougar is extinct; and the first artificial ribosome is created.
Low-dose CT coronary angiography with a novel IntraCycle motion-correction algorithm in patients with high heart rate or heart rate variability


Eur Heart J Cardiovasc Imaging. 2015;16:1093-1100

While coronary computed tomography angiography (CCTA) has achieved good diagnostic performance, motion artifacts due to a high heart rate or high heart rate variability significantly affect the image quality of CCTA. As a result, a motion-correction algorithm has been developed. In this study by Andreini et al, the impact of this algorithm when used in conjunction with low-dose prospective ECG-triggering CCTA on motion artifacts, image quality, and coronary assessability was evaluated. Only one previous study assessed the diagnostic performance of the motion-correction algorithm in conjunction with retrospective ECG-triggering CCTA in a small patient population referred for transcatheter aortic valve implantation. A secondary aim of the study was to evaluate the diagnostic accuracy of CCTA performed with the motion-correction algorithm and standard reconstruction in comparison with invasive coronary angiography—the gold-standard imaging technique.

Of the 410 consecutive patients undergoing CCTA for suspected coronary artery disease who were considered for inclusion in this study, 120 patients with a prescanning heart rate >70 bpm or a heart rate variability >10 bpm during scanning irrespective of prescanning heart rate or both were selected. Mean prescanning heart rate and heart rate variability were 70±7 bpm and 10.9±4 bpm, respectively. Overall, the mean effective dose of radiation was 3.4±1.3 mSv, while a lower dose (2.4±0.9 mSv) was measured for padding of 80 ms. In a segment-based analysis, coronary assessability was significantly higher (P<0.0001) with motion correction (97%) when compared with standard reconstruction (81%) due to a significant reduction (P<0.0001) in severe artifacts (54 vs 356 cases, respectively). An artifact subanalysis showed a significantly lower number of motion artifacts and artifacts related to chest movement with motion correction (16 and 4 cases) than with standard reconstruction (286 and 24 cases, P<0.0001 and P<0.05, respectively).

In conclusion, this study showed that in a subset of patients with high prescanning heart rate, increased heart rate variability, and high mean maximum heart rate during scanning, CCTA with motion-correction reconstruction achieved good image quality, very high coronary assessability, and a lower radiation exposure.

The genes responsible for the 200-year lifespan of the bowhead whale are mapped; astronomers identify a method to determine a star’s age from how fast it spins; and an exoplanet with a gigantic ring system that is 200 times larger than that around Saturn is discovered.
Single-photon emission computed tomography (SPECT) myocardial perfusion imaging is well-established for the prognostic evaluation of patients with suspected coronary artery disease. However, this functional imaging modality is not able to detect nonflow-limiting coronary artery disease. The increased interest in using coronary artery calcium (CAC) to identify subclinical atherosclerosis has demonstrated a close correlation with atherosclerotic plaque burden. With the advent of combined SPECT and computed tomography cameras, it is possible to acquire both SPECT images and CAC scores in a single session.

Engbers et al investigated the prognostic value of CAC scoring as an adjunct to SPECT in a population who are at a low-to-intermediate-risk for stable coronary artery disease. A total of 4897 symptomatic patients with no history of coronary artery disease who were referred for SPECT and CAC scoring were included. Major adverse cardiac events were defined as late revascularization (>90 days after scanning), nonfatal myocardial infarction, and all-cause mortality.

The frequency of abnormal SPECT increased with higher CAC scores, from 12% in patients with CAC scores of 0% to 19%, 32%, 37%, and 50% among those with CAC scores 1 to 99, 100 to 399, 400 to 999, and ≥1000, respectively ($P<0.001$). During a median follow-up of 940 days (25th to 75th percentile, 581-1377), 278 major adverse cardiac events were observed, and the overall incidence of major adverse cardiac events was 2.3% per year. A stepwise increase in major adverse cardiac events was present with increasing CAC scores, both in patients with a normal SPECT result (annual event rate CAC score 0, 0.6%; CAC score ≥1000, 5.5%) and an abnormal SPECT result (annual event rate CAC score 0, 0.4%; CAC score ≥1000, 7.6%). After multivariate analysis, both SPECT results and CAC scores were independent predictors of major adverse cardiac events (CAC score ≥1000: hazard ratio, 7.7; $P<0.001$ and large perfusion defect on SPECT: hazard ratio, 3.7; $P<0.001$).

CAC score and SPECT are independent predictors of major adverse cardiac events in patients suspected of coronary artery disease. Our findings strongly support acquiring a CAC score in addition to SPECT in symptomatic patients to define the risk of events during follow-up better.
Workstation-based calculation of CTA-based FFR for intermediate stenosis


Coronary computed tomography angiography (CCTA) is a common diagnostic test indicated in patients with an intermediate probability of coronary artery disease. However, it often ends up in a diagnosis of intermediate coronary stenosis that leads to further functional testing. CCTA-based fractional flow reserve (CCTA-FFR) is an emerging method for the noninvasive functional diagnosis of coronary artery disease. This imaging technique is the result of the fusion of both an anatomical test and a computationally simulated surrogate of FFR, providing a “one-stop shop” diagnostic tool. Both method developers and clinicians pursue a better understanding of the technique and aim to compare the clinical value across different CCTA-FFR results.

Kruk et al conducted a study to evaluate the proportion of patients with intermediate coronary stenosis diagnosed on CCTA, who may be saved from any further testing due to the use of CCTA-FFR. The study involved determining the upper and lower CCTA-FFR thresholds that predict nonischemic and ischemic stenosis, respectively, (based on an invasive FFR cutpoint ≤ 0.80) with ≥90% accuracy, and subsequently determining the proportion of patients who fall between these thresholds.

A total of 90 patients were included in this prospective, single-center, cohort study, and 96 lesions were analyzed. The patients who underwent routine CCTA due to an intermediate probability of having a significant coronary artery stenosis and who had a CCTA diagnosis of at least one intermediate coronary stenosis (50% to 90% by visual estimation) in an artery ≥2 mm in diameter were scheduled to undergo invasive FFR within 6 months of the CCTA examination.

The study demonstrated that an invasive FFR ≤0.8 was observed in 41 of 96 lesions (42.7%). According to a Bland-Altman analysis, CCTA-FFR underestimated FFR by 0.01 and the 95% limit of agreement was ±0.19. The CCTA-FFR thresholds for which the positive and negative predictive values were each ≥90% (corresponding to an FFR ≤0.80) were >0.87 or <0.74, respectively, and they involved 49 lesions (51%) and 45 of the 90 patients. The authors concluded that this hybrid diagnostic approach (the prototype CCTA-FFR based on CCTA) may discriminate between ischemic vs nonischemic stenoses in around 50% of patients with an intermediate coronary stenosis, potentially saving them from further functional testing. Further studies are needed for the validation of the methodology in an independent multicenter cohort.

2016

Yoshinori Ohsumi is awarded the 2016 Nobel Prize in Physiology or Medicine; the world’s first baby is born using the controversial new “three parent” technique; and asprosin, a fasting-induced glucogenic protein hormone, is discovered
Echocardiographic and fluoroscopic fusion imaging for procedural guidance: an overview and early clinical experience


During the last few years, there has been an exponential growth in the novel percutaneous structural heart interventions developed to treat valvular and structural heart conditions through a transcatheter approach. Investigational device-based therapies, such as transcatheter aortic valve replacement, transcatheter mitral valve repair, left atrial appendage occlusion, and percutaneous paravalvular leak closure, have necessitated increased sophisticated imaging guidance that is not supported solely by fluoroscopy.

There has been increased interest in the multimodality imaging that has fueled the development of fusion imaging to facilitate procedural guidance. Echocardiographic and fluoroscopic fusion imaging combines the precise catheter and device visualization of fluoroscopy with the soft tissue anatomy and color flow Doppler information afforded by echocardiography in a single image. This type of fusion imaging allows for precise catheter manipulations under fluoroscopic guidance while visualizing critical tissue anatomy provided by echocardiography. Thaden et al elegantly review this emerging technology’s strengths, limitations, and potential clinical applications.

Image registration is the first step of fusion imaging, and it involves reorientation of one image (echocardiography image) to match the orientation of a second image (fluoroscopy). These fusion images are compatible with 2D echocardiographic imaging with or without color Doppler, simultaneous multiplane echocardiographic imaging, and 3D echocardiographic imaging.

Three-dimensional volume data sets can also be displayed as the complete volume of data, which can be cropped in the plane of the fluoroscopic image to display soft tissue anatomy relevant to the procedure or as a partial-thickness slice that can be moved from near to far and in the direction of the fluoroscopic beam. Procedure-specific considerations have been made concerning transseptal puncture, left atrial appendage occlusion, paravalvular leak closure, and transcatheter mitral valve repair.

In conclusion, echocardiographic guidance for transcatheter mitral valve repair is essential for procedural success and remains challenging in current clinical practice. As with many new devices and technologies, a learning curve is involved. In some cases, performing the imaging study while also manipulating the fusion imaging system can be a challenge. Furthermore, it would be interesting to know whether this technology and its accuracy will be important to improve the outcomes of patients undergoing structural procedures.

Oxygen is detected in the Martian atmosphere; a successful monkey head transplant is conducted; and a pregnant *Tyrannosaurus rex* is discovered.
Myocardial perfusion single-photon emission computed tomography (SPECT) and coronary computed tomography angiography are distinct diagnostic imaging modalities that provide functional and anatomical information, respectively. SPECT/coronary computed tomography angiography hybrid imaging might be one of the forms that routine myocardial perfusion imaging will take because image fusion significantly improves detection of hemodynamically significant coronary lesions.

Nakahara et al developed a display method to present the fusion data of myocardial perfusion SPECT and coronary computed tomography angiography into a single image that they call the fusion-based bull’s eye. A 3D display is mostly used when reviewing SPECT/coronary computed tomography angiography fusion images, although multidirectional interpretation is required to sweep the entire heart. Fusion-based bull’s eye images are generated from 3D fusion data by determining a cardiac axis, adding a cylindrical object around the aortic root, obtaining a panoramic image from circumferential data of the 3D images, and converting it into a polar coordinate display image. The diagnostic performances between SPECT, conventional 3D fusion, and the fusion-based bull’s eye as regards the presence of hemodynamically relevant coronary vessels were compared in 39 patients with abnormal SPECT findings.

Of an evaluated 105 coronary segments in 35 patients without coronary artery bypass grafting, SPECT showed 17 segments (16%) equivocal to determine hemodynamically relevant coronary vessels. The fusion-based bull’s eye corrected the diagnoses of 5 segments, where SPECT provided a false-negative in 2 segments and a false-positive in 3 segments, with only 2 equivocal segments (P=0.0017).

The fusion-based bull’s eye also revealed 4 culprit lesions in all 4 patients with coronary artery bypass grafting. There was no discordance between the fusion-based bull’s eye and conventional 3D fusion.

DNA is sequenced in outer space for the first time; the second largest meteorite ever found is exhumed near Gancedo, Argentina; and Jemma Redmond, Irish biochemist and a pioneer of 3D bioprinting, dies at age 38.
Coronary Artery Disease Imaging

Bibliography of One Hundred Key Papers

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