Non-invasive imaging in coronary syndromes: recommendations of The European Association of Cardiovascular Imaging and the American Society of Echocardiography, in collaboration with The American Society of Nuclear Cardiology, Society of Cardiovascular Computed Tomography, and Society for Cardiovasc

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Non-Invasive Imaging in Coronary Syndromes: Recommendations of The European Association of Cardiovascular Imaging and the American Society of Echocardiography, in Collaboration with The American Society of Nuclear Cardiology, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance

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Reviewers: This document was reviewed by members of the 2018–2020 EACVI Scientific Documents Committee: Philippe B. Bertrand, Marc Dweck, Kristina H. Haugaa, Leyla Elif Sade, and Ivan Stankovic; by the 2020–2022 Chair of the EACVI Scientific Documents Committee: Erwan Donal; and by the 2020–2022 EACVI President: Bernard Cosyns. The CAD guideline was reviewed by members of the ASE Guidelines and Standards Committee, ASE Board of Directors, and ASE Executive Committee. Reviewers included: Scott Choyce, Benjamin Freed, Lanqi Hua, Thomas Johnson, Anuj Mediratta, Monica Mukherjee, David Orsinelli, Alan Pearlman, Andy Pellett, Michael Picard, Min Pu, Mark Taylor, and David Wiener.

Conflict of interest: F.M.A. received institutional research grant from Neovasc, Corflow. V.D. received speaker fees from Abbott Vascular, Edwards Lifesciences, Novartis, MSD and Medtronic. A.D. received instrument grant from Hitachi, Inc. D.C.L. is conducting research sponsored by Abbott Laboratories. J.R.L. received research grant from Lantheus Medical Imaging. B.A.P. received research support and lecture honoraria from General Electric Healthcare, Hitachi Aloka and Bracco.

0894-7317/$36.00

https://doi.org/10.1016/j.echo.2021.12.012

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PREAMBLE

Coronary artery disease (CAD) is one of the major causes of mortality and morbidity worldwide, with a high socioeconomic impact.[1] Non-invasive imaging modalities play a fundamental role in the evaluation and management of patients with known or suspected CAD. Imaging endpoints have served as surrogate markers in many observational studies and randomized clinical trials that evaluated the benefits of specific therapies for CAD.[2] A number of guidelines and recommendations have been published about coronary syndromes by cardiology societies and associations but have not focused on the excellent opportunities with cardiac imaging. The recent European Society of Cardiology (ESC) 2019 guideline on chronic coronary syndromes (CCS) and 2020 guideline on acute coronary syndromes (ACS) in patients presenting with non-ST-segment elevation (NSTE-ACS) highlight the importance of non-invasive imaging in the diagnosis, treatment, and risk assessment of the disease.[3,4] The purpose of the current recommendations is to present the significant role of non-invasive imaging in coronary syndromes in more detail.

These recommendations have been developed by the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE), in collaboration with the American Society of Nuclear Cardiology, the Society of Cardiovascular Computed Tomography, and the Society for Cardiovascular Magnetic Resonance, all of which have approved the final document.

The experts of the writing panel provided declarations of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest.

BACKGROUND

Definition and Pathophysiology of Coronary Artery Disease—Basic Concepts Relevant to Non-Invasive Imaging

Myocardial ischemia and infarction caused by epicardial coronary atherosclerosis are the main manifestations of CAD. Stenotic or occluded coronary arteries impair downstream blood flow, reduce myocardial perfusion, cause contractile dysfunction, and ultimately lead to angina or, in acute syndromes, myocardial infarction. Coronary syndromes may have stable periods, but can suddenly lead to an unstable event caused by plaque rupture or erosion. The nature of the disease is progressive, resulting in various clinical presentations—from subclinical to CCS and ACS, all of which are covered in this recommendations paper.

The distinctive pathophysiological characteristics of CAD can be evaluated with various imaging modalities such as echocardiography,[3] single-photon emission computed tomography (SPECT), positron emission tomography (PET), cardiac magnetic resonance (CMR), or coronary computed tomography angiography (CTA).[5,6] Combining anatomical and functional imaging modalities by either sequential stand-alone tests or hybrid approaches [e.g. SPECT/computed tomography (CT), PET/CT] would allow a more comprehensive characterization of obstructive CAD.[7-11] When choosing a specific imaging test, one needs to take into consideration the multiple factors that interact in the development of ACS and chronic CAD. The preferred imaging technique to confirm the diagnosis of acute or chronic CAD and guide the treatment will depend on the clinical presentation and characteristics of the patient, the local availability and expertise at the clinical centre.

While this document provides a set of recommendations, many situations encountered in daily clinical practice may not be covered. Ultimately, understanding how each imaging modality assesses different aspects of CAD remains critical to deciding which modality would be most helpful in providing optimal care for each patient. This document aims to provide guidance on how to select the optimal imaging approach for individual patients.

Epidemiology—Focused Towards the Pre-Test Probability of CAD and Bayesian Predictive Models

Age, gender, coronary risk factors, and symptom characteristics are used in clinical practice to estimate the probability of CAD and risk for cardiac events and to identify patients who may benefit from non-invasive testing.

The European and American guidelines recommend the Duke clinical score and the revised Diamond and Forrester models as preferred clinical tools to calculate pre-test probability (PTP) of obstructive CAD in symptomatic patients without known coronary syndromes.[3,12] While other scores have been proposed for various other CAD scenarios, it is important to estimate the PTP using any of these clinical scores to optimize cost/benefit and to reduce false results in individual patients. However, all of these models might overestimate the prevalence of CAD, and several studies have suggested

that the prevalence of obstructive disease among patients with suspected CAD is lower than previously reported.[13,14] The PTP has therefore recently been reconsidered in CCS.[3]

Bayes' theorem of conditional probability applies to the interpretation of all non-invasive imaging test results, since none has 100% sensitivity or specificity to establish either the anatomical presence of obstructive CAD or the functional presence of ischemia. Based on this theorem, optimal performance of most non-invasive tests occurs when PTP is intermediate. The proportion of false positive results increases as PTP decreases. Conversely, the proportion of false negative results increases as PTP increases. Other significant factors that may affect the diagnostic performance of individual tests are the quality of the exams, acquisition protocols and technology used, adherence to protocol standards, patient compliance, heart rate, and body habitus.[3,7,15]

Since imaging tests used for the diagnosis of CAD have different performance characteristics, it is common practice to preferentially select tests with high sensitivity in high disease prevalence groups and with high specificity in lower prevalence groups in order to reduce false negative and false positive results, respectively. Hemodynamic significance of coronary stenotic lesions varies according to anatomical location, degree of stenosis, extent and composition of obstructive plaque, amount of subtended myocardium, microvascular integrity, presence of collaterals, myocardial oxygen consumption, and many other factors.

Clinical Role of Imaging and Current Guidelines for Chronic Coronary Syndromes

Diagnostic testing is most useful and recommended when the likelihood of CCS is intermediate. According to current American and European clinical practice guidelines, patients with intermediate PTP of underlying CAD should undergo initial evaluation with non-invasive anatomical or functional diagnostic tests for the assessment of CAD (Figure 1).[3,5] Patients with very low PTP may not need evaluation (a positive test would be most likely false positive) and patients with high PTP may need direct coronary visualization with angiography (a negative test would most likely be false negative). The new and reconsidered PTP calculation, however, also permits anatomical or functional diagnostic testing in individual patients with a PTP of 5–15% if considered necessary in certain clinical situations.

A resting transthoracic echocardiogram (TTE) is recommended in all patients with a suspicion of CCS for assessment of wall motion and structural abnormalities.[3] The evidence of inducible myocardial ischemia or abnormal perfusion by functional imaging testing, coronary atherosclerosis by coronary CTA, or both, may allow the diagnosis of CAD requiring medical treatment. In cases of either failure of medical therapy to control symptoms or of imaging findings suggesting a high risk of coronary events, invasive coronary angiography (ICA) is indicated to address the possible need for revascularization.[3,5,6,16]

Thus, non-invasive functional imaging tests serve not only to diagnose the presence of CAD, but also to guide clinical decision-making, and are preferable in patients with high intermediate PTP. The documentation of ischemia involving more than 10% of left ventricular (LV) myocardium or in a multivessel pattern are relevant hallmarks of high risk,[3] as reducing ischemia may favorably impact symptoms and outcome.[17,18]

Coronary CTA is the preferred test in patients with the lowest intermediate range of clinical likelihood of CCS, no previous diagnosis of CAD, and characteristics associated with a high likelihood of good image quality, based on its high negative predictive value (the ability to exclude significant CAD).[3] Functional testing with imaging is preferred in patients with a higher likelihood of CCS, known CAD, high burden of calcified atherosclerosis on prior CT imaging, and in patients who are not ideal candidates for coronary CTA (Figure 1).

Coronary CTA may also be utilized in patients with chronic chest pain syndrome and equivocal findings with functional imaging. Conversely, functional testing with imaging may be performed in patients with intermediate stenoses on coronary CTA when the results of these tests may lead to changes in patient management (e.g. medical vs. revascularization strategy) (Figure 2).[11] Recently, evaluation of fractional flow reserve (FFR) by CTA has offered the potential to obtain anatomic and functional information from a single exam. Anatomic testing can be useful when a functional test is equivocal or uninterpretable, and vice versa.

Radiation risks associated with CT or nuclear imaging with contrast agents should be considered when choosing a specific exam and weighed against alternate procedures and the risk of missing a diagnosis.[19] All efforts are recommended to reduce imaging-related risks by using adequate protocols, proper technologies, and avoiding useless/redundant procedures.[19,20]

In about 20% of all patients with stable symptoms and evidence of ischemia, obstructive epicardial disease will be absent (ischemia and non-obstructive coronary artery disease, INOCA); thus, the apparent ischemia may be due to microvascular disease or non-cardiac causes. Whether the endothelium, the smooth muscle cells in the microvasculature or both are the culprits of such disease is unknown. Nevertheless, both are possibly associated with cardiovascular risk factors or structural myocardial abnormalities such as hypertrophy, dilatation, or a mix of them.[21-23] Recognition of these conditions by non-invasive imaging is relevant for risk stratification even if the clinical impact of pharmacological treatment is not yet defined[23,24] (Figure 3).

Clinical Role of Imaging and Current Guidelines for Acute Coronary Syndromes

Transthoracic echocardiography, using either fully equipped units or point-of-care ultrasound systems, should be available to all emergency rooms and should be performed and interpreted by trained expert operators, in all patients referred for chest pain, except in limited situations such as ST-elevation myocardial infarction (STEMI) where imaging would delay reperfusion.[4] Bedside echocardiography is beneficial when complications are suspected or when an alternative diagnosis is considered (Figure 4). Alternative diagnoses include aortic dissection, pericarditis with or without pericardial effusion, hypertrophic cardiomyopathy, mitral valve prolapse, or right ventricular (RV) dilatation that could be suggestive of acute pulmonary embolism (PE).

In patients presenting with acute chest pain syndromes, European guidelines and American appropriate use criteria recognize the value of coronary CTA or functional testing as an alternative to ICA to rule out ACS in patients at very low or low risk for ACS.[4] This includes patients with indeterminate electrocardiogram (ECG) changes, negative troponins, and no recent chest pain. Functional imaging in this situation has higher accuracy and is clearly favored over a stress ECG. This strategy is, however, not recommended in STEMI or NSTE-ACS with high-risk features, where prompt ICA should be pursued [primary percutaneous coronary intervention (PCI) for STEMI, within 24 h for NSTE-ACS].[4,5,25]

	Typical angina		Atypical angina		Non-Anginal		Dyspnea	
Age \ Sex	Men	Women	Men	Women	Men	Women	Men	Women
30-39	3%	5%	4%	3%	1%	1%	0%	3%
40-49	22%	10%	10%	6%	3%	2%	12%	3%
50-59	32%	13%	17%	6%	11%	3%	20%	9%
60-69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

Imaging test option: No test | CACS / CTA | Functional test | Invasive angiogram

Chest Pain to be evaluated by 3 characteristics:
1- location in the chest, epigastrium, neck, jaw, back, left shoulder or left arm.
2- Precipitated by exercise or stress
3- Relieved by resting or sublingual nitrates within 3-5 minutes

TYPICAL ANGINA: meets all 3 characteristics
ATYPICAL ANGINA: meets any 2 characteristics
NON-ANGINAL Chest Pain: meets only 1 or none of these characteristics.

Figure 1 Pre-test probability (PTP) of epicardial CAD (modified Diamond and Forrester) and value of imaging testing. This simple (age, sex, and symptoms) assessment of pre-test probability can be complemented with other data for an improved PTP estimation. Complementary data include traditional risk factors for atherosclerosis (family history of early CAD, dyslipidemia, smoking, diabetes, etc.) and other biomarkers such as Q or ST abnormalities in ECG, low EF, or WMA on resting imaging, etc. The value of each diagnostic approach in each box and its variance based on complementary data is reflected in the colors and their shades. Adapted from 2019 ESC guidelines.[3]

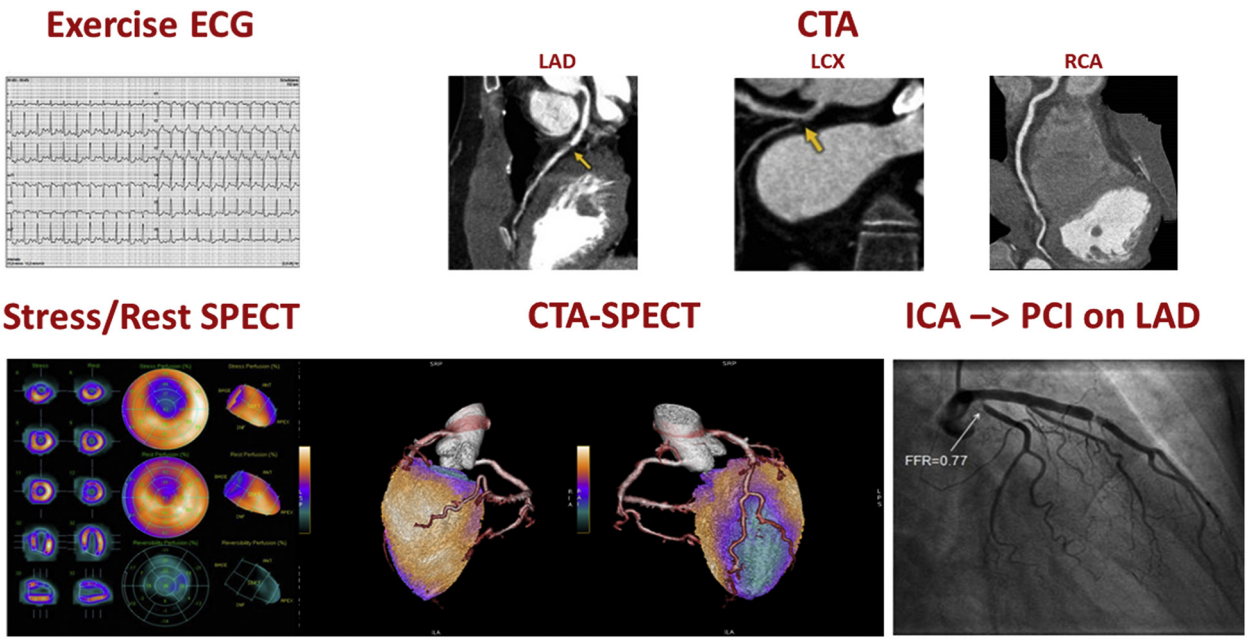

Figure 2 Chronic coronary syndrome. A 49 years old lady with family history of CAD, hypercholesterolemia, and recent onset of effort angina with non-diagnostic ST-segment depression (0.1 mV in the anterior leads) at maximal exercise ECG. Her PTP of obstructive CAD is 10% but the clinical likelihood is higher. She performed CTA as the initial test which allowed the diagnosis of obstructive CAD (LAD middle third and proximal LCX) without high-risk features. Stress SPECT was sequentially performed. CTA-SPECT images demonstrated a severe reversible perfusion defect (>10% LV myocardium) in the LAD territory with preserved perfusion in the LCX territory. These high-risk findings prompted invasive coronary angiography and revascularization (PCI and stenting) of LAD was decided.

OVERVIEW OF IMAGING METHODS IN CAD

Non-invasive imaging methods used to evaluate patients with known or suspected CAD rely on assessing: (i) presence and anatomic severity of stenosis, (ii) abnormal flow in epicardial arteries, (iii) abnormal myocardial perfusion, or (iv) abnormal myocardial contractility. LV regional assessment of perfusion or systolic function is important for the detection of CAD, characterizing the spatial distribution of ischemia (i.e. coronary territories involved), and for identifying patients who are at high risk for adverse events and may benefit from

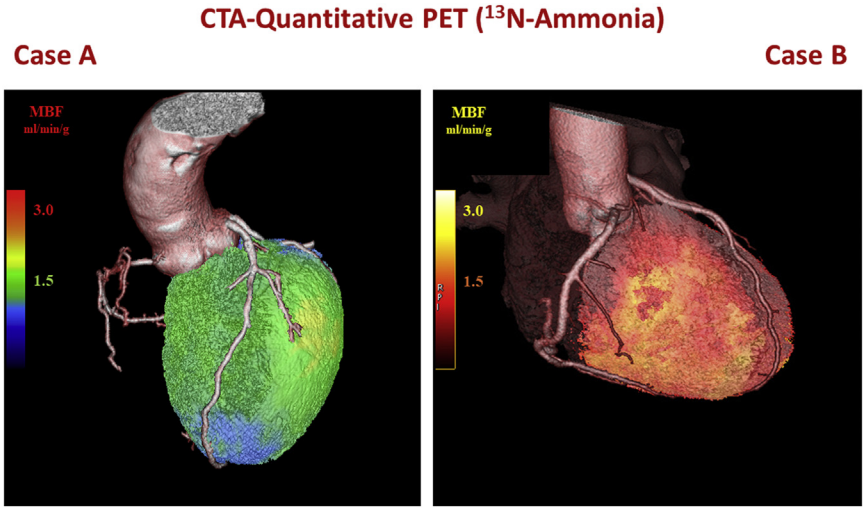

Figure 3 CTA-PET imaging. CTA-PET imaging in two patients with recent onset dyspnea. Case A is a 67 years old man with multiple risk factors, LBBB, systolic LV dysfunction (LVEF 30%), and diffuse non-obstructive CAD at CTA. Case B is a 60 years old man with glucose intolerance, mild hypertension, systolic LV dysfunction (LVEF 33%), and normal coronary arteries at CTA. In both cases, quantitative hyperemic (after i.v. dipyridamole) myocardial blood flow values with N-13 ammonia PET are globally reduced (normal values > 2 mL/min/g, please note different color codes have been used in these cases) (see also Ref.[21] Liga et al. and Ref.[24] Neglia et al.).

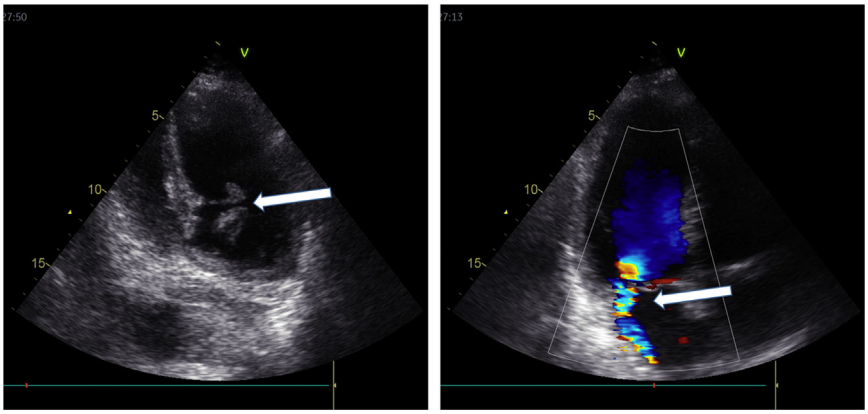

Figure 4 Echocardiography can quickly reveal complications in ACS. Large papillary muscle rupture after acute myocardial syndrome in a 69 years old male. Left panel is a modified apical four-chamber view and the ruptured papillary muscles are easily seen (*white arrow*). Right panel reveals the associated severe mitral regurgitation (*white arrow*).

revascularization. By convention, regional myocardial involvement is described using either a 16-segment model (the LV is divided into six segments at the base and mid-level, and four at the apex) or a 17-segment model (including the additional area of an 'apical cap'), which was added to standardize reporting among imaging modalities. A wall motion score can be derived by assigning each segment a numerical value (e.g. one for normal/hyperkinesis, two for hypokinesis, three for akinesis, four for dyskinesis, and five for aneurysm) and computing a mean value for all segments.[26-28] While standards for assigning each segment to a major coronary artery perfusion territory have been developed, there is considerable inter-subject variation in coronary artery anatomy. Correlation between methods is imperfect and therefore understanding the physiology and technical aspects of each methodology is of critical importance for optimal test performance and image interpretation.

Anatomical vs. Functional Imaging

Both anatomical and functional non-invasive imaging play important roles in the diagnosis and management of CAD. Non-invasive anatomical imaging is today almost exclusively performed using CT, while multiple functional tests are available including echocardiography, nuclear imaging, CMR, and dynamic CT. Recommendations for the use of anatomical and functional imaging in CAD are specific to clinical scenarios and local expertise. In the initial assessment of patients with suspected stable CAD, current European and American practice guidelines recommend either coronary CTA or functional imaging in patients with intermediate PTP, as outlined below.[3,12] These recommendations are supported by the results of the Scottish Computed Tomography of the HEART (SCOT-HEART) and Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trials, in which a strategy of initial coronary

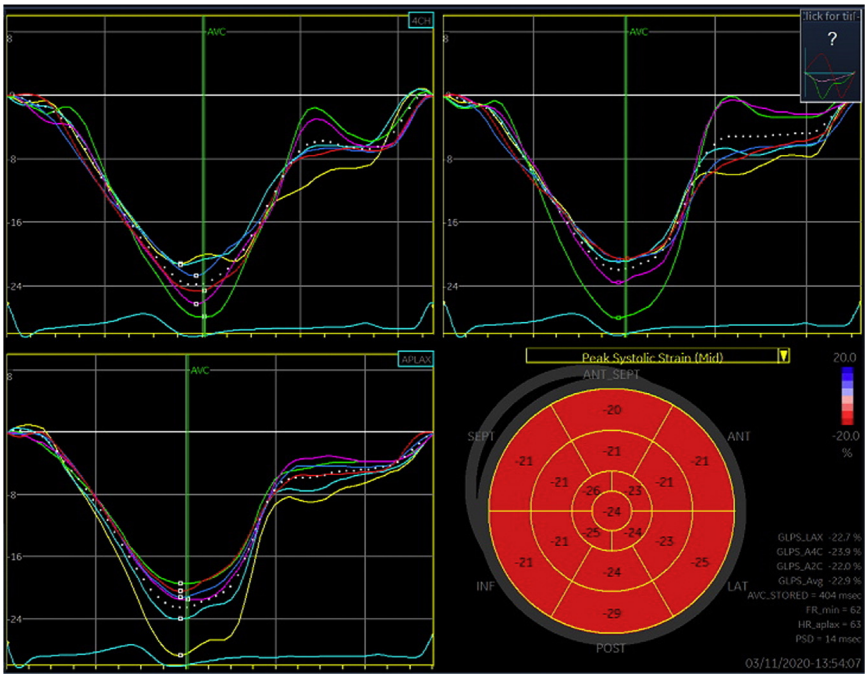

Figure 5 Global longitudinal strain. Normal global longitudinal strain (GLS) in a patient with chest pain. GLS = −22.9% and the bull-eye plot (lower right panel) is colored red, indication of normal LV function. The regional strain traces from six LV segment of the apical four-chamber (upper left), two-chamber (upper right), and long-axis (lower left) are shown.

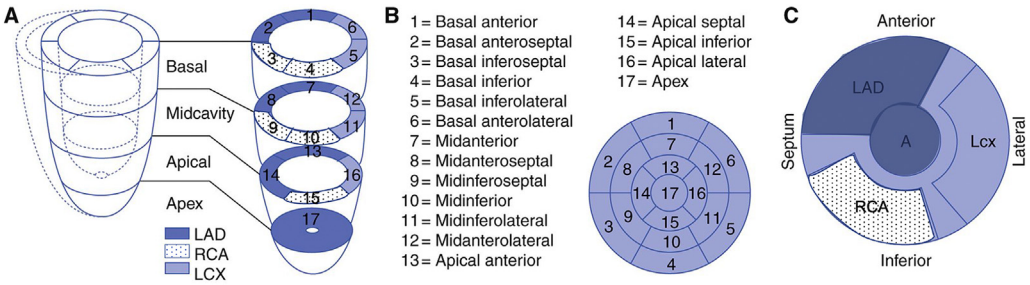

Figure 6 Left ventricular segmentation. The figure illustrates left ventricular segmentation according to the most common anatomical distribution of the coronary arteries (RCA dominance). The boundaries of such distribution varies from patient to patient. In cases of circumflex dominancy, most of the right coronary artery territory shown in this figure would correspond to the circumflex artery. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery. (Adapted from Dilsizian V. SPECT and PET Myocardial Perfusion Imaging: Tracers and Techniques. In Dilsizian V, Narula J, [eds]; Atlas of Nuclear Cardiology, edn 5, Philadelphia, Springer, Inc., 2021, pp 79-124).

CTA was generally shown to be equivalent to functional testing in patients with stable chest pain syndromes.[29-31]

Echocardiography

Echocardiography, both at rest and during stress induced by exercise or administration of an inotrope or vasodilator, is used to detect several aspects of CAD, including resting wall motion abnormalities (WMA), impaired contractile response, microvascular perfusion, or flow in the epicardial arteries. In addition, resting echocardiography is useful in the identification of other causes of chest pain, such as pericardial effusion, aortic dissection, PE, etc.

Echocardiography is most frequently used in patients with CAD to assess global and regional systolic function at rest or during stress. Global systolic function is commonly evaluated by measurement of the LV ejection fraction (LVEF), which can be quantified by two-dimensional (2D) or three-dimensional (3D) echocardiography. The recommended 2D method is the biplane method of disks (modified Simpson's rule). In patients with regional WMA, 3D assessment of LV volumes and ejection fraction (EF) is preferred as it is not dependent on geometric assumptions, and if image quality is good, is more accurate and reproducible. Compared to 2D, however, 3D echocardiography has a few limitations: lower temporal resolution, limited availability, and requirement of a higher level of expertise in echocardiography.[26,27,32] Because LVEF is entirely dependent on proportional volumetric change, it may not accurately reflect mechanical contractile function of the myocardium, particularly in situations where the LV chamber size is abnormally enlarged or reduced, or in increased wall thickness.

Strain echocardiography is more sensitive in detecting LV dysfunction than LVEF in a variety of myocardial diseases, including ischemia (Figures 5 and 16).[33-35] The subendocardial longitudinally oriented

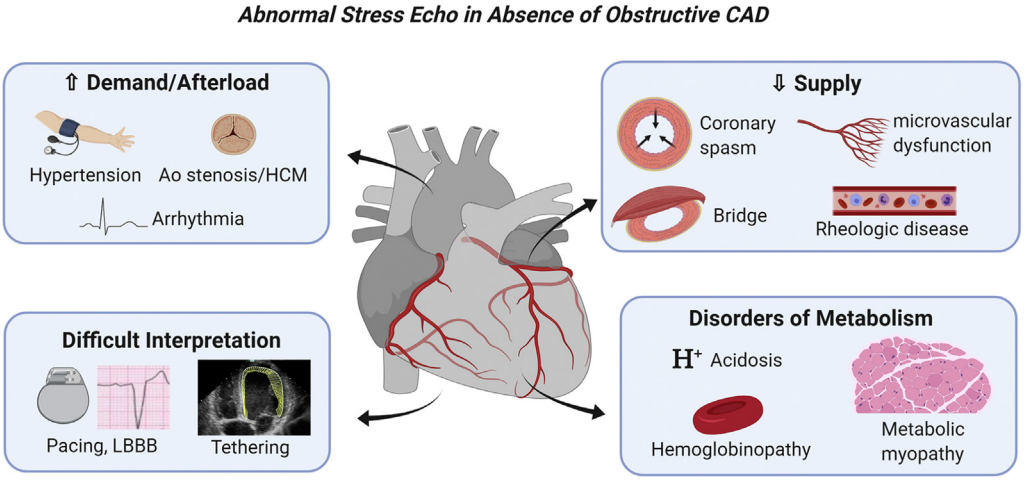

Figure 7 Wall motion abnormalities not related to CAD. Illustration of some of the potential causes, other than obstructive coronary artery disease, for development of wall motion abnormalities during exercise or inotropic stress. Categories are grouped according to pathobiology (increased demand, decreased supply, and metabolic derangements) or situations that make visual interpretation difficult.

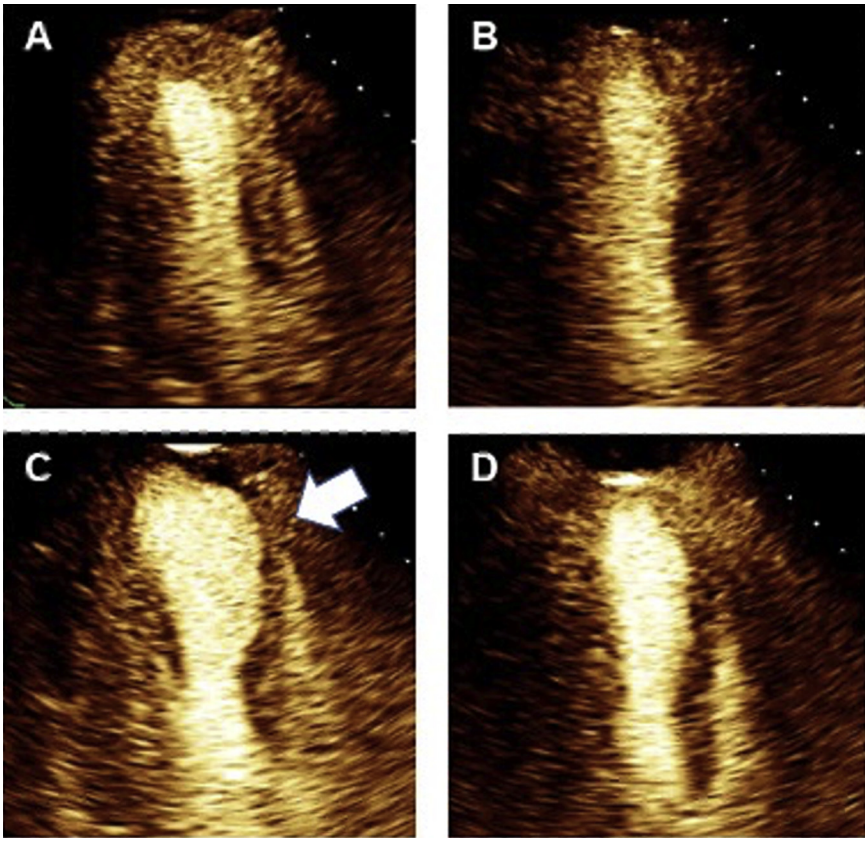

Figure 8 Contrast echocardiography. Contrast echocardiography in the apical three-chamber (long-axis) view during graded supine bicycle exercise stress echocardiography in a patient who required ultrasound-enhancing agents for left ventricular. End-systolic images are shown (**A**) at rest, (**B**) early in exercise, (**C**) at peak exercise, and (**D**) during recovery. At peak stress, the lack of endocardial excursion of the anteroseptal segments (*arrow*) can be appreciated.

muscle fibers are most vulnerable to ischemia, and assessment of global longitudinal strain (GLS) at rest has therefore shown superiority to wall motion analysis in ACS.[36] The speckle tracking technique is the method of choice for assessment of LV strain and is particularly useful in the acute setting when LVEF is normal or WMA are not visible.[37,38]

In addition to evaluating global LV function, regional systolic function should be assessed. Regional systolic function is most frequently

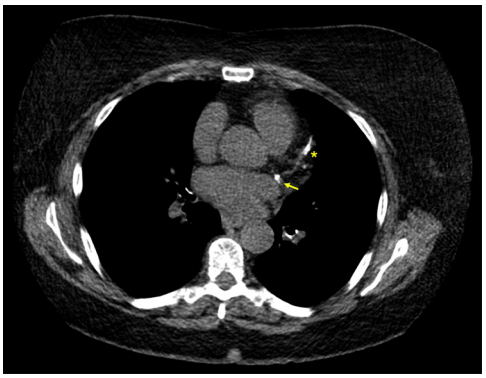

Figure 9 Coronary artery calcium scan. Non-contrast CT scan for coronary artery calcium detection and quantification demonstrating dense calcification in the proximal left circumflex (*arrow*) and mid left anterior descending (*) coronary arteries.

assessed by visual interpretation of wall thickening, although newer quantitative methods have also been applied and will be discussed below. Each myocardial segment can be analyzed separately and combined into a score according to its thickening. Importantly, the segments with WMA due to CAD should be contiguous and correspond with coronary territories (Figure 6). When evaluated by echocardiography, regional WMA must be detected visually in at least two echocardiographic views, as artefactual WMA could be the result of the angle of insonation. This is not necessary when wall motion is evaluated by other imaging modalities (CT, CMR, nuclear).[26,27] Of note, WMA during stress testing may be caused by a variety of other conditions not related to CAD (Figure 7).

Understanding flow-function relationships is key to the interpretation of wall thickening responses in ischemic disease. Under resting conditions, in the presence of severe coronary stenosis or collateral dependency, hypokinesis and even akinesis can occur with hypoperfusion of only the endocardial portion of the myocardium.[39] Akinesis or dyskinesis at rest may be due to transmural flow reduction[39,40] or previous myocardial infarction, even if not transmural.[41]

Regional contractile response to exercise or inotropic stress can be used to identify inducible myocardial ischemia. ACS (within 2 days for non-ST-segment elevation MI) and other contraindications such as uncontrolled arrhythmias, acute heart failure, and severe hypertension must be excluded before proceeding with stress echocardiography. The criteria for an abnormal response involve not only abnormal contraction but also failure of a segment to manifest an appropriate increase in contractility in response to stress. Patients who are able to exercise should undergo exercise stress testing since it represents a true physiologic response. Exercise stress provides additional prognostic information (compared to pharmacological stress) based on ECG results, exercise capacity, time to symptoms, and blood pressure response.[42] Pharmacological stress echocardiography is mostly reserved for patients who cannot exercise or for some specific clinical conditions such as baseline left bundle branch block.[28] These tests can be performed with inotropic agents such as dobutamine, which acts mostly by increasing myocardial oxygen demand, or vasodilators such as adenosine, regadenoson, or dipyridamole, which result in reduced hyperemic subendocardial flow in the presence of stenosis.[43] In addition to detection of CAD, stress echocardiography has a significant role in estimating patient risk and prognosis. This is based on quantification of the global ischemic burden using multiple scores: (i) the number of segments with an abnormal response; (ii) the percentage of myocardium with an abnormal response (>20%); (iii) the global myocardial ischemic severity (wall motion score index >1.4); (iv) abnormal response in multiple coronary territories; and (v) development of wall thickening abnormalities early during stress.[28] The use of more novel echocardiographic techniques (speckle-tracking strain, velocity vector, 3D, tissue Doppler) for stress testing in patients with known or suspected CAD require further validation.

It is important to note that all approaches for evaluating systolic function, including strain imaging, are influenced by loading conditions.

The use of approved ultrasound enhancing agents (UEAs, a.k.a. ultrasound contrast, or microbubbles) is recommended when two or more contiguous segments cannot be adequately visualized at rest or are likely to not be adequately visualized during stress[44] (Figure 8). The use of UEA for assessment of myocardial perfusion has not yet been approved by the US Food and Drug Administration (FDA) or other regulatory agencies by the time of publication of this document. A full review of the principles of myocardial contrast echocardiography perfusion imaging is available in recently published guidelines on the use of UEA.[44,45] The technology requires special expertise and training for both image acquisition and interpretation.

Finally, direct echocardiographic evaluation of epicardial arterial flow may be possible with Doppler ultrasound.[46] In general, the arterial flow is detected by color Doppler in typical locations of the coronary arteries in the interventricular or atrioventricular grooves. Unfortunately, only large primary vessels can be reliably imaged, and difficulty in imaging all three major coronary arteries is a significant limitation, preventing the wide clinical use of this technique.

Computed Tomography

ECG-gated cardiac CT imaging techniques provide an accurate assessment of CAD severity and future cardiovascular risk in asymptomatic and symptomatic patients.

Calcium is part of the reparative process of the body, is incorporated in most plaques, and therefore is a marker of atherosclerosis, although not obstruction. Cardiac CT for the detection and quantification of coronary artery calcium (CAC) scoring is performed as a rapidly acquired non-contrast CT study of the heart (Figure 9). Calcium scans do not require patient preparation, nitroglycerine, iodinated contrast, beta blockers, or fasting. Scans are performed using prospective ECG triggering and 2.5–3.0 mm slice thickness and should be performed at a low patient-effective radiation dose of approximately 1 millisievert (mSv), with high-pitch helical acquisition-achieving doses of <0.5 mSv.[47] The most common and prognostically robust method for quantifying CAC, a proven measure of overall coronary atherosclerosis burden, is via the Agatston score where the area of calcified atherosclerosis is multiplied by a density weighting factor (higher if increased density) for each slice and summed across the entire coronary arterial tree. Other methods of quantifying CAC, such as volume or mass scores, may have higher reproducibility for assessing CAC progression across serial scans but have not been proven to predict patient outcomes. Clinically, CAC scoring has been consistently shown to be excellent for long-term (>10 years) risk prediction of adverse events in asymptomatic individuals, and to have an additive value to traditional cardiovascular risk factors and risk scores.[47-49] CAC scoring is generally reserved for asymptomatic patients at intermediate 10-year risk (5–20%) for atherosclerotic cardiovascular disease events and may guide in the decision to prescribe preventive medications, such as statins.[50,51]

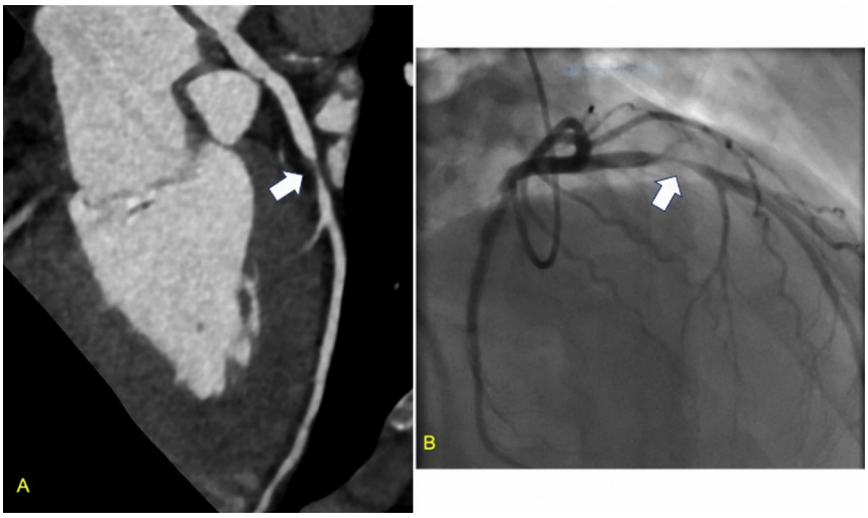

Figure 10 Coronary CT angiography. Curved multiplanar reformatted image of the left anterior descending (**A**) demonstrating a severe mid-vessel stenosis (*arrows*) that corresponded to severe stenosis on invasive coronary angiography (**B**).

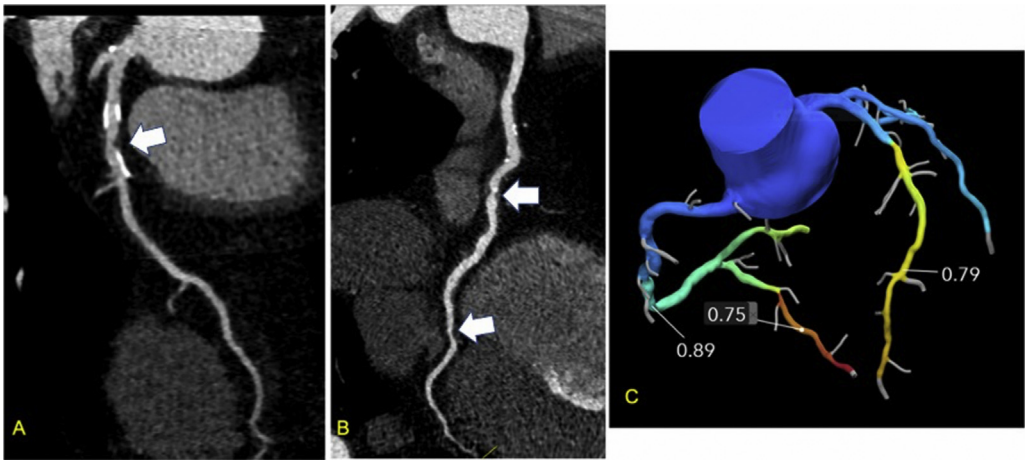

Figure 11 Cardiac CT-derived fraction flow reserve. Curved multiplanar reformatted images of the left anterior descending (**A**) and right coronary arteries (**B**) demonstrating multiple areas of moderate stenosis and diffuse plaque (*arrows*) that corresponded to decreased CT-FFR values (**C**). A CT-FFR value ≥0.80 is considered normal.

Coronary CTA is performed using modern (≥64 slice) ECG-gated/triggered multi-detector CT scans whereby high-resolution, isotropic images of the coronary arteries are obtained following the administration of iodinated contrast. Most coronary CTA scans are performed using prospective ECG triggering at radiation doses typically below 6 mSv.[52] Doses may be further reduced using low tube potential (<100 kVp) and high-pitch helical acquisition, when appropriate, and consequent heart rate lowering. Image quality is significantly improved with the administration of sublingual nitroglycerine (0.4–0.8 μg), producing coronary dilation, and oral and intravenous beta-blocking agents to reduce heart rate, ideally to around 60–65 beats per minute. Scans should be performed in accordance with Society of Cardiovascular Computed Tomography guidelines in order to achieve high image quality at the lowest possible patient radiation and contrast dose.[47] Patients with highly irregular heart rhythms or inability to achieve adequate heart rate control according to local scanner technology, with known CAD, or who are unable to safely undergo contrast or nitroglycerine exposure are not ideal candidates for coronary CTA.

In symptomatic patients, coronary CTA provides a unique, direct 3D visualization of the coronary arteries, allowing assessment of the presence, extent, and severity of luminal stenosis. Stenosis is typically assessed as minimal (<25%), mild (25–49%), moderate (50–69%), severe (70–99%), and occluded (100%) in arteries of at least 1.5 mm in diameter (Figure 10).[53] Arteries smaller than 1.5 mm in diameter are often difficult to visualize on coronary CTA. Studies have demonstrated that absence of stenosis >50% on coronary CTA has 97% and 93% sensitivity for excluding stenosis >50% with ICA and invasive FFR <0.80, respectively.[3] While stenosis severity <50% with coronary CTA has high sensitivity for excluding significant CAD, CTA has only modest specificity of 53% for predicting lesions shown to result in invasive FFR <0.80.

FFR can be estimated from static coronary CTA datasets using computational fluid dynamic or machine learning techniques

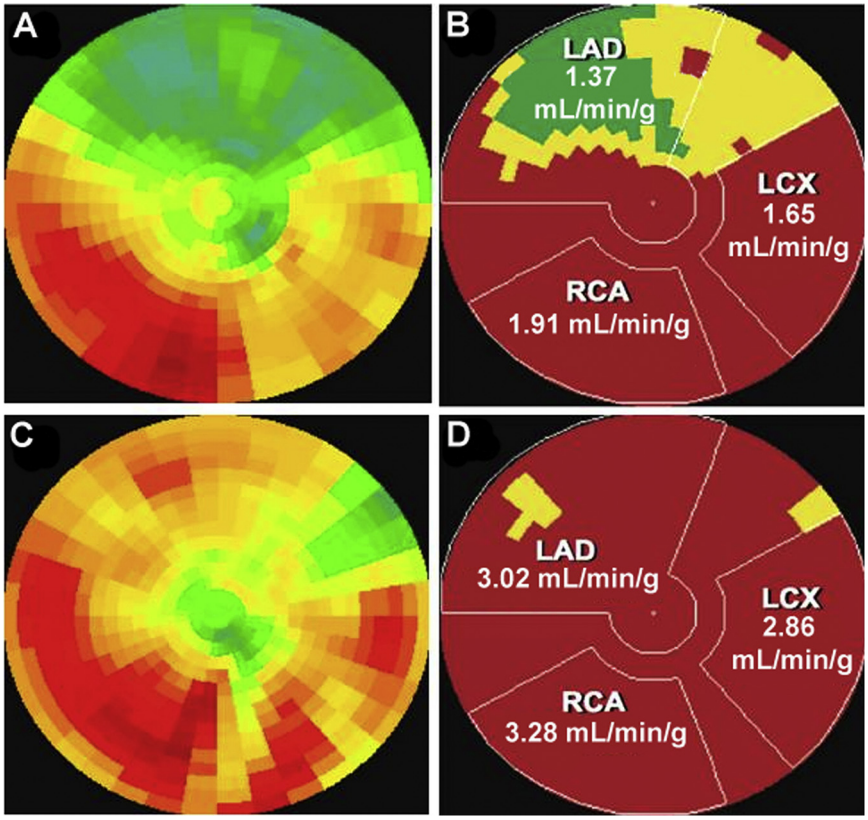

Figure 12 Adenosine-stimulated hyperemia after 1-year treatment with pravastatin. When compared with baseline quantitative hyperemic myocardial blood flow values with N-13 ammonia PET (**A** and **B**), follow-up polar maps show significant improvement in hyperemic myocardial blood flow in all three coronary artery vascular territories (**C** and **D**). The extent of the stress-induced defect decreased from 51% of the left anterior descending (LAD) vascular territory to only 3% 1-year post-medical therapy. (Adapted from Schindler TH, Schelbert HR. Quantitation of myocardial perfusion: Absolute blood flow versus relative uptake. In: Dilsizian V, Narula J, (eds); Atlas of Nuclear Cardiology, edn 4, Philadelphia, Current Medicine-Springer, Inc., 2013:145–194.)

(Figure 11) and is of highest value on patients with higher PTP of CAD. Such CT-derived FFR has been shown in several clinical trials to improve the specificity and accuracy of coronary CTA, especially when assessing intermediate stenosis, and may improve decision-making when selecting patients who are most likely to benefit from ICA and revascularization.[54-56] Myocardial perfusion with CT performed at rest and during vasodilator stress is a novel promising technique that is not currently widely utilized in the clinical setting and does require additional contrast and radiation beyond the baseline coronary CTA study.

SPECT and PET Nuclear Imaging

Both SPECT and PET technologies use similar reconstruction processes to obtain tomographic images of the heart but they differ in the type of radiopharmaceuticals and the kind of instrumentation used to acquire the images. SPECT myocardial perfusion imaging is the most commonly performed nuclear cardiac imaging procedure. After the injection of a myocardial perfusion radiotracer (technetium-99m labelled tracers), the isotope is extracted from the blood by viable myocytes and retained within the cells for a time that is dependent on the dynamics of the radiotracer and the physiological conditions of the tissue. This timing mandates the optimal moment for acquisition of the gamma ray photons, which are emitted from the myocardium in proportion to the magnitude of myocardial tracer uptake, therefore reflecting regional myocardial perfusion. The final result of SPECT imaging is the creation of multiple tomograms of the heart in three conventional projections (short-axis, vertical long-axis, and horizontal long-axis) or a polar map, digital displays that represent radiotracer distribution throughout the heart and also allows evaluation of LVEF.[57]

PET allows non-invasive quantification of regional myocardial blood flow (MBF) and metabolism using physiologic substrates prepared with positron-emitting isotopes.[58] Scanners that combine PETor SPECT technology with radiographic CT provide a tool for obtaining complementary anatomic and functional information that are spatially aligned and can be acquired during a single imaging session. Hybrid scanners might also document impairment of myocardial perfusion not directly related to obstructive CAD that may have prognostic relevance[23,24] and may indicate the need for specific treatment. In addition, quantitative assessment of absolute MBF as provided by PET and SPECT adds diagnostic and prognostic value in the assessment of CAD[59,60] (Figure 12).

All contemporary camera-computer systems have fully automated software capable of obtaining highly reproducible values of LVEF. Radionuclide ventriculography, also known as gated blood pool imaging, may be performed using first-pass or equilibrium-gated techniques. The latter is often referred to as multiple-gated acquisition scanning. For labelling of the blood pool, Tc-99m is bound to red blood cells or albumin. While both first-pass and equilibrium-gated techniques provide a highly reproducible means to quantifying both

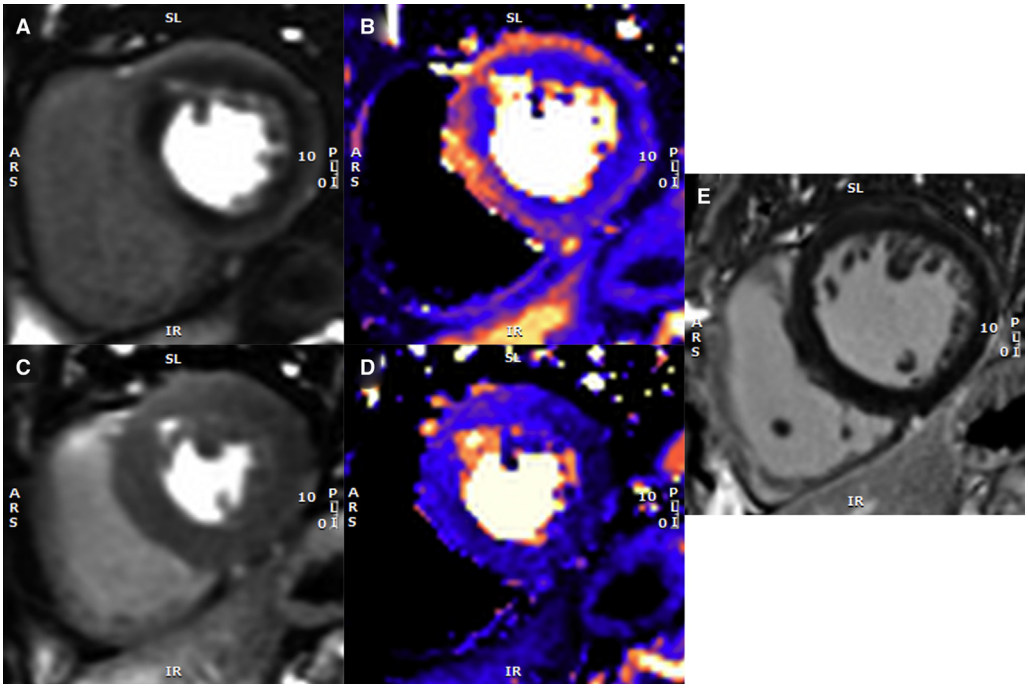

Figure 13 Cardiovascular magnetic resonance imaging in chronic coronary syndrome. Patient presenting with stable exertional angina. **(A)** Adenosine stress perfusion imaging demonstrates subendocardial perfusion defects in all three coronary territories. A still image at peak contrast uptake in the mid-ventricular slice is shown. **(B)** Quantitative perfusion map shows reduced myocardial blood flow (blue color) in the subendocardial anterior and antero-septal segments and transmurally in the inferior and lateral wall. **(C)** Corresponding myocardial perfusion imaging at rest shows homogenous contrast distribution. **(D)** Myocardial perfusion map shows homogenous myocardial blood flow in all segments. **(E)** Late gadolinium enhanced images show no evidence of myocardial infarction and all coronary territories are viable. Cine images (not shown) showed normal contraction in all segments. Invasive coronary angiography showed severe three vessel coronary artery disease.

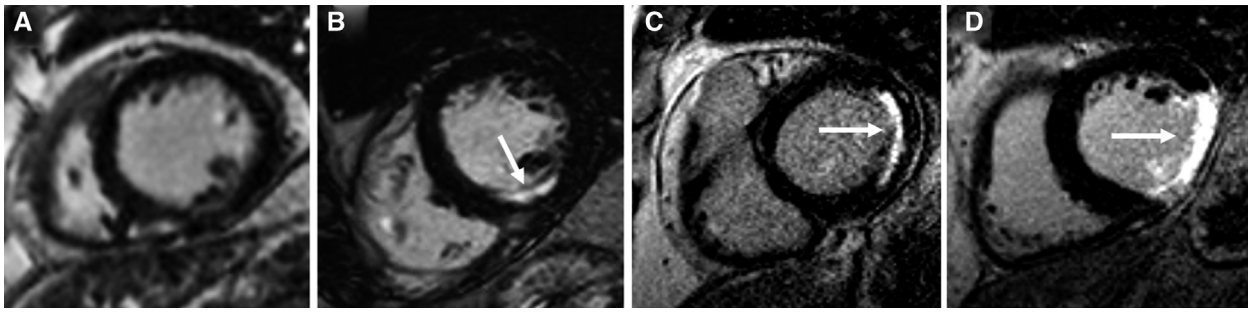

Figure 14 Cardiovascular magnetic resonance imaging assessment of myocardial viability and infarction using late gadolinium enhancement (LGE). **(A)** LGE image in a mid short-axis location showing homogenous signal in all segments with no evidence of myocardial infarction. **(B)** LGE image in short-axis orientation showing subendocardial infarction (25–50% transmural extent) in the inferior wall. **(C)** LGE image in short-axis orientation showing myocardial infarction involving 50–75% of wall thickness in the lateral wall. **(D)** LGE image in short-axis orientation showing transmural infarction in the lateral wall (*white arrow*).

left and RV EFs, in contemporary practice, the equilibrium technique is performed far more commonly.

SPECT imaging with 99mTc-labelled radiotracers (sestamibi and tetrofosmin) provides information on myocardial perfusion and to some extent, cellular viability. The uptake and retention of the tracers is dependent on regional blood flow and mitochondrial membrane integrity, thus areas with reversible defects from stress to rest indicate inducible ischemia while areas with persistent lack of uptake indicate non-viable myocardium. Stress-redistribution-reinjection or rest-redistribution thallium-201 protocols or modified stress-rest 99mTc-labelled myocardial perfusion radiotracer protocols are used to optimize myocardial viability detection.[61] PET perfusion imaging with the generator-produced rubidium-82, the cyclotron-produced N-13 ammonia, O-18 water, or more recently F-18 flurpiridaz, provides more accurate information regarding MBF.[24,62,63]

Cardiovascular Magnetic Resonance

CMR imaging offers a wide range of methods to evaluate patients with known or suspected CAD, including assessment of global and regional ventricular function, myocardial perfusion, scar, and viability.

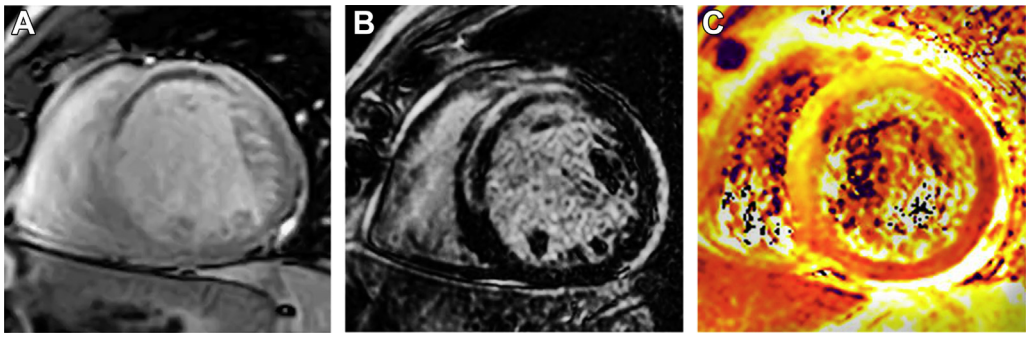

Figure 15 Cardiovascular magnetic resonance imaging in acute myocardial infarction. Male patient over 12 h after onset of chest pain with ST-elevation myocardial infarction. Cine CMR imaging after contrast administration (only mid slice of a whole heart short-axis stack shown) shows low signal in the subendocardial portion of the anterior and antero-septal segments—suggesting microvascular obstruction. **(B)** Late gadolinium enhanced images in corresponding short-axis orientation at mid ventricular level shows near-transmural contrast enhancement in the anterior and antero-septal segments with low signal in the subendocardial portion. This finding suggests microvascular obstruction. **(C)** T2 mapping in corresponding short-axis orientation shows high signal in the anterior and antero-septal segments consistent with myocardial edema.

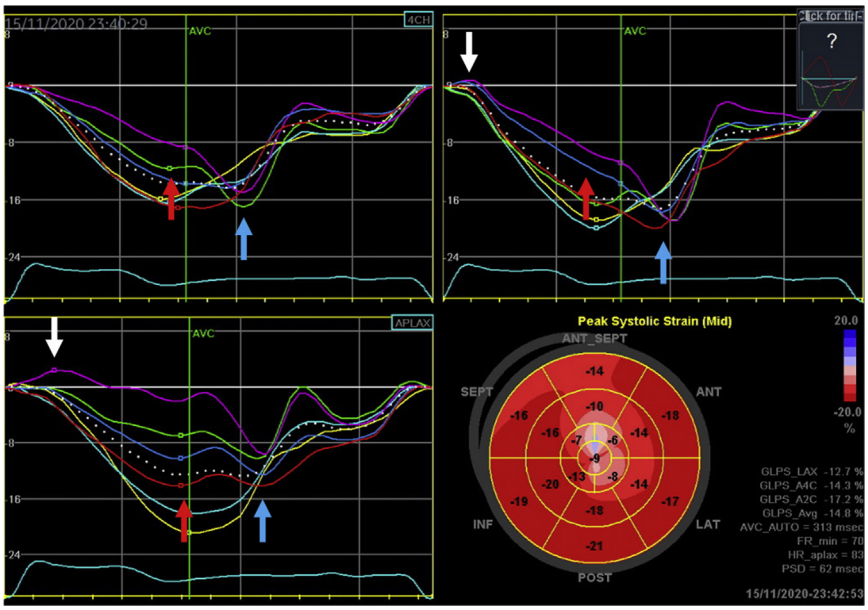

Figure 16 Strain in a patient with LAD infarct. Typical strain patterns in acute myocardial ischemia are early systolic lengthening (*white arrows*), reduced systolic strain (*red arrows*), and post-systolic shortening (*blue arrows*). The bull-eye plot contains areas with lighter colors which indicate LV segments with decreased function.

However, its value for evaluation of coronary anatomy is limited to the proximal segments or to detect anomalous origins and therefore there is no current clinical indication for coronary CMR in the assessment of chest pain. Standardized acquisition and post-processing protocols have been proposed for CMR assessment of function, ischemia, and viability.[64] A typical CMR examination for the assessment of stable and acute CAD combines several of these methods into a single imaging session. Volumetric measurement by CMR is based on cine imaging using balanced steady-state free precession acquisition, which provides high spatial and temporal resolution and high intrinsic endocardial-to-blood-pool contrast. Because data are conventionally averaged over several cardiac cycles to optimize resolution and signal, image quality may be impaired in patients unable to breath hold or with irregular heart rhythm. In these patients, ultra-fast 'real-time' cine imaging can provide good image quality. Cine datasets are typically acquired in a contiguous stack of sections in the LV short-axis plane, covering the entire heart. These datasets allow volumetric analysis free of geometric assumptions about the shape of both the left ventricle and the right ventricle. In the context of CAD, cine imaging is used to determine resting regional and global ventricular function, wall thickness, and LV mass, which provide high levels of reproducibility.[65] In clinical practice, interpretation of WMA is typically by visual estimation using the same hierarchical scoring system and 16- or 17-segment model as other non-invasive imaging tests. Wall thickening can also be quantified using post-processing tools that allow manual or semi-automated tracing of the endocardial and epicardial borders. While quantitative analysis of strain and strain rate can be performed using myocardial tagging or feature-tracking methods, the relatively low frame rate limits its clinical value.[66] In addition, cine imaging allows the detection of some CAD-related valve pathologies, such as functional mitral regurgitation due to tethering from myocardial infarction.

Akin to stress echocardiography, cine CMR can be performed during inotropic stimulation with dobutamine to determine both functional reserve and the presence of inducible ischemia.[67] An advantage of CMR is that imaging planes are highly reproducible and image quality and endocardial border definition are consistently high. A limitation of CMR compared with echocardiography is that patient monitoring is more challenging in an MRI scanner, exercise stress is generally not feasible, and the ECG cannot be used to detect ischemia.

The most commonly used CMR approach to ischemia imaging is evaluation of myocardial perfusion[68] (Figure 13). In this method, a dynamic series of images is acquired following the intravenous injection of a gadolinium-based contrast agent. For ischemia detection, hyperemia is induced using adenosine, dipyridamole, or regadenoson and imaging is performed at maximal hyperemia. Typically, the pulse sequences used for myocardial perfusion CMR cover the heart in at least three LV short-axis slices (base, mid, and apex), with modern acquisition methods allowing the acquisition of additional sections or even 3D whole heart acquisition. The in-plane spatial resolution of the acquired images is typically better than 3×3 mm, allowing the confident detection of subendocardial perfusion defects. Resting perfusion may be added to the protocol, assisting to distinguish artifacts, such as the endocardial dark rim, from true perfusion defects. Clinical perfusion studies are evaluated visually for areas with relative reduction or delay in the myocardial contrast passage. Quantitative MBF (in mL/min/g) can be calculated using kinetic models, with recent methods providing automated in-line quantification of blood flow.[69]

Myocardial infarction is most commonly detected by CMR with the late gadolinium enhancement (LGE) method (Figure 14). LGE images are acquired >10 min following the injection of a gadolinium-based contrast agent using pulse sequences that are designed to maximize the signal difference between tissues with distinct T1 recovery times.[70] Images are typically acquired in a contiguous short-axis stack and multiple long-axis planes using the same orientations as cine images to allow direct correlation of function and morphology. Because gadolinium-based contrast agents are exclusively extracellular, they have a relatively low volume of distribution in normal myocardium, resulting in a longer T1. Myocardial regions containing chronic collagen scar or ruptured membranes from acute necrosis have a higher contrast distribution volume and slower contrast washout than normal myocardium, and consequently a shortened T1. Conventionally, infarcted tissue on LGE imaging appears bright and is mostly subendocardial, while normal myocardium is dark. Careful selection of the inversion time is critical to ensure good image contrast and avoidance of over-reporting of scar or fibrosis. The high spatial resolution of LGE images allows the detection of small infarcts that may go undetected with other imaging modalities. The transmural extent and overall scar size can be precisely measured from LGE images covering the whole heart and are of high diagnostic and prognostic relevance (Figure 15). It is important to acknowledge that the region of LGE in the acute phase contains a combination of scar and edema or inflammation, and the size decreases over several months after ACS.[71,72] LGE, as well as images acquired early after contrast administration, are useful in detecting thrombus and microvascular obstruction in acute infarction. T1 mapping before and after contrast administration allows estimation of the myocardial extracellular volume fraction, as a quantitative marker of fibrosis and scar. T2 mapping provides a quantitative assessment of myocardial edema, which is increased in the setting of acute myocardial injury.

Although CMR is no longer contraindicated in patients with most modern implantable cardiac devices, image quality may be reduced due to device- and lead-related artifacts.

DIAGNOSIS OF ACUTE CORONARY SYNDROMES AND THE ROLE OF IMAGING

The role of imaging in ACS is to confirm diagnosis of a condition that is otherwise inconclusive and to evaluate LV function. Whenever an urgent or emergent cardiac catheterization is indicated, performing non-invasive imaging tests should not delay the performance of ICA. Indications for such catheterization are beyond the scope of the current document.

Left Ventricular Function Assessment

In patients with suspected NSTE-ACS and non-specific ECG changes, the addition of non-invasive imaging modalities to clinical examination and blood biomarkers can help in establishing the diagnosis by detecting regional or global WMA. The detection of WMA by TTE in ACS patients can be useful, but the presence of regional contractile abnormalities may be either chronic or acute, and this is best resolved if prior studies are available for direct comparison. A regional contractile abnormality is highly suspicious of ACS. Sensitivity is best when TTE is performed during active symptoms, but diminishes rapidly after chest pain resolution. Contrast echocardiography should be considered when visual assessment of the left ventricle is non-diagnostic (two or more contiguous segments not visualized) or for myocardial perfusion abnormalities in patients with suspected ACS but without WMA.[73,74] Assessment of myocardial strain can be of value when visual assessment for LV dysfunction is indeterminate. Typical changes in the strain curves during acute ischemia are early systolic lengthening, reduced systolic strain, and post-systolic shortening (Figure 16).[36,75-77]

In patients with suspected NSTE-ACS without ischemic changes on the ECG, no signs of WMA during a resting echocardiogram, and normal troponins, myocardial ischemia could be evaluated by means of a functional imaging test. Importantly, the use of imaging in functional testing in this scenario has significant clinical value compared to the stress ECG in assessing CAD and subsequent revascularizations, resulting in a more cost-effective strategy.[78,79]

An urgent TTE should always be performed in hemodynamically unstable patients to rule out complications of acute MI such as LV or RV systolic dysfunction, acute mitral regurgitation, myocardial rupture, or cardiac tamponade (Figure 4). Transesophageal echocardiography (TOE) should be considered as an alternative only if TTE is not feasible or inconclusive or if aortic dissection is suspected.

CMR is an alternative test for assessment of LV/RV function, usually in combination with at least LGE for infarct detection, when echocardiography is inconclusive, if the patient's clinical condition allows the test to be performed.

Key Points

1. Performing non-invasive imaging tests in ACS should never delay ICA if the latter is clinically indicated.
2. The presence of a new regional contractile abnormality, or one of unknown duration, is highly suggestive of ACS.
3. Use of myocardial strain at rest can be valuable when visual assessment of LV function is uncertain.

4. An ultrasound-enhancing agent is indicated when visual assessment of LV function is uncertain.
5. An urgent TTE should be performed in hemodynamically unstable patients with suspected or confirmed ACS, to evaluate LV/RV function, mechanical complications, or pericardial effusion/tamponade.
6. CMR is an alternative test for assessment of LV/RV function if echocardiography is inconclusive and the patient is stable.

Myocardial Perfusion Imaging

In suspected ACS, resting myocardial perfusion imaging may show a lack of coronary blood flow even without regional wall motion abnormality, but this is quite rare.[73,80] Hypoperfusion at rest (as opposed to during stress) almost always causes a WMA. Contrast echocardiography permits real-time bedside evaluation of myocardial perfusion as well as contractile function following intravenous injection of a UEA. Ischemia is identified by a delay in the replenishment of UEA after a high-energy destructive pulse. Identifying the absence of a perfusion defect in conjunction with normal ventricular function virtually excludes ongoing acute ischemia in a symptomatic patient evaluated for acute chest pain.[73] Conversely, finding a defect in a patient without a history of prior MI supports the diagnosis of ACS.

Stress TTE and MPI studies have shown that early testing in the emergency department (ED) or in an outpatient setting are both safe and diagnostic in acute chest pain patients who do not have recurrent ischemic symptoms, remain hemodynamically stable, and had a negative initial evaluation with biomarkers and ECG. Stress TTE offers the advantage that LV function and assessments for other causes of cardiac symptoms can be evaluated at the time of baseline imaging (Supplementary data online, Movie S1). In randomized controlled trials, compared to standard care, both stress modalities have been shown to be cost-effective and to reduce unnecessary admissions without compromising appropriate admissions.[81] For these reasons, functional testing by any of these modalities might be used also in the chest pain unit or ED, if troponin or/and other parameters fail to establish the diagnosis.

Myocardial perfusion CMR is able to detect perfusion defects with limited evidence in low-risk, hemodynamically stable ACS patients.[82,83] Evidence of microvascular obstruction by CMR has been shown to have incremental prognostic value over evaluation of LV function (Figure 15).

Key Points

1. Myocardial perfusion imaging may show reduction or loss of myocardial perfusion, most often combined with regional wall motion abnormality, in patients with ACS due to obstructive CAD.
2. Stress modalities are cost-effective and may reduce unnecessary admissions.

Coronary Artery Anatomy

Coronary CTA in patients with suspected NSTE-ACS has demonstrated high diagnostic accuracy and efficiency to rule out obstructive CAD and thus allow for safe and early patient discharge from the ED. It can be performed quickly and safely (with minimal radiation and iodinated contrast) and interpreted rapidly (less than 20 min). Coronary CTA can be used to exclude CAD and the need for ICA in patients with unclear NSTE-ACS.[84] Additionally, coronary CTA may be useful in patients with equivocal elevations in troponin that are not clearly due to ACS.[85,86] CTA in patients with known prior CAD might be less useful in patients with prior stents.

A normal CTA might facilitate early discharge from the ED. On the other hand, coronary CTA may be associated with increased downstream testing and revascularization procedures (Figure 10). It is often difficult to differentiate bystander from culprit coronary disease. The choice of coronary CTA vs. stress testing will mostly depend on local availability and expertise. In a meta-analysis that compared the diagnostic accuracy of coronary CTA, stress echocardiography, and MPI for the assessment of chest pain in the ED, there were no significant differences between all these modalities in terms of their negative predictive accuracy for short-term cardiac events.[87] The utilization of CT-derived FFR in patients with possible ACS has been shown to result in the safe deferral of ICA in a large prospective observational study and may further enhance the diagnostic accuracy of coronary CTA.[88] The clinical utility of non-contrast CT in the ED is limited.[89]

Key Points

1. Coronary CTA in patients with suspected ACS has demonstrated high diagnostic accuracy and efficiency to rule out obstructive CAD.
2. Coronary CTA might result in a shorter length of stay in the ED.

Myocardial Scar and Edema Assessment

In patients presenting with acute chest pain of uncertain etiology and unrevealing initial diagnostic workup (TTE, coronary CTA), non-invasive imaging of edema (and scar in subacute cases) can be used to confirm ACS vs. other causes of chest pain and elevated troponin such as myocarditis or stress-induced (takotsubo) cardiomyopathy. Imaging might also guide identification of culprit vessels in patients with established ACS, but with uncertainty on which vessel to revascularize. The high resolution of LGE CMR enables detection of micro-infarctions involving as little as 1 g of myocardial tissue and is more sensitive for the detection of subendocardial infarcts than is SPECT.[90] Edema by CMR can be detected with T2-weighted imaging or parametric mapping, and can also often be seen on standard steady-state free precession cine images, in which signal is determined by the T2/T1 ratio of tissues. In clinical practice, edema by CMR contributes to the detection of ACS and allows identification of the culprit artery in patients with multi-vessel disease. It is important to remember that in ACS the edema and/or scar should reflect the coronary territories and is usually transmural or subendocardial in CAD. Myocardial edema and mid-myocardial or epicardial LGE are indicative of acute myocarditis.

Key points

1. Myocardial edema is an early manifestation of myocardial damage that can be evaluated with edema-sensitive CMR methods.
2. LGE CMR detects infarction and edema in ACS and can contribute to the diagnosis of other causes of acute chest pain.

Differential Diagnosis in Acute Chest Pain

The main goal of the initial diagnostic evaluation is to confirm or exclude the most frequent life-threatening conditions, namely ACS, acute aortic syndromes (AAS), and acute PE. Although the vast majority of patients with acute chest pain are not critically ill, the diagnostic process can be challenging and imaging can be of great help. Possible differential diagnoses are many and comprise both ischemic and non-ischaemic cardiovascular causes (Table 1), as well as a multitude of non-cardiac conditions. All cardiac imaging tests can aid in the

Table 1 Frequent cardiac or cardiac-like causes of acute chest pain that can be evaluated by non-invasive imaging modalities during routine diagnostic work-up*

	TTE	TEE/TOE†	Nuclear	CMR	CT	Other techniques‡
Acute coronary syndrome	• RWMA • Mechanical complications	Mechanical complications	Perfusion defects	• RWMA • Myocardial edema	• Coronary anatomy • Culprit lesion	FoCUS
Acute aortic syndrome	• Intimal flap • Aortic dilatation • Acute AI	Intimal flap		Intimal flap	Intimal flap	
Acute pulmonary embolism	• Increased TR velocity • Right heart dilation • PA dilation • Right heart thrombi	Central thrombi in the main pulmonary artery and/or its branches	Lung V-Q scan: multiple, pleural-based segmental Perfusion defects		Thrombi in pulmonary artery tree	FoCUS
Acute pericarditis	• Pericardial effusion • Tamponade	Pericardial effusion Tamponade		• Pericardial effusion • Pericardial LGE	Pericardial effusion	• Chest X-ray • FoCUS
Acute myocarditis	• RWMA • Global hypocontractility			Myocardial edema • RWMA • Global hypocontrac-tility	Normal coronary anatomy	FoCUS
Pneumothorax						• Chest X-Ray • Lung US
Chest trauma	RWMA, acute valve insufficiency, pericardial /pleural effusion, signs of AAS	Signs of AAS		Signs of AAS	Signs of AAS	• Chest X-ray • Lung US • FoCUS
Aortic stenosis	Thickened leaflets/ gradient				Thickened leaflets	
Hypertrophic cardiomyopathy	• Myocardial hypertrophy • SAM		Perfusion defects	• Myocardial hypertrophy • SAM • Scar		
Takotsubo cardiomyopathy	• Apical ballooning • Various RWMA			• Apical ballooning • Various RWMA • Myocardial edema		Contrast left ventriculography

AAS, acute aortic syndrome; *AI*, aortic insufficiency; *CMR*, cardiac magnetic resonance; *CT*, computed tomography; *FoCUS*, focused cardiac ultrasound; *RWMA*, regional wall motion abnormalities; *SAM*, systolic anterior motion; *TEE/TOE*, transesophageal echocardiography; *TTE*, transthoracic echocardiography; *US*, ultrasound.

*Not all causes of acute chest pain are listed. Depicted imaging techniques are used early in diagnostic work-up for index disease/condition presented with acute chest pain. Only the main findings that can be obtained by each imaging technique in index diseases/conditions are shown. Of note, not all signs that can be detected by individual imaging techniques are listed; details can be found in related literature. Empty cells denote that particular imaging technique is not in use or not routinely used in diagnostic work-up for index disease/condition. Shaded cells denote imaging technique recommended for initial use in diagnostic work-up.

†TEE/TOE can be used in case of non-diagnostic TTE and could evaluate for each differential diagnosis similarly to TTE.

‡Chest X-ray is routinely used in patients presented with acute chest pain in many institutions. Trained individuals may use FoCUS in emergency settings to identify global left and right ventricular dysfunction and pericardial effusion/tamponade, or as technique integrated into advanced cardiovascular life support (ACLS) algorithm in patients with cardiac arrest.

detection of differential diagnoses of acute chest pain.[25,91] Lung ultrasound has diagnostic value in certain indications (e.g. pneumothorax). Although TTE can reveal clues to aid the diagnosis of AAS and acute PE, its diagnostic accuracy for both conditions is insufficient.[92,93] Additional diagnostic work-up for suspected AAS includes TOE or CT. For definite diagnosis of acute PE, patients should undergo CT. The choice of the optimal imaging technique involves consideration of the prioritized differential diagnosis, patient clinical stability, and institutional availability (particularly after hours) and expertise.

Cardiac imaging plays an important role in the diagnosis of myocardial infarction with non-obstructed coronary arteries (MINOCAs). The diagnosis of MINOCA excludes specific diagnoses

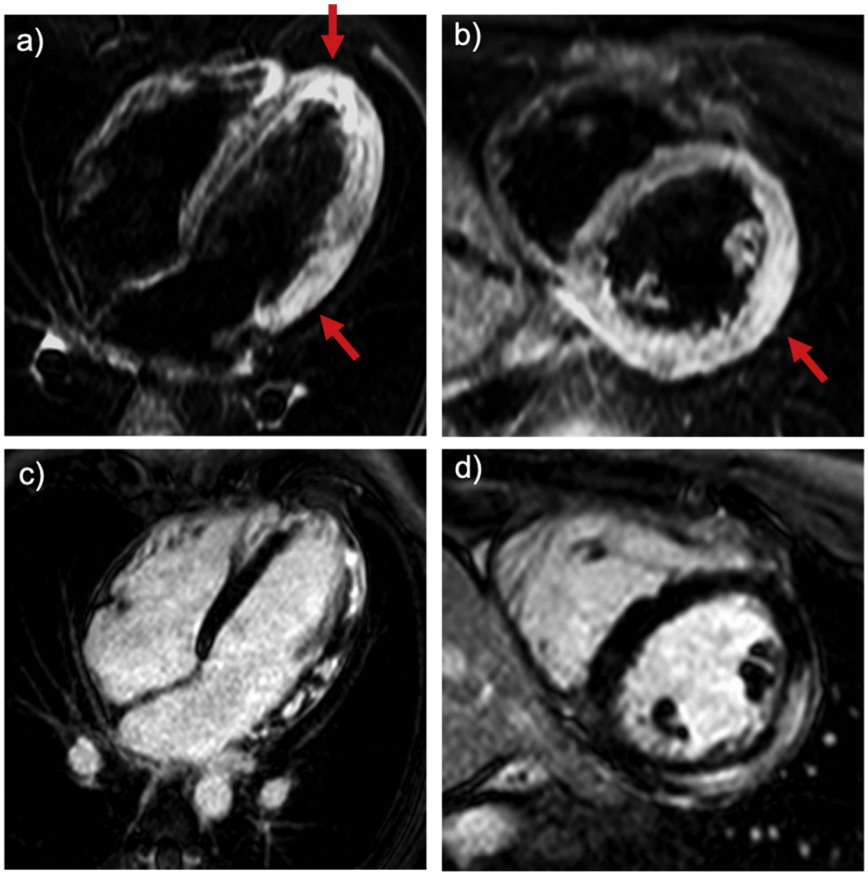

Figure 17 Cardiovascular magnetic resonance imaging in MINOCA. A 19-year-old male presenting with recent viral illness, chest pain, and elevated troponin levels. **(A)** T2-weighted short tau inversion recovery image in the four-chamber view showing increased signal in the lateral wall and apex, suggestive of inflammation and edema (*red arrows*). **(B)** T2-weighted short tau inversion recovery image in short-axis orientation at mid ventricular level showing increased signal in the lateral wall, suggestive of inflammation and edema (*red arrow*). **(C)** Late gadolinium-enhanced images in the four-chamber view showing patchy epicardial contrast enhancement in the lateral wall and apex, suggestive of inflammation and infiltration. **(D)** Late gadolinium-enhanced images in short-axis orientation at mid ventricular level showing patchy epicardial contrast enhancement in the lateral wall, suggestive of inflammation and infiltration.

as sepsis, PE, aortic dissection, and other non-cardiac causes of troponin rise.[4] An early echocardiographic study could help exclude other causes of troponin rise and also demonstrate LV wall motion. CMR is a very important tool to diagnose or exclude myocarditis, takotsubo cardiomyopathy, and Type 1 MI, as well as other possible causes of troponin rise. The presence (and pattern) or absence of LGE can help clarify the differential diagnosis[94] (Figure 17).

Key Points

1. Non-invasive imaging is critical in the differential diagnosis of ACS and frequently requires multi-modality imaging.
2. CMR is the most useful imaging test in the diagnostic work-up of MINOCA and can detect or exclude other cardiac causes of troponin rise.

Risk Stratification After Revascularization

Following revascularization, patients with CAD are at risk for sudden cardiac death (SCD), heart failure, and/or recurrent ischemic events. Patients with ischemic LV dysfunction experience a variable degree of functional recovery after PCI or coronary artery bypass grafting (CABG). Persistence of reduced LVEF represents an indication for continued pharmacologic therapy for heart failure, and implantable cardioverter-defibrillator (ICD) is indicated for primary prevention of SCD if LVEF is <35% beyond 40 days after the acute coronary event.[95]

The majority of patients suffering from a cardiac arrest have an EF >35%, but the prognosis is worse for those with low EF. GLS has repeatedly shown to add information beyond LVEF in risk prediction of heart failure, ventricular arrhythmias, and mortality.[37,38,96,97] A dyssynchronous LV contraction pattern (increased mechanical dispersion) has been demonstrated to be a risk marker for malignant ventricular arrhythmias after an ischemic event but has not been evaluated as a single-risk parameter for ICD implantation.[38,98]

A routine echocardiographic study before discharge from the hospital, including evaluation of LVEF and GLS, is recommended.[38,96] Time to maximum recovery also varies from days to several months. Based on data collected from large revascularization trials, it is reasonable to re-evaluate LV function 1–3 months after an ACS. A heterogeneous contraction pattern might imply a higher risk of malignant arrhythmias during the follow-up.[99,100]

The size and transmural extent of scar by CMR predict wall motion recovery and adverse LV remodelling.[101,102] Furthermore, scar size is a powerful predictor of adverse cardiac events following ACS.[103-105]

The presence of microvascular obstruction, seen as a dark area within a region of bright LGE on CMR or a dark defect with myocardial contrast echocardiography, provides additional prognostic value.[106,107]

Cardiac imaging is also considered appropriate at any moment post-ACS for the evaluation of a change in patient symptoms or clinical signs (e.g. new murmur). In the early post-revascularization period, cardiac imaging using any of the non-invasive methods may help to differentiate ischemic from non-ischemic chest pain syndromes. Pericarditis or pericardial effusion may be present after acute MI. The presence of new wall motion or perfusion abnormalities may support the diagnosis of acute stent thrombosis or graft closure, although in their absence these diagnoses cannot be necessarily excluded. Coronary CTA should not be performed routinely to evaluate for stent thrombosis or re-stenosis post-PCI.[108] If there is sufficient clinical suspicion, ICA is required for both diagnosis and treatment in these cases.

There is not sufficient evidence to support serial evaluation of asymptomatic patients following revascularization, as it does not seem to improve long-term outcomes. Evaluation of LV function and/or detection of ischemia may be reasonable, however, in patients who present with new ECG abnormalities and when symptoms are too vague to justify ICA. Evaluation of LV function may also be performed in high-risk patients with limited functional capacity who require high-risk elective non-cardiac surgical procedures.[109]

Key Points

1. A routine echocardiogram, including evaluation of LVEF and GLS, is recommended before hospital discharge.
2. An evaluation of LV function 1–3 months after an ACS should be performed if the pre-discharge echo demonstrated an abnormal EF, and used as post-MI reference for subsequent risk stratification.
3. Serial evaluation of asymptomatic patients following revascularization is not recommended.
4. Scar size by nuclear imaging or CMR, and microvascular obstruction by echocardiography or CMR, are predictors of outcome.
5. Coronary CTA should not be routinely utilized to evaluate stent thrombosis or re-stenosis post-PCI.

DIAGNOSIS OF CHRONIC CORONARY SYNDROMES—THE ROLE OF IMAGING

Non-invasive diagnostic modalities can evaluate resting LV function, assess the presence of myocardial scar/viability or ischemia, and directly assess coronary anatomy (by coronary CTA).

Left Ventricular Function Assessment

The assessment of resting LV function should be performed in all patients with suspected CAD for diagnostic and prognostic purposes (Table 2). While these patients often demonstrate normal LV function at rest, abnormal findings may indicate the presence of CAD and trigger further diagnostic work-up.[110] CMR may be considered in patients with suspected CAD when the echocardiogram (with UEA) is inconclusive.[111]

Resting global LV function is strongly related to long-term prognosis with a significant inverse relationship between mortality rate and LVEF.[44] LVEF should be calculated from 2D and 3D echocardiographic measurements of LV volumes, and normal reference values for both methods are available.[26,27] Other modalities, notably CMR and CT, use 3D data sets routinely to measure LV function. Overall, any 3D imaging would be preferable over 2D, to avoid geometrical assumptions, which could be particularly significant in CAD due to regional wall motion variations.

Table 2 Causes of regional wall motion abnormalities

Regional WMA related to CAD
• Ischemia
• Myocardial scar (acute or prior myocardial infarction)
• Myocardial stunning
• Myocardial hibernation
Regional WMA not directly related to CAD
• Myocarditis
• Takotsubo cardiomyopathy
• Sarcoidosis
• Abnormal septal motion
• Post-operatively (after open heart surgery)
• LBBB (septal 'flash' and apical 'rocking')
• RV pacing
• RV pressure or volume overload

CAD, coronary artery disease; *LBBB*, left bundle branch block; *RV*, right ventricular; *WMA*, wall motion abnormality.

Echocardiographic speckle tracking-derived GLS is a sensitive, reliable, and reproducible measure of global LV function, and may have incremental prognostic value over EF.[37] Similar methods tracking standard cine images or dedicated tagged cine imaging are available for CMR measurement of strain.

In patients with CAD and normal segmental wall motion by 2D echocardiography, myocardial deformation imaging might reveal subtle abnormalities that can be attributed to clinically relevant ischemia or ischemic memory.[112] Reduced regional longitudinal strain, as well as regional diastolic asynchrony expressed as post-systolic shortening (detected either by strain curve analysis or by M-mode), may also indicate the presence of ischemia (Figure 18).[35,113-115] When using strain in patients with suspected CAD, it seems therefore more prudent to look for specific patterns of contraction/deformation than to rely on numerical values of regional segmental strain.[44]

In most cases, 2D TTE will provide sufficient information about LV function. In cases of suboptimal visualization of LV cavity and endocardial borders, a UEA should be used for better diagnostic accuracy.[44,116] However, in cases of suboptimal or non-diagnostic echocardiographic studies (including UEA) or conflicting clinical information, CMR is an excellent alternative, offering highly accurate and reproducible assessment of LV volumes, EF, and regional wall motion.[117,118]

The use of other imaging modalities for the purpose of LV function assessment (i.e. CT or radionuclide ventriculography) should be restricted to specific clinical circumstances.

Key Points

1. Initial/baseline assessment of resting LV function should be performed in all patients with suspected CAD for diagnostic and prognostic purposes.
2. TTE should be used as the initial imaging modality for the assessment of LV systolic function. If initial echocardiographic images are of limited quality (two or more contiguous segments cannot be properly seen), a UEA should be used for better endocardial delineation.
3. CMR is the reference standard for LV/RV assessment and is an excellent alternative to echocardiography, especially when image quality from echocardiography is suboptimal.

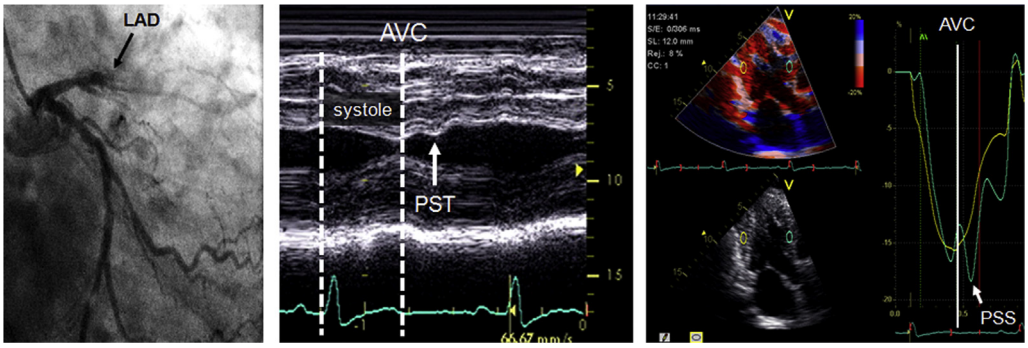

Figure 18 Altered deformation of the septum in a patient with suspected coronary artery disease. The patient had a two-dimensional echocardiogram at rest. M-mode recording (middle panel) showing the 'double peak' contraction pattern of the septum (*white arrow* pointing at post-systolic thickening of the septum). Tissue Doppler-derived segmental longitudinal strain curves (right panel) of normal posterior wall (yellow curve with a single peak systole) and ischemic septum (double peak green curve with the post-systolic peak occurring after the aortic valve closure). Coronary angiography (left panel)—proximally occluded (*black arrow*) left anterior descending coronary artery (LAD). AVC, aortic valve closure; PSS, post-systolic shortening; PST, post-systolic thickening. (Adapted from Nešković AN, Flachskampf FA, Picard MH (eds). Emergency Echocardiography, 2nd Edition. CRC Press, Taylor & Francis Group, Boca Raton, London and New York, 2017, ISBN - 13: 978-1-4822-4385-7 (Pack-Book and Ebook)).

4. Currently, the recommended method to measure LVEF by 2D echocardiography is the biplane method of disks (modified Simpson's rule).
5. Whenever feasible, 3D echocardiographic measurements of LV volumes and EF should be used for higher accuracy and reproducibility.
6. Speckle tracking-derived GLS offers a reliable and reproducible measure of global LV function and may have incremental prognostic value over EF.
7. Regional WMA are visually detected and scored by echocardiography (2D or 3D) or by CMR.

Myocardial Ischemia Assessment

When screening for CAD, cardiac imaging has a pivotal role in the diagnostic work-up of those who have clinical likelihood of CAD. The recent ISCHEMIA trial highlights the significant role of ischemia testing. This pivotal trial did not find difference in outcomes (death or MI) when patients with stable CAD and significant ischemia underwent an invasive vs. a conservative strategy, although symptom relief was better after revascularization.[119] Patients with left main stenosis were excluded by CTA in this trial; an initial strategy of medical therapy in patients without left main stem disease therefore appears safe and reasonable. The additional value of anatomical non-invasive imaging with CTA in this study is still being debated. The choice of imaging tests to be performed is based on pre-test likelihood, patient characteristics and preference, availability and local clinical expertise. Coronary CTA or stress tests are the preferred choices, but patients might be referred directly for ICA if the likelihood of CAD is very high. Myocardial ischemia can be evaluated through myocardial perfusion or wall motion.

An exercise ECG stress test might be used to diagnose myocardial ischemia only if a functional imaging test or coronary CTA are not available or not feasible.

Some studies have indicated that MPI during vasodilator, inotropic, or exercise stress is particularly advantageous compared to wall motion response when the degree of stenosis is moderate rather than severe, and for situations where a low workload is achieved.[120]

Available data consistently demonstrate that diagnostic modalities based on myocardial perfusion (SPECT, CMR, or PET), wall motion (stress echocardiography), those complementing flow information with wall motion (CMR) or with coronary anatomy (CTA with FFR or PET/CT) have high accuracy.[3,7-9,111,121] This writing group agrees with the new ESC guidelines that functional testing is preferred in patients with intermediate to high PTP of CAD, while coronary CTA is preferred in those with low to intermediate PTP of CAD.[3]

A functional test with evaluation of wall motion can be performed by echocardiography (exercise, dobutamine, or vasodilator) or CMR (dobutamine or vasodilator). An imaging-based functional test is more specific compared to standard exercise ECG,[122] and the various non-invasive imaging functional tests have similar accuracy.[3,123] The choice of method will depend on local expertise, test availability, and the patient's characteristics as already discussed.

Importantly, in the setting of left main or multivessel CAD, stress echocardiography may have greater sensitivity compared to perfusion imaging, as the latter compares relative differences in perfusion and may miss ischemia when it is balanced (similarly affecting most territories) or global.[124] This affects modalities with high spatial resolution less than those with lower spatial resolution. Quantification of MBF by CMR or PET can overcome this limitation of relative perfusion assessment.

Stress echocardiography allows combined assessment of ischemia with diastolic function, valvular structure and function, presence of LV hypertrophy, atrial enlargement, RV size and function, and pulmonary hypertension.[125,126]

Antianginal medical therapy (in particular, beta-blocking agents) significantly affects the diagnostic accuracy of all forms of stress. Therefore, whenever screening obstructive CAD by exercise and dobutamine stress echo and dobutamine CMR for, it is recommended to withhold beta-blockers at the time of testing to avoid a false negative result.[122,127] When the goal is to evaluate the response to therapy, however, it is recommended that the test be performed while maintaining anti-anginal therapy.

Key Points

1. Anatomical or functional imaging should be used as first-line test for diagnostic and prognostic purposes in patients with known or suspected CAD and low to high PTP.
2. Myocardial ischemia can be detected by stress-induced perfusion defects or WMA.

3. Echocardiography, SPECT, PET, CMR, and CT-FFR can detect ischemia with high accuracy.
4. The choice of one test over the other will depend on relative contraindications, patient characteristics, and local availability and expertise.
5. With all techniques, the presence of ischemia, as well as its location, extent, and severity should be reported as they all have diagnostic and prognostic value.

Assessment of Coronary Artery Stenosis

In patients with stable and chronic symptoms, multiple studies have compared coronary CTA to usual care strategies based on functional testing.[5,29] Patients that undergo coronary CTA have similar incidence of events and a significant reduction in incidence of myocardial infarction during short-term follow-up.[128]

The SCOT-HEART trial demonstrated a significantly lower rate of cardiovascular death or non-fatal MI during 5-year follow-up when coronary CTA was performed in addition to routine testing with exercise ECG.[30] Diagnostic testing with coronary CTA is associated with clinical outcomes similar to those for functional imaging in patients with suspected CAD in several randomized, prospective clinical trials.[29,129] However, coronary CTA is associated with an increase in referral for ICA at 2 years, but similar referral at 5 years.

Prognosis in patients who undergo coronary CTA is strongly correlated with the extent and severity of both non-obstructive and obstructive (≥50% stenosis; potentially flow-limiting) CAD.[130,131] In addition to coronary stenosis, plaque composition (e.g. low-attenuation, spotty calcification) and morphology (e.g. positive remodeling) affects risk of future ACS and death,[132,133] while the role of coronary plaque volume is still unclear. Assessments of plaque burden however offer the most powerful prediction of future myocardial infarction.[134] Importantly, the absence of CAD on CAC and coronary CTA identifies patients at very low risk for subsequent atherosclerotic cardiovascular disease events. A negative CAC was shown to have 1.4% chance of having a cardiovascular event or death during 26.1 months of follow-up.[135]

Coronary CTA should be used in patients with chest pain at low to intermediate pre-test likelihood of obstructive CAD according to current guidelines.[3] This indication is predicated on the high sensitivity and negative predictive value of coronary CTA to rule out CAD among appropriately selected symptomatic patients. A disadvantage of coronary CTA that makes it less attractive for coronary imaging in patients likely to have extensive calcified lesions is the overestimation of lesion severity. However, coronary CTA and ICA suffer from reduced specificity, particularly among patients with intermediate stenosis (most frequently defined as 50–70%) when compared with invasive FFR as the reference standard.[54,121]

The roles of anatomic and functional imaging are complementary. Coronary CTA should be considered as an alternative to invasive angiography if another non-invasive test is non-diagnostic or indeterminate. Similarly, functional imaging for myocardial ischemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic. Coronary CTA, however, is usually not recommended in patients with irregular heart rhythm, significant obesity, inability to cooperate with breath-hold commands, or other conditions that might make good image quality unlikely. The presence of extensive coronary calcification is associated with lower diagnostic accuracy.

The exposure to ionizing radiation associated with coronary CTA must also be considered, especially in young patients.[19] The use of non-contrast CT for CAC scoring is generally not recommended for the assessment of symptomatic patients.[3]

Newer, evolving techniques of CT-derived functional evaluation (CT-FFR- and stress CT perfusion) may provide additive insight into the ischemic significance of lesions identified by coronary CTA. These methods have been shown to improve the specificity of coronary CTA for the evaluation of intermediate stenoses, while others have showed reduced diagnostic accuracy. Among these, CT-FFR has been most widely studied and utilized clinically to date but both techniques continue to evolve.

Key Points

1. Coronary CTA should be considered in patients with stable symptoms and suspected CAD with low and intermediate risk.
2. Coronary CTA should be considered as an alternative in patients with equivocal findings on non-invasive functional tests who are not at high risk for obstructive CAD.

Myocardial Viability and Scar Assessment

Each imaging modality assesses different aspects of viability, and therefore defines viability with specific characteristics or imaging phenotypes, whether contractile reserve (dobutamine echocardiography or cine CMR), metabolic activity (PET), membrane integrity (SPECT), or increased extracellular space (LGE CMR). The choice of imaging modality to identify viability is largely dependent upon local availability of equipment and expertise. Studies thus far have demonstrated general equivalence among methods.

The presence of myocardial hibernation or stunning (both reflecting dysfunctional but viable myocardium) can be identified either by (i) wall motion imaging, as areas of resting dysfunction with preserved contractile reserve during stress (echocardiography, cine CMR); (ii) dysfunctional myocardium without scar (LGE CMR); or (iii) mismatched areas of reduced perfusion with preserved glucose metabolism (SPECT/PET). Therefore, the imaging assessment of myocardial viability includes different parameters linked to distinctive pathophysiological aspects of dysfunctional myocardium.[136,137]

Multiple small non-randomized observational clinical studies have suggested that viability testing should be the gatekeeper for determining which patients with CAD and low EF would benefit from coronary revascularization.[138] On the basis of these studies and expert consensus, the standard clinical practice and American College of Cardiology/American Heart Association practice guidelines suggest significant symptomatic and/or survival benefit among HF patients with significant myocardial viability who undergo revascularization, a concept challenged by a recent large clinical trial. The STICH (Surgical Treatment for Ischemic Heart Failure) trial enrolled 1212 ischemic HF patients who were randomly assigned to receive medical therapy alone or medical therapy plus CABG. The rates of death from any cause, death from cardiovascular causes, and hospitalization for cardiovascular causes were significantly lower over 10 years among patients who underwent CABG in addition to receiving medical therapy than among those who received medical therapy alone.[139] The viability sub-study of STICH, which consisted of 601 patients, was a non-randomized sub-study that failed to determine which patients (with or without significant viability) would fare better with CABG and optimal medical therapy as opposed to optimal medical therapy alone.[140] As with all the previous non-randomized studies, the STICH sub-study had some significant limitations such as potential for patient selection bias or sub-optimal viability techniques utilized [^{18}F fluorodeoxyglucose (FDG) PET and LGE CMR were not studied], among others. In this sub-study, the presence of myocardial viability

predicted better outcomes overall and improvement in EF, although such EF improvement did not translate into better long-term clinical outcomes.[141] Therefore, the role of viability imaging in clinical practice remains unclear.

Myocardial Viability Evaluation by Nuclear Imaging. PET myocardial FDG metabolic imaging combined with PET or SPECT perfusion imaging is the current nuclear imaging approach of choice for the evaluation of myocardial viability.[136] In the presence of repetitive ischemia and after a glucose load, viable myocardium shows an increased uptake of FDG, reflecting preferential utilization of glucose over free fatty acids. The typical viability study consists of FDG PET images paired with resting myocardial perfusion images. In regions with resting hypoperfusion a concordant reduction in both flow and metabolism ('match') represents myocardial scar while an increase in FDG uptake compared with flow ('mismatch') represents hibernating but viable myocardium.[142] PET FDG has been reported to have a high negative predictive value (mean 90%, confidence interval 86–95%) and a good positive predictive value (mean 73%, confidence interval 66–80%) for recovery of segmental contractile function after revascularization.[137] An ongoing randomized clinical trial will further test the hypothesis that ^{18}F FDG viability imaging improves patient outcomes (IMAGE-HF Project I-A).[143]

Myocardial Viability Evaluation by Dobutamine Echocardiography. The stress echocardiographic sign of myocardial viability is a stress-induced improvement of function during low levels of stress in a region that is abnormal at rest. Most of the experience is available with low-dose dobutamine stress echocardiography, the preferred stressor for assessing myocardial viability,[5,12,19] although viability may also be detected by dipyridamole stress echocardiography or during low-level bicycle exercise. In patients with CAD, proof of viability is an improvement of myocardial function, which may occur spontaneously (e.g. after stunning), on medical therapy, or after revascularization (Supplementary data online, Movie S1).

In patients with dysfunctional but viable myocardium, regional function can be improved by low-dose (5–10 μg/kg/min) dobutamine, typically worsening at higher doses (biphasic response). Dobutamine stress echocardiography has similar overall accuracy as nuclear imaging techniques.[5,23]

Myocardial Viability and Scar Evaluation by Cardiac Magnetic Resonance. Similar to echocardiography, cine CMR imaging can be performed at rest and during a low-dose infusion of dobutamine to determine viability based on improvement of wall motion.[144] This technique does not require gadolinium contrast. However, the vast majority of viability imaging by CMR utilizes the LGE method. Rather than detecting viable tissue, LGE CMR detects scar (non-viable myocardium) (Figure 15). With LGE images acquired approximately 10–12 min after the administration of gadolinium, myocardium that is infarcted, fibrotic or scarred appears bright, while viable myocardium is conventionally set to appear dark. Given its high spatial resolution, the size, location, and transmural extent of myocardial infarction by LGE CMR closely matches histopathology.[145] Myocardial segments with more than 50% transmural infarction have a low likelihood of functional recovery, while segments exhibiting less than 50% transmural enhancement are more likely to recover contractile function.[41] The presence and extent of scar detected by LGE is a powerful predictor of prognosis, independent of LVEF.[146,147]

Key Points

1. Non-invasive imaging to detect ischemia and viability is reasonable in patients presenting with heart failure who have known CAD and no angina, unless the patient is not eligible for revascularization, although its value is unclear.
2. Nuclear imaging, low-dose dobutamine echocardiography, or CMR and LGE CMR are all options to evaluate viability.
3. LGE CMR is the method of choice for scar detection.

Risk Stratification in Chronic Coronary Syndromes

All non-invasive imaging methods have demonstrated important prognostic relevance in CCS, and the choice of imaging method should be based on intended clinical assessment and the best local choice to diagnose CAD.[3]

A resting TTE assessment of LV function is important for risk stratification in CCS. Assessment of GLS will add incremental information about risk, particularly in patients with EF >35%.[37,38,148]

A resting echocardiogram should usually be followed by anatomical or functional tests for diagnostic purposes. All non-invasive imaging methods have demonstrated important prognostic relevance in chronic CAD. A normal stress echocardiogram, CMR, or myocardial perfusion scan implies excellent prognosis and coronary angiography can safely be avoided in patients with suspected CAD.[149] Results of the stress tests can be further stratified by evaluating clinical parameters (diabetes, renal dysfunction, and therapy at the time of test), resting echocardiography (global LV function), and stress echocardiography parameters (LV cavity dilatation, coronary flow reserve, and previous revascularization). The ischemic response can be further stratified with additive stress echocardiographic parameters, such as the extent of inducible WMA and the maximum workload/dose achieved. Survival rate correlates directly with ischemia-free stress time and inversely with wall motion score index. The incidence of death in patients with a negative functional test off therapy is very low. At intermediate risk are those patients with a negative test on medical therapy or a positive test off medical therapy. The findings of a negative functional test cannot, however, rule out lower degrees of coronary atherosclerosis, and patients should always receive advice and treatment according to current risk charts and recommendations.

The presence of scar by SPECT and CMR is associated with poor prognosis, and absolute quantification of MBF with PET and CMR adds prognostic information.[150]

Assessment of coronary atherosclerotic plaque burden provides powerful prediction of myocardial infarction. Numerous large-scale studies have demonstrated the long-term prognostic value of CAC testing among diverse populations, even additive to standard risk scores.[1] The absence of CAC is associated with a very good prognosis, with 1.0–1.5% risk of atherosclerotic cardiovascular disease outcomes over 10 years of follow-up, while those with advanced CAC (>300 Agatston score) have at least a six-fold increased relative risk for long-term events.[151,152]

The use of CAC scoring in symptomatic patients is more controversial. Non-calcified plaque and obstructive CAD uncommonly occur in the absence of CAC, especially in patients at higher pretest CAD risk.[153,154] Therefore, the absence of CAC has been shown to have very high negative predictive value to exclude obstructive CAD in observational and prospective studies and has been suggested as a possible gatekeeper test in low-risk patients.[155,156]

In patients with suspected stable CAD, coronary CTA demonstrates the coronary lumen as well as the characteristics of the vessel wall and has a very high negative predictive value in excluding coronary atherosclerotic disease. In addition, CTA is able to document the presence, severity and extent of non-obstructive and obstructive coronary lesions as well as the composition of coronary plaques, providing strong prognostic information.

Key Points

1. GLS adds incremental prognostic information to EF in CCS.
2. A normal functional or anatomical non-invasive imaging test implies an excellent prognosis and ICA can safely be avoided.
3. Presence of high scar burden by SPECT and CMR is associated with poor prognosis.
4. Markers of coronary plaque burden provide powerful prediction of myocardial infarction.
5. Coronary CTA is an excellent prognostic tool in patients with suspected CAD.

CONCLUSIONS AND FUTURE DIRECTIONS

While multiple technologies and approaches to diagnose CAD in the acute and chronic stages have been developed, they address different aspects and stages of the disease. The imaging modality applied in any clinical situation should depend upon the information that is being sought. All modalities can provide information regarding LV structure and function, although echocardiography and CMR clearly have advantages. Similarly, with the general exception of CTA, all techniques can detect ischemia and viability; although echocardiography and nuclear imaging have the largest imprint in clinical practice, CMR is increasingly being utilized. CTA is the non-invasive procedure of choice to visualize coronary anatomy. As none of them is perfect or can provide all the needed information, there is a need for clinicians to have a deep understanding of the disease within the coronary arteries and beyond. Such critical view of the disease and of our patients, together with the comprehensive knowledge of each diagnostic tool, will allow for development of the appropriate diagnostic strategies for each patient and situation, which is ultimately the goal of this document.

With the advent of newer technologies such as hybrid systems that combine nuclear imaging with CT, opportunities for obtaining complementary anatomic and functional information in a single imaging session may prove to have higher value than do current approaches. Furthermore, developments in high-definition imaging such as CT or CMR may allow for more detailed plaque evaluation and provide an opportunity to evaluate coronary plaques with a different goal, by assessing not only for stenosis and ischemia, but to also evaluate plaque morphology and activity to improve the identification of patients at risk of acute coronary events.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2021.12.012.

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