New Images in Cardiology

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Invited Editorial

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NEW IMAGES IN CARDIOLOGY:
GOOD TIMES NOW—AND BETTER STILL AHEAD

This issue of Dialogues in Cardiovascular Medicine is devoted to “New Images in Cardiology.” The Editors-in-Chief were wise to pick this topic, as history has never seen a more exciting time for imaging in cardiology. Imaging is the bread and butter of cardiology. Almost every patient cared for by cardiologists will at some point undergo some form of diagnostic imaging. Cardiac imaging has been developed with ever-increasing levels of sophistication over the past century, and there have been three phases of major development (Figure 1). The first started with the discovery of the x- (or Roentgen) rays by W. C. Roentgen in 1895, with the subsequent development of the chest x-ray during the beginning of the 20th century. For many decades, this method was the only option for imaging the heart. Then, over the 1960s and 70s, three parallel developments entered clinical practice that revolutionized the way the heart was imaged—nuclear scintigraphy, M-mode-/2-D echocardiography, and invasive catheterization laboratory-based x-ray imaging methods. Thereafter, however, the principal approach to cardiac imaging remained relatively unaltered, and indeed, many cardiologists pride themselves of the sophisticated diagnostic imaging techniques we have had at our disposal over the past three decades. However, in reality, the current conventional cardiac imaging methods all have severe limitations and drawbacks, related to issues such as insufficient resolution and information content, and use of radiation and invasive procedures associated with risk and patient discomfort.

Figure 1. The three evolutionary stages of cardiac imaging modalities. Abbreviations: CCT, cardiac computed tomography; CMR, cardiac magnetic resonance.
Over the past 10 to 15 years, a third phase of cardiac imaging development has gradually gained pace and is now in full swing: cardiac magnetic resonance (CMR) imaging, cardiac computed tomography (CCT), and advanced echocardiography methods. While magnetic resonance (MR) and computed tomography (CT) imaging methods initially became available much earlier, in the 1980s, the heart poses particular challenges to these highly computerized methods. The structures we need to image are small, there are many parameters that interest the cardiologist, including physiologic and dynamic aspects of cardiac function, such as contraction, perfusion, or viability. Unlike, for example, the brain, the heart represents a constantly moving target for imaging. The more recent developments in CMR and CCT (and also in advanced echocardiography) that have made cardiac imaging by these methods feasible have been possible due to the enormous advances in computing power (which is critical both for acquisition and interpretation of MR and CT images) and in MR and CT hardware development (such as, for example, better gradient performance and phased array imaging coil technology in MR, or faster gantry rotation times/dual x-ray source in CT).

In the current issue of *Dialogues in Cardiovascular Medicine*, a select group of experts in the field provide their views on a number of recent developments in advanced cardiac imaging. Sanjay K. Prasad and Dudley J. Pennell from the Royal Brompton Hospital, London, provide the lead article, critically appraising the new advanced cardiac imaging techniques. In the Expert Answers articles, Jeroen J. Bax from Leiden University Medical Center discusses the use of echocardiographic tissue Doppler and strain imaging for the identification of patients likely to benefit from resynchronization therapy; Juerg Schwitter from the University Hospital Zurich focuses on a question that is currently at the forefront of many noninvasive cardiologists’ minds—whether perfusion CMR will replace single photon emission computed tomography (SPECT) measurements of myocardial perfusion, and finally, Udo P. Sechtem from Stuttgart gives a critical account of “the hype, the reality, and the future” of CT coronary angiography. These articles will provide the reader with major insight into many current capabilities of these new imaging methods.

We are now at a time when one can no longer assume that diagnostic imaging pathways firmly established in cardiology for several decades (conventional echocardiography, nuclear scintigraphy, and invasive coronary angiography) are the optimal diagnostic strategy, both in terms of *best patient care* and *best value for money* for health care funders. With the advent of advanced techniques, the field of cardiac imaging has been thrown wide open once again. A systematic effort, including a substantial number of multidisciplinary, multimodality, and multicenter clinical studies, will be required to determine which diagnostic approaches are to be recommended for which specific clinical scenarios. It is also clear that the new imaging methods will lead to an unprecedented level of understanding of cardiac pathophysiologic mechanisms and of the...
effects of established and novel forms of treatment. In parallel to the methodological developments, several national and international cardiac imaging societies have blossomed in recent years, and new cardiac imaging specialist meetings and journals abound (for more information see www.scmr.org; www.bscmr.org; www.escardio.org/bodies/WG/wg26/ for CMR; www.scct.org for CCT; http://asecho.org/; www.bsecho.org/; www.escardio.org/bodies/associations/EAE/ for echocardiography).

Apart from the existing technical and clinical research challenges for advanced imaging techniques, many other hurdles will have to be overcome before some of the advanced imaging methods described in this issue fully enter mainstream cardiology. Standardization of imaging approaches among centers, simplicity and speed of imaging, appropriate capacity for training a new generation of cardiac imagers, and avoidance of turf wars among disciplines, are just some of the challenges that need to be mastered on our journey to the cardiac imaging world of the future.

However, given the outstanding and unprecedented array of novel imaging tools that have now become available, the next 10 years in cardiac imaging promise to be much more exciting—and undoubtedly controversial—than recent decades have been. For a cardiac imager, there has never been a better time to be around…
Clinical role of advanced imaging in cardiology

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The last decade has seen an unprecedented development in imaging technologies that are able to noninvasively characterize cardiovascular conditions. At the forefront of these modalities have been cardiovascular magnetic resonance (CMR) and multidetector computed tomography angiography (MDCTA). Linked to advances in software and hardware, current CMR scanners are able to provide a comprehensive evaluation of the cardiac patient with a range of information on anatomy, function, perfusion, viability, tissue characterization, flow patterns, as well as coronary and vascular angiography. MDCTA is able to provide accurate characterization of coronary luminal stenosis and plaque burden in a short scan, frequently avoiding the need for subsequent x-ray angiography with its attendant risks and complications—particularly in the intermediate risk group. Developments in echocardiography have enabled better tissue characterization, real-time three-dimensional visualization, and, using specific contrast agents, assessment of myocardial perfusion. Tissue Doppler techniques have facilitated better understanding of myocardial mechanics—particularly useful, eg, in assessment of dyssynchrony. In this review article we provide a brief overview of how these techniques work and discuss current and future applications. We highlight the strengths, as well as limitations, of these imaging modalities, and discuss when to consider these tests in clinical practice.

Keywords: cardiovascular magnetic resonance (CMR); echocardiography; multidetector computed tomography angiography (MDCTA); cardiomyopathy; coronary artery

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SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CMR</td>
<td>cardiovascular magnetic resonance</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>DCM</td>
<td>dilated cardiomyopathy</td>
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<td>HCM</td>
<td>hypertrophic cardiomyopathy</td>
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<tr>
<td>LGE</td>
<td>late gadolinium enhancement</td>
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<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>MCE</td>
<td>myocardial contrast echocardiography</td>
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<tr>
<td>MDCTA</td>
<td>multidetector computed tomography angiography</td>
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<td>MSCT</td>
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FUNCTIONAL IMAGING T2-weighted spin echo sequences contain a water-excitation pulse that can be used to highlight myocardial inflammation or edema. Other influences on signal intensity are proton density, blood flow, and the use of magnetic contrast media.

Assessment of cardiac volumes and function

Determining biventricular dimensions, mass, and function is the first step in cardiac evaluation. CMR is the gold standard for this. Initial ECG-gated cine scans are obtained of the left ventricle (LV) and right ventricle (RV) in the standard vertical and horizontal long axes, typically with 30 to 50 frames per cardiac cycle and provide a rapid qualitative assessment of biventricular function. Quantitative assessment of cardiac function is made by acquiring a stack of contiguous 7 to 10 mm short-axis cine slices, encompassing both ventricles from base to apex. From these scans, end-diastolic volume and end-systolic volume are calculated in a 3-D fashion, by defining endocardial borders in systole and diastole (Simpson’s method) Figure 1.

Myocardial mass is calculated by multiplying the myocardial volume by the specific gravity of muscle (1.05 g/mL). In comparison to 2-D echo, no geometric assumption is made that the left ventricle is ellipsoidal, so that there is better accuracy of derived values. This is particularly important for heart failure patients with distorted morphology due to DCM or infarction and regional differences in wall motion. Likewise, the RV has traditionally been difficult to evaluate due to its crescentic shape. The wide field of view and 3-D evaluation provide a reliable way to assess both global and regional RV function. Each one of the contiguous short-axis cines is acquired in a single breath-hold; with current fast steady-state precession, gradient echo sequences the total scanning time for volume and mass assessment is under 10 minutes. For patients experiencing dyspnea, navigator-based respiratory gating techniques allow acquisition of a short-axis stack during free breathing with similar quality, although acquisition times are longer. With newer techniques such as parallel imaging, complete short-axis 3-D data sets can be acquired in a single breath-hold of around 12 seconds. In patients with arrhythmias such as fast atrial fibrillation or frequent ventricular ectopics, real-time imaging may provide images of an adequate resolution to be clinically helpful.1-4

Diastolic function is assessed by various methods. Ventricular inflow measurements can be made in a manner similar to echocardiography with velocity...
mapping of the E and A waves. Temporal resolution is about 20 ms. Alternatively, the peak filling rate of the LV can be established by differentiation of the time-volume curve from the high temporal resolution short-axis cine stack. Relaxation strain patterns can also be assessed from tagging patterns.\(^5\)

An important benefit of the excellent interstudy reproducibility of CMR is the ability to detect early changes in longitudinal follow-up. For clinical trials, this manifests in reduced sample sizes and costs compared with other imaging modalities.

**Assessment of regional ventricular function**

For assessment of regional wall motion, the 17-segment model of the LV is used as recommended by the American Heart Association (AHA). Wall motion can be analyzed from the sinoatrial stack at rest and also with low-dose dobutamine for the detection of viable myocardium and high-dose dobutamine for the detection of ischemia. Accuracy is improved using myocardial tagging—a unique CMR-based technique that allows very accurate quantitative assessment of wall motion, strain, and strain-rate based on cine CMR. With echo, a quantitative assessment can be difficult since myocardial dynamics are composed of a complex interaction of contraction, expansion, twisting, and through-plane motion rather than the more simplistic view of just thickening and 2-D motion. CMR permits the alteration of signal properties of the myocardium before imaging, with deposition of planes of presaturation (tags) at end-diastole. These tags intersect the myocardium to form grids, prior to play-out of the imaging sequence itself, and distortion of the grids can be analyzed during the cardiac cycle (Figure 2) by computer algorithms giving a quantitative measure of cardiac deformation and strain. Tagging allows tracking of the same section of the heart throughout the cardiac cycle and enables assessment of radial, circumferential, and longitudinal ventricular contraction. It also allows assessment of changes at subendocardial and subepicardial layers. Thus, function can be analyzed and cor-

**Figure 1.** Viability assessment. This patient had impaired left ventricular function with severe 3-vessel disease. A cine and late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) study was performed to assess myocardial viability. **Panel A:** Cine 4-chamber view in diastole. **Panel B:** Cine 4-chamber view in end-systole demonstrating thinned akinetic lateral wall. **Panels C and D:** LGE study showing transmural infarction of lateral wall (arrows). There is no evidence of infarction of the septal wall. The septal wall shows viability. The lateral wall was subtended by an occluded circumflex vessel and is nonviable.

**Figure 2.** Microvascular obstruction. Late gadolinium enhancement study in a patient with a recent lateral wall acute infarct (short-axis view at midcavity level). The inner core of the infarct shows hypoenhancement (dark) reflecting microvascular obstruction (arrows) surrounded by a bright rim of late enhancement reflecting fibrotic change.
related according to the internal structure of the heart rather than assuming the myocardium to be a uniform object as with most noninvasive imaging modalities.5,6

**CMR IN ISCHEMIC HEART DISEASE**

The main current clinical applications of CMR in coronary artery disease (CAD) are assessment of anatomy, function, amount of hibernating myocardium, and myocardial perfusion.

**Assessment of viability**

Dysfunctional myocardium in patients with CAD may be made up of scar tissue, viable tissue that is hypococontractile (stunned or hibernating), or a mixture. Determining which is present is important as it predicts both prognosis and response to revascularization. From animal studies, following myocardial infarction, the region of myocardium most vulnerable to scarring is the subendocardium as this is the most distal from the epicardial coronary artery. Using a technique called late gadolinium enhancement (LGE), it is now possible to directly visualize regions of infarction in-vivo in high resolution, and in particular with the ability to quantify the transmural extent of infarction. Gadolinium is a metal that is chelated to form a water-soluble paramagnetic contrast medium. One typical chelate is diethylenetriamine pentaacetic acid (DTPA) and this distributes into the extracellular space. Gadolinium creates signal contrast by shortening T1 relaxation time in direct proportion to the local concentration, which increases signal intensity (brightness). Following intravenous administration, gadolinium chelate diffuses from the intravascular space and accumulates in interstitial tissue, but is unable to enter intact cells. Accumulation after 10 to 15 minutes (late after injection) is greater in areas of necrosis and fibrosis than normal myocardial tissue. Thus, late gadolinium enhancement is seen at sites of myocardial necrosis or scar (Figure 1). Postmortem analysis in animal models has demonstrated that in both acute and chronic infarction the region of enhancement correlates accurately in size and territory to the area of irreversible injury, while nonenhancing regions are viable. This has thus given rise to the principle that “bright is dead.” Postinfarction LGE of scar tissue always involves the subendocardium. Depending on the extent and duration of ischemia, the necrotic processes spread transmurally toward the epicardium in a region subtended by the occluded coronary artery. The amount of infarction can be easily and accurately quantified by LGE in both absolute terms and also as the relative transmural extent per segment (Figure 1). In a seminal study by Kim et al,7 the transmural extent of infarction as determined by LGE was shown to correlate with the likelihood of functional recovery of the affected tissue at 6 months post-revascularization. Areas of hypokinesia with subendocardial infarction less than 50% of transmural extent have up to 80% likelihood of improvement. By contrast, hypokinetic segments with myocardial infarction involving more than 50% of the wall thickness have a low probability of recovery. LGE can therefore be used to guide decisions on revascularization based on the detection of dysfunctional myocardium with limited infarction in a region subtended by a diseased coronary artery.7,11 These findings are also resulting in a paradigm shift. Thinned (<5 mm) hypokinetic myocardium was previously assumed to be scar tissue. CMR studies are demonstrating that the absence of LGE (and thus infarction) can be associated with restoration in wall thickening and function post revascularization, thus challenging previous assumptions than thinned myocardium is always scarred. LGE has additional applications in demonstrating the complications of infarction, including the walls of true and false aneurysms, and apical thrombi. In patients in whom cardiac resynchronization therapy (CRT) is being considered, the presence of lateral wall scarring is associated with a lower likelihood of responsiveness.

Compared with established imaging techniques for viability assessment, there is excellent correlation with positron emission tomography (PET) findings. In a study by Wagner et al,11 CMR had a higher sensitivity and specificity to detect infarcted myocardium compared with single photon emission computed tomography (SPECT) in canine hearts. Due to its better spatial resolution, it was better in the detection of smaller subendocardial infarcts, with no use of ionizing radiation. These small infarcts have been shown to have significant prognostic importance.11

Viability and hibernation can also be detected with high sensitivity and specificity using a low- and high-dose dobutamine infusion protocol to gauge changes in wall thickness and motion, similar to stress echo. Typically, systolic wall thickening of 2 mm or more reliably predicts reversibility of contractile function post-revascularization.

In the acute infarction setting, microvascular obstruction (MVO) can be demonstrated, reflecting blockage of capillaries by microemboli and endothelial edema. It is characterized by dark subendocardial areas where gadolinium chelate cannot penetrate, which is sur-
rounded by a rim of enhancement (Figure 2). It reflects more severe disease and a high likelihood of adverse remodeling in spite of successful upstream revascularization. T2-weighted imaging is currently being evaluated to determine areas of salvageable myocardium surrounding regions of infarction, which are edematous, but not irreversibly injured.

Myocardial perfusion

Most approaches to CMR perfusion analysis use IV injected gadolinium chelate. After injection, the initial transit (first pass) of gadolinium chelate is visualized through the heart. Ischemic myocardial regions show up as areas with reduced signal intensity change in comparison with well-perfused myocardium, which appears bright. These defects may be present at rest and are hence fixed, or may be inducible if they only become evident after the infusion of stressor agents such as adenosine. To visualize the passage of a bolus of contrast, fast magnetic resonance imaging sequences are used, which enable repetitive registration of several short-axis cuts at different anatomic levels. The technique has subendocardial resolution that is unique, and myocardial signal changes are assessed during the first pass for quantitative analysis.12-14

The parameters measured are the rate and level of enhancement, time taken to reach peak signal intensity, and mean transit time. Parametric maps can be generated to show perfusion parameters and the anatomic location of abnormalities. Myocardium perfused by a diseased vessel shows lower peak signal intensity and rate of signal increase and a longer time to reach peak. Intervention with angioplasty or surgery to revascularize that territory can reverse this with an increase in the peak signal intensity and slope. Pharmacologic stress with adenosine enables calculation of the myocardial perfusion reserve, with results similar to nuclear imaging techniques.

In patients with suspected CAD who have been referred for coronary angiography, stress/rest adenosine, gadolinium chelate first-pass myocardial perfusion with semiquantitative analysis has a sensitivity of 88%, a specificity of 90%, and an accuracy of 89% for detecting coronary artery disease. Semiquantitative analysis can be time-consuming and, therefore, many centers use visual interpretation for clinical studies. With a combined protocol of stress/rest myocardial perfusion and LGE, the diagnostic accuracy of visual interpretation is better than stress/rest perfusion alone for the detection of significant coronary artery steno-

sis (accuracy of 88% vs 68%) in patients with an intermediate pretest probability of coronary atherosclerosis referred for coronary angiography.

Overall, CMR perfusion is useful to both detect coronary stenoses and assess their severity. It is helpful both in the initial screening assessment of patients with suspected ischemic etiologies for their LV dysfunction and also as a complementary adjunct to x-ray angiography when the significance of documented lesions is unclear. Combined with the LGE technique, CMR perfusion provides a powerful means of the functional assessment of coronary artery disease in a timeframe of just 45 minutes. Perfusion assessment with CMR is likely to improve further in the future. Intravascular contrast agents are being developed that may allow for improved quantification. In addition, methods that eliminate the need for invasive contrast agents, such as spin-labeling and BOLD (blood oxygen level-dependent) sequences, are also in development. Issues that need to be addressed are the reduction of artifacts and consensus over the optimal CMR sequence to use.13

Assessment of coronary arteries

Imaging of the coronary arteries by magnetic resonance imaging has proved technically challenging. Coronary arteries are small and often tortuous vessels that move during the cardiac cycle as a result of both cardiac contraction and respiratory motion. In addition, these vessels are often surrounded by epicardial fat, which can sometimes compromise the contrast-to-noise ratio (CNR). Despite these challenges, coronary CMR can achieve imaging resolutions of less than 1 mm.

For patients with disease of the left main coronary artery or three-vessel disease, coronary CMR was demonstrated in a large prospective multicenter study of 109 patients with suspected coronary disease to have a high sensitivity (100%), specificity (85%), and accuracy (87%). The negative predictive value for this group was 100%. However, in the detection of any coronary disease, the accuracy was only 72%, with a negative predictive value of 81%. At present, coronary CMR is therefore not used routinely to exclude stenoses in epicardial vessels. Its use is mainly limited to identifying the origin and course of anomalous coronary arteries and bypass grafts. Recent developments using whole-heart imaging, more powerful 3-tesla scanners, and developments in intravascular MR contrast agents, may have an impact on the clinical applications of coronary CMR. Compared with multislice computed tomography (MSCT), coronary CMR has inferior spa-
tial resolution. However, it is less sensitive to calcium deposition. Also, the typical MSCT scan exposes the patient to about 12 mSv (millisieverts) of radiation so that serial evaluation is problematic—such concerns do not affect coronary CMR.15-21

CMR IN CARDIOMYOPATHY

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by the dilatation and functional impairment of the LV in the absence of significant CAD. In a proportion of patients the RV is also affected and this is associated with a poorer prognosis. Histologically, it is characterized by progressive interstitial fibrosis and degeneration of myocytes. Replacement fibrosis is also often seen and, unlike in CAD, there is midwall rather than subendocardial fibrosis due to involvement of the circumferential fiber layer.

Clinically, in the patient presenting with new-onset heart failure, it can sometimes be difficult to establish if the etiology is ischemic or due to DCM, as patients often present without a history of angina or prior myocardial infarction. The current discriminatory diagnostic tool considered to be the gold standard is x-ray coronary angiography. However its invasive nature and use of ionizing radiation and nephrotoxic contrast media exposes patients to a small, but significant, risk of serious complications.

In a prospective study of fibrosis patterns in 63 patients with a clinical diagnosis of DCM and normal coronary angiograms, 60% of patients, showed no LGE, while in about 30% of patients, a patchy midwall pattern of enhancement was seen that is distinct from that observed in CAD. Moreover, this pattern of midwall LGE correlates well with autopsy and explanted hearts from patients with DCM (Figure 3). Interestingly, in 12% of patients, a subendocardial pattern typical of infarction was seen. Thus, in spite of the normal coronary angiogram, an ischemic etiology is likely due to either recanalization or arterial emboli. This study highlights some of the limitations of luminography in assessing patients with heart failure. The clinical implications are important prognostically, as this latter cohort of patients would have been mislabeled as having idiopathic DCM when in fact they warrant treatment for secondary prevention of ischemic heart disease with agents such as aspirin and statins. In addition, some patients with coexistent minor CAD on invasive coronary angiography (eg, single-vessel disease) may be misdiagnosed as having an ischemic etiology when the primary pathology is a nonischemic DCM and the coronary disease is merely a bystander. LGE is therefore useful to differentiate etiology in such patients. It has a complementary role to angiography and in many cases may avoid the need for the latter.22-24

It has also been proposed that in patients with the typical pattern of subendocardial enhancement in a coronary artery territory, primary DCM can be excluded as a sole cause. Subsequent prospective studies using LGE to differentiate the underlying etiology have already produced promising results with a high accuracy. Ongoing trials using augmented protocols with coronary CMR and/or CMR perfusion with LGE in this group may produce even better results, thereby providing robust evidence for CMR as a valid noninvasive alternative to invasive x-ray coronary angiography.

Figure 3. Dilated cardiomyopathy. Late gadolinium enhancement study demonstrating midwall fibrosis in a patient with dilated cardiomyopathy (arrows) as seen in the 4-chamber (panel A) and short-axis views (panel B).
In DCM, the presence of midwall fibrosis is associated with an increased incidence of all-cause mortality and unplanned hospitalization. There is a trend toward increased significant arrhythmia. These findings are independent of established markers of adverse outcome such as left ventricular ejection fraction (LVEF). Further work is required to examine the value of such findings in the DCM cohort in the decision to implant defibrillators and pacemakers.

**Myocarditis**

In patients presenting acutely with heart failure and troponin elevation, but normal coronaries, an important cause is myocarditis. Biopsy-validated CMR studies in such patients have been very informative. T2-weighted images can show focal increases of midwall and subepicardial myocardial signal defining areas of edema. This is particularly the case in the first 3 weeks from symptom onset. In the proportion where there is acute necrosis or residual fibrosis, this can be detected by LGE. CMR is very useful to establish this diagnosis and in addition guide the site of LV biopsy, thereby increasing the yield of this invasive procedure. The pattern of LGE is also related to the type of virus infection and the effect on long-term LV function.25-28

**Hypertrophic cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) is characterized by asymmetric wall thickening, myocyte disarray, and interstitial or replacement fibrosis. The pattern of replacement fibrosis is unlike that seen in DCM or post-infarction. Typically, it is patchy, midwall, and most commonly in areas of maximal wall thickening. Microvascular ischemia is a potential mechanism. A cohort of these patients is at risk of developing the progressive variant with heart failure. Transthoracic echocardiography is the most commonly used noninvasive method to study HCM. However, the 3-D nature of CMR allows for the precise definition of the site and the extent of hypertrophy, especially at the basal anterolateral wall and apex, which are less well assessed by echocardiography, sometimes leading to missed diagnoses. Small cavity volumes with good systolic function can also be readily assessed. In-vivo CMR studies have confirmed that the patchy, midwall patterns of LGE found in HCM correlate well with pathological patterns of fibrosis (Figure 4). LGE may have a role in diagnosis and identifying high-risk patients.29-34

About 4% of patients who present clinically with HCM actually have Fabry’s disease (an X-linked disorder of sphingolipid metabolism causing idiopathic left ventricular hypertrophy). LGE shows a distinct and unusual pattern of lateral wall enhancement in these patients with a concentric pattern of hypertrophy.

CMR is also useful in distinguishing heart failure linked to HCM from hypertensive heart disease. In the latter, there is a concentric pattern of wall thickening that usually does not exceed 15 mm, with increased cavity volumes and reduced or normal range systolic function. While these patients have increased interstitial fibrosis, replacement fibrosis of the type detected by CMR is very unusual. By contrast, over half of patients with HCM have evidence of patchy fibrosis.

**Amyloidosis**

Amyloid heart disease is characterized by fibril deposition within the myocardium. There is concentric wall thickening, but poor contractility with marked diastolic dysfunction. The interatrial septum is often thickened and there is atrial dilatation. CMR is useful to document these abnormalities. Following gadolinium chelate, there is a unique pattern of circumferential late enhancement of the subendocardium with variable penetration through the myocardium of the LV. The interventricular septum may show a zebra pattern because it has two effective subendocardia. A typical sign is that the blood pool is dark on the LGE images, which seems to be specific to this condition and marks rapid blood washout of gadolinium. This reflects high myocardial uptake, fast blood washout, and similar T1 values of the blood-pool and myocardium in this condition.35
**Sarcoidosis**

Among patients with sarcoidosis at autopsy, 20% to 30% have evidence of cardiac involvement. Typically, granulomatous changes most commonly affect the LV lateral wall, papillary muscles, RV subendocardial surface, and RV free wall. The diagnosis of cardiac involvement is important to establish, as a proportion of patients may present with sudden cardiac death due to malignant ventricular arrhythmias. Patients with cardiac sarcoidosis may also develop progressive heart failure due to LV dilatation and functional impairment. LGE is useful to detect cardiac granulomatous disease, and may provide a potential therapeutic marker (Figure 5). In addition, the use of T2-weighted sequences identifies myocardial inflammation, which can be used as a guide to disease activity. Work is still under way to determine the sensitivity and specificity of CMR in this difficult condition.

**Arrhythmogenic right ventricular cardiomyopathy**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by RV dilatation and functional impairment resulting from fibrofatty replacement of the RV myocardium. LV dilatation is a late manifestation. It is a genetic condition caused by abnormal cell connections through the desmosome, suggesting that the fibrofatty phenotype is a result of repair of injury. Progression of ARVC may be exacerbated by physical exercise. It can cause sudden death from arrhythmia or progressive heart failure. The diagnosis is made on the basis of defined taskforce criteria. There is biventricular dilatation in about 20% of cases, so that it can sometimes be difficult to distinguish from DCM. The disproportionate RV enlargement in conjunction with regional RV wall abnormalities is a useful guide. The RV is difficult to visualize by echo due to near-field signal dropout and the crescentic shape. CMR obtains 3-D images to depict structural and functional abnormalities and so is well suited to demonstrate regional wall-motion abnormalities, thinning, and aneurysmal changes in the RV free wall, increased RV and LV volumes, and increased T1 myocardial signal, suggesting fatty infiltration. The role of LGE to identify RV or LV fibrosis is currently being evaluated in this condition. The RV myocardial tissue is significantly thinner than that of the LV and has a higher degree of trabeculation so that detection of RV wall fibrosis is more difficult. Recent work in genotyped cohorts suggests that about 20% of patients have evidence of LV fibrosis.

**Iron-overload cardiomyopathy**

CMR has established itself as the gold-standard investigative tool for the noninvasive assessment of myocardial iron overload. In patients with transfusional iron overload (especially β-thalassemia major), heart failure is an important cause of death. The amount of myocardial iron can be quantified using the T2* relaxation parameter, which is the component of T2 that is sensitive to microscopic magnetic variations caused by small iron deposits. This simple scan can be performed in a single breath-hold and is validated against both biopsy samples and other markers of myocardial dysfunction such as LVEF. The normal myocardial T2* is 50 ms, with a lower limit of 20 ms. Of patients with thalassemia presenting with heart failure, 89% have a T2* <10 ms, making this measure a very powerful early warning of impending myocardial dysfunction. Scans can also directly guide iron-chelating drug regimens.
**CMR IN VALVULAR DISEASE**

CMR is gaining acceptance as an accurate and highly reproducible method for evaluation of the structural and functional variables associated with valvular disease. It provides complementary information to echocardiography. While echocardiography and catheterization are most widely used for the evaluation and follow-up of valvular disease, it can be challenging in the individual patient to quantify the severity of the lesion, determine the impact on ventricular morphology and function, and evaluate prognosis with respect to timing of surgical versus pharmacologic treatment.

Breath-hold spin echo sequences (for morphology) and the cine sequences (for dynamic visualization) can reliably characterize both normal and abnormal valves. Turbulence of flow resulting from stenosis or regurgitation causes signal loss on cine sequences, allowing identification of the abnormality. The size and extension of the signal loss, however, is only a semiquantitative measure for lesion severity because of the influence of hemodynamics, shape of the valve, and parameters of the sequence, just like in color flow mapping in echo-Doppler. Multiplanar imaging enables direct and accurate planimetry of the stenotic or the effective regurgitant orifice area. Through plane motion, signal voids due to turbulence or calcification and distorted valve morphology may interfere with this measurement, but there is good correlation with derived valve areas determined by echocardiography and cardiac catheterization. Quantification of peak and mean flow velocities (m/s) as well as volume flow (mL/s) at multiple sites in the heart can be measured by phase contrast velocity mapping. The velocity of blood flow through vessels or cardiac valves is measured. The integral product of blood velocity and cross-sectional area over time allows calculation of cardiac output, valvular regurgitant fraction, and shunt ratios.

The combination of stroke volume, flow mapping, and peak velocity measurements enables the accurate calculation of gradients, resistance, valve area, and regurgitant volumes and fraction. The impact of valvular dysfunction on cardiac remodeling can be monitored serially by measuring myocardial mass and ventricular volumes. Automated tracking of valve through plane motion may in the future improve the reliability of velocity encoded measurements and may make CMR the optimal technique to quantify some forms of valvular dysfunction. Aortic regurgitation can be quantified by measuring retrograde diastolic flow immediately above the valve. The regurgitant fraction represents the percentage fraction of the retrograde-to-forward flow. For mitral regurgitation, direct flow measurement is difficult due to annular through-plane motion, the altering valve plane, the presence of multiple or eccentric jets, and the larger, less circular mitral ring area. The difference between the stroke volume obtained from cavity measurements and antegrade flow in the aorta is therefore a more accurate and widely used technique. For stenosis assessment, both in-plane and through-plane velocity measurements can be used, but in both instances multiple parallel planes are required to optimize alignment and to obtain true maximal velocities that can be inserted in the modified Bernoulli equation for calculation of gradients and valve area with the continuity equation.

There were previous safety concerns about performing CMR in patients with prosthetic metal valves, based largely on anecdotal evidence. Current guidelines state that it is safe to perform CMR in all prosthetic valves although the metal in the prostheses causes local artifacts that can obscure small jets. Quantification of valvular regurgitation remains possible, but even more care has to be taken to adjust the acquisition plane to the motion of the valve.

Compared with echocardiography, the temporal resolution is not as good with CMR, so that leaflet motion is more difficult to assess. Endocarditis lesions can therefore be difficult to visualize and echocardiography is recommended. Software and hardware upgrades that improve real-time CMR may offer improvements on this front.

Overall, in valve disease, CMR is particularly useful when echo images are suboptimal, transesophageal echo cannot be performed, or the results of echo and catheterization conflict. It is the technique of choice for individual patient follow-up with respect to volumes and mass. Combined with other aspects of the CMR study such as the detection of infarction, CMR has an important role both when the valve disorder is the primary and the secondary pathology to be evaluated.39-41

**CMR IN CONGENITAL HEART DISEASE**

The management of patients with congenital heart diseases needs an accurate characterization of underlying cardiac morphology and hemodynamics. Due to the multiplanar 3-D imaging and wide field of view, together with comprehensive anatomical and functional information available, congenital heart disease represents a major indication for CMR. The ability to quan-
tify local flow and therefore shunts has avoided the need for catheter studies in many patients. Serial evaluation is facilitated by the lack of ionizing radiation exposure. The problems of using echocardiography post-surgery where scar tissue around the heart impedes ultrasound penetration and views are often suboptimal, have all contributed to the successful use of CMR in this indication. A range of CMR sequences is used in congenital heart disease: (i) gradient echo cine and single frame sequences for overall anatomy and function (LV, RV, and atrial volumes, stroke volumes and ejection fraction, and myocardial mass); (ii) spin echo for morphologic details, (iii) T2 imaging for tissue characterization, (iv) velocity mapping of local flow for valvular function (aorta, pulmonary artery, caval veins, pulmonary veins, grafts and conduits, and valve planes); and (v) gadolinium angiography for 3-D representation of the great vessels and complex anatomy. More recently, LGE has been useful in risk stratification of patients with previous surgical repairs based on the presence of RV fibrosis.

Anatomical arrangement

The visceroatrial situs (situs solitus, situs inversus, situs ambiguus) and the malposition of the heart (dextrocardia) can be easily obtained with CMR since the technique offers a large field of view that includes the surrounding structures, including the abdomen, and identification of the different chambers from morphologic and functional characteristics. A full set of images in the three orthogonal planes (transverse, sagittal, coronal) is the basis for this analysis. Depending on the anomalies observed, further images, taken in oblique planes, can be combined with functional imaging.

Assessment of atria and ventricles

While atrial septal defects are usually seen with echocardiography (especially transesophageal echo), their hemodynamic impact on the circulation (shunt quantification, RV dilatation, and function) is more accurately assessed with CMR. Flow measurements in the ascending aorta and in the pulmonary artery are used to derive shunt flow and size. RV dimensions and function are reproducibly measured; CMR can quantify volumes, ejection fraction, and pulmonary valve flow.

In patients with partial anomalous pulmonary venous return the route and drainage of the aberrant vein can be established, together with the shunt fraction. Contiguous 2-D slices or 3-D volume acquisitions are used to pick up systemic venous abnormalities or variants (left superior vena cava, interrupted inferior vena cava) that are useful both for diagnosis and guiding routes for intervention. An important group is the postsurgical repair set. Baseline evaluation and early detection of problems are important and common reasons for referral, eg, following a Mustard or Senning procedure.

Atrioventricular concordance

CMR can be used to identify systemic and pulmonary chambers based on typical morphologic features. Atrioventricular discordance or abnormal morphology or function of the valves (straddling, atresia, regurgitation, stenosis) can be visualized. A reliable quantification of ventricular volumes and function can be used to guide surgical decisions (eg, would a patient benefit from a total cavopulmonary connection [TCPC]?).

Ventricles

Complex ventricular anomalies (tetralogy of Fallot, univentricular hearts, valve atresia) can be seen by CMR and the shunt fraction and morphologic and hemodynamic consequences can be quantified. Ventricular septal defects can be visualized (jet on cine images) and the shunt quantified, but it is particularly in complex lesions (eg, double outlet) where the strengths of CMR are demonstrated.

Valvular assessment

While the temporal resolution of CMR is inferior to echocardiography, so that valve morphology is not so well seen, CMR is better at quantification of regurgitation, since it can measure flow directly, and the impact on the receiving chamber, especially for the RV, is better assessed. In pulmonary regurgitation (eg, post-patch surgery for tetralogy of Fallot), it is clinically difficult to decide on the appropriate timing for valve replacement. Serial follow-up in these patients can gauge the severity and rate of any deterioration.

Large vessels and conduits

The commonest anomaly of the thoracic aorta is coarctation. CMR can visualize the affected part of the aorta, the presence of any residual membrane, and in addition demonstrate the collateral circulation. By comparing flow before the coarctation and at the level of the diaphragm, the collateral circulation can be quantified and used to judge the success of invasive treatment. Diastolic tailing, Vmax, and dilatation of inter-
nal mammary arteries provide a guide to the severity. Other abnormalities of the aorta (double aortic arch, aneurysm of the sinus of Valsalva, dilatation in Marfan and Ehler-Danlos syndromes) can be followed over time. Patent ductus arteriosus can be easily seen with echo in newborns, but in older patients CMR can be more reliable. Abnormalities of the pulmonary circulation in patients with reduced pulmonary artery flow or systemic-to-pulmonary collaterals, as well as pulmonary anomalies can be shown with CMR.

Follow-up postoperatively

CMR is useful after surgery for complex anomalies where the echocardiographic quality is often suboptimal and a need exists for a quantitative technique that can reliably follow volumes, function, and morphology over time. This is particularly true for conduits and for the RV, which is often overloaded as it copes with systemic circulation or due to pulmonary insufficiency.

Coronary arteries

CMR is the current gold standard for anomalous coronary arteries. It can show the abnormal origin of the artery and its subsequent course with respect to aorta and pulmonary artery. This is important for risk and surgical planning in congenital heart disease.

Comparison with other modalities

In newborns and young infants, echocardiography is the imaging modality of choice, since image quality is typically very good and CMR would require sedation or anesthesia in this cohort. By contrast, in adolescents and adults with complex pathology or after surgery, CMR is better. The CMR information may allow cardiac catheterization to be avoided, significantly shortened, or reserved for interventional procedures. For serial follow up, CMR usually offers all the necessary clinical information required, while cumulative radiation can be avoided.

CMR AND THE GREAT VESSELS

CMR is useful for assessing diseases of the aorta and the involvement of branch vessels. Gradient echo images are useful for measuring the size, shape, and compliance of vessels, while spin echo images provide information on the vessel walls and periaortic soft tissue. Gadolinium CMR angiography yields high resolution 3-D angiograms that are very useful in surgical planning.

Routine indications for performing CMR in aortic disease are to diagnose or follow up aneurysms or dissections. Based on the range of sequences, distinction can be readily made between common causes of an acute aortic syndrome, including dissection, intramural hematoma, and penetrating aortic ulcers.

In aortic dissection, the presence and extent of any intraluminal intimal flap is seen from transverse cine slices. Gadolinium CMR angiography may provide additional information regarding branch vessel involvement. The presence of pericardial effusions and the function of the aortic valve can also be depicted, and quantification of aortic regurgitation is possible using velocity mapping. The speed of acquisition (a dissection can be assessed within 15 minutes) means that even moderately unstable patients can be scanned safely.

For intramural hematoma black-blood spin echo sequences with T1 weighting are useful for depicting the bright crescentic thickening of the aortic wall. Penetrating aortic ulcers are usually seen in the elderly with diffuse and severe forms of atherosclerosis. These ulcers can lead to large aneurysms that may need placement of endovascular stent-grafts. Such ulcers can be distinguished from small and benign ulcers by using both black blood CMR and angiography.

Carotid imaging is now well established by CMR and, in addition to anatomical delineation, much attention is focused on plaque characterization and its regression with therapy.

MULTIDETECTOR COMPUTED TOMOGRAPHY ANGIOGRAPHY (MDCTA)

One of the most exciting recent advances in noninvasive cardiac imaging has been the detection of CAD by MDCTA. Technical developments have enabled better temporal and spatial resolution through the use of multiple detector rows. Coronary artery lumen stenosis can be assessed both visually and quantitatively using reconstruction and analysis software. Information is obtained as well on nonobstructive atherosclerotic plaque in the coronary artery wall.

Typically, there are two aspects to the study. Firstly, assessment of the calcium score; and secondly, assessment of stenotic lesions. A calcium score is usually obtained from an unenhanced computed tomography (CT) technique using a 3-mm collimator and prospective ECG gating with tube current modulation in systole. The calcium score is calculated using the Agatston
method modified for MDCTA and is useful both as a marker of CAD and as a predictor of CAD events independent of standard risk factors. In patients at intermediate Framingham risk, it is useful for stratifying patients into either a lower- or higher-risk group. In one study, patients with a Framingham risk of 10% to 15% and a calcium score above 300 had a 19.5% incidence of myocardial infarction or coronary death over a median of 7 years, while patients with the same Framingham risk and a lower calcium score had an incidence of only 4.2% over the same time period. Coronary artery calcium scoring is less useful in patients who are at very low or very high risk for coronary events. Therefore, in patients who are known to have significant CAD, and thus are at high risk for clinical events, coronary artery calcium score is not necessarily performed prior to contrast-enhanced MDCTA.

For assessment of the coronary artery lumen, typically, a bolus of 80-100 mL of isotonic contrast medium is administered. The contrast attenuation or brightness is the result of the product of the iodine content times the injection rate (iodine flux). Scanning is initiated based on either a timing bolus (15 to 20 mL of contrast medium) or an automated bolus tracking system in the ascending or descending aorta, which detects a threshold of 100-150 Hounsfield units (HU). A breath-hold of 8 to 16 seconds is required for native coronary arteries and 12 to 20 seconds for patients with bypass grafts, depending on the scan field covered by the detectors with each gantry rotation. Longer breath-holds are required for scanners with fewer detectors. Segment-based analyses have a sensitivity of 73% to 99% and specificity of 86% to 97% with current 64-slice scanners. It remains unclear how MDCTA will perform in the low-to-intermediate-risk patients as a primary investigation, although it has a role as an adjunctive diagnostic test in patients at low-to-intermediate risk of CAD and an indeterminate cardiac stress test result. An scan showing no significant stenosis (>50%) predicts an excellent short-term prognosis in this population (event rate of 0.2% at 6 months), but further work is required to evaluate the long-term incremental value.

MDCTA has also been studied in patients who have undergone coronary artery stenting, but due to the blooming artifact and partial volume effects of the stent struts, the sensitivity for detecting in-stent restenosis remains suboptimal. Bypass grafts are, however, well-visualized and with high diagnostic accuracy due to their larger diameter and relative lack of motion. MDCTA is also helpful in identifying anomalous coronary arteries.

The main limitation is exposure to ionizing radiation. The effective radiation dose with 64-detector MDCTA is currently around 8 to 10 mSv, but can range from 6.4 and 21.4 mSv per study depending on the scan. The effective radiation dose of MDCTA can be reduced using ECG-dependent dose modulation and reduced tube voltage. By contrast, the effective radiation dose with invasive diagnostic coronary x-ray angiography is typically around 2 to 3 mSv. Although the lifetime risk of dying from cancer due to the dose of radiation absorbed during a 64-detector CT scan is estimated to be less than 0.1%, radiation exposure should be taken into consideration when subjecting a patient to an MDCTA. Other limitations are difficulty interpreting segments due to severe calcifications, frequent need for β-blockers to slow heart-rate, and suboptimal scans due to rhythm and breathing artifacts.

**ECHOCARDIOGRAPHY**

Myocardial contrast echocardiography (MCE) is a new technique that utilizes acoustically active gas-filled microspheres (microbubbles), which remain exclusively in the intravascular space and allow the simultaneous assessment of global and regional myocardial structure, function, and perfusion. An increasing body of data supports its role in assessing myocardial viability and predicting the recovery of function. The ultrasonic contrast agents are microbubbles that resonate when excited by diagnostic ultrasound frequencies producing an increasing ultrasound backscatter from the blood. Recent advances in echocardiography have resulted in improved detection of microbubbles within the myocardium allowing combined acquisition of function and perfusion data, thus making MCE suitable for bedside use. MCE detects changes developing in the coronary microcirculation, providing important information for the evaluation of severity of CAD and for the detection of viable myocardial tissue in acute or chronic CAD. It accurately differentiates “stunning” from necrosis, delineates transmural extent of infarction, predicts recovery of regional and global left ventricular systolic function in the recuperative phase, identifies patients at high risk of left ventricular remodeling, and provides incremental viability data when performed in conjunction with low-dose dobutamine echocardiography.

Another significant development over the last decade has been the introduction of 3-D echocardiography and its evolution from slow and labor-intense offline reconstruction to real-time volumetric imaging. The major advantage of this technique over more conven-
CONCLUSION

Over the last 5 years there have been tremendous developments in imaging tools to evaluate cardiac patients. CMR is safe, noninvasive, and with no radiation exposure. Within a single study, a comprehensive evaluation is possible, aiding diagnosis and treatment strategies. In considering the applications of CMR, information is obtainable on anatomy, function, flow, viability, perfusion, tissue characterization, as well as definition of the great arteries. No other single test has this range. For cardiomyopathies and congenital heart disease, the role of CMR is now fully established. For CAD, with the exception of coronary artery depiction, a wide range of function information is derived. While MSCT currently offers better resolution images of the coronary arteries, the high radiation exposure even with dual-source scanners and lack of functional information limits its broader appeal. Future applications are likely to emanate from improved hardware and software as well as the use of targeted contrast agents. Advances in echocardiography now enable excellent characterization of myocardial mechanics. Contrast echo is useful to look at perfusion and define viable myocardium. 3-D real-time echo is guiding management of patients with valve disease and complex congenital conditions. Important areas that may change clinical practice are; (i) the role of echo in predicting response to cardiac resynchronization therapy; (ii) whether assessment of perfusion by CMR will replace SPECT; and (iii) evaluating the clinical role of coronary CT in routine clinical practice. These issues will be addressed in the following Expert Answer review articles.

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New Images in Cardiology

*Expert Answers to Three Key Questions*

1. What is the role of echocardiography in predicting response to cardiac resynchronization therapy?
   *J. J. Bax*

2. Perfusion cardiovascular magnetic resonance: will it replace SPECT?
   *J. Schwitter*

3. Computed tomography coronary angiography: what is the hype, the reality, and the future?
   *U. P. Sechtem*
What is the role of echocardiography in predicting response to cardiac resynchronization therapy?

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Cardiac resynchronization therapy (CRT) is a promising technique in patients with end-stage heart failure. Current selection criteria include New York Heart Association class III or IV heart failure, left ventricular (LV) ejection fraction ≤35%, and wide QRS complex (>120 ms). The majority of patients selected according to these criteria respond well to CRT, but 20% to 30% do not respond. Selection criteria could be improved by including assessment of LV dyssynchrony, which appears mandatory for response to CRT. LV dyssynchrony may be evaluated using conventional echocardiography (eg, M-mode echocardiography), although tissue Doppler or strain imaging is preferred. Which technique will provide optimal information on LV dyssynchrony is currently unknown, as is the precise extent of LV dyssynchrony needed to predict response to CRT. Large multicenter studies are being performed to elucidate these issues.

Keywords: cardiac resynchronization therapy (CRT); echocardiography; heart failure; left ventricular dyssynchrony; response to treatment; strain imaging

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SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CRT</td>
<td>cardiac resynchronization therapy</td>
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<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<td>PROSPECT</td>
<td>Predictors Of reSPonsE to Cardiac resynchronization Therapy</td>
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<tr>
<td>SPWMD</td>
<td>septal-to-posterior wall motion delay</td>
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<td>TDI</td>
<td>tissue Doppler imaging</td>
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DEFINITION OF RESPONSE TO CRT

It is hard to define a responder to CRT and definitions vary significantly from one study to another. The response is generally assessed after 6 months of CRT, and clinical trials have used clinical markers for this purpose, including NYHA class, 6-minute walking distance, quality of life score, heart failure hospitalization, and mortality (Table II, page 106). Echocardiographic markers have also been used, including LVEF, LV volumes, and mitral regurgitation (Table II). The prevalence of nonresponse to CRT is around 30% when clinical markers are used, but increases to 40% when echocardiographic markers are used. This issue was specifically addressed recently, in a direct comparison between these clinical and echocardiographic markers of response in 144 patients with end-stage heart failure, LVEF ≤35%, and ORS duration ≥120 ms who underwent CRT implantation. Clinical markers and LV volumes/LVEF were assessed at baseline and 6-month follow-up. An improvement of at least 1 NYHA class occurred in 70% of patients, indicating clinical response to CRT. Echocardiographic response (defined as a decrease >15% in LV end-systolic volume) was observed in 56% of patients. Clinical improvement without echocardiographic response was observed in 19% of...
patients, whereas only 5% of patients failed to show clinical response in the presence of echocardiographic response (resulting in a 24% disagreement between clinical and echocardiographic response) (Figure 1).

In addition, it is unclear when exactly to assess the response to CRT. Invasive and echocardiographic studies have demonstrated an immediate response to CRT, and it is uncertain whether this translates into a response at 6-month follow-up. In particular, gradual response to CRT with gradual improvement in LV volumes has been demonstrated recently, and may be more pronounced in patients with ischemic cardiomyopathy.10

**WHAT PREDICTS RESPONSE TO CRT?**

In the failing heart, cardiac dyssynchrony is present on three levels: (i) atrioventricular; (ii) interventricular (right versus left ventricle); and (iii) intraventricular (within the left ventricle). Initially, it was considered that interventricular dyssynchrony was the major predictor of response to CRT and was reflected by QRS duration. Accordingly, wide QRS complex (>120 ms) was considered a major selection criterion for CRT. However, it has recently been questioned whether baseline QRS duration is a predictor of response to CRT, since a clear relation was demonstrated in only 1 of 34 CRT studies.11 One study in 61 patients with heart failure specifically addressing this issue demonstrated that QRS duration was similar in responders and nonresponders (179±32 ms vs 171±32 ms, NS), and thus failed to predict response to CRT.12

**Clinical markers used to define response**

Improvement in:
- NYHA class
- 6-minute walking distance
- Quality-of-life score
- Exercise capacity (VO₂ max)
- Hospitalization for heart failure
- Mortality

**Echocardiographic markers used to define response**

Improvement in:
- LVEF
- LV volumes (remodeling)
- Mitral regurgitation

More recent (echocardiographic) studies have focused on the utility of intraventricular or LV dyssynchrony as a predictor, and have reported no relation between QRS duration and LV dyssynchrony, as assessed by tissue Doppler echocardiography (Figure 2).13 On the other hand, the majority of echocardio-
graphic studies demonstrate that LV dyssynchrony predicts response to CRT. So, QRS duration reflects interventricular dyssynchrony, whereas LV dyssynchrony is needed for accurate prediction of response to CRT. A wide variety of echocardiographic techniques have been introduced for assessment of LV dyssynchrony and prediction of response to CRT (Table III).

**Table III.** Echocardiographic methods of assessing left ventricular dyssynchrony.

<table>
<thead>
<tr>
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<th>M-mode echocardiography</th>
<th>Pulsed-wave tissue Doppler imaging</th>
<th>Color-coded tissue Doppler imaging</th>
<th>Tissue synchronization imaging</th>
<th>Strain/strain rate imaging</th>
<th>3-D echocardiography</th>
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**M-MODE ECHOCARDIOGRAPHY**

M-mode echocardiography is the simplest technique for assessment of LV dyssynchrony, and was proposed by Pitzalis et al. A parasternal short-axis view is used to measure so-called septal-to-posterior wall motion delay (SPWMD), the interval between the systolic excursions of the anteroseptum and of the posterior wall. An example is shown in Figure 3, Panel A (page 108).

Pitzalis et al. evaluated 20 patients (mainly with nonischemic cardiomyopathy) and showed that responders to CRT had a significantly larger SPWMD than nonresponders. When a cutoff value of 130 ms for LV dyssynchrony was used, response to CRT was predicted with a sensitivity of 100% and a specificity of 63%.

The M-mode approach was further explored by Marcus et al. who performed a retrospective analysis of the CONTAK-CD (not an acronym; name of device combining an implantable cardioverter defibrillator with CRT, manufactured by Guidant Corporation) patients (n=79 patients), 72% of whom had ischemic cardiomyopathy. SPWMD could not be assessed in 50% of the patients, as the anteroseptum is frequently akinetic in patients with ischemic cardiomyopathy (Figure 3, Panel B, page 108). The authors reported a sensitivity of 24% and a specificity of 66% in predicting response to CRT.

**TISSUE DOPPLER IMAGING AND TISSUE SYNCHRONIZATION IMAGING**

At present, tissue Doppler imaging (TDI) is probably the most popular technique for assessing LV dyssynchrony. It measures peak systolic velocities in different regions of the myocardium and the time-intervals...
between electrical activity (the QRS complex) and the mechanical activity (segmental peak systolic velocity). The myocardial velocity curves can be constructed online using pulsed-wave TDI (Figure 4, Panel A) or reconstructed offline from the color-coded TDI images (Figure 4, Panel B).

Color-coded TDI has clear advantages over pulsed-wave TDI: (i) offline analysis is possible; (ii) multiple segments can be analyzed in one cardiac cycle, and (iii) peak systolic velocity is displayed more accurately. LV dyssynchrony is then assessed by comparing delays between peak velocities between different regions, permitting assessment of delays between peak velocities between different regions as a marker of LV dyssynchrony (Figure 5).

Studies vary in the number of segments used to assess LV dyssynchrony, but 2 or 4 basal segments (septal, lateral, inferior, anterior) are frequently evaluated. The 4-segment approach was used in 85 heart failure patients with follow-up data obtained up to 1 year. The optimal cutoff value of 65 ms in identifying significant LV dyssynchrony resulted in 80% sensitivity and specificity in prediction of clinical response, and 92% sensitivity and specificity for prediction of LV reverse remodeling. Moreover, patients with ≥65 ms LV dyssynchrony who underwent CRT had a 6% 1-year event-rate, as compared with 50% for patients with <65 ms LV dyssynchrony (Figure 6). When a 6-segment model was employed, response to CRT was predicted with a sensitivity of 97% and a specificity of 55%. Using a cutoff value of 31 ms, the 12-segment model has been used to derive the so-called asynchrony index; with a sensitivity of 96% and specificity of 78%.

Tissue synchronization imaging is similar to TDI, but is more visually oriented. It automatically calculates the peak systolic velocities from TDI and displays them as a color map, for direct visualization of the early activated segments (displayed in green) and late activated seg-

Figure 3. Panel A. Assessment of the septal to posterior wall motion delay (SPWMD) as derived by M-mode echocardiography. The delay between the anteroseptal systolic excursion is compared with that of the posterior wall (arrows). Panel B. In ischemic cardiomyopathy, the anteroseptum is frequently akinetic and assessment of SPWMD is not possible.

Figure 4. Panel A. Pulsed-wave tissue Doppler tracing of a normal individual. The pulsed-wave sample is placed online in the region of interest and the myocardial velocity curve is derived. Panel B. Color-coded tissue Doppler tracing in a normal individual. The sample is placed offline in the basal part of the septum, demonstrating PSV and diastolic parameters (E’ and A’).

Abbreviations: AVC, aortic valve closure; AVO, aortic valve opening; PSV, peak systolic velocity, E’ and A’ represent diastolic parameters.
ments (displayed in red) (Figure 7, page 110). This technique predicted response to CRT with 82% sensitivity and specificity.20

**STRAIN AND STRAIN RATE IMAGING**

Strain imaging techniques can be derived from color-coded TDI. Strain and strain rate imaging measures (the rate of) myocardial deformation, and has the advantage of differentiating between active and passive myocardial motion. This is particularly important in regions with extensive infarction and scar formation, where passive motion occurs. With strain (rate) imaging, the extent of LV dyssynchrony is assessed by measuring time to peak systolic strain.

Initial studies used apical views and derived longitudinal strain, whereas more recent work used short-axis images to derive radial strain. One study assessed LV dyssynchrony by circumferential strain, using a cut-off of 130 ms, which yielded 95% sensitivity and 88% specificity.21

The more robust and less operator-dependent 2-dimensional (2-D) strain technique (also referred to as speckle tracking) was recently introduced for strain imaging and predicted response to CRT with 91% sensitivity and 75% specificity.22 The speckle tracking software makes use of natural acoustic markers, or speckles, that are present on standard ultrasound tissue images. These speckles move together with the myocardium, and can be followed accurately from frame to frame. 2-D tissue velocity vectors are then derived and strain can be assessed.

![Figure 5. Panel A. Two-segment color-coded tissue Doppler imaging of a normal individual without left ventricular dyssynchrony (yellow tracing septum, green tracing lateral wall). The peak systolic velocities (arrow) of both walls appear simultaneously. Panel B. Two-segment color-coded tissue Doppler imaging of a heart failure patient with left ventricular dyssynchrony (yellow tracing septum, green tracing lateral wall). The peak systolic velocities (arrows) of both walls show a delay. Abbreviations: AVC, aortic valve closure; AVO, aortic valve opening.](image)

![Figure 6. Kaplan-Meier survival curves of patients with severe LV dyssynchrony (>65 ms) indicate a low event rate over 1-year follow-up after CRT implantation, whereas patients without severe LV dyssynchrony (<65 ms) have a high event rate. Reproduced from reference 17: Bax JJ, Bleeker GB, Marwick TH, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol. 2004;44:1834-1840. Copyright © 2004, American Heart Association.](image)
3-D ECHOCARDIOGRAPHY

LV volumes and LVEF can be assessed with great accuracy using 3-dimensional (3-D) echocardiography. Evaluation of LV dyssynchrony requires analysis of regional function as a function of time, and a series of plots is obtained representing the change in volume for each segment throughout the cycle. Sixteen or 17 segments are often used. In the presence of LV synchrony, each segment would be expected to achieve the minimum volume at the same time in the cardiac cycle. In the presence of LV dyssynchrony, however, minimum volume will be reached for each segment at different times, and the extent of this dispersion reflects the LV dyssynchrony and can be used to determine the systolic dyssynchrony index. Parametric “polar-map” displays (of the 3-D data) of the timing of LV contraction have been developed to simplify interpretation of results (Figure 8). Color coding is used to identify the region of latest activation. Kapetanakis and coworkers\(^\text{23}\) recently demonstrated the use of this technique in 26 patients undergoing CRT. A significant difference in the systolic dyssynchrony index between responders and nonresponders was demonstrated, but no prediction of response to CRT was made.

WHICH ECHO TECHNIQUE TO USE?

No large, multicenter studies have yet directly compared prediction of response to CRT by these different echo techniques, which use from 2 to 12 segments and different cutoff values for LV dyssynchrony. The prospective, multicenter PRedictors Of reSPonsE to Cardiac resynchronization Therapy (PROSPECT) trial is specifically designed to directly compare the most widely used echocardiographic techniques in predicting response following CRT.\(^\text{24}\) Three hundred patients will undergo CRT implantation and echocardiographic techniques will be compared in predicting the response. Follow-up after CRT implantation is 6 months, and the results are expected during 2007.

VALUE OF OTHER IMAGING TECHNIQUES IN CRT

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is not used extensively to evaluate LV dyssynchrony. Tagged MRI has proved feasible for assessment of LV dyssynchrony in animal models of heart failure and in normal individuals, but we lack data in patients. It has been demonstrated recently that LV dyssynchrony can be derived

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Figure 7. Tissue synchronization imaging. The colors represent time to peak systolic velocity. Green corresponds to early mechanical activation; yellow/orange/red indicates a delayed peak systolic velocity (in this case in the lateral wall).

Figure 8. Parametric polar-map displays (lower left and right) of left ventricular dyssynchrony of the real-time 3-dimensional images. Blue indicates early activation, red indicates late activation. Left ventricular dyssynchrony is present before cardiac resynchronization therapy (CRT) in the anteroseptal region (indicated in red, lower left panel). Almost complete resynchronization has occurred after CRT, with disappearance of “red” regions (lower right panel).

from velocity-encoded MRI. In a small group of heart failure patients with depressed LVEF and wide QRS complex, excellent agreement between MRI and TDI was reported for assessment of LV dyssynchrony. These results are of interest, since MRI can also provide information on LV function, size, and shape, and scar tissue (when contrast-enhanced MRI is used), whose importance is highlighted in a study indicating that LV lead positioning in a large area with scar tissue did not result in response to CRT. The main limitations of MRI include time-consuming data acquisition and analysis, and the fact that repeat analysis after device implantation is not possible, since pacemakers are still a contraindication for MRI.

**Nuclear imaging**

Radionuclide angiography has been used to assess LVEF, but can also be used for evaluation of cardiac dyssynchrony. Inter- and intraventricular delay can be quantified using functional images, as assessed by Fourier analysis, with high reproducibility. This technique may potentially be useful for prediction of response to CRT, but solid data are lacking. Quantitative assessment by positron emission tomography (PET) showed that myocardial blood flow did not increase after CRT, but there was more homogenous distribution of myocardial perfusion. Recent observations with 64-slice CT revealed that patients with large infarctions may have limited venous anatomy not feasible for transvenous LV lead placement, which has to be done surgically.

**Computed tomography**

Computed tomography (CT) techniques cannot presently be used to assess cardiac dyssynchrony, but do allow noninvasive visualization of the cardiac venous system. In daily practice, retrograde invasive venography is used to determine venous anatomy during CRT implantation, and high variation in venous anatomy shows that not all patients are suited to transvenous LV lead implantation. With 16- and 64-slice technology, the venous system can be adequately visualized (Figure 9). Recent observations with 64-slice CT revealed that patients with large infarctions may have limited venous anatomy not feasible for transvenous LV lead placement, which has to be done surgically.

**CONCLUSION**

It has become clear that LV dyssynchrony is mandatory in evaluating the response to CRT, and is best assessed by TDI or strain imaging using echocardiography. A wide variety of ultrasound imaging techniques is available, and information is urgently needed on the optimal technique, optimal number of myocardial segments to evaluate, and optimal extent of LV dyssynchrony needed to predict the response to CRT. Other imaging techniques (MRI, nuclear imaging, CT) presently play a minor role in the evaluation of patients for CRT.
REFERENCES


What is the role of echocardiography in predicting response to CRT? - Bax


Perfusion cardiovascular magnetic resonance: will it replace SPECT?

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and Consultant Cardiac MR Center - Children’s University Hospital Zurich - Zurich - SWITZERLAND

While innovations in the treatment of coronary artery disease (CAD), eg, by the introduction of drug-eluting stents, are now entering a phase of consolidation, major changes in diagnostic imaging are still ahead of us, and most likely will occur in the very near future. This prediction is based on two major considerations: (i) newer imaging technologies will give rise to diagnostic strategies that were not available in the past; and (ii) exploitation of the information technology such as the World Wide Web will develop an increasing awareness of the need for better diagnostics through the knowledge gathered by international surveys and registries, which will direct our view from (restricted) academic settings to the population as a whole. This article discusses point 1 in detail, but let us take a brief look at point 2, which states that better diagnostics are needed.

According to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2006 Update,1 approximately half of all sudden cardiac deaths in the US occur before patients reach the catheterization laboratory for emergency treatment. These data clearly demonstrate that detection of CAD is suboptimal with current diagnostic strategies. Moreover, approximately half of men and almost two thirds of women dying of a heart attack in the US did not exhibit symptoms before the fatal event, which suggests that focusing on symptoms may be inappropriate in regard to a large portion of the patients at risk.

In the USA, in 2005, about half of patients who died of a heart attack did not reach the hospital for emergency treatment, indicating the need for earlier detection of coronary artery disease (CAD). Single photon emission computed tomography (SPECT) imaging has a high diagnostic and prognostic power despite some technical limitations. Perfusion- and late-enhancement cardiovascular magnetic resonance (CMR) are not limited by such restrictions. Multicenter trials have found a high diagnostic performance of CMR for the detection of CAD, with one trial additionally showing superiority of CMR over SPECT. The advantages of CMR, eg, lack of radiation exposure, will likely promote a shift toward early CAD detection by CMR. Nevertheless, more efforts are needed to standardize the technique, train physicians and personnel, and improve access to infrastructures.

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CMR</td>
<td>cardiovascular magnetic resonance</td>
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<tr>
<td>CXA</td>
<td>coronary angiography</td>
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<tr>
<td>LE-CMR</td>
<td>late-enhancement cardiac magnetic resonance</td>
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<tr>
<td>MDCT</td>
<td>multidetector computed tomography</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>MR CM</td>
<td>magnetic resonance contrast media</td>
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<tr>
<td>MR-IMPACT</td>
<td>Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial</td>
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<td>PCI</td>
<td>percutaneous coronary intervention</td>
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Keywords: cardiovascular magnetic resonance (CMR); coronary artery disease; infarction; ischemia; pharmacological stress; single photon emission computed tomography (SPECT); viability

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No identification of CAD in asymptomatic patients will be possible, however, if tests are costly and/or inconvenient and/or harmful for patients. The comparative features of an “ideal” cardiovascular magnetic resonance (CMR) and single photon emission computed tomography (SPECT) test are given in Table I.

Shaw and coworkers, in a large multicenter study (Economics of Noninvasive Diagnosis [END]), looked at the economic consequences of diagnostic strategies used in patients with suspected CAD. In this study, approximately 11 000 patients with stable angina pectoris were prospectively allocated to either invasive x-ray coronary angiography (CXA) or noninvasive SPECT imaging, the later being followed by CXA only if SPECT was positive. Over a 3-year follow-up period, 2.8% cardiac deaths and 2.8% myocardial infarctions (MI) occurred in the SPECT arm vs 3.3% and 3.0%, respectively, in the invasive arm (statistically not significant). In the intermediate- and high-risk group, the reduction in deaths or MI with SPECT was 8% and 6%, respectively, and 16% in the low-risk group vs the invasive strategy. Interestingly, although use of SPECT was only associated with a tendency toward lower complication rates, costs (including treatment costs during the 3-year follow-up period) were reduced by as much as 40% in the SPECT arm in comparison with the invasive arm. Studies like this one demonstrate that newer diagnostic algorithms can potentially improve outcome while reducing costs. So the obvious question is, with this and other large studies and meta-analyses showing an excellent diagnostic and prognostic yield of SPECT, why should CMR be considered to replace SPECT?

Table I. Comparison of CMR and SPECT with the “Ideal Test.” Evaluation of test performance considers both accuracy (area under the receiver-operator-characteristics curve) and reproducibility (intra-/interobserver/inter-test variability).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Ideal Test</th>
<th>CMR</th>
<th>SPECT</th>
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<tr>
<td>Stenosis or ischemia detection</td>
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<td>- Spatial resolution</td>
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<td>- No attenuation</td>
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<td>- Standardization</td>
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<td>Flow-dependent distribution</td>
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<td>of MR CM into vascular (interstitial) space</td>
<td>Flow-dependent distribution of radiolabeled tracer into viable myocytes</td>
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<tr>
<td>Viability and scar detection</td>
<td>+++</td>
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<tr>
<td>- Spatial resolution</td>
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<td>- Mechanism</td>
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<td>Redistribution (at steady-state)</td>
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<td>of MR CM into extracellular space</td>
<td>Redistribution (at steady-state) of radiolabeled tracer into viable myocytes</td>
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<td>Repeatability*</td>
<td>+++</td>
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<td>Low costs†</td>
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<td>Comfort</td>
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<td>- Short study duration</td>
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<tr>
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<td>Repeatability*</td>
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<td>Low costs†</td>
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<td>Abbreviations: CI, contraindication; CMR, cardiovascular magnetic resonance; LE-CMR, late-enhancement cardiovascular magnetic resonance; MR CM, magnetic resonance contrast media; SPECT, single photon emission computed tomography.</td>
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*Repeatability refers to the various risks associated with the tests (eg, side effects of contrast media, vascular injury in invasive coronary angiography, radiation, etc). It does not refer to reproducibility (which is included in the category: Stenosis or ischemia detection).
† Costs may differ considerably between different countries and centers.
**PERFUSION- AND LATE-ENHANCEMENT-CMR**

The most salient feature of CMR is probably its versatility. CMR creates image information by modifying the local frequency and phase of signals from the body. These MR signals, ie, their evolution over time, depend on the type of tissue from which they originate, and these characteristics can be further enhanced and/or modified by magnetic resonance contrast media (MR CM). The magnetic resonance technique can visualize these different tissue characteristics, and high-end scanner hardware and software enable this information to be acquired today with excellent spatial and temporal resolution in two- (2-D) or three-dimensional (3-D) formats. Consequently, CMR imaging provides comprehensive information on cardiac and vascular anatomy, myocardial and valvular function, blood flow, and metabolism, and in conjunction with MR CM, it delineates distribution of myocardial perfusion and viability in 2-D and 3-D high-resolution data sets.

**Principles of perfusion-CMR**

Myocardial perfusion is typically assessed using MR CM first-pass CMR techniques. To this end, a conventional MR CM is injected as a rapid bolus into a peripheral vein and its first-pass through the myocardium is monitored by a very fast and contrast-sensitive magnetic resonance pulse sequence. An example of this approach is shown in Figure 1. In this setting, a flow-limiting coronary artery stenosis causes a delayed wash-in of MR CM into the myocardium, and consequently a delayed evolution of signal in this region of the myocardium. These data are acquired with state-of-the-art equipment with spatial resolutions of 2 to 3 mm/pixel, evidencing transmural differences in perfusion and coverage of the heart with 3 to 7 slices. These slices are typically oriented in the left ventricular short axis for easy assignment of myocardial territories to the major coronary arteries. It is important to realize in this context, that the high nominal spatial resolution is preserved in CMR through the fact that: (i) respiratory motion is eliminated from the data by breath-holding, since MR CM first-pass during vasodilation typically lasts less than 15 seconds; and (ii) cardiac contraction and relaxation is eliminated by ECG triggering, the use of which became very widespread over recent years thanks to the vector-ECG application now available on all CMR-systems. Unlike SPECT, CMR imaging is not associated with artifacts arising from signal attenuation or scattering (Figure 2), which is crucial for the technique achieving high specificity, particularly as regards the inferior wall and inferolateral wall. Furthermore, the ability to differentiate transmural gradients in perfusion by perfusion-CMR explains the high sensitivity of the method in detecting CAD, which is even able to detect completely balanced CAD (Figure 3, page 118).

The diagnostic performance of perfusion-CMR for analysis of transmural (full wall thickness) and subendocardial perfusion data is also shown in Figure 3. Importantly, perfusion-CMR is not compromised in patients after percutaneous coronary interventions (PCI) and stenting (see...
Perfusion cardiovascular magnetic resonance: will it replace SPECT?

- Schwitter

While providing excellent information, application of the perfusion-CMR technique requires sound knowledge of cardiac pathophysiology and CMR physics, and of course access to high-end hardware and software. The challenge now is to define standards for these requirements, based on the findings from the large international multicenter trials that have confirmed the high level of performance of the perfusion-CMR technique. The dependence of diagnostic performance on image quality is shown in Figure 4 derived from multicenter data.

Safety of perfusion-CMR

When assessing myocardial perfusion during hyperemia, regions of compromised perfusion reflect those developing ischemia during inotropic stress. Hyperemia testing achieved by standard adenosine infusion over 3 minutes (at 0.14 mg/min/kg) is advantageous, since ischemia (due to coronary steal) is induced only by very severe stenoses and, consequently, the test generally does not trigger angina pectoris or ischemia-induced arrhythmias, as shown in large multicenter trials using scintigraphy and/or CMR. It should also be pointed out that CMR does not expose the patient to ionizing radiation. For contraindications, see Table I.

Perfusion- and late-enhancement-CMR in combination

Once myocardial regions of compromised hyperemic perfusion are mapped within the left ventricular wall (Figure 1A,B), it is crucial for further clinical decision making to determine whether the perfusion abnormality is due to scar formation (which does not require revascularization) or whether it resides in viable myocardium, which would
be considered for revascularization. Thus, for a comprehensive workup of patients with CAD, it is obvious that perfusion-CMR and late enhancement–CMR (LE-CMR) should be performed in combination, at least in patients with wall-motion abnormalities. For viability assessment, CMR exploits the fact that conventional MR CM are excluded from myocytes with intact cell membranes. Thus, in acute myocyte necrosis, where cell membrane integrity is lost,13 or in chronic scar tissue, where extracellular space is large,14 conventional MR CM accumulate and induce a high signal (Figure 1D), when probed with appropriate pulse sequences. Thus, LE-CMR relies on the redistribution of MR CM from the intravascular compartment into the enlarged extracellular space (acute necrosis or scar), analogous to viability imaging with SPECT, which also relies on redistribution, in this case however, of tracer from the blood pool into viable myocytes. Thus, at steady-state after redistribution, LE-CMR shows scar and necrosis as bright areas, whereas SPECT after redistribution shows these regions as dark, ie, cold spots.

While both techniques rely on redistribution, LE-CMR acquires these data during a breath-hold with ECG-triggering, thereby preserving the nominally high spatial resolution of CMR. Since MR CM exchange between blood pool, intra-, and extracellular compartments at steady-state is considerably slower than first-pass kinetics, LE-CMR imaging is performed over a period of several minutes, resulting in even higher spatial resolutions (compared with perfusion-CMR) in the order of 1-2 mm\(^2\) in 2-D or 3-D formats. Thus, scar tissue as small as 0.5 gram is reliably detectable with LE-CMR15 and recovery of function after revascularization is predictable when considering the transmural extent of scar and thickness of viable rim tissue.14,16

Perfusion-CMR performance
In a single-center study, a stress-only perfusion-CMR protocol yielded a sensitivity and specificity of 87% and 85%, respectively, for detection of CAD (defined as ≥50% diameter stenosis in at least one coronary artery in quantitative coronary angiography) corresponding to an area under the receiver-operator characteristics curve (AUC) of 0.91. A comparison with PET perfusion data as standard of reference in these patients yielded even higher sensitivity and specificity of 91% and 94%, respectively, for perfusion-CMR (AUC: 0.93). Excellent results were also reported from other groups using perfusion-CMR at rest and stress with sensitivities and specificities of 88% to 90% and 84% to 90%, respectively.17-19 Finally, a multicenter, single-vendor study yielded a sensitivity and specificity of 91% and 78%, respectively, for CAD detection with an AUC of 0.91 using a semiautomatic analysis approach.
Perfusion cardiovascular magnetic resonance: will it replace SPECT?

SPECT imaging in combination with $^{99m}$Tc-tracers is a powerful technique for the detection of perfusion abnormalities during hyperemia induced by pharmacological or physical stress and it also allows assessment of viability. In the early 90s, the first applications of $^{99m}$Tc-tracers yielded sensitivities and specificities for the detection of angiographically documented CAD of 81% and 90%, respectively. For dual-isotope rest $^{201}$Tl/stress $^{99m}$Tc-sestamibi SPECT protocols, sensitivities and specificities of 91% and 75% were reported, respectively. The performance of diagnostic SPECT is also well established in disease states such as complete left bundle-branch block (sensitivity and specificity of 79% and 81%, respectively) or diabetes (sensitivity and specificity of 86% and 56%, respectively). In women, who are more prone to attenuation artifacts in the anterior myocardium due to breast tissue, gender-specific diagnostic SPECT performance achieves a sensitivity and specificity of 72% and 71%, respectively. Slightly lower performances were reported from multicenter trials with overall sensitivities in the range of 77% to 85% and specificities of 36% to 58%. While attenuation artifacts represent a substantial limitation for SPECT imaging, attenuation correction algorithms can mitigate this problem, albeit at the expense of some reduction in sensitivity. Another improvement is provided by gated-SPECT, which was shown to increase three-vessel disease detection (typical perfusion/function abnormality pattern in 25% of patients with gated-SPECT vs typical perfusion abnormality pattern in only 10% of patients with ungated SPECT), while specificity was not altered, with 72% vs 69%, respectively, for gated- vs ungated SPECT. Since assessment of diagnostic performance typically requires invasive coronary angiography as the standard of reference, these studies are often restricted to smaller patient groups. Considerably larger studies are available for the assessment of prognostic performance with SPECT3 than with CMR. Despite the technical restrictions for SPECT imaging mentioned above, this technique was shown to discriminate patients with preserved prognosis vs those with complications in studies involving thousands of patients. In summary, single-center and particularly multicenter studies show adequate SPECT performance for the detection of CAD. Limitations in sensitivity may arise from suboptimal spatial resolution of the technique, as well as from attenuation artifacts. For perfusion-CMR these two types of limitations are less of a concern, which explains its high diagnostic performance in CAD detection. With this in mind, studies were undertaken to directly compare perfusion-CMR and SPECT imaging.
Comparison of CMR and SPECT performance

Ishida and coworkers reported on a single-center comparison between perfusion-CMR and SPECT for the detection of CAD in patients without prior MI. Perfusion-CMR performed significantly better than SPECT, with an AUC of 0.89-0.91 vs 0.71-0.75, respectively, \( P < 0.001 \). The overall high performance of perfusion-CMR for the detection of angiographically defined CAD was the basis for a large multicenter, multivendor perfusion-CMR trial in order to determine the optimum MR CM dosage for perfusion-CMR and for its comparison with SPECT.

The MR-IMPACT (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial) was conducted in 18 centers in the US and Europe in 234 patients with known or suspected CAD. Three blinded readers each assessed the perfusion-CMR and SPECT images at rest, and stress and quantitative coronary angiography was used as the standard of reference (with diameter stenoses ≥50% in at least one coronary artery of ≥2 mm diameter defining CAD). A total of 4.8% and 5.3% of the perfusion-CMR and SPECT studies, respectively, were not evaluable. At the dose of 0.1 mmol/kg of a conventional MR CM (Gd-DTPA-BMA, Omniscan, GE Healthcare), perfusion-CMR yielded an excellent AUC for the detection of CAD, of 0.86 (sensitivity and specificity: 91% and 67%), which was significantly superior to SPECT, with an AUC of 0.67 (sensitivity and specificity: 74% and 57%). Similarly, perfusion-CMR was also superior to SPECT for the detection of multivessel disease (AUC: 0.89 vs 0.70). This large multicenter, multivendor trial confirmed the impressive performance of perfusion-CMR, particularly when considering the number of participating centers and the multivendor design. This led to an even larger clinical phase 3 trial, MR-IMPACT II, being carried out in 34 centers in Europe and US, the first results of which were presented in late 2006, further confirming the superiority of perfusion-CMR.

**PERSPECTIVES OF CMR AS A COMPONENT IN FUTURE DIAGNOSTIC ALGORITHMS**

The prevalence of CAD is expected to increase in the next decades due to the older age of the population and an increase in other risk factors such as diabetes and obesity. As economic resources may not develop in parallel, cost-effectiveness will become an increasingly important issue. Since costs for CAD treatment by PCI and surgery are substantial and drug therapy typically lasts for many decades, accurate diagnosis is crucial for appropriate allocation of expensive treatments. CMR provides a comprehensive assessment of patients with suspected or known CAD and is also helpful for the diagnosis of cardiomyopathies, myocarditis, valvular heart disease, and congenital heart disease in the adult. Perfusion-CMR and LE-CMR are ideally suited for the detection and workup of CAD and will most likely become a “backbone” diagnostic modality in cardiology of the future, where patients at risk should be detected earlier than with current diagnostic algorithms. This active strategy will make it possible to treat CAD earlier and hence will hopefully reduce the high rate of fatal MIs in the prehospital phase. To this end, the diagnostic strategy should be expanded from the “very high risk” to the “high-intermediate risk” population. In this population, however, with a lower incidence of CAD, tests must not cause any harm to patients, and avoiding ionizing radiation of CMR is important, considering that 10 mSv of exposure induces cancer in about 1 per 1000 expositions. While radiation exposure is 6 to 8 mSv for SPECT (depending on tracers and protocols), approximately 15 mSv is required for Multidetector CT (MDCT) coronary angiography, which is increasingly utilized for exclusion of CAD. In comparison, in a recent multicenter single-vendor MDCT coronary angiography trial (n=11 centers), 42% of all patients were excluded from analysis due to inadequate quality, yielding a sensitivity and specificity of 80% and 70%, respectively, for CAD detection in the remaining population. The multicenter single-vendor CMR study yielded a sensitivity and specificity of 91% and 78%, respectively, after exclusion of only 14% of patients. In MR-IMPACT (n=18 centers and multivendor), sensitivity and specificity were 91% and 67%, respectively, after exclusion of only 5% of the CMR studies.

Currently, CMR examinations are still demanding with respect to cardiological and imaging knowledge, and also with respect to infrastructure, as demonstrated by the recent multicenter CMR trials. Based on these trials, perfusion-CMR and LE-CMR, in experienced centers, may be considered as a valuable alternative to SPECT for the workup of patients with suspected CAD or post revascularization. Considering the advantages of CMR over SPECT a shift toward CMR is expected in the near future. However, before this transition occurs, it appears wise to put major effort into standardizing CMR protocols, training physicians and technical personnel, and improving the accessibility of CMR units.

Juerg Schwitter is Consultant of GE-Healthcare and Primary Investigator of the MR-IMPACT program.
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Computed tomography coronary angiography: what is the hype, the reality, and the future?

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The number of computed tomography (CT) scanners capable of imaging the coronary arteries is increasing exponentially in the Western world. Expectations are that CT coronary angiography (CTCA) will replace conventional angiography in many patients. However, there is hardly any evidence showing that multislice CT is better than conventional stress testing in selecting patients for coronary interventions. The high negative predictive value of CTCA may provide help for some patients who are very concerned about the presence of coronary artery disease. Chest pain, however, may be caused by myocarditis and coronary vasospasm and CTCA is not able to exclude these conditions. The future will show whether CTCA is able to depict the development of atherosclerosis in the arterial wall by serial examinations at a reduced radiation exposure.

Patients and doctors are often fascinated by the same concepts. They both want to learn more about the future and make prophecies about the patients' individual path in this direction. Both are also fascinated by pretty pictures showing the patients' inner self, hopefully providing the ultimate evidence that the patients are healthy and that their symptoms do not indicate an ominous outcome. The desire to predict the future and the belief that medical imaging can be helpful in this respect led to an explosion of the number of imaging services all over the world, notably in the US. Modern computed tomography (CT) holds the promise to image the coronary arteries noninvasively. Expectations are great, but what is the reality? What does the future hold?

THE HYPE

The number of CT-scanners capable of imaging the coronary arteries is increasing at an exponential growth in the Western world. Membership in the Society of Cardiovascular Computed Tomography (SCCT) is rapidly growing and now exceeds 2200 with 15 to 20 new applications being received daily. The Society was only founded in March 2005. The public is flooded with predictions that CT angiography will take the place of single photon emission computed tomography (SPECT) and cardiac catheterization for the majority of clinically important cardiac disorders. Indeed, 72% of US cardiologists order CT angiography procedures every month and many cardiologists plan to purchase the CT equipment necessary for performing this examination for their own practice. The SCCT as well as other interest groups are pushing hard for Medicare reimbursement for the procedure and experts predict that nationwide reimbursement will emerge by 2008 at the latest. An estimate for local Medicare reimbursement in the US is between $400 and $600. The promise made to Medicare is that CT coronary angiography (CTCA) will save the patient an unnecessary and more costly invasive cardiac catheterization procedure. The question of whether looking at the coronaries of so many people makes any sense is never asked.

The prospect of being able to noninvasively have a look at the coronary arteries motivates radiologists and cardiologists to line up for learning CTCA. However, few physicians have accumulated enough experience to competently perform this procedure. Fewer still are qual-
ified to teach physicians how to conduct and interpret examinations. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) clinical competency statement requires 150 supervised cases. These include 50 cases in which a physician is directly involved in scanning to establish skill in interpreting a coronary artery CT scan. In contrast, the American College of Radiology requires board-certified radiologists to perform only 75 supervised scans to achieve competence. This difference recognizes the training in thoracic CT interpretation that radiologists receive during their residencies. There are, however, also warning voices such as that of Dr Pamela Douglas, the outgoing ACC President. “If imaging were a drug, approval would be denied” she said at the opening of the 55th Annual Scientific Session of the American College of Cardiology in 2006 speaking of problems with cardiovascular imaging research. “New diagnostic tools and creative treatments have sparked an exciting evolution in medicine,” she said. Her warning, however, was: “While this would seem to be a positive change, sometimes we adopt these new tools with not enough thought to ensuring quality.” Despite this call for diligence and patience, requirements for cardiology fellowship education were already changed and now include at least one month of cardiac CT applications. CTCA advocates argue that this is necessary as cardiac CT is becoming integral to cardiology practice. Despite the fact that randomized multicenter trials remain the basis for evidence-based medicine and that such studies are conspicuously absent, many radiologists and cardiologists embrace cardiac CT as the new standard of care for patients at intermediate risk for the development of an acute coronary syndrome. Some already see CTCA in the emergency room to immediately define the status of the coronaries. Pilot studies show that cardiac CT speeds diagnosis and hence allows for earlier discharge of patients at intermediate or low risk for myocardial infarction. The market is huge, as approximately 3 million patients report to emergency rooms with chest pain every year. Excitement over the 64-slice scanners has not yet subsided and already new technology is available: dual source CT will extend the applicability of CTCA to larger patient groups such as those with faster heart rates or rhythm disturbances like atrial fibrillation, avoiding the current obligatory use of β-blockers to slow down the heart rate. High heart rates are detrimental to image quality with current 16- to 64-slice scanners and lead to blurring and artifact generation. Recent findings indicate that heart rate is predictive of image quality and that a low heart rate substantially improves vessel visibility and stenosis detection.

Why all the excitement? Calcium-scoring of the coronary arteries has been around for many years. Although more and more solid data are gathered by clinical researchers that indicate that quantification of coronary calcium provides increased prognostic ability to predict cardiovascular events beyond and independent of traditional coronary risk factors, calcium-scoring has not ignited the imagination of patients and physicians. The breakthrough for cardiac CT came with the availability of 4-slice helical CT-systems, which were introduced in the year 2000. These systems showed the coronary artery lumen after intravenous injection of contrast material, but were limited in many patients because of image artifacts. Yet, the possibility of visualizing the coronaries without inserting an arterial catheter quickly exerted a strong fascination on physicians and engineers, leading to rapid improvements in CT technology over the following years. Only 4 years after the introduction of the 4-slice system, systems offering 64 slices became available. These systems have shorter gantry rotation times, higher slice collimation, and higher tube output, all of which improve the temporal and spatial resolution of the machines. The number of slices itself is just helpful for shortening imaging times. Sixty-four-slice machines now permit coronary imaging within a breath-hold of approximately 6 seconds. The result is a stack of about 300 cross-sectional images with a slice thickness of between 1/2 and 1 millimeter. Three-dimensional reconstructions of the coronary arteries often in color attract the attention of radiologists, cardiologists, cardiac surgeons, and general practitioners alike. And all this beauty comes without hospital stay, without catheters inserted into the body, and without heaps of consent forms to be signed informing the patient about the risk of death and myocardial infarction as is the case with invasive cardiac catheterization.

Of course, CT exposes the patient to about 3 times more radiation than conventional coronary angiography (for multislice CT [MSCT] angiography effective dose [ED] 14 mSv and for conventional coronary angiography ED 6 mSv) although estimates differ considerably. These exposures yield lifetime risks of 0.07% and 0.02%, respectively, of inducing a fatal cancer in the general (ie, age- and gender-averaged) population. However, CT proponents point to the fact that conventional coronary angiography poses additional serious risks associated with cardiac catheterization, yielding a nonradiogenic risk of mortality—exclud-
ing contrast media reactions—of 0.11%. The argument continues that combining the radiogenic and non-radiogenic risks (0.02% and 0.11%, respectively) yields a 0.13% overall risk of mortality from conventional coronary angiography—nearly 2-fold higher than that for MSCT angiography (0.07%). If one were to use the lower, more age-appropriate risk factors for the older patient population in question, the radiogenic risks of both conventional coronary angiography and MSCT would be reduced by about half, further widening the overall safety ratio of MSCT relative to conventional coronary angiography, by a factor of nearly 2 in favor of MSCT.8

If that is not enough to convince you, consider the following: some believe that widespread use of this “soft and safe” new CT tool could even save huge numbers of lives. This interesting argument goes as follows: if the entire 18 800 000 people comprising the 50- to 55-year-old population of the US were screened for coronary artery disease using MSCT, the anticipated increase in the number of fatal cancers would be 14 900. If this screening were repeated every 5 years until the population reached the age of 70, the aggregate increased risk would be increased by approximately 3-fold, to 42 900. Because the average age of patients with their first infarction is 65.8 for men and 70.4 for women and because 94% of patients have >75% stenosis in at least one vessel, these sequential procedures should identify patients with significant stenoses before their initial event. Hence, if this procedure prevented even 10% of the estimated 355 000 sudden deaths each year, the proponents of MSCT feel the trade-off would be well worthwhile.8 At this point, however, it appears necessary to mention the robust data demonstrating the low predictive value of stenosis severity for the probability of vessel occlusion at the site of the stenosis.9

Now we understand the fascination of MSCT coronary angiography: beautiful, easily obtained images of coronary artery stenoses, which otherwise would go undetected, provide the opportunity to intervene early enough and put an end to sudden death. One just has to perform enough MSCT coronary angiograms. We will deal later with the fallacy of these arguments.

**THE REALITY**

Where—at this point in time—is the appropriate position of MSCT in the armamentarium of the clinical cardiologist who has to deal with the expectations and the fears of those suffering from coronary artery disease or at risk of developing the disease? When appropriately performed in appropriately selected patients, 64-slice CTCA will result in sensitivities between 86% and 99% and specificities of 93% to 97% for detecting stenoses considered significant by conventional coronary angiography (Table I).10-16 However, one has to remember that 9% of vessel segments with a diameter >1.5 mm evidenced by conventional coronary angiography cannot be evaluated by 64-slice CTCA due to degraded image quality. An important asset of the technique, hailed by all proponents, is the high negative predictive value of between 95% and 99%.17 The values given represent the accuracy data if per segment or per artery analysis were performed. For a patient-based analysis, CTCA is even better with sensitivities of between 94% and 100% and specificities ranging from 90% to 100% (Table I). The negative predictive value for the patient-based analysis is between 93% and 100% for the 64-slice scanners. However, data are still preliminary and the studies published today incorporated a maximum of 134 participants.

![Table I. Accuracy of 64-slice computed tomography in identifying patients with at least one coronary artery stenosis.](image-url)
obstacles to the correct interpretation of CTCA scans.\textsuperscript{19} Blooming effects expand the apparent size of calcified plaques and hence lead to overestimation of plaque volume, resulting in false-positive diagnoses. This is of course well known to experienced CT interpreters. In order to preserve their high negative predictive value they tend to overrate such scans and misinterpret calcifications as stenoses rather than risk missing a stenosis. Although blooming effects have become less important with the higher spatial resolution of newer machines, they continue to be a source of artifacts even with the latest scanner generation (Figures 1 and 2). It has hence become customary in experienced centers to first perform a low-dose radiation nonenhanced MSCT scan to evaluate coronary calcium and omit CTCA if the Agatston-score is more than 600. However, some believe that, with dual-source CT, CTCA can be reliably performed in patients with calcium scores up to 1000. In the study of Garcia et al.,\textsuperscript{18} only 201 patients (84%) had Agatston scores <600 and were thus evaluated by MSCT angiography. However, there were additional problems with the procedure leading to further exclusions. Two patients had arrhythmias that were missed at the initial screening procedure. Stented segments were excluded from analysis because stents carry similar problems as severe calcifications (Figure 3). There was also a large number of nonevaluable segments by MSCT (29%) due to respiratory or cardiac motion or excessive calcification, poor opacification, or small vessel size. Hence, after censoring all nonevaluable segments as positive, the sensitivity for detecting more than 50% luminal stenoses was 89%, with a specificity of only 65%. The positive predictive value was 13%, but the negative predictive value remained high at 99%—albeit at the cost of an unacceptably low predictive value. In a patient-based analysis, which is the clinically more important analysis compared with segmental analysis, the sensitivity for detecting patients with at least one narrow segment was 98%, with a specificity of 54%. This study indicates that in order to preserve an attractive negative predictive value, a very high number of false positives need to be accepted when MSCT coronary angiography is performed with 16-row-scanners. Even though
appropriate tube current modulation led to a relatively low radiation exposure of 8±2.5 ms, this radiation burden is still higher than for conventional coronary angiography plus left ventricle angiography. The authors conclude that routine implementation of CTCA in clinical practice is not justified. They feel, however, that CTCA is of potential use in excluding coronary artery disease in selected patients in whom false-positive or inconclusive stress test results are suspected.

The discussion on when to use MSCT in clinical practice is still greatly influenced by the belief that imaging of coronary artery anatomy is of greater clinical value than functional assessment of the consequences of impaired coronary blood flow. It is surprising that this superstition continues to influence scientific statements because a wealth of robust data showing the contrary is available. When does it make sense to examine the coronary arteries? In order to approach this question it is useful to look at the recommendations for performing conventional coronary angiography issued by the ACC/AHA. There are few Class I recommendations. One is for patients with severe grades of angina despite intensive medical treatment. The other Class I indication is for patients who, regardless of angina severity, are at high risk for severe ischemia or sudden cardiac death according to noninvasive functional testing. In these patients, coronary angiography makes sense because there is a high probability that high-grade coronary lesions will be detected, resulting in appropriate revascularization. In contrast, patients with mild symptoms or atypical symptoms do not need coronary angiography because this test does not provide any additional prognostic or therapeutic benefit.

Let us briefly have a look at the prognostic implications of coronary angiography in asymptomatic or mildly symptomatic patients. Usually, prognosis is estimated on the basis of conventional risk factors, but calcium-scoring by MSCT may further improve risk stratification in these patients. Coronary angiography can only provide additional information about the severity of stenosis in patients who would already be known to have coronary artery disease by calcium scoring. The low predictive value of stenosis severity for the probability of vessel occlusion at the site of the stenosis, however, has been amply documented. On the other hand, in those who by risk factor analysis and/or CT-calcium scoring are already known to be at low risk, coronary angiography could just confirm this by excluding the presence of coronary artery stenosis. What about the intermediate-risk group? The guidelines recommend noninvasive tests rather than invasive coronary angiography because the posttest probability after these tests may help to decide whether or not to use invasive coronary angiography. Do these recommendations still hold true when noninvasive coronary angiography by MSCT is broadly available? Some claim that the additional dye load and radiation exposure of MSCT argue against the broad use of this new technique in intermediate-risk patients. If many patients need invasive coronary angiography following a positive MSCT result, patients would unnecessarily be exposed to the same risks twice. As invasive coronary angiography is not recommended in patients with a low pretest probability of significant coronary artery disease and MSCT coronary angiography is not likely to alter the statistically good prognosis in this patient group, where could be the place for MSCT coronary angiography in the prognostication of patients with coronary artery disease? If the pretest probability of coronary artery disease is less than 50%, a negative result on MSCT coronary angiography is associated with a posttest probability of coronary artery disease below 10%. In order to achieve a posttest probability below 5% by a
negative MSCT, the pretest probability needs to be below 30%. This would be the case in a person with nonspecific chest pain and equivocal results of functional noninvasive testing. Excluding coronary artery disease would be important in such a patient if the patient’s symptoms require multiple hospitalizations. In fact, such patients constitute a significant subgroup of those undergoing coronary angiography in countries with easy access to invasive coronary angiography as in Germany. The main benefit for such a patient with a low pretest probability in whom the response to treatment or other noninvasive tests is inconclusive, is that he will be reassured if MSCT results are negative. Based on this negative MSCT, the patient might then not be sent by his or her physician who is also anxious to not miss a disease with potential fatal consequences to invasive coronary angiography.

But is the exclusion of coronary stenoses by MSCT really helpful when the chest pain symptoms described by the patient sound like real angina, when they occur mainly at rest or both at rest and with exercise? Will patients really be content if the physician tells them that their symptoms are completely innocent and that there is no heart disease? Is it not the obligation of the patient’s doctor to find an explanation for the patient’s symptoms especially when the patient frequently contacts other physicians or emergency facilities and is even hospitalized? Aren’t there alternative explanations for chest pain symptoms in patients known to be reliable historians to their general practitioners? Chest pain at rest is frequently associated with regional myocardial inflammation as demonstrated by late gadolinium enhancement cardiac magnetic resonance imaging. Coronary vasospasm is another almost completely forgotten cause of chest pain. Among patients who had acute coronary syndromes with hospital admission severe enough to warrant immediate coronary angiography, 20% to 30% have no coronary stenosis. Even among those with evidence of myocardial necrosis by troponin elevation, 6% have no significant angiographic coronary stenosis. Coronary vasospasm is present in 50% of patients with significant coronary artery disease, but normal or near-normal coronary angiograms. Vasospasm as the cause of a patient’s chest pain can be confirmed by invasive coronary angiography. In a patient with stress-induced angina or more commonly repeated episodes of resting angina, the injection of acetylcholine following exclusion of significant coronary artery disease often results in coronary vasospasm with reproduction of the patient’s symptoms. This test can be performed during conventional coronary angiography at negligible additional risk when acetylcholine is infused slowly with increasing concentrations. Vasospasm is quickly and safely reverted by intracoronary injection of nitroglycerine. Similar testing cannot be performed using MSCT coronary angiography. Hence, even in patients with a low probability of coronary artery disease and inconclusive results at noninvasive testing, MSCT coronary angiography is inferior to invasive coronary angiography for making a definitive diagnosis in patients who often suffer from severe and repetitive symptoms. If MSCT coronary angiography is not helpful to improve prognosis, would it not be a suitable tool to select the low-risk patient who might benefit from a coronary intervention? Unfortunately, all available data indicate that coronary interventions in patients with mild stable angina do not improve outcome. Patients with severe angina, however, should undergo invasive coronary angiography to give them the opportunity of immediate percutaneous coronary interventions.

**THE FUTURE**

Even with the recently introduced 64-slice CT systems, motion artifacts remain the most important challenge for CTCA. Even with 64-slice CT, the administration of beta-blocking agents and nitroglycerine is necessary to provide acceptable image quality in many patients. In order to achieve temporal resolutions of less than 100 ms, which would eliminate the need for heart-rate control, new concepts are necessary. Multisegment reconstruction approaches from imaging over various cardiac cycles give variable results and are not robust enough for standard clinical performance. Although electron beam CT (EBCT) provides short scan times, its spatial resolution and signal-to-noise ratio in larger patients is insufficient for state-of-the-art cardiac imaging or for general radiology applications. Shorter imaging times could be achieved by shorter rotation times of the currently available mechanical scanners. However, mechanical forces with current scanners providing 330 ms rotation time are already at 28G and these forces would increase to more than 75G at rotation times of less than 200 ms. Therefore, a new dual-source CT system was developed, which is equipped with two x-ray tubes and two corresponding detectors. The two acquisition systems are mounted onto the rotating gantry with an angular offset of 90 degrees. Each detector comprises 40 detector rows, the 32 center rows have an 0.6-mm collimated slice. Using the z-flying focal spot technique two subsequent 32-slice readings are...
Computed tomography coronary angiography: what is the hype, the reality, and the future?

- Sechtem

The key benefit of dual source CT for cardiac scanning is improved temporary resolution. The scanner provides temporary resolution of approximately one fourth of the gantry rotation time, which is approximately 83 ms. As the system can cover almost 30 cm in the longitudinal direction, data from one cardiac cycle only are necessary to reconstruct the images. Initial experience with this system shows that high-quality images can be obtained without the use of β-blockade. Image quality is further improved due to the short temporal resolution, which avoids the blur of motion artifacts. The improved temporal resolution may allow the time window during which the full x-ray tube current is used to be shortened. Without such measures the radiation dose is even further increased with the new dual-source CT as compared with the 64-slice CT.

Although MSCT coronary angiography is not suitable for replacing invasive coronary angiography or noninvasive tests for the detection of ischemia on a broad basis, we have not yet fully explored the possibilities of this fascinating and rapidly developing technology. There are interesting niche applications such as the preoperative evaluation of patients with valvular heart disease where MSCT coronary angiography may play a clinical role. Although no large-scale clinical trial has assessed the contribution of coronary angiography, this invasive investigation is recommended in the preoperative assessment of patients with valvular heart disease. A limiting factor to the widespread use of MSCT-coronary angiography is the presence of high calcium scores in the patients with aortic stenosis, but three fourths of these patients may have calcium scores low enough to permit reliable exclusion of coronary artery disease by MSCT. Hence, the use of MSCT may in the future help to avoid conventional coronary angiography in up to 80% of patients with aortic stenosis. With improved temporal resolution MSCT coronary angiography may also become useful in patients with mitral valve disease who frequently suffer from atrial arrhythmias. This currently precludes reliable coronary imaging with 64-slice MSCT. With the more widespread availability of dual-source CT patients with mitral valve incompetence might be even more suitable than those with aortic stenosis because they usually have less coronary calcification.

Figure 4. A: Exclusion of significant coronary stenoses by 3-D MSCT reconstruction: 16-slice multislice computed tomography (MSCT), 3-dimensional reconstruction of coronary arteries of a patient with repetitive attacks of resting angina. Exercise tests were repeatedly normal. The CT does not show significant coronary artery disease. B: Left anterior descending (LAD) coronary artery vasospasm. Left: when 100 µg acetylcholine is selectively infused into the LAD, the patient experienced identical symptoms as those that brought him into the hospital, and subtotal occlusion of the distal LAD was observed. Right: After injection of 0.2 mg nitroglycerin (NTG), the vessel opened wide and the symptoms disappeared immediately.

Patients with left bundle-branch block pose serious problems to noninvasive stress testing. False-positive results are common with myocardial perfusion scintigraphy, but the abnormal motion of the interventricular septum also makes dobutamine stress echocardiography a challenge. However, it is important to identify the underlying cardiac pathology as it primarily determines prognosis. MSCT may become an interesting modality in the management of these patients. It detects significant coronary artery stenoses with excellent accuracy and identifies 95% of patients without significant stenosis and 97%
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with significant stenosis by conventional coronary angiography. Other new and exciting possibilities provided by MSCT are the visualization of nonstenotic plaque including noncalcified soft plaque. This opens a fascinating window to the serial study of the development of atherosclerosis, ie, in patients with a high genetic risk. However, the excitement raised by this new possibility of noninvasive study of the development of atherosclerosis must be tempered when thinking of the radiation burden resulting from serial studies. MSCT may also offer the possibility to differentiate between fibrous and lipid-rich plaques on the basis of differences in the attenuation values measured in Hounsfield units.

Although there are interesting new applications in difficult clinical situations, the availability of MSCT coronary angiography also poses significant challenges to the medical community. Rates of invasive testing and treatment of coronary artery disease nearly doubled from 1993 to 2001. However, hospitalization rates for acute myocardial infarction remained stable over that period. The well-known differences in rates of cardiac testing and treatment between nonblack men and other subgroups persisted over time. Hence, temporal increases in the use of noninvasive and invasive car-

### Table III. Indications for computed tomography coronary angiography considered to be inappropriate by the American College of Cardiology Foundation (ACCF) Task Force. Assume the logical operator between each variable listed for an indication is “AND.”

<table>
<thead>
<tr>
<th>Indications</th>
<th>Abbreviations:</th>
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<tbody>
<tr>
<td>1. Detection of CAD in symptomatic patients</td>
<td>CAD, coronary artery disease, CHD, coronary heart disease, PCI, percutaneous coronary intervention.</td>
</tr>
<tr>
<td>• Evaluation of chest pain syndrome</td>
<td></td>
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<tr>
<td>• Intermediate pretest probability of CAD</td>
<td></td>
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<tr>
<td>• ECG uninterpretable or unable to exercise</td>
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<tr>
<td>2. Detection of CAD in symptomatic patients</td>
<td></td>
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<tr>
<td>• Evaluation of suspected coronary anomalies</td>
<td></td>
</tr>
<tr>
<td>3. Detection of CAD in symptomatic patients</td>
<td></td>
</tr>
<tr>
<td>• Acute chest pain</td>
<td></td>
</tr>
<tr>
<td>• Intermediate pretest probability of CAD</td>
<td></td>
</tr>
<tr>
<td>• No ECG-changes and serial enzymes negative</td>
<td></td>
</tr>
<tr>
<td>4. Detection of CAD with prior test results</td>
<td></td>
</tr>
<tr>
<td>• Evaluation of chest pain syndrome</td>
<td></td>
</tr>
<tr>
<td>• Uninterpretable or equivocal stress test (exercise, perfusion, or stress echo)</td>
<td></td>
</tr>
<tr>
<td>5. Assessment of morphology</td>
<td></td>
</tr>
<tr>
<td>• Assessment of complex congenital heart disease including anomalies of coronary circulation, great vessels and cardiac chambers and valves</td>
<td></td>
</tr>
<tr>
<td>• Evaluation of coronary arteries in patients with new-onset heart failure to assess etiology</td>
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</table>

### Table IV. Indications for computed tomography coronary angiography considered to be appropriate by the American College of Cardiology Foundation (ACCF) Task Force. Assume the logical operator between each variable listed for an indication is “AND.”

<table>
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<tr>
<th>Indications</th>
<th>Abbreviations:</th>
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<tbody>
<tr>
<td>1. Detection of CAD in symptomatic patients</td>
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<tr>
<td>• Evaluation of chest pain syndrome</td>
<td>CAD, coronary artery disease.</td>
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<tr>
<td>• High pretest probability of CHD</td>
<td></td>
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<tr>
<td>2. Detection of CAD in symptomatic patients</td>
<td></td>
</tr>
<tr>
<td>• Acute chest pain, and</td>
<td></td>
</tr>
<tr>
<td>• high pretest probability of CHD</td>
<td></td>
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<tr>
<td>• ECG-ST-segment elevation and/or positive cardiac enzymes</td>
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<tr>
<td>3. Detection of CAD in asymptomatic patients</td>
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<tr>
<td>• Low CHD risk by Framingham risk criteria</td>
<td></td>
</tr>
<tr>
<td>or • Moderate CHD-risk by Framingham risk criteria</td>
<td></td>
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<tr>
<td>4. Detection of CAD with prior test results</td>
<td></td>
</tr>
<tr>
<td>• Evaluation of chest pain syndrome</td>
<td></td>
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<tr>
<td>• Evidence of moderate to severe ischemia on stress test (exercise, perfusion, or stress echo)</td>
<td></td>
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<tr>
<td>5. Risk assessment with prior test results in asymptomatic patients</td>
<td></td>
</tr>
<tr>
<td>• High CHD-risk (Framingham)</td>
<td></td>
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<tr>
<td>• Within 2 years prior cardiac CT angiogram or invasive angiogram without significant obstructive disease</td>
<td></td>
</tr>
<tr>
<td>or • High CHD risk (Framingham)</td>
<td></td>
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<tr>
<td>• Prior calcium score ≥400</td>
<td></td>
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<tr>
<td>6. Risk assessment: preoperative evaluation for noncardiac surgery</td>
<td></td>
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<tr>
<td>• Low-risk surgery</td>
<td></td>
</tr>
<tr>
<td>• Intermediate perioperative risk</td>
<td></td>
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<tr>
<td>7. Detection of CHD: post revascularization (PCI or CABG) in asymptomatic patients</td>
<td></td>
</tr>
<tr>
<td>• Evaluation of bypass grafts and coronary anatomy</td>
<td></td>
</tr>
<tr>
<td>• &lt;3 years after CABG</td>
<td></td>
</tr>
<tr>
<td>or • Evaluation of bypass grafts and coronary anatomy</td>
<td></td>
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<tr>
<td>• ≥5 years after CABG</td>
<td></td>
</tr>
<tr>
<td>or • Evaluation for in-stent restenosis and coronary anatomy after PCI</td>
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</table>
Cardiac services could not be explained by changes in disease prevalence and did not succeed in narrowing preexisting treatment differences. One also has to remember that such increases, although bringing benefit to some, will expose others to risk and cost without appropriate benefit. The Foundation of the American College of Cardiology has responded to the rapid and uncontrolled increase of medical imaging procedures by defining appropriateness criteria for cardiac computed tomography. Table II lists indications that are currently viewed as appropriate for performing CT angiography. However, the panel also defined clinical situations where the performance of a CT-angiogram is considered to be inappropriate (Table III).

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**SUMMARY**

MSCT coronary angiography is a fascinating new technical tool that has not yet found a definite place in clinical cardiology. It is certainly premature to speculate that this new noninvasive technique will replace invasive coronary angiography. If indeed too many invasive coronary angiograms were currently performed it does not follow that we should replace them by even more noninvasive coronary angiograms. The possibility to get excellent images of the coronary arteries surrounding their lumen without the need to stab holes in the femoral arteries and insert catheters into the ostia of the coronary arteries should not seduce us into an indiscriminate use of this new technique. Looking at the coronary arteries will not solve the main medical problems associated with coronary artery disease: the suboptimal use of preventive measures and the suboptimal allocation of medical resources to those who need it most.
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Matters @ Heart

Franklin Delano Roosevelt and the treatment of hypertension

Richard J. Bing, MD

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Franklin Delano Roosevelt, President of the United States, died on April 12, 1945 in Warm Springs, Georgia, of a cerebral hemorrhage resulting from hypertension. As related by his attending cardiologist, Howard G. Bruenn, his blood pressure on the day of his death was 300/190 mm Hg. The President had suffered from hypertension since 1935. Bruenn ends his article written in 1970, “I have often wondered what a turn the subsequent causes of history may have taken if the modern methods of the control of hypertension had been available.” Since Roosevelt’s death, treatment of hypertension has been spectacular. This is astonishing when one considers that there were questions in 1940 as to the rationale of treating high blood pressure; it was

Harry Goldblatt (1891-1977) showed, in his celebrated landmark experiments, that clamping the kidney arteries of dogs resulted in production of a “pressor substance,” causing constrictions of the arterioles throughout the body. In its April 15, 1940 edition, Time Magazine ventured the pessimistic opinion that, “although fellow physicians had Dr Goldblatt’s work as one of the great medical contributions of the last 20 years, they admit that, so far, nothing much can be done with it…” © National Library of Medicine, History of Medicine Division.

Irvine Heinly Page (1901-1991) was active in the field of hypertension for almost 60 years with major discoveries relating to serotonin, the renin-angiotensin system (coining the word “angiotonin”), and the mosaic theory of hypertension. © National Library of Medicine, History of Medicine Division.

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Irvine Heinly Page (1901-1991) was active in the field of hypertension for almost 60 years with major discoveries relating to serotonin, the renin-angiotensin system (coining the word “angiotonin”), and the mosaic theory of hypertension. © National Library of Medicine, History of Medicine Division.
thought that one could not treat a disease without knowing its exact cause. We know now that even an elevation of 5-6 mm Hg in the diastolic pressure is sufficient to result in complications.

Amongst the pioneers, Harry Goldblatt, Irvine Page and Eduardo Braun-Menéndez stand out. Goldblatt’s studies focused on the kidneys. Braun-Menéndez and Page pioneered the work on which much of the modern treatment of hypertension is based. The work of Braun-Menéndez and Page goes back to the discovery of renin by Tigerstedt and Bergman who showed that extracts of rabbit’s kidneys and renal vein blood raised the blood pressure when injected into nephrectomized animals. Braun-Menéndez, an Argentinean born in Chile, belonged to the circle around Houssay, a Nobel prize winner; his group showed that the renal vein blood from kidneys grafted into the neck was pressor in nephrectomized dogs and that renin activated a substrate in the plasma to produce a substance which they called hypertensin. Almost simultaneously, thousands of miles to the north in Indiana, Irvine Page and O. M. Helmer published an article in 1940, which also described that renin acts with a renin activator to form a strong pressor substance which is heat stable and which they called angiotensin.
What sort of men were Page and Braun-Menéndez? Eduardo Braun-Menéndez was born into a family of great wealth. He had nine children. Braun-Menéndez died in a plane accident together with one of his daughters. When I met Braun-Menéndez in the early 1950s, Houssay and his group had left the University in Buenos Aires because of the severe restrictions of academic freedom by Perón, the dictator of Argentina. They worked in a private villa which had been converted into laboratories away from the University and its political intrigues and restrictions. Braun-Menéndez was a quiet, polite, cultured man, who was totally unpretentious. Irvine Page was mercurial, a man who did not shy from arguments. He was one of those individuals who are propelled to success and into political difficulties by a personality which does not shy away from political fights. As a result, Page was not elected to the Society of Clinical Investigation and the Association of American Physicians, although amazingly he was elected to the National Academy. In 1955, the American College of Cardiology asked Page to resign because he had criticized the way scientific meetings were conducted. Page became a chemist, working at the Rockefeller Institute and the Kaiser Wilhelm Institute (later the Max-Planck Institute), in Munich.

Two individuals had come to the same conclusion which influenced the treatment of thousands of patients. Braun-Menéndez and Page compromised by naming the pressor substance “angiotensin.”

The consequences of this discovery were stunning. The group at Western Reserve University in Cleveland demonstrated the existence of two forms of angiotensin, and confirmed the existence of the angiotensin-converting enzyme. It was now only one step from the discovery of the angiotensin-converting enzyme to the discovery of blocking agents which inhibit the conversion of angiotensin I to II. This was accomplished by a group from the University of Colorado, the University of Ribeirao Preto in Brazil, and the Biology Department, Brookhaven National Laboratory. A peptide from a poisonous snake inhibits the enzyme that normally inactivates bradykinin and is identical to the enzyme responsible for the conversion of angiotensin I to angiotensin II. Angiotensin-converting enzyme inhibitors are now one of the most important treatment modalities for progressive heart failure, acute myocardial infarction, and hypertension.

After Roosevelt’s death, hypertension had become a treatable disease.
New Images in Cardiology

Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med. 2007;12:137-147

1. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease
   R. Y. Kwong and others. Circulation. 2006

2. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction

3. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance
   J. A. McGrohon and others. Circulation. 2003

4. Presentation, patterns of myocardial damage, and clinical course of viral myocarditis
   H. Mahrholdt and others. Circulation. 2006

5. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy

6. Lipid-lowering by simvastatin induces regression of human atherosclerotic lesions: two years’ follow-up by high-resolution noninvasive magnetic resonance imaging
   R. Corti and others. Circulation. 2002

7. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy

8. Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission tomography and coronary angiography
   J. Schwitter and others. Circulation. 2001

9. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload
   L. J. Anderson and others. Eur Heart J. 2001

10. Coronary magnetic resonance angiography for the detection of coronary stenoses

Selection of seminal papers by Sanjay K. Prasad, MD, MRCP; Dudley J. Pennell, MD, FRCP, FACC, FESC
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round 25% of myocardial infarctions (MI) are subclinical. Their presence is identified by Q waves on the ECG, although they go clinically unrecognized. While the absence of pain and distress may be a potential relief to the patient, this cohort has a high incidence of major adverse cardiac events (MACE). Over a 10-year period, the mortality rate is estimated to be somewhere between 45% and 55%—similar or higher to patients with recognized MI. A number of imaging modalities have tried to characterize these silent MIs in high-risk groups, but have had variable success. Segmental wall imaging has a variable sensitivity. Nuclear scintigraphy has a spatial resolution of 6 to 8 mm and therefore will miss small infarcts. There is also a substantial radiation exposure. Serum biomarkers such as troponin have made a valuable contribution in the acute setting, but have less value when performed after the acute phase of injury. Recent developments in the technique of late gadolinium enhancement (LGE) by cardiovascular magnetic resonance (CMR) imaging have now enabled the detection of infarcts with a spatial resolution of around 2 mm and with both high sensitivity and accuracy.

In this study, 195 consecutive patients with a clinical suspicion of coronary artery disease, but no history of MI, underwent CMR to assess the prognostic impact of unrecognized scar tissue on clinical outcomes over a median period of 16 months. Patients were referred for a CMR scan on clinical grounds to either evaluate left ventricular function and myocardial scar as part of a noninvasive workup or for viability assessment following angiography where segmental wall-motion abnormalities had been identified.

The presence of LGE turned out to be among the strongest multivariable predictors of MACE and cardiac mortality. A threshold effect was observed where even small infarcts (<2% of average left ventricular mass) was associated with a >7-fold increase in MACE hazards. Using two different multivariable regression approaches, LGE yielded substantial prognostic information for MACE and cardiac mortality; after adjustment for clinical predictors alone or when combined with angiographic predictors, patient risk factor scores, or left ventricular segmental and global functional markers. Limitations of the study were, firstly, that it was single center and, secondly, that coronary angiography was performed at the discretion of the treating physician rather than as a standard part of the protocol. It therefore remains unclear if the incremental prognostic value would still hold if angiographic findings had been considered throughout the whole cohort. The ideal study would ensure impartiality by not divulging the scan findings to the physician providing clinical care. In this study, scan results were available on the same day as the scan so that the influence on clinical management is unclear.

The importance of this paper was 2-fold. Firstly, in identifying a subset of patients at high risk for MACE who are not well characterized by other noninvasive techniques—providing adjunctive risk stratification of patients with signs or symptoms of coronary artery disease. Secondly, this was one of the first CMR papers with prognostic outcome data—something that was urgently required to understand the significance of in vivo fibrosis detection.
ibernating myocardium reflects a downregulation of myocyte metabolism as a consequence of prolonged hypoperfusion or repetitive episodes of myocardial stunning. A spectrum of histological and structural alterations occurs, including cellular dedifferentiation (fetal phenotype) and cellular degeneration (with more extensive fibrosis) associated with loss of contractile and cytoskeletal proteins. The extent of histological changes matches the degree and chronicity of hypoperfusion. Accurate and timely detection of viable myocardium is an important guide to both prognosis and therapy. Until recently, nuclear medicine techniques and stress echocardiography were the mainstay of diagnosis. In patients with chronic ischemic left ventricular dysfunction, improvements in ejection fraction and exercise capacity after revascularization have been well documented. The prognostic importance of detecting viable myocardium is based on two key factors. First, medically treated viable myocardium is a harbinger of further nonfatal ischemic events and higher overall mortality. In patients with significant viable myocardium, the annual mortality rate is more than 4-fold in those treated medically versus optimal revascularization. Second, discrimination between viable and nonviable dysfunctional myocardium can guide the optimal treatment strategy. Patients are able to avoid the risks associated with revascularization when they are unlikely to benefit. Although limited by the lack of large randomized studies, meta-analysis data indicates that the annual mortality rate in patients with dysfunctional myocardium undergoing revascularization is more than twice as great in those without significant viability (7.7%) when compared with those with viable myocardium (3.2%). Moreover, the perioperative mortality rate is substantially increased (to approximately 10%) in the absence of viability.

Direct imaging of myocardial fibrosis by cardiac magnetic resonance (CMR) is with the use of an inversion-recovery prepared T1-weighted gradient-echo sequence after the intravenous administration of a gadolinium-chelate (Gd)—the so called late gadolinium enhancement (LGE) technique—and demonstrates nonviable tissue as “hyperenhanced” or bright. The technique can be performed under resting conditions and without patient exposure to radiation. For assessment of viability, LGE is performed in conjunction with segmental wall-motion assessment by resting cine images. Kim and colleagues performed LGE-CMR in 50 patients with known left ventricular dysfunction before they underwent surgical or percutaneous revascularization. This study showed that CMR has the unique ability to evaluate several markers of myocardial viability that are of proven clinical effectiveness. Based on the functional recovery at a mean of 2 months, lack of hyperenhancement or mild degrees of hyperenhancement (<25% of the segment) in the presence of segmental dysfunction correlated with a 60% to 80% likelihood of functional recovery. In contrast, a segmental wall-motion abnormality in combination with >75% hyperenhancement had a less than 10% likelihood of recovery.

The main limitation of the technique is that the outcome after revascularization is less clear in dysfunctional segments that show intermediate degrees of hyperenhancement (>25% and <75%). The available data suggest heterogeneity of response to revascularization, as such, the potential for contractile recovery of these segments is uncertain. The validation of the LGE technique has enabled a paradigm shift in how viable myocardium is detected. Importantly, in conjunction with the other strengths of CMR such as perfusion analysis, a comprehensive assessment could be made. Analysis is literally “black or white” based on the pattern of late enhancement and therefore more transparent, reproducible, and less operator-dependent.

Former US First Lady Hillary Rodham Clinton is elected to the United States Senate; the first joint US-Russian crew arrives at the International Space Station; and Valentin Paniagua becomes interim president of Peru following the resignation of Alberto K. Fujimori.
Heart failure is not a diagnosis, but a consequence. The underlying etiology will guide subsequent management. The commonest cause is ischemic heart disease followed by a dilated cardiomyopathy. Differences occur in treatment, e.g., antiplatelet therapy and statins, as well as prognosis. The mainstay of distinguishing between the two has traditionally been the x-ray coronary angiogram. This is invasive and carries a tangible risk of complications. There is also exposure to ionizing radiation. There is limited prognostic correlation between degree of stenosis and clinical outcomes.

This paper highlighted additional concerns—particularly the focus on luminography. Consecutive series of patients with left ventricular dysfunction underwent cardiovascular magnetic resonance with late gadolinium enhancement. All patients with a known infarct showed a typical pattern of late enhancement that involved the subendocardium and extended toward the epicardium. In patients with dilated cardiomyopathy (DCM) (normal coronaries), most commonly, there was no detectable fibrosis or scarring. However, about 33% of patients showed a mid-wall pattern of fibrosis that matches the pattern seen in autopsy hearts. Also about 13% of patients assigned a diagnosis of DCM in the presence of normal coronaries showed a typical infarct pattern of fibrosis that is either due to recanalization or an embolic episode.

This study showed that CMR was effective in establishing the etiology in this cohort of patients and also in highlighting the inaccuracies of luminography. Patients with left ventricular dysfunction are also prone to bystander disease where both an infarct and a DCM pattern may be evident. Knowing the relative contribution of each part is useful.

This paper came on the back of previous work showing typical infarct patterns with LGE. However, prior to this study, it was thought that patients with DCM did not have evidence of late enhancement. The mid-wall pattern seen reproducibly in patients with DCM challenged that dogma and was reaffirmed in cases where postmortem analysis was possible. In clinical context, CMR is most useful in the workup of patients with a low or intermediate likelihood of coronary artery disease as a cause for heart failure. It is less appropriate for patients with left ventricular dysfunction and angina. Another issue is whether balanced severe ostial stenoses of the left anterior descending (LAD) coronary artery and right coronary (RCA) could be masked—this is, however, uncommon and almost always accompanied by some detectable infarction.
Myocarditis is a relatively common myocardial disease that can be identified in up to 9% of routine postmortem examinations. It may progress to chronic dilated cardiomyopathy and is an important cause of sudden cardiac death in patients below the age of 40 years. The commonest cause is probably viral. The majority of patients will present with chest-pain or shortness of breath. Troponin levels may be elevated and ECG changes can mimic an infarction. The majority of cases will resolve spontaneously; however, about one third of patients will show clinical deterioration. In some cases the deterioration can be rapid. It is this group that represents the biggest clinical challenge. There is hesitancy to perform myocardial biopsies due to potential risks and experience. Sampling errors mean that the result when it does come is often nondiagnostic. The challenge then is how to make the diagnosis. This has important implications in prognosis, management, and frequently patient reassurance. Distinguishing myocarditis from an acute myocardial infarction will determine whether patients are placed on long-term statins and aspirin.

Previous reports have shown that the pattern of late enhancement, as determined by cardiac magnetic resonance (CMR), in myocarditis is usually mid-wall and that the T2-weighted signal is a useful guide to the presence of active inflammation. What has been unknown is whether there are specific “footprints” attributable to the common viral pathogens. Also, until recently there has been little in the way of targeted therapy toward the underlying viral pathogen. Ventricular remodeling was also different according to the viral type. Patients with herpesvirus infection (HHV6) had a worse outcome than those with parvoviral (PVB 19) infections. The worst adverse remodeling was in patients that had evidence of both parvovirus and herpesvirus infection. Another interesting finding was the mode of presentation and viral etiology. Patients with PVB 19 all had chest-pain and either no or only mild left ventricular dilatation. By contrast, patients with HHV6 may have had chest pain, but the dominant clinical feature and reason for seeking medical attention was dyspnea and increasing peripheral edema.

Limitations of this study are whether these observations are reproducible in different cohorts and the lack of a mechanistic basis to account for the observed differences.

Nonetheless, these findings are likely to guide diagnosis, and be useful in implementing and monitoring therapeutic measures in patients who demonstrate early signs of deterioration. Furthermore, they provide a platform to follow the disease process and stratify patients according to predicted risk. Following on from this study, a multicenter trial is now being planned to replicate these findings and to trial viral-targeted therapy.
Dilated cardiomyopathy (DCM) is the end-result of a number of underlying etiologies with shared final common pathways. It is associated with an increased morbidity and mortality rate and this is reflected by the reduced 5-year survival. A challenge has been to establish who is at highest risk of sudden cardiac death (SCD) or exacerbation of heart failure. The advent of implantable cardioverter defibrillator (ICD) devices has meant that for the former group there is now effective treatment. The problem is that implanting the devices has a tangible risk of complications and the procedure comes with a considerable cost. There are also major psychological problems for many patients. Our current methods of risk stratification have their limitations—demonstrated by the low annual discharge rate of these devices. How can we refine this process?

The answer is unlikely to be found in a single test, but one pathological feature that has attracted much recent attention is the presence of fibrosis. Wherever there is an interaction between normal myocardium and fibrous tissue, normal myocardial electrical automaticity is affected, with the potential to act as a focus for ventricular arrhythmias. This is something that electrophysiologists have recognized for some time, but in vivo, it is only through recent advances in the late gadolinium enhancement (LGE) technique by magnetic resonance imaging (MRI) that we are now able to detect these areas of fibrosis. Likewise, hospitalization for heart failure is distressing for patients and a major burden on health care resources. Potentially, the detection of fibrosis may reflect myocardium that is more prone to diastolic dysfunction.

In this study, a consecutive cohort of 101 patients with DCM was followed up for a mean of just under 2 years. Patients were categorized into two groups based on the presence or absence of mid-wall replacement fibrosis detected using the LGE technique. Mid-wall fibrosis was noted in 35% of the cohort. It was associated with a significantly higher rate of the primary combined end point of all-cause mortality and indexed cardiac dimensions. Patients with fibrosis also had a higher incidence of SCD or sustained ventricular tachycardia (hazard ratio 5.2). There was no significant difference in all-cause mortality, but this may reflect the duration of follow-up and sample size. So is this an all-none phenomenon? Is it the mere presence of fibrosis that is the problem or the amount? Linear regression analysis showed a strong association between the probability of having an event and the extent of late enhancement.

The findings suggest that a potential role for cardiac magnetic resonance is the risk stratification of patients with DCM. Further work is required to replicate these findings in a multicenter setting and to determine whether new patterns of fibrosis develop with disease chronicity. Clearly, it will not be possible to randomize patients to receive an ICD or not on the basis of these findings, but the hope is that they will provide important incremental value in guiding patient management and, importantly, in identifying those patients for whom more aggressive therapy should be considered at an early stage.

Russia cuts delivery of natural gas to Ukraine over a pricing dispute; a stampede during the Stoning of the Devil ritual kills 362 pilgrims in Saudi Arabia; and “Deus Caritas Est,” the first encyclical of Pope Benedict XVI, is promulgated.
The role of lipid-lowering therapy to reduce cardiovascular mortality has been well documented. Such has been the enthusiasm that some have advocated putting statins in drinking water—a panacea for all! However, there is still much to understand before advocating anything quite so dramatic. Several mechanisms have been attributed to account for the observed clinical success. De novo cholesterol synthesis is inhibited with a correlating reduction in both total and low-density-lipid (LDL) cholesterol levels. Statins also promote plaque stabilization, particularly of vulnerable plaques by decreasing their lipid content and amount of inflammation. An important question has been whether there is additional plaque regression.

In this study, magnetic resonance imaging (MRI) was used for longitudinal study of large atherosclerotic arteries following treatment with simvastatin. The study examined aortic and carotid artery plaques in asymptomatic hypercholesterolemic patients. Patients had an LDL cholesterol >130mg/dL. The effects of statins on these lesions were evaluated as changes versus baseline in lumen area, vessel wall thickness, and vessel wall area. A range of MRI sequences was deployed to include fast-gradient echo and black-blood fast spin-echo scans. The typical study time was 60 to 90 minutes. A series of 25 to 30 transverse slices were taken in the region of interest with a typical resolution of 780 μm for the aorta and 469 μm for the carotid artery. In order to ensure matched image acquisition between baseline and follow-up scans, anatomic landmarks were used. Patients were followed up at 12, 18, and 24 months. The main finding was that maintained lipid-lowering therapy with simvastatin is associated with significant regression of established atherosclerotic lesions and sustained vascular remodeling. The vascular atherosclerotic burden and arterial luminal area were both reduced. Changes were not so readily recognized at 12 months and really only accrued with longer-term use. This supports both animal data and human outcome data. Plaque shrinkage and vascular remodeling appear to be achieved before more profound effects on luminal dimensions. The main limitation of this study is whether these findings apply equally to coronary arteries. These are much more difficult to image by MRI as they are small, tortuous, and moving, with only a narrow acquisition window during diastole.

The importance of this study is in highlighting and reinforcing the need for chronic therapy in patients. It confirms Glagov’s original findings that the early stage of atherogenesis is characterized by lipid deposition with outer remodeling of the arterial wall. By contrast, it is the arterial lumen that is compromised in the later stages. This is something that angiography may not appreciate by its focus on lumenography. More clinical data are required to follow through on these original findings and confirm clinical significance in this cohort. It remains therefore too early to place statins in the drinking water just yet!

**Lipid-lowering by simvastatin induces regression of human atherosclerotic lesions: two years’ follow-up by high-resolution noninvasive magnetic resonance imaging**


*Circulation.* 2002;106:2884-2887

The opposition National Rainbow Coalition wins a landslide victory over the ruling KANU party in the Kenyan election, ending 40 years of single party rule; the Raeli sect announces to the world press that they have successfully cloned a human being, named Eve, after aliens taught them how to perform the procedure; and Hans Enoksen is elected prime minister of Greenland.
Cardiac resynchronization therapy (CRT) has emerged as an important therapeutic option in patients with advanced heart failure. The patients characterized in several recent multicenter trials had left ventricular ejection fractions less than 35%, in New York Heart Association (NYHA) Class III or IV and wide QRS complexes (>120 ms). CRT was associated with significant improvements in clinical outcomes. However, one persistent feature has been that up to 30% of patients fail to respond and indeed in some cases are positively worse. Better selection criteria are needed to obviate device implantation in this nonresponder group. A number of echocardiographic parameters have been suggested and, while useful, some guide to their present uncertainty has been highlighted by the number of different markers.

In this study, Bleeker et al took a different angle. They hypothesized that part of the problem may relate to deploying the left ventricular (LV) lead in regions of scar tissue (usually in the inferolateral wall region) resulting in ineffective LV stimulation in patients with underlying coronary artery disease (CAD). Forty patients with CAD and meeting current standard inclusion criteria for CRT underwent cardiac magnetic resonance (CMR) to identify the pattern, location, and transmurality of scar tissue by late-enhancement CMR. Parameters of LV dyssynchrony were measured at baseline and post implant. Clinical evaluation was based on NYHA status, 6-minute walking tests, and Minnesota quality-of-life questionnaires. LV volumes and function were assessed by echocardiography. The response rate in patients with transmural inferolateral infarctions was 14% versus 81% in patients without scar tissue in this region. Patients without inferolateral scar tissue and severe baseline dyssynchrony (>65 ms) showed an excellent response rate of 95% compared with patients with an inferolateral scar and/or absent LV dyssynchrony.

The importance of this paper was in providing a mechanistic basis for part of the observed failure rate. The findings supported the hypothesis that pacing the left ventricle in nonviable or scarred myocardium may result in ineffective LV pacing, resulting in a failure of device therapy. The main limitation is whether the difference in echocardiographic and 6-minute walking test correlates with more hard clinical end points. These studies are under way—potentially, in patients with LV dysfunction secondary to CAD, CMR may refine patient selection. Advice could be given to the implanting physician to avoid the inferolateral wall if the region of infarction is localized—whether it should be avoided in the context of more extensive infarction remains to be tested. Another challenge is that scanning these patients post implant is currently a contraindication. Looking at volumetric changes and any progression in fibrosis is therefore a problem. A number of companies are presently working to develop magnetic resonance imaging (MRI)-compatible devices, but these are still some time away. The role of fibrosis in dilated cardiomyopathy patients was not examined in this study and needs further work.
Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission tomography and coronary angiography

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Circulation. 2001;103:2230-2235

In the assessment of patients with coronary artery disease (CAD), interventional strategies regarding the need for angioplasty or bypass surgery are based mainly on the evaluation of coronary anatomy. This is fine where there is a single tight stenosis and the patient has angina. The problem arises when there are multiple lesions or when the hemodynamic response of a borderline lesion—and thus potential benefit from intervention—are unclear. In this situation, perfusion assessment by single photon emission computed tomography (SPECT) is useful. However, the technique has a number of limitations. These include attenuation artifacts and exposure to ionizing radiation. Positron emission tomography (PET) imaging allows the quantification of perfusion and corrects for attenuation, but is also associated with radiation exposure, has limited access, and is costly. In the early 1990s, first-pass cardiac magnetic resonance (CMR) perfusion imaging was shown to detect CAD in patients. Because the extent of disease relates to the patient’s prognosis, multislice approaches were developed.

In this prospective study, the authors hypothesized that using a fast readout sequence would yield highly reliable perfusion data for the detection of stenosed coronary arteries, even in a multislice mode, and moreover, it would allow evaluation of perfusion indexes quantitatively within distinct myocardial layers. The main method was monitoring contrast medium wash-in kinetics in hyperemic myocardium. Findings were compared with PET and quantitative coronary angiography. \(^{13}\)N-ammonia PET was used as a reference for myocardial perfusion. The diagnostic performance of CMR perfusion imaging was evaluated with respect to anatomically and functionally defined CAD.

Overall, 48 patients and 18 healthy subjects were studied by MR using a multislice hybrid echo-planar pulse sequence for monitoring the myocardial first pass kinetics of Gd-DTPA (0.1 mmol/kg injected at 3 mL/s IV) during hyperemia (dipyridamole 0.56 mg/kg). Signal intensity upslope as a measure of myocardial perfusion was calculated in 32 sectors per heart from pixelwise parametric maps in the subendocardial layer and for full wall thickness. Before coronary angiography, coronary flow reserve (hyperemia induced by dipyridamole 0.56 mg/kg) was determined in corresponding sectors by \(^{13}\)N-ammonia PET. Receiver-operator characteristic analysis of subendocardial upslope data revealed a sensitivity and specificity of 91% and 94%, respectively, for the detection of CAD as defined by PET (mean coronary flow reserve minus 2 SD of controls) and a sensitivity and specificity of 87% and 85%, respectively, vs quantitative coronary angiography (diameter stenosis $\geq 50\%$). The number of pathological sectors per patient on PET and CMR studies correlated linearly (slope, 0.94; r=0.76, $P<0.0001$). The authors concluded that the presented CMR first-pass perfusion approach: (i) reliably detects and quantifies perfusion deficits in patients with CAD; and (ii) provides information on the amount of compromised myocardium resolving transmural differences in perfusion and generating polar maps of perfusion deficits in the subendocardium. The best results for the detection of CAD by CMR perfusion imaging were obtained when contrast media wash-in was assessed in the subendocardial layer, which is most sensitive to an ischemic challenge. Patients with previous myocardial infarctions were excluded from this study, and the performance of the CMR technique in these patients remains to be determined.

This paper was important as one of the first papers to validate the novel CMR approach and to show that it reliably identified and quantified perfusion deficits in an unselected patient population, allowing the assessment of perfusion in distinct myocardial layers.

The foot and mouth disease crisis begins in the UK; Blanche Barton, High Priestess of the Church of Satan, steps down and gives the position to Peter Gilmore and Peggy Nadramia; and Sherpa Temba Tsheri becomes the youngest person to conquer Mount Everest, at age 16.
Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload


Eur Heart J. 2001;22:2171-2179

The most common cause worldwide of iron overload cardiomyopathy is β-thalassemia major (due to transfusional iron overload), but it can also be found in patients with other forms of transfusion-dependent anemia and in primary hemochromatosis. While less of a problem in most Western countries, it is a major problem in the Mediterranean regions and Far East. Patients with thalassemia major have a high morbidity and mortality rate. Around 50% of this is due to cardiac dysfunction. Such was the concern that it is widely reported that the Greek Orthodox Church prohibited marriage between two known thalassemia carriers!

Traditionally, assessment of iron overload has focused on liver biopsies. This is invasive, difficult for serial monitoring, has risk for complications, and to compound these, does not always reflect cardiac patterns of iron overload. Myocardial iron content cannot be predicted from serum ferritin or liver iron, and conventional assessments of cardiac function can only detect patients with advanced disease. There was a need for a noninvasive means of measuring cardiac and liver iron. Iron has paramagnetic properties and therefore affects the signal on T1- and T2*-weighted sequences. The typical epicardial deposition of iron noted at autopsy is visualized in vivo by gradient echo images.

The aim of this study was to develop and validate a noninvasive method for measuring myocardial iron in order to allow diagnosis and treatment before overt cardiomyopathy and failure develops. This group developed a new magnetic resonance T2-star (T2*) technique for the measurement of tissue iron, with validation to chemical estimation of iron in patients undergoing liver biopsy. To assess the clinical value of this technique, they subsequently correlated myocardial iron measured by this T2* technique with ventricular function in 106 patients with thalassemia major. There was a significant, curvilinear, inverse correlation between iron concentration by biopsy and liver T2* (r=0.93, P<0.0001). Interstudy cardiac reproducibility was 5.0%. As myocardial iron increased, there was a progressive decline in ejection fraction (r=0.61, P<0.001). All patients with ventricular dysfunction had a myocardial T2* of <20 ms. There was no significant correlation between myocardial T2* and the conventional parameters of iron status, serum ferritin, and liver iron. Multivariate analysis of clinical parameters to predict the requirement for cardiac medication identified myocardial T2* as the most significant variable (odds ratio 0.79; P<0.002).

The amount of cardiac iron deposition can be quantitatively and reproducibly assessed by myocardial T2* measurements and this information is helpful in both directing treatment and observing the therapeutic response. It has been incorporated clinically for predicting the need for ventricular dysfunction treatment. Early intensification of iron chelation therapy, guided by this technique, has subsequently been shown to reduce mortality from this reversible cardiomyopathy.

Using this technique in a separate cardiac magnetic resonance-naïve population, myocardial siderosis was found in two thirds of thalassemia major patients on maintenance deferoxamine treatment. This was combined with a high prevalence of impaired LV function, the severity of which tracked the severity of iron deposition. Brain natriuretic peptide was not useful to assess myocardial siderosis. Work is under way to look at oral chelating agents.

Wikipedia, the free-content encyclopedia, goes online; UN war crimes prosecutor Del Ponte demands that Serbia hand over Slobodan Milosevic; and the submarine USS Greeneville strikes and sinks a Japanese fishing vessel near Hawaii during an ill-fated maneuver, killing 9 crew members, among which 4 high-school students
Coronary magnetic resonance angiography for the detection of coronary stenoses


In cardiology, any new imaging modality has to contend with the widely held view that, even if it offers exquisite images with high spatial and temporal resolution, if it does not show the coronaries—the so-called Holy Grail of imaging—it ranks as second tier. Over the last 15 years, much attention has focused on the ability of magnetic resonance imaging to noninvasively demonstrate the coronary arteries. The appeal is obvious: a noninvasive safe test with no ionizing radiation that can be carried out as an outpatient. The challenge is, however, formidable: coronary arteries are tortuous, of small caliber (<6 mm), and with both cardiac and respiratory motion the window to image them while relatively stationary in mid-diastole is narrow.

This study investigated the accuracy of magnetic resonance coronary angiography (MRCA) among patients with suspected coronary artery disease (CAD). MRCA was performed in 109 patients before elective x-ray coronary angiography, and the results of the two diagnostic procedures were compared. All images were independently assessed by blinded observers.

Overall, a total of 636 of 759 proximal and middle segments of coronary arteries (84%) could be interpreted on MRCA. In these segments, 78 (83%) of 94 clinically significant lesions (>50% reduction in diameter on x-ray angiography) were also detected by MRCA. Overall, MRCA had a slightly disappointing accuracy of 72% (95% confidence interval [CI], 63% to 81%) in diagnosing CAD, ie, not good enough for routine clinical practice. MRCA was more promising in patients with left main [coronary] artery (LMA) or 3-vessel disease, where sensitivity, specificity, and accuracy were 100% (95% CI, 97% to 100%), 85% (95% CI, 78% to 92%), and 87% (95% CI, 81% to 93%), respectively. Also importantly, the negative predictive values for any CAD and for LMA or 3-vessel disease were 81% (95% CI, 73% to 89%) and 100% (95% CI, 97% to 100%), respectively.

The authors concluded that among patients referred for their first x-ray coronary angiogram, MRCA allowed the accurate detection of CAD of the proximal and middle segments and that this noninvasive approach reliably identified (or ruled out) LMA or 3-vessel disease.

MRCA is currently regarded as the gold standard for the evaluation of anomalous coronary arteries. It is therefore useful in young patients with congenital heart disease or atypical chest pain. It can be used to assess bypass grafts, which are straighter and move less. In patients with heart failure with a low prescan probability of CAD, MRCA is useful to exclude severe proximal disease. Stents are not a contraindication to MRCA and can be visualized although there will be some signal dropout so that stenosis may not be clearly identified.

Since the study was performed, there has been much improvement in both scanner software and hardware. Already the spatial resolution by MRCA has come down to single figures. Additionally, flow mapping may help in identifying the severity of defined lesions.

Computed tomography has the advantage at present in terms of image quality and positive and negative predictive value—but this comes at the cost of 8 to 12 mSv of radiation—thus restricting its value in younger patients and for serial monitoring. If MRCA can improve its diagnostic accuracy, the appeal is in the comprehensive information gleaned—of function, viability, perfusion, and anatomy.

New Zealand sailor Sir Peter Blake, winner of two America’s Cups, is murdered by pirates during an environmental exploration trip in South America; a record barometric pressure of 1085.6 hPa (32.06 inches Hg) is recorded in Tosontsengel, Mongolia; and Peter Jackson’s “The Lord of the Rings: The Fellowship of the Ring” is released into movie theaters.
## New Images in Cardiology

### Bibliography of One Hundred Key Papers

selected by **Sanjay K. Prasad, MD, MRCP; Dudley J. Pennell, MD, FRCP, FACC, FESC**

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