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Functional Cardiac Magnetic Resonance Imaging (MRI) in the Assessment of Myocardial Viability and Perfusion

An Evidence-Based Analysis

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Abbreviations/Acronyms

CA	Coronary angiography
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CFR	Coronary flow reserve
CI	Confidence interval
CMRI	Contrast enhanced MRI
DMRT	Dobutamine MRI tagging
DSE	Low dose dobutamine stress echo
FDG	Fluorine 18-fluorodeoxyglucose
FDI	Functional diagnostic imaging
HF	Heart failure
INAHTA	International Agency for Health Technology Assessment
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
MPR	Myocardial perfusion reserve
MPRI	Myocardial perfusion reserve index
MRI	Magnetic resonance imaging
MV	Myocardial viability
NHSC	National Horizon Scanning Centre
NYHA	New York Heart Association
PET	Positron emission tomography
PCTA	Percutaneous coronary transluminal angioplasty
RF	Radiofrequency
SE	Standard error
SI	Signal intensity
SPECT	Single photon emission tomography
T	Tesla
Tl	Thallium
TEE	Transesophageal echocardiography
TEI	Transmural extent of infarction
WM	Wall motion
WMS	Wall motion study or wall motion score
WT	Wall thickness

Glossary

Coronary angiography: Radiography of the vascular system of the heart muscle after injection of a contrast medium.

Coronary flow reserve (CFR): The ratio of maximal achievable coronary flow under pharmacologic stimulation/exercise and baseline coronary flow.

Cine magnetic resonance imaging: A type of imaging technique used primarily in the field of cardiology. By triggering a MRI sequence with prospective ECG gating, numerous short time frames evenly spaced in the cardiac cycle are produced. These images are sequenced together in a cinematic display so that wall motion of the ventricles, valve motion, and blood flow patterns in the heart and great vessels can be visualized.

Gating: Use of an electronic signal from the cardiac cycle to trigger an event, such as in imaging separate phases of cardiac contraction.

Infarct: An area of tissue death due to a local lack of oxygen.

Magnetic Resonance Imaging (MRI): A special imaging technique used to image internal structures of the body, particularly the soft tissues. It uses the influence of a large magnet to polarize hydrogen atoms in the tissues and then integrates this polarization in threee dimensions using magnetic field gradients and radiofrequency pulses.

Myocardium: A term used to describe the middle layer of the heart wall (heart muscle).

Myocardial hibernation: Dysfunctional cardiac muscle and the functional impairment due to chronic ischemia which can be improved by revascularization. Hibernating cardiac myocytes downregulate metabolic needs to compensate for decreased nutrient supply. On restoration of normal blood flow via revascularization, normal metabolic activity and contractile function resume.

Myocardial perfusion reserve (MPR): The ratio of maximum tissue blood perfusion, i.e., flow achieved during maximal exercise or pharmacological stress, to resting/baseline perfusion.

Myocardial perfusion reserve index (MPRI): An index calculated from the slopes of a signal intensity tissue curves under resting and hyperemic conditions and used as an estimate of the perfusion reserve. It is the ratio of the normalized hyperemic over resting up-slopes.

Myocardial stunning: A form of myocardial contractile dysfunction occurring in response to a transient but fully restored cessation of blood flow. No revascularization is needed and full recovery of the cardiac function is expected but may take minutes to weeks.

No reflow phenomenon: The failure to restore perfusion to acutely ischemic myocardium despite angiographic coronary artery patency.

Parametric map analysis: The myocardium contained within a region of interest is subjected to a pixel by pixel analysis for the entire series of images. The data is then fitted by a statistical method. The end result is a computer generated image of the myocardium in which each pixel represents a hemodynamic parameter such as perfusion.

Pixel: A single two dimensional picture. A computer image corresponds to n rows and m columns of pixels.

Positron emission tomography (PET): A digital imaging method that produces tomographic images of the three dimensional distribution of positron emitting radionuclides.

Scintigraphy: A diagnostic procedure consisting of the administration of a radionuclide with an affinity for the organ or tissue of interest, followed by recording the distribution of the radioactivity with a stationary or scanning external scintillation camera.

Single photon emission tomography (SPECT): A digital imaging method that produces tomographic images of metabolic and physiologic functions in tissues, the image being formed by computer synthesis of photons of a single energy emitted by radionuclides administered in suitable form to the patient.

Tesla (T): Unit of magnetic flux density.

Tomography: The recording of three dimensional images of the internal body often in the form of stacks of two dimensional images.

Executive Summary

Objective

The objective of this health technology policy assessment was to determine the effectiveness safety and cost-effectiveness of using functional cardiac magnetic resonance imaging (MRI) for the assessment of myocardial viability and perfusion in patients with coronary artery disease and left ventricular dysfunction.

Results

- Functional MRI has become increasingly investigated as a noninvasive method for assessing myocardial viability and perfusion. Most patients in the published literature have mild to moderate impaired LV function. It is possible that the severity of LV dysfunction may be an important factor that can alter the diagnostic accuracy of imaging techniques.

- There is some evidence of comparable or better performance of functional cardiac MRI for the assessment of myocardial viability and perfusion compared with other imaging techniques. However limitations to most of the studies included:
  - Functional cardiac MRI studies that assess myocardial viability and perfusion have had small sample sizes.
  - Some studies assessed myocardial viability/perfusion in patients who had already undergone revascularization, or excluded patients with a prior MI (Schwitter et al., 2001).
  - Lack of explicit detail of patient recruitment.
  - Patients with LVEF >35%.
  - Interstudy variability in post MI imaging time(including acute or chronic MI), when patients with a prior MI were included.
  - Poor interobserver agreement (kappa statistic) in the interpretation of the results. Traditionally, 0.80 is considered "good".

- Cardiac MRI measurement of myocardial perfusion to as an adjunct tool to help diagnose CAD (prior to a definitive coronary angiography) has also been examined in some studies, with methodological limitations, yielding comparable results.

- Many studies examining myocardial viability and perfusion report on the accuracy of imaging methods with limited data on long-term patient outcome and management.
  - Kim et al. (2000) revealed that the transmural extent of hyperenhancement was significantly related to the likelihood of improvement in contractility after revascularization. However, the LVEF in the patient population was 43% prior to revascularization. It is important to know whether the technique has the same degree of accuracy in patients who have more severe LV dysfunction and who would most benefit from an assessment of myocardial viability.
  - "Substantial" viability used as a measure of a patient's ability to recover after revascularization has not been definitively reported (how much viability is enough?).

- Patients with severe LV dysfunction are more likely to have mixtures of surviving myocardium, including normal, infarcted, stunned and hibernating myocardium (Cowley et al., 1999). This may lead to a lack of homogeneity of response to testing and to revascularization and contribute to inter- and intra-study differences.

- There is a need for a large prospective study with adequate follow-up time for patients with CAD and LV dysfunction (LVEF<35%) comparing MRI and an alternate imaging technique. There is some evidence that MRI has comparable sensitivity, specificity and accuracy to PET for determining myocardial viability. However, there is a lack of evidence comparing the accuracy of these two techniques to predict LV function recovery. In addition, some studies refer to PET as the gold standard for the assessment of myocardial viability.

Therefore, PET may be an ideal noninvasive imaging comparator to MRI for a prospective study with follow-up.

- To date, there is a lack of cost-effectiveness analyses (or any economic analyses) of functional cardiac MRI versus an alternate noninvasive imaging method for the assessment of myocardial viability/perfusion.

Conclusion

- There is some evidence that the accuracy of functional cardiac MRI compares favourably with alternate imaging techniques for the assessment of myocardial viability and perfusion.

- There is insufficient evidence whether functional cardiac MRI can better select which patients [who have CAD and severe LV dysfunction (LVEF <35%)] may benefit from revascularization compared with an alternate noninvasive imaging technology.

- There is insufficient evidence whether functional cardiac MRI can better select which patients should proceed to invasive coronary angiography for the definitive diagnosis of CAD, compared with an alternate noninvasive imaging technology.

- There is a need for a large prospective (potentially multicentre) study with adequate follow-up time for patients with CAD and LV dysfunction (LVEF<35%) comparing MRI and PET.
  - Since longer follow-up time may be associated with restenosis or graft occlusion, it has been suggested to have serial measurements after revascularization (Cowley et al., 1999).

Objective

The purpose of this health technology assessment was to determine the effectiveness, safety and cost-effectiveness of using functional cardiac magnetic resonance imaging (MRI) for the assessment of myocardial viability and perfusion in patients with coronary artery disease and left ventricular dysfunction.

Background

Clinical Indications

Of patients who are diagnosed with heart failure each year, coronary disease is a major etiological factor (Ho et al., 1993). The number of acute myocardial infarction (MI) patients (>20 years of age) in Ontario surviving their index hospitalization in the 1996/1997 fiscal year was 15,773 (Tu et al., 1999). The prognosis of patients after a MI is related to the extent of tissue necrosis, preserved viability, LV dysfunction and degree of stress induced ischemia (Miller et al., 2003; Expert reviewer, 2004).

Viable myocardium is defined as myocardial segments characterized by reduced function at rest but potentially recoverable either spontaneously (stunned) or with revascularization [usually associated with reduced myocardial perfusion (i.e., hibernating myocardium)] (Marwick, 2002) (Figures 2 and 3). Furthermore, dysfunctional segments may contain: mixtures of normal tissue and nontransmural scar (unlikely to recover); stunned myocardium with maintained perfusion that can recover spontaneously; repetitively stunned myocardium that has persistent dysfunction that can only recover with revascularization; and hibernating myocardium that has reduced perfusion and maintained metabolism that can recover with adequate revascularization (Expert reviewer, 2004).

For patients with ischemic cardiomyopathy, which is characterized by extensive CAD and diminished global left ventricular function, the five year rates of survival range from 50 to 60% (Beller, 2000). Survival worsens as left ventricular ejection fraction (LVEF) decreases, the extent of CAD increases and the age of the patient increases (Bart et al., 1997). Chronic LV dysfunction in patients with ischemic cardiomyopathy most often results from either scarring due to myocardial necrosis or myocardial hibernation (Beller, 2000). The presence of myocardial hibernation suggests that there is sufficient residual blood flow to sustain the viability of myocytes but not enough to maintain systolic contraction (Rahimtoola, 1989). In the case of hibernating myocardium, systolic function improves as perfusion increases such as after coronary revascularization (Beller, 2000). Many patients can have both scarring and hibernation in different regions.

The recognition of viable myocardium may permit improvement of regional left ventricular (LV) function after revascularization, with potential benefits in global ventricular function, functional capacity and prognosis (Marwick, 1998). Similarly, patients with hibernation as the predominant cause of LV dysfunction appear to have a better prognosis after revascularization than after medical therapy (Afridi et al., 1998; Chaudhry et al., 1999).

An important issue for undertaking interventional procedures after a MI or in the presence of chronic ischemia mediated LV dysfunction is viability. For patients with relatively preserved LV function (ejection fraction >35%) and severe symptoms of angina pectoris that interfere with daily lifestyle, coronary revascularization may be indicated without the need of viability studies (Bax et al., 1998). However, it is the subgroup of patients with poor LV function (ejection fraction <35%) and symptoms of heart failure (ischemic cardiomyopathy), in whom viability studies are indicated (Bax et al., 1998). Therapeutic options for these patients include: medical therapy, revascularization, or heart transplantation. Due to the relative shortage of donor hearts, the choice of therapy for most of these patients will be medical therapy or revascularization. Revascularization procedures in these patients are associated with an increased risk of perioperational complications (Bax et al., 1998).

It has been suggested that patients with moderate LV dysfunction and heart failure may also benefit from viability imaging (Expert reviewer, 2004).

Techniques to Assess Myocardial Viability

Any assessment of myocardial viability must include an assessment of coronary artery anatomy by coronary angiography (CA) in order to determine the potential for revascularization if viability in ischemic tissue is suggested by noninvasive imaging methods (Thornhill et al., 2002). For example, atherosclerosis can be very diffuse, and may limit the possibility of performing angioplasty or bypass surgery (Thornhill et al., 2002). Coronary angiography may not be necessary if the extent of viable tissue is limited (Expert reviewer, 2004).

All noninvasive techniques can only identify tissue that might benefit from revascularization (Thornhill et al., 2002). Viable hibernating tissue may not recover, but it has been suggested that patients may still benefit because there is less ischemic tissue (potentially prone to arrhtymias) or eventually some delayed recovery occurs (Expert Reviewer, 2004). The gold standard for the assessment of viability in the clinical setting is therefore limited. The determination of viability is indirect and depends on a region's functional response to revascularization and this remains a limitation of all clinical studies of viability using noninvasive markers (Thornhill et al., 2002).

Thornhill et al. (2002) stated that if the assessment of viability is defined as the detection and discrimination of four tissue states (normal, stunned, hibernating, and infarcted) then viability assessments should in effect include measurements of tissue blood flow.

Four broad categories of techniques have focussed on various surrogates of hibernating myocardium (Marwick, 1998):

- **metabolic function**: assessed by examination of uptake of the glucose tracer flurodeeeoxyglucose (FDG) by positron emission tomography (PET) or single photon emission tomography (SPECT) or with tracers of oxidative metabolism such as labeled acetate and fatty acids.
- **cell membrane integrity**: assessed by uptake of tracers (thallium-201)
- **perfusion**: examined by absolute flow (PET) or tests that focus on microvascular integrity (myocardial contrast echocardiography).
- **contractile reserve**: can be assessed by dobutamine echocardiography.

Allman et al. (2002) conducted a meta-analysis to examine late survival with revascularization versus medical therapy after myocardial viability testing in patients with severe CAD and LV dysfunction. Twenty-four viability studies, pooled using a random effects model, reported patient survival using thallium perfusion imaging, FDG PET or dobutamine echocardiography. MRI was not included in the meta-analysis.

There were 3,088 patients with an average LVEF of 32$\pm$8% were followed for 25$\pm$10 months. In patients with viability, revascularization was associated with 79.6% reduction in annual mortality (16% versus 3.2%, $p<0.0001$) compared with medical treatment. Patients without viability had intermediate mortality, with a trend to higher rates with revascularization versus medical therapy (7.7% versus 6.2%, $p>0.05$). Patients who demonstrated viability revealed a direct relationship between severity of LV dysfunction and magnitude of benefit with revascularization ($p<0.001$). There was no measurable performance difference for predicting revascularization benefit between the three different testing techniques.

Allman et al. (2002) concluded:

- A search for preserved myocardial viability in patients with CAD and significant LV dysfunction using noninvasive imaging techniques identified patients at substantial risk of death which may be reduced by successful revascularization.
- The magnitude of the potential reduction in mortality increased as the severity of LV dysfunction increased.
- Noninvasive imaging of myocardial viability can be used to inform the clinical decision regarding revascularization in such patients.

Allman et al. (2002) stated that limitations to the meta-analysis included:

- Individual studies that were observational, nonrandomized, unblinded and subject to other biases including patient selection bias to enter the studies and proceed to either medical or revascularization treatment.
- The technical aspects and completeness of revascularization and individual patients' medical therapy regimens may have varied widely.
- There was little information in the reports on background medical therapy, and whether the results would hold under the conditions of contemporary medical therapy with aggressive use of statins and b blockers.
- For each imaging technique, there were substantial differences in methodology, protocols and criteria for definition of clinically significant viability. In the meta-analysis, viability could only be interpreted as "present" or "absent" based on the individual study definitions.
- The potential significance of the extent of demonstrated viability or the presence of inducible ischemia in relationship to the degree of subsequent prognostic benefit could not be examined. As well, the extent of viability leading to revascularization was probably variable.
- The individual studies did not report late LVEF, so the relationship between any improvement in LV function and potential prognostic benefit could not be explored. Allman et al. (2002) stated that this may have been instructive since it was recently reported that patients with CAD and LV dysfunction who are revascularized may have similar survival regardless of improvement/no improvement in late LVEF (Samady et al., 1999).
- Recent technical innovations were not routine at the time the included studies were published, therefore, imaging techniques may not reflect current usage.
- Ascertainment of events was not fully complete.
- The findings may not be applicable to all CAD patients with severe LV dysfunction being assessed for prognostic coronary revascularization.
- A limitation to the literature on viability in general is the question of applicability to patients with very advanced degrees of heart failure symptoms and more severe LV dysfunction.

A further limitation to the study by Allman et al. (2002) was the test for homogeneity. For the overall meta-analysis, 3 studies were considered "outliers" and rendered the primary chi square homogeneity test significant ($p<0.05$); i.e., indicating that there was significant heterogeneity between the studies. When the 3 studies were removed from the analysis, the test for homogeneity was no longer statistically significant. However, all the studies were included in the meta-analytic calculations. There was no further discussion by Allman et al. (2002) about the lack of homogeneity or the 3 studies that were "outliers".

Why Use functional cardiac Magnetic Resonance Imaging (MRI)?

Cardiac MRI can offer superior spatial resolution compared with other noninvasive imaging , does not use ionizing radiation, is not subject to attenuation or scatter artifacts and allows 2 or 3 dimensional imaging without orientation constraints. However, imaging without compensation for cardiac or respiratory motion results in image degradation. During the last several years, MRI has been used for the assessment of myocardial perfusion by measuring the alteration of regional myocardial magnetic properties after the intravenous injection of contrast agents.

Treatment Protocol

Typically, a patient is placed on a sliding table and asked not to move during the imaging process. The radiologist and technologist leave the room and the individual MRI sequences are performed. The patient is able to communicate with the technologist at any time using an intercom. Depending on how many images are needed, the exam will generally take from 15 to 45 minutes.

Safety

MRI is safe and no long-term adverse effects have been noted (TFESC, 1998). Claustrophobia occurs in approximately 10-15% of patients (Francis and Pennell, 2000), however, the more recent open construction of many new MRI systems may reduce this. Metallic implants such as hip prostheses, mechanical heart valves and sternal

sutures are not hazardous since the materials used are not ferromagnetic. Patients with electrical stimulators such as pacemakers or cardioverter defibrillators should not be studied due to the risk of causing arrhythmias (TFESC, 1998). However, Greatbatch et al. (2002) recently revealed that a newly developed fiber optic pacemaker lead may be safe for patients who have electrical stimulators and undergo MR imaging using systems operating at 1.5 Tesla (T) or less.

Mechanism of Action

Magnetic resonance imaging uses radio waves and a magnetic field to produce images of internal organs and tissues. Radio waves are directed at protons, the nuclei of hydrogen atoms. The protons are excited and relaxed causing radio signals that can be computer processed to form an image. The pulse sequences create images over hundreds of heartbeats thereby "averaging out" ventricular performance in the process (Fogel, 2000).

MRI systems consist of 3 major components (Pohost et al., 2003):

a) The magnet
b) The radiofrequency coils – generate radio waves at a frequency determined by the field strength of the magnet and by hydrogen to be imaged. The RF coil has two functions: to transmit signal into the body and induce resonance, and to receive the signal emitted from the body.
c) The gradient coil – produce small magnetic fields that vary in a programmed way needed to encode positional information.

Early in the development of clinical MRI, magnetic field strength was relatively low (e.g., 0.1T) (Pohost et al., 2003). The field strength of imaging systems capable of performing cardiac MRI has increased to 1.5T. Most recently, the newer hardware trends for cardiac MRI scanner systems include magnets at 3.0T for whole body imaging since higher fields may lead to improved image quality, greater acquisition speed and increased ability to evaluate nuclei in addition to hydrogen (Pohost et al., 2003).

Techniques have been developed to assess the presence or absence of hibernating myocardium. These include contrast agents (Kim et al., 1999; Pereira et al., 1999; Kim et al., 2000) and dobutamine (Baer et al., 1995; Dendale et al., 1995; Baer et al., 1996; Baer et al., 1998).

MRI Techniques for Myocardial Viability Studies

1. Dobutamine cine MRI

The technique of dobutamine MRI is similar to dobutamine stress echocardiography. Dobutamine MRI assesses changes in LV wall motion in dysfunctional segments using cine cardiac MRI sequences with low and or high dose dobutamine (Galasko et al., 2003).

Normal wall thickness without significant wall thickening during systole is a feature of myocardial stunning and hibernating myocardium. Low dose dobutamine stimulation with the infusion of 5-10 ug/kg/min of dobutamine together with cine MRI has been used to determine viable from nonviable myocardium (Poon et al., 2002). Higher doses of dobutamine (up to 40 ug/kg/min) with or without the addition of atropine at peak dose of dobutamine are mainly used for evaluation of the presence of coronary stenosis or cardiac ischemia (Poon et al., 2002).

2. Contrast Enhanced MRI – Perfusion Imaging and Delayed Enhancement

Specific contrast agents are available for MRI and these are mainly gadolinium complexes. MRI contrast media probe cellular membrane integrity and therefore viability. Gadolinium based contrast agents do not enter intact myocytes but are incorporated into damaged cells; therefore relative hyperenhancement will occur in permanently damaged myocardium (Galasko et al., 2003). By using a combination of contrast and cine MRI, myocardial scar (hyperenhanced with reduced contractile function), hibernating myocardium (not hyperenhanced with reduced contractile function) and normal myocardium (not hyperenhanced with normal contractile function) can be assessed (Galasko et al., 2003). The mechanism of hyperenhancement is believed to be due to tissue accumulation of gadolinium possibly due to differences in contrast distribution volume (Pereira et al., 1999; Thornhill et al., 2002; Kim and Judd, 2003). Since tissue volume in normal myocardium is predominantly intracellular (approximately 75% to 80%), the distribution volume of gadolinium is normally quite low. In acute necrosis, gadolinium will be

able to passively diffuse across ruptured myocyte membranes in the intracellular space, which results in increased gadolinium concentration at the tissue level (Kim and Judd, 2003). It has been postulated that the absence of viable myocytes leads to myocardial hyperenhancement, rather than any inherent properties that are specific for nonviable tissue (Thornhill et al., 2002; Kim and Judd, 2003).

Retention of contrast agent in the myocardium indicates the presence of nonviable myocardium regardless of the age of the infarct (Poon et al., 2002). By using the method of constant infusion of contrast agent, the difference between recent infarcts and older scar tissue can be delineated (Thornhill et al., 2002; Flacke et al., 2001).

2a. Myocardial Perfusion Imaging

A comprehensive assessment of myocardial viability should include an assessment of perfusion (Thornhill et al. 2002). The presence of intact microvasculature can help discriminate between ischemic (but viable) and infarcted myocardium. Myocardial regions that do not enhance during first pass of a bolus dose are supplied by critically stenosed coronary vessels with associated perfusion defects.

Gadolinium is useful as both a contrast agent and a perfusion agent. Perfusion imaging may help to distinguish stunning (normal or near normal perfusion) from hibernating myocardium (hypoperfusion) (Poon et al., 2002). The addition of adenosine stress may further accentuate the baseline perfusion defect in hibernating myocardium and help differentiate normal from near-normal regions in stunned myocardium.

Similar to the detection of contractile reserve with low dose dobutamine, vasodilator-induced perfusion defects detect myocardial perfusion reserve (Poon et al., 2002). Pharmacological vasodilation can increase resting flow 4-8 fold in normally perfused viable tissue, whereas a lesser increase occurs in areas supplied by stentotic arteries (Klocke et al., 2001). Klocke et al. (2001) stated that 70% diameter stenoses reduce vasodilated flow by approximately 50%. Techniques for identifying and quantifying perfusion reserve should be capable of detecting small (2 fold) regional differences in flow to be of real clinical value (Klocke et al., 2001).

The "no reflow phenomenon" refers to the failure to restore perfusion to acutely ischemic myocardium despite angiographic coronary artery patency (Laddis et al., 2001). It is believed to be due to microvascular and myocyte damage resulting from acute ischemia. Small size infarcts show homogeneous contrast hyperenhancement on MRI, however, large infarcts reveal a dark central subendocardial area during the first few minutes after contrast administration. When imaging is performed later, these areas show gradual hyperenhancement as contrast accumulates. Lima et al. (1995) suggested that such a MRI perfusion pattern may be an indication of delayed contrast delivery due to no reflow and may indicate worse prognosis (Wu et al., 1998).

Myocardial perfusion imaging is an active area of cardiac MRI research, however, there are ongoing issues including (Thornhill et al., 2002):

- Hardware requirements
- Choice of contrast medium
- MR pulse sequence
- Tracer kinetic model

2b. Delayed Enhancement

Delayed imaging occurs several minutes after a bolus injection of contrast agent. Approximately 10-20 minutes post-injection of the bolus, infarcted tissue manifests as regions of hyperenhancement.

An alternative approach to gadolinium chelate enhancement is to follow the bolus injection by a constant infusion of the contrast agent (Flacke et al., 2001; Pereira et al., 2000; Thornhill et al., 2003). Small studies have suggested that the partition coefficient of gadolinium chelate in infarcted myocardium exceeds that of normal tissue.

Thornhill et al. (2002) created a protocol that could be used to determine the existence and extent of normal, stunned, and infarcted myocardium (when used in conjunction with cine MRI assessments of contractility):

1. Viable tissue (normal or reversibly damaged) versus nonviable tissue can be discriminated based on differences in the signal intensity or partician coefficient. Both stunned and infarcted tissue will exhibit contractile dysfunction, so a distinction cannot be based on a cine MRI assessment alone.

2. Normal versus reversibly ischemic tissue can be discriminated based on differences in regional contractile function, as assessed by cine MRI. Both normal and stunned tissue will demonstrate a similar signal – therefore a distinction cannot be based on contrast enhancement alone.

MRI for Diagnosis and Management of Coronary Artery Disease

In addition to the possibility of distinguishing viable myocardium, MR perfusion imaging may be capable of the detection and follow-up of patients with CAD (Muhling et al., 2003). Clinical applications for MR first pass perfusion imaging are for the assessment of:

Patients with suspected CAD
Collateral flow and myocardial angiogenesis
Patients with chest pain and a normal coronary angiogram
Myocardial perfusion in heart transplant recipients

Coronary angiography is considered the "gold standard" for defining the site and severity of coronary artery lesions. CA provides mainly anatomical information and can measure the degree of stenosis. However, CA findings are not always a reliable indicator of the functional significance of a coronary stenosis. The routine use of CA without prior noninvasive testing has been considered unadvisable, due to the high cost and associated mortality and morbidity including nonfatal MI and cerebrovascular accidents (NICE, 2003). Exercise electrocardiography (ECG) is widely used for noninvasive detection of CAD due to easy access and relatively low cost. Imaging techniques may be added to improve detection and or localization of exercise induced ischemia (NICE, 2003).

The specific role of MRI perfusion imaging as a noninvasive adjunct (following stress ECG) to coronary angiography for the diagnosis of CAD is unknown. The role of perfusion imaging to stratify patients into appropriate at risk groups and influence the decision on how to optimally manage their conditions is unclear. Furthermore, it is unknown if normal perfusion imaging, excluding clinically significant CAD, can justify avoiding invasive CA.

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Magnetom Open Viva MRI System (License # 35553) (Class 2 device)
Magnetom Sonata MRI System (License # 35573) (Class 2 device)
Magnetom Symphony MRI System (License # 35569) (Class 2 device)
Magnetom Vision MRI System (License # 8427) (Class 2 device)
Magnetom Trio (License # 60276) (Class 2 device)

Gadolinium, gadodiamide, gadopentetate and gadoteridol are included in the listing of drugs currently regulated as new drugs by the Therapeutic Products Directorate (TPD) (Health Canada, 1999). The listing represents substances and formulations which have been assessed by TPD on the basis of an application to market or further to promotion of products for medicinal purposes where safety and efficacy for such purposes have not been established.

An expert consultant to MAS, stated that to the best of his/her knowledge, clinical trials applications (CTAs) for the use of gadolinium (Gd-DTPA) in cardiac patients have not been required.

Alternative Technologies

In patients suspected of having coronary artery disease (CAD), noninvasive testing has a role in selecting patients who would require coronary angiography for either the "definitive" diagnosis of CAD or as a prelude to planning myocardial revascularization (Maddahi and Gambhir, 1997).

A number of techniques have been used to noninvasively assess cardiac viability. These include:

Fluorine-18 fluorodeoxyglucose (FDG) PET
FDG SPECT
Magnetic resonance spectroscopy (MRS)
Functional MRI
Echocardiography
Technetium (Tc-99m)-SPECT
Thallium (TI)-201 SPECT

Techniques used for cardiac perfusion imaging (rest and stress) include MRI, PET and SPECT, and stress echocardiography.

Literature Review on Effectiveness

Objective

- To assess the safety, effectiveness and cost-effectiveness of initial functional cardiac MR imaging as an adjunct to coronary angiography for the diagnosis of CAD.
- To assess the safety, effectiveness, and cost effectiveness of functional cardiac MR imaging used for the assessment of myocardial viability.
- To compare pre-revascularization assessment of myocardial viability in patients, using functional cardiac MRI compared with other imaging modalities, to patient outcomes post-revascularization.

Methodology

Inclusion criteria:

- English language articles (1998- July 2002).
- Journal articles that report primary data on the effectiveness or cost effectiveness of functional MRI obtained in a clinical setting, or analysis of primary data maintained in registries or databases.
- Study design and methods must be clearly described.
- Systematic reviews, randomized controlled trials (RCTs), non-randomized controlled trials and/or cohort studies that have ≥20 patients, cost effectiveness studies.

Exclusion criteria

- Studies that are duplicate publications (superceded by another publication by the same investigator group, with the same objective and data).
- Non-English articles
- Non-systematic reviews, letters and editorials
- Animal and in-vitro studies
- Case reports

Patients

- Human subjects who receive functional cardiac MRI compared to an alternate imaging modality for the assessment of myocardial viability.
- Human subjects who receive functional cardiac MR imaging as an adjunct to coronary angiography for the diagnosis of CAD.

Questions

- Is functional cardiac MRI useful as an adjunct to angiography for diagnosis of CAD?
- How does functional cardiac MRI compare with other imaging modalities (e.g., SPECT, PET, Echo) in terms of sensitivity and specificity for determining myocardial viability in patients with CAD and LV dysfunction?
- How does pre-revascularization assessment of myocardial viability using functional cardiac MRI compare with other imaging modalities (SPECT, PET, Echo) in terms of patient outcomes post-revascularization?
- Is the use of functional cardiac MRI to assess myocardial viability prior to revascularization cost-effective compared to alternate imaging techniques?

Intervention

Functional cardiac MRI.
The comparator is an alternate imaging modality.

Literature Search

Cochrane database of systematic reviews
ACP Journal Club
DARE
INAHTA
Embase
Medline
Reference section from reviews and extracted articles

Outcomes of Interest

Sensitivity
Specificity
Safety
Predictive value of MRI for functional recovery
Economics analysis data

Results of Literature Search

The Cochrane and INAHTA databases yielded 2 health technology assessments. A search of Medline and Embase 1998- July 2003 was conducted using key words myocardial viability, myocardial perfusion, myocardial infarction, revascularization. This search produced 196 studies of which 22 met the inclusion criteria. The quality of the included articles is presented below.

Quality of Evidence

Study Design	Level of Evidence	Number of Eligible Studies
Large randomized controlled trial, systematic reviews of RCTs	1	
Large randomized controlled trial unpublished but reported to an international scientific meeting	1(g)	
Small randomized controlled trial	2	
Small randomized controlled trial unpublished but reported to an international scientific meeting	2(g)	
Nonrandomized study with contemporaneous controls	3a	22
Nonrandomized study with historical controls	3b	
Nonrandomized study presented at international conference	3(g)	
Surveillance (database or register)	4a	
Case series (multi-site)	4b	
Case series (single site)	4c	
Retrospective review, modeling	4d	
Case series presented at international conference	4(g)	

g=grey literature

Assessment of Evidence

Two health technology assessments were identified: Cowley et al. (1999) from the Alberta Heritage Foundation for Medical Research and the National Horizon Scanning Centre (2001) from the United Kingdom.

A. Alberta Heritage Foundation for Medical Research [AHFMR] (1999)

Cowley et al. (1999) conducted a health technology assessment of functional diagnostic imaging in the assessment of myocardial viability. Part of the review evaluated functional MRI in the assessment of myocardial viability (Cowley et al., 1999). Cowley et al. (1999) concluded that MRI has considerable promise as a method for assessing viability. Although the MRI studies assessed by Cowley et al. (1999) had a number of limitations, Cowley et al. (1999) stated that there appears to be useful evidence that MRI compares favourable with other functional diagnostic imaging techniques in terms of accuracy and predictive ability. In addition, Cowley et al. (1999) concluded that further studies would be required to establish its status in the area of diagnostic imaging.

The advantages and limitations of the cardiac functional diagnostic imaging techniques have been summarized by Cowley et al. (1999) (Table 1). In a review, Bax et al. (1997) compared SPECT to dobutamine echocardiography and stated that SPECT had a higher sensitivity (85% to 90% versus 75% to 80%) but a lower specificity (65% to 70% versus 80% to 85%) for predicting whether LV function will improve after revascularization. Beller (2000) stated that the drawbacks of SPECT include limited spatial resolution, poor quality of the images obtained in some obese patients, occurrence of attenuation artifacts that may be misinterpreted as perfusion defects, and the inability of SPECT to differentiate endocardial from epicardial viability. Furthermore, like SPECT, PET has a higher sensitivity (85% to 90%) and a lower specificity (70-75%) than dobutamine echocardiography (Bax et al., 1997). Limitations to PET include the inability to distinguish endocardial from epicardial viability, high cost, and limited availability (Beller, 2000). The limitations of dobutamine echocardiography include the incomplete visualization of all myocardial segments in 15-20% of patients, reliance on visual assessment of wall thickening, and the observation that some severely ischemic segments without thickening at rest may not respond to inotropic stimulation despite persistent evidence of substantial viability (Beller, 2000).

Cowley et al. (1999) commented on the clinical issues and studies of functional diagnostic imaging methods for assessment of viability. Some general points were:

- Most studies have based their analysis on regional functional outcome rather than on global functional outcome.
- Segmental analysis is statistically relevant but may not be clinically relevant.
- When patient based analysis was used, different measures of substantial viability were used for global function recovery.
- Not all studies have stated clearly the degree of anticipated improvement of LV function.

The following is a commentary by Cowely et al. (1999) on the limitations of cardiac FDI studies included in their 1999 review:

1. Definition

The terms viability and potential reversibility were used synonymously in many papers although the pre-revascularization MV assessment is most clinically relevant in patients with chronic impaired LV function for detection of hibernating myocardium. Various cardiac imaging modalities use different markers for MV. In addition, the clarity with which chronic impaired LV function can be defined as hibernation, repetitive stunning or a combination of the two is still limited.

2. Quantification of Viability

A given myocardial region may not be entirely scarred or entirely hibernating and the detection of viable myocardium is not in itself an indication for revascularization. Some patients may have some myocardial regions that include normal, infarcted, stunned and hibernating "micro regions".

Several investigators suggested that the relative proportion of hibernating myocardium to other abnormalities in a given segment and the total extent of hibernation in the LV myocardium will determine the extent of recovery of regional and global LV function after revascularization. It has been previously estimated that $\geq$20% of the myocardial region should be reversibly dysfunctional before an improvement in ejection fraction can be expected (Marwick, 1998). The "substantial viability" used as a measure of a patient's ability to recover functionally after revascularization has been inconsistently defined in the reviewed literature.

3. Patient Selection

The specific category of patients most likely to benefit from MV assessment is not fully understood. It was suggested that patients with severely impaired LV function who have no disabling angina pectoris (which alone may guide therapy) but have HF are most likely to benefit from MV assessment (Bax et al., 1998; Iskandrian et al., 1996; Marwick, 1998). Furthermore, it was suggested that viability results are clinically most relevant in patients with severe global LV dysfunction and in myocardial regions with resting wall motion abnormalities (Schoeder et al., 1993).

Schoeder et al. (1993) considered that viability is important for a subset of patients with akinesia or severe hypokinesia, significant stenosis in the related coronary arteries and severe reduced uptake of Tl-201 or sestamibi during scintigraphy. Beller (1997) stated that accurate viability detection allows for selection of patients with CAD and resting LV dysfunction characterized by severely depressed LVEF (undefined), "who will most benefit from revascularization". There is limited information about revascularization techniques in patients with very severe LV dysfunction (Castro et al., 1998). In a review, Castro et al. (1998) noted the severity of LV dysfunction is defined by different values of LVEF, ranging from <20% to ≤40%.

It is generally believed that viability assessment is not relevant in patients with mild LV dysfunction, however, most patients included in the published primary studies evaluating viability had mild to moderate impaired LV function. Selection bias may explain the comparable accuracy of the various cardiac imaging techniques in predicting recovery of function after revascularization. The results reported by the reviewed primary studies suggested that severity of LV dysfunction is an important factor that is likely to alter the diagnostic accuracy of imaging techniques.

4. Follow up after Revascularization

The optimal time for follow-up after revascularization has yet to be determined. The reviewed accuracy studies provided follow-up data at three months. It has been suggested that in some patients recovery may occur at 6-12 months post revascularization. Of note, longer follow-up may be associated with restenosis or graft occlusion; therefore it may be important to have serial measurements after the procedure.

Outcome endpoints after revascularization need to be determined. Objective endpoints such as improvement in wall motion abnormality or EF may be important, however, improvement in symptoms and survival are clinically important. The standard used in most of the reviewed studies was the echographic determination of improved wall motion (improvement of regional dysfunction). It has been argued that wall motion may have limited significance in terms of improvement in EF, symptoms and survival.

5. Effect on Outcomes

Assessment of the extent of MV may help to select patients who may benefit from revascularization. However, following such selection, many other factors may affect recovery of LV function after revascularization including coronary anatomy, presence/absence of perioperative MI, completeness of revascularization and graft patency (Cowley et al., 1999).

B. National Horizon Scanning Centre [NHSC], (2001)

For a new and emerging technology briefing, the National Horizon Scanning Centre (NHSC, 2001) reviewed imaging in coronary heart disease in general, since a number of noninvasive diagnostic tests were available to determine whether or not a patient with CAD would benefit from coronary angiography. Coronary angiography is considered the "gold standard" for defining the site and severity of coronary artery lesions (NHSC, 2001). NHSC stated that the routine use of coronary angiography without prior noninvasive testing is not advisable, partly due to the high cost and also because of the associated mortality and morbidity.

MRI was one of the imaging technologies briefly reviewed by NHSC (2001). NHSC concluded that MR first pass myocardial perfusion imaging has the potential, if widely diffused to have a large impact on first line perfusion imaging tests. Similarly, NHSC concluded that contrast MRI could have a large clinical impact on coronary imaging before revascularization.

Viability Studies Comparing MRI and SPECT

Kitagawa et al. (2003) compared contrast enhanced MRI with resting ^{201}Tl SPECT for predicting myocardial viability in patients early after acute MI. Thirty consecutive patients admitted to the coronary care units were prospectively enrolled. Patients were included if:

- no history of MI
- underwent successful percutaneous transluminal coronary angioplasty with less than 50% residual stenosis
- clinically stable

Exclusion criteria were not reported by Kitagawa et al. (2003). Eight patients were excluded from data analysis because follow-up cine MR images were not obtained.

CMRI and SPECT images were evaluated in 22 patients (mean age 61.0 years, standard error [SE] 2.4). No clinical evidence of a recurrent coronary event was recorded before follow-up cine MRI in the 22 patients. SPECT was performed 4.3 days (SE 0.2) after onset of MI, and CMRI was obtained at a mean of 7.9 days (SE 1.6) (range 1-20 days) after SPECT. Follow-up cine MRI was performed a mean of 67 (SE 17) days after CMRI.

Contrast MRI, SPECT and follow-up cine MRI were evaluated on separate days and were presented in a different randomized order of patients for each imaging modality. Regional myocardial enhancement on inversion recovery MRI images was graded by assessing the transmural extent of hyperenhanced tissue in each segment:

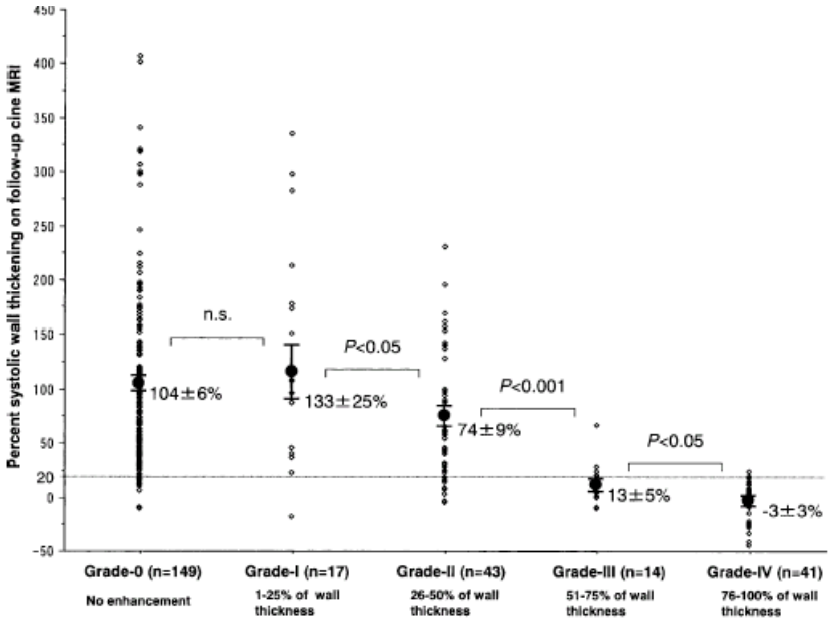
Grade 0	No enhancement
Grade I	Hyperenhancement of 1-25% of wall thickness
Grade II	Hyperenhancement of 26-50% of wall thickness
Grade III	Hyperenhancement of 51-75% of wall thickness
Grade IV	Hyperenhancement of 76-100% of wall thickness

Two authors graded regional myocardial enhancement with consensus before evaluating cine MRI. In each patient, the myocardial region of interest with the maximum count was used as the normal reference region for that patient. ^{201}Tl uptake was graded on the basis of severity of reduction in ^{201}Tl activity:

Grade 0	86-100% of peak activity
Grade I	60-85% of peak
Grade II	50-59% of peak
Grade III	0-49% of peak

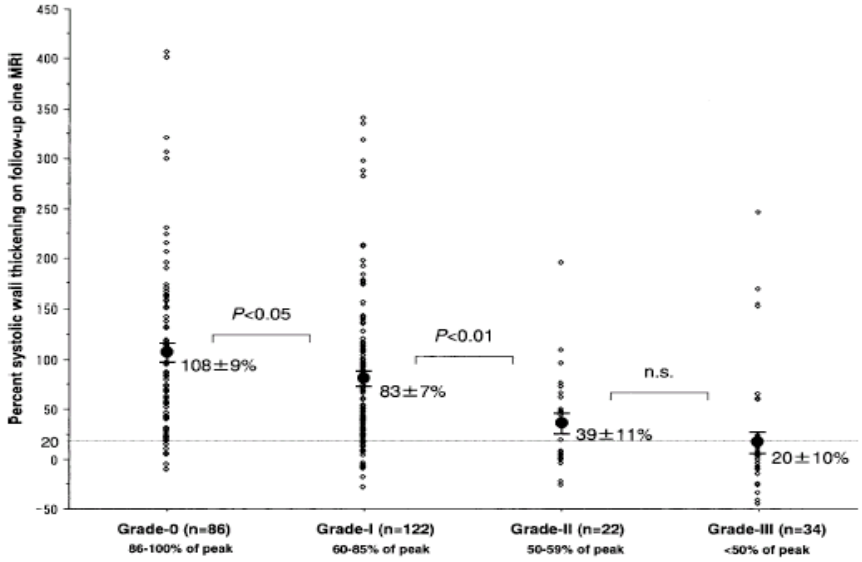
Wall thickening on cine MRI was determined with commercial software. Wall thickening is an indication of contractile function. The hyperenhancement grade for CMRI and SPECT uptake were compared with the regional LV wall thickening on follow-up cine MRI. For calculation of sensitivity and specificity of CMRI, hyperenhancement of 0-50% of the wall thickness (Grade 0-II) was used to determine viable myocardium. This is a clinical definition. Fifty percent hyperenhancement means that half of the myocardial wall is dead and suggests that contractility will retun if only 50% of the wall is viable and there is tissue blood flow. For resting SPECT, 60-100% of the peak activity (Grade 0-I) was used to detect viable myocardium.

Coronary angiography was used to determine the infarct-related artery. However, Kitigawa et al. (2003) did not report when coronary angiography occurred (e.g., before/after MRI, SPECT or both). The transmural extent of hyperenhancement on CMRI, which increases with myocardial injury, revealed a significant correlation with the regional wall thickening on follow-up cine MRI. The proportion of segments with preserved wall motion decreased as the transmural extent of hyperenhancement increased ($p<0.001$). For example, preserved wall thickening greater than 20% was observed in 95% (141/149) of grade 0 segments; 94% (16/17) of grade I segments; 81% (35/43) of grade II segments; 21% (3/14) of grade III segments; and 2% (1/41) of grade IV segments. In addition, the mean percentage of systolic wall thickening between segments of grades I and II, II and III, III and IV was significantly different:



Plot illustrates the relationship between transmural extent of hyperenhancement on contrast-enhanced MR images and percentage of systolic wall thickening on follow-up cine MR images in 264 segments in 22 patients after acute myocardial infarction. Significant differences were observed in mean percentage of systolic wall thickening between segments of grades I and II, grades II and III, and grades III and IV. Solid dot: mean percentage of systolic wall thickening in each hyperenhancement grade, Clear dot: myocardial wall segment, *n.s.:* not significant. Error bars represent standard error.
Used with permission from the Radiological Society of North America and the autho; from: Kitagawa K, Sakuma H, Hirano T, Okamoto S, Makino K, Takeda K. Acute myocardial infarction: myocardial viability assessment in patients early thereafter – comparison of contrast enhanced MR imaging with resting T1 SPECT. Radiology. 2003;226:138-144

The ^{201}Tl uptake, which decreases with myocardial injury showed a significant relationship with the regional wall thickening on follow-up with cine MRI:



Plot illustrates the relationship between resting 201Tl uptake and percentage of systolic wall thickening on follow-up cine MR images in 264 segments in 22 patients after acute myocardial infarction. Significant differences were observed in mean percentage of systolic wall thickening between segments of grades 0 and I and grades I and II. Solid dot: mean percentage of systolic wall thickening in each 201Tl uptake grade; Clear dot: myocardial; wall segment, *n.s.:* not significant. Error bars represent standard error.
Used with permission from the Radiological Society of North America and the author; from: Kitagawa K, Sakuma H, Hirano T, Okamoto S, Makino K, Takeda K. Acute myocardial infarction: myocardial viability assessment in patients early thereafter – comparison of contrast enhanced MR imaging with resting T1 SPECT. Radiology. 2003;226:138-144

Myocardial viability was defined as preserved wall thickening (>20%) at follow-up cine MR imaging. The sensitivity, specificity, and accuracy of CMRI in the prediction of myocardial viability were 98.0% (95% confidence interval 96.0%-100%), 75.0% (64.7%-85.3%) and 92.0% (88.7%-95.3%) respectively. For resting ^{201}Tl SPECT, the sensitivity, specificity, and accuracy of the prediction of myocardial viability were 90.3%(86.2%-94.4%), 54.4% (42.6%-66.2%), and 81.1%(76.4%-85.8%). Significant differences were observed between the two modalities in sensitivity ($p<0.05$), specificity ($p<0.05$) and accuracy ($p<0.001$) in favour of CMRI.

Decreased ^{201}Tl uptake (<60% of peak) resulted in false negative findings in 19 (34%) of 56 grade II or III segments in the prediction of myocardial viability. The false negative segments on ^{201}Tl SPECT images were frequently found in the inferior wall; 14(74%) of 19 segments. Kitigawa et al. (2003) reported that false negative results were found in 4(7%) of the 55 grade III or IV segments on CMRI.

Limitations to the study by Kitigawa et al. (2003) include:

- Details as to why hyperenhancement of 0-50% of the wall thickness (Grade 0-II) was used as a cutoff to detect viable myocardium was not provided.
- Patients were included if they had already undergone successful percutaneous transluminal coronary angioplasty.
- Feasibility study with small number of patients (n=22).
- LVEF was not reported.
- CMRI and ^{201}Tl SPECT were not performed the same day. The area with hyperenhancement on CMRI may decrease from the acute phase to the subacute and chronic phases. Therefore, the area of nonviable myocardium can be slightly larger if contrast enhanced MR images were acquired earlier after onset of MI.
- Redistribution scanning was not used during ^{201}Tl SPECT. It was reported in the early 1990s that delayed SPECT after ^{201}Tl injection was useful for detecting myocardial viability. However, authors of several studies demonstrated that initial resting SPECT images provided significantly equal or greater accuracy than did redistribution SPECT images in the prediction of myocardial viability after revascularization (Pace et al., 1998; Perrone-Filardi et al., 1999).

Wagner et al. (2003) conducted a cohort study of 91 consecutive patients who underwent clinically indicated stress-rest SPECT perfusion imaging for known (n=35) or suspected (n=56) CAD. Known CAD was defined as 50% or greater stenosis in one or more of the coronary arteries at cardiac catheterization or a history of MI or both. For contrast MRI (CMRI), two observers randomly scored the transmural extent of MI by consensus. SPECT images were interpreted in a random order by consensus of two observers who were blinded to the CMRI results.

All patients had CMRI and SPECT within 2 months (mean 10 days, SD 17) of each other. No patient had a clinically recognized MI within the 3 months before CMRI or between the CMRI and SPECT scan. Both SPECT and CMRI revealed agreement for the diagnosis of MI with large transmural extent (>75%). However, there was discordance in the detection of subendocardial infarcts. Of 181 segments that showed subendocardial infarcts when analyzed with CMRI (<50% transmural extent of the LV wall), 85 (47%) showed no sign of infarcts when analyzed with SPECT.

No difference was detected in the rate of missed infarcts (MRI versus SPECT) in patients with suspected (40/87 segments, 46%) compared with known CAD (45/94 segments, 48%, $p=0.682$). There was no difference in the rate of missed infarcts in patients who received pharmacological compared with exercise stress test ($p>0.99$).

Analysis of SPECT images indicated that of all 95 segments with evidence of infarction seen with CMRI but not with SPECT, 48(51%) revealed evidence of induced ischemia on the stress images. Four of the 6 patients (67%) in whom SPECT did not detect an infarction had evidence of induced ischemia in the stress SPECT images.

When patients were analyzed individually, all patients with large infarcts identified by CMRI (>30% infarction of the LV) also had evidence of infarction by SPECT. However, one of the 30 patients with a medium sized infarct and 5 of the 10 patients with smaller infarcts (11-30% and <11% infarction of the LV respectively) defined by CMRI had no evidence of infarction by SPECT.

Overall, Wagner et al. (2003) revealed that although SPECT and CMRI detect transmural myocardial infarcts at similar rates, contrast enhanced MRI detects subendocardial infarcts that are missed by SPECT.

Limitations to Wagner et al. (2003) include:

- Lack of information about the extent of the patients' LV dysfunction.
- Lack of information about whether a coronary angiogram was performed, and if so, when and in how many patients.

Wahba et al. (2001) analyzed the concordance between wall motion and thickening scores derived by gated (electronic signal from the cardiac cycle to trigger imaging of cardiac contraction in separate phases) SPECT and MRI imaging in 21 patients. MRI was used as the reference standard. Wahba et al. (2001) stated that since "gated SPECT imaging allows the simultaneous assessment of both perfusion and function through one study, assessment of ventricular function (e.g., ejection fraction, wall motion and thickening) during myocardial perfusion SPECT can serve as a cost-effective technique for providing more diagnostic data with fewer diagnostic tests".

Patients with known or suspected CAD were referred for gated myocardial perfusion SPECT or MRI. The time between the 2 tests was less than 6 weeks and there were no cardiac events during that interval. Thirteen patients (62%) had a previous MI. The time interval between MI and imaging studies ranged between 4 months and 6 years (mean 3.2 years). The average LVEF in patients with a prior MI was 37±16% and 51±15% in patients without a prior MI. Six patients underwent gated SPECT post stress and 15 patients were imaged at rest.

SPECT

Six patients (29%) underwent a 2 day rest/stress protocol. SPECT using ^{99m}Tc-tetrofosmin was performed 30 minutes post stress. Fifteen patients (71%) had a 2 day stress rest protocol in which SPECT was performed during the rest study due to logistic reasons. Regional function (wall motion and thickening) from the gated SPECT was visually assessed by 2 experienced observers blinded to the MRI results. Nongated SPECT images were used for the assessment of myocardial perfusion.

MRI

For assessment of regional wall motion and thickening, the short axis MRI images were visually interpreted by two observers blinded to the SPECT results. Agreement between gated SPECT and MRI were measured using the kappa statistics.

Segmental wall motion scores by gated SPECT and MRI were identical in 229 of 273 segments, $\kappa=0.72$, $p<0.001$. For patients with MI, $\kappa=0.66$ (no p value provided) or without MI, $\kappa=0.81$ (no p value provided). Segmental wall thickening scores by gated SPECT and MRI yielded $\kappa=0.77$, $p<0.001$. For patients with MI, $\kappa=0.70$ and for patients without MI, $\kappa=0.86$ (no p values provided).

Segmental wall motion and thickening scores between gated SPECT and MRI for segments with normal or mild to moderate hypoperfusion produced $\kappa=0.80$ ($p<0.001$), and $\kappa=0.84$ ($p<0.001$) respectively. For segments with severe hypoperfusion $\kappa=0.45$ ($p<0.001$) or no perfusion, $\kappa=0.57$ ($p<0.001$).

Limitations of the study by Wahba eta l. (2001) included:

- Small number of patients studied (n=21).
- A combination of patients with and without prior MI. Patients with a MI may have had severe perfusion defects and lower agreement than patients without a previous MI.
- The use of coronary angiography was not reported.
- Traditionally, a kappa value of 0.80 is considered "good". Wahba et al. (2001) did not discuss the low kappa values or statistical significance of kappa values in the paper.
- The patients had a mean LVEF >35%, i.e., they did not have severe LV dysfunction.
- Details of the patient recruitment (e.g., prospective or retrospective) were not reported.

Bax et al. (2000) performed a head-to-head comparison between MRI and gated SPECT for the evaluation of LV function in patients with ischemic cardiomyopathy. Patients were referred for evaluation of LV function and myocardial viability. The inclusion criteria were:

Sinus rhythm
Angiographically proven coronary artery disease
Impaired LV function (documented on 2 dimensional echocardiography or LV angiography)

Exclusion criteria consisted of:

Recent MI (<1 month) or episode of unstable angina and or heart failure requiring hospitalization (<1 month)
Cardiac pacemakers or intracranial aneurysm clips

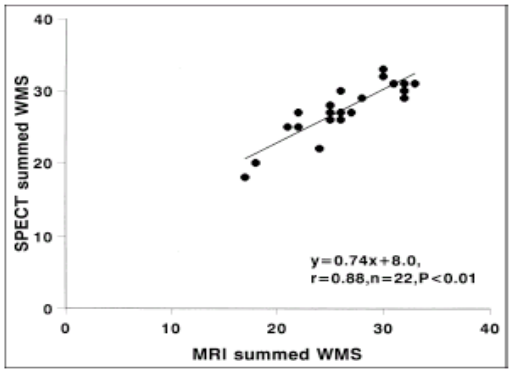
Resting gated SPECT and resting MRI were performed within 30 days (range 2-27) . All patients were clinically stable during the study period. Regional function from the gated SPECT was visually assessed by 2 observers blinded to the MRI results. A 13 segment model was used. Each segment was assigned a wall motion score (WMS) of 1 to 3:

1=normal
2=hypokinetic
3=akinetic or dyskinetic

A summed wall motion score was calculated for each patient as the sum of the individual scores of the 13 segments. MRI studies were performed using a standard 1.5 T MRI system.

Initially, 29 patients were selected for the study protocol. Seven patients were excluded and or incompletely evaluated due to HF (n=5) or unstable angina (n=2).

The agreement for segmental wall motion by MRI and gated SPECT produced a kappa of 0.77 (95% CI 0.71-0.83). The relation of the summed wall motion scores per patient between MRI and gated SPECT was statistically significant ($p<0.01$):



Relation between the summed wall motion score (WMS) per patient on MRI and gated SPECT.

Reprinted from the American Journal of Cardiology, Vol. 86, Bax JJ, Lamb H, Dibbets P, Pelikan H, Boersma E, Viergever EP et al. Comparison of gated single photon emission computed tomography with magnetic resonance imaging for evaluation of left ventricular function in ischemic cardiomyopathy, 1299-1305, Copyright 2000, with permission from Excerpta Medica Inc.

The mean LVEF measured by MRI was 29±4% (range 17-47) and gated SPECT was 29±9% (range 13-50), p=0.76.

The largest share of discrepancies between the 2 modalities was due to 25 segments with normal wall motion out of a total of 286 segments analyzed on MRI that were classified hypokinetic on gated SPECT. This may be due to "mismatching" of segments in the MRI and gated SPECT image volumes.

Limitations to Bax et al. (2000) include:

- It is unknown if the study patients were recruited consecutively.
- 12 patients in the study had already undergone a previous revascularization.

Gunning et al. (1998) compared ^{201}Tl SPECT, ^{99m}Tc-tetrofosmin SPECT, and dobutamine cine MRI for identifying regions of reversible myocardial dysfunction in patients with significantly depressed LV function. Thirty patients with ischemic LV dysfunction were identified prospectively from a waiting list for coronary bypass surgery. Inclusion criteria were:

LVEF<35%
dyspnea as a dominant symptom
3 vessel CAD (defined as >70% luminal diameter stenosis)
a prior MI

Exclusion criteria consisted of:

- Significant valve disease
- Uncontrolled atrial fibrillation
- Permanent pacemaker
- Previous coronary bypass surgery

Preoperative assessment was performed within 3 months of surgery, and postoperative assessment between 3 and 6 months after surgery. Preoperative assessment included stress/redistribution thallium SPECT, separate-day rest/redistribution thallium SPECT, stress/rest tetrofosmin SPECT and cine MRI at rest and during infusion of low dose dobutamine. Postoperative assessment included stress/redistribution thallium SPECT, rest MRI and x-ray coronary angiography.

MR and radionuclide images were analyzed by 2 blinded observers. Postoperative coronary arteriograms were analyzed by a single observer unaware of the other imaging findings.

Agreement for scoring tracer uptake was κ=0.77; for MR wall motion κ=0.54, thickening κ=0.41, and thickness κ=0.41.

Twenty-three patients completed the study. Median time to follow-up imaging was 5 months. For patients completing the study, mean LVEF increased from 24% (SD 8.3%) to 29.7% (SD 11.1%), $p<0.05$. For patients who died, LVEF was 17% (SD 6%).

In the 23 patients with complete imaging data, 207 segments were analyzed. Before surgery, 145 segments had severe hypokinesis and 82 of these improved after revascularization by $\geq$1 wall motion grade. These segments were classified retrospectively as hibernating and this classification was taken as the standard against which the ability of the imaging techniques to predict hibernation was compared.

The majority of segments that recovered function were graded as severely hypokinetic on preoperative MRI.

For radionuclide techniques, late rest thallium images showed the highest sensitivity (76%) compared with stress redistribution thallium (68%), and rest tetrofosmin (66%), $p<0.05$. The three tracer techniques were nonspecific (44%, 51% and 49% respectively). The response to dobutamine cine MRI was specific (81%) yet insensitive (50%).

Limitations to the study by Gunning et al. (1998) include:

- Postoperative assessment occurred within 3-6 months after surgery. Functional recovery may occur later than 6 months after revascularization.
- Interobserver agreement (kappa values) was very poor and p values or confidence intervals were not reported. Traditionally, a kappa value of 0.80 is considered "good" (Einarson et al, 1988).

Gunning et al. (1997) investigated the value of ECG gated 99m Technetium tetrofosmin SPECT in the assessment of myocardial motion, thickening and thickness in comparison to cine MRI. Twenty-eight patients who were referred for routine myocardial perfusion scintigraphy were recruited prospectively. Eight patients had 3-vessel coronary disease, 2 had 2-vessel disease, 5 had single vessel CAD, and 13 had not previously undergone CA. Twelve patients had a previous MI. CAD was defined by CA as stenosis of 50% diameter or more.

For MRI images, endocardial motion in each segment was scored using a 6-point scale: normal, mildly hypokinetic, severely hypokinetic, akinetic, paradoxical or unclassified where no judgement was possible. Systolic myocardial thickening was scored using a 5-point scale: normal, mildly reduced, markedly reduced, absent, or unclassified. Diastolic myocardial thickening was scored using a 4-point scale: normal, mildly reduced, markedly reduced, unclassified.

Two hundred and thirty-seven segments were analyzed. The segmental agreement (kappa) between SPECT and MRI for the whole study group was 0.66 for wall motion, 0.62 for thickening, and 0.55 for thickness. For patients with normal regional function in all myocardial segments (n=90) kappa values were 1.0, 1.0, and 1.0 respectively. For patients with LVEF>35% having abnormal regional function in one or more segments the kappa values were

0.54, 0.39 and 0.34 respectively. For patients with LVEF<35% having abnormal regional function in one or more segments, the kappa values were 0.48, 0.41 and 0.37 respectively.

Subgroups were defined according to the uptake of the SPECT tracer. However, with decreasing tracer uptake, agreement became poorer and agreement for wall thickness was generally worse than for the other 2 categories. For tracer uptake grade 3 (normal) kappas were 0.75 (motion), 0.74 (thickening), and 0.64 (thickness). For uptake grade 2 (mild reduction) kappa values were 0.61, 0.60 and 0.45 respectively. For uptake grade 1 (moderate reduction) kappa values were 0.44, 0.34, and 0.31. Lastly, for uptake grade 0 (severe reduction), kappa values were 0.61, 0.12 and 0).

SPECT and MRI had poor interobserver agreement in poorly functioning ventricles.

Limitations to Gunning et al. (1997) included:

- Poor kappa values reflecting interobserver agreement.
- Small number of patients assessed.
- Some patients had previously undergone CA.

Viability Studies Comparing Functional Cardiac MRI to PET

Klein et al. (2002) compared MRI hyperenhancement with PET as a gold standard for detection and quantification of myocardial scar tissue in patients with chronic ischemic heart failure. Thirty-one patients with CAD (determined by angiography) and reduced LV function (LVEF<35%) assessed by echocardiography or contrast ventriculography and scheduled for a PET study were included in the study. Twenty-six patients had documented MI. Exclusion criteria consisted of:

MI within 6 weeks before PET or MRI
Contraindication to MRI
Unstable angina pectoris
Advanced HF (NYHA IV)

PET and MRI were performed within 1 week with none of the patients having a change in clinical status.

Nonviable tissue (scar) was defined as increased signal intensity 20 minutes after administration of gadolinium. The extent of hyperenhancement was divided into transmural and subendocardial. An inversion recovery 3D turbo gradient echo technique with echo planar readout was used. For PET, different viability criteria combining interpretation of perfusion and metabolism were used:

1. normal blood flow with normal or increased FDG uptake (normal)
2. reduced blood flow with preserved or increased FDG uptake (mismatch)
3. reduced blood flow with reduced metabolism (matched defect) was divided into mild (nontransmural) or severe (transmural) defect and considered scar tissue.

A receiver operating characteristic (ROC) analysis was used to assess hyperenhancement and wall thickness/thickening in differentiating scar from viable tissue.

Sensitivity and specificity of MRI in detecting patients with scar tissue defined by PET were 0.96 and 1 respectively. Five patients (16%) had transmural and 4 patients (13%) had subendocardial hyperenhancement only; 18 patients (58%) had a combination of both, 4 patients (13%) showed no hyperenhancement. For PET, eleven patients (35%) had a severe matched PET defect, 7 patients (23%) had a mild matched PET defect, 10 patients (32%) showed a combination of both, and 3 patients (10%) were normal.

Sensitivity and specificity for detecting transmural defects only were 0.86 and 0.94 respectively, and for detecting any defect (transmural or nontransmural) were 0.83 and 0.88 respectively. In 11% of segments defined as normal by PET, MRI showed hyperenhancement, whereas 5% with a matched PET defect showed no hyperenhancement. Fifty-five percent of segments with subendocardial hyperenhancement were classified as normal by PET. Of 34 segments showing a mismatch, reflecting hibernating myocardium in PET (i.e., decreased perfusion with FDG uptake), 3 showed transmural, 8 nontransmural and 23 no hyperenhancement.

The extent of scar tissue showed a weak inverse correlation (p=0.05) with EF. There was a significant difference between end diastolic and end systolic wall thickness and wall thickening in viable segments compared with segments with transmural scar defined by PET (p<0.001). However, ROC analysis revealed smaller area under the curve for wall thickness and thickening compared with hyperenhancement suggesting that these wall thickness parameters had only limited diagnostic value of differentiation.

Klein et al. (2002) concluded that in patients with chronic CAD and severe LV dysfunction, hyperehnancement correlated closely concerning location and extent with infarct size using PET with NH3 for perfusion and FDG as a metabolic tracer. The results were independent of the severity of contractile dysfunction.

Limitations to this study included:

- Only a few segments revealed a mismatch in PET (hibernating myocardium) 34/1023. Of note, 68% of these segments revealed no hyperenhancement, whereas transmural enhancement occurred in 8%. This weakly suggests that hibernating myocardium was diagnosed correctly by MRI as viable in many cases. Patients with a higher incidence of hibernation need to be examined before final conclusions can be made.
- It is unknown if patients were enrolled consecutively.
- Without a measure of recovery of function or other outcome, no decision can be made regarding which modality was correctly identifying tissue capacity for recovery after revascularization.

Viability Studies With No Comparator to MRI

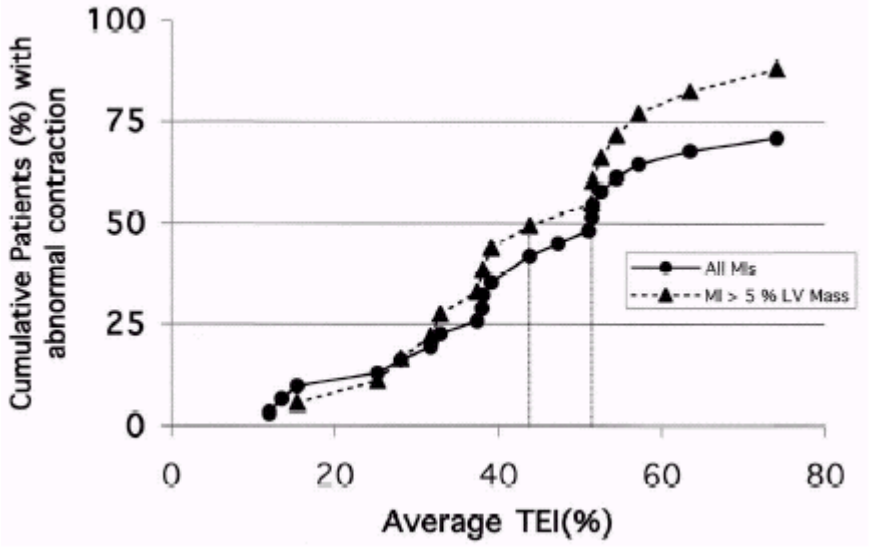
Mahrholdt et al. (2003) examined the relationship of contractile function to the transmural extent of infarction (TEI) in patients with chronic MI in the same imaging session. Thirty-one patients admitted to coronary care units and presenting with first MI were sequentially enrolled. Inclusion criteria consisted of:

No previous history of MI
Single vessel disease defined by cardiac catheterization (no additional stenosis>50%)
Underwent successful primary angioplasty
No contraindications to MRI.

Specific exclusion criteria were not reported. All patients were scanned approximately 5 months after reperfused first MI (162$\pm$62 days). Twelve patients were also scanned acutely as part of another study (Choi et al., 2001). No patient was excluded from the study due to technical or image quality reasons, and none of the patients had clinical evidence of recurrent ischemia between revascularization and MRI. Segmental WT was scored by consensus according to the following scheme: 0=normal, 1=mild to moderate hypokinesis, 2=severe hypokinesis, 3=akinesis, and 4=dyskinesis.

Of all 516 segments with any infarction, blinded observers were unable to detect abnormal thickening in 193 (37%) and WT measured quantitatively in these segments was 66$\pm$28%. Of the 193 segments, 163 (84%) were infarcts limited to the subendocardium with a TEI of $\leq$50%.

The average TEI reached 53% before half of the patients had abnormal contractile function. When patients with small MI ($\leq$5% of the total LV mass) were excluded, the average TEI reached 43% before half the patients had abnormal function:



Summary of the results by patient. LV=left ventricular; MI=myocardial infarction; TEI=transmural extent of infarction.

Reprinted from the Journal of the American College of Cardiology, v. 42, Mahrholdt H, Wagner A, Parker M, Regenfus M, Feino DS, Bonow RO et al. Relationship of contractile function to transmural extent of infarction in patients with chronic coronary artery disease, 505-512, Copyright 2003, with permission from the American College of Cardiology Foundation.

In patients with small MI (≤5% of total LV mass [n=13]), segments with TEI>75% had normal function (14 of 14) if they were surrounded by normally moving "neighbour segments" (the appearance of improved contractile function in infarcted segments due to contraction of neighbouring segments).

Mahrholdt et al. (2003) discussed the "threshold phenomenon" (i.e., sizing of MIs based on contractile function resulting in an overestimation of infarct size) that is observed in an acute and/or nonreperfused setting is not observed in the setting of chronic reperfused infarction. This is because in the setting of acute MI, contractile function may be reduced secondary to myocardial stunning which resolves within days to weeks post MI. As well, contractile function may be reduced in the setting of nonreperfused infarction due to ongoing ischemia.

Mahrholdt et al. (2003) concluded that in the absence of biochemical evidence of infarction and in the absence of significant wall thinning which only occurs in larger transmural infarcts, imaging techniques in which the primary definition of infarction is impaired contractile function may systematically miss patients with subendocardial chronic infarcts.

Limitations to Mahrholdt et al. (2003) included:

- The study patients had an average LVEF of 58±16% and prior angioplasty. The applicability of the results to patients with severe LV dysfunction (LVEF <35%) is unclear.
- Lack of a comparator imaging technique.

Gerber et al. (2002) evaluated the diagnostic accuracy of contrast enhanced MRI (CMRI) late after contrast injection versus early after contrast injection in acute MI (since CMRI reveals a pattern of hypoenhancement early after acute MI) to predict late functional improvement of regional contractility. Inclusion criteria consisted of:

Hospitalization for a first acute MI
Hemodynamically stable

Exclusion criteria consisted of contradictions to MRI.

Twenty patients underwent CMRI and tagged MRI at 4±2 days and tagged MRI again at 7±2 months after acute MI. The resting circumferential shortening strain (contractile function) was analyzed in 24 segments per patient and

diagnostic accuracy of early hypoenhancement was compared with delayed hyperenhancement in predicting recovery of resting circumferential shortening strain 7 months after MI.

The receiver operating characteristic analysis demonstrated that the absence of delayed hyperenhancement compared with the absence of early hypoenhancement had better sensitivity (82% versus 19% respectively; $p<0.001$) and accuracy (74% versus 49% respectively; $p<0.001$), but worse specificity (64% versus 89% respectively; no p value reported) in predicting recovery of resting circumferential shortening strain to any given level.

Gerber et al. (2002) concluded that compared with lack of early hypoenhancement, lack of delayed hyperenhancement had better diagnostic accuracy in predicting functional improvement in dysfunctional segments. Furthermore, the early hypoenhanced regions which represented the fraction of infarcted tissue with concomitant microvascular obstruction, underestimated the amount of irreversibly injured myocardium present after an acute MI.

Limitations to the study by Gerber et al. (2002) included:

- Small sample size.
- Lack of a p value and discussion of the poor specificity for delayed hyperenhancement.
- Interobserver reliability was not reported for the MRI results.

Choi et al. (2001) designed a study to determine if the transmural extent of infarction (TEI) assessed using MRI within the first week after a MI can predict improvement in contractile function 2-4 months later. Thirty-one consecutive patients with a diagnosis of MI defined by cardiac enzymes were prospectively enrolled. Patients were included if:

no prior history of MI
were reperfused (thrombolytics or angioplasty)
clinically stable
no contraindications to MRI
could be scanned within 7 days (scan 1).

The study population consisted of 24 patients who had a second MRI scan 2-4 months later (scan 2). No patient was excluded for technical or image quality reasons. No patients had clinical evidence of a new MI between scan 1 and scan 2.

Cine and CMRI images were analyzed using a 72 segment model (6 slices; 12 segments per slice). Cine images from scan 1 and 2 were randomized and interpreted by 2 observers who were blinded to patients' identity, CMRI, and the chronological order of the 2 sets of images for each patient. Segmental wall thickening was scored according to:

0	normal
1	mild to moderate hypokinesis
2	severe hypokinesis
3	akinesis
4	dyskinesis.

Transmural extent of infarction was scored by consensus of 2 observers on the basis of the transmural extent of hyperenhanced tissue according to:

0	no infarction
1	TEI of 1% to 25% of LV wall thickness
2	TEI of 26% to 50% of LV wall thickness
3	TEI of 51% to75% of LV wall thickness
4	TEI of 76% to 100% LV wall thickness

Subendocardial hypoenhanced regions surrounded by hyperenhancement were included as part of the infarct territory.

A total of 157 of the 1728 segments (9%; 24 patients x72 segments=1728) were within the LV outflow tract or could not be visualized on both MRI scans. Of the remaining 1571 segments, 1047 (67%) had normal wall thickening and 524 (33%) were dysfunctional. Of the 524 segments revealing dysfunction, 316 (60%) improved on scan 2 (change in wall thickening score of $\geq$1) and 208 (40%) did not improve.

When analyzing the percentage of improved segments on scan 2 as a function of the TEI on scan 1, the percentage of improved segments decreased with increasing TEI ($p<0.001$).

When the dysfunctional segments were analyzed using the mixed-effects model, which took into account the multiple measurements from the same patient and a variable number of segments from each patient, TEI remained the best predictor of improvement ($p<0.001$).

There was a high correlation between future improvement in global contractile function (mean wall thickening score) and the percent of LV that was dysfunctional but viable ($p<0.001$). Similarly, there was a correlation between future improvement in ejection fraction (EF) and the percent of LV that was dysfunctional but viable ($p=0.02$).

For both change in mean wall thickening score and change in ejection fraction, the only statistically significant predictive variables were the dysfunctional region by MRI ($p=0.0002$ and $p=0.037$ respectively) and the dysfunctional but viable region by MRI ($p<0.0001$ and $p=0.0022$ respectively). The best single predictor of global improvement was the dysfunctional but viable region by MRI.

Limitations to the study by Choi et al. (2001) include:

- The range of time to follow-up (55-225 days). Patients with a short follow-up time may not have had full recovery of all dysfunctional segments.
- It is unknown whether infarct shape plays an independent role in contractile improvement.
- The LVEF was not reported.
- Some patients in the study had already received angioplasty.

Wu et al. (2001) investigated whether healed myocardial infarction could be visualized as hyperenhanced regions with contrast enhanced MRI. MRI was performed several months after the acute event. In all patients, findings on contrast enhanced MRI were compared with the results of coronary angiography, electrocardiography, cine MRI and creatine kinase measurements. To assess the specificity of the findings, contrast enhanced MRI was also done in 20 patients with nonischemic cardiomyopathy and in 11 healthy volunteers with no clinical risk factors for CAD. Exclusion criteria consisted of:

Unstable angina
New York Heart Association Class IV heart failure
Contraindications to MRI (pacemaker)

Forty-four patients were admitted to hospital with enzymatically proven myocardial necrosis and were prospectively enrolled for future MRI scanning. The study group consisted of 32 patients who returned 3 months after the index event for MRI scanning. Of the remaining 12 patients, five declined to return for MRI scanning, 4 were lost to follow-up, and 3 died. No patient was excluded due to technical limitations or poor image quality and no patient had clinical evidence of a recurrent coronary event prior to MRI scanning. Twenty-one (66%) of patients had clinically successful reperfusion therapy (n=20 percutaneous transluminal coronary angioplasty [PTCA]; n=2 thrombolysis; n=1 one coronary artery bypass grafting [CABG]).

Another group of 19 patients with more "remote infarction" underwent MRI a mean of 14 months after the enzymatically proven index event. This group included 11 patients from the group studied at 3 months, who were followed up for an additional year and had repeat scanning (Wu et al., 2001).

All images were obtained during repeated breath holds and were gated to the ECG. Contrast enhanced images were acquired in the same views as for cine images 15 minutes later. Regional wall motion was scored on a scale:

0=normal
1=mild to moderate hypokinesis
2=severe hypokinesis
3=akinesis
4=dyskinesis

Regional contrast enhancement was scored independently of wall motion. Coronary angiography was performed by standard techniques at the time of the index event in 31 of the 32 patients who were studied at 3 months, and 14 of the 19 "remote infarction"patients who were studied at 14 months.

Among the patients with healed myocardial infarctions, hyperenhancement ranged from large, fully transmural regions that extended over several short axis slices to small subendocardial regions that were visible only in a single sector of a single view. For patients with hyperenhancement, the mean difference in image intensity between hyperenhanced and remote myocardium was 17 SDs of remote region intensity.

Twenty-nine (91%) of the 32 patients with healed MIs examined at 3 months and all of the 19 patients examined at 14 months showed hyperenhancement.

For patients with hyperenhancement in whom the infarct related artery territory could be determined by coronary angiography, 24/25 examined at 3 months 14 patients examined at 14 months had hyperenhancement in the territory of the infarct related artery. None of the twenty patients with nonischemic dilated cardiomyopathy showed hyperenhancement despite the presence of significant LV systolic dysfunction and none of the healthy volunteers showed hyperenhancement.

Wu et al. (2001) reported the sensitivity of contrast enhanced MRI for the detection of healed infarction was 91% at 3 months and 100% at 14 months. The specificity was 100% when patients with nonischemic dilated cardiomyopathy and normal volunteers were considered.

Seven hundred and fourteen segments were analyzed for both contrast enhancement and wall motion in the patients with healed infarction. Hyperenhancement was observed in 250 segments; 188 (75%) had abnormal wall motion and 62 (25%) had normal wall motion. Eighty-nine percent of the segments with hyperenhancement and normal wall motion had hyperenhancement that extended less than 50% of the transmural thickness of the ventricular wall. Of 259 segments with abnormal wall motion, 73% exhibited hyperenhancement and 71 (27%) did not.

The absence of hyperenhancement in patients with nonischemic dilated cardiomyopathy suggests that hyperenhancement may be highly specific for previous myocardial infarction and therefore the presence of ischemic heart disease. However, other nonischemic cardiac disorders may cause hyperenhancement. For example, Friedrich et al. (1998) reported that myocardial hyperenhancement occurs in patients with acute viral myocarditis.

Wu et al. (2001) demonstrated that patients with similar cardiac enzyme release may have equal volume loss of myocardial tissue, but one may have a transmural infarct, whereas the other may have a subendocardial infarct with a larger circumferential size. The clinical implications could be different since a transmural infarct may be likely to expand and remodel the ventricle more than a subendocardial infarct, whereas a subendocardial infarct represents a larger area at risk for future infarction in the infarct related artery area (Wu et al., 2001; Kaul, 1998).

Limitations to the study by Wu et al. (2001) include:

- The result reflects the study population, which was skewed towards patients with small infarcts; more than 50% of the patients had peak enzyme (creatine kinase MB) concentrations less than five times the upper limit of normal.
- 66% of patients had already received clinically successful reperfusion therapy, including PTCA and CABG.
- The study by Wu et al. (2001) had a small sample size.
- The baseline LVEF was not reported.

Kim et al. (2000) investigated the value of cine MRI after the administration of a gadolinium in 50 consecutive patients to assess whether contrast enhanced MRI could be used to predict whether regions of abnormal ventricular contraction improve after revascularization in patients with CAD. Inclusion criteria consisted of:

scheduled to undergo revascularization
abnormalities in regional wall motion on either contrast ventriculography or echocardiography
did not have stable angina, NYHA class IV heart failure, or contraindications to MRI (e.g., pacemaker)
gave written informed consent

Specific exclusion criteria were not reported. No patient was excluded from the study due to technical reasons or reasons of image quality.

Twenty-one patients (42%) had a documented history of MI and 6 were studied within 2 weeks after MI. The mean interval between MRI and revascularization was 18±25 days, and no patient had clinical evidence of infarction

during this period. The transmural extent of hyperenhanced regions was postulated to represent the transmural extent of nonviable myocardium. The extent of regional contractility at the same locations was determined by cine MRI before and after revascularization in 41 patients. MRI was repeated a mean of 79$\pm$3 days after revascularization. Of the remaining 9 patients, one died, 2 were lost to follow-up, 2 had a pacemaker implanted, and 4 declined to return. Two patients had biochemical evidence of MI after coronary artery bypass surgery and before the follow-up MRI.

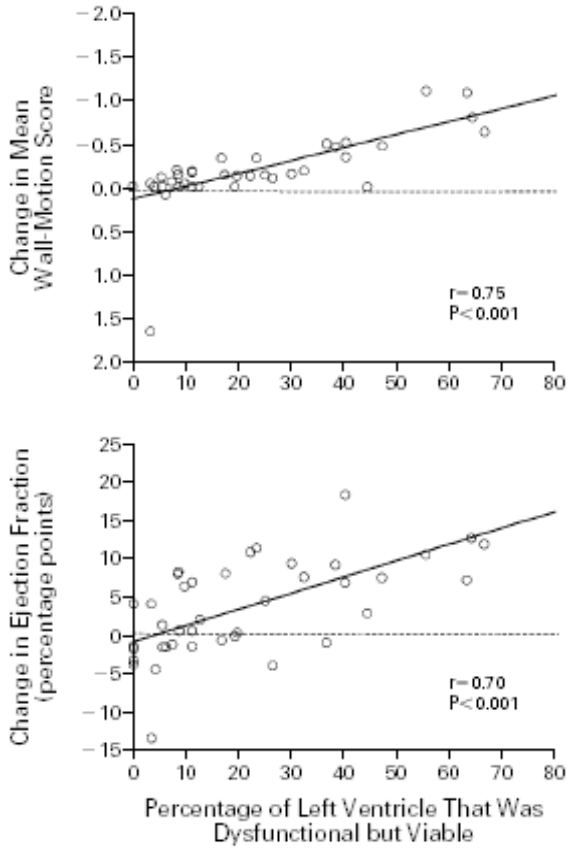
Cine MRI images and contrast enhanced images obtained before and after revascularization were placed in random order and analyzed by 2 observers who were unaware of the findings on contrast enhanced MRI or cine images. The extent of segmental wall thickening and extent of hyperenhanced tissue within each segment were graded on 5-point scales.

Contrast enhanced MRI demonstrated hyperenhancement in 40 out of 50 patients (80%) before revascularization. The mean intensity of hyperenhanced regions was 530$\pm$195 % of that of regions without hyperenhancement. For the 41 patients who underwent imaging after revascularization, the mean EF was 43$\pm$13 % before revascularization and 47$\pm$12 % after the procedure.

When all segments that were dysfunctional before revascularization were analyzed, the proportion with improved contractility decreased progressively as the transmural extent of hyperenhancement increased ($p<0.001$). Contractility increased in 256 of 329 segments (78%) with no hyperenhancement but in only 1 of 58 segments with hyperenhancement of more than 75% of tissue. A similar relation between the transmural extent of hyperenhancement and contractile improvement was found in segments with at least severe hypokinesia at baseline ($p<0.001$) and in segments with akinesia or dyskinesia at baseline ($p<0.001$). The mean transmural extent of hyperenhancement was 10$\pm$7 % for the group of dysfunctional segments with improved contractility and 41$\pm$14 % for the group with no improvement in contractility ($p<0.001$).

For 1,075 segments that were assessed by a third independent observer, the kappa value for improvement in contractility was 0.59 (95% CI 0.53-0.64). For all 5 categories of hyperenhancement, there was a positive relation (Spearman $r=0.74$, $p<0.001$) between the scores determined by the first set of observers and the third observer. The concordance was 99% (defined as scores that were within 1 point of each other).

For each patient, the percentage of the LV that was dysfunctional but viable before revascularization was calculated. The total number of segments that were dysfunctional but predominantly viable (defined as hyperenhancement of no more than 25% of the tissue in each segment) were divided by the total number of segments in the LV. An increasing extent of dysfunctional but viable myocardium before revascularization correlated with greater improvements in both the mean wall motion score ($p<0.001$) and the EF after revascularization ($p<0.001$).



Relation between the percentage of the LV that was dysfunctional but viable in 41 patients before revascularization and the changes in the mean wall motion score and ejection fraction after revascularization. Decreases in wall motion scores indicate increases in contractility. The mean ejection fraction was 43±13 percent before revascularization and 47±12 percent after revascularization. One patient had significantly worse function after revascularization and required the insertion of an intraaortic balloon pump aft3r bypass surgery because of a perioperative myocardial infarction.
From Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O et al. The use of contrast enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. New England Journal of Medicine. 2000;343:1445-1453; Copyright 2003 Massachusettes Medical Society. All rights reserved.

Several factors may account for the lack of functional improvement in some regions that were considered viable (Kim et al., 2000):

1. Use of a single evaluation of ventricular function soon after revascularization may lead to an underestimation of the true rate of functional recovery.
2. Tethering of regions may inhibit the response of viable regions to revascularization.
3. Even if technically successful, coronary revascularization may be incomplete particularly in patients with extensive atherosclerosis and diffuse disease.

Contrast enhanced MRI had greater accuracy in segments with the most severe dysfunction, possibly due to the ability of contrast enhanced MRI to delineate the transmural extent of viable and nonviable myocardium (Kim et al., 2000).

The high predictive accuracy in severely dysfunctional segments (akinesia or dyskinesia) is important, as was the ability to determine the transmural extent of myocardial injury. This is important since Dakik et al. (1997) revealed that on the basis of myocardial biopsy data that transmural scarring of >20-30% of tissue correlates with a lack of improvement in function after revascularization.

Kim et al. (2000) stated that the use of a single cutoff value for hyperenhancement on which to base predictions of functional improvement would not have a physiologic basis and therefore would be suboptimal. If a cutoff value of 25% were chosen, the positive and negative predictive values would be 71% and 79%, respectively for regions with

any degree of dysfunction and 88% and 89% respectively for regions with akinesia or dyskinesia. If a cutoff value of 75% were chosen, none of the 57 segments with at least severe hypokinesia at baseline would be considered to have increased contractility after revascularization, yielding a negative predictive accuracy of 100%.

Limitations to the study by Kim et al. (2000) included:

- The patient population had an average EF of 43% before revascularization. This value is higher than in other assessments of myocardial viability. It is important to know whether the technique has the same degree of accuracy in patients who have more severe LV dysfunction and who would most benefit from an assessment of myocardial viability.
- Kim et al. (2000) visually evaluated the degree of wall motion and extent of hyperenhancement rather than quantitative measurements of these indices. The kappa value for interobserver agreement including all 3 observers was only 0.59. An arbitrary cut-off value for "good" agreement is usually 0.80.
- Regional function was evaluated 11 weeks post revascularization. This may be too soon to see the full functional improvement expected in patients with hibernating myocardium (Beller, 2000).
- Prospective randomized studies should be undertaken to determine the worth and cost-effectiveness of noninvasive testing of viability as a means of guiding therapeutic strategies in patients with ischemic cardiomyopathy.
- No comparator imaging modality.

Viability Studies Comparing MRI versus Dobutamine Echocardiography

Kramer et al. (2002) compared the qualitative response of low dose dobutamine by echocardiography (DSE) with the quantitative response of dobutamine MRI tagging (DMRT) in the prediction and evaluation of functional improvement after reperfused MI. Twenty-seven patients with reperfused ST elevation MI were initially enrolled. Inclusion criteria consisted of:

recent MI
documented open infarct related artery after thrombolytic therapy or primary angioplasty with or without stenting.

Exclusion criteria consisted of patients with:

post MI angina
active HF
atrial fibrillation
sustained ventricular arrhythmia
inability to lay flat
standard contraindications to MRI such as pacemakers, defibrillators or cerebral aneurysm clips

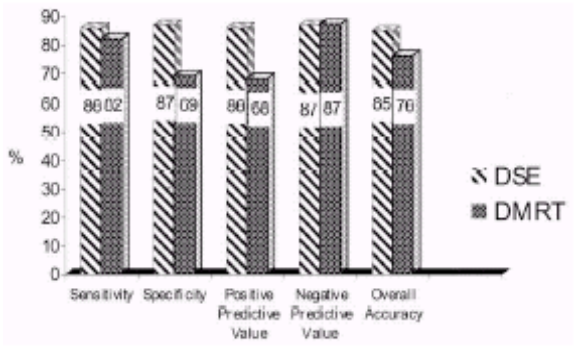
On day 3±1 after MI, patients underwent both DSE and breath hold DMRT at baseline and during infusion of dobutamine. The patients returned at week 8±1 for follow-up echocardiogram and MRT at rest.

Low dose dobutamine echocardiography was used to determine contractile reserve and functional improvement in dysfunctional segments. The DSE was scored by use of the American Society of Echocardiography scoring system (1=normal, 2=mild hypokinesis, 3=severe hypokinesis, 4=akinesis, 5=dyskinesis). Functional improvement was defined as any improvement in wall motion in a given segment by 1 grade with dobutamine and at follow-up respectively. By DMRT, a 5% increase in percent intramyocardial circumferential shortening at peak response to dobutamine was defined as evidence of contractile reserve. Functional improvement by echocardiography was defined as the gold standard.

Twenty-two patients completed the study. Agreement for functional improvement at 8 weeks post-MI between the techniques yielded a kappa=0.52 ($p<0.001$).

For echocardiography, wall motion score fell from 1.8±0.1 at baseline to 1.6±0.1 with dobutamine and 1.5±0.1 at 8 weeks post MI ($p<0.05$). In the same 67 segments, the percent intramyocardial circumference shortening (%S) by MRI was 4%±1% at baseline and improved to 10%±1% at peak dobutamine ($p<0.0001$ vs. baseline), and 11%±1% at week 8 ($p<0.0001$vs. baseline); overall $p<0.001$.

The sensitivity, specificity, and overall accuracy of low dose dobutamine echocardiography and low dose dobutamine MR tagging are presented below. Kramer et al. (2002) stated that the overall accuracies were similar between techniques with a difference in agreement of –9% (95% CI –23, 5).



Reprinted from the American Heart Journal, v. 143, Kramer CM, Malkowski MJ, Mankad S, Theobald TM, Pakstis DL, Rogers WJ. Magnetic resonance tagging and echocardiographic response to dobutamine and functional improvement after reperfused myocardial infarction,1046-1051, Copyright 2002, with permission from Elsevier.

Kramer et al. (2002) suggested that potential reasons for the lower specificity of DMRT are the known lower specificity for dobutamine response in the subendocardium and difficulties in registering locations between the 2 different imaging modalities when one is used as the gold standard.

Limitations to the study by Kramer et al. (2002) include:

- Imaging a very early post-MI and matching to 8-week images. How soon after a MI should imaging take place?
- Longer follow-up may have identified more functional improvements.
- Patient recruitment details were not explicitly described (consecutive?).
- There was poor interobserver agreement (κ=52%).
- Some patients had already received angioplasty. Examination of contractility prior to revascularization may allow prediction of which patients would benefit from revascularization.

Saito et al. (2000) assessed the viability of myocardium by an analysis of the improvement of the regional wall motion using a MRI tagging method. Nine patients had a prior MI. All patients had abnormal ventricular wall motion on echocardiography at rest. A cine MRI with tagging sequence was used before and during dobutamine infusion. Stress MRI was initiated after 3 minutes of dobutamine infusion. The wall motion was compared before and during dobutamine infusion in 22 patients and 7 healthy volunteers.

To determine viability, 19 of the 22 patients also underwent ^{201}Tl SPECT, 14 patients were examined by PET, and follow-up echocardiography without the use of dobutamine was performed in 10 patients 1 month after CABG or percutaneous transluminal coronary angioplasty (Saito et al., 2000). Some patients were evaluated for viability by 2 or 3 examinations "and the estimation by these methods showed no discrepancies in any of the patients" (Saito et al., 2000). It is uncertain if the investigators meant some patients were evaluated for viability by 2 or 3 of the same or different examinations. No further information was provided for the SPECT, PET or follow-up echocardiography without dobutamine.

For healthy patients, the wall thickening ratio increased significantly with dobutamine infusion ($p<0.05$). The results of the evaluation of myocardial viability with dobutamine stress MRI and echocardiography "were similar in 19 (86.4%) of the 22 patients with ischemic heart disease". The sensitivity, specificity and accuracy of the two technologies in determining viability in 60 vessel areas in the 20 patients in whom both procedures were performed are presented below.

	Sensitivity	Specificity	Accuracy
Dobutamine MRI	75.9% (22/29)	85.7% (6/7)	77.8% (23/36)
Dobutamine echocardiography	65.5% (19/29)	100% (7/7)	72.2% (26/36)

Reprinted with permission from the Japanese Circulation Society; from Saito I, Watanabe S, Masuda Y. Detection of viable myocardium by dobutamine stress tagging magnetic resonance imaging with three dimensional analysis by automatic trace method. Japanese Circulation Journal. 2000;64:487-494.

Limitations to the study by Saito et al. (2000) include:

- Lack of clarity in reporting study details in methods and results.
- Lack of data for the alternate imaging methods that were also used.
- Lack of patient inclusion/exclusion criteria.
- Small sample size.
- LVEF was not reported.
- Patient recruitment was not sufficiently described.

Baer et al. (2000) compared dobutamine transesophageal echocardiography (dobutamine TEE) and dobutamine MRI for the detection of viable myocardium and the prediction of LV functional recovery in patients with chronic CAD following successful revascularization procedures. Baer et al. (2000) prospectively studied 103 patients. Forty-eight of these patients were also included in a previous MRI study on myocardial viability (Baer et al., 1998).
Inclusion criteria consisted of:

Chronic CAD (infarct age > 4 months)
Persisting akinetic or dyskinetic infarct region as demonstrated by left ventriculography
Severe stenosis of the infarct related coronary artery – reduction in resting flow or repetitive ischemic episodes in the infarct region (>80% diameter reduction)
Angiographically documented successful revascularization after 6 months.

Exclusion criteria consisted of:

Unstable angina
Congestive heart failure (NYHA IV)
Atrial fibrillation
Permanent pacemaker
History of multiple myocardial infarctions
History of sustained ventricular tachycardia

Dobutamine TEE and dobutamine MRI were performed in random order within 3 days without intervening cardiac events. β blockers were withdrawn 48 hours preceding the pharmacological stress tests and the control studies after revascularization. After 4.9 ± 0.7 months, 65 patients underwent control coronary angiography. Patients with restenosis/obstruction (>70% diameter reduction) of the infarct related coronary vessel or bypass were excluded from the final evaluation. A subset of 52 patients who fulfilled the inclusion criteria underwent an additional rest MRI study for quantitative evaluation of LV functional recovery. The mean baseline LVEF of the patients was 41%.

Dobutamine TEE images were analyzed on a segment-by-segment basis by two observers independently and without knowledge of the findings of the other imaging techniques. Akinetic and dyskinetic segments at rest were graded viable if dobutamine-induced wall thickening could be observed. Individual infarct regions were graded viable if 50% of akinetic or dyskinetic segments showed dobutamine induced systolic wall thickening.

For MRI, wall motion and systolic wall thickening were assessed semiquantitatively on a segmental basis. Akinetic and dyskinetic segments at rest were graded viable if dobutamine induced wall thickening could be observed. The reference standard "contractile recovery after successful revascularization" was evaluated quantitatively by measuring end diastolic and end systolic wall thickness. Improvement of LV function was defined as systolic wall thickening at rest $\geq$2 mm. Functional recovery of the entire infarct region was defined as systolic wall thickening $\geq$2 mm in $\geq$50% of the dysfunctional segments prior to revascularization.

The sensitivity, specificity and accuracy of dobutamine TEE and dobutamine MRI for the recovery of regional LV function after successful revascularization were (82%, 83%, 83%) and (86%, 92%, 88%) respectively.

The mean LVEF before revascularization was not significantly different between patients with and without a dobutamine induced contraction reserve by TEE and MRI in infarct related segments. In contrast, the LVEF increased significantly in patients with predominantly viable infarct regions by TEE ($p<0.001$) and MRI ($p<0.001$) compared to those infarct regions graded to have predominantly scar tissue. The magnitude of the increase in LVEF was significantly correlated with the number of dobutamine responsive segments assigned to an individual infarct region (TEE $r=0.71$, $p<0.0001$; MRI $r=0.73$, $p<0.0001$) in both imaging techniques.

The mean baseline LVEF of the patients was 41%. However, patients with severe LV dysfunction may be more likely to have a lower sensitivity using dobutamine MRI (Baer et al., 2000; Gunning et al., 1998).

Limitations in the study by Baer et al. (2000) include:

- The mean LVEF was 41±10.0%. The number of patients with LVEF <35% was n=15 (29%).
- Baer et al. (2000) stated that the patient group was a "heterogeneous patient population" and that it is difficult to relate changes of LVEF solely to the effect of adequate reperfusion and functional improvement of a specific infarct region of interest because CABG may have influenced global left ventricular function by revascularizing myocardial other areas not assigned to the dysfunctional infarct region of interest. Baer et al. (2000) further stated that change sin medication may have also lead to variations in global LV function. Further explanation of these limitations stated by Baer et al. (2000) is required.
- 103 patients fulfilled the inclusion criteria, however, during follow-up (4.9+0.7 months) only 52 patients had a successful revascularization ("52 patients still had an angiographically controlled open target vessel") and MRI assessment.

Viability Studies Using Dobutamine Tagged MRI and Contrast Uptake

Kramer et al. (2000) examined the ability to predict functional recovery using MRI contrast uptake patterns and contractile response to dobutamine by tagged MRI within the same myocardial tissue early after reperfused first MI in a single noninvasive examination. Twenty-seven patients with reperfused first MI were enrolled. Inclusion criteria consisted of:

Recent MI
Documented open infarct related artery after thrombolytic therapy or primary angioplasty with or without stenting and dysfunction in the infarct zone documented by left ventriculography or echocardiography.
Documented Thrombolysis in MI trial (DTM) grade 3 flow in the infarct related artery after therapy.

Exclusion criteria were:

Patients with postinfarction angina
Active congestive HF
Atrial fibrillation
Aortic stenosis
History of sustained ventricular arrhythmia
Inability to lay flat
Standard contraindications to MRI such as pacemakers or cerebral aneurysm clips

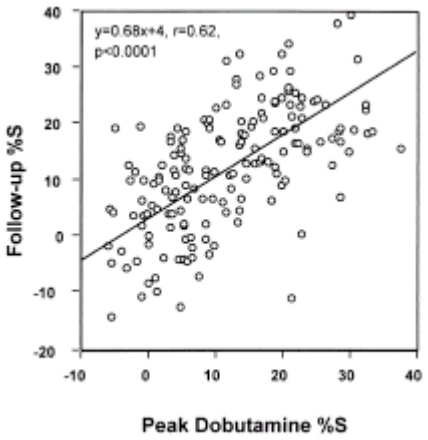
Breath hold tagged imaging, using a grid tagged method, in the LV short axis from apex to base was performed. Dobutamine was infused for tagged imaging. Contrast enhanced imaging was performed using an intravenous bolus dose of gadolinium. At least 1 set of 10 delayed images in each of the same three planes was acquired 5-7 minutes after the first pass imaging. The patients returned 9±1 weeks after the MI for a repeat MRI that consisted of MR tagging without dobutamine.

The first pass images and a set of delayed enhancement images were reviewed in cine format for qualitative determination of abnormal contrast uptake patterns. Myocardial regions with hyperenhancement through more than two-thirds of the transmural extent of the wall on delayed postcontrast imaging were identified. The regions were subdivided into those demonstrating first pass hypoenhancement and those demonstrating normal first pass enhancement.

Only end diastolic and end systolic images were used to measure intramyocardial-circumferential-shortening. Measurements were made at baseline and at each dobutamine dose. Percent shortening was measured at nine weeks after MI.

Twenty-three patients completed the study. No patients had interval cardiac events between the two exams. Eighty-four transmural regions with an abnormal contrast pattern were identified and therefore function in 168 segments within these regions were measured. When improvement was defined as a 5% (%S) increase from baseline to follow-up, 88 of 168 segments improved (52%). The percent shortening in normal first-pass enhancement regions was greater than those regions demonstrating first pass hypoenhancement at baseline, peak dobutamine and follow-up ($p<0.0003$ for each).

There was good correlation between follow-up 5% intramyocardial-circumferential-shortening and 5% intramyocardial-circumferential-shortening with peak dobutamine:



Plot of linear regression analysis for %S at nine weeks after myocardial infarction (follow-up) on the y-axis and at peak dobutamine day 3 after myocardial infarction for all 168 segments. A significant correlation is demonstrated (y=5 0.68x 1 4, r=5 0.62, p< 0.0001). %S=5 percent intramyocardial circumferential shortening.

Reprinted from the Journal of the American College of Cardiology, v. 36, Kramer CM, Rogers WJ, Mankad S, Theobald TM, Pakstis DL, Hu YL. Contractile reserve and contrast uptake pattern by magnetic resonance imaging and functional recovery after reperfused myocardial infarction, 1835-1840, Copyright 2000, with permission from the American College of Cardiology Foundation.

Kramer et al. (2000) suggested that the region with normal first pass enhancement represented predominantly viable myocardium defined as both normal dobutamine response and functional recovery in the setting. The region with first pass hypoenhancement represented a mixture of viable and nonviable tissue with some late functional improvement. According to Kramer et al. (2000), the presence of first pass hypoenhancement reflected a greater extent of myocardial injury than seen in regions with normal first pass enhancement.

This study assessed both myocardial contractility and perfusion.

Limitations to the study by Kramer et al. (2000) include:

- The study did not include patients with a residual stenosis in the infarct-related artery, chronic MI, or with less than grade 3 flow after reperfusion.
- Only data from two short axis slices per patient were analyzed.
- The perfusion imaging was performed without a breath hold whereas the tagged imaging was breath hold, thereby creating a potential matching problem. Kramer et al. (2000) stated that the perfusion images were registered and thereby allowed matching of landmarks including apex to base location and papillary muscles.

Summary of Viability Studies Using Cardiac MRI

- One level 3a study (Klein et al., 2002) found that in 31 patients with chronic CAD and severe LV dysfunction, hyperehnancement correlated closely concerning location and extent with infarct size using PET with NH_3 for perfusion and FDG as a metabolic tracer. The results were independent of the severity of contractile dysfunction.
- In a recent study, significant differences were observed between contrast enhanced MRI and SPECT in sensitivity, specificity and accuracy in favour of contrast enhanced MRI (Kitigawa et al., 2003). However, there were also methodological limitations.
- One level 3a study (Wagner et al., 2003) revealed that SPECT and contrast enhanced MRI detect transmural myocardial infarcts at similar rates, however, contrast enhanced MRI detects subendocardial infarcts that are missed by SPECT.
- Many studies have methodological limitations including small sample size, inclusion of patients who had already undergone a revascularization procedure, LVEF not reported, variable times when imaging was performed (<1 month post MI or acute MI, >1month post MI or chronic MI, or in patients without a documented MI). Knowledge of viability after revascularization is of limited use since adequate perfusion has already been achieved. No studies have looked at recovery of global function in patients with severe LV

dysfunction where viability is most relevant. In addition, no studies have looked at long-term clinical outcomes.

- Many studies (for example Gunning et al., 1998; Bax et al., 2000; Wahba et al., 2001) reported poor interobserver agreement (kappa less than 0.80) (See Table 3 in Appendix).
- There is variability in the definition of CAD determined by coronary angiography in studies (for example, stenosis ≥50% diameter, or >75% diameter).
- General limitations to viability assessment by cardiac MRI include:
  - Thornhill et al. (2002) stated that given the cellular adaptations that can occur during hibernation, it is possible that contractile reserve may not always be present in hibernating myocardium compared to stunned myocardium. As such, dobutamine stress testing may not be sufficient on its own for predicting functional recovery post-revascularization.
  - With current technologies, no one test is used to guide patient management. For example, the combination of cine MRI and contrast enhanced MRI with gadolinium.
  - A need to evaluate MR contrast enhancement characteristics of hibernating tissue itself (Thornhill et al., 2002).
  - There are ongoing differences in the determination of viability when one method is compared against another (e.g., perfusion vs. cellular membrane integrity vs. preserved but altered myocardial metabolism vs. systolic and diastolic function) as each technique examines different cellular or vascular functions.
- The current method of detecting permantently damaged myocardial tissue with CMRI is dependent on a biological assumption that heart muscle cells become significantly permeable to the exgtracellular contrast agent gadolinium only if they are permanently damaged. The methodological assumption consists of two parts:
  - Gadolinium administration results in increased concentration in the infarcted tissue at the time of MR image collection.
  - MRI pulse sequence used can detect this increased concentration.
  - False positives and false negatives will arise if either or both of thse assumptions are violated.
- According to expert opinion, it is still unclear whether or not false positives and false negatives arise from violation of only the methodological assumption or if there are some uses in which the biological assumption can be violated in such a way as to result in false positives or false negatives. Hence, a CMRI studies must involve centres with sufficient methodological expertise to assure than an optimal study is performed.
- Breath holding is a difficulty in patients with severe LV dysfunction. International experts in the field indicate that these problems are potentially solvable for MRI scar imaging.

Perfusion Studies Comparing MRI as a Noninvasive Adjunct to Coronary Angiography for the Diagnosis of CAD

National Institute for Clinical Evidence [NICE], United Kingdom (Mowatt et al., 2003)

NICE conducted a systematic review of the effectiveness and cost-effectiveness and economic evaluation of myocardial perfusion scintigraphy using SPECT for the diagnosis and management of coronary artery disease. The NICE document does not constitute the Institute's formal guidance on the technology at this time since the recommendations are preliminary and may change after consultation.

The Appraisal Committee's preliminary recommendations were:

1. Myocardial perfusion scintigraphy using SPECT is recommended for use in the diagnosis and management of CAD, particularly under the circumstances described in 2 and 3.
2. SPECT before CA is recommended as the preferred initial diagnostic tool in people with a low likelihood of CAD and a low risk of future cardiac events.
3. SPECT is also recommended as the preferred initial diagnostic tool in people for whom stress electrocardiography poses particular problems of poor sensitivity or difficulties in interpretation, including women, patients who have undergone ravascularization procedures, patients with cardiac conduction defects, people with diabetes and people for whom treadmill exercise is difficult or impossible. SPECT is also recommended in addition to stress electrocardiography in the assessment of prognosis following myocardial infarction.

Mowatt et al. (2003) recommended that the value of SPECT in relation to other tests of cardiac function such as stress ECG, MRI and PET should be investigated in order to inform future assessment of the needs of the UK National Health Service (NHS) for the investigation of CAD patients.

Perfusion Studies Comparing MRI to SPECT

Panting et al. (2001) investigated the feasibility of using a first pass MRI technique to detect perfusion defects at rest and during adenosine stress in 26 patients with CAD and an abnormal thallium SPECT. Panting et al. (2001) also developed a parametric map analysis in order to analyze the MRI data. First pass perfusion imaging was performed within a mean of 2±2 months of abnormal thallium SPECT scans undertaken for the investigation of CAD. Of these patients, 22 also had conventional angiography "within a mean of 7±6 months of their MRI study". It is unclear whether coronary angiography occurred before or after the MRI study. Coronary angiography was defined as at least one narrowing of more than 50% diameter. There was a history of 16 MIs in 14 patients. No specific inclusion criteria were reported. Patients were excluded if there was worsening of angina symptoms or if a MI occurred between investigations.

Method

The results of the MR assessments at rest and during adenosine stress were analyzed by a newly developed parametric map analysis by the authors (the myocardium was subjected to a pixel to pixel analysis for the entire series of images) of time to peak, peak intensity and slope of contrast washing. These results were compared with the results of conventional visual analysis of the perfusion cine series.

Coronary angiography was reported visually without knowledge of the thallium findings from SPECT. All the SPECT studies were analyzed by using a semiquantitative scale in each segment in comparison to the maximum pixel in the heart:

- 80-100% normal
- 60-80% mild
- 40-60% moderate
- 20-40% severe
- 0-20% absent

Panting et al. (2001) stated that the rest and stress studies were analyzed separately and change in activity were recorded if an improvement of at least one level was noted. However, Panting et al. (2001) did not explicitly state whether this was for SPECT, MRI or both. Segments were described as:

- Normal
- Reversible ischemia (normal at rest)
- Partially reversible ischemia (resting defect with superimposed ischemia) or
- Fixed defect (resting defect with no superimposed ischemia)

No further details were provided for the segment descriptions.

The entire SPECT study was analyzed. However, for the comparison with MRI, a single midventricular slice was used. The MRI studies were scored for image quality:

- Good
- Satisfactory
- Poor
- Not interpretable

All abnormalities were scored as for SPECT on a 5 point scale:

1. Normal perfusion
2. Mild impairment
3. Moderate impairment
4. Severe impairment
5. Absent perfusion

SPECT

All 26 patients had abnormal thallium SPECT scans. In the 22 patients where CA could be used as the gold standard, the overall sensitivity and specificity of detecting by SPECT was 83%. Panting et al. (2001) stated that the SPECT slice had an accuracy of 73% with a sensitivity of 70% and specificity of 78%.

MRI

None of the first pass studies was deemed to be uninterpretable. Overall, interobserver agreement for the assignment of segmental perfusion defect was good for both rest and stress studies, except for the time to peak during stress. The rest and stress kappa values for visual MRI were 90% and 88%. The rest and kappa values for the parametric map analysis were: time to peak (88% and 63%); peak (94% and 91%); and slope (91% and 93%).

However, the segmental agreement of perfusion severity was very poor. The kappa values for visual rest and stress MRI were 31% and 49% respectively. Rest and stress kappa values for the parametric map analysis were: time to peak (9% and 20%); peak (26% and 51%); and slope (27% and 49%).

Panting et al. (2001) stated that there was no significant difference in the accuracy of rest thallium and rest MRI for detecting abnormalities in areas of infarction. The sensitivity, specificity and accuracy for rest thallium was 63%, 86%, and 79%. The sensitivity, specificity and accuracy for rest visual MRI was 81%, 64% and 69% respectively. For the parametric map analysis, sensitivity, specificity and accuracy were: time to peak (44%, 67%, 60%), peak (81%, 58%, 65%), and slope (81%, 76%, 77%).

Also, in patients who had also undergone CA, Panting et al. (2001) stated the MRI and the thallium results were comparable in the detection of abnormal coronary regions:

Detection of Abnormalities by Angiography

	Sensitivity	Specificity	Accuracy
Thallium	70%	78%	73%
MR Visual	77%	83%	79%
MR Parametric map			
Time to peak	60%	43%	60%
Peak	72%	83%	76%
Slope	79%	83%	80%

Reprinted with permission from Wiley Publishers; From Panting JR, Gatehouse PD, Yang GZ, Jerosch-Herold M, Wilke N, Firmin DN, Pennell DJ. Echo planar magnetic resonance myocardial perfusion imaging: parametric map analysis and comparison with thallium SPECT. Journal of Magentic resonance imaging. 2001;13:192-200.

The usefulness of individual parametric maps was assessed. In 12 patients, parametric maps were thought to be more useful in making the final diagnosis than was visual analysis and in 3 patients was visual analysis considered more useful ($p<0.04$). The slope and peak parametric maps performed relatively similar, but the time to peak map was significantly less useful ($p<0.001$).

The feasibility study by Panting et al. (2001) examined limited ventricular coverage since a short axis MR slice was used to establish the clinical utility of the technique. Despite the use of single slice imaging, comparison with CA as a gold standard indicated good results and near equivalence between MR and SPECT during stress. Panting et al. (2001) hypothesized that MR results would be expected to improve with a multislice approach.

Limitations of the study by Panting et al. (2001) included:

- Details of patient recruitment were not reported. In 5 patients, coronary artery bypass grafts had previously been performed.
- The study examined a small number of patients (n=26).
- Not all patients had coronary angiography. A subanalysis was performed for the group of patients who received coronary angiography (n=22).
- It was not explicitly stated whether coronary angiography occurred before or after the MRI study.
- The interobserver agreement (kappa values) for assessing segments with perfusion severity was very poor. This raises concern with the subsequent sensitivity/specificity/accuracy values.

Perfusion Studies Comparing MRI to PET

Ibrahim et al. (2002) investigated CMRI estimates of regional myocardial blood flow in patients with CAD compared to PET flow measurements. Healthy volunteers with a low likelihood for CAD were examined by MRI or PET in order to provide reference data. Twenty-five clinically stable patients with angiographically documented CAD and normal LV function (LVEF 64$\pm$13.5%) were examined by MRI and PET at rest and during adenosine stress within the same day. CMRI was performed using a multislice ultrafast hybrid sequence and a rapid gadolinium bolus injection.

Twenty healthy volunteers underwent MRI (group I). During adenosine infusion, the rate pressure product significantly increased compared to baseline conditions (7,333$\pm$1,221 vs. 10,9888$\pm$2,092; $p<0.001$). Fourteen different volunteers (group II) underwent PET. The rate pressure product significantly increased under adenosine (9,048$\pm$2,133 vs. 12,646$\pm$1,863; $p<0.001$). The MRI flow ratios in normal volunteers were significantly smaller than the coronary flow reserve as assessed by PET ($p<0.0001$).

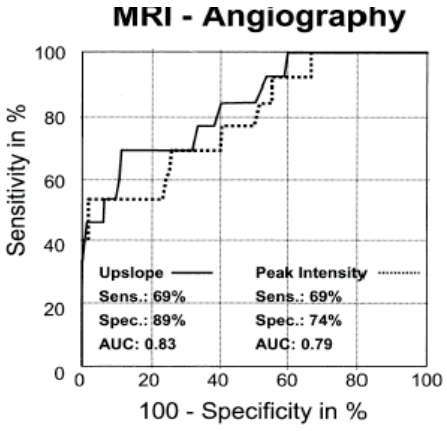
For CAD patients, 3 patients had a history of MI, 10 patients had balloon angioplasty and 4 patients underwent coronary artery bypass graft surgery at least 6 months prior to entering the study. Upslope and peak-intensity indices were regionally determined from first-pass signal intensity curves and compared to N-13 ammonia PET flow reserve measurements. The rate pressure product during stress was comparable between CMRI and PET studies (11,209±2,192 vs. 11,707±2,328, p=0.2). Eleven patients developed typical angina and 4 had significant ST segment depression which recovered rapidly after cessation of adenosine. Compared to healthy volunteers, patients with CAD showed reduced MRI indices, even in regions without angiographically detectable lesions:

	CAD Patients			
	0% Stenosis (31/75)	**<50% Stenosis (19/75)**	**50-75% Stenosis (11/75)**	**>75% Stenosis (14/75)**
MRI upslope index	1.6±0.3	1.5±0.4	1.4±0.5	1.2±0.3
MRI peak intensity index	1.3±0.3	1.2±0.4	1.2±0.3	1.0±0.4
PET coronary flow reserve	3.0±1.1	2.5±1.1	2.2±0.8	1.9±0.7

Modified from the Journal of the American College of Cardiology, v. 39, Ibrahim T, Nekolla SG, Schreiber K, Odaka K, Volz S, Mehilli J, Guthlin M, Delius W, Schwaiger M. Assessment of coronary flow reserve: comparison between contrast enhanced magnetic resonance imaging and positron emission tomography, 864-870, Copyright 2002, with permission from the American College of Cardiology Foundation.

The MRI indices (upslope and peak intensity) in CAD patients were significantly lower than the coronary flow reserve in PET, which was consistent with findings in the healthy volunteers ($p<0.001$).

The sensitivity, specificity and diagnostic accuracy rates for the detection of regional stenosis (>75%) were 69%, 89%, and 79% for the upslope index (cutoff 1.20) and 69%, 74% and 72% for the peak intensity index (cutoff: 1.10):

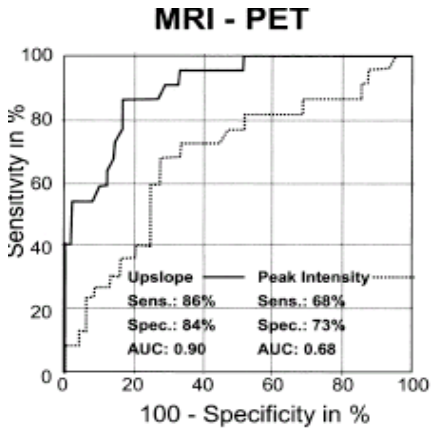


The receiver operating characteristic analysis using varying magnetic resonance imaging (MRI) upslope and peak-intensity flow indices as threshold for the detection of severe coronary artery stenosis (>75%). AUC=area under the curve; Sens.=sensitivity; Spec.=specificity.

Reprinted from the Journal of the American College of Cardiology, v. 39, Ibrahim T, Nekolla SG, Schreiber K, Odaka K, Volz S, Mehilli J, Guthlin M, Delius W, Schwaiger M. Assessment of coronary flow reserve: comparison between

contrast enhanced magnetic resonance imaging and positron emission tomography, 864-870, Copyright 2002, with permission from the American College of cardiology Foundation.

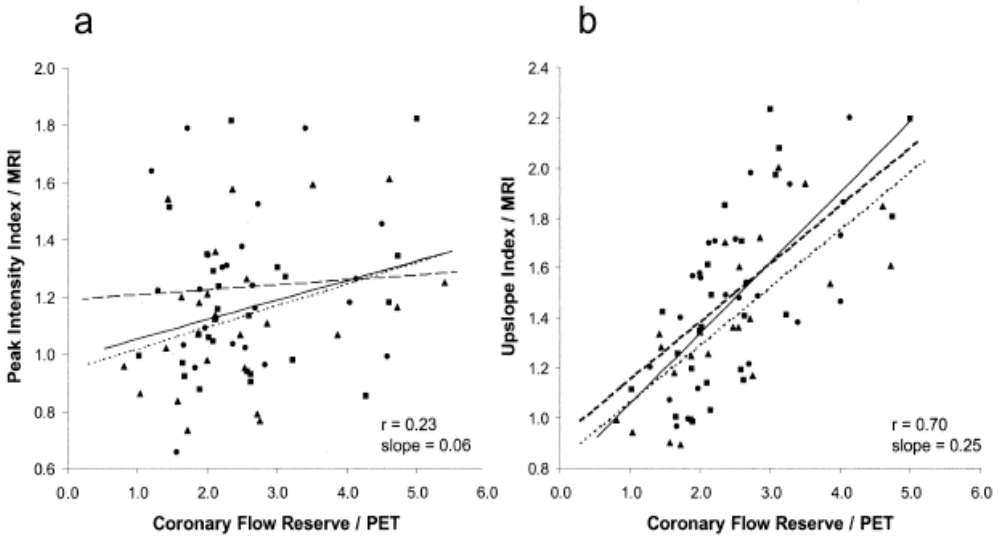
The sensitivity, specificity and diagnostic accuracy levels for detection of regional coronary flow reserve <2.0 were 86%, 84%, and 85% respectively for the upslope index (cutoff: 1.3) and 68%, 73%, and 71% respectively for the peak intensity index (cutoff: 1.1):



The receiver operating characteristic analysis using varying magnetic resonance imaging (MRI) upslope and peak-intensity flow indices as threshold for the detection of reduced coronary flow reserve by positron emission tomography (PET) (<2.0). AUC=area under the curve; Sens.=sensitivity; Spec.=specificity.

Reprinted from the Journal of the American College of Cardiology, v. 39, Ibrahim T, Nekolla SG, Schreiber K, Odaka K, Volz S, Mehilli J, Guthlin M, Delius W, Schwaiger M. Assessment of coronary flow reserve: comparison between contrast enhanced magnetic resonance imaging and positron emission tomography, 864-870, Copyright 2002, with permission from the American College of cardiology Foundation.

Poor correlation was found for the MRI peak intensity index in comparison to PET flow measurements (r=0.23; slope=0.06). The p values were not reported. The MRI upslope index and the coronary flow reserve by PET were comparably correlated within different vascular territories as shown below (r=0.70; slope=0.25).



Correlation of magnetic resonance imaging (MRI) peak-intensity index **(a)** and upslope index **(b)** with positron emission tomography (PET) measurements of coronary flow reserve in different vascular segments. **Circle** - left anterior descending; **square -** left circumflex; **triangle -** right coronary artery.

Reprinted from the Journal of the American College of Cardiology, v. 39, Ibrahim T, Nekolla SG, Schreiber K, Odaka K, Volz S, Mehilli J, Guthlin M, Delius W, Schwaiger M. Assessment of coronary flow reserve: comparison between contrast enhanced magnetic resonance imaging and positron emission tomography, 864-870, Copyright 2002, with permission from the American College of cardiology Foundation.

The results indicated that the CMRI upslope index provides estimation of regional myocardial flow reserve as measured by PET and coronary artery stenosis as measured by angiography. However, Ibrahim et al. (2002) concluded that the CMRI flow reserve is underestimated due to a low extraction of extravascular paramagnetic contrast agents such as gadolinium, and that further development of contrast agents that have better physiological characteristics is required.

The study by Ibrahim et al. (2002) had limitations:

- The results may not be generalizable to patients with CAD. The patients had a very low incidence of prior MI and impaired LV function (LVEF 64$\pm$13.5%). Therefore, the selected patient population may not represent the entire spectrum of clinical disease representation in which both localization and characterization of coronary stenoses are important.
- The diagnostic thresholds were determined based on a ROC analysis yielding 1.3 for the upslope index and 1.1 for the peak intensity index. Other investigators used higher cutoff values for the detection of ischemic regions which were defined using normal databases (Al Saadi et al., 2000). Ibrahim et al. (2002) acknowledged that these thresholds are lower than those used in PET, hence further studies are necessary to refine diagnostic criteria prospectively in larger patient cohorts to optimize the diagnostic performance of MRI.
- Despite groups I and II being closely matched in terms of age, low likelihood of CAD, and hemodynamics, the data from volunteers were obtained in 2 separate cohorts thereby limiting the direct comparison of individual data.
- Patients were already diagnosed with CAD at the start of the study, then subsequently underwent MRI and PET.
- Efforts should be made to develop CMRI methodology and tracer kinetic modeling that would account for the variation in contrast agent extraction fraction as tissue flow is increased. It is this dependence of extraction fraction on tissue blood flow that results in an underestimation of MPR and MPRI.

Koskenvuo et al. (2001) investigated whether velocity encoded cine MRI of coronary sinus blood flow could accurately measure global myocardial blood flow and global coronary flow reserve in patients with CAD compared to PET using ^{15}O labeled water.

Twenty men with angiographically confirmed CAD were enrolled. The patients first underwent MRI and PET at rest and then after administration of dipyridamole in order to obtain blood flow data at baseline and after vasodilation. Coronary sinus flow was considered to represent global myocardial blood flow in the left ventricular myocardium. The average delay between MRI and PET was 8±10 days.

The Spearman correlation coefficients of myocardial blood flow and coronary flow reserve between the two methods were 0.80 ($p<0.01$) and 0.5 ($p<0.01$) respectively. These results suggest that MRI flow quantification could potentially be used for measuring global myocardial blood flow in patients in whom intervention treatment for CAD is being evaluated. The patients' left ventricular ejection fraction was not reported by Koskenvuo et al. (2001).

Limitations to Koskenvuo et al. (2001) include:

- MRI and PET were used after angiographically confirmed CAD was performed. The role of MRI or PET using O^{15} labeled water to help determine which patients should further undergo angiography is unclear.
- Detailed patient inclusion/exclusion criteria were not reported.
- Small sample size.

Schwitter et al. (2001) conducted a prospective study to assess myocardial perfusion by comparing the quality of a multislice MRI approach to PET and coronary angiography (CA). ^{13}N ammonia PET was used as the reference for myocardial perfusion.

Forty-eight patients with suspected CAD and referred for CA were prospectively identified. Exclusion criteria consisted of:

Unstable angina
Atrial fibrillation
Valvular heart disease
History of revascularization
Prior MI as indicated by history, Q waves, or wall motion abnormalities at rest

Within 2 weeks before CA, patients underwent MRI and PET perfusion studies in random order.

After MRI assessment of resting cardiac function (baseline), vasodilation was induced by dipyridamole. During a breath-hold, gadolinium was injected and the first pass was monitored. For PET, measurements were performed for baseline and vasodilation using a whole body PET scanner and intravenous bolus administration of ^{13}N ammonia. Hyperemia was induced by dipyridamole.

A total of 48 patients were studied by MRI, PET and CA and an additional 18 healthy volunteers were examined by MRI. All examinations were tolerated by the patients without any complications. Forty-one PET exams were available for comparison with MRI.

The ROC analysis revealed a high diagnostic reliability of subendocardial MRI upslope data for detection of hemodynamically significant CAD as defined by PET, or anatomically by CA.

The number of pathological sectors measured by MRI and PET correlated linearly (slope 0.94, $r=0.76$, $p<0.0001$). MRI sectors with transmurally reduced flow underestimated the extent of disease (4.9±5.34 sectors vs. 9.0±5.7 sectors with PET, $p<0.005$).

Sensitivities and specificities to detect CAD as defined by quantitative CA were not different for 1, 2, or 3-vessel disease. In addition, for all 3 coronary arteries the sensitivities and specificities of subendocardial MRI data to detect > 50% stenoses as defined by CA were similar indicating that the quality of MRI data was similar throughout the LV myocardium.

Limitations to the study by Schwitter et al. (2001) included:

- The influence of altered hemodynamics on contrast medium first pass kinetics and the applicability of thresholds for myocardial upslope data warrants further investigation.

- Further investigation and explanation as to differences between MRI assessed subendocardial versus transmural sectors.

Perfusion Studies Comparing MRI to Angiography

Nagel et al. (2003) assessed the value of myocardial perfusion reserve for the noninvasive detection of CAD in ninety consecutive patients with suspected CAD. Inclusion criteria consisted of:

Scheduled for a primary diagnostic invasive CA

Exclusion criteria consisted of:

MI <7 days
Unstable angina pectoris
Arterial hypertension (>160/140 mmHg)
Diabetes mellitus
LVEF<50%
Atrial flutter or fibrillation
Sick sinus rhythm
SA or AV block>I
Ventricular premature beats
Relevant obstructive pulmonary disease or valvular disease
Contraindications to MR exam (metallic implants, claustrophobia)

After the MR exam, all patients underwent CA. CAD was defined as ≥75% area reduction with respect to prestenotic segment area in at least 1 major epicardial coronary artery or major branch (>2.5 mm diameter). An index for myocardial perfusion index reserve was calculated by dividing the results at maximal vasodilation through the results at rest.

Eighty-four patients successfully completed the MRI. The prevalence of CAD was 51% (43 patients). For comparison of MR perfusion with angiography, the best results were achieved when 3 inner slices were assessed and a threshold value of 1.1 was used for the second smallest value as a marker for significant CAD: sensitivity 88%, specificity 90% and accuracy 89%.

Nagel et al. (2003) concluded that MR can be used to assess myocardial perfusion reserve and detect significant CAD. Additionally, MR may be used to screen patients with suspected CAD and avoid cardiac catheterization in patients with negative MR. Nagal et al. (2003) stated that before MR perfusion measurements can be routinely used in clinical practice, further improvement and automization of quantification algorithms is required.

Limitations to Nagal et al. (2003) included:

- Large exclusion criteria – may decrease generalizability of the results.
- Rapid diffusion of the contrast agent into the extracellular space. Intravascular contrast agents that are currently under development may aid analysis.
- Perfusion reserve indices that were calculated versus true alterations of flow may require assessment.
- The inner 10% and outer 30% of the myocardium were excluded from the analysis.
- A retrospective analysis was used to generate the ROC curves. There may be a difference when prospectively applying a reported cutoff value.

Al Saadi et al. (2000a) used a single slice approach to assess the diagnostic accuracy of MR perfusion reserve measurement in comparison with angiography. The study population consisted of patients who were referred for coronary angiography. CAD was defined as >75% coronary artery stenosis. Forty patients were prospectively examined by the use of the previously defined threshold value. Patients were excluded if:

< 18 years old
history of MI, unstable angina, hemodynamic relevant valvular disease, ventricular extrasystole Lown class ≥III, atrial fibrillation, EF<30%, blood pressure >160/95 mm Hg or <100/70 mm Hg, obstructive pulmonary disease, claustrophobia.
contraindications such as incompatible metal implants.

For all MR images, the examiner was blinded to the angiographic results. To determine intraobserver and interobserver variabilities, 200 myocardial segments were reevaluated by the same examiner and by a different examiner. If the myocardial perfusion reserve was less than the predefined cutoff value, the segment was classified as pathological; if it was more than the cutoff value, it was defined as normal.

Stress MR perfusion imaging was successfully performed in 34 of the 40 (85%) patients. Three (7.5%) patients were excluded due to claustrophobia and in 3 patients ECG triggering was insufficient.

Myocardial perfusion reserve was significantly different between ischemic (1.16±0.29) and nonischemic (2.17±0.62) segments ($p<0.001$). Fifty-four of the 60 segments supplied by stenotic coronary arteries and 35 of the 42 segments supplied by nonstenotic coronary arteries were correctly classified by the use of the predefined myocardial perfusion reserve cutoff value of 1.5, resulting in a sensitivity of 90%, a specificity of 83% and a diagnostic accuracy of 87%.

The limitations to this study include:

- Coronary angiography was used as the reference method for the detection of coronary artery stenosis. Since coronary angiography detects luminal morphology rather than the functional significance of a stenosis, Al Saadi et al. (2000) suggested that "false-positive" MR results might in fact be "false-negative" angiograms. Three of the seven segments that had a "false positive" reduction of myocardial perfusion reserve showed ≥1 stenosis <75% area reduction of the corresponding coronary artery on angiography. Also, 2 false positive segments were found in 1 patient with diffuse atherosclerosis of the nonstenotic coronary arteries.
- Use of a single slice technique. The myocardium was only partially visualized and significant myocardial ischemia might have been missed. The value of multislice techniques was not assessed.
- The combined use of nonischemic segments from patients with single vessel disease and patients without significant coronary artery disease for the definition of the ischemic threshold.
- Patient recruitment was not explicitly described (consecutive patients?).

Al Saadi et al. (2000b) evaluated the changes of myocardial perfusion reserve (MPR) within 24 hours of a successful coronary intervention in a patient population with CAD. Another purpose of the study was to determine the possible impact of this technique in the diagnosis and follow-up of patients with CAD who have undergone balloon PTCA or stenting.

Thirty-eight patients with previously angiographically proven significant single or double vessel CAD referred for elective coronary intervention were prospectively included in the study. Patients were excluded if:

History of prior MI
Unstable angina
Hemodynamic relevant valvular disease
Ventricular extrasystole >Lown III
Atrial fibrillation
EF<30%
Blood pressure >160/95 mmHg or <100/70 mmHg
Obstructive pulmonary disease
Claustrophobia
Contraindication for an MR exam

After the MR exam, all patients underwent cardiac catheterization and coronary angiography.

The signal intsnsity time curves of the first pass of a gadolinium bolus injection were evaluated before and after dipyridamole infusion. The MR study was repeated 24 hours after coronary intervention using an identical protocol to that used before the intervention.

The MPR index was calculated for all segments. If the MPR index was less than or equal to 1.5, the segment was classified as pathological and defined as ischemic.

Dipyridamole stress MR perfusion imaging was successfully performed in 35/38 patients (92%). Fifty-two coronary artery stenoses were found by angiography. In 793 of 840 segments (94%) evaluated before and after dipyridamole a linear fit was performed. Forty-seven segments could not be analyzed due to noise or artifacts.

Before intervention, the MPR index was 1.13±0.25 in segments supplied by a stenotic coronary artery and 2.18±0.35 in control segments ("p<0.00"). Forty-seven of the 53 territories supplied by stenotic coronary arteries and 43 of the 52 territories supplied by nonstenotic coronary arteries were correctly diagnosed as ischemic and

nonischemic, respectively by use of the previously defined threshold of 1.5. This resulted in a sensitivity of 89% and a specificity of 83% with a diagnostic accuracy of 86%.

The group effect for the three groups (control, stent and balloon revascularization) was significant ($p<0.001$). After intervention, the MPR index increased significantly in segments supplied by successfully treated vessels (1.07 ± 0.24 before and 1.89 ± 0.39 after intervention, $p<0.001$); however it remained below the level of the control segments ($p<0.01$).

After coronary intervention, sensitivity and specificity for the detection of a stenotic coronary artery were 82% and 84%, respectively, which resulted in a diagnostic accuracy of 84%.

Limitations to the study by Al Saadi et al. (2000) include:

- Only a single slice technique was used, therefore small perfusion defects at basal or apical segments may have been missed.
- No comparison of the cardiac MRI perfusion measurements with scintigraphy or PET was performed. Al Saadi et al. (2000) chose invasive angiography as the comparator since in clinical practice invasive angiography serves as a reference standard to decide whether a significant coronary artery stenosis is present and if an intervention is required.
- To optimize kinetics of the contrast agent bolus, a central venous catheter was placed in all patients which cannot be done if this technique is used routinely in larger patient populations due to the semi invasiveness of the procedure. However, Al Saadi et al. (2000) stated that analysis can also be performed with peripheral injection and will be used in further studies by the investigators.
- The long acquisition time resulted in a significant through plane motion during acquisition and may result in discrepancies in the assignment of the segments to the territories and an error in comparing similar segments. Al Saadi et al. (2000) compared large segments rather than a pixel to pixel analysis which can be more sensitive to through plane motion.

Keijer et al. (2000) investigated the feasibility of quantifying myocardial perfusion parameters and to localize perfusion abnormalities in three circumferential layers of the myocardium in 22 patients with single vessel CAD. Inclusion criteria consisted of:

> Referred for diagnostic cardiac catheterization after either a previous positive exercise test or an episode of unstable angina with subsequent hospital admission.

Exclusion criteria was not reported. At coronary angiography, all patients had significant single vessel CAD. Patients were all in sinus rhythm and had no valvular heart disease, diabetes mellitus, left ventricular hypertrophy or pathologic Q waves on ECG or other clinical evidence of previous MI. Eleven patients underwent additional CA two hours after the MRI protocol.

MRI was done within 4 weeks of cardiac catheterization. First pass images were acquired before and after intravenous dipyridamole. Each myocardial segment yielded separate values for subendocardial, mesocardial and subepicardial myocardium.

The abnormal/normal ratio (A/N) of the maximum myocardial contrast enhancement (MCE) in subendocardial regions at rest was 0.89 ± 0.18 and decreased during hyperemia to 0.74 ± 0.15 ($p<0.003$). There were no significant transmural differences in A/N ratios at rest. During dipyridamole, the A/N ratio of MCE in subendocardial myocardium was lower than in subepicardial myocardium (0.74 ± 0.15 vs. 0.84 ± 0.21, $p<0.02$).

Under resting conditions, the endo/epi ratio of MCE in normal myocardium was 1.25 ± 0.29 and in the abnormal myocardium 1.18+0.18 (not significant). During stress these ratios decreased to 1.08 ± 0.23 (not significant, pre vs. postdipyridamole) and 0.96 ± 0.21, respectively ($p<0.0002$ pre vs. postdipyridamole, $p<0.002$ normal vs. abnormal myocardium).

There were no statistically significant relationships between severity of coronary artery stenosis and subendocardial A/N ratio ($r=-0.52$, $p=0.1031$) and with endo/epi ratio ($r=-0.34$, $p=0.3062$) in abnormal myocardium.

In summary, Keijer et al. (2000) concluded that MRI was capable of approximating the transmural redistribution of myocardial perfusion during pharmacologic stress. Also, perfusion abnormalities due to coronary stenosis were found to be more pronounced in the subendocardium than in the subepicardium.

Limitations to Keijer et al. (2000) include:

- A single short axis slice was imaged. This may save temporal and spatial resolution but does not allow comprehensive imaging of the whole heart.
- Small sample size.
- Highly selected group of CAD patients.

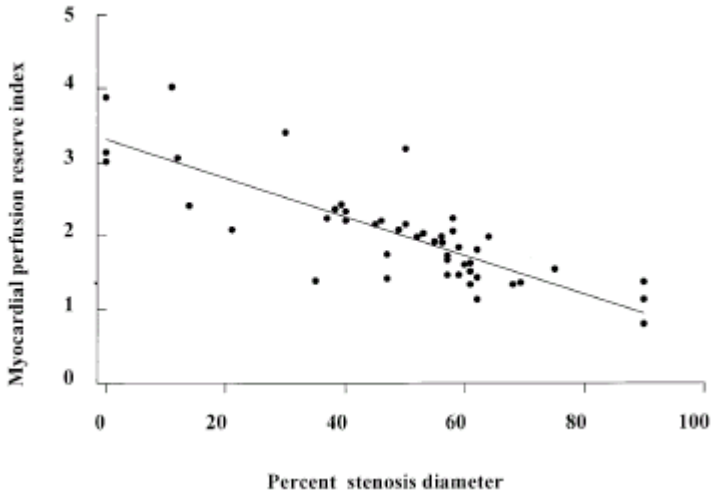
Cullen et al. (1999) evaluated the myocardial perfusion reserve index (MPRI) derived from a MRI technique in normal human volunteers and patients with CAD. Twenty patients with angiographically proven CAD and 5 normal volunteers underwent both resting and stress (adenosine) first pass contrast enhanced MRI exams. Exclusion criteria consisted of:

Intracranial clips
Pacemaker, cochlear or intraocular implants
History of metal fragments in the eye
Claustrophobia
Contraindication to receiving adenosine

All patients underwent MRI exams within 2 weeks after their coronary angiogram. Three double oblique short axis planes through the left ventricle were acquired sequentially: 1) basal, 2) mid-left ventricular (through the papillary muscles) and 3) apical using an inversion recovery snapshot FLASH method. The patients and volunteers underwent both a resting and a stress MRI exam separated by 24 hours. Perfusion was assessed by injecting gadolinium. A tracer kinetic model was used to calculate MPRI.

MPRI was significantly reduced in patients compared with healthy volunteers (2.02 ± 0.7 vs. 4.21 ± 1.16, $p<0.02$). Regions that were supplied by vessels with <40% diameter stenosis ("nonflow limiting") had a significantly higher MPRI than regions supplied by stenoses of "intermediate" severity (i.e., >40%-59% diameter stenosis), 2.80 ± 0.77 and 1.93 ± 0.38 respectively, $p<0.02$. Regions that were supplied by vessels with <40% diameter stenosis had a significantly lower MPRI than volunteers ($p<0.01$).

For regions supplied by individual vessels, there was a significant negative correlation of MPRI with percent diameter stenosis:



Scatterplot of relation between myocardial perfusion reserve index and percent diameter stenosis of coronary arteries assessed by arteriography (r = -0.81, p<0.01).

Reprinted from the Journal of the American College of Cardiology, v. 33, Cullen JHS, Horsfield MA, Reek CR, Cherryman GR, Barnett DB, Samani NJ. A myocardial perfusion reserve index in humans using first pass contrast enhanced magnetic resonance imaging, 1386-1394, Copyright 1999, with permission from the American College of Cardiology Foundation.

Limitations to the study by Cullen et al. (1999) include:

- The perfusion model used for the calculation of gadolinium was subject to a number of assumptions.
- The technique was not compared to another noninvasive technique.

Perfusion Studies Comparing Stress MRI to Angiography

Al Saadi et al. (2002) evaluated the value of dobutamine stress MRI for the detection of significant coronary artery stenosis from the alterations of myocardial perfusion. Twenty-seven patients were prospectively included in the study. Inclusion criteria consisted of:

Suspected or proven single or double CAD
Admitted to hospital for invasive coronary angiography

Exclusion criteria consisted of:

History of prior MI
Unstable angina
Triple vessel disease
Hemodynamic relevant valvular disease
Ventricular extrasystole ≥Lown III
Atrial fibrillation
EF<40%
Blood pressure >160/95 or <100/70 mmHg
Known claustrophobia
Contraindication for MR exam such as incompatible metallic implants

All patients underwent cardiac catheterization and coronary angiography. Dobutamine was administered in increasing doses. The myocardial perfusion reserve index was calculated for all segments. Patients without CAD were used as controls and a threshold value was determined from all myocardial segments of controls. Segments with an index below the threshold value were defined as ischemic. MR was regarded as true positive if at least one segment within the territory of the stenotic coronary artery was found to be ischemic. Segments with an index above the threshold value were defined as nonischemic.

Twenty-three patients had significant CAD. Median area reduction was 88%. Dobutamine stress perfusion imaging was successfully performed in all patients. In 268 (89%) segments, a linear fit could adequately be performed. In 14 patients with single CAD, myocardial perfusion reserve index in segments supplied by a stenotic coronary artery was significantly lower than the remote segments (0.90 ± 0.18 vs. 1.73 ± 0.32, $p<0.0001$) or segments of the control

patients without CAD (2.0±0.39, p<0.0001). No difference was found between the segments of patients without significant coronary stenosis and the remote control segments of patients with single vessel disease (p=0.67). In all patients with CAD, perfusion reserve index in segments supplied by a stenotic coronary artery was significantly lower than segments of patients without significant CAD (0.97±0.20 vs. 2.0±0.39, p<0.001).

A threshold value of 1.22 was calculated from the segments of patients without CAD. A significant coronary artery stenosis of >75% area reduction was correctly diagnosed in 26 of 32 stenotic coronary arteries. Twenty-seven of the 37 coronaries without significant stenosis were correctly identified resulting in a sensitivity and specificity of 81 and 73% respectively and a diagnostic accuracy of 77%.

Limitations to the study by Al Saadi et al. (2002) include:

- Evaluation of a single slice.
- Long acquisition time that results in a significant through plane motion during image acquisition and may result in discrepancies in the assignment of the segments to the territories and an effort in comparing similar segments.
- High heart rate results in an image acquisition of only every second heart beat. Improvements of the MR technique allow faster acquisition which will minimize this effect.
- The small CAD patient sample size was highly selected and therefore the results cannot be extrapolated to a general patient population.
- By using a comparison to angiography; differences between luminal morphology and myocardial perfusion may occur.
- The index threshold was set with the same database as was used for the study.

Hundley et al. (1999) assessed the safety and clinical utility of fast cine MRI stress testing for determination of inducible ischemia in patients not suitable for stress echocardiography. Inclusion criteria consisted of 163 patients who:

> Were referred for diagnosis of ischemia with dobutamine echocardiography
> Did not have adequate endocardial visualization.

Exclusion criteria consisted of:

> Patients who had a pacemaker, intracranial metal, claustrophobia or a known contradiction to receiving dobutamine.

Ninety percent of referrals had ≥8 and 10% had 5-8 of 16 endocardial segments not visualized with echocardiography. At baseline, single slice images were acquired continuously during intravenous dobutamine infusions. LV segments were continuously assessed by a 4 point scoring system in which 1=normal, 2=hypokinetic 3=akinetic, 4=dyskinetic. Myocardial segments were identified as ischemic if the score increased by 1 during infusion or a hypokinetic segment at rest failed to improve contractility or elicited a biphasic response (Hundley et al., 1999).

One hundred and fifty-three patients were examined. At baseline, 97 patients had abnormal and 56 had normal LV regional wall motion. After baseline imaging, 10 patients could not receive dobutamine.

Thirty-six patients had evidence of inducible myocardial ischemia and 103 patients did not. Forty-one patients who received dobutamine and did not have a coronary event within 6 months underwent contrast coronary angiography (8 because of results of noninvasive testing: 4 MRI and 4 due to results of another test; and 33 patients on the basis of clinical characteristics). The average time from MRI to catheterization was 35 days.

The sensitivity and specificity of MRI for detecting a coronary arterial luminal narrowing >50% was: 75% (1 vessel), 82% (2 vessel), and 92% (3 vessels or left main). The specificity of detecting a >50% narrowing was 83%.

The sensitivity of detecting a coronary artery luminal narrowing >70% was: 82% (1 vessel), 88% (2 vessel), and 100% (for 3 vessels or left main). The specificity of detecting a >70% narrowing was 58% (7 patients had a positive MRI scan and a luminal narrowing >60% but <70%).

There were many limitations to the study by Hundley et al. (1999) included:

- Comparison of MRI to CA was not the primary objective of the study.

- Many patients were in sinus rhythm. It was uncertain whether this technique provides reliable results in subjects with irregular rhythms.
- Coronary angiography was not performed in all patients. It is possible that the sensitivity and specificity data for detecting coronary arterial luminal narrowings may have influenced by referral bias.
- Patients possessed a relatively high pretest probability of CAD, therefore, application of the results would be appropriate for similar patients.
- Specificity data are based on 6 patients.

Hundley et al. (2002) conducted a 20-month follow-up of Hundley et al. (1999) to determine if the presence of inducible ischemia identified during MRI stress tests could be used to identify patients at risk of having a future cardiac event. Three hundred and thirty eight consecutive patients were referred (owing to initial unsuccessful echocardiography) for dobutamine/atropine MRI to diagnose inducible ischemia. The outcomes of 143 patients described in Hundley et al. (1999) were also included in Hundley et al. (2002). After MRI stress testing, the occurrence of MI, cardiac death, death attributable to any cause, revascularization, and unstable angina or HF requiring hospitalization was determined.

Eighteen LV myocardial segments were identified at rest and during graded doses of dobutamine/atropine that were administered to achieve 80% of the maximum predicted heart rate response (MPHRR) for age. Images at peak stress were collected at all slice positions after the peak heart rate response occurred. Throughout stress MRI, LV segmental wall motion was assessed as normal, hypokinetic, akinetic or dyskinetic. Inducible ischemia was defined as a deterioration in wall motion within a myocardial segment during the course of testing observed in 2 orthogonal views.

Contact was made with 295 patients. Sixteen patients underwent coronary arterial revascularization within 60 days of their MRI stress tests and none experienced a subsequent "hard event" (i.e., MI or cardiac death). To exclude the possibility that immediate revascularization prevented subsequent hard events, the 16 patients were excluded from further analyses. The remaining 279 patients formed the study population:

LVEF ≥40% Negative ischemia	LVEF ≥40% Positive ischemia	LVEF <40% Negative ischemia	LVEF <40% Positive ischemia
n=164	n=71	n=22	n=22

From Hundley WG, Hamilton CA, Thomas MS, Herrington DM, Salido TB, Kitzman DW et al. Utility of fast cine magnetic resonance imaging and display for the detection of myocardial ischemia in patients not well suited for second harmonic stress echocardiography. Circulation. 1999;100:1697-1702.

No raw data was reported specifically for the number of event free patients who survived the followup period. The proportion of patients free of hard events was analyzed. For patients with a LVEF<40% at rest, the presence or absence of inducible ischemia did not significantly influence the 2 year incidence of hard events (25.6% versus 26.5%, p>0.9, respectively).

Multivariate analysis revealed that MRI evidence of inducible ischemia (hazard ratio [HR] 3.3, 95% confidence interval [CI] 1.1-9.7) or a LVEF<40% (hazard ratio 4.2, 95%CI 1.3-13.9) was associated with MI and cardiac death independent of the presence of risk factors for coronary arteriosclerosis. Compared with patients with a LVEF≥40% and no evidence of inducible ischemia, event free survival was significantly lower in patients with inducible ischemia (p<0.0004) or an LVEF <40% (p<0.00005).

Overall, 5022 segments were assessed during testing. Sixty-six patients (50 with and 16 without inducible ischemia), showed an improvement in wall motion in segments that were akinetic at baseline. Improvement in wall motion in segments akinetic at rest was associated with MI and cardiac death (HR 4.9, CI 1.8-13.2, p=0.001) but not all cause mortality (HR 2.4, CI 0.7-8.9, p=0.19) or other events (HR 1.8, CI 0.8-4.2, p=0.16). Together, improvement in wall motion in resting akinetic segments and ischemia (HR 4.8, CI 1.8-12.9, p=0.002) revealed no additional increase in the HR of hard or other events than the risk associated with each alone.

The chronic use of β blockers was associated with the presence of inducible ischemia (p=0.027). A test for interaction between β blocker use and LVEF <40% in predicting hard events was significant (p=0.01). Additionally, the lack of β blocker use was associated with MI and cardiac death in patients with LVEF<40% (p=0.04) but not LVEF >40% (no p value reported).

The corresponding limitations to Hundley et al. (1999) apply to Hundley et al. (2002) and include:

- Raw data for the number of patients who survived and were event free was not reported.
- No discussion of MRI vs. CA results as reported in Hundley et al. (1999) was made in terms of cardiac outcomes.
- Unable to determine if inducible ischemia predicted hard events for LVEF<40%. There were 44 patients with a LVEF <40% and 7 hard events were observed in that group. To determine with 80% power if inducible ischemia produced a 3-fold increase in the risk of sustaining a hard event, a study would need 27 events distributed among patients with a LVEF<40%.
- Wide confidence intervals were statistically significant, however, the clinical significance is uncertain.
- 60% of the patients attained >80% of the maximum predicted heart rate response for age during testing. The diagnostic accuracy of noninvasive stress tests may be higher when patients achieve >80% of the maximum rate for age during testing.

Summary Perfusion Studies Comparing MRI as an Adjunct to Coronary Angiography

- One level 3a study, with methodological limitations, compared MRI to SPECT (Panting et al. (2001). Comparison to coronary angiography as a gold standard indicated good results and near equivalence between MR and SPECT during stress perfusion imaging in 22 patients.
- Three level 3a studies, with methodological limitations, compared MRI to PET.
  - Ibrahim et al. (2002) revealed that MRI upslope index provided estimation of regional myocardial flow reserve as measured by PET and coronary artery stenosis as measured by angiography.
  - Koskenvuo et al. (2001) suggested that MRI flow quantification could potentially be used for measuring global myocardial blood flow in patients in whom intervention treatment for CAD is being evaluated.
  - Schwitter et al. (2001) showed a high diagnostic reliability of subendocardial MRI upslope data for detection of hemodynamically significant CAD as defined by PET or anatomically by coronary angiography.
- Several studies, also with methodological limitations and variable inclusion criteria, compared MRI to the reference standard angiography.
  - Nagel et al. (2003) demonstrated a sensitivity of 88%, specificity of 90% and accuracy of 89% for comparison of MR perfusion with angiography.
  - Al Saadi et al (2000a) revealed sensitivity 90%, specificity 83%, and accuracy 87%.
  - Al Saadi et al. (2000b) calculated sensitivity 89%, specificity 83% and accuracy 86%.
- One small sample size (n=23) level 3a study assessed dobutamine stress MRI for the detection of significant coronary artery stenosis from alternations of myocardial perfusion reserve (Al Saadi et al., 2002) and found sensitivity 81%, specificity 73% and accuracy 77%.
- Most studies had very small sample sizes.
- Variation in the definition of CAD between studies (>50% diameter, >70% diameter).
- Limitations to evaluating cardiac MRI perfusion studies include:
  - Primarily representations of the experience of single centers that used different imaging approaches.
  - In some (mostly earlier) studies, limited myocardial sections (single slice) were assessed; more recently the assessment of multiple slices has been successfully attempted.
  - Small number of patients, most of whom were highly selected for CAD and who did not necessarily have prior MI or significant LV dysfunction (LVEF≤35).
- Myocardial perfusion and perfusion reserve are dependent on the administration methodology, the imaging methodology and the data analysis/kinetic modeling approach. Hence future studies must be done at MRI centres with sufficient expertise in these areas.
- CMRI perfusion imaging has limited cardiac coverage, i.e., the whole myocardium cannot be assessed because only one slice at a time can be studied.

- MRI does not have a definitive method for quantification of flow. In addition, further study is required to examine how flow quantification information can be used clinicall (e.g., define microvascular disease or severe balanced disease).

Economic Analysis

Literature Review

The literature search did not reveal any economic analyses of functional cardiac MRI specifically for the assessment of myocardial viability or perfusion. To date, economic analyses of MRI examine costs associated with standard diagnostic MRI. Functional cardiac MRI economic studies will need to account for the added time and cost of perfusion MRI imaging (perfusion imaging requires a rest and stress study).

Cardiac MRI has experienced: rapid advances in coil and magnet design; higher processing speed of modern computer hardware as well as ongoing development of software; improved pulse sequences; and better cardiac and respiratory gating systems (Poon et al., 2002).

The expert consultant revealed that the cost of gadolinium (Gd-DTPA) for an average myocardial viability study using methodology currently considered the best, i.e., a double dose injection, costs between $2.40/kg to $3.80/kg or for a 70 kg patient between $168 and $266. The cost for a perfusion study would be another $1.20/kg.

The Canadian Coordinating Office for Health Technology Assessment (**CCOHTA, 1995**) stated that the fixed costs associated with the purchase and installation of a general fixed MRI ranged between $2,085,000 and $4,130,000 with annual operating costs (maintenance, staff, supplies) between $705,000 and $810,000. Of note, the general fixed MRI system was 1.0T.

Costs of a 1.0T fixed MRI (in $000 CAD).

Costs	1.0 T Fixed MRI
Equipment costs	
1.0T MR system (Configuration dependent)	1,650 - 2,150
Building costs	
New	900-1,800
Renovative	350-650
Radio frequency shield (site dependent)	85-110
Magnetic shield (site dependent)	0-70
Total Fixed Costs	2,085-4,130
Operating Costs (yearly)	
Staff*	150-180
Service Contract	120-140
Cryogens & magnet maintenance	35-40
Equipment upgrades	150
Operating supplies	230-270
Facilities maintenance	20-30
Total Operating Costs	705-810

- Staff costs were based on two technologists and one nurse.

Modified with permission from CCOHTA; From Canadian Coordinating Office for Health Technology Assessment. A comparison of fixed and mobile CT and MRI scanners. CCOHTA. 1995; November: 1-17

Fletcher et al. (1999) analyzed the costs associated with operating a MRI facility in a UK National Health Service setting. Costs arising immediately after the introduction of a MRI facility in 1988 were compared with the costs arising towards the end of the scanner's useful life during the 1995/1996 financial year. With regard to the comparative global costs for the MRI facility from 1989-1996, but excluding contrast medium, Fletcher et al. (1999) revealed that the nominal total costs of MRI increased marginally, from £403,223 to £434,037, the increase in total costs was below the rate of inflation and the nominal average costs of MRI fell from £179.20 to £115.77 over the period.

Costs	Annual Costs (1989 prices)(£)	Annual Costs (1996 prices)(£)
Capital Costs		
Equipment costs	157,830	5,071
Accomadation costs and furniture and fittings	17,898	8,919
Total capital costs	175,728	13,990
Revenue Costs		
Staffing costs	105,272	273,326
Consumable costs*	52,452	70,377
Service and maintenance costs	63,419	68,750
Total operating costs	221,114	412,449
Indirect Costs (cleaning/building maintenance and rates)	6,350	7,598
Total Costs	403,221	434,037
No. of examinations per annum	2,250	3,749
Average cost per scan	179.20	115.77

*Excluding contrast medium

Reproduced with permission from The British Institute of Radiology; From Fletcher J, Clark M, Sutton F, Wellings R, Garas K. The cost of MRI: changes in costs 1989-1996. The British Journal of Radiology. 1999;72:432-437.

Fletcher et al. (1999) reported that the annual cost for contrast medium in 1989/90 was £11,000-20,000 and in 1996/97 the annual cost was £16,798. Further details of the contrast medium were not provided by Fletcher et al. (1999) and no explanation was provided as to why the cost of contrast medium was excluded from the calculation of global costs for the years examined.

Mowatt et al. (2003) conducted an economic analysis as part of the NICE systematic review of myocardial perfusion scintigraphy for the diagnosis and management of coronary artery disease. The systematic review included studies that compared costs and outcomes of SPECT with alternative diagnostic strategies.

In summary, at low levels of prevalence of CAD, stress ECG→SPECT→CA and SPECT→CA can be viewed as cost effective whereas CA, which generated more quality adjusted life years (QALYs), did so at an incremental cost per QALY that might be viewed as too high. At higher prevalence rates (50-85%), stress ECG→CA and CA strategies generate more QALYs at a relatively low incremental cost.

One of the recommendations from the NICE systematic review was that the other tests of cardiac function such as stress ECG, MRI and PET should also be investigated in order to inform future assessment of the needs of the National Health Service (NHS) for the investigation of CAD patients.

Garber et al. (1999) evaluated the cost-effectiveness of alternative approaches to diagnose coronary artery disease in the United States. A meta-analysis of the accuracy of alternative diagnostic tests plus decision analysis to assess the outcomes and costs of alternative diagnostic strategies for patients at intermediate pretest risk for coronary disease was conducted.

Method

The target population for the analysis were men and women 45, 55 and 65 years of age with a 25%-75% pretest risk for coronary disease. The time horizon was 30 years using a societal perspective. The diagnostic strategies investigated were initial angiography and initial testing with one of 5 noninvasive tests (exercise treadmill testing , planar thallium imaging, SPECT, stress echocardiography and PET) followed by CA in noninvasive test results were positive. Testing was followed by observation, medical treatment, or revascularization. The outcome measures included life years, quality adjusted life years (QALYs), costs and costs per QALY.

Results of Base Case Analysis

Life expectancy varied little with the initial diagnostic tests. Echocardiography improved heath outcomes and reduced costs relative to stress testing and planar thallium imaging. The incremental cost effectiveness ratio was $75,000/QALY for SPECT relative to echocardiography and was greater than $640,000 for PET relative to SPECT. Compared with SPECT, immediate angiography had an incremental cost effectiveness ratio of $94,000 per QALY.

Garber et al. (1999) concluded that echocardiography, SPECT, and immediate angiography were each cost-effective alternatives to PET and other diagnostic approaches.

Since noninvasive tests are often used to estimate prognosis, these tests can serve as adjuncts to CA (Garber et al., 1999). Garber et al. (1999) cautioned that there is no consensus about how management should be modified by such information but the value of such uses, which support an initial strategy of testing with echocardiography or SPECT rather than angiography, should be considered in choosing among testing strategies. Furthermore, noninvasive tests must detect the most severe forms of CAD to prolong life. Garber et al. (1999) noted that noninvasive tests were highly sensitive for 3 vessel and left main disease, therefore, improved test performance characteristics were unlikely to greatly affect mortality unless treatment of less severe forms of disease is also shown to prolong life substantially.

A limitation to the study by Garber et al. (1999) includes use of published assessments of test performance that met predefined quality criteria. Studies of diagnostic test performance reporting lower figures for sensitivity or specificity may be less likely to be submitted or accepted for publication. Test accuracy may also be different in different populations.

Maddahi et al. (1997) assessed the cost-effective selection of patients for coronary angiography. A mathematical model was used that defined cost effective utility of nuclear cardiology testing for diagnosis of CAD and selection of appropriate candidates for coronary angiography according to a decision analysis. The medical literature was surveyed to obtain a baseline for the variables of interest. Clinical utility or effectiveness was defined in terms of percent correct diagnosis of CAD and cost was defined as US dollars of medical expenditure.

Strategies using coronary angioplasty, exericise ECG, SPECT or PET were compared in subsets of patients with different pretest likelihoods of CAD, based on age, sex and symptoms (Maddahi et al., 1997). The authors concluded:

- Nuclear cardiology testing was the most cost-effective initial method of choice in patients with an intermediate pretest likelihood of CAD.
- In patients with a low pretest likelihood of CAD, nuclear cardiology testing was cost-effective in the subgroup of patients who had abnormal exercise treatdmill ECGs.
- In patients with a high pretest likelihood of CAD, direct referral to coronary angiography was the most cost-effective strategy for diagnosis of CAD.

Limitations to tbe study by Maddahi et al. (1997) included use of a model that was not confirmed by a randomized controlled trial. The study was published in 1997; more recent studies may use updated techniques including imaging, optimal surgical revascularization, stent therapy and aggressive medical management.

In the United States, **Patterson et al. (1995)** compared the cost effectiveness and utility of four clinical algorithms to diagnose CAD: exercise ECG, stress SPECT, PET and coronary angiography. Published data and a mathematical model were used to compare strategies. Effectiveness was defined as the number of patients with diagnosed CAD and utility was defined as the clinical outcome, specifically the number of quality adjusted life years (QALYs) extended by therapy after the diagnosis of CAD. The model used published values for costs, accuracy and complication rates of tests.

Results were as follows:

- The direct cost (fee) for each test differed considerably from total cost per QALY.
- As pretest likelihood of CAD (pCAD) in the population increased, there was a linear increase in cost per patient tested but a hyperbolic decrease in cost per effect and cost per utility unit, i.e., increased cost effectiveness and decreased cost per utility unit.
- At pCAD<0.70 analysis of the model indicated that stress PET is the most cost-effective test, with the lowerst cost per utility followed by SPECT, exercise ECG and angiography in that order.
- Above a threshold value of pCAD of 0.70, proceeding directly to angiography as the first test revealed the lowest cost per effect or utility.

Limitations to the study by Patterson et al. (1995) included the use of a mathematical model that was not confirmed by a randomized controlled trial. Furthermore, the study was published in 1995; more recent studies may have used updated techniques including imaging, optimal surgical revascularization, stent therapy and aggressive medical management.

Underwood et al. (1999) assessed the cost-effectiveness of diagnostic strategies in a retrospective study from the UK comparing cost-effectiveness of diagnosis and management between centres that routinely use myocardial

perfusion imaging scintigraphy (MPI) with those that do not. The primary outcome measures were the cost and accuracy of diagnosis, the cost of management, and clinical outcome in patients newly presenting with symptoms suggestive of CAD. Secondary measures included prognostic power, normal angiography rate and rate of angiography not followed by revascularization. Patients presenting with acute coronary syndromes (MI or unstable angina) were excluded as were patients in whom coronary disease had been previously confirmed or excluded.

Fifty consecutive cases were identified from outpatient and inpatient records of 8 hospitals (Underwood et al., 1999). Two hospitals were selected in each of four countries: France, Germany, Italy, and UK. All hospitals had access to myocardial perfusion imaging butr its use was at the discretion of individual cardiologists. All myocardial perfusion imaging was tomographic but no account was taken of the tracer used or the method of stress. Information was gathered retrospectively on presentation, investigations, complications, and clinical management and patients were followed up for 2 years in order to assess outcome.

Pre and post test probabilities of CAD were computed for diagnostic tests and each test was also assigned as diagnostic or part of management. Diagnostic strategies defined were:

1 Exercise ECG/coronary angiography
2 Exercise ECG/MPI/coronary angiography
3 MPI/coronary angiography
4 Coronary angiography

For each investigation performed, Bayes' theorem was used to calculate posttest probability.

Cardiac events were defined as soft or hard. Soft events were complications of any diagnostic or therapeutic procedure, worsening of angina, coronary angioplasty, or bypass grafting. Hard events were unstable angina, MI or death (of any cause).

Each center supplied information on costs and charges for principal investigations and procedures. The aim was to obtain one hospital in each country as a regular user of MPI and the other as a nonuser. All hospitals had access to MPI but its use was at the discretion of individual cardiologists. All MPI was tomographic but no account was taken of the tracer used or the method of stress. Underwood et al. (1999) stated that to simplify amalgamation of patients between centres, data were analyzed using a single table of costs applied to all centres. Items included were consumerables, labour, fixed costs (including equipment maintenance), apportioned according to average throughput, and capital charges. The cost did not include nominal figures for rental and maintenance of space. The costs were derived by averaging 1996 figures from 3 UK centres which were judged to be the most consistent.

Costs used for the analysis in all centres (rounded to the nearest £10 below £1000 and the nearest £100 above £100). The cost of coronary angiography includes one overnight bed.

Item	Cost (£)
Rest ECG	20
Exercise ECG	70
Rest echocardiogram	100
Myocardial perfusion imaging	220
Coronary angiography	1100
Coronary angioplasty	3700
Coronary bypass grafting	6900
Outpatient visit	70
Hospital bed (1 night)	300

U*nderwood SR, Godman B, Salyani S, Ogle JR, Ell PJ. Economics of myocardial perfusion imaging in Europe – the EMPIRE study. European Heart Journal. 1999;20:157-166, by permission of Oxford University Press.*

The financial perspective was from the provider of health care and the intent was to assess cost as true consumption of resources.

Strategies were defined according to the order in which investigations were performed:

Strategy	Ex-ECG	Myocardial Perfusion Imaging	Angiography
#1	1	-	2
#2	1	2	3
#3	-	1	2
#4	-	-	1

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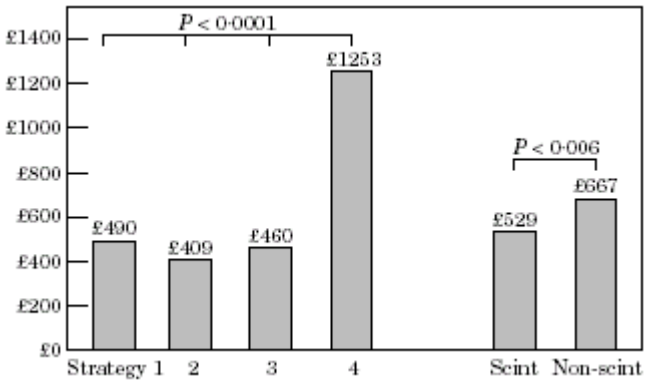
Three hundred and ninety six patients were included, 189 from MPI user centres and 207 from MPI non-user centres.

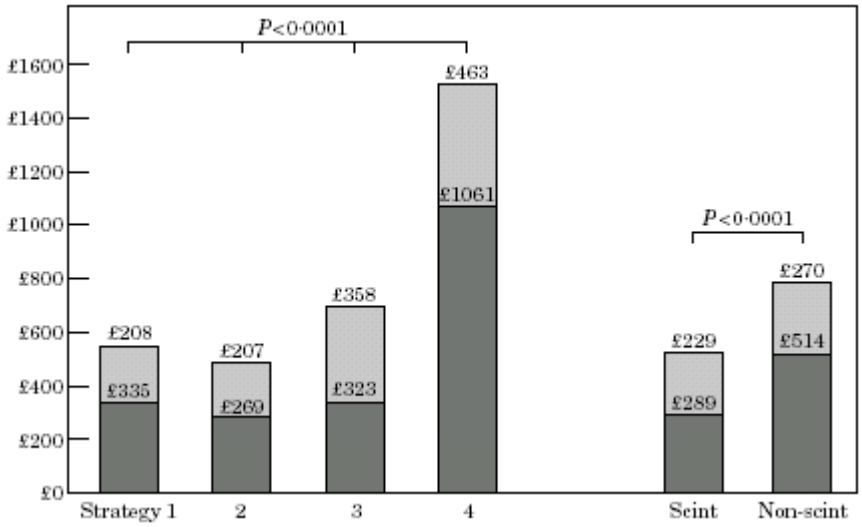
There were significant differences between strategies with the scintigraphic strategies cheaper than the nonscintigraphic strategies. The cost of diagnosis for each patient was defined as the sum of costs of outpatient attendances and investigations up to the point of diagnosis. The cost of inpatient days was not included due to discrepancies in practice between centres. Hidden and induced costs were not included (e.g., travel to hospital, cost of absence from work).



Mean cost of diagnosis according to strategy and type of centre (MPI user or non MPI user)

U*nderwood SR, Godman B, Salyani S, Ogle JR, Ell PJ. Economics of myocardial perfusion imaging in Europe – the EMPIRE study. European Heart Journal. 1999;20:157-166, by permission of Oxford University Press.*

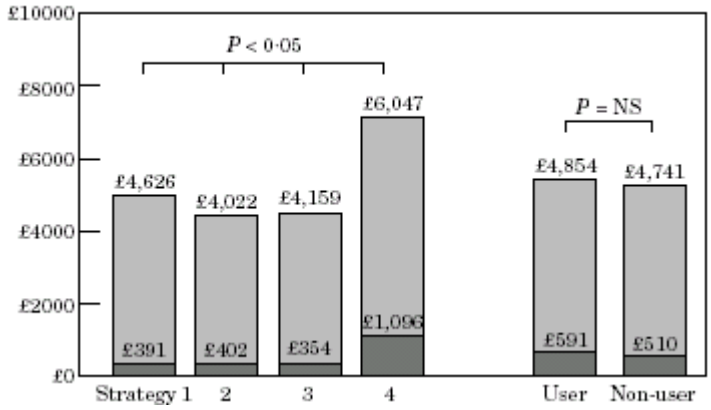
The following figures show the total diagnostic and management costs over 2 years in patients without and with CAD. The cost of management was defined as the sum of costs over 2 years from the point of diagnosis including outpatient attendances, inpatient admissions, further investigations, drug and other therapy and complications.



Mean two year cost per patient separated into diagnostic (dark) and management (light) costs and according to diagnostic strategy and type of centre, for patients without CAD.

U*nderwood SR, Godman B, Salyani S, Ogle JR, Ell PJ. Economics of myocardial perfusion imaging in Europe – the EMPIRE study. European Heart Journal. 1999;20:157-166, by permission of Oxford University Press.*

According to Underwood et al. (1999), the above figure indicated that in patients without disease, there were significant differences between strategies (p<0.0001), with strategy 2 being 15% cheaper than strategy 1, and strategy 3 being 54% cheaper than strategy 4. The facilities using myocardial perfusion imaging had a 32% saving over the nonuser facilities (p<0.0001).



Mean two year cost per patient separated into diagnostic (dark) and management (light) costs and according to diagnostic strategy and type of centre, for patients with CAD.

U*nderwood SR, Godman B, Salyani S, Ogle JR, Ell PJ. Economics of myocardial perfusion imaging in Europe – the EMPIRE study. European Heart Journal. 1999;20:157-166, by permission of Oxford University Press.*

In patients with disease, total costs were reported to be much higher and the percentage differences between strategies were less, but strategy 2 was 12% cheaper than strategy 1 and strategy 3 was 36% cheaper than strategy 4 (p<0.05) (Underwood et al., 1999). There was no significant difference in total costs between myocardial perfusion imaging user and nonuser facilities.

There were significantly more deaths in patients in strategies 3 and 4 (*P<0·05), but two of these deaths were non-cardiac. There was no difference in total number of hard events between strategies or user class:

	Patients	Unstable angina	Myocardial infarction	Death	Any event
Strategy 1	144	1	10	4	15
Strategy 2	130	1	9	2	12
Strategy 3	48	0	3	*5	8
Strategy 4	75	0	9	*4	13
MPI users	190	1	18	8	27
MPI non-users	207	1	13	7	21

Numbers of hard cardiac events according to diagnostic strategy and class of hospital

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Patients in strategy 4 had significantly more revascularization procedures (*P<0·001), but there were no differences between classes (MPI user or nonMPI user) of hospital:

	Compl'n	Worse angina	CABG	PTCA	Other	Any event
Strategy 1	3	2	11	8	1	25
Strategy 2	1	1	2	10	2	16
Strategy 3	1	0	4	6	1	12
Strategy 4	3	1	*14	*19	2	*39
MPI users	3	1	11	27	2	44
MPI non-users	5	3	20	16	4	48

Compl'n=complication of investigation or therapeutic procedure; Other=non-cardiac events.

Numbers of soft cardiac events according to diagnostic strategy and class of hospital. (For number of patients, see previous table).

U*nderwood SR, Godman B, Salyani S, Ogle JR, Ell PJ. Economics of myocardial perfusion imaging in Europe – the EMPIRE study. European Heart Journal. 1999;20:157-166, by permission of Oxford University Press.*

There were significant differences between strategies and type of centre in patients with CAD. In patients with CAD after 2 years, 98 of 187 (52%) patients were free of any symptom (cardiac or noncardiac) (Underwood et al., 1999). There was no significant difference in the proportion when separated by diagnostic strategy or type of hospital. In patients with CAD, 86 of 175 (49%) were free of symptoms, but there were differences between strategies and types of centre, with strategy 1 having the lowest freedom from symptoms (37%) and strategy 4 the highest (64%) (p=0.05) (Underwood et al., 1999). MPI users had significantly greater freedom from symptoms (63%) than nonusers (37%) (p<0.001) (Underwood et al., 1999).

Strategy	CAD		No CAD	
	Free of Symptoms	Any Symptoms	Free of Symptoms	Any Symptoms
1	23	40	31	32
2	21	16	41	39
3	14	17	8	8
4	28	16	18	10
MPI Users	50	29	49	49
MPI Nonusers	36	60	49	40

Numbers of patients free of any symptom at 2 year follow-up or with any symptom (cardiac or non-cardiac), according to the presence of coronary artery disease (CAD) on final diagnosis, diagnostic strategy, and type of hospital

U*nderwood SR, Godman B, Salyani S, Ogle JR, Ell PJ. Economics of myocardial perfusion imaging in Europe – the EMPIRE study. European Heart Journal. 1999;20:157-166, by permission of Oxford University Press.*

The number of coronary angiograms were studied as a secondary outcome measure. In the myocardial perfusion imaging user hospitals, 42/75 angiograms were diagnostic of which 11 (26%) were normal. In the nonusers, 79/88 angiograms were diagnostic, of which 34 (43%) were normal, p=0.07. Underwood et al. (1999) stated that both of these rates were relatively high because of exclusion of the management angiograms which by definition had at least a 90% likelihood of being abnormal. Considering all angiograms, 35/75 (47%) of patients undergoing angiography in the myocardial perfusion imaging user hospitals were revascularizaed, compared with 27/88 (31%) in the nonuser hospitals (p<0.05). Therefore, Underwood et al. (1999) stated that more patients undergoing angiography in the user hospitals proceeded to revascularization than in the nonusers.

Prognostic power at diagnosis was higher (p<0.0001) in the scintigraphic centres and strategies.

Underwood et al. (1999) concluded that investigative strategies using myocardial perfusion scintigraphy imaging are cheaper and at least equally effective compared with strategies that do not use MPI, both for the cost of diagnosis and for overall 2 year costs. As well, two-year outcomes were the same.

Limitations include:

- Differences between individual hospitals and some country specific differences, however, Underwood et al. (1999) stated that these differences "evened out" in the longer term.
- Patients undergoing strategies 3 and 4 had a higher likelihood of disease than patients who received strategies 1 and 2. Underwood et al. (1999) commented that many physicians reserve the more aggressive strategies for such patients and therefore the results should not be surprising, however, this restricts comparisons between strategies 1 and 2 between 3 and 4.
- The description of "angina" or "atypical" was not uniform from the hospital records.
- The issue of generalizability to other settings or countries was not fully addressed.
- No difference in prognostic power was observed in the study but a much larger and longer study would have been required in order to do so.
- It was reported that actual sensitivity and specificity achieved in the study were similar to the values reported in the literature, but it was considered more appropriate to use published values due to the relatively small numbers of patients studied and the lack of confirmatory angiography in some cases.
- Lack of power calculation to justify sample size.
- Lack of systematic literature review.

The impact of stress SPECT perfusion imaging on downstream resource utilization has been assessed. In a US study, **Mishra et al. (1999**) examined the downstream utilization rate in 2 cohorts of patients with intermediate pretest probability of CAD. In 1 group, coronary angiography was used as an initial screening test and in the second group stress SPECT perfusion imaging was the initial screening test and coronary angiography was subsequently performed if deemed necessary. Medicare reimbursements were used to calculate the cost savings.

Patients were identified from a database. Inclusion criteria consisted of:

All patients evaluated for chest pain syndromes suspected of being due to CAD

Exclusion criteria consisted of:

Previous coronary revascularization
Known cardiomyopathy
Primary valvular heart disease

Patients in group 1 (n=4,572) underwent coronary angiography and patients in group 2 (n=2,022) underwent stress SPECT perfusion imaging as the initial screening test. The subsequent need for coronary angiography in group 2 within 3 months and revascularization procedures in both groups (angioplasty or CABG) within 2 weeks of coronary angiography were documented. CAD was defined as $\geq$50% diameter stenosis in $\geq$1 of the major vessels.

In group 1, there were 1,536 patients (33%) with no significant CAD and 3,036 patients (67%) with CAD. Coronary revascularization was performed in 1,692 patients, which constituted 51% of the patients with CAD and 35% of the entire group 1.

In group 2, 1,626 patients (80%) were managed conservatively whereas 396 (20%) underwent coronary angiography. Among patients who underwent coronary angiography, 71 (18%) had no significant CAD ($p<0.0001$ versus group 1) and 325 (92%) had CAD. There were 123 patients in group 2 who underwent coronary revascularization after coronary angiography; this represented 38% of patients with CAD by angiography ($p<0.0001$ versus group 1) and only 6% fo the total group 2 patients ($p<0.001$ versus group 1).

Mishra et al. (1999) assumed a Medicare reimbursement of $840 US for stress SPECT and $2,800 US for coronary angiography. The selective use of coronary angiography in group 2 appeared to be an economically superior method to coronary angiography in all patients (savings of $1,420/patient). The cost in group 2 included $840 in each of 2,022 patients who underwent SPECT imaging and $2,800 in 396 patients who underwent coronary angiography, whereas the cost in group 1 was based on $2,800 in each of the 4,572 patients who underwent coronary angiography.

Mishra et al. (1999) stated that the higher rate of coronary revascularization in patients who initially had coronary angiography without SPECT imaging may have been due in part to the "occulostenotic reflex", whereas the lower rate in group 2 suggested that coronary revascularization was more appropriate because it targeted the high risk patient with evidence of ischemia.

Mishra et al. (1999) stated that there are factors that may affect the use of coronary angiography and coronary revascularization that are beyond the analysis:

- The treating physician's perception of the value of stress SPECT imaging
- Patient's expectations
- Economic factors related to self-referral whether in a private setting or in an academic institution.

Limitations to the study by Mishra et al. (1999) included:

- The cost analysis did not include costs of subsequent patient care or the need for intervention beyond the narrow study time frame.
- Short follow-up time

Jacklin et al. (2002) developed a UK economic model to examine if PET would be cost effective in selecting patients with poor LV function for revascularization. Jacklin et al. (2002) collected data from two main sources: records from a UK hospital and published literature. Hospital data were used to calculate the cost of performing CABG and PET scans in the authors' institution, to measure perioperative mortality rate and estimate the cost of providing drug treatment for 1 year. The published literature was used to estimate the prevalence of hibernating myocardium, the annual survival rates of patients on medical and surgical treatment, and the accuracy of the PET scan.

A decision analysis model was developed. Quality of life was not assessed by the authors. The cost and outcome of treating hypothetical patients using the model for 3 different strategies was estimated:

1. Patients were treated with operation without a PET scan in the preoperative workup.
2. Patients had PET scans first and were treated with medical therapy or with operation according the result of the scan.
3. Patients were treated with medical therapy and never offered operation as an option.

A sensitivity analysis was also performed due to uncertainty surrounding data values assigned to some of the model variables.

Jacklin et al. (2002) determined that PET was cost-effective in selecting patients for operation. Results from using the default values are shown below:

Treatment strategies	Total cost (£)	Total effect (life-years)	Incremental cost (£)	Incremental effect (life-years)	Incremental cost-effectiveness (cost per life-year saved)
Medical therapy	666,900	855.00	…	…	-
Preoperative PET + CABG	5,359,146	915.79	4,692,246	60.79	£77,186
CABG	8,146,717	913.79	2,787,572	-2.00	Dominated*

*Dominated: A strategy that is more expensive and produces less benefit than another is said to be dominated by the cheaper and more effective alternative

Reprinted from the Annals of Thoracic Surgery, v. 73, Jacklin PB, Barrington SF, Roxburgh JC, Jackson G, Sariklis D, West PA, Naisey MN. Cost-effectiveness of preoperative positron emission tomography in ischemic heart disease, 1403-1410, Copyright 2002, with permission from the Society of Thoracic Surgeons.

The sensitivity analysis showed that the prevalence of hibernation and the survival rate of patients refused revascularization on the basis of the PET scan were the areas most likely to influence cost-effectiveness.

Limitations to the study by Jacklin et al. (2002) included:

- Use of a decision analysis model to collate available data compared to using trial data.
- The sensitivity analysis confirmed that there was uncertainty surrounding the available data. The areas of uncertainty that may alter the cost-effectiveness conclusion were the prevalence of hibernation in the referral population and the survival of patients with myocardial necrosis on medical therapy.
- Quality of life was not measured.
- The accuracy of PET may affect cost-effectiveness conclusions. The threshold analysis suggested that the sensitivity of PET was more important than specificity.
- The cost of medical therapy was underestimated because Jacklin et al. (2002) did not include the cost of medical consultations or admissions to hospital.
- The model examined only the use of PET in the preoperative workup of patients. Jacklin et al. (2002) chose to examine PET since it was "generally regarded as the most accurate imaging technique for hibernation".
- Alternative imaging techniques were not analyzed.

Jacklin et al. (2002) stated that a prospective trial of medical therapy versus surgical treatment is desirable. **Kappetein (2002)**, in an accompanying editorial to the study by Jacklin et al. (2002), recommended that there is a need for well designed studies that reproducibly quantify the amount of hibernating myocardium, assess the

accuracy of different tests, and evaluate whether optimal medical therapy or revascularization is of benefit. As well, Kappetein (2002) stated that there is a need for studies to assess the cost-effectiveness of different diagnostic and therapeutic strategies.

Summary and Conclusions

- Functional MRI has become increasingly investigated as a noninvasive method for assessing myocardial viability and perfusion. Most patients in the published literature have mild to moderate impaired LV function. It is possible that the severity of LV dysfunction may be an important factor that can alter the diagnostic accuracy of imaging techniques.

- There is some evidence of comparable or better performance of functional cardiac MRI for the assessment of myocardial viability and perfusion compared with other imaging techniques. However limitations to most of the studies included:
  - Functional cardiac MRI studies that assess myocardial viability and perfusion have had small sample sizes.
  - Some studies assessed myocardial viability/perfusion in patients who had already undergone revascularization, or excluded patients with a prior MI (Schwitter et al., 2001).
  - Lack of explicit detail of patient recruitment.
  - Patients with LVEF >35%.
  - Interstudy variability in post MI imaging time (including both acute MI and chronic MI), when patients with a prior MI were included.
  - Poor interobserver agreement (kappa statistic) in the interpretation of the results (See Table 3 Appendix). Traditionally, 0.80 is considered "good".

- Cardiac MRI measurement of myocardial perfusion as an adjunct tool to help diagnose CAD (prior to a definitive coronary angiography) has also been examined in some studies, with methodological limitations, yielding comparable results.

- Many studies examining myocardial viability and perfusion report on the accuracy of imaging methods with limited data on long-term patient outcome and management.
  - Kim et al. (2000) revealed that the transmural extent of hyperenhancement was significantly related to the likelihood of improvement in contractility after revascularization. However, the LVEF in the patient population was 43% prior to revascularization. It is important to know whether the technique has the same degree of accuracy in patients who have more severe LV dysfunction and who would most benefit from an assessment of myocardial viability.
  - "Substantial" viability used as a measure of a patient's ability to recover after revascularization has not been definitively reported (how much viability is enough?).

- Patients with severe LV dysfunction are more likely to have mixtures of surviving myocardium, including normal, infarcted, stunned and hibernating myocardium (Cowley et al., 1999). This may lead to a lack of homogeneity of response to testing and to revascularization and contribute to inter- and intra-study differences.

- There is a need for a large prospective study with adequate follow-up time for patients with CAD and LV dysfunction (LVEF<35%) comparing MRI and an alternate imaging technique. There is some evidence that MRI has comparable sensitivity, specificity and accuracy to PET for determining myocardial viability. In addition, some studies refer to PET as the gold standard for the assessment of myocardial viability. Therefore, PET may be an ideal noninvasive imaging comparator to MRI for a prospective study with follow-up.

- To date, there is a lack of cost-effectiveness analyses (or any economic analyses) of functional cardiac MRI versus an alternate noninvasive imaging method for the assessment of myocardial viability/perfusion.

Conclusion

- There is some evidence that the accuracy of functional cardiac MRI compares favourably with alternate imaging techniques for the assessment of myocardial viability and perfusion.

- There is insufficient evidence whether functional cardiac MRI can better select which patients [who have CAD and severe LV dysfunction (LVEF <35%)] may benefit from revascularization compared with an alternate noninvasive imaging technology.

- There is insufficient evidence whether functional cardiac MRI can better select which patients should proceed to invasive coronary angiography for the definitive diagnosis of CAD, compared with an alternate noninvasive imaging technology.

- There is a need for a large prospective (potentially multicentre) study with adequate follow-up time for patients with CAD and LV dysfunction (LVEF<35%) comparing MRI and PET.
  - In a 2003 review of SPECT for the diagnosis and management of CAD, NICE recommended that the other tests of cardiac function such as stress ECG, MRI and PET should also be investigated in order to inform future assessment of the needs of the National Health Service (NHS) for the investigation of CAD patients.
  - In an editorial to the MRI viability study by Kim et al. (2000), Beller et al. (2000) stated that "prospective randomized studies should now be undertaken to determine the worth and cost-effectiveness of noninvasive testing of viability as a means of guiding therapeutic strategies in patients with ischemic cardiomyopathy and congestive heart failure".
  - Since longer follow-up time may be associated with restenosis or graft occlusion, it has been suggested to have serial measurements after revascularization (Cowley et al., 1999).
  - Both MRI and PET measurements should be made in the same patient.
  - The study centres should have the technical expertise to conduct such studies including in depth knowledge of PET and MRI methodologies.

Existing Guidelines Regarding the Utilization of the Technology

Task Force of the European Society of Cardiology (ESC), in Collaboration with the Association of European Paediatric Cardiologists (1998)

The classification of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures was adapted by the ESC (1998).

Class I	Provides clinically relevant information and is usually appropriate; may be used as a first line imaging technique.
Class II	Provides clinically relevant information and is frequently useful, but similar information from other imaging techniques is usually adequate.
Class III	May provide clinically relevant information but is infrequently used because information from other imaging techniques is usually adequate.
Class IV	Does not provide clinically useful information.
Inv	Potentially useful, but still under investigation.

Indications for MRI in patients with coronary artery disease:

Indication	Class
Assessment of myocardial function	III
Detection of coronary artery disease	
Analysis of LV function during stress	III
Assessment of myocardial perfusion	Inv
Coronary angiography	Inv
Bypass graft angiography	III
Assessment of coronary flow	IV
Detection and quantification of acute MI	IV
Sequelae of MI	
Myocardial viability	II
Ventricular septal defect	III
Mitral regurgitation	III
Intraventricular thrombus	II

American College of Cardiology (ACC)/American Heart Association (AHA)/ American Society of Nuclear Cardiology (ASNC) Guidelines for the Clinical Use of Cardiac Radionuclide Imaging (Klocke et al., 2003)

For myocardial viability, Klocke et al. (2003) stated:

> *"MRI has emerged as an alternative noninvasive imaging approach for discrimination of fixed scar versus viable but dysfunctional myocardium. Reports indicate that infarct avid imaging analogous to that formerly performed with Tc-99m pyrophosphate can be performed by using MRI and a conventional gadolinium-based contrast agent [Kim et al., 2000; Wu et al., 2001]. Potential advantages included the improved resolution now available with MRI and an ability to image chronic and acute infarctions. Additional clinical experience will be needed to place this approach in proper context".*

No ACC/AHA classification or level of evidence was provided for cardiac MRI in the assessment of myocardial viability.

National Institute of Clinical Excellence (NICE) -UK (Mowatt et al., 2003) Appraisal Committee's Preliminary Recommendations for Myocardial Perfusion Scintigraphy for the Diagnosis and Management of CAD:

- Myocardial perfusion scintigraphy using SPECT is recommended for use in the diagnosis and management of CAD, particularly under the circumstances described below:
- SPECT before CA is recommended as the preferred initial diagnostic tool in people with a low likelihood of CAD and a low risk of future cardiac events.
- SPECT is also recommended as the preferred initial diagnostic tool in people for whom stress electrocardiography poses particular problems of poor sensitivity or difficulties in interpretation, including women, patients who have undergone ravascularization procedures, patients with cardiac conduction defects, people with diabetes and people for whom treadmill exercise is difficult or impossible. SPECT is also recommended in addition to stress electrocardiography in the assessment of prognosis following myocardial infarction.

NICE recommended that the value of SPECT in relation to other tests of cardiac function such as stress ECG, MRI and PET should be investigated in order to inform future assessment of the needs of the National Health Service (NHS) for the investigation of CAD patients.

Appendix

Table 1. Comparison of cardiac functional diagnostic imaging techniques to assess viability

Technology	Basis of data	Main Advantages	Main Limitations
FDG PET	Detects changes in energy metabolism	High resolution and good spatial localization of defects. Possibility for attenuation correction. Data can be analyzed qualitatively and quantitatively. Can be applied to measure various abnormalities (using different tracers).	High overall technical cost. Limited availability. Does not have capabilities of displaying anatomy. Need for a cyclotron for FDG production.
FDG SPECT	Detects changes in energy metabolism.	Lower overall technical cost than for PET. Widely available SPECT equipment.	Need for cyclotron for FDG production. Poorer spatial resolution than PET; lower sensitivity than PET. Requires specialized equipment and staff. Requires attenuation correction technique.
PET/CT	Detects changes in energy metabolism/ provides a detailed picture of the internal anatomy revealing location, size, and shape	Results of PET and CT scans are "fused" together; the combined image provides information on location and metabolism. Both scans - PET and CT - done at the same time. CT angiography provides coronary anatomy. Combined coronary anatomy and function; myocardial function, perfusion and metabolism.	High overall technical cost. Limited availability.
MRS	Detects metabolic changes.	Noninvasive. Offers possibility of in vivo measurement of myocardial biochemistry. Can be performed with available MRI equipment. 3-D capability with unlimited field of view.	Very limited spatial resolution. Time consuming. Patients with ferromagnetic objects n their bodies must be excluded. Requires specialized software and expertise. Abnormalities of phosphocreatine and adenosine triphosphate (ATP) are not specific for ischemia or absence of viability.
Functional MRI	Measures contractile reserve (thickness and wall motion)	Can be performed on available MRI scanners (permits direct correlation of function with the underlying anatomy). Does not use ionizing radiation. Good spatial resolution of LV cavity and wall thickness in diastole and systole.	Patients with ferromagnetic objects in their bodies must be excluded. Relatively long scanning time. Relatively high costs of additional equipment, software. Breath holding required.
Echocardiography	Measures contractile reserve (thickness and wall motion).	Versatile imaging method for a variety of heart diseases. All cardiac structures visualized and pump function assessed. Relative low cost; no needles or radiation; easily portable. Does not depend on ECG gating (rhythm). Good resolution of LV wall thickness during cardiac cycle.	Dependent on operator's skill to acquire images and requires specialized equipment and experienced interpreters (especially stress echo). Stress echo cannot evaluate myocardial perfusion adequately on a routine basis. Uncertain definition of LV cavity size.
Tc-99m-SPECT	Measures myocardial perfusion and membrane integrity.	Lower overall technical cost than for PET. Widely available SPECT equipment. Tc-99m sestamibi has better radiation characteristics than TI-201. Time fo TC-99m sestamibi imaging is not critical (minimal redistribution).	The utility of Tc-99m sestamibi alone as an indicator of MV is limited (reduced value as MV agent under ischemic and hypoxic conditions). Improves with adequate attenuation correction technique, but often done without.
TI-201 SPECT	Measures myocardial perfusion and membrane integrity.	Lower overall technical cost than for PET. Widely available SPECT equipment.	Redistribution/uptake depend on time after injection and blood concentration. Suboptimal radiation characteristics compared to Tc-99m SPECT.

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Table 2. Included Studies.

Study	Intervention	Patients	Outcome	Comment
Kitigawa et al. (2003)	Delayed contrast enhanced MRI vs. Resting ^{201}Tl SPECT Followup cine MRI to assess wall thickness. Objective: to compare MRI and resting SPECT in the prediction of preserved wall thickening at follow-up cine MRI.	30 prospectively enrolled patients. Patients had MI defined as typical chest pain, characteristic abnormal findings at ECG and increased cardiac enzyme level.	Sensitivity MRI: 98.0 Specificity MRI: 75.0 Accuracy MRI: 92.0 Sensitivity SPECT: 90.3 Specificity SPECT: 54.4 Accuracy SPECT: 81.1	Delayed contrast enhanced MRI may help predict myocardial viability as seen on followup cine MRI images after acute MI with improved sensitivity, specificity, and accuracy compared to resting SPECT. Small sample size. MRI and SPECT not performed same day. LVEF not reported.
Panting et al. (2001)	MRI vs. SPECT. Objective: to detect perfusion defects at rest and during adenosine stress in 26 patients with CAD and an abnormal Tl SPECT.	26 patients (retrospective/prospective enrollment?)	In patients who had undergone coronary angiography, MRI and rest SPECT results were comparable in detection of abnormal coronary regions: Sens. Spec. Accur. Thallium 70 78 73 MR Visual 77 83 79 MR Parametric Map Time to peak 60 43 60 Peak 72 83 76 Slope 79 83 80	There was good overall agreement in the overall patient findings. The segmental agreement (kappa) of perfusion severity was poor. Patient recruitment not explicitly described. LVEF not reported.
Wahba et al. (2001)	MRI vs. SPECT Analyzed concordance between wall motion and thickening scores derived by SPECT and MRI. Also, agreement for wall motion and thickening according to myocardial perfusion was analyzed by both techniques.	21 patients (retrospective/prospective enrollment?) Average LVEF in patients with a prior MI was 37±16%, and 51±15% in patients without a prior MI.	Segmental wall motion and thickening scores between gated SPECT and MRI for segments with normal or mild to moderate hypoperfusion produced k=0.80 (p<0.001) and k=0.84 (p<0.001). For segments with severe hypoperfusion, k=0.45 (p<0.001) or no perfusion, k=0.57 (p<0.001).	Combination of patients used (MI and no MI). Average LVEF indicated that patients did not have severe LV dysfunction. Details of patient recruitment not explicit.
Bax et al (2000)	MRI vs. SPECT Assessed LV function and myocardial viability.	29 patients. Inclusion criteria: sinus rhythm, angiographically proven CAD, impaired LV function.	7 patients excluded: heart failure (n=5), unstable angina (n=2). The relation of the summed wall motion scores per patient between MRI and gated SPECT was statistically significant (p<0.01).	Patient recruitment not explicitly described. Mean LVEF measured by MRI was 29±4% (range 17-47) and gated SPECT was 29±9% (range 13-50), p=0.76.
Gerber eta l. (2002	MRI Cohort Objective: to evaluate the diagnostic accuracy of delayed contrast enhanced MRI versus early hypoenhancement.	20 patients underwent CMRI and tagged MRI at 4 days. Tagged MRI was again conducted at 7 months after acute MI. Inclusion criteria: hemodynamically stable, hospitalization for MI. Exclusion criteria: contraindication to MRI	Hypoenhanced region: Sensitivity 19% Specificity 89% Accuracy 49% Hyperenhanced region: Sensitivity 82% Specificity 64% Accuracy 74%	No comparator imaging method. Small sample size. No interobserver reliability reported.
Choi et al. (2001)	MRI Cohort Objective: to determine if the transmural extent of infarction (TEI) assessed using MRI within the first week after an event can predict	31 consecutive patients with diagnosis of MI (enzymatically determined) prospectively enrolled. Inclusion criteria: no prior MI, were	7 patients did not receive a second scan: 2 lost to followup, 3 refused to return and 2 had CABG. The percentage of improved segments	No comparator modality. It is unknown whether infarct shape plays an independent role in contractile improvement. Patients with a short follow-up may not have had full recovery of all dysfunctional

	improvement in contractile function 2-4 months later.	reperfused, clinically stable, no contradictions to MRI, could receive a scan within 7 days of MI.	decreased with increasing TEI (p<0.001). High correlation between future improvement in global contractile function (mean wall thickening score) and the percent of LV that was dysfunctional but viable (p<0.001).	segments. LVEF not reported.
Wu et al. (2001)	MRI Cohort Objective: To determine if healed myocardial infarction can be visualized as hyperenhanced regions with contrast enhanced MRI.	44 patients with enzymatically proven myocardial necrosis were prospectively enrolled for repeat MRI scanning (at 3 months). 19 patients with more "remote" MI. This group included 11 patients from the group studied at 3 months who were followed up for an additional year and had repeat scanning. 20 patients with idiopathic dilated cardiomyopathy. 11 healthy patients with no clinical risk factors for CAD.	32 patients returned for the 2nd scan. Five declined to return, 4 lost to followup, 3 died. 29/32 patients with healed Mis examined at 3 months and all 19 patients examined at 14 months showed hyperenhancement. None of the 20 nonischemic cardiomyopathy patients displayed hyperenhancement. Sensitivity of contrast enhanced MRI for detection of healed infarction was 91% at 3 months and 100% at 14 months. Specificity was 100% when patients with nonischemic dilated cardiomyopathy and normal volunteers were considered.	LVEF not reported. Small sample size. It is possible that other cardiac disorders may cause hyperenhancement.
Kim et al. (2000)	MRI Cohort Objective: Investigate value of contrast enhanced MRI in determining the transmural extent of myocardial viability.	61 patients prospectively enrolled. Inclusion criteria: Scheduled to undergo revascularization Abnormalities in regional wall motion (ventriculography or echocardiography) Not have stable angina, NYHA class IV HF, or contraindications to MRI Informed consent	11 patients did not participate: 9 decided not to undergo revascularization 2 could not have MRI performed prior to revascularization 50 consecutive patients were studied. 9 patients were excluded: 1 died, 2 lost to follow-up, 2 had pacemaker implanted, 4 declined to return. For 41 patients who underwent imaging after revascularization, mean EF was 43±13% and 47±12% after the procedure. The proportion of segments with improved contractility decreased progressively as the transmural extent of hyperenhancement increased, p<0.001. Increasing extent of dysfunctional but viable myocardium before revascularization correlated with greater improvements in both the mean wall motion score (p<0.001) and EF after revascularization (p<0.001).	Patient population had a LVEF=43% prior to revascularization. Visually evaluated the degree of wall motion and extent of hyperenhancement. Kappa value of 0.59 among 3 observers. Regional function was evaluated 11 weeks post revascularization. No comparator imaging modality.
Klein et al (2002)	Contrast enhanced MRI vs. PET Objective: To compare the extent and location of hyperenhancement with nonviable tissue defined by PET in patients with chronic ischemic heart failure. PET and MRI performed within 1 week.	31 patients with CAD Inclusion: LVEF<35% (assessed by echocardiography or ventriculography) Scheduled for PET Informed consent	Sensitivity and specificity for detecting transmural defects only were 0.86 and 0.94 respectively, and for detecting any defect (transmural or nontransmural) were 0.83 and 0.88 respectively.	Prognosis after revascularization is unknown. Patient recruitment was not explicitly described.

Ibrahim et al. (2002)	Contrast enhanced MRI vs. PET Objective: To compare MRI estimates of regional myocardial blood flow in patients with CAD compared to PET flow measurements. MRI and PET performed the same day at rest and during adenosine stress.	25 clinically stable patients with angiographically documented CAD and normal LV function (EF =64±13.5%). Two different groups (group I n=20 and group II n=14) of healthy volunteers with a low likelihood for CAD based on history and clinical examination were either examined by MRI or PET in order to provide reference data.	MRI indices (upslope and peak intensity) in CAD patients were significantly lower than the coronary flow reserve in PET. The sensitivity, specificity and diagnostic accuracy levels for detection of regional coronary flow reserve <2.0 were 86%, 84%, and 85% respectively for the upslope index (cutoff: 1.3) and 68%, 73%, and 71% respectively for the peak intensity index (cutoff: 1.1).	The results may not be generalizable to patients with CAD. The patients had a very low incidence of prior MI and impaired LV function. The data from volunteers were obtained in 2 separate cohorts thereby limiting the direct comparison of individual data.
Koskenvuo et al. (2001)	MRI vs. PET Objective: To investigate whether velocity encoded cine MRI of coronary sinus blood flow could accurately measure global myocardial blood flow and global coronary flow reserve in patients with CAD compared with PET using ^{15}O labeled water. Average delay between MRI and PET was 8±10 days. MRI and PET at rest and after dipyridamole infusion.	20 men with angiographically confirmed CAD were enrolled.	3 patients excluded: 2 and unsatisfactory MRI flow curves possibly due to gating errors. 1 atrial fibrillation during PET. The Spearman correlation coefficients of myocardial blood flow and coronary flow reserve between the two methods were 0.80 ($p<0.01$) and 0.5 ($p<0.01$) respectively.	Patient recruitment not explicitly described (retrospective/prospective). LVEF not reported.
Schwitter et al. (2001)	MRI vs. PET Objective: To assess myocardial perfusion by comparing the quality of multislice MRI to PET and quantitative coronary angiography (CA). Two weeks before CA patients underwent MRI and PET in random order. MRI and PET at rest and dipyridamole infusion.	48 patients with suspected CAD and scheduled for CA were prospectively identified. 8 healthy volunteers for reference data. 10 healthy volunteers added to the patient cohort "to stimulate the relatively high proportion of normal subjects that are typically referred for noninvasive testing to achieve a more reliable calculation of specificity" For comparison of PET versus quantitative CA, the study cohort of 41 patients (33 with documented CAD, 8 without CAD) was supplemented by 8 "additional low likelihood subjects" who were randomly collected from the authors "normal database".	41 PET exams were available for comparison with MRI. (1 PET study was cancelled for logistic reasons and 4 were lost due to storage failure). The number of myocardial sectors with impaired subendocardial flow on MRI and reduced coronary flow reserve on PET were compared (8.1±6.5 sectors vs. 9.0±5.7 sectors respectively; overall p=0.22). The number of pathological sectors measured by MRI and PET correlated linearly (slope 0.94, r=0.76, p<0.0001). MRI sectors with transmurally reduced flow underestimated the extent of disease (4.9±5.34 sectors vs. 9.0±5.7 sectors with PET, p<0.005).	Patients with a prior MI were excluded from the study. Therefore, the applicability of the results to these patients was not determined. LVEF was not reported. Patient recruitment was not explicitly described.
Al Saadi et al. (2000)	MRI Cohort Objective: To use a single slice MRI method to assess the diagnostic accuracy of MR perfusion reserve measurement in comparison with angiography. "After" MR exam, patients underwent cardiac catheterization and CA.	40 patients were prospectively examined by use of a previously defined threshold value. (Group B) 15 patients with single vessel disease and 5 patients with chest pain but no significant stenoses of the coronary arteries were examined to define the cutoff values in perfusion measurements for detection of significant coronary artery stenosis. (Group A)	34/40 patients in Group B successfully underwent perfusion imaging. 3 patients excluded due to claustrophobia 3 ECG triggering was insufficient In group B, myocardial perfusion reserve was significantly different between ischemic (1.16±0.29) and nonischemic (2.17±0.62) segments (p<0.001). Fifty-four of the 60 segments supplied by stenotic coronary arteries and 35 of the 42 segments supplied	Patients were excluded if EF<30%. However, overall LVEF not reported. Patient recruitment was not explicitly described (consecutive?). Use of a single slice technique. The myocardium was only partially visualized and significant myocardial ischemia might have been missed. The value of multislice techniques was not assessed. The combined use of nonischemic segments from patients with single vessel disease and patients without significant coronary artery

			by nonstenotic coronary arteries were correctly classified by the use of the defined myocardial perfusion reserve cutoff value of 1.5, resulting in a sensitivity of 90%, a specificity of 83% and a diagnostic accuracy of 87%.	disease for the definition of the ischemic threshold.
Kramer et al. (2002)	Dobutamine MRI vs. Dobutamine Echocardiography Objective: To compare the qualitative response of low dose dobutamine by echocardiography (DSE) with the quantitative response of MRI tagging (DMRT) in the prediction and evaluation of functional improvement after reperfused MI. 3+1 days after MI, patients underwent DSE and DMRT at baseline and during dobutamine infusion. Patients returned at week 8+1 for followup echocardiogram and MRT at rest.	27 patients with reperfused MI were initially enrolled. Inclusion: Recent MI and documented open infarct related artery with TMI grade 3 after thrombolytic therapy or primary angioplasty with or without stenting.	22 patients completed the study. 4 did not return for followup echocardiography or MRI 1 had inadequate image quality of DSE for interpretation. The overall accuracy of DSE and DMRT were 85% and 76% respectively.	LVEF was not reported. Patient recruitment details were not explicitly described. Imaging a very early post MI and matching to 8 week images. Longer follow-up may have identified more functional improvements. Results were qualitative.
Saito et al. (2000)	Dobutamine MRI vs. Dobutamine Echocardiography Objective: To assess myocardial viability by a quantitative analysis of the improvement of the regional wall motion using a MRI tagging method.	22 patients with ischemic heart disease 7 health volunteers.	To determine viability, 19 of the 22 patients also underwent ^{201}Tl SPECT, 14 patients were examined by PET, and follow-up echocardiography without the use of dobutamine was performed in 10 patients 1 month after CABG or percutaneous transluminal coronary angioplasty (Saito et al., 2000). Some patients were evaluated for viability by 2 or 3 examinations "and the estimation by these methods showed no discrepancies in any of the patients" (Saito et al., 2000). It is uncertain if the investigators meant some patients were evaluated for viability by 2 or 3 of the same or different examinations. No further data were provided for the SPECT, PET or follow-up echocardiography without dobutamine. For healthy patients, the thickening ratio increased significantly with dobutamine infusion ($p<0.05$). The results of the evaluation of myocardial viability with dobutamine stress MRI and echocardiography "were similar in 19 (86.4%) of the 22 patients with ischemic heart disease". Among these 22 patients, 20 were studied by PET, ^{201}Tl SPECT, or were examined for improvement in wall motion following coronary intervention. No further detail was provided.	Lack of clarity in reporting study details in methods and results. Long acquisition time during dobutamine stress MRI, taking 4-5 minutes per slice per patient. This problem may be solved by high speed MRI techniques. The time of the appearance of tagging on the LV wall. The tags remained on the wall for up to 350 ms but as the automatically available and precise image data from the tags in all patients was only up to 270 ms, they could not be observed until the end of systole. LVEF was not reported. Patient recruitment was not sufficiently described.
Baer et al. (2000)	Dobutamine transoesophageal echocardiography (dobutamine TEE) and dobutamine MRI for the detection of viable myocardium and the	103 patients were prospectively studied. 48 of these patients were also included in a previous MRI study on myocardial viability (Baer et al., 1998).	Dobutamine TEE and dobutamine MRI were performed in random order within 3 days without intervening cardiac events. After 4.9±0.7 months, 65 patients underwent	LVEF was >35%.

	prediction of LV functional recovery in patients with chronic CAD following successful revascularization procedures. 4 year period.	Inclusion: Chronic CAD (infarct age > 4 months) Persisting akinetic or dyskinetic infarct region as demonstrated by left ventriculography Severe stenosis of the infarct related coronary artery – reduction in resting flow or repetitive ischemic episodes in the infarct region (>80% diameter reduction) Angiographically documented successful revascularization after 6 months.	control coronary angiography. Mean baseline LVEF was 41%. 52 patients had a successful revascularization and MRI followup to the study. Mean LVEF before revascularization was not significantly different between patients with and without a dobutamine induced contraction reserve by TEE and MRI in infarct related segments. LVEF increased significantly in patients with predominantly viable infarct regions by TEE ($p<0.001$) and MRI ($p<0.001$) compared to those infarct regions graded to have predominantly scar tissue. Magnitude of the increase in LVEF was significantly correlated with the number of dobutamine responsive segments assigned to an individual infarct region (TEE $r=0.71$, $p<0.0001$); MRI $r=0.73$, $p<0.0001$) in both imaging techniques.	
Kramer et al. (2000)	Contrast enhanced dobutamine tagged MRI Objective: ability to predict functional recovery using MRI contrast uptake patterns and contractile response to dobutamine by tagged MRI within the same myocardial tissue early after reperfused first MI in a single exam.	27 patients with reperfused first MI were enrolled. Patients returned 9±1 weeks after MI for a repeat MRI without dobutamine.	23 patients completed the study. There was a good correlation between followup %S and %S with peak dobutamine.	LVEF not reported.
Al Saadi et al. (2000b)	MRI Objective: to evaluate changes of myocardial perfusion reserve (MPR) within 24 hours of a successful coronary intervention in a patient population with CAD. Secondary objective: to determine the possible diagnostic impact of this technique in the diagnosis and followup of patients with CAD who have undergone balloon PTCA or stenting.	38 patients with previously angiographically proven significant single or double vessel CAD referred for elective coronary intervention were prospectively included. After MR exam, all patients underwent cardiac catheterization and biplane selective coronary angiography. MR exam could not be performed for: 1 claustrophobia 1 insufficient ECG triggering 1 occurrence of uncomplicated ventricular arrhythmias after PTCA which required continuous monitoring.	Before intervention, 47/53 of the 53 territories supplied by stenotic coronary arteries and 43/52 territories supplied by nonstenotic coronary arteries were correctly diagnosed as ischemic and nonischemic respectively by use of a previously defined threshold of 1.5. This resulted in a sensitivity of 89%, and a specificity of 83% with a diagnostic accuracy of 86%. After intervention, MPR index increased significantly in segments supplied by successfully treated vessels (1.07±0.24 before and 1.89±0.39 after intervention, $p<0.001$). However, it remained below the level of control patients ($p<0.01$). After intervention, sensitivity and specificity for the detection for a stenotic coronary artery were 82% and 84% respectively and a diagnostic accuracy of 84%.	Single slice technique was used. No comparator for MRI perfusion measurements. Analysis time was approximately 60 min per patient. Large segments were compared rather than a pixel to pixel analysis which can be more sensitive to through plane motion.
Hundley et al. (1999)	Assessed the clinical safety and utility of fast cine MRI stress testing for determination of inducible ischemia in patients not suitable for stress echocardiography.	163 patients referred for diagnosis of ischemia with dobutamine echocardiography who did not have adequate endocardial visualization. Quantitative angiography was performed without knowledge fo patient characteristics	The sensitivity and specificity of fast cine MRI for detecting coronary arterial narrowings assessed with quantitative CA were: # of Coronary Arteries with >50% luminal diameter narrowing 0 1 2 3 or left main MRI positive 1 9 9 11 MRI negative 5 3 2 1	Coronary angiography was not performed in all patients. Patients possessed a high pretest probability for CAD. Specificity data are based on 6 patients.

		or MRI results in all patients who underwent angiography within 6 months of MRI.	Sensitivity 75% 82% 92% Specificity 83%	
Al Saadi et al. (2002)	Evaluated the value of MRI for the detection of significant coronary artery stenosis from alteration s of myocardial perfusion using dobutamine stress.	27 patients with suspected or proven single or double CAD admitted for invasive coronary angiography were prospectively included.	23 patients had significant CAD. In all patients with CAD, perfusion reserve index in segments supplied by al stenotic coronary artery was significantly lower than segments of patients without significant CAD (0.97+0.20 vs. 2.0+0.39, p<0.001). 27/37 coronaries without significant stenosis were correctly identified resulting in a sensitivity and specificity of 81 and 73% respectively and a diagnostic accuracy of 77%.	Single slice was evaluated. Patient population was highly selected.
Nagel et al. (2003)	Assessed the value of MRI for the noninvasive detection of CAD in patients with suspected CAD (vs. angiography).	84 consecutive patients.	Prevalence of CAD was 51%. Sensitivity 88%, specificity 90% and accuracy 89%.	Large exclusion criteria – decreases generalizability of results. Rapid diffusion of the contrast agent into the extracellular space. Intravascular contrast agents that are currently under development may aid analysis. Perfusion reserve indices that were calculated versus true alterations of flow will require assessment. The inner 10% and outer 30% of the myocardium were excluded from the analysis. A retrospective analysis was used to generate the ROC curves. There may be a difference when prospectively applying a reported cutoff value.

Table 3. Comparison of Interobserver Agreement (Kappa Statistic) Among Studies.

Study	Kappa (κ)
Wahba et al. (2003)	Segmental wall motion scores by gated SPECT and MRI were identical in 229 of 273 segments, k=0.72, p<0.001. For patients with MI, k=0.66 (no p value provided) or without MI, k=0.81 (no p value provided). Segmental wall thickening scores by gated SPECT and MRI yielded k=0.77, p<0.001. For patients with MI, k=0.70 and for patients without MI, k=0.86 (no p values provided). Segmental wall motion and thickening scores between gated SPECT and MRI for segments with normal or mild to moderate hypoperfusion produced k=0.80 (p<0.001), and k=0.84 (p<0.001) respectively. For segments with severe hypoperfusion k=0.45 (p<0.001) or no perfusion, k=0.57 (p<0.001).
Gunning et al. (1998)	Agreement for scoring tracer uptake was k=0.77; for MR wall motion k=0.54, thickening k=0.41, and thickness k=0.41.
Kramer et al. (2002)	Agreement for functional improvement at 8 weeks post-MI between the techniques yielded a kappa=0.52 (p<0.001).
Gunning et al. (1997)	The segmental agreement (kappa) between SPECT and MRI for the whole study group was 0.66 for wall motion, 0.62 for thickening, and 0.55 for thickness. For patients with normal regional function in all myocardial segments (n=90) kappa values were 1.0, 1.0, and 1.0 respectively. For patients with LVEF>35% having abnormal regional function in one or more segments the kappa values were 0.54, 0.39 and 0.34 respectively. For patients with LVEF<35% having abnormal regional function in one or more segments, the kappa values were 0.48, 0.41 and 0.37 respectively. Subgroups were defined according to the uptake of the SPECT tracer. However, with decreasing tracer uptake, agreement became poorer and agreement for wall thickness was generally worse than for the other 2 categories. For tracer uptake grade 3 (normal) kappas were 0.75 (motion), 0.74 (thickening), and 0.64 (thickness). For uptake grade 2 (mild reduction) kappa values were 0.61, 0.60 and 0.45 respectively. For uptake grade 1 (moderate reduction) kappa values were 0.44, 0.34, and 0.31. Lastly, for uptake grade 0 (severe reduction), kappa values were 0.61, 0.12 and 0).
Panting et al. (2001)	The rest and stress kappa values for visual MRI were 90% and 88%. The rest and kappa values for the parametric map analysis were: time to peak (88% and 63%); peak (94% and 91%); and slope (91% and 93%). However, the segmental agreement of perfusion severity was very poor. The kappa values for visual rest and stress MRI were 31% and 49% respectively. Rest and stress kappa values for the parametric map analysis were: time to peak (9% and 20%); peak (26% and 51%); and slope (27% and 49%).

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