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CONSENSUS PANEL REPORT

Clinical Indications for Cardiovascular Magnetic Resonance (CMR): Consensus Panel Report[#]

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INTRODUCTION

Cardiovascular magnetic resonance (CMR) is established in clinical practice for the diagnosis and management of diseases of the cardiovascular system. However, current guidelines for when this technique should be em ployed in clinical practice have not been revised since a Task Force report of 1998 (Sechtem et al., 1998). Considerable technical and practice advances have been made in the intervening years and the level of interest from clinicians in this field is at an unprecedented level. Therefore the aim of this report from a Consensus Panel of established experts in the field of CMR is to update these guidelines. As CMR is a multidisciplinary technique with international interest, the Consensus Panel was composed of European and American cardiologists and radiologists with major input from members with additional established expertise in paediatric cardiology, nuclear cardiology, magnetic resonance physics and spectroscopy, as well as health economics. The Consensus Panel was originated, approved and funded in its activities by the Working Group on CMR of the European Society of Cardiology and the Society for Cardiovascular Magnetic Resonance.

The Consensus Panel recommendations are based on evidence compiled from the literature and expert experience. If there is insufficient evidence in the literature, this is indicated in the report but usually no recommendations are made under these circumstances. The appropriateness of using CMR is described for the frequent disease entities where imaging information may be warranted. The diagnostic use of CMR will be described in the context of other, competing imaging techniques, with particular emphasis on the differential indications with respect to echocardiography.

The usefulness of CMR in specific diseases is summarized by means of the following classification:

Class I = provides clinically relevant information and is usually appropriate; may be used as first line imaging technique; usually supported by substantial literature.

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Class II = provides clinically relevant information and is frequently useful; other techniques may provide similar information; supported by limited literature.
Class III = provides clinically relevant information but is infrequently used because information from other imaging techniques is usually adequate.
Class Inv = potentially useful, but still investigational.

This classification is not meant to equate to AHA/ ACC/ESC consensus documents. We have used the classification system that was used for the first consensus report (Sechtem et al., 1998), with minor amendments in order to maintain parity with that report so that advances in the field can be readily identified. It should also be noted that the classification system for imaging technologies does not easily marry with that of therapeutic trials because the datasets are smaller, multi-centre trials are unusual and randomized controlled trials the exception. In addition, the experience worldwide with the clinical applica tions of CMR is still limited.

It should also be noted that this consensus report reflects opinion at the start of 2004. The rapidly continuing technical and clinical advances in CMR will change the indication's tables. Between formal reports, the consensus panel may post updates on the ESC CMR Working Group or SCMR websites.

OUTLINE OF CMR TECHNIQUES

A brief description of the technical aspects of CMR is included here to facilitate understanding of the technical terms used in the clinical part of this report. It is necessarily brief and fuller texts give much greater detail (Higgins and de Roos, 2003; Manning and Pennell, 2002). A key point to understanding clinical CMR is that the interaction required for clinical imaging is at the level of the nucleus, which means that CMR is fundamentally safe and does not interfere with the electron shells involved in chemical binding (particularly in DNA) that can be altered by ionizing radiation such as X-rays. Only atomic nuclei with unpaired spin can exhibit the phenomenon of magnetic resonance as first described in 1946. Although this includes important elements such as carbon, oxygen, sodium, potassium and fluorine, these elements are rarely used for imaging in clinical practice. Phosphorus is used for clinical CMR spectroscopy, but the majority of clinical CMR interrogates the hydrogen nucleus which is abundant in water, fat and other biochemical compounds in the human body.

The hydrogen nucleus (a single proton), behaves as a small spinning magnet which aligns itself parallel to an external magnetic field and precesses about the field in the same way that a spinning top precesses in a gravitational field. The frequency of precession is 63 MHz for a field strength of 1.5 Tesla which is in the radiofrequency range. The ensemble of nuclei in a body region can be excited by radiowaves only at this resonant frequency, which has the effect of rotating the net magnetisation vector by an amount termed the *flip angle*. After this excitation, the net magnetization vector precesses around the direction of the main field, returning to its former position (*relaxation*). Whilst there is a component of magnetization perpendicular to the applied magnetic field, energy is transmitted as a radio signal and this can be received by a receiver coil placed over the chest. The return of the net magnetisation vector to equilibrium has two components: The vector component parallel to the main field returns to equilibrium by interacting with surrounding molecules which is a relatively slow process and is known as *T1 relaxation*. The vector component transverse to the field is more rapid and results from interaction between individual spins, and is termed *T2 relaxation*. CMR images can be weighted to show the distribution of T1 or T2, or just the density of protons. In order to localize the signals coming from the body, additional magnetic fields are required which are switched on and off at appropriate times; these are termed *gradient fields*. An MR image therefore simply represents the spatially resolved signal coming from the relaxing spins.

A CMR *scanner* has six major components. The *magnet*, which is usually superconducting, produces the static magnetic field whose strength is measured in Tesla. This field needs to be homogeneous and stable with time, and yet large enough to contain a human body. Resistive gradient coils within the bore of the magnet produce the gradient fields, and the currents within these coils are driven by the *gradient amplifiers*. The performance of the gradient system determines how fast magnetic resonance acquisition can be. A *radiofrequency coil* (antenna) is coupled to a *radiofrequency amplifier* to excite the patient with the radiofrequency pulses, and this (or another more localized surface coil) is coupled to the receiver to measure the signals coming from the patient. A *computer* is required to control the scanner and generate the images. Images are then displayed in static, dynamic (cine) modes or as multi-planar reconstructions.

An MR *pulse sequence* is a combination of radiofrequency pulses and magnetic gradient field switches, and can be considered as an orchestral score with multiple aspects of the scanner acting in concert and control led by the scanning computer. For CMR, *spin* *echo, gradient echo, steady state free precession* (SSFP) and *echo-planar imaging* (EPI) sequences are the most commonly used for the signal read-out. Spin echo sequences are routinely used for multi-slice anatomical imaging and rapidly moving blood is typically displayed as black, whilst gradient echo and SSFP sequences are used for physiological assessment of function through cine acquisitions, and blood is typically white. Pre-pulses may be added to sequences and these may change the contrast appearances. For example, an *inversion recovery* prepulse is typically used for infarct/viability imaging, where myocardium is nulled to be black, infarct is white and blood is an intermediate grey. With modern scanners, many sequences are now performed during a 4–20 s breath-hold. This reduces image artefacts from respiratory motion. ECG gating is required for most CMR in order to coordinate the acquisition to the correct phases of the cardiac cycle.

Some specialized sequences exist which have particular application for the cardiovascular system. CMR angiography (MRA) is usually performed with three dimensional (3D) coverage of the vessel during a short breath-hold and after intravenous injection of a *gadolinium*-based contrast agent. Gadolinium has seven unpaired electrons in its outer shell which hastens T1 relaxation, and usually thereby increases the signal in the area of interest. Non-contrast MR angiographic techniques are also sometimes used. Myocardial perfusion CMR follows the effect of a first pass of a bolus of intravenous gadolinium through multiple planes of the myocardium using ultrafast sequences such as Fast Low Angle Shot (*FLASH*), EPI or SSFP which can allow entire images to be acquired in <200 ms. For coronary CMR, some high resolution acquisitions cannot be completed within a breath-hold, and respiratory motion is reduced by using a *navigator*, whereby the diaphragm (or other interface) is monitored in real-time. In order to study regional myocardial contraction, a sequence called *tagging* may be used, which superimposes a grid of dark lines across the image in diastole. These tags subsequently deform through the cardiac cycle allowing the calculation of regional myocardial strain. Finally, velocity *mapping* is a sequence used to measure velocity and flow in blood vessels or within the heart somewhat analogous to Doppler echocardiography, in which each pixel in the image displays the phase of the radiofrequency signal rather than its magnitude. The signal phase is encoded for velocity, and flow is calculated from the product of mean velocity and the vessel area measured throughout the cardiac cycle.

CMR is very safe and no long-term ill effects have been demonstrated. Claustrophobia may be problematic in about 2% of patients, but mild anxiolysis is often effective (Francis and Pennell, 2000). One of the most important safety issues for CMR is the prevention of introduction into the scanner area of ferromagnetic objects which can become projectiles. Metallic implants such as hip prostheses, prosthetic heart valves, coronary stents and sternal sutures present no hazard since the materials used are not ferromagnetic (although an artefact local to the implant may be present). Care is required in patients with many cerebrovascular clips however, and specialist advice is needed for such patients. Patients with pacemakers, implanted cardioverter defibrillators (ICD), retained permanent pacemaker leads and other electronic implants are not scanned, although some reports of success do exist (Martin et al., 2004), and there is progress towards manufacture of CMR-compatible devices.

CONGENITAL HEART DISEASE

General Aspects

Evaluation of patients with congenital heart disease (CHD) is a significant strength of CMR because 3D contiguous data sets are very effective for the complete depiction of the pathological anatomy of both simple and complex CHD. Moreover, the lack of ionizing radiation is an important consideration when performing sequential studies in children and young adults. However, the clinical use of CMR depends on the age and the clinical condition of the patient. Sedation is required in small children and monitoring is demanding in critically-ill infants. Thus, CMR is usually performed following, and as an adjunct to, transthoracic echocardiography in neonates and infants. In contrast, CMR becomes the first line technique when in older children, in adolescents or adults, in more complex anatomy, or at any age after surgery because body habitus and interposition of scar tissue and lungs become an increasing problem for transthoracic echocardiography (Hirsch et al., 1994; Hoppe et al., 1996). The need for and duration and risks of diagnostic catheterisation can be minimised by prior use of CMR (Geva et al., 1994; Hirsch et al., 1994). Thus, diagnostic catheterisation is likely to become a one stage process with concurrent interventional procedures. Precise depiction of cardiac and arterial/venous great vessel anatomy using CMR should also decrease the duration and radiation dose associated with interventional procedures. In recent years, dual X-ray/CMR facilities have been proposed for more efficient diagnostic and interventional procedures during a single anaesthesia session (Razavi et al., 2003).

Expertise in CMR is highly recommended in centres specialised in the care of patients with congenital heart disease (Hirsch et al., 1994).

CMR techniques are generally less operator dependent than echocardiography, but a thorough understanding of the anatomic and functional principles of CHD is nevertheless required for a reliable study. This requires experience and training guidelines have been published (Pohost et al., 2000). All parts of the cardiovascular system can be imaged, a feature which makes a CMR evaluation especially useful in complex cases. For a complete CMR examination, the following sequences should be performed:

1. Anatomical images in the transaxial and at least one additional orthogonal plane (sagittal or coronal depending on the case). For thoracic aortic anomalies, additional oblique sections are acquired. Usually these are spin echo acquisitions.
2. Functional information with SSFP sequences in contiguous short axis planes for the evaluation of biventricular function, volumes, and mass.
3. When clinically indicated, measurements of velocity and flow volume in the heart and great vessels/conduits.
4. Gadolinium-enhanced MRA for 3D representation of the thoracic aorta, pulmonary arteries, and veins. For specific indications, it may also be employed for the 3D display of complex cardiovascular anatomy.

CMR may be used in the following specific congenital anomalies (see Table 1):

1. *Anomalies of the viscero-atrial situs*. The viscero-atrial situs (situs solitus, inversus, ambiguus) and malposition of the heart (dextrocardia, levocardia) are easily identified by conventional diagnostic methods. However, in the presence of additional lesions (atrio ventricular or ventriculoarterial discordance, anomalous pulmonary or systemic venous connections) difficulties may arise in the definition of the topographic relation of the major cardiac segments. CMR provides anatomical data which is easily related to the surrounding structures of the body (Geva et al., 1994), and thus provides reliable diagnoses with a sensitivity approaching 100% (Kersting-Sommerhoff et al., 1990a). In patients with complex anomalies, especially in older patients, CMR may be the primary imaging technique so as to maximise non-invasive information prior to catheterisation.

Table 1. Indications for CMR in congenital heart disease.

Indication	Class
General indications	
1. Initial evaluation and follow-up of adult congenital heart disease	I
Specific indications	
1. Assessment of shunt size (Qp/Qs)	I
2. Anomalies of the viscero-atrial situs	
Isolated situs anomalies	II
Situs anomalies with complex congenital heart disease	I
3. Anomalies of the atria and venous return	
Atrial septal defect (secundum and primum)	II
Anomalous pulmonary venous return, especially in complex anomalies and cor triatriatum	I
Anomalous systemic venous return	I
Systemic or pulmonary venous obstruction following intra-atrial baffle repair or orrection of anomalous pulmonary venous return	I
4. Anomalies of the atrioventricular valves	
Anatomic anomalies of the mitral and tricuspid valves	II
Functional valvular anomalies	II
Ebstein's anomaly	II
Atrioventricular septal defect	II
5. Anomalies of the ventricles	
Isolated ventricular septal defect	III
VSD associated with complex anomalies	I
Ventricular aneurysms and diverticula	II
Supracristal VSD	I
Evaluation of right and left ventricular volumes, mass and function	I
6. Anomalies of the semilunar valves	
Isolated valvular pulmonary stenosis and valvular dysplasia	III
Supravalvular pulmonary stenosis	II
Pulmonary regurgitation	I
Isolated valvular aortic stenosis	III
Subaortic stenosis	III
Supravalvular aortic stenosis	I
7. Anomalies of the arteries	
Malpositions of the great arteries	II
Post-operative follow-up of shunts	I
Aortic (sinus Valsalva) aneurysm	I
Aortic coarctation	I
Vascular rings	I
Patent ductus arteriosus	III
Aortopulmonary window	I
Coronary artery anomalies in infants	Inv
Anomalous origin of coronary arteries in adults and children	I
Pulmonary atresia	I
Central pulmonary stenosis	I
Peripheral pulmonary stenosis	Inv
Systemic to pulmonary collaterals	I

2. *Anomalies of the atria and venous anomalies*. CMR may be valuable in the assessment and identification of atrial septal defects. Quantification of shunt size (pulmonary to systemic flow ratio) by CMR compares favourably to other imaging techniques and should be considered a primary method (Hundley et al., 1995a). The best technique for assessing the interatrial septal morphology is transesophageal echocardiography (TEE) (Taylor et al., 1999). In infants, CMR may be used as a second line technique following transthoracic echocardiography. A drawback of echocardiography is the difficulty of evaluating anomalous pulmonary venous return. CMR appears to be the best non-invasive technique for the evaluation of pulmonary veins (Greil et al., 2002a; Valsangiacomo et al., 2003), as complete and selective demon stration may not be achieved by echocardiography or X-ray angiocardiography (Prasad et al., 2004). CMR may also be indicated to identify partial anomalous venous return in patients with atrial septal defects (White et al., 1997). CMR may identify atrial septal defect (ASD) or partial anomalous pulmonary venous connection in adults with right-sided chamber enlargement, hypertrophy or dysfunction of unknown aetiology. CMR may be particularly useful for demonstrating pulmonary venous stenoses or occlusions postoperatively, or after ablation (Dill et al., 2003). It is effective for demonstrating stenoses of intra-atrial baffles after repair of transposition of the great arteries (Chung et al., 1988). Moreover, systemic venous anomalies (bilateral superior cava, interrupted inferior cava) are correctly identified by CMR (Kersting-Sommerhoff et al., 1989).
3. *Anomalies of the atrioventricular connections*. CMR is an excellent technique for defining the morphologic features of each atrium and ventricle (Geva et al., 1994). Consequently, it can demonstrate discordant atrioventricular connections and crisscross atrioventricular connections (Araoz et al., 2002). CMR is also indicated for demonstrating double inlet ventricle (Yoo et al., 1999), straddling atrioventricular valve, tricuspid atresia, and mitral atresia. Echocardiography is usually employed initially for these abnormalities and CMR is used to supplement this information. CMR is superior to echocardiography for quantifying ventricular volumes in these abnormalities which may be critical for surgical decisions regarding biventricular repair versus the Fontan procedure.
4. *Anomalies of the ventricles*. CMR is highly sensitive and specific for the quantification and detection of ventricular septal defects (Didier and Higgins, 1986; Mirowitz et al., 1989), and detection and localisation of jets is helpful (Sechtem et al., 1987b). However, CMR may add little anatomical information in isolated ventricular septal defect when the diagnosis is already established by echocardiography, except that CMR can readily quantify shunt volume (Hundley et al., 1995a). This may become more relevant if clinicians come to rely on noninvasive diagnostic information prior to surgery. CMR has an important role in depicting ventricular anatomy in complex anomalies such as in tetralogy of Fallot, pulmonary atresia, tricuspid atresia, and univentricular hearts (Kersting-Sommerhoff et al., 1990b; Razavi et al., 2003). CMR can precisely depict the location of the ventricular septal defect in relation to the great arteries in double outlet ventricles (Mayo et al., 1990). CMR is the most accurate technique for quantifying left and right ventricular mass and volumes.
5. *Valves*. Echocardiography is the primary imaging modality for defining valve morphology, and estimating valvular regurgitation. However, CMR velocity mapping can quantify the severity of regurgitation in many cases, and this is valuable for sequential monitoring of the severity of pulmonary regurgitation after outflow patch surgery for tetralogy of Fallot (Rebergen et al., 1993a), and after placement of RV to pulmonary artery conduits (Holmqvist et al., 1999). Thus, CMR may be useful for decision making on valve replacement. CMR has also been shown to be effective for the morphologic depiction of tricuspid atresia and Ebstein's anomaly (Link et al., 1988). Moreover, it can provide a precise RV volumetric and functional assessment in these anomalies (Choi et al., 1994).
6. *Anomalies of the great arteries and conduits*. CMR is very effective for the evaluation of anomalies of the thoracic aorta. Although 2D echocardiography with Doppler is usually sufficient to diagnose and estimate the haemodynamic severity of coarctation of the aorta in infants, difficulties may be encountered in older children or adults. Under these circumstances

the severity and extent of stenosis including diffuse narrowing of the aortic arch, the collateral circulation as well as the shape and size of the ascending aorta can be demonstrated by CMR. Velocity mapping can estimate the pressure gradient across the coarctation and the volume of collateral flow (Mohiaddin et al., 1993; Steffens et al., 1994). Thus, CMR is now regarded as the optimal modality for the evaluation of coarctation of the aorta. CMR is also the procedure of choice for evaluation of coarctation after surgery or angioplasty (Bogaert et al., 2000; Rees et al., 1989b; Simpson et al., 1988). CMR is also useful for the evaluation of sinus of Valsalva aneurysm, aortic dilatation, aneurysm associated with Marfan and Ehler–Danlos syndromes, and in the general monitoring of aortic dimensions over time. CMR is the procedure of choice for the diagnosis of aortic arch anomalies (vascular rings) (Jaffe, 1990; Kersting-Sommerhoff et al., 1987). In infants, visualisation of a patent ductus arteriosus is commonly achieved by echo cardiography. CMR has a role in older patients and is often better suited to depict the lesion (Bijl et al., 1993). In patients, in whom an aortopulmonary window is suspected, CMR may be helpful to establish the differential diagnosis or demonstrate the additional defect.

CMR is also valuable in the visualisation of the pulmonary artery and its main branches, which is essential in the surgical management of patients with diminished pulmonary artery blood flow. Echocardiography may often be limited due to reflection of the ultrasound by the chest wall and lungs. Angiocardiography can be dangerous in cyanotic children, as very small pulmonary arteries may be difficult to catheterise and non-confluent vessels may not be seen even with pulmonary venous wedge X-ray angiography. The blood supply to the lungs in patients with tetralogy of Fallot and pulmonary atresia is well defined by CMR (Gomes et al., 1990; Julsrud et al., 1989; Kersting-Sommerhoff et al., 1988; Vick et al., 1990). MRA is the most effective non-invasive technique for demonstrating systemic to pulmonary collateral vessels (Geva et al., 2002). MRA is also indicated for demonstrating the status of the pulmonary vessel after shunt (Rebergen et al., 1993b), or unifocalization procedures. Both before and after surgery, CMR, especially 3D gadolinium MRA, is indicated for demonstrating stenoses of the central (Greenberg et al., 1997), and segmental pulmonary arteries (Kondo et al., 2001). The severity of stenoses of the central pulmonary arteries can be estimated using velocity mapping to measure flow separately in the right and left pulmonary arteries.

CMR is valuable to assess the patency of systemic-to pulmonary shunts and extracardiac conduits (Canter et al., 1989; Canter et al., 1991; Gomes et al., 1990; Jacobstein et al., 1984). Patients with extracardiac ventriculopulmonary shunts often experience graft degeneration and echocardiographic imaging is difficult due to the retrosternal position of the graft. CMR provides accurate anatomic and functional information and is the technique of choice for following these patients (Martinez et al., 1992).

7. *Post-operative CHD*. Echocardiography is usually employed for the serial evaluation of most CHD patients after transcatheter or surgical treatment. The sequential monitoring of ventricular dimensions and function is important during follow-up. CMR provides more precise and reproducible quantification of ventricular volumes, mass and function than 2D echocar diography (Grothues et al., 2002; Helbing et al., 1995a). This is especially the case for the RV (Grothues et al., 2004), which is usually the chamber implicated in and stressed by repair of CHD (Holmqvist et al., 1999; Roest et al., 2002). Sequential measurements of RV volumes, mass and function are important for post-operative management after intraatrial repair of transposition and repair of tetralogy of Fallot (Niezen et al., 1996), and other abnormalities requiring pulmonary transannular patch or conduit insertion. The consequences of pulmonary regurgitation on RV and left ventricular (LV) function can be comprehensively evaluated by the combined use of volume measurements and assessment of diastolic ventricular function by velocity mapping CMR (Helbing et al., 1996). This unique information may have prognostic and therapeutic implications for the management of patients with (repaired) CHD. Pulmonary blood flow and regurgitant volume can also be measured in the presence of some stents (Kuehne et al., 2001). CMR is indicated for evaluation of the morphology and function after repair of complex congenital heart disease and during the stages of various surgical repairs, such as those used for hypoplastic left heart syndrome (Kondo et al., 1991b), and single ventricle (Fogel et al., 1996).

8. *Adult CHD*. CMR and TEE are complementary for the evaluation of adult CHD (Hirsch et al., 1994) The limited field of view and sometimes inadequate acoustic window renders echocardiography less effective in adults. Compared to echocardiography, CMR tends to be better for the evaluation of the morphology of abnormalities of the aorta, pulmonary arteries, and pulmonary veins and for quantification of RV function and blood flow. It is also indicated when the quality of echocardiographic images is limited and interpretation is ambiguous.
9. *Coronary artery anomalies*. CMR is useful in defining congenital or inflammatory changes of the coronary arteries as in Bland-White-Garland syndrome (Rees et al., 1989a), and Kawasaki disease (Duerinckx et al., 1997; Greil et al., 2002b; Niwa et al., 1990). Congenital abnormalities in the course of the proximal coronary arteries can be reliably depicted by CMR both in patients with CHD (prevalence of 30% in CHD) (Taylor et al., 2000), and especially tetralogy of Fallot (Felmeden et al., 2000; Li et al., 1998), and also in those with otherwise normal cardiac anatomy (1% of the general population) (Bunce et al., 2003; McConnell et al., 1995; Post et al., 1995). CMR has advantages over X-ray angiography in clarifying the spatial relationship of these arteries with respect to the aorta and the pulmonary artery, which is crucial for estimating the risk associated with these abnormalities and for surgical planning.

ACQUIRED VASCULAR DISEASE

CMR is well-established for evaluation of a wide variety of acquired vascular diseases. CMR is particularly useful for vascular lumen imaging with its ability to generate projection angiograms (MRA). These can be generated either with time-of-flight techniques, or with intravenous gadolinium, which has similar pharmacokinetic properties to iodinated X-ray contrast but with the advantage of minimal nephrotoxicity. Consequently, it is well-suited for use in patients with contraindications to X-ray contrast (allergy, renal insufficiency). In addition to angiography, the wide variety of soft tissue contrast available on CMR (proton density, T1, T2, lipid-saturation) can be applied to vascular imaging to assess features of vessel wall such as haematoma/thrombus, inflammation, and atherosclerotic plaque. In addition to morphologic imaging of blood vessels, velocity mapping can be used to assess and measure the blood flow. Blood velocity and flow can be integrated across the cardiac cycle and the vessel lumen for reliable volume flow measurements (see Table 2).

Table 2. Indications for CMR in acquired diseases of the vessels.

Indication	Class
1. Diagnosis and follow-up of thoracic aortic aneurysm including Marfan disease	I
2. Diagnosis and planning of stent treatment for abdominal aortic aneurysm	II
3. Aortic dissection	
Diagnosis of acute aortic dissection	II
Diagnosis and follow-up of chronic aortic dissection	I
4. Diagnosis of aortic intramural haemorrhage	I
5. Diagnosis of penetrating ulcers of the aorta	I
6. Pulmonary artery anatomy and flow	I
7. Pulmonary emboli	
Diagnosis of central pulmonary emboli	III
Diagnosis of peripheral pulmonary emboli	Inv
8. Assessment of thoracic, abdominal and pelvic veins	I
9. Assessment of leg veins	II
10. Assessment of renal arteries	I
11. Assessment of mesenteric arteries	II
12. Assessment of iliac, femoral and lower leg arteries	I
13. Assessment of thoracic great vessel origins	I
14. Assessment of cervical carotid arteries	I
15. Assessment of atherosclerotic plaque in carotid artery/aorta	III
16. Assessment of pulmonary veins	I
17. Endothelial function	Inv

AORTA

For the thoracic and abdominal aorta, CMR accurately displays the size, extent, and shape of aneurysms (Lutz et al., 2003). Multi-planar imaging is helpful in tortuous segments to evaluate and follow cross-sectional diameters and areas as well as to assess the relationship of the aneurysm to major branch vessels. Both black-blood and white-blood imaging can be used to differentiate patent lumen from intraluminal thrombus (Castrucci et al., 1995). Gadolinium MRA is a necessary adjunct for visualizing any associated branch-vessel occlusive disease or relationship of the aneurysm to smaller vessels (Meaney et al., 1997).

Flow-sensitive imaging cannot be relied upon in the setting of aneurysmal disease due to the stagnant flow patterns that may be present and gadolinium MRA is more robust. Post-gadolinium T1-weighted CMR, especially with fat saturation, is helpful in identifying areas of peri-aortic inflammation in mycotic aneurysms (Akins et al., 1991; Engellau et al., 1998; Mosca et al., 2000). Inflammatory abdominal aortic aneurysms can have a thick rind of tissue encircling the anterior and lateral aspects of the aorta, which typically enhances with gadolinium (Anbarasu et al., 2002). Although not as widely used as CT for pre and post-operative evaluation of aortic stent-grafts, CMR provides comparable information with regard to pre-stent anatomy and post-stent leaks (Cejna et al., 2002). The only limitation of CMR in this setting is its inability to visualize calcium, which is important for stent graft planning. For this purpose, it can be supplemented with non-contrast computed tomography (CT).

Aortic dissection is a well-established indication for CMR, and accuracy is very high (Cesare et al., 2000; Nienaber et al., 1993; Sommer et al., 1996). With increasing ability to monitor acutely ill patients in the CMR suite combined with advances in imaging speed, CMR is competitive with CT for speed of diagnosis of aortic dissection (Pereles et al., 2002). However, scanner availability and location may limit the utility of CMR in the acute setting. The intimal flap can be demonstrated and staging with regard to involvement of the ascending aorta and branch vessel involvement can be made (Cesare et al., 2000). Gadolinium MRA is typically acquired in the aortic long-axis plane and reformatted into the axial plane for definition of the intimal flap and branch vessel involvement. Associated aortic regurgitation can be detected with cine gradient echo CMR and quantified using velocity mapping (Sondergaard et al., 1993). Pericardial fluid is also easily identified and characterised (Tscholakoff et al., 1987). CMR is ideal for measuring aortic diameter and intimal flaps in the chronic setting, making it ideal for evaluation and follow-up of patients following surgery (Deutsch et al., 1994), and those with Marfan's syndrome (Kawamoto et al., 1997). Compared with CT, CMR avoids radiation exposure, an especially important consideration in children. When compared with transthoracic echocardiography, CMR should be considered as the first line technique in Marfan's syndrome for imaging the aorta, because CMR is capable of visualising its entire length.

Intramural haematoma is a variant of dissection, where the false channel in the aortic wall is filled with thrombus. Dissections can include segments of both patent false lumen and intramural haematoma in the same patient, depending on the location of intimal tears, pressure in the false lumen and stage of dissection development (Fattori and Nienaber, 1999). Flow-sensitive techniques are less accurate for the diagnosis of intramural haematoma (Murray et al., 1997), and more use ful is spin echo imaging with T1 weighting which can detect red cell breakdown products (methaemoglobin) as a bright signal within the aortic wall in the acute and subacute stages. The use of fat saturation is helpful for distinguishing haematoma within the aortic wall from the surrounding mediastinal fat (Ionescu et al., 1998). Penetrating ulcers are a form of dissection where there is intimal erosion with either ulceration extending into the media and/or focal intramural haemorrhage (Hayashi et al., 2000). Penetrating aortic ulcer is associated with more extensive atherosclerosis, ectasia, older age but less severe hypertension than typical aortic dissection. CMR shows focal ulcerated atherosclerotic plaque on gadolinium MRA, and/or focal intramural haematoma, best seen on T1-weighted images with fat saturation (Yucel et al., 1990). Ulceration may also be seen as an incidental, benign finding in asymptomatic elderly patients with no or atypical symptoms and is not a cause for concern (Troxler et al., 2001).

There has been recent interest in the use of CMR for the detection of potentially embologenic aortic plaque (Tunick and Kronzon, 2000). Both gradient echo or double inversion-recovery black-blood scans define aortic plaque and can monitor progression (Helft et al., 2002). There is good correlation between TEE and double inversion-recovery black-blood CMR for aortic plaque characterisation and thickness (Fayad et al., 2000b). A potential limitation of CMR is the identification of highly mobile plaques, which may move asynchronously with the cardiac cycle. The real-time feature of echocardiography may be advantageous for fully characterizing plaque mobility. On the other hand, CMR may be superior to echocardiography for detecting plaques in the aortic arch. CMR may be able to replace the more invasive TEE for this application if confirmed in larger studies.

PULMONARY ARTERIES

The most common acquired disease of the pulmonary arteries is pulmonary embolism. Promising results have been obtained in several small series using gadolinium MRA (Goyen et al., 2001; Oudkerk et al., 2002). However, these scans currently require prolonged breath-holds which may be difficult to reliably achieve in this population. For this reason, as well as improved spatial resolution and access, CT remains the study of choice at many centres. MRA may be useful in patients with contraindications to X-ray contrast. Although rarer, pulmonary artery aneurysms (Ugolini et al., 1999) and dissections (Stern et al., 1992) can also be evaluated by CMR.

EXTREMITIES

The primary indication for CMR of the lower extremities is assessment of suspected atherosclerotic occlusive disease. While time-of-flight imaging is well-validated for imaging of the tibial and pedal vessels (Owen et al., 1992), it has been supplanted by 3D gadolinium MRA for inflow (aorta, iliac, femoral, popliteal) evaluation (Ruehm et al., 2001b). Imaging of the tibial vessels using the bolus-chase approach may be compromised by venous contamination. One straightforward solution to this problem is to image the calves with an initial injection, followed by two-station bolus-chase of the pelvic and thighs. The pedal vessels can also be imaged with gadolinium MRA, although it may be difficult to integrate a dedicated pedal contrast-enhanced scan into a full lower extremity study due to contrast limitations (Dorweiler et al., 2002). For limb-threatening ischaemia, gadolinium MRA has been validated for the evaluation and pre-interventional planning of peripheral occlusive disease (Leyendecker et al., 1998). CMR may also be used to identify patients who may be suitable for directed endovascular interventions. There has been much less experience with imaging of the upper extremity. Gadolinium MRA works well for the great vessel origins from the aortic arch out to the axillary artery (Cosottini et al., 2000). Beyond that, time-of-flight imaging may be used with the arms positioned over the head. Gadolinium MRA has also been used for the vessels of the hand with promising results (Wentz et al., 2003).

RENAL AND MESENTERIC ARTERIES

Gadolinium MRA is the dominant approach for the renal and mesenteric vessels due to its reproducibility, ease of use, and efficacy (Leung et al., 2002; Mittal et al., 2001). Limitations include lower spatial resolution than X-ray angiography, which remains better for quantitative stenosis measurement as well as evaluation of branch vessels and small accessory vessels. For this reason, X-ray angiography may be preferred for renal donor evaluation. On the other hand, MRA may provide more information about venous anomalies, which may be important in patients undergoing laparoscopic nephrectomy. Adjunctive imaging with either time-of flight or phase-contrast imaging may be performed to provide additional imaging information about the renal arteries. In particular, dephasing effects seen at areas of stenosis using 2D MRA may provide qualitative information about the haemodynamic significance of lesions. CMR remains complementary to captopril renal scintigraphy and duplex Doppler evaluation of resistive index. The former provides a non-invasive arterial map, while the latter provides highly quantitative information about renal perfusion and function under conditions of stress. Several approaches to functional imaging with CMR have been described (Vallee et al., 2000); none have achieved the level of acceptance of nuclear medicine renal functional evaluation.

Published experience with mesenteric gadolinium MRA is limited. Experience suggests similar results as for renal angiography and gadolinium MRA provides excellent images of the proximal mesenteric vessels for screening for atherosclerotic occlusive disease (Hagspiel et al., 2002). Velocity mapping of the superior mesenteric artery and vein after a fatty meal challenge may be helpful for providing information about the functional significance of mesenteric occlusive disease. For more distal or detailed evaluation, X-ray angiography is currently still required.

EXTRACRANIAL CAROTID ARTERIES

Carotid CMR angiography using 3D time-of-flight is as accurate as X-ray angiography for measurement of internal carotid stenosis (Nederkoorn et al., 2002). Rapid screening of the carotid arteries for clinically significant occlusive disease can be performed using 2D time-of-flight MRA. Gadolinium MRA has been limited by the rapid jugular venous return which obscures the carotid bifurcation, but this can be improved by high temporal resolution imaging with lower spatial resolution during the arterial phase and high resolution with contrast encoding (centre of k-space) heavily weighted toward the start of the acquisition (elliptical centric). Published data has shown results with gadolinium MRA that is comparable to 3D time-of-flight MRA (Fellner et al., 2000). Advantages of gadolinium MRA include speed, improved coverage in the superior-inferior direction, including the arch origins, and higher sensitivity to slow flow in carotid pseudo-occlusion.

ARTERIAL WALL IMAGING

The arterial wall is affected with atherosclerosis long before clinical manifestations (Glagov et al., 1987), and this provides an opportunity for early detection of CAD prior to irreversible clinical consequences. Because atherosclerosis is a systemic disease, CMR can be used to image arteries outside of the heart such as the carotid and aorta (Fayad et al., 2000b; Shinnar et al., 1999; Yuan et al., 1998). Arterial wall CMR identifies the plaque burden and plaque constituents using a combination of T1, T2 and proton density weighted images (Cai et al., 2002; Coombs et al., 2001; Fayad and Fuster, 2000). This has allowed the imaging of the cholesterol pool component (Yuan et al., 2001), which is believed to significantly influence the likelihood of plaque rupture. In addition, the fibrous cap can be identified (Mitsumori et al., 2003), and thin or disrupted caps have been linked with cerebrovascular events (Yuan et al., 2002). Contrast agents have been used to further characterize plaque, show inflammation (Ruehm et al., 2001a; Schmitz et al., 2001), neovasculature (Kerwin et al., 2003), and the fibrous cap (Wasserman et al., 2002). Longitudinal study of the plaque by CMR has been used to gauge the effectiveness of anti-atheroma therapy such as statin treatment, showing reduction in plaque volume (Corti et al., 2001; Corti et al., 2002), and the lipid pool (Zhao et al., 2001). More recently, coronary wall CMR has been reported, and wall thickening and plaque constituents have been identified (Botnar et al., 2000; Botnar et al., 2001; Fayad et al., 2000a; Kim et al., 2002).

BRACHIAL ARTERY REACTIVITY

Endothelial function can be examined non-invasively with stimuli which cause arterial vasodilation. Flow mediated dilation is used to examine endothelial function directly, by occluding usually the forearm using a blood pressure cuff inflated above systolic pressure for a standard time period. On release of the cuff, reactive hyperaemia causes increased endothelial shear and the release of nitric oxide (NO) which causes the brachial artery to dilate. Endothelial independent responses can also be tested by using glyceryl trinitrate, typically as a sublingual spray. Visualisation of brachial dilation with these stimuli was first described using ultrasound (Celermajer et al., 1992), but it may be difficult to ensure that the transducer is correctly positioned perpendicular to the artery and without movement, and that repeated measurements are made with good reproducibility. CMR techniques are considered to have advantages in both these areas and comparisons of CMR and ultrasound for accuracy and reproducibility favour CMR (Sorenson et al., 2002). In addition to measuring brachial dilation, CMR can also measure flow changes directly in response to the standard stimuli (Mohiaddin et al., 2002; Silber et al., 2001).

CORONARY ARTERY DISEASE

CMR has opened new avenues for assessing coronary artery disease (CAD) and its consequences. It provides valuable information which may not be available from other diagnostic tools such as echocardiography and nuclear cardiology which currently dominate non-invasive diagnosis in patients with CAD (see Table 3).

ASSESSMENT OF VENTRICULAR FUNCTION AND MASS

CMR is accurate, reproducible and well validated for measuring LV and RV volumes and mass; this makes it valuable for the assessment of fundamental parameters of cardiac function as well as longitudinal follow-up of patients over time. The absolute accuracy of global LV volume measurements, with a 3D approach that has no geometric assumptions, has been established ex vivo (Longmore et al., 1985; Rehr et al., 1985). In vivo accuracy of LV volume measurements is more

Table 3. Indications for CMR in coronary artery disease.

Indication	Class
1. Assessment of global ventricular (left and right) function and mass	I
2. Detection of coronary artery disease	
Regional left ventricular function at rest and during dobutamine stress	II
Assessment of myocardial perfusion	II
Coronary MRA (CAD)	III
Coronary MRA (anomalies)	I
Coronary MRA of bypass graft patency	II
MR flow measurements in the coronary arteries	Inv
Arterial wall imaging	Inv
3. Acute and chronic myocardial infarction	
Detection and assessment	I
Myocardial viability	I
Ventricular septal defect	III
Mitral regurgitation (acute MI)	III
Ventricular thrombus	II
Acute coronary syndromes	Inv

difficult to prove, but validation work strongly suggests that CMR is accurate by 2 methods: First by showing equivalence in normal human subjects of the stroke volumes measured by the 3D contiguous slices approach of the LV and RV which must be equivalent in normals (Helbing et al., 1995b; Longmore et al., 1985; Sechtem et al., 1987c); and second by using flow mapping (Bryant et al., 1984; Firmin et al., 1987; Nayler et al., 1986), to show equivalence of LV stroke volume and aortic flow (Firmin et al., 1987; Kondo et al., 1991a). RV volumes have likewise been validated in vitro (Jauhainen et al., 1998), and in vivo (Helbing et al., 1995b). The accuracy of LV mass (Myerson et al., 2002a), has been established directly compared with autopsy hearts from humans (Bottini et al., 1995; Katz et al., 1988), and animals (Florentine et al., 1986; Keller et al., 1986; Lorenz et al., 1999; McDonald et al., 1993; Shapiro et al., 1989). The accuracy of RV mass measurements has also been established in ex vivo animal hearts (Bloomgarden et al., 1997; Katz et al., 1993; McDonald et al., 1992). Comparisons of CMR with echocardiography and scintigraphy are useful for guiding clinical interpretation, but are less useful for absolute validation because they show wide individual discrepancies in results compared with CMR because of their lower accuracy (Bellenger et al., 2000a).

The interstudy reproducibility of CMR-derived quantitative parameters of ventricular function and mass is excellent for both the LV (Bellenger et al., 2000b; Germain et al., 1992; Grothues et al., 2002; Mogelvang et al., 1993; Semelka et al., 1990a; Semelka et al., 1990b), and RV (Grothues et al., 2004), and has been shown to be considerably superior to 2D andm mode echocardiography (Bottini et al., 1995; Grothues et al., 2004). This allows the reduction of sample sizes in drug studies (Bellenger et al., 2000b; Mogelvang et al., 1993). Phase 2 trials and sub-studies in phase 3 trials are being conducted using CMR as primary endpoints (Bellenger et al., 2004; Osterziel et al., 1998). Regional contractile function is also well-assessed by CMR with visual inspection of cines or quantification of wall motion and thickening for both the RV (Johnson and Rubin, 1987; Suzuki et al., 1991), and LV (Azhari et al., 1990; Peshock et al., 1989; Sechtem et al., 1987d; Underwood et al., 1986). However, the CMR tagging technique permits the determination of the strain of the myocardium as a measure of contractility (Zerhouni et al., 1988), By monitoring the progressive distortion of the tags during the course of the cardiac cycle, regional ventricular strain myocardial rotational deformation, ventricular non-uniformity, and differences in endocardial and epicardial wall motion can be calculated (Buchalter et al., 1990). This can be fully resolved in 3D to cover the entire heart (Young and Axel, 1992). CMR tagging has been validated against invasive sonomicrometer studies (Lima et al., 1993), and has been used to discriminate infarcted from remote myocardium (Gotte et al., 2001).

DETECTION OF CORONARY ARTERY DISEASE

There are several approaches to detecting CAD using CMR. These include the visualization of the effects of induced ischaemia (wall motion, perfusion) and direct visualization of coronary arteries (coronary angiography and flow). Early detection of atherosclerosis and endothelial dysfunction is also possible (arterial wall imaging, brachial artery reactivity).

Stress Wall Motion Abnormalities

Physical exercise within the magnet leads to degradation of image quality from motion artefacts, and therefore pharmacologic stress is more commonly used. Dobutamine is ideal for this (Baer et al., 1994a; Baer et al., 1994b; Pennell et al., 1992; van Rugge et al., 1993), with superior results compared with dipyridamole (Baer et al., 1992; Baer et al., 1993; Casolo et al., 1991; Pennell et al., 1990; Zhao et al., 1997). Dobutamine stress CMR is well established as a technique for identifying ischaemia-induced wall motion abnormalities in CAD, with guidelines for clinical practice (Nagel et al., 2001). Breath-hold gradient echo or SSFP cines are used to examine regional wall function throughout the LV before and during stress. Diagnostic results are very good and direct comparison data with dobutamine stress echocardiography have shown superiority of CMR (Nagel et al., 1999a), due to higher quality imaging (Nagel et al., 1999b). Dobutamine stress CMR has been shown to be very effective in the diagnosis of CAD in patients who are unsuitable for dobutamine echocardiography (Hundley et al., 1999b). Quantification of LV wall motion and thickening using CMR using the centreline method may improve the accuracy for detection of patients with single vessel CAD (van Rugge et al., 1994). There is a low event rate when dobutamine CMR is normal (Hundley et al., 1999b; Hundley et al., 2002; Kuijpers et al., 2003), and a higher event rate in the presence of ischaemia (Hundley et al., 2002). CMR has also been used for pre-operative risk assessment (Rerkpattanapipat et al., 2002).

Other CMR techniques have been used to assess CAD during dobutamine. Tagging methods (Power et al., 1997; Scott et al., 1999) have shown increased sensitivity for diagnosis of CAD (Kuijpers et al., 2003). Objective analysis using tagging would be expected to reduce observer interpretation variability, which is well recorded for dobutamine stress echocardiography (Hoffmann et al., 1996), and application of this CMR technique in a large clinical trial is awaited. In the MR environment, the ECG is uninterpretable with regards to STT wave change. Real-time CMR may be used to monitor wall motion and may eliminate the need for breath-holding (Schalla et al., 2002). Diastolic function has been shown to be abnormal using dobutamine CMR in CAD (Karwatowski et al., 1994a; Karwatowski et al., 1994b), and parameters of global ventricular function such as flow acceleration are affected by dobutamine-induced ischaemia (Pennell et al., 1995). Further work is required to determine the clinical role of these techniques.

Myocardial Perfusion

Myocardial perfusion CMR now achieves comprehensive ventricular coverage using multi-slice imaging in contiguous short axis, or mixed short and long axis planes. An intravenous bolus of gadolinium contrast agent (up to 0.1 mmol/kg) is given usually in the antecubital fossa with a power injector to allow a fast and consistent injection rate (typically 5–7 mL/s). Ideally, imaging is performed on every ventricular plane with each cardiac cycle. Visual interpretation to identify dark areas of low perfusion may be performed, or the myocardial signal may be measured during the first pass for computer analysis. Quantification can be performed by measuring the upslope of myocardial signal increase and the plotting of colour parametric perfusion maps (Panting et al., 2001; Schwitter et al., 2001). More complex analysis includes respiratory motion correction (Yang et al., 1998), and deconvolution analysis allowing for the input function from the LV blood pool signal curve (Jerosch-Herold et al., 1998), in order to generate regional values for quantitative perfusion index and myocardial perfusion reserve. These techniques have been extensively reviewed (Kroll et al., 1996; Wilke et al., 1994), and validated in animal models (Epstein et al., 2002; Kraitchman et al., 1996; Wilke et al., 1993). In humans in vivo, validation against perfusion reserve and absolute blood flow by PET has been performed (Schwitter et al., 2001).

For clinical application, CMR perfusion is still in development, and two clinical scenarios are being tested. First, the simple approach of assessing stress myocardial perfusion only during vasodilation, and using late gadolinium enhancement to define areas of non-viability. Second, is the use of both stress and rest myocardial perfusion scans, which is more akin to conventional nuclear cardiology procedures, and has the benefit of allowing the generation of myocardial perfusion reserve measurements (Al-Saadi et al., 2000a; Cullen et al., 1999). In clinical studies for the detection of CAD, the results of myocardial perfusion CMR are very good in comparison with X-ray coronary angiography, (Panting et al., 2001; Schwitter et al., 2001; Wolff et al., 2004) PET (Schwitter et al., 2001), and SPECT (Panting et al., 2001). CMR has shown improvement in myocardial perfusion reserve after coronary angioplasty (Al-Saadi et al., 2000b), reduced perfusion in hypertrophic cardiomyopathy (Sipola et al., 2003), and impaired subendocardial perfusion in cardiac syndrome-X (Panting et al., 2002). A technique called T2* blood oxygen level dependent (BOLD) has also recently been described, which allows measurement of myocardial perfusion without the use of a contrast agent (Bauer et al., 1999; Beache et al., 2001; Wright et al., 2001; Wacker et al., 2003). The clinical role of the BOLD technique is promising (Friedrich et al., 2003), but not yet fully defined.

Coronary Angiography and Flow

MRA is used routinely for evaluation of the arteries and veins throughout the body, but coronary MRA is technically more difficult due to their small size, tortuosity, complex 3D anatomy, and near incessant cardiac and respiratory motion. Using 3D acquisitions and modern optimized sequences, both breath-hold (Wielopolski et al., 1998), and navigator techniques (Botnar et al., 1999), have been used. A multi-centre trial has shown 81% negative predictive value for the exclusion of multi-vessel proximal CAD (Kim et al., 2001). However, the current spatial resolution and residual motion during the acquisition period, restricts the assignment of diameter stenosis severity to broad categories, and distal vessel assessment of run-off for surgical planning is still problematic. The application of coronary MRA for the assessment of the course of anomalous coronary arteries is well established however, and is usually undertaken after X-ray angiography to ensure that the proximal portion does not have a malignant course between the aorta and pulmonary artery (Bunce et al., 2003; McConnell et al., 1995; Post et al., 1995; Taylor et al., 2000). A different approach to detecting CAD by CMR is the noninvasive measurement of coronary flow velocities (Hofman et al., 1995; Keegan et al., 1994).

Determination of coronary flow by CMR at rest and after adenosine has been reported in animals (Clarke et al., 1995), and in humans (Davis et al., 1997; Hundley et al., 1996; Sakuma et al., 1996). The use of coronary flow reserve in humans has been reported for identifying stenosis of the left anterior descending artery (Hundley et al., 1999a), and in stent restenosis (Nagel et al., 2003).

CMR sequences can also be used to image coronary vein grafts. Both spin echo (Gomes et al., 1987; Jenkins et al., 1988), and gradient echo imaging (Aurigemma et al., 1989; White et al., 1987), yield accuracies in predicting graft patency of around 90%. This may prove useful in early post-operative chest pain syndromes in order to exclude graft occlusion. Bypass graft flow has proved useful in identifying diseased vein grafts through reduced baseline flow and flow reserve (Hoogendoorn et al., 1995; Galjee et al., 1996; Langerak et al., 2002a). and may further define focal stenoses (Bedaux et al., 2002; Langerak et al., 2002b; Langerak et al., 2003).

ASSESSMENT OF CHRONIC CORONARY SYNDROMES

Myocardial infarction (MI) can be detected with high accuracy and sensitivity using late gadolinium-enhanced CMR (Simonetti et al., 2001). Gadolinium (0.1–0.2 mmol/kg) is given intravenously and after 10–20 min, CMR is commenced using an inversion recovery sequence, where the inversion time is chosen to null myocardial signal. Because normal myocardium is uniformly tightly packed with muscle, and gadolinium is an extracellular contrast agent, there is uniformly low signal in the normal heart. In areas of MI, the extracellular compartment is expanded, and in addition, gadolinium wash out from these areas is slow. This leads to a higher gadolinium concentration on the late enhancement scan, which shows as bright signal, and has lead to the aphorism ''bright is dead.'' Because CMR has high resolution, it is possible to determine the transmural distribution resolution of MI in vivo. The technique has been extensively validated in animal MI models (Fieno et al., 2000; Judd et al., 1995; Kim et al., 1996; Kim et al., 1999), and has now replaced other CMR techniques for detecting MI. In humans, late gadolinium enhanced CMR has been shown to accurately detect both Q-wave and non-Q wave MI (Wu et al., 2001). Because the technique is so sensitive, CMR has been shown to identify subendocardial MI when wall motion and perfusion by SPECT are normal (Wagner et al., 2003a).

In the assessment of myocardial viability for the clinical scenario of consideration of bypass surgery for improvement of LV function, CMR has been shown to be very useful. As CMR accurately measures wall thickness, which is reduced in chronic transmural MI (Dubnow et al., 1965), this has been used to exclude the presence of viable myocardium in chronic infarcts with good correlation to positron emission tomography (PET) findings using fluorodeoxyglucose (FDG) (Baer et al., 1995). In dysfunctional areas where wall thickness is preserved, viability can be established by demonstrating improved thickening during low-dose dobutamine infusion, and again correlation with FDG PET is good (Baer et al., 1995). Late gadolinium-enhanced CMR has also been tested for prediction of viability (Ramani et al., 1998), and when the transmural extent of infarction is <50%, the likelihood for functional recovery in acute MI (Gerber et al., 2002), or with bypass surgery is good (Kim et al., 2000). Reproducibility is good (Mahrholdt et al., 2002), direct comparisons with PET are excellent (Klein et al., 2002; Kuhl et al., 2003), and CMR has been shown to be superior to thallium SPECT (Kitagawa et al., 2003).

EVALUATION OF ACUTE CORONARY SYNDROMES

CMR has been used in the emergency room in the assessment of chest pain (Kwong et al., 2003).CMR showed a sensitivity and specificity of 84% and 85% for identifying patients with CAD, and multi-variate analysis including standard clinical tests (ECG, troponin, TIMI risk score) showed that CMR was the strongest predictor of CAD and added diagnostic value over clinical parameters, including identification of enzyme-negative unstable angina. This promising data needs to be confirmed in other centres.

CMR also identifies microvascular obstruction in acute MI (Rochitte et al., 1998; Wu et al., 1998a). This is demonstrated early (1–2 min) after intravenous injection of gadolinium. At this time, which is well before late gadolinium-enhancement CMR would be performed, inversion recovery CMR shows areas within the MI which have severely compromised perfusion as black, and this indicates areas with microvascular collapse. Microvascular obstruction detected by CMR has been linked to ventricular remodelling (Gerber et al., 2000), and adverse cardiovascular events (Wu et al., 1998b). Finally, the transmural extent of late gadolinium-enhancement CMR predicts recovery of function following acute MI (Choi et al., 2001).

CMR is effective in demonstrating the complications of acute MI including ventricular aneurysm (Ahmad et al., 1987), pseudoan eurysms (Harrity et al., 1991), ventricular septum perforation (Sechtem et al., 1987b), and mitral regurgitation. As echocardiography may yield false positive and false negative results when looking for LV thrombi in post-infarction patients (Sechtem et al., 1989), CMR is useful (Jungehuelsing et al., 1992; Mollet et al., 2002; Semelka et al., 1992).

CARDIOMYOPATHIES AND CARDIAC TRANSPLANTATION

The cardiomyopathies include a variety of diseases where the primary pathology directly involves the myocardium excluding CAD. CMR is proving increasingly valuable in the identification and management in these conditions (see Table 4).

HYPERTROPHIC CARDIOMYOPATHY

Clinically, hypertrophic cardiomyopathy (HCM) requires an accurate diagnosis, determination of the distribution of hypertrophy and its functional consequences, and assessment of the likelihood of sudden death and progression to heart failure. Two-dimensional and Doppler echocardiography are the most commonly used non-invasive methods to study HCM (Devereux et al., 1986; Gardin et al., 1985). However, the 3D nature of CMR allows for the precise definition of the site and the extent of hypertrophy, especially at the LV apex which may not be well assessed by echocardiography (Sardanelli et al., 1993), which can lead to underdiagnosis of apical HCM (Moon et al., 2004a). Cardiac function and flow dynamics of the outflow tract are also well characterised by CMR (Arrive et al., 1994; Higgins et al., 1985; Suzuki et al., 1993). CMR myocardial tagging identifies abnormal patterns of strain, shear and torsion in HCM, demonstrating significant dysfunction in hypertrophic areas (Dong et al., 1994; Kramer et al., 1994; Young et al., 1994). Late enhancement gadolinium CMR has also been used in HCM to demonstrate areas of fibrosis (Moon et al., 2004b), and the extent of this abnormal uptake is linked to the risk of sudden death and development of LV dilation and heart failure (Moon et al., 2003a). CMR has also been used to identify the functional and anatomical consequences of septal resection (White et al., 1996), and percutaneous ablation (Sievers et al., 2002). Serial CMR therefore permits complete assessment of the morphologic and functional consequences of the disease, is ideal for screening of relatives of probands because of its phenotypic accuracy, and its ability to identify abnormal myocardial substrate linked to adverse events. Therefore, especially in patients in whom echocardiography is technically unsatisfactory, CMR should be considered the technique of choice for diagnosing and following patients with all variants of HCM. Finally, it is now known that about 4% of patients who present clinically with HCM actually have Fabry's disease. Gadolinium enhanced CMR shows unusual lateral wall enhancement in these patients (Moon et al., 2003b), and further work is required to evaluate this finding.

Table 4. Indications for CMR in patients with pericardial disease, cardiac tumours, cardiomyopathies, and cardiac transplants.

Indication	Class
1. Pericardial effusion	III
2. Constrictive pericarditis	II
3. Detection and characterization of cardiac and pericardiac tumours	I
4. Ventricular thrombus	II
5. Hypertrophic cardiomyopathy	
Apical	I
Non-apical	II
6. Dilated cardiomyopathy	
Differentiation from dysfunction related to coronary artery disease	I
7. Arrhythmogenic right ventricular cardiomyopathy (dysplasia)	I
8. Restrictive cardiomyopathy	II
9. Siderotic cardiomyopathy (in particular thalassemia)	I
10. Non compaction	II
11. Post-cardiac transplantation rejection	Inv

LEFT VENTRICULAR HYPERTROPHY

LV hypertrophy is an important independent risk factor for cardiac events. CMR is the best technique for assessing LV mass (Myerson et al., 2002a; Myerson et al., 2002b), and following its progression over time (both for research trials (Brull et al., 2001; Eichstaedt et al., 1989; Hoffman et al., 2001; Myerson et al., 2001) and for clinical patients), because of excellent interstudy reproducibility (Bellenger et al., 2000b; Bottini et al., 1995; Grothues et al., 2002).

LEFT VENTRICULAR NON-COMPACTION

This condition has become more recognised (Jenni et al., 2001), and appears to have autosomal dominant inheritance (Sasse-Klaassen et al., 2003). There is a failure of normal embryonic development of the myocardium from loosely arranged muscle fibres to the mature compacted form of myocardium. This has been linked with microvascular dysfunction (Jenni et al., 2002), and ventricular arrhythmias (Jenni et al., 2001). Variant forms seem to include left ventricular trabeculation which appears as a fine network or is more bizarre. CMR appears ideal for identification of this condition (McCrohon et al., 2002), but there are no large comparison studies with echocardiography.

DILATED CARDIOMYOPATHY

The morphological and functional abnormalities of dilated cardiomyopathy (DCM) are clearly demonstrated and quantified by CMR. These findings may not distinguish DCM from other forms of LV dysfunction, such as that resulting from CAD. An advantage of CMR over echocardiography is the use of late gadolinium enhancement CMR, which shows no uptake in a majority of DCM patients. This confirms the diagnosis and precludes the need for invasive coronary angiography (McCrohon et al., 2003). In some DCM patients, late gadolinium enhancement is seen, but only in the mid-myocardium in a non-coronary pattern which is clearly distinguishable from CAD, and is recognized by pathologists as mid-wall fibrosis seen at post-mortem. Another advantage of CMR is the superior depiction of dilation of the RV which is typical of DCM (Doherty et al., 1992a). The quantitative effects of therapy can also be assessed by CMR (Doherty et al., 1992b; Groenning et al., 2000; Osterziel et al., 1998).

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

CMR is an ideal technique to depict the structural and functional abnormalities of the RV and a substantial clinical role for CMR in the investigation of arrhythmogenic right ventricular cardiomyopathy (ARVC) has developed (Blake et al., 1994; Casolo et al., 1987). The diagnostic criteria of ARVC (McKenna et al., 1994), which CMR can show in the RV include regional wall motion abnormalities, increased RV volumes with quantification, morphological abnormalities (aneurysms, trabecular disarray) and increased myocardial signal suggesting fatty infiltration. Early work suggests that abnormal CMR findings predict an adverse outcome in ARVC (Keller et al., 2003). Experience in interpretation of CMR is required however, because of the normal variants of the RV which are in general greater than for the LV. Therefore isolated findings must be interpreted with caution. Focal wall motion abnormalities, especially focal dyskinesia, is generally felt to be a more reliable indicator of ARVC than intramyocardial fat. Overall, in centres with good experience however, CMR is a first line technique for investigating ARVC and following any progression in RV volumes, structure and function over time.

SIDEROTIC CARDIOMYOPATHY

An often overlooked cause of heart failure which is important worldwide, is iron overload cardiomyopathy arising in patients with haemochromatosis or the inherited severe anaemias which require regular blood transfusions from birth. The most important of these conditions is beta-thalassemia major, with 60 000 affected children born annually (Weatherall, 2001). Over 70% of these patients die from heart failure (Borgna-Pignatti et al., 1998). Repeated assessment of myocardial iron using biopsy is difficult because of safety issues, sampling error and patchy iron distribution. Recently, measurement of T2* using CMR has been shown to reflect tissue iron, and there is a clear relation between reduced myocardial T2* (<20 ms) indicating iron overload, and LV dysfunction (Anderson et al., 2001b). Myocardial T2* increases in concert with LV function recovery in thalassemia patients with heart failure (Anderson et al., 2001a). CMR has been used to evaluate different chelation regimes specifically for their action on the myocardium (Anderson et al., 2002). The CMR sequence can be completed quickly in a single breath-hold (Westwood et al., 2003), and has good reproducibility (Anderson et al., 2001b).

RESTRICTIVE CARDIOMYOPATHY

CMR may be useful to depict the anatomic and functional abnormalities associated with infiltrative/

restrictive cardiomyopathy (Sechtem et al., 1987a). Amyloid heart disease can be recognised by its typical alterations of diastolic function and morphology, including thickening of the interatrial septum (Fattori et al., 1998). Another contribution of CMR is the of visualisation of the pericardial thickness with spin echo CMR which aids in the differentiation from constriction (Masui et al., 1992). Computed tomography may have similar accuracy in making this distinction.

CARDIAC SARCOIDOSIS

Although cardiac involvement in sarcoidosis is relatively uncommon, sudden death may be its initial clinical presentation and early detection of such involvement is thus important. However, clinical information and standard imaging techniques suffer from low diagnostic accuracy (Danias, 2001). There are reports of the value of CMR in this condition (Doherty et al., 1998; Riedy et al., 1988). Gadolinium-enhanced CMR demonstrates increased signal in hearts affected by sarcoidosis (Schulz-Menger et al., 2000; Shimada et al., 2001; Vignaux et al., 2002), which reduces with steroid treatment and is therefore a potential therapeutic marker (Shimada et al., 2001; Vignaux et al., 2002).

MYOCARDITIS

The clinical diagnosis of myocarditis is difficult as symptoms are variable and often non-specific. Myocardial biopsy carries some risk and is limited by the patchy involvement of the muscle in the inflammatory process. CMR shows focal increases of myocardial signal on T2-weighted and early gadolinium enhancement CMR (1–2 min) in acute myocarditis (Friedrich et al., 1998; Wagner et al., 2003b), and also with late enhancement (Mahrholdt et al., 2004).

HEART TRANSPLANTATION

The two most common clinical problems in patients following heart transplantation are detection of episodes of acute rejection, and identification of accelerated coronary artery disease commonly considered as chronic rejection. Acute rejection can be identified as an increase in myocardial mass (Revel et al., 1989), areas of high myocardial signal intensity (Kurland et al., 1989), and an increase in T2 values (Marie et al., 1998). These findings correlate with myocardial oedema or infiltration by mononuclear cells. However, these changes, as well as reductions in LV wall thickening, are not reliable indicators of acute rejection, particularly not in the early stages. CMR may help detect CAD associated with cardiac transplantation (Mohiaddin et al., 1996), complications such as pericardial disease or intracavitary masses (Revel et al., 1989), and the beneficial effects of medical treatment (Schwitter et al., 1999), on the remodelling process associated with long term use of cyclosporin (Globits et al., 1997).

PERICARDIAL DISEASE

Both CMR and CT are well suited to define anatomic abnormalities of the pericardium including pericardial thickening and effusions. CMR has the advantage of being able to depict and quantify the functional abnormalities which may be associated with pericardial disease (Mohiaddin et al., 1990). The large field of view of CT and CMR is helpful in providing a better overview of the extent of pericardial disease, and to define the relationship with surrounding anatomic structures. For suspected pericardial thickening, CMR and CT are primary imaging modalities, with CT having an advantage for identification of pericardial calcium.

PERICARDIAL EFFUSIONS

Gradient echo and SSFP cine CMR generally show pericardial effusions with high signal intensity (Tscholakoff et al., 1987). CMR may be of diagnostic value in patients with loculated or complex configurations of pericardial effusions.

CONSTRICTIVE PERICARDITIS

The characteristic anatomic and functional changes associated with constrictive pericardial disease (elongated and narrow RV, abnormal motion of the sigmoid shaped interventricular septum, enlargement of the right atrium and inferior caval vein, stagnant blood in the atria, and pericardial thickening) are clearly identified with spin echo CMR (Masui et al., 1992; Sechtem et al., 1986).

Pericardial thickening is the hallmark of pericardial constriction although cases of constriction without pericardial thickening detectable by imaging techniques have been described (Masui et al., 1992). Both spin echo CMR and CT are superior to echocardiography in measuring pericardial thickness but CMR has the additional advantage of permitting assessment of haemodynamic impairment. However, in patients with severe heart failure and in those with poorly controlled atrial fibrillation, CT may be preferable to CMR because imaging time is shorter and ECG gating is not required. The reliability of CMR in making a diagnosis of pericardial constriction is indicated by its high positive predictive accuracy (Masui et al., 1992).

Velocity mapping of flow may be helpful to assess functional sequelae of pericardial disease (Kaemmerer et al., 1993). Flow mapping may be performed at the level of cardiac inflow through the superior or inferior vena cava, where a normal biphasic flow pattern may be demonstrated. In patients with constrictive physiology and abnormal cardiac filling, the second peak of caval flow may be attenuated.

CONGENITAL ABNORMALITIES OF THE PERICARDIUM

Pericardial cysts can be identified and distinguished from other tumours based on their characteristic signal intensity on spin echo images, which is low on T1-weighted but high on T2-weighted images. Signal is usually high on gradient echo cines. However, differential diagnosis from a necrotic or cystic mediastinal tumour, especially if it is situated in the typical location for a pericardial cyst, the right costophrenic angle, may be difficult. Absence of the pericardium is indicated by a leftward shift of the long axis of the heart visible using CMR (Ratib et al., 2001). The protrusion of a portion of the heart, which is usually associated with partial absence of the left-sided pericardium is easily observed on spin echo images. However, due to the absence of epicardial and epipericardial fat over the left ventricle, the pericardial defect itself may not be seen on spin echo images (Schiavone and O'Donnell, 1985).

CARDIAC TUMOURS

Transthoracic echocardiography is the usual technique which detects intracardiac tumours. However, in many cases the characterization is incomplete, and CMR is particularly helpful in determining the relationship to normal intracardiac structures and tumour extension to adjacent vascular and mediastinal structures (Freedberg et al., 1988), infiltration into the pericardium (Montalescot et al., 1988), and surgical planning (Lund et al., 1989). In addition to this, there are a number of CMR features which can assist in tumour characterization (Frank, 2002; Semelka et al., 1992). The signal intensity of a lesion is dependent on the interaction of the tissue composition and the CMR parameters employed for imaging. The differential diagnosis of a high signal intensity lesion on T1-weighted images includes fatty tumours (lipoma, liposarcoma), recent haemorrhage (due to methaemoglobin breakdown products), some cystic lesions (due to the high protein content of the contents of the cyst), and melanoma (due to the effects of melanin). A lesion with low signal intensity on T1-weighted images may represent a cyst filled with low protein fluid, a signal void in a vascular malformation, a calcified lesion or the presence of air. Cysts typically have high signal intensity on T2-weighted independent of the protein concentration of the fluid. Fat saturation can be used to diagnose fatty content definitively. Further differentiation of the tumour can be made with gadolinium. During the first pass, vascular tumours (haemangioma, angiosarcoma) show early enhancement and small vessels may be easily identifiable. In the early phase, after injection at 1–2 min, necrotic areas in malignant tumours show as dark areas surrounded by enhancement elsewhere. In the later phase, malignant tumours typically show contrast enhancement indicating tissue vascularity. Such enhancement is usually absent in cystic lesions, and most benign tumours (haemangiomas and myxomas being exceptions). Thrombus in the ventricles is well shown by modern CMR sequences, including SSFP cines, and late gadolinium enhancement (Mollet et al., 2002), and for this application may be more sensitive than echocardiography.

VALVULAR HEART DISEASE

The low cost, flexibility and ease of handling make transthoracic echocardiography the primary clinical tool for evaluation of valvular heart disease. Moreover, TEE is superior to CMR in assessment of valve morphology and detection of small and rapidly moving vegetations at tached to the valves in endocarditis. However, CMR may play a complementary role when transthoracic acoustic windows are poor and a TEE approach is undesirable, or when results of echocardiography and catheterization are conflicting. Furthermore, CMR is a valuable tool for individual follow-up of the severity of regurgitant lesions and for quantification of the effects of valvular lesions on ventricular volumes, function and myocardial mass (see Table 5).

Table 5. Indications for CMR in patients with valvular heart disease.

Indication	Class
1. Valve morphology	
Bicuspid aortic valve	II
Other valves	III
Vegetations	Inv
2. Cardiac chamber anatomy and function	I
3. Quantification of regurgitation	I
4. Quantification of stenosis	III
5. Detection of paravalvular abscess	Inv
6. Assessment of prosthetic valves	Inv

TECHNICAL ASPECTS

As normal heart valves are thin and rapidly moving, visualization on conventional spin-echo images may be difficult but breath-hold spin-echo techniques allow complete visualization of normal aortic valve leaflets in 85% of patients (Arai et al., 1999). Abnormal valves are more easily seen because they are thicker and may be less mobile. Calcifications give rise to loss of signal and may lead to underestimation of valve pathology on spin-echo images. Generally, gradient echo cines are more informative as myocardial and valvular function are dynamically displayed. A phenomenon characteristic of older gradient echo cine CMR is referred to as intravoxel dephasing which leads to signal loss demonstrating turbulence found in heart valve lesions. This signal-loss can be seen in the proximity of rapidly moving valves or at sites of stenoses where flow is accelerated and turbulent. Jets of signal-loss indicate valvular stenosis or incompetence. Whilst the length and area of the signal-loss jet help to indicate the severity of the valvular defect, they are only semi-quantitative (Wagner et al., 1989), because the extent of the jet depends on the combination of haemodynamic variables such as size and shape of the valve orifice, the pressure gradient, and technical parameters of the pulse sequence (Suzuki et al., 1990). Modern CMR systems with high gradient performance typically acquire cines using the SSFP technique, which is less dependent on the inflow of magnetically non-saturated blood within the imaging slice. This makes the blood appear brighter, and it is less sensitive to intravoxel dephasing thereby reducing the jet of signal loss.

Velocity mapping CMR is a well validated approach to quantify blood flow velocity in large vessels, and is useful to quantify the severity of regurgitant and stenotic valve lesions. The direction of velocity is generally obtained through-plane with the imaging plane perpendicular to the direction of flow. Integration of velocities over the cross-section of a vessel yields flow rate (mL/s) when multiplied by the vessel cross-sectional area. By integration over the entire cardiac cycle, the stroke volume is obtained. New technical developments include adaptation of the imaging slice to motion of the valve annulus with simultaneous correction of the velocity measurements to through-plane motion of the heart, and realtime colour flow CMR (Kozerke et al., 1999; Nayak et al., 2000).

REGURGITATION

Valvular regurgitation is identified by means of the jet of signal loss on cine gradient echo CMR, but the size of the jet is highly sequence-dependent. A quantitative assessment of single valve lesions can be obtained by calculating the regurgitant volume from the difference of RV and LV stroke volume (Globits et al., 1992; Sechtem et al., 1988). If single valves on both sides of the heart are regurgitant, the method can be extended to determine regurgitant volume from the subtraction of the ventricular stroke volume from the great vessel flow on the same side. Regurgitant fraction is calculated as the regurgitant volume divided by the ventricular stroke volume.

Aortic regurgitation may be associated with a semicircular shaped signal void proximal to the leaking orifice during diastole (Yoshida et al., 1991). Using velocity mapping CMR, the aortic regurgitant volume and fraction can be obtained directly by measuring the retrograde volume flow in diastole in the ascending aorta (Sondergaard et al., 1993). This simple and direct approach is more quantitative than Doppler, and has been used to identify patients responsive to angiotensin-converting enzyme inhibitor therapy (Globits et al., 1996), and hydralazine (Hoffmann et al., 2001). It has high interstudy reproducibility, which is valuable for repeated estimations (Dulce et al., 1992). The flow acquisition should be placed between the aortic valve and the coronary ostia to avoid inaccuracies from aortic compliance and coronary flow (Chatzimavroudis et al., 1997).

Mitral regurgitation may be central or eccentric (Aurigemma et al., 1990; Nishimura et al., 1989), and can be quantified by comparing total LV stroke volume derived from short axis multi-slice volumetry with the net forward stroke volume obtained with velocity mapping CMR in the ascending aorta. This method compares favourably with catheterization and Doppler echocardiography (Hundley et al., 1995b; Kizilbash et al., 1998). More direct methods for measuring systolic regurgitant flow and ventricular inflow at the mitral annulus level are complicated by through plane motion of the annulus and by eccentricity of the regurgitant jet (Fujita et al., 1994). Methods to correct for inaccuracies have been developed but are currently not routinely available (Chatzimavroudis et al., 1998; Kozerke et al., 2001b).

STENOSIS

Bicuspid or fused aortic valves can be identified with accurate positioning of the imaging plane in early systole perpendicular to the doming valve leaflets. Direct planimetry of the orifice area is also feasible (John et al., 2003). Calcification of the leaflet tips may be difficult to differentiate from signal loss due to turbulence and may thus lead to overestimation of the valve opening area, however, calcifications are usually located within the cusps and interference with measurements of valve area is uncommon. Non-uniform and accelerated flow distal to an abnormal valve causes signal loss in cine gradient echo cine CMR and may indicate valve stenosis. The extent of the jet cannot be used as an accurate measure of stenosis severity because of its dependency on settings of CMR parameters. For example, a short TE reduces the magnitude of the signal void. Using velocity mapping CMR, the peak velocity within the core of the jet can be measured in alignment with the jet direction or perpendicular to it, and the modified Bernouilli equation used to estimate the pressure gradient. Short TE sequences are required to avoid loss of velocity information in areas of turbulent flow. Close agreement has been demonstrated between CMR, catheterisation and Doppler echocardiography in patients with mitral and aortic valve stenosis (Caruthers et al., 2003; Kilner et al., 1993). As valve area measurements by cardiac catheterization may be complicated by occult strokes (Omran et al., 2003), CMR could be used to quantify the valve area in aortic stenosis (Friedrich et al., 2002) when echocardiography is not possible or non-concordant data with invasive techniques have been obtained.

PROSTHETIC VALVES

CMR is safe in patients with prosthetic heart valves at 1.5 Tesla, as the heart valve prostheses have no substantial interactions with the magnetic field and heating is negligible (Edwards et al., 2000). However, they do produce focal artefacts and signal loss due to distortion of the magnetic field by the metal contained within the prostheses. The artefacts are least pronounced on spin-echo images and more pronounced with gradient-echo cines. As a consequence, smaller jets of signal loss due to paravalvular leakage may be obscured by the artefact. Heart motion-adapted velocity mapping has allowed the measurement of velocity profiles close to aortic valve prostheses (Kozerke et al., 2001a).

CARDIOVASCULAR MAGNETIC RESONANCE SPECTROSCOPY

CMR spectroscopy for clinical purposes is presently limited to the study of P-31 containing myocardial phosphates present in important biochemical compounds involved in energy metabolism. Compounds such as adenosine triphosphate (ATP), phosphocreatinine (PCr), inorganic phosphate (Pi) and monophosphate esters (MPE) can be studied at rest and during stress. Although other important elements can be studied by CMR spectroscopy, none are currently used clinically. Nevertheless, potentially clinically relevant results have been reported with in vivo human studies of hydrogen (H-1) (Bottomley and Weiss, 1998; Reeves et al., 1989), sodium (Na-23) (Kim et al., 1997), and potassium (K-39) (Fieno et al., 1999). The main reason for their limited clinical application is the low MR sensitivity of other nuclei and their low concentration, which results in a very low signal. At present, CMR spectroscopy can only interrogate anterior portions of the heart, but higher field strength magnets and new coils should improve the coverage.

A primary clinical goal of CMR spectroscopy is to determine the PCr/ATP ratio, which reflects the energetic state of the myocardium. Important conceptual studies suggest that the unique ability to interrogate the high energy pathway has significant diagnostic and prognostic potential. In mild heart failure, the PCr/ATP ratio is in the normal range (Neubauer et al., 1992; de Roos et al., 1992), but falls with advancing severity (Hardy et al., 1991; Neubauer et al., 1992). Reduced PCr/ATP ratios improve with treatment of heart failure (Neubauer et al., 1992), and the level of PCr/ATP is an independent predictor of cardiovascular events which may be more predictive than ejection fraction (Neubauer et al., 1997). In patients with valvular disease, PCr/ATP ratios are reduced only when patients develop heart failure but not in early stages (Conway et al., 1991). Whether PCr/ATP ratios can be used clinically to guide the timing for valve replacement is currently unknown. In CAD, myocardial ischemia induced during handgrip exercise can be detected by transient reduction in the PCr/ATP ratio. This response is abolished by revascularization (Weiss et al., 1990). This ischaemic response is not seen in non-viable regions (Yabe et al., 1994). Viable myocardium has been shown to have normal absolute levels of ATP, but levels are low in non-viable myocardium (Yabe et al., 1995). Stunned myocardium has been shown to have normal PCr/ATP ratios (KalilFilho et al., 1997). Taken together, these results suggest that CMR spectroscopy can provide metabolic evidence for myocardial viability (Bottomley and Weiss, 1998). In early cardiac allograft rejection, decreased PCr/ATP ratios are seen (Canby et al., 1987; Fraser et al., 1990), although this must be distinguished from transient reductions early after transplantation that might occur on the basis of transient allograft ischaemia. In LV hypertrophy, the PCr/ATP ratio is generally normal (Pluim et al., 1996), but reductions are seen in hypertrophic cardiomyopathy (Jung et al., 1998; Rajagopalan et al., 1987). The reasons for this are not currently understood. Finally, a decrease in PCr/ATP ratio has been found in 20% of women with chest pain in the absence of significant epicardial coronary artery stenosis, a result which suggests the presence of microvascular disease and resultant ischaemia (Buchthal et al., 2000).

COSTS AND BENEFITS OF CMR

This section focuses on the USA and UK where cost data and technology assessments of CMR have been under taken; the principles apply however to most European Union (EU) countries and elsewhere (Berry et al., 2002; Mark et al., 2003). There are a number of medical society and governmental position papers on the economic value of CMR and other imaging techniques, and these are a useful further reference source for independent assessments of cost-benefit (Beller et al., 2002; Berry et al., 2002; Greenland et al., 2000; Hunink et al., 1999; Laupacis et al., 1992; Mark et al., 2003; Mowatt et al., 1997; Mushlin et al., 2001; Office of Technology Assessment, 1980; Oortwijm et al., 2001; Pettigrew et al., 2000; Shaw and Redberg, 2001; www.hcfa.gov/quality/3j2-5.htm). A large amount of data reveals that there is a large economic burden placed upon society for the use of imaging tests for cardiovascular disease. For example, high rates of resource consumption are noted in the US (~40 million non-invasive cardiac tests are performed annually for public and private health care payers; Medicare reimbursement of \$372–\$740 million; and high growth rates >20% using Medicare databases for some cardiac imaging modalities). The same applies in most countries of the EU, but in some there is underutilization of procedures (National Institute of Clinical Excellence). In this latter case, the opportunity exists that societal investment in more accurate and diverse technology may supplant the use of inexpensive and less accurate diagnostic testing modalities. This might be feasible in the more urban or centralized health care environments.

Current efforts to contain health care costs in the US and Europe have included developing evidence-based guidelines where a threshold body of clinical and economic evidence is desired to support and guide reimbursement for a given clinical procedure indication. Despite the concern over excessive and rising costs of care, the current armamentarium for cardiac imaging has suffered from technical artefacts, limited resolution, and other challenges that often provide a unidimensional risk evaluation upon which patient management is based. Thus, the promise to society for CMR is to develop strategies that provide a full range of risk markers which would allow health care systems to benefit from improved diagnostic accuracy, risk assessment and therapeutic decision making. The resultant economic effects of these improvements may result in decreases in overall test use, early diagnosis, improved patient outcome, decreased hospitalizations and length of stay, and reduced invasive procedure use. As many countries currently track cardiovascular mortality rates, the impact of early diagnosis on long-term survival may provide a link to shifting health care resources and the decision to utilize differential technology in order to exhibit a more beneficial impact on population-based risk reduction efforts.

COST IMPLICATIONS OF FUNCTIONAL CMR

CMR permits accurate and precise measurements of cardiac chamber sizes and volumes, rendering it ideal to detail abnormalities in complex diseases. A hierarchical testing approach in which lower cost tests are applied to a greater percentage of patients and higher cost tests are limited to high-risk patients where a greater incremental value is determined (Marwick et al., 1995), is based upon high-risk cost effectiveness model in which economic value is greater in higher risk populations who receive a greater proportional benefit to testing and treatment (in the form of disproportionately greater risk reduction when compared to lower risk cohorts). By applying this principle of high-risk cost models, costs can be differentially and selectively allocated to sicker patients and thereby result in more cost efficient care shifting higher risk patients from ultrasound or nuclear-based techniques to CMR. Additionally, the upfront cost differences are minimised by the greater outcome benefit to that patient cohort, rendering the test more cost effective.

COST IMPLICATIONS OF CMR PERFUSION AND VIABILITY TESTING

CMR has the potential to provide myocardial perfusion measures. Evidence in small patient samples reveals a sensitivity and specificity of 87% and 85%, respectively, versus catheterization as the gold standard (Schwitter et al., 2001), and improved detection of infarction versus SPECT (Wagner et al., 2003a). A considerable amount of diagnostic and prognostic data are available with SPECT however and despite a substantial radiation burden of SPECT, it appears that perfusion CMR may take time to become competitive due to the current favourable reimbursement for perfusion SPECT, with function as an add-on (Shaw et al., 2000). The detection of subendocardial ischaemia by CMR techniques could prove to be clinically and cost effective for large segments of the SPECT population (for example women evaluated for chest pain symptoms) (Panting et al., 2002).

Despite this initial caution on the use of perfusion, viability testing with CMR may become the gold standard for the assessment of patients with LV dysfunction presenting for evaluation and consideration of coronary revascularization. Using a model of high risk cost-effectiveness, evidence of CMR viability would result in improved patient outcome with coronary revascularization and reduced cost (due to reduced hospitalisations for heart failure, acute myocardial infarction, etc.). The incremental cost effectiveness ratio of viability testing with CMR when compared with echocardiography, SPECT, or PET techniques could result in a dominant economic strategy of improved life years saved and cost savings.

COST IMPLICATIONS OF CORONARY CMR

Currently, 1.2 million diagnostic coronary X-ray angio grams are performed annually in the USA which carries a small risk due to the invasive procedure, the contrast media, and the radiation exposure. Although under development, coronary MRA provides an opportunity to reduce these risks. If coronary MRA could be utilized to screen lower risk patients currently referred for catheterization, substantial cost savings may be achieved amongst the patients with normal catheterization (current rate in USA approximately 35%). In one report, the total cost savings, when compared to diagnostic coronary angiography, was expected to exceed $1000 per patient (or >60% cost reduction) (Shaw et al., 2000).

In the area of carotid and peripheral MRA, there are existing cost effectiveness analysis that may be used to guide the utilization of these techniques. In a recent review by the UK's National Institute of Clinical Excellence (NICE), the high sensitivity (93%) and specificity (94%) in the detection of carotid disease, resulting in cost-effectiveness ratios of £19 419 (approximately €27 000) per quality adjusted life years saved (Berry et al., 2002). Thus, in the evaluation of carotid disease, MRA was the cost-effective test of choice. A cost-effectiveness analysis was also performed by NICE in the evaluation of peripheral arterial disease comparing MRA (94% sensitivity and 93% specificity) with X-ray angiography. There was little difference in 1 year outcomes, a small complication risk with the invasive angiography and reduced costs with MRA. Thus, MRA was considered the favourable choice, except for the highest risk patients who should be referred to X-ray angiography.

COST IMPLICATIONS FOR THE PHARMACEUTICAL INDUSTRY

It costs an estimated $500 million to bring a new drug to the marketplace. Although the majority of drug development costs are in preclinical research, the average cost of FDA-sponsored Phase I to IIIb clinical trials ranges from $14 to $54 million. There is increasing interest on the part of pharmaceutical manufacturers to reduce the frequency with which large morbidity and mortality outcome trials are utilized by re-focusing resources early on in drug development to areas of distinct clinical promise. An alternative to the use of large outcome trials is to use an imaging or laboratory marker as a surrogate outcome. A surrogate outcome is, by definition, a process of care measure that may be used to reflect a worsening long-term outcome (e.g., worsening ejection fraction). Due to the enhanced reproducibility of CMR measurements (Grothues et al., 2002), it appears ideally suited for use as a surrogate outcome. Prior research supports the view that CMR can reduce the necessary and sufficient sample sizes by as much as 10-fold and decrease overall cost by as much as 80% (Bellenger et al., 2000b; Bottini et al., 1995). Using simple cost calculations, approximately 5–11% of drug development costs may be saved thus providing substantial reductions in costs to society.

COMPARATIVE TEST COSTS

The current estimated costs of cardiac imaging modalities are shown in Table 6. As a number of CMR techniques are currently under development, these cost estimates should be viewed with caution. Despite this, the estimated unit procedural cost (not charge) of CMR ranges from €194 to €1063 based upon multiple sources (Berry et al., 2002; Mark et al., 2003; Shaw et al., 2000). Current estimates of CMR costs are expected to decline over the next decade as training costs, initial protocol development, and equipment costs contribute to higher initial development costs for this modality. An example of lower achieved costs can be seen in the area of more mature CMR techniques, such as can be seen with peripheral MRA techniques (Berry et al., 2002). As is noted with vascular MRA costs, in the UK the unit cost for some MR procedures has been estimated at £110 and £247 for evaluation of carotid arteries and peripheral vasculature (Berry et al., 2002). Upon reviewing the initial cost estimates, it appears that CMR is quite cost competitive when com pared to other modalities. One would anticipate with continued use and protocol refinement, enhanced efficiency and cost reductions for CMR will ensue.

Table 6. Estimated average costs of CMR and other common cardiac imaging procedures when compared to 2D echocardiography.

	Average cost	Cost range
Echocardiography	[a]	[a]
Computed tomography	3.13	(±1.39)
SPECT	3.27	(±2.88)
CMR	5.51	(±3.51)
PET	14.03	(±9.62)
Right and left heart catheterization	19.96	(±13.55)

[a]Echocardiography is the cost comparator where costs of other modalities are a ratio of *x*-fold higher costs. Note: Costs are unit operating costs (not charges) derived from multiple sources (Berry et al., 2002; Mark et al., 2003; Shaw et al., 2000). CMR cost does not include the cost of intravenous contrast agents or stress protocols. Conversion of US Costs to Euros based upon CPT codes: 75552, 75553, 75554, 75555 (based upon average for Atlanta, Georgia, US, August 19, 2003).

Test use is guided by both economic forces, such as reimbursement, and information content. For CMR, the multitudes of test parameters that can be acquired render this test unlike other non-invasive imaging modalities. Its ability to acquire diverse risk markers may, in some cases, raise the overall procedural cost but its up front cost may be minimized by substantial downstream cost savings. Economic value may be achieved by developing a single, non-invasive test that assesses all aspects of the heart, and CMR has the potential to provide this comprehensive examination in one sitting at considerably less risk and cost to the patient. With rapid imaging techniques, it should be possible to complete a comprehensive study in as little as one hour, at an estimated median cost of €435. The effect of this initial test cost may be offset by a reduction in downstream utilization of other redundant imaging tests. Using a rudimentary cost analysis, adding the ability of CMR to perform multiple test functions may therefore provide cost savings to the health care system.

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