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AN INITIATIVE OF THE NATIONAL, STATE AND TERRITORY GOVERNMENTS OF AUSTRALIA AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Delayed enhancement MRI for the detection of myocardial viability in patients who have experienced myocardial infarction

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Enquiries about the content of this summary should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

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This *Horizon scanning prioritising summary* was prepared by Linda Mundy and Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Discipline of Public Health, Mail Drop 511, University of Adelaide, South Australia, 5005.

PRIORITISING SUMMARY

REGISTER ID: **000296** **REFERRAL FROM HEALTHPACT**

NAME OF TECHNOLOGY: **DELAYED ENHANCEMENT MRI**

PURPOSE AND TARGET GROUP: **FOR THE DETECTION OF MYOCARDIAL VIABILITY IN PATIENTS WHO HAVE EXPERIENCED MYOCARDIAL INFARCTION**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☒	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☒	Yes	ARTG number	Numerous
☐	No		
☐	Not applicable		

Numerous MRI units are registered on the TGA for clinical use in Australia.

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia		✓	
Germany		✓	
United States		✓	

IMPACT SUMMARY:

Delayed enhancement magnetic resonance imaging (DE-MRI) aims to assess cardiac viability in patients who have experienced an acute myocardial infarction. This technology would be made available through specialist cardiac facilities.

BACKGROUND

Acute myocardial infarction (AMI), or a heart attack, occurs when a coronary plaque breaks off, causing a blood clot to form which may partially or completely block blood flow to the downstream heart muscle. Lack of blood flow results in the death of cardiac myocytes and the loss of cardiac viability. The clot should be removed promptly to restore blood flow and to prevent further loss of cardiac muscle viability (Mathur 2002). Viable myocardium may still be dysfunctional and can be described as

either “hibernating” or “stunned”. A hibernating myocardium is chronically dysfunctional due to low blood flow and its recovery after revascularisation is slow and often incomplete. Contractile dysfunction occurs in the stunned myocardium possibly as a result of an overload of oxyradicals and calcium; however recovery after revascularisation tends to be early and complete (Senior 2006). Treatment should be aimed at restoring left ventricular systolic function by the revascularisation of the damaged myocardium, either by surgical (percutaneous coronary intervention or a coronary artery bypass graft) or pharmacological means. A delay in the revascularisation process may result in irreversible damage to the myocardium and is associated with an increase in mortality. Revascularisation of patients with *non-viable myocardium* by surgical means is associated with an increase in peri-operative morbidity, an increased risk of mortality and worse long-term outcomes. To determine the most appropriate treatment option for patients (surgical or medical) the viability of the myocardium needs to be rapidly assessed (Isbell & Kramer 2006; Thomson et al 2004). A recent meta-analysis reported that when the left ventricle was 25-30 per cent dysfunctional, but still considered viable as assessed by non-invasive testing, then revascularisation should be considered (Senior 2006).

Cardiac MRI requires the high temporal resolution of scanners of >1 Tesla[1] with high-performance gradients (≥40 mT/m/s) and dedicated software. The number of MRI images obtainable is limited by the heart rate and images should ideally be acquired during diastole when the left ventricle is relatively still. Ideal temporal resolution is attained by acquiring images at intervals less than or equal to the heart rate. There are several means available to shorten the T1[2] of protons in the tissues including the use of the contrast agent gadolinium (De Filippo et al 2006). The T1 weighting is controlled primarily by the inversion time (Ti) with the inversion time set to null the signal from normal myocardium before the contrast agent is injected (personal communication, MRI Research and Development, RAH). The inversion time is an estimate, ranging from 200-380 milliseconds and experienced clinicians may estimate Ti reasonably well, whereas inexperienced clinicians may require the use of Ti scout sequences (Marcu et al 2007). Gadolinium is injected as a bolus (0.1-0.2 mmol/kg) into a peripheral vein. Gadolinium washes out rapidly from *viable* tissue, with a decreased washout of the contrast agent from areas of the myocardium that have been scarred (De Filippo et al 2006). It is thought that this slow washout is

[1] The tesla (T) is the SI derived unit of magnetic flux density (or magnetic induction). It is used to define the intensity (density) of a magnetic field. The tesla is the value of the total magnetic flux (a magnet's "power") divided by area Wikipedia (2007b). *Tesla (unit)* [Internet]. Wikipedia. Available from: http://en.wikipedia.org/wiki/Tesla_%28unit%29 [Accessed 28th March 2007]..

[2] To understand MRI contrast, it is important to have some understanding of the time constants involved in relaxation processes that establish equilibrium. Following radio frequency excitation, the high-energy nuclei of cells relax and realign and emit energy at varying rates. The realignment of nuclear spins with the magnetic field is termed longitudinal relaxation and the time required for a certain percentage of the tissue's nuclei to realign is termed "Time 1" or T1 Wikipedia (2007a). *Magnetic resonance imaging* [Internet]. Wikipedia. Available from: http://en.wikipedia.org/wiki/Magnetic_resonance_imaging [Accessed 28th March 2007]..

due to the gadolinium becoming entrapped in the interstitial oedema associated with the necrotic cells of the infract area (Senior 2006). Determining the difference between viable and non-viable myocardium relies on the washout kinetics of gadolinium, therefore image acquisition is *delayed* by 5-20 minutes post-administration of the contrast agent (Grand & Bluemke 2006). The higher concentration of gadolinium in the infarct area causes rapid T1 relaxation, resulting in a bright signal intensity that is approximately 400 times the intensity observed in viable tissue (De Filippo et al 2006). The extent and depth of the scar is used to assess if that part of the ventricle wall may regain function if reperfused.

CLINICAL NEED AND BURDEN OF DISEASE

In Australia, the age-standardised rate of acute myocardial infarction public hospital admissions has been steadily decreasing since the early 1990s, corresponding to a decline in the incidence of AMI. However, the absolute number of admissions has remained steady or increased due to the increasing average age and overall growth of the population. In Australia, AMI occurs predominantly amongst those aged 40 years and over (97%), with almost two-thirds occurring among people aged 65-90 years of age. Men are twice as likely to be admitted to hospital for AMI as women. One in four Australians experiencing a heart attack or AMI will die within an hour of the first symptoms and almost nine in ten coronary deaths will occur before the patient reaches hospital (Mathur 2002).

In Australia, the number of public hospital separations for patients with acute myocardial infarction, in 2004-05, was 47,633. Of these, there were 31,188 male and 16,443 female separations, representing a total of 270,756 patient days. This equates to a rate of 519 separations per 100,000 population, aged 40 years and over. In Australia, the National Cardiovascular Disease and Diabetes Database recorded that in the year 2000, 14,616 persons died from AMI at a rate of 76.3 per 100,000 (AIHW 2007).

In New Zealand, the number of public hospital separations for patients with acute myocardial infarction, in 2003-04, was 12,127 and of these, there were 7,555 male and 4,572 female separations (provisional data). Provisional 2002 data reported 3,252 deaths with an underlying cause of AMI (data supplied by the NZ Health Information Service).

DIFFUSION

Although DE-MRI for the assessment of cardiac function is conducted in several specialist cardiac centres in Australia, it is not routinely used to assess cardiac viability of patients who have experienced an AMI.

COMPARATORS

Myocardial viability may be assessed by a number of imaging modalities including positron emission tomography (PET), single photon emission computed tomography,

(SPECT), dobutamine stress echocardiography, myocardial contrast echocardiography as well as conventional MRI.

PET is capable of assessing myocardial perfusion, glucose utilisation, fatty acid uptake and oxidation, presynaptic and postsynaptic neuronal activity, oxygen consumption and contractile function (Thomson et al 2004). It is considered the gold standard for myocardial viability assessment (Marcu et al 2007).

SPECT, utilising the tracer thallium-201 (^{201}Tl), can elucidate information on myocardial perfusion and cell viability, however ^{201}Tl has a long half-life and patients are exposed to high levels of radiation. Technetium-99m (^{99m}Tc) may be used with SPECT. This tracer has a shorter half-life compared to thallium, and reducing radiation exposure to patients. However, ^{99m}Tc depends on cardiac perfusion and viability for uptake of the tracer and therefore may underestimate the true cardiac viability (Senior 2006). Both PET and SPECT have limited resolution (8-10mm pixel size) resulting in viability being determined in a binary fashion with an accompanying loss of data (Thomson et al 2004).

Dobutamine infusion during echocardiography can detect myocardium viability through the ability of dobutamine to induce an enhanced contractile response via the recruitment of contractile proteins. A dobutamine responsive myocardium is considered viable (Senior 2006). When compared to nuclear medicine techniques, however, dobutamine stress echocardiography has a low sensitivity and a high specificity (De Filippo et al 2006).

Myocardial contrast echocardiography utilises gas-filled microspheres which are capable of detecting capillary and myocardial blood flow. Patients are considered to have a viable myocardium if contrast opacification is visible in the infracted region. Standard MRI scanners can measure ventricular volumes, ejection fraction, myocardial mass and regional wall motion but may be limited in its applicability due to the requirement for breath-holding, and difficulties with claustrophobic patients and those fitted with a pace-maker (Senior 2006).

EFFECTIVENESS AND SAFETY ISSUES

All the studies included for assessment in this summary compared DE-MRI to other scanning modalities in the assessment of cardiac viability, the evaluation of infarct size (scar) or the number of perfusion defects. None of the studies identified used the assessment of cardiac viability to guide the suitability of patients to undergo either surgical or medical reperfusion strategies. Studies were conducted in patients who had experienced AMI but had already been reperfused or in patients who had chronic ischaemic heart disease. All patients underwent cardiac viability assessment by DE-MRI and PET or ^{99m}Tc-SPECT as the reference standard.

A comparative study assessed cardiac viability in 31 patients with chronic coronary artery disease, 26 of whom had previously documented myocardial infarction,

however patients who suffered AMI 6-weeks prior to evaluation were excluded (level III-1 diagnostic evidence) (Klein et al 2002). DE-MRI was performed with a 1.5 Tesla scanner, with delayed images acquired 20 minutes after gadolinium injection. The sensitivity and specificity[3] of DE-MRI in detecting patients with scar tissue (as defined by the reference standard, PET) were 96 and 100 per cent, respectively. In addition, the sensitivity and specificity of DE-MRI to detect transmural defects were 86 and 94 per cent, respectively, and for detecting any defect (transmural and non-transmural) were 83 and 88 per cent, respectively. Of the total number of segments defined as viable by PET, 11 per cent were classified as having a defect by DE-MRI, whereas five per cent of segments with a matched PET defect were considered viable by DE-MRI.

Kühl et al (2003) assessed the cardiac viability of 23 consecutive patients with left ventricular dysfunction with PET and DE-MRI (level II diagnostic evidence) (Kuhl et al 2003). Seventy eight per cent of patients had experienced a previous AMI event with an average interval between AMI and viability studies of 150 ± 83 months. The sensitivity and specificity of DE-MRI to identify non-viable myocardium when compared to PET were 96 and 84 per cent, respectively.

A similar study by Lund et al (2004) on 60 consecutive patients reported a good correlation (r=0.73, $p<0.001$) between DE-MRI and ^{201}Tl-SPECT in regards to ascertaining infarct size 6-days (±3 days) post-reperfusion after a first myocardial infarction (level II diagnostic evidence). The infarct size detected by both screening modalities was not significantly different from each other at 20.7 ± 11.5 and 19.4 ± 14.3 per cent of left ventricular area for DE-MRI and ^{201}Tl-SPECT, respectively. However, ^{201}Tl-SPECT failed to detect 6/30 (20%) of patients with an inferior myocardial infarction, whereas DE-MRI detected MI in all patients ($p<0.01$) (Lund et al 2004).

The comparative study by Lombardo et al (2006) assessed the number of resting perfusion defects in 14 consecutive patients (mean age 61 ± 9 years) admitted to hospital with a diagnosis of a first AMI (diagnosed by ST elevation, chest pain and 3 times the upper normal level of creatine kinase[4]) (Lombardo et al 2006). All patients underwent myocardial contrast echocardiography (MCE), DE-MRI and ^{99m}Tc-SPECT (the reference standard) within five days of admission to hospital and within 48 hours of each other (level II diagnostic evidence). In addition, all patients underwent standard X-ray coronary angiography within seven days of admission. DE-MRI was performed with a 1.5 Tesla scanner, with delayed images acquired 15 minutes after gadolinium injection with a standard Ti of 325 milliseconds. Patient characteristics

[3] Sensitivity is the ability of a test to correctly identify those individuals who have the disease ie to correctly identify segments *with a perfusion defect*. Specificity is the ability of a test to correctly identify those individuals who do not have the disease ie to correctly identify those segments *without a perfusion defect.*

[4] Normal range of creatine kinase = 230-460 IU/L

after clinical, echocardiographic and angiographic diagnosis/analysis are described in Table 1.

Table 1 Patient characteristics

Anterior MI (n)/ inferior MI (n)	12/2
Peak creatine kinase (IU/L) (mean ± SD)	2693 ± 2385
Number dysfunctional segments (mean ± SD)	6.7 ± 2.7
Left ventricular ejection fraction (%) (mean ± SD)	45 ± 6

Using ^{99m}Tc-SPECT as the reference standard, images of 224 left ventricular segments were obtained for analysis (Table 2). Of these, a perfusion defect was present in 62/224 (27.7%) of segments. Although DE-MRI picked up more segments with a perfusion defect than ^{99m}Tc-SPECT (70 vs 62), only 39 of these were the same segments (39/62=63% sensitivity). The number of left ventricular segments suitable for analysis with MCE was lower than for DE-MRI (68 vs 98%, $p<0.001$), however MCE showed a higher sensitivity than ME-MRI (81 vs 63%, $p<0.03$ NS) in detecting perfusion defects (as defined by the reference standard). Specificity was significantly lower with MCE than DE-MRI (42 vs 82%, $p<0.001$) as well as overall accuracy (53 vs 77%, $p<0.001$). This study concluded that both MCE and DE-MRI are adequate tools for assessing perfusion defects in AMI patients (Lombardo et al 2006).

Table 2 Comparative results of scanning modalities

	LV segments	Perfusion defect	Sensitivity	Specificity	Accuracy
^{99m}Tc-SPECT alone	224	62/224 (27.7%)			
DE-MRI vs ^{99m}Tc-SPECT	220/224 (98.2%)	70/220 (31.8%)	63%	82%	77%
MCE vs ^{99m}Tc-SPECT	153/224 (68%)	75/153 (49%)	81%	42%	53%

LV = left ventricular

The good quality studies included for assessment in this summary indicate that DE-MRI has high sensitivity and specificity values for the detection of scar tissue and cardiac viability when compared to PET. The sensitivity of DE-MRI decreased when compared to assessment with SPECT. However, none of the papers included in this assessment reported on patient outcomes when DE-MRI is used to assess cardiac viability as a decision making tool for the treatment of patients admitted to hospital with acute myocardial infarction.

COST IMPACT

DE-MRI can be conducted on a conventional MRI scanner installed with the appropriate software package. It is not covered by a MBS item number. However, assessment of the cardiovascular system may be conducted on patients with a congenital heart condition, tumour of the heart, an abnormality of the thoracic aorta

using MBS item numbers 63385 ($448), 63388 ($448), and 63391 ($403.20), respectively. It may be possible to assess the cardiac viability of these patients using DE-MRI (personal communication, Adelaide Cardiac Imaging).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

No issues were identified/raised in the sources examined.

CONCLUSION:

Although the good quality studies included in this assessment indicate that DE-MRI correlates and agrees well with both PET and SPECT in the detection of scar tissue and cardiac viability, none of the studies reported on DE-MRI as a decision making tool for the treatment of patients admitted to hospital with acute myocardial infarction.

HEALTHPACT ACTION:

Currently Victoria is undertaking a feasibility trial of delayed enhancement MRI for the assessment of cardiac viability. HealthPACT have therefore recommended that data from this trial be assessed and that this technology be monitored in 12 months time.

SOURCES OF FURTHER INFORMATION:

AIHW (2007). *National Hospital Morbidity Database* [Internet]. Australian Institute of Health and Welfare. Available from: http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi?DC=Q&E=/ahs/principaldiagnosis9899-0405 [Accessed 27th March 2007].

De Filippo, M., Julsrud, P. et al (2006). 'MRI evaluation of myocardial viability', *Radiol Med (Torino),* 111 (8), 1035-1053

Grand, D. & Bluemke, D. A. (2006). *Mri Determination of myocardial viability* [Internet]. Applied radiology. Available from: http://www.medscape.com/viewarticle/534044_4 [Accessed 28th March 2007].

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Klein, C., Nekolla, S. G. et al (2002). 'Assessment of myocardial viability with contrast-enhanced magnetic resonance imaging: comparison with positron emission tomography', *Circulation,* 105 (2), 162-167

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Lombardo, A., Rizzello, V. et al (2006). 'Assessment of resting perfusion defects in patients with acute myocardial infarction: Comparison of myocardial contrast echocardiography, combined first-pass/delayed contrast-enhanced magnetic resonance imaging and 99mTC-sestamibi SPECT', *International Journal of Cardiovascular Imaging,* 22 (3-4), 417-428

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Marcu, C. B., Nijveldt, R. et al (2007). 'Delayed Contrast Enhancement Magnetic Resonance Imaging for the Assessment of Cardiac Disease', *Heart Lung Circ*,

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Wikipedia (2007a). *Magnetic resonance imaging* [Internet]. Wikipedia. Available from: http://en.wikipedia.org/wiki/Magnetic_resonance_imaging [Accessed 28th March 2007].

Wikipedia (2007b). *Tesla (unit)* [Internet]. Wikipedia. Available from: http://en.wikipedia.org/wiki/Tesla_%28unit%29 [Accessed 28th March 2007].

LIST OF STUDIES INCLUDED

Total number of studies	
Level II diagnostic evidence	3
Level II diagnostic evidence	1

SEARCH CRITERIA TO BE USED:

Cardiomyopathies/diagnosis/physiopathology
Coronary Vessels/physiopathology
Diagnostic Techniques, Cardiovascular
Gadolinium
Heart/*physiopathology
Magnetic Resonance Imaging/*methods
Gadolinium DTPA/*diagnostic use
Image Enhancement/*methods
Contrast Media
Ventricular Dysfunction, Left/diagnosis