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Prognostic value of adenosine stress perfusion cardiac MRI with late gadolinium enhancement in an intermediate cardiovascular risk population

Angela G. Bertaso [a], James D. Richardson [a,b], Dennis T.L. Wong [a,b], Michael S. Cunnington [a], Adam J. Nelson [a,b], Hussam Tayeb [a], Kerry Williams [a], Derek P. Chew [c], Matthew I. Worthley [a,b], Karen S.L. Teo [a,b], Stephen G. Worthley [a,b,*]

[a] Cardiovascular Research Centre, Royal Adelaide Hospital, Adelaide, Australia
[b] Department of Medicine, University of Adelaide, Adelaide, Australia
[c] Department of Medicine, Flinders University, Adelaide, Australia

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ABSTRACT

Background: The high diagnostic accuracy of adenosine stress cardiac magnetic resonance (AS-CMR) for detecting coronary artery stenoses, with high sensitivity and specificity, is well documented. Prognostic data, particularly in non-low risk study populations and for greater than 12 months of follow up, is however lacking or variable in its findings. We present prognostic data, in an intermediate cardiovascular risk cohort undergoing adenosine stress perfusion CMR, over approximately 2 years of follow up.

Methods: The study population comprised 362 patients referred for a clinically indicated stress CMR and included patients with proven coronary artery disease (CAD; n = 157) or unknown CAD status, yet an intermediate cardiovascular risk profile (n = 205). Perfusion imaging was performed at stress (adenosine 140 μg/kg/min) and rest on a 1.5 T system. Patient records and state-wide hospital databases were reviewed. Major adverse cardiac events — death, myocardial infarction, revascularisation or ischaemic hospitalisation — were evaluated over a median follow up of 22 months.

Results: Of the 362 cases, 90 had a stress perfusion CMR positive for ischaemia and experienced a MACE rate of 24%. Of the 272 negative CMR scans, 225 were also negative for late gadolinium enhancement, and in this group MACE was encountered in only 6 (2.7%) patients. Accordingly a negative stress CMR afforded a freedom from MACE of 97.3%. Freedom from death/myocardial infarction was 99.6%.

Conclusions: In patients with confirmed coronary artery disease or at intermediate risk for cardiovascular events, a negative stress perfusion CMR is associated with an excellent prognosis over nearly 2 years of follow up.

1. Introduction

Ischaemic heart disease remains one of the leading causes of morbidity and mortality worldwide [1]. Identification of patients with significant myocardial ischaemia provides an opportunity for therapeutic interventions that can reduce symptoms and may improve prognosis [2,3]. Non-invasive investigations may play an important role in detecting ischaemia and risk-stratifying patients with known or suspected coronary artery disease (CAD) to distinguish symptomatic patients that require invasive coronary angiography from those that have a good prognosis who can be safely reassured and continued on medical therapy. A number of non-invasive imaging modalities have been shown to be superior to clinical assessment for risk stratification, including nuclear perfusion imaging, dobutamine stress echo, and CT coronary angiography [4–6]. More recently, adenosine stress perfusion cardiac magnetic resonance (AS-CMR) has emerged as a technique offering high spatial resolution and unrestricted imaging planes providing functional perfusion data without the need for ionising radiation [7,8]. The sensitivity and specificity of AS-CMR has been shown to be at least as good as other non-invasive imaging modalities for the detection of coronary stenoses [9,10]. Although there is some data for risk prediction of AS-CMR in select populations over short follow up periods, its role in unselected populations at higher risk over longer period of follow up remains less clear. Therefore we sought to assess the prognostic value of AS-CMR with respect to major adverse cardiovascular events (MACE) over almost 2 years of follow up in a real-world cohort of intermediate cardiovascular risk including patients with established coronary disease, previous myocardial infarction (MI) and revascularisation.

* Corresponding author at: Cardiovascular Investigational Unit, Level 6 Theatre Block, North Terrace, Adelaide, South Australia, 5000, Australia. Tel.: +61 8 8222 5608; fax: +61 8 8222 2454.
E-mail address: stephen.worthley@adelaide.edu.au (S.G. Worthley).

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2. Methods

2.1. Study population

Consecutive patients undergoing AS-CMR from January 2008 to April 2009 at our centre were included. All scans were clinically indicated for a patient cohort with a broad spectrum of clinical presentations reflecting the real-world nature of populations undergoing this investigation. Many had prior documented CAD and in those without known CAD we performed an assessment of pre-test likelihood to more accurately define this patient cohort [11]. The risk score encompassed: age, sex, typicality of symptoms and cardiovascular risk factors [12]. Standard contraindications to MRI or adenosine administration were applied [13]. Patients with prior coronary artery bypass graft surgery were excluded from this analysis [14,15]. All patients had a minimum estimated GFR of 30 mls/min permitting the use of gadolinium-based contrast and had abstained from caffeine/xanthine-containing products for at least 24 h prior to AS-CMR. Written informed consent was obtained in accordance with research ethics committee approval. We assessed MACE (defined as cardiovascular death, MI, revascularisation or hospitalisation for cardiac ischaemia) over the follow-up period. Baseline data and events during follow-up were ascertained through a combination of inpatient (state-wide hospital database — OACIS™) and outpatient (clinic patient record) sources. MI was defined as the detection of troponin rise above the 99th percentile of the upper reference limit together with symptoms and/or ECG changes. Hospitalisation for cardiac ischaemia was defined as hospital admission with a final diagnosis of myocardial ischaemia (e.g. angina or unstable angina) without MI. Baseline data and events during follow-up were ascertained through a combination of inpatient (state-wide hospital database — OACIS™) and outpatient (clinic patient record) sources.

2.2. CMR imaging

2.2.1. Cine imaging

All CMR studies were performed using a 1.5 T MRI scanner (Siemens Avanto, Erlangen, Germany) with a phased array cardiac coil. Hemodynamic parameters, oxygen saturation and lead vector ECG rhythm were continuously monitored throughout. Following image localisers, ventricular long and short axis cine images were acquired in end expiration with retrospectively ECG-gated steady-state free precession sequences (image matrix 156×192, read field of view (FOV) 340 mm, phase FOV 75–100% of the FOV read, echo time 1.12 ms, flip angle 70°) with slice thickness 6 mm and intersection gaps of 4 mm. The AS-CMR protocol is illustrated schematically in Fig. 1.

2.2.2. Adenosine infusion protocol

Adenosine (Adenoscan®, Sanofi-Synthelabo) was infused at 140 μg/kg/min, via a 20-gauge cannula sited in an antecubital vein, using a syringe pump (Graseby® 3500). Adenosine was infused for a minimum of 3 min before acquiring stress images. Indications for terminating adenosine infusion were persistent or symptomatic 3rd degree atrioventricular block, severe hypotension (systolic blood pressure<90 mm Hg) or bronchospasm. Scans were supervised by an MRI trained clinician with access to immediate resuscitation facilities.

2.2.3. Perfusion imaging

Perfusion imaging was performed using a T1-weighted fast low-angle single shot (FLASH) gradient-echo sequence (Read FOV 340 mm, phase FOV 75% of the read FOV, base matrix 128×96, echo time 1.04 ms, repetition time 3.3 ms, saturation recovery time 100 ms, voxel size 2.7×2.2×10 mm; flip angle 12°). Parallel acquisition method with generalised autocalibrating partially parallel acquisition (GRAPPA) was utilised [16] with an acceleration factor of 2. Image data acquisition time per slice was 100 ms. Three short axis slices with mean slice separation of 150% were acquired during each cardiac cycle over 50 consecutive cycles. Gadolinium-DTPA (Magnevist; Schering, Germany) was administered intravenously at 0.1 mmol/kg body weight (injection rate 7 ml/s), followed by 30 ml normal saline at the same rate [13,17]. Rest perfusion imaging was performed a minimum of 10 min after the stress sequences.

2.3. CMR analysis

2.3.1. Visual analysis

Visual analysis of myocardial perfusion was performed off-line by consensus of 2 CMR specialists. Rest and stress perfusion images of the 3 short axis sections (base, mid and apex) were viewed side by side. If an area of reduced signal intensity persisted for at least 3 frames compared with remote myocardium, it was considered to be ischaemic, as previously described [18]. If the same signal intensity abnormality was observed in the rest and stress perfusion images and there was no evidence of scar on late contrast enhanced images, the defect was considered an artefact as previously described [18]. All cases underwent evaluation for late gadolinium enhancement. A normal scan required the absence of both reversible ischaemia and late gadolinium enhancement. A representative example of a patient with inducible ischaemia is shown in Fig. 2.

2.3.2. Left ventricular function analysis

Left ventricular ejection fraction, volume and myocardial mass were derived from cine images using commercially available software (MASS v7.2, Medis, The Netherlands). Papillary muscles and pericardial fat were excluded from calculations. In brief, the end-diastolic and end-systolic cine frames were identified for each slice and the endocardial and epicardial borders were manually traced. The end-diastolic and end-systolic volumes were then calculated using the true disk summation method [19,20].

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation for normally distributed data or as median (interquartile range) for data which did not follow a normal distribution. The negative predictive value of CMR in predicting cardiac events was determined. Associations between variables were made using Chi square analysis or Mann–Whitney testing as appropriate. Variables with $p<0.2$ on univariate analysis were entered into a multivariate analysis. Multivariate analysis to determine the best independent predictor for MACE was performed by binary logistic regression. A p value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS 17.0 (SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Patient characteristics

All 362 consecutive patients who underwent AS-CMR were included in the analysis, with no patients excluded due to uninterpretable images. Mean age was 62 ± 12 years and 211 (58%) were male. Some patients had additional tests in the 3 months prior to CMR including exercise treadmill testing (70 patients) or angiography with indeterminate stenoses (39 patients). Demographic characteristics of the study population are summarised in Table 1. Documented CAD, defined as angiographically proven disease, previous MI or previous percutaneous coronary intervention (PCI), was present in 157/362 (43%). In the remainder of the cohort, the median pre-test probability of having CAD was calculated as 75% (51–90) (Fig. 3). Therefore the study population occupies a position at the higher end of the 10–90% intermediate risk group as described in contemporary guidelines [11]. The cohort was followed-up for a median of 22 (18–25) months.

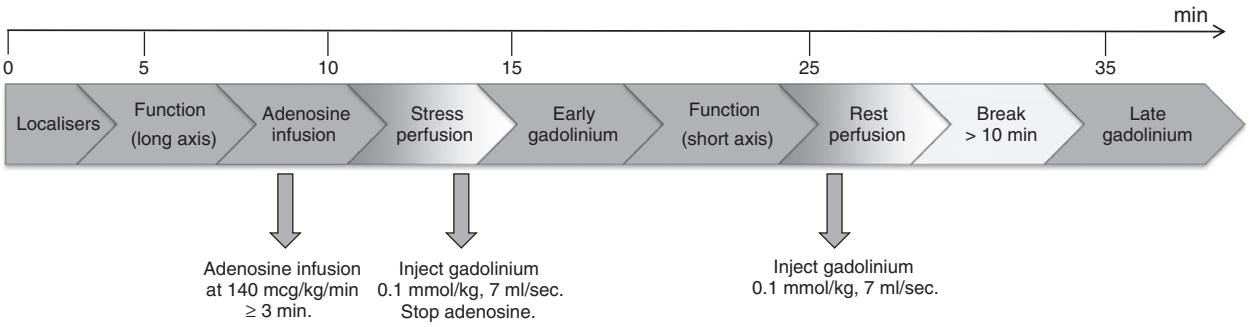

Fig. 1. Adenosine stress CMR protocol. Following image localisers, ventricular long cine images were acquired. Adenosine (140 mcg/kg/min) infused for ≥3 min before stress perfusion imaging at the time of gadolinium injection. Early gadolinium imaging is followed by short axis cine and then rest perfusion imaging. Late gadolinium enhancement images to evaluate scar/viability conclude the scan. Study duration typically 35–40 min.