International Journal of Cardiology 166 (2013) 458–464

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Relationship of cardiac biomarkers and reversible and irreversible myocardial injury following acute myocardial infarction as determined by cardiovascular magnetic resonance☆,☆☆

Adam N. Mather, Timothy A. Fairbairn, Nigel J. Artis, John P. Greenwood, Sven Plein *

Multidisciplinary Cardiovascular Research Centre, University of Leeds, United Kingdom

ARTICLE INFO

Article history:
Received 31 July 2011
Received in revised form 27 October 2011
Accepted 1 November 2011
Available online 26 November 2011

Keywords:
Acute myocardial infarction
Cardiac magnetic resonance imaging
Cardiac biomarkers

ABSTRACT

Background: Cardiovascular magnetic resonance (CMR) can accurately depict myocardial oedema, haemorrhage, infarction and microvascular obstruction. The purpose of this study was to establish the relationships between cardiac biomarkers and reversible and irreversible myocardial injury following AMI, as determined by CMR.
Methods: Forty-eight patients admitted with AMI and successfully treated with primary percutaneous coronary intervention were studied. A comprehensive CMR protocol was performed at day 2, 1 week, 1 month and 3 months after presentation. Blood samples were taken at the same intervals and analysed for highly sensitive C-reactive protein (hs-CRP), Troponin I, N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) and Heart-type fatty acid binding protein (H-FABP). The CMR end points were the extent of myocardial oedema, haemorrhage and infarction as well as left ventricular function and volumes.
Results: Multiple regression analyses demonstrated that hs-CRP on 'day 2' was the strongest independent predictor of left ventricular ejection fraction (LVEF) ($p = 0.007$) and left ventricular end-systolic volume (LVESV) ($p = 0.002$) at 3 months. Troponin I level on 'day 2' was the only independent predictor of infarct size ($p = 0.002$) at 3 months. Patients with haemorrhagic infarctions had significantly higher biomarker levels at 'day 2'. NT-pro-BNP levels were significantly greater in patients with myocardial haemorrhage at all four time points.
Conclusions: C-reactive protein measured two days after reperfusion was the strongest independent predictor of left ventricular remodelling at three months. Elevated biomarker levels in patients with haemorrhagic infarction suggest that reperfusion haemorrhage is a marker of more severe myocardial injury and may be associated with adverse ventricular remodelling.

1. Introduction

The role of inflammation in coronary artery disease (CAD) is well recognized [1]. Inflammatory cells and proteins and inflammatory pathways are instrumental in the pathogenesis of various stages of atherosclerosis. These include the initiation and progression of atheroma, plaque instability and rupture, and restenosis following percutaneous coronary intervention [2–4]. Inflammatory cytokines are also released by myocytes following acute myocardial infarction (AMI) in order to influence tissue healing [5].

C-reactive protein (CRP) is one of the most widely studied inflammatory markers in cardiovascular disease. It is an acute phase protein that has been shown to be a marker of systemic inflammation, elevated in response to infection, injury and other inflammatory stimuli such as myocardial infarction [6]. In healthy individuals only trace levels of CRP can be detected in the circulation. CRP is produced mainly in the liver but there is evidence to suggest that it is also produced in vascular smooth muscle cells and macrophages of atherosclerotic lesions [7]. Its production is controlled by several cytokines, principally interleukin-6, which is released from the viable border zone of reperfused infarctions [8]. Several clinical studies of patients with AMI have demonstrated associations between elevated CRP levels and larger infarcts [9,10] as well as adverse clinical outcomes [11,12]. However, the relationship between CRP and the extent of reversible myocardial injury following AMI has not been elucidated.

Cardiovascular magnetic resonance (CMR) imaging has the unique ability to characterize tissue non-invasively and without the use of ionizing radiation. In the setting of AMI, CMR is particularly useful in accurately assessing myocardial oedema [13], infarcted tissue [14], microvascular obstruction [15] and myocardial haemorrhage [16].

☆ There are no relationships with industry to declare.
☆☆ This research was supported by a project grant from Heart Research UK.
* Corresponding author at: Multidisciplinary Cardiovascular Research Centre, Division of Cardiovascular and Neuronal Remodelling, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, G-floor, Jubilee Wing, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, United Kingdom. Tel.: +44 113 3925404; fax: +44 113 3925405.
E-mail address: s.plein@leeds.ac.uk (S. Plein).

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.11.004

Irreversible injury is detected using late gadolinium enhancement (LGE) imaging which can depict infarcted myocardium with sensitivity comparable only to histology [14,17]. T2-weighted (T2W) CMR performed up to one week after reperfusion can also accurately determine vulnerable myocardium at risk, as it was before recanalization of the occluded coronary artery [18]. Therefore, CMR can quantify reversible (salvaged) myocardium as myocardium at risk minus infarct size.

In this study, we aimed to assess the relationships between highly sensitive C-reactive protein (hs-CRP) and reversible and irreversible myocardial damage, as determined by CMR, in patients with reperfused AMI. CMR was also used to detect myocardial haemorrhage which has been associated with adverse left ventricular (LV) remodelling following AMI [19]. However, the relationship between reperfusion haemorrhage and inflammation has not been addressed clinically and we therefore sought to explore any differences in hs-CRP in patients with haemorrhagic infarction. Finally, by performing serial CMR examinations, we aimed to compare the predictive values of hs-CRP, Troponin I, NT-pro-BNP (N terminal-pro-Brain Natriuretic Peptide) and Heart-type fatty acid binding protein (H-FABP) to determine infarct size, LV function and LV end-systolic volume (LVESV) at three months after reperfusion.

2. Methods

2.1. Study population

We prospectively enrolled 57 patients hospitalised to our institution between August 2008 and December 2009 with first presentation acute ST elevation myocardial infarction and treated successfully with primary percutaneous coronary intervention (PPCI) within 12 h of symptom onset. A successful PPCI result was defined as restoration of Grade 2 or 3 TIMI (thrombolysis in myocardial infarction) flow, as determined by coronary angiography. The study was approved by the institutional Research Ethics Committee and complied with the Declaration of Helsinki; written informed consent was obtained from all patients. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology. Patients with a history of previous coronary revascularization (i.e. PCI or coronary artery bypass surgery), previous myocardial infarction, severe renal failure (defined as estimated glomerular filtration rate <30 ml/min/1.73 m^2) or contraindication to CMR examination, were excluded. Clinical data regarding patient characteristics and procedural details were gathered from the medical notes.

2.2. CMR protocol

All patients underwent CMR imaging within 72 h of their index presentation. Follow up CMR studies, using the identical imaging protocol, were performed at 1 week, 1 month and 3 months. Patients were studied supine in a 1.5 Tesla scanner (Philips Healthcare, Best, The Netherlands) equipped with 'Master' gradients (30 mT/m peak gradients; 150 mT/m/ms slew rate) and a 5-element cardiac phased array receiver coil. Images were acquired using electrocardiographic gating and expiratory breath holds. All data were acquired in the true left ventricular short axis with 10–12 contiguous sections as required to cover the entire left ventricle.

Cine imaging was carried out using a steady state free precession (SSFP) pulse sequence. Next, T2W CMR was performed, also in the short axis orientation, using a dark-blood T2W short tau inversion-recovery (STIR) fast spin echo sequence. This was immediately followed by a dual-echo T2-star sequence in the identical orientation [20].

A dose of 0.2 mmol/kg of Gadolinium-DTPA (dimeglumine gadopentetate, Magnevist, Schering AG, Germany) was then administered. Ten minutes after contrast injection, a 'Look Locker' sequence was performed to obtain the most appropriate inversion time (TI) to null the signal intensity of normal myocardium. This was immediately followed by acquisition of late gadolinium enhanced (LGE) images using an inversion recovery-prepared T1-weighted gradient echo pulse sequence.

2.3. CMR analysis

The CMR images were analysed off-line using commercial software (MASS 6.0, Medis, Leiden, The Netherlands) by two experienced observers blinded to all clinical details. For assessment of LV volumes and mass, 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 summation of discs method. LV mass (g) was calculated from the total volume of myocardium at end-diastole multiplied by the myocardial density of 1.05 g/ml. LV volumes and mass were indexed to body surface area (BSA) as calculated by the Mosteller method [21].

Infarcted tissue was identified using LGE images (Fig. 3). The LV endocardial and epicardial borders on each slice were traced manually. Infarcted tissue was defined as an area of gadolinium hyperenhancement in a subendocardial or transmural pattern and in the territory of a coronary artery. These regions were identified and then quantified using a semi-automated algorithm. Areas of hyperenhancement were defined as myocardium with a signal intensity >2 SD above the mean signal intensity of remote normal myocardium [14]. The mass of infarcted myocardium was then automatically calculated (scar) and expressed as a percentage of LV mass that is infarcted (% LV—scar).

The area at risk (AAR) was quantified on T2W images by using a similar semi-automated algorithm as above (Fig. 3). Myocardium with a signal intensity >2 SD above the mean signal intensity of remote normal myocardium was considered to be oedematous [22]. Areas of increased signal intensity due to slow flow of blood adjacent to the endocardium were excluded. The mass of oedematous myocardium was then automatically calculated (AAR) and expressed as a percentage of LV mass (% LV—AAR). The mass of salvaged myocardium was derived by subtracting the mass of infarcted tissue from the mass of AAR. This was then represented as a percentage of AAR to give a % myocardial salvage index (MSI) [23].

The presence of myocardial haemorrhage was determined using T2-star CMR (Fig. 3). Areas of hypointense signal within the infarcted territory were considered to be haemorrhage [20,24].

2.4. Blood sampling protocol

Venous blood samples were collected from each patient on arrival at each CMR visit (i.e. 2 days, 1 week, 1 month and 3 months after index presentation). The blood samples were collected in four serum separator tubes containing separating gel and clot activator. The samples were then centrifuged within 30 min of collection, at 3000 rpm for 10 min. The serum was then carefully separated and stored at −80 °C. All of the samples were analysed together in one batch at the end of the study.

2.5. Biochemical analyses

Troponin was measured with the Advia Centaur system (Siemens Healthcare Diagnostics). The assay for measuring troponin in routine clinical practice at the recruiting hospital was Advia TnI-Ultra. The cutoff value corresponding to the 99th percentile value of healthy adults for this assay is 0.05 μg/l. This has previously been established locally with a reference population of 299 healthy adults [25]. The intra-assay coefficient of variation (CV) was 10% at a concentration <0.01 μg/l.

H-FABP was measured with the Cardiac Biochip array technology on the fully automated Evidence system (Randox Laboratories, Ltd., Co., Antrim, United Kingdom). This biochip uses a high precision, chemiluminescent immunometric assay for measuring H-FABP with 2 mouse monoclonal antibodies. The intra-assay CV has previously been assessed to be 5% at a concentration of 5.8 μg/l (99th percentile values for subjects with estimated glomerular filtration rate >60 ml/min) [26].

NT-pro-BNP was measured on an Immulite 2000 analyser (Siemens Healthcare Diagnostics, Camberley, UK). The Immulite 2000 NT-pro-BNP assay is a solid phase, two site chemiluminescent immunometric assay with a range of 20–35,000 pg/ml. The intra-assay CV was 5% at concentration of 519 pg/ml.

Highly sensitive CRP was measured on an Advia 2400 Chemistry System (Siemens Healthcare Diagnostics, Camberley, UK) using the Wide Range C-Reactive Protein assay from the same company. The assay range is 0.03–640 mg/l. The intra-assay CV was 5% at a concentration of 1.1 mg/l. This assay measures hs-CRP in serum by a latex-enhanced immunoturbidimetric assay. It is based on the principle that the analyte concentration is a function of the intensity of scattered light caused by the latex aggregates. The latex particles coated with anti-CRP rapidly agglutinate in the presence of C-reactive protein, forming aggregates.

2.6. Statistical analysis

Statistical analysis was performed using commercially available software (SPSS, version 16.0, SPSS Inc, Chicago, USA). Two-sided p values ≤ 0.05 were considered to be statistically significant. Continuous data are summarised as mean (standard deviation, SD) unless otherwise stated and categorical data as numbers (percentages). The distribution of the biochemical data was assessed using the Kolmogorov–Smirnov test. The data did not follow a Gaussian distribution. Therefore, these variables are expressed as mean and interquartile range (IQR) and non-parametric tests were used. Mann–Whitney U-test was used to examine differences between groups. The relationships between factors were assessed using Spearman correlation coefficients. Multiple linear regression analyses were used to predict linear endpoints.

3. Results

3.1. Baseline characteristics

Fifty-seven patients were recruited. Four patients were unable to complete the first CMR scan due to claustrophobia. Four patients refused to attend follow-up and one patient died from an intracranial haemorrhage before final follow-up. Therefore, 48 patients completed