International Journal of Cardiology 167 (2013) 2047–2054

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Cardiovascular magnetic resonance-derived intramyocardial hemorrhage after STEMI: Influence on long-term prognosis, adverse left ventricular remodeling and relationship with microvascular obstruction ☆

Oliver Husser [a,b], Jose V. Monmeneu [c], Juan Sanchis [a], Julio Nunez [a], Maria P. Lopez-Lereu [c], Clara Bonanad [a], Fabian Chaustre [a], Cristina Gomez [a], Maria J. Bosch [d], Ruben Hinarejos [c], Francisco J. Chorro [a], Günter A.J. Riegger [b], Angel Llacer [a], Vicente Bodi [a,*]

[a] Cardiology Department, Hospital Clinico Universitario, INCLIVA, Universidad de Valencia, Valencia, Spain
[b] Klinik und Poliklinik für Innere Medizin II, University of Regensburg, Medical Center, Regensburg, Germany
[c] ERESA, Valencia, Spain
[d] Cardiology Unit, Hospital La Plana, Vila-Real, Spain

ARTICLE INFO

Article history:
Received 12 December 2011
Received in revised form 4 April 2012
Accepted 11 May 2012
Available online 9 June 2012

Keywords:
Cardiovascular magnetic resonance
Reperfusion injury
Prognosis
Adverse remodeling

ABSTRACT

Background: T2 weighted cardiovascular magnetic resonance (CMR) can detect intramyocardial hemorrhage (IMH) after ST-elevation myocardial infarction (STEMI). The long-term prognostic value of IMH beyond a comprehensive CMR assessment with late enhancement (LE) imaging including microvascular obstruction (MVO) is unclear. The value of CMR-derived IMH for predicting major adverse cardiac events (MACE) and adverse cardiac remodeling after STEMI and its relationship with MVO was analyzed.
Methods: CMR including LE and T2 sequences was performed in 304 patients 1 week after STEMI. Adverse remodeling was defined as dilated left ventricular end-systolic volume indexes (dLVESV) at 6 months CMR.
Results: During a median follow-up of 140 weeks, 47 MACE (10 cardiac deaths, 16 myocardial infarctions, 21 heart failure episodes) occurred. Predictors of MACE were ejection fraction (HR .95 95% CI [.93–.97], p = .001, per %) and IMH (HR 1.17 95% CI [1.03–1.33], p = .01, per segment). The extent of MVO and IMH significantly correlated (r = .951, p < .0001). dLVESV was present in 40% of patients. CMR predictors of dLVESV were: LVESV (OR 1.11 95% CI [1.07–1.15], p < .0001, per ml/m^2), infarct size (OR 1.05 95% CI [1.01–1.09], p = .02, per %) and IMH (OR 1.54 95% CI [1.15–2.07], p = .004, per segment). Addition of T2 information did not improve the LE and cine CMR-model for predicting MACE (.744 95% CI [.659–.829] vs. .734 95% CI [.650–.818], p = .6) or dLVESV (.914 95% CI [.875–.952] vs. .913 95% CI [.875–.952], p = .9).
Conclusions: IMH after STEMI predicts MACE and adverse remodeling. Nevertheless, with a strong interrelation with MVO, the addition of T2 imaging does not improve the predictive value of LE-CMR.

1. Introduction

In ST-segment elevation myocardial infarction (STEMI) timely reperfusion is the primary therapeutic goal [1]. Nevertheless, despite re-established epicardial blood flow in the infarct related artery, microvascular perfusion might still be impaired, a phenomenon referred to as microvascular obstruction (MVO) [2]. Moreover reperfusion itself may cause additional myocardial damage termed reperfusion injury with intramyocardial hemorrhage (IMH) [3].

These phenomena can be readily assessed using cardiovascular magnetic resonance imaging (CMR) allowing for a state of the art assessment of the post-infarction patient [4,5]. Using T2 weighted sequences, CMR allows for the appreciation of myocardial edema representing the area at risk in an acute STEMI [6]. Within these hyperdense areas of myocardial edema, hypodense cores can appear and are suspected to reflect IMH [7,8].

Additionally, CMR allows for an exact delineation of infarct size in late gadolinium enhancement (LGE) sequences. Dark areas within the core of the infarct zone have been described as MVO resulting from impaired microvascular perfusion due to multifactorial causes including edema, microembolization and inflammatory response [9,10].

MVO has been linked to adverse outcome and left ventricular (LV) remodeling [5,11,12]. Emerging data indicates that the presence of IMH also brings about a higher rate of cardiovascular events [13], nevertheless the existing prognostic data are scarce and it is unclear whether or not both phenomena represent different entities or

☆ This work was supported by the "Instituto de Salud Carlos III" (PI1102323 grant), the Foundation Gent per Gent, and by the "Microcluster Proteccion Cardiovascular". No conflicts of interests exist in the present study.
* Corresponding author at: Cardiology Department, Hospital Clinico Universitario, Universitat de València, Incliva Blasco Ibanez 17, 46010 Valencia, Spain. Tel./fax: +34 96 3862658.
E-mail address: vicentbodi@hotmail.com (V. Bodi).

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doi:10.1016/j.ijcard.2012.05.055

are representations of the same pathology in different imaging sequences.

In the present study we aimed to assess [1] the long-term prognostic value of CMR-derived IMH in a large unselected population of STEMI patients, [2] the influence of IMH on LV remodeling at the 6th month, [3] to compare the additional value of T2 imaging beyond LGE imaging for these purposes and [4] to assess the relationship of IMH with MVO.

2. Methods

2.1. Study group

We prospectively included patients admitted to our institution with a first STEMI from November 2001 to December 2010. Patients who died or had a reinfarction or otherwise complicated clinical course or cardiac surgery as well as those who denied participation in the registry, were transferred to other hospitals after reperfusion or those who had contraindications to CMR were not included in the study. Patients underwent CMR at 1 week and, in order to evaluate LV remodeling, at 6 months after STEMI.

In total, 335 patients underwent a CMR study at the 1st week after STEMI (median 6 days). Of these, 31 patients (9%) were excluded from the study due to insufficient image quality in T2 imaging, resulting in 304 patients with a complete 1st week CMR study. For evaluation of late LV remodeling after STEMI, CMR was repeated at 6 months (189 ± 32 days) in 234 patients. The reasons for exclusion were: MACE during the first 6 months (n = 23), contraindications to CMR (n = 14), patient/cardiologist decision (n = 26) or patient not contactable (n = 7).

Our institutional ethics committee approved the research protocol and written informed consent was obtained from all subjects. The study was conducted in accordance with the Declaration of Helsinki. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Reperfusion therapy

Reperfusion strategy and medical treatment were left to the discretion of the attending cardiologists. A pharmacoinvasive strategy [14] consisting of thrombolysis with timely angiography was used as a reperfusion therapy in 161 patients (53%) and 107 (35%) were directly submitted to primary percutaneous coronary intervention (PCI). 38 patients underwent rescue angioplasty due to failed thrombolysis. There were 36 patients (12%) who did not receive any reperfusion therapy within the first 12 h after symptom onset due to delayed presentation in all cases.

Overall, 260 patients (86%) were treated with a stent: 100 during primary angioplasty, 28 during catheterization after delayed presentation and 132 during cardiac catheterization performed after thrombolysis (of these 33 during rescue angioplasty). *Thrombolysis in myocardial infarction* (TIMI) flow grade before and after PCI and myocardial blush grade after PCI were determined offline by an experienced observer unaware of CMR results using standard software (Integris HM3000, Philips, Best, the Netherlands). TIMI flow grade 3 and myocardial blush grade 2 to 3 were regarded as normal [15].

2.3. CMR study

CMR (1.5-T, Sonata Magnetom, Siemens, Erlangen, Germany) was performed at a median 6 days (at least 48 h after cardiac catheterization) and at 189 ± 32 days after STEMI according to our laboratory protocol [4,16,17]. All images were acquired by a phased-array body surface coil during breath-holds and were ECG-triggered.

Cine images were acquired at rest in 2-, 3-, 4-chamber views and every 1 cm in short-axis views using steady-state free precession imaging sequences (repetition time/echo time: 3.2/1.6 ms, flip angle: 61°, matrix: 256 × 128, slice thickness: 6 mm, temporal resolution: 26 ms).

Black blood, T2-weighted STIR (short TI inversion recovery) sequences in the same short-axis view as the cine sequences, all in mid-diastole were carried out. A half-Fourier acquisition single-shot turbo spin echo (HASTE) multisection sequence was used (TR, 2 R–R intervals; TE, 33 ms; TI, 170 ms; slice thickness, 8 mm; interslice interval, 2 mm; flip angle, 160°; matrix, 256 × 151; bandwidth, 781 Hz/pixel) [18]. Additionally, a segmented turbo-spin echo (TSE) sequence was obtained with 1 slice per breath-hold (TR, 2 R–R intervals; TE, 100 ms; TI, 170 ms; slice thickness, 8 mm; interval, 2 mm; flip angle, 180°; matrix, 256 × 146; bandwidth, 235 Hz/pixel) [19,20].

LGE imaging was performed in the same projections used for cine images at least 10 min after administering 0.1 mmol/kg of gadoliniumdiethylenetriaminepentaacetic acid (Magnograf, Juste S.A.Q.F., Madrid, Spain). A segmented inversion recovery steady-state free precession imaging sequence was used (repetition time/echo time: 2.5/1.1 ms; slice thickness: 6 mm; flip angle: 50°; matrix: 195 × 192) nullifying myocardial signal.

2.4. CMR data analysis

CMR studies were analyzed by an experienced observer blinded to all patient data using customized software (QMASS MR, 6.1.5, Medis, Leiden, The Netherlands).

LV ejection fraction (%), end-diastolic and end-systolic volume indexes (ml/m^2) and mass (g/m^2) were calculated by manual planimetry of endocardial and epicardial borders in all short-axis views cine images. For segmental analysis, the 17 segment model was applied [21].

For the evaluation of myocardial edema, TSE sequences were used in approximately 80% of the cases due to the superior quality. Since this sequence is prone to motion artifacts, in the remaining cases, myocardial edema was evaluated in the HASTE sequences. Myocardial edema was automatically quantified as areas of high T2 signal intensity (>2 standard deviations greater with respect to remote non-infarcted myocardium) and manually corrected by an expert observer. Myocardial edema was expressed as percentage of LV mass. The finding of a low-signal-intensity area surrounded by a high-signal-intensity area in these images was considered to indicate an area of IMH. In order to avoid the influence of artifacts, a patient was considered to have IMH if a hypodense area was observed in more than one segment (Fig. 1A).

LGE was considered present if signal intensity was >2 standard deviations with respect to a remote non-infarcted area in LGE imaging [4]. Infarct size was calculated as the percentage of LV mass showing LGE.

MVO was visually defined on a segmental basis as a lack of contrast uptake in the core of a segment surrounded by tissue showing LGE [22]. On a patient basis, significant MVO was considered if it was detected in more than one segment (Fig. 1B).

Salvaged myocardium was defined by subtracting the mass of infarcted myocardium from myocardium showing edema and expressed as percentage of LV mass.

Thus, all CMR indexes were quantitatively assessed with the exception of the extent of MVO and IMH. Due to the inherent difficulties to precisely quantify the latter, we regarded them on the basis of the analysis performed by the experienced independent observer, as the number of segments displaying hypointensity in the core of edema (IMH) and LGE (MVO).

The intraobserver variability for the determination these CMR parameters in our group is less than 5% [5,23,24].

2.5. Endpoints and follow-up

The endpoints of the study were MACE and adverse LV remodeling at the 6th month. MACE was defined as cardiac death, admission for nonfatal myocardial infarction [25], and admission for heart failure [26] whichever occurred first. An independent adjudication process, including review of clinical histories was applied and consensus between two cardiologists was required to finally adjudicate an event.

Adverse LV remodeling was defined as a dilated left ventricular end-systolic volume index (dLVESV) according to accepted reference values according to gender, age and body surface area [27] (see online Appendix).

2.6. Statistical analysis

Data were tested for normal distribution using the Kolmogorov–Smirnov test. Continuous normally distributed data were expressed as the mean ± SD and compared using the unpaired or paired samples Student's *t*-test where appropriate. Non-parametric data were expressed as the median with the interquartile range (IQR) and compared using the Mann–Whitney *U*-test or the Wilcoxon signed rank test where appropriate. Group percentages were compared using the Chi-square test or Fisher's exact test where appropriate.

The additional value of T2 imaging on LGE data for the prediction of MACE and dLVESV was assessed by comparing the area under the receiver operating characteristic curve (AUC).

The correlation of IMH with MVO was assessed using Pearson's correlation coefficient.

Multivariate analyses including baseline, angiographic and CMR variables were performed: The association of variables with time to MACE was assessed by means of a Cox proportional hazard regression model using stepwise multivariate procedures adjusted by variables yielding a $p < .2$ in the univariate analyses and traditional risk factors. Hazard ratios (HR) with the corresponding 95% confidence intervals (95% CI) were computed.

For dLVESV, a multivariable logistic regression model was applied, adjusted by variables yielding a $p < .2$ in univariate analyses. Odds ratios (OR) with the respective 95% CI were computed.

Statistical significance was considered for a two-tailed $p < .05$. The SPSS statistical package (version 13.0, SPSS Inc., Chicago, Illinois) was used.

3. Results

The clinical, angiographic and CMR characteristics of the study group are shown in Table 1. IMH was present in 102 patients (34%) and was associated with younger age (57 ± 12 years vs. 59 ± 12, $p = .03$), a higher heart rate on admission (84 ± 20 bpm vs. 79 ± 19, $p = .04$), diabetes (25% vs. 14%, $p = .02$) and a higher rate of Killip