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Utility of galectin-3 in predicting post-infarct remodeling after acute myocardial infarction based on extracellular volume fraction mapping

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ABSTRACT

Aims: ST-segment elevation myocardial infarction (STEMI) triggers remote extracellular matrix expansion. Myocardial extracellular volume fraction (ECV), determined by cardiovascular magnetic resonance, permits quantification of interstitial space expansion. Our aim was to determine the relationship between early serum fibrosis biomarkers and 180-day post-infarct remote myocardium remodeling using ECV.

Methods and results: In 26 patients with STEMI, functional imaging, T1-mapping, and late-gadolinium-enhancement were performed on a 3-T CMR scanner at baseline (days 3 to 5) and 180 days. Biomarkers were measured at days 1, 3, and 7 after STEMI. The mean initial and follow-up left ventricular ejection fraction (LVEF) were 48.3 ± 18.1% and 52.6 ± 12.3%, respectively. Initial infarct size was 11.6 ± 16.8% of LV mass. ECV in the remote myocardium at 180 days correlated with indexed end-systolic volume ($r = 0.4$, $p = 0.045$). A significant correlation was observed between galectin-3 at day 7 and ECV at 6 months ($r = 0.428$, $p = 0.037$). A trend towards a direct correlation was found for BNP ($r = 0.380$, $p = 0.059$). Multivariate analysis revealed that BNP and galectin-3 were independent predictors of long-term changes in ECV and explained nearly 30% of the variance in this parameter ($r^2 = 0.34$; $p = 0.01$). A galectin-3 cutoff value of 10.15 ng/mL was the most powerful predictor of high ECV values (≥28.5%) at follow-up. Galectin-3 at day 7 was an independent predictor of high ECV values at follow-up (OR = 22.51; CI 95%: 2.1–240.72; $p = 0.01$) with 0.76 AUC (CI: 0.574–0.964; $p = 0.03$).

Conclusions: Galectin-3 measured acutely after STEMI is an independent predictor of increased ECV at 6-month follow-up that might be useful for long-term risk stratification.

1. Introduction

Left ventricular (LV) remodeling after STEMI leads to the development of ischemic LV dysfunction, a process characterized by structural and functional alterations involving the myocardium [1], that is related to prognosis and survival [2]. LV remodeling starts early after ST-segment elevation myocardial infarction (STEMI) to an extent that depends primarily on the size of the infarct [3] and involves cellular damage and phenotypic transformation of myocytes and nonmyocyte cells as well as changes in the composition of the extracellular matrix (ECM). ECM that is mainly composed of elastin, glycoproteins, glycosaminoglycans, and collagen fibrils is exposed to a constant homeostatic control of synthesis and degradation mediated by the activity of cardiac fibroblasts and extracellular proteases [4]. In pathological conditions such as after STEMI, alterations in the composition of the cardiac ECM lead to diffuse myocardial fibrosis (DMF) in the remote myocardium as well as replacement fibrosis in the infarcted myocardium, and the exacerbation of these pathological features plays a major role in the

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development of wall stiffness, arrhythmia, and sudden death [5]. In this context, several publications have appeared in recent years documenting that cardiac fibrosis is an independent predictor of major adverse cardiac events [6].

Cardiac magnetic resonance (CMR) is emerging as a modality that enables noninvasive evaluation of the myocardial interstitial space through the measurement of the myocardial extracellular volume fraction (ECV) with T1 mapping techniques. Late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) after administration of gadolinium-based contrast agents (GBCA) is the gold standard for noninvasive detection of focal fibrosis [7]. However, the presence of DMF cannot be evaluated by this technique, and endomyocardial biopsy (EMB) is the gold standard for detecting diffuse fibrosis regardless of sampling errors. ECV has been shown to closely reflect the degree of histologic DMF [8–10].

At present, the ability of circulating biomarkers involved in cardiac ECM turnover and homeostasis to predict ECV expansion following STEMI has not been addressed. The aim of the present study was to determine the relationship between early serum biomarkers, measured during the first week after STEMI, and 180-day post-infarct remodeling of remote myocardium evaluated using ECV by CMR. Our working hypothesis is that the combination of serum biomarkers of ECM turnover may provide additional information on top of LGE-CMR scar characterization to predict adverse LV remodeling.

2. Methods

2.1. Patient population

From June 2013 to September 2014, patients presenting with a first STEMI to the Coronary Care Unit were screened. Patients with early death and those requiring mechanical ventilation or with hemodynamic instability were not included in the study. From 192 patients screened, a total of 29 patients were included. Of them, 26 underwent a complete initial and follow-up CMR study (Fig. 1).

Primary percutaneous intervention was the reperfusion treatment, delivered by experienced on-call interventional cardiologists following unfractionated heparin, aspirin, and a loading dose of clopidogrel. At the physician's discretion and unless contraindicated, captopril or enalapril (at least 6.25 mg every 8 h or 2.5 mg every 12 h, respectively) and beta-blockers were initiated early, usually by 24 h from admission. Serum troponin I was measured over 48 h: every 6 h during the first 12 h and every 12 h thereafter. The main exclusion criteria were the presence of other underlying fibrotic pathologies affecting major organs such as liver, kidney, and lung, as these processes may affect the quantification of cardiac biomarkers for extracellular matrix remodeling and fibrosis. In addition, patients with a previous history of renal or liver failure were also excluded from the study.

2.2. CMR protocol and analysis

CMR examinations were performed at baseline (days 3 to 5) and 180 days after STEMI. CMR images were acquired with a 3-T system (MAGNETOM Trio™, a Tim® System, Siemens Healthcare, Erlangen, Germany) using electrocardiographic triggering and a 32-channel phased array cardiovascular coil. The sequences used in cine image acquisition, inversion-recovery imaging after gadolinium administration [7], and in T1 mapping [11], together with the techniques used in measuring LV volumes, LVEF, ECV [12,13] (Fig. 2), and myocardial infarct size [14] were described elsewhere (further details can be read in the Supplemental material online).

2.3. Laboratory measurements

Blood samples were obtained from study participants at days 1, 3, and 7 after STEMI. Samples were collected and processed as indicated in Supplemental information. Briefly, brain natriuretic peptide (BNP), Enhanced Liver Fibrosis score (ELF™, calculated from the measurement of PIIINP, HA, and TIMP-1), troponin I (TnI), dehydroepiandrosterone sulfate (DHEA-SO_4), insulin-like growth factor 1 (IGF-1), tumor necrosis factor α (TNF-α), pregnancy-associated plasma protein (PAPP-A), the receptor of the cytokine interleukin 2 (IL2R), IL-1β, IL-6, IL-8, IL-10, beta-C-terminal telopeptide (CITP), C-terminal propeptide of type I collagen (PICP), matrix metalloproteinase-1 (MMP-1), MMP-2, MMP-9, apelin, and galectin-3 were quantified as described in Supplemental information. The intra- and interassay coefficients of variation were lower than 5% and 10%, respectively, in all cases. Other biochemical and hematological parameters were measured by standard procedures at the Core Laboratory of the Biomedical Diagnostic Centre of the Hospital Clinic of Barcelona.

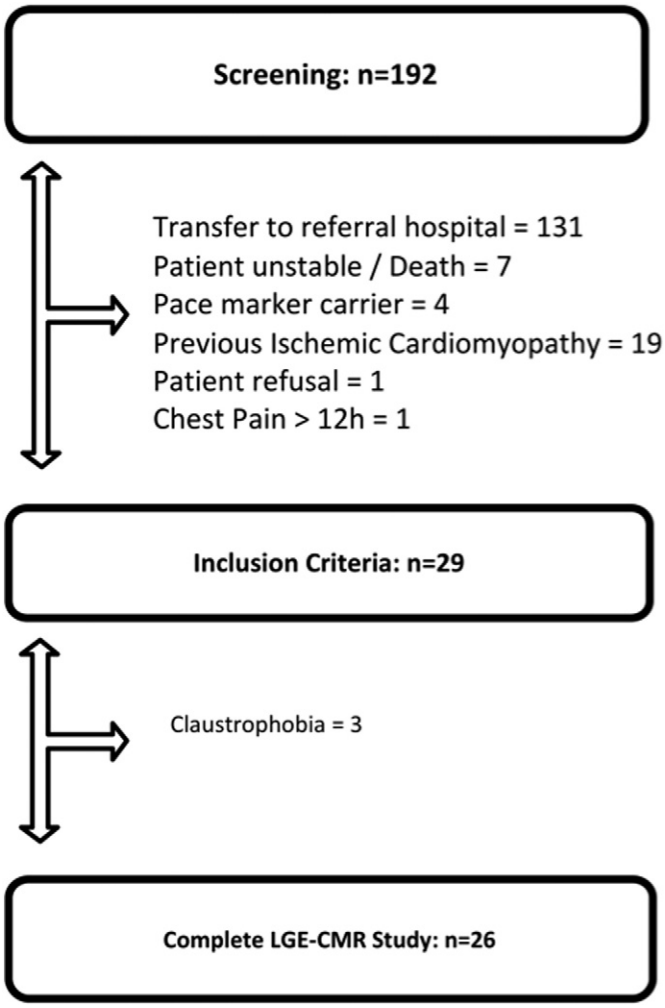

Fig. 1. Patient inclusion flow chart.

2.4. Statistical analysis

Normal QQ plot and the Shapiro–Wilk test were used to identify non-normally distributed variables. Normally distributed data were expressed as mean values ± S.D. Non-normally distributed data were expressed as medians ± interquartile range. CMR measurements were adjusted for total body surface area. The strength of the relationship between the laboratory parameters at days 1, 3, and 7 post-STEMI and the ECV at day 180 was assessed using the Pearson and Spearman correlation coefficients. Correlations between ECV at day 180 and clinical characteristics—age, body mass index, total cholesterol level, and blood pressure—were also conducted. The statistical analysis between ECV