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Soluble IL-1 receptor 2 is associated with left ventricular remodelling in patients with ST-elevation myocardial infarction☆

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ABSTRACT

Background: The inflammatory response following myocardial infarction (MI) is prerequisite for proper healing of infarcted tissue, but can also have detrimental effects on cardiac function. Interleukin (IL)-1α and IL-1β are potent inflammatory mediators and their bioactivity is tightly regulated by IL-1 receptor antagonist (IL-1ra) and soluble (s) IL-1 receptors (R). We aimed to examine whether levels of soluble regulators of IL-1 signalling are changed during ST-elevation MI (STEMI) and their associations with parameters of cardiac injury and ventricular remodelling.

Methods: Plasma levels of IL-1Ra, sIL-1R1, sIL-1R2 and sIL-1R accessory protein (sIL-1RAcP) were measured by immunoassays in repeated samples from patients with STEMI ($n = 255$) and compared to healthy controls ($n = 65$).

Results: IL-1Ra, sIL-1R1 and sIL-1R2 levels were all significantly elevated after STEMI, while levels of sIL-1RAcP were lower compared to controls. sIL-1R2 levels (at different time points) correlated positively with C-reactive protein, myocardial infarct size and change in indexed left ventricular end-diastolic and end-systolic volume (LVEDVi and LVESVi) measured by cardiac MR acutely and after 4 months, and negatively with LV ejection fraction. Patients with >median levels of sIL-1R2 in the acute phase were more likely to have increased change in LVEDVi and LVESVi. Importantly, sIL-1R2 remained significantly associated with change in LVEDVi and LVESVi also after adjustment for clinical covariates.

Conclusion: Levels of sIL-1R2 are independently associated with parameters of LV adverse remodelling following STEMI.

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1. Introduction

Inflammation has a dual role in cardiovascular disease. It is suggested to play a pivotal role in all stages of coronary artery disease from development of atherosclerotic plaques to plaque rupture and thrombus formation, but is also involved in cardiac repair and remodelling following myocardial infarction (MI) [1,2]. The inflammatory response following MI involves cytokine release and infiltration of neutrophils and monocytes, which is prerequisite for proper healing of damaged cardiac tissue. However, excessive inflammation may cause collateral damage and have detrimental effects on cardiac function both in the short and long term [1,2]. Clinical trials have found that targeting interleukin (IL)-1 in acute coronary syndromes by recombinant IL-1 receptor antagonist (IL-1Ra) has anti-inflammatory effects accompanied by reduced ventricular remodelling [3,4], and neutralization of IL-1β was very recently shown to induce a lower rate of recurrent cardiovascular events in patients with previous MI [5]. However, the regulation of IL-1 related molecules, in the complex IL-1 system, following MI, are still not clear.

IL-1α and IL-1β are potent upstream mediators of inflammation and their activity is regulated at several levels (Supplementary Fig. S1) [6]. IL-1α is often classified as an alarmin and is typically membrane associated and rarely detectable in circulation [6]. Activation and secretion of IL-1β is a two-step process involving inflammasomes [6]. IL-1 (both α and β) binds the type I IL-1 receptor (IL-1R1) resulting in recruitment of the co-receptor IL-1 receptor accessory protein (IL-1RAcP), which is required for signal transduction. To avoid an excessive inflammatory response, IL-1 activity is tightly regulated at the receptor level [6]. IL-1 receptor antagonist (IL-1Ra) competes with IL-1 for binding to IL-1R1. Moreover, type II IL-1 receptor (IL-1R2) lacks the ability to initiate signalling and acts as a decoy receptor. Finally, the extracellular domain of all IL-1 receptors may be shed from the cell surface and act as soluble(s) negative regulators of IL-1 signalling (i.e., sIL-1R1, sIL-1R2 and sIL-1RAcP). sIL-1R2 may be of particular importance since binding to IL-1 is nearly irreversible [6], whereas sIL-1R1 also binds IL-1Ra and may therefore also have an inflammatory effect.

We have previously shown elevated levels of IL-1β during acute ST segment elevation MI (STEMI) and an association with subsequent left ventricular (LV) hypertrophy and remodelling [7]. Others and we have also shown that IL-1Ra is increased in the acute phase of MI [7–9], but not much is known about levels of the soluble IL-1 related receptors which clearly influence the net activity in IL-1 related pathways. Herein, we examined levels of soluble regulators of IL-1 signalling in STEMI as well as their associations with parameters of cardiac injury and ventricular remodelling.

2. Material and methods

2.1. Study population

Samples from the previously reported Post-conditioning in ST-Elevation Myocardial Infarction (POSTEMI; www.clinicaltrials.gov; NCT00922675) trial [10] were investigated and consisted of 272 patients included between January 2009, and August 2012, at Oslo University Hospital Ullevål, Norway, with first-time STEMI with symptoms of <6 h and with typical changes in ECG with >1 mm elevation in the ST-segment in at least two contiguous extremity leads or >2 mm elevation of the ST-segment in at least two contiguous precordial leads or new-onset left-bundle branch block and with successful opening of the occluded coronary vessel after one balloon inflation. The study was approved by the Regional Ethics committee and conducted in accordance with the principles of the declaration of Helsinki and all patients provided written informed consent. Study design, including study flow-chart and detailed cardiac magnetic resonance imaging (CMR) protocol has previously been reported [10,11]. Patients with inability to provide informed consent, previous MI, renal failure (serum creatinine > 200 μmol/L), contraindications to CMR, and clinically unstable patients (cardiac arrest, cardiogenic shock, pulmonary congestion, or hypotension), were excluded. POSTEMI compared two reperfusion strategies, primary PCI with ischemic postconditioning (IPost) or conventional PCI. STEMI was defined and treated according to current guidelines [12]. CMR was performed median 2 days after the index event in the acute phase and repeated after 4 months' follow-up, allowing assessment of infarct size, left ventricular ejection fraction (LVEF), LV volumes, myocardial salvage, and microvascular obstruction (MVO). Estimation of myocardial salvage (%) was based on CMR measurements of myocardium at risk in the acute stage and final infarct size at 4 months' follow-up, as previously reported [10]. Clinical end points were recorded at follow-up visits 4 and 12 months after the index infarction, and long-term mortality data were acquired from clinical records median 70 months after inclusion. The effect of IPost on the primary endpoint of the study, final infarct size measured by CMR after 4 months, was neutral [10]. Sixty-five healthy individuals were included as controls.

2.2. Blood sampling protocol

Blood samples were drawn before and immediately after the percutaneous coronary intervention (PCI) procedure, at day 1 following the procedure and after 4 and 12 months. EDTA-blood was placed on crushed ice and within 30 min centrifuged at 3000*g* for 20 min at 4 °C to obtain platelet-poor plasma. Samples were stored at −80 °C until analysis.

2.3. Immunoassays

EDTA-plasma levels of sIL-1R1, sIL-1R2, sIL-1RAcP were analysed by enzyme immunoassays from R&D Systems (DuoSet), while IL-1Ra was measured using an enzyme immunoassay from Peprotech (Rocky Hill, NJ).

2.4. Statistical analyses

Differences between groups were analysed with the use of Mann-Whitney *U* test. Due to differences in some demographics (age, sex, smoking and BMI), ANCOVA was used at each time-point when comparing levels of IL-1 related proteins between patients and controls. Univariate repeated measures ANOVA was used to assess changes in protein levels over time during STEMI. Associations between variables were assessed by means of Spearman correlation coefficient. To further assess possible associations between sIL-1R2 and LV remodelling, multiple linear regression analyses were performed with change in indexed LV end-diastolic volume (LVEDVi) and LV end-systolic volume (LVESVi) from STEMI to 4-month follow-up as outcome variables, respectively. The following covariates were entered into the models based on either clinical relevance or an association with either sIL-1R2 or the dependent variable in univariable analyses with a p-value < 0.2: Age, gender, hypertension, diabetes mellitus, time from symptom onset to PCI, infarct localization (anterior MI vs inferior or posterior MI), treatment with ischemic postconditioning, peak troponin T, peak C-reactive protein (CRP), N-terminal brain natriuretic peptide (NT-proBNP) on admission and hemoglobin on admission. As a result of skewness, the following continuous variables were logarithmically transformed with the natural logarithm (ln): Time from symptom onset to PCI, troponin T, CRP, and NT-proBNP. A backward stepwise regression approach was used to produce the final model, with removal of the variable with the smallest contribution to the model (largest p-value above $p < 0.05$) at each step. Pairwise deletion was used to handle missing data in multivariable analyses. Collinearity was assessed by the variance inflation factor in all multivariable models. A p-value < 0.05 was considered statistically significant. All analyses were performed by IBM SPSS Software, version 23.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

3.1. Temporal changes in plasma levels of IL-1 signalling regulators after STEMI

We analysed plasma levels of regulators of IL-1 signalling in 272 patients with STEMI from the POSTEMI trial [10], and 65 healthy controls. Baseline characteristics are shown in Table 1 showing that patients were younger, had a higher BMI and proportion of smokers and males. Samples were acquired immediately before and immediately after the PCI procedure, at day 1 after PCI (median 18.3 h after PCI) and at 4-month and 12-month follow-up. At baseline, before PCI, the STEMI population was characterised by increased levels of IL-1Ra, sIL-1R1 and sIL-1R2 and decreased levels of sIL-1RAcP as compared with healthy controls (Fig. 1). IL-1Ra levels peaked right after PCI, but remained elevated even one year after STEMI. sIL-1R1 levels were at their highest before PCI and thereafter decreased, ending up lower than controls at 4 and 12-month follow-up. Notably, however, the elevated levels of sIL-1R2 and decreased sIL-1RAcP levels remained stable throughout the study. The IPost procedure did not affect levels of IL-1 regulators (data not shown).

3.2. Levels of soluble IL-1 modulators in relation to measures of myocardial injury and remodelling as assessed by CMR after STEMI

We then studied the associations between soluble regulators of IL-1 signalling and markers of myocardial damage and remodelling. There

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