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Original article

Angiotensin II receptor blockers suppress the release of stromal cell-derived factor-1α from infarcted myocardium in patients with acute myocardial infarction

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ABSTRACT

Background: Although angiotensin II receptor blockers (ARBs) have been shown to have anti-inflammatory effects on infarcted myocardium in experimental models, little is known in humans. Stromal cell-derived factor-1α (SDF-1α), a pro-inflammatory chemokine, is released from infarcted tissue in patients with acute myocardial infarction (AMI). This study examined whether ARBs suppress SDF-1α production in the infarcted lesion in patients with AMI.

Methods: SDF-1α levels were measured by enzyme-linked immunosorbent assays in plasma obtained from the aortic root (AO) and the anterior interventricular vein (AIV) in 50 patients with an anterior AMI. Measurement of SDF-1α levels and left ventriculography were repeated at discharge and 6 months after AMI. Patients were divided into 2 groups according to treatment with ARBs, which were administered at the discretion of the attending physician after admission.

Results: The AIV–AO gradient of SDF-1α, reflecting SDF-1α release from the infarcted myocardial region, decreased between the time of discharge and 6 months after AMI in patients taking an ARB. In contrast, the SDF-1α transcardiac gradient did not change in patients not taking an ARB. Among the clinical parameters tested, only the use of ARBs was significantly associated with percent changes in the SDF-1α transcardiac gradient from the time of discharge to 6 months after AMI in a linear regression analysis ($r = -0.31$, $p = 0.03$). The SDF-1α transcardiac gradient 6 months after AMI was inversely correlated with the percent change in left ventricular (LV) ejection fraction ($r = -0.52$, $p < 0.01$) and positively correlated with the percent change in LV end-diastolic volume index ($r = 0.57$, $p < 0.01$) and LV end-systolic volume index ($r = 0.54$, $p < 0.01$) during 6 months after AMI.

Conclusions: ARB treatment suppressed SDF-1α release from the infarcted myocardial region, which was associated with improvement in LV dysfunction and adverse remodeling in AMI survivors.

Introduction

Left ventricular (LV) dysfunction and adverse remodeling after myocardial infarction (MI) are important predictors of mortality and adverse cardiac events [1,2]. MI is followed by an early inflammatory response that clears dead cells and matrix debris [3]. However, prolonged inflammation in the infarcted lesion leads to dysfunction and adverse remodeling of the infarcted myocardium through matrix degradation and cardiomyocyte apoptosis [3].

A variety of cytokines, chemokines, and growth factors are involved in the post-MI inflammatory response in the infarcted lesion [4,5]. Stromal cell-derived factor-1α (SDF-1α)/CXCL12 is a CXC chemokine with chemotactic effects for CXCR4-expressing progenitor cells [6]. Several previous animal studies showed that SDF-1α expression is up-regulated in the infarcted lesion [7], and that SDF-1α exerts beneficial effects on the healing process after MI by enhancing the regenerative capacity of mobilized CXCR4-expressing progenitor cells [7], increasing angiogenesis [8], and decreasing cardiomyocyte apoptosis [9]. However, other animal

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experiments showed that SDF-1α/CXCR4 signaling worsened post-infarction LV function through pro-inflammatory mechanisms, including an increased influx of inflammatory cells and enhanced cardiomyocyte apoptosis [10,11]. Thus, animal studies have shown conflicting results regarding the effects of SDF-1α on post-infarction LV function [12]. In recent clinical studies, we found that release of endogenous SDF-1α from the infarcted lesion was associated with LV dysfunction and adverse remodeling after MI [13]. Therefore, endogenous SDF-1α expressed in the infarcted lesion may exert detrimental effects on the post-infarction reparative process in humans.

The renin–angiotensin–aldosterone system (RAAS) is activated after MI, both in the infarcted lesion and in the peripheral circulation [14–16]. The activated RAAS enhances collagen deposition, inflammatory responses, apoptosis, and coronary constriction in the infarcted myocardium, leading to LV dysfunction and adverse remodeling after MI [17–19]. There is increasing evidence that RAAS inhibitors attenuate LV dysfunction and adverse remodeling in acute MI (AMI) survivors [20,21]. Although animal studies showed that RAAS inhibitors reduced the expression of pro-inflammatory molecules in the infarcted lesion [22,23], there is little clinical evidence to suggest that RAAS inhibitors have an anti-inflammatory effect on the infarcted lesion in patients with AMI.

This study aimed to determine whether angiotensin II receptor blockers (ARBs) suppress SDF-1α production in the infarcted lesion in patients with AMI. In this study, we measured SDF-1α levels in plasma obtained from the aortic root (AO) and the anterior interventricular vein (AIV) in patients with AMI due to occlusion of a proximal segment of the left anterior descending coronary artery (LAD) [24,25]. We calculated the AIV–AO gradient of SDF-1α, reflecting SDF-1α release from the myocardial region supplied by the LAD. The transcardiac difference in SDF-1α levels served as an indicator of SDF-1α production in the infarcted myocardial region.

Methods

Study patients

This prospective study registered 212 consecutive patients, with a first AMI due to occlusion of a proximal segment of the LAD, who were admitted to Yamanashi University Hospital between January 2005 and December 2013. All of the study patients received emergent coronary angiography and successful reperfusion therapy by primary percutaneous coronary intervention (PCI) within 24 h after the onset of symptoms. The diagnosis of MI was based on the presence of all of the following criteria [26]: typical chest pain persisting for ≥30 min, ST-segment elevation of ≥0.2 mV in ≥2 contiguous leads on a standard 12-lead electrocardiogram (ECG), and creatine kinase-MB increase ≥2-fold the upper limit of normal or troponin T >0.1 ng/ml. The exclusion criteria were as follows: (1) use of RAAS inhibitors within 3 months prior to admission, (2) residual organic stenosis ≥30% in the LAD, (3) previous PCI in the LAD, (4) previous coronary artery bypass surgery, (5) congestive heart failure at 1 week after AMI, (6) persistent atrial fibrillation and pacing rhythm, (7) age >80 years old, (8) valvular heart disease, secondary hypertension, stroke, renal dysfunction (serum creatinine concentration >2.0 mg/dL), or other serious diseases. Ultimately, the study included 72 patients (Fig. 1). The study also included 25 age- and sex-matched control patients who were selected from 61 consecutive angiographically normal patients. The control patients served as a reference group for plasma SDF-1α concentrations. All of the control patients underwent diagnostic coronary angiography for atypical chest pain at rest at Yamanashi University Hospital. The control patients also fulfilled all of the following inclusion criteria: (1) no significant ST segment changes during chest pain on 12-lead ECG and ambulatory ECG; (2) neither chest pain nor ST segment changes during an exercise treadmill test; (3) no coronary artery spasm during a provocation test with intra-coronary infusion of acetylcholine [27]. Clinical characteristics of AMI patients and controls are shown in Table 1. Written informed consent was obtained from all patients before the study. The study was approved by the ethics committee at Yamanashi University Hospital.

Study protocol and blood sampling

Patients with AMI were divided into 2 groups according to ARB treatment after admission. The prescription of ARB treatment, daily doses, and types of ARB were determined by the discretion of the attending physician. Patients were prohibited from being treated with other RAAS inhibitors. All patients received standardized cardiac medications, except for RAAS inhibitors, during the 6 months following AMI, as shown in Table 2.

After emergency coronary angiography upon admission, cardiac catheterization was repeated twice: at the time of discharge (mean time after the onset of AMI, 12 ± 5 days) and 6 months after AMI in all AMI patients. Blood sampling from the AIV, the AO, and the antecubital vein was performed during cardiac catheterization at the time of discharge and 6 months after AMI, before systemic heparinization, as described in our previous reports [24,25,28]. Furthermore, coronary angiography and left ventriculography were performed at the time of discharge and 6 months after AMI. All control patients had similar blood sampling during cardiac catheterization, but this occurred only once. Initial parts of each sample, including those forcibly drawn, were discarded. Blood samples were immediately centrifuged at 3000 rpm for 10 min at 4 °C, and the serum and EDTA-plasma were aliquoted and stored at −80 °C until analyzed.

Assays, left ventriculogram, and definition of coronary risk factors

Enzyme-linked immunosorbent assays with commercially available kits were used for measurement of plasma SDF-1α levels (R&D Systems, Minneapolis, MN, USA). The minimal detection limit of this assay was 18 pg/ml. Radioimmunoassay was used for measurement of plasma renin activity (PRA) (Renin RIA beads, Fujirebio Inc., Tokyo, Japan) and plasma aldosterone concentration (PAC) (SPAC-S aldosterone kit, Fujirebio Inc.). C-reactive protein (CRP) levels in the serum were assayed by rate nephelometry (Dade Behring, Tokyo, Japan). Plasma levels of brain natriuretic peptide (BNP) were measured by an immunoradiometric assay (Shionogi Pharmaceutical LTD., Osaka, Japan). LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV), and LV end-systolic volume (LVESV) were calculated by area-length methods using computer-assisted analysis (CAAS5.9, PieMedical Imaging, Maastricht, the Netherlands). Risk factors for cardiovascular disease were defined as current smoking (≥10 cigarettes/day for >10 years), hypertension (blood pressure >140/90 mmHg, or taking antihypertensive medications), and diabetes mellitus (fasting plasma glucose level ≥126 mg/dL, 2-h post-load ≥200 mg/dL in a 75-g oral glucose tolerance test, random plasma glucose level ≥200 mg/dL, hemoglobin A1c ≥6.5%, or taking medications for diabetes mellitus) [29].

Statistical analysis

Data are expressed as mean ± SD, median and interquartile range (IQR, 25th and 75th percentile), or frequency (%). Continuous

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