International Journal of Cardiology 155 (2012) 442–447

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

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

Beneficial effects of statin treatment on coronary microvascular dysfunction and left ventricular remodeling in patients with acute myocardial infarction ☆

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ARTICLE INFO

Article history:
Received 22 June 2011
Received in revised form 21 September 2011
Accepted 4 November 2011
Available online 5 December 2011

Keywords:
Acute myocardial infarction
Statins
Myocardial flow reserve
Cardiac remodeling
Asymmetric dimethylarginine

ABSTRACT

Background: Statin treatment has been shown to improve coronary endothelial function, irrespective of lipid-lowering effects. This study's aim was to elucidate the effects of statin treatment on coronary microvascular dysfunction and left ventricular remodeling in acute myocardial infarction (AMI) patients.
Methods: Thirty-five patients undergoing successful reperfusion following AMI were assigned to a statin-treated (Group S, 16) or a non-statin-treated (Group NS, 19) group, according to fasting serum low-density lipoprotein-cholesterol. ^{13}N-ammonia positron emission tomography was performed to assess myocardial flow reserve (MFR) in the infarct area.
Results: Infarct sizes and lipid profiles during the chronic period were similar between the two groups. At 2 weeks after AMI onset, mean MFR in the infarct area was significantly higher in Group S than in Group NS (2.34 ± 0.63 vs. 1.91 ± 0.43, $p = 0.0214$). At 6 months post-AMI, Group S had a smaller left-ventricular end-diastolic volume index (69.4 ± 11.7 mL/m^2 vs. 88.5 ± 32.5 mL/m^2, $p = 0.0328$) and higher left-ventricular ejection fraction ($67.7 \pm 9.2\%$ vs. $59.2 \pm 13.3\%$, $p = 0.0394$) than Group NS. Serum asymmetric dimethylarginine was significantly increased in Group NS at 1 month post-AMI (0.43 ± 0.12 μmol/L (baseline) vs. 0.52 ± 0.14 μmol/L, $p = 0.0186$), but unchanged in Group S.
Conclusions: Statin treatment appears to beneficially attenuate left ventricular remodeling after AMI, which may be associated with restoring coronary endothelial function via endogenous nitric oxide.

1. Introduction

Microvascular dysfunction in the infarcted myocardium soon after acute myocardial infarction (AMI) onset is known to be related to left ventricular remodeling [1]. We recently demonstrated that microvascular dysfunction in the non-infarcted myocardium is also associated with left ventricular remodeling [2]. Hence, it is clinically important to ameliorate global microvascular dysfunction, as well as to achieve angiographic reperfusion by percutaneous coronary intervention (PCI).

The coronary endothelium plays an important role in regulating coronary blood flow. Endothelial dysfunction is partially characterized by L-arginine-nitric-oxide pathway dysregulation. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of endothelial nitric oxide synthase [3], is elevated in patients with dyslipidemia [4], diabetes [5], hypertension [6], and acute coronary syndrome [7]. In addition, elevated ADMA is associated with decreased hyperemic myocardial blood flow (MBF) [8].

Recent studies have focused on pleiotropic effects of 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors, i.e. statins, including anti-inflammatory [9], antioxidant [10] and anti-thrombotic effects [11], as well as directly up-regulation of endothelial nitric oxide synthase expression and function [12,13]. Statins improve mortality and cardiovascular morbidity in patients with coronary artery disease, irrespective of lipid-lowering effects [14]. The Management of Elevated Cholesterol in the Primary Prevention of Adult Japanese (MEGA) study showed that low-dose statin treatment reduces incidences of major cardiovascular events by 26 to 37% [15]. Furthermore, in Japanese AMI patients, Teshima et al. [16] reported early beneficial effects of atorvastatin on left ventricular systolic dysfunction and Ohara et al.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ADMA, asymmetric dimethylarginine; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; ATP, adenosine triphosphate; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEDVI, left-ventricular end-diastolic volume index; LVEF, left-ventricular ejection fraction; MBF, myocardial blood flow; MFR, myocardial flow reserve; PCI, percutaneous coronary intervention; PET, positron emission tomography; QGS, quantitative gated single photon computed tomography; RPP, rate pressure product; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction.

☆ None of the authors have any conflicts of interest to disclose.

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doi:10.1016/j.ijcard.2011.11.015

[17] reported short-term statin treatment to attenuate post-infarct left ventricular remodeling. However, these effects and the mechanism by which statins improve left ventricular function, after AMI, have not been clarified in detail.

We investigated whether statin treatment improves coronary microvascular function with changes in serum ADMA levels and attenuates left ventricular remodeling after AMI, using adenosine triphosphate (ATP)-loaded ^{13}N-ammonia positron emission tomography (PET).

2. Materials and methods

2.1. Subjects

Thirty-five consecutive AMI patients (25 men, 10 women, mean age 66.1 ± 10.5 years; range 52–89) who were successfully treated by PCI within 12 h after onset, and 6 controls (4 men, 2 women, mean age 62.3 ± 8.2 years; range 48–74) with no clinical or echocardiographic evidence of cardiac disease were enrolled. Patients were assigned to a statin-treated group (Group S, 16) or a non-statin-treated (Group NS, 19) group, according to the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2007 (fasting serum low-density lipoprotein-cholesterol (LDL-C) > 100 mg/dl). Group S patients were given pravastatin (10 mg/day; 7), atorvastatin (10 mg/day; 5), or pitavastatin (2 mg/day; 4) starting within 96 h of AMI onset.

Inclusion criteria were: (1) first AMI (2) successful recanalization by PCI [<25% residual stenosis and thrombolysis in myocardial infarction (TIMI) flow grade 3] within 12 h of AMI onset. Patients with previous myocardial infarction, hepatic disease, severe renal dysfunction, bronchial asthma and those taking statins on admission were excluded. None had left-ventricular hypertrophy, valvular disease or left-bundle brunch block. AMI diagnosis was based on typical chest pain lasting at least 30 min, ST-segment elevation of at least 1 mm in 2 contiguous electrocardiograpic leads and a subsequent increase in serum creatinine kinase to more than twice the normal upper limit. Coronary angiography was performed using the standard femoral approach. All patients were given 200 mg oral aspirin and 5000 U of intravenous heparin after admission. Intra-coronary isosorbide dinitrate (2 mg) was administered before coronary angiography. After an additional intra-arterial bolus of 5000 U of heparin, all patients underwent PCI. All patients were given dual anti-platelet therapy (100 mg/day of aspirin with either 200 mg/day of ticlopidine or 75 mg/day of clopidgrel), following PCI. All patients received nicorandil. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and β-blockers were administered at the attending physician's discretion. Concomitant drugs were continued during the study period. All patients underwent follow-up angiography to assess restenosis of the infarct-related artery at 6 months after AMI onset. Left-ventricular end-diastolic volume index (LVEDVI) and left-ventricular ejection fraction (LVEF) on left ventriculography were also measured.

This study protocol was approved by the local ethics committees according to the Declaration of Helsinki guidelines. Written informed consent was obtained from all patients prior to study participation.

2.2. Blood sampling

Blood samples were collected from peripheral veins. Serum creatinine kinase was measured in 4 h intervals, after recanalization. Fasting serum LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride were measured at the beginning of the study and 6 months after AMI onset employing commercially available assays. Serum ADMA was measured immediately after PCI and at 1 month post-AMI in 19 patients (Group S, 7; Group NS, 12). Serum ADMA was determined by ELISA (Immundiagnostik AG, Bensheim, Germany) in samples frozen to −20°. Intra- and inter-assay coefficients of variation were <5%. Analytical sensitivity of the test was 0.05 μmol/L.

2.3. PET studies

Perfusion imaging with ^{13}N-ammonia was performed using a whole body PET scanner (Advance; General Electric Medical Systems, Milwaukee, WI) at 15.8 days (mean) after AMI onset. The scanner allows simultaneous acquisition of 35 image slices in two-dimensional mode with an inter-slice spacing of 2.5 mm. Administration of all vasoactive medications was stopped 24 h before PET studies. Blood pressure, heart rate and cardiac rhythm were recorded during rest and ATP stress imaging. After a 10-min transmission scan using ^{68}Ge/^{68}Ga rod sources, all patients received a 30-second injection of 740 MBq ^{13}N-ammonia (in 10 mL of saline) via the antecubital vein. A 5-min dynamic PET scan was performed with 12 × 10 s, 2 × 30 s and 2 × 60 s frames. Fifty minutes later, ATP (0.16 mg/kg/min) was infused intravenously over 6 min using an infusion pump. At the 3-min points of this infusion, another 740 MBq of ^{13}N-ammonia was injected and dynamic PET acquisition was repeated.

MBF images were calculated using the Patlak plot method [18,19]. An operator blinded to the clinical information placed regions of interest in the left ventricular cavity using two slice levels to obtain a time–activity curve for arterial blood, which was used as an input function. Time frames of 30 s to 2.5 min were used to obtain influx rate constants in a pixel-by-pixel manner from dynamic data. The table-lookup method was applied to convert influx rate constants into MBF. A constant recovery coefficient of 0.75 was used to calculate influx rate constants by the graphical-plotting method [18,19]. The polarmap of MBF was divided into 20 segments, to permit regional comparison with corresponding quantitative gated single photon computed tomography (QGS) findings (Fig. 1). MBF was calculated in each segment and myocardial flow reserve (MFR) was defined as the ratio of MBF during hyperemia to baseline MBF.

2.4. ^{99m}Tc-tetrofosmin myocardial scintigraphy

All patients underwent ^{99m}Tc-tetrofosmin myocardial scintigraphy during the same time period as the PET study to examine the extent and severity of AMI. Two nuclear variables were defined using a 20-segment 5-point scoring model [20]. All segments were visually assessed by two experienced observers using a 5-point scoring system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severely reduced tracer uptake, and 4 = no detectable tracer uptake). The summed defect score representing AMI severity was obtained by adding scores of the 20 segments in the tetrofosmin images, and the summed extent score representing AMI extent was obtained from the total number of segments with abnormal tracer uptake. Infarct area was defined as segments showing <70% of maximum (100%) end-diastolic tracer uptake on QGS analysis, because the number of segments showing <70% of maximum tracer uptake correlated, most significantly, with the extent score in all subjects ($r = 0.825$, $p < 0.0001$).

2.5. Statistical analysis

All descriptive data are expressed as the means ± SD for continuous variables and as percentages for categorical variables. Intergroup differences were evaluated using Student's unpaired *t* test, while the Mann–Whitney *U* test for continuous variables and the paired *t* test were applied to evaluate changes between measurements within groups. The groups were compared using the one-way analysis of variance followed by Scheffe adjustment. Categorical variables were compared by the chi-square or Fisher's exact test. Correlations between variables were analyzed using Pearson's correlation coefficient. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed with StatView Ver. 5.0 software (SAS Institute, Cary, North Carolina).

3. Results

3.1. Baseline characteristics of patients

There were no significant differences in age, gender distribution, body mass index, coronary risk factor prevalences or medication profiles between Groups S and NS. Furthermore, culprit artery distribution, elapsed time, prevalences of stent implantation and thrombectomy during PCI, prevalence of congestive heart failure after PCI, peak creatinine kinase, summed extent score and summed defect score did not differ significantly between the two groups (Table 1). Although slow flow during PCI occurred in two patients in Group NS and 2 in Group S, TIMI flow grade 3 was achieved after PCI in all patients. No significant restenosis was detected in any patients on follow-up angiography.

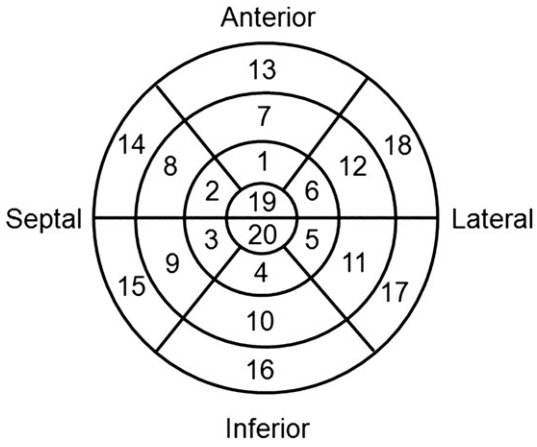

Fig. 1. Polarmap image. The polarmap of myocardial blood flow (MBF) was divided into 20 segments, to permit regional comparison with the corresponding quantitative gated single photon computed tomography findings.