Oxidative Stress Correlates with Left Ventricular Volume after Acute Myocardial Infarction

Clinical Studies

Oxidative Stress Correlates with Left Ventricular Volume after Acute Myocardial Infarction

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SUMMARY

It has been suggested that oxidative stress may play a role in the pathophysiology of heart failure. However, little is known about the clinical relationship between oxidative stress and left ventricular dilatation after acute myocardial infarction (AMI). We prospectively studied 28 consecutive patients, successfully treated with primary coronary angioplasty, after their first AMI. To evaluate oxidative stress, plasma oxidized low-density LDL levels (U/mL) were measured serially 1 day, 7 days, 14 days, 30 days, and 90 days after the onset of AMI using a specific sandwich enzyme-linked immunosorbent assay. Left ventriculography and coronary angiography were obtained in all patients 3 months after the AMI and infarct-related arteries were all patent. Peak plasma oxidized LDL levels were seen 7 days after AMI (after 1 day: 14.7±1.5, 7 days: 21.0±2.8, 14 days: 20.2±2.8, 30 days: 18.3±2.5, 90 days: 16.5±2.3 U/mL). Plasma oxidized LDL levels 7 days after AMI were significantly correlated with left ventricular end-diastolic volume (115±7 mL; $r=0.54$, $P=0.0025$) and end-systolic volume (58±5 mL; $r=0.49$, $P=0.008$) 3 months after the AMI. Moreover, they were also correlated with end-diastolic volume index (68±4 mL/m², $r=0.40$, $P<0.05$). However, no correlation was seen between peak plasma oxidized LDL levels and ejection fraction. These findings suggest that oxidative stress may play an important role in the development and progression of left ventricular remodeling after AMI. (Jpn Heart J 2002; 43: 203-209)

Key words: Left ventricular remodeling, Lipoproteins, Myocardial infarction, Oxidative stress

LEFT ventricular remodeling after acute myocardial infarction (AMI) is a serious problem because it leads to progressive left ventricular dilatation, impaired cardiac performance, and chronic heart failure. Previous studies have demonstrated that infarct size[1-2] and persistent occlusion of the infarct-related artery[3-5] are two major factors that promote ventricular remodeling. However, multiple

factors may in fact contribute to left ventricular remodeling at different stages, from the time of coronary occlusion until the development of ventricular dilatation and dysfunction.[6-7] The assessment of the relative role and determinants in the natural history of the left ventricular remodeling process is of crucial importance for planning risk stratification and management strategies.

Oxidative stress and the production of intracellular reactive oxygen species have been implicated in the pathogenesis of cardiovascular disease. Recent data have suggested that oxidant product levels increase significantly in patients with heart failure.[8-9] In particular, atherogenic oxidized low-density lipoprotein (LDL)[10-13] can be measured *in vivo* and is useful as a diagnostic marker for cardiovascular disease.[14-16] However, the time course of oxidative stress after AMI and its clinical significance remain uncertain. In this prospective study, we investigated the serial changes in plasma oxidized LDL levels as one of the oxidative markers and their correlation with clinical variables, especially with left ventricular volume after AMI.

METHODS

Study population: We prospectively studied 28 consecutive AMI patients (24 men and 4 women; mean age, 61±2 years) treated at our institution between August 1998 and March 1999. All patients had ischemic chest pain with ST-segment elevation on the electrocardiogram and were admitted within 6 hours. Coronary angiography was performed on all patients, after informed consent was obtained, and 22 infarct-related arteries were found to be completely occluded. Primary percutaneous transluminal coronary angioplasty (PTCA) was performed using conventional techniques. During the procedures, the patients received an initial bolus injection of heparin (100 units/kg [body weight]) and additional heparin (2000 units) each hour. Investigators attempted to achieve an optimal result with conventional balloon angioplasty, defined as residual stenosis of <25% of the luminal diameter, according to a visual estimate. Stent placement was permitted as a bailout procedure in the case of abrupt or threatened closure, and was defined as a dissection. Angiographic success was defined as <50% diameter narrowing after the procedure. Follow up coronary angiography and left ventriculography were performed 3 months after the AMI. None of the patients had major adverse cardiac events, renal failure, or infectious disease during the 3 month period following the AMI. Left ventricular ejection fraction, volume, and volume index were evaluated by left ventriculography using an area-length method.

Blood sampling: Blood samples were obtained from the antecubital vein serially 1 day, 1 week, 2 weeks, 1 month, and 3 months after the onset of AMI. All blood samples were collected in the fasting state. Serum was obtained by centrifugation

and stored at 4°C until use. To determine maximum creatine kinase-MB and C-reactive protein levels, blood samples were also obtained every 6 hours and every day, respectively, until peak levels were attained.

Oxidized LDL assay: Plasma oxidized LDL concentrations were measured by a sandwich enzyme-linked immunosorbent assay using a specific monoclonal antibody against oxidized phosphatidylcholine and anti-human apolipoprotein B antibody.[17-18] Before each assay, the plasma samples were diluted with dilution buffer (1/250), and DLH3-coated plates were washed 3 times with phosphate-buffered saline and patted dry. Dilution buffer (100 μL) was added to the wells of the plates and 20 μL of patient or calibration sample was added to wells and mixed with dilution buffer. The plates were incubated for 2 hours at 37°C. After washing 5 times with wash buffer, horseradish peroxidase-labeled anti-human apolipoprotein B-100 goat IgG was added to each well and the plates were incubated for 1 hour at 37°C. After washing 5 times with wash buffer, 100 μL of tetramethylbenzidine solution was added to the wells, and the plates were incubated for 30 minutes at 37°C. To stop the reaction, 100 μL of 1M H_2SO_4 was added, and the absorbance at 450 nm was measured with a MTP-120 plate reader (Corona Electric Co., Ltd., Tokyo). The levels of plasma oxidized LDL were expressed in arbitrary units (U/mL). This assay has good sensitivity (detection limit: 1 U/mL), reproducibility (coefficient variation <10%), and accuracy (recovery: 90.6-103.8%). The dosages of heparin did not affect the measurements

Statistical analysis: Data are expressed as mean±SEM. For changes in oxidized LDL levels, a nonparametric analysis (Wilcoxon signed rank test) was performed. A simple linear regression line was calculated to assess the correlations between two parameters. Stepwise regression analysis was performed to determine whether clinical variables were independently related to left ventricular volume. All statistical analyses were performed using StatView Version 4.5 (Abacus Concepts, Inc., Berkeley, CA). Statistical significance was defined as *P*<0.05.

RESULTS

The AMI among the 28 patients included 11 anteroseptal, 10 inferior, and 7 lateral AMI. No patient had any previous myocardial infarction, however 7 patients had hypertension (25%), 10 hyperlipidemia (36%), and 5 diabetes mellitus (18%). The mean of the maximum creatine kinase-MB was 322±48 IU/L and the mean of the maximum C-reactive protein was 5.56±0.72 mg/dL.

Figure 1 shows the changes in plasma oxidized LDL levels in patients with AMI from 1 to 90 days after the onset. Peak elevation in plasma oxidized LDL was found on day 7 (21.0±2.4 U/mL), which was significantly higher than that on day 1 (14.1±1.6 U/mL). The day on which plasma oxidized LDL levels reached

their maximum in each patient was distributed between days 7 and 30 after the onset of AMI.

Correlations between plasma oxidized LDL levels and laboratory data: As shown in Figure 2, a significant positive correlation was found between peak oxidized
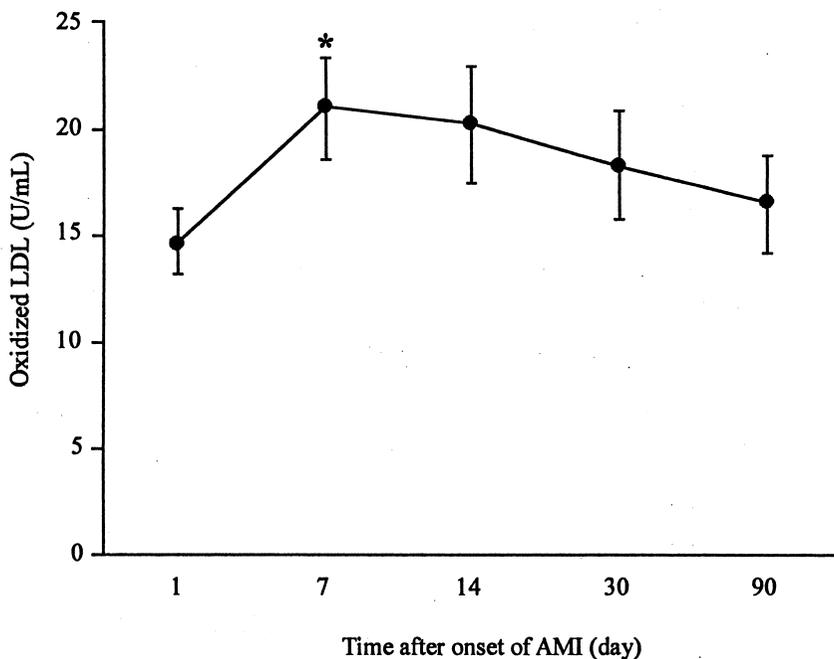

Figure 1. Serial changes in plasma oxidized LDL after the onset of AMI. Circles: mean plasma oxidized LDL in AMI patients. *$P<0.0001$ compared with plasma oxidized LDL level on day 1.
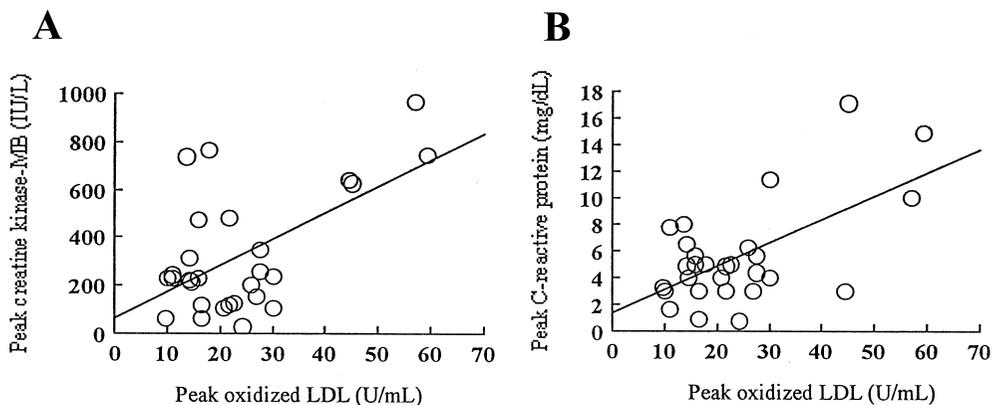

Figure 2. Correlations between oxidized LDL levels and laboratory data. **A:** A significant positive correlation was found between peak oxidized LDL and peak creatine kinase-MB ($r=0.58$, $P=0.001$). **B:** A significant positive correlation was also found between peak oxidized LDL and peak C-reactive protein ($r=0.61$, $P=0.0004$).
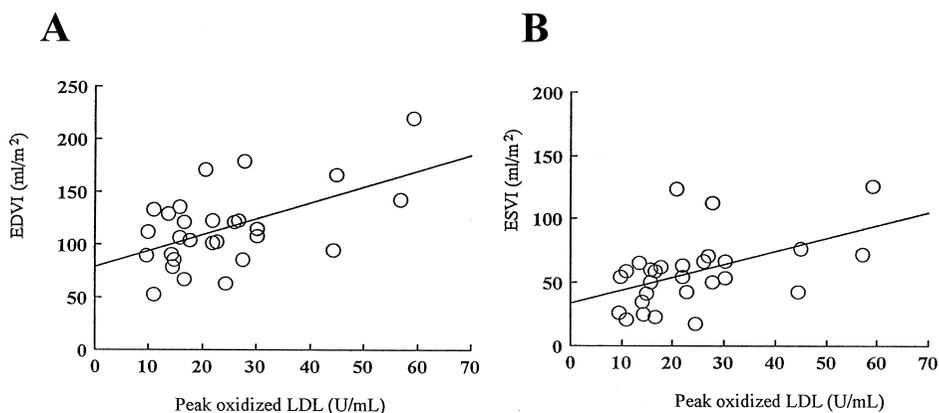
A

B

Figure 3. Correlations between oxidized LDL and left ventricular volume. **A:** A significant positive correlation was found between peak oxidized LDL and end-diastolic volume (r=0.54, P=0.0025). **B:** A significant correlation was found between peak plasma oxidized LDL and end-systolic volume (r=0.49, P= 0.008).

LDL and peak creatine kinase-MB levels (r=0.41, P=0.001). A significant positive correlation was also observed between peak oxidized LDL and peak C-reactive protein levels (r=0.61, P=0.0004).

Correlations between plasma oxidized LDL levels and left ventricular volume: End-diastolic and end-systolic volume after 3 months were 115±7 mL and 58±5 mL, respectively. In Figure 3, a significant positive correlation was found between peak oxidized LDL and end-diastolic and end-systolic volume, respectively. Moreover, peak oxidized LDL levels were also correlated with end-diastolic volume index (68±4 mL/m^2, r=0.40, P<0.05). However, no correlation was seen between peak plasma oxidized LDL levels and ejection fraction (52±2%, P=NS). Multivariate stepwise analyses were performed to find the major determinants of end-diastolic and end-systolic volume using 4 variables: peak C-reactive protein, peak creatine kinase-MB, peak oxidized LDL, and angiotensin-converting enzyme inhibitor therapy. These analyses revealed that only peak plasma oxidized LDL was a significant independent predictor of both end-diastolic and end-systolic volume.

DISCUSSION

The major findings in this study are that plasma oxidized LDL levels increased significantly after AMI and the peak levels were significantly associated with end-diastolic and systolic volume 3 months after the AMI.

Plasma oxidized LDL levels have been found to be significantly elevated in patients with coronary artery disease.[15] The source of elevated oxidized LDL lev-

els may be back-diffusion from the arterial wall into blood.[14-16] On the other hand, Tsutamoto, *et al* reported transcardiac elevation of oxidized LDL levels in patients with dilated cardiomyopathy with the same assay used in this study.[19] Their results suggest that elevated levels of plasma oxidized LDL are due to oxidative stress in the failing heart. Overstretching of the myocardium leads to enhanced generation of reactive oxygen species,[8] and there is evidence of free radical production in coronary artery disease.[20] Therefore, the peak elevation in oxidized LDL levels is thought to be due to increased myocardial oxidative stress after AMI[21] rather than back-diffusion from the coronary artery wall.

We observed a significant correlation between plasma oxidized LDL and peak creatine kinase-MB as well as peak C-reactive protein, suggesting that peak oxidized LDL levels may reflect damaged myocardium after AMI. Several variables have been identified that predict an increase in left ventricular volume after AMI. These include infarct size and the patency of the infarct-related artery.[1-5] However, the role of oxidative stress, which may play an important role in heart failure, has not been fully investigated after AMI. In the present study, peak oxidized LDL levels were significantly correlated with end-diastolic and end-systolic volume and were the best predictor of left ventricular volume. This suggests oxidative stress may affect left ventricular remodeling after AMI.

In conclusion, this is the first study demonstrating that left ventricular dilatation after AMI is associated with a significant increase in plasma oxidized LDL levels, which is likely to reflect oxidative stress in the heart. These feasible approaches to quantify oxidative stress in damaged myocardium could be used to predict left ventricular dilatation and to manage therapeutic strategies after AMI.

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