論　文　内　容　要　旨

Impact of Lipoprotein (a) on Long-Term Outcomes in Patients With Acute Myocardial Infarction

（急性心筋梗塞における Lipoprotein (a)の長期予後に与える影響）

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Objective; Patients who survive acute myocardial infarction (AMI) are reported to have poor clinical outcomes. Identification and management of the residual risk factors for major adverse cardiac events (MACE) after AMI is necessary because substantial residual CVD risk remains after AMI despite optimal management. Lipoprotein (a) (Lp (a)) is an apolipoprotein B-containing lipoprotein bound to a hydrophilic, highly glycosylated protein called apolipoprotein (a) (apo (a)). Lp (a) levels are approximately 70% to ≥90%, genetically determined by the *LPA* gene. Although high levels of Lp (a) are considered an independent and causal risk factor for atherosclerotic cardiovascular disease (ASCVD) through mechanisms associated with increased atherogenesis, inflammation, and thrombosis, the influence of Lp (a) on the long-term outcomes after AMI remains unknown. We aimed to assess the influence of Lp (a) on the long-term outcomes including cardiac death, non-fatal myocardial infarction, and readmission for heart failure after AMI.

Methods; Between December 2015 and January 2018, 397 consecutive patients with AMI underwent primary percutaneous coronary intervention (PCI) within 24 h of the onset of chest pain at Hiroshima City Hiroshima Citizens Hospital. We enrolled 262 of the surviving patients in whom Lp (a) was measured several days after AMI prior to their discharge. The study patients were divided into two groups according to the Lp (a) level, a high Lp (a) group (≥32 mg/dL: n=76) and a low Lp (a) group (<32 mg/dL: n=186). The primary endpoint was MACE, which was defined as a composite of cardiac death, non-fatal myocardial infarction, and readmission for heart failure (HF). Cardiac death was defined as death from pump failure, sudden cardiac death, or death from arrhythmia. The receiver-operating characteristic (ROC) curve analyses were performed to determine the optimal cut-off values of Lp (a) for predicting MACE. Event curves after AMI were constructed using the Kaplan-Meier method and compared using log-rank test. Risk factors associated with the outcomes were determined using univariate analysis. Variables with a p-value <0.1 in the univariate analysis were included in the multivariate analysis. Cox proportional hazard regression was used to identify independent predictors of MACE, adjusting for baseline clinical and angiographic variables. Statistical significance was set at $p < 0.05$, and two-tailed tests were applied.

Results; The median (interquartile range) value of Lp (a) was 21 (11-35.25) mg/dL, ranging from 1 mg/dL to 158 mg/dL. Patients with high Lp (a) levels had a significantly higher prevalence of atrial fibrillation (AF), higher N-terminal pro-hormone brain natriuretic peptide (NT-ProBNP) level at admission, and lower left ventricular ejection fraction (LVEF) at discharge. Patients with high Lp (a) levels had significantly higher apolipoprotein B levels than those with low Lp (a) levels. The median (interquartile range) follow-up period was 4.6 (1.9-5.9) years. The incidence of MACE was significantly higher in patients with high Lp (a)

than in those with low Lp (a) (32.8% vs. 19.6%, p=0.004). Cardiac death (9.5% vs. 2.1%, respectively; p=0.033) and readmission for HF (19.4% vs. 5.9%, respectively; p=0.003) were significantly higher in patients with high Lp (a) than in those with low Lp (a), although the incidence of non-fatal MI was comparable between two groups (18.0% vs. 15.6%, respectively; p=0.196). Multivariate analysis showed that a Lp (a) level ≥ 32 mg/dL was an independent predictor for MACE (odds ratio (OR) 2.84, 95%CI 1.25-6.60, p=0.013).

Discussion; Lp (a) has long been recognized as a genetically determined, independent risk factor for atherothrombotic cardiovascular disease. Lp (a) can become trapped within the arterial wall to participate in the initiation and progression of atherosclerotic plaques. Lp (a) particles may be more atherogenic than other apolipoprotein B-containing lipoproteins despite carrying less cholesterol because of their long circulating half-life and high concentration of oxidized phospholipids. Mendelian randomization studies have consistently demonstrated a causal relationship between the plasma concentrations of Lp (a) and the risk of myocardial infarction, stroke, peripheral arterial disease, and cardiovascular death. Previous study demonstrated that high Lp (a) levels are significantly associated with long-term cardiovascular outcomes in patients with acute coronary syndrome, which is consistent with our findings. However, the primary endpoints in our study included readmission for HF, which also significantly occurred more frequently in patients with high Lp (a). To the best of our knowledge, this is the first report of a higher incidence of readmission for HF in AMI patients with high Lp (a) levels. Previous study demonstrated that elevated Lp (a) levels were associated with increased risk of HF, consistent with a causal association in the general population. A total of 63% of HF risk was mediated by combined myocardial infarction and aortic valve stenosis. Upon exclusion of individuals with myocardial infarction or aortic valve stenosis, risk estimates were attenuated to approximately two-thirds; however, the association between Lp (a) and HF remained significant. The mechanism behind the atherosclerotic stenotic effect of high Lp (a) levels may be due to their effect on increased arterial stiffness, including vascular noncompliance in the aorta, which would increase afterload. This has been strongly associated with an increased risk of HF. Patients with high Lp (a) levels were associated with a significantly higher prevalence of AF, which might have led to a higher incidence of readmission for HF in this study. A previous study showed that patients with AF have a greater risk of heart failure. Lp (a) particles have additional thrombogenic and inflammatory properties that could provide other mechanisms, independent of ASCVD, by which an effect on AF could be mediated.

Conclusions; The present study demonstrated that a high Lp (a) level was an independent predictor of long-term MACE after AMI. Measurements of Lp (a) levels may enable us to identify high-risk patients after AMI.