Mitochondrial Dysfunction and Left Ventricular Structural Remodeling After Acute Myocardial Infarction
— Usefulness of Leukocyte Mitochondrial Copy Number —

Ryuji Tsuburaya, MD, PhD

Although recent progress in emergency care systems and percutaneous coronary intervention (PCI) substantially reduced mortality due to acute myocardial infarction (AMI), left ventricle (LV) remodeling after AMI remains an important concern worldwide. Adverse LV remodeling after AMI is the most common cause of worsening heart failure with resultant poor prognosis.

The process of LV remodeling after AMI starts from infarct expansion followed by hypertrophy in the non-infarct region and progressive LV dilation. During this process, the LV shape changes from elliptical to spherical, leading to a dilated LV and reduced systolic function. Sphericity index (SI) evaluated on 3-D echocardiography, which indicates spherical LV shape changes, is a strong predictor of LV remodeling after AMI. Furthermore, surgical ventricular reconstruction, a procedure to restore the elliptical LV shape, could improve LV function and prognosis in patients with ischemic cardiomyopathy. Thus, it is important to evaluate LV shape changes as well as LV volume after AMI.

Although infarction size is the most important factor for adverse LV remodeling, some patients with small infarction size progress to LV remodeling, and some patients with large infarction do not. Thus, other mechanisms of LV remodeling after AMI should be considered. Mitochondria play a pivotal role in the maintenance of cardiac function.
through energy production and the regulation of apoptosis and reactive oxygen species (ROS), and mitochondrial dysfunction might lead to myocardial dysfunction, progression of LV remodeling and worsening of heart failure. Mitochondria contain several copies of circular mitochondrial DNA molecules, and this mitochondrial copy number (MCN) is important for preserving mitochondrial function. In previous experimental studies, reduction of MCN caused dilated cardiomyopathy in an in vivo mice model, and, inversely, genetic preservation of MCN can protect LV remodeling after AMI in mice in vivo. Thus, MCN might reflect the process of LV remodeling. In fact, in a previous clinical study, decrease in mitochondrial DNA content was correlated with LV remodeling in end-stage heart failure.

In this issue of the Journal, Huang et al report on the usefulness of basal leukocyte MCN for predicting adverse LV remodeling in patients with ST-elevated myocardial infarction (STEMI; Figure). They measured leukocyte MCN prior to primary PCI in 55 patients with de novo STEMI and evaluated the time course of LV function, volume, and shape on 3-D echocardiography. They found that (1) the patients with AMI had significantly lower baseline leukocyte MCN than healthy controls; and (2) the patients with low baseline leukocyte MCN (<82 per cell; categorized according to the cohort median), had significant increase in LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and SI at 3 and 6 months after STEMI, whereas there were no differences in baseline characteristics and echocardiographic parameters between the low and high MCN groups. Furthermore, on multiple regression analysis baseline leukocyte MCN was a strong predictor for LV remodeling compared with peak creatine phosphokinase, any echocardiographic findings, and baseline characteristics.

Although Huang et al have shown the potential of MCN as a promising novel biomarker for LV remodeling after AMI, several issues remain regarding the interpretation of that study. First, the sample size and single-center design were insufficient to determine the real cut-off to predict LV remodeling after AMI. Thus, further studies with a large sample size and multicenter design are needed in future. Second, that study used a single point measurement of MCN only prior to PCI for STEMI. Thus, the relationship between the time course of MCN and LV remodeling after AMI remains to be elucidated. Third, they evaluated MCN using leukocytes collected from peripheral venous blood. Although leukocyte MCN has been correlated with cardiomyocyte MCN in end-stage heart failure patients, leukocytes are the key players in inflammation. Recent reports focus on the crucial role of the inflammatory response in LV remodeling after AMI. Although an inflammatory response immediately after AMI accelerates wound healing in the infarcted myocardium, a prolonged and excessive inflammatory response could delay tissue repair and enhance fibrotic changes, leading to adverse LV remodeling. The inflammatory response induces ROS production, further enhancing inflammation and progressing mitochondrial dysfunction during ischemia-reperfusion injury. In fact, leukocyte MCN was associated with an inflammatory marker, fibrinogen, in the Huang et al study.

Thus, leukocyte MCN might be influenced not only by cardiomyocyte mitochondrial dysfunction, but also by systemic inflammation induced by acute ischemia and reperfusion injury.

In conclusion, Huang et al suggest that mitochondrial dysfunction plays an important role in LV remodeling after AMI through a spherical LV shape change. Leukocyte MCN, which reflects mitochondrial dysfunction during acute ischemia and reperfusion, might be a useful biomarker to identify AMI patients at high risk of developing heart failure, and for researching new treatments to inhibit LV remodeling after AMI.

Disclosures

The author declares no conflict of interest.

References