Cardiac Rehabilitation-Mediated Molecular Mechanisms of Cardiovascular Protection
– What Should We Focus on Next? –
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Cardiac rehabilitation (CR) and secondary prevention (SP) programs are recognized as key components of the management of patients with various cardiovascular conditions, including stable angina, recent myocardial infarction or acute coronary syndrome, and heart failure, and of those who have undergone coronary revascularization procedures, aortic disease, valve surgery, and cardiac transplantation. Numerous reports have established the benefits of CR with regard to reduction of total risk of cardiovascular disease and necessity for SP measures, thereby improving the patient’s prognosis and quality of life. A recent study showed that participation in CR/SP programs reduces the 5-year mortality by 25–46%, and recurrent nonfatal myocardial infarction by 31%. However, the underlying mechanisms of CR remain unclear.

Consequently, the revelations in this issue of the Journal by Takashima et al provide a remarkable insight into CR/SP research. Although many biomarkers, including inflammatory and antiinflammatory cytokines, reactive oxygen species (ROS)-related molecules, and soluble form of lectin-like oxidized low-density lipoprotein (ox-LDL) receptor-1, have been investigated for their potential to monitor CR success, none has been completely successful for this purpose. However, Takashima et al found that the malondialdehyde-modified LDL (MDA-LDL) level was significantly reduced by CR, concomitant with LDL oxidation may provide a greater understanding of the underlying molecular mechanisms responsible for prevention of cardiovascular diseases.

Certain factors, such as smoking, hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease (CKD), obesity, sleep apnea syndrome, excessive salt intake, estrogen deficiency, physical inactivity, and ox-LDL levels, decrease vascular endothelial function. However, endothelial function can be significantly improved by smoking cessation, weight loss in obese patients, and consumption of a favorable diet. In addition, appropriate exercise increases the shear stress on the endothelium, thereby inducing an immediately favorable effect on vascular endothelial function. In fact, CR was shown to improve endothelial function in elderly patients with heart failure. These findings indicate that vascular endothelial function serves as an independent predictor for cardiovascular diseases. Consequently, improving endothelial function in patients with hypertension, diabetes mellitus, and hypercholesterolemia is a critical step in cardiovascular disease risk reduction. The major pharmacological interventions in this cohort of patients comprised statins and renin-angiotensin system inhibitors. In SP research, endothelial function is typically evaluated by non-invasive measurement of the percentage flow-mediated dilation or reactive hyperemia-peripheral arterial tonometry by EndoPAT. Although both types of endothelial measurement are useful for predicting cardiovascular events, has it been established that circulating levels of biomarkers readily determine the efficacy of CR in the clinical setting? MDA-LDL may represent such a candidate biomarker.

Recently, a protective gel-like coating layer of the endothelium, the vascular endothelial glycocalyx, has received considerable attention in vascular biology (Figure 1). Accumulating evidence emphasizes the importance of the endothelial glycocalyx for physiological and pathological endothelial functions. Moreover, recent cryo-electron microscopy studies have shown that the endothelial glycocalyx can extend up to 11 µm into the lumen, inevitably making it the endothelial structure first exposed to changes in fluid shear stress. The vascular endothelial glycocalyx is impaired in areas lacking shear stress, and in conditions such as diabetes mellitus, dyslipidemia, CKD, and ischemia-reperfusion injury. The glycocalyx component, syndecan-1, has been shown to control the shear stress-induced signaling and flow-mediated phenotypic modulation in endothelial cells, whereas an elevated capillary tube hematocrit reflects degradation of the endothelial glyocalyx by ox-LDL.

Therefore, whether patients with cardiovascular diseases show such molecular changes at the intravascular endothelial cell surface level remains to be addressed. It is evident that...
Endothelium as a Target of Cardiac Rehabilitation

Perturbation of the endothelial glycocalyx readily induces endothelial dysfunction, which leads to excessive ROS production, LDL oxidation, and potentially inhibition of normal LDL cholesterol clearance (Figure 2B). Effective CR may have the potential to repair the damaged endothelial glycocalyx and improve endothelial function through an increase in shear stress (Figure 2A). Although to date the precise mechanisms by which MDA-LDL is decreased by CR remain unclear, the antioxidative properties of CR may contribute to lower levels of ox-LDL and protect the endothelium from pro-atherogenic risk factors, thereby restoring the endothelial glycocalyx layer by favoring shear stress-related effects. To conclude, further investigations into the maintenance of a healthy endothelial glycocalyx may present a novel approach to cardiovascular disease prevention.

References


