Rho-Kinase in Leukocytes – An Emerging Biomarker for Heart Failure–

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Heart failure (HF) is a highly prevalent disease associated with repeated hospitalization and is a leading cause of death in developed countries. Accumulating evidence suggests that pharmacological therapies (eg, β -blockers and renin-angiotensin-aldosterone system inhibitors) and cardiac resynchronization therapy can improve the clinical symptoms and reduce the mortality of patients with HF.^{1–3} Despite this progress in both therapeutic agents and cardiac devices, the fact that the mortality rate of patients with HF remains high has increased the demand for alternative therapeutic approaches. Therefore, it is desirable to elucidate the distinctive features of HF and discover a novel therapeutic target.

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Rho-kinase was identified as an effector of the small GTPase Rho in 1996.⁴ Several actomyosin-associated proteins (eg, myosin light chain phosphatase, adducin, LIM-kinase, ezrin-radixin-moesin proteins, etc.) serve as physiological substrates

for Rho-kinase (**Figure**). It is now widely established that the Rho-kinase pathway is an integral component of various pathophysiological conditions because of its role in actin cytoskeleton organization, migration, adhesion, proliferation, and gene expression. In the cardiovascular system, Rho-kinase signaling influences vascular tone by regulating the balance of myosin light chain phosphorylation and dephosphorylation,⁵ and contributes to the development of various vascular diseases.⁶

Previous studies have indicated that systemic Rho-kinase activity can be detected by examining the phosphorylated myosin binding subunit, a substrate of Rho-kinase, in circulating leukocytes.⁷ Indeed, Rho-kinase in leukocytes is significantly activated in patients with hypertension, stable angina, vasospastic angina, and acute ischemic stroke.^{8,9} Rho-kinase activity in circulating leukocytes, therefore, is recognized as a marker of atherosclerotic burden. However, this situation has begun to change in recent years. Novel behaviors of Rho-kinase have been proposed in patients with HF in human clinical studies.

Based on the phosphorylation profiles of the myosin-bind-

Figure. Role of Rho-kinase in the pathogenesis of heart failure. MLCP, myosin light chain phosphatase; ERM, ezrin-radixin-moesin proteins.

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ing subunit in leukocytes, 2 research groups have shown that systemic Rho-kinase activity appears to be elevated in chronic HF. Ocaranza et al found increased Rho-kinase activity in patients with chronic HF with left ventricular remodeling and systolic dysfunction,¹⁰ and Dong et al reported a possible association of Rho-kinase activity with mortality in patients with congestive HF.¹¹

In this issue of the Journal, Zhulanqige Do et al describe Rho-kinase activation in patients with HF and provide further insight into the role of Rho-kinase signaling in HF.¹² Unlike previous reports in which elevated Rho-kinase activity is shown only in chronic HF, Zhulanqige Do et al show direct evidence of Rho-kinase activation in patients with acute HF as well as those with chronic HF. Moreover, they found that elevated Rho-kinase activity in the acute phase was significantly decreased in the chronic phase during the time course of HF. The biomarkers for HF severity established in the clinical setting currently include natriuretic peptides, cardiac troponins, and C-reactive protein (CRP). Interestingly, Zhulanqige Do et al found no significant correlation between Rho-kinase activity and the BNP or high-sensitivity cardiac troponin I concentration. Their results imply that Rho-kinase activation in patients with HF occurs independently of the context of elevated intracavity filling pressures, increased wall stress, or cardiomyocyte damage. No significant correlation between Rho-kinase activity and high-sensitivity CRP was shown in their study. Moreover, of great interest is that no correlation was noted between Rho-kinase activity in leukocytes and or myocardial biopsy specimens in patients with chronic HF. These results are likely related to the fact that HF develops through various underlying mechanisms involving cardiac and extracardiac pathologies (Figure). Because a number of factors are thought to influence Rho-kinase activation, the functional significance of the Rho-kinase signal is likely connected to the integration of multiple factors causing HF. Because biomarkers reflecting such extracardiac pathologies in HF have not been clearly defined, systemic (in blood) Rho-kinase activity might have emerged as the preferred biomarker for the integrated features of HF.

Unlike BNP or cardiac troponins, Rho-kinase itself appears to contribute to the pathogenesis of HF. Evidence from animal studies suggests the involvement of Rho-kinase activation in cardiac remodeling induced by ischemia¹³ or hypertrophic stress,¹⁴ leading to cardiac decompensation and HF. Thus, in addition to its utility as a diagnostic biomarker for HF, Rho-kinase is a potential therapeutic target. Fortunately, we have available a specific intervention that reduces Rho-kinase activity. Fasudil, a selective inhibitor of Rho-kinase, has already been used for the treatment of cerebral vasospasm complicating intracranial hemorrhage. Clinical trials of fasudil have demonstrated its efficacy in angina and pulmonary hypertension. Although fasudil is the only Rho-kinase inhibitor available for clinical use, other Rho-kinase inhibitors are currently under development. Moreover, some of the cardiovascular benefits of statins are independent of lipid lowering and might be mediated, at least in part, by the inhibition of Rho-kinase.¹⁵ Therefore, Rho-kinase inhibitors are promising candidates for HF treatment.

Although there is noteworthy evidence for Rho-kinase activity as a potential novel biomarker and therapeutic target for HF, some questions remain unanswered. First, our understanding of the mechanisms of Rho-kinase activation in patients with HF is superficial. Second, the downstream Rho-kinase pathway and the related molecular mechanisms implicated in the pathogenesis of HF are less well understood compared with

those of vascular diseases. In particular, the precise role of the Rho-kinase signal in the myocardium is not completely understood. Third, how does activated Rho-kinase in leukocytes affect each target organ? Fourth, whether Rho-kinase activity correlates with the ejection fraction (EF) is a matter of controversy. In contrast to previous reports,^{10,11} Zhulanqige Do et al show that Rho-kinase activity in leukocytes has no correlation with EF; they found no significant difference in Rho-kinase activity between HF with preserved EF (HFpEF) and HF with reduced EF (HFrEF). Large clinical studies of HF are needed to clarify the role of Rho-kinase as a biomarker of HF, assess whether the measurement of Rho-kinase will improve HF risk prediction, and determine the prognostic significance of systemic Rho-kinase activity.

The recent explosion in research on Rho-kinase has broadened our knowledge regarding cardiovascular diseases. In particular, the association of Rho-kinase activity with extracardiac pathologies in HF is of specific interest. Thus, the functions of Rho-kinase make it an attractive target for future research into therapeutic strategies for treating HF. The value of the study by Zhulanqige Do et al lies in the fact that it proposes new treatment avenues.

Disclosure

None declared.

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