Anderson-Fabry disease (AFD) is an X-linked lysosomal storage disease caused by a loss-of-function mutation in the lysosomal enzyme α-galactosidase A (GLA) gene, resulting in progressive intracellular accumulation of neutral glycosphingolipids, particularly globotriaosylceramide (Gb3), in different tissues including skin, kidney, central and peripheral nervous systems, and the heart. Patients with AFD suffer from various cardiac complications, including hypertrophic cardiomyopathy, valvular diseases, conduction defects and arrhythmias, as well as coronary artery stenosis, caused by Gb3 accumulation in vascular endothelial and smooth muscle cells (VSMCs) (Figure); however, the prevalence of coronary spastic angina (CSA) has not been clearly demonstrated among AFD patients previously.

In this issue of the Journal, Kitani et al describe the clinical presentations and results of intracoronary acetylcholine provocation test in 9 consecutive patients with AFD. They found a high prevalence (8/9 patients) of acetylcholine-induced CSA without coronary artery stenosis. It should be noted that all 9 patients complained of angina at rest, which suggests possible self-selection bias to undergo cardiac assessment, and therefore, raises prior probability of a positive diagnosis of CSA even among consecutive AFD patients. Nonetheless, this report is the first to describe a high prevalence of CSA in a series of Japanese patients with AFD. Interestingly, 6 of the 8 acetylcholine-positive patients were female in this study, in contrast to the fact that as low as 13% of Japanese CSA patients are female. However, the significance of either sex or ethnicity in the prevalence of CSA was indeterminate in this study.

**Endothelial Dysfunction in AFD**

Vascular endothelial cells produce endothelium-derived relaxing factors (EDRFs), including prostanoids, nitric oxide (NO) and endothelium-derived hyperpolarizing factor, and orchestrate VSMCs to regulate vascular tonus and blood flow. CSA is a result of endothelial dysfunction, or VSMC hypercontractility, or both. Several reports have described an altered NO pathway in AFD. Moore et al reported that enhanced nitrotyrosine staining was observed in dermal and cerebral blood vessels by immunohistochemical analysis, which indicates dysregulated NO production as well as reactive oxygen species (ROS).
Moore et al also suggested that ERT could improve altered vascular cells.

vascular cells.

perturbations among vascular hypertensive and arteriosclerotic changes of the fundus and high serum adhesion molecule levels in Japanese AFD patients.9 Also, exogenous Gb3 downregulates KCa3.1 in cultured endothelial cells, which may inhibit EDRF production.10,11 These notions underpin the endothelial dysfunction per se caused by the accumulation of Gb3 in AFD (Figure).

VSMC Hypercontractility in AFD

Hypercontractility of VSMCs is another mechanism of CSA.4,5 VSMC contraction is determined by phosphorylation of myosin light chain (MLC), which is regulated by MLC kinase and myosin phosphatase. Rho-kinase (ROCK) inhibits myosin phosphatase, promoting MLC phosphorylation, and therefore induces Ca2+ sensitization and hypercontractility of VSMCs.12 Ravarotto et al13 examined myosin phosphatase target protein-1 in the peripheral mononuclear cells as a marker of ROCK activation in vascular cells.14 They found enhanced ROCK activation, as well as with oxidative stress and lipid peroxidation in AFD patients compared with healthy subjects.15 Collectively, AFD is associated with oxidative stress and ROCK activation, which may lead to VSMC hypercontractility per se, and predispose the coronary artery to vasospasm and also atherosclerosis, not just hypertrophic changes in the media. It is worth mentioning that ROCK activation destabilizes eNOS messenger RNA in endothelial cells, which is another mechanism associating AFD with endothelial dysfunction (Figure).15

Clinical Perspectives

In this report by Kitani et al, 8 AFD patients complicated with CSA were treated with anti-anginal agents and galactosidase enzyme replacement therapy (ERT).4 The relief of angina was fairly attained; 6 of 8 patients were free from angina. Thurberg et al reported that ERT could clear vascular endothelial Gb3 deposits in the kidney.16 Moore et al also suggested that ERT could improve altered NO-mediated cerebrovascular responses.7,17 Although clinical evidence is awaited, the effects of ERT are expected to ameliorate endothelial dysfunction and VSMC hypercontractility in AFD, especially in the early stage of AFD-associated CSA. Regarding the role of endothelial dysfunction as an initial step in atherogenesis, the management of coronary risk factors is also important for patients with AFD, for whom statins may be effective for improving endothelial and VSMC function by inhibiting ROCK activity.14 Antioxidants such as vitamin C2 may also have positive effects.

Finally, Kitani et al provide an important clinical finding of the high incidence of CSA among patients of AFD without coronary artery stenosis.4 Gb3 accumulation can induce not only altered morphology, but also endothelial dysfunction and VSMC hypercontractility through oxidative stress-mediated impairment of endothelial-derived relaxing factors and activation of ROCK. Further investiga-

gation of the basic mechanisms of Gb3-induced pathophysiology and clinical evidence of therapeutic interventions may improve the care and prognosis of AFD patients with cardiovascular complications.

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Conflicts of Interest

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