Coronary artery spasm is defined as abnormal contraction of an epicardial coronary artery resulting in myocardial ischemia. Coronary artery spasm plays an important role in the pathogenesis of not only variant angina but also the other forms of ischemic heart disease such as myocardial infarction. Considering the fact that esophageal motility is enhanced in patients with angina pectoris due to coronary spasm (i.e., vasospastic angina (VSA)), the presence of a generalized disorder of smooth muscle contraction is strongly suggested. To date, the clinical features of VSA have been well characterized, and the treatment almost established. However, the underlying mechanisms for coronary spasm are not fully determined, and useful biomarkers also have not been identified. Endothelial dysfunction through abnormalities of nitric oxide (NO) synthase and its reduced bioavailability, and hypercontractility of vascular smooth muscle in spastic arteries, are factors in the development of VSA. Mutations (Glu298Asp variation in exon 7 and T-786 C in the 5' flanking region) of the endothelial NO synthase gene have been shown to be associated with coronary spasm. In other reports, NO is not necessarily decreased at the sites of spasticity of the coronary arteries, suggesting additional mechanisms inducing focal smooth muscle cell hypersensitivity in patients with variant angina. We recently showed the pivotal role of phospholipase C (PLC)-δ1 in the genesis of VSA in humans. PLC-δ1 is an isoform of PLC that is more sensitive to Ca2+ than the other isozymes; therefore, the initial increase in Ca2+ induced by G protein-linked PLC induces the prolonged activation of PLC-δ1 via positive feedback. PLC-δ1 activity was 3-fold higher in the cultured skin fibroblasts obtained from VSA patients than that from control subjects, and its activity positively correlated with coronary artery vasomotility. A single base variant (864G-A) in the entire coding region of the PLC-δ1 gene, resulting in the amino acid replacement of arginine 257 by histidine and enhanced activity, was found in 10% of the VSA patients, whereas p122 protein, which was recently cloned to potentiate PLC-δ1 activity, was increased 3-fold in patients with VSA compared with control subjects. Another enzyme related to constriction, ROCK/Rho kinase, was also reported to play an important role in the genesis of VSA. The porcine models of coronary artery spasm were developed by chronic application of interleukin-γ to the coronary artery and by removal of the endothelium with high-cholesterol feeding. Increased expression of ROCK/Rho kinase messenger RNA was demonstrated at the spastic segment compared with the control in the porcine model. In patients with VSA, the Rho-kinase inhibitor, fasudil, attenuated the constrictor response of the coronary artery to acetylcholine (ACh) and prevented the occurrence of chest pain.

The current report by Matsumoto et al focuses on the determination of the serum level of lipocalin-type PGD synthase (L-PGDS) in VSA patients and the relationship between the level of L-PGDS and coronary vasomotor function. L-PGDS has 2 functions: as a PGD2-producing enzyme within cells and as a lipophilic ligand-binding protein after secretion to the extracellular space. Of note, L-PGDS is localized in human cardiovascular tissue, including smooth muscle cells and endothelial cells, and coronary atheromatous plaques, thereby being secreted into the coronary circulation. Therefore, it has been shown that the L-PGDS level is increased in patients with stable angina pectoris, essential hypertension, and renal dysfunction. The current report by Matsumoto et al first demonstrated that the serum level of L-PGDS was significantly elevated in patients with VSA compared with those without VSA. The authors speculated that vasoconstriction increases arterial shear stress, and thereby promotes PGD2 production by stimulation of L-PGDS expression in vascular endothelial cells. The serum level of L-PGDS was statistically elevated in patients with VSA (Figure 2); however, since most of the values of L-PGDS overlapped between patients with and without VSA, it should be determined by further analysis of a larger population whether an elevated level of L-PGDS is clinically useful. The serum level of L-PGDS was more elevated in smokers and in patients with VSA who also smoke, and the serum level of L-PGDS was higher in patients with VSA than in those without VSA. The authors further showed that the L-PGDS level was associated with smoking status by univariate analysis. Since smoking is reported to be closely related to coronary spasm, L-PGDS findings seem reasonable. The precise mechanism for the linkage with smoking is unclear, but chronic low-grade inflammation, which is in part induced by smoking, may be a contributing factor in coronary spasm.

It is intriguing and noteworthy that the serum level of L-PGDS negatively correlated with the degree of LAD vasomotility. The higher the serum level of L-PGDS, the greater...
the decrease in coronary diameter (constriction) induced by intracoronary infusion of ACh. Because PGD2 produced by L-PGDS functions as an endothelium-derived coronary vasodilator, the serum level of L-PGDS may reflect a compensatory response to coronary spasm, and a high level of L-PGDS may be associated with the current status of disease activity. These findings raise an interesting aspect about the relationship between changes in the serum level of L-PGDS and coronary diameter after intracoronary infusion of ACh. It is also important whether the serum level of L-PGDS changes in patients with VSA by either the treatment with medicines, such as the Ca2+ antagonists, or the disease activity. These detailed observations may provide the answer as to whether L-PGDS is a novel biomarker for coronary spasm. Since L-PGDS is secreted in the systemic circulation and its serum level correlates with the decrease in coronary diameter (constriction) induced by intracoronary infusion of ACh, measuring the serum L-PGDS level may be useful for screening for coronary artery disease prior to coronary angiography, as suggested by the authors. In contrast to vessel diameter, the serum level of L-PGDS did not correlate with the change in coronary blood flow induced by intracoronary infusion of ACh. The authors discuss how PGD2 induces endothelium-dependent vasodilatation and suppresses the inflammatory process and maintains vascular homeostasis by functioning as an antivasospasm factor, which may explain the disparity in the coronary artery responses, but further investigation is needed to elucidate the vasomotor mechanisms underlying the elevated level of L-PGDS.

The increase in the serum level of L-PGDS was reported in patients with VSA, but the difference in the levels between non-VSA and VSA was small and the deviation was large. Therefore, further examination is needed to clarify the clinical role of L-PGDS. Furthermore, it should be emphasized that the present findings cannot explain the pathogenesis of VSA.

References