Drug-eluting stents (DES) are widely used in percutaneous coronary intervention because of their excellent early results with regard to the reduction in the rates of angiographic restenosis and associated clinical events. However, it has been shown that, compared with bare-metal stents, DES do not improve the long-term survival of patients with coronary artery disease (CAD), and that they have the potential to cause late stent thrombosis associated with delayed or absent endothelialization, or coronary endothelial dysfunction post implantation.\(^1\)\(^-\)\(^6\)

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In this issue of the Journal, Aizawa et al\(^7\) investigate the role of Rho-kinase activation in the DES-induced coronary hyperconstrictive response in CAD patients. In their study, they used fasudil, a Rho-kinase inhibitor, a downstream effector of the small GTP-binding protein Rho. They examined the structural changes in coronary segments with DES-induced hyperconstrictive response using optical coherence tomography (OCT) technique. The authors demonstrated enhanced coronary vasoconstrictive responses to acetylcholine (ACh) and attenuation of such response by fasudil. This is the first report that demonstrates the involvement of Rho-kinase activation in the pathogenesis of DES-induced hyperconstrictive response in patients with CAD, highlighting the therapeutic importance of the Rho-kinase pathway after DES implantation.

Previous clinical studies concluded that implantation of sirolimus-eluting stents (SES) could be followed by coronary endothelial dysfunction. These conclusions are based on the results of exercise\(^5\) or ACh-provocation\(^8\) tests. How peri-stent endothelial dysfunction develops after SES implantation remains unclear at this stage. The Cypher\(^\text{TM}\) stent used in the present study contains a 5-µm thick sirolimus coating mixed with non-erodable polymers.\(^1\) Sirolimus (rapamycin) is an immunosuppressant drug that binds to its cytosolic receptor, FKBP12, and inhibits downregulation of the cyclin-dependent kinase inhibitor p27\(^\text{kip1}\), blocking the transition from G1 to S phase in the cell cycle\(^a\) and inhibiting vascular smooth muscle cell proliferation and migration. Rapamycin is reported to impair endothelium-dependent relaxation in an in vitro model of porcine epicardial coronary arteries,\(^9\) and to enhance tissue factor expression in human aortic endothelial cells,\(^10\) suggesting coronary endothelial dysfunction and enhanced thrombogenicity at the site of DES implantation. However, there is no proof that this also occurs after the clinical use of SES. Because sirolimus is fully eluted from the polymer coating within 60 days, the abnormal vasomotion observed at 6–10 months in the current study does not seem to represent the direct effect of sirolimus itself. However, one cannot exclude the induction of a permanent abnormality in intact or regenerating endothelium occurring during the elution of sirolimus. Alternatively, the polymer from which the drug elutes, which may contribute to a marked hypersensitivity reaction, could be involved in the observed abnormal vasomotion.

It is also unclear if the DES-induced hyperconstrictive response was caused by the direct action of sirolimus on coronary smooth muscle cells, because functional tests specific for endothelial and smooth muscle cells were not performed in the present study. However, the authors performed OCT imaging analysis to provide detailed information on the intimal area of the coronary artery.\(^7\) The results demonstrated a lack of correlation between intimal hyperplasia and DES-induced coronary hyperconstrictive response. This result is consistent with the previous finding that coronary vasospasm is associated with a variable degree of intimal hyperplasia in a swine model of coronary vasospasm.\(^11\) Furthermore, the authors showed that the Rho-kinase inhibitor, fasudil, markedly attenuated the enhanced coronary vasoconstrictive response to ACh at the segments adjacent to the stents. It is possible that the Rho-kinase-mediated mechanism in coronary smooth muscle cells plays an important role in the DES-induced coronary hyperconstriction in response to ACh in CAD patients. On the other hand, the inflammatory response in the coronary artery, especially at the adventitia, is reported to be accelerated at the site of SES implantation.\(^12\) Furthermore, the expression levels and activity of Rho-kinase are accelerated by inflammatory stimuli, such as angiotensin II and interleukin-1β, through the protein kinase C/nuclear factor-κB pathway.\(^13\) Based on these observations, the present results suggest that in CAD patients the DES-induced local inflammatory response in the coronary artery activates the Rho-kinase pathway, leading to a coronary hyperconstrictive response by ACh provocation. However, further functional studies are needed to elucidate whether or not the Rho-kinase pathway is directly activated in the DES-induced hyperconstrictive response.

Fasudil is the only clinically available Rho-kinase inhibitor at present. Its intravenous form is used for the treatment of cerebral vasospasm in Japan only. Clinical studies using fasudil have suggested that Rho-kinase inhibitors may be useful...
for the treatment of a wide range of cardiovascular diseases in addition to cerebral vasospasm, including angina pectoris, hypertension, pulmonary hypertension, stroke, and heart failure. In patients with vasospastic angina, intracoronary fasudil markedly inhibits ACh-induced coronary spasm and related myocardial ischemia, demonstrating the involvement of the Rho-kinase pathway in the pathogenesis of coronary spasm in humans. Furthermore, intracoronary fasudil is effective in the treatment of intractable coronary spasm resistant to maximal vasodilator therapy with calcium channel blockers and nitrates after coronary artery bypass surgery. Although clinical studies of fasudil have demonstrated its efficacy and safety profile in humans, further studies are needed to confirm the potential therapeutic importance of the Rho-kinase pathway and clinical usefulness of Rho-kinase inhibitors in cardiovascular disease. We hope Rho-kinase inhibitors help optimize the efficacy and safety of DES in CAD patients.

References