Drug-eluting stents (DES) considerably reduce rates of restenosis and related target vessel revascularization compared with bare-metal stents (BMS). Although patient survival is not significantly increased by DES, concern has been growing that delayed endothelialization, incomplete neointimal healing, inflammatory events, or hypersensitivity reactions after DES implantation may lead to serious adverse events such as vasospasms and stent thrombosis, and consequently may trigger myocardial infarction and death (1).

Drugs released from DES exert distinct biological effects, such as (in)activation of signal transduction pathways and inhibition of cell proliferation. Although primarily aimed at preventing vascular smooth muscle cell (VSMC) proliferation and migration, these drugs also impair re-endothelialization and induce tissue factor expression, resulting in a prothrombogenic environment (2). DES implanted in noninjured common swine coronary arteries provoke an extensive granulomatous, eosinophil-rich inflammatory response with circumferential vessel involvement in all stented sections. Inflammation was also observed in BMS control subjects, but at a much lower prevalence and with less intensity (3). DES, but not BMS, are associated with acetylcholine- or exercise-induced paradoxical coronary vasoconstriction of the adjacent vessel segments (4,5). These observations suggest a drug-induced endothelial and/or vascular dysfunction as the underlying mechanism. Whether this effect is directly and specifically drug-induced or whether this is the result of a prolonged inflammatory response with concomitant delayed recovery of the endothelium and other vascular tissues remains unclear.

In this issue of the Journal, Shiroto et al. (6) showed that paclitaxel increases Rho-kinase (ROCK) expression and activity in cultured human coronary VSMCs. After paclitaxel- or sirolimus-eluting stent implantation in porcine coronary arteries, serotonin-mediated vasoconstriction at the stent edges was more enhanced in DES than in BMS. This hyperconstriction could be diminished by intracoronary pre-treatment with hydroxyfasudil, a selective ROCK inhibitor. Bradykinin-mediated vasodilation was not altered. Histological analyses showed a suppression of neointimal formation and re-endothelialization in DES sites compared with BMS sites. Microthrombus formation and inflammatory response at DES sites were enhanced. Immunohistological analyses also detected a higher expression of ROCK at the DES sites.

This nice work by Shiroto et al. (6) suggests that the ROCK pathway plays an important pathogenetic role in coronary hyperconstriction after DES implantation. The present study deals with a very important issue, provoking additional questions:

1. Although it is well accepted that stent thrombosis is succeeded by serious clinical end points, it is unsettled whether vascular hyperconstriction is frequently the cause of adverse events. Coronary vasospasm has been postulated to play an important role, especially in the Japanese population (7), in variant angina, but also in unstable angina, myocardial infarction, and sudden cardiac death (8). Coronary artery spasms caused by a local hyper-reactivity of the arterial wall may contribute to the development of occlusive coronary thrombosis by fissuring a plaque or the vessel wall and by leading to blood stasis (9). However, the link between adverse clinical events and persistent abnormal vasomotion after DES implantation has yet to be established.

2. It would be interesting to know whether DES-induced hyperconstriction predominately occurs in individuals who are a priori predisposed to abnormal vasospasms. This could shed some light on the underlying mechanisms. Is Rho-kinase generally instrumental for the development of clinically relevant vasospasms?

3. Obviously, it remains to be determined whether investigation and treatment of healthy porcine vessels is transferable to the clinical scenario in humans, where we commonly deal with vascular structures severely altered by atherogenesis. So far, patients with atherosclerotic lesions may display paradoxical exercise- and acetylcholine-induced vasoconstriction of vessel segments adjacent to sirolimus-eluting stents, although the endothelium-independent dilatory response to nitroglycerin was maintained (4,5,10). The underlying mechanisms (possibly Rho?) were not clarified.

4. Is the coronary hyperconstriction, especially found at DES sites, a direct and specific drug effect of paclitaxel or sirolimus, or is it rather a result of prolonged and

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*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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enhanced inflammatory response in DES? Both ROCK-
messenger ribonucleic acids and ROCK-proteins are
up-regulated through protein kinase C- and nuclear
factor kappa B-dependent pathways by proinflammatory
factors such as angiotensin II and interleukin-1 beta. The
ROCK pathway modulates the phosphorylation level of
myosin light chain through inhibition of myosin phos-
phatase and contributes to the agonist-induced calcium
sensitization in smooth muscle contraction (8). Activat-
tion of the ROCK pathway down-regulates endothelial
nitric oxide synthase and thereby reduces bioavailability
of nitric oxide, promoting endothelial dysfunction (11).
Thus, ROCK activation might be a central mechanism
for both endothelial dysfunction and VSMC hypercon-
striction, causing general vascular dysfunction.

Because long-term inhibition of ROCK with fasudil
suppresses the in-stent neointimal formation by multiple
mechanisms, including inhibition of vascular inflamma-
tion, enhanced apoptosis, and reduced collagen deposi-
tion (12), increased ROCK activity at the stent site could
also be an epiphenomenon of the inflammatory process
of the vessel wall, which is aggravated by paclitaxel or
sirolimus at the DES sites. At least, a recent study
observed more extensive inflammatory reactions at DES
-especially in sirolimus-eluting stents- than at BMS sites
in a porcine model (3). After all, the expression of
ROCK itself is accelerated by inflammatory stimuli.
These inflammatory processes may partly explain the
hyperconstricting responses after DES implantation.

5. What is the impact of anti-inflammatory treatment on
the observed events? Although a recent study observed
an antirestenotic efficacy of oral prednisone treatment
after percutaneous coronary intervention with conven-
tional BMS (13), the impact of steroid administration
after DES implantation especially with respect to hyper-
constriction is unknown, but may help to elucidate the
role of the DES-induced inflammatory response of the
vessel wall.

6. By the same token, is the inflammatory cascade directly
initiated by the eluting drugs? What is the role of the
polymer? The exemplary data in cultured VSMCs sug-
gest direct effects of paclitaxel (sirolimus?). However,
those cells are not comparable with the quiescent and
contracting cells residing in the media of an adult vessel.
In addition, in vivo hyperconstriction may not be purely
mediated via VSMC action, but may also be influenced
by other adjacent cells (endothelial or inflammatory cells)
as well as by extracellular factors (matrix, cytokines,
growth factors, and so on). If we are looking at a
cell-specific mechanism taking place only in smooth
muscle and not in endothelial cells, the underlying
mechanisms need attention imperatively because this
could guide us to the desperately needed differential
vascular therapy required to selectively foster the endo-
thelial and afflict the muscle cells. Thus, further research
would need to definitely exclude the possibility that the

7. Is the pathway specific for serotonin? In coronary an-
giography, serotonin provokes more focal coronary vaso-
spasm, whereas acetylcholine induces more diffuse and
distal vasospasm (8,14). Obviously, coronary artery spasms
frequently occur at the atherosclerotic lesions of the coro-
nary artery. Revealing a close topological correlation
between the serotonin-induced spastic site and the athero-
sclerotic lesion, serotonin seems to better mimic spontaneous
coronal spasms than acetylcholine in vivo (8,15). It would
be nice to know whether vasoconstrictors, such as nor-
epinephrine, angiotensin II, or endothelin, also provoke
hyperconstriction after DES implantation. If so, effective
treatment options to test this hypothesis would be
available.

8. Would statin treatment ameliorate the DES-associated
vasoconstriction? By inhibiting the 3-hydroxy-3-
methylglutaryl coenzyme A reductase, statins reduce cho-
esterol synthesis, thus preventing the formation of
geranylgeranyl pyrophosphate required for membrane
translocation and activation of Rho-A, the main up-
stream activator of ROCK (16). Because ROCK inhibi-
tion results in the stabilization of endothelial nitric oxide
synthase–messenger ribonucleic acid and an increased
bioavailability of nitric oxide (17,18), this, as one of the
so-called pleiotropic effects of statins, is thought to be
responsible for the observed improvement in flow-
driven vasodilation by statin administration. Do we
need a drug such as fasudil, with an uncertain safety
profile, if we could instead select the widely used statins?

The findings of Shirote et al. (6) add valuable informa-
tion to the DES issue and underline the importance of
better understanding the mechanisms responsible for the
vascular performance, and supposedly, the clinical outcome
after DES implantation. As almost always, we implemented
with DES a treatment option in humans that we have (at
best) not fully mechanistically anticipated. Although no one
will dispute the clinical success of this venture, much work
needs to be accomplished not only to better understand the
molecular and cellular events critical for vascular pathology
with or without stents, but also to develop therapeutic
measures that will improve patient outcome. Certainly, the
ROCK pathway is one attractive candidate.

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late coronary thrombosis secondary to a sirolimus-eluting stent: should


Key Words: vasoconstriction • stents • smooth muscle • inflammation.