Patrick M. McCarthy, MD, FACC
Mario J. Garcia, MD, FACC

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REFERENCES

1. Firstenberg MS, Vandervoort PM, Greenberg NL, et al. Noninvasive estimation of transmitral pressure drop across the normal mitral valve in humans: importance of convective and inertial forces during left ventricular filling. J Am Coll Cardiol 2000;36:1942–9.
2. Beppu S, Izumi S, Miyatake K, et al. Abnormal blood pathways in left ventricular cavity in acute myocardial infarction. Experimental observations with special reference to regional wall motion abnormality and hemostasis. Circulation 1988;78:157–64.
3. Greenberg NI, Vandervoort PM, Firstenberg MS, Garcia MJ, Thomas JD. Estimation of diastolic intraventricular pressure gradients by Doppler M-mode echocardiography. Am J Physiol Heart Circ Physiol 2001;280:H2507–15.
4. Vlassak J, King LM, Greenberg NL, Firstenberg MS, Thomas JD, Garcia MJ. Early apical relaxation increases ventricular suction during exercise in normal volunteers (abstr). J Am Coll Cardiol 2001;37:442A.
5. Courtois MA, Kovacs SJ, Ludbrook PA. Physiologic early diastolic intraventricular pressure gradient is lost during acute myocardial ischemia. Circulation 1990;81:1688–96.
6. Firstenberg MS, Smedira NG, Greenberg NI, et al. Relationship between early diastolic intraventricular pressure gradients, an index of elastic recoil, and improvements in systolic and diastolic function (abstr). Circulation 2000;102:II647.
7. Tonti G, Riccardi G, Denaro FM, Trambaiolo P, Salustri A. From digital image processing of colour Doppler M-mode maps to noninvasive evaluation of the left ventricular diastolic function: a dedicated software package. Ultrasound Med Biol 2000;26:603–11.

Paclitaxel-Coated Stent: Is There a Light at the End of the Tunnel?

We read with great interest the study by Drachman et al.(1). Their study determines long-term effects of stent-based paclitaxel delivery and its influence on neointimal thickening in a rabbit injury model.

Their report highlights the importance of stents with drug delivery capabilities and therefore signals the beginning of the era of "smart" stents. An important question unanswered in their study is the gender bias in paclitaxel therapy. It is well established that the chemotherapeutic effect of paclitaxel is mediated through the plasma membrane estrogen receptors (2). It is also widely accepted that this is particularly effective in breast and ovarian neoplasms (3–5).

In contrast, the estrogen receptors in the human cells, including arterial smooth muscle cells (SMC), are probably less developed in the male cell system. Therefore, it will be extremely interesting to investigate the effect of paclitaxel-coated stents on myointimal hyperplasia in male and female animals.

Another issue of this antiproliferative approach for restenosis is the nonselective nature of this modality, which also includes suppression of endothelial cell growth. Although the Drachman et al. (1) study along with others demonstrates complete endothelialization of the coated stents at follow-up, histology is not always an absolute indicator of the endothelialization process. Many believe there is the phenomenon of pseudo-endothelialization. Synthetic or proliferative SMC that line the surface of the vessel after injury may perform many, but not all, functions of endothelial cells. Therefore, functional studies are necessary to address the issue of true endothelialization and, subsequently, late thrombosis.

Finally, the issue of modulation of collagen production by SMC needs to be addressed. The arrest of SMC migration and proliferation will not be enough to reverse the process of restenosis. It might be that paclitaxel therapy of the vessel wall also abolishes collagen production. Importantly, further in vitro and in vivo studies will help to understand antirestenotic properties of this compound.

Thus, additional experimental studies that will address all these issues might indeed allow us to see the beginning of the end of a long and difficult journey of restenosis prevention.

Nicholas Kipshidze, MD, PhD
Lenox Hill Heart and Vascular Institute of New York
130 East 77th Street
Black Hall—9th Floor
New York, New York 10021
E-mail: nkipshidze@lenoxhill.net

Jeffrey W. Moses, MD
Martin B. Leon, MD

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REFERENCES

1. Drachman DE, Edelman ER, Seifert P, et al. Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months. J Am Coll Cardiol 2000;36:2325–32.
2. Razandi M, Pedram A, Levin ER. Plasma membrane estrogen receptors signal to antiapoptosis in breast cancer. Mol Endocrinol 2000;14:1434–47.
3. Kuter I. Breast cancer update. Oncologist 2000; 5:285–92.
4. Lin HL, Liu TY, Chau GY, Lui WY, Chi CW. Comparison of 2-methoxyestradiol-induced, docetaxel-induced, and paclitaxel-induced apoptosis in hepatoma cells and its correlation with reactive oxygen species. Cancer 2000;89:983–94.
5. Wang Z, Yang D, Mohanakrishnan AK, et al. Synthesis of B-ring homologated estradiol analogues that modulate tubulin polymerization and microtubule stability. J Med Chem 2000;43:2419–29.

REPLY

We very much appreciate the comments of Kipshidze et al. regarding our report on long-term reduction of experimental restenosis using a paclitaxel-releasing stent (1). Their insights underscore the challenges we all face in translating "bench-top" triumphs to techniques that benefit our patients.

It is interesting to consider the role played by the estrogen receptor in smooth muscle cell migration and proliferation (2), and it will be important to determine whether paclitaxel's antirestenotic effects are, at least in part, effected through this receptor system. It is worth noting, however, that paclitaxel's effects are myriad, and that attributing all to plasma membrane estrogen receptors may not be accurate. Such mechanistic insight may extend our understanding of clinical restenosis.

We reiterate concerns that experimental models of endothelial cell function are incomplete and may not always mirror responses in humans. Following experimental arterial injury, the endothelium plays an important role in guiding the healing process, modulating neointimal proliferation, controlling extracellular matrix deposition, regulating vasomotor tone, and protecting against luminal thrombus deposition. Although present laboratory methods allow us to examine the histologic impact of arterial injury on endothelial viability, specific aspects of endothelial cell function are