Since the earliest use of coronary stents for treating symptomatic coronary stenosis, maintaining patent arteries after treatment has remained an elusive goal. Although the first bare metal stents opened stenotic arteries, they injured the arterial wall. The buildup of intimal scar tissue caused restenosis, a frustrating problem for prevention or treatment. After a dozen years of research, however, drug-eluting stents were developed; armed with polymer coating and paclitaxel or sirolimus, they prevented restenosis and were hailed as a major therapeutic breakthrough.

By the time drug-eluting stents were approved by the U.S. Food and Drug Administration in 2003, clinical trials first raised concern about increased thrombosis and efficacy of drug-eluting stents surfaced as reports of late stent thrombosis began to appear.1,2 Cardiologists wondered if prevention of restenosis was always a good thing. If no protective cellular layer formed over the struts of the drug-eluting stent—even months or years after implantation—would thrombus develop on the exposed metal scaffolding or other damaged or inflamed areas on the blood vessel wall? Over months or years, would progressive inflammation or late “catchup” tissue growth cause drug-eluting stents to lose their early advantage over bare metal stents?

The pendulum in this debate has swung back and forth as clinical trials first raised concern about increased thrombosis and then later quelled our fears as our understanding of how drug-eluting stents work in real life has matured. An important issue has been the increased use of stents in patients with more complex coronary and other disorders, raising the question of whether the established standards of safety and efficacy still apply.

Answers for these challenging questions have come from 2 worlds: clinical studies of patients with stents and animal studies that elucidate the mechanisms of biological response to drug-eluting stents. In this issue of Circulation, Wilson and colleagues3 studied pig coronary arteries treated with pairs of overlapping bare metal stents, sirolimus-eluting stents, or paclitaxel-eluting stents. They examined the histopathology of the stented arteries 30, 90, or 180 days later. The authors found granulomatous inflammation and positive remodeling in some vessels treated with sirolimus-eluting stents, which they ascribed to a late inflammatory response to the polymer coating of the stent. In paclitaxel-eluting stent–treated vessels, there was an excess of fibrin deposition next to the struts, with a loss of medial smooth muscle cells. Stent strut malapposition (50 to 100 µm) was found in paclitaxel-eluting stent–treated vessels at 30 days, but not later and not in the other treatment groups. Neither drug-eluting stent reduced restenosis compared with bare metal stent controls, a finding previously established in the pig coronary model,4–6 and endothelialization, which is notoriously robust in the pig model, was complete in all vessels studied. The restenosis and endothelialization underline the differences between pig and human studies.

How can we relate the Wilson et al observations to coronary stenting in humans? If overlapping drug-eluting stents provoke inflammation or delay healing of the vessel wall in pig coronary arteries, the findings of Wilson et al, does this predict a similar response in humans? Does this imply that the risk for stent thrombosis is increased with drug-eluting stents?

In humans, the data are inevitably incomplete because during life our view of patients’ coronary arteries lacks the microscopic detail of animal histopathology. Although examining thrombosed human vessels at postmortem can give some insights into the human pathology, it presents an inherently biased view: Only the failures are available, making generalization of the pathological findings questionable at best. What would the stented coronaries of the healthy survivors show?

Several similarities have been shown, however, in human and animal histopathology after drug-eluting stent use. Pig and rabbit studies show slightly different results for each drug-eluting stent, but overall, the findings usually include greater inflammation, delayed wound healing, increased fibrin deposition, medial smooth muscle cell loss, and incomplete endothelialization; in some, late stent malapposition also is noted.4–9 In postmortem human studies, histopathology shows increased inflammation, incomplete stent strut endothelialization, poor apposition of stent struts to vessel wall, and other signs of delayed healing. These changes are much greater in patients with stent thrombosis than in those without thrombosis.10,11

These animal and human pathological observations raise several important questions: Are these changes present to some extent in all patients with drug-eluting stents? Why do only a small minority of drug-eluting stents thrombose? Can

Four legs good, two legs better.
—George Orwell, Animal Farm, 1945
we determine what factors modify the reaction to these stents, whether they are related to stent deployment, lesion type, patient characteristics, or arterial biological response? And most important, how critical are these changes clinically, and how (if at all) do they affect the value of drug-eluting stents in the real-world, patient-care setting? Three imaging techniques, intravascular ultrasound, optical coherence tomography, and angioscopy, provide some potential insights into these questions. Several large intravascular ultrasound studies showed that up to 20% of patients treated with drug-eluting stents may, over time, develop incomplete stent apposition to the vessel wall. Despite similar findings in both animal models and human pathological specimens associated with thrombosis, intravascular ultrasound–documented incomplete stent apposition has never prospectively identified a patient who later developed thrombosis. The predictive value of identifying incomplete stent apposition for thrombosis risk remains unclear.12,13

Angioscopy (currently a research tool) visualizes the human arterial lumen in vivo. In a recently published study, angioscopy showed heterogeneity of neointimal coverage 9 months after drug-eluting stent implantation, greater in paclitaxel-eluting than in sirolimus-eluting stented vessels. No clinically apparent thrombosis occurred, but small amounts of thrombus were seen in patches of vessel wall that were less well covered. One day, this technique, which shows the completeness of stent strut coverage, may predict the risk for stent thrombosis.14

Optical coherence tomography provides greater spatial resolution than intravascular ultrasound and may eventually reveal the correlation between incomplete stent apposition, neointimal strut coverage, and the risk for associated thrombus. Ideally, however, improved molecular imaging techniques may soon be able to label and image endothelial cells, macrophages, fibrin, or other elements of the arterial wall, helping us to understand the biological response, for which the anatomic changes are a surrogate measure, and to establish whether healing has occurred after stenting.15

Although animal studies and human autopsy evaluations suggest some risks for drug-eluting stent thrombosis, the true measure of their value must be the long-term results from meticulous clinical trials. In these studies, drug-eluting stents have routinely reduced the need for repeat revascularization compared with bare metal stents, and early concerns for an increased risk of thrombosis have been put to rest by recent animal studies. On balance, however, the mounting long-term human data tip the scales decisively in favor of drug-eluting stents, which reduce restenosis without additional risk of death or myocardial infarction, even in the most complex patients. When considering the implications of drug-eluting stent therapy in animal and clinical models in 2009, we find that insights obtained from creatures with 4 legs may be good, but outcomes measured in those with 2 legs are better and a more germane guide for clinical practice.

Disclosures

Dr Drachman has served on the speakers’ bureau for Bristol-Myers Squibb/Sanofi-Aventis.

References


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