Editorial Comment

A Dilemma for the 1990s
Choosing Appropriate Experimental Animal Model for the Prevention of Restenosis

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Percutaneous transluminal coronary angioplasty (PTCA) has become a successful and widely used treatment for patients with coronary disease since its first clinical application by Andreas Gruentzig in 1977. Despite the increase in procedure and case complexity, primary success rates have improved. However, late restenosis, which constitutes the most important problem after successful angioplasty, continues to occur in 30–40% of patients within 3–6 months. Experimental, pathological (autopsy and atherectomy specimens), angioscopic, and angiographic observations, coupled with recent observations in cell culture and in situ hybridization, indicate that restenosis after PTCA involves a fibroproliferative response to vascular injury in the setting of mural thrombosis with platelet activation, thrombin generation, and the release of mitogens. An alternative or associated mechanism of restenosis after PTCA is recoil at the site of PTCA injury.

Attempts to modify the fibroproliferative response to PTCA in humans by pharmacological interventions have met with very limited success. Therefore, despite more than a decade of intensive research, PTCA interventions that have shown promise in limiting restenosis in laboratory animal models have not led to similar findings in patients.

Difficulty applying the results of animal models to humans is not surprising, considering the complexity of the response of the arterial wall to injury. Therefore, differences in techniques used to initiate injury, degree of stretch, and the type of injury (deep versus mild) that results may modify the outcome of pharmacological manipulation in a given animal model; complex mechanisms regulating the initial deposition of platelets and fibrin on and within the damaged vessel wall and the subsequent fibroproliferative response are not fully understood and may vary among species; the influence of atherosclerotic plaque composition on the response of the vessel wall to mechanical insult is not considered by most animal models of acute balloon injury and confounds the problem of extrapolating experimental results to clinical settings; most importantly, drug metabolism, tissue penetration, and end-organ effects of pharmacological interventions may vary among species such that an equal dosage per kilogram does not ensure equal biological effects.

Of interest, most of the data obtained in the pig and primate models of restenosis after PTCA, contrary to those obtained in the smaller size of the animal species, appear to be more closely related to the data obtained in humans. In this context, the study by Lam et al in this issue of Circulation considers the regulation of the fibroproliferative component of restenosis in the pig model. The experiments examine the effects of pretreatment with an angiotensin converting enzyme (ACE) inhibitor, cilazapril, on vascular healing following balloon-mediated carotid artery injury. The dose of cilazapril nearly abolished plasma ACE activity and significantly lowered the mean arterial blood pressure in the treatment group. The study was not able to demonstrate any attenuation of carotid neointimal myoproliferation after either "deep" or "mild" balloon-mediated injury in the treatment group. This study is in agreement with two recent preliminary reports in which ACE inhibition did not limit restenosis in the coronary circulation in the pig model. Similarly, Hanson et al reported that ACE inhibition with cilazapril did not reduce intimal thickening over a 3-month period in arteries injured by either endarterectomy, balloon denudation, or synthetic vascular grafting in a primate model. In contrast, Powell et al demonstrated that pretreatment with an ACE inhibitor in the rat decreased neointima formation by 80% at 14 days after balloon injury of the carotid artery. Subsequently, others have confirmed a similarly profound decrease in smooth muscle cell proliferation after balloon injury by pretreatment with cilazapril in the rat model. These discordant studies have important implications for the Multicenter European Trial with Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis in which more than 700 angioplasty patients have been randomly chosen to receive either cilazapril or placebo starting 4–6 hours after PTCA. A similar trial involving 1,400 patients is under way in the United States. As noted by Lam et al, the dose of cilazapril in some of the animal experiments was almost 100-fold that which might be used in the clinical setting and resulted

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in significant blood pressure–lowering effects and therefore may have little physiological relevance for humans. Moreover, the variable effects of ACE inhibition on restenosis in various animal species (beneficial in small animals but ineffective in the pig and primate) serve to highlight the problems of extrapolating data from experimental animal models of restenosis to the clinical setting. Recent reviews have underscored the paucity of interventions that have been effective in preventing or attenuating restenosis in clinical trials after PTCA, in contrast to the numerous methods that have been of benefit in small animal models. Although it seems logical to initiate investigations of new interventions for preventing restenosis in small animal models for reasons of cost-effectiveness, ease of experimentation, and the ability to generate statistically significant numbers of animals, the pitfalls of this approach are now evident as the complexities of restenosis are unraveled and differences between species become apparent.

Before undertaking large and costly patient PTCA-restenosis trials, it would be ideal to conduct trials in an experimental animal model of arterial injury that closely simulates this condition in humans with regard to natural history, thrombus deposition, and fibroproliferative response to injury. In addition, the model should have a similar pharmacological profile. Unfortunately, no such model exists. At present, research conducted in the pig and the primate appears to be the most predictive of results in humans, and it would seem prudent to verify laboratory findings obtained using smaller animals in these models before undertaking large-scale human trials. Furthermore, measurements of a specific biological activity and duration that are measurable in animals may also be measurable and translatable to smaller studies in humans for assessment of dosage and duration of therapy before embarking on large-scale and expensive trials with clinical efficacy end points.

In the absence of an ideal experimental animal model, the ongoing challenge for investigators is to identify effective therapies within the constraints of available models that will translate into patient benefit in clinical trials of restenosis after PTCA. However, given the complex biology of restenosis and the multiple influences that are active, including injury, thrombosis, cellular proliferation, growth factors, coronary spasm, and vessel recoil, it is unlikely that a single intervention will be effective in limiting restenosis in humans. The solution will more likely involve a multifactorial approach predicated on an understanding of the basic biological processes involved and targeted at the individual components.

References


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