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The Porcine Model of Coronary Restenosis

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INTRODUCTION

Human coronary restenosis remains an elusive problem, and a major limitation of all percutaneous interventional coronary revascularization procedures, despite intracoronary stenting (1–9). Restenosis has recently gained even greater importance, since trials comparing PTCA with coronary bypass surgery (BARI, EAST, CABRI) suggest that angioplasty is comparable therapy for cardiac events and symptoms, but the two differ strikingly regarding the need for repeat interventions and cost (10–12). Restenosis lies at the center of these problematic differences.

A wide spectrum of pharmacologic strategies have demonstrated either complete failure, or at best equivocal success (13–27). New devices have also failed to show substantial effect (28). The incidence, clinical time course, and angiographic correlates of coronary restenosis have been well described, yet a limited understanding of its pathophysiology has prevented the formulation of

From: *Contemporary Cardiology: Vascular Disease and Injury: Preclinical Research*
Edited by: D. I. Simon and C. Rogers © Humana Press Inc., Totowa, NJ

Table 1
Clinical Problems Involving Exuberant
Neointimal Hyperplasia

Small-diameter vascular grafts
Prosthetic grafts
Vasculitis
Transplant coronary artery disease
Atherosclerosis

a truly effective therapy. Only recently has vascular brachytherapy with β or γ radiation suggested that neointimal hyperplasia may be limited.

While many animal arterial injury models have been developed and extensively studied to test potential therapies, a limited knowledge of the relevance of such models to human restenosis poses a major drawback. These models have been used to test preclinical therapies, and to provide a better understanding of the pathophysiology of the restenosis problem. Studies using such models have provided a framework for a better knowledge of the arterial response to injury (29–31).

Published results from many animal studies often fail to translate to clinical trials, resulting in confusion about the models, restenosis mechanisms, and potential solutions. However, in most instances, a careful review and consideration of such studies frequently reveals that the interpretation of the results, and not the models themselves, have failed. In general, the porcine model of restenosis seems practical, and substantially representative of human remodeling and neointimal formation. We must formulate a better understanding of this useful model to determine when and how far to apply it in understanding the restenosis problem.

Restenosis in its simplest form is the healing response following arterial injury caused by revascularization (32–38). It is commonly attributed to several factors, including acute and chronic remodeling, (39–42) thrombus at the injury site, medial smooth-muscle-cell (SMC) migration and proliferation, and extracellular matrix production (43–49). In these times, when coronary stent placement is ubiquitous, remodeling at the angioplasty site is minimized. However, the stent itself enhances neointimal hyperplasia, reducing the problem to understanding and limiting neointimal thickening (50). Neointima plays an important role in many arterial diseases (*see* Table 1).

PORCINE CORONARY ARTERY INJURY MODELS

The coronary arteries of domestic crossbred pigs respond in a very similar fashion to human coronary arteries after sustaining deep injury (51). A hyper-

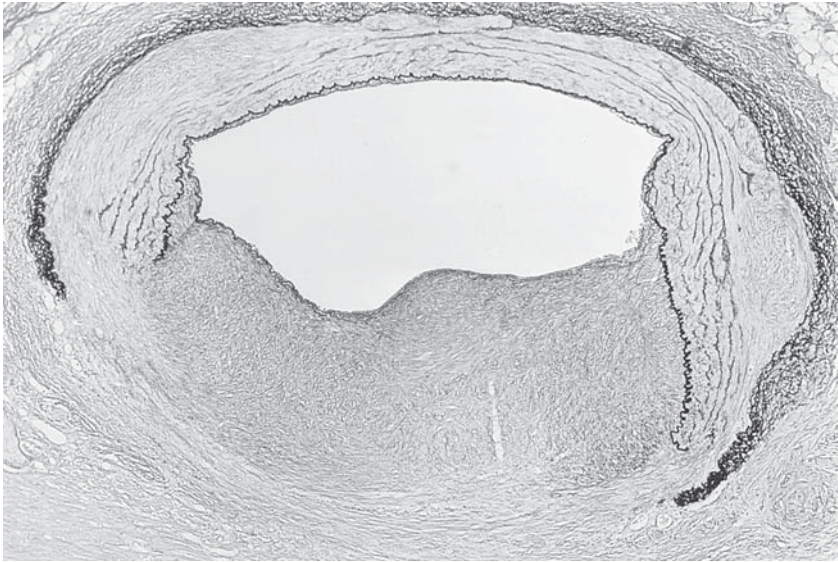


Fig. 1. Photomicrograph of a porcine coronary artery 28 d after oversized balloon injury. Not all wires penetrated into the vessel media. The balloon lacerated the media and created a large dissection (*bottom*) that filled with neointima. The neointima grows only at sites of internal elastic lamina and medial rupture. The amount of neointimal formation is variable, and in general is proportional to the size of the fracture length. A typical response index is intimal area/fracture length. Elastic van Gieson's stain, magnification $\times 10$.

cholesterolemic diet produces lesions which are histopathologically identical, but more severe than those produced by standard laboratory diets (52).

The carotid arteries are typically used for arterial access in this model, although the femoral arteries may also be used without difficulty. Standard human coronary-guide catheters and curves for human coronary angioplasty fit the porcine aortic root well (20–40 kg animals) for engagement of the left main or right coronary arteries.

Severe mechanical arterial injury is done to the coronary arteries either by a coronary angioplasty balloon alone, (30,53,54) or by delivering an oversized metal coronary stent to the artery for chronic implant. Both methods create an injury that results in a thick neointima within 20–28 d (*see* Figs. 1–3). The histopathologic features of this neointima are identical to human restenotic neointima (Fig. 4), and the neointima is often voluminous enough to cause relevant luminal narrowing.

Specimens from balloon-injured vessels without stents typically show a single laceration of media, filled at 28 d by a variable amount of neointima. Oversized stent placement in arteries show multiple injuries in each section.

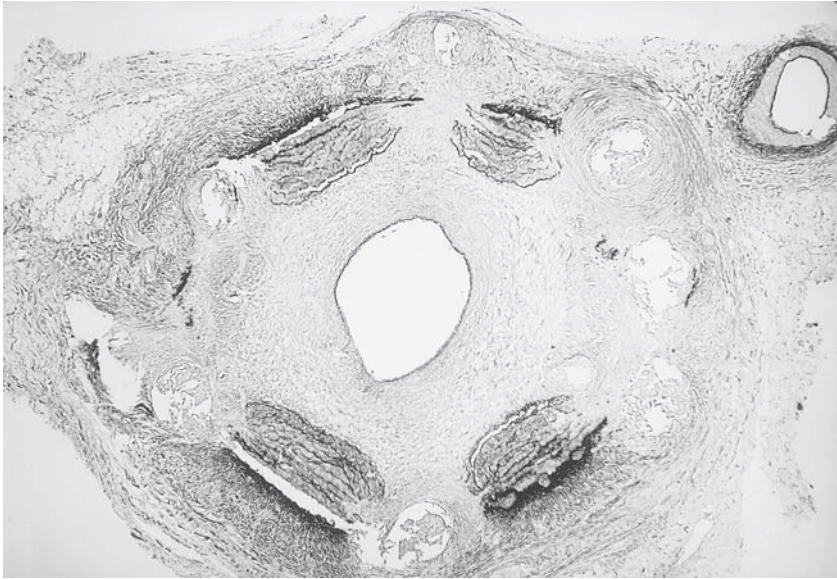


Fig. 2. Section showing severe injury in a normal porcine coronary artery at 28 d after coronary artery injury. All wires have produced severe damage, as evidenced by voluminous neointimal thickening at all sites circumferentially around the lm. The lm is markedly compromised by this injury. Elastic van Gieson's stain, magnification $\times 10$.

Each injury site is characterized in the porcine oversized stent-injury model as a mean injury score (Table 2) that is ordinarily proportional to injury depth (53,54). The amount of neointimal thickening is directly proportional to this score (Fig. 5). This permits creation of an injury-response regression line that can be used to quantitate the response to potential therapies (55).

An interesting consideration is whether neointimal formation resulting from injury by balloon alone differs from that caused by oversized stents, and several considerations are important to answering to this question. The first is whether the stent alters the mechanism of neointimal formation. Neointimal thickness is strongly related to the depth of injury in the stented injuries—an observation which has important implications. At low or zero levels of arterial injury, neointima at stent-wire sites is quite thin—essentially the same as that of “appropriately sized” stents. It is only when stent wires fracture the internal elastic lamina, lacerate media, or perforate through the external elastic lamina that neointimal thickness grows substantially to the point of creating macroscopic stenoses. This set of observations suggests that it is the *injury* from the stent wires, rather than the wires themselves, that is responsible for neointimal generation. The stent is thus a means of reliably producing injury to the arterial

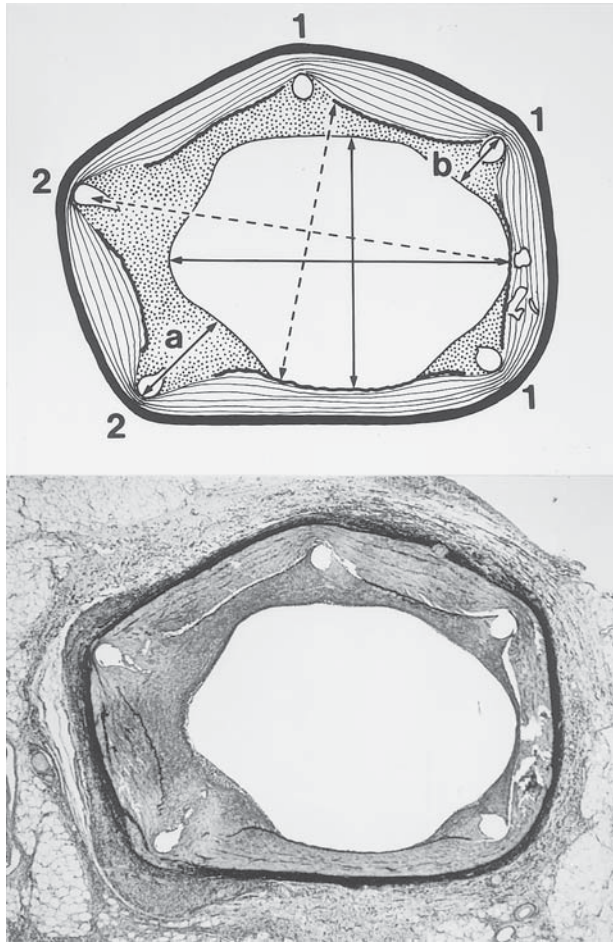


Fig. 3. Photomicrograph of a porcine coronary artery 28 d after severely oversized coil injury. Not all wires penetrated into the vessel media. In this section, the two coils at the bottom of the vessel lacerated the media and resulted in substantial neointimal thickening. Conversely, the farthest right wire did not, and less thickening resulted. A short segment of vessel media at the bottom-most portion of the figure is entirely normal, without any neointima, although this segment was stretched by the balloon. This normal-appearing segment has the farthest distance between any coil wires. The top image shows the method of quantitating injury produced by the stent wires. The Elastic van Gieson's stain, magnification $\times 10$.

wall. When the stent itself is not a cause of injury, it does not produce substantial neointimal thickening. Evidence from studies with rabbit femoral arteries indicates that oversized, injurious stent wires provide a strong, prolonged stimulus to mitosis in the intima of the vessel. It is also clear that the stent metal

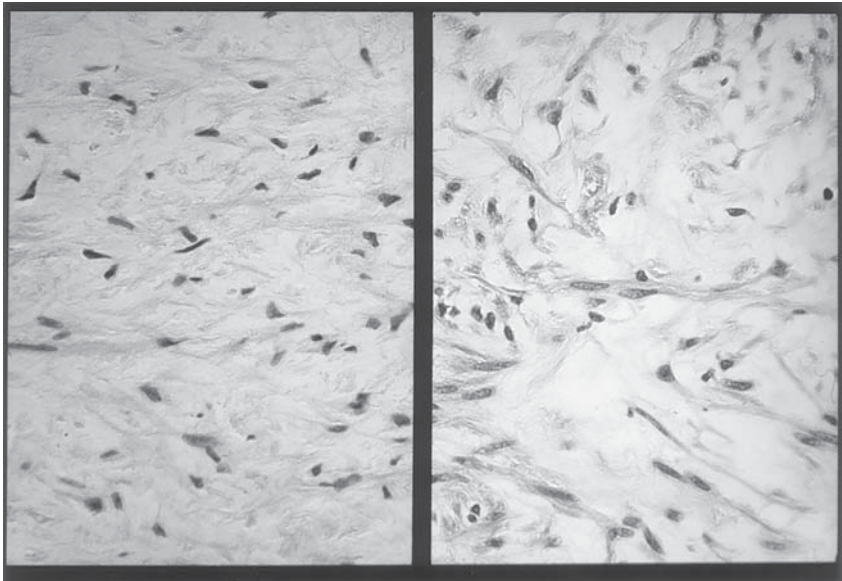


Fig. 4. High-power side-by-side comparison of a representative sample of human restenotic neointima (*left*) and tissue from the porcine restenosis model (*right*). The character of cells and proportion of ground substance is histopathologically identical. Hematoxylin Eosin stain, magnification $\times 300$.

Table 2
Ordinal Arterial Injury Score

<i>Score</i>	<i>Injury</i>
0	Internal elastic lamina intact; endothelium typically denuded; media compressed but not lacerated
1	Internal elastic lamina lacerated; media typically compressed but not lacerated
2	Internal elastic lacerated; media visibly lacerated; external elastic lamina intact but compressed
3	External elastic lamina lacerated; typically large transluminal lacerations of media; coil wires sometimes residing in adventitia

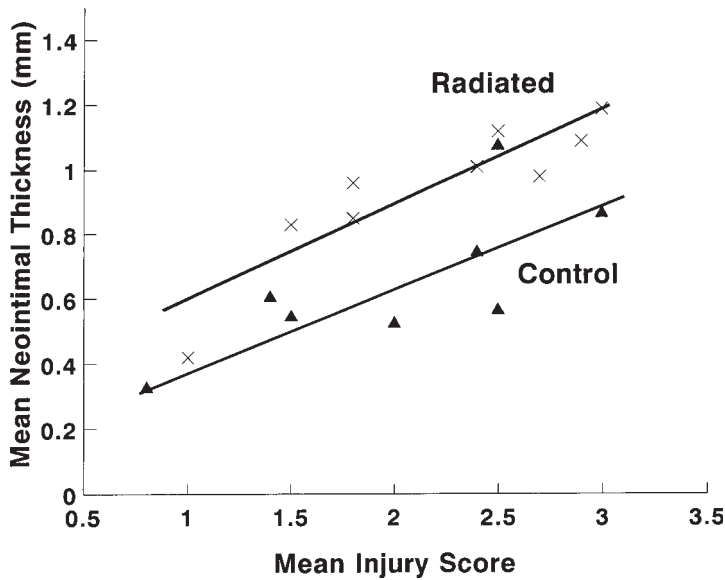


Fig. 5. Regression lines of mean neointimal thickness vs mean injury score for porcine 26 coil-injured coronary-artery segments. The two regression lines are from a study comparing external-beam radiation with control, no radiation. The external radiation exacerbated the injury, and worsened the neointimal thickening. This is shown by a parallel regression line, but with a larger y-intercept.

causes essentially no foreign-body reaction, since many studies have shown little or no chronic inflammatory cellular response at wire sites (i.e., no giant cells). Most importantly, the stent in this model assumes even greater importance when considering that a majority of patients receiving angioplasty also receive stents.

One reason for the greater neointimal thickening with oversized stent placement is that typically, five or more injury sites result in a localized region around the vessel circumference, each generating neointima. This type of injury pattern differs from the inflation-only injuries, where a single large dissection is typical (Fig. 1). This injured location is the site of neointimal development.

In the oversized stent model, quantitation of vessel injury is facilitated by the discrete stent injury points, and the exact size and extent of injury can be measured and compared directly with the neointimal thickening response using regression methods. A similar proportional response between injury and neointimal thickness has been shown by Bonan for the inflation-only injury method (56). This consistency with the injury-neointimal-thickness response found for the oversized stent injury method is reassuring; the neointima of both models is likely formed by similar mechanisms. It is possible that thrombus volume dif-

fers at the injury sites for inflation-only and oversized stent-injury models. This may be caused either by the stent itself, or the increased injury present in the vessel wall that in turn causes increased thrombus deposition. It is likely that increased thrombus is partially responsible for the greater amount of neointima occurring in the stented model. The mechanisms of healing—whether from balloon inflation only or oversized stent—are the same. These photomicrographs, (Fig. 1) from a balloon-only coronary artery injury, show a typical single medial dissection beginning to heal. Thrombus is present early, and is healed from the *luminal* side toward the adventitial surface. A thin cap of SMCs is present on the luminal surface of the thrombus. This finding should not be surprising—it would be unusual to find stented arterial injuries healing through different mechanisms than inflation-only injuries. Recent findings from irradiated arteries in both human patients and pigs suggest that mural thrombus attached to and covering the stent struts and the injury site is the earliest response in the healing process. In cases of irradiated vessels, healing is halted and only such layers of thrombus are present, without cellular organization.

The oversized stent and inflation-only porcine coronary-injury models are thus quite comparable. Reliability of lesion generation depends primarily on the operator's ability to cause enough arterial injury to generate neointima in either model, but not so much that acute vessel thrombosis occurs with resultant animal death. This finite incidence of thrombosis is considered a problem by investigators, but is in fact a representation of stent thrombosis that occurs in human patients.

Quantitation of vessel injury and the neointimal thickening response is facilitated in the oversized stent model, because discrete injury points are observed and quantitated. The differences and similarities of these two models are summarized in Table 3. The importance of proper, blinded quantitation cannot be overemphasized in this context.

ANIMAL RESTENOSIS MODEL TESTING: DIVERGENT RESULTS FROM CLINICAL TRIALS

Many pharmacologic agents have been tested in the animal models described above, and representative results are summarized in Table 4. These data indicate that many agents are effective in animal models, yet these same agents are *ineffective* when tested in human clinical trials. Examples are antiplatelet drugs, (27,57–61) anticoagulants, (62) calcium-channel blockers, (63,64) angiotensin converting enzyme inhibitors, (15,65) and antiproliferatives (13). The disparity of results between animal-model research and clinical trials has led to skepticism about the validity of animal models in restenosis research.

Table 3
Comparison of Oversized Stent and Inflation-Only Porcine Model

	<i>Oversized stent</i>	<i>Balloon injury only</i>
Number of injury sites	Multiple	Single
Size of injury sites	Smaller, constant	Larger, variable
Injury quantitation	Easier (injury score)	More difficult (fracture length)
Response variables	Neointimal thickness	Intimal area (IA)
	Neointimal area	Fracture length (FL)
	Lumen area	Quotient IA/FL
	Injury-NI thickness Regression	
Neointimal response to injury	Proportional	Proportional
Thrombus at injury site	Present	Present

Many therapies effectively limit proliferation and migration in rat carotid arteries. Why do the results of so many animal studies not reflect those seen in clinical trials of the same agents? A number of interpretations explain this observation. One consideration is that the rat carotid model is the oldest. More agents have been tried, and thus more have been found successful in this model. The rabbit iliac model has also been extensively studied and tested. Since the porcine models are newer, fewer agents have been tested and found effective. Are the mechanisms of neointimal formation different among these animal models and in human patients? Are other factors in the models themselves or their analysis methods responsible for the discrepancies? The answers to these questions are unknown, but are essential for developing solutions based on animal-model data.

In the rat carotid model, proliferation of SMCs has been documented in detail (66–68). Yet neointimal volume in these injured arteries is small, and rarely causes arteriographically detectable luminal stenoses. The porcine model also shows cellular proliferation, but hemodynamically significant stenoses regularly occur. Are the pathophysiologic mechanisms different across species? Strong teleologic arguments must be raised against the hypothesis that the arterial response to injury occurs differently across species. The apparent disparity in animal-model results must be examined if they are to be reconciled by a unifying hypothesis of restenosis pathophysiology.

Table 4
Porcine Coronary Model

<i>Agent</i>	<i>Efficacy</i>	<i>References</i>
Angiopeptin	++	95–97
Lovastatin	+/-	98, 99
Hirudin	+	100, 101
Methotrexate	N	102
Probucol	++	103
Trandolapril/Captopril	N	104
Enalapril	N	105
ACE Inhibition	N	106
X-Irradiation	N/++	73, 107–117
Endothelin Inhibition	+/-	118
Antisense: CDC2/PCNA	N	119
Vitamins C/E	N	120

Key: ++ Effective in Neointimal Reduction
N Not Effective

TRANSLATING RESULTS OF ANIMAL MODELS TO CLINICAL TRIALS

The porcine coronary models using either the stent or overstretch injury alone have increasingly become the standard by which potential restenosis therapies are applied. In the past, negative trials in the pig have corresponded to negative clinical trials, suggesting that this model has specificity. Since there were few or no therapies available that showed positive results in human patients, the effective sensitivity of the model was uncertain. Recent clinical trials suggest that ionizing radiation may limit neointimal hyperplasia in human patients (69–72). Interestingly, the pig model showed that external-beam radiation was not only ineffective against neointima—it actually *stimulated* growth (73). More recently, other investigators have examined intravascular radiation and found this modality effective against neointima. Interestingly, subsequent clinical trials suggest the efficacy of intravascular radiation in human patients. This seminal observation—if demonstrated with subsequent larger randomized trials—will add useful data to our understanding of precisely how the porcine model will translate when applied to human patients. Specifically, the multiple methods of assessing efficacy in the pig coronary (percent stenosis and reduction, neointimal thickness, remodeling) (*see* Fig. 6A–C) will be considered, and the best correlate of human data determined. Subsequent new or modified therapeutic modalities may then be tested to rapidly converge on the best treatments for the problem.

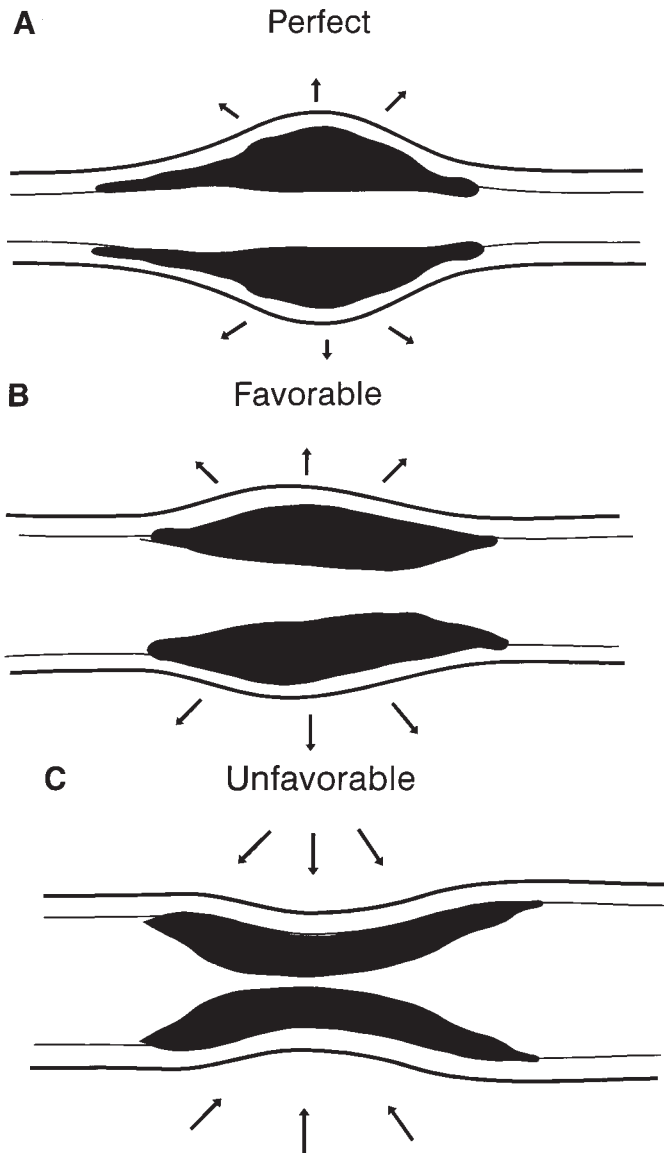


Fig. 6. Schematic representation of three types of remodeling: perfect, favorable, and unfavorable. (A) In perfect remodeling, the artery expands its diameter perfectly to compensate exactly for the vol of neointima that grows. The lumen is not compromised in this situation. (B) This figure shows favorable remodeling. In this case, the artery cannot perfectly remodel, but is able to partially expand in an attempt to accommodate neointimal thickening. The lumen is only partially compromised by the neointimal thickening, while expanding outwardly and incompletely. (C) In unfavorable remodeling, the artery either does not expand at all, or actually contracts. The artery develops a severe stenosis as a result.

The thrombotic response to arterial injury may differ substantially across species. In the rat carotid model, a thin layer of platelets accumulates at the endothelial denudation site. However, significant fibrin-rich thrombus is virtually never found in this model. Conversely, in the rabbit iliac model, macroscopic thrombus does occur, as characterized in a preliminary report (74,75). In the porcine carotid and coronary models, fibrin-rich mural thrombus also plays a significant role in the response to injury. In the coronary arteries, fibrin-rich thrombus provides a framework for colonization by medial SMCs. This foundation eventually forms the organized neointima, a mechanism also suggested in the rabbit. The question of mural thrombus vol and its relation to eventual neointimal vol is critical, and is under investigation. Differences in mural thrombus vol formed in the days and weeks following angioplasty could govern the occurrence of restenosis, as suggested by the rabbit and porcine models. Differences of native thrombolytic potential across species might partially explain differences in mural thrombus. The distinction between “proliferation” and “thrombus” may be blurred, since proliferation may be occurring within thrombus. The rat carotid artery may not generate substantial neointimal vol (and macroscopic stenoses), because it does not form macroscopic thrombus. This suggests an explanation for agents effective in the rat carotid model, yet ineffective in human clinical trials. These agents might be very effective in reducing SMC migration and proliferation, yet exhibit little effect on chronic mural thrombus deposition. Only a part of restenotic neointimal formation may be addressed by these strategies, resulting in clinical failures.

REASONS FOR THE FAILURE OF ANIMAL MODELS TO PREDICT CLINICAL RESULTS

Questions remain about why certain therapeutic strategies which successfully inhibit neointima in some animal models fail to predict clinical trial results. Several potential explanations exist for these discrepancies.

There is still uncertainty regarding how doses of pharmacologic agents given to rodents and other small animals translate to comparable human doses. Two examples from the literature are noteworthy. Studies have shown that Angiotensin Converting Enzyme (ACE) inhibition effectively limits neointimal formation in the rat (76–81). In a key study, (77) the common carotid arteries of rats were denuded of endothelium in the usual fashion, and animals were treated with either captopril 100 mg/kg or cilazapril 10 mg/kg body weight per d beginning 6 d before arterial injury and continuing until the time of euthanasia. An impressive reduction in the percentage of neointimal coverage of the internal elastic lamina was found in both drug treatment groups ($42 \pm 11\%$ captopril treated vs $111 \pm 10\%$ control, and $35 \pm 9\%$ cilazapril treated vs $93 \pm 5\%$ control). This important study provided the stimulus for two large, well-executed

clinical trials of cilazapril in Europe (MERCATOR) and the United States (MARCATOR).

Both clinical trials showed this agent had essentially no impact on restenosis (65,82). The highest cilazapril dose used in MARCATOR was 20 mg/d for 24 wk. In a 70-kg patient, this dose corresponds to 0.29 mg/kg body weight, or 2.5% of the dose reported effective in rats on a body weight basis. In patients, even 20 mg/d was high, because many patients were intolerant as a result of orthostatic hypotension and other side effects. A marked discrepancy thus existed between the effective dose in rats compared to humans. Furthermore, the most effective regimen in rats involved 6 d of drug pretreatment before injury. This pretreatment regimen was not used in either the MERCATOR or MARCATOR trials.

A similar situation is found in a study of colchicine in the rabbit iliac artery model (83,84). Colchicine was administered to rabbits at either 0.02 mg/kg-d or 0.2 mg/kg-d. The endpoints of this study were angiographic luminal diameter. Neointimal thickening in the control group changed from a mean of 1.7 ± 0.3 mm immediately following angioplasty to 0.6 ± 0.4 mm. In the group receiving colchicine (0.2 mg/kg), mean luminal diameter was reduced from a mean of 1.7 ± 0.3 mm following angioplasty to 1.1 ± 0.6 mm. In the 0.02 mg/kg-d colchicine group, mean luminal diameter dropped from 1.7 ± 0.3 mm following angioplasty to 0.9 ± 0.5 mm—a result not statistically different from control. In the high-dose colchicine group, the incidence of restenosis was reduced by 50%. However, studies of colchicine in patients have shown no evidence of clinical benefit when used in doses of 1.2 mg/d or 1 mg/d, with angiography or exercise thallium scintigraphy as endpoints (26,85,86). The equivalent doses in a 70-kg human were 0.01 mg/kg-d, or only 5% of the most effective dose in rabbits. The side-effect profile of colchicine is well-known. Colchicine doses as high as 0.2 mg/kg-d in patients would be impossible to achieve without severe side effects.

In the pharmacology of drug testing across species (including human patients), dosing is generally begun at comparable weight-adjusted (mg/kg) levels. It is possible, but unlikely, that the high doses used in rats and rabbits were comparable in efficacy to the doses used in the clinical human trials.

The normal coronary artery of a young rat, rabbit, or pig differs markedly from the atherosclerotic coronary artery of an older human patient. The arteries of these animal models—even those of the hyperlipidemic rabbit (developing over a period of 4 wk instead of decades as in humans)—do not show densely fibrous and acellular plaques with ulceration, calcification, thrombosis, and hemorrhage into the vessel wall. The impact of this atherosclerotic environment on restenosis is unknown. Whether the use of models that produce atherosclerosis will have advantages over nonatherosclerotic models is unknown. Yet, considering that restenosis is a response to arterial injury, there are only minimal differences in healing time as a function of age.

The positive relationship between arterial injury and neointimal thickness has been documented in the porcine coronary and carotid arteries. Clinical patient studies are emerging that also support a proportionality between increased vessel injury during revascularization and increased neointimal thickness. This proportional response in patients must be inferred only indirectly, since arterial injury cannot be assessed angiographically. Surrogate parameters for vessel injury include balloon:artery ratio, severity of initial stenosis (i.e., more severe stenoses undergo a larger relative dilation), acute complications, and the size of the initial lumen immediately following angioplasty. Most have correlated with increased restenosis risk in clinical studies (87,88). A major advantage of histopathologic assessment in animal models is that vessel injury can be directly and semiquantitatively assessed. If a proportionality exists between depth of injury and neointimal response in animal models other than the porcine coronary model, it might be of substantial benefit in the models. Typically, artifact results when vessel injury is not accounted for as a covariate in animal studies, since conclusions regarding differences in efficacy might result from differences in injury among the treated and control groups.

The methods used to determine biologic response play a pivotal role in the outcome of any study. The most quantifiable and tangible outcome of clinical trials is quantitative coronary angiographic measurement of absolute lumen size, or percent luminal stenosis. The issue of defining restenosis has been fully explored in published studies (89). Restenosis rates using quantitative coronary angiography vary widely even within the same patient data set, depending on the definition used.

In animal-model studies, quantitative histopathologic measurements are generally the endpoints used to determine efficacy. Much quantifiable information is available from microscopic examination of histopathologic specimens. The area of neointima, media, and residual lumen size can be measured precisely and compared across treatment groups using digital microscopic methods.

The study of cilazapril in rats would have reported a negative conclusion if the accepted angiographic criteria of 0.72 mm minimum luminal diameter change had been applied to the histologic lumen diameter data. Data from this study were analyzed using three measurements: neointimal area, the quotient of (neointimal/media area), and percent coverage of the internal elastic lamina by neointima. Since the media is typically 50 μ in the rat, neointimal formation is typically 50–100 μ thick. Although the inhibition of neointimal thickness by cilazapril was 80%, the *absolute* inhibition was only 90 μ (0.09 mm). Inhibition of neointimal thickness must be at least 0.36 mm to be minimally detectable using angiography (90–93).

In another example, lovastatin was studied for its ability to reduce neointimal thickening in the nitrogen-desiccated hypercholesterolemic rabbit iliac artery, using angiographic endpoints (94). The mean angiographic arterial diameter in

the control group immediately following angioplasty was 1.73 mm. At follow-up it was 0.91 mm—a difference of 0.82 mm. In the lovastatin-treated group, the immediate postangioplasty result was 1.44 mm, decreasing at follow-up to 1.16 mm—a change of 0.28 mm. Although statistically significant, these changes (1.82–0.28, or 0.54 mm) would not be discernable within angiographic definitions of clinical trials. While the data from this study clearly demonstrate a modestly beneficial effect from lovastatin, the identical angiographic result in a human trial would be interpreted as having no effect.

The assessment of histopathologic efficacy is important, and should be performed in all animal studies. However, to better predict results in human trials when performing animal studies, microscopically planimetered minimal luminal diameters and percent stenoses should be measured. These measurements more accurately represent surrogate parameters for what would be found in a human angiographic restenosis trial. Variability of efficacy measurement may thus be a major factor in explaining why successful animal-trial results have not translated to clinical efficacy.

CONSISTENCY AMONG ANIMAL RESTENOSIS MODELS: A UNIFIED APPROACH

Many similarities exist among the animal restenosis models. Neointima forms through SMC migration, proliferation, and matrix synthesis in response to injury in all models. How can the apparent differences be reconciled?

The primary differences among animal models lie in the *volume* of neointima from a certain amount of arterial injury. As noted previously, studies of neointimal formation over time in both porcine and rabbit models suggest that mural thrombus at the injury site is a major determinant of neointimal vol. The healing process occurs from the *luminal side outward toward adventitia*. Smooth-muscle-cell migration from nearby medial sites has been documented in the porcine model, both for balloon inflation-only injuries and oversized stent injuries.

CONCLUSION

The importance of using analysis methods comparable to clinical trials (angiography, intravascular ultrasound) should be applied to animal trials. The many response variables to injury for the artery should be studied to determine which can best predict results in human trials. Different data analysis methods may play a major role in the variability of studies. Coronary angiography is the “gold standard” in patients against which all treatments will eventually be tested; thus arterial lumen size (absolute and relative or percent stenosis) must be evaluated when analyzing data from animal-model studies.

The importance of using similar drug doses and timing for animal models and clinical trials cannot be overstated. Effective agents may have already been tested in the wrong doses or timing, with false-negative results. If concentration is a problem because of side effects, local delivery to the angioplasty site may be considered.

The variability of restenotic neointimal formation in different species is substantial. At either end of the spectrum of neointimal vol, species should be carefully analyzed for clues explaining why some species generate very little neointima following coronary-artery injury. The current animal models may be far more alike than at first apparent from the divergent results in published studies.

A stratified approach to testing potentially effective agents in multiple animal models should be implemented *before* clinical trials to minimize the possibility of negative results. Agents may be screened in the rat carotid-artery model before testing in other animal restenosis models and before human trials.

While there may be no perfect animal model for human restenosis, modeling a biologic process should be conducted to first understand the mechanisms of that process, followed by formulating and testing therapeutic strategies based on well-founded hypotheses. Strategies should be designed and tested to verify or refute these individual hypotheses. For restenosis, this process has been reversed: in the rush to solve the problem, understanding the biologic process is far from complete. Numerous pharmacologic agents and new device technologies have been tested in models without firm hypotheses for mechanisms. The limitations of these models are poorly understood, because of the markedly divergent results in human studies.

A solution to restenosis will result from the continued, meticulous study of neointimal formation in many models, leading to a full understanding of the limitations of the models and preventing erroneous conclusions from those models when applied to clinical trials.

REFERENCES

1. Holmes D, Fitzgerald P, Goldberg S, LaBlanche J, Lincoff AM, Savage M, et al. The PRESTO (Prevention of restenosis with tranilast and its outcomes) protocol: a double-blind, placebo-controlled trial. *Am Heart J* 2000; 139:23–31.
2. Ruygrok PN, Melkert R, Morel MA, Ormiston JA, Bar FW, Fernandez-Aviles F, et al. Does angiography six months after coronary intervention influence management and outcome? Benestent II Investigators. *J Am Coll Cardiol* 1999; 34:1507–1511.
3. de Feyter PJ, Kay P, Disco C, Serruys P. Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative coronary angiography. *Circulation* 1999; 100:1777–1783.
4. van Domburg RT, Foley DP, de Jaegere PP, de Feyter P, van den Brand M, van der Giessen W, et al. Long term outcome after coronary stent implantation: a 10 year single centre experience of 1000 patients. *Heart* 1999; (Suppl 2)II82:27–34.

5. Di Luzio V, De Remigis F, De Curtis G, Paparoni S, Pecce P, Di Emidio L, et al. Coronary restenosis after optimal (stent-like) initial angiographic results obtained by traditional balloon angioplasty. (Review). *Giornale Ital Cardiol* 1997; 27:645–653.
6. Kastrati A, Schuhlen H, Hausleiter J, Walter H, Zitzmann-Roth E, Hadamitzky M, et al. Restenosis after coronary stent placement and randomization to a 4-week combined antiplatelet or anticoagulant therapy: six-month angiographic follow-up of the Intracoronary Stenting and Antithrombotic Regimen (ISAR) Trial (see comments). *Circulation* 1997; 96:462–467.
7. Kastrati A, Schomig A, Elezi S, Schuhlen H, et al. —Predictive factors of restenosis after coronary stent placement *J Am Coll Cardiol* 1997; 30:1428–1436.
8. Hoffmann R, Mintz G, Dussaillant G, Popma J, Pichard A, Satler L, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation* 1996; 94:1247–1254.
9. Shiran A, Mintz GS, Waksman R, Mehran R, Abizaid A, Kent KM, et al. Early lumen loss after treatment of in-stent restenosis: an intravascular ultrasound study. *Circulation* 1998; 98:200–203.
10. BARI, CABRI, EAST, GABI, and RITA: coronary angioplasty on trial. *Lancet* 1990; 335:1315–1316 (editorial).
11. Alazraki NP, Krawczynska EG, Kosinski AS, DePuey EG, 3rd, Ziffer JA, Taylor AT, Jr., et al. Prognostic value of thallium-201 single-photon emission computed tomography for patients with multivessel coronary artery disease after revascularization (the Emory Angioplasty versus Surgery Trial [EAST]). *Am J Cardiol* 1999; 84:1369–1374.
12. Dages N, Erbel R. Comparison between PTCA and bypass operation. Results of large randomized studies. *Med Klin* 1998; 93:22–26, 58.
13. Freed M, Safian RD, O'Neill WW, Safian M, Jones D, Grines CL. Combination of lovastatin, enalapril, and colchicine does not prevent restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1995; 76:1185–1188.
14. Schulman SP, Goldschmidt-Clermont PJ, Topol EJ, Califf RM, Navetta FI, Willerson JT, et al. Effects of integrelin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina. A randomized multicenter trial. *Circulation* 1996; 94:2083–2089.
15. Faxon DP. Effect of high dose angiotensin-converting enzyme inhibition on restenosis: final results of the MARCATOR Study, a multicenter, double-blind, placebo-controlled trial of cilazapril. The Multicenter American Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MARCATOR) Study Group. *J Am Coll Cardiol* 1995; 25:362–369.
16. Califf RM, Lincoff AM, Tchong JE, Topol EJ. An overview of the results of the EPIC trial. *Eur Heart J* 1995; 16:43–49.
17. Ohman EM, Harrington RA, Lincoff AM, Kitt MM, Kleiman NS, Tchong JE. Early clinical experience with integrelin, an inhibitor of the platelet glycoprotein IIb/IIIa integrin receptor. *Eur Heart J* 1995; 16:50–55.
18. Schafer AI. Antiplatelet therapy with glycoprotein IIb/IIIa receptor inhibitors and other novel agents. *Tex Heart Inst J* 1997; 24:90–96.
19. Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS. Preventing restenosis with fish oils following coronary angioplasty. A meta-analysis. *Arch Intern Med* 1993; 153:1595–1601.
20. Austin GE. Lipids and vascular restenosis. *Circulation* 1992; 85:1613–1615.
21. Bell L, Madri JA. Original Contributions: effect of Platelet Factors on Migration of Cultured Bovine Aortic Endothelial and Smooth Muscle Cells. *Circ Res* 1989; 65:1057–1065.

22. Bowles MH, Klonis D, Plavac TG, Gonzales B, Francisco DA, Roberts RW, et al. EPA in the prevention of restenosis post PTCA. *Angiology* 1991; 42:187–194.
23. Califf R, Ohmann E, Frid D, Fortin D, Mark D, Hlatky M, et al. Restenosis: the clinical issues. In: Topol E., ed. *Textbook of Interventional Cardiology*. W.B. Saunders, Philadelphia, 1990, pp. 363–394.
24. Finci L, Hofling B, Ludwig B, Bulitta M, Steffenino G, Etti H, et al. Sulotroban during and after coronary angioplasty. A double-blind, placebo controlled study. *Z Kardiol* 1989; 3: 50–54.
25. Israel DH, Gorlin R. Fish oils in the prevention of atherosclerosis. *J Am Coll Cardiol* 1992; 19:174–185.
26. OKeefe JHJ, McCallister BD, Bateman TM, Kuhnlein DL, Ligon RW, Hartzler GO. Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty. *J Am Coll Cardiol* 1992; 19:1597–1600.
27. Taylor R, Gibbons F, Cope G, Cumpston G, Mews G, Luke P. Effects of low dose aspirin on restenosis after coronary angioplasty. *Am J Cardiol* 1991; 68:874–878.
28. Kimura T, Kaburagi S, Tamura T, Yokoi H, Nakagawa Y, Hamasaki N, et al. Remodeling of human coronary arteries undergoing coronary angioplasty or atherectomy. *Circulation* 1997; 96:475–483.
29. Schwartz RS, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE. Restenosis occurs with internal elastic lamina laceration and is proportional to severity of vessel injury in a porcine coronary artery model. [abstract]. *Circulation* 1990; 82:III-656.
30. Schwartz RS, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR. Restenosis after balloon angioplasty: a practical proliferative model in porcine coronary arteries. *Circulation* 1990; 82:2190–2200.
31. Schwartz RS, Murphy JG, Edwards WD, Camrud AR, Garratt KN, Vlietstra RE, et al. Coronary artery restenosis and the “virginal membrane”: smooth muscle cell proliferation and the intact internal elastic lamina. *J Inv Card* 1991; 3:3–8.
32. Bonan R, Paiement P, Scortichini D, Cloutier MJ, Leung TK. Objective Evaluation of a restenosis-injury index in porcine arteries. *Proceedings of the Restenosis Summit IV*, Cleveland, OH, 1992.
33. Bonan R, Paiement P, Scortichini D, Cloutier MJ, Leung TK. Coronary restenosis: evaluation of a restenosis injury index in a swine model. *Am Heart J* 1993; 126:1334–1340.
34. Bonan R, Paiement P, Leung TK. Swine model of coronary restenosis: effect of a second injury. *Catheterization Cardiovasc Diagn* 1996; 38:44–49.
35. Ellis SG, Muller DW. Arterial injury and the enigma of coronary restenosis. *J Am Coll Cardiol* 1992; 19:275–277.
36. Ferns GA, Stewart LAL, Anggard EE. Arterial response to mechanical injury: balloon catheter de-endothelialization. *Atherosclerosis* 1992; 92:89–104.
37. Indolfi C, Esposito G, Di Lorenzo E, Rapacciuolo A, Feliciello A, Porcellini A, et al. Smooth muscle cell proliferation is proportional to the degree of balloon injury in a rat model of angioplasty. *Circulation* 1995; 92:1230–1235.
38. Karas SP, Gravanis MB, Santoian EC, Robinson KA, Anderberg KA, King SB, 3d. Coronary intimal proliferation after balloon injury and stenting in swine: an animal model of restenosis. *J Am Coll Cardiol* 1992; 20:467–474.
39. Back MR, White RA, Kwack EY, Back LH. Hemodynamic consequences of stenosis remodeling during coronary angioplasty. *Angiology* 1997; 48:99–109.
40. Mintz GS, Kent KM, Pichard AD, Satler LF, Popma JJ, Leon MB. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses. An intravascular ultrasound study. *Circulation* 1997; 95:1791–1798.

41. Schwartz RS, Topol EJ, Serruys PW, Sangiorgi G, Holmes DR, Jr. Artery size, neointima, and remodeling: time for some standards. *J Am Coll Cardiol* 1998; 32:2087–2094.
42. Sabate M, Serruys PW, van der Giessen WJ, Ligthart JM, Coen VL, Kay IP, et al. Geometric vascular remodeling after balloon angioplasty and beta-radiation therapy: a three-dimensional intravascular ultrasound study. *Circulation* 1999; 100:1182–1188.
43. Strauss BH, Chisholm RJ, Keeley FW, Gotlieb AI, Logan RA, Armstrong PW. Extracellular matrix remodeling after balloon angioplasty injury in a rabbit model of restenosis. *Circ Res* 1994; 75:650–658.
44. Chesebro JH, Badimon L, Fuster V. Importance of antithrombin therapy during coronary angioplasty. *J Am Coll Cardiol* 1991; (suppl B): 96B–100B.
45. Clowes A, Reidy M, Clowes M. Kinetics of cellular proliferation after arterial injury: I. Smooth muscle growth in absence of endothelium. *Lab Invest* 1983; 49:327–332.
46. Foley DP, Hermans WM, Rensing BJ, de Feyter PJ, Serruys PW. Restenosis after percutaneous transluminal coronary angioplasty. *Herz* 1992; 17:1–17.
47. Lam JYT, Chesebro JH, Steele PM, Dewanjee MK, Badimon L, Fuster V. Deep arterial injury during experimental angioplasty: relationship to a positive Indium-111 labeled platelet scintigram, quantitative platelet deposition and mural thrombus. *J Am Coll Cardiol* 1986; 8:1380–1386.
48. Liu MW, Roubin GS, King SB, 3rd. Restenosis after coronary angioplasty. Potential biologic determinants and the role of intimal hyperplasia. *Circulation* 1989; 79:1374–1387.
49. Zijlstra F, den Boer A, Reiber JH, van Es GA, Lubsen J, Serruys PW. Assessment of immediate and long-term functional results of percutaneous transluminal coronary angioplasty. *Circulation* 1988; 78:15–24.
50. Mintz G, Kent K, Pichard A, Popma J, Satler L, Leon M. Intravascular ultrasound insights into mechanisms of stenosis formation. *Cardiol Clin* 1997; 15:17–29.
51. Schwartz R, Holmes DJ. Pigs, Dogs, Baboons, and Man: lessons for Stenting from Animal Studies. *J Interv Cardiol* 1994; 7:355–368.
52. Carter AJ, Laird JR, Farb A, Kufs W, Wortham DC, Virmani R. Morphologic characteristics of lesion formation and time course of smooth muscle cell proliferation in a porcine proliferative restenosis model. *J Am Coll Cardiol* 1994; 24:1398–1405.
53. Schwartz R, Huber K, Murphy J, Edwards W, Camrud A, Vlietstra R, et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. *J Am Coll Cardiol* 1992; 19:267–274.
54. Schwartz RS, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR, Jr. Restenosis and the Proportional Neointimal Response to Coronary Artery Injury: results in a Porcine Model. *J Am Coll Cardiol* 1991.
55. Huber KC, Schwartz RS, Edwards WD, Camrud AR, Murphy JG, Jorgenson MA, et al. Restenosis and angiotensin converting enzyme inhibition: effects on neointimal proliferation in a porcine coronary injury model. *Circulation* 1991; 84:II–298.
56. Bonan R, Paiement P, Leung TK. Swine model of coronary restenosis: effect of a second injury. *Catheterization Cardiovasc Diagn* 1996; 38:44–49.
57. Barnathan E, Schwartz J, Taylor L, Laskey W, Kleavland J, Kusssmaul W, et al. Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. *Circulation* 1987; 76:125–134.
58. Grigg LE, Kay TW, Valentine PA, Larkins R, Flower DJ, Manolas EG, et al. Determinants of restenosis and lack of effect of dietary supplementation with eicosapentaenoic acid on the incidence of coronary artery restenosis after angioplasty. *J Am Coll Cardiol* 1989; 13:665–672.

59. Koster JK Jr., Tryka AF, H'Doubler P, Collins JJJ. The effect of low-dose aspirin and dipyridamole upon atherosclerosis in the rabbit. *Artery* 1981; 9:405–413.
60. Riess H, Hofling B, von Arnim T, Hiller E. Thromboxane receptor blockade versus cyclooxygenase inhibition: antiplatelet effects in patients. *Thromb Res* 1986; 42:235–245.
61. Schwartz L, Bourassa MG, Lesperance J, Aldridge HE, Kazim F, Salvatori VA, et al. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med* 1988; 318:1714–1719.
62. Thornton MA, Gruentzig AR, Hollman J, King SB, 3rd, Douglas JS, Jr. Coumadin and aspirin in prevention of recurrence after transluminal coronary angioplasty: a randomized study. *Circulation* 1984; 69:721–727.
63. Corcos T, David PR, Bal PG, Renkin J, Dangoisse V, Rapold HG, et al. Failure of diltiazem to prevent restenosis after percutaneous transluminal coronary angioplasty. *Am Heart J* 1985; 109:926–931.
64. O'Keefe JHJ, Giorgi LV, Hartzler GO, Good TH, Ligon RW, Webb DL, et al. Effects of diltiazem on complications and restenosis after coronary angioplasty. *Am J Cardiol* 1991; 67:373–6.
65. Anonymous. Does the new angiotensin converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal coronary angioplasty? Results of the MER-CATOR study: a multicenter, randomized, double-blind placebo-controlled trial. *Circulation* 1992; 86:100–110.
66. Fingerle J, Johnson R, Clowes AW, Majesky MW, Reidy MA. Role of platelets in smooth muscle cell proliferation and migration after vascular injury in rat carotid artery. *Proc Natl Acad Sci USA* 1989; 86:8412–8416.
67. Hanke H, Strohschneider T, Oberhoff M, Betz E, Karsch K. Time course of smooth muscle cell proliferation in the intima and media of arteries following experimental angioplasty. *Circ Res* 1990; 67:651–659.
68. Hanke H, Haase KK, Hanke S, Oberhoff M, Hassenstein S, Betz E, et al. Morphological changes and smooth muscle cell proliferation after experimental excimer laser treatment. *Circulation* 1991; 83:1380–9.
69. Williams DO. Radiation vascular therapy: a novel approach to preventing restenosis. *Am J Cardiol* 1998; 81:18E–20E.
70. Kay IP, Sabate M, Van Langenhove G, Costa MA, Wardeh AJ, Gijzel AL, et al. Outcome from balloon induced coronary artery dissection after intracoronary beta radiation. *Heart* 2000; 83:332–337.
71. Meerkink D, Tardif JC, Crocker IR, Arsenault A, Joyal M, Lucier G, et al. Effects of intracoronary beta-radiation therapy after coronary angioplasty: an intravascular ultrasound study. *Circulation* 1999; 99:1660–1665.
72. Teirstein PS. Prevention of vascular restenosis with radiation. *Tex Heart Inst J* 1998; 25: 30–33.
73. Schwartz R, Koval T, Edwards W, Camrud A, Bailey K, Browne K, et al. Effect of external beam irradiation on neointimal hyperplasia after experimental coronary artery injury. *J Am Coll Card* 1992; 19:1106–1113.
74. Preisack MB, Karsch KR. The paradigm of restenosis following percutaneous transluminal coronary angioplasty. *Eur Heart J* 1993; 14(1):187–192.
75. Bauters C, Labalanche J, McFadden E, Hamon M, Bertrand M. Angioscopic thrombus is associated with a high risk of restenosis. *Circulation* 1995; 92:1912.
76. Powell J, Muller R, Baumgartner H. Suppression of the vascular response to injury: the role of angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 1991; 17:137B–142B.

77. Powell J, Clozel J, Muller R, Kuhn H, Hefti F, Hosang M, et al. Inhibitors of angiotensin-converting enzyme prevent myointimal proliferation after vascular injury. *Science* 1989; 245:186–188.
78. Bilazarian S, Currier J, Haudenschild C, Heyman D, Powell J, Ryan T, et al. Angiotensin converting enzyme inhibition reduces restenosis in experimental angioplasty. *J Am Coll Cardiol* 1991; 17:268A.
79. Berk B, Vekshtein V, Gordon H. Angiotensin II-stimulated protein synthesis in cultured vascular smooth muscle cells. *Hypertension* 1989; 13:305–314.
80. Brozovich FV, Morganroth J, Gottlieb NB, Gottlieb RS. Effect of angiotensin converting enzyme inhibition on the incidence of restenosis after percutaneous transluminal coronary angioplasty. *Catheterization Cardiovasc Diagn* 1991; 23:263–267.
81. Daemen MJ, Lombardi DM, Bosman FT, Schwartz SM. Angiotensin II induces smooth muscle cell proliferation in the normal and injured rat arterial wall. *Circ Res* 1991; 68: 450–456.
82. Faxon DP. Angiotensin converting Enzyme Inhibition and restenosis: the final results of the MARCATOR Trial [abstract]. *Circulation* 1992; 86:I–53.
83. Bauriedel G, Heimerl J, Beinert T, Welsch U, Hofling B. Colchicine antagonizes the activity of human smooth muscle cells cultivated from arteriosclerotic lesions after atherectomy. *Coron Artery Dis* 1994; 5:531–539.
84. Gradus-Pizlo I, Wilensky RL, March KL, Fineberg N, Michaels M, Sandusky GE, et al. Local delivery of biodegradable microparticles containing colchicine or a colchicine analogue: effects on restenosis and implications for catheter-based drug delivery. *J Am Coll Cardiol* 1995; 26:1549–1557.
85. O'Keefe J, McCallister B, Bateman T, Kuhnlein D, Ligon R, Hartzler G. Colchicine for the prevention of restenosis after coronary angioplasty. *J Am Coll Cardiol* 1991; 17:181A.
86. Grines C, Rizik D, Levine A, Schreiber T, Gangadharan V, Ramos R, et al. Colchicine angioplasty restenosis trial (CART) [abstract]. *Circulation* 1991; 84:II–365.
87. Roubin GS, Douglas JS, Jr, King SB, 3rd, Lin SF, Hutchison N, Thomas RG, et al. Influence of balloon size on initial success, acute complications, and restenosis after percutaneous transluminal coronary angioplasty. A prospective randomized study. *Circulation* 1988; 78:557–565.
88. Nichols A, Smith R, Berke A, Shlofmitz R, Powers E. Importance of balloon size on initial success, acute complications, and restenosis after percutaneous transluminal coronary angioplasty. A prospective randomized study. *J Am Coll Cardiol* 1989; 13:1094–2000.
89. van der Giessen WJ, Hermans WRM, Rensing BJ, Foley DP, Serruys PW. Clinical and angiographic definitions of restenosis: recommendations for clinical trials. In Schwartz RS, ed. *Coronary Restenosis*. Blackwell Scientific, Boston, 1992, pp 169–191.
90. Serruys PW, Luijten HE, Beatt KJ, Geuskens R, de Feyter PJ, van den Brand M, et al. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. *Circulation* 1988; 77:361–371.
91. Serruys PW, Juilliere Y, Bertrand ME, Puel J, Rickards AF, Sigwart U. Additional improvement of stenosis geometry in human coronary arteries by stenting after balloon dilatation. *Am J Cardiol* 1988; 61:71G–76G.
92. Serruys P, Hermans R. The new angiotensin converting enzyme inhibitor cilazapril does not prevent restenosis after coronary angioplasty: the results of the MERCATOR trial [abstract]. *J Am Coll Cardiol* 1992; 19:258A.
93. Strauss BH, Juilliere Y, Rensing BJ, Reiber JH, Serruys PW. Edge detection versus densitometry for assessing coronary stenting quantitatively. *Am J Cardiol* 1991; 67:484–490.

94. Gellman J, Ezekowitz MD, Sarembock IJ, Azrin MA, Nochomowitz LE, Lerner E, et al. Effect of lovastatin on intimal hyperplasia after balloon angioplasty: a study in an atherosclerotic hypercholesterolemic rabbit. *J Am Coll Cardiol* 1991; 17:251–259.

Additional Reading and Background

95. Hong MK, Kent KM, Tio FO, Foegh M, Kornowski R, Bramwell O, et al. Single-dose intramuscular administration of sustained-release Angiopeptin reduces neointimal hyperplasia in a porcine coronary in-stent restenosis model. *Coron Artery Dis* 1997; 8:101–104.
96. Howell MH, Adams MM, Wolfe MS, Foegh ML, Ramwell PW. Angiopeptin inhibition of myointimal hyperplasia after balloon angioplasty of large arteries in hypercholesterolaemic rabbits. *Clin Sci* 1993; 85:183–188.
97. Santoian ED, Schneider JE, Gravanis MB, Foegh M, Tarazona N, Cipolla GD, et al. Angiopeptin inhibits intimal hyperplasia after angioplasty in porcine coronary arteries. *Circulation* 1993; 88:11–14.
98. Veinot JP, Edwards WD, Camrud AR, Jorgenson MA, Holmes DR, Jr., Schwartz RS. The effects of lovastatin on neointimal hyperplasia following injury in a porcine coronary artery model. *Can J Cardiol* 1996; 12:65–70.
99. Ragosta M, Barry WL, Gimple LW, Gertz SD, McCoy KW, Stouffer GA, et al. Effect of thrombin inhibition with desulfatohirudin on early kinetics of cellular proliferation after balloon angioplasty in atherosclerotic rabbits. *Circulation* 1996; 93:1194–2000.
100. Meyer BJ, Fernandez-Ortiz A, Mailhac A, Falk E, Badimon L, Michael AD, et al. Local delivery of r-hirudin by a double-balloon perfusion catheter prevents mural thrombosis and minimizes platelet deposition after angioplasty. *Circulation* 1994; 90:2474–2480.
101. Schwartz R, Holder D, Holmes DJ, Veinot J, Camrud A, Jorgenson M, et al. Neointimal thickening after severe coronary artery injury is limited by short term administration of a factor Xa inhibitor: results in a porcine model. *Circulation* 1996; 83:1542–1548.
102. Muller DWM, Topol EJ, Abrams GD, Gallagher KP, Ellis SG. Intramural methotrexate therapy for the prevention of neointimal thickening after balloon angioplasty. *J Am Coll Cardiol* 1992; 20:460–462.
103. Schneider J, Berk B, Santoian E, Gravanis M, Cipolla G, Tarazona N, et al. Oxidative stress is important in restenosis: reduction of neointimal formation by the antioxidant probucol in a swine model of restenosis. *Circulation* 1992; 86:I–186.
104. Huber KC, Schwartz RS, Edwards WD, Camrud AR, Bailey KR. Effects of angiotensin converting enzyme inhibition on neointimal hyperplasia in a porcine coronary injury model. *Am Heart J* 1993; 125:695–701.
105. Churchill DA, Siegel CO, Dougherty KG, Raizner AE, Minor ST. Failure of enalapril to reduce coronary restenosis in a swine model [abstract]. *Circulation* 1991; 84:II–297.
106. Huckle WR, Drag MD, Acker WR, Powers M, McFall RC, Holder DJ, et al. Effects of subtype-selective and balanced angiotensin II receptor antagonists in a porcine coronary artery model of vascular restenosis. *Circulation* 1996; 93:1009–1119.
107. Waksman R, Robinson KA, Crocker IR, Wang C, Gravanis MB, Cipolla GD, et al. Intracoronary low-dose beta-irradiation inhibits neointima formation after coronary artery balloon injury in the swine restenosis model. *Circulation* 1995; 92:3025–3031.
108. Waksman R, Robinson KA, Crocker IR, Gravanis MB, Palmer SJ, Wang C, et al. Intracoronary radiation before stent implantation inhibits neointima formation in stented porcine coronary arteries. *Circulation* 1995; 92:1383–1386.
109. Waksman R, Robinson KA, Crocker IR, Gravanis MB, Cipolla GD, King SB, 3rd. Endovascular low-dose irradiation inhibits neointima formation after coronary artery balloon injury in swine. A possible role for radiation therapy in restenosis prevention. *Circulation* 1995; 91:1533–1539.

110. Waksman R, Robinson KA, Crocker IR, Wang C, Gravanis MB, Cipolla GD, et al. Intracoronary low-dose beta-irradiation inhibits neointima formation after coronary artery balloon injury in the swine restenosis model. *Circulation* 1995; 92:3025–3031.
111. Waksman R, Robinson KA, Crocker IR, Gravanis MB, Palmer SJ, Wang C, et al. Intracoronary radiation before stent implantation inhibits neointima formation in stented porcine coronary arteries. *Circulation* 1995; 92:1383–1386.
112. Waksman R, Robinson KA, Crocker IR, Gravanis MB, Cipolla GD, King SB, 3rd. Endovascular low-dose irradiation inhibits neointima formation after coronary artery balloon injury in swine. A possible role for radiation therapy in restenosis prevention. *Circulation* 1995; 91:1533–9.
113. Waksman R, Robinson KA, Crocker IR, Wang C, Gravanis MB, Cipolla GD, et al. Intracoronary low-dose beta-irradiation inhibits neointima formation after coronary artery balloon injury in the swine restenosis model. *Circulation* 1995; 92:3025–3031.
114. Waksman R, Kosinski AS, Klein L, Boccuzzi SJ, King SB, 3rd, Ghazzal ZM, et al. Relation of lumen size to restenosis after percutaneous transluminal coronary balloon angioplasty. Lovastatin Restenosis Trial Group. *Am J Cardiol* 1996; 78:221–224.
115. Wilcox JN, Waksman R, King SB, 3rd, Scott NA. The role of the adventitia in the arterial response to angioplasty: the effect of intravascular radiation. *Int J Radiat Oncol Biol Phys* 1996; 36:789–796.
116. Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J. Intracoronary irradiation markedly reduces restenosis after balloon angioplasty in a porcine model. *J Am Coll Cardiol* 1994; 23:1491–1498.
117. Weinberger J, Amols H, Ennis RD, Schwartz A, Wiedermann JG, Marboe C. Intracoronary irradiation: dose response for the prevention of restenosis in swine. *Int J Radiat Oncol Biol Phys* 1996; 36:767–775.
118. Burke SE, Lubbers NL, Gagne GD, Wessale JL, Dayton BD, Wegner CD, et al. Selective antagonism of the ET(A) receptor reduces neointimal hyperplasia after balloon-induced vascular injury in pigs. *J Cardiovasc Pharmacol* 1997; 30:33–41.
119. Robinson KA, Chronos NA, Schieffer E, Palmer SJ, Cipolla GD, Milner PG, et al. Endoluminal local delivery of PCNA/cdc2 antisense oligonucleotides by porous balloon catheter does not affect neointima formation or vessel size in the pig coronary artery model of postangioplasty restenosis. *Catheterization Cardiovasc Diagn* 1997; 41:348–353.
120. Nunes GL, Sgoutas DS, Redden RA, Sigman SR, Gravanis MB, King SB 3rd, et al. Combination of vitamins C and E alters the response to coronary balloon injury in the pig. *Arterioscler Thromb Vasc Biol* 1995; 15:156–165.



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Vascular Disease and Injury

Preclinical Research

Simon, D.I.; Rogers, C. (Eds.)

2001, XVIII, 348 p., Hardcover

ISBN: 978-0-89603-753-3

A product of Humana Press