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Articles

Marked Inflammatory Sequelae to Implantation of Biodegradable and Nonbiodegradable Polymers in Porcine Coronary Arteries

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Abstract

Background With the thrombogenic tendency and permanent implant nature of metallic stents, synthetic polymers have been proposed as candidate materials for stents and local drug delivery designs. We investigated the biocompatibility of several synthetic polymers after experimental placement in the coronary artery.

Methods and Results Five different biodegradable polymers (polyglycolic acid/polylactic acid [PGLA], polycaprolactone [PCL], polyhydroxybutyrate valerate [PHBV], polyorthoester [POE], and polyethyleneoxide/polybutylene terephthalate [PEO/PBTP]) and three nonbiodegradable polymers (polyurethane [PUR], silicone [SIL], and polyethylene terephthalate [PETP]) were tested as strips deployed longitudinally across 90° of the circumferential surface of coil wire stents. Appropriately sized polymer-loaded stents were implanted in porcine coronary arteries of 2.5- to 3.0-mm diameter. Four weeks after implantation, stent patency was assessed by angiography followed by microscopic examination of the coronary arteries. The biodegradable PCL, PHBV, and POE and the nonbiodegradable PUR and SIL evoked extensive inflammatory responses and fibrocellular proliferation (thickness of tissue response: 0.79±0.22, 1.12±0.01, 2.36±0.60, 1.24±0.36, and 1.43±0.15 mm, respectively). Less but still severe responses were observed for the

biodegradable PGLA and PEO/PBTP (0.46±0.18 and 0.61±0.23 mm, respectively) and for the nonbiodegradable PETP (0.46±0.11 mm).

Conclusions An array of both biodegradable and nonbiodegradable polymers has been demonstrated to induce a marked inflammatory reaction within the coronary artery with subsequent neointimal thickening, which was not expected on the basis of in vitro tests. The observed tissue response may be attributable to a combination of parent polymer compound, biodegradation products, and possibly implant geometry.

Key Words: stents • arteries • angioplasty • coronary disease

Introduction

Percutaneous transluminal coronary angioplasty to deform or ablate obstructive coronary atherosclerotic narrowing is performed increasingly with inflatable balloons, excisional and rotational atherectomy devices, stents, and lasers. Progress has been made since the introduction of this technology with respect to procedural success as well as the increasing complexity of coronary lesions treated. Early coronary reocclusion as well as late restenosis, however, remain limitations of PTCA. Recently, high-dose systemic antiplatelet drug therapy has been shown to limit early complications after PTCA by ≈35%; however, bleeding complications have ensued.[1] The beneficial effect was shown to be sustained, as a trend toward a reduction in the need for later revascularization was also observed.[2] The only approach proven to reduce the incidence of late restenosis (by 30%) is the use of coronary stents.[3] [4] However, despite recently promoted high-pressure deployment and antiplatelet therapy with aspirin and ticlopidine, the use of stents is not free from complications, with an incidence rate of ≤20% at 6 months.[5] [6] [7] Therefore, a combination of drugs and stents has been touted as a possibility to overcome both early and late complications of PTCA.[8] [9]

Synthetic polymers have been proposed as a solution to improve the quality of stents, to serve as a vehicle for local (high-dose and site-specific) drug delivery, or both.[10] [11] Therefore, efforts are under way to develop polymer compounds that can be implanted within the coronary artery.[12] [13] [14] [15] [16] [17] In addition, biodegradable polymers may be formulated with dispersion of drug within the polymeric preparation. Drug release would then occur by diffusion through and/or breakdown of the base polymer. Several biodegradable polymers have been screened for medical-device applications, and a few have been used for local (subcutaneous) drug delivery systems or wound healing. It is unknown, however, whether tissue compatibility data generated from in vitro systems, animal subdermal implant models, or nonvascular human application adequately reflect blood compatibility.[18] [19] Therefore, we studied the biocompatibility of five biodegradable polymers and three nonbiodegradable polymers after implantation within porcine coronary arteries.

Methods

Polymer Test Samples

Five different biodegradable polymers were studied (Table 1✦). They were selected by known medical application and favorable screening results in vitro and in vivo.[20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] To control for the effects of the biodegradation process, three different non biodegradable polymers were also tested in the same experimental protocol.[33] [34] [35]

Chemical Name	Abbreviation	Structure	MW, kD	Degradation Rate	Medical Application	Reference
Biodegradable polymers						
Polyglycolic acid/polylactic acid copolymer (85193/	PGLA	Amorphous	40-100	100% in 60-90 days (rat SC)	Sutures; fracture fixation; oral implants; drug delivery microspheres	20-24
Polycaprolactone	PCL	Semicrystalline	40-72	50% in 4 years (rat SC)	Contraceptive delivery implant; prosthetics; sutures	25,26
Polyhydroxy-butyrate/-valerate copolymer (78/22)	PHBV	Semicrystalline	100-750	0-20% in 26 weeks (rat SC)	Sutures; drug delivery microspheres	27,28
Polyorthoester	POE	Amorphous	100-130	60% in 46 weeks (saline bath 37°C)	Prosthetic nerve grafts; contraceptive delivery implant	29,30
Polyethyleneoxide/polybutylene terephthalate copolymer (30/70)	PEO/PBTP	Semicrystalline	Not available	50% in 52 weeks (rat middle ear)	Tympanic membrane	31,32
Nonbiodegradable polymers						
Polyurethane	PUR	Semicrystalline	48	NA	Artificial heart; vascular prostheses; pacemaker lead insulation	33
Poly(dimethyl)-siloxane	SIL	Amorphous	Not available	NA	Drug-eluting pacing lead; electrostimulation device	34
Polyethene terephthalate	PETP	Semicrystalline	26	NA	Vascular prostheses; heart valve sewing ring; annuloplasty ring	35

MW indicates molecular weight; NA, not applicable; and SC, subcutaneous.

Table 1. Biodegradable and Nonbiodegradable Polymer Test Samples

The polymer specimens were processed to obtain strips 75 to 125 µm in thickness. The strips were cast longitudinally onto a balloon-expandable stent (Wiktor, Medtronic Inc) that served as the vehicle for polymer deployment. The polymer covered ≈90° of the stent circumference (Fig 1). Polymer-loaded stents were mounted on standard angioplasty balloon catheters (manufacturer-specified balloon diameter, 3.0 to 3.5 mm). The implant systems were produced in a clean laboratory environment but not sterilized because of concern about changing the physicochemical properties of the polymers.

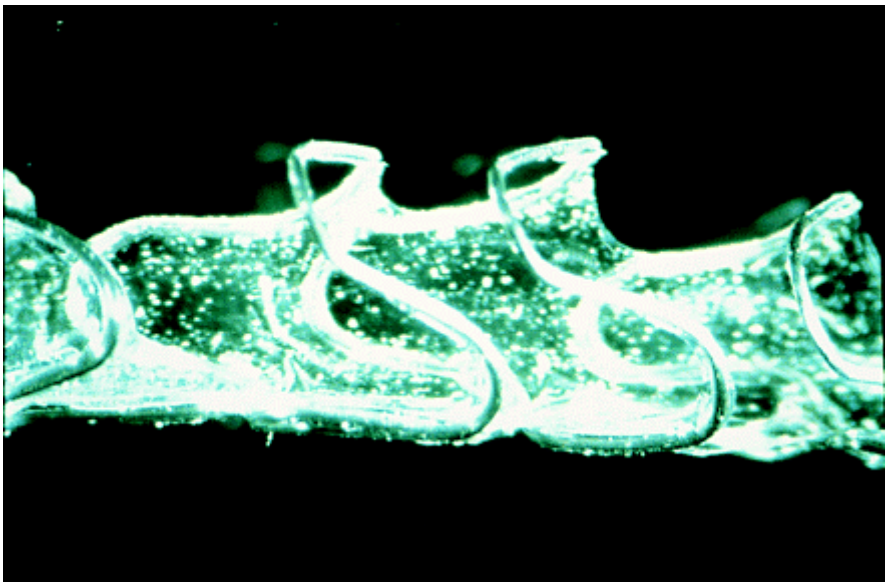

Figure 1. Polymer test strip cast asymmetrically on the coil stent vehicle. Magnification x20.

Animal Preparation

Experiments were performed in farm-bred pigs (weight, 20 to 30 kg) fed a normal, nonatherogenic chow. The investigations were performed according to the *Guide for the Care and Use of Laboratory Animals* (NIH publication 85-23, 1985), and the protocol was approved by the Experimental Animals Ethics Committee of the three participating centers. The experimental protocol of this first multicenter animal trial of restenosis was uniform for the three study sites, and each site strictly adhered to this protocol. The polymers studied at each center were as follows: polyglycolic acid/polylactic acid (PGLA), polyorthoester (POE), and polyurethane (PUR) (Cleveland Clinic); polyhydroxybutyrate valerate (PHBV) and silicone (SIL) (Mayo Clinic); and polycaprolactone (PCL), polyethyleneoxide/polybutylene terephthalate (PEO/PBTP), and polyethylene terephthalate (PETP) (Thoraxcenter).

After an overnight fast, the animals were sedated. After endotracheal intubation, the pigs were connected to a ventilator, and anesthesia was maintained with gas anesthetics. After administration of antibiotic prophylaxis, arterial access was obtained under sterile conditions by femoral or carotid artery cutdown. Thereafter, angiography was performed to select the part of the coronary tree in which to leave the implant. Heparin (5000 IU) was administered during the procedure only. Aspirin (325 mg) was given before the procedure and continued daily during the 4-week follow-up period.

Polymer-Loaded Stent Implantation

The method of implantation of the polymer-loaded stent in porcine coronary arteries was similar to that described for the conventional stent.[36] Briefly, on the basis of the angiograms, at least one segment in one of the three epicardial coronary arteries (LAD, LCx, and RCA) was selected with a diameter of ≈2.5 to 3.0 mm. Thereafter, an angioplasty catheter with the polymer-loaded stent crimped on its deflated balloon was advanced to that site for implantation over a standard PTCA guidewire. The balloon was inflated to a maximal pressure of 8 atm for 30 seconds, deflated, and slowly withdrawn, leaving the stent in place. This procedure was eventually repeated in a second coronary artery. After repeat angiography of the stented coronary arteries to confirm patency, the arteriotomy was repaired, the skin was closed, and the animals were allowed to recover from anesthesia.

Follow-up Examination

The catheterization procedure for follow-up angiography at 4 weeks was identical to that described above. Coronary angiography was performed in the same projection as used during implantation. Thereafter, the thorax was opened by a midsternal split and a lethal dose of sodium pentobarbital was injected intravenously, immediately followed by in situ fixation of the coronary arteries according to routine procedures in the three study centers, with use of a pressure of ≈120 mm Hg. Subsequently, the stented vessels were dissected free and placed in 4% formaldehyde in phosphate buffer (pH 7.3) for ≥48 hours in preparation for microscopy.

Microscopic Examination

Serial sections over the entire length of the polymer-containing coronary segment were embedded in methacrylate or, after removal of the metal stent wires, paraffin. After routine staining (hematoxylin-azaphloxin or hematoxylin-eosin) and application of an elastin stain (resorcin-fuchsin or elastica–van Gieson), at least three representative sections of each artery were examined at each center for fibrocellular tissue response and inflammatory changes on the polymer side, after which the slides were sent to one institute (Erasmus University Rotterdam) for central review.

Morphometry

For the measurement of the constituent layers of the arterial wall, at least three elastin-stained sections from the proximal, central, and distal parts of each stented coronary segment were examined. The extent of the tissue response at the side of the polymer test sample was assessed as shown in Fig 2. In each section, only the middle area at the polymer side was analyzed so that the potential damaging effect of the polymer edges could be excluded.

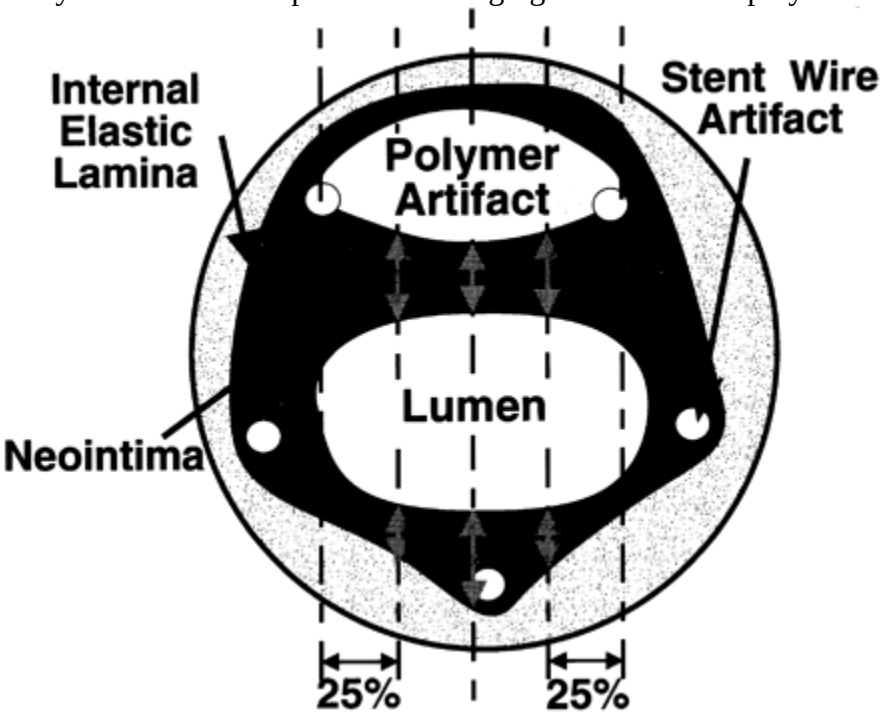

Figure 2. Diagrammatic representation of a coronary artery cross section with the polymer test sample removed. The arrows at both the polymer and opposite sides indicate the central 50% of the tissue reaction that was used for the assessment of neointimal area and thickness.

Gram Staining

To check for bacterial contamination of the implants, alternate histological sections of the stent-containing segments with the polymers PGLA, POE, and PUR were also stained with Gram's stain.

Statistical Analysis

All data are expressed as mean±SEM. Histological measurements were analyzed by unpaired Student's *t* test. Because of repeated testing, only values of $P<.01$ were considered statistically significant (Bonferroni correction).

Results

Polymer Test Sample Implantation

For each polymer, 5 to 10 test samples were placed in four to six animals (Table 2). In all but five cases, the polymer test sample could be placed in the predetermined coronary segment. Damage to the metal stent or premature detachment of the polymer strip was the cause of failure in three cases. In two cases, air embolism during angiography caused the implantation procedure to be aborted. Angiography after successful implantation showed that all coronary arteries were patent, with no signs of intraluminal defects.

Polymer	Animals, n	LAD Stents	LCx Stents	RCA Stents	Failures to Implant
PGLA	4	4	0	4	None
PCL	6	2	4	2	One stent damaged
PHBV	4	3	0	2	None
POE	4	4	0	4	One air embolism; one polymer strip detachment
PEO/PBTP	5	5	2	3	None
PUR	4	4	1	3	One air embolism; one polymer strip detachment
SIL	4	1	2	2	None
PETP	6	3	1	3	None

Table 2. Implantation Data of Polymer-Loaded Stents

Follow-up and Restudy at 4 Weeks

Stent occlusion resulting in premature death of the animal occurred in three groups (PHBV, PEO/PBTP, and SIL) in the first 48 hours after implantation (Table 3). In the groups receiving PGLA, PCL, POE, PUR, and PEO/PBTP, silent occlusion of one of the stents was angiographically demonstrated at 4 weeks. When both early and late stent occlusion were considered together, the arterial patency rate at 4 weeks varied between 70% (PEO/PBTP) and 100% (PGLA, POE, PUR, and PETP), with other groups having one or two arteries occluded (Table 3). In most other cases, repeat angiography showed an eccentric lumen reduction at the site of the test sample implant at 4 weeks.

Polymer	Angiographic Patency at 4 Weeks	Complications	Time to Occlusion (Cause of Occlusion)
PGLA	8/8	None	Not applicable
PCL	8/8	One stent, angiographic severe narrowing at 4 weeks	(Proliferative response)
PHBV	5/7	One animal died of acute occlusion of two stents	<24 hours (platelet thrombus)
POE	8/8	One stent subtotally narrowed at 4 weeks	(Proliferative response)
PEO/PBTP	7/10	One animal (two stents) died of thrombosis of both implants	<8 hours
		One animal (two stents) died at 3 weeks (only one stent occluded)	(Severe inflammatory response)
PUR	8/8	None	Not applicable
SIL	4/5	One animal died with acute occlusion (one of two stents)	<24 hours (platelet thrombus)
PETP	7/7	None	Not applicable

Table 3. Angiographic Patency and Complications During Follow-up

Histology

Macroscopic examination demonstrated that the eccentric lumen reduction apparent on angiography was due to a localized tissue reaction on the polymer side of the implants (Fig 3). Light microscopy confirmed that the eccentric tissue response was located mainly on the polymer side. All polymers seemed to evoke a similar reaction; only the extent of the reaction differed (Fig 4), ranging from a relatively benign response (Fig 4A) to a malignant or severe inflammatory response (Fig 4D). Thrombus remnants containing mainly fibrin but also platelet and erythrocyte remnants and hemosiderin deposits were present near the polymer strips. At the interface between polymer and tissue, multinucleated giant cells and macrophages surrounded this proteinaceous debris (Fig 5). However, signs of acute

inflammation were also observed frequently, evidenced by granulocytes (predominantly eosinophils), lymphocytes, and occasional plasma cells. This thrombotic and inflammatory reaction was seen on all sides of the polymer strips, ie, also toward the adventitial side.

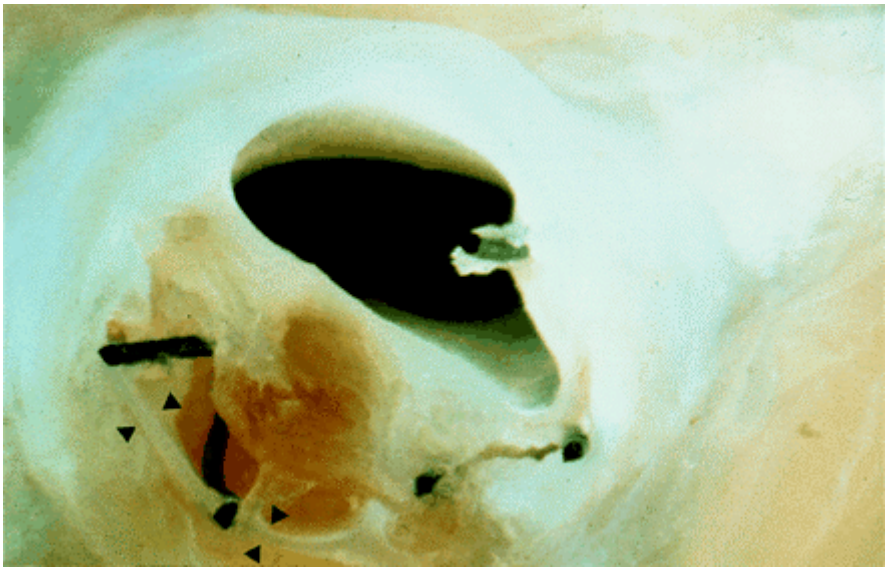

Figure 3. Macroscopy of transverse section through a PHBV test sample–containing coronary artery 4 weeks after implantation. The asymmetric luminal narrowing is consistently associated with the polymer strip (between arrowheads). Magnification x40.

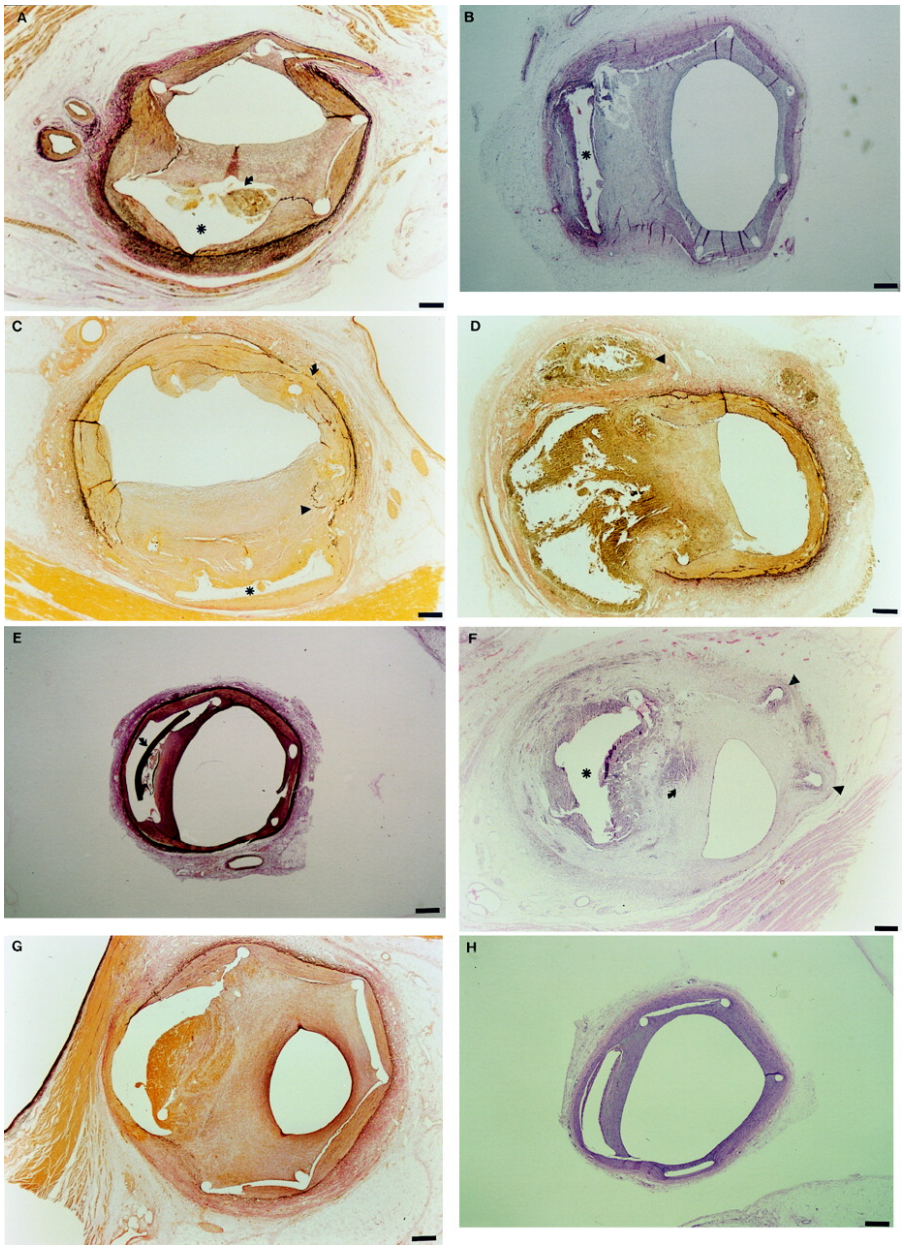

Figure 4. (Facing page.) Various tissue responses to the individual biodegradable (A through E) and nonbiodegradable (F through H) polymer test samples. In each panel, the bar indicates 375 µm. A, PGLA. The large open area was occupied by the polymer (✱) and proteinaceous debris (arrow) and covered by a distinct fibrocellular layer. (Elastic stain.) B, PCL showed a smaller polymer artifact (✱) but a more pronounced eccentric fibrocellular response. (Hematoxylin-eosin-stain.) C, PHBV. At the site of the polymer implant (✱), the media ruptured (arrowhead), but at the opposite side, lysis of the elastic membranes had occurred (arrow) as a phenomenon secondary to the inflammatory response. (Elastic stain.) D, POE induced an immense inflammatory response with a granulomatous appearance (arrowhead) that extended into the adventitia and resulted in destruction of the architecture of the vessel. (Elastic stain.) E, PEO/PBTP. The vascular response to this polymer (arrow) was limited in nature and had a more benign character. (Elastic stain.) F, PUR demonstrated a circumferential inflammatory reaction to both the polymer (✱) and damaging bare wire (arrowheads) that extended into the neointima (arrow). (Hematoxylin-eosin-stain.) G, SIL. In contrast to the reaction to PUR, the intense inflammatory response was restricted to the polymer but with a circumferential fibrocellular response. (Elastic stain.) H, PETP showed a benign tissue response and a limited neointimal growth. (Hematoxylin-eosin stain.)

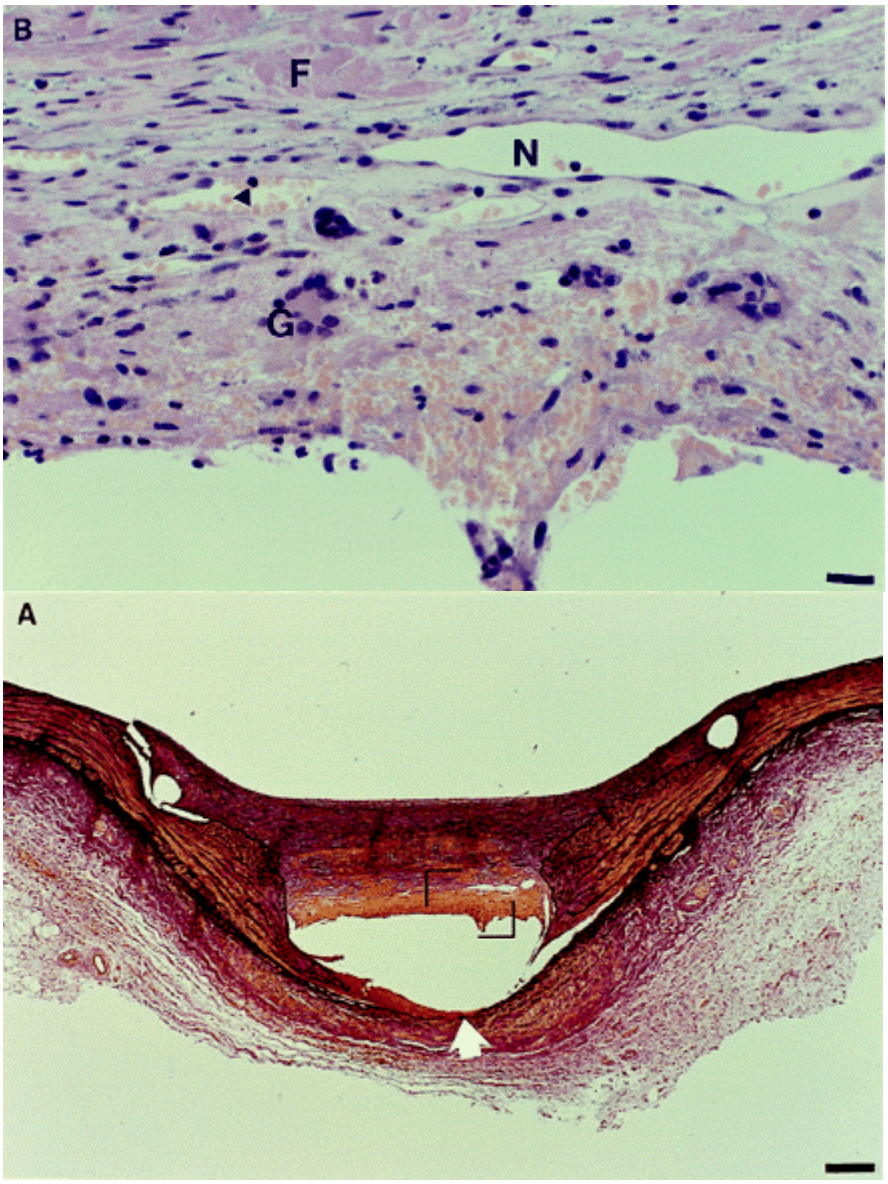

Figure 5. A, A segment of the PETP test sample shows laceration of the internal elastic membrane and media and obliteration of the external elastic membrane (arrow). (Elastic stain; bar=200 µm.) B, Detail of the cadre indicated in Fig 5A showing fibrin thrombus remnants (F), neovascularization (N) with ongoing leukocyte infiltration (arrowhead), and abundant multinucleated macrophage giant cells (G). (Hematoxylin-eosin stain; bar=20 µm.)

A thick layer with a predominantly fibrocellular component was seen around this layer but was most pronounced between the polymer and the lumen. This layer contained smooth muscle cells (confirmed by immunostaining with smooth muscle cell–specific α-actin antibody) in a matrix of collagen and proteoglycans with many neocapillaries and spilled over to the bare wire sites of the specimen. Moderate to severe disruption of the architecture of the arterial wall was present in most specimens. This consisted of rupture or lysis of the elastic membranes and in some cases also of the media and was always accompanied by adventitial inflammatory infiltrates (Fig 5✦). This pattern of thrombus remnants, acute and chronic inflammation, and fibrocellular hyperplasia was observed with both biodegradable and nonbiodegradable polymers.

Morphometry

Thickness and area of the tissue response per polymer test sample are summarized in Table 4. Regardless of the type of polymer, the vessel wall reaction was more pronounced on the polymer than on the metal wire alone. The thickness or area of the tissue reaction to PHBV, POE, PUR, and SIL was significantly larger than the reaction to all other polymers. No significant differences between the other polymer groups were observed.

Polymer	Neointimal Thickness: Polymer, mm	Neointimal Area: Polymer, mm^2	Neointimal Thickness: Bare Wire, mm	Neointimal Area: Bare Wire, mm^2
PGLA	0.46±0.18	0.34±0.15	0.08±0.03	0.09±0.05
PCL	0.79±0.22	0.70±0.23	0.11±0.06	0.04±0.03
PHBV	1.12±0.01	3.32±0.71*	0.21±0.14	0.38±0.02*
POE	2.36±0.60*	1.56±0.55*	0.38±0.17*	0.23±0.11
PEO/PBTP	0.61±0.23	0.52±0.29	0.14±0.09	0.09±0.05
PUR	1.24±0.36*	0.89±0.36	0.34±0.26	0.22±0.17
SIL	1.43±0.15*	3.13±1.1*	0.41±0.17*	0.66±0.19*
PETP	0.46±0.11	0.35±0.11	0.11±0.06	0.06±0.04

*P<.01 vs PGLA, PCL, PEO/PBTP, and PETP.

Table 4. Thickness and Area of Neointima Covering Polymer Sample and Bare Wire

Gram Staining

Signs of bacterial contamination were not observed in any of the samples that underwent Gram staining.

Discussion

Study Objective and Design

The purpose of this study was to screen which polymers may be candidate materials for construction of new stents or local drug delivery modalities. Therefore, polymers were screened for their biocompatibility in the coronary circulation in a format that bypassed the need to construct new stents. In addition, because a metal stent was used as the carrier, the reactions to polymer and metal could be compared. The polymers were selected because of favorable results of in vitro test systems or (preliminary) medical applications.[20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] This choice was also based on the premise that the biodegradation rate of the polymers should be in the range of months, to allow early disappearance of the implant or a rapid rate of drug diffusion from the polymeric matrix. The reasoning was that the mechanical scaffolding function of stents would only be needed in the first few weeks after angioplasty, and the local tissue response to an implant or after arterial injury (PTCA) could be influenced by drugs in the early phase.[37]

A unique feature of the present approach is that we chose to perform this study using identical experimental protocols at three centers experienced in the evaluation of new vascular techniques. Therefore, we were able to screen a variety of polymers within a limited period of time while at the same time allowing comparison of results between the polymers and the centers involved.

Main Findings

The main study results of this multilaboratory approach are summarized as follows: (1) after a follow-up period of only 4 weeks, all polymer implants were associated with a significant inflammatory and proliferative response; (2) this response was observed with both biodegradable and nonbiodegradable polymer implants; (3) in some groups, implants were complicated by acute thrombotic vessel occlusion, although with no more frequency than that experienced with stainless steel coronary stents.[17] [38] Occlusion occurred more frequently, however, than with the tantalum carrier stent alone.[36]

Polymer Implants in the Coronary Circulation

Implants in the cardiovascular system are more demanding than those in other parts of the human body. The requirement for blood compatibility is added to the requirements for biological performance, absence of toxic reactions (toxic, immunologic, carcinogenic), and long-term mechanical properties (fatigue life, wear resistance, kink resistance) in this dynamic environment.[39] This means favorable behavior is required in an environment in which complex and integrated cellular and humoral systems (coagulation, complement, and immune systems) unite to isolate and exclude the foreign body from incorporation into the vascular wall.[35] Therefore, in retrospect, it is not surprising that polymer implants in the coronary circulation elicit a more severe reaction than that predicted from subcutaneous implants. In three groups (PHBV, PEO/PBTP, and SIL), early thrombotic occlusion was observed (5 [23%] of 22 stents). This is not an exceptionally high number, because earlier studies in the same model reported even higher rates of thrombosis with stainless steel stents.[17] [38] Moreover, during the initial clinical experience with the Palmaz-Schatz stent, an 18% incidence of subacute closure was observed when anticoagulation treatment was withheld.[40] Furthermore, it has been reported recently[41] that noncoated, slotted-tube stents show a 42% thrombotic occlusion rate in the rabbit iliac model.

However, local mechanical and hemodynamic factors may influence the success or failure of a specific material.[42] [43] For instance, vascular grafts of PETP (Dacron) seem to perform best in larger vessels, whereas in smaller vessels, expanded polytetrafluoroethylene (Gore-Tex) yields good results. However, in vessels <4 mm in diameter, all synthetic materials fail, and the use of vein grafts offers the best solution. Our results in the coronary circulation extend this effect of recipient vessel diameter to the coronary circulation.

The results of the present study may only be applicable to the specific polymers investigated. Differences in molecular weight, polymerization catalysts, plasticizers, and fillers may all change the physicochemical behavior of the implants. Studies by others who used a PGLA stent yielded superior results,[12] but the toxicity of PGLA microspheres in smooth muscle cell culture has also been reported recently.[44] Furthermore, the use of PETP stents of different sources resulted in equivocal vascular responses.[15] [16]

In the present study, a significant inflammatory response was observed with all implanted polymers. In all cases, this consisted of a chronic inflammatory reaction with an acute component and a persistent foreign-body response. In most cases, a substantial part of the overall inflammatory and proliferative response may have been aggravated by damage due to the asymmetric geometry of the implant. It is very likely that the aggressive inflammatory response may have increased the injury to the arterial architecture by the action of released proteases and elastases. This may have been influenced by by-products of the polymer. A role for greater stretch injury of the polymer side of the stent cannot be excluded, but it seems more likely that the presence of the hard polymer structure merely prevented overstretch on that side. Indeed, after in vitro expansion of some stent specimens by inflation, followed by removal of the balloon, it was evident by subsequent high-power microscopy that the polymer strip covered a smaller part of the circumference than in the unexpanded condition. In addition, the uncovered part expanded more than the part covered by the polymer. The possibility that this acute damage adds to the final outcome should be substantiated by acute experiments in future studies testing the intracoronary biocompatibility of other synthetic polymers.

In addition to the general reaction to the bulk material and the physicochemical properties of the implant surface, the surface texture could be an important determinant of the early reaction.[37] A limitation of the present study is that we cannot retrospectively correlate the overall response with its several components.

It should also be emphasized that the implants in the present study were not sterilized but were manufactured in a clean laboratory environment. This may have influenced the response. Gram staining in those polymer samples that demonstrated the most vigorous responses, however, did not show bacterial contamination. Furthermore, it has been shown that the addition of steroids to one of the polymers ameliorated the inflammatory response.[45] However, this does not exclude completely the possibility of bacterial or nonbacterial contamination.

Conclusions

The present study demonstrates the marked inflammatory and neointimal response to an array of biodegradable as well as nonbiodegradable polymers after implantation in the porcine coronary artery. This reaction must be fully understood biologically before we can make use of these or other polymers as implant materials in stents or drug delivery devices.

Selected Abbreviations and Acronyms

LAD	=	left anterior descending coronary artery
LCx	=	left circumflex coronary artery
PCL	=	polycaprolactone
PEO/PBTP	=	polyethyleneoxide/polybutylene terephthalate
PETP	=	polyethylene terephthalate
PGLA	=	polyglycolic acid/polylactic acid
PHBV	=	polyhydroxybutyrate valerate
POE	=	polyorthoester
PTCA	=	percutaneous transluminal coronary angioplasty
PUR	=	polyurethane
RCA	=	right coronary artery
SIL	=	Silicone

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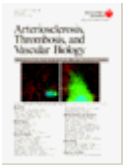

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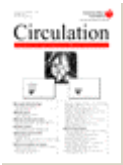

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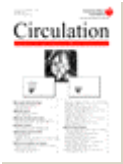

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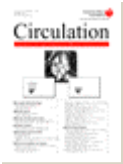

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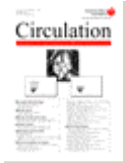

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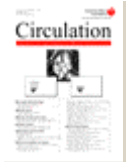

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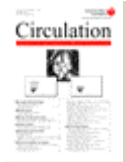

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