Evaluation of fluorinated polymers as coronary stent coating

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In this report, some fluorinated polyphosphazenes and polymethacrylates were selected for evaluation as coronary stent coating. After applying the polymer film by dipcoating, the stents were implanted in porcine coronary arteries. No acute thrombotic occlusions were observed. The neointimal proliferation was studied by a 6 week follow-up of the minimal lumen stented diameter, using quantitative coronary analysis. All polymers demonstrated a slight hyperplasia, resulting in a 10–20% lumen narrowing at follow-up. Only for one fluorinated polymethacrylate, PFM-P75, a minimal neointimal response (3% lumen narrowing) was found.

Nomenclature

PFP poly(fluoroalkoxy)phosphazene
PFP-E95P5 Poly(fluoroalkoxy)phosphazene, containing 95 mol % trifluoroethyl- and 5 mol % octafluoropentyl-side chain
PFP E90P10 Poly(fluoroalkoxy)phosphazene, containing 90 mol % trifluoroethyl- and 10 mol % octafluoropentyl-side chain
PFP-E95O5 Poly(fluoroalkoxy)phosphazene, containing 95 mol % trifluoroethyl- and 5 mol % pentadecafluor-ooctyl-side chain
FM (fluoroalkyl)methacrylate
PFM poly(fluoroalkyl)methacrylate
PFM-E50 Poly(fluoroalkyl)methacrylate, containing 50 mol % trifluoroethyl- and 50 mol % 2-ethylhexylacry-late-side chain
PFM-P75 Poly(fluoroalkyl)methacrylate, containing 75 mol % octafluoropentyl- and 25 mol % 2-ethylhexyla-crylate-side chain
PFM-O65 Poly(fluoroalkyl)methacrylate, containing 65 mol % pentadecafluoro-octyl- and 35 mol % 2-ethyl-hexylacrylate-side chain
PFM-ESA-O Poly(fluoroalkyl)methacrylate with an ethylsulphonamido-pentadecafluorooctyl side chain
PFM-BSA-O Poly(fluoroalkyl)-methacrylate with a butysulfonamidopentadecafluorooctyl side chain.

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1. Introduction

Percutaneous transluminal coronary angioplasty (PTCA) has become of major importance in angioplasty. In the last 15 years, PTCA has expanded rapidly as a modality for coronary revascularization in Western countries. In 1990 more than 300 000 procedures were performed worldwide, progressively increasing to 500 000 in 1994 [1]. However, PTCA remains limited by the problems of acute occlusion and restenosis [2–5]. Because of the cracking and breaking of the atherosclerotic plaques, intimal dissections, occlusive flaps and thrombus formation occur and can cause acute reclosure of the treated artery. Furthermore, balloon dilatation causes injury to the intima and media of the arterial wall, inducing a myofibroblastic hyperplasia resulting in restenosis. Restenosis is a biological complex process and has not yet been fully understood. The basic mechanism is the infiltration of actively proliferating myocytes from the media into the intima, accompanied by the production of abundant extracellular matrix components (collagen, proteo-aminoglycans). The immediate platelet deposition at the site of vessel angioplasty injury and the subsequent production of myoproliferative substances (growth factors such as platelet-derived growth factor (PDGF), β-transforming growth factor (β-TGF), endothelium-derived growth factor (EDGF), etc.) are probably initiating factors [6–8].

The use of intravascular stents addresses the acute closure by prolapsing flaps and elastic recoil of the vessel

wall. Reduction of restenosis is obtained by maximizing initial luminal enlargement to compensate for the late luminal loss induced by the neointimal hyperplasia [9–10]. Notwithstanding the success of metallic stent implantation, acute thrombotic occlusion and late restenosis are still observed [11–14], though to a lesser extent. Thrombogenicity of the stent material and intimal hyperplasia, induced by vessel injury and a foreign body response against the implant, are the responsible factors.

The ideal intracoronary stent has been defined by Schwartz *et al*. [15] as a device that is easy to deploy, with good fluoroscopic visibility. It should be non-thrombogenic and temporary, i.e. remaining in place as long as needed to permit adequate arterial healing. It should abolish restenosis, creating a thin, smooth, re-endothelialized fibrocellular conduit of sufficient diameter to permit unimpeded blood flow. Though the ideal stent may not be realizable in practice, some synthetic polymers may be good alternative materials, either as a cover of metallic stents or as a non-metallic, biodegradable endovascular prothesis.

Synthetic polymers are good alternatives because their physico-mechanical properties can be adapted easily by the choice of suitable monomers and polymerization conditions and because of their capacity to be used for drug delivery systems. Antithrombotic, anti-inflammatory and antiproliferative agents can be dispersed in the polymer and released locally over long time periods. Higher dosages at the site of injury are reached and systemic side effects are avoided. Tanguay *et al*. [16] described in their review different stent designs using inert and bioabsorbable polymers. Kruft *et al*. [17] recently prepared a polymethacrylate terpolymer for stent coating with unique radio-opacity and good haemocompatibility. Slepian and Hubbell [18] reviewed the possibility of polymer human endoluminal gel paving. A variety of stent designs have been patented [19]. However, there still remain difficulties in preparing polymer stents with a good blood biocompatibility and the right physico-mechanical properties to ensure mechanical support to the vessel wall and a sufficient opened lumen. Strength and inertness, as well as polymer stent flexibility, are needed.

Polymer coating of metallic stents has been applied by different groups [20–26]. Palmaz stainless steel stents were modified by gamma graft polymerization of *N*-vinylpyrrolidone and potassium sulfopropyl acrylate monomers [20]. Lincoff *et al*. [21] and Van Der Giessen *et al*. [22] have coated stents with a variety of polymers (polyethyleneterephthalate, polyurethane, silicone, polyglycolic acid/polylactic acid, polycaprolactone, polyhydroxybutyrate valerate, polyorthoester and polyethyleneoxide/polybutylene terephthalate). They were deployed in porcine coronary arteries for 4 weeks of angiographical evaluation and histological assessment. De Scheerder *et al*. [23] evaluated the biocompatibility of poly(organo)phospazenes and amphiphilic polyurethanes coated stainless steel stents. A few studies with polymer coated stents, loaded with drug, were performed. One polylactic acid coated stent, loaded with dexamethasone, was described to release drug for up to 28 days [24] and intramural forskolin bioactivity was demonstrated for 48 h after local delivery from polymer-coated stent [25, 31]. In the patent literature [26] the preparation of an intravascular stent, coated with different classes of polymer and loaded with antiplatelet, anticoagulant, antimitotic, antimetabolite or/and anti-inflammatory agents are described.

For the present study some tailor made fluorinated polyphosphazenes and polymethacrylates were selected for evaluation as coronary stent coating. The polymer-coated stents were implanted in porcine coronary arteries for the study of subacute thrombotic occlusion and neointimal response. The *in vivo* biocompatibility was analyzed by follow-up of the minimal stented lumen diameter (MSLD).

2. Materials and methods

2.1. Products

The poly(fluoroalkoxy)phosphazenes were prepared [27] by reaction of polydichlorophosphazene with the alkoxides of trifluoroethanol, octafluoropentanol or pentadecafluorooctanol.

The fluorinated polymethacrylates were prepared by radical copolymerization of the selected monomer, using 2,2′-azobis-(2-methylpropionitrile) (AIBN) as initiator.

The polymer structures are given in Fig. 1. The synthesis, characterization and surface analysis has been reported in more detail elsewhere [27].

2.2. Stents and stent coating

Self-designed balloon-expandable stainless steel stents (manufactured in the Department of Cardiology, University Hospital Gasthuisberg, KUL) were made of 0.18 mm 316L stainless steel wire, folded in a zig-zag shape over a 6F tubular device. These stents can easily be mounted onto any conventional angioplasty balloon and deployed with a minimal pressure of 6×10^5 Pa [28, 29]. The stents were coated with the polymers by dipping them in a 0.75 g/v% polymer solution. The solvent was selected according to the type of polymer: tetrahydrofuran for the polyphosphazenes; chloroform/acetone:95/5 for PFM-E50 and PFM-P75; 1,1,2-trichlorotrifluoroethane for PFM-O65 and PFM-BSA-O. Subsequently they were allowed to dry in a clean air chamber at room temperature. The stent surface, before and after expansion, was investigated by scanning electron microscopy (SEM: Philips 505, 30 kV).

2.3. Stent implantation

Stent implantation in the right coronary artery of domestic cross-bred pigs was performed according to the method described by De Scheerder *et al*. [30, 31]. Either a coated or a bare stent was randomly deployed in the right coronary artery of pigs (one stent/pig). At 6 weeks follow-up, final angiograms were obtained. The pigs were sacrificed and the right coronary artery was harvested for histopathology and morphometry.

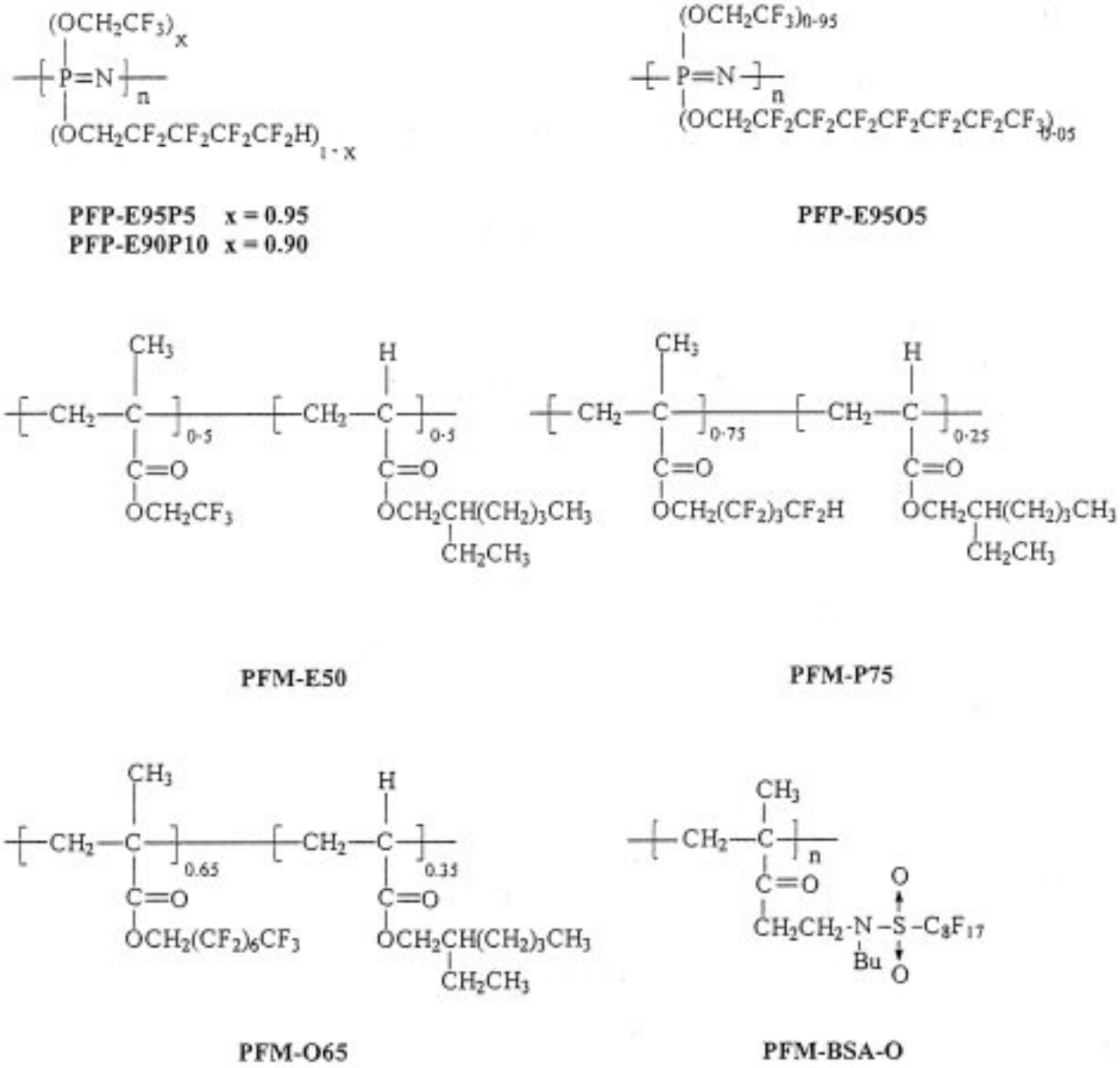

Figure 1 Chemical composition of the flourinated ploymers.

2.4. Quantitative coronary angiography

Angiographic analysis of stented vessel segments was performed before, immediately after stenting, and at follow-up using the Polytron 1000®-system as described previously by De Scheerder *et al*. [30, 31]. The Polytron 1000®-system was previously validated *in vitro* and *in vivo* [32–34] with a metal bar as a calibration device [35]. The diameters of the vessel segments were measured before, immediately after stent implantation and at follow-up. The degree of oversizing was expressed as measured maximum balloon size – selected artery diameter divided by selected artery diameter. Recoil was expressed as measured maximum balloon size – minimal stent lumen diameter measured 15 min after stent implantation divided by measured maximum balloon size. The late loss represents the loss in stented lumen diameter and the % narrowing is calculated by reference – measured diameter divided by reference diameter.

2.5. Statistics

Arteriographic measurements before, immediately after and 6 weeks after stent deployment were compared using paired *t*-tests. For comparison among different groups non-paired *t*-tests were used. Data are presented as mean value $\pm$ SD. A P-value < 0.05 was considered statistically significant.

3. Results

Since the surface smoothness can influence thrombus formation and neointimal hyperplasia, an SEM study of non-coated and coated stents was carried out. Clearly it could be demonstrated that the stent surface is more smooth after polymer coating (SEM Figs 2 and 3). Repeated expansion of the coated stent, up to 6×10^5 Pa, did not affect the polymer coating. No cracking or peeling of the polymer film was observed.

Arteriographic measurements of the MLSD before,

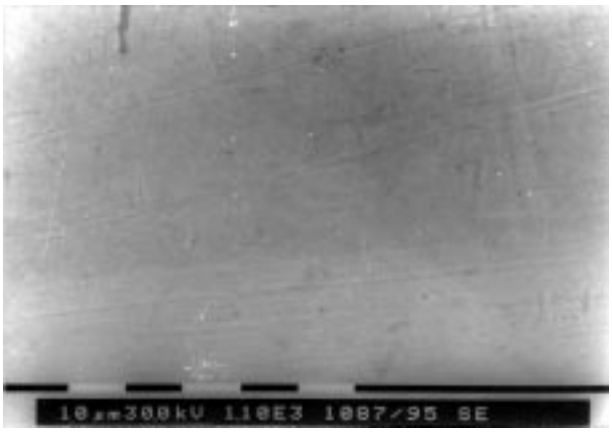

Figure 2 SEM image of an uncoated stainless steel stent.

Figure 3 SEM image of a PFP-E95P5.

TABLE I The results of the quantitative coronary angiography

Code	Balloon diameter	Pre-implantation diameter (mm)	Post-implantation MLSD (mm)	Over-sizing (%)	MLSD (mm) after 6 weeks of implantation	Late loss	% narrowing
bare stent	3.02 ± 0.05	2.49 ± 0.23	2.91 ± 0.13	22 ± 11	2.87 ± 0.16	0.05 ± 0.15	1.72 ± 5.16
PFP-E95P5	2.94 ± 0.06	2.41 ± 0.10	2.70 ± 0.11	22 ± 3	2.40 ± 0.16	0.29 ± 0.16	10.74 ± 5.94
PFP-E90P10	2.95 ± 0.05	2.18 ± 0.16	2.60 ± 0.14	36 ± 12	2.12 ± 0.21	0.49 ± 0.28	18.77 ± 10.78
PFP-E9505	3.15 ± 0.16	2.30 ± 0.37	2.97 ± 0.16	39 ± 18	2.44 ± 0.22	0.53 ± 0.11	17.85 ± 3.83
PFM-E50	2.83 ± 0.16	2.24 ± 0.32	2.56 ± 0.2	29 ± 16	2.26 ± 0.41	0.31 ± 0.37	12.11 ± 14.58
PFM-P75	2.98 ± 0.05	2.52 ± 0.16	2.91 ± 0.09	18 ± 8	2.83 ± 0.13	0.08 ± 0.17	2.75 ± 5.84
PFM-O65	3.01 ± 0.06	2.57 ± 0.15	2.98 ± 0.05	18 ± 6	2.45 ± 0.30	0.51 ± 0.29	17.45 ± 9.74
PFM-BSA-O	2.95 ± 0.10	2.50 ± 0.17	2.87 ± 0.11	18 ± 9	2.56 ± 0.09	0.32 ± 0.13	11.15 ± 4.55

immediately after, and at least 6 weeks after stent implantation are listed in Table I. Before implantation the size of the selected vessel segments was not significantly different. The balloon used for stent implantation had a 3 mm diameter. After implantation a significant enhancement of MSLD was observed for all groups. After 6 weeks the MSLD was significantly decreased. The results showed a superior behavior of PFM-P75. With a late loss of 0.08 mm and a 3% stenosis it revealed the best *in vivo* biocompatibility.

4. Discussion

Some biostable fluorinated polyphosphazenes and polymethacrylates are evaluated as coating for stainless steel coronary stents aiming to reduce the main problems of thrombogenicity and neointimal hyperplasia, related to these metallic devices. Perfluorinated polymers have proved in the past to be successful for the preparation of biomaterials. Examples of fluorinated biomaterials can be found in the production of intra-ocular lenses [36], dental prostheses and filling materials [37], and cardiovascular devices [38, 39], e.g. artificial veins and heart valves. The advantage of the fluorinated polymers, reported here, in comparison with the commonly used commercially available expanded polytetrafluoroethylene, is their ease of synthesis and processing and the possibility to dissolve them and apply as coatings. The chemical structure of polyphosphazenes can be varied by modification of the precursor polymer poly(dichloro)-phosphazene. Polymethacrylate copolymers can be easily prepared by radical polymerization.

A stent device, implanted in the coronary arteries, has a permanent function. Requirements of blood compatibility are extremely high. Hydrophobic polymers, especially fluorinated ones, have a potential as biocompatible materials. Tissue and blood compatibility seems to be connected with the formation of a tightly bound, irreversible protein layer [40]. Masked by the strong homogeneous protein film, the artificial material device is not able to activate the coagulation cascade or complement system, nor induce inflammatory response, calcification and tissue cell reactions.

Conventional stainless steel stents were dipcoated and sterilized by gamma-radiation. The coated stents were implanted for a period of 6 weeks in porcine coronary arteries. The porcine model was used because this model appears to offer specific advantages compared to other animal models [41–44]. Domestic pigs are relatively inexpensive, readily available and easy to use. Injury to porcine arteries leads to a neointimal proliferation, resembling human restenotic lesions after balloon angioplasty.

For none of the polymers acute thrombotic stent occlusion was observed. As is shown in Table I, the polymers involved, except PFM-P75, belong to class 2: a neointimal proliferation leading to less than 50% lumen narrowing. PFM-P75 showed superior properties in contact with the blood stream. Only a 3% narrowing and a minimal neointimal proliferation, comparable to the bare stainless steel stent, were found.

PFM-P75 is characterized by a high degree of pendant octafluoropentyl side chains with terminal CF_2H unit. In previous work [27], using X-ray photoelectron spectro-

TABLE II Dynamic contact angle measurements of the studied materials

Polymer Code	δadv (H_2O)	Harmonic mean method (10^{-3} J m^{-2})			
		δ*d*	δp γd/γp	δ*t*	
PFP-E95P5	111.4 δ 0.8	11.9	4.3	16.2	2.8
PFP-E90P10	113.1 δ 0.8	13.9	2.6	16.5	5.4
PFP-E95O5	113.5 δ 0.5	18.4	1.5	19.9	12.3
PFM-E50	111.4 δ 0.7	17.3	1.9	19.2	9.1
PFM-P75	103.1 δ 0.5	17.4	4.7	22.1	3.7
PFM-O65	121.9 δ 0.7	13.3	0.6	13.9	22.2
PFM-BSA-O	120.0 δ 0.8	14.0	0.6	14.6	23.3

scopy (XPS), it could be demonstrated that the fluorinated sidegroup is preferentially orientated to the surface, minimizing surface free energy. Atomic force microscopy (AFM) and SEM imaged a very smooth polymer surface. In stress–strain experiments PFM-P75 behaved as an elastic material, with an elasticity modulus of 1 MPa and an elongation at break of 672%. Dynamic contact angle (DCA) measurements showed the lowest advancing contact angle ($\theta adv(H_2O) = 103^\circ$) and the highest surface tension ($\gamma = 24 \times 10^{-3}$ J m^{-1}) for PFM-P75 in comparison with the other polymers. Because of the presence of the CF_2H endgroup a dipole moment along the surface is created, decreasing the polymer hydrophobicity. This may explain the superior behavior of PFM-P75 in the present study.

Many authors correlated surface hydrophobicity to blood compatibility [45]. The polymers, included in this study, can be classified as materials with high dispersion energy and low polar surface free energies. According to Kaeble, such materials will be more blood compatible than those with low dispersion and high polar surface free energy. The superiority of PFM-P75 also fits the hypothesis of Ratner who stated that the balance of polar and apolar sites on a surface may be important for its blood compatibility: $\gamma_d/\gamma_p \rightarrow 1$. Table II presents the advancing contact angle in water and the dispersive, polar and total surface free energy of the polymers. The smallest γ_d/γ_p ratio is found for PFM-P75 and PF-E95P5, corresponding to the smallest percentage of artery lumen narrowing, 3 and 10%, respectively.

5. Conclusions

In this report fluorinated polyphosphazenes and fluorinated (meth)acrylate copolymers are evaluated as coronary stent coating. Stainless steel stents were coated with the polymers and implanted in pig coronary arteries. No acute thrombotic occlusion occured. A 6-week follow-up of the minimal stented lumen diameter revealed superior blood compatibility of PFM-P75. Only 3% lumen narrowing and a minimal neointimal response was observed. This may be caused by the presence of the CF_2H terminal group of the fluorinated pentyl chain, situated at the surface layer. They can induce a dipole moment along the material surface and a decrease in hydrophobicity.

The angiographic results for PFM-P75 coated stents are comparable to those of the bare stainless steel stents. However, this polymer material offers possibilities as coronary stent coating. The polymer film can be loaded with anti-inflammatory, antithrombogenic and/or anti-proliferative drugs. As such the device can act as a local drug delivery system and reduce problems, typically related to stent implantation. The results obtained with drug loaded coatings will be reported in a subsequent paper.

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