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Viability, proliferation and adhesion of smooth muscle cells and human umbilical vein endothelial cells on electrospun polymer scaffolds

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Abstract. A major clinical problem of high relevance in the cardiovascular field is late stent thrombosis after implantation of drug eluting stents (DES). Clinical widely used DES currently utilize durable polymer coatings, which can induce persistent arterial wall inflammation and delayed vascular healing resulting in an impaired endothelialization. In this study we explored the interaction of smooth muscle cells (SMC) and human umbilical vein endothelial cells (HUVEC) with electrospun scaffolds prepared from resorbable polyetheresterurethane (PDC) and poly(*p*-dioxanone) (PPDO), as well as polyetherimide (PEI), which can be surface modified, in comparison to poly(vinylidene fluoride-*co*-hexafluoropropene) (PVDF) as reference material, which is established as coating material of DES in clinical applications.

Our results show that adhesion could be improved for HUVEC on PDC, PPDO and PEI compared to PVDF, whereas almost no SMC attached to the scaffolds indicating a cell-specific response of HUVEC towards the different fibrous structures. Proliferation and apoptosis results revealed that PPDO and PEI have no significant negative influence on vitality and cell cycle behaviour compared to PVDF. Hence, they represent promising candidates for temporary blood vessel support that induce HUVEC attachment and prevent SMC proliferation.

Keywords: Endothelialization, drug eluting stent, degradable polymer, electrospinning, cell selectivity

1. Introduction

Coronary artery disease (CAD) is still one of the world's leading causes of death. Current therapy of first choice to treat CAD is percutaneous coronary intervention (PCI) with bare-metal stent (BMS) implantation. However, up to 20% of the patients still developed in-stent restenosis due to neointima formation [6]. Considerable success to further reduce restenosis rates was achieved by coating stents

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with a polymer film that contains pharmacological agents [11]. Such drug eluting stents (DES) release small amounts of active substances that inhibit neointima formation, e.g. sirolimus or paclitaxel, over a period of 30 to 90 days. Nevertheless, DES-implantation is limited by late stent thrombosis due to delayed re-endothelialization, a major complication resulting in a life-threatening event [12, 22].

Clinical widely used DES, e.g. the Xience® coronary stent system [4, 14], elute the anti-proliferative drug everolimus on both the luminal side, which is exposed to the blood flow, and the abluminal side, which stays in direct contact to the vessel wall. Everolimus inhibits proliferation of abluminal smooth muscle cells (SMC) and matrix deposition. Thereby, the rapamycin-derivate limits restenosis but also impedes sufficient re-endothelialization favouring late stent thrombosis. The maintenance of an intact functional endothelial monolayer is crucial for early re-endothelialization and prevention of late stent thrombosis after vascular injury. Vascular remodeling after arterial injury is dependent on mobilization and recruitment of bone marrow derived progenitor cells [12, 17]. Therefore, one of the most promising approaches to support endogenous regeneration is realization of an effective re-endothelialization by recruitment of adjacent endothelial cells (EC) and endothelial progenitor cells (EPC) [13]. This requires a selective adherence of EC and EPC to a biomaterial surface, whereas recruitment of smooth muscle cells is prevented [21].

The majority of clinically established DES employ hydrophobic polymeric coatings, e.g. poly(vinylidene fluoride-*co*-hexafluoropropene) (PVDF) in case of the Xience® stent [4], which are not intended to degrade. Degradable polymers have attracted great interest as promising candidate materials for biomaterial-based regenerative therapy approaches e.g. as resorbable stent, since a permanent coating may contribute to inflammatory and platelet activating responses that eventually lead to late stent thrombosis [12, 13].

In this 4-armed comparative study we explored electrospun scaffolds prepared from three different polymers and PVDF as reference material. Electrospun test specimens were chosen as their structural characteristics can beneficially influence cell attachment, cell growth and cell differentiation [9, 20]. The aim of the present study was to investigate the influence of different electrospun polymer scaffolds on the cellular behaviour of primary HUVEC and SMC and to identify promising candidates for future cardiovascular applications like stent coatings. As degradable polymers a polyetheresterurethane (PDC) [8, 19] containing poly(*p*-dioxanone) (PPDO) and poly(ε-caprolactone) (PCL) segments, as well as PPDO homopolymer, a clinically established degradable implant material, were chosen. Finally, polyetherimide (PEI) was selected as material for long-term applications, which allows the surface chemistry to be altered and which has already been intensively investigated as candidate material for blood contacting applications [5, 23, 24]. PDC was selected as candidate material due to its multifunctional character combining a unique controllable degradation behaviour with an almost linear mass loss in *in-vitro* hydrolytic and enzymatic degradation experiments [15, 16, 18, 19], high elasticity as well as a shape-memory capability and furthermore a pro-angiogenic effect was reported for PDC *in vivo* [10].

2. Materials and methods

2.1. Polymers

The polyetheresterurethane (PDC) was synthesized via co-condensation from precursor macrodiols poly(ε-caprolactone)diol ($M_n = 2000\ g\,mol^{-1}$, Solvay Caprolactones, Warrington, U.K.) and poly(*p*-dioxanone)diol with $M_n = 5300\ g\,mol^{-1}$ using an aliphatic urethane linker (HDU) as junction unit,

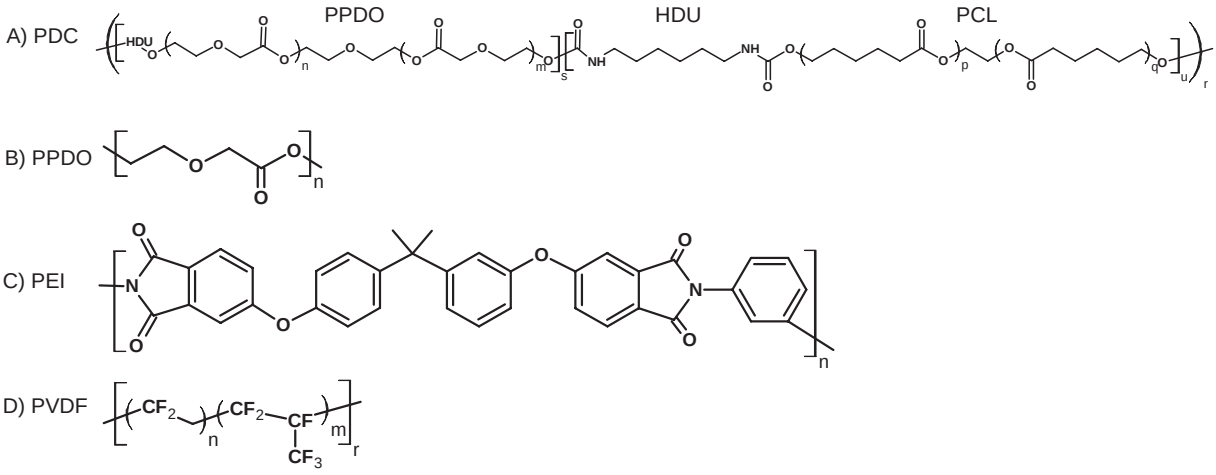

Fig. 1. Chemical structure of the polymers used for this study. (A) PDC, (B) PPDO, (C) PEI and (D) PVDF.

whereby poly(*p*-dioxanone)diol was prepared by ring-opening polymerization according to a method reported in [8]. Here a PDC composition with identical weight contents of the telechelic oligomers in the starting reaction mixture was chosen. PPDO (Resomer X®, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany), PEI (Ultem® 1000, General Electric, New York, USA) and PVDF (Solef®, Solvay Solexis, Tavaux, France) were used as received. The chemical structures of the investigated polymers are shown in Fig. 1.

2.2. *Electrospinning of fibrous scaffolds*

Electrospinning of PDC and PPDO was conducted from a 1,1,1,3,3,3 hexafluoro-2-propanol (HFP) solution with a concentration of 11% (w/v) according to the method recently described in [15]. PEI was electrospun using dimethylacetamide (DMAc) as solvent with a concentration of 31% (w/v), while the solution was handled under argon atmosphere to prevent precipitation of PEI, which occurs especially at high humidity levels. Finally, PVDF was dissolved in a dimethylformamide/acetone mixture (3 : 1 v/v) solution with a concentration of 40% (w/v). The thickness of the scaffolds was measured using a digital caliper, whereas the porosity was obtained according to equation (1):

$$Porosity\ [\%] = \left(1 - \frac{m_{sc}}{\rho \cdot V_{sc}}\right) \cdot 100 \tag{1}$$

where m_{sc} and V_{sc} are the weight and the volume of the electrospun scaffold and ρ is the density of the polymer.

2.3. *Thermal and mechanical characterization*

Differential scanning calorimetry (DSC) experiments were performed on a Netzsch DSC 204 Phoenix (Netzsch, Selb, Germany). The temperature range of -100 to 150°C was chosen for PDC, PPDO and PVDF samples, whereas PEI was evaluated from 0 to 300°C. All experiments were conducted under nitrogen atmosphere at a constant heating rate of 10°C min^{-1} with a waiting period of 2 min at the

maximum and minimum temperature. The glass transition T_g and the melting temperature T_m were analysed from the second heating run.

The mechanical properties of the electrospun scaffolds were examined by tensile tests (Zwick, Ulm, Germany) at ambient temperature, while the test specimens were cut into rectangular stripes with the dimensions $40 \times 10 \times 0.1\,\text{mm}^3$. Five consecutive measurements were performed for each electrospun polymer. For determination of the Young's modulus of the porous scaffolds an effective thickness d_{eff} was calculated according to equation (2):

$$d_{eff} = \frac{m_{sc}}{w_{sc} \cdot l_{sc} \cdot \rho} \tag{2}$$

where w_{sc}, l_{sc} and m_{sc} are the width, length and weight of the test specimen and ρ is the density of the polymer.

2.4. Morphological characterization of the electrospun scaffolds

For scanning electron microscopy (SEM) analysis the samples were cut into small rectangular pieces and mounted on a SEM sample holder. SEM pictures of Pt/Pd sputtered samples were taken at 1–3 keV acceleration voltage with 500–2000× magnification. For assessing the HUVEC ultrastructure after seeding on the scaffolds SEM was performed after 20 h culture time. The seeded samples were rinsed three times in PBS before and after fixation of the cells on the seeding substrate with a 3% glutaraldehyde PBS solution at 4°C in the dark. Finally, the samples were dehydrated in an ascending alcohol series at room temperature and dried using hexamethyldisilazine for 3×10 min.

2.5. Investigation of endotoxin load and cytotoxicity testing

The endotoxin content was analyzed by measuring the release of *p*-nitroaniline of a proenzyme in the lysate of Limulus Amebocytes from a synthetic substrate. Detection was performed photometrically and the concentration correlates linearly with the endotoxin content (QCL-10001 Limulus Amebocyte Lysate assay, Lonza, Basel, Switzerland).

The cytotoxicity tests in direct contact were performed using L929 mouse fibroblasts. Electrospun scaffolds fixed in 13 mm Minusheet® (MINUCELLS and MINUTISSUE Vertriebs GmbH, Bad Abbach, Germany) were sterilized by gas sterilization with 600 mg/ml ethylene oxide for 3 hours in 50–80% humidity and subsequently left for 3 days at 35–45°C to induce desorption. The samples were seeded with L929 cells (ATCC, 60×10^3 cells/cm^2) and the mitochondrial activity was measured after 48 h using a tetrazolium compound. Additionaly, the cell plasma membrane integrity was analyzed with the lactate dehydrogenase assay (LDH-assay, Roche, Penzberg, Germany) and the cell morphology was investigated by transmission light microscopy in phase contrast mode.

2.6. Cell culture and adhesion to polymer scaffolds

Human coronary smooth muscle cells (SMC, Clonetics, USA) and human umbilical vein endothelial cells (HUVEC, Lonza) were cultured at 37°C under an atmosphere of 5% CO_2. HUVEC were cultured in endothelial basal medium (EBM-2, Lonza) supplemented with EGM-2 SingleQuots® kit (Lonza) and 15% FCS. SMC were cultured in smooth muscle cell basal medium (SmBm, Lonza) supplemented with SmGM-2 SingleQuot® kit and 15% FCS.

Approximately 2×10^5/well HUVEC or SMC cells were seeded in 24-well plates onto polymer scaffolds fixed in 13 mm Minusheet® or glass coverslips as positive control. For the biological evaluation four samples per group and cell type were tested, while the study was performed in accordance with the ethical guidelines of Clinical Hemorheology and Microcirculation [1]. Polymer scaffolds were preincubated with medium for 6–12 h. After 0 min, 10 min, 30 min and 60 min scaffolds were washed three times with PBS, cells were trypsinized from polymer scaffolds using 0.25% (w/v) trypsin/PBS and cells were counted in a Neubauer counting chamber. The percentage of adhered cells (normalized to starting cell number) for each time point was calculated.

2.7. Proliferation and apoptosis studies

SMC or HUVEC were labelled with 0.2 μM carboxyfluorescein succinimidyl ester (CFSE) for 15 min at 37°C. Cells were washed twice with PBS and subsequently seeded for three days onto scaffolds or glass coverslips as positive control. The non-fluorescent dye CFSE is cleaved by intracellular esterase and irreversibly couples to amines to form fluorescent conjugates. The fluorescent CFSE-conjugates are distributed equally between daughter cells. Proliferation correlates with reduction of CFSE fluorescent and was assessed by flow cytometry using FACSCanto II with FACSDiva and FloJo software (BD Biosciences, Heidelberg, Germany). Viability/apoptosis of HUVEC was evaluated by Flow cytometry after AnnexinV/PI-staining (AnnexinV Apoptosis Detection Kit II, BD Bioscience). Annexin binds to phosphatidylserine (PS) early in the apoptotic process (AnnexinV$^+$ PI$^-$), where PS is translocated from the internal to the external layer of the plasma membrane. The DNA-binding dye Propidium iodide (PI) is used to distinguish cells, which are in the later stage of apoptosis or already dead (AnnexinV$^+$ PI$^+$).

2.8. Statistics

Data were reported as mean value ± standard deviation, and were analyzed by two-tailed unpaired Student's *t*-test. A p value of less than 0.05 was considered significant.

3. Results

3.1. Thermal, mechanical and morphological characterization of electrospun scaffolds

Electrospun non-woven fabrics with an average deposit thickness of 100 ± 30 μm and a porosity in the range from 70% to 90% were achieved for all four polymers, where the single fiber diameters were around 2–3 μm (Fig. 2). Table 1 summarizes the thermal and mechanical properties of the scaffolds. The multiblock copolymer PDC exhibited two distinct glass transitions (T_g) as well as two melting transition temperatures (T_m) at 36 and 90°C associated to the PCL and PPDO domains indicating a phase segregated morphology of the multiblock copolymer, which were in good agreement with previously reported data [15]. A thermal transition at around body temperature occurs only for PDC, which has been implemented into the multiblock copolymer system to induce a shape-memory effect suitable for biomedical applications.

The results of the tensile tests performed at room temperature indicate that the electrospun homopolymers PEI and PPDO were the scaffold materials with highest stiffnesses, while PEI exhibited a low elongation at break of $\varepsilon_B = 13 \pm 5\%$. By contrast, both copolymers PDC and PVDF showed high

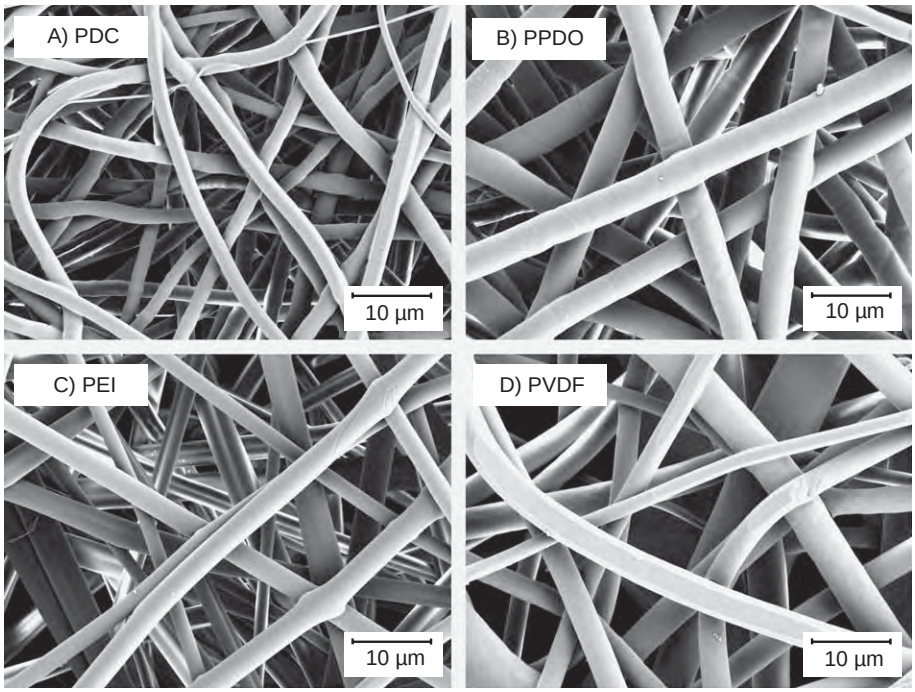

Fig. 2. SEM images of (A) electrospun PDC, (B) PPDO, (C) PEI and (D) PVDF scaffolds.

Table 1
Thermal and mechanical properties of the electrospun scaffolds

Sample	E[a] [MPa]	ε_B[a] [%]	$T_{g,\,onset}$[b] [°C]	$T_{g,\,offset}$[b] [°C]	T_m[b] [°C]
PVDF	173 ± 25	226 ± 30	-47 ± 1	-14 ± 1	134 ± 1
PDC	51 ± 8	210 ± 25	-62 ± 1, -27 ± 1	-54 ± 1, -13 ± 1	36 ± 1, 90 ± 1
PPDO	349 ± 30	127 ± 10	-12 ± 1	-4 ± 1	106 ± 1
PEI	534 ± 150	13 ± 5	212 ± 1	217 ± 1	–

[a]Young's modulus (E) and elongation at break (ε_B) were determined by tensile tests at room temperature.
[b]Glass transition ($T_{g,\,onset}$, $T_{g,\,offset}$) and melting temperature (T_m) were obtained by DSC measurements.

elongation at break values above 200%, whereby PDC was the softest scaffold material with a Young's modulus of 51 ± 8 MPa.

3.2. Biological evaluation of cell behaviour on polymeric scaffolds

Prior to HUVEC and SMC exposure the endotoxin content of the sample extracts was analyzed based on the endotoxin induced activation of a proenzyme in the lysate of Limulus Amebocytes. All investigated scaffolds exhibited a low endotoxin load <0.06 EU/ml and showed only slight cytotoxic effects according to mitochondrial activity and cell plasma membrane integrity when tested with L929 cells in direct contact. The adhered L929 cells were found to circum-grow the scaffold fibers.

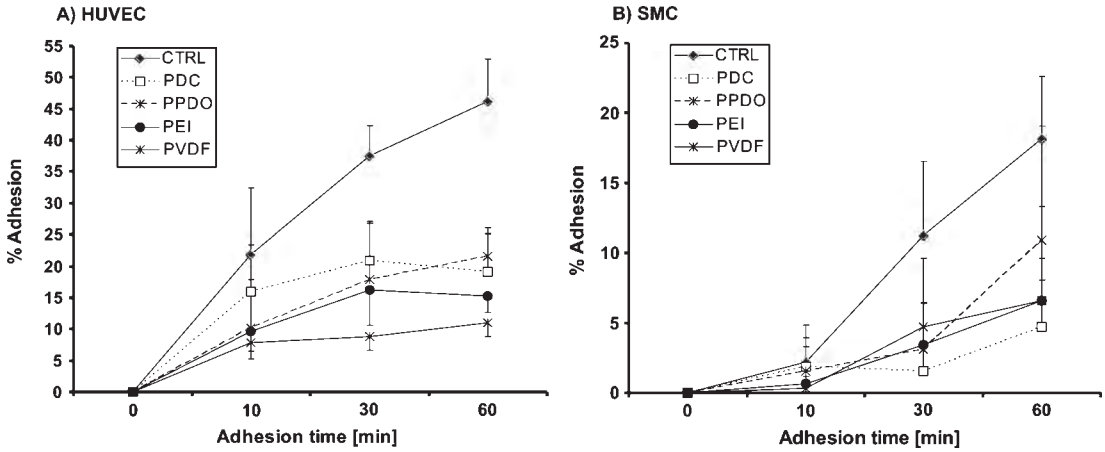

Fig. 3. Adhesion of HUVECs and SMCs on electrospun scaffolds. Endothelial HUVEC (A) and SMC cells (B) were cultured for 10, 30 and 60 min on polymer scaffolds and glass coverslips as positive control (Ctrl). The percentage of adhered cells was counted in a Neubauer counting chamber. (A) Compared to reference polymer (PVDF), adhesion of HUVECs is improved for: PDC (19%), PPDO (22%) and PEI (15%) *vs*. PVDF (11%); Ctrl (46%) *vs*. PVDF (p for all at 60 min <0.05). (B) No significant amount of SMCs adhered to polymeric structure. Due to low cell numbers, it is not feasible to test significances. The experiment was performed in duplicates and was repeated one time.

Endothelial recovery after acute vascular injury from stent implantation is essential for vascular healing. Therefore, we assessed the cellular behaviour of EC on the different polymer surfaces using HUVEC as model cells. Quantitative evaluation of *in vitro* cell adhesion towards the polymeric scaffolds revealed that PVDF showed the lowest adhesion properties for HUVECs (11% adhesion) and cell attachment was improved significantly for all fabricated polymers, PPDO (22% adhesion); PDC (19%) and PEI (15%) (Fig. 3A). However, all electrospun scaffolds exhibited reduced cell adhesion compared to glass coverslips (Ctrl; 46% adhesion), which was used as positive control for cell adhesion of endothelial cells. On the other side, almost no SMC adhered to scaffolds (PDC 5%; PPDO 11%; PEI 6%; PVDF 7%) compared to the glass coverslips (18%) (Fig. 3B). Due to very low cell numbers it was not feasible to test significances.

Proliferative capacity of HUVEC on electrospun scaffolds were assessed by CFSE labelling and FACS analysis, in which proliferation correlates with reduction of mean fluorescence intensity (MFI). Table 2 and Fig. 4 (representative histogram plots) show that proliferation rate of HUVEC detected by CFSE fluorescence dilution was largely unaffected among the PPDO, PEI and PVDF polymeric scaffolds and the glass coverslip Ctrl (set to 100%) (PPDO = 105 ± 6%; PEI = 97 ± 5%; PVDF = 109 ± 2%). Only the PDC polymeric scaffold induced a significant reduction in proliferation indicated by an increase in CFSE MFI (PDC = 188 ± 21%) compared to Ctrl and the PVDF reference polymer.

Although interestingly, the electrospun scaffolds did not have a substantially impact on cell proliferation of HUVEC, all tested scaffolds facilitated significantly apoptosis leading to a reduced percentage of viable cells: PPDO = 73 ± 5% living cells; PDC = 63 ± 7%; PEI = 58 ± 7%; PVDF = 71 ± 9% compared to glass coverslips Ctrl (set to 100%) (Table 2 and Fig. 5 representative histogram plots). Here, the durable PEI scaffold showed the strongest facilitation of apoptosis, while on the other hand, electrospun PPDO scaffolds exhibited the lowest induction of apoptosis as compared to PVDF. The ultrastructure of HUVECs on PDC, PPDO and PEI scaffolds was visualized using SEM as shown in Fig. 6, while no

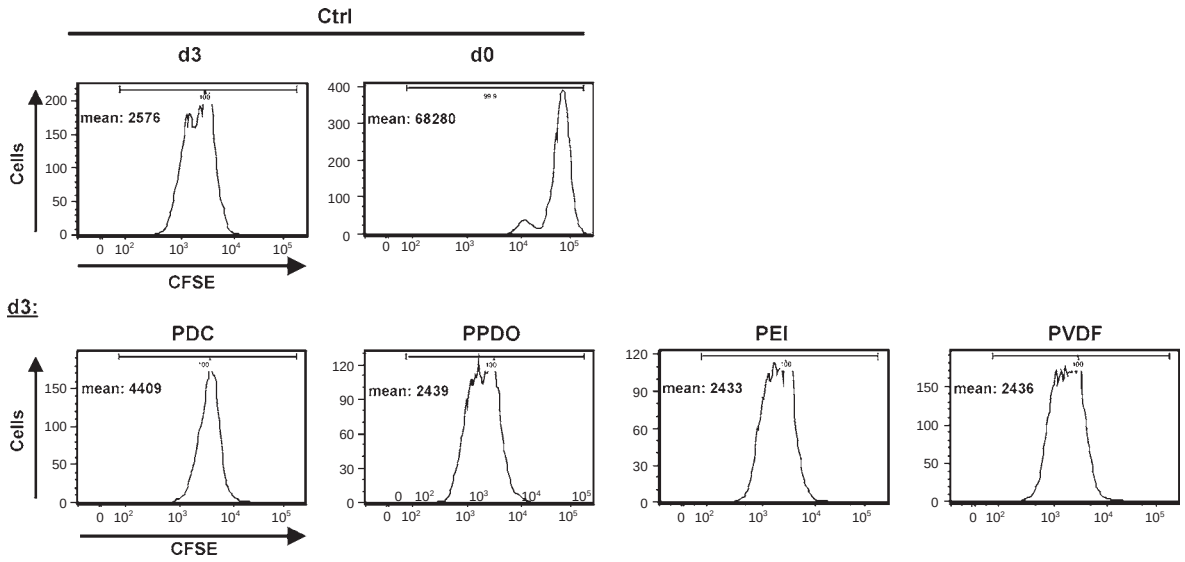

Fig. 4. Impact of electrospun scaffolds on HUVEC proliferation. HUVECs were seeded onto polymer scaffolds or glass coverslips as positive control (Ctrl). CFSE-Fluorescence was monitored immediately after CFSE-labeling at day 0 (d0) and after three days (d3) of culture. Mean CFSE fluorescence intensity (MFI) was calculated using FloJo software. Representative histogram plots gated on live cells are shown. The experiment was performed in duplicates and was repeated one time.

Table 2
Proliferation and viability of cultured HUVEC on electrospun scaffolds

Sample	Proliferation[a] [CFSE MFI; % of Ctrl]	Living cells[b] [% of Ctrl]
Ctrl	100 ± 0	$100 \pm 0^{*2}$
PDC	$188 \pm 21^{*1}$	63 ± 7
PPDO	105 ± 6	73 ± 5
PEI	97 ± 5	58 ± 7
PVDF	109 ± 12	71 ± 9

Percentages compared to glass coverslip Ctrl (set to 100%) are shown.
[a]Proliferation of HUVECs was analyzed after 3 culturing days by FACS analysis and calculating the CFSE-mean fluorescence intensity (MFI).
$*^1 p < 0.05$, Student's *t* test (PDC *vs* PVDF or Ctrl).
[b]Viability of HUVECs was evaluated by Flow cytometry after 3 culturing days using AnnexinV/PI-staining.
$*^2 p < 0.05$, Student's *t* test (Ctrl *vs* all tested scaffolds).

viable cell could be found on PVDF scaffolds. HUVECs on PDC and PEI scaffolds, as indicated by white arrows, remained rounded and tended to circum-grow around and along the fiber, whereas the HUVECs on PPDO scaffolds spreaded and created their own fibrous microenvironment as newly formed nanofibers could be observed within the scaffold.

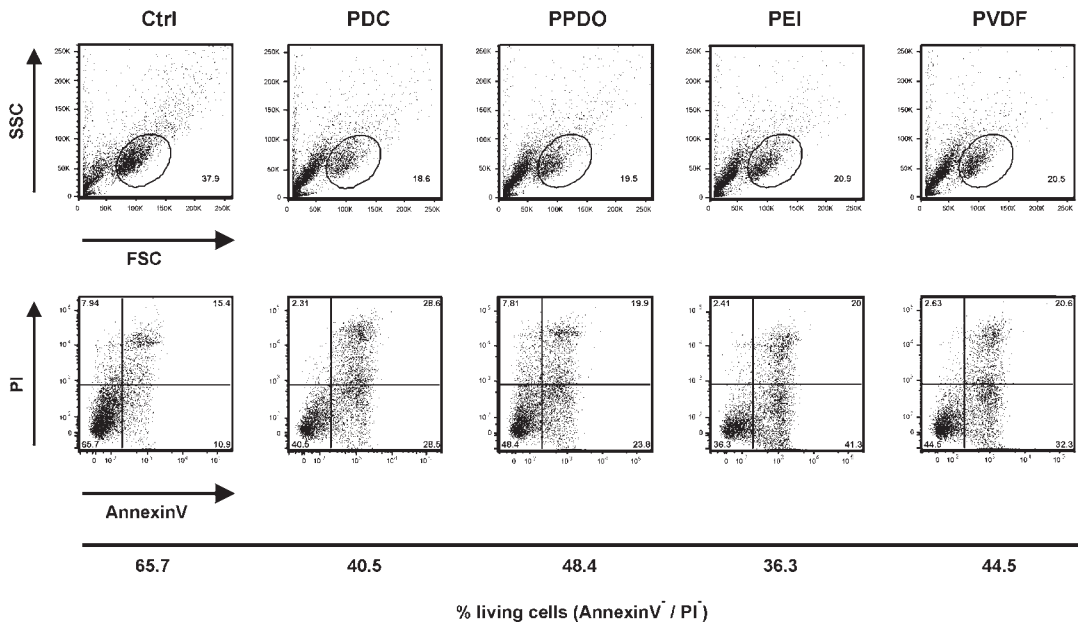

Fig. 5. Viability of HUVECs cultured on electrospun scaffolds. HUVECs were seeded onto electrospun scaffolds or glass coverslips as positive control (Ctrl). After three days (d3) living cells were discriminated by AnnexinV/PI-staining (Annexin-/PI-) and analysed by flow cytometry. Representative dots plots are shown. The experiment was performed in duplicates and was repeated one time.

4. Discussion

Fibrous scaffolds as obtained from the electrospinning technique might be applied for stent coating applications to represent a tunable matrix in terms of pore size, fiber diameter and surface chemistry. A cell-selective biomaterial processed by the electrospinning technique, which can suppress SMC proliferation but does not influence HUVEC attachment, would be a promising approach to develop a new DES stent platform with enhanced re-endothelialization properties and reduced risk of late stent thrombosis.

The tested scaffolds PDC, PPDO and PEI exhibited an increased adhesion of HUVECs as compared to the reference polymer PVDF used in the Xience® coronary stent system. With the exception of the multiblock copolymer PDC, cell survival and proliferation was largely unaffected among the different polymers. Interestingly, almost no SMCs adhered to all tested polymers indicating a cell-selective behaviour for the different fibrous structures. The topography and porosity of scaffolds play significant roles in attachment, proliferation and differentiation of cells and EC might prefer structures with high porosity and large surface area for cell attachment and proliferation as warranted by electrospun scaffolds [1]. Although in vitro assays can provide essential information, the *in vivo* situation is more complex. Therefore, the *in vivo* biocompatibility and tissue integration is currently under investigation in ongoing experiments by subcutaneous scaffold implantation into mice.

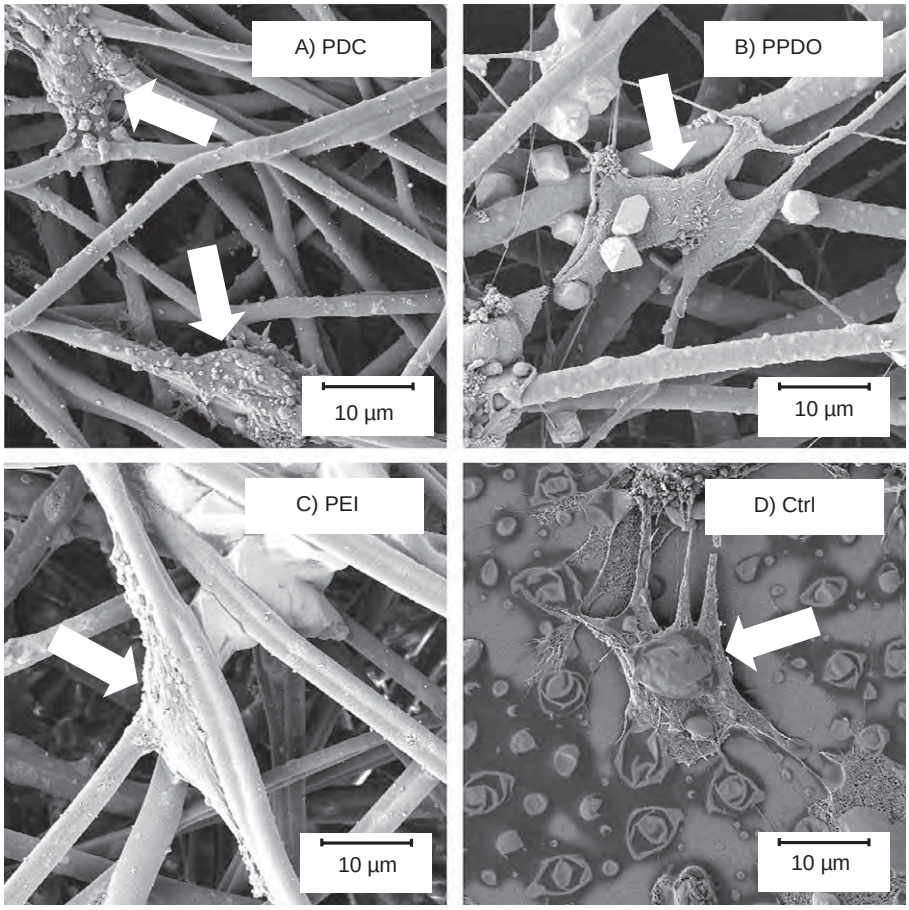

Fig. 6. SEM images of HUVECs on different electrospun scaffolds after 20 h culture time. (A) PDC, (B) PPDO and (C) PEI scaffolds as well as (D) glass coverslips as positive control (Ctrl). No viable cells could be found on PVDF scaffolds.

5. Conclusion

The tested PDC, PPDO and PEI scaffolds improve adhesion of HUVEC compared to the reference polymer PVDF. Cell survival and proliferation was largely unaffected for the PPDO and PEI polymeric scaffolds. In contrast, adhesion of SMCs is suppressed for all electrospun scaffolds indicating a cell-specific response of HUVECs towards the scaffolds. In conclusion, electrospun PPDO and PEI might be promising candidates for future cardiovascular applications like e.g. biodegradable (PPDO) or durable and functionalizable (PEI) stent coatings. For future studies multifunctional polymers, such as depsipeptide-based multiblock copolymers with non-toxic degradation products [7] or modular degradable blends made from PPDO- and PCL-based multiblock copolymers [3], might be employed to combine the advantages of improved material properties with a tunable electrospun matrix. As we observed here that the cells preferably circum-grow the single fibers of the electrospun scaffolds, a comparative study with films of the same polymers will be conducted subsequently in order to separate effects of different chemical composition of the polymers and the influence of the substrate morphology.

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References

[1] Anonymous, Ethical guidelines for publication in clinical hemorheology and microcirculation, *Clinical Hemorheology and Microcirculation* **44** (2010), 1–2.
[2] N.L. Angeloni, et al., Regeneration of the cavernous nerve by Sonic hedgehog using aligned peptide amphiphile nanofibers, *Biomaterials* **32** (2011), 1091–1101.
[3] M. Behl, U. Ridder, Y. Feng, S. Kelch and A. Lendlein, Shape-memory capability of binary multiblock copolymer blends with hard and switching domains provided by different components, *Soft Matter* **5** (2009), 676–684.
[4] S. Bezenek, et al., Low stent thrombosis risk with the XIENCE V(R) everolimus-eluting coronary stent: Evidence from randomized and single-arm clinical trials, *J Interv Cardiol* **24** (2011), 326–341.
[5] S. Braune, M. Lange, K. Richau, K. Lutzow, T. Weigel, F. Jung and A. Lendlein, Interaction of thrombocytes with poly(ether imide): The influence of processing, *Clin Hemorheol Microcirc* **46** (2010), 239–250.
[6] G.D. Dangas, B.E. Claessen, A. Caixeta, E.A. Sanidas, G.S. Mintz, R. Mehran, In-stent restenosis in the drug-eluting stent era, *J Am Coll Cardiol* **56** (2010), 1897–1907.
[7] Y. Feng, M. Behl, S. Kelch, A. Lendlein, Biodegradable multiblock copolymers based on oligodepsipeptides with shape-memory properties, *Macromol Biosci* **9** (2009), 45–54.
[8] H. Grablowitz, A. Lendlein, Synthesis and characterization of α,ω-dihydroxy-telechelic oligo(p-dioxanone), *J Mater Chem* **17** (2007), 4050–4065.
[9] L.G. Griffith, Emerging design principles in biomaterials and scaffolds for tissue engineering, *Ann N Y Acad Sci* **961** (2002), 83–95.
[10] B. Hiebl, R. Fuhrmann, F. Jung, K. Kratz, A. Lendlein, R.P. Franke, Degradation of and angiogenesis around multiblock copolymers containing poly(p-dioxanone)- and poly(epsilon-caprolactone)-segments subcutaneously implanted in the rat neck, *Clin Hemorheol Microcirc* **45** (2010), 117–122.
[11] R. Hill, et al., Coronary artery stents: A rapid systematic review and economic evaluation, *Health Technol Assess* **8** (2004), iii-iv, 1–242.
[12] M. Joner, et al., Pathology of drug-eluting stents in humans: Delayed healing and late thrombotic risk, *J Am Coll Cardiol* **48** (2004), 193–202.
[13] F. Jung, C. Wischke and A. Lendlein, Degradable, multifunctional cardiovascular implants: Challenges and hurdles, *MRS Bulletin* **35** (2010), 607–613.
[14] C. Kaiser, et al., Drug-eluting versus bare-metal stents in large coronary arteries, *New Engl J Med* **363** (2010), 2310–2319.
[15] K. Kratz, R. Habermann, T. Becker, K. Richau, A. Lendlein, Shape-memory properties and degradation behavior of multifunctional electro-spun scaffolds, *Int J Artif Organs* **34** (2011), 225–230.
[16] A. Kulkarni, J. Reiche, J. Hartmann, K. Kratz, A. Lendlein, Selective enzymatic degradation of poly(epsilon-caprolactone) containing multiblock copolymers, *Eur J Pharm Biopharm* **68** (2008), 46–56.
[17] N. Langwieser, J.B. Schwarz, C. Reichenbacher, B. Stemmer, S. Massberg, N.N. Langwieser, D. Zohlnhofer, Role of bone marrow-derived cells in the genetic control of restenosis, *Arterioscler Thromb Vasc Biol* **29** (2009), 1551–1557.
[18] A. Lendlein, R. Langer, Biodegradable, elastic shape-memory polymers for potential biomedical applications, *Science* **296** (2002), 1673–1676.
[19] A. Lendlein, M. Behl, B. Hiebl, C. Wischke, Shape-memory polymers as a technology platform for biomedical applications, *Expert Rev Med Devic* **7** (2010), 357–379.
[20] S. Liao, B. Li, Z. Ma, H. Wei, C. Chan and S. Ramakrishna, biomimetic electrospun nanofibers for tissue regeneration, *Biomed Mater* **1** (2006), R45–R53.

[21] N. Scharnagl, S. Lee, B. Hiebl, A. Sisson and A. Lendlein, Design principles for polymers as substratum for adherent cells, *J Mater Chem* **20** (2010), 8789–8802.
[22] P.W. Serruys, et al., Angiographic follow-up after placement of a self-expanding coronary-artery stent, *N Engl J Med* **324** (1991), 13–17.
[23] R. Tzoneva, B. Seifert, W. Albrecht, K. Richau, T. Groth, A. Lendlein, 2008. Hemocompatibility of poly(ether imide) membranes functionalized with carboxylic groups, *J Mater Sci Mater Med* **19** (2008), 3203–3210.
[24] R. Tzoneva, B. Seifert, W. Albrecht, K. Richau, A. Lendlein, T. Groth, Poly(ether imide) membranes: Studies on the effect of surface modification and protein pre-adsorption on endothelial cell adhesion, growth and function, *J Biomater Sci Polym Ed* **19** (2008), 837–852.