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Improvement of stenting therapy with a silicon carbide coated tantalum stent

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State of the art cardiovascular stent materials are a compromise between bulk properties and surface related properties. As a consequence, deficiencies in both characteristics lead to serious limitations of stenting therapy. Beside a dissatisfying X-ray visibility of current stent materials, which hinders precise angiographic control of the stent during implantation, insufficient hemocompatibility causes subacute vessel occlusions despite stringent anticoagulant medication. Additionally, bleeding complications result which further limit the therapeutical success. Therefore it is essential to develop a new coronary stent with improved material properties for the bulk of the stent and its surface. This is realized by a hybrid concept. The stent is manufactured from tantalum, having a high inherent radio-opacity. The stent is coated with amorphous silicon carbide, optimized for hemocompatibility. An appropriate deposition technology to maximize coating adhesion was developed. Amorphous silicon carbide was investigated *in vitro* and *in vivo* to assess its suitability for coronary stents.

1. Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is a successful clinical method to treat coronary artery obstructions. However, its clinical efficacy is limited by the major problems of acute vessel occlusions in approximately 5 to 10% of all patients and restenosis in 20 to 57% in the first six months after implantation, despite a stringent pharmacological treatment [1, 2].

In order to reduce these deficiencies, which are seriously limiting the applicability of PTCA, a new clinical therapy was introduced with the implantation of metallic stents. These stents are mainly used to treat significant dissections occurring during conventional PTCA as well as to reduce restenosis rate [3]. Recent studies confirmed a reduction of restenosis of more than 10% in the stent group compared to the PTCA group [4, 5].

However, due to the inherent thrombogenicity of currently used stent materials, a high rate of subacute stent thrombosis must be accepted despite a rigorous anticoagulant and antithrombotic pharmaceutical regime [6]. As a consequence, anticoagulant related bleeding and vascular complications occur, requiring blood transfusions and surgical repair of the vessels. Further limitations result from difficulties in controlling stent implantation precisely because of the poor X-ray visibility of the device.

Therefore, it is essential to develop a new cardiovascular stent with low thrombogenicity and adequate radio-opacity.

2. Materials and methods

2.1. Hybrid design of the coronary stent

In order to reduce the deficiencies of stenting therapy, the material properties of the bulk of the stent as well as surface-related properties have to be improved. Unfortunately both aspects cannot be realized by one alloplastic material. Therefore the proposed coronary stent consists of two different materials, which are optimized independently of each other with regard to the bulk-related and surface-related requirements of a coronary stent.

The body of this hybrid designed stent is manufactured from tantalum in order to enhance the radio-opacity while preserving well-known mechanical properties. The material is machined using electric discharge machining having optimized process parameters to obtain burr-free edges and smooth-cut edges.

In order to improve the hemocompatibility, different physical properties of a material are required. Considering the mechanisms of protein degeneration at alloplastic surfaces, a physical model was proposed which enables the development of an amorphous silicon carbide (a-SiC: H) coating [7, 8], deposited using the plama-enhanced chemical vapour deposition technique (PECVD).

2.2. Deposition technology of a-SiC:H with respect to adhesion optimization

Besides defined physical properties of a-SiC:H, the technological performance of a hybrid design requires

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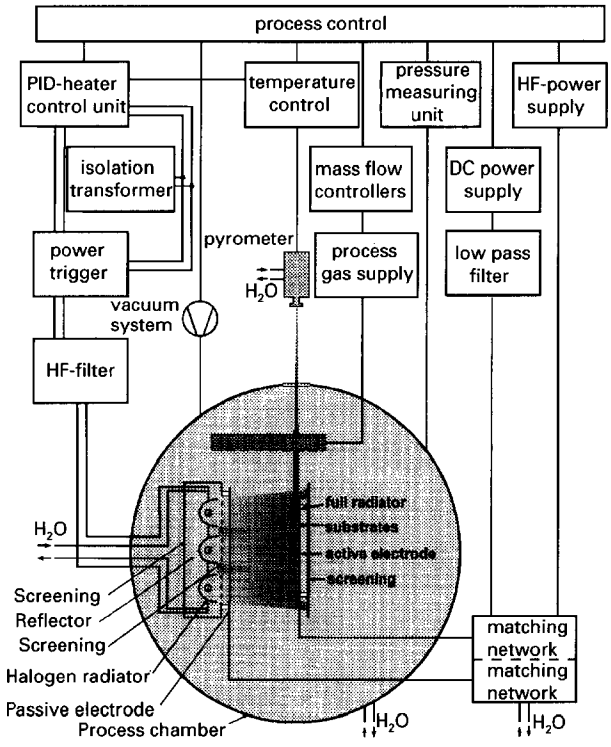

Figure 1 PECVD equipment to deposit a-SiC:H.

strong adhesion of the coating on the metallic stent, a particular problem being the high expansion ratio of the device during dilatation. Due to the fixed chemical composition of a-SiC:H, an important method to improve adhesion is modification of the substrate surface prior to the deposition of a-SiC:H. Therefore various plasma pretreatments were performed. The PECVD equipment which allows a-SiC:H deposition as well as other plasma pretreatments is shown in Fig. 1.

To perform the plasma pretreatments and to deposite a-SiC:H, the potential distributions of Fig. 2 were applied. Interaction of the DC source with the RF power source and vice versa was prohibited by appropriate electronic high-pass and low-pass filters.

2.3. Adhesion measurement

The adhesion of a-SiC:H was measured using the scratch test [9, 10]. A diamond tip was pulled across the coated substrate with a variable normal load at a constant velocity. By light microscopy the failure mechanism [10] and lowest force F_{crit} which caused delamination of a-SiC:H or defect formation in the layer was determined. F_{crit} is a measure of the adhesion of the coating.

2.4. *In vitro* properties of a-SiC:H

To investigate the *in vitro* behaviour of a-SiC:H, the following tests were performed.

2.4.1. Cytotoxicity

The cytotoxicity test uses mice fibroblasts L929 cell cultures. The cells were covered with an agar-overlay in order to prevent damage of the sensitive cells by the solid test material. Three samples, coated with a-SiC:H and filters saturated with saline as the negative control and 0.04 M $CuSO_4$ as the positive control were directly contacted to the agar-overlay and incubated for 24 h at 37 °C. The cell response to the material was evaluated after colouring with trypian blue and further incubation (2 h, 37 °C).

2.4.2. Hemolysis

For hemolysis testing, 1 ml of a solution of sheep erythrocytes was mixed with 4 ml of an a-SiC:H extract. For the negative and positive control, saline and aqua dest. (100% hemolysis degree) were used. After incubation (2 h, 37 °C) and centrifugation the concentration of hemoglobin, which is measure of the degree of hemolysis, was quantified by adding calciumhexacyanoferrat III and caliumcyanid to the centrifugation excess. The resulting chemical complex (hemoglobin-cyanid) changes the optical absorption of the test fluid at 546 nm which was converted into a concentration.

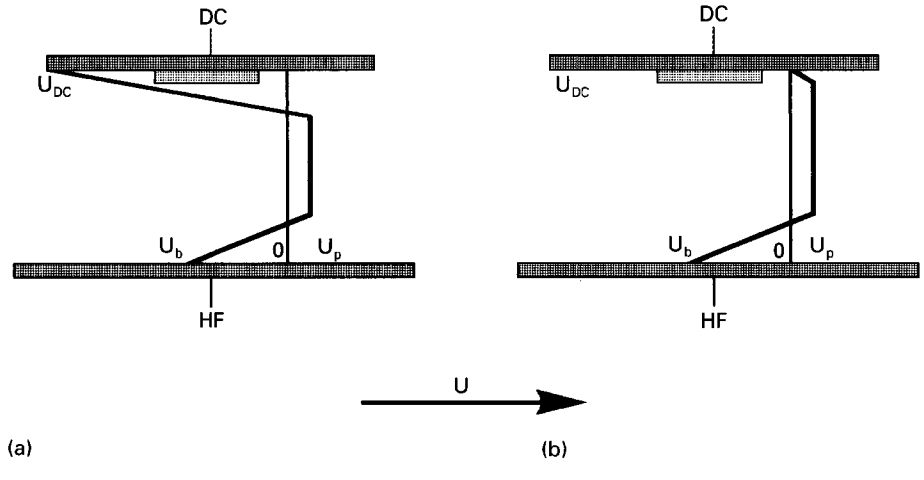

Figure 2 Potential distribution between the asymmetric plates of the PECVD equipment: (a) plasma pretreatment; (b) deposition of a-SiC:H.

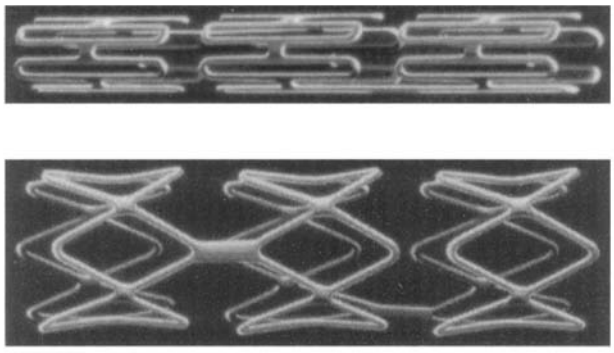

Figure 3 (a) Silicon carbide coated tantalum stent and (b) its dilated form.

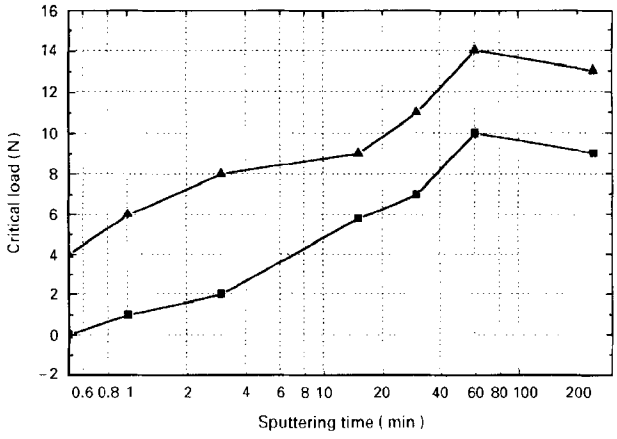

Figure 4 Adhesion depending on the presputtering time using argon (200 W RF, 1000 V DC, p_{Ar} 3.6 Pa): —▲— Ta; —■— 316 L.

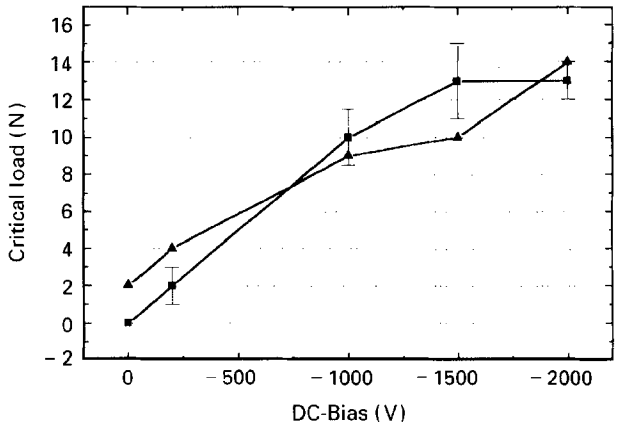

Figure 5 Adhesion of a-SiC: H depending on the DC-bias (200 W RF, p_{Ar} 3.6 Pa, 60 min) : —▲— Ta; —■— 316 L.

2.4.3. *Mutagenicity (Ames test)*

The degree of mutation caused by a-SiC:H was investigated on the *Salmonella typhimurium* mutants TA98, TA100, TA 1535 and TA1537. After covering the salmonella bacteria with a top agar, a-SiC:H coated substrates together with filters saturated with mutagenic chemicals (positive control) and saline (negative control) were directly contacted to the cell culture. After incubation (3 days, 37 °C) the degree of inverse mutation of *Salmonella typhimurium* around the test substances was measured by the amount of histidin produced by the mutant bacteria.

2.4.4. *Endothelial cell growth*

The growth behaviour of endothelial cells on a-SiC: H was investigated using human endothelial cells isolated from the umbilical vein. The cells were seeded into wells containing the test specimens with a density of 10 000 per cm^2. After 1, 4 and 7 days of incubation, adherent cells were detached with a trypsin/ETDA solution. The number of cells was measured with a counter.

2.5. *In vivo* investigation of a-SiC:H

2.5.1. *Hemocompatibility testing*

The *in vivo* investigation of a-SiC:H was performed by two methods. In the first examination one coated and one uncoated stent were dilated in a PVC tube, which was implanted in the carotis communis of a female pig as a bypass. This was performed in order to exclude the influences of the vessel. After a 90 min period of blood perfusion, the stents were explanted and investigated with respect to aggregation of blood components and morphology of the layer. The uncoated stent was used as a reference.

2.5.2. *Implantation test*

In the second examination, one uncoated and three a-SiC:H coated Palmaz–Schatz stents were implanted in the arteria femoralis region of a pig for three days. To simulate worst-case conditions, no treatment against anticoagulation or thrombocytic aggregation was applied. After explanation the specimens were examined histologically.

3. Experimental results

3.1. Hybrid designed coronary stent

The new silicon carbide coated tantalum stent before and after dilatation is shown in Fig. 3. The stent consists of three parts connected via bridges with a total length of 14.6 mm. By dividing the device into three elements, a high flexibility results which allows implantation of the stent even into tortuous vessels. The tantalum body of the stent shows very high X-ray visibility of the device under angiographic control.

3.2. Adhesion measurements

The results of the adhesion measurements of a-SiC: H on metallic substrates, depending on the presputtering time using argon and on the DC-bias, are shown in Figs 4 and 5, respectively.

Without sputtering, the adhesion of a-SiC:H on metallic substrates was quite low (Fig. 4). With increasing presputtering time, the adhesion increased linearly. This was according to the amount of adsorbents which were removed from the substrate surface by argon bombardment. With increasing DC-bias the adhesion was enhanced quantitatively as well as qualitatively which was identified by the type of failure mechanism. Bias voltages higher than 1500 V did not

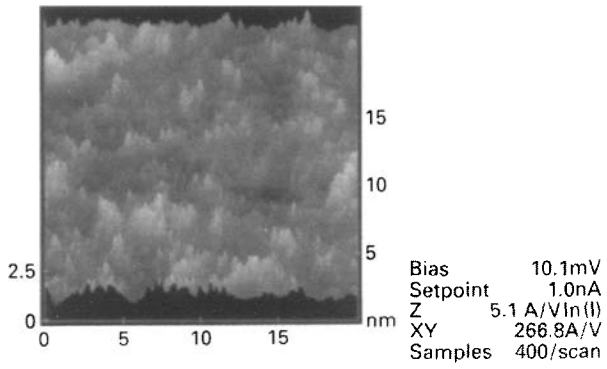

Figure 6 Scanning tunneling microscopy (STM) image of the surface after sputtering with argon (750 V, 3 min).

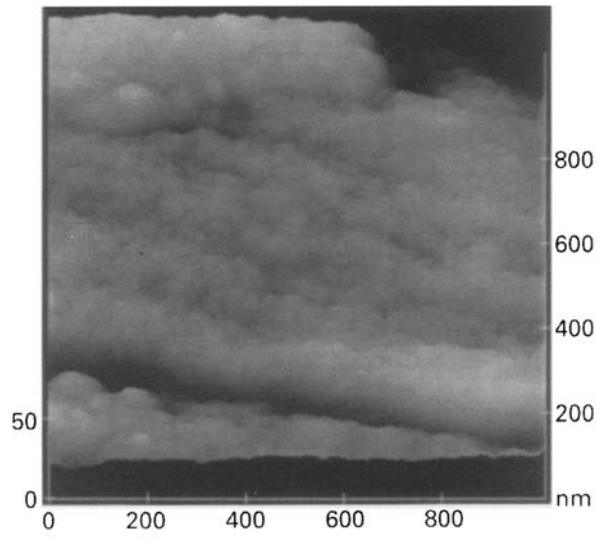

Figure 7 Surface morphology of a-SiC:H.

improve adhesion, suggesting complete removal of adsorbents. Auger-electron spectroscopy depth profiling investigations revealed that the plasma pretreatment led to a broadening of the interface region. This broadening could be attributed to a morphological change of the surface. Induced by sputtering, the surface changed from a smooth structure to a rough morphology on an atomic scale (Fig. 6), significantly increasing the chemical active surface area. This lead to an increased number of chemical bonds thus enhancing adhesion of a-SiC:H. However, despite the roughness of the substrate surface induced by sputtering, the a-SiC:H layer forms a very smooth surface structure as shown in Fig. 7.

3.3. *In vitro* results

3.3.1. Cytotoxicity

Fig. 8 shows the results of the cytotoxicity tests. The indices 0 to 5 symbolize gradual reactions from non-toxic (0 and 1) to a moderate toxicity (2 and 3) and toxic behaviour (4 and 5) of the test material to the L929 cells.

Amorphous silicon carbide did not show any cytotoxic reaction to mice fibroblasts L929, which was confirmed by the negative reaction of the saline reference. The $CuSO_4$-solution demonstrated the expected toxic reaction.

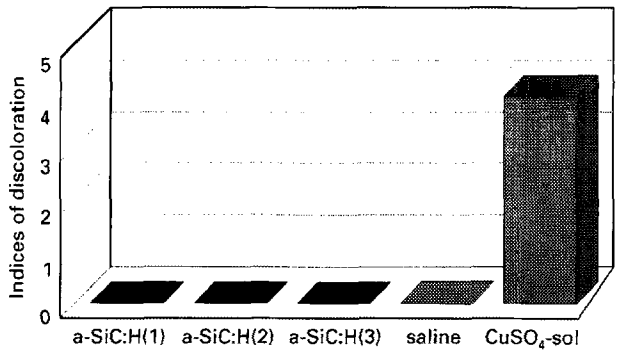

Figure 8 Index of discoloration representing the degree of cytotoxicity.

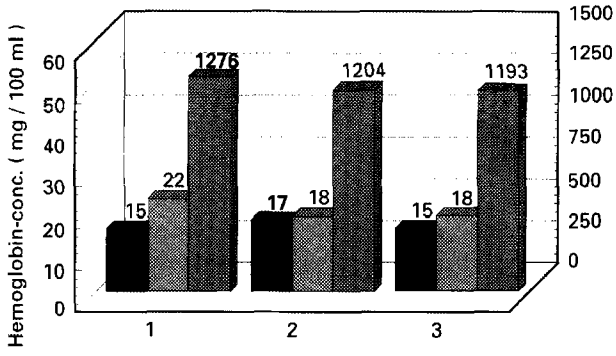

Figure 9 Concentration of hemoglobin indicating the degree of damage to erythrocytes: ■ a-SiC:H; ▩ saline; ▨ aqua dest.

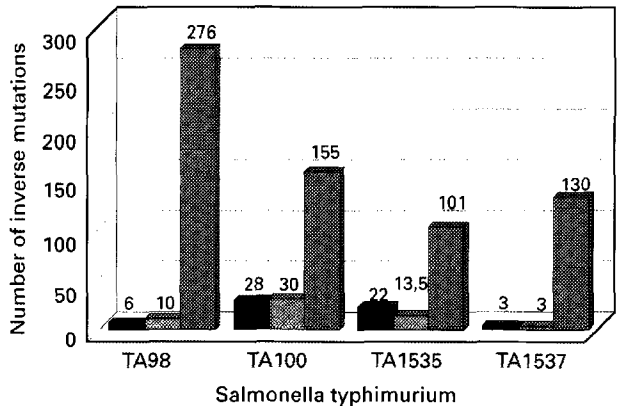

Figure 10 Mutagenicity of a-SiC:H: ■ a-SiC:H; ▩ saline; ▨ mutagenic solution.

3.3.2. Hemolysis

The degree of damage to erythrocytes was measured by the concentration of hemoglobin (Fig. 9).

Amorphous silicon carbide caused no damage to red blood cells. Its behaviour is similar to the saline reference.

3.3.3. Mutagenicity (Ames test)

The number of inverse mutations of *Salmonella typhimurium* as an indication of a material's mutagenicity is summarized in Fig. 10. The number of inverse mutations caused by a-SiC:H is comparable with the saline reference therefore indicating no mutagenic potential of a-SiC:H.

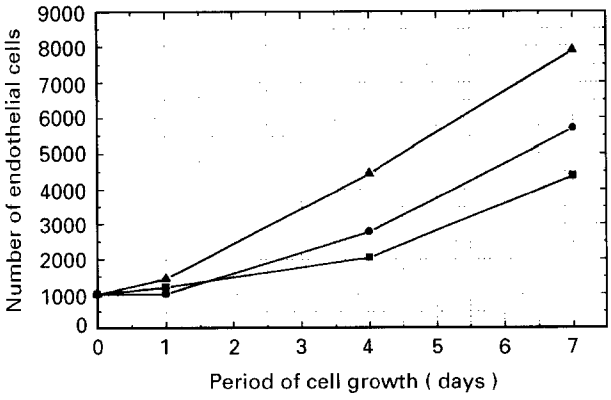

Figure 11 Growth of endothelial cells on a-SiC:H compared to reference materials: —■— a-SiC: H; —●— glass; ▲— polystyrene.

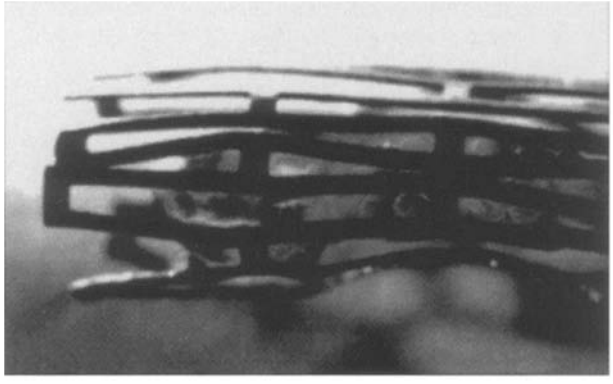

Figure 12 Image of an uncoated Palmaz–Schatz stent after perfusion for 90 min.

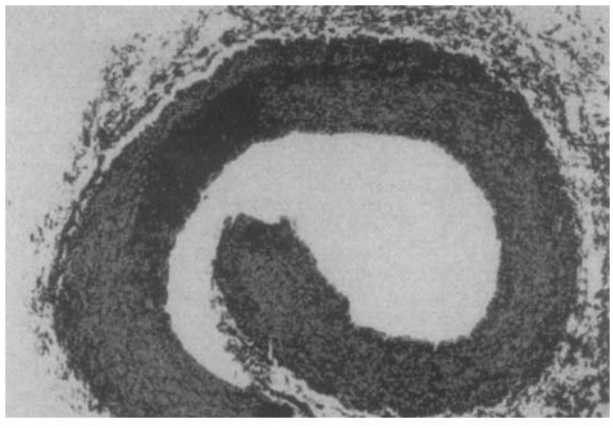

Figure 13 Scanning electron microscopy image of the surface of the a-SiC:H coated Palmaz–Schatz stent.

3.3.4. *Endothelial cell culture*

The growth behaviour of endothelial cells on a-SiC:H is shown in Fig. 11. The number of endothelial cells grown on a-SiC:H after 7 days was 55% of that grown on a polystyrene tissue culture.

3.4. *In vivo* behaviour of a-SiC:H

After removing the uncoated stent from the plastic tube, a large amount of adherent blood components and thrombus formation was verified by macroscopic investigation (Fig. 12). Compared with the uncoated stent, the a-SiC:H-coated stent surface showed no

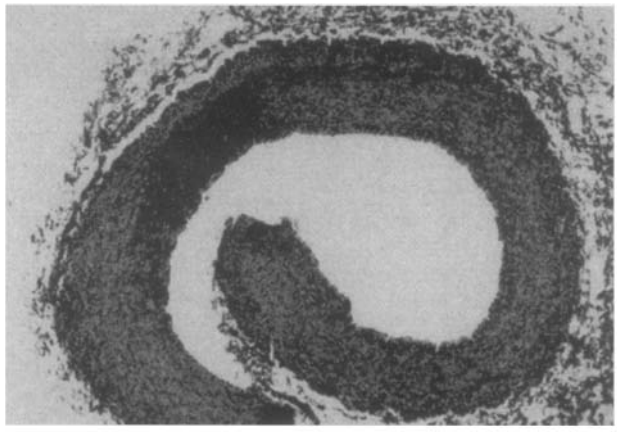

Figure 14 Histology of fibrin-coloured stented vessels with a-SiC:H coated Palmaz–Schatz stents (macroscopic overview).

Figure 15 Histology of fibrin-coloured stented vessels with a-SiC:H coated Palmaz–Schatz stents (section of Fig. 14).

further blood coagulation on its surface except one small thrombus (Fig. 13). Furthermore the strong adhesion of the a-SiC:H coating is confirmed because no spallations or other defect formations are visible despite the high dilatation ratio.

After a perfusion period of 3 days the lumina of all stented vessels remained open. The histological evaluation of the vessels with the silicon carbide-coated stents showed no signs of thrombus formation. This was verified by haematoxylin and fibrin colouring techniques in Figs 14 and 15 at higher magnifications.

However the histological examination of the uncoated Palmaz–Schatz stent showed proliferations of the intima, cell degenerations and localized thrombus formation. In Fig. 16a fibrotic layer as well as a completely destroyed intima was identified.

4. Conclusions

The new coronary stent consists of a hybrid design using different materials for the stent body and its surface. Each of these materials is optimized independently according to the specific requirements of the stent. The tantalum body comprises well-known mechanical properties with excellent radio-opacity. The amorphous silicon carbide coating prevents adversary effects to cells *in vitro* as well as damage to the sensitive endothelial cells of arterial vessels *in vivo*. The hemocompatibility of a-SiC:H is confirmed by the absence of any thrombus formation *in vivo*. The combination of the a-SiC:H coating on metallic substrates is realized by an optimized adhesion through an appropriate deposition technique.

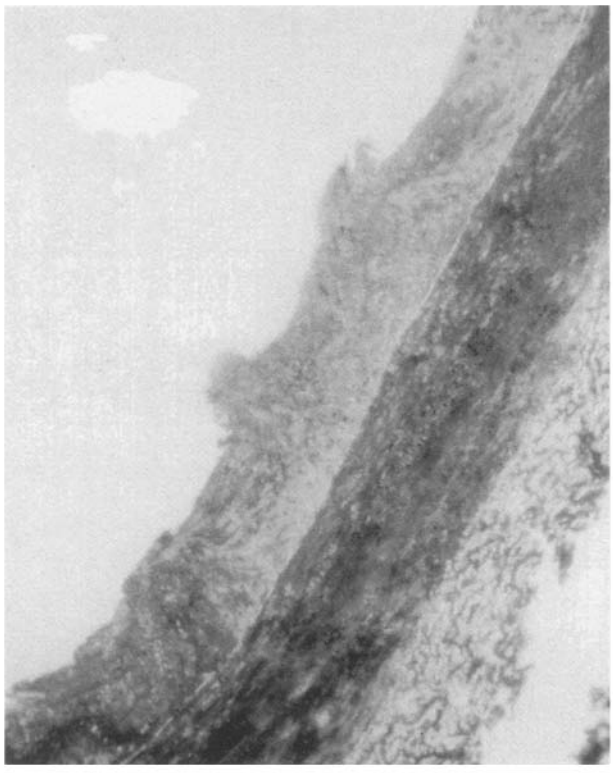

Figure 16 Histology of a vessel stented with a conventional Palmaz–Schatz stent.

Due to the specific advantageous properties of the applied materials, the new coronary stent improves stenting therapy.

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