

Arterial stenting with self-expandable and balloon-expandable endoprostheses

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Key words: arteries, coronary, grafts, pigs, prosthesis

Summary

Coronary angioplasty is complicated by acute occlusion (within 24 hours) and late restenosis (within 6 months) in 2–5% and 20–40% of the cases, respectively. Vascular endoprostheses (stents) may provide the cardiologist with a solution to some of these complications. Several stent-devices are now available for experimental and clinical evaluation. In this study we describe our experience with two metallic stents in normal arteries of swine.

Self-expandable, stainless steel stents (3.5 mm diameter) were implanted in 17 peripheral arteries, eight of which were deendothelialized by prior balloon angioplasty. Following implantation, the animals received antithrombotic therapy with acenocoumarol and aspirin (8 stents), or aspirin alone (9 stents). After 1 week repeat angiography was performed, which showed patency of all stented arteries. Microscopy showed complete covering by neointima, 80 μ m in thickness. This self-expandable stent (SES) and a balloon-expandable stent (BES), constructed of tantalum, were implanted in normal coronary arteries. SES (3.0 and 3.5 mm) receiving animals were treated with coumadines (10 stents) or received no antithrombotic treatment (16 stents) after implantation. BES receiving animals were also not treated (10 stents). Three untreated animals with SES died suddenly within 48 hours. Postmortem examination showed partial or complete thrombosis of all six stents in these animals, resulting in a patency rate of 62% after 1 week. All animals with SES, which were treated with coumadines, and all animals with BES (untreated) had patent stents after one week. It is concluded that SES implanted in normal coronary arteries of pigs, which do not receive additional antithrombotic treatment, show a 38% occlusion rate within 48 hours, but show 100% patency after 1 week, when the animals are treated with coumadines. BES implanted in normal coronary arteries of pigs, which do not receive antithrombotic drugs, are 100% patent after 1 week.

Introduction

The application of percutaneous transluminal coronary angioplasty (PTCA) for the treatment of atherosclerotic coronary artery disease has increased considerably in recent years. The initial success rate is high [1, 2], with an incidence of acute

or subacute occlusion at the site of angioplasty of 2–5% [3, 4]. Restenosis several months after the procedure occurs frequently with an incidence of 20–40% [5–7]. The effect of pharmacological therapy on acute complications [8–11] and late restenosis [12] is still unclear. The implantation of vascular endoprostheses was already attempted in the early

days of angioplasty for the treatment of procedure-related complications and the prevention of restenosis [13]. Narrowing of the stented segment caused by neointimal hyperplasia limited the use of these devices. Changes in design, the use of other metal alloys, and miniaturization of the endoprotheses has resulted in the availability of several types of stents for experimental and clinical evaluation [14–17]. Early experimental and clinical experience, however, indicates that the thrombogenic nature of most devices remains a concern [18, 19]. We therefore studied the short-term angiographic patency of two different stents in pigs, treated with different antithrombotic regimen.

Materials and methods

Description of the stents

Self-expandable stent (SES)

The SES used (Wallstent®, Medinvent SA, Lausanne, Switzerland) is a stainless steel, open-weave wire mesh. The wires are 80 µm in thickness. The elastic properties of this prosthesis are such that its diameter can be substantially reduced by elongation. It can thus be constrained on a small-diameter delivery-catheter (diameter catheter plus stent is approximately 1.6 mm), which consists of two coaxial catheters. The proximal regions of the two coaxial catheters are joined by an invaginated rolling membrane, which effectively retains the prosthesis. Withdrawal of the outer catheter rolls back the membrane progressively, thus releasing the stent, which tends to return to its original diameter, thereby anchoring itself against the arterial wall. The unconstrained diameters of the stents used in this study were 3.0 and 3.5 mm, with a length of 15 to 19 mm.

Balloon-expandable stent (BES)

The BES used (Wiktor®, Medtronic Inc., Minneapolis, USA) is constructed of a single tantalum wire, which is coiled in interdigitating loops. This prosthesis is crimped onto the balloon of a standard angioplasty catheter. The features of this prosthesis design are such that by inflating the balloon the

diameter of the stent increases without altering its length. The maximal diameter of the balloon after inflation determines the ultimate diameter of the prosthesis after implantation. One inflation at 8 Atm is sufficient to open the stent and allows the safe withdrawal of the deflated balloon. The balloon-diameters of the mounted angioplasty catheters used in this study were 3.0 and 3.5 mm, and the lengths of the prostheses 14–16 mm.

Application of the stents

Peripheral implantations of self-expandable stents

After an overnight fast 6 Yorkshire swine (18–25 kg) were sedated with 20 mg · kg⁻¹ ketamine hydrochloride. Following endotracheal intubation the animals were connected to a respirator for artificial ventilation with a mixture of oxygen and nitrous oxide (1 : 2). Anaesthesia was maintained with 1–4 vol% enflurane, while pancuronium bromide was used as a muscle relaxant. An 8F introduction sheath was placed via the left carotid artery in the descending aorta. After intravenous administration of 5,000 IU heparin and 100 mg aspirin, an 8F guiding catheter was advanced to the aorto-iliac bifurcation. After baseline angiography of both femoral arteries an angioplasty balloon catheter (balloon size 3.5 mm) was advanced over a long guidewire in the left femoral artery. From the angiograms, and using the diameter of the guiding catheter as a reference, a segment of the left femoral artery was chosen with a diameter of 3.0 mm.

Table 1. Diameters and numbers of self-expandable ('Wallstent') and balloon-expandable ('Wiktor') stents implanted in peripheral and coronary arteries of pigs. RCA = right coronary artery; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery.

stent type	stent diameter	n	artery
'Wallstent'	3.5 mm	9	right femoral
	3.5 mm	8	left femoral
'Wallstent'	3.0 mm	13	RCA 3, LAD 6, LCX 4
	3.5 mm	13	RCA 5, LAD 4, LCX 4
'Wiktor'	3.0 mm	6	LAD 4, LCX 2
	3.5 mm	4	RCA 2, LCX 2

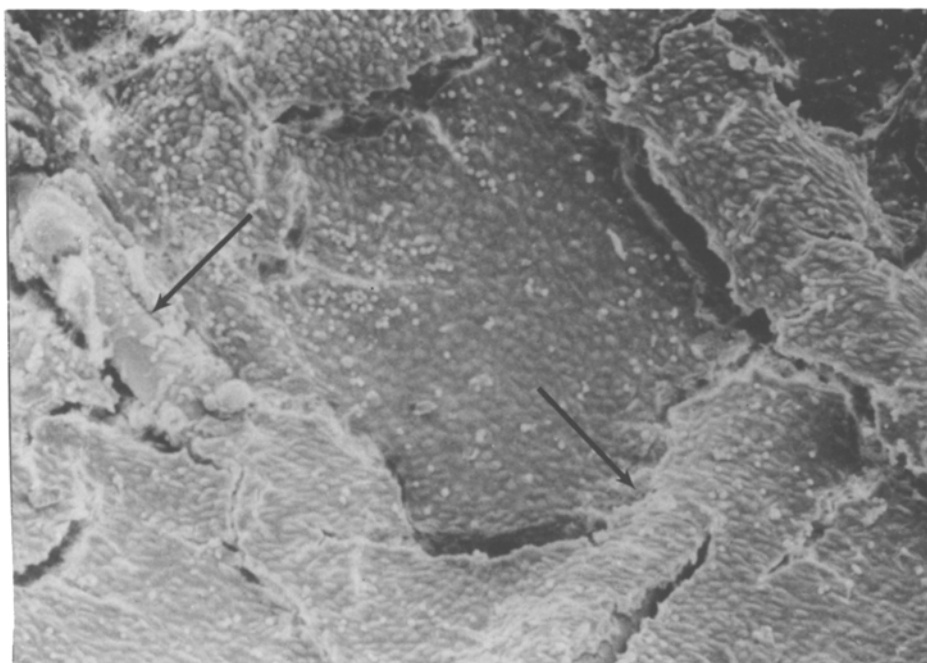


Fig. 1. Scanning electron microscopical picture (magnification 1,250 \times) of porcine femoral arterial segment 7 days after implantation of a SES. The wires (arrow) are covered with a continuous layer of spindle shaped endothelial cells. Fissures in the endothelial layer are caused by the preparation of the specimen.

At that point the angioplasty balloon was inflated twice for 60 s. at 10 Atm inflation pressure. Thereafter the angioplasty catheter was withdrawn, and angiography was repeated. A SES (unconstrained diameter 3.5 mm) mounted on the tip of the delivery catheter was positioned over the long guidewire at the dilated arterial segment. After the stent was released repeat angiography was performed. The same procedure was followed for placement of a stent in the right (contralateral) femoral artery, except for the fact that angioplasty was not per-

formed at this side. The catheters were removed, and the animals were allowed to recover from anaesthesia. After 6–10 days the animals were again anaesthetized and angiography of the stent-related arteries was performed. Immediately thereafter, the stent-containing arterial segments were perfused in vivo with saline (perfusion pressure 75 mmHg), removed and placed in buffered glutaraldehyde until preparation for microscopy. Thereafter the animals were sacrificed with an overdose of pentobarbitone sodium.

Table 2. Angiographic patency one week after implantation of stents in peripheral and coronary arteries of pigs, which received different antithrombotic treatment. ASA = acetylsalicylic acid; F/U = follow up.

stent type	treatment	n	F/U (days)	patency (%)
'Wallstent' (peripheral)	ASA/coumadines	9	6	100
'Wallstent' (coronary)	ASA	8	8–10	100
'Wiktor' (coronary)	–	16	7	62.5
'Wallstent' (peripheral)	coumadines	10	7	100
'Wiktor' (coronary)	–	10	7	100

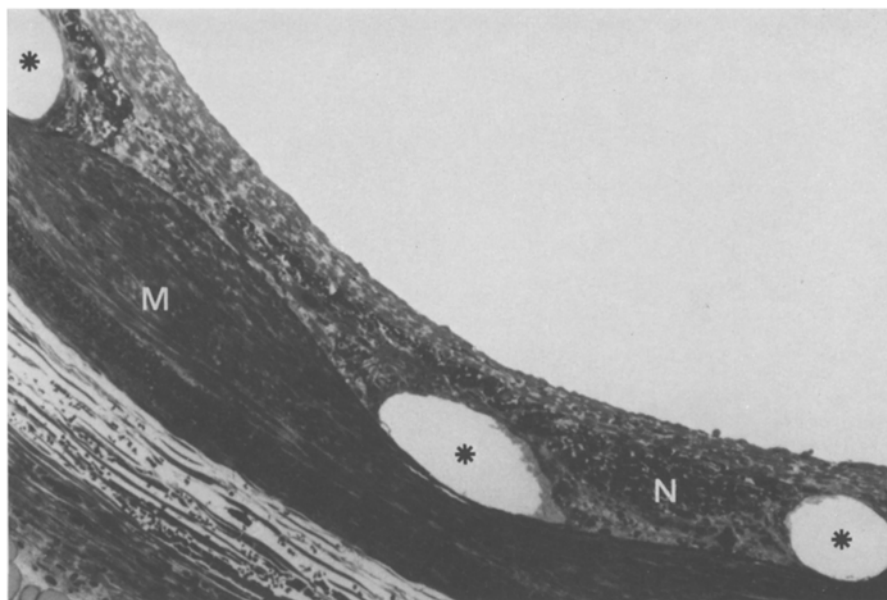


Fig. 2. Light microscopy of a porcine femoral artery 8 days after implantation of a SES (magnification 200 \times). The voids (asterisk) formerly occupied by the stent wires exert pressure to the media muscularis (M), and are covered by neointima (N).

Antithrombotic treatment after femoral implantation of self-expandable stents

Starting the day of the procedure two animals (8 stents) received daily calciparin 25,000 IU subcutaneously until oral acenocoumarol had prolonged the prothrombin time threefold. Aspirin 100 mg \cdot 24h $^{-1}$ intravenously was also added. The other four animals (9 stents) received only 100 mg of aspirin in one daily oral dose.

Coronary implantations with self-expandable stents

After an overnight fast 13 Yorkshire swine (40–46 kg) were sedated with 20 mg \cdot kg $^{-1}$ ketamine hydrochloride. Following endotracheal intubation, mechanical ventilation and anaesthesia as described above, a 9F sheath was placed via the left carotid artery in the ascending aorta. After intraarterial administration of 5,000 IU heparin, baseline coronary angiography was performed using an 8F guiding catheter. Using the diameter of the guiding catheter as a reference, two coronary segments with a diameter of approximately 2.5 and/or 3.0 mm were chosen from the angiograms

from two of the three major coronary arteries (left anterior descending coronary artery: LADCA; left circumflex coronary artery: LCXCA; right coronary artery: RCA). A SES, constrained on the delivery catheter, was advanced over a long guide-wire and positioned in one of the two selected coronary segments. After the stent was released, angiography was repeated to confirm its proper placement. The second stent was released in the other coronary segment. Stents with an unconstrained diameter of 3.0 mm were placed in coronary segments with a measured diameter of 2.5 mm, and those with an unconstrained diameter of 3.5 mm in 3.0 mm vessels. The number of stents, diameters and selected coronary arteries are summarized in Table 1.

After 7 days the animals were again anaesthetized and angiography of the stent-containing coronary arteries was performed.

Antithrombotic treatment after coronary implantation of self-expandable stents

Eight animals (16 stents) received no antithrombotic treatment after implantation. During one

week the other five animals (10 stents) received acenocoumarol, in a dose that lowered the Quick-test to less than 10% of normal, starting the day before the procedure.

Coronary implantations with balloon-expandable stents

After an overnight fast 5 Yorkshire swine (41–48 kg) were anaesthetized as described above. A 9F sheath was placed via the left carotid artery in the ascending aorta. After intraarterial administration of 5,000 IU of heparin, baseline coronary angiography was performed using an 8F guiding catheter. From these angiograms two coronary sites in two of the tree major coronary branches (LADCA; LCXCA; RCA) were chosen as described for the SES. Thereafter, a BES was placed at both sites as follows: the catheter with the stent crimped onto its balloon was positioned at a desired position, and the balloon was inflated for 30 s with an inflation pressure of 8 Atm. Stents mounted on a 3.0 mm balloon were placed in vessels with an approximate diameter of 2.5 mm, and stents mounted on a 3.5 mm balloon were implanted in vessels with a diameter of 3.0 mm. Stent diameters, numbers and selected coronary vessels are summarized in Table 1.

After 7 days the animals underwent repeat angiography under anaesthesia. Thereafter the thorax was opened by a midsternal split. The ascending aorta was cross clamped and 500 ml of saline, followed by 400 ml of a phosphate buffered mixture of 1% glutaraldehyde and 4% formaldehyde, was infused in the aortic root immediately above the coronary ostia at a pressure of 120 mmHg. The heart was excised, the coronary arteries dissected out, and placed in 4% formaldehyde and 1% glutaraldehyde in phosphate buffer (pH 7.3) for at least 48 hours until preparation for microscopy.

Antithrombotic treatment after coronary implantation of balloon-expandable stents

Antithrombotic drugs were not administered after the implantation of the BES.

Microscopical examination

After fixation, the stent-containing arterial seg-

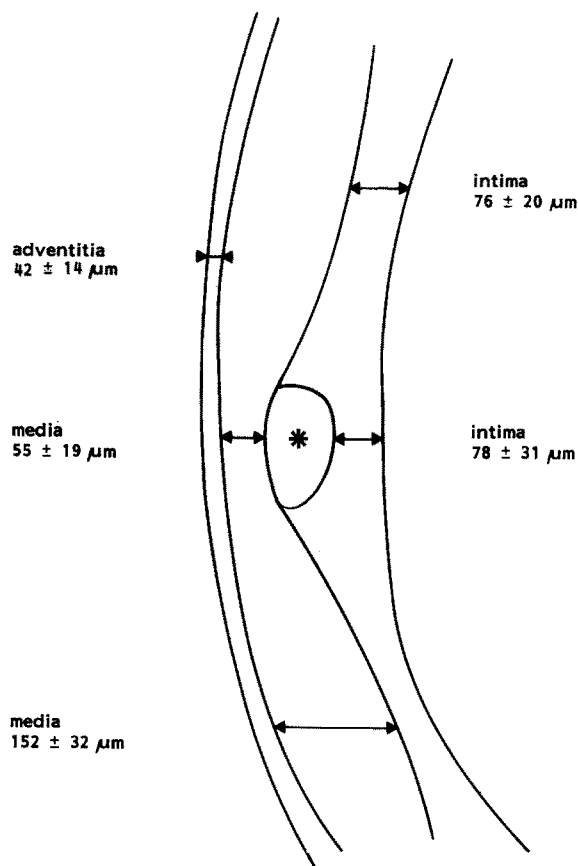


Fig. 3. Schematic drawing of a section of a stented porcine artery (e.g. as in Fig. 2). The average values of the measurements of the layers of 4 porcine femoral arteries 6–10 days after placement of a SES are included.

ments were divided lengthwise into two equal parts using a pair of fine scissors. From one half of each vessel the stent wires were removed. Both halves were washed in 0.1 M cacodylate buffer (pH 7.3), postfixed in 1% osmium tetroxide and washed overnight in 0.1 M cacodylate. The specimen were placed in 1% tannic acid for 60 min, 1% Na₂SO₄ for 10 min and again washed in 0.1 M cacodylate buffer. The half of the vessel containing the stent wires underwent dehydration in graded ethanol and critical point drying with liquid CO₂. This part of each vessel was mounted on a specimen table and sputtercoated with gold before examination in a scanning electron microscope (ISI-DS-130). The other half was dehydrated in graded acetone and embedded in Epon. After sectioning and staining trans-



Fig. 4. Angiogram of the right coronary artery of a pig 7 days after implantation of a BES. The fine arrows indicate the stented coronary segment, which appears patent without narrowing of the lumen. The solid arrow marks a clearly visible stent in the LADCA.

mission microscopy was performed using a Zeiss light microscope and a Philips EM 400 electron microscope.

Results

Peripheral implantations of self-expandable stents

One femoral artery (6%) showed complete occlusion after balloon-denudation, and could not be reopened by the intraarterial administration of isosorbide dinitrate. As a result, 9 stents were placed in right femoral arteries (without angioplasty) and 8 stents in left femoral arteries (after angioplasty). After 6–10 days all stent-containing arteries were angiographically patent, without signs of stenosis or intraluminal defects (Table 2). This means that

all stents were patent, irrespective of earlier endothelial damage or the addition of coumadines to aspirin. Scanning electron microscopy showed that all stents were covered by an endothelial lining as early as 6 days after implantation (Fig. 1). Transmission microscopy showed that the stent wires were incorporated in the arterial wall and covered by a neointima (Fig. 2). Measurement of the arterial layers showed that the media was considerably compressed at the site of the wires (Fig. 3). Median thickness of the neointima on top of or between the wires was $80\ \mu\text{m}$ (range $50\text{--}125\ \mu\text{m}$).

Coronary implantation of self-expandable stents

Three of the 8 animals (6 stents) which did not receive additional anticoagulant treatment, died

suddenly within 48 hours after implantation. Post-mortem examination showed partial or complete thrombotic occlusion within all 6 stents. The other 5 animals in this group survived, and repeat angiography after 1 week revealed normal patency of all 10 stented coronary arteries in these animals (Table 2). All 5 animals (10 stents), which received anti-thrombotic prophylaxis with coumadines survived. Repeat angiography in this group after 1 week revealed normal patency of all stented coronary segments.

Coronary implantations of balloon-expandable stents

All 5 animals, which received a total number of 10 BES, survived for one week. Repeat angiography at this time showed normal patency of all stented coronary arteries, without signs of intraluminal defects (Table 2; Fig. 4).

Scanning electron microscopy revealed that the stent wires were completely covered by normal appearing endothelium after 1 week (Fig. 5). Furthermore, the luminal surface of the arteries showed corrugation between the stent wires. Transmission microscopy of the stented segments confirmed the incorporation of the stent in the wall of the coronary arteries, and considerable compression of the arterial media.

Discussion

Metallic vascular endoprostheses are currently under investigation in the coronary arterial tree of experimental animals and man. The most important limitations of its widespread use in clinical practice are thrombogenicity and restenosis in the stent due to neointimal hyperplasia. The most promising clinical indications seem to be implantations in stenosed aortocoronary venous bypass grafts or when used as a 'bail-out'-device for acute occlusion after angioplasty [20–22]. Turbulent flow, exposure of the subendothelium and accumulation of prothrombotic factors require, however, that a stent-device is athrombogenic. Stainless steel

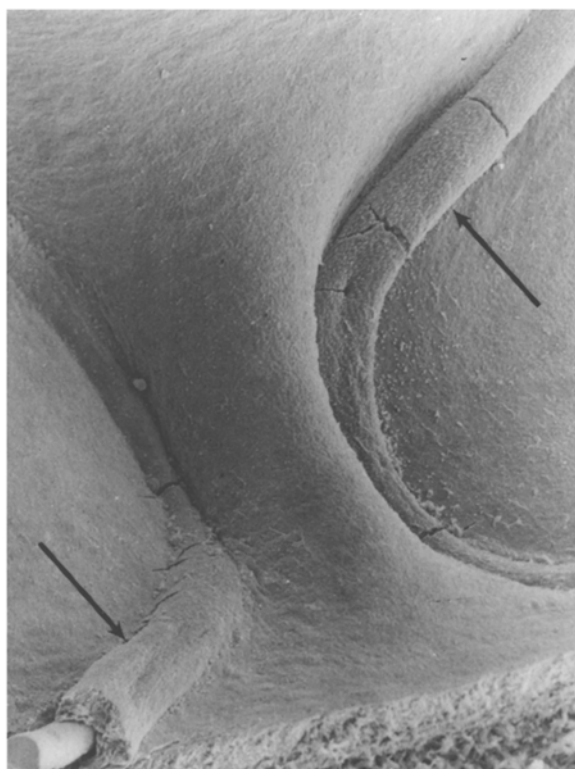


Fig. 5. Scanning electron micrograph (magnification 75 ×) of a segment of a left circumflex coronary artery 7 days after implantation of a BES. The stent wire (arrows) is completely covered with an endothelial lining.

is not the material of choice for use in such a situation. Physicochemical and biological surface modification of the stent-wires may provide a solution [23, 24], but up till now these attempts have not been fruitful.

Stent implantation in the native coronary circulation immediately after angioplasty for the prevention or treatment of restenosis seems less promising than originally envisaged [15]. Although the stent improves the immediate post-dilatation result [25–27], restenosis within the stented segment occurs frequently [20, 28, 29]. The present study describes for the first time an attempt to compare two stent-devices in the same animal model and in the same laboratory. Results suggest that the stainless steel self-expandable stent may be more thrombogenic than the tantalum balloon-expandable stent. As both devices are covered by endothelium within

7 days, the need for additional antithrombotic treatment may be of short duration. However caution is required when interpreting the results of the present study. Apart from the metallic composition and the mode of delivery to the coronary arterial tree, many other variables are present between the devices. For instance the significance of wire thickness, density of the mesh or loops, and active or passive radial force after placement are not known.

Acknowledgements

The authors wish to thank Mrs Marjo van Ee for her secretarial assistance in the preparation of this manuscript, and Mr. B. Klazema (General Electric Plastics, Bergen op Zoom) for the use of the scanning microscope. This project is supported by the Netherlands Heart Foundation under grant no. NHS 88.077.

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