Review

Are resorbable implants about to become a reality?

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RESORBABLE IMPLANTS ARE AVAILABLE, WE implant them every day. To date, there is no permanent material which is also chemically inert used for biomedical implants. Degradation, most often due to corrosion of the implant, has been demonstrated in an abundance of alloys used for various applications. The accumulation of compounds of alloys from the implants in the surrounding tissue has been demonstrated for those used in orthodontics, orthopaedic, and cardiovascular practice.[1–8] It was the observation of total decomposition, such as occurred after implantation of tungsten coils, which further elucidated the fact that corrosion is a major problem for implants inserted in the cardiovascular system.[9]

When searching for biodegradable implants suitable for cardiovascular purposes, therefore, it is the kinetics of degradation of the alloy used to make the implant which should be the focus of attention. Biodegradation, in this respect, would stand for the timely degradation of an implant after it has fulfilled its mission at the site of implantation.

To date, however, there is no detailed information available regarding the length of time a cardiovascular implant needs to maintain its integrity. The site of implantation, and the pathophysiology of the obstruction, will be the determinants for the desired rates of degradation. Degradation of stents has to be planned in accordance with the cause of the obstruction. It is obvious, for example, that external compression is not

the setting for a biodegradable stent. For stenoses occurring after previous surgical procedures, we currently do not know how long the stent needs to maintain its mechanical integrity so as to prevent further restenosis of the vessel. Detailed knowledge from histological experimental studies, as well as from intravascular ultrasonic studies, exists on the time course of endothelialization of stents implanted in vascular obstructions.[10] Degradable devices used to close septal defects may decompose after complete ingrowth of the device, or complete cellularization of the matrix. Cellularization of such devices has been studied in experimental animals, and after removal of devices implanted in humans.[11–14] From those studies, ingrowth of the device can be anticipated to be completed after a period of 3 to 6 months.

Why search for degradable implants?

Most devices and stents used in interventional applications serve a temporary purpose dictated by the purpose of the implantation. In the setting of interventional closure of atrial and ventricular septal defects, the device serves as a matrix for autologous cells. After overgrowth of the device covering the defect, a stable layer of cells is formed, and the matrix is no longer needed. Interference with the surrounding tissue, however, is known to occur after non-degradable devices are inserted to close atrial septal defects. After such closure, the interaction of the device with the surrounding tissue has been found to lead to perforation of either the atrial wall or the aortic root.[15,16] Especially in defects with a deficient aortic rim, the compression of the aortic root may result in geometrical changes that may lead to aortic regurgitation.

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Stents serve a temporary purpose if they are implanted in stenoses not due to compression or distortion of the treated vessel. If stents are implanted with the indication of treating surgical or native stenoses, they can avoid recoil of the vessel, and thereby prevent early restenosis. They do interfere, nonetheless, with the positive remodelling of the vessel.[17] Insertion of a permanent implant can negatively interfere with that process of remodelling, and lead to restenosis within the stent itself due to inflammation and neointimal proliferation.[18] Despite the possibility of adapting the diameter of the stent to the growth of the vessel by re-dilation,[19,20] implantation of stents in children is currently limited by the maximal diameter that can be achieved after re-dilation to avoid fixed obstruction of the growing vessel. Stents are currently implanted, therefore, only if it is possible to re-dilate to the dimensions of the receiving vessel as anticipated in adult life, or if the stents are used as a final resort in palliative situations. Were they available, degradable stents would allow for alternative therapeutic strategies, for example in neonates with native aortic coarctation. Restenosis angioplasty in this group was reported to be high after balloon angioplasty. Because of this, surgery has become the recommended treatment.[21] Degradable stents would be able to address the issue of early restenosis after balloon angioplasty. Furthermore, by limiting the injury produced by overstretch, and by serving to attach intimal flaps to the vessel wall, implantation of stents into the coarcted aorta has the potential to reduce the risk of postinterventional formation of aneurysms.[22] If, after their degradation, residual stenosis would necessitate further therapy, implantation of a still larger degradable stent would allow us to keep these patients out of the operating theatre. Another potentially beneficial aspect of degradable stents is the lack of negative interference with potential subsequent surgery of the stented vessels.

Having the potential to deliver drugs locally, biodegradable stents could also be used during the process of decay of the carrier. Stents produced currently with the capability of delivering drugs locally are produced with a sandwich technique, most frequently with a degradable polymer cover that carries the drug.[23] This technique itself produces problems. During expansion of the stent, the polymer cover becomes loose, giving the stent a rough luminal surface. Release of pro-inflammatory debris from the polymeric coating, with a subsequent hypersensitivity reaction, has been shown to result in late thrombosis of the drug-eluting stents.[24,25] Prolonged and aggressive antithrombotic treatment is then needed to decrease the risk of acute and late thrombosis, particularly since cellular passivation of the surface is slowed by adding anti-proliferative drugs.[26]

Historical review

Biodegradable implants produced from polymers

In the early 1990s, biodegradable polymers were studied extensively for use in coronary arterial stents. It was Stack et al.[27] who were the first to report the use of a woven poly-l-lactide stent in an experimental setting, the so called Duke-stent. The stent had an excellent profile of collapse under pressure, and the authors reported complete degradation after 9 months. Although no significant adverse events were observed in their study using animals, there were no clinical applications. After this pioneering work, others evaluated the use of different polymers. Polyglycolic acid was studied by Susawa et al.[28] in a canine model, but was complicated by deposition of thrombus. Van der Giessen et al.[29] then evaluated different degradable and stable polymers in a porcine coronary arterial model. They encountered a massive inflammatory response of the artery subsequent to the implantation of various biodegradable polymers. It was not before Tamai et al.[30] reported their successful implantation of a self-expanding stent into humans with coronary atheroma that the concept of biodegradable stenting was transferred into clinical practice. The Tamai stent is a coil composed of a poly-l-lactic acid monofilament with a molecular mass of 183,000 Dalton. Visibility of the stent is achieved by two gold markers that label its proximal and distal parts. It expands by infusion of hot contrast medium at a temperature of 80 degree Celsius. Expansion is uncontrolled, and is characterized by equilibrium of the forces of recoil of the vessel and expansion of the stent. Since the original report, however, there have been no publications on future applications of the Tamai stent. Nor has there been any report on the long term follow-up of the initial patients treated.[30] It is suspected, therefore, that long-term results were not encouraging, and that the concept of biodegradable stenting with the Tamai stent had to be abandoned. Interestingly, the characteristics of degradation of the stent were not reported prior to the clinical trials, and still remain to be defined.

The characteristics of expansion of biodegradable polymeric stents, nonetheless, have been studied by Venkatraman et al.[31] Their study revealed that such biocompatible polymeric stents as currently available lack a force of expansion sufficient to cope with surgical lesions such as might be encountered in patients with congenital cardiac malformations. It remains uncertain, therefore, whether polymeric stents will have a role for future treatment of patients with congenital cardiac anomalies.

Corrosion of metallic cardiovascular implants

None of the currently available material used to construct cardiovascular implants can be considered chemically inert. Corrosion was proven for a variety of different alloys used in cardiovascular applications. For example, stainless steel of category 316 of the American Iron and Steel Institute shows corrosion in a saline environment.[6] The same holds true for superelastic nitinol alloys.[8] Profound knowledge exists on the behaviour of corrosion and biocompatibility of tungsten used for the production of microcoils. Although complete dissolution was observed 2 years after implantation, and elevated levels of tungsten were found in the serum and urine of these patients during follow-up, there were no reports of clinical problems related to the elevated levels.[9,32–34]

Present state and clinical indications

Recent research has focused on corrosion as a principle for biodegradation of cardiovascular implants. As stated above, all alloys currently used for cardiovascular implants show varying degrees of corrosion in a saline environment. The kinetics of corrosion, however, are slow and, apart from tungsten coils, have not been shown to result in a complete decomposition of the implant.

Those seeking to produce implants which are biodegradable by means of corrosion have used non-toxic elements in the alloys, hoping to produce timely corrosion of the implant after incorporation at the site of implantation. Efforts are made to modify the kinetics of degradation by modification of the surface and composition of the alloys. Two basic metals have so far been used as the basis of corrodible stents, namely iron and magnesium.

Pure iron stents have been tested in a design for coronary arteries,[35] as well as for use peripherally. Degradable stents produced from magnesium-based alloys, with varying additional elements used in the alloy, have been tested for small peripheral vessels,[36] and for stenting coronary arteries in the experimental setting.[37] Currently, patients are being recruited for fist clinical trials with coronary arterial stents made of magnesium.

Iron-based alloys

Iron was the first metal to be studied as a corrodible implant.[35] The profound knowledge on uptake, transport, and excretion of iron in the intact organism makes it attractive for degradable cardiovascular applications. Furthermore, iron shares a number of mechanical features with other alloys currently available for making stents, like stainless steel classified as 316-L by the American Institute of Iron and Steel.

Iron is an essential element. In adults, the total content is from 4 to 5 grams, with seven-tenths being bound to haemoglobin. The daily loss is about 1 milligram in men, and 2 milligrams in females, mostly due to epithelial loss via desquamation of the intestine or skin, and through menstrual losses in women. Iron cannot be actively excreted. The regulation of homeostasis, therefore, is dependent on the regulation of its intestinal resorption. Elementary iron is known to have a low toxicity, since its rate of corrosion is rather slow, and the release of ferric and ferrous ions is low.

After resorption from the intestinal mucosa, ferric iron is oxidized immediately by the copper-dependent enzyme ferrioxidase, also known as Coeruloplasmin, to its ferrous form. It is then bound to plasmatic transferrin. The total iron-binding capacity of transferrin is from 280 to 400 micrograms for each 100 millilitres of plasma. In an adult, the total iron-binding capacity is up to 12 milligrams of iron. Usually, only one-third of the total transferrin is saturated with ferrous iron. If the total iron binding capacity of transferrin is reached, ferrous iron will bind loosely to plasma proteins, predominantly to albumin. In this bound form, iron cannot be eliminated by excretion via the renal system. Only if chelate-building agents are used to force iron out of the protein binding can it be excreted renally. Parenteral substitution, and use of iron-releasing implants, therefore, should be aimed at a slow release of iron in order to prevent complete saturation of transferring, with the subsequent risk of toxicity.

A coronary arterial stent made of iron weighs about 40 milligrams, with a peripheral stent weighing around 250 milligrams. Considering the rates of degradation as described below, systemic toxicity is not to be anticipated even after the implantation of multiple stents.

Composition and material scientific description of the iron stent

Initial laboratory studies were performed with pure iron, with less than 1% belonging to minimal contamination by the elements Aluminum, Calcium, Cobalt, Chromium, Manganese, Nickel, Selenium, Carbon and Sulphur. At the given concentrations in the stent, systemic toxic side effects cannot be expected due to the release of these ions even after complete degradation of the implant.

The stents are manufactured in 2 different designs, similar to commercially available stents from Devon Medical and Bard. They are cut by laser in a "slotted tube" design, and electropolished to achieve a thickness of the struts of 80 micrometres for the coronary arterial stent, and 120 micrometres for the peripheral
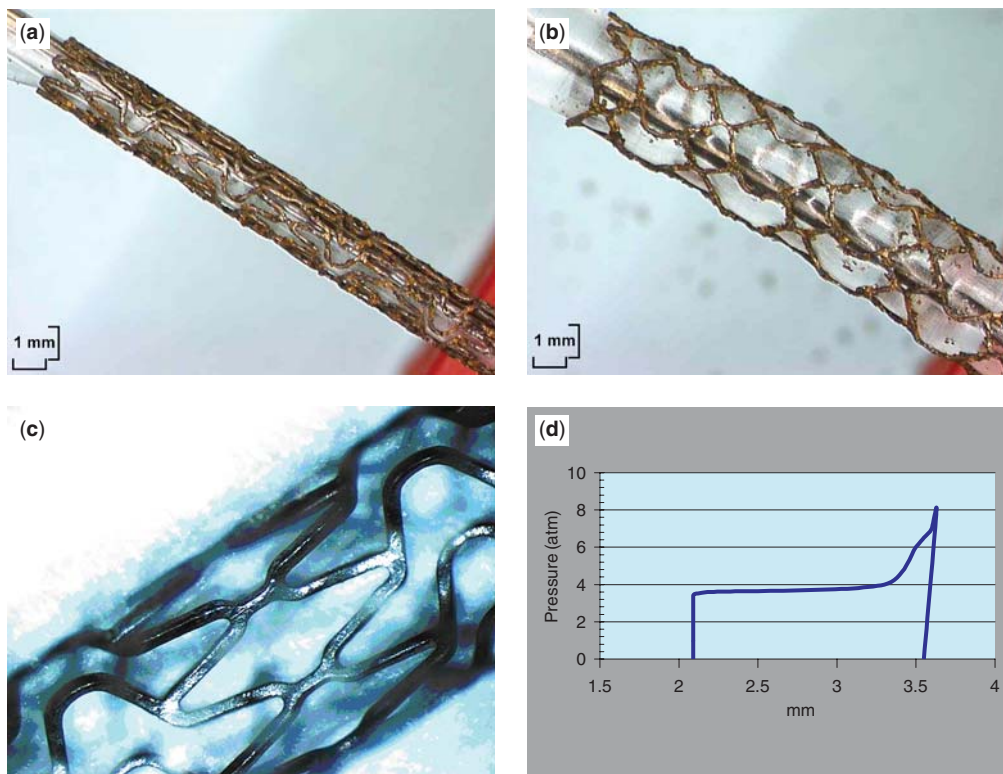
Figure 1.

A corrodible iron stent crimped on a coronary angioplasty catheter (a) and after inflation to 3.5 millimetres (b). Since the stent was not stored in protective gas, there is accumulation of corrosion products surrounding the struts. After laser-cutting and electropolishing, the stent shows no corrosion and a smooth surface (c). The dilation-pressure curve shows a recoil of the stent of 2.2%, and an opening pressure of approximately 4 atmospheres (d).

stent. Elastic recoil of the stent was evaluated in bench tests, and found to be 2.2% (Fig. 1).

Corrosion and biocompatibility of iron-based stents

To evaluate the rates of degradation in a standard setting, iron samples with a diameter of 26 millimetres and a thickness of 0.91 millimetres were placed in an electrolytic solution and incubated under continuous stirring at a constant temperature of 37 degree Celsius for 2 weeks. After short intervals of time, electrolyte samples were examined by inductive coupled plasma atomic emission spectroscopy to determine the concentration of iron. The calculations (Fig. 2) revealed a loss of 15% of mass of an iron chip cut from iron foils after 1 week's incubation in human serum, and of 20% after incubation in 0.9% salt solution.

Experimental studies with iron stents

In vitro cell cultural and proliferation assays. To assess biocompatibility in the cardiovascular system, chips with a diameter of 10 millimetres diameter, and a thickness of 0.2 millimetres, were evaluated in cell culture and metabolic assays, and did not show any
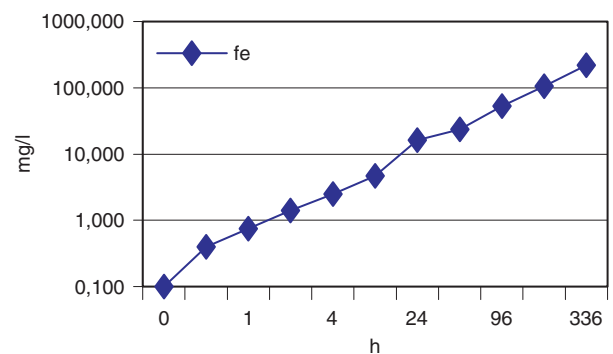
Figure 2.

Accumulation of iron ions after incubation of an iron sample with a diameter of 26 millimetres and a thickness of 0.91 millimetres in Ringer's solution at 37 degree Celsius. There is rapid accumulation of iron in the electrolyte.

toxicity on either human vascular endothelial cells or human fibroblasts. There was a confluent growth of the tested cells on the surface of the probes, and vitality was confirmed by staining. Human vascular smooth muscle cells, however, showed decreased growth after incubation with iron samples. It was speculated that decreased proliferation of smooth muscle cells could decrease the incidence of neointimal
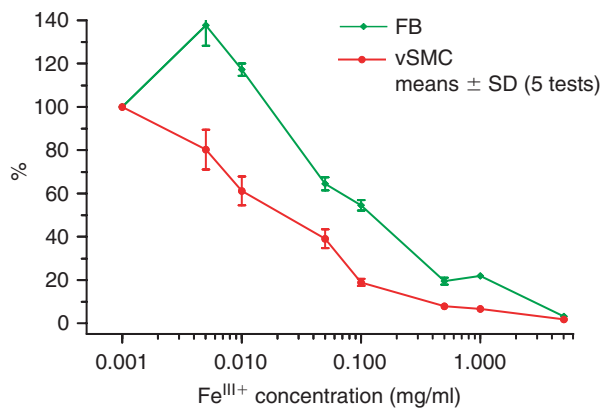
Figure 3.
Results of metabolic activity assays (WST, Roche) after incubation of human fibroblasts and human vascular smooth muscle cells with varying concentrations of ferrous iron in the growth medium. The cells show a reduced metabolic activity compared to control cells at 100-fold elevated serum concentrations.
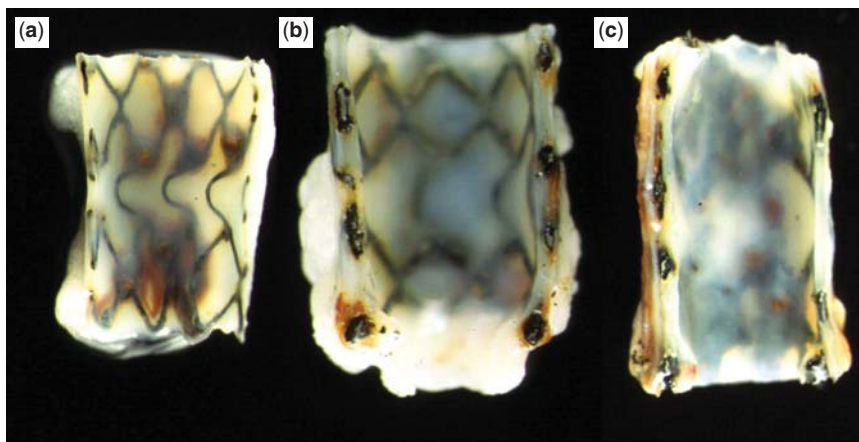

Figure 4.
The macroscopic aspect 12 months after implantation of a corrodible iron stent (left) and an American Iron and Steel Institute 316-L control stent (right) into the descending aorta of a minipig. There is no macroscopic pathology. Vascularization seems to be more pronounced on the adventitial side at the region of the iron stent.

proliferation after implantation of a stent. This hypothesis was tested in the in vivo experiments described below.

Using assays of cellular proliferation, toxic thresholds were determined using different concentrations of irons in the growth medium of human vascular cells. It was demonstrated that physiologic concentrations in the serum can be elevated to 100-fold before they result in decreased metabolic activity of human endothelial cells, human fibroblasts, and human smooth muscle cells (Fig. 3).

In vivo studies of a coronary arterial stent in the descending aorta of rabbits. The first studies to evaluate the safety of a corrodible iron stent were conducted in the descending aorta of rabbits. The iron stents, produced in a design similar to the commercially available stent from Devon Medical, Germany, were manually crimped on coronary angioplasty catheters with a balloon diameter of 3.5 to 4.0 millimetres, giving a mean ration of the diameter of the balloon to the diameter of the descending aorta of 1.13, with a range from 1.09 to 1.18. Angiography after the implantation of the stents showed patency of the descending aorta in all animals, with no signs of intraluminal defects or dissection of the vessel wall. The animals were followed for a period of up to 18 months. There were no deaths during the study period, and no signs of clinical pathology in any of the rabbits. Angiography 6, 12 and 18 months after the implantation demonstrated complete patency of the descending aorta in all, with no obstruction or thrombosis at the site of implantation. Compared to the native descending aorta, the loss of luminal diameter or area was less then 10%. Macroscopic evaluation of the stented vessels demonstrated a continuously smooth and intact endothelial surface, without evidence of formation of thrombus. Pronounced accumulation of degradation products was seen at the junctions of the struts, which led to a slight elevation of the vessel wall, and a focal discoloration of the intima. Histologically, degradation of the iron struts was revealed by loss of distinct border lines. The inflammatory reaction was variable within and between the animals independent of the thickness of the struts and the time of follow-up. Accumulation of iron-laden macrophages and multinucleated giant cells ranged from a sparse isolated localization to accumulation in clusters. Macrophages with brownish pigments were often found within the adjacent media and/or the fibrous adventitia of the aorta.

In vivo studies of a peripheral iron stent in the porcine descending aorta. The safety of a degradable iron stent with a similar design to the commercially available peripheral stent made by Bard has been tested over a period of 12 months in minipigs. Iron stents were implanted into the descending aorta, with a mean ratio of balloon to vessel of 1.2, and a range from 1.1 to 1.4 (Fig. 4). Follow-up angiography was performed at 30, 90, 180 and 360 days. There was no thrombosis observed, and all the stents were patent. Quantitative angiography demonstrated no loss of luminal area up to 90 days. After 180 days, the median loss was around 10%, and reached up to 25% after 360 days. No significant difference was found between stents made of stainless steel conforming to classification 316-L of the American Iron and Steel Industry or those made of iron with regard to neointimal proliferation. No serious adverse events were encountered during the period of follow-up. Degradation was evident by progressive loss of integrity of the stent incorporated into the vessel wall (Fig. 5)

Figure 5.
*Macroscopic aspects of the corrosion process after implantation into the descending aorta of minipigs after 3 (**a**) 6 (**b**) and 12 (**c**) months. At 3 months, the struts of the stent are clearly visible, with corrosion plaques limited to the intersections. At 6 months, there is progressive loss of structure, and accumulation of corrosion products in the wall of the stented vessel. After 12 months, there is loss of integrity. The stents are completely covered with a thin layer of neointima without excessive proliferation.*

Magnesium-based alloys

Magnesium is an attractive material for biodegradable implants because of its low thrombogenicity and well-known biocompatibility. It is an essential trace element, and the daily recommended intake is 6 to 10 milligrams per kilogram body weight. The body stores a total of 20 to 28 grams, and the normal concentration in the serum is from 0.5 to 1.3 millimols per litre. Systemic toxic effects can be expected when the concentration in the serum is from 7 to 10 millimols per litre. Magnesium has vasodilator effects, is a cofactor of adenosintriphosphatase, and acts as a physiologic antagonist of calcium, thereby preventing intracellular overload in ischaemic settings. Its low thrombogenicity is due to its fibrinolytic and anticoagulative properties.

Composition of magnesium alloys used in cardiovascular applications. Initial studies with Magnesium based alloys were performed by Heublein et al.,[37] who used the alloy "AE21" for the production of a biodegradable metal stent. Later work, and the first human trials, were performed with the Magic stent, made by Biotronik, which consists of an alloy containing magnesium, zirconium, yttrium and lanthanides. Since the exact composition of the stent is not disclosed by the company, neither its potential toxicity nor its degradation products can be determined, and we have to rely on the biocompatibility testing carried out by the manufacturers.

Material scientific description of the magnesium stent. Untreated magnesium alloys are very brittle, thereby interfering with the plastic deformations occurring during implantation of the stent. During drawing of the tube from the extruded alloy bar, thermic treatment is added to increase the ductility of the tube during drawing, and of the stent during expansion. The magnesium stent is currently available in a design for coronary arteries that was specifically developed by finite element analyses to account for the plastic deformations during implantation. By applying a specific design, the stress on the implant is distributed equally, with anticipated reduction in the incidence of fractures. The surface is finished by electropolishing, leading to a smooth and atraumatic surface (Fig. 6).

Corrosion and biocompatibility of magnesium-based alloys. In a salinic environment, magnesium-based alloys will show degrade to magnesium chloride, oxide, sulphate, or phosphate. A single coronary arterial stent has a content of approximately 3 to 6 milligrams of magnesium. Given the above physiological data, complete degradation releases about 1% of the recommended daily intake of magnesium for a normal adult. Since degradation occurs over a period of months, the release of the magnesium incorporated in the stent should not negatively interfere with the body as a whole, Local effects have also to be considered. Concentrations of magnesium in the tissue surrounding the stent might be much higher, and may interfere with cellular physiology of endothelial cells as well as smooth muscle cells. To date, there has been no evidence for such toxicity in ex vivo experiments with human vascular endothelial and smooth muscle cells incubated with magnesium salts at high concentrations.

Aluminum has a well known toxicity which is dose-dependent. Normal levels in the serum vary from 0.5 to 10 microlitres per litre. Toxic effects can be expected at a concentration of 100 micrograms per litre, while encephalopathy and osteodystrophic findings can be expected from 250 micrograms per litre.

Little is known on the effects of the compounds of the alloys besides magnesium and aluminium. Rare earth metals have not been tested concerning their biocompatibility after intravascular application. The dosage after oral intake of such elements with no clinical effects was found to be as high as 60 milligrams per kilogram body weight.[38] Zirconium and yttrium are not thoroughly evaluated concerning their biocompatibility. Yttrium has only been tested as radiolabeled pharmacon, or in dental ceramics with zirconium.[39]
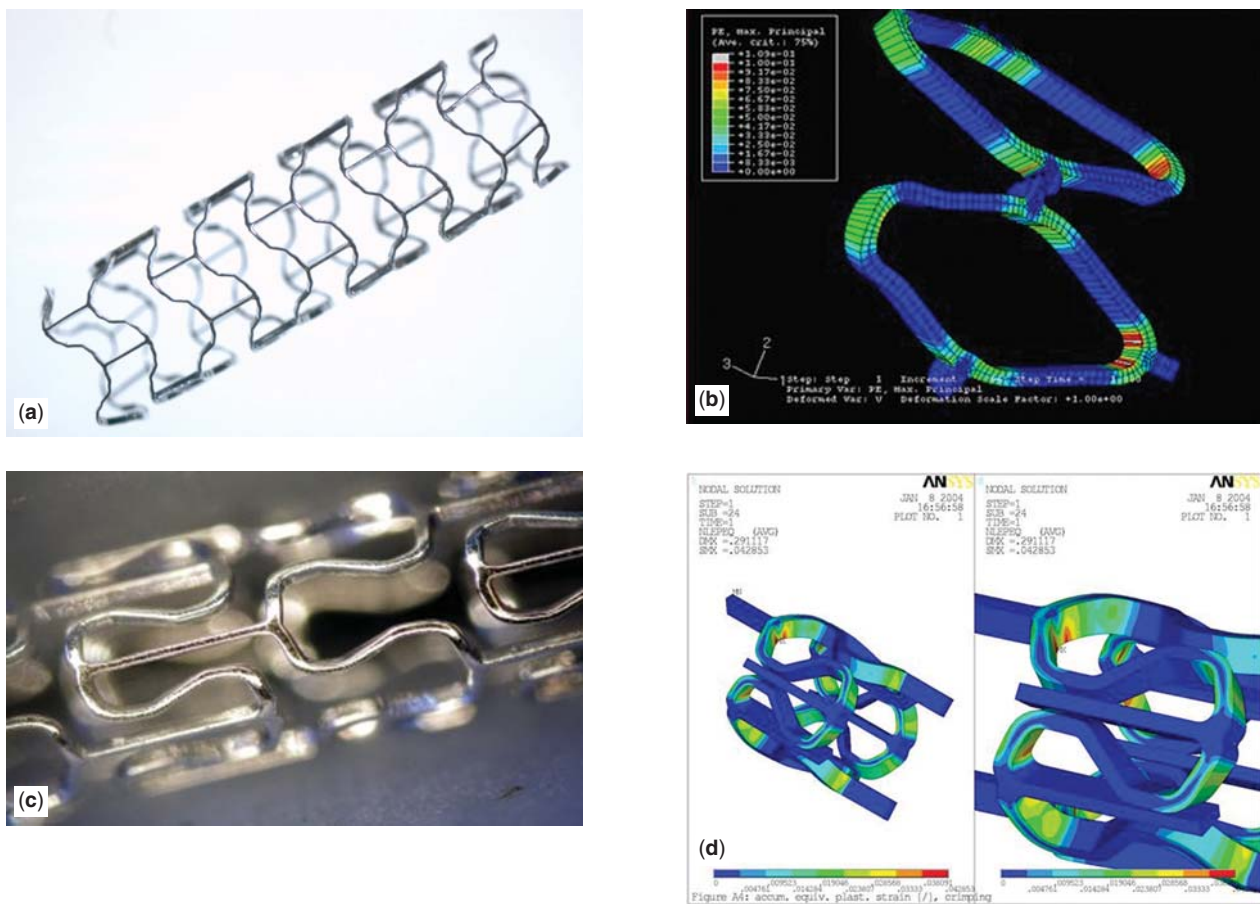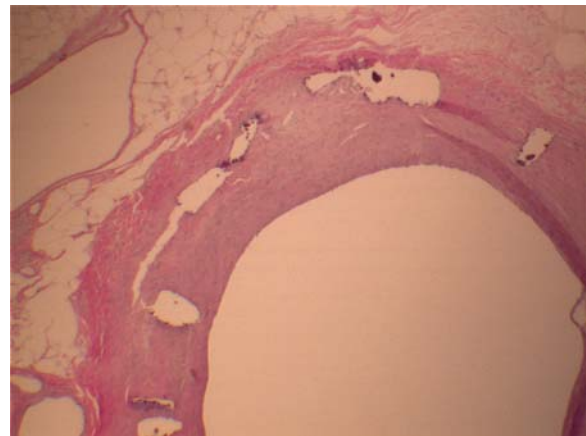
Figure 6.
*Expanded (**a**) and non-expanded (**b**) view of a magnesium stent (MAGIC, Biotronik). Finite element analyses show regions of stress within the stent during expansion (**c**) and during crimping of the stent (**d**). (Photographs courtesy of Biotronik).*

Clinical applications. Magnesium-based alloys have been proposed for the production of a corrodible stent with rapid degradation after deployment. Different alloys are in experimental evaluation to achieve ideal degradation kinetics in a clinical setting. As described, the initial work was done by Heublein et al.[37] who implanted the "AE21" alloy which spawned the Magic coronary arterial stent. Recoil of the Magic stent is about 5%, and its collapse pressure is 0.8 atmospheres. The beneficial characteristic of the alloy with regard to compatibility with magnetic resonance imaging is obscured by a complete radiolucency. Embolization or migration during expansion, therefore, is not visible on fluoroscopy.

Experimental studies with the Magic stent have focused on the late luminal loss and neointimal proliferation in minipigs (Fig. 7). Mean luminal diameters were in favour of the Magic stent if compared to implantation of a conventional stent made of stainless steel. Preliminary clinical application in humans, implanting the stent below the knee in 20 patients, has shown no adverse events. One month after the implantation, normal flows were found in 18 patients,

Figure 7.
Histopathology 3 months after implantation of a MAGIC stent into the coronary artery of a domestic pig. Neointimal proliferation is low.

with stenosis of 30 to 40% in two. To date, there have been two late occlusions, one recognized in an unstented feeding artery of the stented vessel. No toxic or allergic reactions were encountered. Application of such magnesium stents is currently under
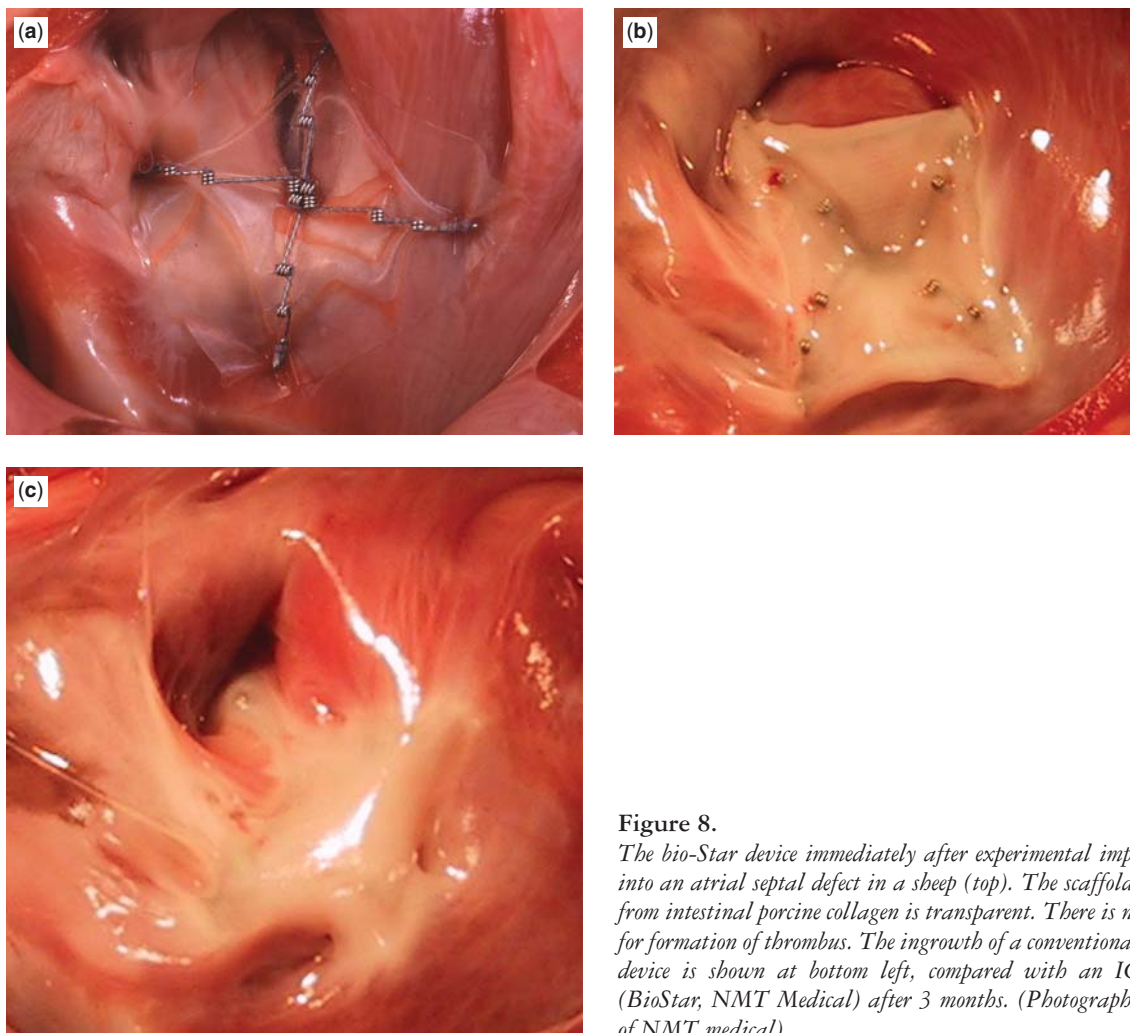
Figure 8.
The bio-Star device immediately after experimental implantation into an atrial septal defect in a sheep (top). The scaffold produced from intestinal porcine collagen is transparent. There is no evidence for formation of thrombus. The ingrowth of a conventional Starflex device is shown at bottom left, compared with an ICL device (BioStar, NMT Medical) after 3 months. (Photography courtesy of NMT medical).

evaluation in the PROGRESS study, with 63 patients enrolled.

Future aspects: Degradable devices for closing defects

It is the late Gerd Hausdorf who should be credited for the idea of developing a completely biodegradable umbrella. He initiated the use of iron-based alloys to produce a corrodible framework of the Cardioseal/ Starflex device. Degradation of the corrodible framework was slow, with fatigue observed at the junctions of the "arms" of the device (Fig. 8). Despite the fact that no adverse events were associated with those fatigue fractures, the concept of the corrodible framework was not further pursued. Current research is focused on degradable polymers with mechanical properties compatible with use in implantation to close holes at the oval fossa.

In a second step, the scaffolding material of the currently available Starflex device was replaced by a degradable matrix of small intestinal submucosa or intestinal collagen. The degradable scaffold used as a matrix for fast ingrowth of the device was successful (Fig. 9). Experimental studies have been performed in sheep. Short and long-term follow-up after creation and subsequent closure of defects demonstrated a good biocompatibility. Compared to "permanent" Starflex devices, the degradable devices created by NMT Medical, from Boston, and mounted on the "MP35N" alloy used in the Starflex device, demonstrated a faster cellular seeding, along with a low thrombogenicity.

So, now that we can replace the synthetic Dacron covering the defect with biological material, the first step towards production of a biodegradable occluder has been made. It was after the death of Hausdorf that results of the study using the intestinal collagen layer in the Starflex device were published.[40] A clinical trial with this BioStar device is currently in preparation.

Summary

Current research on degradable cardiovascular implants from corrodible alloys has demonstrated promising experimental results. To date, corrosion of iron-based stents shows a slow degradation kinetic,
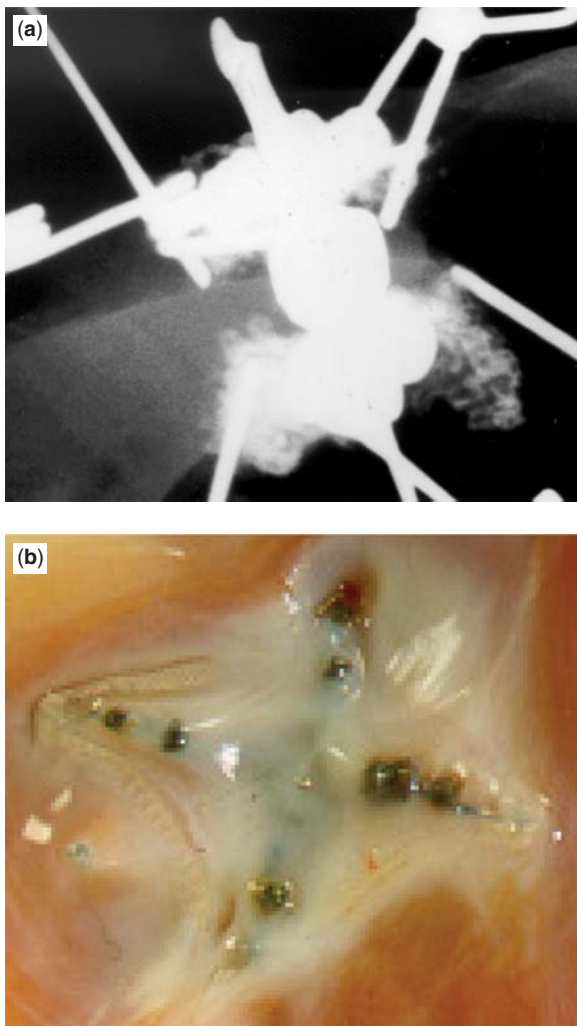
Figure 9.

*Radiographic aspect of a "Music wire" corrosive framework of a Cardioseal/Starflex device (**a**). There is accumulation of corrosive wear around the centre of the device. The central wires have fractured. Ingrowth of the Music wire device was complete after 3 months, with evidence for corrosive attacks around the springs (**b**). (Photography courtesy of Harald Bertram, MD.)*

with complete degradation expected to occur after years, whereas stents made from magnesium-based alloys show a fast degradation, within weeks. Collapse pressures are higher for the iron stent. To date, therefore, iron stents may be superior to stents based on magnesium for the treatment of post-surgical and calcified vascular obstructions. Research, therefore, is focused on the modification of the composition of the alloy, and the surface, seeking to influence the rate of degradation and incorporation of the corrodible stent into the vessel.

Acknowledgement

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