Chapter 7

Cardiovascular Applications of Magnesium Alloys

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Additional information is available at the end of the chapter

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Abstract

Therapy in cardiovascular medicine often relies on implantation of prosthetic materials or application of stents. The diseases of many cardiovascular structures require their complete and immediate repair by utilising prosthetic materials. The ideal cardiovascular prosthesis involves good functional properties, capability of regeneration and does not activate the host's immune system. Ideally, the graft can be applied for a temporary use and degrades after a predefined period according to controlled degradation kinetics. Only biological grafts would provide this spectrum of properties by today's level of knowledge. However, biological prostheses exhibit some relevant drawbacks as well, such as insufficient mechanical stability or restricted availability. Implants or supporting structures of magnesium alloys would bridge this gap and would either provide a substrate for innovative and temporary grafts or would—as supporting structures—transiently add some missing properties to regenerative biological prostheses. This chapter reviews the different fields of cardiovascular therapeutic applications of magnesium alloys. The required properties of magnesium alloys and their preparation, fabrication and testing will be discussed under the specific cardiovascular perspective.

Keywords: cardiovascular prostheses, cardiac surgery, aortic surgery, aortic aneurysm, congestive heart failure, coronary heart disease, sternum cerclage wires, cardiology, stents, degradation kinetics, magnesium alloys, coating, in vitro test, in vivo test

1. Introduction

The treatment of cardiovascular disease often requires the implantation of prosthetic material [1–7] or insertion of stents [8–14]. The ideal cardiovascular prosthesis has good functional

properties and the ability to regenerate, without activating the immune system of the host organism [15]. In some cases, the implant should only remain in place for a limited period of time in the patient, followed by controlled degradation. Up to date, only biological grafts meet most of the spectrum of these relevant requirements (see **Figure 1** and **Table 1**). However, biological prostheses have specific disadvantages, such as insufficient mechanical stability or limited availability (see **Figure 1** and **Table 1**).

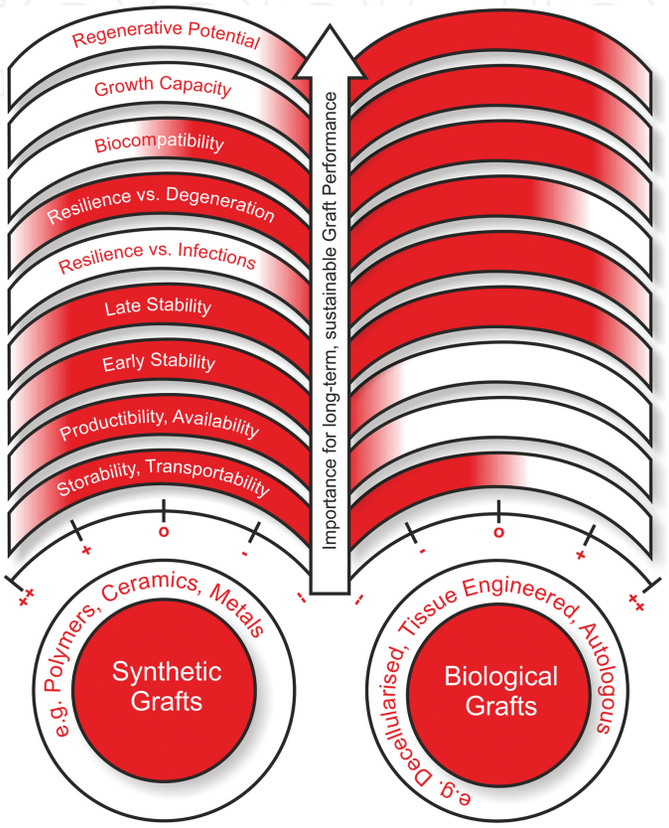

Figure 1. Rough estimation of the average characteristic and extent of relevant properties of grafts made of synthetic or biological materials that influence sustainable and long-term graft performance in cardiovascular applications (Properties of individual grafts may of course deviate). + +, excellent/very high; +, good/high; o, medium/average; –, bad/low; – –, insufficient/very low.

Tissue	Application, success (+) and limitation (–)	Year	Authors
Cardiac muscle	Reconstruction RVOT (rat model) + Good functional and histomorphological outomes – Not applied in left ventricular high pressure system	2012	Wainwright et al. [16]
Skeletal muscle	Epicardial fixation of skeletal muscle (human) + Better vascularisation of myocardium – No transmural reconstruction	1935	Beck et al. [17]
Pericardium	Transmural reconstruction of right ventricle (rat model) + Vascularisation of patch and presence of cardiomyocytes	2007	Chang et al. [18]

Tissue	Application, success (+) and limitation (–)	Year	Authors
	– Not applied in left ventricular high pressure system		
Diaphragm	Epicardial fixation of autologous diaphgram (dog model) + Optimised hemodynamics – No transmural reconstruction	1973	Kusaba et al. [19]
Urinary bladder	Transmural right ventricular reconstruction (pig model) + Improved contractility, repopulation of patch with host cells – Not applied in left ventricular high pressure system	2008	Ota et al. [20]
Peritoneum	Epicardial fixation of stem cells and peritoneum (rat model) + Improved left ventricular function, immigration of cells – No transmural reconstruction	2006	Huang et al. [21]
Myometrium	Epicardial fixation of uterine myometrium (rabbit model) + Good biological integration and angiogenesis of patch – No transmural reconstruction	2008	Taheri et al. [22]
Small intestine	Transmural reconstruction of right ventricle (pig model) + Improved contractility, cardiomyocytes found in patch – Not applied in left ventricular high pressure system	2009	Tudorache et al. [5]
Stomach	Epicardial fixation of stomach on left ventricle (pig model) + Improved angiogenesis of infarcted area – No transmural reconstruction	2003	Ruel et al. [23]
Aorta	Decellularisation of xenogeneic aorta segments (mouse model) + Adhesion of cells – Small diameter, small animal model, no implantation into circulation	2016	Song et al. [24]
Natural polymers	Engineering of small diameter bypass grafts with degradable polymers (rabbit model) + Cell infiltration, good graft patency – Implantation in carotid position (lower stress than in aorta)	2016	Antonova et al. [25]
Fibrin	Engineering of vascular grafts with compacted fibrin (human) + On-the-fly generation of regenerative grafts – Mechanical stability up to 230 mm of mercury	2016	Aper et al. [26]
Induced pluripotent stem cells	Abdominal aorta interposition of engineered blood vessels from induced pluripotent stem cells (rat model) + No rupture of grafts, cellular proliferation – 2 weeks observation period, small animal model	2016	Gui et al. [27]

Table 1. Overview of exemplary studies to test diverse biological materials as grafts for selected cardiovascular applications.

Structures of degradable magnesium alloys could temporarily compensate for such disadvantages, through means of complementing some of those missing features of biological prostheses (see **Figure 2**).

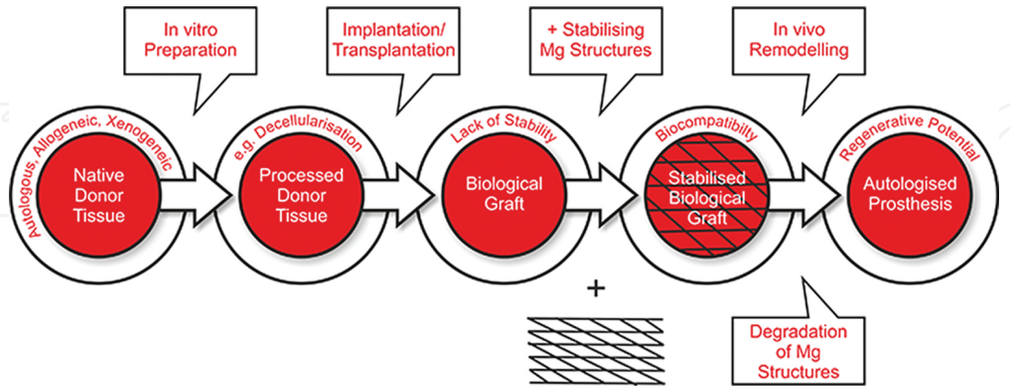

Figure 2. Schematic principle of temporarily stabilising biological grafts with degradable magnesium structures, resulting in highly biocompatible, autologised, and therefore regenerative prostheses.

However, implants made of magnesium alloys remain in an outsider position with regard to cardiovascular medicine so far. While the experimental application of coronary stents made of magnesium alloys was performed for some decades [11], degradable magnesium has hardly ever played a role in the development of other cardiovascular implants.

This chapter introduces scenarios for a beneficial application of degradable magnesium implants or supporting structures in clinical settings. Desirable and essential requirements of the materials are presented here as well as research emanating from experimentally well studied alloys in other disciplines. This chapter does not claim to be exhaustive, but rather to convey the essential principles that need to be considered in the development of cardiovascular implants made of magnesium alloys for various application scenarios.

2. Fields of potential applications for magnesium alloys in cardiovascular medicine

2.1. Coronary heart disease

Coronary heart disease (CHD) is associated with the pathological reduction in the lumen of the coronary arteries, which can eventually lead to a total closure and thus the clinical picture of the life-threatening myocardial infarction. Cardiovascular diseases are among the most common causes of death. According to WHO, in 2012, about 17.5 million people died from cardiovascular disease, of which approximately 7.4 million can be attributed to a coronary heart disease [28].

The treatment of coronary heart disease is dependent on the extent of the disease. The common guidelines of the European Society of Cardiology and the European Society for Cardiothoracic

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Surgery recommend interventional balloon dilation of stenotic vessels or the application of coronary stents for patients with one- or two-vessel-CHD [29]. For this purpose, a tubular metal structure under X-ray fluoroscopy is positioned into the affected coronary artery, usually through a femoral arterial puncture. Subsequently, the initially crimped stent is dilated with an inflatable balloon via the same catheter. The specific framework design and a partial plastic deformation of the stent ensure that this does not collapse.

According to current studies, patients with left main coronary artery disease or two- or three-vessel-disease benefit more in the long term from surgical coronary artery bypass grafting [12–14, 30, 31]. Segments of autologous saphenous vein, radial artery or internal mammary artery are herewith connected via a proximal anastomosis to the ascending aorta and via a distal anastomosis to the affected coronary vessel behind the stenosis. This intervention takes place, in most cases, using a heart-lung machine. In heart-lung machine interventions, systemic anticoagulation with heparin is necessary to prevent clotting of blood along the long synthetic tube surfaces of the machine. Patients who have to undergo a surgical revascularisation due to a secondary closure of the inserted stent are subject to a higher perioperative risk of bleeding because of chronic, medical, dual anticoagulant therapy with platelet inhibitors, and vitamin K antagonists [32]. Furthermore, the surgeon is faced with a sealed coronary in such cases, where—because of the inserted metal stents—only a few sites to connect the bypass graft remain. But even in cases where no secondary surgical intervention is required, permanent stents may have a chronically negative impact. This may lead to a long-term endothelial dysfunction, a permanent physical irritation, the release of toxic metal ions or a local chronic inflammation [11]. Removal of these stents poses a significant risk to the patient and is associated with high additional costs.

In the last two decades, therefore, innovative stents from polymers [33, 34] and degradable metals such as iron and magnesium were developed, which initially ensure the openness of the coronary vessel and are degraded without residue after a sufficient regeneration phase [35–40]. The coating of degradable metal stents should slow the corrosion [35]. The hydrolytic degradation in vivo of certain polymer coatings as PLA or PGA, however, leads to an acceleration of the metal corrosion because of the acidic degradation products, such as carboxylic acid acidifying the milieu, which promotes the oxidation of the magnesium alloys [41, 42]. Bioabsorbable stents made of magnesium alloys [43] with an absorbable polymer coating, from which antiproliferative drugs are released represent a promising future treatment alternative. With this combination, the in-stent restenosis, which occurs in 20–30% of patients should be prevented whilst exploiting the advantages of a transient implant.

2.2. Congestive heart failure

Heart failure is associated with an insufficient function of the heart whereby the heart is no longer able to provide the required output. Between 800,000 and 1,600,000 people in Germany suffer from heart failure [44]. According to the Federal Statistics Office, heart failure is currently the third leading cause of death in Germany [45], resulting in costs of €3.2 billion in 2008 [46], showing that heart failure is also of economic relevance. As a result of demographic change and improved chances of survival from triggering diseases—for example, after a heart attack

—this number is expected to increase in the future, leading to an increase in related health expenditures [47].

Surgical treatment of severe heart failure focuses on regaining a sufficient pumping function primarily of the left ventricle, which results from a physiological volume and the natural geometry of the left ventricle [48]. Since the 1980s, therefore, myocardial reconstruction according to Dor has been applied [6, 7] whereby, the damaged, non-functioning heart tissue is resected and reinforced by synthetic grafts such as Dacron. The use of grafts currently available allows for reconstruction of the physiological volume of the left ventricle, but not the ellipsoidal shape, which is required for an optimal pumping function [4]. In addition, the currently available synthetic materials are neither capable of growth nor regeneration and do not contribute actively to the left ventricular function. The dyskinetic cardiac tissue is therefore replaced by equally dyskinetic grafts. Innovative surgical procedures that address the use of regenerative materials, the physiological volume, and the physiological ellipsoidal shape are therefore necessary in order to offer the patients a sufficient and sustainable therapy.

In this sense, the replacement of damaged myocardium has been tested with decellularised bladder [49], skeletal muscle [50], intestinal mucosa [5], stomach [23, 51] (see **Figure 3** and **Table 1**) amongst others [52].

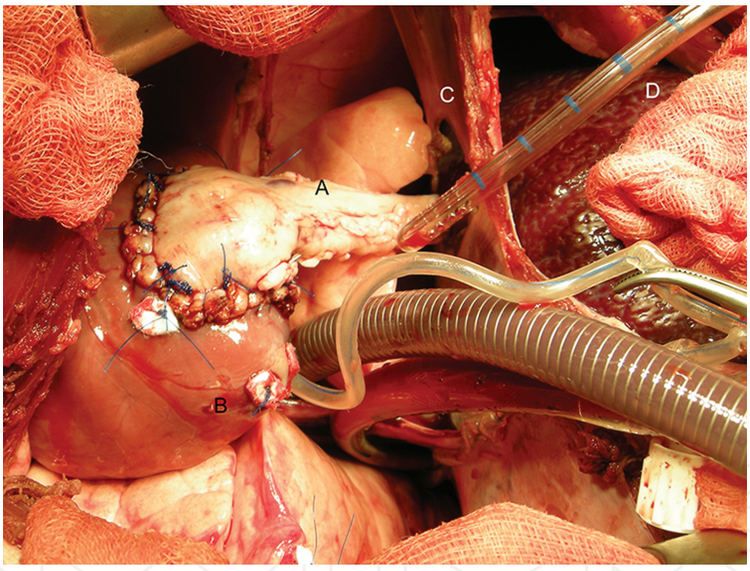

Figure 3. Transdiaphragmatic autologous transplantation of a vascularised segment of the stomach as a myocardial patch for the anterolateral facies of the left ventricle. (A) Gastric patch; (B) apex cordis; (C) diaphgram; (D) spleen.

The feasibility of a clinical application of these potentially regenerative grafts has already been shown for the replacement of right ventricular or atrial cardiac muscle tissue. However, the mechanical strength of most of these biological grafts is too low for use in the left ventricular high-pressure area with up to 240 mmHg of blood pressure. Especially in the early phase after implantation, there is a great risk for an aneurysm or even a fatal rupture of the delicate, prosthetic tissue. Nevertheless, a physiological transformation process of heterotopically applied tissue has been ascertained, which raises hope for an acquisition of specific cardiac

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functions, but also an increase in the mechanical stability [5]. Stabilising structures from degradable magnesium structures could support biological grafts by attaining sufficient mechanical stability through the physiological transformation, thus making regenerative therapy options available to all needy patients [53].

Implants such as the Paracor HeartNet or the Acorn CorCap can be used for left ventricular support and reduction in the wall load. The aim is to reduce the mechanical stress acting on the (damaged) heart wall with reticular structures that span the epicardial layer of the myocardium, so that the high intraventricular blood pressure cannot further dilate the myocardial wall. The Acorn CorCap is a polyester net that is placed circumferentially from the apex to the atrioventricular fossa around the heart. The network supports end-diastolic resistance and reduces left ventricular wall stress, thus preventing further dilatation of the ventricle [54, 55]. The nitinol elastic Paracor HeartNet device acts in a similar manner [56, 57].

2.3. Aneurysm and dissection of the aorta

Congenital (Marfan syndrome, Ehlers-Danlos Syndrome) and acquired (atherosclerosis) disease of the aorta lead to about 7000 surgical procedures annually in Germany and thus to a high demand for prosthetic material [58]. In acute aortic dissection, the true number of cases is often underestimated because many patients die from unknown causes of death before reaching the hospital [59]. The incidence of diseases of the aorta in 2011 consisted of 34 hospital-based main diagnoses per 100,000 inhabitants. Of this amount, 17.4% belonged to the group of aortic dissection, which corresponds to an incidence of 5 per 100,000 inhabitants in Germany.

In particular, in many cases, aortic aneurysms (ballooning of the aortic wall) or aortic dissection (tearing of the aorta) require surgical therapy. However, the surgical treatment of aortic disease does not always lead to complete cure of patients. In a study over a period of 14 years, it was shown that reoperation is required in approximately 13% of all performed surgical procedures of the thoracic aorta. Reoperation may be required for progressive aneurysms, persistent or recurrent aortic dissection or false aneurysms at the suture lines, on the one hand, while on the other hand, stenoses and infections of implanted grafts may occur and proximal or recurrent aneurysms distal to the grafts may be observed, requiring a reoperation [60].

2.3.1. Aortic prostheses and their limitations

In the last 50 years, aortic prostheses were produced essentially of polyethylene terephthalate (PET, Dacron), polytetrafluoroethylene (PTFE, Gore-Tex®) or polyurethanes (PU) [61]. The disadvantages of synthetic vascular grafts include the risk of thromboembolism, a subsequent stenosis and occlusion of the prosthesis by intimal hyperplasia. Infections resulting from synthetic implants are difficult to handle. In addition, prostheses consisting of artificial materials have no regenerative potential and are not able to grow [62, 63]. Finally, synthetic grafts have a low elasticity, so that the function of Windkessel of the aorta, which is responsible for the uniform and muted forwarding of the pulse wave, is restricted. Especially in cases of the application of very extensive vascular grafts, there may occur refractory hypertension, which can lead to further organ damage in the long term (see **Figure 4**).

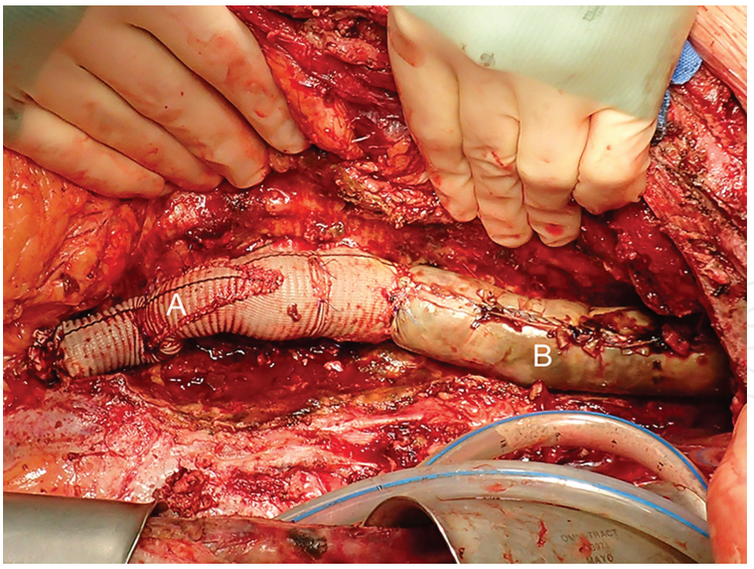

Figure 4. Operative situs following replacement of thoracic (with Dacron prostheses (A), left side) and abdominal (Pericardium graft (B), right side) aorta. Now re-operation because of graft infection.

Bio prostheses or hybrid grafts represent an alternative to synthetic implants [3, 64, 65]. The gold standard for biological grafts is allogeneic native vessels made from fresh and cryopreserved human donor tissue. Fresh homografts, which tend to have a later expiration than the cryopreserved homograft, bear the risk of forming aneurysms and are only of limited availability. The cryopreserved homograft is prone to calcific degeneration approximately 10–15 years following implantation. Usage in younger patients therefore entails at least one reoperation [66, 67]. The long-term degeneration of biological implants is thus far, a significant, unresolved limitation of these prostheses [68].

2.3.2. The ideal vascular prosthesis

Artificial blood vessels, which consist of viable tissue, constitute the ideal vascular prosthesis. An ideal prosthesis must have physiological mechanical resistance and compliance. The graft should be non-toxic and non-immunogenic. The graft must be biocompatible and always available in various sizes. In addition, the graft should be surgically easy to handle. It should not, if possible, trigger any thrombogenic effects. The graft must integrate into the host tissue and have the ability to grow, when used in children [69–71]. Furthermore, an easy manufacturing process, the shelf life of the vascular prostheses and readily available supply for an acute emergency, all play very important roles. According to the principles of tissue engineering, innovative biological aortic prostheses can be produced, which can overcome the previous limitations of available grafts. One option is the implantation of a decellularised allogeneic or xenogeneic donor aorta. After the original cells have been removed from the donor tissue chemically or enzymatically, these can colonise after implantation in vivo with cells of the host organism. In this way, a regenerative, biological implant, which will not be attacked immunologically by the host, is converted successively to truly endogenous tissue in the course of

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the physiological remodelling. Tubular structures of fibrin and collagen can be constructed in vitro as an alternative to decellularisation of preformed donor tissue [26, 72].

However, both grafts have a limited mechanical stability at the time of implantation. To avoid premature rupture or aneurysm formation, a stabilising biodegradable clip of magnesium could be placed around the biological graft until the latter reaches sufficient stability. Subsequently, this support structure of magnesium should be degraded, preferentially in a biologically inert manner.

2.4. Closure of sternotomy following cardiac surgery

In cardiac surgery, many procedures are already performed using minimally invasive approaches that do not require traditional median sternotomy. But the indication for minimally invasive access paths is still conservative due to the difficulty involved in the operation [73, 74]. In addition, most cardiac surgical interventions are not isolated, but combined procedures. The average age of cardiac surgical patients is steadily increasing, and in many cases, the requirement is not just for a single heart valve or bypass surgery, but rather a combination of both procedures or the replacement of several valves all taking place in a single operative session [75]. In such cases, the safest and most effective access path is the median sternotomy. Here, the sternum is opened with an oscillating bonesaw starting from the xiphoid process—the lowest point of the sternum—to the manubrium sterni. After the surgical treatment of the heart, the separate halves of the sternum are brought together with non-degradable metal wires and fixed under tension. For this purpose, the wires are guided laterally from the sternum with a needle through the intercostal spaces. Thereafter, the free ends of the wires are twisted with pliers. The twisted ends are placed as flat as possible along the bony structures (see **Figures 5** and **6**).

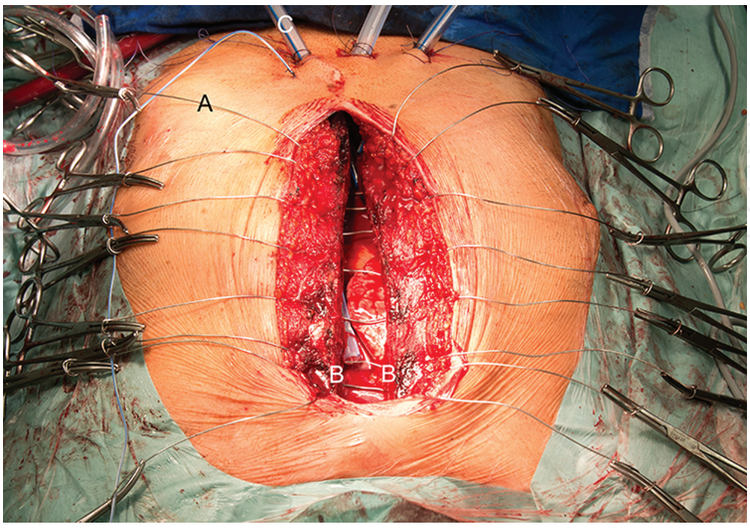

Figure 5. Intraoperative situs. Closure of sternotomy (B) with conventional sternum cerclage wires (A). Cerclages already inserted and just prior to fixing and drilling. Chest tubes in position (C).

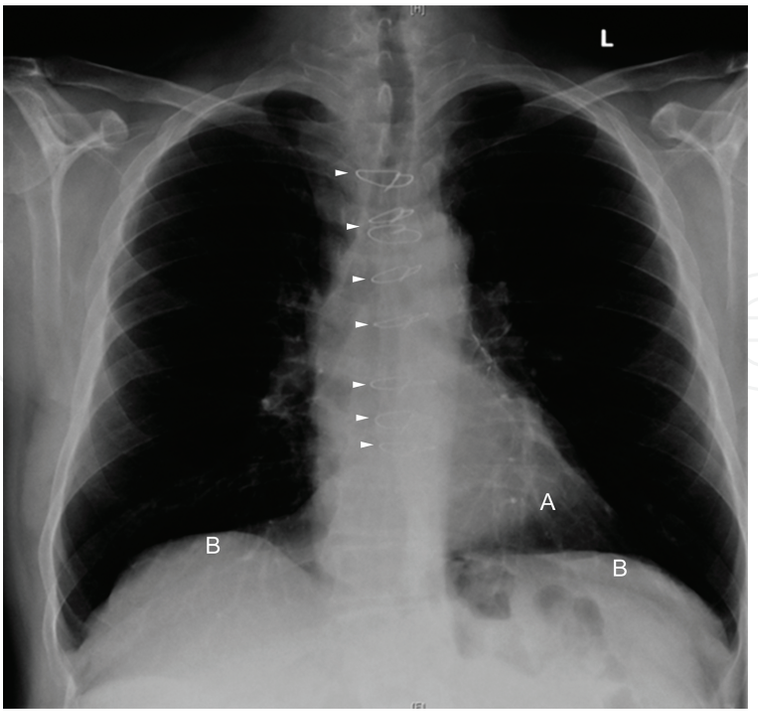

Figure 6. X-ray of thorax in posterior-anterior beam path with clearly visible sternum cerclage wires (arrow heads). (A) Apex cordis; (B) diaphragm.

2.4.1. Limitations of current available sternal cerclage wires

In some cases, these wires lead to postoperative complications. Some patients perceive the twisted ends of sternal cerclage as truly painful [76]. Other patients can get the twisted ends with its tip to curve in the direction of body skin, and even penetrate it by mechanical stress or remodelling of the bony skeleton. This leads to impairment of wound healing, wound pain and wound infections, which, under unfavourable configuration can lead to secondary bone or mediastinal infections. The latter require an extremely burdensome, tedious and sometimes highly complex wound therapy often using reserve antibiotics. Multiple re-operations for rehabilitating serious findings in such cases constitute a very high-risk stress factor for patients. Even the development of sternal cerclage systems made of polyester did not lead to an improvement of the postoperative complication rate or the subjective well-being of the patients [77].

2.4.2. Degradable sternal cerclage and release of active agent

Against this background, the ideal cerclage wire material consists of controllable degradable metal. The healing of the bone to physiological stability following sternotomy requires about 3–6 months. A degradation process of resorbable sternal cerclage should lie roughly within this time frame.

It is conceivable that the coating of degradable magnesium wires would not only provide an additional protective layer for the magnesium but would allow the possibility for controlled

local delivery of drugs. First, cardiac surgical patients immediately receive painkillers after surgery to alleviate the pain [78]. It is conceivable that for a limited period of time, local anaesthetics could be released from the coatings of magnesium wires. This could lead to considerable local relief of postoperative pain and perhaps reduce the administration of systemically acting analgesics. Second, the infection of the sternotomy wound is a common complication after cardiac surgery, which is often associated with mediastinitis and the most protracted wound healing problems with instability of the sternum [79]. A reoperation for revision of the infected and unstable sternum is essential in such cases and not only provides an extremely stressful engagement with additional risks and pain for the patient himself but is usually directly associated with increased postoperative mortality [80]. Although sternal infections are largely reduced to a minimum following utmost care and hygiene, this burdensome and costly complication cannot be avoided in all cases [81]. Particularly, elderly patients or patients with an impaired immune system and diabetics are at an increased risk of infection where wound healing processes are complicated due to microcirculatory disorders [82]. The immediate postoperative period, commencing with the release of antibiotic or at least bacteriostatic substances from the wire cerclages used in the closure of the sternum, could further reduce the likelihood of wound infection [83]. Robinson et al. could show that—at least in in vitro experiments—the degradation of magnesium and the degradation products exert an inhibitory effect on the growth of bacteria. The local increase of pH in the medium as a result of degradation corresponded approximately to the effect of an antibiotic [84].

3. Magnesium alloys for cardiovascular implants

Magnesium alloys are currently being investigated for use as biodegradable implants. The implants should take over the desired function for the needed duration and then biologically degrade as biocompatibly as possible. Magnesium, although a very promising material is, in principle, far from being perfect material for implants because it is electrochemically highly active and easily corrodes in biological milieus [85]. The corrosion of magnesium is therefore to be controlled by alloying with other components. The most-studied alloy components for magnesium are calcium, aluminium, lithium and rare earth (RE) elements [39, 86]. Cardiovascular implants will also benefit from the modification of magnesium by these alloys, because a uniform and temporally controllable corrosion as well as a long-term mechanical stability or even elasticity is a common requirement for most implants.

Calcium is the most abundant mineral in the human body. It is mainly found in the bones and teeth [39]. In the alloy with magnesium, there is a reduction in the tendency to dissolve. It also leads to a refinement of the grain structure [39, 87]. Wan et al. found an increase in the compressive and elastic moduli. Wu et al. were able to show that the addition of calcium to a magnesium-aluminium-zinc alloy improved the corrosion properties of this alloy [88]. With an alloy of 9 ma.-% Al, 1 ma.-% Zn, 1 ma.-% REE and 1 ma.-% Ca, they were able to achieve the best results and to reduce the corrosion rate compared to the AZ91 alloy without calcium by 19% [88]. Due to their good biocompatibility, good mechanical properties and desirable

influence on the corrosion kinetics, magnesium-calcium alloys constitute a particularly attractive material for implant development.

Aluminium is used for alloying of magnesium, because it increases the corrosion resistance of magnesium [89]. A corrosion product of aluminium in physiological solution is Al_2O_3, which forms an insoluble outer protective layer on the alloy [87]. Moreover, aluminium tends to precipitate and reduces the tendency to dissolve [39].

Alloys with rare earth elements also often show positive results, although these are not always easy to reproduce. This is also because rare earth elements are often used as so-called master alloys for the production of a magnesium alloy, which already contains a mixture of many rare earths [39]. While this system is used for industrial applications without major limitations, the exact composition of the material must be known in the development of medical implants, as even minor changes can dramatically impair the function and longevity of the product that is used in a biological environment [90]. The effects of rare earth on solubility and precipitation behaviour are mediated by the formation of intermetallic phases. This results in an improved corrosion resistance, creep resistance, as well as an optimisation of the mechanical properties [39, 88, 91]. Following the implantation of magnesium alloys, a foreign body reaction involving macrophages and giant cells (giant cells) takes place. The pH in phagolysosomal vacuoles of macrophages and giant cells can be as low as 3, therefore, their activity results in an acidification of the granulation tissue surrounding the magnesium implant after a short time. A low pH of the environment in turn accelerates the oxidation of the magnesium. Therefore, lithium is used in magnesium alloys in order to stabilise the corrosion layer on its alkalising effect [86]. This effect during the degradation of magnesium is further enhanced by the solution and accumulation of magnesium hydroxide as the main degradation product [92].

4. Degradation of cardiovascular implants

The degradation of magnesium implants influences the host's organism through the (corroded) surface, the release of degradation products such as magnesium ions, hydroxide ions and hydrogen gas [87, 93]. Both the gas development and the alkalisation of the medium by the released hydroxide ions lead to an enhanced localised corrosion as well as to a reduced cell adhesion [85, 94].

There are four basic types of corrosion possible for Mg alloy biomaterials [95]. **Galvanic corrosion**, also known as couple corrosion, occurs when two metals with differing electrochemical potentials are in electronic contact in an ionic conduction fluid such as serum or interstitial fluid [95]. This kind of corrosion plays only a minor role in cardiovascular applications, because cardiovascular implants are basically made of only one alloy. **Pitting corrosion** occurs when small, distinct areas of a material are rapidly corroded while most of the surface remains unaffected. Corrosion pits can also cause crack formation, leading to further breakdown. Magnesium is very susceptible to pitting corrosion. **Corrosion fatigue** takes place in materials undergoing cyclic loading, such as the pressures that would occur under normal blood flow past a stent. This form of corrosion is heavily dependent on a material's micro-

structure. Whether testing is carried out in a dry or aqueous environment strongly influences a material's performance under cyclic loading conditions. **Erosion corrosion** occurs due to the mechanical action of surrounding liquids or particles. Although not as influential as the other corrosion types listed here, erosion corrosion must also be considered when discussing biodegradable implants [95].

Corrosion rate and type are very important when evaluating an implant's performance. It is of paramount importance that localised corrosion attack in stents is avoided, as localised corrosion in the thin portions of the device can lead to premature loss of mechanical integrity [96].

Moreover, the rapid corrosion of magnesium implants leads to undesirable formation of gas bubbles in the tissue [37, 86, 97–99]. Song et al. determined a rate of 0.01 ml/cm^2/day as a conservative, acceptable level for the development of hydrogen gas in the human body [100]. The effects of gas generation vary with the implantation site. In a hardly flexible bony environment, the rapid development of high volumes of hydrogen gas undoubtedly has serious effects on bone remodelling due to an increase in pressure. In an epicardial application of magnesium structures, negative effects due to the development of higher gas volumes are hardly to be expected because of the relatively larger space available in the pericardium and mediastinum. In intraluminal stents, there is an immediate and effective removal of the released gas through the blood. Adventitially fixed clips for stabilising biological, large lumen aortic prostheses find sufficient thoracic as well as abdominal space into which the released gas can diffuse without damaging the surrounding tissue [101].

5. Biocompatibility

Many of the early Mg-based implants researched were pure magnesium. In truth, “pure” Mg will always have some level of impurity. The characteristic impurities in magnesium alloys are copper, nickel, iron and beryllium. The composition and production of the alloys will influence the levels of these impurities [39]. In general, it is best to have as low an impurity level as possible, not only because some of these impurities are considered carcinogenic or can become toxic at higher levels, but also because having higher levels of uncontrolled impurities can skew results. With impurities as well as alloying or coating elements, it is important to keep in mind the tolerable upper intake levels of these elements in humans so that improved strength or corrosion resistance does not come at the expense of biocompatibility. Pure Mg alloys for biomedical applications have mostly been replaced by other alloys, though some studies still contain pure magnesium, often as a control [102–105].

Pure magnesium is biocompatible in the highest degree. It is ubiquitous in the human body and plays an important role as a cofactor in many enzymatic reactions [106]. Calcium is also a cofactor for biochemical reactions and an essential component of bone metabolism. Therefore, it shows a comparably higher biocompatibility as an alloying component.

Magnesium aluminium alloys were initially developed for non-biomedical applications. As such, their biocompatibility was initially not important. Naturally occurring aluminium in the

human body is practically non-existent. The inclusion of high concentrations of aluminium, for example, in the metal working industry or with drugs, is associated with the aetiology of neurodegenerative diseases [39, 107–109]. The required concentrations for those effects are not to be expected during the degradation of relatively small cardiovascular implants made of alloys that usually contain only small amounts of aluminium. Above all, the degradation process ideally extends over a period of months, and only small amounts of aluminium are released in given intervals [101]. Following the implantation of epicardial degradable support structures of the magnesium alloy LA63, which contains lithium and aluminium, no adverse effects on the surrounding myocardium were determined in a pig model [101]. Feyerabend et al. found that aluminium and lithium exert toxic effects on perivascular cells only at concentrations above 1000 micromole [90]. Except for gadolinium, rare earth elements are only toxic at high concentrations, although calcium antagonistic effects could be shown, which in principle could affect many biochemical reactions, particularly muscle and heart muscle contractions as well as cardiac conduction [110]. Many RE elements have even been said to show some anti-carcinogenic properties [39].

In general, even cardiovascular implants made of magnesium alloys, and their degradation products cause the usual foreign body reactions of the host. The foreign body reaction, which is characterised as an inflammatory healing process through the activity of macrophages and giant cells, represents the natural reaction to the implantation of magnesium alloys [111].

6. Developing innovative implants made of magnesium alloys for cardiovascular application

6.1. Design and shapes

Magnesium is a versatile material that can be used for different cardiovascular implants of almost any shape. Using finite element simulation, various geometric shapes and designs of the stent or support structures can be analysed for possible weak spots [112]. The most promising approaches can be identified with these simulations in many cases prior to costly and tediously manufacturing them. Even the degradation of magnesium alloys can be simulated to a certain extent, at least for in vitro experiments [113].

In support of biological myocardial prosthetic devices, degradable magnesium lattices can be individually adapted to the patient's own geometry and anatomy of the damaged heart region. The preforming of implants reduces the plastic deformation of the implants in vivo, which induces high stress and consequently premature breakage of the implants [114]. Cardiac MRI or CT data could thus be employed to adjust the geometry of magnesium structures to the individual anatomy of each patient [114].

Magnesium alloys can be cut with a very high resolution into almost any shape by means of water abrasive jet cutting, laser or plasma beam. Nevertheless, it is mandatory to take into account the specific properties of each cutting process and its impact on the material. It is certainly possible to achieve finest structures down to 0.1 mm kerf width with a laser beam

[115]. However, the laser and plasma cutting bring about a significant heating of the surrounding material. The resulting melting and oxidation processes can significantly affect the integrity of the structures, so that the a-thermic water abrasive jet cutting, although considerably more complex and expensive, certainly is the gentlest method. Hence, the most precise cuts can be performed with water abrasive jet cutting due to the lack of heat.

6.2. Increasing the corrosion resistance

Three experimental routes are essentially taken in order to control the magnesium corrosion and to optimise the mechanical properties of the implants: The **alloying of magnesium**, the **manufacturing process** such as the reduction of grain size and phase transitions and the **surface modifications and coatings** [85]. Wang et al. provide a compact overview of the basic methods available for surface treatment [35]. They hint to microarc oxidation [116], anodising [117], evaporation [118], alkaline heat treatment [119], fluoride coating [120], electro deposition [121], phosphate coating [122], shock peening [123], ion implantation [124], physical vapour enrichment [125] and polymer coating [126]. The aim of the process is always to reduce the oxidation tendency of the surface of the magnesium alloy or to provide the surface with a protective layer. This protective layer may occur as the result of a reaction product of the alloy, such as magnesium fluoride via immersion of the implant in hydrofluoric acid, or a dedicated polymer layer, which is applied to the metal. To optimise cardiovascular implants made of magnesium alloys, procedures should be used, which are satisfactory for the field of use and are biocompatible. The adhesion of cells should also be made more difficult by an appropriate surface modification, which can be unequivocally desirable for coronary stents as well as for other applications.

6.3. In vitro and in vivo tests

As different alloys and coatings are developed to improve the mechanical and corrosion behaviour of these implants, in vivo and in vitro testing techniques must be developed. Unfortunately, since these techniques have not been standardised, it is difficult to compare results from different studies. There is difficulty in establishing a set corrosion rate for magnesium implants, because the experimental degradation varies based on so many variables, including composition of alloy, manufacturing method, coating, implant shape, in vivo location of implant, type of surrounding tissue, species of testing subject, temperature, local pH, ions or proteins present in an in vitro solution and more [37, 85, 126–128]. The same alloy tested in different in vitro scenarios can yield different corrosion rates, and often, in vitro corrosion tests do not accurately predict in vivo behaviour [93, 129].

Although in vitro experiments are helpful to get a first indication of the desired properties of the alloy, large animal experiments are essential to characterise the degradation of magnesium alloys in vivo before it can be used clinically for humans.

Scientific discoveries in medicine have to be gradually shifted into practical application. This path extends from basic research in the laboratory to preclinical models and ultimately to clinical trials. Preclinical models allow a forecast of possible future clinical reality without the

risks and costs associated with clinical trials [130]. Careful review of the biological responses to the implant, and the surgical procedure is necessary especially with complex, in vitro-generated products. It is important to be aware of the overall reaction of the organism to the implant, which may differ significantly from the tissue reactions that had taken place previously, or that have been detected in in vitro tests. This applies in particular to possible immunological reactions.

When choosing an animal model, many factors must be considered, including ease of operation, cost of acquisition and upkeep, susceptibility to disease or infection and similarity to human physiological mechanisms. Researchers may also need to consider the ethics of their animal model choice; some animals, such as dogs, cats, non-human primates, and perhaps horses might fulfil the other requirements of an animal model, but are considered inappropriate for medical research. No one animal model will be appropriate for all purposes, but no model should be dismissed entirely [131, 132]. Animal model size is an important consideration. Larger animals may have more in common with humans, but they will also be more difficult and expensive to care for.

To study cardiovascular implants, the pig can well be used as an experimental animal. The vascular systems of humans and pigs show similar behaviour under acute stress, and the fine structural elements of the porcine heart are particularly useful for morphological studies, given the analogy to the human morphology. Another suitable animal model is provided by the sheep, which serves as a model for rapid calcific degeneration. Degenerative changes can thus be observed particularly well in the sheep model.

In the field of implant biodegradation, there is a further concern: the total amount of fluid in the body seems to influence degradation rate, with less fluid leading to less corrosion. Yamamoto et al. used this line of thinking to discourage the use of small animals as models for implant corrosion studies [133]. Thus, they recommend not using small animal models to perform corrosion studies.

Once a more accurate in vitro testing protocol is designed and implemented by as many research groups as possible, magnesium alloy implant technology will finally be able to move forward as a united front, rather than a plethora of loosely connected individual lines.

7. Conclusion and outlook

This chapter gives a brief overview of potential cardiovascular applications of different magnesium alloys. Stents, grafts, support structures and sternal cerclage of degradable magnesium provide innovative and promising approaches for combating cardiovascular diseases, which are not only among the leading causes of death worldwide, but significantly reduce quality of life of affected patients and represent a high financial burden on healthcare systems worldwide. Cardiovascular implants made of magnesium alloys are currently still in an experimental or preclinical stage, but have a high potential in the foreseeable future for clinical applications, since magnesium can easily be processed and offers a good biocompatibility.

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There is a significant need for temporary, degradable implants in cardiovascular medicine. The drug-eluting degradable magnesium stent is just the next logical development of the currently available magnesium stents. Support structures using magnesium catalyse on the clinical use of renewable biological myocardial prostheses enabling the survival of patients with terminal heart failure who cannot receive a donor organ due to donor organ shortage. The same applies to patients who have to undergo an aortic intervention. Biological aortic prostheses that might exhibit low mechanical stability in the early phase after implantation could be made available to a large number of patients through stabilising, degradable magnesium clips. Finally, some months after successful bony healing of the sternum following sternotomy, it is in principle no longer necessary that the sternal cerclages remain in the patient and bear risks such as pain, infection and dermal puncturing. The development of degradable wires made of magnesium alloys is therefore a predictable consequence of the ongoing highly active magnesium research.

The high variety of available alloys, coatings, manufacturing processes and the high variability of the myriad of potential in vitro and in vivo test methods—including a plethora of different result parameters to be investigated—currently complicate the comparability of studies for the analysis of magnesium implants. The development of analytical standards would not only unify magnesium research, making studies comparable, but would give an immense boost to the field. With the expected advances in magnesium research, there is hope to offer reliable, renewable and sustainable therapeutic options to the millions of patients with cardiovascular disease in the near future.

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