



Endothelialization and Inflammatory Reactions After Intracardiac Device Implantation

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Abstract

Background: Due to the advances in catheter-based interventional techniques, a wide range of heart diseases can now be treated with a purely interventional approach. Little is yet known regarding biological effects at the intracardiac implantation site or the effects on endothelialization and vascular inflammation in an in vivo environment. Detailed knowledge of

ongoing vascular response, the process of endothelialization, and possible systemic inflammatory reactions after implantation is crucial for the clinical routine, since implants usually remain in the body for a lifetime.

Methods: For this narrative review, we conducted an extensive profound PubMed analysis of the current literature on the endothelialization processes of intracardially implanted devices, such as persistent foramen ovale (PFO) occluders, atrial septal defect (ASD) occluders, left atrial appendage (LAA) occluders, transcatheter aortic valve implantations (TAVIs), and leadless pacemakers.

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Additionally, the known biological activities of common metallic and synthetic components of intracardiac devices in an “in vivo” setting have been evaluated.

Results: Nitinol, an alloy of nickel and titanium, is by far the most commonly used material found in intracardiac devices. Although allergies to both components are known, implantation can be performed safely in the vast majority of patients. Depending on the device used, endothelialization can be expected within a time frame of 3–6 months. For those patients with a known allergy, gold coating may be considered as a viable alternative.

Conclusion: Based on our analysis, we conclude that the vast majority of devices are made of a material that is both safe to implant and nontoxic in long-term treatment according to the current knowledge. The literature on the respective duration of endothelialization of individual devices however is highly divergent.

LAA	Left Atrial Appendage
MERTK	Myeloid–Epithelial–Reproductive Tyrosine Kinase
MMPs	Matrix Metalloproteinases
MI	Myocardial Infarction
NOAC	New/“Non-Vitamin K” – Oral Anticoagulants
PCI	Percutaneous Coronary Intervention
PDGF	Platelet-Derived Growth Factor
PET	Polyethylene Terephthalate
PFO	Persistent Foramen Ovale
PRRs	Pattern Recognition Receptors
RAGE	Receptor for Advanced Glycation End Products
ROS	Reactive Oxygen Species
SMCs	Smooth Muscle Cells
TAVI	Transcatheter Aortic Valve Implantation
TGF- β	Transforming Growth Factor Beta
TLRs	Toll-Like Receptors
Treg	Regulatory T-cells
VEGF	Vascular Endothelial Growth Factor
VSD	Ventricular Septal Defect

Keywords

Cardiac injury · Endothelialization · Endovascular inflammation

Abbreviations

ASD	Atrial Septal Defect
ASO	Amplatzer Septal Occluder
ATP	Adenosine Triphosphate
CMs	Cardiomyocytes
DAMPs	Damage-Associated Patterns
ECs	Endothelial Cells
ECM	Extracellular Matrix
EPCs	Endothelial Progenitor Cells
GSO	Gore Septal Occluder
HMGB1	High-mobility Group B1
HSPs	Heat Shock Proteins
ICAM-1	Intercellular Adhesion Molecule 1
IFN- γ	Interferon Gamma

1 Introduction

Interventional cardiology is a rapidly evolving field in modern clinical medicine. Although the enormous therapeutic potential was not immediately recognized after Forßmann carried out the first catheterization of the right heart in 1929 in a heroic self-experiment, the idea was taken up and further developed by Cournand et al., who are today regarded as founders of interventional cardiology (Forssmann-Falck 1997; Nicholls 2020).

Grüntzig’s first successful percutaneous coronary intervention (PCI) in 1977 marked the dawn of a new era in clinical cardiology as catheter-based therapy changed from a purely diagnostic tool to an interventional treatment option for acute coronary syndrome (Ar et al. 1979).

During recent years, interventional cardiology has undergone an enormous transformation as catheter technology has developed rapidly and is

used in many different cardiological diseases. Today, in addition to coronary heart disease, a wide range of valvular diseases or congenital heart defects, such as atrial septal defect (ASD) (Sievert et al. 1998) and persistent foramen ovale (PFO) can be successfully treated using a catheter-based interventional approach. Even the catheter-based implantation of cardiac pacemakers is widely used in countless clinics today.

Permanent intracardiac placement of devices represents an enormous challenge for product engineers, as all components must offer exceptional stability and durability combined with low weight and small size. In addition, any device exposed to blood flow in an “in vivo” environment must be safe in terms of hemostasiological interactions; more precisely, the device must not initiate thrombogenic or even hemolytic cascades. Furthermore, the materials components must have an extremely low allergic potential, both at the implantation site and, in case of systemic reactions, in the entire organism.

All the devices must undergo extensive testing on safety and durability for market approval in order to achieve CE certification. In addition, an optimally designed intracardiac device should also have acceptable biocompatibility, especially rapid endothelialization, to reduce the duration of anticoagulant use with the goal of reduced bleeding risk and to safely discontinue use of endocarditis prophylaxis.

The aim of this narrative review is to provide an overview of the current state of knowledge on endothelialization in common intracardiac devices

as well as an overview of the known in vivo interactions, and the important components of different devices.

2 Intracardiac Devices

2.1 PFO Occluders

The patent foramen ovale (PFO) is an essential component of intrauterine circulation, allowing blood to bypass fetal lungs. Although spontaneous occlusion should occur shortly after birth, this physiological process is absent or incomplete in up to 27.3% of the population (Hagen et al. 1984).

In the vast majority of cases, a PFO does not have a clinical relevance. Nevertheless, it may play a crucial role in the genesis of migraine headaches or even cryptogenic stroke (Saver et al. 2017). In symptomatic patients, interventional treatment with an occluder can be considered to permanently close the opening. Recent studies (CLOSE, REDUCE, RESPECT LT, and DEFENSE PFO) showed that interventional PFO occlusion (Fig. 1a) was associated with a significant reduction in recurrent stroke compared to drug therapy (Mas et al. 2017; Saver et al. 2017; Søndergaard et al. 2017). Based on the long-term results of RESPECT and the results of the REDUCE study, two occluder devices, the AMPLATZER PFO closure and GSO (GORE Medical, Flagstaff, AZ, USA) received US Food and Drug Administration (FDA) approval for secondary stroke prevention in 2016 and 2018, respectively.

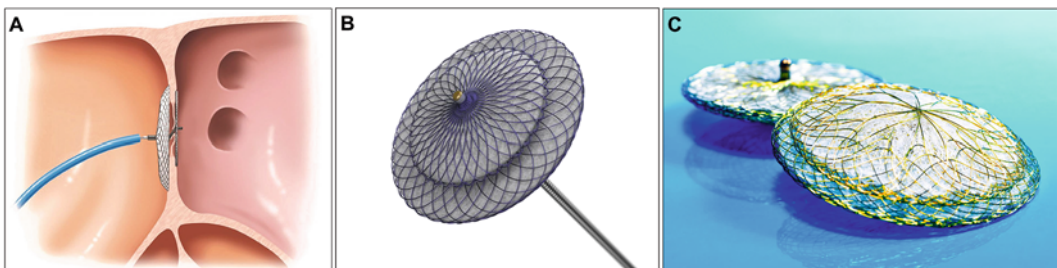


Fig. 1 PFO occluders. (a) Schematic representation of the regular position of a PFO occluder. (b) Amplatzer™ PFO Occluder. (c) Figulla Flex II® PFO Occluder. Pictures provided by Occlutech International AB

The later developed Flex II PFO occluder (Occlutech, Jena, Germany) received CE certification for clinical use in Europe in 2009. According to the manufacturer, more than 33,000 such devices have been delivered worldwide.

2.1.1 Amplatzer PFO Occluder

The Amplatzer occluder (Abbott Cardiovascular, North Chicago, Illinois, USA), first implanted in 1997, has been very well described elsewhere (Meier 2005; Madhkour et al. 2019). In brief, it is a double disc made of Nitinol mesh, the inside of which is made of polyester fabric.

A thin neck, which consists of the tightly woven wires of the discs, serves as a connector. The neck is rotated around its longitudinal axis so that it can be extended in principle (Fig. 1b). The two discs are sewn together with polyester fabric for better stabilization (Scalise et al. 2016).

The special feature is the so-called “shape memory,” which means that the device returns to its original shape after being stretched through the guiding catheter.

The Amplatzer PFO Occluder is available in three different sizes (18 mm, 25 mm, 35 mm), whereby the size specification is based on the size of the right-sided disc. The most frequently implanted occluder is the medium size. The small version has its special value in the case of a small PFO with a largely stable septum primum, whereas the 35 mm version is used in the case of an extremely redundant septum primum and possibly in the case of an atrial septal aneurysm.

According to the current literature, the chances of success are very high, so that complete closure of the shunt can be assumed in well over 90% of cases (Bruch et al. 2002; Greutmann et al. 2009).

Residual shunts require surgical intervention only in rare cases, although the actual average duration until complete endothelialization “in vivo” is not completely clear. In a recent position paper, the German Cardiology Society recommends dual antiplatelet therapy with aspirin and clopidogrel for a period of 6 months. Should there be a concomitant indication for oral anticoagulation, this will be given as monotherapy, with NOACs being preferred.

2.1.2 Gore Septal Occluder

The Gore Septal Occluder (GSO) has been approved for the treatment of PFOs in Europe for 10 years now by means of CE certification.

In contrast to the more commonly implanted Amplatzer Occluder, it is intended to offer advantages in difficult anatomical conditions. The device consists of five nitinol wires formed into a left atrial and a right atrial disc. The outer frame is coated with polytetrafluoroethylene film. For implantation, the device comes already loaded on a 10 French introducer catheter. A special safety feature is the integrated retrieval cord, which can be used to retrieve the device if necessary. When fully deployed, two circular discs are formed, facing each other, which can be fixed in place by a locking mechanism in the center.

2.1.3 Flex II PFO Occluder

The Flex II PFO occluder (Occlutech, Jena, Germany) consists of two self-expanding woven nitinol discs (Fig. 1c). The special feature of this device is a central pin on the left atrial disc and also a ball socket joint connection. The complete closure is achieved by two biocompatible polyethylene terephthalate patches.

The superiority of this device is the flexibility and ability to angulate in order to achieve the maximal adaptation to the interatrial septum. This offers an advantage for the complex anatomical variations (Neuser et al. 2016).

2.2 ASD Occluders

Atrial septal defect (ASD) is a relatively common congenital heart defect with a birth prevalence of 1.43:1000 live births and an expected survival rate into adulthood of 97% (Anderson et al. 2002; Anderson 2016; Lee et al. 2018). ASD of the ostium secundum is the most common type, occurring in 70% of all patients with ASD, followed by ASD of the ostium primum (10%) and ASD of the sinus venosus (5–10%) (Moons et al. 2009). The “true atrial septum,” that is, the tissue directly separating the atrial cavities, is

restricted to the base of the oval fossa and the surrounding inferoanterior margins. Defects of the true atrial septum are called “secundum defects.” Atrial septal defects are usually well tolerated in children, but can cause significant complications in adults (Campbell 1970). Early closure is therefore recommended and can be achieved using catheter deployment in the majority of cases. A symptomatic benefit can be seen at any age (Komar et al. 2014) Since left ventricular compliance decreases with age or in the presence of conditions that can increase left atrial pressure (e.g., high blood pressure, ischemic heart disease, cardiomyopathy, aortic and mitral valve disease), the left–right shunt can increase due to ASD (Le Gloan et al. 2018; Kumar et al. 2019). However, conditions that reduce right ventricular compliance (e.g., pulmonary arterial hypertension, pulmonary stenosis, right heart disease, tricuspid valve disease) may eventually reverse the shunt and cause cyanosis (Le Gloan et al. 2018).

A left–right shunt leads to right ventricular volume overload, which in turn results in right ventricular dilatation. It is well tolerated throughout childhood, despite a pulmonary–systemic flow ratio that can exceed 3:1. The pulmonary vascular system is also able to absorb the increased blood flow at low pulmonary artery pressure for many years. A persistent large left–right shunt leads to increased right atrial and right ventricular dilatation from late childhood onwards, which in some patients leads to arrhythmia and a progressive increase in pulmonary

vascular resistance (Le Gloan et al. 2018). Severe pulmonary vascular disease is rare (<5%), unless there are other associated factors (Nashat et al. 2018).

2.2.1 Amplatzer Septal Occluder

The Amplatzer® Septal Occluder (ASO) (Abbott Cardiovascular, North Chicago, Illinois, USA; former: St. Jude Medical, Inc., St. Paul, Minnesota) consists of nitinol–titanium memory wire mesh infused with polyester patches that facilitate occlusion and endothelialization (Fig. 2a). It consists of a smaller right and a larger left disc connected by a waist; the difference in size of both discs is 4 mm (Nassif et al. 2016).

ASO has been shown to be a practical, safe, and effective treatment option for ASD (Masura et al. 1997; Podnar et al. 2001; Masura et al. 2005; Cardoso et al. 2007; Knepp et al. 2010). Nevertheless, complications such as implant embolization, mispositioning, and fracture may occur in rare cases. Moreover, cases of erosion/perforation, cardiac arrhythmia, cardiac tamponades, and even infectious endocarditis have been reported (Sievert et al. 1998; Chessa et al. 2002; Fischer et al. 2003; Balasundaram et al. 2005; Sadiq et al. 2012).

2.2.2 Occlutech ASD Occluder

The Figulla Occlutech ASD closures (Occlutech, Jena, Germany) consist of individually braided, very thin (40–150 μm or 0.00157–0.00590 inches) nitinol strands. All strands end proximally

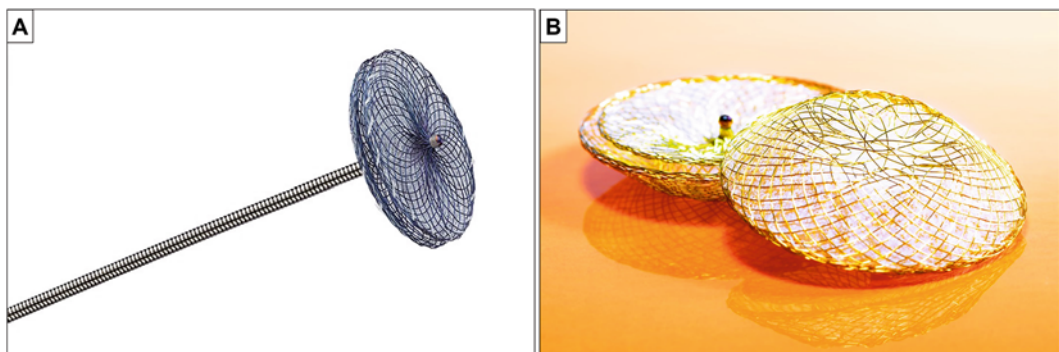


Fig. 2 ASD occluders. (a) Amplatzer™ Multi-Fenestrated Septal Occluder – “Cribriform”. (b) Occlutech® Fenestrated Atrial Septal Defect Occluder. Pictures provided by Occlutech International AB

and therefore do not require clamping to the left disc (Fig. 2b). This results in a smaller amount of uncovered metallic material. The ultrathin fabrics made out of polyethylene terephthalate (PET) of the device promote the endothelial growth after implantation as well as the defect closure (Pedra et al. 2016). The design of the Flex II ASD occluder is intended to allow ideal alignment of the septum, which in turn should increase feasibility and patient safety during implantation. The device is made of Titanium oxide-covered nitinol, which should result in the lowest possible release of nickel.

2.3 Left Atrial Appendage Occluders

The term “LAA occluder” refers to devices that can be used to close the left atrial appendage (LAA). In patients with atrial fibrillation, the LAA is anatomically particularly important, as this is where the vast majority of cardio-embolic strokes originate (Alli and Holmes, 2015). In patients at high risk for bleeding complications, implantation of an occluder allows discontinuation of anticoagulants after the initial endothelialization phase. The most common product is the Watchman Device, which has been CE certified since 2005. Another product, CE certified in 2013, is the Amulet device, which is designed to provide benefits due to its wide range of available sizes, according to the manufacturer.

2.3.1 Watchman Device

The Watchman device (Boston Scientific, Marlborough, MA, USA) consists of a nitinol frame coated with a permeable 160 micron polyethylene terephthalate knit fabric on the left atrial surface (Fig. 3a) (Fountain et al. 2006). It is a parachute-shaped, self-expanding device (Kramer and Kesselheim, 2015). The PET knit fabric facilitates endothelialization over the device and serves as a filter for emboli that originate from the LAA pouch (Della Rocca et al. 2019). After femoral vein access and transseptal puncture, the Watchman device is delivered using a 12-Fr delivery catheter and is then deployed until its titanium dowel pin separates from the catheter (Fig. 3b). The Watchman device is affixed to the LAA wall by 10 fixation barbs, which are arranged around the mid-perimeter. To match different LAA orifice sizes, the device is manufactured in five sizes (21 mm, 24 mm, 27 mm, 30 mm, and 33 mm) to allow adequate placement. An adequate seal is defined as a leakage < 5 mm.

2.3.2 Amulet Occluder

The AMULET is a second-generation Amplatzer Cardiac Plug (Abbott Cardiovascular, North Chicago, Illinois, USA; former: St. Jude Medical, Inc., St. Paul, Minnesota). The self-expanding device is made of flexible, braided nitinol filled with polyester tissue. It consists of a proximal disc and a distal lobe shaped like a hockey puck

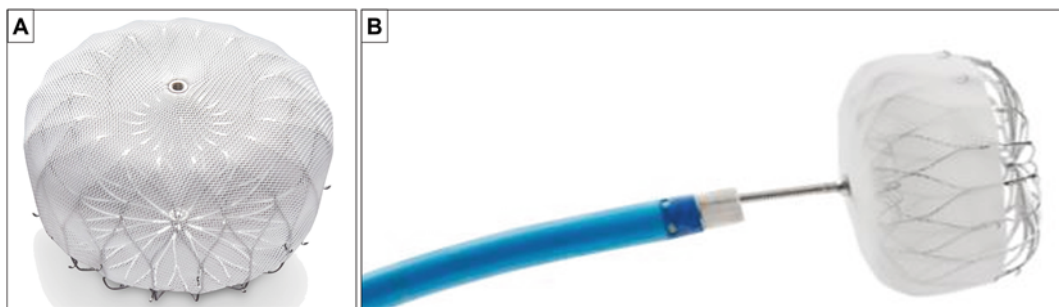


Fig. 3 Watchman Devices. (a) Watchman™. (b) Watchman™ on a 12 French delivery catheter. Pictures provided by Boston Scientific

connected by a flexible waist (Meerkin et al. 2013). The proximal disc covers the LAA orifice and the distal lobe with stabilization hooks that secure the engagement of the occluder to the LAA wall. The LAA Occluder is delivered by a 12-F or 14-F sheath into the left atrium after a transseptal puncture. It is available in eight sizes. Pre-interventional standard imaging, including transesophageal echocardiography and computerized tomography (CT) scan, is performed in order to determine the proper occluder size. The proximal disc is always slightly larger than the lobe and has a central screw.

2.4 Transcatheter Aortic Valve Implantation

Transfemoral aortic valve replacement, first performed in 2001 by Cribier et al., is beyond doubt one of the greatest achievements in interventional cardiology (Cribier et al. 2002). As alternative to conventional surgical aortic valve replacement, a minimally invasive transcatheter implantation of a valve prosthesis is possible. The intervention was originally reserved for medium- to high-risk elderly patients, also due to material durability profiles. In recent years, its indication has been extended to younger patients age

<75 years. Recently, transcatheter valve replacement has been approved by the FDA as the method of choice for all patients (Edlinger et al. 2020). The most important challenge is the material compatibility and the special required characteristics of the valve. Those consist of “durability, low thrombogenicity, hydrodynamics, hemocompatibility, low calcification susceptibility and crimping and deployment stability” (Rotman et al. 2018).

Various models have been developed over the years, whereby the self-expanding Medtronic valves (CoreValve, Evolut R) (Medtronic, Minneapolis, MN, USA) and the balloon-expanding Edwards valves (Sapien, Sapien XT, Sapien 3) (Edwards Lifesciences, Irvine, CA, USA) are the most widely implanted valve types (Chakos et al. 2017). The SAPIEN 3 and SAPIEN 3 Ultra are the latest generation of balloon-expanding Edwards valves. The Evolut R and Evolut PRO are the latest self-expanding valves from Medtronic (Renker and Kim, 2020). In several hospitals they consist more than 70% of the total transcatheter aortic valve implantation (TAVI) procedures.

Another important aspect concerns the valve-in-valve procedures. Here is the geometric orifice area that plays the most significant role. Therefore a valve-in-valve procedure should only be used after careful planning, because it can diminish the

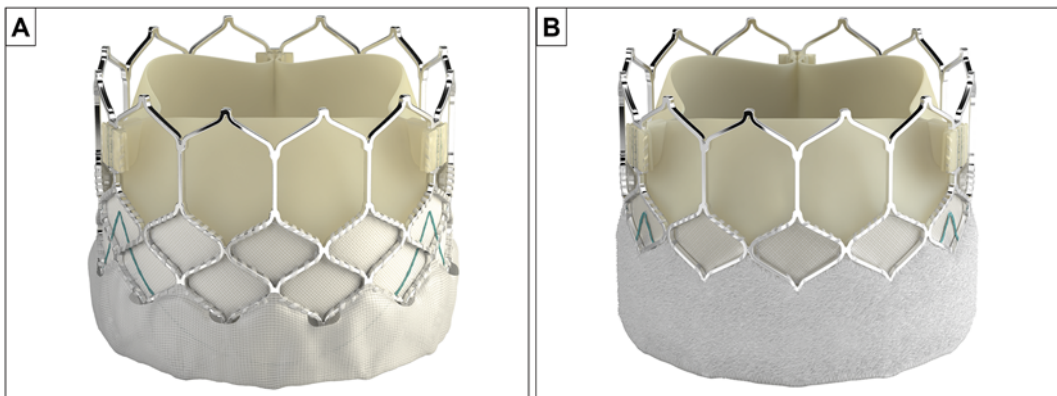


Fig. 4 Transcatheter aortic valve products of Edwards Lifesciences. (a) Edwards SAPIEN™; Edwards SAPIEN 3™ transcatheter heart valve. Picture provided by

Edwards-Sapien. (b) Edwards SAPIEN™ 3 Ultra; Edwards SAPIEN 3 Ultra™ transcatheter heart valve. Picture provided by Edwards-Sapien

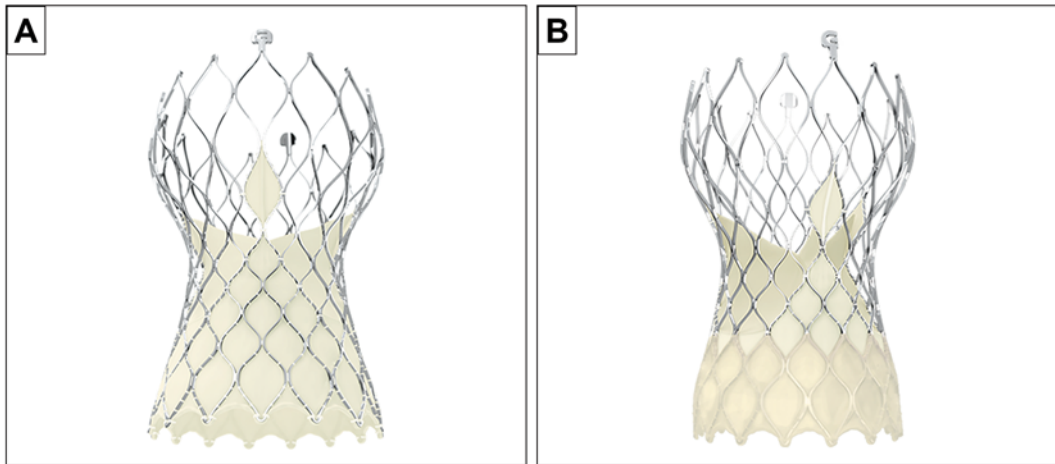


Fig. 5 Transcatheter aortic valve products of Medtronic. (a) CoreValve™ Evolut™ R. (b) CoreValve™ Evolut™ Pro. (Source: Medtronic GmbH)

hydrodynamic performance of the valve and significantly reduce the opening area (Rotman et al. 2018).

2.4.1 Edwards SAPIEN 3/SAPIEN 3 Ultra

The Edwards SAPIEN 3 (Fig. 4a) and SAPIEN 3 Ultra (Fig. 4b) consist of a cobalt–chromium stent frame, three leaflets of bovine pericardium, an inner and an outer skirt. The SAPIEN 3 has an internal skirt and an outer sealing skirt made of polyethylene terephthalate (PET) (Jose et al. 2015). In the SAPIEN 3 Ultra, the outer portion is textured PET material with a greater height in comparison to the SAPIEN 3 (Renker and Kim, 2020). The valves are manufactured in four sizes (20 mm, 23 mm, 26 mm, and 29 mm).

2.4.2 Medtronic Evolut R/Evolut PRO

Both valves consist of a self-expandable nitinol stent frame and three leaflets of porcine pericardium positioned in a supra-annular location. In contrast to the Evolut R (Fig. 5a), an external porcine pericardial sleeve has been added to the Evolut PRO (Fig. 5b) as a sealing sleeve. The Evolut R model is manufactured in four sizes: 23 mm, 26 mm, 29 mm, and 34 mm, while the Evolut PRO is only available in 23 mm, 26 mm, and 29 mm.

The valve size selection is of paramount significance for the physician and for the patient and

is highly associated with the success of a TAVI procedure. In order to choose the right valve size, an MSCT Scan must be performed. Then the appropriate software should be used to quantify the aortic root.

The cut-off values of the manufacturer’s sizing plan should be considered. There is often a difference between clinical valve selection and selection based on the computer software. The “device–host interaction” is very important in order to prevent complications such as obstruction of the coronary arteries, relevant aortic regurgitation after implantation as well as conduction disorders such as atrioventricular (AV) block (El Faquir et al. 2020).

A rare but sometimes life-threatening complication is the transcatheter heart valve migration into the outflow tract of the left ventricle. In this case is a balloon repositioning of the valve necessary as well as possibly a valve-in-valve procedure in order to prevent severe aortic regurgitation (Ito et al. 2017).

One of the deciding mortality as well as success parameters of a TAVI procedure – also long term – is the paravalvular regurgitation. This reinforces the importance of correct valve selection and the experience of the physician. In several publications, it is observed that in the second part of the study or cohort there are a greater number of good final results as the technique of

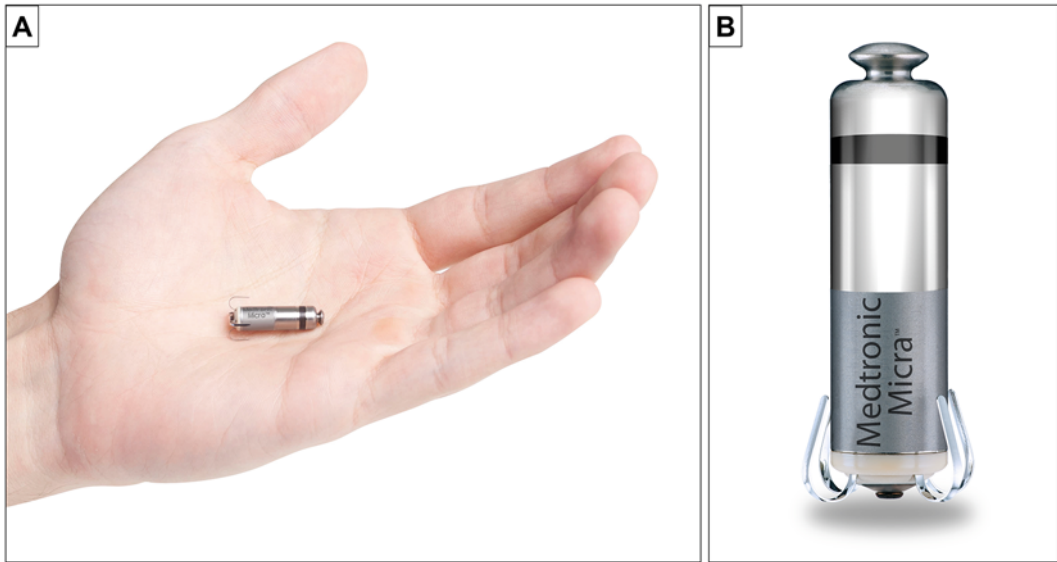


Fig. 6 Micra Pacemakers. (a) Illustration of **Micra™** pacemaker size compared to a human hand. (b) **Micra™**. (Source: Medtronic GmbH)

the interventional cardiologist improves exponentially (Wang et al. 2021).

2.5 Leadless Pacemakers

Within the last decade, single-chamber leadless pacemaker devices have been developed, which are implanted to the inner side of the right ventricle via a steerable catheter insertion system (Reynolds et al. 2016). Currently, the most common device in clinical use is the Micra™ (Medtronic Inc., Minneapolis, MN, USA). Despite its small size of 0.8 m^3 , a light capsule weight of 2.0 g, a length of 25.9 mm, and an outer diameter of 6.7 mm, it has all the features of a conventional single-chamber pacemaker system (Reddy et al. 2015). The Micra pacemaker itself consists of nitinol, gold, steel, titanium, and tungsten (Figs. 6a and 6b). The tines, with which the device is affixed to the endocardium of the right ventricle, consist entirely of nitinol.

There are now numerous clinical studies that prove both, the effectiveness and safety of the product. Medtronic postulates that the device would float in an *in vivo* environment at the inside of the right ventricle. According to the manufacturer, the only connection to the endothelium is

through the pacemaker's anchoring system. As lead-free pacemaker technology is a relatively new topic, the effects on the intracardiac endothelium at the anchor point are not yet well understood. However, individual cases have also been published in which unexpected encapsulation was observed. First data from autopsies show partial or even complete encapsulation (Tjong et al. 2015; Kypta et al. 2016). In the two published cases, complete endothelialization or even encapsulation is reported after 12 months and 19 months, respectively. Within one of our prior *in vitro* studies, we could identify a potential impact of the tungsten component in these processes of endothelialization (Edlinger et al. 2019).

3 Common Device Components

3.1 Nitinol

Nitinol, a material used in the majority of intracardiac devices, is a 55:45 nickel–titanium alloy. It is of enormous value for medical applications due to its thermal shape–memory effect and super elasticity (Ryhänen et al. 1998). Nitinol is not considered cytotoxic or thrombogenic, although its individual components, nickel and titanium,

can be detected in peripheral blood samples (Shayan and Chun 2015).

It is assumed that the immunological effects are comparable to those of stainless steel without any toxic effects (Ryhänen et al. 1998). Nitinol is widely used, for example, in many PFO and ASD occluders, as well as the tines of the Micra pacemaker are made of this material.

3.2 Titanium

Due to its good *in vivo* compatibility, titanium is a widely used component for implants and alloys (Ungersboeck et al. 1995). Concentrations of 50–150 µg/l can be measured in peripheral blood samples, a level considered nontoxic (Ipach et al. 2012). Data from orthopedic studies could show an increase in classical inflammatory cytokines such as tumor necrosis factor alpha (TNF- α), interleukin-1beta (IL-1 β) and IL-6 in patients with titanium implants. However, there is no evidence of toxicity to date (Sun et al. 2000; Östberg et al. 2015). In cardiology, for example, titanium is used in pacemaker generators with no long-term adverse effects. It is particularly important as a component of the nitinol alloy.

3.3 Tungsten

Tungsten is another component that is commonly used in medical devices. Certain publications point to toxic effects during long-term treatments (Witten et al. 2012). However, according to the current knowledge, no toxic effects are expected at normal corrosivity rates and slightly elevated serum levels are considered as normal (Peuster et al. 2003). It is considered to be a very strong and durable material as well as very resistant to corrosion. In cardiology, tungsten is widely used as a component of pacemaker probes. The Micra pacemaker also partly consists of this material.

3.4 Gold

Implants made of gold and its nanoparticles are known to be noncytotoxic and nonimmunogenic

(Shukla et al. 2005). Cytokine elevations of interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF- α), interleukin 1-beta (IL-1 β), and mononuclear chemotactic protein 1 (MCP-1) are frequently found. However, these cytokine reactions are insignificant and have no influence on the cell viability (Zhang et al. 2011). For this reason, gold is of paramount value as a reserve material if the patient to be implanted suffers from a previously known allergy, for example to titanium. This is a rare allergy, which affects only the 0.6% of the total population. There are reports of patients who have been successfully implanted with a gold-plated leadless pacemaker for this indication. This was described in a 65-year-old man with a type IV allergy to titanium in the case report by Kypta et al. (Kypta et al. 2015; Goli et al. 2012).

3.5 Steel

Steel is considered to be a material of manufacturing precision, good hygiene, as well as high resistance against corrosion. It has been reported that the toxic effects of steel implants are higher than those of other components (Haynes et al. 1998). Lacey et al. observed a decrease in monocyte and macrophage survival in response to steel (Lacey et al. 2009), as well as a reduced leukocyte migration to the implant site or prosthetic implants. In addition, steel has been shown to induce abundant elevation of cytokines such as IL-1 β (Haynes et al. 1998).

4 Cardiac Injury, Wound Healing, and Regeneration – A Brief Overview

Cardiac injury causes a severity-related damage of the myocardium, followed by cardiac repair or wound healing where damaged tissue is usually replaced by a fibrotic scar, as described in the literature (Deb and Ubil 2014; Talman and Ruskoaho 2016). Moreover, it has recently been reported that adult cardiomyocytes (CMs) have a slight ability to proliferate, raising the promise of promoting cardiac regeneration in humans

(Beltrami et al. 2001; Bergmann et al. 2009; Mollova et al. 2013). However, the feasibility of cardiac regeneration is largely dependent on the type and extent of immune responses, thus leading to an inflammatory response (Sattler and Rosenthal 2016; Cheng et al. 2017).

Although the implantation of an intracardiac device is necessary for the maintenance of proper cardiac pacing in various cardiac diseases, it is also accompanied by the injury of the cardiac tissue at the site of implantation. This inevitable injury initiates a complex series of tissue repair processes that comprise of the interaction and timely coordination of several cell types, cytokines, chemokines, and signaling cascades. Furthermore, there is a host reaction following the implantation of foreign biomaterial into the cardiac implantation site. This also includes blood–material interactions, inflammation, granulation, provisional matrix formation, and the fibrotic remodeling of the injured area (Gretzer et al. 2006; Luttkhuizen et al. 2006).

Generally, the immune response to cardiac injury is accomplished by the innate and the adaptive immune systems in synergy and can be divided into three phases: the pro-inflammatory phase, the proliferative phase, and the reparative phase (Lai et al. 2019).

4.1 Pro-inflammatory Phase

In the very early process after the implantation of a foreign biomaterial, a material–blood interaction occurs, whereby proteins from the blood adhere to the implant's surface. A provisional matrix based on the blood's components forms, that is, the initial thrombus or blood clot where further protein adsorption proceeds. This provisional matrix and the injured tissue are responsible for the recruitment of structural, biochemical, and cellular compartments that are essential for wound healing (Gristina 1994; Gretzer et al. 2006; Luttkhuizen et al. 2006). In this period, inflammatory cells are recruited to the site of injury to clear the damaged wound of dead cells and tissue, as well as to degrade the matrix debris. Furthermore, it initiates the processes necessary

to form the reparative scar. However, it has been described that prolonged or excessive inflammation is accompanied by a poor tissue remodeling and worse outcomes in patients or animal models with myocardial infarction (MI) (Timmers et al. 2008; Arslan et al. 2010; Frangogiannis 2012).

The initial immune response is driven by molecules released from necrotic cells, the so-called damage associated patterns (DAMPs) (Arslan et al. 2010). In addition, during tissue death, dying proteases, hydrolases, and mitochondrial reactive oxygen species (ROS) are also released into the extracellular space, generating further DAMPs that trigger the inflammatory response (Kono and Rock 2008). Subsequently, these DAMP molecules bind to pattern recognition receptors (PRRs), including toll-like receptors (TLRs) and the receptor for advanced glycation end products (RAGE), that are expressed by both tissue resident cells and recruited leukocytes (Muzio et al. 2000; Chavakis et al. 2004). Among other DAMPs present in cardiac inflammation, high-mobility group B1 (HMGB1) is one of the best characterized (Andrassy et al. 2008). HMGB1 is responsible for the initiation of inflammation in myocardial infarction (MI) and cardiac ischemia by promoting the migration of immune cells through its interaction with PRRs, such as TLR2/4 (most abundant TLRs in the heart) and RAGE (Nishimura and Naito 2005; Klune et al. 2008; Sims et al. 2009). Moreover, it induces tissue healing by changing the macrophages' phenotype, favoring neoangiogenesis and promoting stem cell activation and proliferation (Bianchi et al. 2017).

Physiologically, the extracellular matrix (ECM) is responsible for the support and the maintenance of the heart's structural integrity. However, during inflammation the ECM is degraded by matrix metalloproteinases (MMPs), activated by necrotic cells, neutrophils, and macrophages. This degraded ECM can in turn act as a DAMP, driving the inflammatory pathway forward (Dobaczewski et al. 2010a). In the context of cardiac injury, a switch to a transient fibrin-based ECM is achieved (González-Rosa et al. 2011; Frangogiannis 2017), further

modulating and guiding inflammatory cells through TLRs (Corbett and Schwarzbauer 1998; Smiley et al. 2001; Flick et al. 2004) and promoting the proliferation of endothelial cells and fibroblasts (Frangogiannis 2017).

As mentioned above, dying cardiomyocytes release intracellular components, such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), as well as intracellular components like adenosine triphosphate (ATP) and heat shock proteins (HSPs), that might accelerate the ongoing immune response (Arslan et al. 2011; Kono et al. 2014). Furthermore, reactive oxygen species (ROS), which stem from mitochondria of necrotic cells or are secreted by neutrophils, constitute a key player in the promotion of immune cells to infiltrate the injured tissue. ROS contributes to the onset of the nuclear factor kappa light chain enhancer of activated B-cells (NF- κ B), a main chemotactic and pro-inflammatory protein complex (Thannickal and Fanburg 2000; Gloire et al. 2006), and directly activates the so-called inflammasome, as well as cardiac resident cells, such as fibroblasts and mast cells (Gilles et al. 2003; Kawaguchi et al. 2011). The inflammasome, a multiprotein complex of receptors and cytokines, in turn promotes the immune response and triggers the expression and activation of other cytokines (Latz et al. 2013).

After the immune response has been initiated by damage-associated molecular patterns (DAMPs) and related pattern recognition receptors (PRRs), resident immune cells and non-immune cells, such as resident macrophages, endothelial cells (ECs), and fibroblasts, drive the expression of pro-inflammatory cytokines and chemokines. In cardiac device implantation, the extent of immune responses is primarily mediated by the extent of injury that happened during the implantation procedure (Zdolsek et al. 2007; Tang et al. 1998). In the presence of DAMPs, cytokines, chemokines, activated platelets, and histamine, neutrophils are the first innate immune cells that are rapidly recruited to the injured tissue (McDonald et al. 2010; Soehnlein and Lindbom 2010). Contemporaneously, the cardiac endothelium is activated by pro-inflammatory cytokines, such as TNF- α , IL-1 β , and histamine (Duperray

et al. 1995; Dewald et al. 2004; Debrunner et al. 2008). This ensemble of pro-inflammatory cytokines constitutes the inflammasome and facilitates the neutrophil transmigration between and through the endothelial wall to the site of tissue injury (Frangogiannis et al. 1998; Singh and Saini 2003). Furthermore, IL-6 seems to be a main mediator of tissue injury, since it is expressed by CMs and recruited neutrophils and macrophages (Youker et al. 1992). IL-6 in turn upregulates intercellular adhesion molecule 1 (ICAM-1) on CMs that mediates neutrophil binding and is associated with cytotoxic events (Entman et al. 1992; Youker et al. 1992).

4.2 Cell Proliferation Phase

The cellular proliferative phase is the second phase and is characterized by the expansion of neutrophils and macrophages that degrade dead cells and the matrix debris, further promoting the expression of cytokines and growth factors. Due to the pro-inflammatory and cytotoxic activity of neutrophils, excessive amounts or a prolonged presence of neutrophils have been associated with remodeling and a poor prognosis after MI (Mocatta et al. 2007; Akpek et al. 2012). On the other hand, they constitute a key factor in the resolution of inflammation and lead to a shift of the macrophages' phenotype to a reparative one (Čulić et al. 2002; Pase et al. 2012). Furthermore, they contribute to the initiation of angiogenesis during inflammation by expressing vascular endothelial growth factor (VEGF) (Gong and Koh 2010).

Generally, monocytes are a type of leukocytes that have the ability to differentiate into macrophages and dendritic cells. There are two different subpopulations of monocytes present in cardiac inflammation: the Ly6C^{high} and Ly6C^{low} (Hettinger et al. 2013; Yona et al. 2013). Ly6C^{high} monocytes belong to the primary subset that is recruited to the injured heart, driven by MCP-1. Therefore, Ly6C^{high} monocytes are commonly active in the early pro-inflammatory phase and are responsible for proteolytic and inflammatory processes. In contrast, Ly6C^{low} are sometimes

known as resident monocytes due to their appearance of not being actively recruited into the injured myocardium (Geissmann et al. 2003; Nahrendorf et al. 2007). They have been shown to emerge later, in the resolution phase, demonstrating decreased inflammatory properties, as well as the expression of VEGF (Yao et al. 2012). It is not definitively clear if Ly6C^{low} arise from differentiation of Ly6C^{high} (Hanna et al. 2011; Yona et al. 2013), although it has been speculated that they arise from the same progenitor cells (Hettinger et al. 2013; Yona et al. 2013). In addition, two macrophage subsets (M1 and M2 macrophages) correspond with these different monocyte concentrations. M1 macrophages are present early after heart injury and are known to secrete pro-inflammatory cytokines, like IL-1 β , TNF- α , IL-6, and IL-10 (Dewald et al. 2005), whereas M2 monocytes become active at the later stage of reparative heart tissue healing (Nahrendorf et al. 2010). However, the simple division of macrophages into two subsets should be considered due to the great variety of macrophage phenotypes (Martinez and Gordon 2014). The initial acute inflammatory response usually resolves within 1 week after device implantation, though it is also dependent on the extent of injury at the implant site (Gretzer et al.).

4.3 Endothelialization and Resolution of Inflammation

Finally, the conversion from inflammation to the repair phase is crucial for wound healing as a prolonged inflammatory response would lead to CM death, excessive fibrosis, cardiac remodeling, and damage. In cardiac device implantation, acute inflammation is often followed by a chronic inflammation period that is characterized by the presence of mononuclear cells, such as monocytes and lymphocytes. This chronic inflammation lasts for a short time of approximately 2 weeks and is strictly located to the site of implantation. The prolongation of the inflammation phase for greater than 3 weeks, usually a device infection is indicated (Luttikhuisen et al. 2006). Once the inflamed/injured area is cleared

of apoptotic cells, the repair process is initiated and a new ECM is produced (Frangogiannis 2014). The resolution phase is mainly characterized by the recruitment of lymphocytes, the activation of fibroblasts, and the proliferation of ECs, as well as the activation of smooth muscle cells (SMCs).

Originally, it was thought that circulating endothelial progenitor cells (EPCs), as progenitors of ECs, were a source of new endothelial cells, as first described by Asahara et al. in 1997 (Asahara et al. 1997). They originate from different hematopoietic progenitor cells located in the bone marrow, such as hematopoietic stem cells, myeloid precursors, and mesenchymal stem cells (Balistreri et al. 2015). However, EPCs also stem from different nonhematopoietic tissues, such as the umbilical cord etc. (Ingram et al. 2004; Mund et al. 2012; Chan et al. 2013). In response to tissue damage, they are released into the circulation and invade the site of injury attracted to inflammatory cytokines and chemoattractant proteins. As progenitor cells, EPCs constitute a source for ECs by differentiation and further promoting the proliferation of resident ECs (Buijs et al. 2004; Li et al. 2012). Furthermore, they release several growth factors, such as VEGF and angiopoietins, and other pro-endothelial factors that promote the healing process (MCP-1), stromal cell-derived factor 1, insulin-like growth factor 1, platelet-derived growth factor (PDGF), and macrophage inflammatory protein 1a (Rehman et al. 2003; Caiado et al. 2008). In turn, these factors stimulate ECM proteins and the proliferation of SMCs. An overview of the factors released by ECs, SMCs, and inflammatory cells was already provided by Welt and Rogers (Welt and Rogers 2002).

Both lymphocytes, B- and T-cells, comprise the main cellular components of the adaptive immune system. T-cells are further divided into CD8⁺ and CD4⁺ subsets, whereas CD4⁺ T cells are the main actors in the healing process. According to their secreted cytokines they are further classified into Th1 (IL-2, TNF- α , and interferon gamma (IFN- γ); Th2 (IL-4, IL-4, IL-13); Th17 (IL-17, IL-21, IL-22); and regulatory T-cells (Treg) (transforming growth factor

beta (TGF- β), IL-35) (Hofmann and Frantz 2015). More precisely, especially Tregs play a key role in the healing phase through suppressing the immune response in the damaged tissue, promoting revascularization, and initiating the shift to a reparative phenotype of the macrophages (M2 microphages; as mentioned above) (Zougari et al. 2009; Dobaczewski et al. 2010b; Weirather et al. 2014). Particularly, TGF- β was shown to be mainly responsible for the deactivation of inflammatory macrophages in MI (Dobaczewski et al. 2011). These M2 macrophages then have the ability to express high amounts of several different MMPs and secrete anti-inflammatory cytokines, such as IL-4, IL-13, and mainly IL-10 (Frangogiannis et al. 2000). Consequently, the extent of IL-4 and IL-13 expression also determines the extent and duration of the inflammatory response. Furthermore, it was found that myeloid–epithelial–reproductive tyrosine kinase (MERTK) (Wan et al. 2013) and platelet-derived growth factor (PDGF) (Zymek et al. 2006) are crucial for the transition to a reparative status too. Furthermore, TGF- β signaling and the decline in pro-inflammatory cytokine signaling result in the activation of interstitial and perivascular fibroblasts, EC proliferation, followed by reparative myocardial fibrosis and angiogenesis (Chen and Frangogiannis 2013). Any failure of accurate regulation of Treg or TGF- β signaling may lead to excessive scar formation, an ongoing chronic inflammation (Kypita et al. 2016), such as described in the case report by Kypita et al. (Dobaczewski et al. 2011).

5 Discussion

In the last decades, an immense increase in the number of implanted intracardiac devices could be observed (Mond and Proclemer, 2011). At the same time, patients implanted with a device are getting older and therefore may live for decades with this foreign material embedded in the endocardium and exposed to blood flow (Leon et al. 2010; Proclemer et al. 2010). This is of relevance

insofar as little is known about long-term toxic effects of implantable devices (Eliaz 2019; Nasakina et al. 2019). Furthermore, at present it is not known with certainty whether there is a “critical concentration” of the metallic components which, if exceeded, can be expected to cause consequential damage to health. Nitinol, by far the most commonly used alloy for intracardiac devices, appears to have a number of good properties especially during implantation and durability in long-term treatment. On the one hand, it is highly malleable, which is of enormous importance in the context of implantation (Stoeckel et al. 2004; Henderson et al. 2011; Maleckis et al. 2018); on the other hand, it is considered to be extremely durable with overall good tolerance (Eliaz 2019).

We know from numerous preliminary reports that as a result of intracardiac positioning, endothelialization on nitinol surfaces is expected to occur after only a few weeks (Zahn et al. 2001; Sigler et al. 2005a; Schwartz et al. 2010) and depends on numerous factors, such as the size of the device or, in the case of occluders, the primary interventional outcome (Granier et al. 2018). Incomplete endothelialization could lead to complications at site of the implantation, such as thrombus formation (Sigler et al. 2005b; Sellers et al. 2019). Moreover, patient-specific factors must be taken into consideration. For instance, there are known cases of patients with multiple allergies where excessive endothelialization was found in the autopsy (Kypita et al. 2016). Vice versa, it seems conceivable that endothelialization processes or the healing phase can be negatively influenced by the intake of immunosuppressive substances such as glucocorticoids (Radovsky et al. 1988) or TNF- α inhibitors (Sandberg et al. 2012). The same is conceivable for patients in whom cytotoxic substances or radiation therapies are used (Hopewell 1990). As a wide overall variation in anatomic conditions is to be expected in PFO, ASD, or LAA occlusions, positional control by transesophageal echocardiography appears essential (Krizanic et al. 2010; Saw et al. 2016).

Intracardiac pacemakers are a special case in this context, as no endothelial surface usually

forms over the implanted cardiac device due to direct contact with the blood flow (Jana 2019). According to the manufacturers, the devices should only be anchored to the endocardium at their base, while the majority of the device should remain floating in the blood flow. However, there are now several published cases reporting the contrary. Namely, a complete or at least partial endothelialization/encapsulation of the device in the right ventricular wall (Candinas et al. 1999; Esposito et al. 2002; Tjong et al. 2015; Keiler et al. 2017). Interestingly, there are also reports from autopsies where histological processing has shown a clear evidence of inflammatory processes around the encapsulated pacemaker (Dvorak et al. 2012). Exact knowledge of any expected endothelialization is of enormous clinical relevance, since an influence on the stimulation threshold is at least conceivable through the encapsulation (Stokes et al. 1991). There are also issues of what to do in the event of battery exhaustion. An extraction, as originally intended by the developers, seems unlikely in the case of complete encapsulation. It remains to be seen whether the limited space at the surface of the inner heart is sufficient to safely implant an additional device. For the Micra pacemaker, it could be shown in an animal model that up to three devices can be implanted without any problems (Omdahl et al. 2016).

Another major uncertainty is the importance of allergies in long-term use. Nitinol is an alloy which consists of 45–50% nickel (Eliaz 2019), a relevant allergen. Nickel allergies are type IV allergies, that is, a contact allergy caused by long-term exposure, usually after 24 h to a few days (Tramontana et al. 2020), and are relatively common with a prevalence of approximately 8% to 19% in adults (Diepgen et al. 2016). Whether the allergenic potential within the blood flow is particularly high, or whether a weakening occurs once endothelialization has been achieved, remains completely unclear to date. Allergies are also known to occur with exposure to titanium, which is the other component of the nitinol alloy (Fage et al. 2016). However, the incidence is

significantly lower for titanium; consequently therefore the clinical relevance is probably of secondary importance (Grosse Meininghaus et al. 2020). In case of a confirmed allergy, it is possible to coat the device with a less/nonallergenic substance such as gold, which has already been done in individual cases (Kypta et al. 2015). The measurement of any metal released from cardiac devices has already been performed (Ries et al. 2003; Saylor et al. 2018). An open question for the future will be whether there are measurable parameters that can be used to estimate the degree of endothelialization. For example, it is conceivable that the metallic components could be measured as nanoparticles in peripheral blood, but their concentration would decrease during the healing phase. It may also be assumed, that with complete endothelialization achieved, the metal content might fall below the detection limit, which in turn provides important additional information for the estimated duration of the healing process.

6 Conclusion

In summary, we conclude that the vast majority of intracardiac devices meet very high safety standards from a hemostasiological point of view, and that there is currently no evidence of any therapy-limiting toxic effects in long-term treatment. Nitinol, as a component of many devices, is of particular importance in this context. However, there are currently gaps in knowledge for patients who are under immunosuppressive medication. Moreover, the impact of an optimal implantation technique on the initial healing phase and endothelialization phase has not been fully understood in many cases.

For these reasons, it seems indispensable to us that patients continue to be treated at the respective healthcare center after primary implantation and are followed up by means of imaging, so that individualized coagulation management can be determined if necessary.

7 Limitations

We could only include devices which are already in broad clinical use. Nevertheless, a number of less-established devices in the field of interventional cardiology might already have received market approval or might be in the preclinical testing phase. However, in our opinion, the current knowledge of the established devices provide a fundamental basis for the above review and the obtained conclusions.

Contributions C.E planned and coordinated the study, compiled and analyzed data, wrote the manuscript, and contributed in the final submission. V.P., E.B., S.H.K., and M.B. analyzed data, prepared figures, and contributed to manuscript preparation. F.K. analyzed data and contributed to final submission. V.D. contributed in data acquisition. K.K. carried out English-language editing of the paper. E.L., C.B., and U.C.H. revised the article critically for the content. M.L. planned the study and provided the final approval of the article.

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