Review

Neointimal fibrotic lead encapsulation – Clinical challenges and demands for implantable cardiac electronic devices

Jonas Keiler (PhD)\textsuperscript{a,e}, Marko Schulze (Dipl.-Biol.)\textsuperscript{a}, Martina Sombetzki (PhD)\textsuperscript{b}, Thomas Heller (PhD)\textsuperscript{c}, Tina Tischer (PhD)\textsuperscript{d}, Niels Grabow (PhD)\textsuperscript{e}, Andreas Wree (PhD)\textsuperscript{a}, Dietmar Bänsch (PhD)\textsuperscript{a}

\textsuperscript{a}Department of Anatomy, Rostock University Medical Center, Rostock, Germany
\textsuperscript{b}Department for Tropical Medicine and Infectious Diseases, Rostock University Medical Center, Rostock, Germany
\textsuperscript{c}Institute of Diagnostic and Interventional Radiology, Rostock University Medical Center, Rostock, Germany
\textsuperscript{d}Heart Center Rostock, Department of Internal Medicine, Divisions of Cardiology, Rostock University Medical Center, Rostock, Germany
\textsuperscript{e}Institute for Biomedical Engineering, Rostock University Medical Center, Rostock, Germany
\textsuperscript{f}KME Clinics Güstrow, Germany

\textbf{A R T I C L E  I N F O}

Article history:
Received 20 December 2016
Accepted 16 January 2017

Keywords:
Lead failure
Lead tissue encapsulation
Vascular fibrosis
Neointimal formation

\textbf{A B S T R A C T}

Every tenth patient with a cardiac pacemaker or implantable cardioverter-defibrillator implanted is expected to have at least one lead problem in his lifetime. However, transvenous leads are often difficult to remove due to thrombotic obstruction or extensive neointimal fibrotic ingrowth. Despite its clinical significance, knowledge on lead-induced vascular fibrosis and neointimal lead encapsulation is sparse. Although leadless pacemakers are already available, their clinical operating range is limited. Therefore, lead/tissue interactions must be further improved in order to improve lead removals in particular. The published data on the coherences and issues related to lead associated vascular fibrosis and neointimal lead encapsulation are reviewed and discussed in this paper.

© 2017 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

\textbf{Contents}

<table>
<thead>
<tr>
<th>Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>8</td>
</tr>
<tr>
<td>Lead issues</td>
<td>8</td>
</tr>
<tr>
<td>Lead longevity</td>
<td>8</td>
</tr>
<tr>
<td>Lead/tissue interactions: thrombosis and fibrosis</td>
<td>8</td>
</tr>
<tr>
<td>Lead-induced venous obstruction</td>
<td>8</td>
</tr>
<tr>
<td>Characterization and etiology of fibrotic lead encapsulation</td>
<td>9</td>
</tr>
<tr>
<td>Transvenous lead extraction (TLE)</td>
<td>11</td>
</tr>
<tr>
<td>Strategies to avoid lead issues</td>
<td>12</td>
</tr>
<tr>
<td>Leadless pacemakers</td>
<td>12</td>
</tr>
<tr>
<td>Requirements for future cardiac device leads</td>
<td>13</td>
</tr>
<tr>
<td>Summary</td>
<td>13</td>
</tr>
<tr>
<td>Funding</td>
<td>13</td>
</tr>
<tr>
<td>Conflict of interest</td>
<td>13</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>13</td>
</tr>
<tr>
<td>References</td>
<td>13</td>
</tr>
</tbody>
</table>

\textsuperscript{*} Corresponding author at: Department of Anatomy, Rostock University Medical Center, Gertrudenstraße 9, 18057 Rostock, Germany. Fax: +49 381 494 8402.
E-mail address: jonas.keiler@uni-rostock.de (J. Keiler).

http://dx.doi.org/10.1016/j.jcc.2017.01.011
0914-5087/© 2017 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
Introduction

The worldwide demand for implantable cardiac electronic devices (ICEDs) such as pacemakers (PMs) for bradyarrhythmia treatment, devices for cardiac resynchronization therapy (CRT), and implantable cardioverter-defibrillators (ICDs) is continuing to increase due to the aging society [1–3] and socioeconomic changes in several countries [4]. Due to the aging society, the life expectancy in the European Union is approximately 81 years [7] – but also due to patients with congenital cardiac defects who receive a cardiac device at an early age [8–10].

However, transvenous leads are the Achilles' heel of ICEDs and problems with leads are the most common indication for revision of PMs and ICDs [11–13]. Inactive PM leads, however, are rarely explanted; e.g. in 2013 in Germany in about 50% of patients, only [12]. This is due to the often risky extraction procedure, which should be performed only in specialized centers and with cardiac surgical backup [14–17]. In recent years, major complication rates during lead extraction ranged from 0% to 7% and procedure-related mortality rates ranged from 0% to 2.6% [12,18–23]; e.g. in 2013, 307 PM: 1.2%; ICD: 1.6% of patients died during or after revision or explantation in German hospitals [12,13]. The main reasons for the fatal and non-fatal complications during extraction are neo-intimal fibrotic encasulations of the transvenous leads which tend to occur in ICED patients over time [16]. Although it is of high clinical and economic relevance, relatively little is known about the causes and biological processes of lead-associated neo-intimal fibrosis. However, detailed knowledge of lead-related defects on the one hand and neo-intimal fibrotic lead encasulation on the other are both necessary prerequisites to respond to actual and future challenges in heart rhythm therapy. In this paper, we focus on the phenomenon of neo-intimal fibrotic lead encasulations by discussing published data on lead/tissue interactions and strategies for avoidance of lead encasulation in the light of our own experiences.

Lead issues

On the one hand, leads present an increased risk potential for the development of thrombosis and acute vessel occlusions [24–36]. On the other hand, complications are frequently encountered during the explantation of defective leads due to fibrous adhesion sites with the vessel wall or an almost complete encapsulation into a neo-intimal tissue pocket created by the lead (Fig. 1) [9,15,37–42]. Moreover, it is believed that the newly formed tissue sheath at the lead coils in ICDs can also result in an unfavorable higher threshold [43,44]. The most common causes for ICED revision and lead explantation are dislodgement of the lead, loss of pacing, lead fractures, insulation defects, and infection [12,13,16,18,21,45,46]. Moreover, lead removal can be indicated in the course of a system upgrade [19,47–50]. Although technical improvements in recent years have improved their performance, ICED leads, especially those of ICDs, still demonstrate an unacceptable high failure rate in the form of defects and lead fractures [13,51–56].

Led longevity

PM leads for bradycardia therapy have experienced the longest period of product evaluation and evolution [57] and reach a long-term cumulative survival rate of about 95% for 10 to 97% for 15 years, based on manufacturers' product performance reports [58,59] – a rate that is consistent with previous studies on PM lead longevity [57]. Technical malfunction rates of PM leads (e.g. conductor fracture, insulation breach, or crimps) returned to manufacturers are, however, very small (0.0–0.42%) [60].

The longevity of ICD leads is worse. The mean 5-year-survival rate ranges from 85% to 98% [52,61–63]. Long-term survival rates range from 60% to 72% for eight years, the annual lead defect rate increases with 20% for 10-year old leads [52,63]. A recent meta-data based analysis, however, concludes that at worst about 90% of ICD leads would survive 10 years [64].

In pediatric patients with congenital heart disease, leads have a higher failure rate [65–67]. This is attributed to enhanced lead stretching and distortion due to growth and more intense physical activity in younger patients [68,69].

Although their implant numbers are increasing continuously [70], CRT devices are applied relatively seldomly among pacemakers (in 2013: 1.8% in Germany, 5.0% in Sweden) [12]. Therefore, information on the survival of CRT leads implanted in the coronary sinus is relatively sparse. Nevertheless, fracture of CRT leads appears far less often than in PM or ICD leads. Besides dislodgement [71] and threshold increase [72] infection is reported as the main indication for the extraction of coronary sinus leads in CRT patients [73–76].

Lead/tissue interactions: thrombosis and fibrosis

The causes for occlusion associated with pacemaker leads were formerly categorized as I. thrombotic occlusion or II. fibrotic occlusion with or without associated thrombosis [34]. However, our experience with autopsied corpses shows that, although further reducing the cross-sectional area of the respective vascular section, neo-intimal fibrotic encasulations themselves do not obstruct the vessel since the tissue sheath is rather thin (<1 mm), with a maximum thickness of 3 mm [41]. Therefore, we assume that lead-associated obstruction is always based on thrombosis, either with or without neo-intimal fibrotic encapsulation.

Lead-induced venous obstruction

The (presumably always thrombotic) occlusion is often not clinically apparent at first [77] due to the formation of venous collaterals [27,28,34,77,78] (Fig. 2A). Therefore, typical symptoms of lead-associated upper extremity deep venous thrombosis (UEDVT) such as swelling and pain in the arm occur infrequently, although these severely impair the patient when they do arise and UEDVT is linked to a significant incidence of pulmonary embolism and an increased mortality [36,79]. Lead-associated superior vena cava obstruction (Fig. 2B) occurs less often but likewise has severe effects [34]. In 12%, a complete occlusion of the subclavian vein or the brachiocephalic vein following PM or ICD implantation occurs without infections and with functional leads [80]. Although it is evident that ICD leads increase the incidence of obstruction it has been shown that UEDVT in the subclavian and brachiocephalic vein can occur independently from lead implantation [77] – thus, a direct coherence between leads and vessel obstruction is possibly not given in all cases. Occurrence of clinically inapparent venous obstruction just before lead placement as previously stated [77] is, however, rather unlikely since lead implantation via obstructed vessels usually requires specialized techniques, such as balloon venoplasty [81].

Computational fluid dynamic models have been constructed for the comparison of vessels with and without leads based on patient-specific computed tomography data. These findings suggest that shear wall stress at the vein wall is about 25% greater in lead-bearing vessels due to their diameter decrease while mean exposure time which is a correlate of prothrombotic blood flow stasis is increased adjacent to the leads [82].

According to venography-based studies, the type of insulation material (silicone or polyurethane) does not appear to affect the
risk of venous occlusion [83,84]. In contrast with popular opinion, it appears to make no difference whether the lead is placed via the cephalic vein or the subclavian vein [84]. Previous ICD implantations and the use of dual-coil leads increase the risk of acute stenosis (>75%) and occlusion [84] (Fig. 2). Mandal and colleagues suspect a correlation between the incidence of lead-induced thrombosis and comorbidities such as diabetes mellitus [85], although clear evidence to this effect or with other comorbidities is lacking. While patient’s age or sex does not seem to play a significant role [22,77,86,87], a systemic infection also appears to increase the risk of lead-induced vessel occlusion [80].

Characterization and etiology of fibrotic lead encapsulation

The duration of the devices’ implantation appears to be an important factor in the formation of adhesions and with it problems with the extraction of leads [18,21,22,40,42,88–92]. However, even brief durations of only a few months can apparently result in pronounced encapsulation [41].

There are currently various studies examining tissue ingrowth of PM, CRT, and ICD leads in patients following lead revisions, post mortem or in animal models. Studies on the topography of adhesion sites and encapsulations of PM and ICD leads have thus far been performed on a modest number of humans [16,38,41,93–95] and in animal models [96–98]. With the aid of contrast venography and fluoroscopy, the degree of blockage in vessels through which leads are guided in patients with ICDs has also been examined [8,84,99], although this does not permit a conclusive statement as to the cause (endothelial encapsulation or thrombosis) of the stenosis.

Almost all vascular areas adjoining the leads can be affected by acute fibrosis. The predominant adhesion areas are the venous puncture sites [37,38], that is, primarily the subclavian vein...
Additionally, the brachiocephalic vein [89], the arch into the superior vena cava [37], the superior vena cava itself [38,89], the right atrium [89], but especially the upper right atrium [97] and the right ventricle [89,97] (Fig. 1A,C) and (in case of CRT) the coronary sinus [95,100] are also affected. Adhesions even occur on the tricuspid valve (Fig. 1D) [41,89,101]. In some cases, the papillary muscles and the chordae of the atrioventricular valves have also grown together with the leads [97]. Only the atrial area of the annulus of the tricuspid valves appears to be less affected [97]. Fibrosis not only binds the leads to the vessel wall but also forms between multiple leads and connects them with each other (lead on lead binding) (Fig. 3) [37].

Mechanical testing (circumferential strain and circumferential stress) of the fibrotic capsules suggest physical properties similar to other semi-elastic human tissues and being independent from patient origin and storage condition [88]. Detectable flow turbulences in the superior vena cava supposedly caused by the neointimal lead fibrosis as previously stated [42] is rather unlikely due to the smooth and usually rather thin nature of the endothelialized capsule.

Histological studies of the adhesion sites and the tissue around the electrode tip are available for PM [88,93,94,102–106], CRT [100,105], and ICD [88,103,105,107,108] leads of deceased patients or from lead extractions as well as for PM [94,98,101] and ICD [88,109–111] in animal models. Accordingly, the fibrotic capsules are largely composed of collagen-rich connective tissue with an acellular interface toward the lead and an endothelial-like layer facing the vessel lumen (Fig. 3). Calcification of the fibrotic tissue has been occasionally reported [37,97,103,105,112–114], especially in young and in very old patients [37], particularly those with chronic renal failure [103]. This mineralization with calcium phosphate salts can massively hamper the extraction procedure since laser and electrosurgical dissection sheaths have difficulties to separate such tissue [89,115].

Initial immunohistochemical studies performed by Esposito and colleagues [102] involved pacemaker leads extracted from patients mechanically or with laser sheaths. Neither an increased number of inflammatory nor inflammatory-type cells – which usually appear during the first 1–2 weeks after implant placement [116] and which were found in the lead-induced fibrotic tissue in canines two to eight months after implantation [98] – could be demonstrated. The fibrotic capsules surrounding the leads were entirely surrounded by CD34-expressing endothelial cells [102]. A more recent study by Rennert et al. [88] revealed that the fibrotic capsule of extracted leads is mainly composed of circumferentially arranged collagen type I and III fibers with a low cellularity. Between the collagen fibers, layers of myofibroblasts positive for α-smooth muscle actin and intermediate vimentin filaments were detected, while desmin filaments were largely absent. Concerning temporal dynamics, the proportion of collagen III fibers decreases with implant time (7–8 months) in favor of collagen I fibers which was interpreted as a process likewise present in early wound healing [88].

According to our own experiences, the neointimal fibrotic capsule can encase the lead along some centimeters without any direct adhesion to the vessel wall except an “initial” adhesion zone more distal. This suggests two different stages of fibrotic
encapsulation: I. around the lead (primary orthogonal outgrowth and encapsulation) and II. along the longitudinal axis of the lead with no direct adhesion (secondary longitudinal outgrowth and encapsulation). The underlying causalities for these processes are hitherto unknown. In our view, adhesive fibrotic encapsulation is mainly mechanically triggered by direct contact pressure or friction emanating from the lead, presumably in all cases causing also endothelial injury. Initially, the persistent contact pressure results in a profibrotic tissue remodeling of the respective vascular wall section (accompanied by inflammatory reactions; Fig. 4) and endothelial depletion followed by the neointimal formation around the lead (encapsulation stage I). Following the remarks by Rennert and colleagues, myofibroblasts may play an important role in the mechanically triggered formation of the capsule [88] – similar to the scar formation after myocardial infarcts [117].

Stokes and colleagues provide theories on the mechanisms of transvenous lead encapsulation, according to which thrombosis and endothelial injuries are the initial events triggering lead encapsulation [101]. Pacemaker leads are, accordingly, a blood flow-perturbing element, which can in turn cause thrombosis due to blood recirculation or stasis. Additionally, it is suspected that thrombosis is also triggered by endothelial injuries caused by contact of the leads with the endothelium lining the vessels and with the endocardium [101]. Epstein and colleagues provide further theories, with a thrombus first forming and activating the complement and fibrinolytic system, upon which liquid, proteins, and blood cells penetrate into the tissue adjoining the lead. This results in acute inflammatory reactions that are mediated by neutrophils, macrophages, foreign-body giant cells, and fibroblasts [108].

The underlying mechanisms for the occasional mineralization in lead-bearing veins are hitherto unknown. In general, veins are not prone to calcification with rare exceptions, e.g. the portal and mesenteric venous system affected by hypertension [118]. Probably, osteogenic regulatory genes are activated and trigger the osteogenic differentiation of mesenchymal stem cells or existing cells such as smooth muscle cells – comparable to the calcification process in atherosclerotic arteries [119–121]. Adequate data are lacking describing factors promoting lead-associated venous calcification. Young patient age and long lead-dwelling time, however, have been suggested to increase the risk of calcification [37]. Chronic renal disease also appears to be an important factor for lead-associated venous mineralization [103]. Mechanical stress is proposed to exacerbate dystrophic tissue mineralization but does not seem to be an obligate trigger [122], while the hemodynamic environment and blood pressure might play an important role [123]. Uremia and diabetes mellitus are associated with arterial calcification [121] and might likewise predispose lead-bearing veins for mineralization.

It is noteworthy that the lead-induced histological changes of the vein wall appear to be similar to the neointimal formation associated with the insertion of a central venous catheter (catheter-related sheath) [124–127]. This is hardly surprising since central venous catheters and ICD leads share similar architectural properties such as a tubular silicone coating and presumably similar mechanics at the implant/vessel interface. The findings with catheter-related sheaths were interpreted by some authors to have thrombus formation as the initial event with subsequent infiltration of smooth muscle cells and final transformation into a collagen-rich endothelialized capsule – which is similar to the theory on lead-induced fibrotic encapsulation by Epstein et al. [108].

This hypothesis for the venous system is supported by some studies on neointimal formation in stent-bearing arteries which revealed similar mechanisms involving initial thrombus formation [128–130].

While factors increasing the risk for thrombotic obstruction have been assessed and discussed in various studies, patient-specific conditions promoting the occurrence of fibrotic lead encapsulation are hitherto not adequately surveyed due to the often lacking histological examination. Deducing from the existing data, we suggest that the fibrotic capsule develops independently from the patient’s constitution, age, or gender, and is generally triggered by focal lead-induced rupture of endothelium and subendothelial stratum. The degree of the fibrosis (small foci vs. full encapsulation) might also be a result of the different degrees of mechanical disturbance.

Transvenous lead extraction (TLE)

Methods have now been developed to allow the explantation of ingrown leads using an extraction sheath without causing significant damage to the vessels [131,132] accompanied by high procedural risks [39,95,114]. Among the common risks are pericardial tamponade, tricuspid valve injury, and the tearing of the superior vena cava associated with the highest mortality, and the subclavian vein. It has been shown that the number of leads to be removed increases the risk of complications [133,134], while other studies have not found such a clear correlation [77,83,86,87] and up to four additional leads in a vessel do not necessarily result in an increased rate of occlusion [80,135]. Leaving inactive PM and ICD leads in the vessels of older patients without infections does
not appear to necessarily increase the risk of complications, although reliable data are still lacking for younger patients [24,80,136].

Extraction of CRT leads can be particularly challenging, since CRT patients are often frail due to multiple comorbidities, and the cardiac veins as implantation site are especially fragile [86]. During a 10-year single center study, 173 CRT lead revisions led to 8.7% complications (1.2% major), mostly hematomas requiring drain- age. Lead-induced fibrotic adhesion represented a significant problem in this context. The slightly higher complication rates in comparison to previous studies were ascribed to the longer implant time, increasing the degree of fibrotic adhesion [137]. However, lacking histological examinations of the lead-adhesive tissue an adequate conclusion whether adhesion is of fibrotic or thrombotic origin (or both) remains speculative.

Besides the direct risks during lead extraction thrombosis and venous obstruction after TLE are serious sequelae [74,137,138]. Reimplantation success of CRT leads after removal can be significa- ntly lower than in de novo implantations into the coronary sinus, mainly due to complete obstruction of the previous implant site [74,137], apparently due to prothrombotic vessel wall rupture. In those cases percutaneous coronary venoplasty to appropriately apply the new lead into the coronary vessel is basically indicated for about 10–15% [81].

Strategies to avoid lead issues

ICED leads usually possess an outer insulation sheath made of silicone or polyurethane or both [54,139–141]. Today, most newer leads are insulated with silicone since it was determined that polyurethane insulations, especially the less biostable 80A polyether polyurethane, result in increased lead failure due to metal oxidation on the conductors [54,140,142]. It was also demonstrated that the lead insulation can be abraded, presumably especially when there is continuous movement of the ICD device (which is usually relatively heavy) and thus the leads and if the leads are implanted too centrally below the clavicle. Multiple leads have also been suggested to promote mutual abrasion [143]. Sili- cone insulations are affected more strongly by this abrasion than are polyurethane insulations [139]. Therefore, in most newer leads manufacturers try to combine the advantageous properties of silicone rubber and (55D) polyurethane either in a polyurethane-coated insulation body made of silicone rubber or in an outer copolymer insulation (e.g. St. Jude Medical’s OptiM™, St. Paul, MN, USA). In addition, the outer lead insulation can be coated with certain lubricious materials, e.g. Fast-Pass™ (St. Jude Medical) or the silicone-derived Silglide® (Biotronik, Berlin, Germany). It has been shown that biostability of polyether polyurethanes can be significantly increased by fluoropolymer coatings [144].

The pacing electrodes and shock coils of recent, mostly bipolar leads are made of corrosion-free alloys, e.g. platinized platinum, platinum-iridium, or platinum-coated tantalum. The electrodes and coils are variously coated; e.g. with fractal titanium nitride (TiN) or fractal iridium to lower the pacing or defibrillation threshold by surface increase [145]. Silicone backfilling of ICD coils help to reduce fibrotic tissue ingrowth [112].

PM and ICD leads are either actively screwed into the endocardium and myocardium of the heart or passively anchored in the right ventricular trabecular muscle with tines (Fig. 1A). Most left-ventricular CRT leads are passively placed within the coronary sinus [86,137], while some newer leads possess active fixation lobes in order to prevent stimulation loss or phrenic nerve stimulation due to lead dislodgement [146,147]. Active fixation strategies as in the Attain StarFix™ (Medtronic, Dublin, Ireland) lead might prevent dislodgement and thus an indication for lead revision; on the downside, if extraction is indicated for other reasons it appears to be much more challenging than in passive leads, particularly if fibrotic or thrombotic adhesions are present [146,148–150]. In the case of a lead-associated infection, however, explantation is rarely avoidable [151]. Placement of the CRT lead via puncture of the interatrial septum [152] or a transapical approach [153] is hitherto sparsely accomplished.

Among the basic benefits of leads with a narrower diameter is that they reduce the venous blood flow less strongly and enable the insertion of additional leads [54]. However, a major challenge in avoiding fibrosis reactions is not the morphological design of the leads, including anchoring, but rather primarily the interaction between the lead surface and the surrounding tissue.

The following solutions, however, are currently available: Steroid-eluting lead tips were developed in the 1980s to suppress inflammatory reactions at the lead tip that are activated during implantation of the lead as a foreign body [154–156]. Steroid-eluting sections on lead tips are particularly beneficial for actively anchored leads reducing the initial fibrotic reaction and thereby preventing a higher pacing or defibrillation threshold [157]. The glucocorticosteroid derivatives used most commonly for silicon- ized pacemaker leads are dexamethasone acetate (DexA) and dexamethasone sodium phosphate (DexP) [43]. The incorporation of drug-eluting systems into the insulation sheath might be a possible strategy to suppress neointimal and fibrotic formation around the lead in being similar to systems already used in coronary stents [158] or stented vascular grafts [159] to reduce neointimal and medial thickening. However, one major limitation of this strategy given a persistent contact pressure and rupture by the ICED leads, is the depletion of the eluted pharmacological substances such as e.g. paclitaxel or sirolimus over time preventing long-term efficiency. On the other hand, preventing the vessel to form a fibrotic “shield layer” which mechanically fixes the lead presumably results in permanent physical stress for the endothelium and its subjacent cell layers. Unfortunately, accurate lead placement within the vessel to avoid disruptive contact pressure is currently not possible.

The use of specially structured surfaces on catheters has made it possible to reduce bacterial contamination as well as to avoid fibrosis [160]. Coating the coils of ICD leads with expanded polytetrafluoroethylene (ePTFE) has shown a significant reduction in fibrotic tissue encapsulation in animal models [109,161,162]. Early endothelialization of the lead surface might inhibit adhesion and the formation of fibrosis, which thus prevents possible occlusion and thrombus formation. While there are promising studies in the field from other devices, such as cardiac and venous valves based on tissue engineering technology [163–167], there is still a considerable need for research with regard to PM, CRT, and ICD leads. It is questionable to what degree leads can be endothelialized without reducing their pacing potential of their electrodes and whether they can be successfully applied transvascually. Moreover, the pressure at the contact zones between the endothelium of the vessel and the endothelial sheath of the lead might still have unwanted effects.

Leadless pacemakers

The strategy of leadless pacemakers involves the endocardial implantation of a miniaturized device with an integrated lead. The main benefit of these devices is the lack of permanent transvascular foreign bodies and thus the avoidance of lead-induced complications [168].

Until recently, three leadless pacemaker systems were in the clinical stage: Nanostim from St. Jude Medical, Micra from Medtronic and WICs from EBR Systems (Sunnyvale, CA, USA). Nanostim and Micra are leadless ventricular pacing, ventricular sensing, inhibition response, rate-adaptive (VVI/VVIR) systems that
are implanted through the femoral vein using a special catheter system and are screwed into or hooked in the right ventricle. Both models have received a CE certificate for the European market [169,170]. The Nanostim model was tested on 526 patients with a 6-month follow-up in a multi-center study (Leadless II) [171]. The Leadless II study, however, was paused in October 2016 due to unforeseen early battery depletion in seven patients (0.5% of 1423 implanted Nanostim devices worldwide). For pacemaker-dependent patients a replacement of the Nanostim device was strongly recommended [172]. The Micra model has thus far been implanted in 719 patients as part of a multi-center study, for which follow-up data on 300 patients after 6 months were recently published [173]. The devices can theoretically be removed [174,175], although comprehensive long-term data are lacking and fibrosis and ingrowth into the surrounding tissue are similar to pacemaker leads [176,177]. The devices are currently designed only for pacing in the right ventricle, which limits their applicability compared with systems equipped with leads [178]. The wireless cardiac stimulation (WiCS) system is designed for use in CRT. In contrast with the VVIIR systems mentioned above, here the lead is anchored in the left ventricle through the femoral artery and is powered via ultrasonic pulses from a transmitter implanted subcutaneously [179]. Despite a significant improvement in ventricular performance, the clinical trial for this system, which had already been started, had to be terminated prematurely due to severe perioperative complications [180]. Long-term data for the assessment of fibrosis are lacking here as well.

Requirements for future cardiac device leads

Certain factors principally influence the durability and long-time functionality of ICED leads: (1) placement constancy at pacing/sensing site, (2) fibrotic reaction at pacing site, (3) robustness of internal lead architecture, (4) robustness of lead insulation, (5) anti-microbial, and (6) anti-thrombotic lead properties. One hundred percent lifetime durability for ICEDs is desirable but likely utopic and system upgrades appear to be necessary once in a while. Therefore, (A) anti-fibrotic/neointima-suppressing (or -minimizing) properties of the lead surface and (B) lead placement with minimal early and long-time disruption of the endothelium and reduced contact pressure between lead and vascular surface are essential to avoid fibrosis-related complications and allow a quick and safe lead removal.

Summary

The longevity of PM, CRT, and ICD leads continues to be unsatisfactory. With a current life expectancy of approximately 80 years about every tenth patient with a cardiac pacemaker or ICD implanted has to expect to have at least one lead problem in his lifetime. Defective leads are however difficult to remove due to extensive ingrowth or thrombotic obstruction. Although leadless pacemakers are already available, it appears strongly advisable that the lead/tissue interaction be further improved in order to improve lead removals in particular. Therefore, processes on cellular and molecular level involved in the formation of fibrotic lead encapsulation must be further studied to gain knowledge for the development of specific responsive lead surfaces.

Funding

The project was funded by the German Federal Ministry of Education and Research within RESPONSE “Partnership for Innovation in Implant Technology” (FKZ: 03ZZ0902A).

Conflict of interest

D.B. received speaker’s bureau from Biotronik, Boston Scientific, Medtronic, and St Jude Medical, and research grants from Biotronik and Medtronic.

Acknowledgments

We thank the technical staff of the Department of Anatomy, Rostock, for assistance with dissection and documentation of postmortem material and slicing and histological staining.

References


transvenous dilation and location of areas of adherence in patients undergoing coronary sinus lead extraction. Euro pacing 2007;9:69–73.


