Histological findings around electrodes in pacemaker and implantable cardioverter-defibrillator patients: comparison of steroid-eluting and non-steroid-eluting electrodes

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Aims

To analyse histological findings surrounding the electrodes in pacemaker/implantable cardioverter-defibrillator (PM/ICD) patients. To compare histology around steroid-eluting and non-steroid ventricular pacing electrodes.

Methods and results

In autopsied PM/ICD patients histopathological findings around the electrodes were determined. Seventy patients were studied, PM(58), ICD(12), mean age 75.1 ± 9.3 years. The implantation—death interval was 4.0 ± 3.3 years. Most causes of death were cardiac (PM 52%, ICD 58%). The majority of atrial electrodes were attached to the endocardium and most ventricular electrodes were found in the myocardium (P ≤ 0.001). The maximum thickness of the fibrous electrode sheath was greatest for the ICD ventricular electrodes. Some electrodes were covered with fibrin thrombi and granulation tissue, most frequently in the ICD ventricular electrodes. The fibrous sheath usually contained chronic inflammatory cells and in some cases particles of foreign material, foreign body giant cells, and haematoxylin pigment. The tissue around steroid-eluting ventricle PM electrodes was compared with the tissue around the non-steroid-eluting ventricle PM electrodes; granulation tissue, foreign material, giant cells being found more frequently around the steroid-eluting electrodes. The fibrous sheath was slightly thinner in the steroid-eluting electrodes. The histology around four coronary sinus electrodes was described.

Conclusions

Atrial electrodes were attached more superficially to the endocardium while PM and ICD ventricular electrodes were more frequently embedded in the myocardium. The electrodes were covered by a connective tissue sheath as a result of thrombus organization. This process persisted most frequently around ICD ventricular electrodes. Only borderline differences were found between the histological findings around steroid-eluting and non-steroid-eluting PM ventricular electrodes.

Keywords

Pacemaker electrodes • ICD electrodes • Histology • Steroid-eluting pacing electrodes

Introduction

Implantable pacemakers (PM), implantable cardioverter-defibrillators (ICD), and biventricular PM/ICDs are used to treat brady/tachycardia and severe heart failure. The causes of death, cardiac findings,1–4 and complications related to the implantation5–11 have been evaluated in the past. Studies that examined the histological changes evoked by the presence of implanted intravascular electrodes have been made with animals12–15 and with human patients4,5,8,16–20 more frequently during the last two decades of the 20th century. Mond and Stokes14 in a review differentiate acute inflammatory response

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with oedema, fibrin depositions, leucocyte migration, fagocytic or foreign body activity, and necrosis from late inflammatory changes inclusive capillary and fibroblast proliferation and collagen formation resulting in the creation of fibrous capsule. Histological findings around steroid-eluting and non-steroid PM ventricular electrodes have been compared in animals.12–14 These studies revealed less connective tissue formation and fewer inflammatory cells in peri-electrode fibrous connective tissue in steroid-eluting electrodes. In humans such histological studies have been rare.19

The aim of the current study was to compare histology around PM and ICD electrodes in deceased patients. This study especially described histological findings around steroid-eluting pacemaker ventricular electrodes in comparison with non-steroid-eluting electrodes.

Methods

Between February 2005 and August 2008, autopsies were performed on 70 deceased PM/ICD patients with intravenous electrodes. The electrode attachment to the endocardium and myocardium was evaluated. A standard histopathological examination of the electrode channel was performed. Formalin-fixed paraffin-embedded tissue blocks were longitudinally sectioned and stained by haematoxylin–eosin and van Gieson staining, and selectively by other special methods. The histological findings were evaluated around the electrode tip and the retractable screw. The maximum thickness of fibrous and granulation tissue around the electrode tip was measured in a distance of 5 mm (Figure 1A).

The binomial distribution homogeneity test was used to describe the frequency of histological parameters for electrodes of various types, whereas the t-test was used to compare the maximum thickness of the sheath around the electrodes.

Results

Autopsies were performed on 70 deceased patients (42 men), mean age 75.1 ± 9.3 (48–92) years with implanted PM (n = 58) or ICD (n = 12). In 17 cases atrial and in 4 cases coronary sinus (CS) electrodes were present. The interval between initial lead implantation and autopsy was 4.0 ± 3.3 years.

The patients were polymorbid and suffered from these main diseases: coronary artery disease (69), hypertension (49), dilated (5), hypertrophic (1) cardiomyopathy, amyloidosis (3), valve disorders (4), endocarditis (1), myocarditis (1). Diabetes mellitus (33), malignant tumours (10), respiratory system disorders (6), and gastrointestinal tract diseases (7) were also found.

The cause of death was cardiac in 30 patients (52%) with PM and 7 (58%) with ICD. The cardiac causes were heart failure (34) and

Figure 1 (A) Fibrous sheath (F) around the pacemakers ventricular electrode (EL, space after electrode extraction) anchored in the myocardium (M) and formed by dense to hyaline connective tissue. An arrow indicates the maximum width of the fibrous sheath. Haematoxylin–eosin stain, magnification ×40. (B) Fibrous sheath (F) around the pacemakers atrial electrode (EL) in the endocardium (E). Myocardium (M). Haematoxylin–eosin stain, magnification ×40. (C) Thrombus from an electrode surface with foreign body giant cells in the edge (arrows). Pacemakers atrial electrode, 8 days after implantation. Fibrin–Weigert stain, magnification ×400. (D) Necrotic muscle fibres (arrows) and mixed inflammatory infiltration near the pacemakers ventricle electrode, 4 days after implantation. Haematoxylin–eosin stain. Magnification ×400.
acute myocardial infarction (3). Non-cardiac circulatory causes of death were pulmonary embolism (8), encephalomalacia (3), brain haemorrhage (1), thrombosis of the arteria mesenterica superior (1), and ruptured aneurysm of the abdominal aorta (1). Non-circulatory disorders included bronchopneumonia (10), sepsis (3), and other (6).

Hypertrophy and dilatation of the right and left ventricle, in various combinations, was present in all but one patient. Most often hypertrophy and dilatation of both ventricles (35) or of the left ventricle (19) was found. The heart mass averaged 533.6 ± 157.3 (300–980) g.

The following PM and ICD generators were found: PM VVI (39), VDD (5), DDD (12), CRT-P (2); ICD VVI (9), DDD (1), CRT-D (2). There were 24 (34%) pacing-dependent patients. Implantable cardioverter-defibrillator shocks during the follow-up were applied in 5 (42%) of 12 patients. (Two or more shocks were applied during the implant of all ICD patients.)

The numbers and types of PM and ICD ventricular, atrial, and CS electrodes are given in Table 1.

The sample included PM ventricular active fixation electrodes (4 out of 58), ICD ventricular active fixation electrodes (10 out of 12), and atrial active fixation electrodes (7 out of 17).

The atrial electrodes were most frequently anchored in the endocardium or at the endocardium/myocardium border (often in the trabeculae), while the ventricular PM or ICD electrodes were situated most frequently in the myocardium. The difference between the number (percentage) of atrial electrodes anchored in the myocardium, in comparison with ventricular PM (P = 0.001) and ventricular ICD (P = 0.0001) electrodes anchored in the myocardium, was statistically significant. The ICD ventricular electrodes were more often situated in the myocardium in comparison with PM ventricular electrodes. This difference was not statistically significant (Table 2, Figures 1A and B).

Within 10 days of the implantation three PM patients died. In one case the ventricular electrode was not fixed and a mixed thrombus with foreign body multinuclear giant cells was present around the atrial electrode (Figure 1C). In the two other cases there was a thrombus around the ventricular electrode. In one case there were necrotic muscle fibres in the myocardium (Figure 1D).

During the period of 1 month to several years after implantation the remaining 67 patients died (55 PM, 12 ICD). The histological findings around the electrodes of all types were similar. The study detected an electrode channel sheathed with mostly dense hyaline (Figures 1A and 2A), less frequently loose, vascular (Figure 2A), and proliferating connective tissue of varying thickness. Sometimes there was a granulation tissue around the electrodes present even a year or longer after implantation (Figure 2B), and sometimes fibrin thrombi (Figure 2C), which were almost always present during the first 6 months. The presence of granulation tissue was significantly more frequent (P = 0.02) in ventricular ICD electrodes in comparison with the atrial electrodes. The presence of fibrin thrombi was significantly more frequent (P = 0.006) in ventricular ICD in comparison with the ventricular PM electrodes (Table 3).

There was usually chronic inflammatory cell infiltration (Figures 2B and D) in the sheath around the electrodes. The presence of leucocytes, erythrocytes, histiocytes, and macrophages was sporadic. The foreign body giant cells (Figure 2D), particles of foreign material (Figure 2E), the pigment haematoidin or haemosiderin (Figure 2F), and sporadic calcifications (Figure 2G) were found several times. In one case necrotic muscle fibres around the ventricular PM electrode were discovered more than a year after implantation. There was a microabscess with Gram-positive cocci (Figure 2H) near the PM ventricular electrode in one case of myocardiitis during sepsis.

Comparisons were made of the maximum thickness (Figure 1A) of the connective tissue sheath. The sheath around the ventricular ICD electrodes (1.08 ± 0.60, 0.30–2.50 mm) was thicker than the sheath around both the ventricular PM electrodes (0.76 ± 0.43, 0.10–2.30 mm, P = 0.04) and atrial electrodes (0.79 ± 0.44, 0.23–1.80 mm, P = NS).

### Table 1 Number and types of pacemaker and implantable cardioverter-defibrillators ventricular, atrial, and coronary sinus electrodes

<table>
<thead>
<tr>
<th></th>
<th>PM ventricular electrodes</th>
<th>ICD ventricular electrodes</th>
<th>PM or ICD atrial electrodes</th>
<th>PM or ICD coronary sinus electrodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroid-eluting (Biotronik)</td>
<td>28</td>
<td>1</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Non-steroid-eluting (Medico Italia)</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Steroid-eluting (St Jude Medical)</td>
<td>20</td>
<td>5</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Steroid-eluting (Biotronik)</td>
<td>2</td>
<td>–</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Steroid-eluting (Guidant)</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Steroid-eluting (Medtronic)</td>
<td>–</td>
<td>3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Not identified</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>12</td>
<td>17</td>
<td>4</td>
</tr>
</tbody>
</table>

*PM electrodes: IRT1, IRTJ, TIR, TIIJ, SX, PX, SD, Arox, MEX, SL, SLX. ICD electrode: Kairox RV.

*ICD electrodes: El200, M340, P Windoll 940.

*PM electrodes: Membrane 1452, E 1472 E 1474, Tendril 1486 and 1688, Isoflex 1636. ICD electrode: Riata 1580. Coronary sinus electrode: QuickSite.

*PM electrodes: Setrox, Corox.


*PM electrodes: 3076. ICD electrodes: 6943, 6949.
The findings around ventricle steroid-eluting (dexamethason) electrodes (St Jude Medical, n = 16) and non-steroid-eluting electrodes with fractal surface (Biotronik, n = 28) were compared, both types with passive fixation. The histological findings around the steroid vs. non-steroid electrodes were in many aspects similar. The differences were as follows. The occurrence of the granulation tissue in 4 vs. 3 (P = NS), foreign material in 4 vs. 1 (P = 0.03), and foreign body giant cells in 3 vs. 0 (P = 0.02) was slightly higher for the steroid-eluting electrodes. The maximum thickness of the sheath around the steroid-eluting electrodes was

Table 2 Depth of electrode anchoring

<table>
<thead>
<tr>
<th></th>
<th>In endocardium</th>
<th>In endocardium/myocardium border, or in trabeculae</th>
<th>In myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular PM electrodes (n = 57)*</td>
<td>5 (9%)</td>
<td>16 (28%)</td>
<td>36 (63%)*</td>
</tr>
<tr>
<td>Ventricular ICD electrodes (n = 12)</td>
<td>–</td>
<td>1 (8%)</td>
<td>11 (92%)**</td>
</tr>
<tr>
<td>Atrial PM and ICD electrodes (n = 17)</td>
<td>7 (41%)</td>
<td>7 (41%)</td>
<td>3 (18%)*</td>
</tr>
</tbody>
</table>

*One electrode was not fixed; probably it was released during the autopsy.
**P=0.001, ***P=0.0001.

Table 3 Histological findings around the pacemakers and implantable cardioverter-defibrillator electrodes of patients deceased later than 1 month after implantation (n = 67)

<table>
<thead>
<tr>
<th></th>
<th>Dense to hyaline connective tissue</th>
<th>Loose, vascular, and proliferating connective tissue</th>
<th>Granulation tissue</th>
<th>Fibrin thrombi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular PM electrodes (n = 55)</td>
<td>50 (90.9%)</td>
<td>30 (54.5%)</td>
<td>10 (18.2%)</td>
<td>14 (25.5%)**</td>
</tr>
<tr>
<td>Ventricular ICD electrodes (n = 12)</td>
<td>11 (91.7%)</td>
<td>9 (75.0%)</td>
<td>5 (41.7%)*</td>
<td>8 (66.7%)**</td>
</tr>
<tr>
<td>Atrial PM or ICD electrodes (n = 16)</td>
<td>15 (93.8%)</td>
<td>8 (50.0%)</td>
<td>1 (6.3%)*</td>
<td>8 (50.0%)</td>
</tr>
</tbody>
</table>

*P=0.02, **P=0.006.
0.72 ± 0.28 (0.25–1.30) vs. 0.79 ± 0.51 (0.15–2.3) mm around non-steroid electrodes (P = NS).

The small groups of ventricle PM electrodes with active (n = 4) and passive (n = 16) fixation (both steroid-eluting) were compared. The histological findings were similar. The maximum thickness of the sheath around active fixation electrodes was 0.87 ± 0.44 (0.47–1.50) vs. 0.72 ± 0.28 (0.25–1.3) mm around electrodes with passive fixation (P = NS).

Coronary sinus leads with passive fixation implanted a year or more before death were examined in four cases (two PM, two ICD). One lead ended in the CS (Figure 3A), two in the left posterior ventricular vein (Figure 3B), and one in the left anterior ventricular vein. All the leads exhibited fibrous encapsulations, and in three cases thrombi were found (Figure 3A). Microscopically, there was a fibrin thrombus with an admixture of foreign body giant cells around the tip of one electrode (Figure 3C) while the tips of the other electrodes were sheathed by dense connective tissue (Figure 3D).

**Discussion**

The average age of deceased patients in our study was 75.1 years with male predominance, similar to the Šindler,4 Chatelain et al.,16 and Mase et al.19 populations.

The depth of electrode attachment in the cardiac wall varied among the samples studied. Mase et al.19 distinguished tight and loose contact between the electrode and the endocardium. This study used an evaluation based on the depth of electrode anchoring. Atrial electrodes were mostly fixed in the endocardium or on the border with the myocardium while ventricular electrodes were anchored in the myocardium. This situation was in more than one half of the ventricular PM electrodes, and in almost all the ventricular ICD electrodes. The thickness of ventricular myocardium as compared to atrial myocardium and the larger diameter of the ventricular ICD electrode may play a role. The depth of electrode insertion should influence the possibility of the right atrium and right ventricle perforation. Sterliński20 found that the number of
cardiac perforations does not differ between PM and ICD implants. All perforations were associated with active fixation. Late lead perforations were described by Refaat et al. \( ^{21} \) None was in our group.

The limited number of patients deceased soon after implantation did not allow for a description of the acute inflammatory response as was reported by Mond and Stokes \( ^{14} \) and assess the chronological development of the reaction to the implanted electrode. Thrombi were formed in the first 6 months in almost all cases. We confirmed the occurrence of foreign body giant cells in the thrombus as a reaction to the foreign material in the first days after implantation, in agreement with Mond and Stokes. \( ^{14} \) Necrosis of muscle fibres around the PM electrodes was reported in dogs by Mond and Stokes, \( ^{14} \) in a small number of patients by Šindler, \( ^{4} \) Lysenkova \( ^{5} \), and Chatelain et al. \( ^{16} \) and around ICD leads by Epstein et al. \( ^{8} \) and Singer et al. \( ^{17} \) Such necroses were quite sporadic in our population: the first occurred in the first few days and the second more than a year after PM implantation. This could be explained by the better mechanical properties of electrodes used in recent years.

The formation of connective tissue around the electrodes has been described in animals, \( ^{12–14} \) and in humans. \( ^{5,8,9,16–19,22} \) Mond and Stokes \( ^{14} \) in their review reported the resorption of fibrin and acute cellular infiltration during the 4 weeks after implantation and the formation of a fibrous capsule between the electrode and the myocardium. Lysenkova \( ^{5} \) and Mase et al. \( ^{19} \) concluded that connective tissue encapsulation of the electrode was due to the organization of thrombi. This is in agreement with our research and that of Chatelain \( ^{16} \) identification of fibrin thrombi, granulation tissue, and connective tissue of various degrees of maturation. In contrast to Mond's report \( ^{14} \) this process took place \( >1 \) year after implantation with our population. Chatelain et al. \( ^{16} \) explained this process as the expression of the lead instability. This study observed a stronger reaction to the electrode, manifested by the more frequent persistence of fibrin thrombi, granulation tissue, less maturated connective tissue, and a larger thickness of the sheath around the electrodes in the ICD patients. The effects of the larger electrode dimensions and defibrillation charges can be assumed.

This research draws attention to the presence of foreign material, probably originating from the protective electrode cover or lead insulation, and foreign body giant cells, also described by Chatelain et al. \( ^{16} \) Chawla et al. \( ^{23} \) studied the surface of the polyurethane insulation from explanted leads, using a scanning electron microscopy analysis. He found cracks of lead insulation that could explain the release of particles. The lead isolation degradation cannot be influenced by clinicians. Histological reaction to foreign material could be decreased by minimalization of contact of lead and the electrodes with patient sterile cover and with other materials used during the operation.

A layer of macrophages and foreign body giant cells within the late inflammatory reaction was reported by Mond et al. \( ^{14} \) In our study these cells did not form a continuous layer and were not found regularly. Mineralization of the necrotic myofibres was reported by Radovský and Van Vleet. \( ^{13} \) In our study’s patients, calcifications were occasionally found in the connective tissue of the fibrous sheath. Both differences could be explained by the extended time from implantation.

One patient in our study group had purulent myocarditis around the ventricular PM electrode. A similar case was reported by Lysenkova \( ^{5} \) and Mase et al. \( ^{19} \) From the clinical point of view maximum sterility is imperative during implantation. Exclusion of any infection before PM/ICD implantation is mandatory.

Kistler et al. \( ^{24} \) described rapid decline of pacing threshold in 10 min after implantation of steroid-eluting active fixation lead. It has been shown in several studies that steroid-eluting electrodes lower the stimulation thresholds for a long-term follow-up after the initial implantation. \( ^{12–14,25–28} \)

Among the PM ventricular electrodes in our study, the non-steroid (Biotronik) and steroid-eluting electrodes (St Jude Medical) formed two groups (both with passive fixation) enabling a statistical evaluation. The maximum thickness of the connective tissue sheath around these electrodes was slightly thinner around the steroid-eluting electrodes (\( P = \text{NS} \)). Radovsky, \( ^{12} \) and Radovsky and Van Vleet \( ^{13} \) described the formation of a thinner sheath of reactive connective tissue around steroid-eluting electrodes than around the similar non-steroid-eluting electrodes in dogs in a 3-week and a 6-week study. This sheath tended to be thinner after 6 weeks in non-steroid-eluting electrodes. In the patients of our study, the time from implantation was much longer, and so the sheath thickness in non-steroid-eluting electrodes could decrease more and the difference in sheath thickness did not differ significantly.

There was a moderately higher occurrence of granulation tissue, foreign material, and foreign body giant cells around the steroid-eluting electrodes. These findings are explicable by more frequent release of particles from the steroid-eluting electrodes.

The comparable groups of electrodes with passive and active fixation (both steroid eluting) were small and so statistical significance could not be established.

The following describes the reaction to the CS pacing leads. Around the electrode tip, histology confirmed a thrombus with an admixture of foreign body giant cells in one case and a connective tissue encapsulation in three other cases. Similar findings around CS defibrillation leads were described by Jones et al. \( ^{18} \)

### Study limitations

Incomplete clinical documentation in some patients (deceased in different hospitals, death soon after admission). Small numbers in some lead types.

### Conclusions

Atrial electrodes were usually attached superficially in the endocardium, compared with ventricular PM/ICD electrodes, which were usually embedded in the myocardium (\( P \leq 0.001 \)).

Around the electrodes there was a sheath of connective tissue, formed from organized thrombi. Thrombi and granulation tissue were preserved more often around ventricular ICD than ventricular PM and atrial PM or ICD electrodes. The sheath around the ICD ventricular electrodes was thicker than around the ventricular PM (\( P < 0.05 \)) and atrial PM/ICD (\( P = \text{NS} \)) electrodes. The sheath...
usually contained chronic inflammatory cells, less frequently particles of foreign material, and foreign body giant cells.

Borderline differences were found between the histological findings around steroid-eluting and the non-steroid-eluting PM ventricular electrodes, the sheath thickness was slightly thinner in the steroid-eluting electrodes \( (P = \text{NS}) \).

**Conflict of interest:** none declared.

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