Differences in encapsulating lead tissue in patients who underwent transvenous lead removal

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Aim
The aim of our study was to characterize specific tissue reaction of encapsulating lead tissue in patients who underwent transvenous lead removal and evaluate condition of the outer leads’ insulation.

Methods and results
Fifty-six leads (27 atrial, 24 ventricular, 5 implantable cardioverter-defibrillators) were removed from 31 patients (mean age 70 years). Indications for removal were chronic pocket infection (CPI) (9 patients), infective endocarditis (IE) (6), and non-infective indications (NI) (16). Leads with their surrounding tissue were fixed in paraformaldehyde. Tissues were embedded in paraffin wax, stained with haematoxylin–eosin, and examined histologically. The outer leads’ insulations were examined in stereomicroscope. The mean lead age encapsulated by connective tissue sheath was 89, whereas encapsulated by granulation tissue was 47.34 months ($P = 0.03$). Calcification was present in 13 patients. Haemosiderine was observed only in patients with severe abrasion with perforation in the pocket ($P = 0.04$). Vasculogenesis was present in one (6%) with NI, five (56%) with CPI, and three (50%) with IE ($P = 0.02$) and was associated with elevated white blood cells (WBC) ($P = 0.04$). Eosinophilia was associated with elevated WBC ($P = 0.04$). The most frequently observed are third level of degradation (severe with perforation) in the intracardiac part of the silicone leads. Insulation damage due to environmental stress cracking concerned all leads with polyurethane overlay.

Conclusions
Granulation in encapsulating tissue was present in patients with younger leads. Vasculogenesis was observed more often in IE and CPI patients, which might indirectly indicate thickness of the sheath. Eosinophilia may indicate allergic component of inflammation. Insulation damage frequently concerned the intracardiac part.

Keywords
Encapsulating lead tissue • Fibrocollagenous sheath • Lead removal • Silicone-insulated leads abrasion • Infective endocarditis

Introduction
Pacemaker (PM) and implantable cardioverter-defibrillator (ICD) therapy provide better quality of life and prolonged lifetime to patients.1,2 Complications like infection, malfunction, wire fracture, insulation damage, and lead removal may occur.3–5 The safety of the extraction procedure depends on the PM or ICD system reliability and the complex reaction of a patient’s tissue to the device. The interactions between the implantable electronic device and heart muscle, venous system, as well as immunological response to pacing, shocks, and insulation materials were investigated. Many studies were performed in animal models (dogs and sheep)6–12 and only few concern humans, from autopsy examination,13–21 cardiac transplantation,22 and rarely histological analysis of tissue remnants attached to transvenously explanted endocardial leads.23

During the first week of implantation, fibrin deposits surround the lead with partial features of organization, and then the

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encapsulating connective tissue forms.\textsuperscript{24} Fibrous sheath formation appears first at the level of tricuspid valve, near the tip, and at the border between the superior vena cava and the right atrium, and then spreads and finally may surround the whole lead body.\textsuperscript{13,14,16} Silicone-insulated leads were covered by prominent scar-like tissues in the ventricle, and less-expressed fibrotic recontacting surfaces around PM materials, thus providing a mechanism for long-term persistence of foreign materials in the blood.\textsuperscript{23} Endothelialization of the fibrous encapsulation indicates a functionalization of bloodcontacting surfaces around PM materials, thus providing a mechanism for long-term persistence of foreign materials in the blood.\textsuperscript{23} Lagergren et al.\textsuperscript{26} did not find any association between encapsulating tissue thickness and time from implantation. Parsonnet et al.\textsuperscript{27} described thicker sheaths around semirough and rough polyurethane-insulated catheters in comparison with the smooth ones. Early venous thrombosis and fibrosis as a result of mechanical trauma of venous endothelium created during lead insertion may lead to late venous stenosis or occlusion.\textsuperscript{28,29}

In the heart, two different contact patterns were distinguished between the lead and the endocardium: loose with dead space and tight. Fibrosis under the tip was observed only in the tight contact due to mechanical compression pressure on the tip of the electrode, which caused oppression of capillaries and decreased blood supply that leads to the process.\textsuperscript{30} Mase et al.\textsuperscript{30} observed disappearance of cardiomyocytes and rarely adipose tissue presence.

Foreign-body granuloma secondary to broken insulating material may be observed.\textsuperscript{12,24} Calcification as a degenerative process in response to the loss of cellular activity and necrosis may also occur.\textsuperscript{8,31} The macrophages could accumulate at the insulation side with vascularization of the outer tissue layer.\textsuperscript{12,23} Haemosiderin granules were found in macrophages and extracellularly in the connective tissue.\textsuperscript{8,23} The encapsulating sheath can differentiate into cartilage, mineralized tissue, and even bone.\textsuperscript{11}

Complex interaction among leads, surrounding tissue, venous endothelium, endocardium, and host immunological response decide about the difficulty of transvenous lead extraction. The aim of our study was to characterize specific tissue reaction of encapsulating tissue of modern leads in patients who underwent transvenous lead removal and evaluate the outer insulation condition of the endocardial leads.

Methods

Fifty-six leads (27 atrial, 24 ventricular, 5 ICD) were removed from 31 patients (12 females), the mean patient age being 70.4 years (range 20–87). Reasons for removal were chronic pocket infection (CPI) (9; 29%), infective endocarditis (IE) (6; 19.3%), and non-infective indications (NIs) (16; 51.6%). The mean number of implanted leads was 1.9 and the mean dwell time was 82.2 months (range 9–168). The mean number of procedures like device exchange or upgrade until removal was 2 (range 1–5). The mean time from the last procedure was 32.5 months (range 1–109).

Leads were produced by different manufacturers (Biotronik, Medtronic, St Jude Medical). The outer insulation material was polyether polyurethane (PEU) in five leads (Medtronic 6932 Sprint, 6931 Sprint Fidelis, Sprint Quattro). Active tip fixation was seen in 17 (30.3%) leads.

All extraction procedures were performed under general anesthesia and aided by fluoroscopy. Leads were removed by mechanical traction and outer sheaths (Cook Vascular, Inc.) were used to mechanically free the lead.

Leads with their surrounding tissues were immediately fixed in 4% paraformaldehyde for 24–48 h at 4°C. Tissues were embedded in paraffin wax, stained with haematoxylin–eosin, and examined histologically.

The outer insulation of the endocardial leads were examined in the stereomicroscope and classified according to Banacha classification of the silicone-insulation abrasions.\textsuperscript{22} In Banacha classification, three levels of degradation were distinguished into two subtypes: a and b (type 1 mild, type 2 moderate, and type 3 severe with perforation). The first-level degradation type 1a with the characteristic cloudiness of the silicone and type 1b with linear damages. The second-level degradation type 2a resembles a cone (with the ends narrowing and a gradual decrease in the silicone towards the central part of the abrasion), and type 2b resembles a canyon (the longitudinal lesion diameters at most points are the same, and the depression walls descend vertically).

In the third level of degradation, severe abrasion with perforation of the outer insulation created at the base of type 2a and 2b changes. Leads with polyurethane overlay were examined using a scanning electron microscope.

Descriptive statistics are presented as the number (%) for categorical variables and mean [± standard deviation (SD) or median (25th–75th percentile)] for continuous variables. Mann–Whitney, Pearson, and Fisher’s tests were used. Tests were two-tailed, with $P \leq 0.05$ considered to be statistically significant.

Results

Pacemaker leads were surrounded with encapsulating connective tissue; larger fragments of the sheath were attached to leads with passive fixation (Figure 1A) than with the active one. The mean lead age encapsulated by connective tissue (Figure 1B and C) was 89, whereas that encapsulated by granulation tissue (Figure 1D and D’) was 47.3 months ($P = 0.03$). In all five cases of encapsulating granuloma tissue, the outer insulation was damaged in the intracardiac part (two patients due to environmental stress cracking, two with third level of silicone degradation—severe with perforation, one with the first level of degradation—1b). There existed an association between infective indications for removal and degree of acute inflammatory response ($P = 0.025$).

Eosinophils were present in the encapsulating tissue of three patients who underwent leads removal due to infective indications (2, IE: $P = 0.06$) and were associated with elevated white blood cells (WBC) ($15.23 ± 2$) ($P = 0.045$). The examination of the outer leads’ insulation revealed the presence of the third level of silicone degradation (severe abrasion with perforation) in the intracardiac part in all three patients.

Calcification (Figure 1E and F) in the encapsulating tissue was present in 13 patients (41.9%), 8 females ($P = 0.059$), and was associated with older leads (110.1 ± 2 months; $P = 0.037$). Eleven leads were silicone insulated and 2 had polyurethane (PTU) overlay. In five patients, leads were extracted due to infective indications. Three patients had chronic renal disease and 10 had reduced estimated glomerular filtration rate (eGFR).

Vasculogenesis (Figure 1G) was present in one (6%) patient who underwent leads removal due to NIs, five (56%) with CPI, and three (50%) with IE ($P = 0.01$) and was associated with elevated...
Figure 1 Encapsulating leads sheaths. (A) Encapsulating tissue attached to leads with passive fixation; (B) encapsulating tissue surrounding the tip; (C) connective tissue partly hyalinized; (D) granuloma tissue; (D') granuloma tissue; (E) calcification of inner part of the capsule, collagen bundle impregnation; (F) calcification of the encapsulating sheath in a focal pattern; (G) vasculogenesis; and (H) haemosiderin deposits.
WBC (mean WBC 11.0 ± 2; \( P = 0.046 \)). Vasculogenesis was observed in six males and three females, the mean patients' age was 76.8 years, the mean dwell time was 90.9 months, the mean number of procedures to removal was 2.5, and the mean time from the last procedure to extraction was 16.4 months (range 2–42).

Haemosiderin deposits (Figure 1H) in connective tissue sheath were associated with the presence of the abrasion with perforation of the outer silicone insulation of the endocardial lead in the pocket region (\( P = 0.045 \)).

All ICD leads were PTU insulated and partially covered by encapsulating tissue (Figure 3F), three leads with passive fixation and three others two coiled. The high-voltage coils were significantly adhered to scar tissue and bind to the veins, right atrium, and right ventricle, which increased the difficulty of subsequent leads removal and where most procedures were estimated as problematic. The ICD leads PEU overlay damage in the mechanism of environmental stress cracking (ESC) were observed in all patients, but with different advancement degrees: from mild-to-deep cracks and breaches (Figure 3G). The lesions were located only under surrounding tissues: in the intracardiac part in five (100%) leads, in the intravenous part in two, and in the pocket region in one lead. In four patients, leads were removed due to NIs. The scar tissue surrounding high-voltage coils seem like coagulated and amorphous without distinguishable cells. Collagen bundles of encapsulating ICD leads tissue characterize irregular and chaotic orientation. Larger fragments of the sheath were attached to ICD leads with passive fixation.

In 12 patients, cardiac muscle fragments were obtained, in all cases attached to the leads with passive fixation (Figure 2A). In eight cases interstitial fibrosis was observed (Figure 2B and C). Two patients had cardiomyocytes hypertrophy. The lymphocytes and granulocytes infiltrations were observed in five (41.6%) patients who underwent leads removal due to NIs, without inflammatory markers elevation (C-reactive protein, WBC). Adipose tissue was observed in one patient (Figure 2C), with EF 70%, without heart motion abnormalities, without metabolic disorder, or renal failure.

The outer silicone-insulation abrasions of the endocardial leads according to Banacha classification are presented in Table 1. The most frequently observed are severe abrasion with perforation (third level of silicone degradation) in the intracardiac part of both atrial and ventricular leads (Figure 3C–E). The insulation damage in the intracardiac part was associated with younger leads and mean implantation time being 68.15 ± 2 vs. 103.3 ± 2 months (\( P = 0.03 \)). Removed leads with PTU overlay were younger (mean implantation time 35.8 ± 2 months) than silicone-insulated ones (mean implantation time 91.2 ± 2 months) (\( P = 0.0007 \)). Severe insulation damage in the intracardiac part was present in 8/26 silicone-insulated leads and 5/5 with PTU overlay (\( P = 0.004 \)).

### Figure 2
Heart muscle fragments. (A) heart muscle attached to lead with passive fixation; (B) interstitial fibrosis; and (C) adipose tissue, interstitial fibrosis, cardiomyocytes hypertrophy.

### Discussion
This is one of the largest histological analyses of tissue fragments attached to transvenously explanted leads, also in relation to new phenomena of intracardiac leads' abrasions. Associations in relation to vasculogenesis, calcifications, granulation, eosinophils, and haemosiderine presence were discovered.

The sheath formation is well documented. In most patients, fragments of very dense encapsulating connective tissue were observed with collagen bundles mainly orientated parallel to the electrode surface and were partially hyalinized. In five patients, granuloma tissue appeared and was associated with younger leads. In one case, the ICD-DR system was extracted due to NIs with concomitant polyurethane overlay degradation. In four other patients, acute inflammatory response was associated with infective indication for leads removal. In the literature,
encapsulating connective tissue of different thicknesses is often covered with a layer of endothelial-like cells, and rare immunological cells infiltrations may be distinguished. The sheath surrounds lead body in vein; right atrium and right ventricle sometimes cause tricuspid valve insufficiency.13,33

Vasculogenesis in encapsulating lead’s tissue was observed in 9/31 patients and was associated with infective indication for leads removal and elevated WBC. Sheath thickening and vegetation formation may induce relevant tissue hypoxia and vasculogenesis. Yue and Tomanek34 indicated the role of hypoxia in the stimulation of coronary vasculogenesis by upregulating vascular endothelial growth factor in heart development. Esposito et al.22 observed an increased vascularization of the outer tissue layer.

Haemosiderin deposits in connective tissue sheath were associated with the presence of abrasion with perforation of the outer silicone insulation of the endocardial lead in the pocket region. Haemosiderin is an iron-storage complex, most commonly found in macrophages, and may follow haemorrhage. Damaged

Figure 3 (A–E) Silicone-insulated leads removed transvenously due to clinical evidence of pocket infection [(A) subclavian region and pocket; (B) X-ray image of crossing ventricular leads in the right heart; (C) explanted endocardial leads with damage of insulation in the intracardiac part; (D and E) mutual abrasions (sever abrasion with perforation type 3a) of ventricular leads with conductor compression). (F–G) polyether polyurethane overlay degradation [(F) stereomicroscopic image and (G) scanning electron microscope image].
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Table 1: Abrasion of the outer silicone insulation according to Banacha classification [given as no. (%)]

<table>
<thead>
<tr>
<th>Abrasion type</th>
<th>Intracardiac part of the lead</th>
<th>Venous part of the lead</th>
<th>Pocket part of the lead</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atrial</td>
<td>Ventricular</td>
<td>Atrial</td>
</tr>
<tr>
<td>1a</td>
<td>9 (33.3)</td>
<td>5 (20.8)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>1b</td>
<td>14 (51.8)</td>
<td>10 (41.6)</td>
<td>10 (37)</td>
</tr>
<tr>
<td>2a</td>
<td>2 (7.4)</td>
<td>4 (16.6)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>2b</td>
<td>9 (33.3)</td>
<td>6 (25)</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>3a</td>
<td>5 (18.5)</td>
<td>7 (29.1)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>3b</td>
<td>1 (3.7)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abrasion of the outer silicone insulation according to Banacha classification [given as no. (%)]

outer insulation in the pocket region could have injured encapsulating tissue vasculature leading to bleeding followed by haemosiderin storage.

Calcifications were present in encapsulating tissue of 13 (41.9%) patients, more often females, and were associated with older leads. Ectopic calcification may occur in uremic patients (metastatic calcifications), as a result of injury, disease, and ageing (dystrophic mineralization), or induced by prosthetic devices. In our patients, mineralization in the fibrous capsule has got mixed aetiology, because it concerns mostly older patients with chronic renal failure and with reduced eGFR, with degenerative reaction to silicone implantation for >9 years. Legrand et al. described degenerative mineralization of fibrous capsule in 18 explanted silicone breast prostheses after 20 or more years of implantation and distinguished two different morphologies: granular deposits (focal calcification of the collagen fibers) and impregnated bundles of fibres. In our study, two different mineralization patterns were observed. Foci of calcifications were observed also in sheaths covering intraventricular part of the leads in dogs. The mineralization may concern not only the encapsulating tissue but also the lead’s body. Stokes et al. introduced hypothesis of calcification as a consequence of encapsulating tissue hypoxia due to its thickening leading to capillary atrophy, cell death, and mineralization even to cellular differentiation (ossification). The eosinophils were present in sheaths of three patients who underwent leads removal due to infective indications and were associated with elevated WBC. The examination of the outer leads’ insulation revealed the presence of third level of silicone degradation (severe with perforation) in the intracardiac part in all three patients. Eosinophilia may be an expression of allergy to inner parts of the lead, e.g. conductors or made of cobalt–chrome–nickel alloys. Châtelain et al. observed foreign-body giant cell reaction around the coil in cases with broken insulating material. Oprea et al. described allergy to PM silicone compounds. Some materials were proven to be allergenic like titanium and polyurethanes. Foreign-body giant cells reaction were also reported in animal model studies.

Heart fragments were obtained only in the case of passive fixation leads, and revealed interstitial fibrosis with cardiomyocytes disappearance, immunological cells infiltrations, in two cases cardiomyocytes hypertrophy, and in one case adipose tissue near the tip. In the literature, the most frequently described phenomenon was cardiac muscle fibrosis without necrosis or myocytolysis, rarely macrophages and multinucleated giant cells, and some focal inflammatory cell accumulation was observed. In dogs, focal fatty infiltrations, small, focal infiltrates of lymphocytes with no necrosis or fibrosis were described.

Polyether polyurethane elastomers are widely used as the outer endocardial lead insulation (overlay) due to their superior fatigue and tear resistance, excellent biocompatibility, strength, toughness, and resiliency. Polymers undergo biodegradation in the mechanism of environmental stress cracking that concerns the outer insulation and metal ion oxidation that is related to inner insulation. The ESC is degradation of PEU that was in direct contact with tissue, associated with macrophage and foreign-body giant cell adhesion to the device and the release of lysosomal oxidants. Polyurethane exposure to activated human neutrophils, hypochlorous acid, peroxynitrite lead to in vitro polymer damage (degradation). We observed fragments of the outer insulation damage in all ICD endocardial leads that were removed due to clinical evidence of non-functional lead. The most frequent polymer degradation place was located in the intracardiac part of the lead. All high-voltage coils were tightly surrounded by scar tissue, which made the removal difficult.

The outer insulation abrasions with perforation were observed by Kutarski and Malecka. The stereomicroscopic analysis of the silicone insulation resulted in Banacha morphological classification of abrasions. The abrasion of the outer silicone insulation in the intracardiac part was observed in ICD leads. In our study, severe abrasion with perforation (third level of degradation—type 3), was most frequently observed in the intracardiac part of the atrial as well as ventricular leads. The insulation damage was associated with younger leads.

We indicate that leads with active fixation are safer for heart muscle and veins during removal. Passive fixation facilitates heart muscle fragment (especially with increased fibrosis) extraction. We prefer ICD leads with one coil because amorphous, coagulated tissue that surrounds coils is problematic to detach during the removal procedure, and collagen bundles of encapsulating tissue except for coils present irregular and chaotic orientation that also may increase difficulty of extraction. Clinical importance of eosinophilia as a marker of allergy to leads with the third level of outer silicone insulation degradation with perforation needs evaluation. We should search for immunological markers...
of abrasions because even severe abrasions may be clinically and electrically silent but create a safe area for pathogen colonization, and are the risk factor of the lead-dependent endocarditis. Tissue calcification is the risk factor of type b linear abrasions formation.\(^{32}\)

Patients with tendency to calcification may be at risk of outer silicon insulation damage. The complex reaction of a patient’s tissue to the device with respect to modern immunological knowledge should be evaluated, especially at the allergic and infectious response fields. To improve the safety of patients with implanted intracardiac electronic devices, we should better understand specific tissue interaction, and insulation damage in pathological condition, for example, in the lead-dependent endocarditis as it could help improvements in lead design.

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**References**


