Tissues attached to retrieved leadless pacemakers: Histopathological evaluation of tissue composition in relation to implantation time and complications

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BACKGROUND Leadless pacemakers (LPs) have proven safe and effective, but device revisions remain necessary. Either replacing the LP or implanting a new adjacent LP is feasible. Replacement seems more appealing, but encapsulation and tissue adhesions may hamper the safety and efficacy of LP retrieval.

OBJECTIVE We determined the incidence and cellular characteristics of tissue adherent to retrieved LPs and the potential implications for end-of-life strategy.

METHODS All 15 consecutive successful Nanostim LP retrievals in a tertiary center were included. We assessed the histopathology of adherent tissue and obtained clinical characteristics.

RESULTS Adherent tissue was present in 14 of 15 retrievals (93%; median implantation duration 36 months; range 0–96 months). The tissue consisted of fibrosis (n = 2), fibrosis and thrombus (n = 9), or thrombus only (n = 3). In short-term retrievals (<1 year), mostly fresh thrombi without fibrosis were seen. In later retrievals, the tissue consisted of fibrosis often with organizing or lytic thrombi.

Fibrosis showed different stages of organization, notably early fibrocellular and later fibrosclerotic tissue. Inflammatory cells were seen (n = 4) without signs of infection. Tricuspid valve material was retrieved in 1 patient after 36 months, resulting in increased tricuspid regurgitation.

CONCLUSION Our results suggest that fibrosis and thrombus adherent to LPs are common and encapsulate the LP as seen in transvenous pacemakers. LPs may adhere to the tricuspid valve or subvalvular apparatus affecting retrieval safety. The end-of-life strategy should be optimized by incorporating risk stratification for excessive fibrotic encapsulation and adhesions.

KEYWORDS Encapsulation; End-of-life; Histopathology; Leadless pacemaker; Nanostim

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Introduction

Patients with bradyarrhythmias are increasingly treated with leadless pacemakers (LPs) because of its growing indication area and low complication rate.1,2 However, because of finite battery longevity and device defects, device revisions remain necessary. Moreover, in the next 10 years, the number of device revisions will increase notably because of the rising implantation rate and the first LPs reaching their end of battery life.3

Either retrieving the LP and implanting a new one or abandoning the LP and implanting a new adjacent one have both been demonstrated to be feasible.4 Although the replacement strategy seems more appealing because it minimizes abandoned intracardiac devices, there are concerns about retrieval failure due to device encapsulation and tricuspid damage due to adhesions. We can learn more about the incidence and cellular characteristics of encapsulation and adhesions in LPs to better understand the mechanism of retrieval failures and subsequently design better LPs and retrieval tools.

Early Nanostim LP retrieval studies with implantation-retrieval intervals of 0.2–6 years show a retrieval failure rate of 10%–15%, which led to the abandonment of LPs in those cases.5,6 The most common cause of retrieval failure was inaccessibility of the docking button because of its position near the tricuspid valve or hindrance of adjacent structures (10 of 12 retrieval failures [83%]). Although encapsulation and adhesions were not formally quantified,
their presence was suggested by Minami et al.\textsuperscript{6} as all irretrievable LPs showed no swinging movement under fluoroscopic imaging. In addition, in the study by Lakireddy et al,\textsuperscript{5} adhesions to chordae tendineae and/or tricuspid valve leaflets caused tricuspid valve damage in 2 patients. The incidence of encapsulation and adhesions after longer implantation durations is unknown because of the novelty of LP therapy. In long-term implanted transvenous pacemakers (TV-PMs), lead encapsulation occurs almost invariably, which can result in adhesions to cardiac (right ventricle [RV]) up to 72%; tricuspid valve 13%–64%) and venous structures.\textsuperscript{7–9} This increases the risk of serious complications during extraction.\textsuperscript{8,10} If the pathophysiology in LPs is similar to TV-PM lead encapsulation, the incidence of encapsulation and adhesions is expected to be high in the growing group of patients reaching end of battery life during the upcoming years. This may cause potential difficulties in retrieving the LP and thus increase the risk of tricuspid valve damage or other serious complications with the currently used retrieval tools.

Therefore, we addressed the following research questions: What is the incidence of tissue adherent to retrieved Nanostim LPs, what are the cellular characteristics, and does this have implications for the end-of-life strategy?

\textbf{Methods}

\textbf{Study population}

In this descriptive study, all consecutive Nanostim LP (Abbott Medical Inc., Chicago, IL) retrievals between January 1, 2014, and February 1, 2021, in a single experienced tertiary center (Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands) were included. Demographic and baseline data including age, sex, indication for pacing, RV implantation location, indication for LP retrieval, implantation-retrieval interval, cardiovascular disease history, and several comorbidities were obtained from the medical records. The presence of swinging movement of the LP before retrieval was assessed retrospectively. \textit{Swinging movement} was defined as a swinging angle of the docking button of $\geq 15^\circ$ on fluoroscopic imaging.\textsuperscript{6} Further follow-up data were obtained at regular outpatient visits at 2 weeks, 3 months, 6 months, and every 6 months after retrieval. When indicated, transthoracic echocardiography (TTE) and/or laboratory testing was performed. All patients gave informed consent. The study was approved by the institutional review board of our center.

\textbf{Retrieval procedure}

All retrievals were performed by the same experienced operator. A dedicated Nanostim retrieval catheter (Figure 1) was used. The retrieval catheter was inserted through an 18-F introducer sheath into the femoral vein. Under fluoroscopy, the single-loop snare and its protective sleeve were advanced into the right atrium. The protective sleeve was retracted and the snare positioned near the LP. The snare was closed around the docking button, and the LP was rotated to detach it from the endocardium. The protective sleeve was advanced over the LP, and the retrieval catheter was pulled back.\textsuperscript{11}

\textbf{Macroscopic and histopathological examination}

Two pathologists assessed the retrieved LPs and performed macroscopic and histopathological evaluation of all specimens. Adherent tissues were carefully removed from the LPs, and after routine formalin fixation and paraffin embedding, hematoxylin and eosin–stained slides were screened for the presence of thrombus, inflammatory cell infiltration, fibrosis, and myocardial tissue. The adjacent sections were stained with Alcian blue and Elastica van Gieson for evaluation of matrix components and with periodic acid-Schiff with diastase and Gram stains for microorganisms. Additionally, immunohistochemical staining was performed on a selection of cases to further define the type of inflammatory cells (using CD68 antibody for macrophages and myeloperoxidase antibody for granulocytes) and to assess the age of thrombi (with CD34 antibody for endothelial cells and smooth muscle actin antibody for myofibroblasts).

Continuous variables are expressed as median (interquartile range [IQR] or range as indicated) and categorical variables as number (percentage). Differences between groups were tested using Fisher-Freeman-Halton (categorical variables) and Mann-Whitney $U$ (continuous variables) tests. Relations between variables were explored using Spearman correlation coefficients.

\textbf{Results}

In total, we attempted to retrieve 18 LPs. We excluded 3 cases: 2 unsuccessful retrievals in which the LP was abandoned and 1 long-term retrieval in which the LP and possibly adherent material was erroneously not sent to the pathology laboratory. In retrieval with the shortest implantation-retrieval interval (ie, $<7$ days), no tissue was present. Thus, we describe data of 15 retrievals and histopathological findings of 14 retrievals.

Indications for retrieval were premature battery depletion in 7 patients (46.7%), prophylactic replacement in pacemaker-dependent patients because of the medical advisory for 4 (26.7%), loss of capture in 2 (13.3%), end of battery life and upgrade to a transvenous implantable cardioverter-defibrillator both in 1 (6.7%). The median implantation-retrieval interval was 36 months (IQR 10–42 months). The median swinging angle before retrieval was 12$^\circ$ (range 3$^\circ$–14$^\circ$) in the no swinging movement group (<15$^\circ$; $n = 10$) and a median angle of 21$^\circ$ (range 16$^\circ$–37$^\circ$) in the swinging movement group ($\geq 15^\circ$; $n = 5$). The median retrieval duration was 20 minutes (IQR 17–37 minutes) and was not significantly correlated with the implantation-retrieval interval ($r = -0.250; P = .368$). No complications occurred during retrieval. Postretrieval, in 1 patient femoral vein bleeding occurred several hours later and in 1 patient increased tricuspid regurgitation (TR) was seen (described
in more detail below). In 12 patients, retrieval was followed by Micra (Medtronic Inc., Minneapolis, MN) implantation, in 2 by Nanostim LP implantation, and in 1 by transvenous implantable cardioverter-defibrillator implantation. Further clinical characteristics are listed in Table 1.

Histopathological examination and clinical correlation
Table 2 summarizes the histopathological characteristics of all tissues adherent to LPs. These were present in 14 of 15 patients (93.3%). The tissue was located at the docking button in 9 and at the fixation mechanism in 1; in 4 its location could not be determined reliably (unknown). The amount of tissue present after retrieval ranged from minimal to partial encapsulation. Of interest, in 1 patient (study 8; implantation-retrieval interval 40 months), after LP retrieval, a ghostlike tubular structure was observed at the site of the retrieved LP by fluoroscopy (Figure 2; Online Supplemental Video 1), suggesting that the retrieved LP was encapsulated in the RV. The retrieved tissue consisted of fibrosis in multiple maturation stages, suggesting that the tubular structure was fibrotic encapsulation. However, this did not limit the retrievability of the LP. This observation emphasizes the difficulty of exact quantification of adherent tissue on retrieved LPs.

The tissue consisted of only fibrosis (n = 2), fibrosis with thrombus (n = 9), or only thrombus (n = 3). In short-term retrievals with retrieved tissue (<1 year; n = 4), mostly isolated thrombus was found (3 of 4 patients); thrombus in combination with fibrosis was present in 1 patient. In later retrievals (>1 year; n = 10), the tissue consisted invariably of fibrosis (10 of 10 patients), often with the presence of thrombotic material (8 of 10 patients).

Two types of fibrosis were seen: fibrocellular and fibrosclerotic. Figure 3 depicts the presence of either or both types of fibrosis vs implantation-retrieval intervals (panel A) and exemplary histopathological sections of both types (panels B and C). Absence of fibrosis was seen in retrievals after a median of 5 months (range 0–11 months), fibrocellular fibrosis in retrievals after a median of 30 months (range 3–41 months) of implantation, a combination of fibrocellular and fibrosclerotic tissue after implantation with a median of 41 months (range 40–56 months) and fibrosclerotic tissue latest after implantation with a median of 55 months (range 31–96 months).

Three types of thrombotic tissue were distinguished: fresh, organizing, and lytic. Fresh thrombus was found isolated in 2 patients with short-term retrievals. In the other patient with a short-term retrieval, isolated organizing thrombus was found. In later retrievals, organizing and lytic thrombi were found within the fibrotic tissue. Importantly, all patients except 1 patient received anticoagulation therapy.

Inflammatory cell infiltration within the fibrotic tissue was seen in 4 patients. This immune response was mediated by eosinophils and giant cells as shown in Figure 4. In 3 of these patients, replacement was due to battery depletion or prophylactically due to the advisory and there was no
In 1 patient with an implantation-retrieval interval of 36 months, the tissue consisted of tricuspid valve and subvalvular apparatus material, as shown in Figure 5, macroscopical (panel A) and histopathological (panel B). There were no clinical or histopathological signs of tricuspid valve endocarditis. TTE 9 months after retrieval demonstrated an increase in TR to moderate to severe with an eccentric jet, whereas this was minimal at 18 months preimplantation (panel C). The patient was asymptomatic and TR improved spontaneously to moderate over the next years.

In the 2 patients with loss of capture, the LPs were retrieved 9 and 88 days after implantation. In the former, the threshold was high at implantation (but anticipated to improve), but at day 7 capture was lost and at retrieval only thrombotic material was found, suggesting insufficient wall contact. In the latter, the threshold increased over time until complete loss of capture and fibrocellular fibrosis and thrombotic material were found at retrieval. However, it is unknown whether this tissue was attached to the docking button or fixation mechanism, which complicates making a causative relationship.

Furthermore, in 2 patients the fibrous tissue contained microcalcifications (implantation-retrieval intervals: 31 [study 6] and 41 months [study 9]). The swinging movement of the LP (angle ≥15°) was observed in 5 of 15 patients (33.3%). In Figure 6, patients with and without swinging movement are compared in terms of implantation-retrieval interval and fibrosis type. Although in patients without swinging movement, fibrosclerotic tissue was observed more often (30% vs 20%), there was no significant difference between overall fibrosis types (P > .99). When swinging movement was absent, a comparable median implantation-retrieval interval was observed without statistical significance (33.9 months vs 40.5 months; P = 1.00). Importantly, the smallest angle was observed (3°) in the patient with tricuspid valve damage due to adhesions.

**Discussion**

These findings suggest that fibrotic and thrombotic tissue adherence to long-term implanted LPs is common. The maturation stage of fibrosis seems to correspond with the duration of implantation. Inflammation may be present in the fibrotic tissue, which is in some cases accompanied by eosinophils. LPs may adhere to the tricuspid valve or subvalvular apparatus.

Fibrosis was present in the adherent tissue in the majority of patients and all patients with an implantation duration of >1 year. Fibrotic tissue was found predominantly at the docking button at the proximal end of the LP. We hypothesize that the fibrosis found at the docking button does not reflect local overgrowth, but rather encapsulation of the LP. As the LP was withdrawn into a sheath, encapsulation may have been left behind in the RV. We found such a “ghost” in 1 patient. This was not yet described after LP retrieval. We think the ghost consisted of fibrosis as the tissue adherent to the retrieved LP consisted of fibrosis. Earlier autopsy
studies confirm the occurrence of LP encapsulation, extending from the endocardial surface toward the proximal end of the LP.12–14 Encapsulation of TV-PMs also occurs frequently, similarly originating from the endocardium, and ghosts after extraction occur in 8%.9,15,16

In the fibrotic tissue we studied, multiple maturation stages were distinguished and a clear pattern consistent with the implantation duration was seen, ranging from early fibrocellular fibrosis to later fibrosclerotic fibrosis, similar to TV-PMs.7 This is exemplified by a notable case in this study: the retrieval of an LP 8 years after implantation—the longest implantation-retrieval interval currently described. A thin encapsulation of completely fibrosclerotic, fully matured, fibrosis was seen. However, variation with regard to the progression of fibrosis maturation and encapsulation around LPs does exist and might be related to patient-specific factors.12,14,17,18 In TV-PMs, longer implanted leads (>10 years) have a significantly higher risk of extraction failures and in some studies the implantation duration is related to serious complications.9,10,19,20 Likewise, in LPs, progression of encapsulation and maturation of fibrosis to a more fibrosclerotic, collagen-rich type of fibrosis may be related to an increased difficulty of retrieval after longer implantation-retrieval intervals, resulting in an increased risk of retrieval.

Table 2  Histopathological characteristics of tissue adherent to retrieved leadless pacemakers, sorted by implantation-retrieval interval

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Implantation-retrieval interval (mo)</th>
<th>Location tissue</th>
<th>Fibrosis</th>
<th>Thrombus type</th>
<th>Inflammation in the fibrotic tissue</th>
<th>Inflammatory cells in the fibrotic tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>Unknown</td>
<td>—</td>
<td>Lytic and organizing</td>
<td>+</td>
<td>Neutrophils, eosinophils, and giant cells</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Unknown</td>
<td>Fibrocellular</td>
<td>Organizing</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>Unknown</td>
<td>—</td>
<td>Fresh</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>Fixation mechanism</td>
<td>—</td>
<td>Fresh</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>Docking button</td>
<td>Fibrocellular</td>
<td>Organizing</td>
<td>+</td>
<td>Eosinophils (with degranulation) and giant cells</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>Docking button</td>
<td>Fibrosclerotic</td>
<td>Lytic</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>Docking button</td>
<td>Fibrocellular</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>Docking button</td>
<td>Fibrocellular and fibrosclerotic</td>
<td>Lytic</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>41</td>
<td>Unknown</td>
<td>Fibrocellular</td>
<td>Organizing</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>41</td>
<td>Docking button</td>
<td>Fibrocellular and fibrosclerotic</td>
<td>Lytic</td>
<td>+</td>
<td>Eosinophils (with degranulation)</td>
</tr>
<tr>
<td>11</td>
<td>42</td>
<td>Docking button</td>
<td>Fibrosclerotic</td>
<td>Lytic</td>
<td>—</td>
<td>Eosinophils (with degranulation), giant cells, and lymphocytes</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
<td>Docking button</td>
<td>Fibrocellular and fibrosclerotic</td>
<td>Lytic</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>Docking button</td>
<td>Fibrosclerotic</td>
<td>Lytic</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>96</td>
<td>Docking button</td>
<td>Fibrosclerotic</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Figure 2  Tubular notch after leadless pacemaker retrieval (study 8). A: Nanostim in situ, snared to the retrieval catheter. B: Contrast injection during subsequent Micra implantation shows a tubular structure at the site of retrieved Nanostim (see also Online Supplemental Video 1).
For determining optimal individual end-of-life strategies, risk stratification for encapsulation may be useful.

Thrombi were present in the majority of patients in this study. Whereas fresh thrombi were found isolated, organizing, and lytic thrombi were found most often within the fibrotic tissue at the docking button. This pattern is consistent with the hypothesis that thrombus formation and organization are an important denominator in the fibrotic response around LPs. In our study, no instances of pulmonary embolism were noted between implantation and retrieval, suggesting a low risk of clinically relevant embolization. In addition, as all patients except 2 were on anticoagulation therapy, these thrombi do not seem to be amenable to such therapy.

Inflammatory infiltrates containing eosinophils in the tissue adherent to LPs were seen in the minority of patients, unrelated to the implantation-retrieval interval. The presence of eosinophils may suggest the occurrence of a mild hypersensitivity reaction. A similar type of eosinophilic tissue reaction has also been reported in restenosis after coronary stent implantation and has been suggested in transvenous leads. In only 1 patient with inflammatory cell infiltration in the retrieved tissue, infectious endocarditis was considered, but no microorganisms were found in blood cultures before the initiation of antibiotics nor in the retrieved tissue.

Further, microcalcifications were seen in 2 patients. In studies on transvenous leads, calcifications are found occasionally and are related to longer implantation-retrieval intervals and renal failure. Our sample size was too small to

Figure 3 Fibrosis types around leadless pacemakers. A: Fibrosis type plotted against implantation-retrieval interval (months). The boxes represent the middle 50%, with the black line being the median; the whiskers represent 25% each. B: Exemplary section of fibrocellular fibrosis (study 13; retrieval after 40 months). C: Exemplary section of fibrosclerotic fibrosis (study 9; retrieval after 33 months).

Figure 4 Microscopic detail of fibrocellular tissue around the leadless pacemaker, containing an infiltrate of eosinophilic granulocytes (1, black arrow) with degranulation (2, red arrow). Hematoxylin and eosin stain. Bar = 200 µm.
make clinical correlations, but the implantation-retrieval intervals were intermediate and both patients did not have renal failure.

The LP adhered to surrounding structures in at least 1 patient in this study. This LP was implanted apically but over time became attached to the subvalvular apparatus and tricuspid valve. During LP retrieval, which was already hindered by the small body size of the patient (160 cm; relatively large heart [cardiothoracic ratio 0.52]), parts of the valvular tissue were retrieved together with the LP. Afterward, severe TR was seen while previous TTE showed only minimal TR. This was most probably due to retrieval. TR was subclinical and improved spontaneously by 1 grade. In a previous LP retrieval study, damage to the tricuspid valve and subvalvular apparatus was described in 2 patients (2.7%), resulting in worsening TR without further progression at 3 months post-implantation.5 The influence of implantation location cannot be determined yet, as this was not described. After TV-PM lead extraction, TR is seen in 6%–12% and is related to implantation duration.25,26 This is most likely caused by the frequent occurrence of fibrotic adhesions to the tricuspid valve apparatus.7 However, obviously these findings relate to a device in another anatomical position within the heart.

Looking forward, clinical tools are necessary to predict excessive fibrotic encapsulation and adhesions in order to guide the end-of-life strategy. Swinging movement may be a first useful tool.6 In our study, more extensive fibrosclerotic fibrosis was seen and the smallest angle was seen in a patient with severe adhesions. However, overall comparisons were not significant, most likely because of the small number of patients. Further, (intracardiac) echocardiography might be a useful tool to study in future prospective studies.27

Limitations
Several limitations hamper drawing firm conclusions and extrapolating our results. First, this was a descriptive case series with a limited number of 15 patients where extensive statistical analysis was not feasible. Second, we described only the successful retrievals, potentially leading to selection bias by excluding subjects with unsuccessful retrievals due to excessive fibrotization. Third, we described the characteristics of the tissue attached to the LPs, but the exact amount of encapsulation could not be determined because (parts of) the encapsulation tissue may remain in the RV after LP retrieval. Fourth, because of the retrospective nature of this study, a more comprehensive clinical description of patients and procedures was not feasible. Prospective studies may potentially include pre- and postprocedural echocardiography to attempt to assess encapsulation and additional parameters of retrieval difficulty, such as the number of retrieval attempts.
of attempts to capture the LP, required force during retrieval, number of catheter/device rotations, fluoroscopy duration, and cardiac wall invagination by transesophageal echocardiography. Fifth, only Nanostim LPs were included and therefore caution must be taken when extrapolating our results to LPs with other fixation mechanisms than a helix, such as Micra LPs with a tine-based fixation mechanism. Sixth, spontaneous improvement in increased TR after retrieval was seen in this study, but extrapolation of this finding is limited as increased TR occurred only once in this study.

Conclusion
These findings suggest that thrombus formation, thrombus organization, and a fibrotic response around LPs are a common feature. Over time, the fibrosis matures and likely encapsulates the LP similarly to transvenous leads, the timing of which is variable. LPs may adhere—although with unknown frequency—to the tricuspid valve or subvalvular apparatus, decreasing the safety of retrieval. The optimal end-of-life strategy should incorporate risk stratification for fibrosis and adhesions.

In light of aforementioned results, we suggest that large-scale, long-term end-of-life data should be gathered in multicenter registries, studying (1) complication rates of retrieval and abandonment, (2) risk factors for the complicated retrievals or abandonments, and (3) quantification of encapsulation/adhesion at necropsy. Subsequently, risk stratification for fibrosis and adhesions should guide the end-of-life strategy. Meanwhile, new retrieval tools should be designed to
overcome encapsulation or adhesions and it should be studied whether different pacemaker materials can minimize encapsulation and adhesions, considering that encapsulation may also protect against device infections.

Appendix

Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.08.025.

References