Explanted Pacemakers: Observations of the Long-term Foreign Body Response

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Abstract: Implanted cardiac pacing systems are widely used medical devices for the treatment of electrophysiological disorders. This study examines morphological and histological characteristics of the foreign body response observed in postmortem human subjects with long term implanted cardiac pacing devices. Four implanted pacing systems were retrieved from cadavers. Tissues were fixed, sectioned and stained with Hæmatoxylin and Eosin, Wright-Giemsa, and Masson’s Trichrome. Fibrous capsules and inflammatory cells were identified and characterized; each fibrous capsule was measured for thickness and classified according to the identity of the material in the tissue-material interface and anatomical location. The surrounding tissues exhibited defined collagen capsules and other evidence of inflammatory cells adjacent to certain materials. Capsule thickness and amount of cellular activity were correlated with position and material in contact with the tissue as well as duration of implant.

1. INTRODUCTION

1.1 Purpose
Because electrophysiological treatments will not cure the underlying disease, pacemakers are implanted for life. When a battery or lead fails, replacement surgery is done in a manner so as to minimize the risk to the patient, often making analysis of the surrounding tissues difficult if not impossible [8]. Through extensive research of pacemaker and Implantable Cardioverter Defibrillator (ICD) lead implant sites, it may be possible to improve the functionality of the devices in vivo. Postmortem studies address this issue by allowing for the removal of as much tissue as is necessary to analyze the foreign body response (FBR) to a pacing system. The purpose of this study is to examine morphological and histological characteristics of the FBR in postmortem subjects with long-term pacing and defibrillation systems.

1.2 Electrophysiological Therapies
Cardiac pacemakers are devices used to treat cardiac electrophysiological disorders such as arrhythmias, irregular beating of the heart caused by obstructed or damaged electrical pathways through the tissue [7]. The implanted pacing system consists of a pulse generator, a small unit containing a battery and computer system, and the leads: conduction wires and insulation with shocking electrodes at the distal ends, placed in direct contact with the endocardium.

The pulse generator of a pacing system is implanted subcutaneously in the pectoral region, in a pocket created at implantation. The titanium casing is in direct contact with fascia, connective and fat tissues between skin and muscle, and undergoes negligible mechanical stress. This situation allows for an examination of the development of a foreign body capsule and the cellular responses to the titanium with minimal outside influences. The pacing lead is placed in contact with the endocardium of the right ventricle. In this position, there are continuous mechanical stresses as the heart continues to cyclically contract and relax and the electrode causes trauma to the tissue with each therapeutic shock, stimulating buildup of a thicker, denser capsule. These factors have led to visible encapsulation of the lead at normal biological response levels [1,5,9].

1.3 The Foreign Body Response (FBR)
Modern medicine uses therapeutic implanted devices to treat a variety of diseases and disorders. Although these implanted devices are generally effective and helpful to the patient, observations have shown that even without systemic rejection, the device is subject to the FBR, the body’s natural reaction to foreign materials [4,6,10]. This inflammatory response is initiated by tissue-material interactions that
occur during device implantation and when inflammatory cells cannot identify the implanted, unnatural material. When an implant is present, a fibrous capsule isolates the material [10]. Acute inflammation at the time of implantation transitions to chronic inflammation of the tissues, characterized by tissue infiltration of activated monocytes, lymphocytes and certain types of circulating leukocytes. Within a few weeks, as the implant site heals, granulation tissue appears as a response to monocyte and macrophage actions. During granulation tissue formation, small blood vessels are formed and fibroblasts migrate into the tissue. The FBR stimulates foreign body giant cells (FBGC) that are created when macrophages fuse to form multinucleated giant cells at the device-tissue interface [4,11].

The FBR is the body’s defense mechanism, but it can cause problems for the implanted device when integration or communication with host tissue is required for device function. If the device is a sensor, isolating it from the surrounding tissues eliminates effectiveness; if the device delivers a treatment, the treatment must pass through the fibrous capsule to reach the target tissues. With ICDs, a fibrous capsule surrounding the pulse generator does not adversely affect function, but the capsule that encloses a pacing lead will increase the excitation threshold, using more energy from the battery, or perhaps prevent the treatment from reaching the target tissue altogether. In this study, we examined tissues surrounding pacemakers in postmortem subjects in which the cause of death was not device failure.

1.4 Device Retrieval

Much of the research performed to date assesses the FBR in a fixed, comparatively brief, period of time; these are often within weeks or a few months of implantation [3]. Device retrieval provides the ability to examine FBR in vivo over a much longer duration. When a device remains functional (does not fail), the purpose of retrieval as in this particular study, is to study postmortem tissues which were inflamed or fibrosed, but not pathological. Even though the device may perform adequately in vivo, examination of the adjacent implant tissues can aid further development of biomaterials and biocompatible devices [1,10]. Whenever possible, devices are retrieved from the patient as well as some of the surrounding tissues which can be analyzed macroscopically and microscopically. Histology and immunohistochemistry of the tissue are analyzed, occasionally with surface analysis of the device itself, to examine for signs of chronic inflammation and the FBR.

2. MATERIALS AND METHODS

2.1 Retrieval of Tissues

Therapeutic pacing and shocking system components, including pulse generator and leads, along with their surrounding tissues were retrieved from human cadavers in the University of Washington Medical Center gross anatomy lab. Specimens had been donated to the Willed Body Program for the purpose of medical education and research. This research was conducted in accordance with University of Washington human subjects policies. Upon receipt, human subject specimens were chilled until conventional embalming with formaldehyde. Following harvesting during medical school training classes, the pacing systems and tissues were stored in Formalin.

2.2 Tissue Processing and Staining

Pacing systems and adjacent tissues were micro-dissected. The titanium pulse generator was exposed and 3 mm thick sections of tissue at the tissue-device interface were retrieved. Areas of tissue in contact with excess lead material in the pectoral pocket were retrieved, as well as tissue in contact with sutures, lead attachment sites, and other structures of interest. Each lead was examined and 3 mm thick sections were taken from the electrode tip, making sure to examine the tissue-device interface at the site of active or passive fixation as well as the shocking site. Cross sections of the tubular capsule were selected as well as longitudinal cuts adjacent to the lead insulation. Tissue sections were also taken from the lead 2-4 cm away from the electrode.

Micro-dissected tissues were dehydrated and paraffinized using a tissue processor overnight,
then embedded in paraffin blocks to be sectioned. Samples were serially sectioned at 5 μm. Every fourth section was mounted on a slide, yielding 12-16 slides with sections at 20-μm intervals.

Slides were stained in sets of four, with one slide in each set stained with Haematoxylin and Eosin (Sigma-Aldrich, St. Louis, MO), one slide stained with Wright-Giemsa (Sigma-Aldrich, St. Louis, MO), and one stained with Masson’s Trichrome (Sigma-Aldrich, St. Louis, MO). Every fourth slide was reserved for additional staining as necessary. All stains were applied according to standard staining protocols.

2.3 Qualitative and Quantitative Analysis

Tissue samples were classified according to their anatomical origin, the identity of the material in the tissue-device interface, and the age of the implant. In accordance with patient privacy rights, the implant date of the pacing device was approximated to within one year by referring to the manufacture date provided by the manufacturer. Patient death was determined to within one month by the University of Washington Willed Body Program’s records.

Slides were examined using a Nikon E800 upright microscope. A CoolSnap digital camera (Roper Scientific) with Metamorph image capture software (version 6.3r7, Molecular Devices) was used to capture images of the tissues.

Examination of the tissues looked for evidence of a fibrous collagen capsule that had developed as part of the FBR, as well as inflammatory cells such as activated macrophages and lymphocytes. Other identifying factors included healthy tissue surrounding the collagen capsule, indicating that there was no infection or systemic rejection of the device.

Quantitative classification of the body’s response was completed by measurement of the collagen capsule surrounding tissues, as indicated by Masson’s Trichrome staining collagen blue. Within each tissue sample, the same general area was measured four times within the field of view. Average thicknesses of the capsules were compared according to which material the tissue had been in contact with on the pacing system as well as whether the surrounding tissue was cardiac or subcutaneous fascia in the pectoral region of the chest.

3. RESULTS

3.1 Devices Retrieved

All four retrieved pacing devices were Guidant Corporation (Indianapolis, IN) pacemakers and leads used for the treatment of bradycardia. Subject 1 had a Meridian™ model pacemaker with dual lead pacing capabilities. Subjects 2 and 3 had Pulsar Max II™ model pacemakers with single lead pacing capabilities, and subject 4 had a Pulsar Max™ model pacemaker with dual lead pacing capabilities. Durations of implants were determined using the manufacturer’s model and serial numbers inscribed on the pods. Guidant Corporation technical services provided a use-by date for each device, and established manufacture date one year previous. According to protocol, patient month of death data was acquired from the University of Washington Willed Body Program’s records.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Model*</th>
<th>Leads</th>
<th>Manufacture Date</th>
<th>Use by Date</th>
<th>Death</th>
<th>Life of Implant**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Meridian</td>
<td>Dual</td>
<td>14-May-99</td>
<td>14-May-00</td>
<td>Jan-05</td>
<td>62 months</td>
</tr>
<tr>
<td>2</td>
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<td>29-Jan-04</td>
<td>29-Jan-05</td>
<td>Feb-05</td>
<td>7 months</td>
</tr>
<tr>
<td>3</td>
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<td>14-Feb-03</td>
<td>14-Feb-04</td>
<td>Feb-05</td>
<td>18 months</td>
</tr>
<tr>
<td>4</td>
<td>Pulsar Max</td>
<td>Dual</td>
<td>3-Jun-99</td>
<td>3-Jun-00</td>
<td>Mar-05</td>
<td>63 months</td>
</tr>
</tbody>
</table>

*All devices retrieved are pacemakers manufactured by Guidant Corporation.

**Duration of Implant determined from midpoint of manufacture and use by dates to death of the subject.

Figure 1 Summary of each subject and pacemaker model retrieved. Implant duration is approximated from the use-by-date and month of patient death.
Program’s records. Implant duration was calculated from six months after the manufacture date as approximate implant date to the month of the patient death. Two pacemakers (subjects 1 and 4) had implant duration of greater than 5 years, while two (subjects 2 and 3) had implant duration of less than 2 years. The retrieved devices are summarized in Figure 1.

3.2 Collagen Capsules

A collagen capsule surrounded each retrieved device, including components placed in the cardiac tissue as well as pectoral fascia, the subcutaneous region in which the pulse generator was placed. The thickness, morphology, and overall composition of the foreign body capsule surrounding each subject’s pacemaker were slightly different, with some commonalities. To characterize the fibrous capsules, measurements were taken with a light microscope and imaging software. Images of tissues from Subjects 1 and 4 are shown in Figure 2, both with implant duration of greater than five years. The fibrous capsule appeared to be completely formed, with constant composition throughout, whereas in subjects 2 and 3, with implant duration of less than two years, the fibrous capsule appeared to be less complete. Figure 3 shows evidence of transitional tissues and continuing formation of the capsule in subjects 2 and 3. No clear trend was found when the thickness of the capsule was measured; however, differences were apparent between cardiac tissue in contact with the silicone insulation of the leads and the pectoral fascia in contact with the silicone lead insulation, polyurethane connector block, and titanium pulse generator. The results are summarized in Figure 4. Because subject 3 had a large population of active inflammatory cells and inconsistent morphology within the collagen capsules, each measurement was substantially different and therefore data from subject 3 could not accurately represented the tissue response and was therefore not included in the quantified data.

3.3 Cellular Activity Adjacent to Implant

In addition to formation of a collagen capsule, the FBR includes the presence of the different cell types that initially attempt to combat the foreign body. Over a long period of time, the local tissue begins to heal and the collagen capsule isolates much of the cellular activity. In each of these subjects, however, a variety of cell types were observed in direct contact with the implant or within the collagen matrix.

Figure 2 Subject 1(a) and subject 4(b) both had implant duration of greater than 5 years. These images show the collagen capsule directly adjacent to the implant as well as some of the surrounding tissue. The collagen itself has a consistent composition with few or no nuclei present in the immediate area surrounding the implant. The image from subject 1(a) is cardiac tissue, showing some inflammatory cells outside the foreign body capsule. Subject 4(b) shows a tissue sample from the pectoral fascia, with adipose cells present around the foreign body capsule.
Subject 2(a) and subject 3(b) both had implant duration of less than 2 years. These images display the collagen capsule directly adjacent to the implant. Image (a) is cardiac tissue, but foam cells (white arrow) are present within the capsule. Image (b) is pectoral fascia, but the orientation of the collagen is not uniform and nuclei are present throughout the image, indicating some sort of cellular activity as opposed to completely fibrous acellular tissue.

Despite implant duration of greater than 5 years, some signs of chronic inflammation were seen in tissue samples from subject 1. Figure 5 shows one case of chronic inflammation, characterized by plasma cells, immunoglobulin particles, and lymphocytes. Figure 2 is more typical of the tissue samples from subject 1, with tightly formed collagen with very few or no observable cell nuclei or signs of chronic activity. The majority of tissue samples from subject 4 display characteristic collagen capsules of a long term implant with little cellular activity, as seen in Figure 2. Figure 6 displays cardiac tissue surrounding the passive fixation site of a silicone tine near the pacing electrode. The sample includes very little collagen surrounding the tine.

Figure 3 Subject 2(a) and subject 3(b) both had implant duration of less than 2 years. These images display the collagen capsule directly adjacent to the implant. Image (a) is cardiac tissue, but foam cells (white arrow) are present within the capsule. Image (b) is pectoral fascia, but the orientation of the collagen is not uniform and nuclei are present throughout the image, indicating some sort of cellular activity as opposed to completely fibrous acellular tissue.

Figure 4 Summary of collagen capsule measurements (error: 1 standard deviation). Measurements from subject 3 could not be recorded because of the highly inconsistent nature of the collagen capsules with a large presence of active cells.
This tissue sample from subject 1 comes from the pectoral fascia where excess leads had been wrapped around the pulse generator. The implant would have been on the left of the image, with a collagen capsule in direct contact with the implant. To the right of the collagen, however, the dark spots are plasma cells, immunoglobulin particles secreted by the plasma cells, and lymphocytes, all signs of chronic inflammation.

Healthy cardiac muscle and connective tissue is visible nearby, indicating minimal FBR or recovery from the initial wounding. Figure 6, a sample of cardiac tissue from subject 4 contains foam cells, macrophages ingesting lipids, within the capsule. This would not be called active inflammation, but rather macrophage migration into the area. In another sample from the pectoral fascia surrounding the pulse generator, silicone or some other foreign object from the lead insulations that the macrophages are trying, unsuccessfully, to ingest (frustrated phagocytosis), was also observed. The presence of a FBGC was observed as well as some multinucleated macrophages, with indications of possible development into FBGCs.

With implant duration of less than 2 years, tissue samples from subject 2 contained many more examples of the intermediate stages of the FBR. Figure 7(a), from the area of cardiac tissue surrounding the lead, just above the tip displays healthy myocytes and a defined collagen capsule. Brown staining with Haematoxylin and Eosin reveals siderophages, iron-containing macrophages, perhaps ingesting erythrocytes. Inside the collagen capsule there is a layer of foam cells, special macrophages that might appear in atherosclerotic plaque. These may have been engulfing lipid or some other particles of material as the material degraded. The small, dark spots within the foam cells/capsule are most likely erythrocytes. In general, there are inflammatory cells present, but the area is quiescent. There is no evidence of FBGCs or active inflammation.

Both images are cardiac tissue from subject 4. (a) The tissue surrounding one of the passive fixation tines displays a tight collagen capsule around the tine with healthy cardiac muscle and connective tissues outside of the capsule. (b) A trial tissue surrounding one of the pacing leads contains foam cells, macrophages ingesting lipids.
Figure 7 Tissue samples from subject 2(a) is cardiac tissue surrounding the lead, just above the pacing electrode. Inside the well defined collagen capsule are siderophages and foam cells in contact with the lead insulation. In the pectoral fascia (b), granulation tissue is apparent inside the more defined collagen capsule.

Figure 7(b) is from tissue surrounding the pulse generator. There is a clear demarcation of tissue, separating the titanium from the polyurethane lead connector area. Adjacent to the titanium, scar tissue is well established with no inflammation at all. Granulation tissue can be seen around the plastic area, characterized by extensive vascularization and macrophages, which could potentially develop into FBGCs. If using immunohistochemical staining, this tissue would show CD45 expression in some areas, indicating the presence of lymphocytes and other mononucleated cells. The area in the bottom left quadrant of Figure 7(b) is granulation tissue that will eventually develop into scar tissue without inflammation.

Figure 8 is tissue from the pulse generator pocket where excess lead was wound around the pulse generator and sutured into place; areas with FBGCs are well defined. There are also more siderophages, or macrophages with non-hemoglobin iron. Most of the observed inflammation is present around the suture. This could also be used as a positive control for CD68 staining, as the inflammatory macrophages are definitely present; however, the capsule around the lead itself is completely free of any inflammation.

The tissue samples from subject 3 contain examples of many well-formed collagen capsules; however, the morphology and composition are not constant throughout. In Figure 3, the collagen is not uniform, but neither is the granulation tissue. There, as well as Figure 9, more vascularization and fibroblasts are present within the tissue. In the pectoral fascia of Figure 9, there are readily identifiable fibroblasts, bipolar cells, and occasional lymphocytes, rounder cells. The fibroblasts indicate a continued formation of more collagen as would be found in incompletely formed scar tissue from the implantation procedure.

Figure 8 A cross sectional sample of a suture from the pectoral fascia of subject 2 reveals definite FBGCs and siderophages, iron containing macrophages, in direct contact with the suture fibers.
4. DISCUSSION

A correlation exists between duration of implant and degree of inflammatory cell activity. This indicates that the FBR occurs as a result of initial implantation, but complete healing occurs over time. The body’s natural healing mechanisms will isolate a foreign body, if possible, to completely eliminate its effect. This degree of encapsulation hinges upon implantation location, as well as the materials with which the body comes in contact. In tissue samples such as those in subject 2, more easily degradable materials resulted in more cellular activity. Evidence of activated macrophages trying to phagocytose particles of silicone from the lead insulation poses two problems, that of damage to the lead itself and therefore implant malfunction and continued inflammation of the tissue, precluding complete healing. In order to confirm the presence of lipid engulfing macrophages one would need to use frozen sections. These macrophages would stain positive for CD68 if using immuno-histochemistry. In some cases, such as Figure 5 from subject 1, cellular activity is occurring immediately outside of the densely formed collagen capsule. This migration of the cellular activity leads to another question of why the cellular activity is not directly adjacent to the implant as would commonly be the case, even among cases of this particular study, shown in Figure 7. Another question is that raised by complete encapsulation around the silicone fixation tine of the electrode in subject 4, versus cellular activity due to the break down of the silicone lead insulation in subject 2.

We also observed that cardiac tissue generally forms less of a collagen capsule than does pectoral fascia, but is surrounded by a large buildup of fibrin not found in fascia. These cardiac tissues adjacent to the silicone tines and lead body insulation appeared healthy with little evidence of inflammatory cells within the capsule. When a collagen capsule is formed it is very dense with few nuclei present, indicating implanted device isolation from surrounding tissues and cellular activity. In subjects 2 and 3, formation of the foreign body capsule was not complete in all physiological regions or extended to differing degrees. Inflammatory cells remained within the collagen capsule, suture material was surrounded by multiple FBGCs, and granulation tissue was present, including macrophages, fibroblasts and small vessels at the tissue-device interface.

The study completed to date indicates a need for a much larger sample population. Individual patient variables, such as medical history, were also not available to us. In future studies, a partnership with an established autopsy program to gain further insight into factors that may affect the functionality of an implant would greatly aid the study of long-term FBR. With
immediate access to the subjects, fixation of the tissues could be controlled and procedures such as immunohistochemical staining could be performed to positively identify endothelial cells, specific inflammatory cells, and other hypothesized bodies. It would also be helpful to take the scope of this study beyond pacing devices to sensors and drug delivery systems, whose performance and efficacy can be negatively affected more drastically by encapsulation than a pacing electrode. The ability to observe long-term effects of FBR with respect to materials such as titanium and silicone, naturally extends study to current efforts to promote angiogenesis and other innovative biomaterials and examine their performance over a much longer period of time.

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