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Histopathological Study of Tissue Reaction to Pacemaker Electrodes Implanted in the Endocardium

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Abstract

Limited information is available about histopathological reactions to the implanted endocardial electrodes of pacemakers (PM). Gross anatomic and histologic studies of tissue reactions to PM electrodes were made in thirteen autopsy cases (nine men and four women, ages 25~89 years, mean age 71.8) who died two months to twenty-one years after PM implantation. Nine of them had complete atrioventricular (AV) block, three had sick sinus syndrome, and one had bradycardia-tachycardia syndrome. The direct causes of death were not related to their PM. The tip with projecting tines was implanted in the right ventricle in all patients. At the contact area between the electrode and the endocardium, no tissue reaction was observed in one patient with a history of over sixteen years of PM implantation. However, cardiomyocytes under the tip had been replaced by fibrotic tissue in many other patients. In two patients in particular where the electrode had been implanted at the apex of each right ventricle, all cardiomyocytes had disappeared and only fibrotic tissue and adipose tissue were observed under the tip. These findings suggest that mechanical stress caused by attaching the tip tightly damages cardiomyocytes and brings about changes in the pacing thresholds. In three patients, a space was seen between the tip and the endocardium. A fibrous sheath covering the electrode extended to the tip and formed a thick fibrous cap. This non-excitabile fibrous cap acted as a virtual electrode and possibly affected the elevation of the threshold in these patients. In four patients, extensive myocardial fibrosis due to disease, e. g. previous myocardial infarction, dilated cardiomyopathy, amyloidosis, or sarcoidosis, was found in the area surrounding the tip and also might affect the elevation of the threshold. We concluded that elevation of pacing thresholds after PM implantation is not due to reactive endocardial thickening. The space between the tip and the endocardium is occupied by a fibrous sheath, and an overly tight attachment damages cardiomyocytes causing replacement fibrosis. Thus, it is not desirable in some patients to insert the electrodes into the apex, where the myocardium is thin. To avoid the elevation of thresholds, development of further devices is necessary to allow electrode fixation to the endocardium with a more suitable pressure level.

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Introduction

Transvenous cardiac pacemakers (PM) have been of great benefit to many patients with bradyarrhythmia. After implantation of such devices, however, tissue reactions may affect the pacing thresholds¹. In fact, after implantation of pacemaker electrodes, the stimulation threshold increases diachronically². It has been supposed that the cause of the increase in the diachronic threshold is a pathophysiological reaction of the endocardium on physical or electrical stimulation^{1,2}; however, limited information is available on histopathological reactions to the implanted endocardial electrodes of pacemakers. The purpose of this study was to investigate histopathological reactions in the endocardium bordering these electrodes.

Materials and Methods

Gross anatomic and histological studies of tissue reactions to PM electrodes were made in thirteen autopsy cases (nine men and four women, ages 25~89 years, mean age 71.8). Nine of them had complete atrioventricular (AV) block, three had sick sinus syndrome, and one had bradycardia syndrome. Their deaths were not directly related to their pacemakers. The duration of PM use was from two months to twenty-one years. The tip with projecting tines (fins) was implanted in the right ventricle in all patients (**Table 1**).

All hearts were fixed in 10% formalin immediately after autopsy. Cross sections of the right ventricle were made carefully along the pacing leads. After gross examination, macroscopic photos were taken

Table 1

No.	Age	Sex	Cause of PMI	Basic Cardiac Disease	Time from PMI to Death	Main Cause of Death	Contact
1	69	F	CAVB	Cardiac Amyloidosis	2 months	Multiple Myeloma, Systemic Amyloidosis	loose
2	70	M	BTS		4 months	Diabetes Mellitus, Chronic Renal Failure	tight
3	25	M	CAVB	Cardiac Hemochromatosis	4 months	Primary Macroglobulinemia, Hemochromatosis	tight
4	56	M	CAVB	Dilated Cardiomyopathy	6 months	Dilated Cardiomyopathy	tight
5	83	M	SSS	Mitral Regurgitation	1 years and 8 months	Bronchopneumonia	loose
6	89	F	CAVB	Cardiac Sarcoidosis	4 years	Cardiac Sarcoidosis, DIC	tight
7	78	M	CAVB	OMI (post CABG)	5 years	Burn, Bronchopneumonia, Pleuritis (Pleural Effusion)	tight
8	80	M	SSS		5 years and 7 months	Lung Cancer	tight
9	78	M	CAVB		8 years and 7 months	Pneumonia, Chronic Renal Failure	tight
10	78	M	SSS	OMI (involving right ventricle)	13 years and 1 month	Cerebral infarction, Pneumonia	tight
11	79	F	CAVB	OMI, AMI	16 years and 4 months	AMI	tight
12	62	F	CAVB	OMI, Mitral Regurgitation (post CABG and Mitral Valvoplasty)	19 years	Postoperative Multiple Organs Failure	tight
13	87	M	CAVB		21 years	Hepatocellular carcinoma	loose

PMI: Pacemaker implantation, CAVB: Complete atrioventricular block, BTS: Bradycardia tachycardia syndrome, SSS: Sick sinus syndrome, DIC: Disseminated intravascular coagulation syndrome, OMI: Old myocardial infarction, AMI: Acute myocardial infarction, CABG: Coronary Artery Bypass Grafting

and the electrodes were removed. The right ventricular walls including the part where the lead was inserted were excised and processed for light microscopic observation. Paraffin embedded sections were stained with hematoxylin and eosin (H-E) or by the Elastica-Masson Goldner (EMG) method.

Results

The electrode was deeply implanted at the apex of the right ventricle in all patients. There were two patterns of contact between the electrode and the endocardium: tight contact (**Fig. 1**) and loose contact (**Fig. 2**).

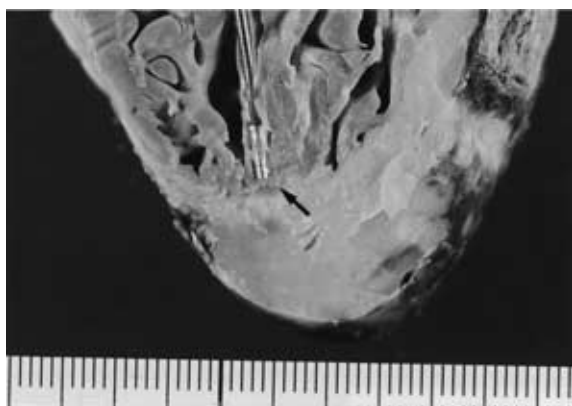


Fig. 1 The electrode is deeply implanted at the apex of the right ventricle and is tightly attached to the endocardium (**arrow**) (Case 12).



Fig. 2 A space (**arrow**) is found between the tip and the endocardium (Case 5).

1. Histopathological Changes in Areas with Tight Contact

In one patient in whom the pacing electrode had been implanted sixteen years and four months prior to death (Case 11), it was in tight contact with the endocardium and no reactive endocardial thickening was observed in the contact area (**Fig. 3**).

In the other patients with tight contact, cardiomyocytes under the tip had disappeared and had been replaced by fibrous connective tissue (**Fig. 4**). In one patient with eight years and seven months of PM implantation (Case 9), fibrosis was observed as a result of the disappearance of cardiomyocytes on one side of the tip. In addition, the fibrotic tissue was formed by an organized thrombus that included capillary proliferation (**Fig. 5-a, b**).

In the two patients (Case 6 and 12) where the electrode had been implanted at the thin apex of the right ventricle, cardiomyocytes had completely disappeared and only fibrous connective tissue and adipose tissue were observed under the tip.

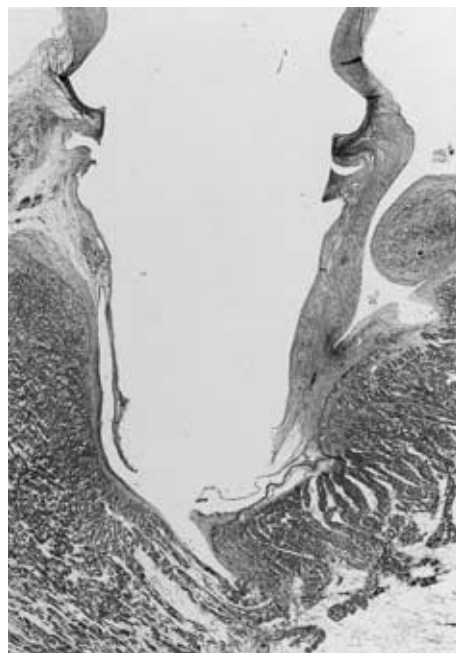


Fig. 3 The electrode is in tight contact with the endocardium and no reactive endocardial thickening is observed in the contact area (Case 11, EMG stain).

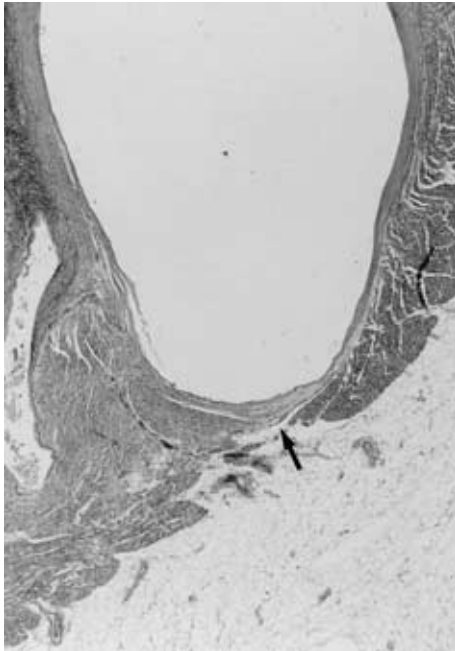


Fig. 4 Cardiomyocytes under the tip have disappeared and are replaced by fibrous connective tissue (**arrow**) (Case 7, H-E stain).

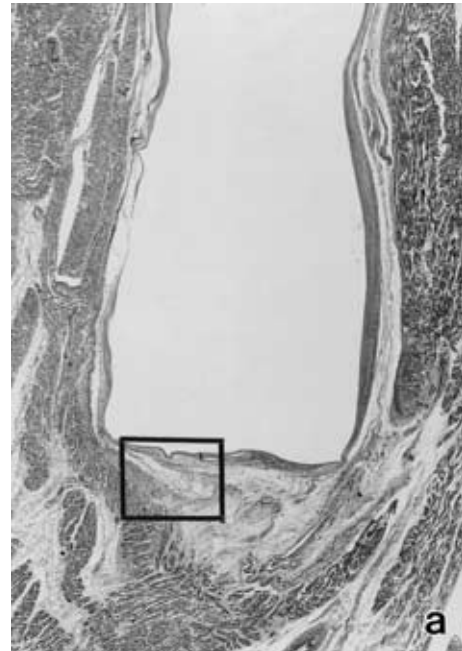


Fig. 5-a Fibrosis results from the disappearance of cardiomyocytes on the left side of the attachment area (Case 9, EMG stain).

2. Histopathological Changes in Areas with Loose Contact

In the three patients (Case 1, 5 and 13) with loose contact between the electrode and the endocardium, a space was seen between the tip and the endocardium. A fibrous sheath covering the electrode extended to the tip, and it formed a thick fibrous cap (**Fig. 6-a, b**). A few capillaries were found in the sheath (**Fig. 6-c**).

3. Histopathological Finding of Fibrous Sheath Formation

In one patient with a short period of implantation (Case 1), a fresh fibrin thrombus was formed on the tip of the electrode. An organized thrombus was observed around the fin in the other patient (Case 6) and the process of organization of these thrombi turning into a fibrous sheath was observed in other patients with a relatively long period of implantation (**Fig. 7-a, b, c**). In all the long-term implantation cases, the pacemaker electrodes were completely covered with fibrous sheaths from lead to tip (**Fig. 8**).

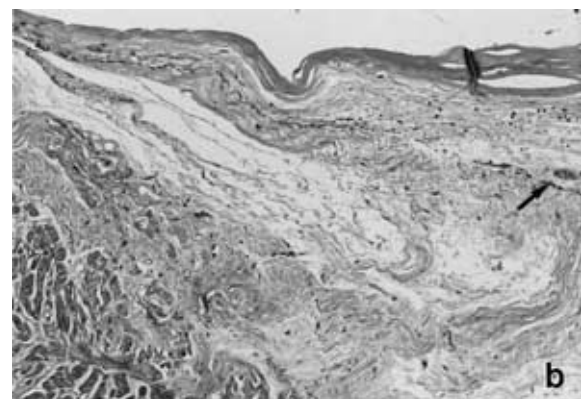


Fig. 5-b A higher magnification view of **a**. Fibrotic tissue is formed by an organized thrombus including a capillary (**arrow**) on the right side of the attachment area, suggesting a small space remained after the electrode insertion (Case 9, EMG stain).

4. Effects of Basic Cardiac Disease

In the patient with cardiac amyloidosis (Case 1), amyloid deposits were found at the tip-attached area and were thought to have influenced the conduction of electrical stimulation. In the patient with dilated cardiomyopathy (Case 4), replacement fibrosis was observed in the myocardium including the

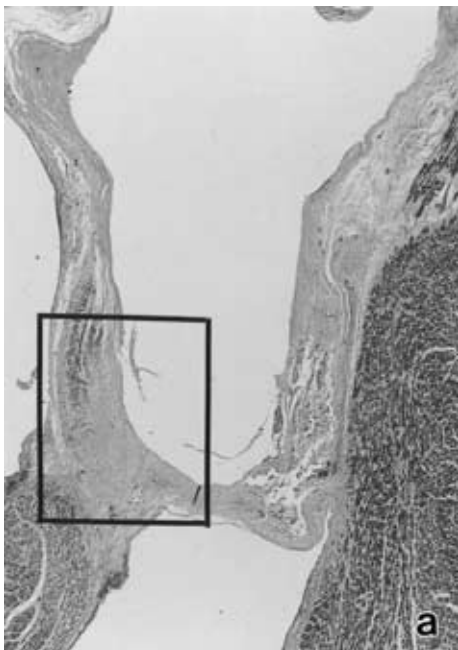


Fig. 6-a A fibrous sheath covering the electrode extends to the tip and forms a thick fibrous cap (Case 5, EMG stain).



Fig. 6-b A higher magnification view of a (Case 5, EMG stain).

subendocardium of the tip-attached area. In this patient, a microabscess was found under the tip because of terminal sepsis. In the patients with previous myocardial infarction involving the right ventricle (Case 10) and cardiac sarcoidosis (Case 6),

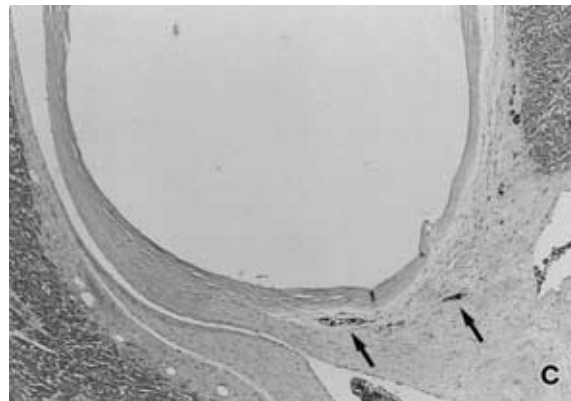


Fig. 6-c A few capillaries (**arrows**) are found in the sheath (Case 13, H-E stain).

fibrosis extended to the subendocardium of the tip-attached area.

Discussion

Implantation of transvenous cardiac pacemakers is a way to control arrhythmia that benefits patients greatly. After the insertion of a PM lead, a histological reaction should occur in the endocardium. Some data have suggested that endocardial thickening causes changes in pacing function after PM implantation³⁴. However, histopathological alterations in the endocardium and surrounding myocardium have not been sufficiently researched, because it is difficult to conduct experimental studies involving long periods of observation of the condition of the endocardium. Our research group investigated the histopathological changes under the tip of pacing leads in autopsies of patients who died between two months and twenty-one years after PM implantation.

This study demonstrated two different contact patterns of the PM electrodes with the endocardium: tight contact and loose contact with dead space. No reactive endocardial thickening was observed in either pattern.

Transvenous implantation is usually performed with the aid of Roentgen fluoroscopy, and the attachment of the PM electrodes to the endocardium is judged only by data from electrophysiology. The state of the electrode—how far the tip has been inserted into the trabecula or how much pressure



Fig. 7-a In the early period after implantation, the electrode is covered with a fibrin thrombus (Case 1, H-E stain).



Fig. 7-c The granulation tissue matures into a fibrous sheath consisting of collagen fiber (Case 7, EMG stain).

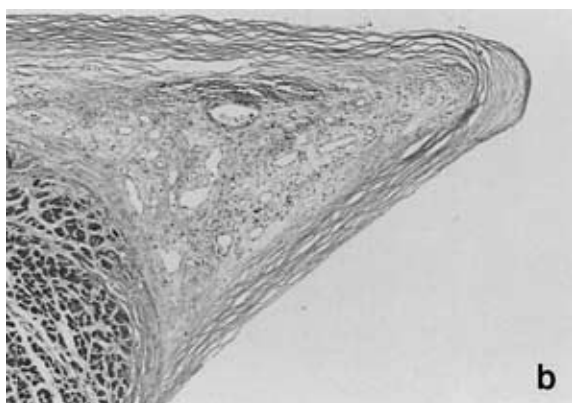


Fig. 7-b The granulation tissue of the organized thrombus is observed between the electrode and the endocardium (Case 6, EMG stain).



Fig. 8 The pacemaker electrode is completely covered with a fibrous sheath from the lead to the tip (**arrowheads**) (Case 10).

the tip exerts on the endocardium—is undetectable. Furthermore, adjustment of the position of the tip may be difficult after insertion when projecting tines are used.

In our cases with tight contact, cardiomyocytes under the tip had disappeared and been replaced by fibrous tissue. This fibrous connective tissue acts as a virtual electrode and does not usually affect the threshold¹⁵⁻⁸. However, in one case where the electrode had been inserted into the thin wall area of the right ventricle, the layer of cardiomyocytes had disappeared completely, and only the adipose tissue of the epicardium surrounded the tip, leading to a possible increase in the pacing threshold. Patients who have an apex with extremely thin endocardium should not have electrodes inserted into it.

In one patient with 16 years and 4 months of PM

implantation, no tissue reaction was observed under the tip-attached area. Thus, it is clear that the disappearance of cardiomyocytes with fibrosis is not caused by electrical stimulation of the PM. Our group concluded that histological alterations under the tip were caused by physical compression pressure on the tip of the electrode. Not only direct damage to cardiomyocytes but also a decrease in blood supply caused by oppression of capillaries leads to fibrosis under the tip, especially in cases where the attachment of the tip causes excessive tension in the tissue.

In the patients with loose contact between the electrode and the endocardium, there were dead spaces between the tip and the endocardium. A thick fibrous sheath had formed and covered the surface of the tip. Observations of cases with different periods of implantation showed that this

fibrous sheath formed an organized fibrin thrombus, which initially adhered to the surface of the tip. The whole length of the PM leads was covered with this sheath in the patients with long periods of implantation.

The dead space remains between the tip and the endocardium if the tip with the fin is fixed above the endocardium. The pacing threshold may not show a high level at the time of implantation, because the blood within the dead space does not affect the electrical stimulation, so it is difficult to determine whether there is a dead space or not from electrical threshold data on implantation. After the formation of a fibrous sheath, this non-excitability fibrous sheath acts as a virtual electrode, and enlargement of the surface area of the electrode may influence the battery longevity.

In patients with heart disease causing interstitial fibrosis in the myocardium, extension of fibrosis should influence the elevation of the pacing threshold and the conduction of electrical stimulation. But the way in which the electrode touches the endocardium is thought to be a common problem even in these patients. Our findings in one patient with microabscess formation in the area adjacent to the electrode suggest that the PM electrode interferes as a foreign body and causes infection.

Study Limitations

This study was hampered by our inability to obtain electrophysiological data together with histopathological results. Many of the subjects of this study had received their PM implantations more than 10 years before death, and it was difficult to obtain data from the time of implantation. Furthermore, their causes of death were not related to their PM, so physiological studies were not performed on admission before death.

Fixation of the tip is important because if the tip moves after implantation, pacing failure may occur. Moreover, long-term bed rest sometimes results in deep vein thrombosis or senile dementia, especially in aged patients. Many types of electrode tip are available, such as a screw-in type, a tined-type, and a

long acting steroid-eluting type to avoid tissue reaction⁹⁻¹². All the patients in this study had been implanted with tined-type electrodes, but they were of many different shapes. Some of these tips may have been steroid-eluting type, but our group could not obtain the PM manufacturers' names, because the PM generators had been returned after autopsy. At any rate, we can say that the leads and electrodes were covered with fibrous sheaths and that steroids did not prevent the sheathing.

Conclusion

Histopathological study of tissue reactions to pacemaker electrodes implanted in the endocardium revealed following:

1. Two different contact patterns were observed in the area where the electrode tip was attached to the endocardium: tight attachment; and loose contact with dead space.

2. In one patient with tight contact, no tissue reaction was observed in the attachment area even more than 16 years after the implantation. However, cardiomyocytes under the tip had disappeared and had been replaced by fibrous connective tissue in many other patients. The disappearance of cardiomyocytes is thought to be caused by mechanical stress (excessive tension in the attachment) in the tip.

3. In patients with loose contact, a fibrous sheath that covered the electrode lead extended around the tip and lay in the space between the tip and the endocardium. The sheath was formed by an organization of thrombus that initially covered the electrode. This non-excitability sheath acts as a virtual electrode and may influence the elevation of the pacing threshold or the battery longevity.

4. Extensive fibrosis of the myocardium may also interfere with the pacing threshold in cases of specific heart disease.

Thus, the elevation of pacing thresholds after PM implantation is not due to endocardial thickening. To avoid the elevation of thresholds, further development of electrodes of a shape that will allow them to be attached to the endocardium with an appropriate level of pressure is necessary.

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