

Pericarditis Following Permanent Pacemaker Insertion

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Abstract

Background: The appearance of pericarditis following insertion of a permanent pacemaker is not widely acknowledged in the literature.

Objectives: To describe our experience with pericarditis following 395 permanent pacemaker implantations over 2 years.

Methods: We retrospectively reviewed the medical records of 395 consecutive patients in whom new pacing systems or pacemaker leads had been implanted over a 2 year period. We searched the records for pericarditis that developed within 1 month after pacemaker implantation according to the ICD-9 code. The incidence, clinical picture, response to treatment, and relationship to lead design and location were studied.

Results: Eight cases (2%) of pericarditis following implantation were detected. Clinical manifestations in all patients were similar to those of post-pericardiotomy syndrome and included chest pain (n=7), friction rub (n=1), fever (n=2), fatigue (n=2), pleural effusion (n=2), new atrial fibrillation (n=2), elevated erythrocyte sedimentation rate (n=4), and echocardiographic evidence of pericardial effusion (n=8). All affected patients had undergone active fixation (screw-in) lead implantation in the atrial position. The incidence of pericarditis with screw-in atrial leads was 3% compared to 0% in other cases ($P < 0.05$).

Conclusions: Pericarditis is not uncommon following pacemaker implantation with active fixation atrial leads. Special attention should be paid to identifying pericardial complications following pacemaker implantation, especially when anticoagulant therapy is resumed or initiated. The use of passive fixation leads is likely to reduce the incidence of pericarditis but this issue should be further investigated.

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Pericarditis is a very well-known complication of cardiac surgery [1]. However, the appearance of pericarditis following permanent pacemaker insertion is not widely acknowledged in the literature and indeed only a limited number of cases is described [3-12]. The first report of probable pericarditis subsequent to a transvenous pacemaker implantation was published in 1975 [2]. Different pacing leads have different methods of fixation to the endocardium. Some are fixated to the tissue by tines, wedges or flanges that anchor into the trabeculae (passive fixation), while others are actively fixated by screws at the distal end of the lead (active fixation leads). It is conceivable to assume that pericarditis is related to mechanical irritation caused by the tip of the pacing lead, and its incidence may therefore depend on the design of the lead and its fixation method, as well as its location (atrium versus ventricle).

We report our experience with the occurrence of pericarditis following 395 permanent pacemaker implantations over 2 years.

The incidence, clinical picture, response to treatment, and the relationship to lead design and location are described.

Patients and Methods

The medical records of 395 consecutive patients who underwent new permanent pacemaker or new lead implantation at the Sheba Medical Center over a 2 year period were reviewed for evidence of pericarditis after implantation (coded by ICD-9).

Pacing lead data of the 395 implants included: 225 with atrial active fixation and ventricular passive fixation, 18 with both atrial and ventricular active fixation leads, 27 with atrial active fixation only (no ventricular leads), 10 with ventricular active fixation only (no atrial lead), and 115 with ventricular passive fixation only (no atrial lead). Models of the atrial leads included Pacesetter 1488 (n=20), Medtronic 5568 (n=41), Medtronic 4568 (n = 98), and Medtronic 4068 (n = 111). All implantations were performed by one of four experienced operators, and no cases were implanted by trainees. All patients were followed by the hospital team for at least 24 hours after implantation. All subjects underwent clinical assessment, chest radiograph and determination of the pacing and sensing thresholds on the day after implantation. Echocardiographic examination was performed in all cases of chest pain or friction rub following the implantation. All patients were examined again at the pacemaker clinic after 2 weeks, 3 months, and every 6 months thereafter. Patients were requested to report any complaints, and were called for unscheduled follow-up visits if any new complaints occurred.

For statistical analysis, incidences in different groups were compared using the chi-square test.

Results

Of the 395 patients with implanted pacemakers, 8 (2%) developed pericarditis (4 males and 4 females). Their median age was 72.7 years (range 54-86 years). Their clinical data are listed in Table 1. Lead models in the eight patients included Medtronic 4068 (n=1), Medtronic 4568 (n = 2), and Medtronic 5568 (n = 5). All affected patients had dual chamber systems implanted via the left subclavian vein approach. All had been implanted with active fixation retractable screw-in leads in the atrium. The incidence of pericarditis among patients with screw-in leads in the atrium was 8/270 (3%), compared to 0/125 among others without atrial screw-in leads ($P < 0.03$). The electrodes had been positioned without any difficulty in all patients. The implant criteria as a measure of a favorable lead position were met in this group of patients. These

Table 1. Demographic characteristics, previous medical history, indication for pacing and pacing mode of the 8 patients with pericarditis

Patient no.	Age (yrs)	Gender	Previous medical history	Anticoagulant/anti-aggregant treatment	Indication for pacemaker	Pacing mode
1	75	M	Cancer of prostate: cured. CRF	Aspirin, stopped 5 days before procedure. Not restarted.	Intermittent CAVB	DDDR
2	70	M	CHF with EF: 30%. CRF	Coumadin, switched to LMWH before procedure and restarted 4 days after procedure. INR on admission for pericarditis was 2.3.	Symptomatic 2° AV block	DDDR
3	53	M	CHF with EF: 40%	Aspirin, stopped for 5 days. Restarted 3 days after procedure.	Symptomatic 2° AV block	DDDR
4	76	F	HTN, hypothyroidism	None	Symptomatic 2° AV block	DDDR
5	76	F	CVA, PAF	Coumadin, switched to LMWH before procedure and restarted 4 days after procedure. INR on admission for pericarditis 5.7	SSS	DDDR
	73	F	IHD, old TB	Aspirin, stopped for 5 days. Restarted 3 days after procedure	2° AV block	DDDR
7	68	M	No	None	CAVB	DDD
8	57	F	ILD, PAF	Aspirin	SSS	DDD

CRF = chronic renal failure, CHF = congestive heart failure, LMWH = low molecular weight heparin, EF = ejection fraction, HTN = hypertension, CVA = cerebrovascular accident, PAF = paroxysmal atrial fibrillation, IHD = ischemic heart disease, TB = tuberculosis, ILD = interstitial lung disease, DDD = dual chamber (atrial + ventricular) pacing, DDDR = dual chamber (atrial + ventricular) rate responsive pacing.

Table 2. Clinical manifestations, laboratory analysis and echocardiographic findings

Patient no.	Time to appearance post-implantation							Pericardial effusion by echo	ESR
		Chest pain	Fever	Fatigue	Pleural effusion	New atrial fibrillation	Pericardial friction rub		
1	1 day	+	-	-	-	-	-	Mild	68
2	2 weeks	+	+	+	+	+	-	Large, signs of tamponade	45
3	2 days	+	-	-	-	-	-	Mild	NA
4	3 weeks	+	-	-	-	-	-	Mild	NA
5	3 weeks	+	+	+	+	+	-	Mild to moderate	56
6	2 weeks	+	-	-	-	-	-	Mild to moderate	NA
7	2 weeks	+	-	+	-	-	+	Mild to moderate	70
8	2 weeks	-	-	+	-	-	-	Mild	NA

NA = not available, AF = atrial fibrillation.

included pacing thresholds: <1.4 V in the atrium and <1.3 in the ventricle; sensing thresholds: >3 in atrium and >12 in ventricle; and range of impedances on both atrial and ventricular leads between 385 and 868.

The clinical and echocardiographic manifestations of the patients with pericarditis are summarized in Table 2. Pericarditis occurred 5–21 days (median 13) after implantation. Common clinical features included the occurrence of chest pain (7 patients), fever (2 patients), elevation of erythrocyte sedimentation rate (4 patients in whom ESR was measured), and new onset of atrial fibrillation (2 patients). Only one of the patients developed tamponade and underwent pericardiocentesis. Pericardial friction rub was audible in one patient. Culture and cytology of the pericardial fluid were negative in all cases. On diagnosis, two patients were on anticoagulant therapy; in one of them the INR level was 5.7, and in the other, who developed tamponade, it was 2.3. Four patients were on low dose aspirin.

Chest X-ray disclosed a marked enlargement of the cardiac silhouette in one patient, whereas normal heart size characterized all the others. All demonstrated properly positioned pacemaker leads in both atria and ventricles, without protrusion beyond cardiac silhouette. Pleural effusion was present in two patients.

Echocardiogram demonstrated pericardial fluid in all affected patients. The amount of fluid was large in one patient with signs of tamponade, small to moderate in three, and small in four. None of the patients demonstrated lead protrusion to the pericardium by echo.

Four patients taking non-steroidal anti-inflammatory drugs and three patients on steroids (due to contraindications to NSAIDs) demonstrated clinical and echocardiographic improvement within 2–3 weeks. Two patients developed relapses following cessation of treatment with NSAIDs and required additional therapy with steroids. The clinical condition of one additional patient did not initially improve on steroids. After removal and re-implantation of

EST = erythrocyte sedimentation rate

NSAIDs = non-steroidal anti-inflammatory drugs

the pacemaker system because of the dehiscence of the pacemaker's pocket, this patient was later treated successfully with steroids.

Discussion

This study describes the occurrence of pericarditis following permanent pacemaker implantation. The first reported case of probable pericarditis following pacemaker implantation was published in 1975, and described a 72 old patient who developed fever and pleuritic chest pain 3 weeks after the transvenous pacemaker implantation [2]. To date only a few reports of pericarditis related to pacemaker implantation have been published in the literature [2–12]. In this study we describe a series of eight patients who developed pericarditis following permanent pacemaker implantation or new pacemaker leads. The diagnosis of pericarditis was based primarily on clinical grounds after the exclusion of other reasons for the occurrence of pericardial effusion, and on the temporal relationship of permanent pacemaker implantation to pericardial complications.

Several clinical observations are noteworthy when assessing the course of pericarditis following permanent pacemaker implantation. Clinical manifestations of pericarditis in our group generally resembled the classic post-pericardiectomy syndrome with pleuritic chest pain, dyspnea, and the presence of pericardial and pleural effusions with a raised ESR, without polyarthropathy. Our clinical findings were similar to those of most previously reported cases. Generally, pericarditis after permanent pacemaker implantation follows a benign and self-limited course [2,7–10]. The occurrence of massive pericardial effusion, resulting in tamponade, is rare and only sporadic cases have been reported [3,5,6,12]. The development of chronic constrictive pericarditis seems to be quite uncommon and only a few cases were previously described [3–4,11].

The pericarditis was treated with NSAIDs, resulting in clinical improvement within 2–3 weeks. Steroids were instituted in patients with contraindications to NSAIDs or in whom recurrences on NSAIDs occurred. In most cases pericardiocentesis was not required because of the small size of effusion, which responded to drug therapy [4,7–9].

All our patients underwent insertion of permanent dual chamber pacemaker with retractable screw-in leads in the atrium. The reported incidence of acute and chronic pericardial complications in our and other series of different lead implantations ranged from 0% to 4.9%, with a higher incidence when active fixation leads were implanted in the atrium [6,13,15,17,18] and a lower incidence when inserted into the ventricle [14]. Passive fixation leads in both the atrium and ventricle were only rarely associated with pericarditis [16,19,20]. It is conceivable that the thin atrial wall is more prone to perforation than the thicker ventricular wall, and that the screw mechanism has a higher tendency to protrude through the walls and to irritate the pericardium or cause low grade perforation resulting in the later development of pacemaker pericarditis [17,18]. Notably, both in our experience and in the literature, this phenomenon is associated with various models of atrial screw-in leads and is not limited to a specific model. Another potential factor for the development of pericarditis as evidenced by our

results was the use of anticoagulants, although there was no direct association with high international ratios during the presentation of pericarditis, and only two of our patients were on anticoagulant therapy.

The mechanism of pericarditis following permanent pacemaker implantation is unclear, but it may involve a direct irritation of the pericardium by minimally protruding electrodes, low grade bleeding with hemorrhagic pericarditis, and a late autoimmune/inflammatory response to those insults [21,22].

Several researchers have proposed pericarditis as a potential cause of rhythm disturbance, especially in patients with evidence of myocardial perforations as demonstrated on echocardiographic studies [23]. It is important to exclude pericarditis as a cause of new-onset atrial fibrillation in patients with recently implanted pacemakers, especially if anticoagulant treatment is initiated. We therefore conclude that pericarditis is not uncommon following pacemaker implantation with active fixation atrial leads. Special attention should be paid to the identification of pericardial complications following pacemaker implantation, especially when anticoagulant therapy is resumed or initiated. Whether the use of passive fixation leads will reduce the incidence of pericarditis is currently being investigated in a randomized trial.

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Capsule

Can we reprogram cancer cells?

Cancer arises as a result of both genetic and epigenetic modifications. Whereas genetic changes permanently alter the DNA sequence of the tumor cell, epigenetic changes act more subtly – for example, by altering the way that critical proteins are packed around DNA. The extent to which these reversible epigenetic changes contribute to tumorigenesis is poorly understood. In two studies, investigators examined whether cancer cells can be reprogrammed into a normal state by transferring nuclei from mouse tumor cells into enucleated mouse oocytes and then assaying their ability to direct early embryo development. Belloch et al. (*Proc Natl Acad Sci USA* 2004;101:10733/pnas.0405015101) found that transfer of nuclei

from embryonal carcinoma cells resulted in normal blastocysts from which embryonic stem (ES) cells could be produced, but the ES cells had the same tumorigenic potential as the donor cells. Hochedlinger et al. (*Genes Dev* 2004;18:1875) likewise found that nuclei from many tumor cell lines could not be reprogrammed. One remarkable exception, however, was a melanoma cell line whose nucleus not only produced ES cells but was able to direct the full development of an adult mouse. These results underscore the important role of genetic changes in tumor development, but raise the possibility that in certain tumor types, epigenetic changes may play a predominant role.

E. Israeli

Capsule

Cancer cells and apoptosis

Cancer cells proliferate because they evade programmed cell-death pathways, and much effort is being devoted to finding ways to activate apoptotic pathways in such cells. Key interactions that determine whether cells live or die are mediated by so-called BH3 (BCL-2 homology 3) domains, which are found in proteins that regulate apoptosis. Such signals can be mimicked or disrupted by peptides that resemble the interaction domains, but such molecules have major shortcomings as experimental or therapeutic agents because of low potency, instability, and inefficient delivery to cells. Walensky et al. (*Science* 2004;305:1466) show that these problems could be overcome when a BH3 domain that promotes apoptosis was held in its native-helical form by a chemical modification they call a hydrocarbon staple. The modified peptide showed increased binding affinity for its target, was relatively protease resistant, and could cross cell mem-

branes. Preliminary studies in animals even showed that the modified peptides could decrease growth of transplanted tumors in mice. The activity of caspases, the cysteine proteases that mediate cell death by apoptosis, is held in check by the inhibitor of apoptosis proteins (IAPs). The protein known as Smac promotes apoptosis by binding to IAPs and relieving inhibition of caspases. Li et al. (p. 1471) show that the effect of the Smac peptide can be potently mimicked by a small membrane-permeable molecule. Studies with the compound revealed that the well-known requirement for inhibition of protein synthesis to allow apoptotic effects of tumor necrosis factor (TNF) likely reflects decreased IAP-mediated inhibition of caspases. The new compound sensitized cancer cells in culture to TNF-induced cell death.

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