Recurrent, late-onset pleural effusions in elderly patients receiving pacemaker therapy

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Abstract

Late-onset pacemaker-related pleural effusions (PEs) are rare and are often misdiagnosed with other entities. Our study aimed to detail the clinical features and management of PEs long after pacemaker insertion.

We conducted a review of 6 consecutive elderly patients with PEs, who had undergone a new pacemaker insertion from September 2014 to January 2017. Also, the clinical characteristics and therapeutic courses of PEs were summarized.

Two cases involved fluids after the first implantations, with pacing durations of 3 and 7 months. Two other cases developed PEs 3 or 4 months after the first replacement, with pacing durations of 6 and 11 years. Another 2 cases developed PEs 3 or 5 months following the second replacement, with total pacing durations of 16 and 18 years, respectively. The average interval was 4.17 months for the 6 cases from the time of the new pacemaker insertion to the occurrence of PEs. During the course, they had to be hospitalized repeatedly for thoracenteses because conventional treatments had only short-term effects. After the pacing settings were adjusted, PEs in all cases disappeared gradually. No patients were readmitted for PEs during the median follow-up period of 13 months.

For elderly patients following implantation of a new pacemaker, PEs should be considered due to improper pacing settings, and corresponding adjustments to the device should be made.

Abbreviations: ADA = adenosine deaminase, AV = atrioventricular, AVD = atrioventricular delay, DDD = dual-chamber, LDH = lactate dehydrogenase, LV = left ventricular, LVEF = LV ejection fraction, NT-proBNP = N-terminal pro-B-type natriuretic peptide, PE = pleural effusion, PMS = pacemaker syndrome, PPD = purified protein derivative, RV = right ventricular, VVI = single-chamber.

Keywords: elderly, pacemaker, pleural effusion

1. Introduction

To imitate normal cardiomyocyte function pacing and to establish the rhythm, implantation of a permanent pacemaker is a commonly used therapeutic strategy for patients with bradyarrhythmias [1] which is becoming more common. [2]

Because this is an invasive procedure, a variety of potential pacemaker-related complications may occur, including those that are periprocedural or late-onset (<30 or >30 days after device insertion). In a cohort study [3] involving 33,519 pacemakers, the 30-day postoperative complications included tamponade, hemothoma, pneumothorax, device failure, superficial, and/or deep infections. The late complications mostly involved lead failure, early battery depletion, pacemaker migration, and/or erosion. [4]

Late-onset pacemaker-related pleural effusions (PEs) are rare and are often misdiagnosed as caused by heart failure, tuberculosis, and so on. [5] The present study describes 6 elderly patients with PEs that developed long after a new pacemaker was implanted, and the resolution of those fluids by adjusting the pacing settings.

2. Materials and methods

From September 2014 to January 2017, 6 consecutive elderly patients with clinical, laboratory, and radiologic evidence of PEs were admitted into Renmin Hospital of Wuhan University, a 4000-bed teaching hospital in Wuhan, China. All patients had undergone a new pacemaker insertion at this hospital, where a total of 1025 pacemakers were implanted during this period. This study had been approved by the Medical Ethics Committee of the Medical School at Wuhan University, and written informed consent for clinical data collection was provided by each of the patients.

At the first admission for PE, each subject received a series of screenings containing their medical history, physical examination, 12-lead electrocardiography (ECG) at rest, echocardiography, chest x-ray or computed tomography (CT) scan, blood biochemical examinations, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), D-dimer, liver and kidney functions, electrolytes, tumor markers, skin test for tuberculin purified protein derivative (PPD), T-SPOT.TB assay, etc. The laboratory characteristics of PEs were always analyzed, and were collected during each patient’s first thoracentesis, with samples simultaneously sent for smears for tuberculosis, cytology, and bacterial cultures. Fluid transudates were assessed according to the criteria described by Light. [5] Each PE was classified by size as...
ejection fraction (LVEF) was 55% (range: 40%–60%).

Data collected from the patients involved demographic characteristics, pacemaker type, and pacing duration, size, and side of PE before and after the pacemaker insertion. Statistical analysis of data was performed using SPSS statistical software 22.0 (IBM Corp, Armonk, NY).

3. Results

3.1. Clinical features

Table 1 summarizes the baseline demographics and characteristics of the subjects at first admission. The series included 4 men and 2 women, whose ages ranged from 78 to 90 years with a median of 81 years. All patients had PEs at the time of admission, a right-sided effusion in 1 patient, and bilateral effusions in the other 5 patients, of which, 4 patients were right-sided predominant and 1 was left-sided predominant. However, their blood pressure (BP), heart rate (HR), and respiration rate (RR) were within the normal range.

All patients had undergone a new permanent dual-chamber pacemaker installation or replacement, with a pacing duration ranging from 3 months to 18 years, with a median of 8.5 years. The median age at primary implantation was 73.5 years (ranging from 63 to 89). The interval was an average of 4.17 ± 1.60 months (ranging from 3 to 7 months) from the new insertion to the occurrence of PEs. The fluids occurred in 2 patients (cases 2 and 6) after the first implantation, with pacing durations of 3 and 7 months, respectively. Cases 1 and 4 developed PEs 3 or 4 months after the first pacemaker replacement (Fig. 1) with a total pacing duration of 6 and 11 years, respectively. The other 2 patients (cases 3 and 5) had PEs 3 or 5 months after the second pacemaker replacement (Fig. 2), with total pacing durations of 16 and 18 years, respectively.

Patients had slightly uncomfortable syndromes shortly after the pacemaker insertion, such as palpitations or precordial discomfort. However, no obvious objective signs were found, and patients with a normal range of vital signs were discharged 1 or 2 days after the pacemaker installation. However, weeks or months later, they were rehospitalized presenting with dyspnea as well as symptoms and signs of PEs. Chest X-rays and ultrasound examinations revealed PEs.

At the time of admission for PEs, 4 cases had edema of the lower extremities. Resting ECG showed that the patients were in sinus rhythm alternating with dual-chamber pacing (DDD) rhythm, pacing rhythm with frequent premature atrial contraction, DDD rhythm with normal pacemaker perception, and pacing function. Others included premature ventricular contraction, complete right bundle branch block, slight ST segment elevation and long QT interval, frequent premature atrial beats in the pacemaker, or atrial fibrillation. However, ventriculoatrial conduction were not evident in paced beats. Several imaging performances on transthoracic echocardiography were revealed separately, including senile degenerative heart disease with slight mitral or aortic stenosis, aorta ascendens dilation, mitral annular calcification with slight mitral insufficiency and aortic regurgitation, ventricular septal base hypertrophy with left ventricular (LV) outflow tract obstruction, right ventricular (RV) hypertrophy, and segmental wall motion abnormality. Three cases had tricuspid incompetence with moderate tricuspid regurgitation and a small amount of pericardial effusion. The median LV ejection fraction (LVEF) was 55% (range: 40%–60%).

Table 1. Demographics and characteristics of subjects in this study.

| Variables | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|-----------|--------|--------|--------|--------|--------|--------|
| Date of first admission for PE (s) | September 14, 2014 | December 12, 2015 | May 1, 2016 | May 18, 2015 | June 18, 1998 | December 10, 2009 |
| Age at admission, y | 78 | 81 | 81 | 86 | 82 | 90 |
| Sex | Male | Male | Female | Female | Male | Male |
| Indication for pacemaker | Third-degree AVB | SSS | Sinus node dysfunction | Slow-fast syndrome | Sinus node dysfunction | Sinus node dysfunction |
| Initial pacing mode | November 02, 2005 | December 02, 2015 | March 22, 2008 | Single-chamber | Single-chamber | Single-chamber |
| Duration of pacing before PE | 11 y | 3 mo | 11 y | 3 mo | 11 y | 3 mo |
| Pleural effusion location | Bilateral, right-sided predominant | Bilateral, left-sided predominant | Right-sided | Right-sided | Right-sided | Right-sided |
| Interval from new pacemaker insertion to PE, months | 4 | 3 | 5 | 3 | 3 | 7 |
| Times of thoracenteses | 6 | 11 | 8 | 7 | 9 | 7 |
| Date of pacemaker setting adjustment | February 07, 2015 | November 21, 2016 | June 02, 2017 | March 06, 2017 | April 12, 2017 | May 29, 2017 |
| Duration of follow-up, mo | 35 | 19 | 16 | 10 | 9 | 7 |

AVB = atrioventricular block; PE = pleural effusion; SSS = sick sinus syndrome.
3.2. Laboratory examinations and fluid results

This group had a normal range of D-dimer, liver and kidney functions, electrolytes, and tumor markers. All the following laboratory results were negative, including PPD, T-SPOT.TB assay, PE samples for smears for tuberculosis, cytology, and bacterial cultures. The main compositions in the fluid are listed in Table 2, the basic characteristics being a serous transudate, low cell count, lymphocyte predominant, low levels of lactate dehydrogenase (LDH) and adenosine deaminase (ADA), and glucose concentration similar to serum, all of which met Light’s

Figure 1. Case 4 was an 86-year-old woman with pleural effusion (PE) after the first replacement of the pacemaker, who was admitted into the hospital for biventricular pacemaker implantation because of slow-fast syndrome on December 17, 2012. On August 12, 2016, she was re-hospitalized for “pacemaker battery depletion” and received a pacemaker replacement. Three months after that replacement, she presented with dyspnea on exertion, fatigue, and diminished strength. Physical examinations were consistent with PE. Chest x-ray (C), CT scan (D, E), and ultrasonography revealed a moderate, right-sided PE. However, there was no fluid on her chest x-ray plates performed 4 days before the replacement procedure (A, B). Therapeutic thoracenteses were performed and 480 mL fluid was removed at the first time. However, in the next 3 months, the PE occurred repeatedly and serial therapeutic thoracenteses were performed, nearly twice a month. Adjustment of the pacing setting made her clinical symptoms and PE gradually disappear. The follow-up time was 10 months.
criteria for transudative effusion. The median LDH level was 106 U/L (range: 61.00–132.00 U/L) and the mean total protein and ADA was 23.91 ± 2.87 g/L (20.70–27.10 g/L) and 7.14 ± 2.25 U/L (4.67–10.97 U/L), respectively. Before the pacemaker settings were adjusted, the value of NT-proBNP was higher, with the median maximum of 2495 pg/mL (1997–3309); however, it decreased to 545 pg/mL (236–1497) 2 weeks after the adjustment.

3.3. Treatment procedure, outcome, and follow-up
No patient had a PE before the pacemaker implantation or replacement. After the pacemaker insertion, the PEs occurred, initially being trace to small in size and gradually becoming moderate or large, mostly bilateral associated with dyspnea. All cases had undergone several managements, including diuretics, and thoracenteses for their unidentified, recurrent PEs. Fluid removal may relieve the dyspnea and provide information about

Figure 2. Case 3 was an 81-year-old woman, who was admitted into the hospital for her second pacemaker replacement (a dual chamber pacemaker) on December 1, 2015. She was initially implanted with an atrial pacing pacemaker because of sinus node dysfunction on June 1998. Ten years later, she received her first pacemaker replacement because of battery depletion, with the same pacing mode as in 1998. On May 18, 2012, that was 4 years after the first replacement, she had x-ray films taken for a cough, which showed no pleural effusion PE (A and B). Also no PE was seen in x-ray images (C) 4 days before the second replacement. Five months later (May 5, 2016), she was admitted into the hospital again for moderate right-sided predominant, bilateral PEs, which were seen on her chest x-ray film (D, E), CT scan (F), and ultrasound examination. Due to no response to diuretic treatment, she was treated 8 times with thoracenteses during the next >3 months, removing 400 to 700 mL of fluid each time. The fluid was typically a transudate according to Light’s criteria. After adjusting the pacemaker setting, the PE gradually disappeared. The follow-up time was 16 months.
the effusion source. Since thoracentesis had only temporary effects to improve the clinical status, patients had to be repeatedly hospitalized and underwent serial therapeutic thoracenteses for the fluid reaccumulation, with an average of $5.50 \pm 1.05$ hospitalizations and $8.00 \pm 1.79$ thoracenteses. During the course, the fluid in 1 case was considered as malignant, 2 cases received antituberculosis therapy, and fluids in another 3 patients were diagnosed as caused by heart failure from the original cardiovascular diseases.

The pacemaker settings in all cases were adjusted with a longer atrioventricular delay (AVD), which may result in an appropriate implantable pacing frequency upper limit reduced. Echo-Doppler-guided AVD optimization was adopted to measure variations in stroke volume for different AVD and pacing rate settings, from the “optimized” AVD [AVD (optimization (OPT))] to shorter [AVD (OPT) – 50 ms] or longer [AVD (OPT) + 50 ms] AVD. Over the next 2 weeks, the patient’s symptoms improved dramatically and fluids gradually reduced or even subsided, with the median LVEF being 56% (42%–60%). During the median follow-up period of 13 months (ranging from 7 to 35 months), none of the 6 patients were hospitalized again and none had evidence of fluid reaccumulation on follow-up ultrasonic examinations and chest x-rays.

4. Discussion

In the present study, we describe a series of patients with PEs that occurred within months following implantation of a new dual-chamber pacemaker. The fluid was initially small to moderate in size, right-sided or bilateral but right-sided predominant, and met transudate criteria. Gradually, the fluid volume increased and was associated with dyspnea. No evidence implied that it was consistent with hepatic hydrothorax, nephrotic syndrome, pulmonary embolism, and tuberculous or neoplastic causes. Before the recognition was made between PEs and pacemaker installment, clinical management of the fluid was usually difficult and ineffective, because spontaneous regression of PEs rarely occurred and they failed to respond to traditional therapeutic alternatives. Physicians could only repeat therapeutic thoracenteses to relieve the symptoms. However, a particular but often forgotten characteristic was a latency period between the pacemaker insertion and the occurrence of PEs. The adjustment of pacing settings improved the resolution and reduced the risk of recurrences.

Pacemaker implantation is performed for bradyarrhythmia patients of all ages, especially in the elderly population. Approximately 70% to 80% of all pacemaker implantations are done for patients older than 65 years of age. Fifteen percent of pacemakers in use are replacements, of which one fifth have been replaced more than twice. Although this procedure is safe, elderly subjects may have more postprocedural complications than younger subjects. Because of age-related physiological changes in cardiovascular and cerebrovascular systems, the

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### Table 2

| Variables          | Value (mean ± standard deviation) | Range       |
|--------------------|-----------------------------------|-------------|
| Pleural fluid      |                                   |             |
| WBC count, $\times 10^9$ | 0.24 ± 0.12                      | 0.12–0.36   |
| Neutrophil, %      | 4.80 ± 2.20                       | 2.00–7.00   |
| Lymphocyte, %      | 93.22 ± 3.42                      | 89.00–98.00 |
| Total protein, g/L | 23.91 ± 2.87                      | 20.70–27.10 |
| LDH, U/L           | 106.00 (Median)                   | 61.00–132.00|
| ADA, U/L           | 7.14 ± 2.25                       | 4.67–10.97  |
| Glucose, mmol/L    | 6.53 ± 0.47                       | 6.00–7.10   |
| CEA, ng/mL         | 0.50 (Median)                     | <0.50–0.80  |
| Serum              |                                   |             |
| Total protein, g/L | 59.81 ± 1.92                      | 56.80–63.40 |
| Albumin, g/L       | 34.61 ± 1.24                      | 32.30–36.60 |
| LDH, U/L           | 278.32 ± 13.20                    | 254.00–294.00|
| ADA, U/L           | 11.35 ± 3.28                      | 6.73–16.46  |
| Glucose, mmol/L    | 6.65 ± 0.26                       | 6.24–7.20   |
| CEA, ng/mL         | 2.62 (Median)                     | <0.50–2.89  |
| Maximum NT-proBNP  | 2495 (Median)                     | 1997–3309   |
| before adjusting, pg/mL |                |             |
| Maximum NT-proBNP  | 545 (Median)                      | 236–1497    |
| 2 weeks later, pg/mL |                |             |

ADA = adenosine deaminase; CEA = carcinoembryonic antigen; LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro B-type natriuretic peptide; WBC = white blood cell.

* Significantly different compared with the NT-proBNP before adjusting ($P < .001$).
adverse consequences of atrioventricular (AV) desynchronization should be more obvious and more common in older patients.[9] In this series, all cases were elderly subjects with a median age of 81 years. The fluids in 2 cases occurred after primary pacemaker replacement, whereas 2 other cases developed PEs after their second replacement.

PEs commonly occur in patients shortly after ventricular assist device implantation,[9,10] or postcardiac injury syndrome after defibrillator implantation,[11] and generally, samples of PEs are exudative in nature. PEs may also be associated with pacemaker placement; patients who experience this may have rapid or slow accumulation and reaccumulation of fluid within the pleural space. Nevertheless, it is a rare but debilitating pacemaker-related complication. The pacemaker syndrome (PMS) may be the symptomatic consequence of the hemodynamic and rhythmic deficiencies of incomplete restoration of the normal pattern of cardiac depolarization,[12] which should include 3 components[12]: the absence of consistent atrial synchrony at a normal physiological AV interval; the retrograde activation of atrial conduction; and an inadequate cardiac rate response to physiological need. Appropriately paced AVDs and upgrading single-chamber pacing (VVI) devices to physiological DDD devices, can usually resolve PMS symptoms.[13] However, PMS has been described in patients with both types of VVI and DDD devices.[14] No significant benefits associated with DDD devices were found compared with VVI devices in a large prospective randomized Pacemaker Selection in the Elderly study[15] and in a study by Harper et al.[16] For a DDD device, an appropriate AVD is important in determining an appropriate implantable pacing frequency, achieving optimal AV synchrony, correcting hemodynamic abnormality, and eliminating clinical symptoms.[17] The ideal A-V interval is that which creates the maximal QRS wave both at rest and while moving.[17] Although the dual-chamber system and operating method contains an automatic test for determining an optimum AVD at a test frequency such as the programmed lower rate limit, the optimal AVD is difficult to determine in each elderly patient. Commonly, empiric programming of the AVD is performed during pacemaker implantation.[18] To solve myocardial electrical propagation, a number of computational models have been developed in simulating electrical activations, such as noninvasive volumetric imaging,[19] cellular automata or reaction-diffusion systems, and meshfree method.[20,21] The primary developing mechanism for pleural fluid formation in our series is speculative; however, it is an indication of volume overload and may be related to the poor coordination of A-V contraction, which causes mild to moderate heart failure and slowly develops PEs. Adjustment of an “optimized” AVD and appropriate pacing frequency caused the pleural fluid to gradually disappear, the BNP to decrease and the edema to be eliminated. Right-sided or right-sided predominant effusions may be influenced by the position of the pacing electrode. Chronic RV apical pacing may have a deleterious effect on LV systolic function,[22,23] by causing intraventricular asynchronous contraction, compromising LV performance and the quality of life. Also, an acute induction of dysynchronous LV contraction was observed, and LV twist, longitudinal shortening were acutely impaired during RV apical pacing.[24]

5. Conclusions

Although uncommon, physicians should consider the possibility of PEs long after insertion of a transvenous pacemaker. An improper pacing setting could be the reason for fluid accumulation and corresponding adjustments should be made, which result in resolution of the symptoms and PEs, without any recurrences at 7- to 35-month follow-up. Recognizing these symptoms is important, otherwise patients may be misdiagnosed with other diseases or can be delayed due to confounding entities and late presentation, so that the fluids persist and cannot be treated in a timely manner. However, therapeutic responses to adjustments of the pacing settings can aid in the diagnosis.

Author contributions

All authors of this research article have directly participated in the designed research (KH, MX), performed research (ZZ, MD, WH), collected data (ZZ, MD, WH), analyzed data (KH, MX), or wrote the article (MX, KH).

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