BMC Cardiovascular Disorders

RESEARCH

Open Access

Pacing therapy for immune checkpoint inhibitors-associated atrioventricular block: a single-center cohort study

Jiaqi Wang[1†], Fanyi Kong[2†], Yifan Wang[2], Jiaqi Yu[1], Yingxian Liu[1], Wei Wu[1], Yongtai Liu[1], Peng Gao[1], Zhongwei Cheng[1], Kang'an Cheng[1], Hua Deng[1], Jinzhi Lai[1], Jingbo Fan[1], Lihua Zhang[1], Quan Fang[1], Taibo Chen[1*] and Deyan Yang[1*]

Abstract

Background ICI-associated myocarditis is an uncommon yet potentially fatal condition, particularly when concomitant with atrioventricular block (AVB) necessitating pacing. The role of pacing therapy for ICI-associated AVB remains unknown.

Objectives The aim of this study is to investigate the efficacy and safety of pacing therapy for ICI-associated AVB.

Methods Patients with ICI-associated myocarditis admitted to Peking Union Medical College Hospital from May 1st 2019 to April 30th 2024 were consecutively screened and the patients with AVB requiring pacing therapy were retrospectively included. Baseline clinical characteristics and initial temporary pacing therapy were evaluated. Follow-up assessments were conducted to evaluate the survival rate and the recovery of atrioventricular conduction.

Results A total of 43 patients with ICI-associated myocarditis were screened. Among them, a total of 11 (11/43, 25.6%) patients (mean age 64.5 ± 8.6 years, female 18.2%) were diagnosed with advanced or complete AVB and subsequently underwent pacing therapy. Short-term (within 90-days after procedure) survival rate was 72.7% (8/11). Atrioventricular conduction recovered in 4 (4/11, 36.4%) patients, without AVB recurrence after temporary pacemaker removal. For safety endpoints, right ventricular (RV) pacing parameters including pacing threshold, sensing amplitude and impedance were acceptable and no procedure-related complications occurred except RV temporary active fixation lead dislodgement in 1 patient (1/11, 9.1%). No pacing system related-infection occurred.

Conclusions Pacing therapy for ICI-associated AVB demonstrates both safety and efficacy. ICI-associated AVB shows a high rate of recovery. Temporary pacemaker with active fixation lead may be a reasonable option for the initial pacing therapy.

Keywords Immune checkpoint inhibitor, Atrioventricular block, Pacemaker

†Jiaqi Wang and Fanyi Kong are First and co-First authors.

*Correspondence:
Taibo Chen
cardio-chen@qq.com
Deyan Yang
swallow_sums@aliyun.com

[1]Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, No.1 Shuaifuyuan, Wangfujing, Dongcheng District, Beijing 100730, China
[2]Department of Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Introduction

Immune checkpoint inhibitors (ICI) have been widely used in the treatment of advanced cancer, significantly improving clinical outcomes. However, the application of ICIs may lead to ICI-associated myocarditis which is uncommon but has a high fatality rate [1]. Atrioventricular block (AVB) is frequently observed among ICI-associated myocarditis patients and related to increased all-cause mortality [2]. Pacing therapy is recommended for patients with complete or advanced AVB [3]. Previous case reports and case series [4, 5, 6] have reported pacemaker implantation in ICI-associated AVB patients. However, data on the safety and efficacy of pacing therapy for ICI-associated AVB remain limited. Furthermore, the clinical course and prognosis of these patients have not been thoroughly investigated. This study aims to investigate the safety and efficacy of pacing therapy in ICI-associated AVB patients.

Methods

Study patients

In this retrospective single-center cohort study, patients admitted to Peking Union Medical College Hospital for ICI-associated myocarditis from May 1st 2019 to April 30th 2024 were consecutively screened. Patients diagnosed with ICI-associated AVB who underwent temporary and/or permanent pacing were included in the analysis. The diagnosis of ICI-associated myocarditis was based on pathohistological or/and clinical criteria according to 2021 International Cardio-Oncology Society (IC-OS) consensus statement [7]. Detailed diagnostic criteria and corresponding clinical manifestations of each patient were provided in Supplementary Table S1. Pacing indications fulfilled the current European Society of Cardiology (ESC) guideline [3]. This study was approved by the ethics committee of Peking Union Medical College Hospital (K6787). All patients had given informed consent to the pacing procedure. The study was conducted in compliance with the principles of the Declaration of Helsinki.

Pacing therapy

Given the potential recovery of atrioventricular conduction, all patients initially received temporary pacing. Depending on the operators' preference, either conventional, transfemoral temporary passive-fixation lead or temporary permanent pacemaker (TPPM) [3, 8] using active-fixation lead via the internal jugular vein or subclavian vein was applied. The pacing lead was placed at the right ventricular apex or septum. The passive-fixation lead was connected to a conventional external generator while the active-fixation lead was connected to a permanent pacemaker pulse generator which was externally secured at the base of the neck or the chest. All generators were programmed to VVI mode. If atrioventricular conduction recovered and no longer fulfilled indications for subsequent pacing, temporary pacing leads and generators were removed. If atrioventricular conduction did not recover, a permanent pacemaker was implanted, or the initial passive-fixation lead was replaced with a TPPM for prolonged temporary pacing. Due to the absence of guidelines or consensus, the duration of waiting for recovery varied and was determined by operator experience. The choice between single- or dual-chamber permanent pacemakers, programmed in VVI or DDD mode, respectively, was based on operator preference and patient-specific factors. For patients with TPPM, pacing threshold, sensing amplitude and impedance of right ventricular lead were measured at implantation. For patients with conventional temporary pacing using passive-fixation lead, only the right ventricular lead pacing threshold was measured at implantation. In patients with permanent pacemakers, pacing parameters for both right atrial and right ventricular leads were measured.

Endpoints

The primary endpoint was the 90-day survival rate of patients with ICI-associated AVB after initial temporary pacing. Secondary endpoints included: [1] recovery of atrioventricular conduction; and [2] long-term survival rate of patients with ICI-associated AVB. The safety endpoint encompassed the rate of pacing procedure-related complications, including lead dislodgement, loss of capture, under-sensing, puncture-related complications (e.g. femoral pseudoaneurysm, pneumothorax, cardiac perforation), and pacing system-related infections. Additionally, pacing parameters were evaluated, including pacing threshold, sensing amplitude and impedance. Predictors of the AVB recovery and 90-day survival were also analyzed.

Data collection and Follow-up

Baseline clinical data, including demographics, comorbidities, previous medications, cancer types, ICI types, time of first ICI dose, clinical manifestations, types of AVB, left ventricular ejection fraction (LVEF), laboratory tests results, ICI-associated complications and treatments was extracted from inpatient electronic medical records. Pacing strategies, pacing parameters and pacing-related complications were obtained from procedure reports. Patients were followed up after initial pacing therapy. All laboratory tests results and LVEF were defined as the first measurements recorded after admission. Follow-up data were collected from our center's electronic medical records and patients treated at local hospitals were followed up via telephone. Details of follow-up visits and electrocardiographic monitoring are

provided in Supplementary Table S2. Follow-up duration was calculated from the date of initial pacing procedure to the date of primary endpoint or the most recent follow-up. All patients were followed up for at least 90 days.

Statistical analysis

Continuous variables were presented as means with standard deviations (SD) for normally distributed data or median with interquartile range (IQR) for non-normal distribution. Normality was assessed using the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages. Continuous variables were compared by student's *t* test for normally distributed data while non-normal distribution data was compared with the Mann–Whitney *U*-test. Categorical variables were compared using Fisher's exact test. Univariate logistic regression analysis was conducted to identify predictors of ICI-associated AVB. Time to endpoints was analyzed using the Kaplan–Meier method. All statistical analyses were performed using SPSS (version 26.0). A two-sided P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

From May 1st 2019 to April 30th 2024, a total of 43 patients with ICI-associated myocarditis were screened. Among them, eleven patients (11/43, 25.6%) with AVB and meeting pacing indications underwent pacemaker (PM) implantation. Clinical characteristics were compared between patients with and without AVB, and risk factors for ICI-associated atrioventricular block (AVB) were evaluated (Supplementary Table *S3*). Univariate logistic regression analysis identified diabetes mellitus (OR 7.200, 95% CI 1.066–48.639, $P = 0.043$), previous use of beta-blocker (OR 8.571, 95% CI 1.300-56.525, $P = 0.026$), previous use of calcium-channel blocker (CCB) (OR 6.577, 95% CI 1.217–35.529, $P = 0.029$), diplopia (OR 11.625, 95% CI 1.062–127.240, $P = 0.045$) and cardiac shock (OR 8.571, 95% CI 1.300-56.525, $P = 0.029$) as significant predictors of atrioventricular block (Supplementary Table S4).

The mean age of ICI-associated AVB patients was 64.5 ± 8.6 years (ranged from 54 to 80 years), and 18.2% (2/11) were female. Hypertension (81.8%) and diabetes mellitus (54.5%) were the two most common comorbidities and coronary artery disease (45.5%) was also prevalent. Previous antihypertensive medications included beta-blocker (36.4%), angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) (36.4%) and CCB (81.8%). None of the patients had previous atrioventricular conduction disorders prior to ICI exposure. Lung cancer (6/11, 54.5%) was the most common malignancy, and pembrolizumab (6/11, 54.5%) was the most frequently used ICI. The median time from the first ICI dose to first pacing therapy was 30 (24,51) days. Besides atrioventricular block, dyspnea (63.6%) and chest pain or tightness (54.5%) were the two most common manifestations. Muscle and ocular involvement were not uncommon. Syncope occurred in 5 patients (5/11, 45.5%). Ventricular tachycardia (36.4%), heart failure (54.5%) and cardiac shock (36.4%) were common. All patients (11/11, 100%) received methylprednisolone and 90.9% (10/11) received intravenous immunoglobulin. Tocilizumab was administered as anti-inflammatory therapy in 6 patients (6/11, 54.5%). ACEI or ARB were used in 45.5% patients. Neither intra-aortic balloon pump (IABP) nor extracorporeal membrane oxygenation (ECMO) was applied, while 4 patients (4/11, 36.4%) received vasoactive drugs for circulatory support.

Six patients (6/11, 54.5%) were refractory to initial intravenous isoproterenol therapy.

Among the remaining 5 patients, temporary pacing was chosen as first-line therapy instead of intravenous isoproterenol due to the following indications: two patients (Case 2 and Case 8) presented with cardiac shock and heart failure, two (Case 1 and Case 5) experienced syncope, and one (Case 10) exhibited an escape rhythm with wide QRS wave, suggesting potential hemodynamic compromise. Temporary right ventricular pacing using passive (7/11, 63.6%) or active fixation (4/11, 36.4%) lead was performed with pacing threshold of 1.3 ± 0.7 V. For the 4 patients using active-fixation lead, the sensing amplitude and impedance were 12.4 ± 10.9mV and 847 ± 227Ω, respectively. initial temporary pacing was performed at the right ventricular septum in 8 patients (72.7%) and at the right ventricular apex in 3 patients (27.3%).

Baseline characteristics and detailed treatments of the 11 patients are summarized in Table 1.

Follow-up

All patients were followed up for at least 90 days until meeting primary endpoint, with a median follow-up duration of 187.0 (14.0,377.0) days. The 90-day survival rate was 72.7% (8/11) and the long-term survival rate was 63.6% (7/11) (Figure 1 A & 1B).

Among the 6 patients who survived after temporary pacing with passive fixation lead, atrioventricular conduction recovered in 1 patient (Case 2) 12 days post-procedure, and the temporary pacing lead was removed. Two patients received permanent pacemakers (single-chamber, programmed in VVI mode) 2 and 8 days later respectively. The remaining 3 patients were upgraded to TPPMs with active-fixation leads due to the potential for atrioventricular conduction recovery. Among these 3 patients, one patient eventually received permanent pacemaker (dual-chamber, programmed in DDD mode) after waiting for another 28 days, atrioventricular

Table 1 Baseline clinical characteristics

Clinical characteristics	All (*n* = 11)	Recovery (*n* = 4)	Non-Recovery (*n* = 7)	*P* value
Female n (%)	2 (18.2)	1 (25.0)	1 (14.3)	> 0.999
Age at pacing, years	64.5 ± 8.6	60.3 ± 3.3	66.9 ± 9.9	0.146
Comorbidities				
Hypertension n (%)	9 (81.8)	3 (75.0)	6 (85.7)	> 0.999
Diabetes mellitus n (%)	6 (54.5)	3 (75.0)	3 (42.9)	0.545
Hyperlipidemia n (%)	2 (18.2)	2 (50.0)	0 (0.0)	0.109
CAD n (%)	5 (45.5)	4 (100.0)	1 (14.3)	**0.015**
Prior MI n (%)	1 (9.1)	1 (25.0)	0 (0.0)	0.364
Current or prior smoking n (%)	7 (63.6)	3 (75.0)	4 (57.1)	> 0.999
Previous medications				
Beta-blocker n (%)	4 (36.4)	2 (50.0)	2 (28.6)	0.576
ACEI or ARB n (%)	4 (36.4)	1 (25.0)	3 (42.9)	> 0.999
CCB n (%)	9 (81.8)	3 (75.0)	6 (85.7)	> 0.999
Statin n (%)	1 (9.1)	1 (25.0)	0 (0.0)	0.364
Cancer types				
Lung cancer n (%)	6 (54.5)	2 (50.0)	4 (57.1)	> 0.999
Liver cancer n (%)	2 (18.2)	1 (25.0)	1 (14.3)	> 0.999
Colorectal cancer n (%)	2 (18.2)	1 (25.0)	1 (14.3)	> 0.999
Esophageal cancer n (%)	1 (9.1)	0 (0.0)	1 (14.3)	> 0.999
Immune Checkpoint Inhibitors				
*Pembrolizumab n (%)	6 (54.5)	3 (75.0)	3 (42.9)	0.545
Tislelizumab n (%)	3 (27.3)	0 (0.0)	3 (42.9)	0.236
Sintilimab n (%)	2 (18.2)	1 (25.0)	1 (14.3)	> 0.999
Atezolizumab n (%)	1 (9.1)	1 (25.0)	0 (0.0)	0.364
Time from first ICI dose to first pacing therapy, days	30.0 (24.0,51.0)	32.5 (22.5,48.5)	24.0 (24.0,51.0)	0.849
Manifestations at admission				
Dyspnea n (%)	7 (63.6)	2 (50.0)	5 (71.4)	0.576
Chest pain or tightness n (%)	6 (54.5)	3 (75.0)	3 (42.9)	0.545
Myasthenia n (%)	4 (36.4)	2 (50.0)	2 (28.6)	0.576
Myalgia n (%)	4 (36.4)	2 (50.0)	2 (28.6)	0.576
Blepharoptosis n (%)	5 (45.5)	1 (25.0)	4 (57.1)	0.545
Diplopia n (%)	3 (27.3)	1 (25.0)	2 (28.6)	> 0.999
Syncope n (%)	5 (45.5)	2 (50.0)	3 (42.9)	> 0.999
Ventricular tachycardia n (%)	4 (36.4)	1 (25.0)	3 (42.9)	> 0.999
Heart failure n (%)	6 (54.5)	2 (50.0)	4 (57.1)	> 0.999
Cardiac shock n (%)	4 (36.4)	1 (25.0)	3 (42.9)	> 0.999
Atrioventricular block				
Complete AVB n (%)	9 (81.8)	3 (75.0)	6 (85.7)	> 0.999
Advanced AVB n (%)	2 (18.2)	1 (25.0)	1 (14.3)	> 0.999
Echocardiography and Laboratory test				
LVEF, %	58.6 ± 16.1	57.8 ± 6.0	59.0 ± 20.3	0.909
Troponin I, ug/L	7.7 (2.0,15.3)	10.0 (1.8,33.7)	7.7 (2.0,12.2)	0.705
CK, U/L	2023.0 (285.0,13876.0)	11431.0 (1223.0,18291.0)	1058.0 (285.0,3130.0)	0.257
CK-MB, μg/L	53.1 (23.6,163.6)	145.9 (44.4,283.7)	43.9 (23.6,85.6)	0.450
NT-proBNP, pg/ml	1236.0 (859.0,3628.0)	1579.0 (996.8,2200.3)	867.0 (503.0,3720.0)	0.705
Serum creatine, μmol/L	65.0 (56.0,80.0)	83.0 (62.0,86.8)	62.0 (47.0,73.0)	0.089
Hyper-sensitive CRP, mg/L	13.0 (0.8,31.4)	14.3 (3.6,53.4)	9.2 (0.8,31.4)	0.776
Other ICI-related adverse events				

Table 1 (continued)

Clinical characteristics	All (*n* = 11)	Recovery (*n* = 4)	Non-Recovery (*n* = 7)	*P* value
Myositis n (%)	7 (63.6)	3 (75.0)	4 (57.1)	> 0.999
Hepatitis n (%)	2 (18.2)	1 (25.0)	1 (14.3)	> 0.999
Treatments				
Intravenous isoproterenol n (%)	6 (54.5)	2 (50.0)	4 (57.1)	> 0.999
Methylprednisolone	11 (100.0)	4 (100.0)	7 (100.0)	/
Methylprednisolone pulse	7 (63.6)	3 (75.0)	4 (57.1)	> 0.999
IVIG n (%)	10 (90.9)	4 (100.0)	6 (85.7)	> 0.999
Tocilizumab n (%)	6 (54.5)	1 (25.0)	5 (71.4)	0.242
ACEI or ARB n (%)	5 (45.5)	1 (25.0)	4 (57.1)	0.545
CCB n (%)	6 (54.5)	2 (50.0)	4 (57.1)	> 0.999
Invasive ventilation n (%)	2 (18.2)	1 (25.0)	1 (14.3)	> 0.999
Vasoactive drugs n (%)	4 (36.4)	1 (25.0)	3 (42.9)	> 0.999
Temporary pacing				
Passive-fixation lead n (%)	7 (63.6)	2 (50.0)	5 (71.4)	0.576
Active-fixation lead n (%)	4 (36.4)	2 (50.0)	2 (28.6)	0.576
Via femoral vein n (%)	7 (63.6)	2 (50.0)	5 (71.4)	0.576
Via internal jugular vein n (%)	3 (27.3)	2 (50.0)	1 (14.3)	0.491
Via subclavian vein n (%)	1 (9.1)	0 (0.0)	1 (14.3)	> 0.999
Temporary pacing site				
RV septum n (%)	8 (72.7)	3 (75.0)	5 (71.4)	> 0.999
RV apex n (%)	3 (27.3)	1 (25.0)	2 (28.6)	> 0.999

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVB, atrioventricular block; CAD, coronary artery disease; CCB, calcium-channel blocker; CK, creatine kinase; CK-MB, creatine kinase isoenzyme; CRP, C reactive protein; ICI, immune checkpoint inhibitor; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; RV, right ventricle

*Case 10 was on both pembrolizumab and atezolizumab

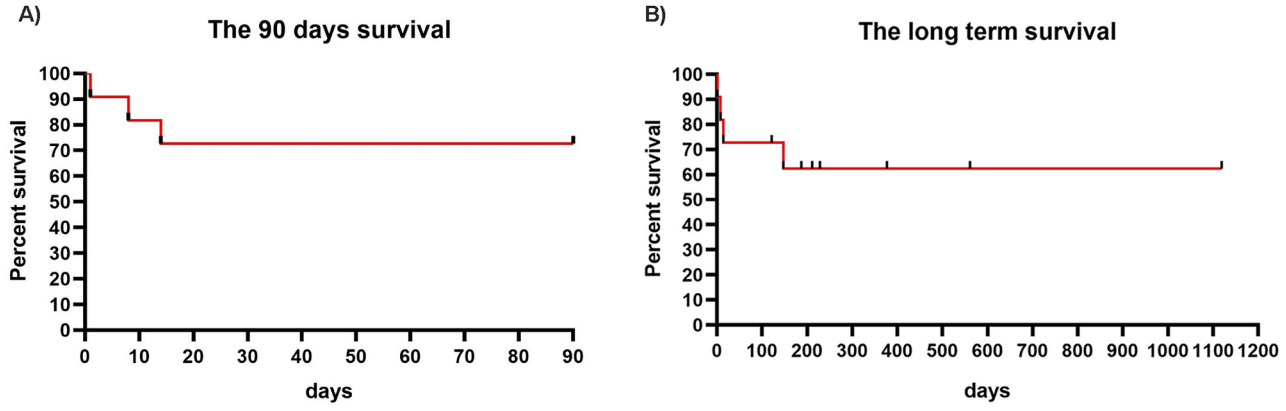

Fig. 1 1**A**. 1**B**.

conduction recovered in 1 patient after 95 days, and 1 patient (Case 6) died 13 days later due to cardiac shock.

Among the 3 patients who survived after TPPM implantation with active fixation lead, atrioventricular conduction recovered in 2 patients after 35 and 39 days, respectively, and the TPPM leads were removed. The third patient did not recover from AVB and received a permanent pacemaker (dual-chamber, programmed in DDD mode) 85 days later.

Among 6 patients who underwent second pacemaker implantation, all ventricular pacing leads were placed at the right ventricular septum. One patient underwent a third pacemaker implantation, with the ventricular lead also positioned at the right ventricular septum.

At approximately 90 days after the initial temporary pacing, 4 patients (4/11, 36.4%) had received permanent pacemakers, and 4 patients (4/11, 36.4%) had recovered from AVB. Three patients (3/11, 27.3%) died from cardiac shock. One patient (Case 2) recovered from AVB but died from cardiac shock 135 days later during further follow-up. Three patients (Cases 7, 9, and 10) who recovered from AVB remained in good clinical condition

without heart failure or bradycardia during follow-up. Pacemaker followed-up interrogation results were available for two patients (Case 3 and Case 5) who underwent permanent pacemaker implantation and are detailed in Supplementary Table S5. Clinical courses of 11 patients during all follow-up are summarized in Figure 2.

Regarding safety endpoints, only 1 case of temporary active-fixation lead dislodgement (Case 11) occurred 77 days after the initial procedure, with no other complications occurred. No device-related infection occurred. Mean pacing parameters of right ventricular lead at implantation are summarized in Figure 3 A-3 C, and pacing parameters of right atrial leads are provided in Supplementary Table S5.

Baseline characteristics were compared between the recovery and non-recovery group (Table 1). Coronary artery disease was more common (100.0% vs. 14.3%, $P=0.015$) in recovery group. The proportions of pacing sites were similar between the AVB recovery and non-recovery group. Comparisons between the deceased ($n=3$) and surviving ($n=8$) patient groups during the 90-day follow-up revealed that left ventricular ejection fraction (LVEF) was lower in the deceased group ($42.7 \pm 22.4\%$ vs. 64.5 ± 8.8, $P=0.036$) and proportions of cardiac shock (100% vs. 12.5%, $P=0.024$) and vasoactive drug use (100% vs. 12.5%, $P=0.024$) were higher in the deceased group. The proportions of pacing sites were similar between the surviving group and deceased group. Detailed data are provided in Supplementary Table S6.

Individual characteristics

Detailed baseline characteristics, initial pacing parameters and follow-up data for each patient are presented in Table 2.

Discussion

In this study, we aimed to evaluate the safety and efficacy of pacing therapy for ICI-associated AVB. Our findings can be summarized as follows: First, the 90-day and long-term survival rates were favorable of 72.7% and 63.6%, respectively. Second, a substantial proportion (36.4%) of ICI-associated AVB cases showed recovery. Third, pacing-related complications were infrequent, and the pacing parameters of right ventricular lead were within acceptable ranges.

AVB is very common among ICI myocarditis patients. In a retrospective multicenter registry study, Power JR, et al. reported that 24.5% (36/147) ICI-associated myocarditis patients developed second-degree heart block (7.5%, 11/147) or complete heart block (17.0%, 25/147) during hospitalization [2]. The incidence of AVB in our study (25.6%, 11/43) was comparable to the previous study. Univariate logistic regression analysis showed diabetes mellitus, previous use of beta-blocker, previous use of calcium-channel blocker, diplopia and cardiac shock were associated with AVB development (Supplementary Table S4). The higher prevalence of antihypertensive medication use reflected a greater proportion of hypertension, although hypertension did not reach statistical

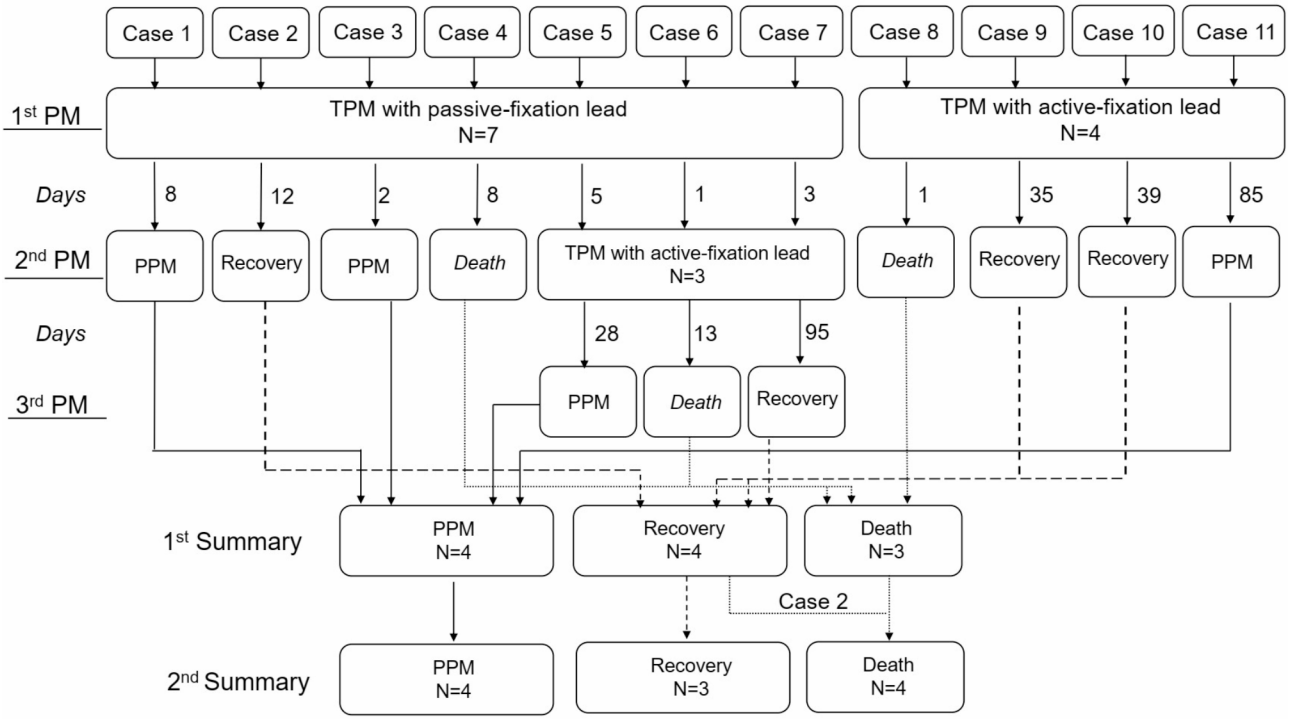

Fig. 2 PM, pacemaker; PPM, permanent pacemaker; TPM, temporary pacemaker

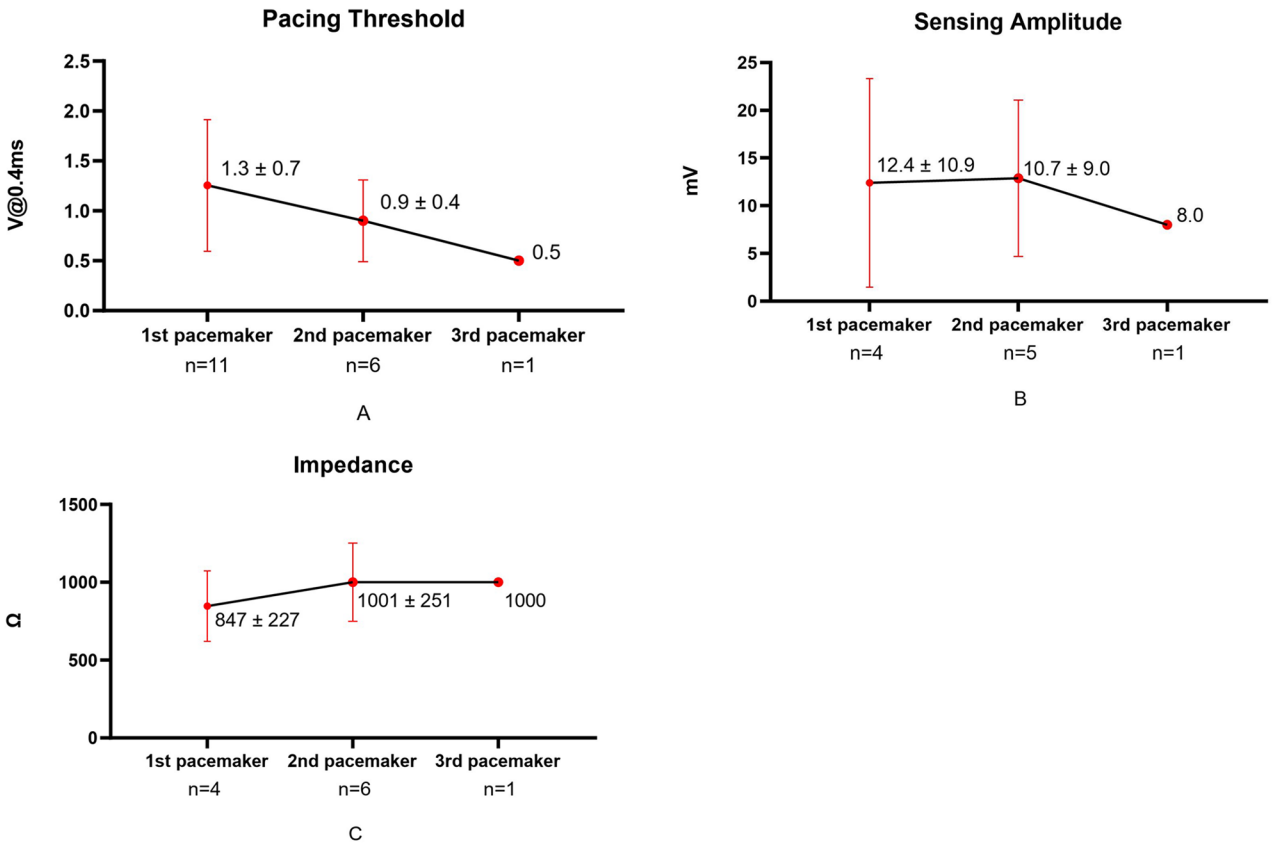

Fig. 3 3**A**-3**C**

* Sensing amplitude and impedance for right ventricular lead of 1st pacemaker were measured in 4 patients with active-fixation lead

** Sensing amplitude for right ventricular lead of 2nd pacemaker were measured in 5 patients because 1 patient (case 1) did not have ventricular escape rhythm

significance ($P=0.08$). We hypothesize that diabetes mellitus and hypertension may indicate underlying conduction system vulnerability, predisposing patients to ICI-induced injury. On the other hand, diplopia and cardiac shock may reflect more extensive and severe ICI-related lesions.

In Power JR's study [2], ICI-associated myocarditis patients who developed complete AVB were more likely to experience all-cause mortality within 30 days (12/25[48.0%] vs. 27/122[22.1%], $P=0.01$) while the mortality of AVB patients underwent pacing therapy was not reported. In a pooled analysis of 21 ICI-associated myocarditis cases requiring pacing for AVB, Chunhong Hu et al. reported that overall fatality rate was 52% and patients with pacemakers had a fatality rate of 38% which was significantly lower than patients without pacemaker (38% vs. 100%; $P=0.035$) and the authors concluded that timely pacemaker implantation played a crucial role in improving outcomes [6]. In our single-center cohort study, the 90-day survival rate of 72.7% suggested that pacing therapy was effective and might provide additional survival benefits beyond intensive anti-inflammatory treatment for patients with AVB requiring pacing. Our data also indicated a favorable long-term survival rate (63.6%) among ICI-associated AVB patients who underwent pacemaker implantation.

In general, the recommended pacing for AVB is a dual-chamber pacemaker programmed in DDD mode [3, 9]. However, due to the lack of guidelines or consensus of on the standard treatment approach for ICI-related AVB, the choice of permanent pacemaker in the present study was largely depended on patient-specific factors and operator preference. Among the four AVB patients who underwent permanent pacemaker implantation, a single-chamber pacemaker of VVI mode was chosen for 2 patients (Case 1 and 3), while a dual-chamber pacemaker of DDD mode was selected in another 2 patients (Cases 5 and 11). In the early phase of our study, single-chamber pacemakers of VVI mode were preferred for their procedural simplicity, due to limited experience in managing ICI-related AVB at that time.

For patients with atrioventricular block, minimizing right ventricular pacing (MVP) was recommended to avoid excessive right ventricular pacing [10]. Among 2

Table 2 Baseline characteristics and follow-up of each patient

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	male	male	male	male	male	male
Age (years)	58	64	80	69	59	76
Hypertension	yes	yes	yes	yes	yes	yes
Diabetes	yes	yes	no	yes	no	no
Hyperlipidemia	no	no	no	no	no	no
CAD	no	yes	no	yes	no	no
Prior MI	no	yes	no	no	no	no
Smoking	no	yes	yes	yes	yes	yes
Previous medications						
Beta-blocker	no	yes	no	yes	no	no
ACEI or ARB	yes	no	yes	yes	no	no
CCB	yes	yes	yes	yes	yes	yes
Statin	no	no	no	no	no	no
Cancer type	lung	lung	liver	lung	esophagus	lung
ICI type	P	P	P	T	T	T
1st ICI to pacing	23 days	30 days	51 days	34 days	24 days	24 days
Dyspnea	no	yes	yes	yes	yes	yes
Chest pain or tightness	no	yes	yes	yes	no	no
Myasthenia	no	no	no	no	yes	no
Myalgia	no	no	no	no	yes	no
Blepharoptosis	no	no	no	yes	yes	yes
Diplopia	yes	no	no	no	yes	no
Syncope	yes	no	no	no	yes	yes
VT	no	no	yes	yes	no	no
HF	no	yes	yes	yes	no	yes
Cardiac Shock	no	yes	no	yes	no	yes
AVB	Comp.	Comp.	Comp.	Comp.	Comp.	Adv.
LVEF (%)	73	56	67	67	77	38
cTnI (μg/L)	7.7	15.3	0.6	11.7	2.0	20.3
CK (U/L)	3130.0	4673.0	2023.0	285.0	1058.0	13876.0
CKMB (μg/L)	53.1	128.1	36.4	43.9	23.6	369.0
NT-proBNP (pg/ml)	503.0	1236.0	3720.0	859.0	171.0	3628.0
SCr, μmol/L	73.0	80.0	47.0	65.0	59.0	74.0
hsCRP, mg/L	24.5	13.0	9.2	0.5	1.36	31.40
Myositis	no	yes	no	yes	yes	yes
Hepatitis	no	yes	no	yes	no	no
Treatments						
Intravenous isoproterenol	no	no	yes	yes	no	yes
MP	yes	yes	yes	yes	yes	yes
MP pulse	yes	yes	no	no	yes	yes
IVIG	no	yes	yes	yes	yes	yes
Tocilizumab	no	no	no	yes	yes	yes
ACEI or ARB	yes	no	yes	yes	yes	no
CCB	yes	yes	yes	yes	no	no
Invasive ventilation	no	yes	no	no	no	yes
Vasoactive drugs	no	yes	no	yes	no	yes
TPM lead	passive	passive	passive	passive	passive	passive
Vein access	femoral	femoral	femoral	femoral	femoral	femoral
RV pacing site	septum	septum	septum	septum	apex	apex
RV T(V@0.4ms)	1.0	1.0	1.0	1.4	1.0	2.2
RV S(mV)	NA	NA	NA	NA	NA	NA
RV I(Ω)	NA	NA	NA	NA	NA	NA
Follow-up(days)	377	147	1119	8	228	14

Table 2 (continued)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
AVC recover	no	yes	no	no	no	no
PPM	yes	no	yes	no	yes	no
Primary endpoint	survival	survival	survival	dead	survival	dead

patients with dual-chamber permanent pacemakers of DDD mode, MVP algorithms was factory default setting. However, due to the small sample size of our study, we were unable to assess differences in outcomes between patients with and without MVP algorithm pacemakers.

Compared with surviving patients, LVEF% in the dead group in our study was significantly lower (42.7 ± 22.4% vs. 64.5 ± 8.8, $P = 0.036$). Previous study has shown that LVEF in ICI-associated myocarditis cases with major adverse cardiac events (MACE) was lower than cases without MACE (45 ± 16% vs. 55 ± 15%, $P = 0.002$) [11]. Our findings aligned with the previous report. We postulated that pacing therapy provided limited benefit to patients with low LVEF, as pacing solely did not ameliorate diffuse cardiomyocyte damage.

Several case reports have described the potential for recovery from ICI-associated AVB, with recovery durations ranging from days to months [4, 5, 6]. Our retrospective cohort study showed the recovery rate was 36.4%. Given that inflammatory activity affected the conduction system [12, 13], ICI-associated AVB might recover following anti-inflammation therapy. Our data revealed that temporary pacemaker, rather than permanent pacemaker, was critical for providing rate and rhythm support during the acute inflammation phase in ICI-associated AVB patients. We attempted to identify the predictors of AVB recovery. Notably, coronary artery disease was more common in the recovery group (100.0% vs. 14.3%, $P = 0.015$). However, the relationship between coronary artery disease/myocardial ischemia and AVB recovery remained unclear. Due to the small sample size and retrospective nature of our study, potential biases could not be excluded.

Consistent with previous case reports, the time from first temporary pacemaker implantation to atrioventricular conduction recovery in our study varied widely, ranging from 12 to 98 days. Therefore, a prolonged period of temporary pacing may be required before recovery or permanent pacemaker implantation. To avoid complications such as electrode displacement and thrombotic events associated with conventional temporary pacemakers using passive-fixation leads during extended use [14], temporary permanent pacemaker using active-fixation leads with better lead stability and allowing patient's mobilization [8] should be considered a reasonable alternative.

In our cohort, temporary pacing for ICI-associated AVB was safe, with a low rate of procedure-related complications (1/11, 9.1%). One temporary active-fixation lead dislodged (Case 11) 77 days after the initial procedure. The exact cause of dislodgment remained unclear, but inadequate suturing of the pacing lead to the patient's neck may have contributed to this event. In general, cardiac implantable electronic devices (CIED)-related infection was uncommon [9]. No device-related infection occurred in our study during follow-up. In Kawata H's study [8], among 23 patients who underwent TPPM implantation due to confirmed or suspected CIED infections, only 1 complication (recurrent vegetation on the temporary pacemaker lead) occurred (1/23, 4.3%). Similarly, in Imberti JF's large prospective study, the incidence of CIED-related infection was very low (0.6%) during a median follow-up of 42.3 months [15]. Our result was consistent with previous report.

There are no prior data on the pacing parameters in ICI-associated AVB patients who underwent pacemaker implantation. In our study, mean value of capture threshold, sensing amplitude and impedance of right ventricular lead were within acceptable ranges [16] and remained stable. A trend toward decreasing pacing thresholds was observed, which we speculated might be attributed to myocardial edema during the acute phase, leading to initially higher thresholds, followed by a reduction as the edema subsided.

Limitations

Several limitations of our study should be acknowledged. First, due to the retrospective design and the small sample size, our findings require validation in larger, prospective cohorts. As ICI-associated AVB was uncommon, only 11 patients were included, which might limit the statistical power to identify predictors of ICI-associated AVB development, recovery, the mortality. Additionally, the small sample size, potential random variability, and selection bias necessitate cautious interpretation and generalization of our results. Due to the retrospective design of our study, variability in therapy and follow-up protocols might potentially influence primary and secondary endpoints. Nevertheless, this study preliminary evaluated the safety and efficacy of pacing therapy in this specific population and might offer valuable insights for future research. Second, due to the lack of guidelines or consensus, the waiting period from temporary pacing to permanent pacemaker implantation was determined at the operator's discretion. The time from ICI-associated AVB onset to recovery varied widely, ranging from days

Table 2 Baseline characteristics and follow-up of each patient (continued)

	Case 7	Case 8	Case 9	Case 10	Case 11
Sex	male	female	female	male	male
Age (years)	60	54	56	61	72
Hypertension	yes	no	no	yes	yes
Diabetes	no	no	yes	yes	yes
Hyperlipidemia	no	no	yes	yes	no
CAD	yes	no	yes	yes	no
Prior MI	no	no	no	no	no
Smoking	yes	no	no	yes	no
Previous medication					
Beta-blocker	yes	no	no	no	yes
ACEI or ARB	no	no	no	yes	no
CCB	yes	no	no	yes	yes
Statin	no	no	yes	no	no
Cancer type	lung	lung	colorectum	liver	colorectum
ICI type	P	P	S	P & A	S
1st ICI to pacing	20 days	213 days	35 days	53 days	24 days
Dyspnea	yes	yes	no	no	no
Chest pain or tightness	yes	yes	yes	no	no
Myasthenia	yes	no	no	yes	yes
Myalgia	yes	no	no	yes	yes
Blepharoptosis	no	no	no	yes	yes
Diplopia	yes	no	no	no	no
Syncope	yes	no	yes	no	no
VT	yes	yes	no	no	no
HF	yes	yes	no	no	no
Cardiac Shock	no	yes	no	no	no
AVB	Adv.	Comp.	Comp.	Comp.	Comp.
LVEF (%)	63	23	62	50	68
cTnI (μg/L)	39.8	12.2	4.6	0.9	7.1
CK (U/L)	18325.0	173.0	73.0	18189.0	712
CKMB (μg/L)	163.6	21.6	16.5	323.7	85.6
NT-proBNP (pg/ml)	2293.0	6768.0	1922.0	917.0	867.0
SCr, μmol/L	86.0	38.0	56.0	87.0	62.0
hsCRP, mg/L	66.0	37.8	0.5	15.5	0.8
Myositis	yes	no	no	yes	yes
Hepatitis	no	no	no	no	no
Treatments					
Intravenous isoproterenol	yes	no	yes	no	yes
MP	yes	yes	yes	yes	yes
MP pulse	yes	yes	yes	no	no
IVIG	yes	yes	yes	yes	yes
Tocilizumab	yes	yes	no	no	yes
ACEI or ARB	no	no	no	yes	no
CCB	no	no	no	yes	yes
Invasive ventilation	no	no	no	no	no
Vasoactive drugs	no	yes	no	no	no
TPM lead	passive	active	active	active	active
Vein access	femoral	subclavian	internal jugular	internal jugular	internal jugular
RV pacing site	apex	septum	septum	septum	septum
RV T(V@0.4ms)	2.5	0.8	0.3	0.8	1.8
RV S(mV)	NA	13.6	4.0	27.4	4.6
RV I(Ω)	NA	606	970	714	1098
Follow-up(days)	561	1	211	187	121

Table (continued)

	Case 7	Case 8	Case 9	Case 10	Case 11
AVC recover	yes	no	yes	yes	no
PPM	no	no	no	no	yes
Primary Endpoint	survival	dead	survival	survival	survival

A, Atezolizumab; ACEI, angiotensin-converting enzyme inhibitor; Adv, advanced; ARB, angiotensin receptor blocker; AVB, atrioventricular block; AVC, atrioventricular conduction; CAD, coronary artery disease; cTnI, Troponin I; CCB, calcium-channel blocker; CK, creatine kinase; CK-MB, creatine kinase isoenzyme; Comp, complete; HF, heart failure; hsCRP, hyper-sensitive C reactive protein; ICI, immune checkpoint inhibitor; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MP, Methylprednisolone; NA, not available; NT-proBNP, N-terminal pro–B-type natriuretic peptide; P, Pembrolizumab; PPM, permanent pacemaker; RV I, right ventricular impedance; RV S, right ventricular sensing; RV T, right ventricular threshold; S, Sintilimab; SCr, serum creatine; T, Tislelizumab; TPM, temporary pacemaker; VT, ventricular tachycardia

to months. Currently, it remains unclear whether ICI-related AVB can recover and how long we should wait for recovery. No guidelines or consensus provided standard treating approach for these patients. Future randomized controlled trials with larger sample sizes and continuous cardiac rhythm monitoring may provide more evidence regarding the duration of AVB and help determine the optimal pacing strategy. Third, predictors of AVB development and recovery were fully evaluated in our study due to the limit number of events. Given the rarity of ICI-associated myocarditis, a multicenter registry study is needed to address this gap. Fourth, as all AVB patients underwent pacing therapy in this study, we did not compare the safety and efficacy between medical and pacing therapy. Determining the relative efficacy of these interventions remains challenging, and further randomized controlled studies are warranted. Finally, the relationship between pacing parameters, which might be markers of myocardial damage, and echocardiographic characteristics should be further investigated.

Conclusions

Pacing therapy for ICI-associated AVB is safe and effective. A substantial proportion of ICI-associated AVB could recover. Temporary pacemaker with active fixation lead might be a reasonable initial therapeutic option.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04764-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Acknowledgements
There is nothing relevant to disclose for any author.

Author contributions
JQ.W. and FY.K. wrote the main manuscript text and did the analysis, YF. W. and JQ. Y. prepared all the figures, YX. W. and W.W. did the analysis, YT. L., P. G., ZW. C. and KA. C. interpretated the data, H.D., JZ. L., JB. F., LH.Z. and Q.F revised the manuscript, TB.C. and DY.Y. contributed to the conception and designed the work. All authors reviewed the manuscript.

Funding
This work was supported by grants from the CAMS Innovation Fund for Medical Sciences (CIFMS#2021-I2M-1-025), National High Level Hospital Clinical Research Funding (2022-PUMCH-B-097), National High-Level Hospital Clinical Research Funding (2022-PUMCH-A-183), and Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2022-RW320-01).

Data availability
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
This study was performed following the Declaration of Helsinki and received approval from the ethics committee of Peking Union Medical College Hospital (K6787). All patients had given informed consent to the pacing procedure.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

Received: 13 December 2024 / Accepted: 14 April 2025
Published online: 24 April 2025

References

1. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol. 2018;71:1755–64.
2. Power JR, Alexandre J, Choudhary A, et al. Electrocardiographic manifestations of immune checkpoint inhibitor myocarditis. Circulation. 2021;144:1521–3.
3. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021;42(35):3427–520.
4. Reddy N, Moudgil R, Lopez-Mattei JC, et al. Progressive and reversible conduction disease with checkpoint inhibitors. Can J Cardiol. 2017;33(10):e133513–5.
5. Lorente-Ros Á, Rajjoub-Al-Mahdi EA, Monteagudo Ruiz JM, et al. Checkpoint Immunotherapy-Induced myocarditis and encephalitis complicated with complete AV block: not all hope is lost. JACC Case Rep. 2022;4(16):1032–6.

6. Hu C, Zhao L, Zhou C, et al. Pacemakers and Methylprednisolone pulse therapy in immune-related myocarditis concomitant with complete heart block. Open Med (Wars). 2022;17(1):2109–16.
7. Herrmann J, Lenihan D, Armenian S, et al. Defining cardiovascular toxicities of cancer therapies: an international Cardio-Oncology society (IC-OS) consensus statement. Eur Heart J. 2022;43(4):280–99.
8. Kawata H, Pretorius V, Phan H, et al. Utility and safety of temporary pacing using active fixation leads and externalized re-usable permanent pacemakers after lead extraction. Europace. 2013;15(9):1287–91.
9. Defaye P, Biffi M, El-Chami M, et al. Cardiac pacing and lead devices management: 25 years of research at EP Europace journal. Europace. 2023;25(8):euad202.
10. Mei DA, Imberti JF, Vitolo M, et al. Systematic review and meta-analysis on the impact on outcomes of device algorithms for minimizing right ventricular pacing. Europace. 2024;26(8):euae212.
11. Awadalla M, Mahmood SS, Groarke JD, et al. Global longitudinal strain and cardiac events in patients with immune checkpoint Inhibitor-Related myocarditis. J Am Coll Cardiol. 2020;75(5):467–78.
12. Champion SN, Stone JR. Immune checkpoint inhibitor associated myocarditis occurs in both high-grade and low-grade forms. Mod Pathol. 2020;33:99–108.
13. Hulsmans M, Clauss S, Xiao L, et al. Macrophages facilitate electrical conduction in the heart. Cell. 2017;169:510–e52220.
14. García Guerrero JJ, Fernández de la Concha Castañeda J, López Quero D, et al. Lower incidence of venous thrombosis with temporary active-fixation lead implantation in mobile patients. Europace. 2010;12(11):1604–7.
15. Imberti JF, Mei DA, Fontanesi R, et al. Low occurrence of infections and death in a Real-World cohort of patients with cardiac implantable electronic devices. J Clin Med. 2023;12(7):2599.
16. Burri H, Starck C, Auricchio A, et al. EHRA expert consensus statement and practical guide on optimal implantation technique for conventional pacemakers and implantable cardioverter-defibrillators: endorsed by the heart rhythm society (HRS), the Asia Pacific heart rhythm society (APHRS), and the Latin-American heart rhythm society (LAHRS). Europace. 2021;23(7):983–1008.

Publisher's note