Review of the epidemiology, pathogenesis and prevention of atrial fibrillation after pacemaker implantation

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Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2023;32(6):707–718

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Funding sources
This work was funded by Guiding Scientific and Technological Project of Quzhou (grant No. 2021007) and Clinical Research Fund Project of Zhejiang Medical Association (grant No. 2021ZYC-A46).

Conflict of interest
None declared

Acknowledgements
We would like to thank Servier Medical Art (https://smart.servier.com) for providing graphical elements required to design Fig. 1.

Abstract

Cardiac pacemaker implantation is an important treatment for symptomatic bradycardia. However, epidemiological data show that the incidence of atrial fibrillation (AF) is significantly higher in patients with implanted pacemakers than in the general population, which may be related to the preoperative presence of multiple risk factors for AF, improvement of diagnostic sensitivity and the pacemaker itself. The pathogenesis of AF after the implantation of pacemaker is related to cardiac electrical remodeling, structural remodeling, inflammation, and autonomic nervous disorder, which are induced by the pacemaker. Moreover, different pacing modes and pacing sites have various effects on the pathogenesis of postoperative AF. Recent studies have reported that reducing the proportion of ventricular pacing, improving the pacing site and setting up special pacing procedures might be highly useful in prevention of AF after pacemaker implantation. This article reviews the epidemiology, pathogenesis, influencing factors, and preventive measures regarding AF after pacemaker surgery.

Key words: pathogenesis, atrial fibrillation, pacemaker implantation, pacing modes, pacing sites

Received on September 28, 2022
Reviewed on November 27, 2022
Accepted on December 7, 2022

Published online on March 6, 2023

Cite as
Wu Y, Xu H, Tu X, Gao Z. Review of the epidemiology, pathogenesis and prevention of atrial fibrillation after pacemaker implantation [published online as ahead of print on January March 6, 2023]. *Adv Clin Exp Med*. 2023;32(6):707–718. doi:10.17219/acem/157239

DOI
10.17219/acem/157239

Introduction

Cardiac pacemaker implantation is an important treatment for symptomatic bradycardia.[1] In recent years, the prevalence of atrial fibrillation (AF) after pacemaker implantation has gradually increased, which may be related to the preprocedural presence of multiple risk factors for AF, improvement of diagnostic sensitivity and the pacemaker itself.[2–4] The parameters and mode setting after the pacemaker implantation, such as atrial and/or ventricular pacing mode, atrioventricular (AV) interval and AV synchronization, may prevent AF, but they might also contribute to the initiation and maintenance of AF.[2,5] This article reviews the epidemiology, pathogenesis, influencing factors, and preventive measures regarding AF after pacemaker surgery.

Epidemiology

Atrial fibrillation is age-related, and the results of various studies have demonstrated that its incidence increases with age.[6] Similarly, in elderly patients, sinus node and AV node diseases requiring permanent pacemaker implantation are more common. Previous findings suggest that the annual incidence of AF after pacemaker implantation is ≥5%, the annual incidence of chronic persistent AF is approx. 3%, the average cumulative incidence of AF is as high as 24.5–40%, and the average cumulative incidence of chronic AF is approx. 20%, which are all significantly higher than for people without pacemaker.[7,8] After analyzing several large-scale clinical trials,[9–14] we concluded that the incidence of AF varied significantly across studies, possibly because of the different study populations, follow-up times, AF-endpoint definitions, and pacing modes.

The mode selection (MOST) trial[13] selected patients with sick sinus syndrome, whereas the United Kingdom Pacing and Cardiovascular Events (UKPACE) trial[14] excluded the sick sinus population and selected patients with AV block who were >70 years old. In the Physical Activity Scale for the Elderly (PASE) trial,[11] the average follow-up time of all elderly patients enrolled was 18 months, and the incidence of AF after pacemaker implantation was 18%. The MOST trial[13] found that the incidence rate of AF was 22.5% after 33 months of follow-up, and the Canadian Trial of Physiological Pacing (CTOPP)[9] had a follow-up time of 42 months, during which the annual rate of AF was 6.0%. Furthermore, the AF-endpoint definition varied among the studies, which may be the main reason for the great differences in the results. The Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACe) trial[12] defined AF as persistent AF lasting ≥22 h per day for >7 consecutive days; the Danish Multicenter Randomized Trial on Single Lead Atrial versus Dual Chamber Pacing in Sick Sinus Syndrome (DANPACE) trial[10] included the incidence of paroxysmal and chronic persistent AF, in which paroxysmal AF was defined as AF first identified in follow-up electrocardiogram (ECG) or pacemaker recording, and persistent AF was defined as AF found in at least 2 consecutive follow-up ECGs; the MOST trial[13] and PASE trial[11] did not distinguish the types of AF and only based their AF definitions on the results of 1 ECG examination. Finally, there were also significant differences in the pacing modes among the studies. The MOST trial[13] and PASE trial[11] mainly observed the effects of rate-adaptive ventricular pacing (VVIR) and rate-adaptive dual-chamber pacing (DDDR) on AF, and the prospective multicenter SAVE PACe clinical trial[12] was the first to evaluate dual-chamber minimal ventricular pacing.

Diagnostic value of pacemakers in AF

The above studies have shown that the incidence of AF was higher with than without pacemaker implantation, which may be related to the pacemaker improving the sensitivity of AF diagnosis and the impact of the pacemaker on AF.[2–4] For patients with implanted pacemakers, the device automatically records and stores the atrial high-rate episodes (AHREs) based on programmable detection algorithms. Studies have shown that AHREs are a reliable indicator for monitoring atrial arrhythmias.[15,16] Kaufman et al. conducted a detailed statistical analysis of 2580 patients with pacemaker implantation, and the results showed that when AF was defined as an atrial-wave frequency >190 beats/min and a duration >6 min, the diagnostic accuracy was 82.7%, and the false positive rate was 17.3%; if the duration of AHRE was extended to 30 min, 6 h and 12 h, the false positive rate decreased to 6.8%, 3.3% and 1.8%, respectively; if the atrial wave frequency was defined as >250 times/min, the diagnostic accuracy for AF would be further improved.[17] Sanna also argued that pacemakers could better detect the occurrence of AF than routine ECG and Holter monitoring.[18]

Although AHREs are associated with the incidence of clinical AF, they also have important independent predictive value for thrombotic stroke and early death.[19,20] In the 2019 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS), the 2020 European Society of Cardiology (ESC), and the 2020 Canadian Cardiovascular Society (CCS)/Canadian Heart Rhythm Society (CHRS) AF guidelines,[21–23] regular evaluation for AHREs among patients with cardiac implantable electronic devices is recommended (class I), which could prompt further evaluation to document clinically relevant AF characteristics and guide anticoagulation treatment decisions. However, the threshold duration of AHREs that warrants anticoagulation is unclear, whereas a wide range of AHRE duration cutoffs (from

10–20 s to >24 h) is reported in studies on the association of subclinical AF with thromboembolism. A meta-study of 18,943 patients found a significantly increased risk of thromboembolic events in patients with an AHRE burden >6 min compared with the no-AHRE group (hazard ratio (HR): 1.82; 95% confidence interval (95% CI): 1.32–2.51), and there was no clear linear relationship between the increasing burden of AF and risk of stroke.[24] In Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT),[25] AHRE duration >24 h significantly increased the risk of ischemic stroke or systemic embolism (adjusted HR: 3.24, 95% CI: 1.51–6.95, p = 0.003) with an event rate of 3.08%/year. There was no increased risk of stroke for AHRE duration between 6 min and 24 h. Hence, the 2019 AHA/ACC/HRS and the 2020 ESC guidelines recommend complete cardiovascular evaluation with the AHRE duration, ECG recording, thromboembolic risk assessment, and preferences to determine whether to initiate long-term anticoagulation, while the CCS/CHRS guidelines recommend that patients with AHRE duration >24 h be treated with anticoagulation if they have stroke risk factors.

Related studies have reported that the incidence of AHREs after pacemaker implantation was approx. 10% in half a year and approx. 35% in 2.5 years.[26] Kawakami et al. found that 48% of patients had at least 1 AHRE during a follow-up period of 52 ±30 months.[27] Implantable devices, such as cardiac pacemakers, can increase the incidence of AHREs, which may be associated with P-wave dispersion in sinus rhythm.[28] Due to the loss of AV synchrony and irregular ventricular cycle, pacemaker-related new-onset AF leads to reduced cardiac output and acute hemodynamic changes, thus increasing the risk of worsening heart failure and reducing patient survival.[29,30]

Mechanism of pacemaker implantation-induced AF

Cardiac electrical remodeling

The nonphysical ectopic pacing of the heart caused by a pacemaker would cause a disorder in the electrical excitation sequence and frequency, and then lead to abnormal changes in cardiac electrical characteristics, including ion channels, electrical coupling and electrical conduction properties. The opening and closing of ion channels in the myocardial cell membrane cause ion transmembrane movement and form an action potential, which produces electrical excitation under the action of cardiac electrical coupling.[31] However, pacemaker-mediated cardiac pacing cannot completely simulate the pacing mode in the physiological state. As an ectopic pacing, it is easy to cause action potential remodeling and abnormal changes in ion channels in the myocardial cell membrane, thus leading to myocardial electrical disturbance.[32,33] Reduction of transient outward K^+ current (Ito), which plays a key role in the first phase of action potential repolarization, is the most important of the changes in ion channels after pacemaker implantation. The decrease in Ito would cause imbalances of potassium and calcium concentrations inside and outside of cells and lead to abnormal changes in electrical conductivity.[34] A long-term electrical remodeling would result in more complex variability in cardiomyocyte transmembrane ion flux, including inactivation of the fast sodium channel (INa), increased expression of slowly activating delayed rectifier potassium (IKs) channels and decreased density of Ito channels and L-type calcium (ICa-L) channels; all 3 disrupt the normal electrophysiological coordination of myocardium.[35–37] Moreover, persistent changes in the properties of ion channels would lead to abnormal myocardial excitation–contraction coupling and changes in the number and distribution of gap junction proteins (such as connexin 43) between cardiomyocytes.[37,38] Therefore, it can be inferred that abnormal changes in ion channels in the myocardial membrane and electrical coupling caused by pacemakers eventually promote re-entry and lead to AF (Fig. 1). In addition, long-term exogenous electrode stimulation produced by a pacemaker causes the enlargement of the left atrium and leads to myocardial stretch, which has been proven to slow myocardial electrical conduction velocity, shorten the effective refractory period and increase the conduction anisotropy in the atrium.[39–41]

Cardiac structural remodeling

Cardiac structural remodeling caused by pacemaker implantation is an adaptive response of the heart to hemodynamic changes or other exogenous factors, including cardiomyocyte hypertrophy, apoptosis and interstitial fibrosis, which would result in cardiac dilation and dysfunction (Fig. 1).[42,43]

The mechanism of cardiomyocyte apoptosis caused by pacemaker implantation includes 2 main aspects. On the one hand, abnormal electrical excitation caused by pacemaker implantation leads to changes in cardiac mechanical contraction. Under the influence of long-term nonphysiological electrical excitation and mechanical contraction, cardiomyocytes in the electrode implantation site and its adjacent areas undergo a series of abnormal changes, including cardiomyocyte arrangement disorder, endoplasmic reticulum aggregation, mitochondrial morphological variation, calcification, and even apoptosis.[44] On the other hand, the hemodynamic changes caused by permanent pacemaker implantation contribute to increased atrial afterload, which leads to compensatory hypertrophy of cardiomyocytes, and induce the release of a series of neuroendocrine substances (such as tumor necrosis factor alpha (TNF-α) and angiotensin II), and leads to cardiomyocyte apoptosis.[42,45,46] Hypertrophy and

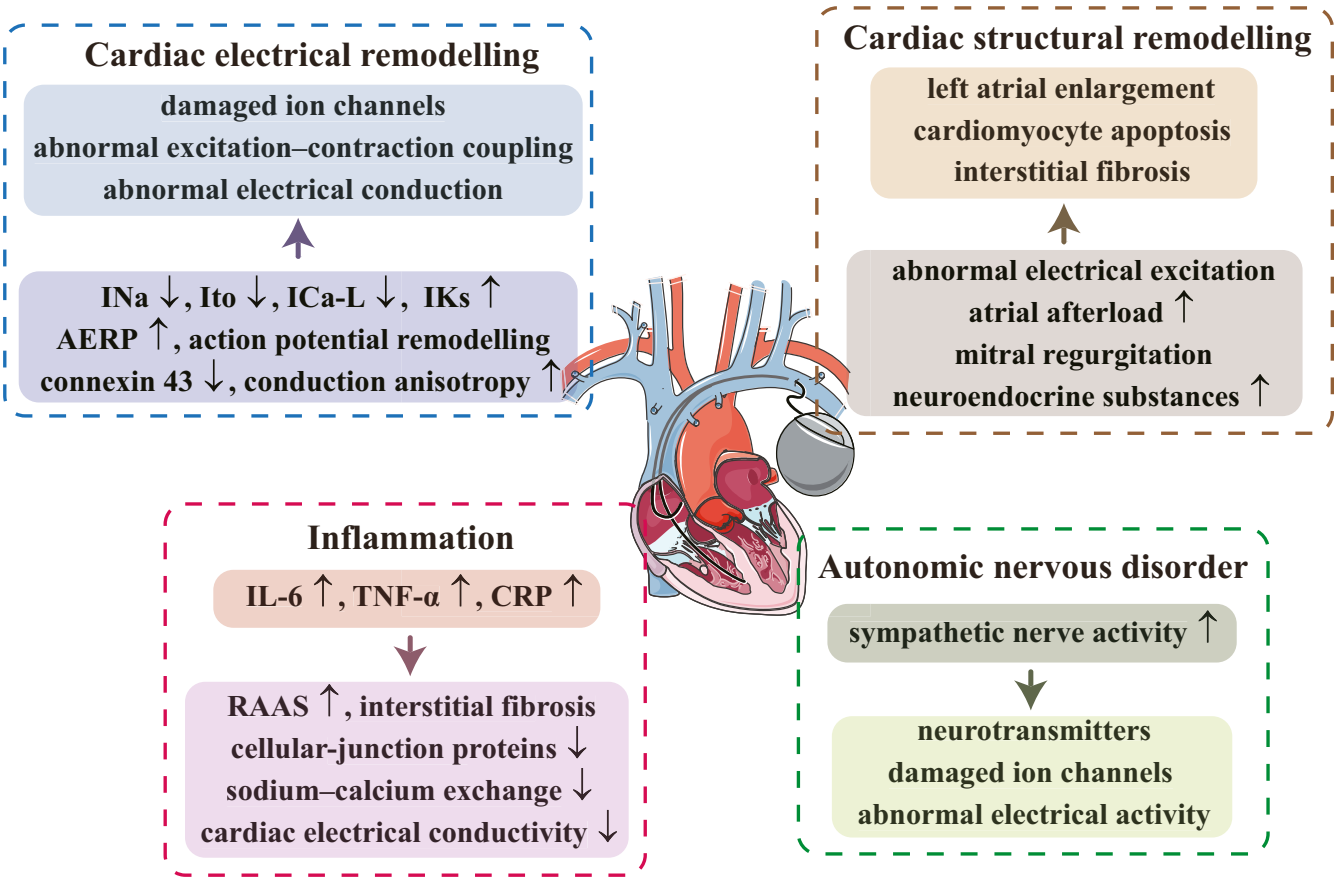

Fig. 1. Mechanism of pacemaker implantation-induced atrial fibrillation (AF)

AERP – atrial effective refractory period; CRP – C-reactive protein; ICa-L – L-type calcium channel; IKs – slowly activating delayed rectifier potassium; IL-6 – interleukin 6; INa – fast sodium channel; Ito – transient outward K^+ current channel; RAAS – renin–angiotensin–aldosterone system; TNF-α – tumor necrosis factor alpha.

apoptosis of cardiomyocytes in the atrial region can cause abnormal changes in local electrical conductivity and eventually lead to AF. Permanent pacemaker implantation can cause changes in myocardial stroma. The myocardial interstitium is mainly filled with fibroblasts, which have electrophysiological characteristics different from those of the surrounding cardiomyocytes. Interstitial fibrosis promotes abnormal changes in cell coupling as well as the nonuniform and multidirectional transmission of electrical pulses, ultimately leading to AF.[47,48]

Under the action of various nonphysiological electrical stimulations, the atrial connective tissue tends toward fibrosis and redistribution, and the atrial morphological structure changes in order to compensate for the effect of various exogenous mechanical, chemical and electrical stimulations caused by the implantation of pacemaker.[43,49] The long-term left and right ventricular systolic and diastolic asynchrony and the change in AV pacing sequence caused by pacemaker implantation leads to hemodynamic changes, such as increased left ventricular end-diastolic pressure, decreased ventricular stroke volume and decreased ejection fraction in terms of mechanical outcomes, resulting in increased left atrial (LA) afterload and an enlarged left atrium.[43,50] Furthermore, abnormal AV systole and diastole would contribute to mitral regurgitation, and increase LA diastolic filling and LA preload, ultimately leading to left atrium enlargement.[51] As a result of clinical observation, the incidence of AF is significantly higher in patients with LA enlargement, and there is a clear causal relationship between the two.[52,53]

Inflammation

Many studies have shown that inflammation is closely related to AF.[54,55] The exogenous stimulation of electrodes and wires of the pacemaker can induce an inflammatory response.[56] Previous studies have found that the inflammatory mediators such as interleukin 6 (IL-6) and TNF-α could downregulate the expression of cellular junction proteins and promote abnormal changes in cardiac electrical conductivity.[57] Moreover, C-reactive protein (CRP), a core expression of the inflammatory response, can bind to phosphatidylcholine on the surface of the cardiomyocyte membrane, thereby affecting sodium–calcium exchange and leading to cardiac electrical remodelling.[58,59] Therefore, the release of inflammatory mediators induced by exogenous stimulation from the implantation of a pacemaker may lead to AF by regulating local cardiomyocyte

junctional proteins and intracellular calcium homeostasis (Fig. 1). Additionally, a long-term pacemaker implantation induces atrial enlargement, and the resulting stretch can strongly stimulate the release of angiotensin II.[60,61] The activation of the renin–angiotensin–aldosterone system could be involved in the inflammatory response, which promotes interstitial fibrosis and eventually leads to AF (Fig. 1).[60,61]

Autonomic nervous disorder

An important cause of the occurrence and development of AF is abnormal autonomic nerve function.[62,63] It can lead to abnormal release of various neurotransmitters and regulate the ion permeability of the cardiomyocyte membrane, causing damage to some ion channel activities and changes in cellular electrical activity, which finally contributes to AF by affecting trigger potential, autonomy and re-entry.[62,63] Right ventricular pacing (RVP) can strongly enhance sympathetic nerve activity, whereas dual-chamber (DDD) pacing has a similar role in the autonomic nervous system.[64,65] Therefore, pacemaker implantation can induce AF through autonomic nervous disorder (Fig. 1).

Effects of different pacing modes on AF

Pacing modes are mainly divided into 2 categories: single-chamber pacing (atrial (AAI) and ventricular single chamber (VVI) pacing) and dual-chamber pacing (DDD pacing).[66,67] Given that the better understanding of natural course of conduction disturbances in patients with pacemakers have rendered AAI pacing clinically obsolete, and VVI pacing is inapplicable in patients without preprocedural AF, they are not to be discussed.

Dual-chamber pacing can maintain synchronization of AV conduction, and thus it has been considered a physiological pacing mode. However, a series of large-scale clinical trials, such as CTOPP, MOST and UKPACE, challenged this traditional thinking.[13,14,68] It has been found that compared with single-chamber pacing, DDD pacing cannot reduce mortality or major cardiovascular events.[13,14,68] Electrophysiological studies of the left atrium found that most patients exhibited intra-atrial conduction block, especially the elderly and those with an enlarged left atrium.[69,70] When the intra-atrial block is 70 ms in sinus rhythm, it may be prolonged to 120 ms during right atrial (RA) pacing. Furthermore, the intra-atrial block can delay LA activation by ≥130 ms.[71] If the AV interval is set to 120 ms (the factory default value for most pacemakers), the AV interval of the left atrium and ventricle will be very short or even negative; that is, the left atrium would be activated after the left ventricle.[71,72] Given the short AV interval setting, DDD pacing patients received a large number of unnecessary RVP, so the seemingly physiological dual-chamber pacing can cause a distinctly "non-physiological" hemodynamic state.[73,74]

In the MOST trial, 2010 patients were implanted with DDD or VVI pacemakers, respectively. The rate of AF was observed in 1399 patients (69.6%). Of these 1339, 707 (52.8%) were randomly assigned to the DDD group and 632 (47.2%) to the VVI group. After 6 years of follow-up, there were no significant differences in various clinical endpoints between the VVI and DDD groups, and the difference in the incidence of AF was 2.1% ($p > 0.05$). In the VVI group, RVP accounted for 58% of the total ventricular events, whereas in the DDD group, it accounted for 90%, especially in patients with pure sinoatrial node disorder. In a further subgroup analysis, Sweeney et al. studied the relationship between the RVP ratio and the incidence of AF.[13] In the VVI group, the incidence of AF was 21% in patients with a RVP ratio <10% and 29% in patients with a RVP ratio of 50–90%. The association was stronger in the DDD group. The incidence of AF was 16% in patients with a pacing ratio <10% and 32% in patients with a pacing ratio of 50–90%. Moreover, Cheung et al. found that in patients with a DDD pacemaker implanted for sick sinus syndrome, a cumulative RVP ratio ≥50% increased the risk of AF by twofold (HR: 2.2, 95% CI: 1.0–4.7, $p = 0.04$).[75] Wu et al. came to a similar conclusion.[76]

Relationship between atrial pacing site and AF

In addition to the pacing mode, the location of the atrial electrodes can also influence the AF occurrence. Atrial electrical asynchrony can be induced during atrial appendage or high RA pacing. Also, the pacing P-wave reflected on the ECG is wider than the sinus P-wave.[77] Moreover, compared with pacing at the low atrial septum (LAS) near the coronary sinus ostium or the high atrial septum near the Bachmann's bundle, atrial appendage or high RA pacing was more likely to induce AF.[78,79] During atrial septal pacing, the P-wave is even narrower than the sinus P-wave, possibly due to the Bachmann's bundle linking to the connecting fibres in the atria and coronary sinus.[78,80] Therefore, in DDD mode, the incidence of AF is lower in the pacing near the Bachmann's bundle than in the right atrial appendage (RAA) pacing. Similarly, atrial overdrive pacing is more effective in preventing AF in the lower atrial septum than in the RAA.[79] Furthermore, the RAA or high RA pacing would prolong AV conduction, resulting in left AV asynchrony (P-wave is located in the T-wave on the ECG) causing pseudo-pacemaker syndrome.[81] During low atrial septal pacing, the duration of AV conduction is shortened, so that under the same AV interval setting, compared with RA pacing, the RVP ratio will be significantly reduced, which can effectively prevent AF.[79,82]

Prevention of AF after pacemaker implantation

The occurrence of AF affects cardiac pacemaker function and increases the risk of embolic events and heart failure, thus significantly reducing the quality of life of patients and causing a huge economic burden. Therefore, it is of great clinical importance to effectively prevent AF after the implantation of a permanent pacemaker.

Reducing the percentage of RVP

Long-term RVP can cause systolic and diastolic asynchrony in various segments of the ventricular wall, which results in decreased ventricular systolic function, increased mitral regurgitation and increased atrial pressure, thereby promoting the occurrence and maintenance of AF.[83,84] Right ventricular pacing with retrograde AV conduction would significantly increase the atrial pressure and cause pulmonary venous reflux, resulting in significant pulmonary vein dilatation, which may be a potential inducement of AF.[85] Even in the absence of retrograde AV conduction, sinus atrial activation can periodically appear after right ventricular (RV) activation, similarly to RVP with retrograde transmission. Another predisposing factor for AF is mitral regurgitation during RVP, which can increase pulmonary wedge pressure and the risk of AF.[86] Elevated brain natriuretic peptide (BNP) during RVP may reflect increased atrial pressure and the potential risk of AF.[87] In addition, animal and human experiments have shown that RVP can increase the ratio of myocardial oxygen consumption to left ventricular output and myocardial oxygen consumption, which can aggravate myocardial ischemia and heart failure, thereby promoting AF.[88,89] Furthermore, long-term AV asynchrony leads to mechanical and electrical remodeling of the atrium, which is conducive to AF and the formation of LA appendage thrombosis. A 10-year follow-up study showed that the incidence of AF was 85.7% in VVI mode compared to 37.4% in non-VVI mode, which confirmed that RVP is more likely to induce AF than AAI or DDD pacing.[90]

Several pacemaker companies have successively developed various functions to reduce RVP, such as AV Search+, Managed Ventricular Pacing (MVP), ventricular intrinsic preference algorithm, and dynamic AV delay (Fig. 2). Although these programs are named differently, the basic principle of preventing AF is to reduce unnecessary ventricular pacing.[83,91] The SAVE PACe trial enrolled 1065 patients with sick sinus syndrome, randomized to the conventional dual-chamber pacing group and dual-chamber minimal ventricular pacing group.[12] During an average follow-up of 1.7 ±1.0 year, the results showed that the median percentage of RVP in the conventional pacing group was 99%, and 68 patients in the group (12.7%) developed persistent AF, whereas the median percentage of RVP in the minimal ventricular pacing group was 9.1%, and 42 (7.9%) patients developed persistent AF ($p < 0.001$ and $p = 0.004$, respectively). Minimal RVP could greatly reduce the risk of ventricular dyssynchrony and persistent AF, with an absolute risk reduction of 4.8% and a relative risk reduction of 40.0%. The MINimizE Right Ventricular Pacing to Prevent Atrial Fibrillation and Heart Failure (MINERVA) trial also showed that MVP significantly reduced mortality, need for hospitalization for cardiovascular events and the incidence of permanent AF.[92] Conversely, a meta-analysis by Shurrab et al. demonstrated that compared with standard DDD pacing, ventricular pacing reduction modalities did not reduce the incidence of persistent AF, nor did they reduce the hospitalization and mortality rates for heart failure.[93] The poor prognosis may be related to the significant prolongation of the AV interval allowed by MVP.[94] Pacing in the DDD mode likely prevented further episodes of atrial tachycardia by preventing long AV intervals, unlike the MVP mode, which permits long AV intervals as long as a ventricular event occurs before the subsequent atrial-paced or atrial-sensed event.

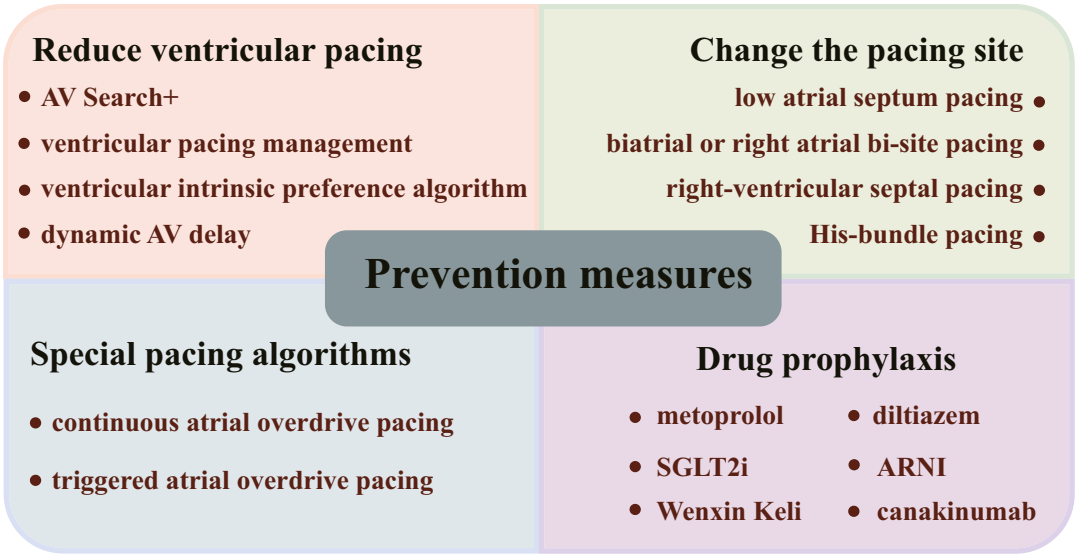

Fig. 2. Prevention of atrial fibrillation (AF) after pacemaker implantation

ARNI – angiotensin receptor-neprilysin inhibitor; AV – atrioventricular; SGLT2i – sodium glucose cotransporter 2 inhibitors.

Changing the pacing site

The RAA contains the pectinate muscle, in which the pacing electrodes are easy to place, so it is the traditional atrial pacing site. However, studies have shown that RAA pacing changes the normal atrial pacing conduction sequence, increases the intra-atrial conduction time and makes the left and right atria asynchronous, which contributes to mitral valve regurgitation, increases the LA pressure and eventually leads to atrial structural and mechanical remodeling and an increased incidence of AF.[95,96] Therefore, scholars have proposed reducing burden of AF after pacemaker implantation by changing the atrial pacing site (Fig. 2).

At present, the feasible atrial pacing sites mainly include LAS pacing and multisite atrial pacing (biatrial or RA bi-site pacing). Minamiguchi et al. found that compared with RAA pacing, LAS pacing could reduce the incidence of AF after pacemaker implantation in patients with sick sinus syndrome from 19.0% to 5.9%, and prevent persistent AF.[97] Zhang et al. agreed that LAS pacing can reduce AF burden, and proved the safety of septal pacing.[98] Multisite atrial pacing mainly refers to biatrial pacing and RA bi-site pacing, and its electrophysiological mechanisms for the prevention of AF include the following: improving atrial depolarization and/or repolarization and ameliorating anisotropic conduction in the atrium, shortening the intra-atrial conduction time and restoring the synchronization of electrical activity in both atria, and shortening the atrial refractory period and reducing the dispersion of the atrial refractory period.[99,100] For patients with intra-atrial block, i.e., the P-wave time in the ECG >120 ms, the benefit of multisite atrial pacing is more obvious. Moreover, biatrial pacing can eliminate premature atrial contraction (an inducement of AF), and prevent AF initiation with programmed atrial stimulation.[101] In a study by Lewicka-Nowak et al. on RA bi-site pacing in 97 patients with sick sinus syndrome, AF was converted to sinus rhythm by preprocedural administration of drugs or electrical cardioversion, and the atrial electrodes were then implanted into the Bachmann's bundle and coronary sinus.[102] After 2 years of follow-up, compared with sinus rhythm, the P-wave time of RA bi-site pacing was significantly shortened, and 90% of the patients showed no AF after surgery. However, some studies have found that RA bi-site pacing could not significantly reduce the incidence of AF, but due to the more complicated and subtle operation, it increased the operation time and X-ray exposure, as well as the dislocation rate of the atrial electrodes.[77] Moreover, it should be noted that the programmed atrial stimulation is not routinely programmed nor endorsed by guidelines. Therefore, further studies are needed.

The ventricular pacing sites also affect the incidence of AF after the implantation of a pacemaker. In patients with RVP, apical activation of the heart gradually spreads to the bottom, causing a significant delay in left ventricular contraction.[103] More ideal ventricular pacing sites, such as the ventricular septum, His bundle or left bundle area, can achieve pacing through the His–Purkinje system and make the ventricular activation close to the physiological conduction sequence, thus enabling synchronization between the left and right ventricles to be maintained, which could help in keeping smooth hemodynamics (Fig. 2).[104–106] A meta-analysis noted that RV septal pacing resulted in narrower QRS complexes than apical pacing, which improved interventricular dyssynchrony and left ventricular ejection fraction (LVEF), ultimately reducing the incidence of AF.[107] Compared with RV apical pacing, RV outflow tract pacing is closer to the physiological state, which has the advantages of ventricular synchronous activation, reduced myocardial perforation complications, shorter QRS wave duration, and better hemodynamics.[108] Furthermore, a retrospective study of patients receiving different ventricular sites found that patients who received His-bundle pacing had a lower rate of AF occurrence (16.9%) than those who received RV septal and RV apical pacing (25.7% and 28.0%, respectively).[109] Another prospective cohort study indicated that, during a mean follow-up of 11.1 months, left bundle pacing resulted in a significantly lower incidence of new-onset AF (7.4% compared to 17.0%, $p < 0.001$) than RVP. Moreover, after adjusting for confounding factors predisposing to AF, only left bundle pacing was an independent protective factor for decreasing the risk of new-onset AF.[110] Researchers are constantly looking for new ventricular pacing sites to avoid asynchronous contraction between ventricles, so as to reduce the risk of AF after pacemaker implantation. His-bundle pacing and left bundle branch area pacing are the 2 most common physiological pacing strategies.[111,112] We look forward to more clinical evidence and experimental data to confirm their benefits.

Algorithms to prevent AF

Several pacemaker companies have introduced special pacing algorithms to prevent AF attacks, mainly in 2 categories: continuous atrial overdrive pacing (CAOP) and triggered atrial overdrive pacing (Fig. 2). The possible mechanisms are as follows: 1) suppressing premature atrial contractions and short bursts of atrial tachycardia through atrial overdrive pacing, thereby eliminating triggering factors of AF; 2) atrial pacing reducing repolarization time; 3) improving bradycardia and long interval to prevent bradycardia-related AF; and 4) shortening the compensatory interval after premature atrial contraction and reducing the short–long sequences.[113,114]

Lewalter et al. observed the heart rhythm before the onset of AF in 126 patients and demonstrated that the AF diagnostics and preventive algorithms could reduce the AF burden by 28% in patients whose AF was mainly triggered by premature atrial contractions.[115] Similarly,

the MINERVA trial evaluated the role of atrial antitachycardia pacing (Reactive ATP) in the development of AF and found that Reactive ATP could reduce the progression of atrial tachyarrhythmias to permanent AF.[92] Moreover, the results of the Study for Atrial Fibrillation Reduction (SAFARI) and the diabetes outcome progression trial (ADOPT) studies both showed that atrial overdrive pacing could significantly lower the risk of AF.[116,117]

However, there are problems with these algorithms. Continuous atrial overdrive pacing aims to prevent the occurrence of AF by increasing the atrial pacing frequency and shortening the compensatory interval after bradycardia and premature atrial contraction. However, symptoms such as heart palpitations may occur.[118,119] The ASSERT trial followed up 2343 patients with DDD pacemaker implantation for 2.5 years, and the results showed that atrial overdrive pacing did not reduce the incidence of AF, whereas COAP could accelerate battery depletion and increase the reoperation rate.[118] The multicenter randomized controlled Septal Pacing for Atrial Fibrillation Suppression Evaluation (SAFE) trial also found no significant benefits of an atrial overdrive pacing program on reducing persistent AF.[120]

Drug prophylaxis

The use of combinations of antiarrhythmic drugs to maintain sinus rhythm or reduce the incidence of AF after pacemaker implantation is advocated (Fig. 2). Metoprolol, a β1-selective adrenoceptor antagonist, can effectively increase the activity of the vagus nerve and maintain the balance of cardiac autonomic nerve function.[121,122] Metoprolol can also inhibit the stimulating effect of endogenous catecholamines on the heart and prolong the refractory period of myocardium, sinoatrial node and AV node, thereby reducing the burden of AF.[121,122] Diltiazem, a non-dihydropyridines calcium channel blocker, can reduce heart rate and sympathetic activity by inhibiting the calcium influx of sinoatrial and AV nodes and decrease left atrium pressure by lowering peripheral blood pressure stress, which could indirectly prevent the onset of AF.[123]

Sodium glucose cotransporter 2 inhibitors (SGLT2i) and angiotensin receptor-neprilysin inhibitor (ARNI) reduce the risk of heart failure and new data show that they can prevent AF.[124,125] In a diabetic rat model, Shao et al. demonstrated that SGLT2i treatment could significantly ameliorate atrial structural and electrical remodeling as well as improve mitochondrial function and mitochondrial biogenesis. Hence, it may be potentially used in the prevention of AF.[126] Similarly, ARNI could effectively decrease LA fibrosis in mice, as well as reduce atrial inhomogeneous conduction in patients with heart failure, which had potential therapeutic value in preventing the incidence of AF.[127,128] Moreover, recent studies have reported that drugs that can improve abnormal changes in ion channels may have a role in preventing AF after pacemaker implantation. For example, Wenxin Keli, a classical Chinese patent medicine, has a selective inhibitory effect on the atrial ion channels and could effectively decrease the incidence of AF.[129,130] Moreover, it is the first Chinese antiarrhythmic medicine to be approved by the China Food and Drug Administration (CFDA), and it has been increasingly used as an alternative approach for AF treatment globally.[131] Canakinumab, a human monoclonal antibody, significantly reduced the levels of inflammatory mediators, such as IL-6 and IL-1β.[132,133] Since inflammatory signaling pathways are associated with the pathogenesis of AF, anti-inflammatory treatment, such as canakinumab, could prevent postprocedural AF,[134,135] which further supports this novel cytokine-based therapy. Modulation of the autonomic nervous system is also helpful because spinal cord stimulation can suppress AF by inhibiting autonomic nerve remodelling.[136,137] In the future, the deepening research on the pathogenesis of AF after pacemaker implantation will inspire more effective and practical prevention methods.

Conclusions

The incidence of AF after pacemaker implantation is relatively high. Various types of exogenous stimulation provided by pacemaker implantation and the resulting cardiac electrical remodeling, structural remodeling, inflammation, and autonomic nervous disorder are all related to the occurrence of postprocedural AF. Moreover, different pacing modes and sites have various effects on the incidence of postprocedural AF. It is of great significance to explore clinical measures in order to reduce the incidence of AF after pacemaker implantation. However, it should be emphasized that optimizing the pacing site and mode may reduce the incidence of postprocedural AF, but there are still few long-term large-scale clinical studies in progress. The safety and effectiveness of special pacing algorithms remain controversial. The impact of the above measures on postprocedural AF is complex and requires additional research.

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