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Literature Review

Understanding pacing-induced cardiomyopathy: a mini-review

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ABSTRACT

Patients with total atrioventricular block or sinus node dysfunction will need pacemaker implantation to improve the heart's physiologic function. It is known that chronic pacing such as right ventricular pacing could deteriorate cardiac function (decreased left ventricular ejection fraction) due to dyssynchrony. This condition is known as pacing-induced cardiomyopathy (PICM). The incidence of PICM could reach 19.5% during 3 years of follow-up. The right ventricle is one of the locations for implantation. Chronic right ventricular pacing may cause interventricular dyssynchrony and disrupt the contraction mechanism in the heart. These will lead to cardiac remodeling and eventually impair the left ventricular function. Therapy is needed in patients with PICM to improve the symptoms and maintain the cardiac function. We included 47 literatures in this review to further highlight the definition, mechanism, risk factor, treatment and preventive strategy for patients with PICM

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INTRODUCTION

The relationship between bradycardia and cardiovascular disease (CVD) or heart disease-related sudden death is not well emphasized. However, this might be an iceberg phenomenon because there is a lack of report or difficulty associating the symptoms with bradycardia condition. Many clinical trial studies demonstrate the relationship between heart rate (HR) and CVD outcome, but bradycardia still does not become appealing compared to tachycardia.(Cook et al., 2006; Fox et al., 2007) Whereas severe bradycardia might relate to prognostic of the CVD.(Diaz et al, 2005; Fox et al., 2007; Jouven et al., 2009). A large sample cohort study, HUNT-2, indicates bradycardia with CVD and all-cause mortality.(Nauman et al.,2011) Base on all the evidences, the bradycardia condition is much more essential than what we thought.(Makita et al., 2014).

Bradycardia defines as a HR <60bpm in adults other than well-trained athletes and visualized by electrocardiogram (ECG) (Kadish et al., 2001). There are some etiologies of bradycardia and conduction abnormalities such as abnormalities of the sinus node, atrial tissue, atrioventricular nodal tissue. Bradycardia more elaborate into two main categories; sick node dysfunction (SND) or formerly known as sick sinus syndrome (SSS) and atrioventricular block.(Kusumoto et al., 2019) There is a wide variety of clinical manifestations form bradycardia, from asymptomatic to abrupt syncope.

SND/SSS is an abnormal cardiac pace function caused by abnormal cardiac impulse formation and the sinoatrial node's alteration. As a consequence, the cardiac rate cannot fulfill body's physiologic need. The ECG manifestation also varies, including sinus bradycardia, sinus pauses/arrest, sinoatrial exit block, or alternating bradyarrhythmia and tachyarrhythmias.(Semelka et al.,2013).Clinical manifestation of the atrioventricular block (AV block) depends on the persistent or intermittent event, ventricular rate or duration of ventricular asystole correlated with AV block (Kusumoto et al., 2019). Bradycardia with or without symptoms alongside high-risk stratification becomes an indication for implantation of permanent pacemaker (PPM) (Kusumoto et al., 2019). Other absolute indications for PPM therapy are; tachycardia-bradycardia syndrome, atrial fibrillation with sinus node dysfunction, complete atrioventricular block (third-degree block), chronotropic incompetence, prolonged QT syndrome, and cardiac resynchronization therapy with biventricular pacing.(Kotsakou et al., 2015)

PPM could improve the quality of life of the patients who have the indication. Many individuals could tolerate the pacemaker implantation on the right ventricle (RV) for many years without adverse effects. Still, chronic RV pacing may lead to impaired left ventricle (LV) function and may result in symptoms of heart failure (HF), a syndrome known as pacing-induced cardiomyopathy (PICM) and significantly increases the incidence of hospitalization.(Dreger et al., 2012; Lu et al., 2018). The incidence of PICM is about 14.1% (Cho et al., 2019). In a study by Khurshid, the incidence of PICM is 19.5% at 3 years follow-up (Khurshid et al., 2014). However, the prevalence and study of PICM in Indonesia are still not available yet. It is important to understand the mechanism of PICM so the clinician can determine the management strategy for the patient. In this review, we included 47 literatures related to the topic. We aim to understand the mechanism of PICM and describe the clinical characteristics so the physician can give the proper management for patients.

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LITERATURE REVIEW

PACEMAKER

It is a small device powered by a battery to regulate a regular heartbeat. There are two primary components of the pacemaker; the generator and the wires/leads. The small generator may be implanted under the skin or a temporary external generator. The generator will send the impulse to the heart through the leads implanted in patient's heart (Kotsakou et al., 2015). Three types of permanent cardiac pacemakers are; (1) single-chamber pacemaker-VVI, (2) dual-chamber pacemaker-DDD, and (3) biventricular pacemaker-BiV.

Pacing Leads

Lead has two edge cable structures: terminal pins inserted to generator and electrode that implanted into cardiac structure act as sensing, pacing, or defibrillation. There are two types of pacemaker leads; unipolar and bipolar lead. In the unipolar lead, a single-implanted lead work as a sensing and pacing lead. Whereas, in the bipolar lead, there is a separate lead between sensing lead and pacing lead. Bipolar lead more superior in eliminating oversense noncardiac signal (Cornacchia et al., 2000). In the Unipolar lead system, the metal part of the pacemaker's generator serves as an anode (positive pole) and lead as a cathode (negative pole). Meanwhile, in a bipolar system, both anode and cathode are located on the same lead, as seen in **Figure 1** (Lazar et al., 2017). Bipolar lead overseeing of myopotentials might be caused by failure of the insulation in pacemaker pocket.

However, unipolar lead has simpler construction and much easier in locating of the pacing artifact. In few cases, the unipolar lead's sensing and capture thresholds might be superior to bipolar lead (Cornacchia et al., 2000). To overcome unipolar lead's problem in over-sense pectoral myopotential, protective coating on the device might contribute in this case.

Generator

The pacemaker generator contains several components: a battery, voltage supply, microprocessor, ROM and RAM memory, telemetry control, system controller, rate-adaptive sensor, filters, sensing amplifier, and pacing output circuit (Swerdlow, Wang, & Zipes, 2015). Batteries refer to total therapeutic energy for pacemakers, and its lifetime must be predicted in the beginning of the implantation. Lithium iodine batteries produce some amount of voltage that the output circuit should convert into the desire amount of voltage.

Sensing

Sensing is the capability of the pacemaker to identify intrinsic cardiac activity. Sensing mode make pacemaker feasible to stop sending impulse in a certain condition. It is easier for pacemaker to sense it in the larger amplitude of the cardiac signal in millivolts (mV). In sensitivity setting mode, the higher sensing value means a lower threshold of the pacemaker's sensitivity, vice versa (Lazar, Huang, & Wissner, 2017). Pacemakers need to analyze cardiac depolarization with time and signal morphology. Further, it also needs to filter out the cardiac signal and separate it from another noncardiac signal before analyzed it (Swerdlow, Wang, & Zipes, 2015) (**Figure 2**).

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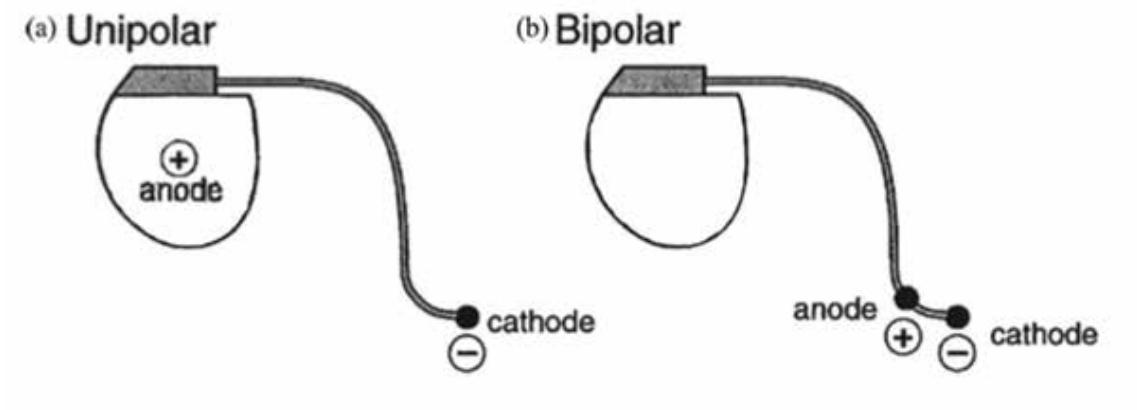

Figure 1. (left) unipolar pacemaker system, (right) bipolar pacemaker system (Lazar et al., 2017).

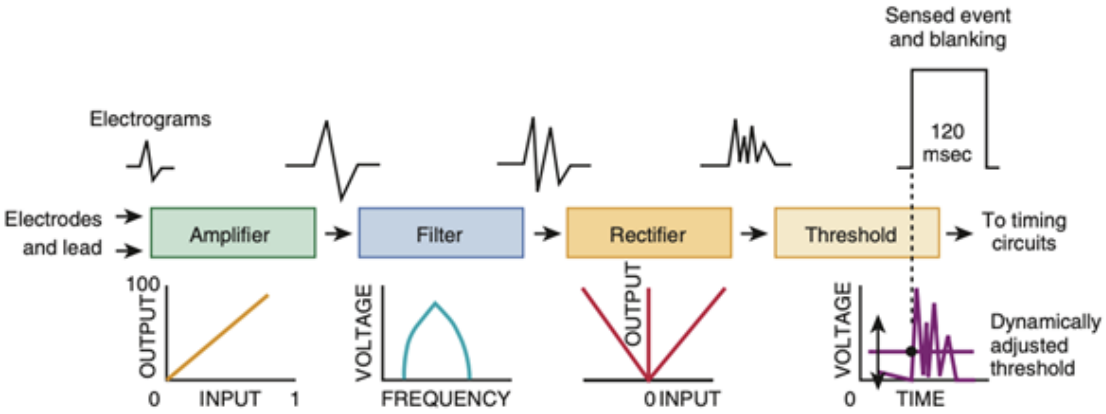

Figure 2. Functional block diagram for pacemaker (Swerdlow, Wang, & Zipes, 2015).

CARDIOMYOPATHY

Definition

Cardiomyopathy is a condition where there is a change in the anatomic of the heart. American Heart Association defines cardiomyopathy as a heterogeneous group of diseases of the myocardium associated with mechanical and/ or electric dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders (Maron et al., 2006) Cardiomyopathy is classified into primary (the disease process is mainly in the heart) and secondary (cardiac involvement in systemic condition). (Table 1) (Maron et al., 2006). The 4 major types are dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and Arrhythmogenic right ventricular Cardiomyopathy.

Classification and Pathophysiology

Dilated cardiomyopathy (DCM) is defined as the dilatation of the left or both ventricles that is not explained by abnormal loading conditions

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Table 1. Classification of Cardiomyopathy

Classification of Cardiomyopathy	
Primary	**Secondary**
Acquired	Inflammatory/autoimmune
Genetic	Endocrine
Mixed	Infectious
	Infiltrative disorder
	Neuromuscular storage disorder
	Nutritional deficiencies
	Toxic

or coronary artery disease. In DCM, there is an enlargement of the cardiac, but the ventricular wall thickness remains normal, and the systolic function is impaired. Patients with DCM can develop heart failure with reduced ejection fraction. DCM is caused by several diseases such as hypertension, coronary artery disease, viral myocarditis, valvular disease, and genetic predisposition (Elliott et al., 2008).

Hypertrophic cardiomyopathy (HCM) is a clinically and genetic disorder. It is characterized by muscle hypertrophy without dilatation of the left ventricle, and there is no other systemic or cardiac disease that can cause hypertrophy of the heart muscle, such as hypertension. HCM is a common genetic heart disease with a prevalence of 1 in 500 people (Semsarian et al., 2015). The etiology of HCM is usually from genetic factors. HCM is caused by 11 mutant genes with more than 500 individual transmutations which; the most common variation involves the beta-myosin heavy chain and myosin-binding protein.

The prevalence of arrhythmogenic right ventricular hypertrophy (ARCV) is lesser than DCM and HCM. It is estimated at 1/2000 to 5000 (Marcus et al., 2010). ARCV occurs when there is a progressive loss of myocytes and replaced by fatty tissue, resulting in functional and morphological right ventricular abnormalities. It involves the right ventricle at the beginning, but the pathologic process can also affect the left ventricle. ARVC is caused by autosomal dominantly inherited mutations in genes encoding plakophilin 2 and other proteins of the desmosome of cardiomyocytes, inherited disorder of the muscle of the right ventricle (Buja et al., 2008; Elliott et al., 2008).

Restrictive Cardiomyopathy is the type of cardiomyopathy that occurs when the ventricles become stiff and rigid without wall thickening which causes an increased chamber pressure in response to relatively small increases in volume. This results in the dysfunction of blood filling. The ventricle does not relax and fill the normal blood volume. This type is the most uncommon type of cardiomyopathy. This process results from several diseases such as sarcoidosis, hemochromatosis, amyloidosis, and abnormalities related to desmin. Desmin is a protein marker found in sarcomeres (Wexler et al., 2009).

Sign and symptoms

These four types of cardiomyopathy present in several sign and symptoms. DCM presents with shortness of breath, fatigue, cough, orthopnea, paroxysmal nocturnal dyspnea, and edema. Clinical presentation of HCM includes chest pain, congestive heart failure symptoms, syncope or pre-syncope, palpitations, and sudden cardiac death. Restrictive cardiomyopathy can

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present with pulmonary congestion, dyspnea on exertion, decreased cardiac output, and syncope. ARCV presents with syncope, atypical chest pain, initial episode of ventricular tachycardia, recurrent ventricular tachycardia. (Wexler et al., 2009)

Diagnostic evaluation

Cardiomyopathy usually presents with signs and symptoms of heart failure, and some diagnostic tools are beneficial to diagnose cardiomyopathy. The diagnostic tools include B-type natriuretic peptide (BNP), echocardiography, electrocardiography, and chest radiography. The rise in volume and filling pressure on ventricle will induce BNP secretion into the bloodstream as a response to ventricular stretching or wall tension (Doust et al., 2006). Imaging modality using echocardiography is also a beneficial diagnostic tool for cardiomyopathy. In DCM patients, th echocardiography will show enlargement of the ventricular chamber with normal or decreased wall thickness and systolic dysfunction. In HCM patient, the echocardiography will show left ventricular hypertrophy with a decreased ventricular volume. Patient with restrictive cardiomyopathy will show biatrial enlargement with a normal or reduced ventricular volume, normal left ventricular wall thickness with normal systolic function, and impaired ventricular filling in echocardiography. The echocardiography in ARVC will show global or segmental wall abnormalities with or without motion abnormalities. Electrocardiography (ECG) can also be used to diagnose cardiomyopathy. In DCM and HCM, the ECG will show left ventricular hypertrophy. ECG in a patient with RCM will show a decreased voltage without signs of left ventricular hypertrophy, and in ARVC patient the ECG will show abnormal repolarization and small-amplitude potentials at the end of the QRS complex.(Maron et al., 2006).

PACING-INDUCED CARDIOMYOPATHY

Definition and Diagnostic Criteria

Pacing-induced cardiomyopathy is a condition which a new onset of left ventricular systolic dysfunction occur due to chronic pacing, with a deterioration of left ventricular ejection fraction (LVEF) ≥10% or regional wall motion abnormality with no other causes can be explained (Khurshid et al., 2014; Sarvari et al., 2017). There are no specific criteria to make a diagnosis of PICM. However, several aspects can be measured that help the physician to diagnose. Decreased LVEF more than 10% after the pacemaker implantation is the common and established criteria to diagnose a PICM. Other than LVEF, the paced beats should be involved > 20% of the whole QRS complex. (Khurshid et al., 2016).

Mechanism of PICM

Chronic RV pacing has been associated with electrical and then mechanical dyssynchrony of the ventricles, leading to ventricular remodeling and causing heart failure (Gebauer et al., 2009). Physiologically, the conduction mechanism will go through the His-purkinje system. In RV pacing, the conduction will go directly to the myocardium and not going through the His-purkinje system (Bank et al., 2012). The abnormality in the conduction system may cause intraventricular. Interventricular, and atrioventricular dyssynchrony. Intraventricular dyssynchrony is associated with prolonged isovolumic contraction and isovolumic relaxation, thus delaying the mitral valve opening. The longitudinal intraventricular dyssynchrony in RV pacing-induced heart failure is even greater than in patients with other causes of heart failure (Bank et al., 2010). Interventricular dyssynchrony causes the septum to be pushed toward the left ventricle during RV ejection. The left ventricular diastolic filling period is impaired due to atrioventricular dyssynchrony (Bank, Gage, & Burns, 2012;

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Mollazadeh et al., 2012; Tops, Schalij, & Bax, 2009). All these mechanisms also lead to abnormal metabolic changes in cardiac tissue level, causing different myocardial blood flow, glucose uptake, and altered regional perfusion (Cicchitti et al., 2016). Other than mechanical dyssynchrony, left ventricular torsion abnormalities may occur. The abnormalities consist of lower basal and apical peak rotation and lower peak systolic torsion (Burns et al., 2011).

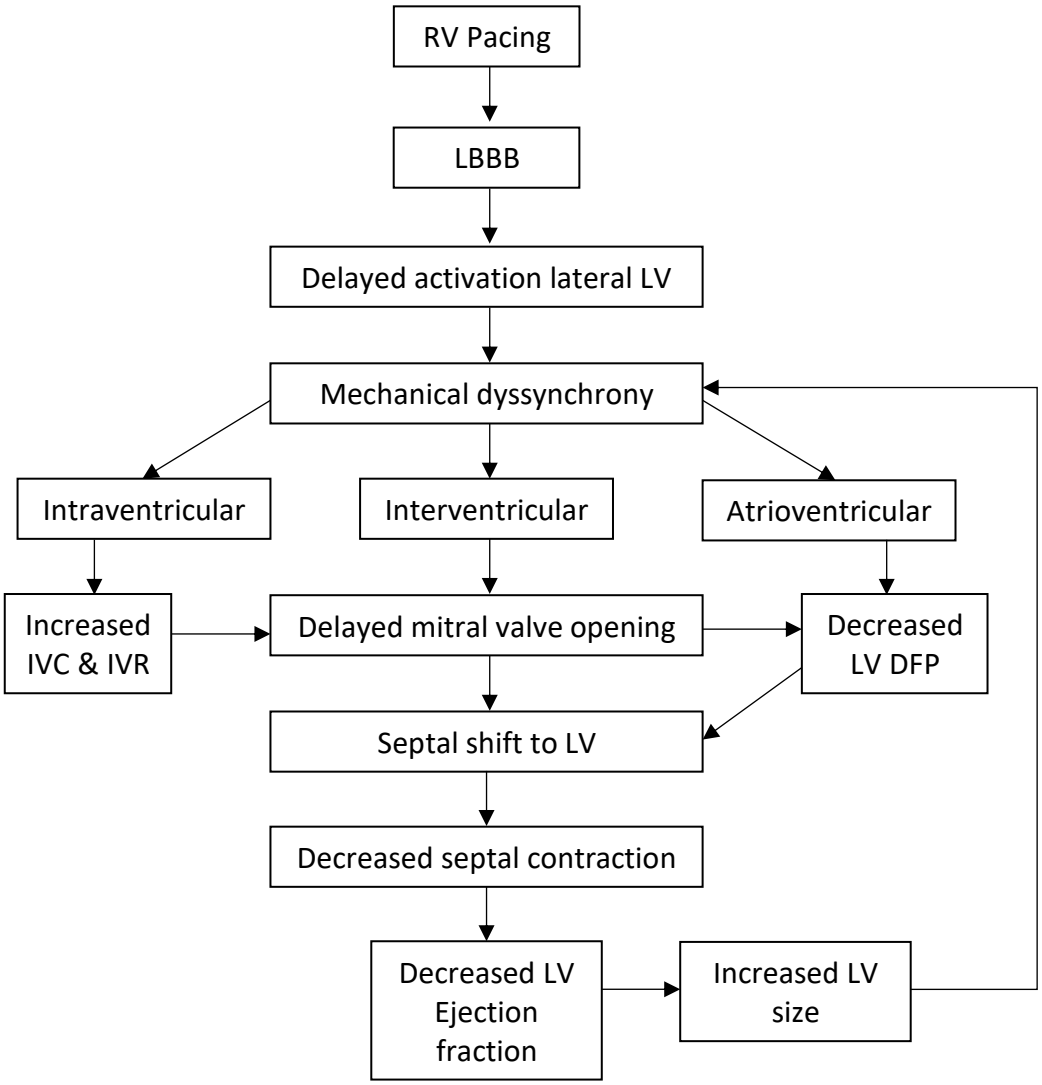

Figure 3. Mechanism of PICM (Bank, Gage, & Burns, 2012) RV: right ventricle; LV: left ventricle; LBBB: left bundle branch block; IVC: isovolumic contraction; IVR: isovolumic relaxation; DFP: diastolic filling pressure.

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Risk factor for developing PICM

Understanding the risk factors for someone to develop PICM will help the clinician to prevent the event. Several risk factors have been related to the likelihood of experiencing PICM, such as older age, male, wider intrinsic QRS, history of atrial fibrillation, and baseline left ventricular dysfunction (impaired left ventricular ejection fraction) (Curtis et al., 2016; Kim et al., 2018; Lee et al., 2016; Merchant et al., 2017; Merchant & Mittal, 2020). Several risk factors could also be evaluated after the pacemaker implantation. Those are the increased RV pacing burden (> 20%) and wider paced QRS duration (Kiehl et al., 2016; Kim et al., 2018). Lead location as another risk factor is still not clear. While several studies showed no association between RV apical (RVA) pacing and non-RVA pacing, a greater deterioration of LVEF might occur in RVA pacing group (Hussain et al., 2015; Kaye et al., 2019; Khurshid et al., 2014; Riahi et al., 2012).

Clinical manifestation

PICM shares similar clinical signs and symptoms with heart failure in general, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema of the extremity, and fatigue. The difference is only at the fact that PICM occurs in patients with pacemaker, and no other etiology of heart failure is identified. The diagnosis of PICM can also be made in the absence of heart failure signs and symptoms (Kim et al., 2018).

Treatment and preventive strategy for PICM

For individuals with PICM, cardiac resynchronization therapy (CRT) is one of the treatment strategies. A study by Khurshid et al showed that 85.5% of the patients with severe PICM responded with a rise of LVEF ≥5% within the first 3 months of treatment (Khurshid et al., 2018). The implantation of CRT in PICM patients also showed a better electromechanical reverse remodelling than other indications for CRT implantation (Gwag et al., 2017).

Another treatment for PICM is an implantation of His-bundle pacemaker (HBP) system. This strategy's benefit is that it plays role as a dual-chamber pacemaker, whereby the ventricular lead is placed on the His bundle and does not cause a dyssynchrony (Shan et al., 2018). A study reported that HBP implantation successfully reversed the electrical and structural changes due to previous chronic RV pacing in 79 (93%) patients, increasing the ejection fraction in 60 patients with reduced ejection fraction due to RV pacing (Vijayaraman et al., 2019).

The patient who needs ventricular pacemaker can be given biventricular pacing instead of RV pacing as a preventive strategy of PICM. It is showed that biventricular pacing patients would have a less mortality, hospital visits, and also an increase ≥15% in LV end-systolic volume index (Curtis et al., 2013).

CONCLUSION

Permanent pacemaker implantation is a definitive therapy for a condition such as total heart block. The pacemaker is usually located on the right ventricle. Chronic RV pacing can lead to pacing-induced cardiomyopathy. Patients with PICM will present with signs and symptoms of heart failure. Risk factors identification is also important to make the right diagnosis. PICM can be treated and prevented with a biventricular pacemaker, cardiac resynchronization therapy which can improve the systolic function, and implantation of the pacemaker on the His-bundle system to avoid dyssynchrony. This review could give the physician more insight about PICM diagnosis and management and could also be used as a basis or reference to conduct a further study related to PICM.

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