Pacing Induced Cardiomyopathy: Diagnosis and Management

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ABSTRACT

Permanent pacemaker is the mainstay treatment indicated for bradycardia caused by sinus node dysfunction. However, heart failure may appear in patients with chronic right ventricle pacing, this is known as Pacing-Induced Cardiomyopathy (PICM). There is no internationally accepted definition for diagnosis of PICM. Studies show the prevalence of PICM is 9% in the first year and increases in proportion to the duration of PPM implantation, but varies widely according to diagnostic criteria used. PICM causes a higher all-cause death, hospital admission, and cardiac death. Therefore, detecting risk factors may be an important part of the prevention and early treatment of PICM. Once PICM develops, several therapy options are available but Cardiac Resynchronization Therapy with biventricular Pacemaker is currently the forefront of treatment. But insight into other more novel therapeutic options such as; His bundle pacing and Left Bundle Branch Pacing shows promising results as an alternative treatment option in the near future.

Keywords
Ventricular dyssynchrony, heart failure, Pacing Induced Cardiomyopathy, Cardiac Resynchronization Therapy

INTRODUCTION

Pacemaker implantation is indicated for bradycardia caused by sinus node dysfunction (SND) as chronic therapy when other potential treatable or reversible etiologies have been excluded. Pacemaker implantation is intended to increase heart rate and improve symptoms.[1] However, long-term use of right ventricle pacing is reported to induce ventricular dyssynchrony which causes disturbances in left ventricular systolic function which further leads to heart failure syndrome or what is called pacing-induced cardiomyopathy (PICM).[2] PICM is defined as a heart failure syndrome characterized by: (i). left ventricular systolic dysfunction (LVEF < 50%) and LVEF reduction ≥10% after pacemaker implantation or (ii). No other cause of left ventricular dysfunction. Incidence of PICM is estimated to occur in 5-20% of patients using right ventricular pacing for more than two years.[3, 4] Symptoms that may appear in patients who develop PICM include dyspnea on exertion, paroxysmal nocturnal dyspnea, unexplained weight gain, and edema on the extremity. Physical examination may show signs of jugular venous pressure elevation, auscultatory crackles, S3 gallop, ascites, pulmonary edema, or pleural effusion.[4] Patients with PICM have higher probability of all cause death, HF admission, and cardiac death compared to non-PICM, so observation and intervention are needed.[5] This study was conducted to provide the latest updates on diagnosing patients with PICM and the best management that can be done in patients by looking at the conditions in each hospital.

Predictors and Risk Factors of Pacing Induced Cardiomyopathy (PICM)

Patient who undergoes RV pacing has up to 26% chance develop LV systolic dysfunction. Many studies have been conducted to find out about the risk factors for PICM. These studies found that men are more likely to experience PICM than women. History of heart diseases such as myocardial infarction, atrioventricular block, atrial fibrillation, and pre-existing LV systolic dysfunction.[5–8] LBBB at baseline ECG, lower baseline LVEF, wider paced QRS duration and pre-LVESD, and higher burden of right ventricular pacing were predictors of PICM.[6, 7, 9, 10] The study shows patient with baseline LVEF under 55% before pacing, wider paced QRS duration (>160msec), and pacing burden more than 33% has a higher risk for developing PICM.[9]

Mechanism of Pacing-Induced Cardiomyopathy (PICM)

Permanent pacing is indicated for patients with total AV block (TAVB) as well as bradycardia caused by SND. Symptomatic SND requiring GDMT or with bradycardia with significant comorbid, single chamber ventricular pacing is recommended unless there is reason to avoid the RV lead (IIa).[1] Studies have found that in patients with higher ventricular pacing burden (> 40%), it is more common to have a decreased LVEF, which causes symptoms of heart failure. This is supported by predictive factors such as lower baseline LVEF and wider-paced QRS duration.[10, 11] Pacing in the distal part of the conduction system disrupts physiological conduction. Conduction does not pass through the his-purkinje system, but rather through the ventricular myocardium which causes ventricular dyssynchrony. Ventricular dyssynchrony furthermore causes abnormal contraction of the ventricle which leads to LV remodeling. Ventricular dilatation, functional MR, reduced LVEF, myocardial fibrosis, and neuro-hormonal activation play a role in LV remodeling.[12] A study conducted by the author previously found that there were neuro-hormonal changes in the remodeling process of LV. The authors found that there was a decrease in miR-155, and an increase in interleukin-6

(IL-6), soluble tumor necrosis factor 2 (sTNFR-2), matrix metalloproteinase-9 (MMP-9), N-cadherin (N-Cad), Occludens Zone-1 (ZO-1).[13]

Diagnosis of Pacing Induced Cardiomyopathy (PICM)

PICM is generally defined as a fall in Left Ventricle Ejection Fraction (LVEF) after implantation of a cardiac pacemaker. This results in symptoms of heart failure such as; dyspnea on exertion, paroxysmal nocturnal dyspnea, unexplained weight gain, edema on extremity, and physical examination may show elevation of jugular venous pressure, auscultatory crackles, S3 gallop, ascites, pulmonary edema or pleural effusion. PICM happens mostly in patients with high right ventricle pacing burden and may happen in months to years following implantation of the pacemaker. No consensus has been reached in determining the diagnostic criteria of PICM. Current literature uses varying criteria for diagnosing PICM. A systematic review and meta-analysis done by Somma et al, states that there are 15 unique diagnostic criteria found in the current literature.[6] Based on a review by Mizner et al, these are the most often used diagnostic criteria for PICM.[14]

1. Decrease of LVEF below 50%, regardless of patients' symptoms, or a reduction of LVEF by 10% or more.
2. Decrease of LVEF below 45%, or reduction of LVEF by 10% or more after implantation of pacemaker device.
3. Decrease of LVEF below 40%, or an indication of upgrading to cardiac resynchronization therapy (CRT).
4. Reduction of LVEF by 5% or more, with signs and symptoms of heart failure, without other etiology of heart failure.

It is estimated that about 6-22% of patients with a permanent pacemaker will fulfill the criteria for PICM within 3-16 years. The wide prevalence of PICM is attributed to differences in diagnostic criteria used, variability of patients included in the studies, and different follow-up duration.[14] One study by Kaye et al, found that in 118 patients with permanent pacemakers and follow-up echocardiography with mean duration of three and a half years, using three unique definitions of PICM, the prevalence of PICM is 5.9% - 39%. This study demonstrates that just based on the diagnostic criteria used, the resulting prevalence may differ exponentially.[11]

Yu et al observed that after one year, 9% of individuals with a right ventricular pacemaker will develop PICM.[15] Khurshid et al, reported a prevalence of 19.5% after a median follow-up of 3.3 years.[4] Zhang et al also reported a prevalence of 26% in patients with a median follow-up of 7.8 years.[16] These three studies mentioned found that the shortest time a patient develops PICM is one month after the implantation of the pacemaker, and the longest time a patient is diagnosed with PICM is nine years following the implantation of pacemaker, suggesting PICM may occur even years after PPM.[4, 15, 16] A systematic review conducted by the author previously, found that the incidence of PICM increases proportionally with the duration of PPM.[17]

Early Detection of Ventricular Dyssynchrony

PICM may occur as soon as one month after PPM implantation.[4] Therefore, detecting pathophysiological changes and identifying risk factors is crucial in the prevention and treatment of PICM.

RV pacing, especially with apex location of the pacemaker, induces a slow myocyte-to-myocyte electrical signal transmission. This electrical signal propagates slowly, through the myocardium and bypasses the physiological conduction system causing disproportional RV and LV contraction. Initial depolarization happens near the pacing site followed by delayed depolarization of more remote segments. This non-physiological cardiac contraction is known as ventricular dyssynchrony.[14]

There are two different types of ventricular dyssynchrony, interventricular (between right and left ventricle) and intraventricular (within one side of the ventricle). Interventricular dyssynchrony can be visualized as delayed aortopulmonary valve opening times and can be assessed with routine Doppler echocardiographic imaging. While an intraventricular dyssynchrony is a delay of mechanical activation between the various segments of the ventricle, and is harder to assess, requiring a Tissue Doppler imaging (TDI) or 2D speckle-tracking strain analysis and real-time 3D echocardiography.[14]

Interventricular dyssynchrony is identified to be an important predictor of ≥10% decrease in LVEF along with high burden RV pacing (>60%) in a study by Bansal et al.[18] Another parameter in echocardiography that may predict LV dysfunction which precedes a decrease in LVEF is the Global Longitudinal Scale (GLS). GLS using 2D echocardiography has high sensitivity (92%) and specificity (89%) for detecting early LV systolic dysfunction. Iqbal et al demonstrate that there is a significant decrease in GLS of patients with PPM after one month, especially those with high RV pacing burden (40%) and apical pacemaker location.[19] This is supported by the PAVD study which found one-month GLS reduction to be highly predictive in assessing patients after implantation of PPM with risk of LV dysfunction and subsequent cardiomyopathy.[20]

Traditionally, ventricular dyssynchrony is assessed with a simple 12-lead ECG. Wide-paced QRS duration (QRSd) (>160msec) is identified as a predictor for PICM. Unfortunately, QRSd is limited as to what it can provide as it is not able to assess separate right and left ventricle activation.[14] Vectorcardiography measuring QRS Area (QRSa) is a parameter that may be acquired using a 12-lead ECG or orthogonal chest leads. Vectorcardiography too is unable to assess separate right and left ventricle activation but may help in CRT optimization as large QRS areas have been found to be associated with better CRT responses and failure to achieve large QRS area reduction is associated with poorer survival and echocardiographic outcomes.[21, 22]

Other more complex and non-invasive modalities to assess ventricular dyssynchrony are the ECG belt system (EBS) and ECG imaging (ECGi). Both use body surface potential mapping (BSPM) to measure a variety of parameters. EBS uses 53 body surface electrodes to produce isochronal activation maps reflecting spatial propagation of ventricular activation as reflected on the body surface.[23] While an ECGi is a more complex and resource-consuming modality, needing 252 body surface electrodes and a CT-Scan to construct 1500

epicardial unipolar electrograms.[24] Both are currently still novel technologies and see the bulk of their use in research rather than clinical settings.

In accordance with the results of the author's previous study which found neurohormonal changes in patients after ppm with LV dysfunction assessed by GLS, the author suggests measuring these biomarkers to assess LV dysfunction in patients after PPM implantation.[13]

Management for Pacing Induced Cardiomyopathy (PICM)

There are many management that can be done in patients who experience PICM. Studies were conducted to determine the best choice for PICM patients who can provide the best benefit with the lowest risk. Patients with PICM who underwent an upgrade to a single or dual chamber biventricular pacing (cardiac resynchronization Therapy/CRT), His Bundle pacing (HBP), and Left bundle branch pacing (LBBP) showed improvements especially in LVEF, symptoms of heart failure, and quality of life although each action has its advantages and disadvantages.

Cardiac Resynchronization Therapy (CRT)

ESC guidelines recommend upgrading to CRTs in patients with conventional pacemakers or an ICD who develop refractory heart failure and LVEF ≤35% and for those with significant RV pacing burden. (Class IIa level B). CRT itself can prevent PICM from happening and more superior to RV pacing in relieving symptoms. Biventricular pacing is proven to be effective and safe in patients with LBBB, as it should remain as first-line therapy. On the other hand, HBP has shown better results in patients with RBBB.[2]

Biventricular pacing (BVP)

Biventricular pacing was first introduced in 1979 to assess arrhythmia. While in 1987, the concept of biventricular was granted a patent then to be widely used. Beginning in 1993, biventricular pacing already shows that this procedure improves functional capacity and LV function.[25] As science develops and research is conducted on BVP, it is found that upgrading to BVP provides many benefits in treating patients with PICM. BVP shows improvement on LVEF, NYHA class, walking distance, and Quality of Life, furthermore, reduces the LV remodeling process.[26–28] A systematic review reported a comparison of the use of BVP and RVP in patients with atrioventricular conduction defects. As a result, it was found that the use of BIV significantly reduced the mortality rate, as well as the incidence of hospitalization due to HF.[26] Transient or permanent loss of biventricular pacing has been reported in some patients. This happens mostly due to Lead dislodgement so reinstallation is required. T-waves oversensing (TWOS) is also seen in some patients. Some old studies suggested a decrease in the ventricular sensitivity (from 0.3 to 0.45 mV or more) and after this was done, no further TWOS was seen.[29, 30] However, reduced ventricular sensitivity can affect the ability of the device to detect VF. Recent studies have shown that reducing ventricular sensitivity is not necessary. This can be avoided by increasing the post-pacing blanking period. That way, the sensitivity does not need to be lowered so that the device can still detect VF.[31]

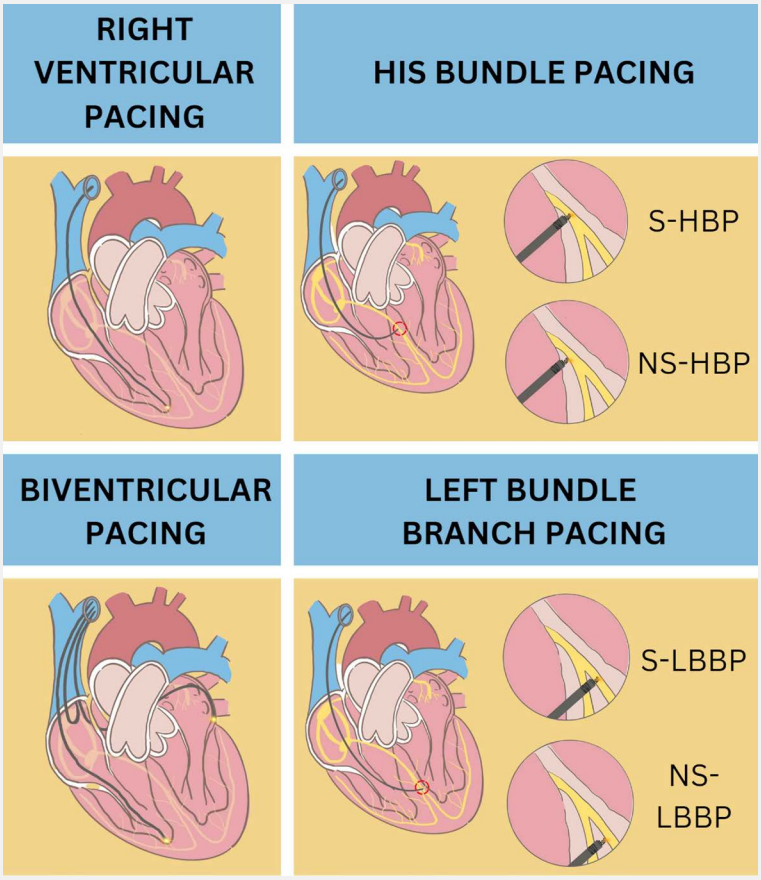
His Bundle Pacing (HBP)

Upgrading from right ventricular pacing to cardiac resynchronization Therapy in patients with PICM, HBP can be superior to BVP. HBP achieves physiological pacing by activating the ventricle via native conduction system. That way, PICM can be avoided.[32] A study by Gardas R et al. shows how HBP is superior to BVP. The group of patients who underwent HBP showed an increase in LVEF from 34.3% to 48.2% after six months of follow-up compared to the group of patients who underwent BVP, which only reached 43.9% from the baseline of 32.9%. Moreover, the study shows improvement in NYHA class, LVEF, and mitral regurgitation more common in patients with HBP.[33] Although all benefit that HBP offer, it has disadvantages such as technical difficulties, reduced R wave amplitudes, and high and unstable threshold. The success rate of HBP reported at ranges from 72 to 92% with re-intervention rate at 6 to 8%. Compared to LBBP which has more than 80% success rate with low re-intervention rate.[32, 34, 35]

Left Bundle Branch Pacing (LBBP)

Among various patient populations with low and stable thresholds, LBBP shows promising results, better in safety, efficacy, and outcomes rather than BVP or HBP.[36–39] This technique is done by placing a pacing device 10-15 mm below his bundle region using an imaginary line drawn from the distal extent of the his bundle to the RV apex.[40] This technique can be an option for patients who develop signs of PICM after long time use of right ventricular pacing. Furthermore, LBBP can produce a near-physiological or true conduction system while bypassing the pathological or vulnerable region in the cardiac conduction system.[41] A cohort study conducted by Li H, et al used 10 patients with PICM that upgraded to LBBP. This study aims to find out how cardiac function and quality of life (QoL) change after upgrading to LBBP. As a result, one month after the procedure, the patient's LVEDD and CTR were lower than before. LVEF was also found to be increased. The 6-minute walking test (6 MWT) was found to increase which means heart failure is relieved and cardiac function is significantly improved.[42] A case reported by Yang D et al, about An 86-year-old Chinese woman with high-degree atrioventricular block who undergo LBBP after two years using a dual chamber pacemaker. The study shows that within 1 week, there is a significant improveme nt in LVEF after post-operation and the QRS complex was significantly narrowed from 152 ms to 105 ms. 6 MWT improved, and the Minnesota Heart Failure Quality of Life scale score decreased indicating that the patient's QoL was significantly enhanced.[43] Though rare, septal perforation and thromboembolism can occur. As the operator, it is important to evaluate the thickness of the basal interventricular septum and lead length. If perforation occurs, the lead need to be re-implanted at different site. When the lead is appropriately repositioned, it is not associated with major adverse event.[40, 44]

Figure 1: Type of Pacing
S-HBP= Selective His-Bundle Pacing; NS-HBP= Non-Selective His-Bundle Pacing; S-LBBP= Selective Left Bundle Branch Pacing; NS-LBBP= Non Selective Left Bundle Branch Pacing



CONCLUSION

PICM is defined as a heart failure syndrome characterized by: (i). left ventricular systolic dysfunction (LVEF < 50%) and LVEF reduction ≥10% after pacemaker implantation or (ii). No other cause of left ventricular dysfunction. LBBB at baseline ECG, lower baseline LVEF, wider paced QRS duration and pre-LVESD, and higher burden of right ventricular pacing were predictors of PICM. Echocardiography, ECG, and GLS examination can also be modalities for assessing a person's risk of developing PICM. Furthermore, GLS can reveal dysfunction of the left ventricle even though there has not been a decrease in LVEF. Several biomarker changes were also found in patients who developed PICM. ESC guidelines recommend upgrading to CRTs in patients with a conventional pacemaker or an ICD who develop refractory heart failure and LVEF ≤35% and for those with significant RV pacing burden. BVP is the recommended pacing technique as the first choice, but at present, developments in the HBP and LBBP techniques show better results, both in terms of increasing LVEF, 6MWT, and quality of life. Compared to HBP, LBBP has more than 80% success rate with low re-intervention rate. Further studies and research are needed that can support LBBP to be the first choice in patients with AV block and SND who need CRT.

Conflict of Interest: None

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