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Pacing-Induced Cardiomyopathy

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Keywords

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INTRODUCTION

The potential for chronic right ventricular pacing (RVP) to cause an acquired cardiomyopathy, termed RV pacing-induced cardiomyopathy (PICM), has been clinically recognized for over 20 years.[1] Nevertheless, over one million pacemakers are currently implanted worldwide,[2] and most of the individuals who are exposed to RVP do not develop PICM.[3] Although more contemporary pacing strategies that can preserve ventricular synchrony (ie, physiologic pacing, such as biventricular pacing [BiV] or conduction system pacing [CSP]) decrease the risk of PICM, higher cost, difficulty of implantation, and increased rate of complications continue to favor traditional RVP in most cases.[4,5] As a result, RVP presently remains the standard of care for most patients who require pacing support in the absence of a pre-existing cardiomyopathy.[6] Such an approach is consistent with current guidelines from the European Society of Cardiology,[7] European Heart Rhythm Association,[8] and American Heart Association/American College of Cardiology/Heart Rhythm Society,[9] which support physiologic pacing with BiV only in the presence of systolic dysfunction and ongoing requirement for ventricular pacing. Therefore, it is imperative for clinicians to understand which individuals are most likely to develop PICM, as well as the optimal strategies for surveillance and treatment after PICM is diagnosed, to minimize adverse outcomes related to RVP.

PATHOPHYSIOLOGY OF PICM

The potential for RVP to result in deleterious cardiovascular outcomes became apparent in the late 1990s and early 2000s. In a small randomized trial reported in 1994, Andersen and colleagues[1] found that individuals with sick sinus syndrome treated with atrial pacing, as opposed to RVP, had a lower incidence of atrial fibrillation (AF) and thromboembolic

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DISCLOSURE

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complications over 5 years of follow-up. Subsequently, the 2002 Dual Chamber and VVI Implantable Defibrillator (DAVID) trial[10] found that individuals randomized to DDD pacing with a lower rate limit of 70 beats per minute (mean RVP percentage 56%) had a 10% increase in death or hospitalization when compared to those randomized to backup VVI pacing at 40 beats per minute (mean RVP percentage 3%). A subset analysis of the 2003 Mode Selection Trial (MOST), another randomized trial of VVI versus DDD pacing, similarly found that higher RVP percentage was a strong predictor of heart failure hospitalization.[11]

PICM is now recognized as an acquired cardiomyopathy caused by exposure to electrical and mechanical dyssynchrony resulting from RVP (Fig. 1). Animal studies suggest that dyssynchrony may lead to clinical cardiomyopathy by inducing alterations in myocardial perfusion, encouraging pathologic remodeling related to regional differences in wall stress, and promoting abnormalities in intracellular and extracellular regulation.[12] As many individuals are exposed to decades of RVP and never develop PICM, it is likely that substrate vulnerability plays an important role in PICM development, although the specific mechanisms underlying such vulnerability are not well-understood.

Although variable definitions exist in the literature, most commonly PICM is defined as a drop in left ventricular ejection fraction (LVEF) of ≥10% to a value <50%, without a clear alternative explanation, in the setting of significant RVP.[13] Some studies have additionally required the occurrence of heart failure symptoms, although such an approach inappropriately excludes the considerable proportion of individuals who develop an asymptomatic cardiomyopathy.[14] As individuals exposed to RVP frequently have competing potential causes of LVEF decline, PICM is most appropriately considered a diagnosis of exclusion, identified as the cause of cardiomyopathy only after a reasonable search for alternative etiologies such as ischemia or uncontrolled hypertension is unrevealing.[13]

PICM FREQUENCY AND RISK FACTORS

Since the initial recognition of PICM as a clinical entity, several studies have examined the incidence of and clinical risk factors for developing PICM. An overview of retrospective observational studies describing PICM incidence and risk factors is compiled in Table 1. A summary of identified risk factors for developing PICM is depicted in Fig. 1.

In 2014, Khurshid and colleagues[13] reported a single-center experience of 257 individuals with normal baseline LVEF undergoing right ventricular pacemaker implantation. They observed an overall PICM incidence of 19% over a median follow-up of 3.5 years. Risk factors for PICM in multivariable models included male sex and wider native QRS duration. In 2016, Kiehl and colleagues[15] published a similarly designed study including 823 individuals and reported a PICM incidence of 12.3% over slightly longer follow-up. In multivariable models, increasing RV pacing percentage, and in particular RV pacing percentage ≥20%, was a strong risk factor for PICM. Notably, only individuals with RV pacing percentage ≥20% were included in the study by Khurshid and colleagues, and therefore both studies support the notion that 20% RV pacing is sufficient to cause PICM.

Several subsequent studies have suggested that postimplant surrogates of dyssynchrony may also identify risk for developing PICM. Lee and colleagues[16] performed a retrospective study of 234 individuals followed for over 15 years, reporting a PICM incidence of 20.5%. Risk factors for PICM included older age and wider paced QRS duration, as well as a greater electrocardiographic myocardial scar score. Kim and colleagues[17] also found that a wider paced QRS duration was associated with PICM. In a cross-sectional study comprising 184 individuals, Khurshid and colleagues[14] reported that paced QRS duration was associated with the presence of PICM at follow-up, with a paced QRS duration ≥150 ms demonstrating 95% sensitivity for the presence of PICM. Within 618 individuals followed for over 7 years, Cho and colleagues[18] found that PICM developed in 14.1%. A paced QRS duration ≥155 ms was again a strong risk factor for PICM, in addition to RVP percentage ≥86% and presence of LBBB before pacemaker implantation. Bansal and colleagues[19] found that echocardiographic evidence of interventricular dyssynchrony was an independent risk factor for PICM, with individuals demonstrating dyssynchrony having a 3-fold increased risk.

UPFRONT PHYSIOLOGIC PACING

Given the key role of electrical and mechanical dyssynchrony in the development of PICM, there has been increasing interest in upfront utilization of pacing strategies that preserve more physiologic ventricular activation (eg, BiV and CSP). The 2013 Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF[6]) study is the largest trial to date comparing RVP to physiologic pacing, randomizing 691 individuals with pre-existing heart failure (ie, New York Heart Association [NYHA] functional class I-III and LVEF ≤ 50%) to BiV or RVP. At 3 years follow-up (median RVP percentage >97% in both groups), BiV was associated with a 10% absolute reduction in the primary outcome of death, urgent heart failure care, and adverse LV remodeling. As a result, physiologic pacing is generally considered first-line therapy among individuals with pre-existing heart failure who have a substantial pacing requirement.

In contrast, the benefit of upfront physiologic pacing as compared to RVP is less clear among individuals without pre-existing heart failure. Several small studies have compared physiologic pacing to RVP as a means of preventing PICM (Table 2). Although larger studies are needed, available evidence supports the concept that PICM can essentially be prevented by use of physiologic pacing. At the same time, it is important to note that although physiologic pacing strategies are becoming increasingly safe and effective, the rates of acute and chronic complications remain higher than those observed with RVP.[20,21]

Biventricular Pacing

Most of the studies investigating upfront physiologic pacing have assessed for echocardiographic evidence of adverse ventricular remodeling (eg, increasing LV volumes) as surrogates for PICM development. In 2011, Albertsen and colleagues[22] randomized 50 patients to BiV or RVP. At 3 years follow-up, the LVEF dropped from a mean of 59% to 53% in the RVP group, with no change in the BiV group. Notably, although sample size was limited, there were no differences in quality of life or NYHA functional class between

the RVP and BiV groups. Similar results were observed in the comparably designed PACE trial,[23] which randomized 177 patients to RVP or BiV. After 2 years, individuals in the RVP group experienced a 10% drop in LVEF, whereas individuals in the BiV group had no change in LVEF. In total, 63% of individuals receiving RVP experienced a drop in LVEF ≥ 5%, as compared to 20% of individuals receiving BiV.

Multiple studies have compared the upfront use of BiV versus RVP following AV node ablation for refractory AF. In the 2005 PAVE trial,[24] 184 individuals undergoing AV node ablation were randomized to BiV or RVP. At 6 months, when compared to individuals receiving BiV, those receiving RVP had a lesser improvement in the 6-min walk test (24% vs 31%) and experienced a mean 5-point decrease in LVEF (no change in BiV group). In the AVAIL CLS/CRT trial,[25] 108 patients undergoing AV node ablation were randomized 4:1 to BiV or RVP. At 6 months, there was no difference in LVEF in the RVP group, but the BiV group had a statistically significant 3-point increase in LVEF.

Conduction System Pacing

More recently, several studies have assessed the use of upfront CSP (specifically His bundle pacing [HBP]) as compared to traditional RVP. In 2018, Vijayaraman and colleagues[21] reported a retrospective study in which individuals undergoing HBP were compared to individuals contemporaneously undergoing RVP at a sister hospital. HBP was attempted in 94 patients, but was successful only in 75 patients (80%). At 5 years, the primary outcome of death or hospitalization for heart failure occurred in 53% of the RVP group compared to 32% in the HBP group. They also reported the incidence of PICM, defined as a decline in LVEF greater than 10% resulting in an LVEF less than 50% among individuals receiving at least 40% RVP. PICM occurred in 22% of the RVP group and only 2% of the HBP group. Of the 2 cases of LVEF decline in the HBP group, one was potentially attributable to myocardial infarction, while the other resolved with transition to BiV pacing, suggesting that conduction system activation may have been suboptimal in that individual. Notably, as compared to RVP, the incidence of lead revision (7% vs 3%) and generator change (9% vs 1%) were both higher with HBP.

A larger, similarly designed study was reported in 2018 by Abdelrahman and colleagues.[20] HBP was attempted in 332 consecutive patients, and successful in 302 (92%), whereas RVP was performed in 433 patients. At approximately 2 years, the primary endpoint of death, hospitalization for heart failure, or upgrade to BiV was significantly lower in the HBP group (25%) than in the RVP group (32%). Of note, improved outcomes with HBP were primarily observed in the subgroup of individuals receiving greater than 20% RVP, consistent with observational data suggesting that 20% RVP may represent a minimum threshold for PICM.[13,15] Again, the need for lead revision was substantially higher in the HBP group (4%) than in the RVP group (0.5%).

TREATMENT OF PICM

Given the increased costs, procedural complexity and complication rates associated with upfront physiologic pacing,[4,5] it is likely that most of the individuals who do not have pre-existing heart failure and require ventricular pacing will continue to receive RVP.

As a result, it is important to understand whether PICM can be effectively treated (Fig. 2). Several recent studies have attempted to characterize the response to provision of physiologic pacing among individuals with established PICM (Table 3). Consistent with dyssynchrony as the underlying mechanism of PICM development, studies generally demonstrate a robust response upon transitioning from RVP to physiologic pacing, even among individuals having had PICM for many years. Nevertheless, recovery of systolic dysfunction is not universally complete, and a minority of individuals with PICM do not respond to physiologic pacing. Further work is needed to assess whether nonresponse to physiologic pacing among individuals with PICM is related to irreversible myocardial injury and fibrosis, or misdiagnosis of PICM in the presence of an alternative cause of cardiomyopathy that is unrecognized (eg, Lamin A/C or sarcoidosis). Of note, as with any nonischemic cardiomyopathy, guideline-directed medical therapy should be provided to individuals with PICM, although the role of specific medical therapies has not been directly assessed in the PICM population.[26]

Biventricular Pacing

The first indication that BiV may effectively reverse PICM was a report by Nazeri and colleagues[27] including 21 patients with PICM. PICM was defined as a decline in LVEF from normal to ≤35% within 6 months of pacemaker implantation among individuals receiving ≥25% RVP and no evidence of an alternative cause of cardiomyopathy. Most individuals had PICM for only several months, with a mean time from PICM diagnosis to BiV upgrade of 5 months. Following upgrade to BiV, the mean LVEF improved from 31% to 37%. Sixteen patients (76%) reported a significant improvement in heart failure symptoms. Among the 5 patients (24%) with no LVEF improvement, no risk factors could be identified for lack of response.

In 2018, Khurshid and colleagues[28] reported a sizable series of individuals with PICM undergoing upgrade to BiV. PICM was defined as a decline in LVEF ≥10% resulting in an LVEF less than 50% among individuals with ≥20% RVP at the time of PICM diagnosis. Among 69 individuals whose medical records were manually adjudicated for the presence of PICM (mean preupgrade LVEF 29%), upgrade to BiV resulted in substantial improvement in LVEF (mean postupgrade LVEF 45%). Notably, the diagnosis of PICM was fairly longstanding, with an average time from diagnosis to BiV upgrade of approximately 1.5 years. Fifty-nine patients undergoing upgrade experienced an improvement in LVEF ≥5% (86%), and 49 patients had an improvement in LVEF ≥10% (71%). Importantly, among individuals with a preupgrade LVEF at or below 35% (ie, the LVEF threshold used to determine candidacy for primary prevention implantable defibrillators[29]), the substantial majority (72%) achieved an improvement in LVEF to above 35%. In multivariable analysis, individuals with a narrower native QRS at the time of initial pacemaker implantation were more likely to respond to BiV upgrade (additional 2% LVEF improvement per 10 ms decrease). Importantly, the vast majority of LVEF improvement occurred within the year following BiV upgrade, and no malignant ventricular arrhythmias were observed in the PICM cohort during that time. Based on these observations, the authors proposed upgrade to physiologic pacing, with the addition of a defibrillator at 1 year in the minority of individuals in whom the LVEF remains ≤35% (see Fig. 3). Such an approach is supported

by independent evidence suggesting a low risk of malignant ventricular arrhythmias in the PICM population.[30]

Conduction System Pacing

Recent studies suggest that HBP may also represent an effective treatment for established PICM. Shan and colleagues[31] reported a series of 18 patients referred for HBP. HBP was successful in 16 patients (89%). Of the 16 patients, 11 had a diagnosis of PICM. Of the PICM patients, the mean LVEF improved from 36% to 53% after HBP. Significant improvements in LV diastolic volume and mitral regurgitation were also observed. NYHA functional class decreased from 3.0 to 1.4 after HBP. No lead revisions were required within 2 years of follow-up.

Vijayaraman and colleagues[4] recently reported results of HBP among 60 individuals with PICM, defined as a decline in LVEF ≥10% resulting in an LVEF less than 50% among those exposed to greater than 20% RVP. HBP was successful in 57 patients (95%). The diagnosis of PICM was even more longstanding than the population reported by Khurshid and colleagues, with a mean time from diagnosis of PICM to upgrade over 6 years. After HBP, the paced QRS duration decreased from 177 ms to 114 ms. Among 55 PICM patients with echocardiographic follow-up, the mean LVEF increased from 34% preupgrade to 48% postupgrade. Improvement in LVEF ≥5% was observed in 52 patients (95%), and improvement ≥10% in 41 patients (75%). NYHA functional class decreased from 2.8 to 1.9 after HBP. Three patients (4%) required lead revision, all because of increased HBP capture thresholds.

AUTHORS' APPROACH

In the vast majority of patients with normal LVEF and high anticipated pacing burden, we initially deliver standard RVP, given simplicity of implantation and low rate of complications. Surveillance echocardiograms are performed every 1 to 2 years, and more frequently should heart failure symptoms develop. If the LVEF decreases ≥10% resulting in an LVEF less than 50%, guideline-directed medical therapy is initiated and a search for alternative etiologies, such as coronary artery disease or uncontrolled arrhythmias, is performed. If PICM is confirmed, upgrade to physiologic pacing is performed. Even if the LVEF is less than 35%, we typically upgrade to physiologic pacemaker only, as most PICM will substantially reverse following physiologic pacing. If the LVEF remains less than 35% after 1 year, consideration is given to further upgrade to a defibrillator (see Fig. 3).

FUTURE OUTLOOK

In recent years, PICM has become appropriately recognized as an important cause of heart failure-related morbidity among individuals undergoing RVP. Since the incidence of bradyarrhythmias appears to be increasing,[32] the public health burden attributable to PICM is likely to grow even further in the coming years. A better understanding of several aspects of PICM epidemiology and management will be critical to minimize the morbidity attributable to PICM.

First, improved methods of risk stratification for PICM development are needed to prioritize individuals for physiologic pacing. Although multiple studies have identified risk factors for PICM, no individual factor or set of factors (outside of preexisting systolic dysfunction[6]) has been shown to portend sufficiently high risk of PICM such that upfront physiologic pacing is considered first-line therapy. Small studies have implicated novel features, such as electrocardiographic scar score[16] or immediate post-implantation dyssynchrony,[19] as potential additional PICM risk factors. It is possible that the ability to predict the development of PICM can be improved further through the development of composite prediction models comprising a multitude of features, potentially including imaging or biomarker data. Prospective validation of such scores would be needed before they could be used to select individuals most likely to benefit from upfront physiologic pacing.

Second, future work is needed to assess the chronic effects of RV pacing beyond decrease in systolic function. After initiation of RVP, the incidence of HF hospitalization and worsening HF-related symptoms appears to increase out of proportion to the degree of LV systolic dysfunction observed.[10,21] Therefore, it is likely that RVP may result in HF symptoms through mechanisms other than induction of LV systolic dysfunction, such as adverse effects on diastolic function,[33] increased risk of incident AF,[34] and worsening of mitral regurgitation.[13,31] A more comprehensive understanding of the mechanisms underlying worsening HF after exposure to RVP may improve our ability to detect individuals earlier in the course of PICM development and facilitate prompt upgrade to physiologic pacing.

Third, continued development of improved methods for delivering physiologic pacing may lead to more opportunities to prevent exposure to RVP in the first place. Although evidence suggests that upfront physiologic pacing using methods such as BiV or HBP can avert the development of PICM, both techniques continue to be associated with greater complication rates and lower long-term durability as compared to traditional RVP.[5,20] Early evidence suggests that left bundle pacing is easier to perform and results in lower capture thresholds than HBP,[35–37] but further work is needed to assess the role of this technique in preventing and treating PICM. In the future, it is conceivable that certain methods of physiologic pacing may become sufficiently safe and effective as to become first-line therapy for most individuals requiring ventricular pacing.

SUMMARY

PICM is a common cause of LV systolic dysfunction, affecting 10% to 20% of individuals exposed to frequent RVP. Factors associated with increased PICM risk include male sex, older age, lower preimplantation LVEF, wider native QRS, wider paced QRS, higher electrocardiographic scar score, and post-implantation dyssynchrony. Physiologic pacing (eg, BiV or CSP) is an effective method to prevent PICM in at-risk individuals, as well as to reverse systolic dysfunction among individuals with established PICM. Future work is needed to improve the delivery of physiologic pacing, and to develop more accurate methods of prioritizing individuals at highest risk for RVP-related morbidity in whom physiologic pacing strategies may be preferred.

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KEY POINTS

- Right ventricular (RV) pacing-induced cardiomyopathy (PICM) is typically defined as left ventricular systolic dysfunction resulting from electrical and mechanical dyssynchrony caused by chronic RV pacing.
- RV PICM is common, occurring in 10% to 20% of individuals exposed to frequent RV pacing.
- Several risk factors for PICM have been identified, yet the ability to accurately predict which individuals will develop PICM remains insufficient.
- Physiologic pacing, including biventricular and conduction system pacing, prevents the development of PICM and can reverse left ventricular systolic dysfunction after PICM has occurred.

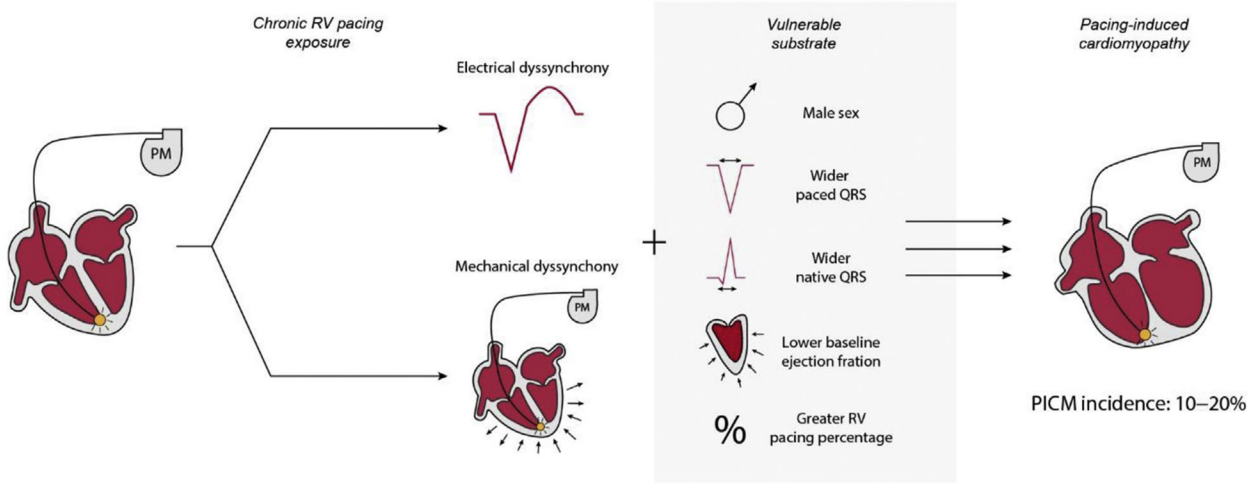

Fig. 1.

Pathophysiology of PICM. An overview of the pathophysiology of PICM is depicted. Chronic exposure to RVP results in electrical dyssynchrony (manifested as a wide paced QRS complex) and mechanical dyssynchrony, including regional differences in myocardial contraction. Particularly in the presence of certain risk factors, electrical and mechanical dyssynchrony can lead to adverse remodeling and development of systolic dysfunction, manifesting in PICM. The prevalence of PICM is 10% to 20% over long-term follow-up.

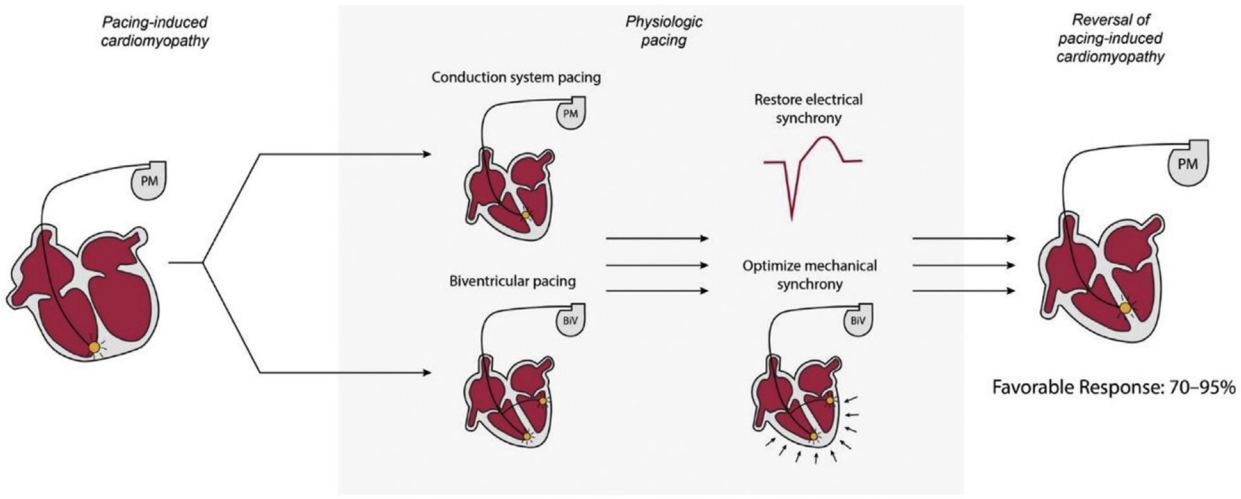

Fig. 2.

Treatment of PICM. An overview of the treatment of PICM is depicted. PICM can be treated effectively with upgrade to a physiologic pacing strategy, either biventricular or conduction system pacing. Physiologic pacing leads to improvement of electrical synchrony (manifesting as narrowing of the paced QRS) and more synchronous intraventricular and interventricular contraction. Physiologic pacing leads to a substantial improvement in LVEF in 70% to 95% of individuals with PICM.

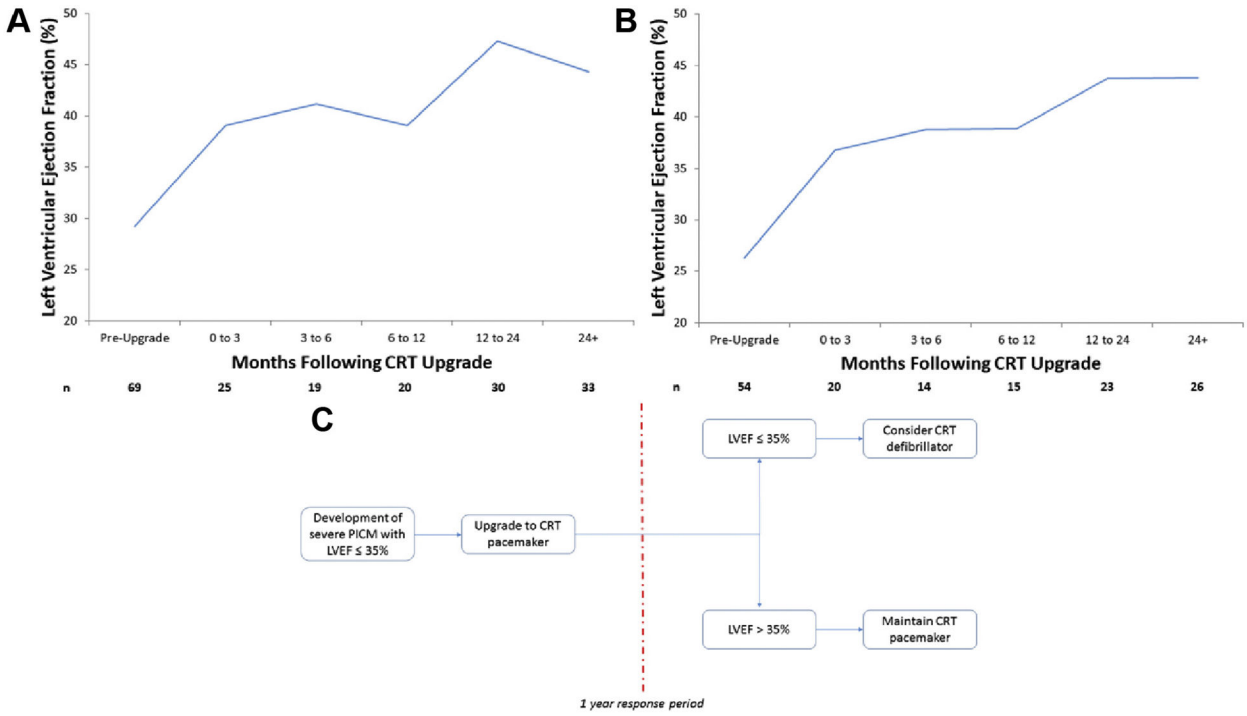

Fig. 3.

Improvement of pacing-induced cardiomyopathy following upgrade to physiologic pacing. Mean improvement in LVEF after cardiac resynchronization therapy (CRT) upgrade is illustrated within the first 3 months, 3 to 6 months, 6 to 12 months, 12 to 24 months, and more than 24 months among (*A*) the entire pacing-induced cardiomyopathy (PICM) cohort and (*B*) the severe PICM cohort (nadir LVEF ≤35%). The number of patients undergoing an echocardiogram during each time range is indicated below the x-axis. A proposed CRT implantation strategy is depicted (*C*) in which patients with severe PICM undergo initial CRT pacemaker with upgrade to defibrillator to be considered among those with LVEF ≤35% after 1 year. LVEF = left ventricular ejection fraction. Reprinted with permission from Khurshid S, Obeng-Gyimah E, Supple GE, Schaller RD, Lin D, Owens AT, Epstein AE, Dixit S, Marchlinski FE, Frankel DS. Reversal of Pacing-Induced Cardiomyopathy Following Cardiac Resynchronization Therapy. JACC Clin Eletrophysiol. 2018 Feb;4(2):168–177.

Table 1

Summary of retrospective observational studies describing PICM incidence and risk factors

Study	Setting	N	Follow-up (y)	PICM Definition	PICM Incidence	PICM Risk Factors
Khurshid et al. 2014[13]	Single-center	257	3.3	LVEF decrease ≥10% to <50% No alternative cause of cardiomyopathy	19.5%	Native QRS duration (HR 1.03 per 1 ms increase) Male sex (HR 2.15)
Kiehl et al. 2016[15]	Single-center	823	4.3	Postimplant LVEF <40% or CRT upgrade	12.3%	Preimplant LVEF (HR 1.05 per 1% decrease) RVP percentage (HR 1.01 per 1% increase) >20% RVP (HR 6.76)
Lee et al. 2016[16]	Single-center	234	15.6	LVEF decrease >5% with HF symptoms No alternative cause of cardiomyopathy	20.5%	Old age (HR 1.62) Paced QRS duration (HR 1.54) Higher myocardial scar score (HR 1.23) Higher RVP percentage (HR 1.31)
Cho et al. 2018	Single-center	618	7.2	LVEF decrease ≥10% to <50% or new regional wall motion abnormality not attributable to coronary heart disease	14.1%	LBBB (HR 8.62) Paced QRS duration ≥ 155 ms (HR 2.61) ≥86% RVP (HR 2.42)
Kim et al. 2018[17]	Multi-center (3 sites)	130	4.5	LVEF decrease >10% to <50%	16.1%	Paced QRS duration (HR 1.05 per 1 ms increase)
Bansal et al. 2019[19]	Single-center	363	1.2	LVEF decrease >10%	13.8%	>60% RVP (HR 4.26) Interventricular dyssynchrony (HR 3.15)
Kaye et al. 2019[38]	Single-center	118	3.5	1. LVEF ≤40% if baseline LVEF >50% or absolute reduction ≥5% 2. LVEF ≤40% if baseline LVEF >50% or absolute reduction ≥10% 3. LVEF ≤40%	1. 9.3% 2. 5.9% 3. 39.0%	RVP percentage (effect size not reported)

Table 2

Summary of studies comparing right ventricular versus physiologic pacing strategies among individuals with preserved preimplant left ventricular systolic function

Study	Setting	N	Mean Preimplant LVEF	Follow-up	Outcomes	Outcome Incidence	Risk Factors for Outcome
Non-randomized							
Abdelrahman et al., 2018[20]	Retrospective multi-center (2 sites)	433 (RVP) 304 (HBP)	54	2 y	Death, HF hospitalization, or upgrade to physiologic pacing	RVP: 32% HBP: 25%	Age (HR 1.02 per 1 y increase) Preimplant LVEF (HR 0.98 per 1% increase) Heart failure (HR 2.09) Chronic kidney disease (HR 1.75) HBP (vs RVP, HR 0.71) >20% RVP (effect size not reported)
Vijayaraman P et al., 2018[21]	Retrospective multi-center (2 sites)	98 (RVP) 75 (HBP)	55–57	5y	Death or HF hospitalization PICM (LVEF decline >10% to <50% w/ RVP >40%)	RVP: 53% (PICM incidence 22%) HBP: 32% (PICM incidence 2%)	RVP (vs HBP, HR 1.9) >40% RVP (effect size not reported)
Randomized							
PAVE, 2005[24]	Multicenter	81 (RVP) 103 (BiV)	45–47	6 mo	LVEF, QoL scores, 6-min walk test	RVP: 24% improvement in 6-min walk, 5-pt decrease in LVEF, no change in QoL BiV: 31% improvement in 6-min walk, no change in LVEF, no change in QoL	Baseline LVEF ≤45%
Occhetta E et al., 2006[39]	Single-center, crossover	16 (RVP) 16 (BiV)	52	6 mo	NYHA class, QoL scores, 6-min walk test	RVP: no change in NYHA class, QoL, or 6-min walk BiV: 0.58-pt improvement in NYHA class, 50% improvement in QoL score and 14% improvement in 6-min walk	None reported
AVAIL CLS/CRT, 2010[25]	Multicenter (22 sites)	20 (RVP) 88 (BiV)	56–57	6 mo	LVEF	RVP: No significant change in LVEF BiV: 3.2-pt increase in LVEF	None reported
Albertsen et al., 2011[22]	Single-center	50 (RVP) 50 (BiV)	59–60	3 y	LVEF, dyssynchrony index	RVP: 6-pt decrease in LVEF; increase in dyssynchrony index BiV: No change in LVEF or dyssynchrony	None reported
PACE, 2011[23]	Multicenter (4 sites)	88 (RVP) 89 (BiV)	62	2 y	LVEF, LVESV	RVP: 9.5-pt decrease in LVEF; 9.9 mL increase in LVESV BiV: No difference in LVEF or LVESV	None reported
PREVENT-HF, 2011[40]	Multicenter (14 sites)	58 (RVP) 50 (BiV)	55–57	1 y	LVEDV	No difference in LVEDV at 12 mo	None reported

Table 3

Summary of studies of pacing-induced cardiomyopathy treatment

Study	Design	N	Mean Pretreatment LVEF (%)	PICM Definition	Response	Factors Predicting Response
Biventricular pacing						
Nazeri et al. 2010[27]	Single-center retrospective	21	31.2	LVEF decrease to ≤35% No alternative cause of cardiomyopathy ≥25% RV pacing	Mean postupgrade LVEF: 37%	None found
Khurshid et al. 2018[28]	Single-center retrospective	69	29.3	LVEF decrease ≥10% to <50% No alternative cause of cardiomyopathy ≥20% RV pacing	Mean postupgrade LVEF: 45% Improvement in LVEF ≥5%: 86% Achievement of LVEF ≥35%: 72%	Native QRS duration (2-pt additional LVEF improvement per 10 ms decrease)
Conduction system pacing						
Shan et al. 2017*,[31]	Single-center retrospective	11	36.1	LVEF decrease ≥10% to <50% No alternative cause of cardiomyopathy ≥20% RV pacing	Mean postupgrade LVEF: 53%	Not reported
Vijayaraman et al. 2019[4]	Single-center retrospective	60	34.3	LVEF decrease ≥10% to <50% No alternative cause of cardiomyopathy >20% RV pacing	Mean postupgrade LVEF: 48% LVEF ≥5%: 95% Achievement of LVEF ≥35%: 75%	Not reported