Přehledový článek | Review article

Pacing induced cardiomyopathy and upgrade to cardiac resynchronization therapy

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SOUHRN

Upgrade na srdeční resynchronizační léčbu je zavedená metoda k léčbě pacientů s trvalým kardiostimulátorem nebo implantabilním kardioverterem-defibrilátorem, u nichž se rozvinou příznaky srdečního selhání a dysfunkce levé komory. Stimulací navozená kardiomyopatie představuje potenciálně reverzibilní příčinu dysfunkce levé komory, která může být plně zlepšena po zavedení biventrikulární stimulace nebo stimulace převodního systému srdečního.

ABSTRACT

Upgrade to cardiac resynchronization therapy is an established method to treat patients with a permanent pacemaker or implantable cardioverter-defibrillator who develop symptoms of heart failure and left ventricular dysfunction. Pacing induced cardiomyopathy represents a potentially reversible cause of left ventricular dysfunction that can fully recover after implantation of biventricular pacing or conduction system pacing.

Introduction

Cardiac resynchronization therapy (CRT) is a method of device treatment for patients with heart failure and wide QRS complexes. Patients with a permanent pacemaker (PM) or an implantable cardioverter-defibrillator (ICD) with a high percentage of right ventricular pacing (RVP) who develop signs of heart failure and have a left ventricular ejection fraction (LVEF) ≤35% despite adequate medical therapy are indicated for upgrade to biventricular pacing.[1] The goal of treatment is to improve heart failure symptoms and reduce mortality. Upgrade accounts for approximately a quarter of all CRT implantations. In the Czech Republic, 29% of all patients who underwent CRT were upgraded in the CRT Survey II study from October 2015 to December 2016.[2] Patients after the upgrade were excluded from first large randomized clinical trials with CRT, however, recently some clinical trials have demonstrated strong evidence for clinical benefit of upgrade procedures. The next research is focusing on pacing-induced cardiomyopathy, which is the most common cause leading to an upgrade to CRT.

Pacing induced cardiomyopathy

Definition and prevalence

Pacing induced cardiomyopathy (PICMP) is defined as left ventricular (LV) systolic dysfunction due to a high percen-

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tage of right ventricular (RV) pacing. Nevertheless, there is no clear definition of PICMP. Most clinical criteria are based on a decrease in LVEF below the cut-off value or the drop of LVEF from the value before PM or ICD implantation. The most used definition is the evidence of LVEF <50% and decrease in LVEF of at least 10% from the baseline before primo-implantation during RV pacing of at least 20%.[3,4] The prevalence of PICMP thus varies depending on the definition used and is reported from 6% to 25%, overall cumulative prevalence is 12%.[3,5] The time from primo-implantation until development of PICMP can vary significantly between patients, with the shortest time interval described being one month, while cases of PICMP developing more than 15 years after implantation have been reported.[6,7] For the diagnosis of PICMP, other causes of left ventricular systolic dysfunction must be excluded – ischemic heart disease, valvular disorders, arrhythmias, cardiomyopathies, and other structural heart diseases.

History of right ventricular pacing and left ventricular systolic dysfunction

Pacing is an effective treatment for patients with symptomatic sinus node (SN) disease. It also reduces symptoms, increases functional capacity, and reduces mortality in patients with atrioventricular (AV) block, and is also used to control heart rate in atrial fibrillation when pharmacological therapy fails. DDD pacing was preferred method for SN disease for a long time because of the maintenance of AV synchrony. However, since the 1990s, studies have begun to appear that RV pacing led to a higher risk of heart failure, atrial fibrillation, and dilation of heart chambers than in patients with atrial pacing.[8–10] The Mode Selection Trial (MOST) study focused on a group of patients with DDDR pacing and a group with VVIR pacing.[11] Subanalysis of the results showed that patients with a higher percentage of ventricular pacing, regardless of the pacing mode, had a higher risk of hospitalization for heart failure and a higher risk of developing atrial fibrillation.[12] Even patients with a DDDR pacemaker with preserved AV synchrony had a 2.6-fold higher risk of hospitalization for heart failure when RV pacing >40% compared to patients with a normal QRS complex. The risk of heart failure progression was also higher in patients with pre-existing left ventricular dysfunction. In the Dual Chamber and VVI ICD Trial (DAVID) study, the authors randomized patients with pre-existing left ventricular dysfunction indicated for ICD implantation.[13] The first group had the device programmed in the VVIR mode at 40/min, the second group had DDDR at 70/min. At the end of the follow-up, a higher number of deaths and hospitalizations for heart failure were demonstrated in the DDDR-70 group. RV pacing >40% had worse overall outcomes – quality of life in questionnaires increased with decreasing percentage of ventricular pacing, and it was also shown that every 10% of RV pacing increased the risk of hospitalization for heart failure. The Multicentre Automatic Defibrillator Implantation Trial II (MADIT II) demonstrated the benefit of ICD in primary prevention in patients with heart failure and ischemic cardiomyopathy compared to conventional drug therapy, but a secondary finding of the study was a twofold higher risk of newly diagnosed heart failure in patients with RV pacing.[14,15] Recently, several studies have been conducted with patients without left ventricular dysfunction and a high percentage of RV pacing. Kiehl et al. followed a group of patients with complete AV block and normal left ventricular systolic function, LVEF >50%. During the 4.3-year follow-up period, PICMP was observed in 12.3% of patients. The main risk factors for the development of PICMP were found to be RV pacing >20% and pre-implantation lower LVEF.

Pathophysiology – electrical and mechanical dyssynchrony

Abnormal electrical and mechanical activation, described as dyssynchrony, are the underlying mechanism for the

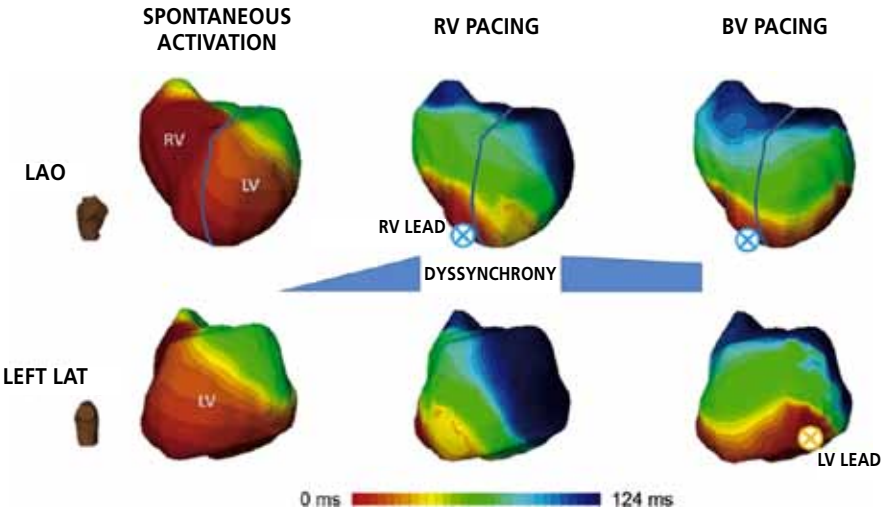

Fig. 1 – Electro-anatomical map of ventricular activation during (A) spontaneous propagation of the impulse (QRS 115 ms), (B) right ventricular pacing, (C) biventricular pacing. Adapted from 19.

development of PICMP. Ventricular dyssynchrony caused by RV pacing leads to chronic LV remodelling, including asymmetric hypertrophy and redistribution of cardiac mass, progression of mitral regurgitation, enlargement of the left atrium, and decreased LVEF.[16] These negative effects of RV pacing explain an increased risk of developing heart failure and atrial fibrillation. **Electrical dyssynchrony** caused by RV pacing is a heterogeneous electric propagation on ventricular myocardium similar to LBBB, where the Purkinje fibre system does not contribute significantly to the electrical activation of the ventricles, and electrical impulses are conducted exclusively by the working myocardium "myocyte to myocyte". The electrical activation of the ventricles leads to a wide QRS complex and is asynchronous, when the interventricular septum is activated first, from which the excitation subsequently spreads to the site of the latest activation, which is usually the base of posterior and lateral left ventricle wall,[17] see **Fig. 1**. Electrical dyssynchrony thus leads to **mechanical dyssynchrony**, which is caused by earlier contraction of the right ventricle – interventricular dyssynchrony, and by impaired contraction within the left ventricle – intraventricular dyssynchrony. RV pacing leads to early activation of fibres near the pacing site (interventricular septum or RV apex) which caused a pre-stretch of later activated LV segments (posterior and lateral left ventricle wall) and does not contribute to the ejection phase of cardiac cycle. Conversely, in the late activated lateral segments, pre-stretch occurs at the beginning of systole and is followed by increased systolic contraction and delayed relaxation.[18] However, part of the contraction later activated segments is used to stretch the already relaxed septal segments. This abnormal pattern of contraction of different LV segments leads to a redistribution of myocardial strain and subsequently less effective contraction.[17] Histopathologically, during long-term RV pacing, changes occur at the cellular level, including myofibrillar disarray, fibrosis, fatty tissue deposits, sclerosis, and mitochondrial changes, see **Fig. 2**, which then cause changes in cardiac metabolism and remodelling, and it leads to the hemodynamical and functional deterioration, see **Table 1**.

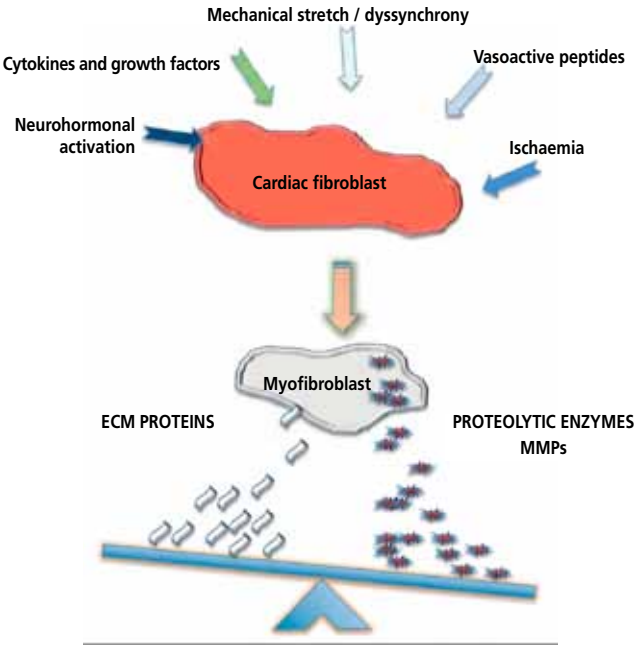

Fig. 2 – Biomechanical factors causing extracellular matrix production and remodelling. Adapted from 20.

Table 1 – Acute and long-term effects of right ventricular pacing	
Metabolism	Changes in local perfusion
	Changes in oxygen consumption
Remodelling	Asymmetric hypertrophy
	Histopathological changes – increased fibrosis, myofibrillar disarray
	Ventricular dilation and systolic dysfunction
	Functional mitral regurgitation
Hemodynamic	Reduced cardiac output
	Increased left ventricular filling pressures
Mechanical function	Changes in myocardial strain
	Interventricular dyssynchrony
	Intraventricular dyssynchrony

Hemodynamic effects of right ventricular pacing

Although LV remodelling due to RV pacing is considered as chronic process that requires months to years to manifest as cardiomyopathy, some acute hemodynamic effects have been observed early in few minutes after RV pacing.[21] During invasive hemodynamic testing, RV pacing versus atrial pacing was found to result in higher wedge pressures, higher pulmonary artery and right atrial pressures, and during exercise testing to lower cardiac output.[22] In addition to the deterioration of left ventricular systolic function, diastolic function is also negatively affected during RV pacing – asynchronous relaxation during RV pacing causes prolonged isovolumic relaxation time and worse ventricular filling.[41] Mechanical dyssynchrony may manifest itself on transthoracic echocardiography as specific dynamics of left ventricular contraction, which can be described in common practice as "septal flash" or "apical rocking".[26] Stankovic et al. in a subanalysis of the PREDICT-CRT study monitored the occurrence of septal flash and apical rocking which was present in 66% of patients with LBBB and in only 23% of patients undergoing an upgrade to CRT.[27] Patients in whom mechanical dyssynchrony was noted had a better volumetric response and a longer overall survival.

The effect of right ventricular pacing on mitral regurgitation, tricuspid regurgitation and atrial fibrillation

RV pacing can lead to the progression of tricuspid and mitral regurgitation. Results suggest that each of these is influenced by different pathophysiological mechanisms. The mechanism of mitral regurgitation can be explained by left ventricular dysfunction during RV pacing, which increases the size and volume of the left ventricle, leading to functional mitral insufficiency, which causes further volume overload and left ventricular dysfunction.[28] Furthermore, mechanical dyssynchrony of the papillary

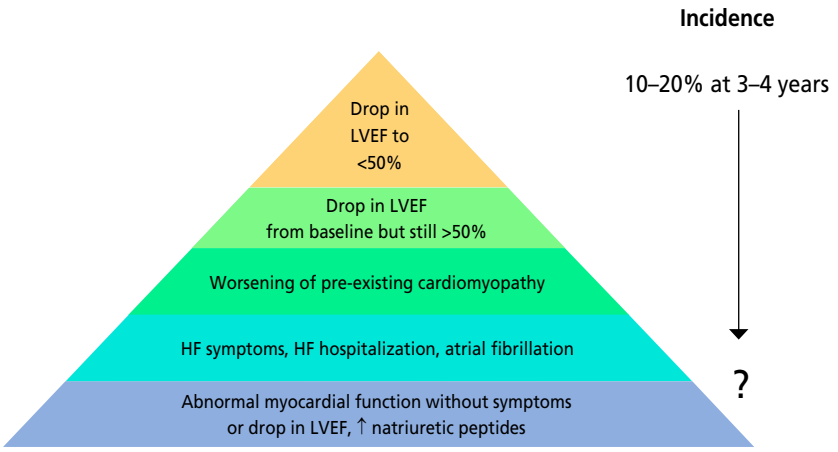

Fig. 3 – The spectrum of potential manifestation of pacing induced cardiomyopathy. Adapted from 21.

muscles affects the mitral leaflets and causes impaired coaptation.[29] The principle of tricuspid regurgitation during RV pacing is not entirely clear, the severity of tricuspid regurgitation is not influenced by the position of the RV lead or the percentage of RV pacing.[28,30] The most likely cause of tricuspid regurgitation seems to be the mechanical effect of the introduced RV lead, which passes through the tricuspid annulus and thus limits movement of the tricuspid valve leaflets. RV pacing is also associated with higher incidence of the new onset of atrial fibrillation, which could be explained by increased left atrial filling pressure, impaired left atrial contraction, and left atrial dilation.[31] Nielsen et al. demonstrated a higher incidence of atrial fibrillation in patients with sick sinus syndrome with dual-chamber pacing compared with the same group with atrial pacing during a mean follow-up of 2.9 years (23.3% versus 7.4%).[32] Similarly, in a subanalysis of the MOST study, the incidence of atrial fibrillation correlated with increasing percentage of RV pacing.[12]

The effect of right ventricular lead position

The apex of the right ventricle has often been chosen as the site of RV pacing because it is easily accessible and allows stable and long-term placement of the lead.[33] Most data on the adverse effects of RV pacing are based on apical pacing. One predictor of the development of left ventricular systolic dysfunction is the duration of the paced QRS complex.[34] Therefore, it is assumed that non-apical pacing of the right ventricle, closer to the cardiac conduction system, will lead to faster electrical activation and less mechanical dyssynchrony. Patients with right ventricular outflow tract pacing and septal pacing were included in the studies, in which there was no difference in acute and chronic pacing thresholds and no difference in lead stability compared to apical RV pacing.[35] Metanalysis have not consistently demonstrated a benefit of non-apical RV pacing on functional class, symptoms, exercise tolerance, and mortality.[36] Janoušek et al. published a multicenter study in which over 100 children with structurally normal hearts and permanent cardiac pacing for complete congenital AV block were included.[37] A total of 7 pacing sites were identified (4 in the right ventricle and 3 in the left ventricle). At long-term follow-up, patients with RV pacing from any site had lower LVEF and greater inter- and intraventricular dyssynchrony compared to LV pacing. These results lead to the conclusion that pacing of the right ventricle from any site will lead to adverse effects and left ventricular dysfunction during long-term follow-up.

Risk factors for pacing induced cardiomyopathy

It is not yet fully understood why PICMP develops only in a subset of patients with a high percentage of RV pacing and why some patients tolerate RV pacing without developing signs of heart failure. The main risk factors reported in most clinical studies include pre-existing left ventricular dysfunction and a longer native QRS complex.[3,21,38] Other risk factors include male gender, ischemic heart disease, atrial fibrillation, and chronic renal failure.[3,21] Risk factors for the development of PICMP that can be assessed after implantation of a permanent pacemaker are the percentage of RV pacing and the wider paced QRS complex.[3,21,38] The threshold value of RV pacing leading to the development of PICMP was reported in the first studies to be around 40%,[12,13] in subsequent studies the threshold value of RV pacing was even around 20%.[7,38] Identification of risk factors is important in preventing the development of PICMP and should be considered before implantation of a permanent pacemaker. However, susceptibility to PICMP is highly individual and the risk factors listed do not have clearly defined thresholds. Therefore, regular monitoring of all patients after implantation of a permanent pacemaker is important.

Upgrade to cardiac resynchronization therapy with biventricular pacing

Clinical effect of upgrade to biventricular pacing

Biventricular (BiV) pacing has been the most widely used strategy for patients with left ventricular dysfunction induced by RV pacing. Patients who have been upgraded to biventricular pacing have been excluded from the first large, randomized trials of CRT. The original data were based on smaller observational studies with short follow-up periods. Recent meta-analysis of patients with retro-

spective evaluation showed a significant increase in LVEF after upgrade to BiV pacing average of 8% and a significant decrease in left ventricular end-systolic volume.[39] In a meta-analysis evaluating only patients with PICMP, a more significant increase in LVEF after upgrade to BiV pacing was reported, ranging from 11% to 19%.[3] The better result may have been influenced by the absence of patients with significant structural heart disorder among patients with PICMP. Similar results were obtained in another meta-analysis evaluating the effect of upgrading to BiV pacing between patients with PICMP and patients with heart failure and a high percentage of RV pacing, where a more significant increase in LVEF was found in the PICMP group (13% vs. 10%), but the difference between the groups was not statistically significant.[40] Severe mitral regurgitation induced by RV pacing often improves after the CRT implantation, the effect on mitral regurgitation begins immediately after the start of therapy and persists during long-term follow-up.[41] BiV pacing is also associated with a significant decrease in BNP compared with RV pacing.[42] The Budapest CRT upgrade study was the first to demonstrate the clinical benefit of the upgrade in a prospectively monitored population, where patients with heart failure, a wide paced QRS complex, and a high percentage of right ventricular pacing were randomized 3 : 2 to upgrade to CRT-D versus ICD. Patients who received the upgrade had a better composite primary outcome of all-cause mortality, hospitalization for heart failure, and reverse left ventricular remodelling at 12 months of follow-up.[43] This effect was also evident in the group of patients with atrial fibrillation.[44]

Comparison of CRT upgrade versus de novo CRT

According to subanalysis of the CRT Survey II focusing on the characteristics of patients undergoing CRT implantation in Europe, upgrade accounted 28% of all implantations in the period 10/2015–12/2016.[45] A lot of studies have often compared patients with CRT upgrade versus patients with *de novo* CRT, however, these are not heterogeneous groups of patients, and therefore the results of those studies have often been contradictory.[46] In general, patients with CRT upgrade versus de novo CRT are older, more male, have more comorbidities such as ischemic heart disease, valvular defects, and more often have atrial fibrillation, chronic renal failure, and anaemia.[45,47] Patients after upgrade are also less likely to have full heart failure medication.[45] The largest review on this topic demonstrated the same benefit of upgrade vs *de novo* on overall mortality and risk of heart failure, as well as there was no clinical difference in improvement in LVEF

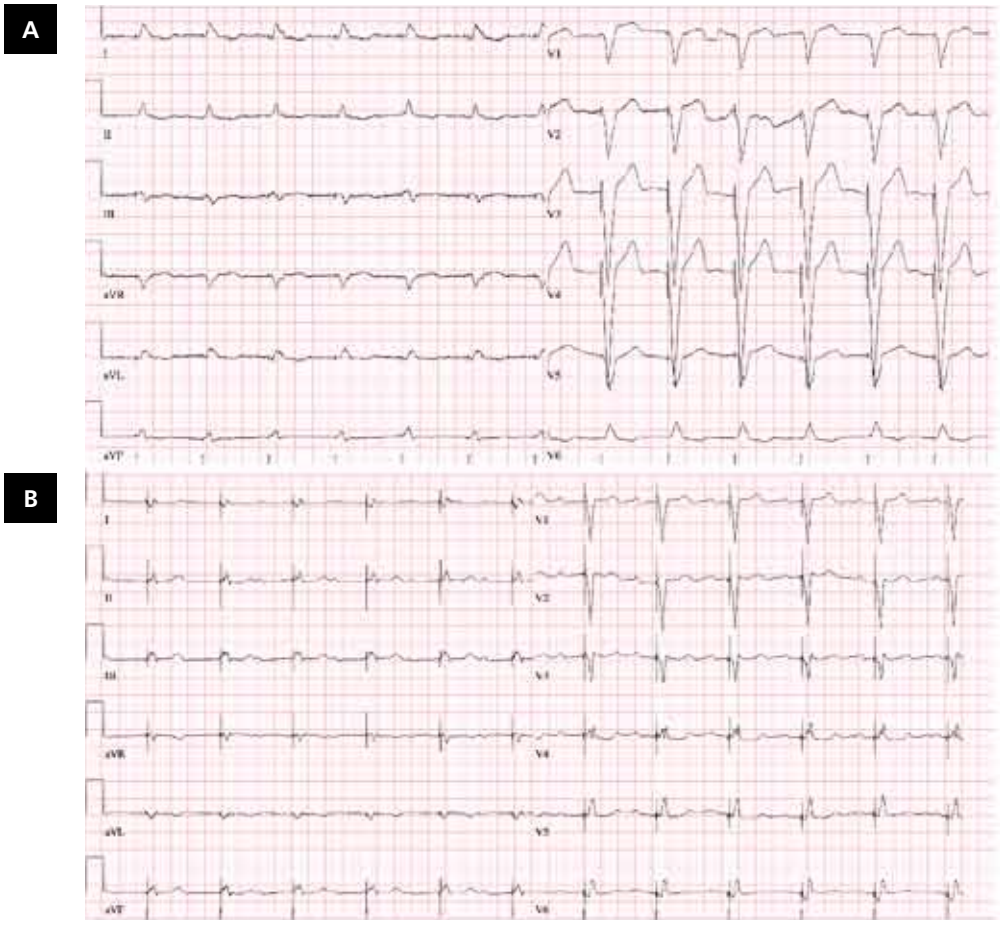

Fig. 4 – Comparison of ECG recordings before and after upgrade to CRT using biventricular pacing. Panel A shows the ECG during RV pacing, with a QRS duration of 184 ms. Panel B shows the ECG during BiV pacing, with a QRS duration of 146 ms.

between the two groups and patients showed similar improvement in functional parameters assessed using the NYHA classification and similar narrowing of the QRS complex.[48]

Comparison of upgrade to CRT-P versus upgrade to CRT-D

Most patients indicated for upgrade to CRT have reduced LVEF below 35% and therefore fulfil the indication class for ICD implantation in primary prevention.[49] The most common indication for upgrade to CRT is PICMP, which is potentially reversible, and with BiV pacing LVEF may improve above the threshold of 35%, which gets the patient outside of the indication for ICD. There is no study that would clearly recommend adding an ICD in primary prevention at the time of upgrade to CRT. Leyva et al. demonstrated the benefit of upgrading to CRT-D in patients without prior ventricular arrhythmia in reducing mortality and hospitalization for heart failure.[50] On the other hand, in a strictly selected group of patients with PICMP, Barra et al. did not demonstrate a difference in the incidence of ventricular arrhythmias between patients with CRT-P and CRT-D patients.[51] Another study demonstrated a reduction in ventricular arrhythmias after upgrade to CRT.[52] Therefore, the adding of ICD to CRT should be made carefully, considering the complications caused by this treatment: inadequate therapy, greater risk of infections and potential restoration of left ventricular function in PICMP patients.

Conduction system pacing and upgrade to cardiac resynchronization therapy

Conduction system pacing is a new emerging modality that includes His bundle pacing (HBP), left bundle branch area pacing (LBBAP). Compared with RV pacing, HBP reduces death, heart failure, and the need for upgrade to BiV pacing in patients requiring permanent pacing, with pacing rates exceeding 20%.[53] HBP is also associated with lower interventricular and intraventricular dyssynchrony, which prevents the development of systolic dysfunction and progression of mitral regurgitation due to asynchronous contraction.[54] HBP results in narrowing of the QRS complex and can be used in the context of CRT when pacing occurs distal to the site of block or delay.[55] In patients with PICMP, HBP compared with conventional RV pacing, leads to narrowing of the QRS complex and leads to reverse remodelling of the left ventricle and improvement of LVEF.56 The success rate of HBP implantation ranges from 88% to 95%, and the number of responders with an improvement of LVEF > 10% was over 75%. Due to the difficulty of lead implantation for HBP and the instability of pacing parameters during follow-up, the way has been opened to LBBAP,[57,58] which provides excellent long-term results with the high implantation success rate of over 90% and the stability of pacing parameters. In patients indicated for CRT, LBBAP led to narrowing of the QRS complex and improvements in echocardiographic and clinical parameters.[59] LBBAP has been shown to significantly narrow the QRS complex, improve LVEF, decrease BNP, and improve NYHA functional class in patients with PICMP and has demonstrated stable pacing parameters over 12 months.[60–62] In other studies, LBBAP has shown greater echocardiographic improvement after upgrade than biventricular pacing, but this effect did not affect clinical outcomes such as mortality or hospitalization for heart failure.[63] Furthermore, HBP or LBBAP can be used in patients in whom a LV lead cannot be implanted, for example for anatomical reasons.

Prevention of pacing induced cardiomyopathy

Percentage of RV pacing is one of the main predictors of the development of PICMP.[64] Therefore individual pacemaker or ICD manufacturers have developed algorithms to program their devices to minimize RV pacing.[65–68] All these algorithms significantly reduced the amount of RV pacing, but often due to the effort to preserve the AV conduction itself, AV synchrony was impaired. These patients often had AV intervals longer than 350 ms and in some cases these algorithms were proarrhythmic. In a published meta-analysis of algorithms for minimizing RV pacing, these algorithms did not reduce the incidence of atrial fibrillation, all-cause hospitalizations, or overall mortality.[69] RV pacing minimalization algorithms have been shown to be effective, but they did not provide the desired clinical benefit for patients.[70]

Another strategy to prevent heart failure due to RV pacing is to implant a CRT device in patients with risk factors for developing PICMP. The HOBIPACE study suggested that patients with left ventricular systolic dysfunction and a predicted high percentage of RV pacing benefit from CRT versus conventional RV pacing.[71] The BLOCK-HF study, which followed patients indicated for permanent pacing with third-degree AV block, pre-existing heart failure with an EF ≤50% showed that BiV pacing had lower overall mortality, fewer heart failure initiations, and smaller left ventricular end-systolic volume than RV pacing.[72] Furthermore, the CRT group had better NYHA functional class and better quality of life. The BioPace study, which enrolled patients indicated for pacing for complete AV block or a PR interval >230 ms with normal LVEF, did not demonstrate a benefit of BiV pacing on mortality and hospitalization for heart failure compared with standard RV pacing.[73] Therefore, BiV pacing is used in patients with expected higher percentage of RV pacing and preexisting LV dysfunction.

Conduction system pacing (CSP) is another method used to prevent PICMP. Due to the significant reduction in the QRS complex, CSP results in smaller electrical and structural changes than RV pacing. In patients with preserved ejection fraction, HBP leads to a significant reduction in hospitalization for heart failure and a trend towards a reduction in overall mortality compared with patients with standard RV pacing.[53] Similarly, LBBAP reduces hospitalization for heart failure and overall mortality in patients with preserved left ventricular function and an indication for permanent pacing.[55] These results, which favor HBP and LBBAP over RV pacing, were achieved with at least 20% pacing.

Another clinical indication for permanent pacemaker implantation is permanent atrial fibrillation with rapid ventricular response, which is indicated for AV junction ablation and permanent pacemaker implantation, the so-called ablate and pace strategy. In the APAF study, including patients with systolic dysfunction undergoing AV

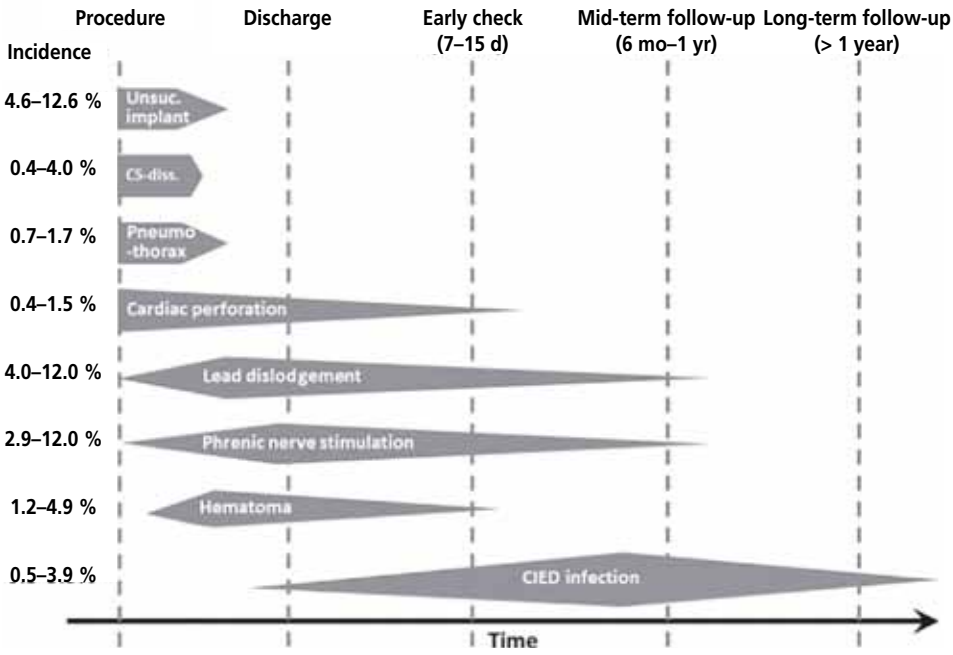

Fig. 5 – Graph showing periprocedural comorbidities and association with de novo CRT implantation or CRT upgrade. Adapted from 87.

junction ablation, the CRT implantation versus RV pacing had a 63% lower risk of hospitalization for heart failure or worsening of heart failure. A recently published study comparing CSP versus RV pacing confirmed that both HBP and LBBAP had lower mortality or fewer hospitalizations for heart failure.[74] A small observational study further confirmed greater success in lead placement and fewer subsequent lead-related complications in the LBBAP versus HBP group in patients undergoing AV junction ablation for atrial fibrillation.[75]

Responders of upgrade to CRT

Pacing induced cardiomyopathy is a potentially reversible cause of left ventricular systolic dysfunction, which can improve after resolution of electromechanical dyssynchrony. QRS complex narrowing from baseline, higher initial RV pacing and sinus rhythm were found as independent predictors of improvement in LVEF after CRT upgrade.[47,76,77] Significantly reduced LVEF <20% at the time of implantation, advanced age, and renal failure were found to be predictors of higher mortality after upgrade.[78,79] The number of responders to CRT varies in individual studies depending on the definition. Khurshid et al. included patients with PICMP and defined a positive response as an improvement in LVEF of ≥5%,[4] and prove 86% of responders in group of patients with PICMP, in addition, 72% of patients who had LVEF ≤35% at baseline had an improvement exceed LVEF >35% and fell outside the indication for primary preventive ICD implantation. The greatest improvement occurred within the first 3 months after the upgrade. A study including patients with all indications for upgrade had a numerically slightly lower rate of responders (76%), but the treatment effect was still significant (80). Patients with CRT upgrade for PICMP have greater QRS narrowing, LVEF improvement and lower hospitalizations for heart failure compared to patients with CRT upgrade for another reason. This result is probably due to the absence of structural damage, especially LV scar and ischemic heart disease, in the PICMP group.[81,82]

Complications after upgrade to cardiac resynchronization therapy

Patients undergoing upgrade to CRT are in general older and have more comorbidities compared to *de novo* patients, indicating greater frailty and are thus potentially at higher risk of developing acute and late complications, which may disadvantage potential responders to therapy. In the large database, major complications such as the need for lead revision, pneumothorax, or coronary sinus perforation were more frequently recorded after upgrading compared to de novo patients.[83] In a subanalysis of the REPLACE registry that focused on upgraded patients, the most common complication was lead dislocation or malfunction in 7.9% of patients, followed by hematoma in 1.5% of cases, and infection in 0.8% during 6-month follow-up.[84] A subanalysis of the recent CRT Survey II study reported similar periprocedural complications in both groups (5.1% upgrade and 5.7% *de novo* CRT). However, patients with *de novo* CRT had longer fluoroscopic time and a higher number of pneumothoraxes. Both complications may be related to the need for multiple lead implantation. On the other hand, patients with upgrade had a higher incidence of bleeding complications, which may be due to the higher number of patients with atrial fibrillation and the need for long-term oral anticoagulant therapy.[85] The most feared complication after CRT upgrade is infection of pacing system, which

has a significant impact on patient mortality and morbidity. This generally prolongs the length of hospital stay and brings a financial burden on the healthcare system. The only effective approach is pacing system explanation. Upgrade to CRT appears to be an independent risk factor for infection of the pacing system. This is consistent with the results of the Danish registry, which showed a higher incidence of late infectious complications in patients after the upgrade.[86]

Conclusion and future perspectives

Upgrading to CRT is an established and effective method of treating patients with preexisting device, left ventricular dysfunction and wide QRS complex. Due to the introduction of CSP, the number of patients with PICMP will decrease in the future, but still there will be a high proportion of patients with an implanted device and progression of their cardiomyopathy. These patients are the most difficult to resynchronize with, where a combination of both CSP and BiV pacing methods such as LOT-CRT (left bundle branch area pacing optimized cardiac resynchronization therapy) or HOT-CRT (His-Purkinje conduction system pacing optimized cardiac resynchronization therapy) can be used.

Conflict of interest
None.

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None.

Ethical statement
The work was written in accordance with the Declaration of Helsinki.

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