Multimodality imaging to guide cardiac interventional procedures

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The effects of right ventricular apical pacing on ventricular function and dyssynchrony: implications for therapy

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ABSTRACT

Cardiac pacing is the only effective treatment for patients with sick sinus syndrome and atrioventricular conduction disorders. In cardiac pacing, the endocardial pacing lead is typically positioned at the right ventricular (RV) apex. At the same time, there is increasing indirect evidence, derived from large pacing mode selection trials and observational studies, that conventional RV apical pacing may have detrimental effects on cardiac structure and left ventricular (LV) function, which is associated with development of heart failure. These detrimental effects may be related to the abnormal electrical and mechanical activation pattern of the ventricles (or ventricular dyssynchrony) caused by RV apical pacing. Still, it remains uncertain if the deterioration of LV function as noted in a proportion of patients receiving RV apical pacing is directly related to acutely induced LV dyssynchrony. The upgrade from RV pacing to cardiac resynchronization therapy (CRT) may partially reverse the deleterious effects of RV pacing. It has even been suggested that selected patients with a conventional pacemaker indication should receive CRT to avoid the deleterious effects. This review will provide a contemporary overview of the available evidence on the detrimental effects of RV apical pacing. Furthermore, the available alternatives for patients with a standard pacemaker indication will be discussed. In particular, the role of CRT and alternative RV pacing sites in these patients will be reviewed.

INTRODUCTION

For decades, cardiac pacing has been an effective treatment in the management of patients with brady- and tachy-arrhythmias (1). New indications for pacing such as drug-refractory heart failure have been introduced (2). However, sick sinus syndrome and atrioventricular (AV) conduction disorders still remain the most important indications for cardiac pacing (3). The endocardial pacing lead is typically positioned at the right ventricular (RV) apex. In general RV apical pacing is very well tolerated and effective. However, it has been suggested that RV apical pacing may have detrimental effects on cardiac structure and left ventricular (LV) function (4). This may be related to the abnormal electrical and mechanical activation pattern of the ventricles (or ventricular dyssynchrony) caused by RV apical pacing. In recent years, the association between RV apical pacing and mechanical dyssynchrony, and their effects on cardiac function have been studied by electrophysiologists, cardiac imaging experts and physiologists. Although the approach to this complex problem may differ among them, the overlapping perspectives have provided important pathophysiologic information.

In this manuscript, the potential detrimental effects of RV apical pacing, and the underlying pathophysiology will be reviewed. In particular, the role of ventricular dyssynchrony will be discussed. Furthermore, the therapeutic options in patients with a pacemaker indication will be reviewed; including the role of CRT and alternative RV pacing sites.

THE EFFECTS OF RV APICAL PACING

Cardiac pacing is the only effective treatment for symptomatic sinus node disease, and can improve symptomatic chronotropic incompetence (1). In addition, numerous studies have demonstrated symptomatic and functional improvement by cardiac pacing in patients with AV block (5). Furthermore, conventional dual-chamber pacing can improve cardiac function in selected patients with LV dysfunction (6). Finally, cardiac pacing is an effective treatment in controlling symptoms of chronic, drug-refractory atrial fibrillation (7). In the last decades, there have been significant increases in the incidence of pacemaker implantations (8).

A number of large randomized clinical trials have provided important information for selection of the optimal pacing mode (9-11). But more importantly, these trials have suggested an association between RV apical pacing and cardiac morbidity and mortality. In addition, a number of clinical (12,13) and pre-clinical (14,15) studies have investigated the exact effects of RV apical pacing on cardiac function. Furthermore, it has been suggested that pacing-induced mechanical dyssynchrony is associated with a deterioration of LV function and clinical status in patients with permanent RV apical pacing (16).

Evidence from pacing mode trials

Several large, randomized clinical trials on pacing mode selection have suggested an association between a high percentage of RV apical pacing and a worse clinical outcome (17). A substudy of the MOde Selection Trial (MOST) demonstrated a strong association between RV pacing and the risk of heart failure hospitalization and atrial fibrillation in both 'physiologic pacing' (DDDR: n=707) and ventricular pacing (VVIR: n=632) (10). It was noted that >40% of ventricular pacing in the DDDR group was associated with an increased risk of heart failure hospitalization (hazard ratio 2.60; 95% CI 1.05 - 6.47; p<0.05) and that >80% of ventricular pacing in the VVIR group was associated with an increased risk of heart failure hospitalization (hazard ratio 2.50; 95% CI 1.44 - 4.36; p<0.05). In the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial patients with a standard indication for a defibrillator implantation, but without an indication for anti-bradycardia pacing, were randomized between 'physiologic pacing' (DDDR mode, lower rate of 70 bpm) or ventricular back-up pacing (VVIR mode, lower rate of 40 bpm) (11). After a median follow-up of 8.4 months, the primary outcome measure (freedom from death and absence of hospitalization for new or worsened heart failure) was lower in the VVIR-40 group than in the DDDR-70 group (relative hazard 1.61; 95% CI 1.06 – 2.44; p=0.03). Interrogation of the defibrillator device revealed a significantly higher percentage of ventricular paced beats in the DDDR-70 group at 3 months follow-up. Importantly, a trend towards a worse survival at 12 months was noted in patients with a high percentage of pacing at 3 months follow-up (11). It should be noted however that not only RV apical pacing itself may have resulted in this worse outcome, but also the higher mean heart rate, and the changes in AV coupling in the DDDR group may have detrimental effects.

These trials suggest that there is no clinical benefit of 'physiologic' DDDR pacing over VVIR. This may be explained by the higher percentage of ventricular pacing in the DDDR groups, as a result of the short programmed AV interval. Thus, the beneficial effect of maintaining AV synchrony by 'physiologic' DDDR pacing may be reduced by the deleterious effects of RV apical pacing itself.

Unfortunately, the exact amount of RV apical pacing that negatively affects cardiac function remains unclear from these trials. A certain amount of ventricular pacing may actually be beneficial since it maintains physiologic AV conduction (6). At the same time, the negative effects of RV apical pacing may be more pronounced in certain patient populations. In particular, patients with underlying conduction disease (18) and patients with ischemic heart disease (19) may be at risk. Furthermore, it has been suggested that in patients who require pacing for a longer period of time, and patients with depressed LV function at baseline are more susceptible for the deleterious effects of RV apical pacing (4). More studies are therefore needed to fully understand the beneficial and deleterious effects of RV apical pacing, and to better identify the patients who are at risk for the detrimental effects of RV pacing. The available studies in which the underlying pathophysiology is studied will be reviewed in the following paragraphs.

Pathophysiology of detrimental effects

In general, the negative effects of RV apical pacing have been attributed to the abnormal electrical and mechanical activation pattern of the ventricles (14). During RV apical pacing, the conduction of the electrical wave front propagates through the myocardium, rather than through the His-Purkinje conduction system. As a result, the electrical wave front propagates more slowly and induces heterogeneity in electrical activation of the myocardium, comparable to left bundle branch block. This is characterized by a single breakthrough at the interventricular septum, and the latest activation at the inferoposterior base of the LV (20-22).

Similar to the changes in electrical activation of the ventricles, the mechanical activation pattern of the LV is changed during RV apical pacing. Importantly, not only the onset of mechanical contraction is changed, but also the pattern of mechanical contraction (14). In several animal studies, it has been demonstrated that the early-activated regions near the pacing site exhibit rapid early systolic shortening, resulting in pre-stretch of the late activated regions (15,23). As a result, these regions exhibit an increase in (delayed) systolic shortening, imposing systolic stretch to the early activated regions exhibiting pre-mature relaxation. This abnormal contraction pattern of the various regions of the LV may result in a redistribution of myocardial strain and work and subsequent less effective contraction (15).

Both the abnormal electrical and mechanical activation pattern of the ventricles can result in changes in cardiac metabolism and perfusion, remodeling, hemodynamics and mechanical function. An overview of the potential harmful effects of RV apical pacing on cardiac function is provided in Table 1. The effects on cardiac metabolism and perfusion have been demonstrated in both clinical and pre-clinical studies (24). Even in the absence of coronary artery disease, myocardial perfusion defects may be present in up to 65% of the patients after long-term RV apical pacing, and are mainly located near the pacing site (12,25).

Table 1. Acute and long-term effects of RV apical pacing

Changes in electrical activation and mechanical activation
Metabolism / perfusion
Changes in regional perfusion
Changes in oxygen demand
Remodeling
Asymmetric hypertrophy
Histopathological changes
Ventricular dilation
Functional mitral regurgitation
Hemodynamics
Decreased cardiac output
Increased LV filling pressures
Mechanical function
Changes in myocardial strain
Interventricular mechanical dyssynchrony
Intraventricular mechanical dyssynchrony

Long-term RV pacing may also result in structural changes, and LV remodeling. Endomyocardial biopsies in 14 patients with congenital complete AV block revealed cellular and intracellular alterations, including mitochondrial variations and degenerative fibrosis, after long-term permanent RV pacing (26). In addition, changes in LV wall thickness (27), and LV remodeling (28) may occur after long-term RV pacing. In addition, functional mitral regurgitation and left atrial remodeling may occur during RV apical pacing (29,30).

Moreover, hemodynamic properties and global mechanical function may be affected by the abnormal electrical and mechanical activation of the LV. Pacing at the RV apex may result in a decrease in cardiac output and may alter LV filling properties (13). Changes in myocardial strain and timing of regional strain may occur during RV apical pacing. Using magnetic resonance imaging in an animal model of cardiac pacing, Prinzen et al. noted a significant decrease in strain in the regions close to the pacing site, whereas an increase in myocardial strain was noted in remote regions (15). Importantly, timing of peak regional strain is also changed during pacing. This is often referred to as 'mechanical dyssynchrony' (31).

Mechanical dyssynchrony during RV apical pacing

Right ventricular apical pacing can induce both interventricular dyssynchrony (between the RV and the LV), as well as intraventricular dyssynchrony (within the LV) (16). It has been demonstrated that the presence of ventricular dyssynchrony is associated with an increased risk of cardiac morbidity (32) and mortality (33) in heart failure patients. In addition, it has been suggested that the presence of mechanical dyssynchrony after long-term RV apical pacing is associated with reduced LV systolic function and deterioration in functional capacity (16). However, there are only a few studies that have demonstrated a direct relation between (pacing-induced) ventricular dyssynchrony and clinical heart failure. At the same time, it has been shown that restoration of normal conduction and 'cardiac synchrony' by cardiac resynchronization therapy (CRT) results in normalization of LV systolic function (34,35). This suggests that an abnormal activation pattern (left bundle branch block during RV apical pacing) or ventricular dyssynchrony may be directly related to a deterioration of LV function. Therefore, the assessment of ventricular dyssynchrony may provide important information in patients with permanent RV apical pacing.

Several echocardiographic techniques are available for the assessment of cardiac mechanical dyssynchrony. These include conventional Doppler techniques, tissue Doppler imaging, strain analysis and novel three-dimensional echocardiography. The majority of the techniques have been used to quantify inter- and intraventricular dyssynchrony in heart failure patients referred for CRT (36). Likewise, these techniques can be used to detect the presence of ventricular mechanical dyssynchrony during acute and long-term RV apical pacing.

For the quantification of interventricular dyssynchrony, conventional Doppler techniques are typically used (Figure 1). For both ventricles, the electromechanical delay is calculated as the time from onset of the QRS complex to the onset of pulmonary systolic flow (RV electromechanical delay) or aortic systolic flow (LV electromechanical delay). The time difference

between the RV and LV electromechanical delay represents interventricular dyssynchrony (37). From previous studies, it has become clear that RV apical pacing can induce significant interventricular dyssynchrony (16,38).

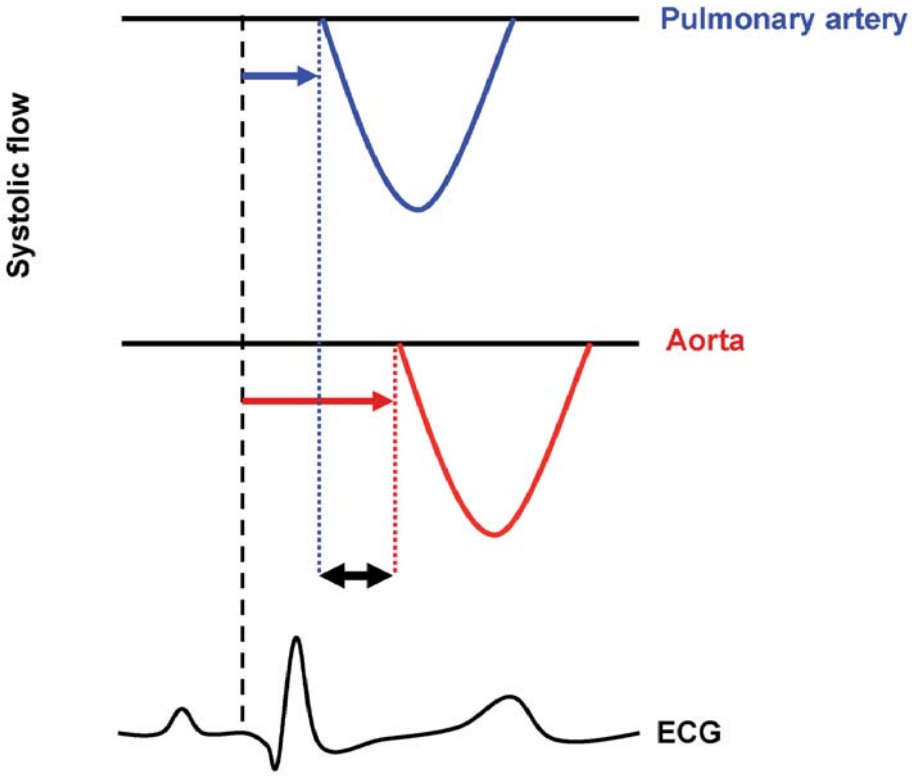

Figure 1. Schematic representation of interventricular dyssynchrony during RV apical pacing. For assessment of interventricular dyssynchrony, the ECG and systolic flow through the pulmonary artery and aorta (assessed with Doppler echocardiography) are typically used. Both the RV and LV electromechanical delay are measured from the onset of QRS (dashed black line). The RV electromechanical delay is the time from the onset of QRS to the onset of pulmonary systolic flow (blue arrow). The LV electromechanical delay is the time from the onset of QRS to the onset of aortic systolic flow (red arrow). Subsequently, the interventricular dyssynchrony can be calculated as the difference between the RV and the LV electromechanical delays (black arrow).

For the assessment of intraventricular (or LV) dyssynchrony, several echocardiographic techniques are available, including tissue Doppler imaging, two-dimensional speckle-tracking strain analysis, and real-time three-dimensional echocardiography (39). In general, LV dyssynchrony is represented by the delay in mechanical activation between the interventricular septum and the posterior or lateral wall (Figure 2). Already in 1977, Gomes et al. demonstrated the effect of RV apical pacing on the mechanical delay between the septum and the posterior wall (40). During the acute onset of cardiac pacing in 12 patients, it was noted that there was an early rapid pre-ejection posterior motion of the interventricular septum. In addition, the posterior wall of the LV exhibited a delayed contraction, resulting in a significant delay between

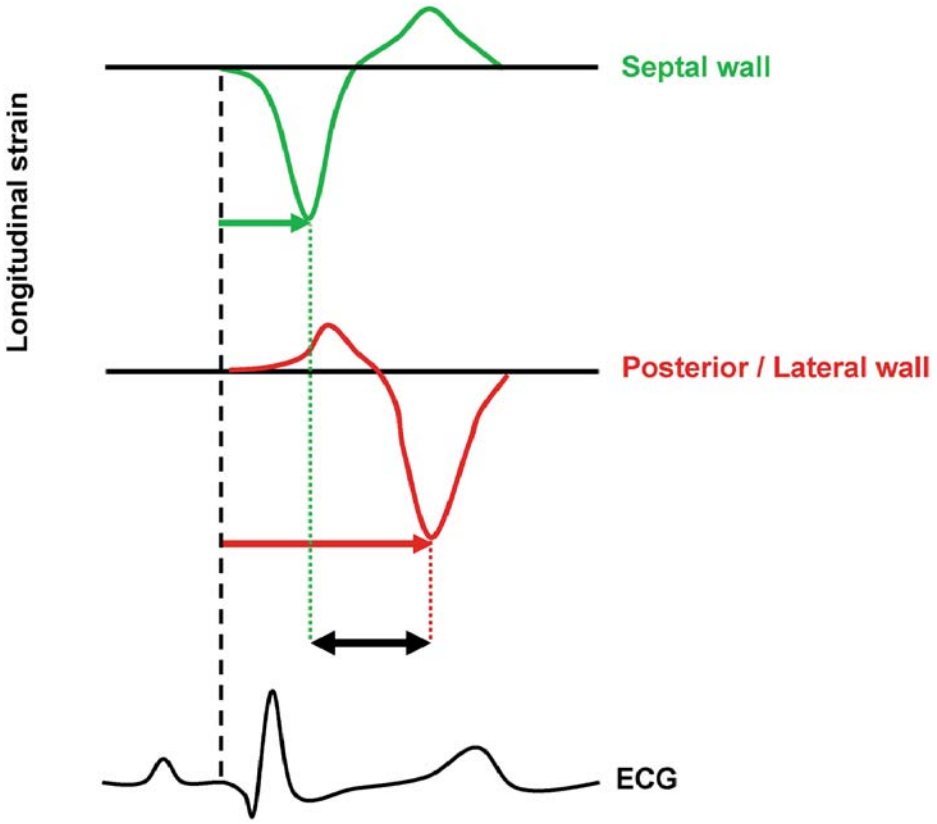

Figure 2. Schematic representation of intraventricular dyssynchrony during RV apical pacing. Intraventricular dyssynchrony is represented by the delay in mechanical activation between different segments within the LV. In this example, longitudinal strain curves of the septum and the posterior or lateral wall are demonstrated. The time from onset of QRS to peak systolic strain for the septum (green arrow) and the posterior or lateral wall (red arrow) is indicated. The difference in time-to-peak strain for the various segments is the delay in mechanical activation, or LV intraventricular dyssynchrony (indicated by the black arrow).

the activation of the septum (61 ± 5 ms) and the posterior wall (116 ± 18 ms) (40). More recently, these findings have been confirmed with dedicated echocardiographic techniques (41-44). From these studies, it has become apparent that RV apical pacing can induce significant intraventricular mechanical dyssynchrony, which has been related to reduced LV function.

CLINICAL IMPLICATIONS

From the large pacing-mode selection trials and observational studies, it has become apparent that conventional RV apical pacing is associated with an increased risk of adverse events (e.g. development of LV dilatation and heart failure). However, in daily clinical practice not all patients who receive RV apical pacing will experience these adverse events (19). In a retrospective study including 286 patients with permanent pacing after AV junction ablation, it was noted that LV

ejection fraction (LVEF) decreased significantly in only 9% of the patients during follow-up (45). In another retrospective study of 304 patients with pacemaker implantation for high degree AV block, the clinical outcome after at least one year of RV apical pacing was studied (46). A total of 79 patients (26%) developed new-onset heart failure after a mean of 6.5 ± 5.7 years of pacing. It appears that some patients are more susceptible to the detrimental effects of RV apical pacing than others, possibly related to mechanical ventricular dyssynchrony.

Ventricular dyssynchrony may be present in up to 50% of the patients after long-term RV apical pacing (38,41,47). Importantly, it has been demonstrated that the presence of mechanical dyssynchrony after long-term RV apical pacing is associated with LV dilatation, and a deterioration of LV systolic function and functional capacity (16). However, it remains unclear if LV dyssynchrony is an acute phenomenon, which may then induce deterioration of LV function at longer follow-up and subsequent development of heart failure.

A recent study in patients with structurally normal hearts, undergoing electrophysiologic testing revealed that significant LV dyssynchrony may be induced acutely in up to 36% of individuals (Figure 3) (48). A concomitant impairment in LV systolic function was observed, reflected by a reduction in LVEF (from 56 ± 8% to 48 ± 9%, p=0.001) and LV longitudinal strain (from -18.3

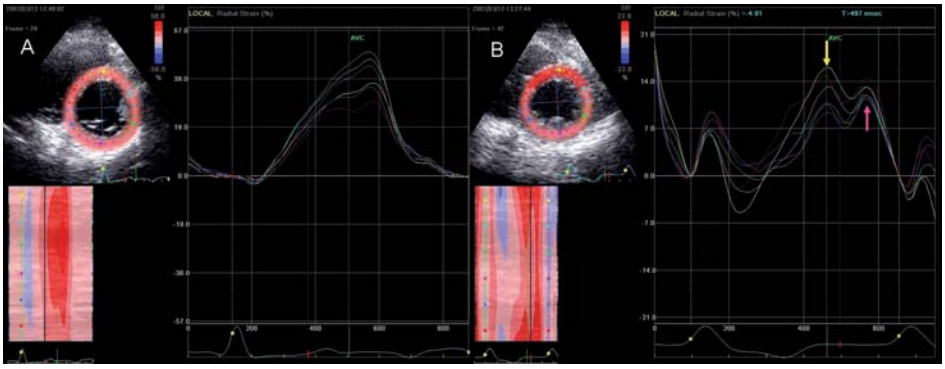

Figure 3. Right ventricular apical pacing acutely induces LV dyssynchrony. Echocardiographic analysis of LV dyssynchrony during intrinsic rhythm (panel A) and immediately after onset of RV apical pacing (panel B). Speckle-tracking strain analysis enables the evaluation of the timing of systolic strain. The color-coded curves represent the time-strain curves of 6 mid-ventricular segments of the LV. During intrinsic rhythm (panel A), a synchronous contraction of all LV segments is present. In contrast, during RV apical pacing, significant LV dyssynchrony is present: there is a significant delay (130 ms) between the time-to-peak strain of the antero-septum (yellow arrow) and the posterolateral segment (purple arrow).

± 3.5% to -11.8 ± 3.6%, p<0.001) (48). In 153 patients undergoing pacemaker implantation for standard indications, Pastore et al. assessed LV dyssynchrony using tissue Doppler echocardiography at baseline and after at least 24 hours (mean 1.7 ± 0.3 days) of continuous RV apical pacing (49). A total of 101 patients (66%) exhibited significant LV dyssynchrony. Interestingly, the amount of pacing-induced LV dyssynchrony was related to the presence of LV dysfunction at baseline (Figure 4). It has been demonstrated previously that the conduction abnormalities induced by RV apical pacing may be enhanced by accompanying conduction disease at

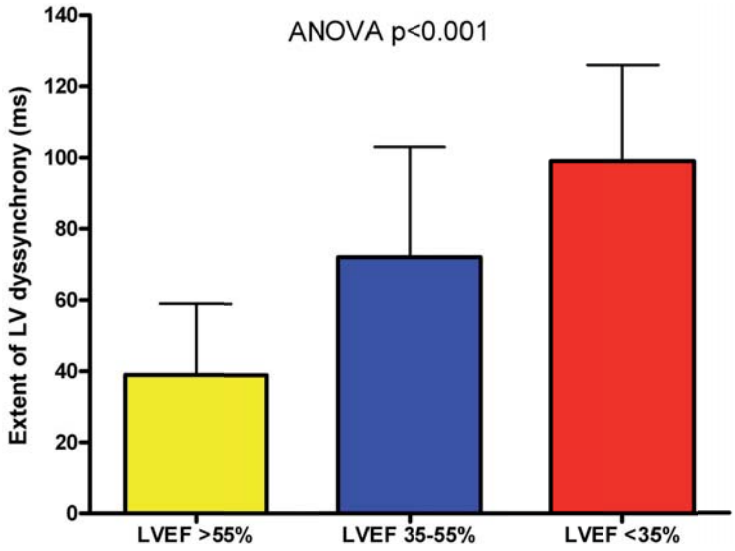

Figure 4. Left ventricular dyssynchrony during RV pacing according to baseline LVEF. In 153 patients undergoing pacemaker implantation, LV dyssynchrony was assessed during RV apical pacing. Patients were classified according to baseline LVEF: normal (LVEF >55%), moderately depressed (LVEF 35-55%), or severely depressed (LVEF <35%). The extent of LV dyssynchrony was strongly related with baseline LVEF. In patients with normal LVEF, 45% of the patients developed LV dyssynchrony (40 out of 89), whereas 39 of the 42 patients (93%) with moderately depressed LVEF developed LV dyssynchrony. In patients with severely depressed LVEF (n=22), all patients exhibited LV dyssynchrony during RV apical pacing (49). LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular

baseline (18). Unfortunately, the abovementioned studies only assessed LV dyssynchrony and LV function in the acute phase. Although it has been demonstrated that the negative effects of the abnormal LV activation sequence may sustain even after termination of RV apical pacing (50), it still remains unclear whether the acutely induced LV dyssynchrony is the basis for the development of LV dysfunction and heart failure after long-term RV apical pacing. In addition, it is still unclear why some patients acutely develop ventricular dyssynchrony, and others do not. This may be due to subtle differences in the location of the pacing lead within the RV apex, and thus the proximity of the Purkinje system. At the same time, some echocardiographic techniques used to assess ventricular dyssynchrony may not be sensitive enough to detect small changes in electromechanical activation (51). Therefore, more studies are needed on acutely induced ventricular dyssynchrony, and its long-term effects.

When future studies show that the acutely induced LV dyssynchrony is associated with deterioration of LV function during follow-up, ventricular dyssynchrony assessment during pacemaker implantation may have important clinical implications. If LV dyssynchrony is present immediately after onset of RV apical pacing, a CRT device may be preferred over conventional RV apical pacing. In contrast, if no LV dyssynchrony is present, conventional RV apical pacing alone may be accepted. Monitoring of LV dyssynchrony and LV function is then warranted.

At the same time, with the increasing evidence of the detrimental effects of RV apical pacing, it has been suggested that the percentage of ventricular pacing should be kept to a

minimum (4). However, in a large proportion of patients, RV pacing is inevitable (1). For these patients, a number of alternative strategies to minimize the induction of mechanical dyssynchrony and other deleterious effects have been proposed. These therapeutic options, including the upgrade from RV pacing to CRT, 'de novo' CRT, and alternative pacing sites, will be discussed in the following paragraphs.

THERAPEUTIC OPTIONS IN PATIENTS WITH RV APICAL PACING

The detrimental effects of RV apical pacing related to cardiac metabolism, remodeling, hemodynamics and mechanical function may be prevented or partially reversed by CRT or alternative RV pacing sites. In the subset of patients who experience detrimental effects of RV apical pacing, CRT may restore the synchronous contraction of the LV and subsequently improve LV function. Alternatively, a number of strategies, including alternative RV pacing sites, have been suggested to avoid the deleterious effects of RV apical pacing. All these therapeutic options will be discussed in the following paragraphs.

Upgrade of RV apical pacing to CRT

Several studies have demonstrated beneficial effects of the upgrade from RV apical pacing to CRT (Table 2). Reverse remodeling of the LV (defined as a reduction in LV end-diastolic or end-systolic volume) after upgrade from RV apical to CRT has been demonstrated in several studies (47,52,53). In addition, the severity of mitral regurgitation may improve after upgrade to CRT (54-57).

Furthermore, LV hemodynamics and mechanical function may improve after upgrade to CRT. In an invasive hemodynamic study in 18 patients with congenital complete AV block who had received RV apical pacing for a mean of 81 ± 10 months, CRT resulted in a significant increase in LV dP/dt_{max} (58). In parallel, a significant decrease in LV end-diastolic pressure and isovolumic pressure half-time was observed (58). Improvements in global LVEF have been demonstrated in various studies, including four prospective studies with more than 110 patients with previous AV junction ablation and pacemaker implantation (52,54,59,60) (Table 2).

Finally, it has been demonstrated that the upgrade from RV apical pacing to CRT may result in a significant improvement in exercise capacity and NYHA functional class (57) (Figure 5). Unfortunately, at present it remains uncertain if the upgrade to CRT in previously paced patients results in an improved prognosis.

Effect on ventricular dyssynchrony In parallel with the improvements in LV function, LV dyssynchrony may improve after upgrade from RV apical to CRT. An acute reduction in the LV pre-ejection interval after onset of CRT in previously paced patients has been demonstrated in several studies (61,62). Importantly, this effect is maintained during mid- and long-term follow-up (47,53,55). In 32 patients receiving upgrade to CRT after a minimum of one year RV apical

Table 2. Studies on mid- and long-term effects of upgrade from RV apical pacing to CRT

			RV pacing		CRT	Outcome after upgrade: RV pacing vs. CRT			
Study (reference)	**Number of patients**	**Inclusion criteria**	**Indication**	**Duration**	**Follow-up duration**	**QRS duration (ms)**	**LVEF (%)**	**NYHA class**	**Other outcome parameters**
Randomized, cross over studies									
Leclercq et al. (57)	44	NYHA III/IV LVEF <35% Ventricular dyssynchrony	Conventional indications	49 ± 34 mo	6 mo	200 ± 20 vs. 154 ± 26 *	30 ± 11 vs. 29 ± 11	2.5 ± 0.7 vs. 2.1 ± 0.4 *	Improvement in 6MWT, QOL Reduction of LV dyssynchrony
Höijer et al. (90)	10	NYHA III/IV No LBBB in pre-pacing ECG	AVB SND Bradycardia	Median 68 mo	6 mo	N/A	N/A	N/A	Improvement in 6MWT, pro-BNP, QOL No changes in echocardiographic parameters
Observational studies									
Leclercq et al. (59)	20	NYHA III/IV LVEF ≤35% Paced QRS ≥200 ms	Conventional indications	N/A	15 ± 10 mo	222 ± 18 vs. 163 ± 30 *	20 ± 6 vs. 24 ± 13 *	3.8 ± 0.4 vs. 2.6 ± 0.5 *	N/A
Baker et al. (60)	60	NYHA III/IV	SND AVB AVJ ablation	N/A	7.7 mo	206 ± 36 vs. 170 ± 34 *	23 ± 8 vs. 29 ± 11 *	3.4 ± 0.5 vs. 2.4 ± 0.7 *	Improvement in QOL
Leon et al. (52)	20	NYHA III/IV LVEF ≤35%	AVJ ablation	26 ± 12 mo	17 ± 5 mo	213 ± 40 vs. 172 ± 31 *	22 ± 7 vs. 31 ± 12 *	3.4 ± 0.5 vs. 2.4 ± 0.6 *	Improvement in QOL
Valls-Bertault et al. (54)	16	NYHA III/IV LVEF ≤35%	AVJ ablation	20 ± 19 mo	6 mo	192 ± 28 vs. 177 ± 23	24 ± 9 vs. 28 ± 12	3.4 ± 0.5 vs. 2.6 ± 1.1 *	No changes in 6MWT and peak VO2
Eldadah et al. (55)	12	NYHA III	AVB Bradycardia	> 1 yr	4 – 6 wks	N/A	31 ± 5 vs. 36 ± 5 *	3.0 ± 0.0 vs. 2.0 ± 0.7 *	Reduction of LV dyssynchrony Improvement in LV systolic strain
Laurenzi et al. (91)	38	NYHA III/IV LVEF <35% QRS >150 ms	N/A	4.7 ± 2.0 yrs	6 mo	179 ± 19 vs. 124 ± 20 *	27 ± 6 vs. 38 ± 10 *	3.1 ± 0.4 vs. 2.0 ± 0.6 *	Reduction of LV dyssynchrony

* Indicates a significant difference after upgrade ($p<0.05$ RV pacing vs. CRT). AVB = atrioventricular block; AVJ ablation = atrioventricular junction ablation; CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; mo = months; QOL = quality of life; RV = right ventricular; SND = sinus node dysfunction; wk = week; yr = year; 6MWT = 6 minute walking-test.

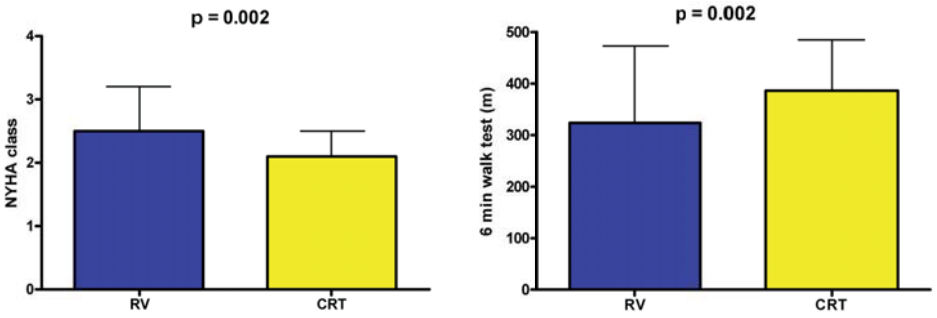

Figure 5. Changes in NYHA functional class and 6 minute walking-test after upgrade from RV pacing to CRT. In 44 patients with conventional pacemaker indications, an upgrade to CRT was performed after a mean of 49 ± 34 months of RV apical pacing. After 6 months of CRT, NYHA class improved from 2.5 ± 0.7 to 2.1 ± 0.4 (left panel), and the distance walked during the 6 minute walking-test increased from 324 ± 20 m to 386 ± 99 m (right panel) (57). CRT = cardiac resynchronization therapy; NYHA = New York Heart Association; RV = right ventricular pacing.

pacing, tissue Doppler imaging was used to assess LV dyssynchrony. After a mean of 144 ± 17 days, a significant decrease in the mean septal-to-lateral delay was noted from 101 ± 12 ms to 10 ± 9 ms ($p<0.001$) (53). Likewise, with the use of novel speckle-tracking echocardiography it has been demonstrated that the difference in time-to-peak strain of various LV segments (as a measure of LV dyssynchrony) decreases significantly after upgrade to CRT (47).

RV apical pacing versus CRT

With the promising results of upgrading patients from RV apical pacing to CRT, it has been suggested that patients with moderate to severe LV dysfunction and a standard pacemaker indication may actually benefit from CRT instead of RV apical pacing alone. A number of observational studies and randomized trials have performed a head-to-head comparison between the two pacing modes.

The effects of the two pacing modes on LV remodeling have been studied in the Homburg Biventricular Pacing Evaluation (HOBIPACE) trial (63). In this trial, 30 patients with standard indications for permanent pacing and a LVEF ≤40%, were randomized between RV pacing and CRT. After 3 months of pacing, cross-over to the other pacing modality was performed. The LV end-systolic volume was 177.3 ± 68.7 ml at baseline, and decreased modestly with RV pacing (160.2 ± 73.4 ml, $p<0.05$). When compared with RV pacing, CRT significantly reduced LV end-systolic volume by 17% (133.1 ± 66.5 ml, $p<0.001$) (63).

In addition to LV remodeling, improvements in LV hemodynamics (64,65) and LV mechanical function (66) during CRT have been demonstrated. In the Post AV Nodal Ablation Evaluation (PAVE) trial, 184 patients were randomized after AV junction ablation in two parallel arms (conventional RV pacing or CRT) (66). Mean LVEF at follow-up was significantly lower in the 81 patients who underwent RV pacing as compared with the 103 patients with CRT (41 ± 13% vs. 46 ± 13%, $p<0.05$) (66). However, it should be noted that other trials, including the Optimal Pacing SITE (OPSITE) trial (67), demonstrated only modest improvement in LVEF during CRT compared to RV pacing.

A number of randomized trials have compared conventional RV apical pacing and CRT (Table 3). Although some trials have demonstrated clear long-term benefit of CRT over RV pacing with regard to peak VO2 or the distance walked during the 6 minute walking-test (63,66), others have demonstrated only modest (67,68) or no benefit at all (69). The ongoing Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BioPace) trial will demonstrate if CRT actually provides benefit in morbidity and mortality over conventional RV apical pacing (70).

Table 3. Randomized clinical trials comparing RV apical pacing versus CRT

Trial (reference)	Number of patients	Design	Inclusion criteria	Primary end-point	Secondary end-point	Comment
MUSTIC (68)	43	Cross-over	Chronic heart failure LV systolic dysfunction Persistent AF Ventricular pacing QRS >200 ms 6MWT <450 m	6MWT	Peak VO2 QOL Heart failure hospitalization Mortality Patient pacing preference	CRT modestly superior over RV pacing for 6MWT and peak VO2 No difference in QOL
OPSITE (67)	56	Cross-over	AVN ablation and PM implantation CRT	QOL 6MWT	Subgroup analysis of: QOL 6MWT	CRT modestly superior over RV pacing for QOL and 6MWT
PAVE (66)	184	Parallel arms	AVN ablation and PM implantation	6MWT	QOL LVEF	CRT superior over RV pacing for 6MWT and LVEF No differences in QOL
HOBIPACE (63)	30	Cross-over	LV systolic dysfunction Permanent ventricular pacing	LVESV LVEF peak VO2	NYHA class QOL NT-proBNP Exercise capacity LV dyssynchrony	CRT superior over RV pacing for LVESV, LVEF, peak VO2 CRT superior over RV pacing for secondary end-points
Albertsen et al. (69)	50	Parallel arms	High-grade AV block	LVEF	LV dyssynchrony LV diastolic function LA volumes LV dimensions NT-proBNP 6MWT	No difference in LVEF No differences in secondary end-points

AF = atrial fibrillation; AV = atrioventricular; AVN = atrioventricular node; CRT = cardiac resynchronization therapy; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; PM = pacemaker; QOL = quality of life; RV = right ventricular; 6MWT = 6 minute walking-test.

Effect on ventricular dyssynchrony For mechanical dyssynchrony, only a few studies have systematically compared RV apical pacing and CRT. In 6 heart failure patients referred for CRT, Matsushita et al. assessed dyssynchrony during RV apical pacing and during CRT (71). During CRT, a decrease in both LV intraventricular dyssynchrony (RV pacing 322 ± 101 ms vs. CRT 209 ± 88 ms, $p<0.05$) and interventricular dyssynchrony (RV pacing 37.2 ± 44.7 ms vs. CRT 16.2 ± 47.4 ms, $p<0.05$) was noted (71). In a randomized study comparing DDDR pacing and CRT in 50 patients with high degree AV block, Albertsen et al. assessed ventricular dyssynchrony using tissue Doppler imaging (69). After 12 months follow-up, the number of LV segments displaying delayed longitudinal contraction (representing LV dyssynchrony) was significantly lower in the patients with CRT, as compared with the patients with DDDR pacing (69). These studies suggest that CRT may be superior over RV apical pacing with regard to the induction of LV dyssynchrony. Together with the promising results on LV remodeling and LV function, it may well be that CRT is a good therapeutic option in patients with moderate to severe LV dysfunction and a conventional indication for cardiac pacing. However, it should be noted that although CRT reduces the amount of ventricular dyssynchrony, normal electromechanical activation is not completely restored (72,73). In addition, it remains uncertain if there is a significant improvement in long-term outcome with CRT, as compared with conventional RV apical pacing. Therefore, more studies are needed to fully appreciate the role of CRT in these patients (1).

Pacing strategies and alternative pacing sites

Alternatives for RV apical pacing may be important in patients who have a depressed LV function at baseline or patients who are expected to be paced frequently (complete AV block) or for a longer period of time (young patients, congenital AV block). Various pacing strategies have been suggested to minimize the amount of RV apical pacing. In addition, strategies to minimize de-synchronization of ventricular contraction using alternative pacing sites have been proposed.

Atrial-based pacing Atrial-based pacing may be preferred over RV apical pacing in selected patient groups, since it prevents cardiac de-synchronization by maintaining normal ventricular electrical activation. Nielsen et al. randomized 177 patients with sinus node disease between AAIR pacing or DDDR pacing with a short AV delay or DDDR pacing with a fixed long AV delay (74). During a mean follow-up of 2.9 ± 1.1 years, left atrial and LV diameters increased and LV fractional shortening decreased in the DDDR groups, whereas no changes occurred in the AAIR group. In addition, atrial fibrillation was less common in the AAIR group as compared to the two DDDR groups (7.4% vs. 23.3% and 17.5%, respectively; $p=0.03$)(74). However, other large randomized trials have not been able to consistently demonstrate an improved outcome of atrial-based pacing. In a recent meta-analysis from 5 randomized clinical trials comparing atrial-based and ventricular pacing, no significant reduction in mortality with atrial-based pacing could be demonstrated (hazard ration 0.95; 95% CI 0.87 – 1.03; $p=0.19$). In addition, no

differences were found in the composite end-point of stroke, cardiovascular death, and heart failure hospitalization between the different pacing modes (Figure 6). However, a significant reduction in atrial fibrillation was noted with atrial-based pacing (hazard ratio 0.80; 95% CI 0.72 – 0.89; p<0.001) (75).

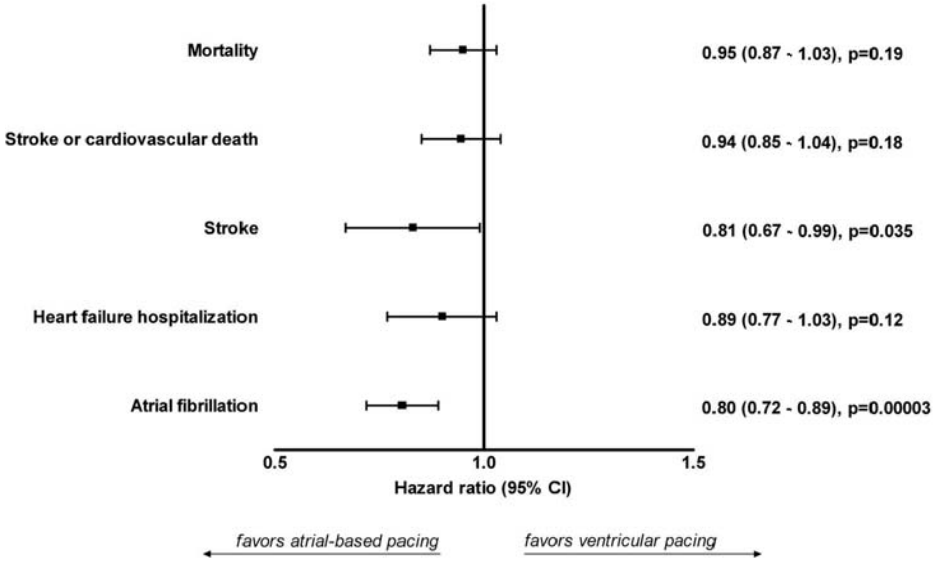

Figure 6. Meta-analysis on atrial-based pacing versus ventricular pacing. A meta-analysis of 5 randomized clinical trials including more than 7000 patients compared atrial-based pacing with ventricular based pacing. This figure demonstrates the effect of the pacing modes on the different outcome parameters (mortality, stroke or cardiovascular death, stroke, heart failure hospitalization, atrial fibrillation), expressed as the hazard ratio and 95% confidence interval (CI). A significant reduction in the incidence of stroke and atrial fibrillation was observed, in favor of atrial-based pacing. The remaining outcome parameters did not show a significant difference between the two pacing modes (75).

Atrial-based pacing to prevent cardiac de-synchronization may only be feasible in selected patients. There is still concern about atrial-based pacing in patients with sinus node disease, because of the development of AV block in these patients (76). In the abovementioned trial, the incidence of progression to symptomatic AV block was 1.9% per year (74). Therefore, atrial-based pacing for the maintenance of ventricular synchrony is only recommended in patients with sinus node disease without AV conduction abnormalities (1).

Minimal ventricular pacing algorithms In addition, specific pacing algorithms have been introduced to minimize unnecessary RV pacing. These algorithms promote normal AV conduction and target maintenance of intrinsic ventricular conduction (77,78). Thereby, the algorithms avoid the induction of LV dyssynchrony. In the Inhibition of unnecessary RV pacing with AVSH in ICDs Study (INTRINSIC RV), the effects of the use of an AV search hysteresis algorithm was studied (77). A total of 988 patients with an indication for an Implantable Cardioverter Defibrillator were randomized between VVI-40 back-up pacing or DDDR pacing with the AV search hysteresis

algorithm. In the DDDR group, 32 patients (6.4%) met the composite primary end-point of all-cause mortality and heart failure hospitalization, as compared with 46 patients (9.5%) in the VVI group ($p<0.001$). It was concluded that the use of the AV search hysteresis algorithm was associated with similar clinical outcomes compared with VVIR backup pacing (77).

Similar, in the Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACe) trial, 1065 patients with sinus node disease and intact AV conduction were randomized between conventional dual-chamber pacing and dual-chamber minimal ventricular pacing (78). With the use of the minimal RV pacing algorithm, the percentage of paced ventricular beats was significantly reduced, as compared with conventional dual-chamber ventricular pacing (9.1 vs. 99.0%, $p<0.001$). After a mean of 1.7 ± 1.0 years, the development of persistent atrial fibrillation was significantly reduced with minimal ventricular pacing (7.9% in minimal RV pacing vs. 12.7% in conventional dual-chamber pacing, $p=0.004$). Although these results suggest that this reduction is directly related to the decrease in RV apical pacing, a better AV coupling may have contributed as well. Unfortunately, no significant difference in mortality or heart failure hospitalizations between the two groups was observed (78). These studies suggest a favorable effect of minimizing ventricular pacing algorithms. However, more studies are needed to fully appreciate the exact clinical benefits in daily practice (1).

Alternative RV pacing sites Pacing at the RV outflow tract, septal pacing and direct His bundle pacing have been suggested as alternatives to the RV apex when pacing is inevitable (79). Because of the closer proximity to the normal conduction system, these sites may result in less electrical activation delay (represented by a shorter QRS duration) and less mechanical dyssynchrony.

From all alternative RV pacing sites, the RV outflow tract has been studied the most extensively. A meta-analysis of 9 studies with 217 patients comparing RV outflow tract and RV apical pacing demonstrated a favorable effect of RV outflow tract pacing on hemodynamics (80). Unfortunately, the majority of the studies involved short-term follow-up studies. A recent retrospective study demonstrated a better survival in patients with RV outflow tract pacing as compared with RV apical pacing (81). The favorable effect of RV outflow tract pacing may be related to the more physiologic activation pattern, resulting in less LV dyssynchrony. However, a small study with 14 patients could not demonstrate a benefit of RV outflow tract pacing over RV apical pacing with regard to LV dyssynchrony (82). More studies with dyssynchrony analysis and long-term follow-up comparing RV outflow pacing and RV apical pacing are therefore needed.

Septal pacing may be another good alternative for RV apical pacing. Short-term studies have suggested good results compared with RV apical pacing (83), with good pacing thresholds and lead stability (84). In addition, less ventricular dyssynchrony may be present during septal pacing as compared with RV apical pacing (85). However, at long-term follow-up, septal pacing may not be superior over RV apical pacing. In a randomized study including 98 patients with AV

block (53 septal pacing vs. 45 apical pacing), no differences in LVEF and exercise capacity were found after 18 months follow-up (86).

Direct His bundle pacing or para-Hisian pacing has also been suggested as an alternative for RV apical pacing. In one of the first clinical studies with permanent direct His bundle pacing, Deshmukh et al. demonstrated the feasibility of this strategy (87). Implantation was successful in 12 of 14 patients (86%), with maintenance of His bundle capture at long-term follow-up in 11 patients (92%). After a mean of 23.4 ± 8.3 months, LV end-diastolic diameter had decreased from 51 ± 10 mm to 43 ± 8 mm ($p<0.01$) and LVEF had increased from 18.2 ± 9.8% to 28.6 ± 11.2% ($p<0.05$) (87). Importantly, it has been demonstrated that His bundle pacing may result in less inter- and intraventricular dyssynchrony (88,89). In a randomized study comparing RV apical pacing and para-Hisian pacing in 16 patients, Occhetta et al. noted a significant reduction in interventricular dyssynchrony during para-Hisian pacing as compared with RV apical pacing (34 ± 18 ms vs. 47 ± 19 ms, $p<0.05$) (89).

Although the various studies have demonstrated beneficial effects of the alternative pacing sites, at present septal and direct His bundle pacing are still not recommended in patients requiring permanent cardiac pacing because of difficulties with lead positioning, and concerns about lead stability and threshold (1). In addition, it should be remembered that any electrical stimulation outside the normal conduction system may ultimately result in electromechanical changes with deleterious effects on LV function. Furthermore, the majority of the studies on alternative pacing sites were non-randomized studies with small study populations and short-term follow-up. Nonetheless, there is increasing evidence that these alternative sites may provide benefit over conventional RV apical pacing.

CONCLUSIONS

From large pacing mode selection trials and observational studies, it has become apparent that a high amount of RV apical pacing may be associated with a worse clinical outcome (deterioration of LV systolic function, development of heart failure and atrial fibrillation). Unfortunately, it remains unclear if there is an 'optimal amount' of RV pacing, and which patients at most susceptible for the deleterious effects of RV pacing. The negative effects may be related to the induction of ventricular dyssynchrony by RV apical pacing. Future studies are needed to address these remaining questions.

Various therapeutic options have been suggested in patients with a conventional pacemaker indication. The upgrade to CRT may partially reverse the deleterious effects of RV apical pacing. New pacing strategies and alternative RV pacing sites may prevent the induction of ventricular dyssynchrony and the deterioration of LV function.

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