REVIEW ARTICLE

The Role of Biventricular Pacing in the Prevention and Therapy of Pacemaker-Induced Cardiomyopathy

Maya Guglin, M.D., Ph.D.,* and S. Serge Barold, M.D.†

*From the *University of Kentucky, Lexington, KY and †University of Rochester School of Medicine and Dentistry, Rochester, NY*

Right ventricular (RV) pacing produces well-known long-term deleterious effects not only on already compromised, but also on the normal left ventricle (LV). The activation pattern mimicks that of left bundle branch block, with delayed activation of the LV free wall, and results in electrical and mechanical dyssynchrony. Long-term mandatory (100%) RV pacing, increases LV dimensions and decreases the ejection fraction. Many of these negative effects of pacing can be overcome by biventricular pacing. In this review, we describe the characteristics of pacemaker-induced cardiomyopathy, its incidence, and the use of cardiac resynchronization therapy (CRT) for its therapy and prevention. The gaps in the current organizational guidelines for using CRT in the treatment of bradycardia are identified, and goals for future research are discussed.

Ann Noninvasive Electrocardiol 2015;20(3):224–239

pacemaker-mediated cardiomyopathy; cardiac resynchronization therapy; heart failure

Right ventricular (RV) pacing produces well-known long-term deleterious effects not only on already compromised, but also on the normal left ventricle (LV). The activation pattern mimicks that of left bundle branch block (LBBB), with delayed activation of the LV free wall, and results in electrical and mechanical dyssynchrony. Frequent RV pacing alters geometry and function of the LV on multiple levels resulting in a variety of manifestations.[1–12] Long-term mandatory (100%) RV pacing, increases LV dimensions (end diastolic and end systolic), LV mass, and left atrial diameter. It also decreases LV ejection fraction (LVEF), and worsens mitral regurgitation.[2,13] On a cellular level, effects of RV pacing include mitochondrial variations and degenerative fibrosis. Morphologically, myofibrillar disarray is seen.[14] Hemodynamically, RV pacing leads to decrease in cardiac output, elevation of pulmonary capillary wedge pressure, and heart failure (HF).[15] Besides, there are other negative consequences such as regional perfusion abnormalities and increased oxygen demand.[16]

In this review, we describe the characteristics of pacemaker-induced cardiomyopathy, its incidence, and the use of cardiac resynchronization therapy (CRT) for its therapy and prevention. The gaps in the current organizational guidelines for using CRT in the treatment of bradycardia are identified, and goals for future research are discussed.

CLINICAL TRIALS: DATA ON LV DYSFUNCTION DUE TO RV PACING

DAVID Trial

The DAVID (The Dual Chamber and VVI Implantable Defibrillator) trial (2002) was designed with the hypothesis that dual-chamber DDDR pacing in patients receiving implantable cardioverters-defibrillators (ICDs) (without bradycardia indications) would result in improved hemodynamics

Address for correspondence: Maya Guglin, M.D., Ph.D., Professor of Medicine, Division of Cardiology, University of Kentucky, 900 S Limestone Street, Lexington, KY 40507; E-mail: mguglin@gmail.com

Authors have no conflicts of interest to disclose.

There was no funding.

DOI:10.1111/anec.12245

and therefore improved outcomes as compared to conventional backup ventricular pacing. The trial compared the clinical effectiveness of dual-chamber ICDs programmed to the DDDR pacing mode at 70 pulses per minute versus the VVI mode at 40 pulses per minute. The atrioventricular (AV) delay was programmed according to the clinical judgment of the investigators and was commonly set at 180 ms thereby favoring ventricular pacing in the majority of patients. The DDDR group exhibited nearly 60% of ventricular beats being paced, and the VVI group showed 1% of ventricular beats being paced. The DAVID trial turned conventional wisdom upside down by clearly showing the hazards of unnecessary RV pacing which was associated with an increased risk of death and HF hospitalizations as a composite endpoint in patients with an impaired LV function (selected for ICD therapy). The study revealed a strong trend toward higher mortality and hospitalization for new or worsened congestive HF in the DDDR group. The VVI group fared better because the programmed rate of 40 pulses per minute minimized RV apical pacing. The depression of LV function by RV apical pacing may be more important in ICD patients with poor LV function and/or a prior history of HF.[17]

In a subsequent study, the group with DDDR RV pacing >40% had a statistically significant higher risk of reaching the endpoint compared with DDDR RV pacing less than or equal to 40% ($P = 0.025$). The latter group had similar or better outcomes to the VVI backup group ($P = 0.07$).[18]

MOST (MOde Selection Trial)

In the MOST, patients with sick sinus syndrome were randomized into two pacing modes: DDDR and VVIR. The investigators found that the cumulative percentage of ventricular pacing was significantly higher in the DDDR group than in the VVIR group (median, 90% vs 58%, respectively; $P < 0.001$), and 50% of the patients in the DDDR group was ventricular paced continuously or nearly continuously, compared with only 20% in the VVIR group.[19] The higher incidence of pacing in the DDDR group was mostly due to overlap of the baseline PR interval with the programmed AV delay. In total, 128 of the 1339 patients (9.6%) had one or more hospitalization for HF during the study. For DDDR pacing, the risk increased with a rising of cumulative pacing until it reaches 40% where it remained stable thereafter with higher values. Ventricular pacing >40% of the time in DDDR mode was associated with a 2.6-fold increased risk of HF hospitalizations, compared with pacing <40% of the time ($P = 0.040$). The data revealed a 20% increase in risk of HF admissions for every 10% increase in RV pacing. This risk increased to threefold when multiple hospitalizations were considered.

In VVIR mode, the risk did not increase until patients were paced >80% of the time. In this group, ventricular pacing >80% of the time was associated with a 2.5-fold increased risk of HF hospitalizations, compared with pacing <80% of the time. The risk of atrial fibrillation increased linearly with cumulative pacing from 0% to 85% in both groups.

In summary, the MOST study demonstrated that not pacing mode but cumulative percentage of RV pacing (as determined by stored pacemaker data) was a major determinant of outcome. These results initiated a profound change in approach to pacing therapy to minimize RV pacing.

MADIT II Study

Steinberg et al.[20] divided the multicenter automatic defibrillator II trial (MADIT II) ICD patients into two groups based on cumulative ventricular pacing under 10% or over 90% (bimodal distribution): the first group ($N = 369$) consisted of patients with very little pacing (median cumulative pacing = 0.2%), and the second group ($N = 198$) consisting of patients being paced most of the time (median cumulative pacing = 95.6%). Group 2 patients showed a significantly higher probability of new or worsened HF at 2 years (30%) versus only 17% in group 1 ($P < 0.001$). A similar pattern emerged with the combined endpoint of HF hospitalization or death ($P < 0.001$), but death alone revealed no significant difference. Group 2 patients were also more likely to experience ICD therapy for ventricular tachycardia/fibrillation ($P < 0.005$) raising the question that RV pacing might be proarrhythmic. It is highly unlikely that the results can be explained solely in terms of the sicker patients requiring more pacing.

During the total 8-year follow-up, high RV pacing was shown to be associated with a significant adjusted 40% ($P = 0.01$) increase in the risk of death compared with low RV pacing.[21] These findings strongly suggest that frequent RV pacing resulted

in LV dysfunction, and HF accounting for increased mortality.

The Danish AAIR versus DDDR Trial

Nielsen et al.[22] reported the results of the first randomized trial comparing the AAIR and DDDR modes of pacing in 177 consecutive patients who received a first pacemaker for sick sinus syndrome. The patients were followed for 2.9 ± 1.1 years and had normal AV conduction, and no bundle branch block. The patients were randomized to three arms: AAIR, DDDR-s (short rate-adaptive AV delay—110–150 ms), and DDDR-l (fixed long AV delay ≥250 ms) modes. The AV delay was not optimized because the study was designed to evaluate the effect of cumulative RV pacing. The AAIR group exhibited no significant change in the left atrial and LV diameters and LV fractional shortening. However, the left atrial diameter increased significantly in both DDDR groups (more marked in the DDDR-s group), while LV fractional shortening decreased significantly in the DDDR-s group (90% proportion of RV pacing) but not in the DDDR-l group (17% proportion of RV pacing). The AAIR versus DDDR trial clearly documented the detrimental effects of LV dyssynchrony produced by long-term unphysiologic RV pacing in patients with sick sinus syndrome. The results of the AAIR versus DDDR study are in accordance with the data from the DAVID and MOST trials (where sequential LV function was not evaluated) with hospitalization for HF as the endpoints.

MECHANISMS

A number of research and review articles have described in detail the adverse structural and pathologic changes associated with pacemaker-induced cardiomyopathy.[1–14,16] We felt that addressing these alterations were beyond the scope of this clinical review.

The detrimental effects of long-term RV pacing may occur in patients with normal and abnormal LVEF and is more prominent in patients with a depressed LVEF. The true incidence of LV remodeling due to RV pacing is not well known but it tends to occur especially if RV paces >40% of the time.[19] Yet, some pacemaker-dependent patients with continual RV pacing do not develop LV dysfunction for reasons that are unclear.

INCIDENCE

Reported data on incidence of pacemaker-induced cardiomyopathy vary. In a retrospective study of 286 patients with atrial fibrillation and normal baseline LVEF, who underwent AV nodal ablation with pacemaker implantation—and paced 100% of time—only 9% of patients experienced at least a 10% drop in LVEF within 1 year, and 15% of patients suffered such a drop in LVEF if followed up over a year.[23] Similar prevalence of cardiomyopathy of 9% after 1 year of pacing was reported by Yu et al.[24]

Zhang et al.[25] analyzed 304 patients who received a pacemaker (RV apical) for AV block and without prior HF. They found 79 patients (26%) who developed new onset HF at a median of 7.8 years since implantation. The baseline LVEF was 64 ± 0.1% and the follow-up LVEF was 47 ± 0.1%, and cardiovascular mortality was significantly higher in the patients with HF (36.7% vs 2.7%, $P < 0.001$). Multivariate analysis revealed that an older age and coronary artery disease were risk factors for the development of HF.

Dreger et al.[26] analyzed patients with no history of structural heart disease, who were paced (>99% of the time) for at least 15 years due to AV block. Pacing-induced cardiomyopathy was defined as LVEF ≤45%. Twenty-six patients met the inclusion criteria. Pacing-induced cardiomyopathy was diagnosed in four patients (15.4%) whose LVEF was 41.0 ± 4.5%, compared with patients with preserved LVEF 61.2 ± 5.8%. The longest intraventricular delay was significantly shorter in patients with preserved LVEF (65.5 ± 43.0 ms) compared with patients with pacing induced cardiomyopathy (112.5 ± 15.0 ms, $P = 0.043$).

Khurshid et al.[27] recently evaluated 277 pacemaker patients for pacemaker-induced cardiomyopathy: preimplantation LVEF ≥ 50% and a drop in LVEF ≥ 10%. Of these 277 patients, 207 remained with preserved LVEF through the end of follow-up (mean 3.3 years, range 0.08–9.4). Of the 70 patients who developed a cardiomyopathy, 20 were excluded for an alternative potential explanation, leaving 50 patients with pacemaker-induced cardiomyopathy (incidence 19.5%). In the patients with pacing-induced cardiomyopathy, the mean baseline LVEF was 62.1%, and at follow-up (3.3 years) the mean LVEF was 36.2%. Among those with ventricular pacing percentages 20–39, 40–59, 60–79, and 80–100, the incidence of

pacemaker-induced cardiomyopathy was 13.0%, 16.7%, 26.1%, and 19.8%, respectively (P = 0.7 for comparison across groups). The shortest time to development of pacemaker-induced cardiomyopathy was 1 month and the longest time was 8.4 years. Pacemaker-induced cardiomyopathy was more likely to occur in men, with a wide native QRS complex, and a lower preimplant LVEF. Native QRS duration >115 ms (excluding typical bundle branch block) was 90% specific for development of pacemaker-induced cardiomyopathy.

If 13% of patients who are only paced 20 to 40% of time, develop cardiomyopathy in three years, threshold of 40% may be, indeed, too high. Interestingly, when number of premature ventricular contractions reaches about 25% of all QRS complexes, it is considered to be enough to cause LV remodeling.[28,29]

WHEN DOES PACEMAKER-INDUCED CARDIOMYOPATHY START?

Like the incidence of pacemaker-induced cardiomyopathy, the timing of onset varies widely in the literature, but it is between few months and few years. Shimano et al.[30] described the development of HF in 18 patients who received permanent pacemakers for complete AV block. The patients were pacemaker dependent, in sinus rhythm and were evaluated 81 ± 10 months after implantation. Before pacemaker implantation, 13 patients presented with a normal LVEF (> 50%) and the mean LVEF in the 18 patients was 54 ± 3.1%. All developed a reduction of LVEF with a mean of 28 ± 2.1% and HF requiring 2.1 ± 0.2 hospitalizations per year. The duration of RV pacing correlated with severity of LVEF reduction. Because this study describes only patients with pacemaker-induced cardiomyopathy, it does not provide any information on its incidence, just on the timing of it.

In the PACE (The Pacing to Avoid Cardiac Enlargement) trial, Yu et al.[24] followed 86 patients after RV apical pacemaker implantation for 1 year with an average ventricular pacing of 97%. The mean LVEF decreased from 61.5 ± 6.6% at baseline to 54.8 ± 9.1% and the LV end-systolic volume increased from 28.6 ± 10.7 to 35.7 ± 16.3 mL (relative increase of 26%). Eight patients (9%) developed an LVEF <45%. The LVEF at 2 years was 53.0 ± 10.1. These observations indicate that LV dysfunction and the clinical manifestations of pacemaker-induced cardiomyopathy in patients with frequent ventricular pacing can begin in the first year. The literature suggests that the incidence peaks at 3 years. It eventually occurs in about 15–20% of pacemaker patients with AV block. Some reports report higher event rate, especially with longer follow-up.

In another study, however, pacemaker-induced cardiomyopathy started developing almost immediately after initiation of pacing. Twelve patients with dual-chamber pacemakers and normal LV function, had LVEF measured after at least 1 week of atrial pacing only (baseline), during and after short-term (2 hours) and midterm (1 week) AV pacing with a short AV delay (>99% ventricular pacing).[31] Baseline LVEF was 66.5 ± 4.5%. Short-term pacing resulted in a decrease in LVEF to 60.3 ± 5.2% (P < 0.0002). After 1 week (midterm) of AV pacing, there was a further decline in EF to 52.9 ± 8.3% (P < 0.0001). After cessation of midterm pacing, EF was 57.3 ± 5.9% (P < 0.0001 vs baseline). A total of 2, 5, 8, and 24 hours later, EF remained depressed (59–60%, P < 0.007). Only after 32 hours, LVEF became statistically similar to baseline 62.9 ± 7.6% (P < 0.11 compared with baseline). The authors concluded correctly that the abnormal activation sequence resulting from RV pacing accounted for only part of the reduction in LVEF as midterm pacing was associated with a lower LVEF than short-term pacing, and LVEF remains depressed after cessation of AV pacing. This study showed that pacemaker-induced cardiomyopathy can become manifest as soon as pacing is initiated and last after pacing is discontinued.[31]

BIVENTRICULAR (BiV) PACING

As in case of intrinsic LBBB, CRT is beneficial in the LBBB-like disorder induced by RV pacing. Current recommendations for CRT in the setting of frequent RV pacing are limited to very few clinical scenarios.

The PAVE (Left ventricular-based cardiac stimulation post AV nodal ablation evaluation) trial[32] was the first randomized study to compare BiV pacing with RV pacing in patients who had undergone ablation of the AV node for refractory atrial fibrillation (Table 1). The ABLATE and PACE trials randomized the same patient population as the

Table 1. Randomized Studies Comparing Effects of Right Ventricular and Biventricular Pacing

Study	n	Patient Characteristics	Rhythm	Treatment	Follow-Up Duration	Endpoints	Results
PACE[24]	177	Bradycardia with preserved LVEF (≥45%)	Persistent AF excluded	RV apical (n = 88) or BiV (n = 89) pacing	2 years for 92% of each group and 18–24 months for the rest	LVEF and LVESV	LVEF decreased in the RV group, but remained unchanged in the BiV-pacing group. Significant difference of 9.9 percentage points at 2 years ($P < 0.001$).
PACE extended follow-up[a35]	149	Bradycardia with preserved LVEF (≥45%)	Persistent AF excluded	RV apical (n = 74) or BiV pacing (n = 72)	4.8 ± 1.5 years	LVEF and LVESV	LVEF decreased while the LV end-systolic volume increased progressively at follow-up, but remained unchanged in the BiV group.
PREVENT-HF[36]	108	Indication for pacing with normal (>50%) LVEF and expected VP ≥ 80%	History of AF in 10% of each group	RV apical (n = 58) or BiV pacing (n = 50)	12 months	LV end-diastolic volume	Endpoint 1: No significant difference between RV and BiV pacing.Endpoint 2: no change in LVEF, LVESV and HF events

(*Continued*)

Table 1. *Continued*

Study	n	Patient Characteristics	Rhythm	Treatment	Follow-Up Duration	Endpoints	Results
BLOCK HF[37]	691	First, second, and third-degree AV block, heart failure, NYHA class I, II, and III and LVEF ≤50%	AF in 51.6% of the BiV group and 54.1% of the RV group VP > 97%	RV (n = 342) or BiV pacing (n = 349)	37 months mean	Composite endpoint of time to death from any cause, or urgent care visit for heart failure requiring intravenous therapy, or ≥15% increase in LVESVI	Endpoint 1: BiV pacing resulted in a 26% statistically significant reduction in the combined endpoint.Endpoint 2: Rates of first hospitalization for HF less for BiV group. Composite outcome of death or hospitalization for HF less in the BiV group.
PAVE[32]	184	Persistent AF with AV node ablation (third-degree AV block)	AF in 100%	RV (n = 81) or BiV pacing (n = 81)LVEF = 46 ± 0.16	6 months	6-minute walk distance and LVEF	RV pacing showed decrease in 6-minute walk distance (P = 0.04) and LVEF compared to BiV pacing (P = 0.03).
ABLATE AND PACE[33]	186	Persistent AF with AV nodal ablation (third-degree AV block)	AF 100%	RV (n = 89) LVEF 37 ±14, or BiV pacing (n = 89) LVET 38 ± 14	20 months median	Composite endpoint of death from HF, hospitalization for HF, or worsening of HF	Endpoint 1: reached in 11% of Biv group versus 26% in the RV group (P = 0.005).Endpoint 2: Fewer BiV pts with worsening of HF (P = 0.001) and fewer BiV for HF hospitalization (P = 0.013).

(*Continued*)

Table 1. *Continued*

Study	n	Patient Characteristics	Rhythm	Treatment	Follow-Up Duration	Endpoints	Results
Albersten[40]	48	Permanent or paroxysmal AV block	AF excluded	DDDR (n = 24)BiV (n = 24). All had 100% pacing. DDD(R): LVEF = 59.7 (57.4 – 61.4)% BiV: LVEF = 58.9 (47 – 62)%	12 months	LVEF	DDDR group: Baseline LVEF = 59.7 (57–61) à12 months = 57.2 (52–61)5 (P = 0.03.BiV group: Baseline LVEF = 58.9 (47–62) à 12 months = 60.1 (55–63)%, P = 0.15.Comparing the changes in LVEF between baseline and 12 months, the difference was highly significant, P = 0.007.
COMBAT[39]	60	AV block	AF excluded, LVEF <40%	DDD versus BiV with time in crossover period = 4.7 ± 2.2 months	17 ± 10.7 months	QoL, NYHA	Both QoL and NYHA class were improved with BiV (P < 0.01).
HOBIPACE[38]	30	Symptomatic bradycardia-Permanent AF = 6, upgrades = 8	LVEF ≤ 40%LVEDD ≥ 60 mm	DDD versus BiV with time in crossover period = 3 months	9 months from start, 6 months in crossover protocol	LVESV, LVEF, peak O_2 consumption	When compared to RV pacing, BiV reduced LVESV by 17% (P < 0.001), increased LVEF by 22% (P < 0.0002), and peak O_2 consumption. AF patients also improved with BiV.

[a] In the first two rows, the data from the same PACE trial are presented. The extended follow-up group was also part of the original trial.

PAVE trial (Table 1).[33] Three randomized trials (PACE,[24,34,35] PREVENT HF,[36] and BLOCK HF [The Biventricular vs Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block][37]) have compared BiV pacing to RV pacing in patients who required close to continual ventricular pacing and included patients in sinus rhythm or atrial fibrillation. All of them except PREVENT-HF demonstrated favorable effects of BiV pacing on functional status, and LV performance and geometry. The PREVENT HF trial was the only inconclusive study possibly because of a relatively short follow-up period and internal inconsistencies.

The four major randomized trials[24,33,36,37] favoring BiV pacing have shown that irrespective of baseline QRS duration, long-term LV remodeling, LV dysfunction, and HF are more common in patients with long-term conventional RV than those with BiV pacing (Table 1). There were 149 patients who had extended follow-up in the PACE trial with a mean duration of 4.8 ± 1.5 years (2.5–7.8 years). The primary endpoint analyses were performed in 146 patients (74 in the RV group and 72 in the BiV group). In the RV-pacing group, the LVEF decreased while the LV end-systolic volume increased progressively at follow-up, but remained unchanged in the BiV pacing group. The differences in LVEF between the RV and BiV groups were −6.3, −9.2, and −10.7% at 1-year, 2-year, and long-term follow-up, respectively (all $P < 0.001$). The corresponding differences in LV end-systolic volume were +7.4, +9.9, and +13.1 mL, respectively (all $P < 0.001$). In addition, patients with RV pacing had a significantly higher prevalence of HF hospitalization than the BiV group (23.9% vs 14.6%, $P = 0.006$).[35]

Three other studies with fewer patients than the above major trials also showed the advantage of BiV pacing (Table 1).[38–40] All the trials have shown so far no reduction in mortality probably because of the relatively short follow-up times. In the case of other studies involving only atrial fibrillation, meta-analyses have suggested functional improvement with BiV pacing after AV junctional ablation as the primary therapeutic procedure.[41,42]

BLOCK HF Trial

BLOCK HF is a major study (2013) enrolled 691 patients with AV block and NYHA class I, II, and III HF and LVEF of 50% or less[6,37] The study population was predominantly male with average in 1970s and NYHA Class II. Patients with an indication for BiV pacing according to organizational guidelines were excluded from the trial. There were 484 patients in the pacing group and 207 in the ICD group. The latter received ICD according to standard guidelines. The patients underwent randomization with either an RV pacemaker or a BiV pacemaker and they were followed for a mean of 37 months. The LVEF was 39.6 ± 8.3% for the RV group and 40.3 ± 8.4% for the BiV group. About 70% of the patients in each group had an LVEF >35%. Importantly, the percentage of ventricular pacing was >97% in all groups. This percentage was probably an overestimation of true ventricular pacing because of ventricular fusion and pseudofusion beats are counted as ventricular paced beats. However, it is very likely that the percentage of pure ventricular pacing was comparable in all the patient groups so that the recorded percentage of ventricular beats remained a valid observation.

The primary outcome was the time to death from any cause, or an urgent care visit for HF that required intravenous therapy or a 15% or more increase in LV end-systolic volume index (LVESVI). The endpoint was driven by the prominent recording of the LVESVI. The composite primary outcome (any of the three endpoints) occurred in 190 of 342 patients (55.6%) in the RV-pacing group, as compared with 160 of 349 patients (45.8%) in the BiV-pacing group resulting in a 26% statistically significant reduction in the combined outcome for BiV pacing. The results were similar in the pacing and ICD groups. Also, the secondary endpoints, rates of first hospitalization for HF and the composite outcome of death or hospitalization for HF differed significantly between the two pacing groups, also in favor of BiV pacing. In the secondary outcome, death alone was not statistically significant.

Some answers are expected from the randomized trial which is currently in progress—the BIOPACE (Biventricular stimulation to prevent cardiac desynchronization).[43]

This randomized trial which is similar to the BLOCK HF trial also evaluates the long-term effects of RV pacing versus BiV pacing. The trial recruited over 1800 patients between May 2003 and September 2007 predominantly from European centers. The patients had a high likelihood of mostly ventricular paced beats (at least 66%

of the time) regardless of sinus rhythm, atrial fibrillation or preimplantation QRS duration, and morphology. The patients will be followed for 5 years. The primary endpoints are survival, quality of life (Minnesota Living with Heart Failure questionnaire), and distance covered in a 6-minute hall walk at 24 months after implantation. The secondary endpoints consist of a relatively large number of observations. The results of the trial should be available soon.

DOES CRT PREVENT PACEMAKER-INDUCED CMP IN PATIENTS WITH A NORMAL LVEF?

The risk of pacemaker-induced cardiomyopathy appears to be less common in patients starting with a normal compared to abnormal LVEF. The true incidence is difficult to determine because many studies present combined data from a normal and near normal mean LVEF. Such studies may contain cases with abnormal LVEF. This evaluation is compounded by the lack of definitions as to what constitutes a normal LVEF and a cutoff of 50% is sometimes used to separate normal and abnormal values. Because echo-derived LVEF is often reported as a range (e.g., 40–45%), and LVEF ≥50% is normal, everything with LVEF >45% may be considered as near normal. The subsets of studies reflecting the effects of CRT in patients with normal LVEF are summarized in Table 2.

In the study of Albertsen et al.,[40] 23 of 25 patients in the DDDR group were analyzed separately because of LVEF >50%. This group of 23 patients started with an LVEF >50%, and the LVEF decreased from 59.8 (58.6–62.2)% at baseline to 57.3(52.7–60.7)% at the 12-month follow-up (P = 0.04). In a study involving 79 patients and a mean LVEF of 64 ± 0.07% strongly suggests that most, if not all, the LVEFs are normal. The same argument can be used in the analysis of the data from Khursid et al.[27] with 50 patients with an initial mean LVEF of 62.1%. In this study, their figure 4 clearly demonstrates that all the initial LVEFs are truly normal. Studies with a normal mean baseline LVEF may have few patients (not specifically stated) with an abnormal LVEF that do not interfere with the overall normal value of the LVEF. However, the incidence of LV dysfunction is greater than the proportion of patients with an abnormal baseline LVEF. This provides further proof that pacemaker-induced cardiomyopathy can affect patients starting with a normal LVEF.

UPGRADE FROM CONVENTIONAL PACEMAKER OR ICD TO CRT

In some registries, upgrading from RV to BiV pacing constitutes about 23–28% of all implanted BiV systems.[44] Patients with pacemaker-induced cardiomyopathy respond favorably (in about 2/3 of cases) to upgrading suggesting that the LV dysfunction is partially reversible. Upgrading to BiV pacing should be considered in patients requiring frequent RV pacing, if they have symptomatic HF and low LVEF (<35–40%) despite the lack of large prospective, randomized trials in this area. This includes patients undergoing routine device replacement. A low LVEF is more important than the presence of HF. The benefit of upgrading to CRT has been evaluated in three clinical scenarios.

(1) Crossover studies

Four small randomized trials with a crossover design were conducted with a 2–6-month period of CRT which was compared with a 2–6-month period of RV pacing.[45–48] The patients had severe symptoms of HF (mostly NYHA class III or IV) and depressed LVEF (mostly <40%). During the CRT phase, the patients consistently showed clinical subjective improvement, less hospitalization, and improved LV function, compared with the RV during the study phase (Table 1).

(1) Nonrandomized studies

The results of CRT upgrade in observational studies involving a relatively small number of patients (almost all in NYHA III or IV, HF, and deterioration of LV function with LVEF <35%) are consistent with the above crossover studies. The patients showed subjective clinical improvement, fewer hospitalizations, and improved LV function.[30,45,49–59]

(1) Upgrading versus de novo cardiac resynchronization

Several studies have shown that patients with RV pacing (and low LVEF) improved after upgrading to BiV pacing with a benefit that was comparable or even better than that observed

Table 2. Randomized Studies Comparing Effects of Right Ventricular and Biventricular pacing in Patients with Normal LVEF

Author, Year	Setting	% Pacing	N	LVEF	Follow-Up	Mean Baseline LVEF	LVEF BiV Arm	LVEF RV Arm	Outcome
PAVE trial, 2005[32]	AV node ablation for AF	100	54	>45%	6 months				Six-minute walk distance unchanged from before AV node ablation/BiV pacing, and not different from patients with RV pacing
Albertsen,[40]	High-grade AV block	100	48 (BiV group 24, DDDR group 24)	>50% in 17 patients	12 months	58% DDDR60.3% BiV	60.1%	57.3%	LVEF did not change from the baseline but was significantly better with CRT than in RV pacing armNo difference between arms in 6-minute walk distanceUnchanged NT-proBNPImproved NYHA class
Yu,[24] The Pacing to Avoid Cardiac Enlargement (PACE) trial[24]	High-degree AV block or sick sinus syndrome	98%	173 (BiV group 87 and RV group 86)	>45%	1 year	61.5 ± 6.6 RV61.9 ± 6.7 BiV	62.2 ± 7.0%	54.8 ± 9.1%	LV end-systolic volume unchanged and 8.1 mL smaller than in patients who were randomized to RV pacing1% in the BiV group versus 9% in the RV group had LVEF <45%6-minute walk and quality of life unchanged
Chan,[34] The Pacing to Avoid Cardiac Enlargement (PACE) trial[34a]	High-degree AV block or sick sinus syndrome	93%	163 (BiV group 82 and RV group 81)	>45%	2 years	61.5 + 6.6% RV61.8+6.7% BiV	62.9 + 8.8%	53.0 + 10.1%	LVEF unchanged and 9.9% better than in patients who were randomized to RV pacing4.5% in the BiV group versus 17% in the RV group had LVEF <45%LV end-systolic volume unchanged and 13 mL smaller than in patients who were randomized to RV pacing 20.2% patients had >5% reduction in LVEF (significantly less than 62.5% in RV pacing arm) 6-minute walk and quality of life unchanged, with no difference between the arms

[a]This row represents same patient population as Yu et al.,[24] but with extended 2-year follow-up.

in HF patients with native LV conduction delay who underwent de novo CRT implantation (follow-up 3–38 months).[60–64] The European CRT survey which compared 692 upgrades with 1675 de novo procedures at 141 centers in Europe, showed that there were no significant differences in clinical outcomes, mortality complication rates between upgrades and de novo procedures.[47] A recent study of 50 patients with unavoidable RV pacing, LV systolic dysfunction, and mild or no symptoms of HF were randomized to either standard RV pacing or BiV pacing at the time of pacemaker replacement.[64] At 6 months, there was a statistically significant improvement in the LVEF in the BiV group ($P < 0.0001$) compared to standard RV pacing. There were also improvements in exercise capacity ($P = 0.007$), quality of life ($P = 0.03$), and NT-proBNP ($P = 0.007$) in those randomized to BiV pacing. Patients with standard RV pacing had more days in hospital during follow-up than those in the BiV group ($P = 0.047$).[64]

Gaps in the Organizational Guidelines

Although the majority of the studies indicate that it is better to pace two ventricles than one, there are not enough data presently to recommend BiV pacing for all patients requiring antibradycardia pacing and more randomized trials are needed to define patients at risk for LV dysfunction and HF, especially in patients with a normal LVEF.

Current recommendations for CRTs or bradycardia in the setting of frequent RV pacing are limited to very few clinical scenarios.

Specifically, indications for CRT include patients with a wide QRS, preferably with a LBBB morphology, and LVEF ≤35%. Some guidelines from different societies recognize mandatory RV pacing as an indication for CRT, but only in the setting of already existing moderate or severe LV systolic dysfunction (Table 3).

Interestingly, only 2013 ACCF/AHA guideline for the management of HF[65] and 2012 ACCF/AHA/HRS Focused Update[66] mention a 40% pacing frequency as a cutoff, after which CRT is indicated. Other recommendations consider CRT only in mandatory (100%) RV pacing or unspecified "high percentage" of RV pacing. Some documents do not even state the importance of the cumulative percentage of RV pacing.[67]

Many guidelines (Table 3) include the clinical syndrome of HF, or even specific NYHA class into the indications. Symptomatic HF merely indicates fluid retention which can easily change on a day-to-day basis, depending on a dietary fluid restriction or the dose of diuretics, and should most probably not play any role in decision on CRT. Fluid retention, in this population, is a consequence of decreased LVEF, or LV remodeling, which should be the indication for CRT regardless of symptoms, as we discussed in detail elsewhere.[68–70] However, patients with an initially normal LVEF, undergoing permanent pacemaker implantation for bradycardia indications, are at risk for LV remodeling and HF. Currently, no indications exist to provide them with a CRT device from the start, in order to prevent the risk.

The Food and Drug Administration (FDA) approved new guidelines for BiV pacing in April 2014 based on the results of the BLOCK HF trial which demonstrated significant clinical advantages of BiV pacing compared with traditional RV pacing. The FDA proposed a class I or IIa indication for AV block expected to require a high percentage of ventricular pacing that would be traditionally require conventional pacing, mild to moderate HF symptoms (NYHA Class I, II, and III) though Class I patients do not have symptoms of HF, and an LVEF ≤50%.[71] This indication should include intermittent second and third-degree AV block because of their propensity to develop sustained third-degree AV block. BiV pacing should be considered only if there is symptomatic marked prolongation of the PR interval that would force sustained traditional RV pacing. The indications should probably exclude patients who exhibit a PR interval >300 ms at an atrial pacing rate of 100 ppm as in the BLOCK HF protocol. In addition, lower cost dual-chamber pacemaker could well be enough for patients with first-degree AV block that does not require much RV pacing.

Adherence to the FDA guidelines does not lead to reimbursement for the BiV procedure which can only occur when the guidelines promulgated by the Centers for Medicare and Medicaid Services are published.

The issues not covered in any of the guidelines are:

- Should CRT be considered if baseline LVEF is normal (>50%) and anticipated cumulative pacing is near 100%? Should it be considered if anticipated cumulative pacing is between 40% and 99% of time? Or ≥20% of the time?

Table 3. Indications for CRT in Patients with Right Ventricular Pacing for Brady Indications

Guidelines, Year	Indication (Excluding Classic CRT Indications for Native QRS >120 ms)	Strength of Recommendation
2013 ACCF/AHA guideline for the management of heart failure[65] and 2012 ACCF/AHA/HRS focused update incorporatedinto the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities[66]	(1) CRT can be useful in patients with atrial fibrillation and LVEF ≤ 35% on recommended medical therapy if • the patient requires ventricular pacing or otherwise meets CRT criteria; and • AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT.	IIA
	(2) CRT can be useful for patients on recommended medical therapy who have LVEF ≤ 35%, and are undergoing placement of a new or replacement device with anticipated requirement for significant (>40%) ventricular pacing	IIA
2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy[44]	(1) CRT is indicated in patients with LVEF <35% and high percentage of RV pacing, who remain in NYHA III or ambulatory NYHA IV despite optimal medical therapy (upgrade).	I
	(2) CRT should be considered in HF patients with reduced LVEF, and expected high percentage of ventricular pacing in order to decrease the risk of worsening HF (de novo implant).	IIA
2012 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[72]	CRT is indicated in patients with an indication for conventional pacing and no other indication for CRT if:	IIA
	• NYHA III or IV with LVEF ≤ 35% irrespective of QRS duration, to reduce the risk of HF worsening • NYHA II with LVEF ≤ 35% irrespective of QRS duration, to reduce the risk of HF worsening	IIB

- Should CRT be considered if baseline LVEF is impaired (35–49%), and anticipated cumulative pacing is near 100%? What if pacing occurs 40–99% or even ≥20% of the time.

Some data already exist but more would be needed for a major change in the pacemaker treatment of bradycardia. These questions will need to be answered definitively in further randomized clinical trials

(1) *Risk versus benefit*

The BLOCK HF trial[37] highlighted the fact that the complications of LV lead implantation are not inconsequential. LV pacing was successful in 93.7% of the patients (acceptable failure rate about 4%). The causes of unsuccessful LV pacing included inability to cannulate the coronary sinus ostium, lead displacement, and unacceptably high threshold. After implantation, LV lead-related complications mostly displacements occurred in 6.4% of the patients. Such lead complications are similar to those reported in the literature (4–6%). The risk of late infection is much greater for CRT-D (with defibrillator) compared to CRT-P (no defibrillator) devices, an important advantage of stand-alone CRT devices.[73] The risk of major complications is four times higher for a CRT upgrading procedure compared to a simple device replacement.[74]

The wider use of CRT for new indications will be limited by the greater complications of LV pacing, unfamiliarity with implantation techniques (more complex than simple RV pacing) and cost. Further trials would be helpful especially with regard to the technical aspects of LV lead implantation and more reliable access sites.[75] Thus, the benefit of CRT should be weighed against the risk of the procedure.

[2] *Alternative sites: Is RV pacing obsolete?*

Alternative RV-pacing sites for pacing should not be considered for the prevention of pacing-induced cardiomyopathy at this juncture because the long-term benefit of pacing at RV sites other than the apex are still controversial. At one time, high hopes were placed on alternative sites of RV pacing, for example, pacing in the RV outflow tract rather than the apex, but results of the studies were discouraging.[76–81]

The long-term effects of pacing RV sites (outflow tract or septum) other than the apex are unknown. Direct His bundle and paraHisian pacing are generally not applicable to patients with AV block. For example, traditional RV pacing could be used in a patient with sick sinus syndrome and occasional pauses between episodes of bradycardia, because RV pacing will be used infrequently particularly when pacing algorithms are used to minimize RV pacing. An intermittent AV conduction disorder could be treated either with traditional RV pacing (with the use of algorithms to minimize pacing) or with BiV pacing, depending on the clinical circumstances and the expected amount of RV pacing.

[3] *Stand-alone BiV devices*

The Block HF trial opens the door for the wider use of a less costly and simpler BiV pacemaker without an ICD for patients with an LV ejection >35%.

[4] *The danger of waiting*

BiV pacing is a good investment in patients who require it and should not be delayed to monitor the deterioration of LV function. In addition, an upgrade procedure is associated with a substantial increase in complications compared to de novo CRT device implantation. In the BLOCK HF trial, 18% of the patients developed an indication for BiV pacing in the first year.[37] The first occurrence of HF carries a dismal long-term mortality.

[5] *Pacemaker follow-up to detect pacemaker-induced cardiomyopathy*

In a regular pacemaker clinic, prevalence of significant LV dysfunction (LVEF < 40%) was reported to be as high as 31%, with almost 80% of the group having HF symptoms.[82] Periodic evaluation of LV function is important to determine the presence of progressive deterioration of LV function. This should include the determination of the paced (RV) QRS duration which is related to the degree of LV dysfunction. The duration of the paced QRS complex should also be determined during follow-up because there is an important correlation between QRS prolongation and LV dysfunction.[83–85]

CONCLUSION

There are not enough data presently to recommend BiV pacing for all patients requiring antibradycardia pacing and more randomized trials are needed to further define patients at risk for LV dysfunction and HF. The cutoff value of the cumulative percent of pacing at 40% for the risk of LV dysfunction and HF is based on old data. New research is needed to reevaluate this measurement and its association with LV dysfunction and HF. A recent study suggests that this index may be too high and perhaps should be 20% or even less. According to the BLOCK HF trial, the mode of pacing (CRT) may be determined only with knowledge of the LVEF (<50%) and the expected frequency of ventricular pacing. This approach would yield many candidates for CRT. It would therefore be important to look further into the Block HF trial to find the subgroups of patients most likely to benefit from BiV pacing.

The use of BiV pacing will increase because more studies like the BLOCK HF trial will most probably continue to confirm the superiority of BiV pacing which may even extend to patients with a normal LVEF. BiV pacing will be favored in pediatric patients and those with congenital heart disease.[86,87] BiV pacing will also increase based on improved technology of LV leads (including better extractability), easier access, better implantation techniques (and better familiarity with all the technical aspects of LV lead implantation, lower cost

(with stand-alone devices), fewer complications, and longer follow-up as in the BIOPACE trial may demonstrate that BiV pacing decreases mortality compared to standard RV pacing. In that case, RV pacing alone will become obsolete for many patients.

REFERENCES

1. Akerstrom F, Pachon M, Puchol A, et al. Chronic right ventricular apical pacing: Adverse effects and current therapeutic strategies to minimize them. Int J Cardiol 2014;173:351–360.
2. Barold SS, Ovsyshcher IE. Pacemaker-induced mitral regurgitation. Pacing Clin Electrophysiol 2005;28:357–360.
3. Karpawich PP, Rabah R, Haas JE. Altered cardiac histology following apical right ventricular pacing in patients with congenital atrioventricular block. Pacing Clinical Electrophysiol 1999;22:1372–1377.
4. Knaapen P, van Campen LM, de Cock CC, et al. Effects of cardiac resynchronization therapy on myocardial perfusion reserve. Circulation 2004;110:646–651.
5. Kyriakides ZS, Manolis AG, Kolettis TM. The effects of ventricular asynchrony on myocardial perfusion. Int J Cardiol 2007;119:3–9.
6. Nielsen JC, Bottcher M, Nielsen TT, et al. Regional myocardial blood flow in patients with sick sinus syndrome randomized to long-term single chamber atrial or dual chamber pacing—Effect of pacing mode and rate. J Am Coll Cardiol 2000;35:1453–161.
7. Prinzen FW, Augustijn CH, Arts T, et al. Redistribution of myocardial fiber strain and blood flow by asynchronous activation. Am J Physiol 1990;259:H300–H308.
8. Prinzen FW, Hunter WC, Wyman BT, et al. Mapping of regional myocardial strain and work during ventricular pacing: Experimental study using magnetic resonance imaging tagging. J Am Coll Cardiol 1999;33:1735–1742.
9. Prinzen FW, Peschar M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. Pacing Clin Electrophysiol 2002;25:484–498.
10. Tse HF, Lau CP. Long-term effect of right ventricular pacing on myocardial perfusion and function. J Am Coll Cardiol 1997;1529:744–749.
11. Ukkonen H, Tops L, Saraste A, et al. The effect of right ventricular pacing on myocardial oxidative metabolism and efficiency: Relation with left ventricular dyssynchrony. Eur J Nucl Med Mol Imaging 2009;36:2042–2048.
12. van Oosterhout MF, Prinzen FW, Arts T, et al. Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. Circulation 1998;98:588–595.
13. Vernooy K, Dijkman B, Cheriex EC, et al. Ventricular remodeling during long-term right ventricular pacing following His bundle ablation. Am J Cardiol 2006;97:1223–1227.
14. Adomian GE, Beazell J. Myofibrillar disarray produced in normal hearts by chronic electrical pacing. Am Heart J 1986;112:79–83.
15. Leclercq C, Gras D, Le Helloco A, et al. Hemodynamic importance of preserving the normal sequence of ventricular activation in permanent cardiac pacing. Am Heart J 1995;129:1133–1141.
16. Tops LF, Schalij MJ, Bax JJ. The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. J Am Coll Cardiol 2009;54:764–776.
17. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: The Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. JAMA 2002;288:3115–3123.
18. Sharma AD, Rizo-Patron C, Hallstrom AP, et al. Percent right ventricular pacing predicts outcomes in the DAVID trial. Heart Rhythm 2005;2:830–834.
19. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107:2932–2937.
20. Steinberg JS, Fischer A, Wang P, et al. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. J Cardiovasc Electrophysiol 2005;16:359–365.
21. Barsheshet A, Moss AJ, McNitt S, et al. Long-term implications of cumulative right ventricular pacing among patients with an implantable cardioverter-defibrillator. Heart Rhythm 2011;8:212–218.
22. Nielsen JC, Kristensen L, Andersen HR, et al. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: Echocardiographic and clinical outcome. J Am Coll Cardiol 2003;42:614–623.
23. Chen L, Hodge D, Jahangir A, et al. Preserved left ventricular ejection fraction following atrioventricular junction ablation and pacing for atrial fibrillation. J Cardiovasc Electrophysiol 2008;19:19–27.
24. Yu CM, Chan JY, Zhang Q, et al. Biventricular pacing in patients with bradycardia and normal ejection fraction. N Engl J Med 2009;361:2123–2134.
25. Zhang XH, Chen H, Siu CW, et al. New-onset heart failure after permanent right ventricular apical pacing in patients with acquired high-grade atrioventricular block and normal left ventricular function. J Cardiovasc Electrophysiol 2008;19:136–141.
26. Dreger H, Maethner K, Bondke H, et al. Pacing-induced cardiomyopathy in patients with right ventricular stimulation for >15 years. Europace 2012;14:238–242.
27. Khurshid S, Epstein AE, Verdino RJ, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy. Heart Rhythm 2014;11:1619–1625.
28. Carballeira Pol L, Deyell MW, Frankel DS, et al. Ventricular premature depolarization QRS duration as a new marker of risk for the development of ventricular premature depolarization-induced cardiomyopathy. Heart Rhythm 2014;11:299–306.
29. Baman TS, Lange DC, Ilg KJ, et al. Relationship between burden of premature ventricular complexes and left ventricular function. Heart Rhythm 2010;7:865–869.
30. Shimano M, Tsuji Y, Yoshida Y, et al. Acute and chronic effects of cardiac resynchronization in patients developing heart failure with long-term pacemaker therapy for acquired complete atrioventricular block. Europace 2007;9:869–874.
31. Nahlawi M, Waligora M, Spies SM, et al. Left ventricular function during and after right ventricular pacing. J Am Coll Cardiol 2004;44:1883–1888.
32. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol 2005;16:1160–1165.
33. Brignole M, Botto G, Mont L, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular

junction ablation for permanent atrial fibrillation: A randomized trial. Eur Heart J 2011;32:2420–2429.
34. Chan JY, Fang F, Zhang Q, et al. Biventricular pacing is superior to right ventricular pacing in bradycardia patients with preserved systolic function: 2-year results of the PACE trial. Eur Heart J 2011;32:2533–2540.
35. Yu CM, Fang F, Luo XX, et al. Long-term follow-up results of the Pacing to Avoid Cardiac Enlargement (PACE) trial. Eur J Heart Fail 2014;16:1016–1025.
36. Stockburger M, Gomez-Doblas JJ, Lamas G, et al. Preventing ventricular dysfunction in pacemaker patients without advanced heart failure: Results from a multicentre international randomized trial (PREVENT-HF). Eur J Heart Fail 2011;13:633–641.
37. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med 2013;368:1585–1593.
38. Kindermann M, Hennen B, Jung J, et al. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: The Homburg Biventricular Pacing Evaluation (HOBIPACE). J Am Coll Cardiol 2006;47:1927–1937.
39. Martinelli Filho M, de Siqueira SF, Costa R, et al. Conventional versus biventricular pacing in heart failure and bradyarrhythmia: The COMBAT study. J Card Fail 2010;16:293–300.
40. Albertsen AE, Nielsen JC, Poulsen SH, et al. Biventricular pacing preserves left ventricular performance in patients with high-grade atrio-ventricular block: A randomized comparison with DDD(R) pacing in 50 consecutive patients. Europace 2008;10:314–320.
41. Chatterjee NA, Upadhyay GA, Ellenbogen KA, Hayes DL, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: A meta-analysis of biventricular vs. right ventricular pacing mode. Eur J Heart Fail 2012;14:661–667.
42. Stavrakis S, Garabelli P, Reynolds DW. Cardiac resynchronization therapy after atrioventricular junction ablation for symptomatic atrial fibrillation: A meta-analysis. Europace 2012;14:1490–1497.
43. Funck RC, Blanc JJ, Mueller HH, et al. Biventricular stimulation to prevent cardiac desynchronization: Rationale, design, and endpoints of the "Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BioPace)" study. Europace 2006;8:629–635.
44. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. Rev Esp Cardiol (Engl Ed) 2014;67:58.
45. Delnoy PP, Ottervanger JP, Vos DH, et al. Upgrading to biventricular pacing guided by pressure-volume loop analysis during implantation. J Cardiovasc Electrophysiol 2011;22:677–683.
46. Hoijer CJ, Meurling C, Brandt J. Upgrade to biventricular pacing in patients with conventional pacemakers and heart failure: A double-blind, randomized crossover study. Europace 2006;8:51–55.
47. Leclercq C, Cazeau S, Lellouche D, et al. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: The RD-CHF Study. Pacing Clin Electrophysiol 2007;30(Suppl 1):S23–S30.
48. van Geldorp IE, Vernooy K, Delhaas T, et al. Beneficial effects of biventricular pacing in chronically right ventricular paced patients with mild cardiomyopathy. Europace 2010;12:223–229.
49. Adelstein E, Schwartzman D, Bazaz R, et al. Outcomes in pacemaker-dependent patients upgraded from conventional pacemakers to cardiac resynchronization therapy-defibrillators. Heart Rhythm 2014;11:1008–1014.
50. Baker CM, Christopher TJ, Smith PF, et al. Addition of a left ventricular lead to conventional pacing systems in patients with congestive heart failure: Feasibility, safety, and early results in 60 consecutive patients. Pacing Clin Electrophysiol 2002;25:1166–1171.
51. Chang PC, Wo HT, Chen TH, et al. Remote past left ventricular function before chronic right ventricular pacing predicts responses to cardiac resynchronization therapy upgrade. Pacing Clin Electrophysiol 2014;37:454–463.
52. Clements IP, Christenson S, Hodge DO, et al. Symptom improvement after upgrade from right ventricular apical to biventricular pacing: Role of right and left ventricular volumes assessed with single-photon emission computed tomographic equilibrium radionuclide angiocardiography. J Nucl Cardiol 2011;18:43–51.
53. Eldadah ZA, Rosen B, Hay I, et al. The benefit of upgrading chronically right ventricle-paced heart failure patients to resynchronization therapy demonstrated by strain rate imaging. Heart Rhythm 2006;3:435–442.
54. Horwich T, Foster E, De Marco T, et al. Effects of resynchronization therapy on cardiac function in pacemaker patients "upgraded" to biventricular devices. J Cardiovasc Electrophysiol 2004;15:1284–1289.
55. Nagele H, Dodeck J, Behrens S, et al. Hemodynamics and prognosis after primary cardiac resynchronization system implantation compared to "upgrade" procedures. Pacing Clin Electrophysiol 2008;31:1265–1271.
56. Scott PA, Whittaker A, Zeb M, et al. Rates of upgrade of ICD recipients to CRT in clinical practice and the potential impact of the more liberal use of CRT at initial implant. Pacing Clin Electrophysiol 2012;35:73–80.
57. Rahmouni HW, Kirkpatrick JN, St John Sutton MG. Effects of cardiac resynchronization therapy on ventricular remodeling. Curr Heart Fail Rep 2008;5:25–30.
58. Vatankulu MA, Goktekin O, Kaya MG, et al. Effect of long-term resynchronization therapy on left ventricular remodeling in pacemaker patients upgraded to biventricular devices. Am J Cardiol 2009;103:1280–1284.
59. Bogale N, Witte K, Priori S, et al. The European Cardiac Resynchronization Therapy Survey: Comparison of outcomes between de novo cardiac resynchronization therapy implantations and upgrades. Eur J Heart Fail 2011;13:974–983.
60. Foley PW, Muhyaldeen SA, Chalil S, et al. Long-term effects of upgrading from right ventricular pacing to cardiac resynchronization therapy in patients with heart failure. Europace 2009;11:495–501.
61. Frohlich G, Steffel J, Hurlimann D, et al. Upgrading to resynchronization therapy after chronic right ventricular pacing improves left ventricular remodelling. Eur Heart J 2010;31:1477–1485.
62. Marai I, Gurevitz O, Carasso S, et al. Improvement of congestive heart failure by upgrading of conventional to resynchronization pacemakers. Pacing Clin Electrophysiol 2006;29:880–884.
63. Paparella G, Sciarra L, Capulzini L, et al. Long-term effects of upgrading to biventricular pacing: Differences with cardiac resynchronization therapy as primary indication. Pacing Clin Electrophysiol 2010;33:841–849.
64. Gierula J, Cubbon RM, Jamil HA, et al. Cardiac resynchronization therapy in pacemaker-dependent patients with left ventricular dysfunction. Europace 2013;15:1609–1614.
65. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.

66. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6–75.
67. Stevenson WG, Hernandez AF, Carson PE, et al. Indications for cardiac resynchronization therapy: 2011 Update from the heart failure society of america guideline committee. J Card Fail 2012;18:94–106.
68. Barold SS, Guglin M, Herweg B. The advent of cardiac resynchronization therapy has created a confusing terminology of heart failure. Cardiol J 2012;19:11–14.
69. Guglin M, Barold SS. Electrical devices for left ventricular dysfunction and heart failure: Do we need revised guidelines? J Interv Card Electrophysiol 2012;34:197–204.
70. Guglin M, Barold SS. Evaluation of heart failure symptoms for device therapy. Pacing Clin Electrophysiol 2012;35:1045–1049.
71. Summary of Safety and Effectiveness Data (SSED). Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/p010031s381b.pdf. Accessed April 10, 2014.
72. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.
73. Romeyer-Bouchard C, Da Costa A, Dauphinot V, et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. Eur Heart J 2010;31:203–210.
74. Poole JE, Gleva MJ, Mela T, et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. Circulation 2010;122:1553–1561.
75. Betts TR, Gamble JH, Khiani R, et al. Development of a technique for left ventricular endocardial pacing via puncture of the interventricular septum. Circ Arrhythm Electrophysiol 2014;7:17–22.
76. Gierula J, Jamil HA, Witte KK. Septal pacing: Still no clarity? Pacing Clin Electrophysiol 2014;37:263–264.
77. Kypta A, Steinwender C, Kammler J, et al. Long-term outcomes in patients with atrioventricular block undergoing septal ventricular lead implantation compared with standard apical pacing. Europace 2008;10:574–579.
78. Molina L, Sutton R, Gandoy W, et al. Medium-term effects of septal and apical pacing in pacemaker-dependent patients: A double-blind prospective randomized study. Pacing Clin Electrophysiol 2014;37:207–214.
79. Shimony A, Eisenberg MJ, Filion KB, et al. Beneficial effects of right ventricular non-apical vs. apical pacing: A systematic review and meta-analysis of randomized-controlled trials. Europace 2012;14:81–91.
80. Wang F, Shi H, Sun Y, et al. Right ventricular outflow pacing induces less regional wall motion abnormalities in the left ventricle compared with apical pacing. Europace 2012;14:351–357.
81. Weizong W, Zhongsu W, Yujiao Z, et al. Effects of right ventricular nonapical pacing on cardiac function: A meta-analysis of randomized controlled trials. Pacing Clin Electrophysiol 2013;36:1032–1051.
82. Thackray SD, Witte KK, Nikitin NP, et al. The prevalence of heart failure and asymptomatic left ventricular systolic dysfunction in a typical regional pacemaker population. Eur Heart J 2003;24:1143–1152.
83. Chen S, Yin Y, Lan X, et al. Paced QRS duration as a predictor for clinical heart failure events during right ventricular apical pacing in patients with idiopathic complete atrioventricular block: Results from an observational cohort study (PREDICT-HF). Eur J Heart Fail 2013;15:352–359.
84. Miyoshi F, Kobayashi Y, Itou H, et al. Prolonged paced QRS duration as a predictor for congestive heart failure in patients with right ventricular apical pacing. Pacing Clin Electrophysiol 2005;28:1182–1188.
85. Pan W, Su Y, Sun A, et al. Native and paced QRS duration in right ventricular apex paced patients. J Card Fail 2010;16:239–243.
86. Manchanda M, McLeod CJ, Killu A, et al. Cardiac resynchronization therapy for patients with congenital heart disease: Technical challenges. J Interv Card Electrophysiol 2013;36:71–79.
87. van der Hulst AE, Delgado V, Blom NA, et al. Cardiac resynchronization therapy in paediatric and congenital heart disease patients. Eur Heart J 2011;32:2236–2246.