Left univentricular pacing for cardiac resynchronization therapy

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REVIEW

Left univentricular pacing for cardiac resynchronization therapy

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This review describes the rationale and published evidence for left univentricular pacing for cardiac resynchronization therapy, gives an overview of the existing optimization algorithms featuring this mode, and discusses future perspectives.

Keywords Cardiac resynchronization therapy • Left ventricle • Pacing • Optimization • Heart failure

Introduction

The cornerstone of cardiac resynchronization therapy (CRT) is improvement of synchrony of cardiac contraction to increase pump function of the heart. There is solid evidence that patients with left bundle branch block (LBBB) benefit most from CRT.[1,2] In these patients, right ventricular (RV) electrical activation may be normal,[3] and the main mechanism explaining benefit of CRT is correction of delayed left ventricular (LV) electrical activation by the coronary sinus lead. Indeed, there is good evidence that fusion pacing, i.e. a mix between intrinsic atrioventricular (AV) conduction (which initiates RV activation, with or without RV pacing) and LV capture (which compensates LV electrical delay) is haemodynamically optimal.[4–11] Another advantage with left univentricular pacing compared with biventricular (BiV) pacing is reduced current drain and prolonged battery longevity. The main issue with LV fusion pacing is that the intrinsic AV conduction delay is variable, both in the short term during various daily activities and over longer periods of time due to changes in disease state and other factors such as medication.

Physiological rationale for left univentricular pacing

The very first studies investigating the acute haemodynamic effects of CRT showed that the effects of left univentricular and BiV pacing were similar, often with LV pacing tending to be even better than BiV pacing.[12–15] Similar acute haemodynamic benefits during LV and BiV pacing were observed in experiments in the canine LBBB model.[16,17]

A reasonable explanation for the good performance of LV pacing seems to be that it can be applied using an AV delay that provides optimal fusion (collision) between the activation wavefronts originating from intrinsic conduction to the RV (via relatively preserved right bundle branch conduction, at least in patients with LBBB) and the LV pacing electrode (*Figure 1*).[5] The benefit of this approach is logical: the impulses from the right bundle branch break out of the Purkinje system at multiple RV locations, thus providing 'multisite activation' and maintaining the synchrony of activation in the RV. It should be noted that with BiV pacing, RV capture results in RV dyssynchrony with prolonged RV electrical activation duration,[3] an aspect that is rarely considered in CRT.

The beneficial effect of fusion pacing has been observed in animals[4,5] and patients.[6–11] However, several studies have demonstrated that even when the AV delay is not programmed to aim at fusion, left univentricular pacing can still create a benefit that is virtually as large as BiV pacing. As left univentricular pacing generally prolongs rather than shortens the QRS complex,[18] this results in the paradoxical situation that electrical dyssynchrony leads to mechanical benefit. Therefore, it may well be that the beneficial haemodynamic effects of left univentricular and BiV pacing result from different mechanisms. Support for this idea has been provided by a combined animal, patient, and computer simulation study.[18] In dogs in which proximal LBBB were created as well as pacing-induced heart failure, LV and BiV pacing resulted in the same increase in LV dP/dT_{max}, despite completely different effects on electrical activation. The same findings were observed in CRT patients, where the lack of fusion during LV pacing was confirmed by ECG imaging. The computer model showed the same findings and provided a possible explanation. The model showed that LV pacing not only prestretched the interventricular septum, but also the RV free wall. Both walls become hypercontractile by virtue of the Frank–Starling mechanism. Whereas the increase in septal contractility was balanced by LV free wall hypocontractility, RV hypercontractility appeared to increase cardiac output by ventricular interaction.[18]

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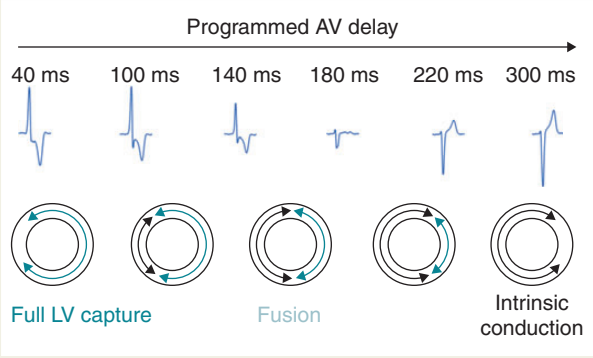

Figure 1 Schematic representation of the effect of left univentricular pacing at various AV delays. Circles indicate the cross-section of the left ventricle (LV), with the left side representing the septum and the right side the LV free wall. Turquoise arrows indicate the activation wavefront generated by LV pacing; black arrows indicate the wavefronts generated by intrinsic conduction. Representative ECGs of a patient study are presented as well, showing the change in QRS morphology illustrating the changing wavefronts and fusion.

Several forms of this interaction may be considered. Serial coupling of the ventricles via the pulmonary and systemic circulations is a first mechanism, i.e. a higher output of the RV will sequentially lead to increased output by the LV and *vice versa*. However, there is also a direct mechanical interaction that is due to the anatomical coupling via the interventricular septum and the surrounding pericardium.[19] Bulging of the interventricular septum by early contraction of the LV free wall will in turn stretch the RV free wall. The animal experiments showed no direct effect of left univentricular pacing on indexes of LV filling, and therefore, the positive effect most probably results from direct mechanical interaction.[18] This explanation has been described as the 'missing link' between electrical and mechanical performance of the heart.[20] It also suggests that the RV can only support the LV if its systolic function is preserved. Therefore, in the case of RV failure, this mechanism may not be effective, and BiV or LV fusion pacing may be superior to left univentricular pacing without significant fusion.

Regarding the haemodynamic impact of AV intervals on BiV and LV pacing, Gold *et al.*[15] showed in an acute haemodynamic study in 28 CRT patients that optimal AV delays were similar in both pacing configurations (with a similar magnitude in d*P*/d*T* improvement). Optimized intervals can therefore be used interchangeably.

Randomized studies evaluating left univentricular vs. biventricular pacing

Starting from acute studies reported almost 20 years ago[12,13,21] which showed that LV pacing induces short-term haemodynamic benefits, mid- and long-term effects have been reported (a summary of these studies is shown in *Table 1*).

The first randomized, single-blind, controlled parallel study in this field was BELIEVE.[22] The study demonstrated in 74 patients with systolic heart failure and LBBB that LV pacing resulted in a comparable rate of response (defined as an absolute increase in LVEF of >5% or increase in 6-min walking test of ≥10%) compared with BiV pacing at 12 months (75 vs. 70% respectively, $P = 0.79$). Improvement in LVEF was comparable in magnitude (+5.2 and +4.2%, respectively, $P = 0.70$). Moreover, chronic LV pacing showed a comparable safety profile as BiV pacing.

The multicentre DECREASE-HF trial[23] randomized 306 CRT patients with LVEF ≤0.35, NYHA III/IV heart failure, and QRS >150 ms to simultaneous BiV, sequential BiV, or left univentricular pacing. Left ventricular volumes and systolic and diastolic function were assessed by echocardiography at baseline, 3 months, and 6 months. All groups had a significant reduction in LV end-systolic and end-diastolic dimensions and improvement in LVEF ($P < 0.001$). Some parameters in LV size showed more improvement in the simultaneous BiV pacing group. Functional parameters were however not reported. The B-LEFT HF study[24] was a prospective, multicentre, randomized, double-blind study in 176 CRT-D recipients aiming to evaluate whether left univentricular pacing is non-inferior to BiV pacing regarding clinical and echocardiographic response. The proportion of responders was in line with current literature on CRT, with improvement in the heart failure composite score in 76.2 and 74.7% of patients in BiV and LV groups, respectively. The study indicated that LV pacing was non-inferior to BiV pacing for a series of response criteria (combination of improvement in NYHA and reverse remodelling, improvement in heart failure composite score, reduction in LV end-systolic volume of at least 10%), both at intention-to-treat and at per-protocol analyses.

The blinded crossover LOLA ROSE pilot study[25] randomized BiV and LV pacing during 8 weeks in 18 patients and found no differences in clinical outcome measures (peak oxygen consumption, 6-min walk distance, and SF36 health questionnaire scores). NYHA class was significantly better in the BiV than in the LV pacing mode, although the small number of patients limits the conclusions one can draw from this study. In a single-centre study that randomized 40 patients with idiopathic dilated cardiomyopathy to LV vs. BiV pacing, Sedláček *et al.*[26] reported worse results with LV pacing at 1 year of follow-up in terms of LV remodelling (LV ejection fraction and end-diastolic diameter). However, the small size of these two studies limits the conclusions that can be drawn.

A meta-analysis was performed in the five previously mentioned randomized studies,[28] evaluating a total of 574 patients. After a midterm follow-up, pooled analysis demonstrated that LV pacing resulted in similar improvements in 6-min walk distance, quality of life, and NYHA functional class and peak oxygen consumption compared with BiV pacing (*Figure 2*). There was a trend toward a superiority of BiV over LV pacing for LV ejection fraction and LV end-systolic volume. In another meta-analysis of the same five studies, Boriani *et al.*[29] report no differences in all-cause mortality/heart transplantation and hospitalization.

The recent GREATER-EARTH[27] study randomly crossed over 121 CRT patients (of whom 103 completed follow-up) to BiV vs. left univentricular pacing for 6-month periods. Exercise duration at 75% of peak VO_2 (the primary outcome), remodelling (improvement in LV ejection fraction and end-systolic volumes), and proportion of responders (≥20% increase in exercise duration) were similar in both groups. It was also observed that 31% of LV non-

Table 1 Summary of trials randomizing left ventricular vs. biventricular pacing for cardiac resynchronization therapy

Study	*n*	Randomization	Inclusion criteria	Primary endpoint	Follow-up	Results
BELIEVE[22]	74	1 :1 BiV vs. LV	NYHA II-IV LBBB, SR QRS ≥130 ms LVEF ≤35% LVEDD ≥55 mm	Increase in LVEF >5% and/or ≥10% in 6MWT	12 months	Similar responder rates in both groups (BiV = 70%, LV = 75%, $P = 0.788$). LVEF increased by 5.2% ($P = 0.002$) in LV group at 12 months.
DECREASE-HF[23]	306	1 :1 :1 Simultaneous BiV vs. Sequential BiV vs. LV	NYHA III/IV QRS ≥150 ms SR LVEF ≤35%	Score combining peak VO_2 and LVESD (not reported in this publication)	6 months	Similar improvement in LVEDD, LVEDV, LVESV, stroke volume, cardiac output, LVEF in all groups. Greater reduction in LVESD with simultaneous BiV group. No difference in adverse events.
B-LEFT HF[24]	176	1 :1 BiV vs. LV	NYHA III/IV QRS ≥130 ms SR LVEF ≤35%	≥1 point decrease in NYHA class and ≥5 mm decrease in LVESD	6 months	No difference in the primary endpoint, heart failure composite score, and adverse events.
LOLA ROSE[25]	18	Crossover BiV vs. LV	NYHA III/IV LBBB, SR QRS ≥120 ms LVEF ≤35%	Peak VO_2	2 × 2 months	No difference in peak VO_2, 6MWD, QOL. Better NYHA during BiV pacing ($P < 0.01$).
Sedlacek *et al.*[26]	40	1:1 BiV vs. LV	NYHA III/IV LBBB, SR QRS ≥120 ms LVEF <35% LVEDD ≥55 mm	Combined score including: improvement in LVEF ≥5%, decrease of LVEDD ≥5 mm, improvement by ≥1 NYHA class, ≥10% increase in peak VO_2 or 6MWD	12 months	Trend in better score with BiV pacing ($P = 0.06$). Greater improvement in LVEF and LVESD with BiV. No differences in groups for improvement in NYHA class, QOL, 6MWD, peak VO_2.
GREATER-EARTH[27]	121	Crossover BiV vs. LV	6MWT ≤400 m SR QRS ≥120 ms LVEF <35%	Submaximal exercise duration	2 × 6 months	No difference in the primary endpoint (>50% improvement in exercise capacity in both groups). Similar improvements in LVEF, LVESV, NYHA class, 6MWD. Similar incidences of adverse events.

6MWD, 6-min walking distance; BiV, biventricular pacing; LV, left ventricular pacing; LVEF, left ventricular ejection fraction; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association functional class; QOL, quality of life; SR, sinus rhythm.

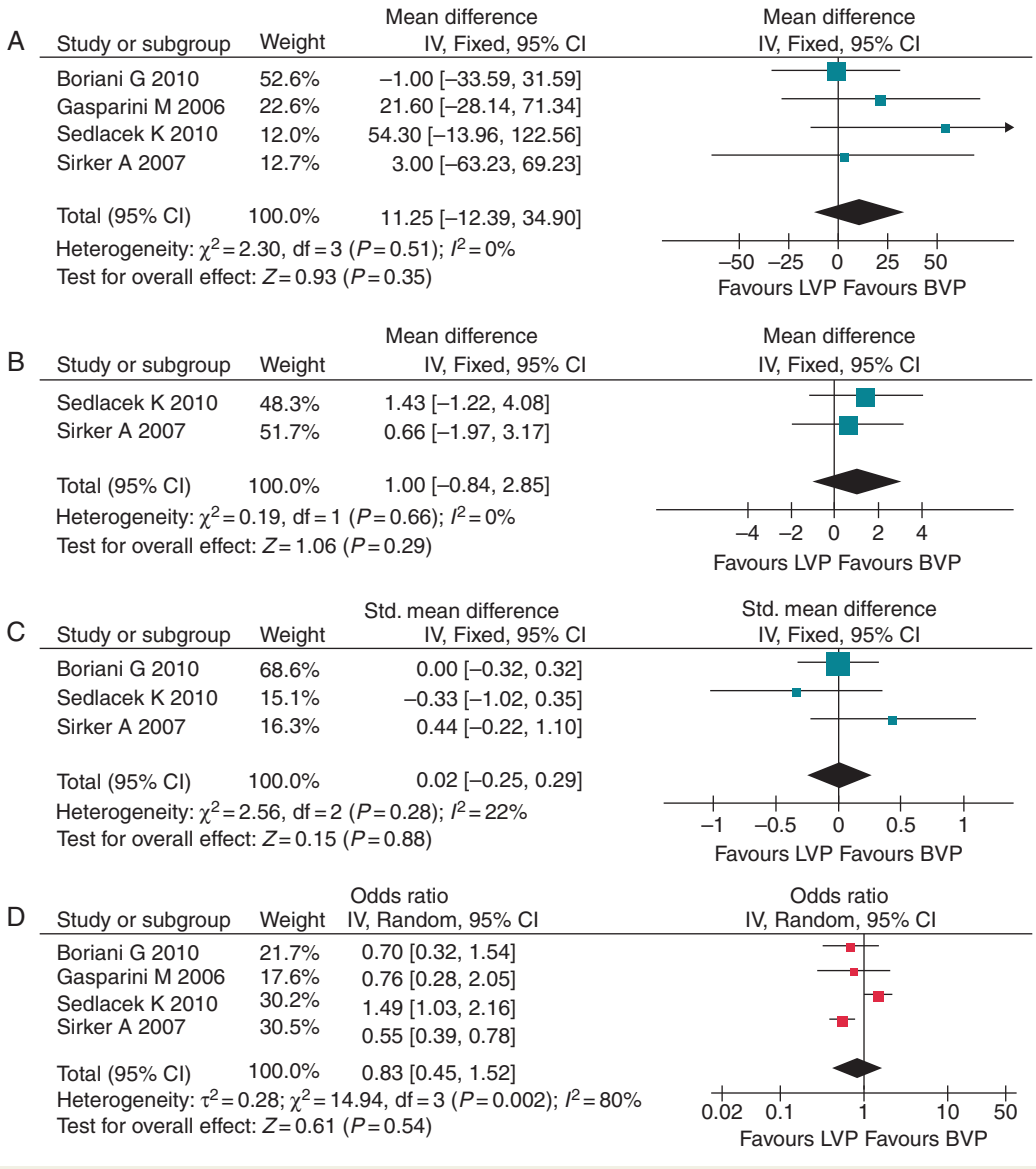

Figure 2 Improvement in clinical status between biventricular pacing and left univentricular pacing for (*A*) 6-min walk distance, (*B*) peak oxygen consumption, (*C*) quality of life, and (*D*) New York Heart Association class. Reproduced with permission from Liang *et al.*[28]

responders improved with BiV pacing and 17% of BiV non-responders improved with left univentricular pacing. There were no differences in adverse events between the groups.

It should be pointed out that these studies did not aim to obtain synchronized LV fusion pacing. The AV intervals were optimized using echocardiography (BELIEVE,[22] LOLA ROSE,[25] Sedlacek *et al.*[26]), automatic algorithms based upon intra-cardiac electrograms (DECREASE-HF,[23] using a precursor of the Smart Delay algorithm described below) or no specific method (B-LEFT HF[24]). In the GREATER-EARTH study,[27] the longest AV delay that fully captured the LV (i.e. without fusion with intrinsic conduction) during left univentricular pacing was programmed. It may be that LV pacing may have shown better results in these studies had fusion pacing been performed using specific device algorithms or the surface ECG.

Algorithms for synchronized left univentricular pacing

Currently, there are three algorithms available that synchronize LV pacing. They result in different extents of fusion between intrinsic AV conduction and LV capture.

VVT pacing mode

This mode is available on all current CRT devices [under different denominations, e.g. Medtronic (Minneapolis, MN, USA) Ventricular Sensed Response, Boston Scientific (Marlborough, MA, USA) BiV Trigger, etc.]. This mode is essentially used to maintain some degree of resynchronization in the case of intrinsic AV conduction during

atrial fibrillation or if the AV delay is programmed too long. Depending on the manufacturer, the device triggers a LV or BiV pacing output immediately upon an RV sensed event, as long as there is no violation of the upper rate limit (which may be programmed separately for this feature in some manufacturers, e.g. Medtronic, Biotronik). In the case of a BiV pacing output, only the LV will capture as the RV will be refractory. The feature is available both in non-atrial tracking, i.e. DDI(R) or VVI(R), as well as atrial tracking, i.e. VDD or DDD(R) modes. In a non-tracking mode, a sensed RV event below the maximum rate triggers an immediate ventricular pacing pulse. In a tracking mode, a sensed RV event during the AV interval triggers an immediate ventricular pacing pulse. Thus, ventricular premature beats occurring during sinus rhythm will usually not trigger a pacing output (except for Boston Scientific devices and as an option on Biotronik devices). The algorithm results in some degree of fusion in patients with LBBB and a very wide QRS (see *Figure 3*). It will however only result in pseudo-fusion in cases with less pronounced intra-ventricular conduction delay or in the case of right bundle branch block (RBBB) due to late detection by the RV lead.

Smart Delay™ (Boston Scientific)

This algorithm is based on acute haemodynamic data from the PATH CHF II studies.[30] The algorithm is executed in-office only and automatically measures intrinsic AV conduction times of the RV and LV leads during atrial sensing and atrial pacing (i.e. AS-RVS; AP-RVS; AS-LVS; AP-LVS). As shown in *Figure 4*, the algorithm recommends either simultaneous BiV or LV pacing (this feature is not available in the USA as it is not FDA approved). Left univentricular pacing is recommended when (i) the LV lead is in an anterior position (this information may be entered manually in the patient data screen or is assumed to be the case the LV−RV sensing delay is $<$40 ms) or (ii) the LV−RV sensing delay is $\geq$20 ms and the average AV interval sensed from the RV lead is $\leq$271 ms. In addition, the algorithm proposes optimal AV delays (for atrial sensing and atrial pacing) based on LV lead location and AV conduction times of the RV and LV leads. The algorithm will not work in the case of second- or third-degree AV block or in case the intrinsic AV conduction delay is $>$400−450 ms (depending on the model). The proposed AV delay may be too short in case of inter-atrial conduction delay (as P-wave duration is not measured). Another shortcoming is that the parameters are not updated automatically and may therefore not correspond to optimal settings under different conditions or over time between in-office visits.

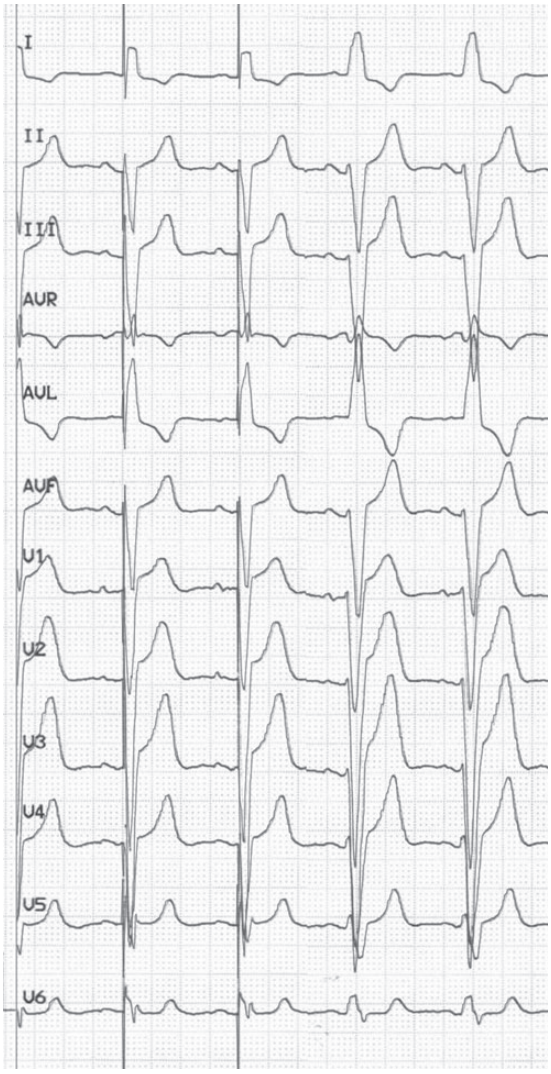

Figure 3 Ventricular fusion pacing using the VVT pacing mode in a patient with a biventricular pacemaker. The first two beats show triggered biventricular pacing, synchronized to right ventricular sensing, whereas the last two beats show intrinsic rhythm with LBBB during temporary inactivation of the algorithm. Note QRS narrowing during VVT pacing. ECG paper speed of 25 mm/s and calibration of 1 mV/cm.

AdaptivCRT™ (Medtronic)

This algorithm dynamically optimizes CRT pacing (BiV vs. LV) and AV/VV delays (see *Figure 5*). The algorithm measures intrinsic AV conduction delays that are updated every minute during one beat (the VVT mode maintains CRT) as well as P-wave and QRS durations measured on the far-field electrogram (can to SVC coil or to right atrial ring), which are updated once every 16 h (during five consecutive beats, without VVT pacing). If the intrinsic AV interval is normal and the heart rate does not exceed 100 bpm, the algorithm provides optimized left univentricular pacing with an AV delay equal to ∼70% of the intrinsic AV interval. Under these conditions, LV pacing has been shown to result in fusion and is haemodynamically preferable.[31,32] Otherwise, the algorithm provides optimized BiV pacing, during which the AV delay is adjusted so that pacing occurs 30 ms after the end of the P-wave, but at least 50 ms before the onset of the intrinsic QRS. This approach is supported by studies showing that optimal AV intervals can be approximated from surface P-wave duration[33] and intra-cardiac electrograms.[34] The algorithm is available in the DDD(R) mode and may be set to switch between adaptive LV and adaptive BiV pacing or set to operate always in adaptive BiV pacing. Thus, the AV and VV delays as well as the ventricular pacing chambers (BiV vs. LV) are automatically updated every minute and will automatically adjust and accommodate for changes in intrinsic conduction (e.g. during sleep). The algorithm functions in case of second- or third-degree AV block, when it

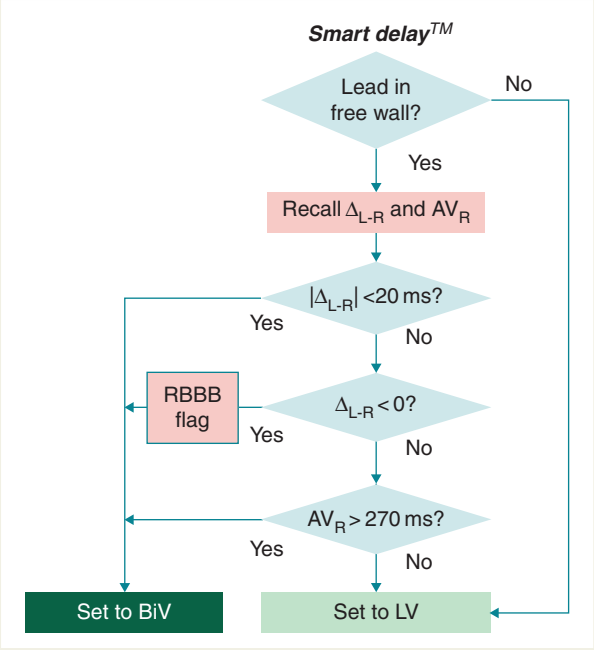

Figure 4 Description of the Boston Scientific Smart Delay algorithm function. Adapted and reproduced with permission from Boston Scientific. AVR, right-sided intrinsic AV delay; BiV, biventricular; LV, left ventricular; N, no; Y, yes; RBBB, right bundle branch block; ΔL-R, difference between left and right ventricular timing; IΔL-RI, absolute difference between left and right ventricular timing.

provides BiV pacing (as there is no fusion with intrinsic AV conduction) and derives the optimal AV interval from the P-wave duration. In case of frequent atrial or ventricular premature beats or during atrial tachyarrhythmias, the algorithm automatically suspends its operation and provides BiV pacing.

A potential shortcoming of this algorithm is that in some patients, measurement of P-wave duration from the far-field electrogram may have limited accuracy due to low-amplitude waveforms. Also, the optimal AV intervals may be influenced by factors other than intrinsic conduction, such as lead position, pacing latency, etc.

Evidence of efficacy of left ventricular fusion pacing algorithms

In a study enrolling 32 CRT patients, the acute haemodynamic effect of the VVT algorithm was compared with echo-optimized BiV pacing.[35] The improvement (studied by the aortic velocity-time interval) was similar with the VVT algorithm as with BiV pacing in patients with LBBB. Patients with RBBB however did not benefit, most probably for the reasons mentioned previously.

The clinical impact of triggered ventricular pacing or the SmartDelay™ algorithm using left univentricular pacing has not been studied to date.

The Adaptive-CRT trial randomized 522 patients in a 2:1 ratio to CRT optimization with the AdaptivCRT™ algorithm vs. echocardiography.[36] The study met all three primary non-inferiority endpoints: clinical composite score (CCS), aortic velocity-time

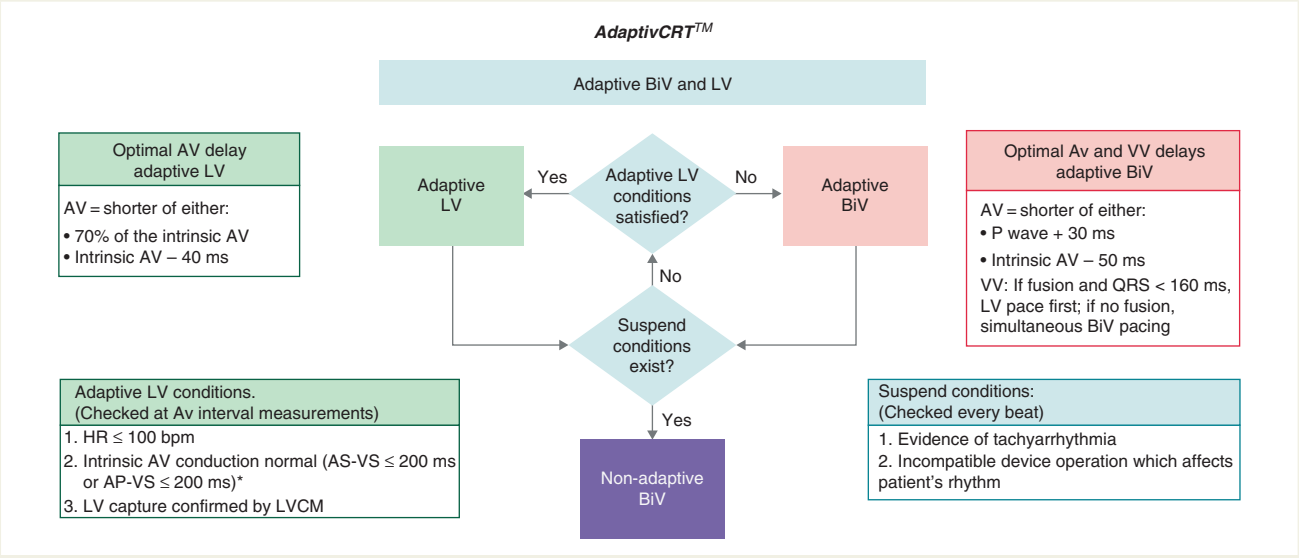

Figure 5 Description of the Medtronic AdaptivCRT™ algorithm function. *In models released as from 2016, the intrinsic AV delays that qualify for LV pacing is extended by 20 ms (i.e. from 200 to 220 ms for the sensed AV delay and from 250 to 270 ms for the paced AV delay). This should increase the percentage of LV pacing by ~20% (personal communication, data on file). Adapted and reproduced with permission from Medtronic. AV, atrioventricular; BiV, biventricular; LV, left ventricular; LVCM, left ventricular capture management.

integral, and safety. The algorithm was associated with a 44% reduction in RV pacing at 6-month follow-up. There were no significant differences between the two groups for mortality and heart failure hospitalization. In a sub-analysis of the study,[37] patients with ≥50% of synchronized LV pacing showed lower heart failure hospitalization and mortality compared with those with <50% synchronized LV pacing (HR 0.49, 95% CI 0.28–0.85; $P = 0.012$). In patients with normal AV conduction, the algorithm significantly increased the rate of CRT response compared with the echo arm (81 vs. 68%; $P = 0.04$) and lowered the risk of death or heart failure hospitalization (HR 0.52; 95% CI 0.27–0.98; $P = 0.044$). A greater proportion of patients in the adaptive CRT arm improved their CCS at 6 months (81 vs. 69%; $P = 0.041$) and at 12 months (77 vs. 66%; $P = 0.076$). Another sub-analysis of the Adaptive-CRT trial[38] focused on the 30-day readmissions rate after discharge (which may be associated with a reduction in reimbursement in some countries). AdaptivCRT™ reduced all-cause and heart failure readmission compared with patients optimized by echocardiography: 19.1 vs. 35.7% (OR 0.41; 95% CI 0.19–0.86; $P = 0.02$) and 14.8 vs. 24.8% (OR: 0.54; 95% CI: 0.31–0.94; $P = 0.03$), respectively. In another report,[39] the active arm of the Adaptive-CRT trial was compared with a pooled historical control derived from the CRT arms of four clinical trials (MIRACLE, MIRACLE ICD, PROSPECT, and InSync III Marquis). A propensity score model was used to adjust 22 potential baseline cofounders of the effect of CRT and showed that patients with AdaptivCRT™ were significantly more likely to have an improved CCS (odds ratio = 1.65, 95% CI: 1.1–2.5). Data presented in abstract form have shown that over long-term follow-up (mean 20 ± 6 months), patients receiving AdaptivCRT™ experienced a reduction in the risk of developing atrial fibrillation (HR = 0.54; 95% CI 0.31–0.93; $P = 0.03$) compared with the control patients.[40]

Thus, current data on the AdaptivCRT™ algorithm are encouraging, but validation by a randomized study with superiority primary endpoints is needed. An ongoing trial is AdaptResponse (NCT02205359) which is enrolling 3000 patients with LBBB and normal AV conduction with a combined primary endpoint of all-cause mortality and intervention for heart failure decompensation.

Future perspectives

Dual-chamber pacemakers with only an LV lead for CRT have been proposed in settings with economical constraints.[41] Even though left univentricular pacing may play an increasing role in CRT, RV leads will probably continue to be implanted, because they are required for defibrillation, provide the option of BiV pacing (which may be superior to LV pacing in subsets of patients), and allow backup pacing and sensing if the LV lead fails. Leadless pacemakers are being investigated to deliver LV pacing,[42] although for the time being, they require a conventional right-sided system with RV pacing to synchronize the LV pacing stimulus.

An important issue will be to identify candidates in whom LV pacing is superior to BiV pacing. Some degree of RV conduction disease may be present in patients with LBBB, who in this instance may benefit from BiV fusion pacing. It is unlikely that patients with pure RBBB will derive any benefit (RV-only fusion pacing may however be an option in this setting, but no algorithms currently exist to deliver this in a consistent manner). Some patients with non-specific, intraventricular conduction delay may be candidates for left univentricular CRT, but it remains to be determined how to identify them and whether pacing timing is the same as for patients with LBBB. Non-invasive ECG imaging is of potential interest but remain investigational for the time being due to limited availability and cost issues.

The current automatic CRT optimization algorithms that deliver left univentricular pacing aim to provide some degree of fusion with intrinsic AV conduction. A template of the RV electrogram during intrinsic AV conduction may be stored to indicate conduction over the right bundle branch and then used to adjust AV intervals during LV pacing. Modification in the electrogram morphology indicates changes in RV activation (i.e. less fusion), which has been shown to be associated with decreasing LV dP/dT.[9]

Conclusions

Left univentricular pacing is an option that may be considered to maximize response to CRT and at least as an alternative in non-responders to BiV pacing. Synchronized left univentricular pacing is based on the concept that ventricular activation may be best obtained by recruiting the intrinsic AV conduction, especially over the right bundle branch which may be intact in many candidates to CRT. To achieve this, algorithms are proposed by different device companies. Ideally, these algorithms should be able to automatically update AV intervals to accommodate for changes in AV delay related to daily activity or to disease progression. The clinical impact of such algorithms is being assessed in randomized studies. Technological progress will hopefully continue to improve these algorithms to best titrate therapy on an individual basis and to allow our patients to derive the greatest possible benefit from CRT.

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