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REVIEW

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ECG optimisation for CRT systems in the era of automatic algorithms: a comprehensive review

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Abstract

Cardiac resynchronisation therapy (CRT) may fail in up to one third of patients, mainly due to anatomical and procedural issues. In the daily practice, ECG optimisation is largely used to address CRT delivery. Ineffective CRT can be related to non-optimal pacing timing as well as inadequate pacing-capture. A rate-competitive atrial fibrillation (AF) or a high daily burden of premature ventricular contractions (PVC) may also affect CRT by means of fusion or pseudo-fusion captures. Growing observations suggest that in a subset of patients with typical left bundle branch block (LBBB), selected LV pacing may be more effective, producing a complete fusion between the left pacing and the intrinsic right bundle activation. The His-ventricular (HV) interval is an invasive measurement (derived from electrophysiological study), which mainly reflects the RV activation (and its contribution to QRS timing) and has been proposed by some authors when addressing LV-paced–RV-sensed fusion. In sinus rhythm CRT patients, with baseline typical LBBB criteria and preserved AV conduction, the "dromotropic" management to achieve RV intrinsic activation with LV fusion is also "AV delay dependent". In this regard, the RV intrinsic activation (detected by RV sensing) and the A (paced/sensed)-RV (sensed) interval are also influenced by the RV lead position within the RV. The current families of CRT devices have implemented automatic algorithms to optimise AV and VV timing intervals. The proof of principle is again the evidence that fusion of an LV-paced beat with intrinsic rhythm may be more beneficial than standard biventricular pacing, provided a preserved AV conduction. In the present review, all the above issues are discussed.

Introduction

Cardiac resynchronisation therapy (CRT) is an established treatment in patients with heart failure, left ventricle (LV) dysfunction, reduced ejection fraction and enlarged QRS. Up to one third of patients may fail to respond to CRT for several reasons, such as anatomical and procedural issues in achieving effective LV pacing [1, 2] or changes in LV threshold over time, which may lead to subthreshold stimulation and concealed loss of capture, or inadequate CRT delivery related to suboptimal AV and VV delays [3–6].

CRT is normally achieved through pacing both ventricles; however, in selected cases, LV-only pacing has also been suggested to be non-inferior compared with biventricular pacing [7, 8].

The His-ventricular (HV) interval is an invasive measure, commonly derived from electrophysiological study, through right ventricle (RV) endocardial mapping, which mainly reflects the contribution of right ventricle activation to QRS timing. In patients with strict left bundle branch block (LBBB) criteria (Strauss criteria) and normal PR interval at ECG (< 140 ms), it may be possible to assume that an intact His-Purkinje conduction along the right bundle branch is present, which is conceptually associated with a normal HV interval [7, 9]. Growing

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observations suggest that a subset of patients with LBBB may benefit mostly from selected LV pacing and/or RV and LV pacing synchronised with intrinsic RV depolarisation to obtain the so-called triple-fusion; these patients may be identified through baseline intact AV conduction (i.e., intact AV-node and right bundle branch conduction) [7, 8].

Recently, permanent His bundle pacing (HBP) has proven to be effective in producing a significant narrowing and often normalisation of QRS duration and morphology. Although not widely accepted to date, QRS narrowing may play a role in achieving a better clinical response [10, 11].

The present review intends to discuss the recent literature and available device settings with regard to dromotropic management of CRT optimisation. A comparison among different CRT settings, as well as different optimisation methods or available automatic algorithms, is not the aim of the present work.

Pacing timing in CRT

Even though literature data show a neutral effect of echocardiographic CRT optimisation, electrocardiographic optimisation of pacing timing reprogramming may play a role [12].

Ineffective CRT can be related to non-optimal pacing timing other than pacing-capture issues.

The former can occur by fusion or pseudo-fusion-paced complexes in the case of sensed atrioventricular interval with preserved or frequent changes in the dromotropic properties of nodal or intranodal His-Purkinje conduction. Both conditions can be corrected by AV reprogramming [13, 14].

In other cases, during simultaneous biventricular pacing, the dominant contribution of RV pacing activation wavefront may render the LV tissue refractory (regionally or temporally) with transient loss or just local capture. This can be fixed by selecting a different LV pacing electrode in multipolar leads, or, more interestingly, by enhancing LV pacing preexcitation by 10 up to 80 ms (to advance LV capture and reduce LV recruitment by RV-sensed or paced activation, in a kind of "dromotropic RV to LV pace conditioning") [15].

A rate-competitive atrial AF or a high daily burden of PVC may also affect CRT by means of fusion or pseudo-fusion captures [16]. In this case, reprogramming has little or no effect. In patients with atrial fibrillation with adequate dromotropic drug control but highly variable R-R cycles, it may be discussed whether a triggered VVT pacing mode, including the "LV preexcitation", may improve LV capture by increasing the fusion captures instead of pseudo-fusion complexes. Based on this concept, most modern devices have "VVT-like" (RV-sensed-triggered) features designed to increase effective pacing during AF and to respond to PVCs; however, few of these devices have been shown to substantially increase CRT pacing percentage, and none has been evaluated for effective CRT pacing. In AF patients with difficult rate control, on top of rate-control drugs, AV-node ablation remains the first choice to ensure effective CRT delivery [16, 17].

The timely delivery of LV pacing and eventual LV-to-RV preexcitation might be addressed by direct electrogram interventricular delay during the CRT implant. Patients with stricter LBBB criteria have been shown to have a better outcome when compared to those with right bundle branch block (RBBB) and nonspecific intraventricular conduction delay (IVCD) patterns. This underlines that QRS absolute width itself may not reflect the real pattern of conduction delay to the LV, which instead may be measured by the Q-LV interval. The Q-LV interval is defined as the interval from the onset of the intrinsic QRS on 12-lead surface ECG to the first large positive or negative peak of the LV EGM [18].

Pastore et al. have recently reported that the Q-LV measure is able to detect a highly prolonged LV conduction delay in patients with strict criteria for LBBB; such delay is limited to the RV in RBBB patients. More important and quite unexpected, patients with nonspecific IVCD showed a very high variability in the Q-LV interval, from poor to very long, with the latter being a better CRT candidate target. Moreover, patients with an ECG pattern resembling RBBB in lead V1, but without the terminal S waves in the lateral limb ECG leads (I and aVL), presented an unexpectedly long Q-LV interval [19].

LV effective pacing

As already known, a higher LV pacing percentage is strongly related to a better clinical outcome.

Koplan et al. compared patients' outcomes and LV pacing percentage and reported a 44% risk reduction of death or HF hospitalisations among those paced > 92% [20].

The current technologies for LV capture automatic confirmation are based on evoked response (ER), available for Boston Scientific, Biotronik and Abbott Medical devices, or "LV pace to RV sense" analysis, available for Medtronic devices. Microport devices are not yet equipped with an ER-based auto-threshold algorithm.

In summary, the efficacy of CRT and the overall pacing percentage over time may be reduced by pacing inhibition (by sensed RV activation). Moreover, an intermittent loss of LV capture, (subthreshold currents or pacing delivered into refractory tissue), represents an important contributor to ineffective pacing, leading to inadequate

CRT delivery assessment, when only the LV pacing percentage is considered [21].

These considerations outline that the traditional LV pacing percentage counter may have a weak value in predicting effective CRT (Fig. 1).

A new algorithm, which evaluates the morphology of a dedicated unipolar LV EGM (LV cathode–RV coil EGM) during biventricular or LV pacing, has been recently proposed to determine, beat to beat, effective LV capture. This algorithm has been validated by comparing its diagnostics with a 12-lead surface ECG, with a 98% sensitivity for effectiveness [22].

This EffectivCRT™ algorithm is available in Medtronic CRT-D systems; it analyses 100 consecutive ventricular events every hour and determines the percentage of effective CRT pacing. All encountered ventricular safety pacing (back-up paced events) and/or ventricular sensing events noted in the 100 consecutive ventricular events are rejected. During data collection, the device transiently switches to the dedicated LV-to-RV coil unipolar EGM [22].

In summary, effective LV capture confirmation may be a helpful tool to fix a pacing/capture mismatch.

RV-LV fusion management

Only a few studies have examined synchronised LV pacing in patients with preserved atrioventricular conduction and normal RV electrical activation [7, 8, 23–27].

In the GREATER-EARTH study, 20.5% of the clinical non-responders to biventricular pacing (defined as $\leq 20\%$ improvement in exercise performance) showed an improvement with RV- synchronised LV pacing. However, it should be underlined that optimal synchronisation with intrinsic conduction was not a target in any of the clinical trials comparing LV pacing [8].

The adaptive CRT algorithm is a Medtronic branded algorithm that periodically measures intrinsic conduction and dynamically adjusts CRT pacing parameters to provide RV-synchronised LV pacing when AV conduction is normal (or to provide biventricular pacing when AV conduction is prolonged). Adaptive CRT has been assessed in a recent trial in which a higher percentage of RV-synchronised LV pacing was found to be associated with a decreased mortality risk and heart failure hospitalisations. In the subgroup of patients with normal AV conduction, the algorithm demonstrated better

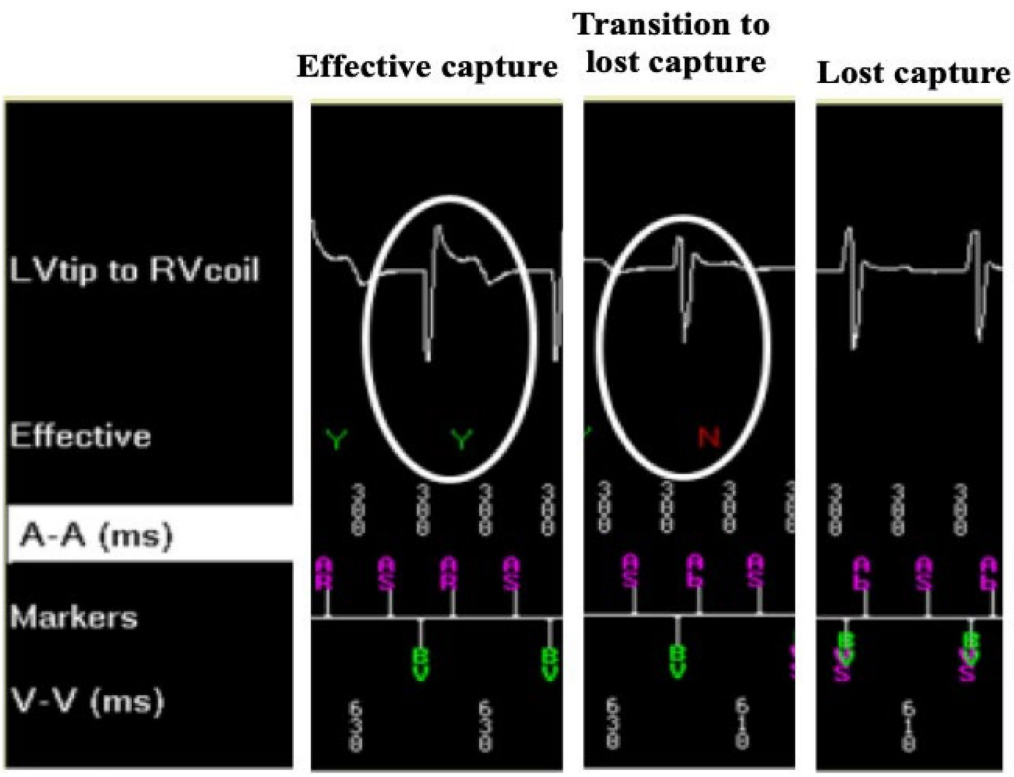


Fig. 1 Left ventricle capture confirmation by "EffectivCRT" algorithm. Dedicated unipolar LV EGM (LV cathode–RV coil EGM) during biventricular or LV pacing; until the third paced beat a "*Qr*" morphology indicate the effective LV capture; the fourth beat represent a kind of fusion and the further beats are represented by an "*rS*" morphology indicating the loss of LV capture. (with permission by Medtronic). *LV* left ventricle; *RV* right ventricle; *Y* LV effective OK; *N* loss of LV effective capture; *AS* atrial sense; *Ab* atrial blanking; *VS* ventricular

clinical outcomes when compared to echo optimised biventricular pacing [15].

Intriguing observations have been published over the last decade, pointing out that a subset of patients with LBBB, identified by a baseline intact AV conduction (i.e., an intact AV-node and right bundle branch conduction), may benefit more from selected LV pacing [7, 8, 23–27].

In a pioneering paper, Van Gelder et al. [23] reported data on acute hemodynamic assessment of LV pacing with fusion compared with biventricular simultaneous pacing. The authors support the hypothesis that synchronised LV pacing with fusion along the intrinsic right bundle conduction is superior in terms of performance as well as in terms of QRS narrowing. They addressed fusion during LV pacing throughout testing four AV delay settings, comparing the QRS morphology with complete LV preexcitation (AV delay 30 ms) to sequential longer AV delays. Fusion has been confirmed by a reduction in QRS width, change in morphology of the QRS complex on surface electrocardiogram and, importantly, the RV EGM recorded by pacemaker telemetry. This study shows that intrinsic conduction over the right bundle significantly contributes to the acute hemodynamic effect of LV pacing, expressed as an increase in LV dP/dt-max, and it is superior to biventricular simultaneous pacing at the longest AV intervals. Importantly, they also underline that ventricular fusion might be a function not only of the AV interval (dromotropic properties), but also of the total ventricular (interventricular dromotropic properties) activation time during LV pacing. The latter depends on the position of LV leads, LV mass and ventricular conduction velocity, which vary in each individual patient. Moreover, LV preexcitation obtained at the longest programmed AV delay proved better results compared with simultaneous pacing.

The physiological reason why LV pre-activation, preceding the RV one, provides better hemodynamic results is addressed as speculative. Interestingly, the authors presume that during fusion with intrinsic conduction, the slower activation resulting from LV (epicardial) pacing compared to intrinsic (endocardial) conduction may require an earlier left-sided activation to balance the whole electrical activation of the left ventricle; thus, the lead position and the epicardial spread of such pacing becomes another important variable. They have also previously demonstrated that this might be a function of the underlying cardiac disease, with patients with ischaemic cardiomyopathy necessitating more LV preexcitation compared to those with idiopathic dilated cardiomyopathy. Scar-related slow conduction might be compensated for by an earlier activation from the LV electrode [23].

A-V delay dependency

Suboptimal AV delay programming can lead to a 15% decline in LV cardiac output [28]. Large randomised clinical trials dealing with the overall efficacy of CRT differed widely in their approach to AV optimisation. For instance, in the CONTAK CD trial, there was no AV optimisation, while in the CARE-HF and MIRACLE trials, AV delay was optimised using Doppler trans-mitral flow [29–31]. Furthermore, the COMPANION trial has adopted an algorithm based on the intrinsic AV interval and baseline QRS width to determine a predicted optimal-programmed sensed AV delay [32].

CRT loss of pacing caused by oversensing, documented by the percentage of pacing, is one of the reasons for CRT failure. Devices' diagnostics may rank oversensing issues into three broad categories: competitive AF, PVCs and the less defined ventricular sensing episodes (VSE), the latter being documentation of lost CRT pacing without specific reason. In an intriguing paper by Cheng et al., VSE may be classified as due to *device programming issues*, such as atrial under-sensing, not-tracking pacing modes (DDI) and post-pacing or sensing AV delay intervals setting, or *clinical issues* such as supraventricular tachycardia, AF (or atrial tachycardia) and junctional rhythm. Considering a 98% CRT pacing percentage as a cut-off, they found roughly 40% (in their very large case series) of CRT patients with a lower CRT pacing rate, where VSE related to suboptimal AV delay programming accounted for one third of cases. Moreover, the contribution of long programmed AV delay (post- atrial-sense or atrial-pacing) to the duration of each VSE was minimal for patients with a CRT pacing percentage from 95 to 98% (5.4%) but became predominant in patients with percentages < 90% (45.6%), mostly for VSE duration of at least 10 beats [33]. While such suboptimal programming can be readily resolved by shorter AV delay intervals (or by rate-adaptive AV programming, as suggested by the authors), on the other hand, these intervals are commonly delayed when CRT optimisation is guided by hemodynamic data derived from echo-based modalities or automated device-based systems, thus mainly resulting in lengthening of AV delays from their nominal settings. One can speculate that a tight AV delay interval window may exist that allows for intrinsic conduction over the right bundle branch, leading to an increase in RV-LV fusion (as documented by echocardiographic improvement of dyssynchrony); otherwise, a shorter interval may favour a reliable sustained biventricular pacing, but, conversely, longer intervals may produce CRT loss. These baseline dromotropic properties should be addressed at each "in-office" device check.

Recently, HBP has been proposed as an alternative to biventricular pacing to achieve CRT [10, 11]. However,

its wide adoption may be limited by the concern of electrical disease progression along the His-Purkinje axis, owing to the lack of long-term performance data. A randomised crossover study by Lustgarten et al. showed that permanent HBP can significantly narrow the QRS in 72% of patients with bundle branch block, showing a 6-month clinical response comparable to traditional CRT [34]. Although HBP can narrow and occasionally normalise the QRS in patients with proximal His-Purkinje disease, there may be, or may occur over time, a residual distal conduction delay. Moreover, in patients with advanced cardiomyopathy, typical LBBB and IVCD can sometimes coexist.

Padeletti et al. performed an acute hemodynamic assessment of simultaneous His bundle and LV stimulation in 11 patients with systolic HF and LBBB. Although HBP did not narrow the QRS width in any of these patients, it led to a consistent improvement in stroke volume and maximum pressure derivative; importantly, these results were independent of A-V delay optimisation. These first observations emphasised the concept and the crucial role of LV pacing with fusion with intrinsic right bundle conduction via the HBP. Moreover, interventricular dromotropic management and "pace conditioning" may be managed at any level of atrioventricular conduction delay up to a complete AV block [35].

In these cases, resynchronisation may be conceptually achieved when an electric bypass acts over the whole specialised conduction system by means of HBP in conjunction with sequential LV pacing. Recently, further data are exploring the consecutive sequential LV pacing when synchronised with HBP, therefore in a His-optimised CRT strategy (HOT CRT) [36, 37].

In this subset of patients, more often affected by advanced cardiomyopathies, the HOT CRT strategy represents a novel approach to further electrical optimisation.

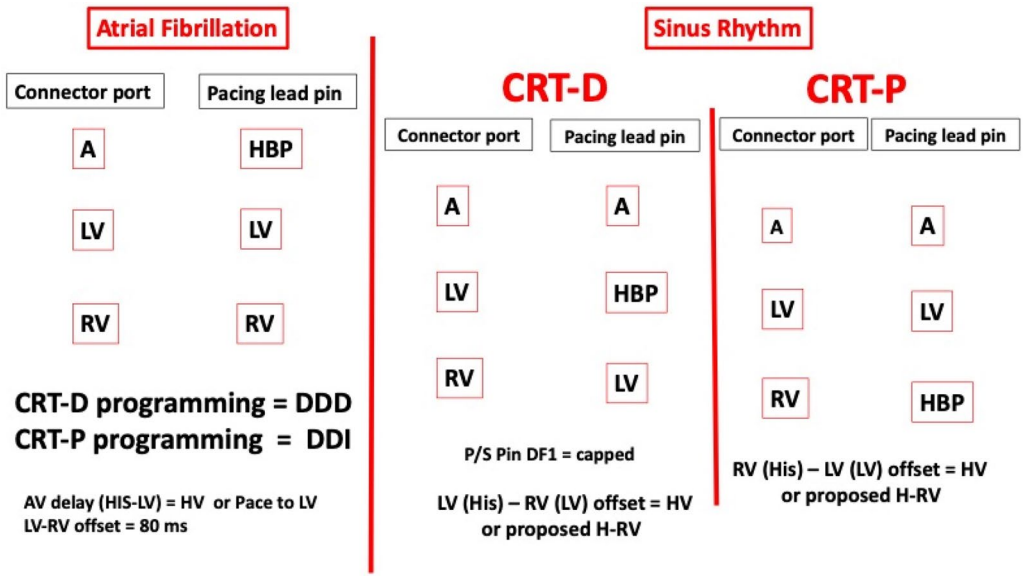
What is new is that fusion optimisation by HOT CRT can be achieved independently from intrinsic atrioventricular conduction, as in the case of AF, long PR intervals, or atrioventricular blocks.

Even though this strategy may offer rescue CRT options in selected cases, the challenge of device programming remains only partially solved because of the limited number of existing connector ports. The lack of an additional port represents an issue in CRT-D patients, while it is easily feasible in patients undergoing CRT-P.

In patients with permanent AF, atrial port availability provides a unique opportunity. In sinus rhythm patients, it is a greater challenge to incorporate the fourth lead without compromising other device functions. An alternative is to exclude the RV pace-sense electrode using a DF-1 ICD lead, provided reliable LV sensing is obtained (Table 1).

The HV interval is commonly measured during HBP implants. To perform HOT CRT in patients with AF, a DDD mode is suitable with an atrioventricular delay (His to LV delay) equal to HV. In the previously mentioned paper by Vijayaraman et al. [36], the LV-RV offset was programmed to a maximum of 80 ms with RV

Table 1 Connector port-pin arrangement and device programming in HOT-CRT strategy



A atrium; *LV* left ventricle; *RV* right ventricle, *His* His bundle; *HBP* His bundle pacing lead pin; *CRT-P* cardiac resynchronisation therapy-pacemaker; *CRT-D* cardiac resynchronisation therapy-defibrillator; *offset* programmable LV to RV delay

output set at 0.5 V at 0.01 ms in nondependent patients to avoid RV apical pacing. In this regard, the position of the RV lead (high RV septum versus apical) may become an important variable, as the RV-sense timing is a function of the progressive fusion with intrinsic right bundle branch conduction. An "advanced" (high RV septum) sensed RV may offer a prompter RV pacing inhibition when compared with a delayed one (apical RV). It may be discussed whether a direct measure of the His-EGM to RV-sense-EGM timing may represent a more useful parameter to guide the His to LV timing programming (therefore "His preexcitation"), as compared with the shorter HV interval to achieve complete fusion, guided by RV sensing.

As also discussed in Vijayaraman's paper, in patients with normal sinus rhythm undergoing CRT-D implants, the His lead must be connected to the LV port and the (bipolar) LV lead in the pace-sense portion of RV port, an arrangement therefore available only with DF-1 ICD lead (with the ICD lead pacing/sensing pin capped); otherwise, in sinus rhythm patients undergoing CRT-P, the His lead pin is connected to the RV port and the LV lead pin to the LV port. In both cases, the device is programmed in DDD with RV (His)-LV delay equal to HV or stimulus to ventricular interval.

In sinus rhythm patients, while managing RV-LV fusion in traditional CRT as compared with HOT CRT, the leading parameter is AV delay "dependency". The LV-to-RV preexcitation programming may achieve fusion with right bundle intrinsic conduction, provided an AV delay programmed "long enough" to permit the complete right ventricle His-Purkinje activation, sensed by the RV lead, which position may again affect its sensing timing. A shorter AV delay may produce such a "rate/cycle-dependent" intranodal or intra-Hisian conduction delay, thus increasing the RV pacing and decreasing the fusion occurrence. The direct measure of the atrial EGM to the RV EGM time interval (A-RV) may help to perform an electrical optimisation by means of LV-to-RV preexcitation programming, set at an interval equal to the A-RV interval minus the A-H or PR interval.

In AF patients implanted with traditional CRT systems, the lack of AV delay dependency may render the management of programmed RV-LV fusion challenging, and often achieved empirically, being the ablate and pace the key strategy in rate-competitive AF patients. On the other hand, as discussed above, in these cases, during HOT CRT, in order to reduce intraventricular dyssynchrony, it is possible to advance the His pacing to the LV one, provided a preserved right bundle branch intrinsic activation allowing acceptable RV-LV fusion.

Automatic "dromotropic" optimisation algorithms

The standard method to optimise CRT setting is still debated. Echocardiography has been used in some clinical studies but is underused due to its complex and time-consuming nature. Even though modern devices provide fast algorithms potentially useful in clinical practice, most electrophysiologists do not optimise AV and VV delays, as reported in a recent international survey [12]. The current families of CRT devices have implemented automatic algorithms to optimise AV and VV timing intervals. The proof of principle is the evidence that fusion of an LV-paced beat with intrinsic rhythm may be more beneficial than standard biventricular pacing, provided a preserved AV conduction (Table 2).

Medtronic

The already-discussed AdaptivCRT algorithm measures intrinsic AV delay and VV timing when a normal AV conduction is present. When programmed, it can be set to either adaptive LV pacing only or adaptive biventricular pacing. In patients with normal AV conduction, adaptive LV-only pre-excites the ventricle by delivering an LV pacing stimulus at about 70% of the measured intrinsic AV conduction, by means of RV sensing following an atrial spontaneous or paced event. The range of sensed AV delays of the AdaptivCRT function is limited between 80 and 140 ms, while the paced AV delays range between 100 and 180 ms. The timings of the VV (RV or LV offset) range between 0 and 40 ms [15].

Boston scientific

The SmartDelay® function enables the optimisation of the sensed and paced AV delays, as well as a choice of LV versus biventricular stimulation. It can be run in post-implant and at in-office device check, taking 2.5 min, and is not automatically repeated by the device during follow-up.

This algorithm is based on the measurements of, respectively, the right and left AV intervals during sensed and paced atrial activity, taking into consideration a programmed V-V delay. The validation studies have demonstrated a correlation with contractile performance and efficiency through LVmax dP/dt measures.

The VV offset and the multisite LV pacing combinations are separately set features.

The algorithm checks the atrial-sensed and paced event to promote RV fusion within the RV activation at the LV offset interval manually programmed, leading to the following automatic AV delay set. For example, if the interval from atrial-sensed and LV-paced is 150 ms

Table 2 Different features of commercially available automatic optimisation algorithms, according to manufacturers

Features	Medtronic *AdaptiveCRT*	Boston *SmartDelay*	Biotronik *AutoAdapt*	Abbott *Sync-AV*	Microport *SonR*
LV sensing capable	−	+	+	−	−
Automatic run during follow-up	+	−	+	+	+
LV preexcitation / LV pacing only	+	+	+	+ fusion with RV always paced	+ fusion with RV always paced
Intrinsic Conduction check	+	+	+	+	+ weekly
Check LBBB pattern by EGM timing	−	−	+	−	−
AV delay (A sense -RV sense)	Range 80–140 ms	+	At 70% A sense-RV sense	50 ms shorter for each A sense-RV sense	Range 30–250 ms
AV delay (A pace -RV sense)	Range 100–18 ms	+	At 70% A pace-RV sense	50 ms shorter for each A pace-RV sense	Range 30–250 ms + Extension 0–125 ms
VV offset	0–40 ms	-Manually fixed	Advance 40 ms for each A sense/pace-RV sense	10–80 ms (in step of 10 ms)	Range 0–48 ms
Hemodynamic sensor	−	−	−	−	+
Validated by available literature	+	+	−	+	+
Available RV pacing minimisation	+ MVP	−	−	+ VIP	+ AAI-SafeR

LBBB left bundle branch block; *LV* left ventricle (pacing); *RV* right ventricle (pacing); *VV offset* VV delay programming with LV-RV which means LV pacing advances the RV pacing or the opposite; *EGM* electrogram; *MVP* Medtronic automatic algorithm to minimise RV pacing; *VIP* Abbott automatic algorithm minimise RV pacing; *AAI-Safe R* Microport automatic algorithm to minimise RV pacing

at a fixed LV offset of 20 ms, the algorithm will set the AV delay from 170 ms, ensuring RV fusion with RV pacing, advanced by 20 ms of LV pacing.

Therefore, the test runs and sets the AV delay on the basis of a fixed programmed VV offset during a chosen multisite or bipolar LV pacing. [38]

Biotronik

The CRT AutoAdapt algorithm operates in LV-only or BiV pacing based on measured conduction time between atrial-sensed or paced events and each RV- and LV-sensed event. If the RV-sensed event occurs before the LV one, then LV-only pacing will be adopted. LV pacing will occur at 70% of the intrinsic A-RV conduction time, or 40 ms earlier, whichever is shorter. Therefore, AutoAdapt continuously adjusts the AV delay and pacing chamber selection by taking individual A-RV and A-LV conduction patterns into account. In LBBB patients, switching to LV-only pacing and adjusting the AV delay can provide optimal interventricular fusion between the activation fronts from the intrinsic RV conduction and the LV pacing lead. In every patient, CRT AutoAdapt continuously evaluates whether an LBBB pattern is present by comparing A-RV and A-LV conduction times [39].

Abbott

The Sync-AV CRT is a closed-loop algorithm that dynamically operates on the AV delay after a sensed or paced atrial event to synchronise with an intrinsic atrioventricular conduction via the right bundle branch. Sync-AV periodically extends the AV delay, and any time intrinsic ventricular events are sensed, the AV delay is reduced by a programmable offset, allowing paced ventricular wavefronts to fuse with the intrinsic ones. Any AV delay interruption by faster ventricular sensed events (shorter PR interval during patient activity) results in further AV delay abbreviation, while periodic AV delay extension accommodates slower conduction (during longer PR interval). The algorithm operates as follows: every 256 beats, the algorithm automatically extends the paced and sensed AV delay for 3 beats to measure the intrinsic atrioventricular interval. The default AV delay offset, 50 ms shorter than the intrinsic AV-sensed interval, may be reprogrammed across a wide range of values (10–120 ms). Additionally, ventricular pacing configuration may be changed from simultaneous biventricular (default) to LV preexcitation. The algorithm operates to promote a discrete right ventricle fusion, as the RV is always paced due to the AV offset advancing the RV sense. During LV preexcitation, according to the degree

of fusion within the RV, an LV-RV fusion is possible, which otherwise is not present during simultaneous biventricular pacing. [40, 41] The newest version of this algorithm, called Sync-AV+, allows for program pacing AV delays as a proportion of the measured intrinsic AV delays [42].

Sorin microport

The SonR® micro-accelerometer hemodynamic automatic sensor is enclosed in a sealed capsule at the tip of an atrial-pacing active fixation lead, which measures in g (m/s^2) the myocardial micro-accelerations throughout the cardiac cycle. The first "sounded" SonR® component (SonR1), reflecting the first heart sound, is selected to check the iso-volumetric contraction (with validated correlation with LVmax dP/dt).

The SonR optimisation runs weekly (at Monday night, 1–2 o'clock for rest testing and at Monday 12 o'clock for exercise intervals confirmation), testing 69 combinations of AV and VV delays, adjusted in a sequence of three adaptive cycles followed by six cycles to measure the SonR.

For the VV optimisation, seven biventricular pacing configurations are tested with both LV and RV offsets (with ranges up to 48 ms) at six AV delays. As for other algorithms, the AV delay test ranges from 30 ms up to the checked RV spontaneous conduction (minus 50 ms), to ensure an RV pacing maximally fused within the RV activation. During the test run, 42 combinations and 252 SonR measurements are included. The VV delay test is then followed by selecting 11 different AV delays (sequentially by atrial-sensed and atrial-paced), from 30 ms to spontaneous conduction minus 50 ms at the previously optimised VV offset. This test includes 11 combinations and 66 SonR measurements for both sensed and paced atrial tracking.

At Monday day time (12 o'clock), optimisation of the AV delay during exercise starts as soon as the heart rate has reached a programmed value, following the described rest test but with shorter sequences: after optimisation of the VV delay, five different AV delays, from 30 ms to spontaneous conduction during exercise minus 50 ms, are tested. This test includes five combinations and 30 SonR measurements. A new VV delay is implemented only after a $\geq$ 14% increase in SonR1. If the new optimal VV delay differs from the previous VV delay by > 16 ms, the VV delay is progressively increased in 16 ms steps until this new optimal VV delay has been reached. Importantly, the AV delay ranges are: sensed AV delay at rest = 60–180 ms; paced AV delay at rest = 92–240 ms [43].

RV lead position

Either in manual or in automatic delay optimisation, the VV offset is strictly AV delay dependent, being the RV Purkinje sequential activation a function of the desired fusion. Apart from the AdaptivCRT algorithm, most of the described automatic algorithms include chasing the RV sequential activation by the RV lead sensing, producing an RV pacing, while seeking to the best fusion *within* the RV itself by slightly advancing the RV pacing after the measured A-RV-sense interval. The position of the RV lead in the right ventricular chamber, either at septum or at apex, is therefore a function of RV sensing timing and can vary the A-RV-sensed interval by several milliseconds, thus affecting the automatic RV-sense-based algorithms.

The position of the RV pacing lead remains therefore crucial to achieve a complete fusion *within* the RV activation, as well *between* LV-to-RV activation fronts, at any level of LV-RV offset programmed.

In case of "AV delay nondependency", such as in AF patients, as well in HOT CRT strategies, the LV-RV delays programming by the use of His to RV time interval (H-RV) may become helpful to guide the LV advance and desired LV-RV pure fusion, which may be set at an interval equal to H-RV, probably more efficiently as compared to the HV interval.

In summary, in sinus rhythm CRT patients with baseline-typical LBBB criteria and preserved AV conduction, the dromotropic management to achieve RV-LV fusion includes the AV delay setting (from A-sensed or -paced to RV-sense interval) that may allow the complete "H-RV axis activation" added to the LV preexcitation offset timing, which might be set at an interval equal to or slightly longer than the A-RV interval minus the PR interval at the ECG. For example, with an A-RV interval = 200 ms, considering a PR interval of 140 ms on ECG, a programmed AV delay should resemble the same baseline PR interval plus an LV-to-RV advance = 60 ms; this setting may allow a virtual LV pacing only, maintaining pure fusion between the LV and RV. Moreover, these measures could be obtained during post-implant standard outpatient devices' control, unlike the HV interval, which is invasively derived.

Moreover, it may now be discussed whether a longer programmed AV delay (equal to the baseline PR), when coupled with such a tailored VV offset, might produce a better contraction performance by achieving the desired fusion, without affecting ventricular filling times. From this point of view, in order to avoid complete E/A waves fusion at the echocardiographic trans-mitral Doppler, a "PR-guided" AV delay setting limit can be measured by echo optimisation or can empirically be considered an upper limit of 200 ms (Fig. 2).

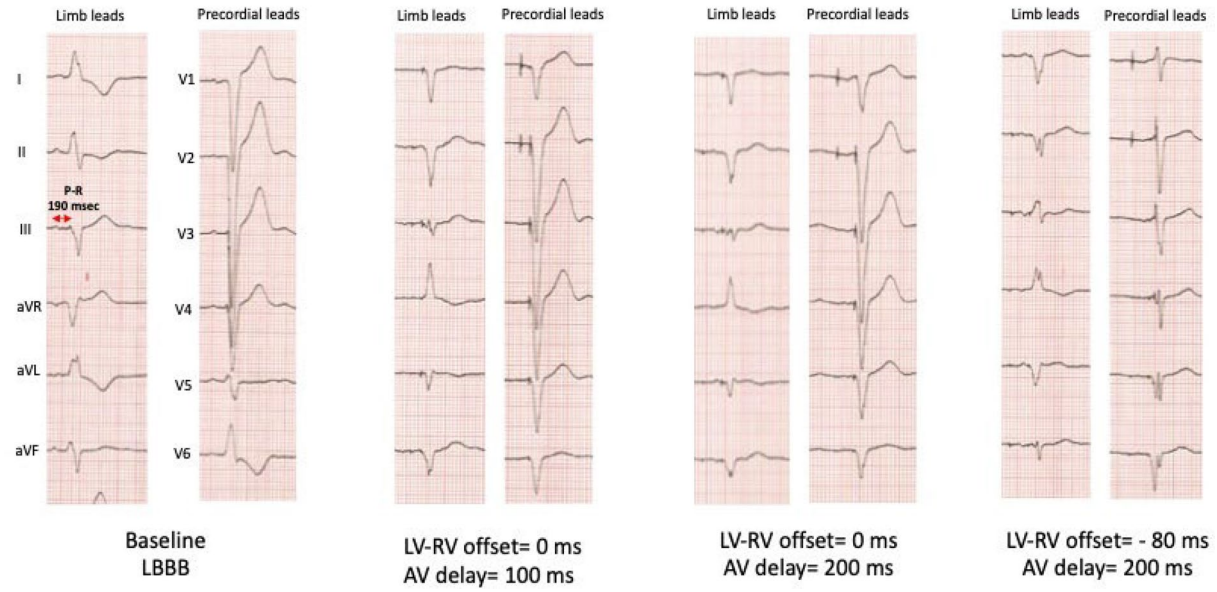


Fig. 2 "In-office" ECG dromotropic CRT optimisation. A case of nonischemic heart failure patient with a baseline LV ejection fraction of 22%, and a baseline ECG with LBBB with "Strauss criteria", who underwent CRT-P implantation followed by routine post-implant ECG optimisation as shown. At 2-month follow-up, the LV ejection fraction raised up to 50%. From left, the first couples of standard 12 leads ECG tracings show the baseline pre-implant ECG with a typical ("Strauss") LBBB pattern with intrinsic RV bundle conduction slightly longer but preserved, being a baseline PR interval = 190 ms. The second and third couples of ECG tracing AV delay settings show the sequential AV delay programming (summarised the shortest at 100 ms and the longest at 200 ms) to reach a RV sensing at a fixed simultaneous LV-RV offset (= 0 ms), in order to check for the RV sense timing and promote fusion also for baseline longer intrinsic AV delays. In the fourth couple of ECG tracings, at the latest AV delay which induce detection of RV sense EGM by device telemetry, the LV offset is then programmed advancing the LV by the formula: sensed/paced A-RV interval minus the P-R interval derived by the baseline EC. *LBBB* left bundle branch block; *LV* left ventricle (pacing); *RV* right ventricle (pacing); *offset* VV delay programming with LV-RV which means LV pacing advances the RV pacing

Conversely, in AF patients (in the lack of AV delay dependency), RV-LV fusion is challenging even by the use of VVT-like RV- or LV-sensed triggered modes. Empirically, an H-RV sensing guided LV preexcitation might be the choice in nondependent, LBBB ("Strauss") AF patients, provided adequate intranodal drug rate control. In all patients undergoing the HOT CRT strategy, in the absence of any AV delay dependency (His pacing), His preexcitation with His-LV offset might be set at an interval equal to the H-RV sense interval, instead of the HV interval, the latter being shorter and therefore decreasing the fusion occurrence, provided a preserved RV intrinsic conduction.

Conclusions

Effective CRT delivery may depend on capture issues as well as sensing issues. The search for intrinsic atrioventricular dromotropic properties may strengthen the CRT clinical outcome by increasing RV-LV fusion instead of pseudo-fusion. The intrinsic His-Purkinje activation along the RV is a function of the desired RV-LV fusion, guiding CRT ECG optimisation. In this regard, the new automatic algorithms consider the sensed/paced A to RV-sense interval to achieve such a fusion. The RV sense timing relates to the RV lead position.

Author contributions

All the authors contributed to the manuscript preparation; in details, Zoppo F, Perazza L and Mangiameli D were involved in the conceptualisation, writing and paragraphs structuring; Cocciolo A and Corrado A were involved in final manuscript review and language editing. All authors read and approved the final manuscript.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

The present manuscript is a literature review; therefore, the required "ethics approval, the Consent to participate and the Consent for publication" have been considered as not applicable.

Competing interests
There are no competing interests to be declared.

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