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# Optimizing Cardiac Resynchronization Therapy Device Programming

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**KEY WORDS:** *AV delay; VV delay; QuickOpt; responders; non-responders; CRT; optimization*

**ABBREVIATIONS**
CRT= Cardiac resynchronization therapy
AV= Atrio-ventricular (interval)
VV= ventriculo-ventricular (between ventricles) (interval)
PVARP= Post-ventricular atrial refractory period
VTI= Velocity time integral
TDI= Tissue Doppler Imaging
IEGM= intracardiac electrogram

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## ABSTRACT

Cardiac resynchronization therapy (CRT) improves symptoms and cardiac function, reduces hospitalizations and increases survival in selected patients with heart failure. It is mandatory to maximize mechanical and electrical synchronicity. Atrio-ventricular and ventriculo-ventricular intervals optimization have a substantial impact on the hemodynamic response to pacing. The number of patients with an implanted CRT system is increasing and many issues have not yet been answered about who and how will benefit the most.

## INTRODUCTION

Cardiac resynchronization therapy (CRT) was introduced to improve symptoms, exercise capacity and cardiac function, to reduce hospitalizations and to increase survival when added to optimal medical treatment in selected patients with refractory heart failure.[1,2] Over the last years, numerous publications have confirmed the beneficial role of CRT.[3-7] As a consequence, the latest guidelines of the European Society of Cardiology for the treatment of heart failure have encompassed this therapy as a Class I Level A recommendation, for the treatment of patients with poor clinical performance (NYHA III-IV), low ejection fraction (EF<35%), prolonged QRS duration (QRS duration >120 ms).[8]

Nevertheless, a quarter of these patients with advanced heart failure fail to respond to this treatment[9,10] based on either clinical or echocardiographic criteria. This pitfall of CRT has been attributed to our inability to predict who of the patients with refractory heart failure may benefit from resynchronization therapy. The criteria for patient selection mentioned in the guidelines do not meet the challenge of identifying with a high level of confidence the population that will respond to treatment.

## PREDICTION OF RESPONSE TO CRT

Changes in the QRS with pacing do not predict CRT efficacy[11] as responders exhibit a significant reduction in QRS duration after CRT, but individual responses are highly variable and do not permit adequate selection[12]. QRS duration alone cannot be used as an accurate index of parameters that may adversely affect the results of CRT. Some of these parameters are: inappropriate patient selection, ischemic vs. non-ischemic

cardiomyopathy as the cause of heart failure, the presence of scar tissue in the failing myocardium, variability in the coronary venous anatomy and incorrect lead positioning, or the suboptimal device programming over time that may have detrimental effect on the outcome of CRT overall.

Some predictors to identify responders to CRT therapy have been suggested but until now, there is no echocardiographic parameter of dyssynchrony that can be recommended[13]. Myocardial contractile reserve (>7.5% increase in the left ventricular ejection fraction (LVEF) during low-dose dobutamine infusion) predicts left ventricular (LV) reverse remodeling after CRT[14]. In a sub-study of the CARE-HF trial it was demonstrated that mitral regurgitation and NT-pro BNP measured 3 months after intervention, were powerful independent predictors of long-term survival[15]. New evidence has shown that change in NT-pro BNP levels from baseline to 3 months after successful CRT device implantation was a strong predictor of long-term response[16]. A prompt blood pressure rise just after resynchronization may also predict short- and long-term clinical improvement in CRT recipients.[17]

Another issue which clearly has not been addressed yet is the definition of non-responders to CRT. Definition of response vary from functional parameters (such as NYHA class, 6 minutes walk test) to reverse left ventricular remodeling, morbidity and mortality. Specific criteria on the lack of improvement of NYHA, the left ventricular dimensions and volumes, the ejection fraction or the cardiac output may all have conflicting responses and cause more confusion[18].

## OPTIMIZATION OF CRT PROGRAMMING

### SIMPLE PACEMAKER PROGRAMMING

Under the need of managing an increasing population with heart failure and in the setting of relative uncertainty about who will gain benefit from this therapeutic strategy, it is mandatory to optimize mechanical and electrical synchronicity by all the means reported in the literature and applied in every day practice so far.

CRT optimization should always start with some common pacemaker troubleshooting such as identification of fusion and pseudofusion beats, the loss of ventricular capture, the percentage estimation of atrial and ventricular pacing, the presence of atrial tachyarrhythmias and ventricular premature beats and tachyarrythmias, the activation of rate response in patients with chronotropic incompetence[19], the presence of inappropriately long atrio-ventricular (AV) interval and the correction of atrial undersensing and ventricular oversensing.

The upper tracking rate should be set to higher values than the default 120 beats per minute (bpm), i.e. to 140 -150 bpm in order to ensure biventricular pacing during rapid heart rates with exercise. However, an ultra short post-ventricular atrial refractory period (PVARP), may result in pacemaker-mediated tachycardia or tracking of atrial arrhythmias. Many devices have the capability to extend PVARP duration especially after a premature ventricular contraction in order to avoid this phenomenon. Loss of atrial sensing and biventricular pacing thereafter, might be a side-effect which has successfully been dealt with algorithms that shorten the PVARP e.g., Atrial Tracking Recovery™ of Medtronic (Minneapolis, MN, USA) or Tracking Preference™ of Guidant (Indianapolis, IN, USA) or AVControl™ of Biotronik (Berlin, Germany). Automatic mode switching should be enabled in all patients since most of them have a history of or will enounter an atrial arrhythmia in the future[20]. Maintenance of left ventricular capture should be carefully monitored as plays a crucial role in left ventricular function[21] keeping in mind that thresholds may rise after implantation[22]. Pacing amplitude and durations should be carefully programmed using unipolar and bipolar configuration, increase of pulse width, pacing between the left and right ring electrodes and automatic measurement of left ventricular thresholds. Ventricular sensing is another parameter that has to be taken into account in order to avoid oversensing of P waves resulting then to inhibition of left ventricular pacing when the left ventricular lead is rarely implanted in a basal position[23]. Either reducing the sensitivity or programming sensing to a unipolar configuration may help oversensing issues.

### ADVANCED CRT OPTIMIZATION

Atrio-ventricular (AV) interval optimization has been used in most clinical trials and may have a substantial impact on the hemodynamic response to pacing, affecting the left ventricular stroke volume and cardiac output; the optimization of AV interval may affect the final outcome either by prolonging AV interval in patients with interatrial conduction delay, or by shortening the AV interval in cases of fusion with intrinsic conduction, long PR, or delayed relaxation of the left ventricle.

Several techniques have been used so far for optimization of AV interval: Echocardiography has been extensively used with the aim to separate fused E and A mitral flow waves leading to prolongation of diastolic filling time. This has been addressed using methods like the Ritter Method, which uses one short and one long AV interval and measures the delay between the onset of QRS and the end of A wave. The optimal AV interval may be calculated as such: AVopt=AVlong – (QAshort – QAlong).[24]

Simpler method is the simplified mitral inflow method measuring once the interval between the end of A wave and the onset of mitral regurgitation which then is subtracted from the long AV delay.[25] Iterative method uses consecutive measurements with different AV delays in order to achieve the best one.

The aortic velocity time integral (VTI ) using Continuous-

Wave Doppler and the mitral VTI using Pulse-Wave Doppler have also been very helpful to individually optimize AV intervals in several studies although they seem time consuming and with relatively low reproducibility. Finger plethysmography and Impedance Cardiography are non-echocardiographic methods with limited clinical applicability.

The limited reproducibility and the need for special equipment have demanded for the development of special algorithms of the devices that calculate automatically the AV delay based on the QRS width and intrinsic AV intervals. The existing algorithms are the Guidant's Expert Ease for Heart Failure™ algorithm[26] and the Peak endocardial acceleration incorporated in the devices of the Sorin group, (Milan, Italy)[27]. These algorithms although helpful in clinical practice may prove insufficient to optimise an actively exercising patient with increased heart rates and in need for prolongation of AV delay during exercise.

Optimizing the between the two ventricles (VV) interval affects interventricular and intraventricular synchrony. Several methods have been tried but echocardiographic ones are the most broadly applied. Optimization can be done by measuring the aortic Velocity Time Integral (VTI)[28] or the highest mean global Tissue Doppler Imaging (TDI) velocity of the ventricular segments at different VV intervals[29]. It is recommended that AV optimization be performed first and then be followed by VV delay optimization. In most studies the majority of patients have optimal VV intervals with left ventricular preexcitation that are within a range of ±20msec. Studies have shown superiority of optimized sequential biventricular pacing over simultaneous biventricular pacing in short-term outcomes such as hemodynamic status, contractility (dP/dt), and tissue Doppler changes. Nonetheless, the VV delay optimization conferred no additional benefit compared with simultaneous biventricular stimulation in NYHA functional class, 6-minute hall walk test and quality of life,[30] has not improved ventricular volumes and systolic function[31], has not promoted additional reverse remodeling at 6 months and has not increased the proportion of echocardiographic responders to CRT.[32] So it seems prudent to apply VV optimization not to all, but restrict it only to non-responders at follow up.

There has been a trend to get away from echo-based optimization with some sort of electrogram-based systems that can be performed during routine device follow-up. Algorithms have been embedded to the pacemaker software to maximize ventricular pacing in atrial tachyarrhythmias like the Medtronic Conducted AF Response™ and Biotronik Rate Fading™ algorithm.

A study that compared an intracardiac electrogram (IEGM) guided optimization and echocardiographic optimization for cardiac resynchronization in heart failure patients with dual-chamber ICD implants demonstrated that the concordance correlation coefficient between the values of the standard method of aortic VTI measurement and the IEGM method aortic VTI values was 97.5%, 96.1%, and 96.6%, respectively.[33] An ongoing but not recruiting participants study, the Frequent Optimization Study using the QuickOpt[34] is looking at the efficacy of the QuickOpt™ system, an algorithm developed by St Jude Medical Inc (Little Canada, MN, USA) based mainly on VV delay modification to optimize CRT with an automated repeatedly done optimization based on IEGM vs. standard programming of the devices. A recent prospective study[35] compares echocardiographic and QuickOpt optimization and shows that echocardiographic optimization gives a superior hemodynamic outcome. Nevertheless it is suggested that easier and quicker QuickOpt system could initially be applied to all patients with recommended echocardiographic optimization to non-responderss.

A second study underway, the Comparison of AV Optimization Methods Used in Cardiac Resynchronization Therapy (SMART-AV) study,[36] is looking again at a more comprehensive electrogram-based system for AV optimization in a three-arm study, using nominal parameters, echo-based optimization, or electrogram-based optimization applying the SmartDelay™ algorithm developed by Boston Scientific (Natick, MA, USA). The results of this study are expected to allow us determine if one mode of optimization is superior to the other. It will also demonstrate the magnitude of that benefit, both in terms of clinical outcomes to the patient as well as magnitude of reverse remodeling.

## CONCLUSIONS

The number of patients with refractory heart failure is steadily increasing. Beyond those who fulfil the classic criteria, patients with QRS duration <120msec or with atrial fibrillation with evident mechanical dyssynchrony may also benefit from CRT. An increasing number of patients with an implanted CRT system develop changes in clinical status, with posture, in exercise, have arrhythmias and show differences in ventricular stress that take place continuously over time. The decision when to study an individual, reprogram and resynchronize the heart is still an unanswered issue. The only certain way to find out who will respond to treatment is to try it and go for the best synchronicity over time focusing on non-responders and on initially responders who deteriorate clinically.

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