Comprehensive cardiac resynchronization therapy (CRT) optimization in the real world

Steffel, J ; Rempel, H ; Breitenstein, A ; Schmidt, S ; Namdar, M ; Krasniqi, N ; Holzmeister, J ; Lüscher, Thomas F ; Ruschitzka, F ; Hurlimann, D

Abstract: BACKGROUND: Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients suffering from chronic heart failure (CHF). Optimal device programming is crucial for maximum patient benefit. The goal of the present study was to assess device settings from CHF patients undergoing CRT optimization in a "real world" setting, and to delineate parameters most frequently requiring adjustment. METHODS: All patients who underwent CRT device implantation in the Cardiology Clinic at the University Hospital Zurich between January 2011 and September 2012 and in whom follow-up was available were included in this analysis. RESULTS: A total of 170 CHF patients were included in this analysis. True biventricular pacing was present in 44.0% of all patients, while QRS fusion was detected in 49.9%. The majority of the patients presented with suboptimal AV delays requiring adjustment. AV delays were therefore shortened due to the presence of QRS fusion in 53.3% and 38.1% of patients (sAV and pAV, respectively) or prolonged because of truncation of the A wave in the LV inflow pulse wave Doppler measurement (17.5% and 28.4% for sAV and pAV, respectively). In contrast, interventricular delay (VV delay) was rarely changed (11.9%). CONCLUSIONS: In our "real world" cohort, a substantial proportion of patients presented to their first post-operative consultation with suboptimal device settings. Our data indicate that the opportunity to optimize device settings is frequently wasted in the "real world", underlining the necessity for expert device follow-up to deliver optimal care to this challenging group of heart failure patients.

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

CARDIOLOGY JOURNAL

Comprehensive cardiac resynchronization therapy (CRT) optimization in the real world

Authors: Jan Steffel, Helene Rempel, Alexander Breitenstein, Susann Schmidt, Mehdi Namdar, Nasmi Krasniqi, Johannes Holzmeister, Thomas F. Lüscher, Frank Ruschitzka, David Hürlimann

Comprehensive cardiac resynchronization therapy (CRT) optimization in the real world

Jan Steffel[1], Helene Rempel[1], Alexander Breitenstein[1], Susann Schmidt[1], Mehdi Namdar[2], Nasmi Krasniqi[1], Johannes Holzmeister[1], Thomas F. Lüscher[1], Frank Ruschitzka[1], David Hürlimann[1]

[1]Cardiology, Cardiovascular Center, University Hospital Zurich, Switzerland
[2]Heart Rhythm Management Centre, UZB, Brussels, Belgium

Address for correspondence:

Jan Steffel, MD FESC, Cardiac Arrhythmia Unit, Department of Cardiology, University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich / Switzerland, tel: +41 44 255 11 11, fax: +41 44 255 87 01, e-mail: j.steffel@gmx.ch

Abstract

Background: Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients suffering from chronic heart failure (CHF). Optimal device programming is crucial for maximum patient benefit. The goal of the present study was to assess device settings from CHF patients undergoing CRT optimization in a "real world" setting, and to delineate parameters most frequently requiring adjustment.

Methods: All patients who underwent CRT device implantation in the Cardiology Clinic at the University Hospital Zurich between January 2011 and September 2012 and in whom follow-up was available were included in this analysis.

Results: A total of 170 CHF patients were included in this analysis. True biventricular pacing was present in 44.0% of all patients, while QRS fusion was detected in 49.9%. The majority of the patients presented with suboptimal AV delays requiring adjustment. AV delays were therefore shortened due to the presence of QRS fusion in 53.3% and 38.1% of patients (sAV and pAV, respectively) or prolonged because of truncation of the A wave in the LV inflow pulse wave Doppler measurement (17.5% and 28.4% for sAV and pAV, respectively). In contrast, interventricular delay (VV delay) was rarely changed (11.9%).

Conclusions: In our "real world" cohort, a substantial proportion of patients presented to their first post-operative consultation with suboptimal device settings. Our data indicate that the opportunity to optimize device settings is frequently wasted in the "real world", underlining

the necessity for expert device follow-up to deliver optimal care to this challenging group of heart failure patients.

Key words: heart failure; cardiac resynchronization therapy; integrative device follow-up

Introduction

Cardiac resynchronization therapy (CRT) has become a cornerstone in the treatment of chronic heart failure (CHF)[1, 2]. Indeed, several clinical trials observed a reduction in morbidity and mortality as compared to medical therapy alone in patients suffering from symptomatic left ventricular (LV) dysfunction (LV ejection fraction $\leq$35%) with a prolonged QRS duration ($\geq$120 ms). Nevertheless, almost 30% of patients do not exhibit an improvement in clinical symptoms or hemodynamic parameters after CRT implantation (so-called "non-responders")[3]. This lack of improvement may be due to pre-implantation characteristics such as large areas of scar tissue due to coronary artery disease or a lack of mechanical dyssynchrony[4]. Suboptimal LV lead position further represents a reason for a lack of benefit[4]. Additionally, however, some patients do not respond to CRT due to suboptimal CRT device settings, impairing LV filling (atrioventricular (AV) dyssynchrony) and / or persistent LV dyssynchrony[5].

At the University Hospital of Zurich, we implemented a standard protocol by which every patient with a CRT device undergoes complete device optimization 3-6 months after implantation and again on a yearly basis or if clinically deemed necessary. The goal of the present study was to summarize clinical presentation, echocardiographic findings, and device settings from chronic heart failure (CHF) patients undergoing CRT optimization in this "real world" setting, unraveling the amount of patients presenting with suboptimal settings, as well as the parameters most frequently requiring adjustment. We provide a rational for the necessity of implementing a routine protocol for the integrated management of these complex CHF patients, including expert device management.

Methods

Study population and CRT implantation

All patients with a CRT device receiving their first device follow-up in our specialized device clinic from January 1st 2011 until September 2012 were prospectively included. The study was approved by the cantonal ethics committee Zurich. Mean time from implantation to optimization was 2.9 months (Tab. 1). Indications for CRT implantation were based on current guidelines[1]. CRT devices were implanted by a standard procedure under local

anesthesia. Devices and leads from Biotronik, Boston Scientific / Guidant, Medtronic and St. Jude Medical were used. For implantation of the left ventricular (LV) lead, percutaneous placement into a lateral or postero-lateral vein was attempted whenever possible. If no suitable vein branch was available epicardial lead implantation was performed.

Follow up protocol

We implemented a standard protocol by which every patient with a CRT device undergoes a comprehensive and standardized device follow-up and optimization procedure. After a complete clinical assessment by a heart failure specialist, a comprehensive device follow-up was performed by implantable electronic cardiac device specialists (JS/DH), including complete check of the system with 12-lead ECG, and review of all brady- and tachycardia parameters. Subsequently, a complete echocardiographic exam was performed (Vivid E9, GE), followed by optimization of the AV- and VV delay if necessary. AV delay optimization was performed starting at a long AV-delay without intrinsic conduction. The AV-delay was then progressively shortened in steps of 20ms until truncation of the A-wave was observed. Then, the AV-delay was prolonged in 10ms steps until the optimal separation of E/A wave without truncation of the A-wave is reached, which was considered the optimal AV-delay.

Results
Study population

A total of 170 chronic heart failure patients were included in this prospective analysis. Baseline demographic data at implantation as well as clinical characteristics at time of follow-up are summarized in table 1. The majority of patients were men (76.5%), and had a cardiovascular risk profile typical of a real-world chronic heart failure cohort as previously shown[6]. All patients were on optimal medical therapy including ACE-inhibitors or angiotensin-II-blockers (95.2%), beta-blockers (93.5%) and diuretics (86.3%) prior to implantation. Furthermore, more than fifty percent of patients were treated with an aldosterone antagonist (55.4%) in addition to standard diuretic therapy, and received anti-arrhythmic treatment with either digitalis (13.1%) or amiodarone (17.9%).

Echocardiographic and electrocardiographic parameters at follow-up

Most patients demonstrated a reduced LVEF (mean 37.3±11.1%) and a dilated left ventricle (enddiastolic volume index 88.4±41.6ml/m2; Tab. 2). Of note, parameters of

dyssynchrony at this time mainly demonstrated values within our lab's predefined normal values (IVMD <40 ms, TDI$_{septal-lateral}$ <60 ms, TDI$_{anteroseptal-posterolateral}$ <60), with an interventricular mechanical delay (IVMD) of 17.5±27.7 as well as 32.7±46.8ms and 33.5±46.3ms for septal-lateral and anteroseptal-posterolateral delay assessed by tissue Doppler imaging (TDI), respectively. The mean intrinsic QRS duration was 150±26.6ms with an ECG pattern of LBBB in the majority of cases (59.5%), and an average PQ interval of 184.7±27.6ms (Table 3). At time of implantation and at first follow-up, most patients were in sinus rhythm (65.9%). While 65.3% of the patients had the same rhythm at our follow-up visit, a minority of patients switched from atrial fibrillation to sinus rhythm (2.4%) and vice versa (4.8%).

Device settings and intervals at time of optimization

True biventricular pacing was present in nearly half of the patients at the time of optimization (44.7%), while QRS fusion could be detected in 39.4% of cases (Table 4, Fig. 1). At time of optimization, average sensed AV (sAV) delay was 110.5± 19ms and paced AV (pAV) 136.5±23.4ms. QRS fusion as diagnosed by 12-lead surface ECG began to appear at an average sAV of 103.9±37.1ms and an average pAV of 136.5±23.4ms, respectively.

A biventricular pacing rate of more than 95% was present in 85.8% of patients from the studied cohort. Main reason for a low biventricular pacing percentage was either atrial fibrillation or frequent ventricular extrasystolies. At time of follow-up, mean programmed interventricular (VV) delay was 8.5±14.4ms (LV first).

Left ventricular lead settings

In a third of all cases, lead pacing configuration was "true" bipolar from the LV lead tip (LvTip) to the LV ring (LvRing; 34.1%) or between LvTip to the right ventricular lead ring (RvRing; 28.2%, Table 5). In every fifth patient, the pacing vector was between the LvTip and the coil of the RV lead (RvCoil; 23.5%). With these configurations, only a minority of patients (n=7, 4.2%) were suffering from diaphragmatic capture (4.2%). The latter was solved in all cases by reprogramming.

Optimization of CRT settings after implantation

In the majority of all patients who underwent CRT device implantation, the programmed AV intervals were deemed suboptimal during follow-up and were subsequently reprogrammed (Table 6). AV delays were shortened (sAV delay in 53.3%, pAV delay in 38.1% of the patients) mainly due to the presence of QRS fusion on the 12-lead ECG. In

contrast, the AV delay was prolonged in only 17.5% and 28.4% (sAV and pAV, respectively), mostly due to truncation of the A wave in the LV inflow pulse wave Doppler measurement. In 77 patients (45% of the entire cohort), some degree of QRS fusion was accepted in order to allow for better LV filling.

In contrast to the adjustments of the AV interval, the VV delay was left unchanged in the majority of patients (88.1%). The main reason for a change in VV delay was intraventricular dyssynchrony observed on TDI (82.4%).

Thirty three (19.4%) of patients in or cohort suffered from atrial fibrillation. By virtue of this, AV optimization was impossible in these patients and VV optimization greatly impaired. Of our patients with AF, 20 (61%) had intrinsic conduction, whereas 7 (21.2%) and 6 patients (18.2%) had no intrinsic AV conduction or underwent AV node ablation, respectively (Tab. 3).

Discussion

The aim of the present study was to give an overview on CRT settings at the time of device implantation and to demonstrate the potential for optimization by comprehensive assessment during follow-up in an integrative device clinic. In view of the substantial discrepancy between programmed parameters and optimal values, our data indicate that this opportunity is frequently missed in the "real world", providing a rational for the necessity of protocol-oriented expert follow-up and optimization procedures for these patients.

AV delay optimization and QRS fusion

Whether and how AV intervals should regularly be evaluated and adjusted remains a matter of debate[8, 9]. In various preliminary studies, optimization of the AV delay has been demonstrated to significantly increase hemodynamic response, NYHA class, LV ejection fraction and brain natriuretic peptide level in the short-time follow-up[10-14]. In contrast, the recently published 'SmartDelay determined AV Optimization: A comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy' (SMART-AV) trial implied otherwise. In this study, CRT device recipients were randomized to a fixed empirical AV delay of 120ms, an echocardiographically optimized AV delay or a device-based AV optimization algorithm (SmartDelay)[15]. The primary endpoint, left ventricular end-systolic volume at 6 months after implantation did not differ between the 3 groups. As discussed by the authors, it may be possible that the observed acute beneficial hemodynamic effects after CRT implantation are not sufficient enough to result in an improvement of hard clinical

endpoints. On the other hand, the follow-up period of only 6 months may have been too short to evaluate such endpoints.

Furthermore, it has to be kept in mind that the optimal AV delay may have a high variability among CRT patients[5, 16]. As such, data from SMART-AV do not imply that individual patients with suboptimal AV delay may not profit from an optimization procedure. Indeed, this has been substantiated most recently in a subanalysis from MADIT-CRT, in which patients with short AV-delays (notably < 120ms) had a superior outcome compared to those with longer AV delays.[17] Our data demonstrate that programming an empirical setting of 120ms for the sensed AV delay was suboptimal in terms of true biventricular stimulation in the vast majority of patients (57.1%), and 8 patients (5.7%) even demonstrated entirely intrinsic conduction or pseudofusion (and hence loss of biventricular pacing) at this setting. Furthermore, a subanalysis of the Clinical Evaluation on Advanced Resynchronization (CLEAR) pilot study revealed that systematic CRT optimization was associated with a higher percentage of improved patients based on the composite endpoint (all-cause mortality, heart failure-related hospitalization, NYHA functional class, and Quality of Life score), fewer deaths and fewer hospitalizations.[18] These data clearly indicate a role for CRT optimization over standard programming in all patients.

Moreover, the mean interatrial delay was markedly longer (71.9±28.2ms, Table 4) than the standard programmed difference between sensed and paced AVD (usually 30-40ms) found in the default settings, further supporting an individualized approach to AVD programming.

The majority of our patients (>70%) underwent reprogramming of the AV delay. One of the most important parameters to guide AV delay optimization is the level of true biventricular pacing or, vice versa, the degree of QRS fusion as a result of intrinsically conducted ventricular excitation[19-21]. In our cohort, 45.3% of patients presented with an AV delay too long to avoid any QRS fusion. However, whether some degree of ventricular fusion may be clinically beneficial remains a matter of debate, as a certain amount of QRS fusion has been shown to improve hemodynamics[22, 23,24]. Fusion allows for intrinsic excitation of the RV via the normal-conducting right bundle branch which may result in improved RV contraction[25]. A recent study further demonstrated that the maximal rate of LV pressure increase (dP/dt) was higher in LV pacing combined with intrinsic conduction as compared to biventricular pacing[22]. Based on these data, we accepted some degree of QRS fusion in order to allow for optimal LV filling in those cases where it was impossible to shorten the AV delay to the point of complete loss of QRS fusion (Fig. 1). Importantly, intrinsic conduction and

pseudofusion could entirely and sustainably be avoided in all patients presenting with these findings.

VV delay optimization

For various reasons, VV delay optimization appears to be less important as compared to AV delay optimization. Even though an improvement in hemodynamic conditions has been observed after optimization of VV intervals[26-28], other randomized trials failed to find a beneficial effect[29, 30]. The latter may, at least in part, be due to the fact that VV delay optimization was performed in the majority of patients on top of AV delay optimization. In a small study investigating the effect of simultaneous AV and VV time optimization, an additional but smaller beneficial effect of VV delay optimization was found[31]. in our cohort, only a minority of patients underwent VV optimization, mainly due to the fact that it was not deemed necessary due to satisfying echocardiographic dyssynchrony parameters and, coherently, visual impression of synchronous LV contraction. In patients who were optimized, the indication was mainly driven by TDI values during echocardiographic evaluation. Conversely, 30 patients (17.9%) were dyssynchronous either visually or by TDI measurements, but could not be corrected by advancing LV or RV activation. As a result, and due to the lack of clear evidence for a benefit, VV optimization is only performed in special cases in our institution.

CRT in patients with AF

19.4% of patients in or cohort suffered from atrial fibrillation. These patients pose a challenge in CRT as the uncoordinated and often rapid intrinsic conduction often results in a substantially impaired rate of biventricular pacing (<95%). Indeed, AF was the main reason for a low percentage of biventricular pacing in our cohort. Pharmacologically, amiodarone has been shown to be most effective and safe for rhythm control in atrial fibrillation patients with heart failure[32], and, as a consequence, is frequently used to increase the percentage of biventricular stimulation. If medical therapy is insufficient, AV nodal ablation is recommended as the next step[33]. In our cohort, 39.4 % of patients with AF ultimately had no intrinsic AV conduction and, consequently, had a high degree of biventricular pacing.

Limitations

Our study has some inherent limitations. Data are only collected from a single tertiary care center, and may hence not be generalizable to other healthcare settings. We do, however,

believe that most interpretations and statements characteristically reflect the situation of "real world" CRT patients, and are therefore important for therapy optimization of these individuals. The study is further limited by the fact that we focused on the necessity and possibilities for CRT optimization, and as such did not assess clinical or echocardiographic outcome in these patients, which was beyond the scope of this study. However, evidence is accumulating as indicated above that empirical AV delay programming cannot generally be recommended.[17] As such, our data do indicate that specialist follow-up of CRT recipients is of crucial importance in order to provide optimal care for these complex patients, which was the primary aim of the current study.

Conclusions and perspective

In our "real world" cohort, a substantial proportion of patients presented with suboptimal device settings. Data from previous studies demonstrate that device optimization is associated with improved outcome.[17, 18] Yet, our data indicate that this opportunity is frequently missed in the "real world", underlining the necessity for expert follow-up to deliver optimal care to this challenging group of heart failure patients in order for them to benefit most of their devices.

Conflict of Interest Statements

Jan Steffel: Research support from St. Jude Medical and Biotronik; consulting honoraria from Biotronik, Medtronic, and St. Jude Medical

Helene Rempel: None

Alexander Breitenstein: None

Susann Schmidt: None

Mehdi Namdar: Research and educational grant from Biotronik and St. Jude Medical

Nazmi Krasniqi: Research and educational grants from Medtronic

Johannes Holzmeister: Consulting fees from St. Jude Medical and Biotronik; research grants and speaker honoraria from Biotronik, St. Jude Medical, Medtronic and Boston Scientific.

Thomas F. Lüscher: Research grants from Biotronik, Medtronic and St. Jude

Frank Ruschitzka: Research grants and consulting fees from Biotronik, speaker honoraria from Biotronik and Boston Scientific.

David Hürlimann: Educational grants from Boston Scientific and Medtronic, speaker honoraria and consulting fees from St. Jude Medical and Medtronic

References

1. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the acc/aha 2005 guidelines for the diagnosis and management of heart failure in adults: A report of the american college of cardiology foundation/american heart association task force on practice guidelines: Developed in collaboration with the international society for heart and lung transplantation. *Circulation*. 2009;119:e391-479

2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, Comparison of Medical Therapy P, Defibrillation in Heart Failure I. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140-2150

3. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J, 3rd, St John Sutton M, De Sutter J, Murillo J. Results of the predictors of response to crt (prospect) trial. *Circulation*. 2008;117:2608-2616

4. Bax JJ, Gorcsan J, 3rd. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: Results of the prospect (predictors of response to cardiac resynchronization therapy) study in perspective. *J Am Coll Cardiol*. 2009;53:1933-1943

5. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Huth C, Schondube F, Wolfhard U, Bocker D, Krahnefeld O, Kirkels H, Pacing Therapies in Congestive Heart Failure Study G. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol*. 2002;39:2026-2033

6. Hürlimann D, Steffel J, Milosevic G, Krasniqi N, Gruner C, Oswald F, Rahn M, Falk V, Noll G, Lüscher TF, Ruschitzka F, Holzmeister J. Cardiac resynchronization therapy - "real world" experience from a swiss tertiary center. *Cardiovascular Medicine (Basel)*. 2010;13:334–341

7. Bertini M, Delgado V, Bax JJ, Van de Veire NR. Why, how and when do we need to optimize the setting of cardiac resynchronization therapy? *Europace*. 2009;11 Suppl 5:v46-57

8.   O'Donnell D, Nadurata V, Hamer A, Kertes P, Mohamed U. Long-term variations in optimal programming of cardiac resynchronization therapy devices. *Pacing Clin Electrophysiol*. 2005;28 Suppl 1:S24-26

9.   Porciani MC, Dondina C, Macioce R, Demarchi G, Cappelli F, Lilli A, Pappone A, Ricciardi G, Colombo PC, Padeletti M, Jelic S, Padeletti L. Temporal variation in optimal atrioventricular and interventricular delay during cardiac resynchronization therapy. *J Card Fail*. 2006;12:715-719

10.   Sawhney NS, Waggoner AD, Garhwal S, Chawla MK, Osborn J, Faddis MN. Randomized prospective trial of atrioventricular delay programming for cardiac resynchronization therapy. *Heart Rhythm*. 2004;1:562-567

11.   Morales MA, Startari U, Panchetti L, Rossi A, Piacenti M. Atrioventricular delay optimization by doppler-derived left ventricular dp/dt improves 6-month outcome of resynchronized patients. *Pacing Clin Electrophysiol*. 2006;29:564-568

12.   Hardt SE, Yazdi SH, Bauer A, Filusch A, Korosoglou G, Hansen A, Bekeredjian R, Ehlermann P, Remppis A, Katus HA, Kuecherer HF. Immediate and chronic effects of av-delay optimization in patients with cardiac resynchronization therapy. *Int J Cardiol*. 2007;115:318-325

13.   Vidal B, Tamborero D, Mont L, Sitges M, Delgado V, Berruezo A, Diaz-Infante E, Tolosana JM, Pare C, Brugada J. Electrocardiographic optimization of interventricular delay in cardiac resynchronization therapy: A simple method to optimize the device. *J Cardiovasc Electrophysiol*. 2007;18:1252-1257

14.   Kedia N, Ng K, Apperson-Hansen C, Wang C, Tchou P, Wilkoff BL, Grimm RA. Usefulness of atrioventricular delay optimization using doppler assessment of mitral inflow in patients undergoing cardiac resynchronization therapy. *Am J Cardiol*. 2006;98:780-785

15.   Ellenbogen KA, Gold MR, Meyer TE, Fernndez Lozano I, Mittal S, Waggoner AD, Lemke B, Singh JP, Spinale FG, Van Eyk JE, Whitehill J, Weiner S, Bedi M, Rapkin J, Stein KM. Primary results from the smartdelay determined av optimization: A comparison to other av delay methods used in cardiac resynchronization therapy (smart-av) trial: A randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. *Circulation*. 2010;122:2660-2668

16.   Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, Klein H, Kramer A, Ding J, Salo R, Tockman B, Pochet T, Spinelli J. Effect of pacing chamber and

atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The pacing therapies for congestive heart failure study group. The guidant congestive heart failure research group. *Circulation*. 1999;99:2993-3001

17. Brenyo A, Kutyifa V, Moss AJ, Mathias A, Barsheshet A, Pouleur AC, Knappe D, McNitt S, Polonsky B, Huang DT, Solomon SD, Zareba W, Goldenberg I. Atrioventricular delay programming and the benefit of cardiac resynchronization therapy in madit-crt. *Heart Rhythm*. 2013

18. Delnoy PP, Ritter P, Naegele H, Orazi S, Szwed H, Zupan I, Goscinska-Bis K, Anselme F, Martino M, Padeletti L. Association between frequent cardiac resynchronization therapy optimization and long-term clinical response: A post hoc analysis of the clinical evaluation on advanced resynchronization (clear) pilot study. *Europace*. 2013

19. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539-1549

20. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845-1853

21. Meluzin J, Novak M, Mullerova J, Krejci J, Hude P, Eisenberger M, Dusek L, Dvorak I, Spinarova L. A fast and simple echocardiographic method of determination of the optimal atrioventricular delay in patients after biventricular stimulation. *Pacing Clin Electrophysiol*. 2004;27:58-64

22. van Gelder BM, Bracke FA, Meijer A, Pijls NH. The hemodynamic effect of intrinsic conduction during left ventricular pacing as compared to biventricular pacing. *J Am Coll Cardiol*. 2005;46:2305-2310

23. Pires LA, Abraham WT, Young JB, Johnson KM, Miracle, Investigators M-I. Clinical predictors and timing of new york heart association class improvement with cardiac resynchronization therapy in patients with advanced chronic heart failure: Results from the multicenter insync randomized clinical evaluation (miracle) and multicenter insync icd randomized clinical evaluation (miracle-icd) trials. *Am Heart J*. 2006;151:837-843

24. Vatasescu R, Berruezo A, Mont L, Tamborero D, Sitges M, Silva E, Tolosana JM, Vidal B, Andreu D, Brugada J. Midterm 'super-response' to cardiac resynchronization

therapy by biventricular pacing with fusion: Insights from electro-anatomical mapping. *Europace*. 2009;11:1675-1682

25. Butter C, Auricchio A, Stellbrink C, Fleck E, Ding J, Yu Y, Huvelle E, Spinelli J. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation*. 2001;104:3026-3029

26. Sogaard P, Egeblad H, Pedersen AK, Kim WY, Kristensen BO, Hansen PS, Mortensen PT. Sequential versus simultaneous biventricular resynchronization for severe heart failure: Evaluation by tissue doppler imaging. *Circulation*. 2002;106:2078-2084

27. Vanderheyden M, De Backer T, Rivero-Ayerza M, Geelen P, Bartunek J, Verstreken S, De Zutter M, Goethals M. Tailored echocardiographic interventricular delay programming further optimizes left ventricular performance after cardiac resynchronization therapy. *Heart Rhythm*. 2005;2:1066-1072

28. Leon AR, Abraham WT, Brozena S, Daubert JP, Fisher WG, Gurley JC, Liang CS, Wong G, InSync IIICSI. Cardiac resynchronization with sequential biventricular pacing for the treatment of moderate-to-severe heart failure. *J Am Coll Cardiol*. 2005;46:2298-2304

29. Rao RK, Kumar UN, Schafer J, Viloria E, De Lurgio D, Foster E. Reduced ventricular volumes and improved systolic function with cardiac resynchronization therapy: A randomized trial comparing simultaneous biventricular pacing, sequential biventricular pacing, and left ventricular pacing. *Circulation*. 2007;115:2136-2144

30. Boriani G, Muller CP, Seidl KH, Grove R, Vogt J, Danschel W, Schuchert A, Djiane P, Biffi M, Becker T, Bailleul C, Trappe HJ, Resynchronization for the HemodYnamic Treatment for Heart Failure Management III. Randomized comparison of simultaneous biventricular stimulation versus optimized interventricular delay in cardiac resynchronization therapy. The resynchronization for the hemodynamic treatment for heart failure management ii implantable cardioverter defibrillator (rhythm ii icd) study. *Am Heart J*. 2006;151:1050-1058

31. Whinnett ZI, Davies JE, Willson K, Manisty CH, Chow AW, Foale RA, Davies DW, Hughes AD, Mayet J, Francis DP. Haemodynamic effects of changes in atrioventricular and interventricular delay in cardiac resynchronisation therapy show a consistent pattern: Analysis of shape, magnitude and relative importance of atrioventricular and interventricular delay. *Heart*. 2006;92:1628-1634

32. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson RA, Kellen JC, Klein RC, Krahn AD, Mickel M, Mitchell LB, Nelson JD, Rosenberg Y, Schron E, Shemanski L, Waldo AL, Wyse DG, Investigators A. Relationships between sinus rhythm, treatment, and survival in the atrial fibrillation follow-up investigation of rhythm management (affirm) study. *Circulation*. 2004;109:1509-1513

33. Gasparini M, Auricchio A, Metra M, Regoli F, Fantoni C, Lamp B, Curnis A, Vogt J, Klersy C, Multicentre Longitudinal Observational Study G. Long-term survival in patients undergoing cardiac resynchronization therapy: The importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. *Eur Heart J*. 2008;29:1644-1652

Table 1: *Demographics at implantation*

Men (years)	130/170 (76.5%)
New implantation	129/170 (75.9%)
CRT Upgrade	41/170 (24.1%)
Time implantation – optimization (months)	2.9 +/- 5
Age at implantation (years)	62.8 +/- 12.5
Ischemic cardiomyopathy	75/169 (44.4%)
CRT-D	156/170 (91.8%)
Sinus rhythm at implantation	107/167 (64.1%)

Table 2: *Clinical parameters at time of optimization*

Clinical	
Height (m)	1.7 +/- 0.1
Weight (kg)	82 +/- 18.5
BMI (kg/m^2)	28.4 +/- 5.9
Systolic BP (mmHg)	116.1 +/- 17.3
Diastolic BP (mmHg)	73 +/- 11.7
NYHA class	
NYHA I	24/134 (17.9%)
NYHA II	54/134 (40.3%)
NYHA III	20/134 (14.9%)
NYHA IV	1/134 (0.7%)
Medication	
Beta blocker	157/168 (93.5%)
ACE-I / ARB	160/168 (95.2%)
Spironolactone	93/168 (55.4%)

Other diuretics	145/168 (86.3%)
Digitalis	22/168 (13.1%)
Amiodarone	30/168 (17.9%)
Calcium channel blocker	11/168 (6.5%)
Nitrates	11/168 (6.5%)
Lipid lowering treatment	103/168 (61.3%)
Aspirin	84/168 (50%)
Clopidogrel	12/168 (7.1%)
Oral anticoagulation	84/168 (50%)

Table 2: *Echocardiography at optimization*

LVEF (%)	37.3 +/- 11.1
LVEDD (mm)	6.2 +/- 1.1
LVESD (mm)	4.9 +/- 1.3
Enddiastolic volume (ml)	169.5 +/- 79.2
Enddiastolic volume index (ml/m2)	88.4 +/- 41.6
Endsystolic volume (ml)	110.8 +/- 71.5
Endsystolic volume index (ml/m2)	58.8 +/- 38.3
Diastolic dysfunction	
No diastolic dysfunction	92/168 (54.8%)
Grade I	7/168 (4.2%)
Grade II	1/168 (0.6%)
Grade III	0/168 (0%)
Mitral regurgitation	
Minimal	88/167 (52.7%)
Mild	59/167 (35.3%)
Moderate	13/167 (7.8%)
Severe	4/167 (2.4%)
LA-ESD (mm)	4.7 +/- 0.9
RV: Area D (cm2)	16.2 +/- 5.1
Fractional shortening RV (%)	39.7 +/- 12.1
TAM (mm)	18.3 +/- 4.9
RV/RA-pressure gradient (mmHg)	27.9 +/- 11.6
RA Size	5 +/- 0.9
Dyssynchrony assessment	
RV-PEP (ms)	118.1 +/- 31.3
LV-PEP (ms)	135.5 +/- 31.5
IVMD	17.5 +/- 27.7
TDI SL	32.7 +/- 46.8
TDI AS-IL	33.5 +/- 46.3
Diastolic filling time / RR-interval	49.5 +/- 32.1

Table 3: *ECG parameters*

Rhythm at optimization	
Sinus rhythm	112/170 (65.9%)
SR, AVB III°, without ventricular escape	15/170 (8.8%)
SR, AVB III°, with ventricular escape	6/170 (3.5%)
Atrial fibrillation with AV conduction	20/170 (11.8%)
AF, AVB III°	7/170 (4.1%)
AF post AVN ablation	6/170 (3.5%)
PQ intrinsic	184.7 +/- 27.6
QRS intrinsic	150 +/- 26.6
Bundle branch block	
No block	14/163 (8.6%)
LBBB	97/163 (59.5%)
RBBB	13/163 (8%)
AVB III°	36/163 (22.1%)
Development of rhythm	
Unchanged	109 (65.3%)
AF --> SR	4 (2.4%)
AF --> PM	2 (1.2%)
SR --> AF	8 (4.8%)
SR --> PM	4 (2.4%)
PM Upgrade	41 (24%)

Table 4: *AV / VV settings at optimization*

Pacing at optimization	
True biventricular stimulation	76/170 (44.7%)
Fusion	67/170 (39.4%)
Pseudofusion	3/170 (1.8%)
Atrial fibrillation	23/170 (13.5%)
AV delays	
sAV (at interrogation)	110.5 +/- 19
pAV (at interrogation)	136.5 +/- 23.4
Begin QRS fusion (sAV)	103.9 +/- 37.1
Begin QRS fusion (pAV)	174.3 +/- 42.7
Intraatrial delay (pAV-sAV)	71.9 +/- 28.2
No fusion (AV block)	33 (19.4%)
Dynamic AV delay on	78/164 (47.6%)
Situation at sensed AV delay 120ms	
Pure biventricular stimulation	58/140 (41.4%)
Fusion	72/140 (51.4%)
Intrinsic rhythm / Pseudofusion	8/140 (5.7%)

Status before optimization	
A-wave truncation	38/147 (25.9%)
QRS fusion	39/147 (26.5%)
Both A-wave truncation and QRS fusion	31/147 (21.1%)
VV (at interrogation) in ms	8.5 +/- 14.4
% Biventricular pacing (average)	94.3 +/- 13.3
≥ 97%	112 (67.9%)
< 97%	53 (32.1%)
< 95%	40 (24.2%)
< 90%	23 (13.9%)
≤ 85%	16 (9.7%)
Reason for low biventricular pacing (<95%)	
Atrial fibrillation	18/39 (46.2%)
VES	13/39 (33.3%)
Intrinsic conduction	3/39 (7.7%)
Other	4/39 (10.3%)
Device manufacturer	
Medtronic	31/170 (18.2%)
St. Jude Medical	49/170 (28.8%)
Biotronik	79/170 (46.5%)
Boston Scientific	10/170 (5.9%)

Table 5: *LV lead parameters*

LV pacing configuration	
LvTip-LvRing	58/170 (34.1%)
LvRing-LvTip (inverse bipolar)	5/170 (2.9%)
LvTip-RvRing	48/170 (28.2%)
LvRing-RvRing	9/170 (5.3%)
LvTip-RvCoil	40/170 (23.5%)
LvRing-RvCoil	7/170 (4.1%)
Unipolar	1/170 (0.6%)
Diaphragmatic capture	
No diaphragmatic capture	161/168 (95.8%)
Diaphragmatic capture, resolved with programming	7/168 (4.2%)
Diaphragmatic capture, not amenable to programming	
changes	0/168 (0%)
Threshold LV (V)	1.3 +/- 0.8
Threshold LV (ms)	0.5 +/- 0.2
LV Sensing mV	12.6 +/- 8.6

LV Impedance	644.4 +/- 228.3

Table 6: Changes during optimization

Change in sensed AV delay	
unchanged	39/137 (28.5%)
shortened	73/137 (53.3%)
lengthened	24/137 (17.5%)
Changes in paced AV delay	
unchanged	45/134 (33.6%)
shortened	51/134 (38.1%)
lengthened	38/134 (28.4%)
Reason for AV delay change	
ECG Fusion	56/97 (57.7%)
LV inflow truncation	23/97 (23.7%)
LV inflow fusion	14/97 (14.4%)
Visual LV filling	3/97 (3.1%)
Other	1/97 (1%)
Status after optimization	
A-wave truncation	22/147 (15%)
QRS fusion	47/147 (32%)
Both A-wave truncation and QRS fusion	34/147 (23.1%)
Change in VV delay	
unchanged	118/168 (70.2%)
LV earlier	13/168 (7.7%)
RV earlier	5/168 (3%)
Dyssynchronous, not improvable	30/168 (17.9%)
Reason for VV delay changes	
Visual	3/17 (17.6%)
TDI	14/17 (82.4%)

Figure 1. Twelve-lead ECGs of a patient presenting for CRT optimization. "True" biventricular pacing (VVI 90 beats per minute, left panel), intrinsic rhythm (right panel) and rhythm at follow-up (middle panel) are shown. Note the significant degree of QRS fusion as demonstrated by 12-lead ECG with the current device settings. The latter are best appreciated in I, avL and V3, indicating the necessity for comprehensive 12-lead ECG analysis in the follow-up of these patients.

Figure 2. CRT patient follow-up algorithm as implemented at the University of Zurich. See text for details
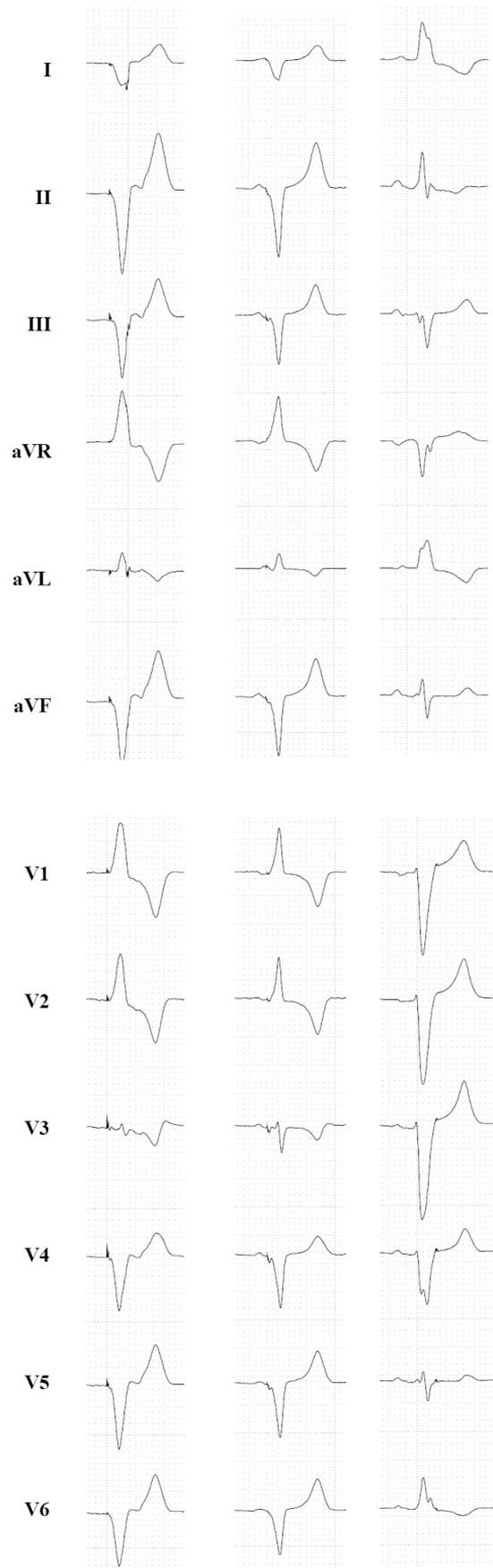
Figure 1:

Figure 2:

```
                    ┌─────────────────────────┐
                    │  Complete Device Check  │
                    └─────────────────────────┘
                                 │
                                 ▼
                    ┌─────────────────────────────┐
                    │ 12-lead ECG, including:     │
                    │   -  Intrinsic rhythm       │
                    │   -  Right ventricular pacing│
                    │   -  Left ventricular pacing │
                    └─────────────────────────────┘
                                 │
                                 ▼
```

AV Delay optimization (12 lead ECG)
- Assess "True biventricular" paced rhythm
- Start at lowest possible AVD
- incremental increase of AVD until signs of fusion on ECG
- Repeat for sensed and paced AVD

Reassess AVD for ECG fusion if VVD has been adjusted

Echocardiography
- Standard examination (if required)
- AVD optimization
- Assessment of VV dyssynchrony (TDI)
- VVD optimization, if required

Wrap up
- Print 12-lead ECG with current setting
- Print current device settings
- Comprehensive report, including rationale for setting changes
- Review with heart failure specialists and discuss pertinent findings