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Long-term follow-up after cardiac resynchronization therapy-optimization in a real-world setting: A single-center cohort study

Running title: CRT-optimization in a real-world setting

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Abstract

Background: Suboptimal device programming is among the reasons for reduced response to cardiac resynchronization therapy (CRT). However, whether systematic optimization is beneficial remains unclear, particularly late after CRT implantation. The aim of this single-center cohort study was to assess the effect of systematic atrioventricular delay (AVD) optimization on echocardiographic and device parameters.

Methods: Patients undergoing CRT optimization at the University Hospital Zurich between March 2011 and January 2013, for whom a follow-up was available, were included. AVD optimization was based on 12-lead electrocardiography (ECG) and echocardiographic left ventricular inflow characteristics. Parameters were assessed at the time of CRT optimization and follow-up, and were compared between patients with AVD optimization (intervention group) and those for whom no AVD optimization was deemed necessary (control group).

Results: Eighty-one patients with a mean age of 64 ± 11 years were included in the analysis. In 73% of patients, AVD was deemed suboptimal and was changed accordingly. After a median follow-up time of 10.4 (IQR 6.2 to 13.2) months, the proportion of patients with sufficient biventricular pacing (> 97% pacing) was greater in the intervention group (78%) compared to controls (50%). Furthermore, AVD adaptation was associated with an

improvement in interventricular mechanical delay (decrease of 6.6 ± 26.2 ms vs. increase of 4.3 ± 17.7 ms, p = 0.034) and intraventricular septal-to-lateral delay (decrease of 0.9 ± 48.1 ms vs. increase of 15.9 ± 15.7 ms, p = 0.038), as assessed by tissue Doppler imaging. Accordingly, a reduction was observed in mitral regurgitation along with a trend towards reduced left ventricular volumes.

Conclusions: In this "real-world" setting systematic AVD optimization was associated with beneficial effects regarding biventricular pacing and left ventricular remodeling. These data show that AVD optimization may be advantageous in selected CRT patients.

Key words: cardiac resynchronization therapy, atrioventricular delay, biventricular pacing, left ventricular remodeling

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a life-saving treatment in selected patients with symptomatic heart failure and reduced ejection fraction (HFrEF) [1–3]. In patients with persistent symptoms (New York Heart Association II to ambulatory IV) on optimal medical therapy, a left ventricular ejection fraction (LVEF) of 35% or less, and a wide QRS complex (> 130 ms), CRT has been shown to prolong life and reduce the risk for recurrent heart failure (HF) hospitalizations [4–8]. However, about one third of patients remain unresponsive to biventricular pacing and do not exhibit improvement in clinical or hemodynamic parameters [5, 6]. Several factors may account for this unsatisfactory therapeutic response in this relevant proportion of patients. Apart from ineffective synchronization secondary to suboptimal left ventricular (LV) lead placement or extensive scar tissue, and indeliberate patient selection remains a major source of error [7, 9]. However, even after correct LV lead placement and in the absence of extensive scar tissue, response to CRT may not be evident. Such therapy failure may be attributed to suboptimal device programming, specifically with regard to the atrioventricular delay (AVD) and interventricular (VV) interval [10, 11]. Yet, whether systematic AVD optimization is of prognostic benefit, remains unclear. To date, a number of studies suggest an improvement of clinical, echocardiographic and hemodynamic parameters after AVD optimization. However, the number of patients is very low and follow-up times are short [12–15].

At the documented institution, a standard protocol of echocardiography- and 12-lead electrocardiography (ECG)-guided device optimization after CRT implantation was implemented. It was previously demonstrated that a majority of patients undergoing CRT optimization after implantation presented with suboptimal device settings, particularly regarding AVD [16]. The aim of this study was to evaluate the clinical course after AVD optimization and to study whether patients, in whom the AVD was changed, fared better than those in whom the AVD was left unchanged in this real-world setting.

METHODS

All patients with a CRT-device who underwent CRT optimization at the documented device clinic between March 2011 and January 2013 and in whom at least one follow-up including echocardiography was available were included. CRT devices were implanted according to standard protocols at the University Heart Center Zurich. Patients for CRT implantation were selected based on current guideline recommendations [17]. After implantation, a baseline CRT-optimization was performed on a routine basis, patients referred for CRT implantation from elsewhere underwent baseline optimization in cases of explicit referral. Baseline optimization included a comprehensive device optimization protocol with a complete clinical assessment by a HF specialist, a device interrogation, 12-lead ECGs of intrinsic and paced (BiV, RV, LV) rhythms, and a complete echocardiograph exam with optimization of AVD, if deemed necessary [16]. After baseline optimization, follow-up CRT-optimization was performed in cases of non-response or signs of disease progression, i.e. patients were referred for follow-up CRT optimization if there was a decrease or insufficient increase of LVEF after unexplained HF decompensation or in cases of unexplained progressive decline in exercise capacity.

The need for optimization of AVD was based on the degree of QRS fusion on 12-lead ECG and the presence of LV inflow truncation or fusion as assessed by pulsed wave Doppler echocardiography. For detection of electrical fusion, QRS morphology was assessed on 12-lead ECG during intrinsic rhythm, in biventricular stimulated VVI mode (representing “true” biventricular pacing), during right/left ventricular pacing only, and during CRT pacing under current settings. AVD was then programmed for as long as possible without signs of fusion with intrinsic conduction. Optimal LV filling was subsequently determined according to the iterative method [18, 19], i.e., AVD was shortened in steps of 20 ms under parallel assessment of QRS morphology on a 12-lead ECG and mitral inflow on pulsed wave Doppler echocardiography until truncation of the A-wave indicated impairment of LV filling. In a

third step, AVD was increased in steps of 10 ms until an optimal separation of E and A wave occurred. This was considered an optimal atrioventricular coupling.

For the current study, clinical, echocardiographic and device parameters at the time of echocardiography, a 12-lead ECG-guided CRT optimization (baseline visit) and at the time of the follow-up visit were analyzed. Parameters were compared between patients, in whom the AVD was changed at baseline ("intervention group") and those, in whom no adaptation of the AVD was made ("control group") (Fig. 1, **Suppl. Fig. 1**). Reasons for not changing the AVD were either an interval that was deemed optimal as assessed by the method described above, or if a change in AVD would lead to new QRS fusion or truncation of the A wave.

Statistical analysis

Continuous variables are expressed as mean and standard deviation; categorical variables are expressed as proportions. Within-group comparisons (baseline vs. follow-up) were performed using the paired Student t-test for continuous variables and the paired Wilcoxon signed-rank tests for categorical variables. Between-group comparisons (intervention group vs. control group) were done using the unpaired Student t-test and the Mann-Whitney-U-test, where applicable. Distribution of data was assessed by the Shapiro-Wilk test and quantile-quantile (Q-Q) plots. Both data at baseline optimization and at follow-up as well as differences in parameters over time were assessed for normal distribution. Proportions were compared using Chi-square tests. Statistical significance was accepted for $p < 0.05$. All p-values are two-sided. Statistical analyses were performed using SPSS version 22.

RESULTS

Eighty-one patients undergoing baseline CRT optimization between March 2011 and January 2013 and in whom a consecutive follow-up was available were included in the analysis. Baseline characteristics are summarized in Table 1. With the exemption of atrial fibrillation (AF), which was absent in the intervention group, and complete atrioventricular block, which was more frequent in the control group, no significant differences were present (Table 1). Median time between CRT implantation and baseline CRT-optimization was 1.7 (IQR 0.4 to 4.2) years. Median follow-up time between baseline optimization and follow-up was 10.4 (IQR 6.2 to 13.2) months. Out of 81 patients, 3 patients were hospitalized for HF during follow-up (2 in the intervention group, 1 in the control group). At baseline, 59 (73%) patients presented with AVD, which was deemed suboptimal either secondary to the presence of QRS fusion on a 12-lead ECG or due to unfavorable LV-filling patterns as assessed by

echocardiography [16]. In these patients, AVD was reprogrammed according to the method described above; in the majority of these patients (n = 42, 52%) AVD was decreased, secondary to QRS fusion and/or LV inflow fusion. In 17 (21%) patients AVD was prolonged secondary to LV inflow truncation. Accordingly, the average AVD was significantly shorter at follow-up compared to baseline (120 ± 20 ms at baseline and 100 ± 29 ms at follow-up, p = 0.001). 12 (15%) patients were in AF.

In the overall population, clinical parameters did not change significantly between baseline and the follow-up visit. The proportion of patients with New Year Heart Association (NYHA) class II or higher was 79% (n = 58/73) at baseline and 76% (n = 57/75) at follow-up (p = 0.109).

Interestingly, biventricular pacing increased in patients after AVD adjustment over time. While there was no difference in biventricular pacing at baseline, the proportion of patients with a biventricular pacing rate of > 97% increased significantly by the time of follow-up (78% in the intervention group vs. 50% in the control group, p = 0.021; Fig. 2). As proof of concept, reassessment of biventricular pacing at follow-up was performed after exclusion of 6 patients with AF and intact atrioventricular conduction. Biventricular pacing proportions remained significantly higher in the intervention compared to the control group (mean biventricular pacing rate: 94.5 ± 6.8% in the control group, 97.5 ± 4.0% in the intervention group, p = 0.022; percentage of patients with > 97% biventricular pacing: 44% in the control group, 78% in the intervention group, p = 0.031; **Suppl. Table 1**).

Moreover, both interventricular mechanical delay (IVMD) and septal to lateral delay (SLD), as assessed by tissue Doppler imaging (TDI), decreased in the intervention group (AVD changed) compared to the control group (AVD unchanged), in which both IVMD and SLD increased from baseline to follow-up (Fig. 3). Although left ventricular ejection fraction was not different between the intervention and the control group at follow-up (Fig. 4A), a trend was observed towards reduced end-diastolic LV volumes (Fig. 4B) in the intervention group. Along this line, the proportion of patients with mitral regurgitation, which did not differ between both groups at baseline (Fig. 4C), decreased in the intervention group while it increased in the control group resulting in a significant difference at follow-up (Fig. 4D).

DISCUSSION

This retrospective is a single-center cohort study in a real-world setting. AVD optimization was associated with an improvement of biventricular pacing, inter- and

intraventricular synchronicity, as well as a reduction in mitral regurgitation along with a trend towards reduced end-diastolic LV volumes.

These results corroborate previous findings from several smaller studies with shorter follow-up [12–14]. However, the role of regular evaluation and adjustment of the atrioventricular interval in patients with CRT and the method of AVD optimization remain a matter of debate [20]. In contrast to other studies, the prospective, randomized, controlled SMART-AV trial showed no benefit of general AVD optimization as opposed to a fixed AVD of 120 ms with regard to the primary outcome of LV end-systolic volume at 6 months [21]. It was concluded that regular AVD assessment and optimization was not necessary and a fixed interval of 120 ms would suffice. However, these results may not apply to selected individuals, especially those with a suboptimal response to CRT in combination with suboptimal diastolic ventricular filling. Indeed, Mullens et al. [11] observed suboptimal AVD settings in 45% of those patients who suffered from persistent advanced HF symptoms and/or adverse remodeling after CRT implantation. Furthermore, a sub-analysis of MADIT-CRT, one of the guideline-defining, large randomized, controlled trials, demonstrated that patients programmed to a short AVD (< 120 ms) had a reduced risk of HF or death over the 3 years following CRT implantation compared to those patients with an AVD > 120 ms, further indicating a role of AVD settings on long-term outcome in selected CRT patients [22]. Finally, a post-hoc analysis of the CLEAR study demonstrated an improved outcome for the composite endpoint of all-cause mortality, HF hospitalization, NYHA class and quality of life with regular, systematic AVD optimization as opposed to “non-systematic” optimization, irrespective of the optimization method applied [23].

Although an assessment of the effect of CRT optimization on morbidity and mortality was beyond the scope of this real-world study, the data support a potential role for CRT optimization with regard to long-term outcome. The present results further underline the importance of the evaluation and adjustment of device settings, given that a substantial part of CRT patients presented with inadequate atrioventricular intervals at baseline.

A high percentage of biventricular pacing is associated with an improved outcome in CRT patients [24]. Koplan et al. [25] demonstrated that the greatest benefit in reduction of HF hospitalization and all-cause mortality was achieved with a biventricular pacing above 92%. The rationale for an even higher proportion of biventricular pacing was provided by Hayes et al. [26] in a cohort of over 30,000 patients, where mortality was found to be inversely related with the percentage of biventricular pacing. Since a reduced percentage of biventricular pacing is among the main reasons for suboptimal response to CRT [11], these data imply that

regular assessments and efforts to increase biventricular pacing are central. However, there are no data assessing this hypothesis prospectively, and whether certain interventions to improve biventricular pacing such as antiarrhythmic therapy in patients with AF truly impact hard clinical outcomes remains elusive.

Loss of biventricular pacing can occur as a result of a long AVD due to intrinsic atrioventricular conduction. In such patients, shortening of AVD may increase the degree of biventricular pacing [24–26]. In the present study, patients in whom the AVD was changed (mostly shortened) during CRT optimization had a higher percentage of biventricular pacing at follow-up. The favorable development of hemodynamic parameters in the intervention group may well be a consequence of the higher biventricular pacing proportion in these patients. As adaptation of AVD in order to prevent intrinsic conduction can be performed on the basis of QRS morphology on 12-lead ECG, this raises the question, if echocardiographic assessment during AVD optimization is necessary. It is however important to note that ensuring constant biventricular pacing based on 12-lead ECG alone may lead to programming excessively short AV delays in order to prevent QRS fusion. In this context, echocardiographic monitoring of mitral inflow is crucial in order to avoid impaired left ventricular filling. Herein, echocardiography was therefore regarded as an essential component in the process of AVD optimization.

Taken together, the present findings support the role of systematic AVD optimization to achieve the highest possible percentage of biventricular stimulation and improve hemodynamic parameters. The absolute effect of this improvement, however, was small and it remains to be determined whether this will translate into a reduction in morbidity and mortality.

Limitations of the study

This study has to be interpreted in light of several limitations, most of which are inherent to any “real-world” registry study. All patients analyzed were recruited at a single center, which may introduce a selection and/or referral bias, and may therefore not reflect the situation in other healthcare facilities.

Furthermore, the control group included 12 patients with AF. In CRT-patients AF can lead to loss of biventricular pacing secondary to high ventricular rates. Importantly, several studies have shown similar benefit of CRT in patients with AF and those in sinus rhythm [27–30]. However, more recent evidence points to a worse prognosis of CRT in the context of AF [31, 32]. This is primarily due to high ventricular rates and consecutive electrical fusion or

loss of biventricular pacing, highlighting the importance of adequate rate control [33]. This was evident in the CERTIFY registry by Gasparini et al. [33], in which CRT-patients in sinus rhythm were compared to CRT-patients with AF either after atrioventricular junction ablation (AVJA) or without AVJA [34]. After a median follow-up of 37 months, mortality was similar between AF patients after AVJA and patients in sinus rhythm, while AF patients on medical rate control alone had a worse outcome compared to both patients in sinus rhythm and patients with AF and AJVA. This implies that patients with AF and complete atrioventricular block derive equivalent benefit from CRT as do patients in sinus rhythm [33]. Out of the 12 patients with AF in the present cohort, 6 patients had intact intrinsic conduction. Upon exploratory exclusion of these patients, the difference in biventricular pacing between the intervention group and the control group remained significantly different. It can therefore be assumed that the difference in biventricular pacing proportions at follow-up were not driven by patients in AF.

Since this study ought to reflect real-world data, not all variables are distributed evenly between groups. Importantly, there was a higher proportion of patients with complete atrioventricular block in the control group (50% vs. 7%), an effect due to the fact that in these patients AV optimization is oftentimes not necessary as no fusion with intrinsic conduction can occur. Few data exist on the direct comparison between CRT-patients with LBBB and those with complete atrioventricular block. However, in patients with atrioventricular block and reduced LVEF biventricular pacing has been shown to reduce the risk of mortality and morbidity and lead to better clinical outcomes [35]. In the absence of intrinsic conduction, complete atrioventricular block is associated with higher biventricular pacing proportions. Therefore, if present, confounding, may lead to an underestimation of the difference in biventricular pacing proportions in the context of this study. However, as this study was intended to reflect a real-world setting, the current study refrained from excluding patients from the analyses wherever possible. Of note, QRS-width, which is the primary determinant of response in CRT [7], was evenly distributed among the groups in this real-world cohort.

Finally, and as with every registry study, residual confounding between groups may have contributed to the findings; as such, only associations and no causality may be inferred [36]. This notwithstanding, the data herein does reflect a “real-world” setting of CRT patients, which may contribute important insight into evolving therapy concepts such as CRT optimization in daily practice.

CONCLUSIONS

The present study results imply that AVD optimization may result in an increased biventricular pacing percentage, which has been shown to be associated with better hemodynamic parameters and reduced mortality. Whether these hypotheses hold true, remains to be determined in a well-controlled randomized setting.

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Table 1. Parameters at baseline during cardiac resynchronization therapy-optimization.

Parameters	**Overall population (n = 81)**	**Control group (n = 22)**	**Intervention group (n = 59)**	**P**
Age at implantation (years)	64 ± 11	63 ± 16	64 ± 9	0.725
Men (n/total)	63/81 (78%)	17/22 (77%)	46/59 (78%)	0.947
Co-morbidities				
Diabetes mellitus	20/80 (25%)	7/22 (31.8%)	13/58 (22.4%)	0.386
Hypertension	44/81 (54.3%)	13/22 (59.1%)	31/59 (52.5%)	0.87
Dyslipidemia	45/81 (55.6%)	13/22 (59.1%)	32/59 (54.2%)	0.875

Coronary artery disease	32/81 (39.5%)	8/22 (36.4%)	24/59 (40.7%)	0.724
Atrial fibrillation	12/81 (15%)	12/22 (55%)	0/59 (0%)	< 0.001*
Medication				
ACEI/ARBs	79/80 (98.8%)	21/22 (96%)	58/58 (100%)	0.102
Beta-blockers	77/80 (96.3%)	21/22 (96%)	56/58 (96.6%)	0.818
Calcium channel blockers	6/80 (7.5%)	0/22 (0%)	6/58 (10%)	0.117
Spironolactone	47/80 (58.8%)	12/22 (55%)	35/58 (60%)	0.638
Diuretics	69/80 (86.3%)	21/22 (96%)	48/58 (83%)	0.141
Digitalis	10/80 (12.5%)	4/22 (18.2%)	6/58 (10.3%)	0.344
Amiodarone	12/80 (15%)	4/22 (18.2%)	8/58 (13.8%)	0.624
Clinical parameters				
NYHA class: NYHA I NYHA II NYHA III NYHA IV	 15/73 (20%) 40/73 (55%) 18/73 (25%) 0/73 (0%)	 5/21 (24%) 10/21 (48%) 6/21 (28%) 0/21 (0%)	 10/52 (19%) 30/52 (58%) 12/52 (23%) 0/52 (0%)	0.946
Weight [kg]	81 ± 19	85 ± 21	80 ± 18	0.32
Systolic BP [mmHg]	118 ± 18	118 ± 18	118 ± 18	0.955
NT-proBNP [pg/mL]	1462 ± 1964	2015 ± 2186	1256 ± 1856	0.152
Echocardiographic parameters				
LVEF [%]	38 ± 10	38 ± 11	37 ± 9	0.78
EDVI [mL/m^2]	88 ± 38	85 ± 39	89 ± 37	0.697
IVMD [ms]	17.3 ± 28.0	12.9 ± 20.6	18.8 ± 30.0	0.41
TDI septal to lateral [ms]	41.7 ± 44.7	15.5 ± 51.2	48.3 ± 40.8	0.013*
TDI anteroseptal to inferolateral [ms]	38.2 ± 48.4	18.8 ± 48.8	42.8 ± 47.7	0.108
ECG and device parameters				
Biventricular pacing [%]	95.6 ± 9.6	93.8 ± 13.0	96.3 ± 8.0	0.304
Bundle branch block* LBBB RBBB IVCD	 54/65 (83%) 5/65 (8%) 6/65 (9%)	 7/11 (64%) 1/11 (9%) 3/11 (27%)	 47/54 (87%) 4/54 (7%) 3/54 (6%)	0.070
Complete AVB	15/80 (19%)	11/22 (50%)	4/58 (7%)	< 0.001*
QRS width [ms]	150 ± 28	142 ± 25	152 ± 28	0.264
PQ interval [ms]**	184 ± 28	172 ± 40	185 ± 27	0.38
Sensed AV interval [ms]	112 ± 20	122 ± 22	110 ± 19	0.156
Paced AV interval [ms]	136 ± 23	146 ± 31	135 ± 22	0.223
VV delay [ms]	10 ±17	11 ± 21	9 ± 16	0.78
VV delay changed	16/81 (20%)	2/22 (9%)	14/59 (24%)	0.141

Continuous variables are presented as mean ± standard deviation; categorical variables are presented as proportions. *Complete AVB excluded. **Patients with complete AVB and patients with AF excluded

ACEI/ARB — angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker; AV — atrioventricular; AVB — atrioventricular block; BP — blood pressure; CRT — cardiac resynchronization therapy; EDVI — end-diastolic volume index; IVCD — intraventricular conduction delay; IVMD — interventricular mechanical delay; LBBB — left bundle branch block; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; RBBB — right bundle branch block; TDI — tissue Doppler imaging; VV — interventricular delay

Table 2. Parameters in patients with changed atrioventricular delay and patients with unchanged atrioventricular delay at follow-up visit.

	Control group (n = 22)	**Intervention group (n = 59)**	**P**
Clinical parameters			
NYHA class: NYHA I NYHA II NYHA III NYHA IV	 7/21 (33%) 9/21 (43%) 4/21 (19%) 1/21 (5%)	 11/54 (20%) 34/54 (63%) 9/54 (17%) 0/54 (0%)	0.745
Weight (kg)	83 ± 24	81 ± 19	0.603
Systolic BP [mmHg]	115 ± 17	120 ± 16	0.331
NT-proBNP [pg/mL]	1674 ± 1446	1092 ± 1602	0.169
Echocardiographic parameters			
LVEF [%]	39 ± 12	39 ± 10	0.903
EDVI [mL/m^2]	90 ± 43	87 ± 38	0.794
IVMD [ms]	16.0 ± 20.6	12.8 ± 22.3	0.553
TDI septal to lateral [ms]	31.9 ± 44.5	47.6 ± 46.2	0.184
TDI anteroseptal to inferolateral [ms]	36.2 +/- 52.3	44.1 ± 42.5	0.515
Electrocardiography and device parameters			
Biventricular pacing [%]	95.3 ± 6.0	97.5 ± 4.0	0.034*
Bundle branch block* LBBB RBBB IVCD	 7/11 (64%) 1/11 (9%) 3/11 (27%)	 46/54 (85%) 5/54 (9%) 3/54 (6%)	0.075
Complete AVB	1**1**/22 (50%)	4/58 (7%)	< 0.001*
QRS width [ms]	141 ± 31	147 ± 23	0.47
PQ interval [ms]**	189 ± 40	195 ± 41	0.92
Sensed AV interval [ms]	121.8 ± 20.4	96.4 ± 28.2	0.006*
Paced AV interval [ms]	144.6 ± 29.8	130.7 ± 30.5	0.17
VV delay [ms]	7.6 ± 15.4	15.7 ± 22.1	0.144

Continuous variables are presented as mean ± standard deviation; categorical variables are presented as proportions. *Complete AVB excluded. **Patients with complete AVB and patients with AF excluded

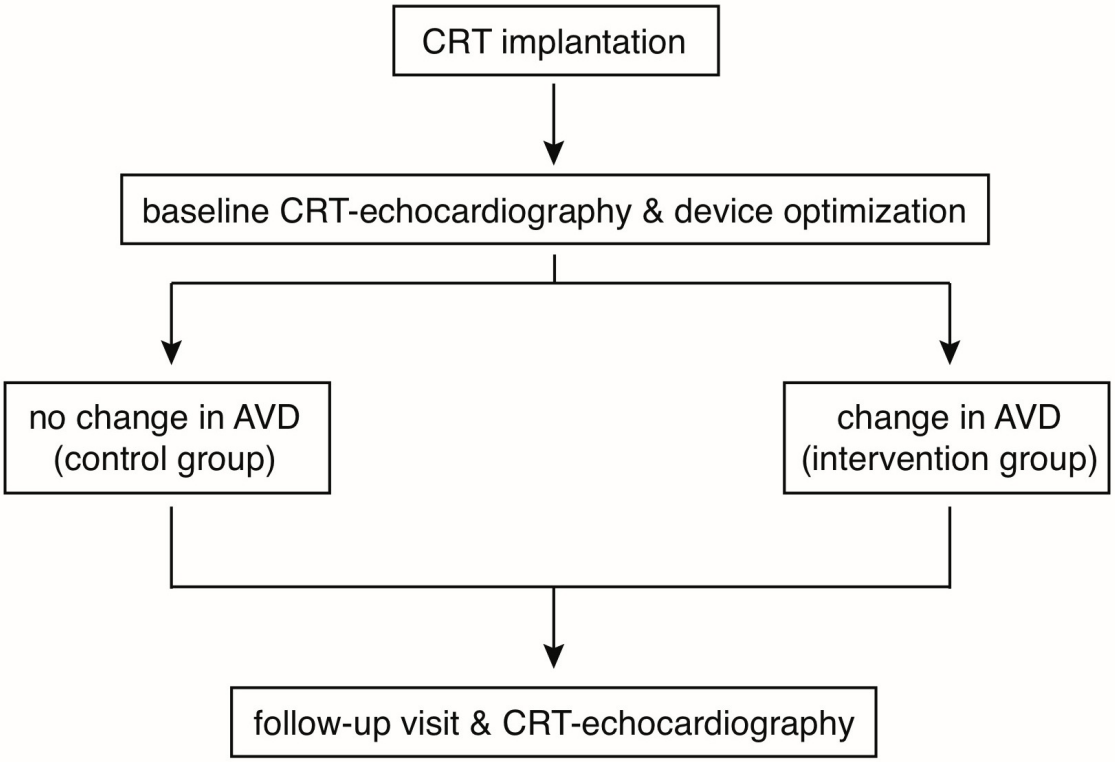
AV — atrioventricular; AVB — atrioventricular block; BP — blood pressure; CRT — cardiac resynchronization therapy; EDVI — end-diastolic volume index; IVCD — intraventricular conduction delay; IVMD — interventricular mechanical delay; LBBB — left bundle branch block; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; RBBB — right bundle branch block; TDI — tissue Doppler imaging; VV — interventricular delay

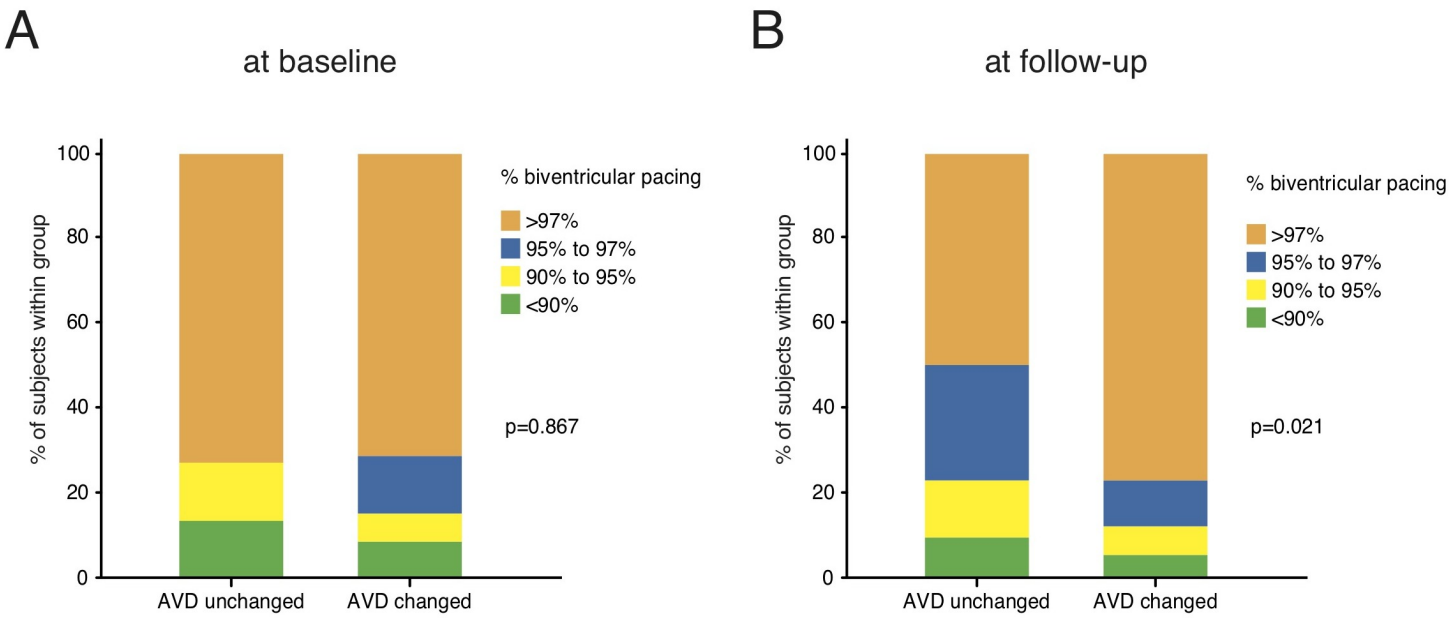
Figure 1. Follow-up flow chart; AVD — atrioventricular delay; CRT — cardiac resynchronization therapy.

Figure 2. Distribution of biventricular pacing proportions before and after atrioventricular delay (AVD) optimization. Comparison of the intervention (AVD changed) and control (AVD unchanged) group; **A.** Assessment at baseline; **B.** Assessment at follow-up. Mann-Whitney U tests.

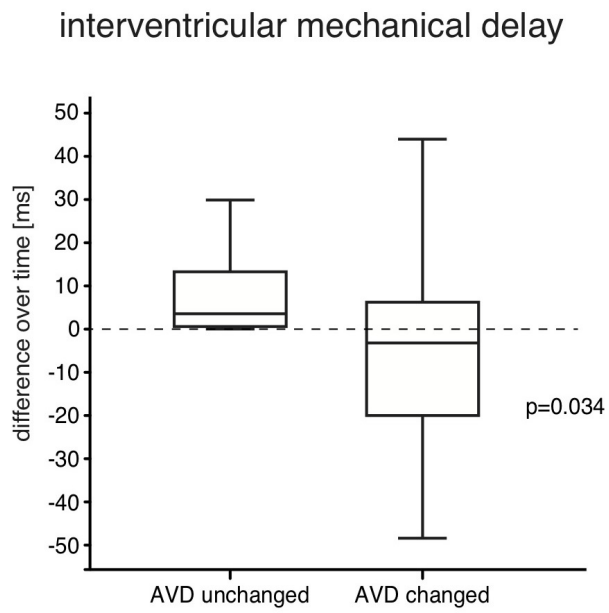
Figure 3. Interventricular mechanical and septal-to-lateral delay in the intervention (atrioventricular delay [AVD] changed) and control (AVD unchanged) group; **A.** Interventricular mechanical delay; **B.** Septal to lateral delay. Box plots indicate interquartile ranges, whiskers indicate minima and maxima. Mann-Whitney U tests.

Figure 4. Reverse remodeling upon adapting atrioventricular delays (AVD); **A, B.** Change in left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume index (LVEDVI), respectively, in the intervention (AVD changed) and control group (AVD unchanged) over time. Box plots indicate interquartile ranges, whiskers indicate minima and maxima; **C.** Mitral regurgitation at baseline; **D.** Mitral regurgitation at follow-up. Mann-Whitney U tests.

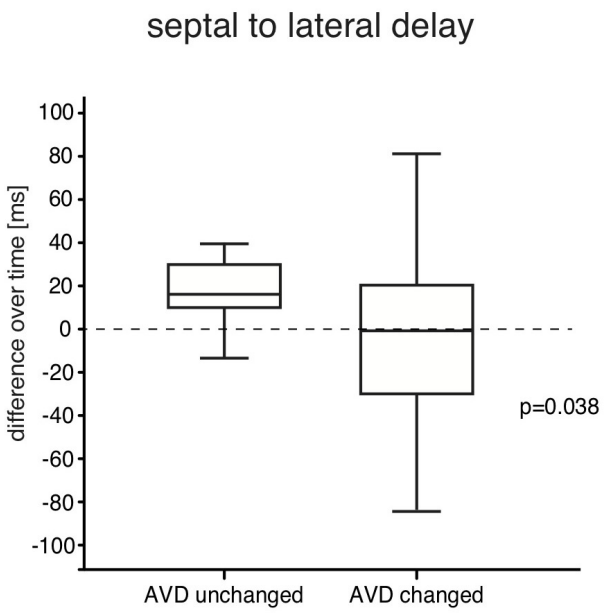

CRT implantation
baseline CRT-echocardiography & device optimization
no change in AVD
(control group)
change in AVD
(intervention group)
follow-up visit & CRT-echocardiography

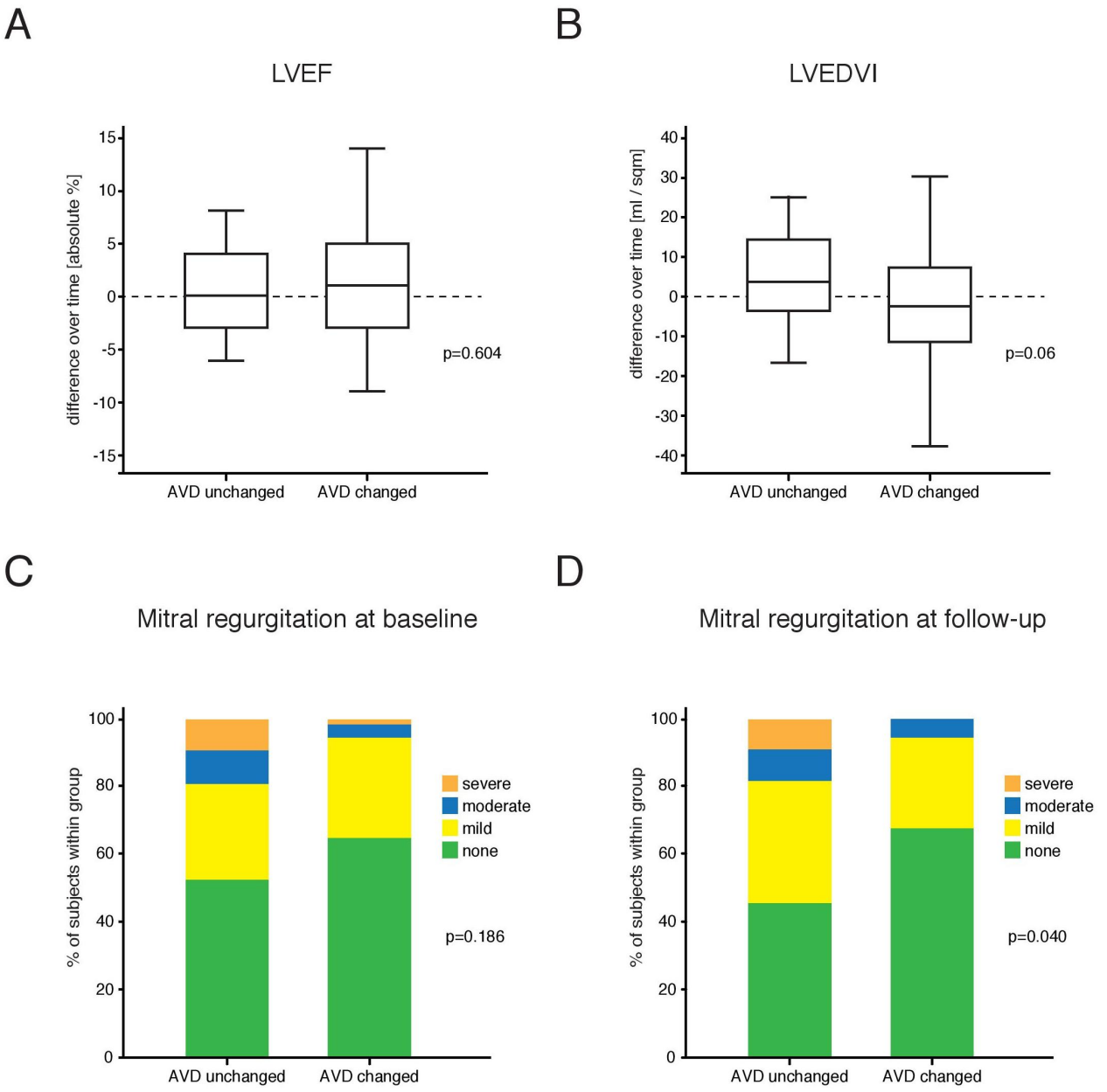

A
at baseline
% of subjects within group
100
80
60
40
20
0
AVD unchanged
AVD changed
% biventricular pacing
>97%
95% to 97%
90% to 95%
<90%
p=0.867
B
at follow-up
% of subjects within group
100
80
60
40
20
0
AVD unchanged
AVD changed
% biventricular pacing
>97%
95% to 97%
90% to 95%
<90%
p=0.021

A


interventricular mechanical delay
difference over time [ms]
50
40
30
20
10
0
-10
-20
-30
-40
-50
p=0.034
AVD unchanged
AVD changed

B


septal to lateral delay
difference over time [ms]
100
80
60
40
20
0
-20
-40
-60
-80
-100
p=0.038
AVD unchanged
AVD changed


A
LVEF
difference over time [absolute %]
15
10
5
0
-5
-10
-15
p=0.604
AVD unchanged
AVD changed
B
LVEDVI
difference over time [ml / sqm]
40
30
20
10
0
-10
-20
-30
-40
p=0.06
AVD unchanged
AVD changed
C
Mitral regurgitation at baseline
% of subjects within group
100
80
60
40
20
0
severe
moderate
mild
none
p=0.186
AVD unchanged
AVD changed
D
Mitral regurgitation at follow-up
% of subjects within group
100
80
60
40
20
0
severe
moderate
mild
none
p=0.040
AVD unchanged
AVD changed

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