Predictors of response to cardiac resynchronization therapy in patients with chronic right ventricular pacing

Benjamin Rath1 · Kevin Willy1 · Julian Wolfes1 · Christian Ellermann1 · Florian Reinke1 · Julia Köbe1 · Lars Eckardt1 · Gerrit Frommeyer1

Received: 16 July 2020 / Accepted: 23 November 2020 / Published online: 15 December 2020
© The Author(s) 2020

Abstract

Background The benefits of de novo cardiac resynchronization therapy (CRT) in patients with QRS-prolongation and impaired left-ventricular function (LVEF) are well established. Current guidelines also recommend CRT-upgrade in patients requiring permanent or frequent right ventricular pacing (RVP) with symptomatic heart failure and reduced LVEF. Whereas several predictors of response to de novo CRT-implantation such as female gender, QRS-duration, non-ischemic cardiomyopathy (NICM) are known due to large prospective trials, similar factors regarding CRT-upgrade are currently lacking.

Methods and results We examine 114 patients 3–6 months after CRT-upgrade due to frequent RVP (> 50%) and symptomatic heart failure. Response to CRT was evaluated by improvement in NYHA class referring to the Minnesota Living With Heart Failure Questionnaire. Only cardiomyopathy type and use of Angiotensin-converting-enzyme (ACE) inhibitor had an impact on response to CRT-upgrade in a linear regression model. Patients with NICM presented a greater responder rate than patients with ischemic cardiomyopathy (ICM) (80.4 vs. 60.3%, p < 0.05). Other traditional response predictors in de novo CRT recipients (e.g. QRS-width, female gender) showed no effect on CRT-response in this cohort.

Conclusion Only underlying heart disease (NICM vs. ICM) and the use of ACE inhibitor were significant predictors of response to CRT-upgrade. In contrast to de novo CRT-recipients, where pre-implant QRS-duration is a key predictor, QRS-duration during RV-pacing has no significant impact on CRT-response in this cohort.
**Graphic abstract**

**Predictors of CRT-Response in chronic right ventricular pacing**

**Ischaemic Cardiomyopathy**

- Responder: 39.70%
- Non-Responder: 60.30%

**Non Ischaemic Cardiomyopathy**

- Responder: 19.60%
- Non-Responder: 80.40%

**Non-significant parameters**

- EF prior (%)
- QRS width prior (ms)
- QRS reduction (ms)
- RV pacing burden (%)
- BP pacing (%)

**Keywords** CRT - Chronic right ventricular pacing - NICM

**Introduction**

Cardiac resynchronization therapy (CRT) is an established treatment for selected patients with heart failure (HF) and prolonged QRS-duration [1]. The vast majority of patients enrolled in clinical CRT trials had de novo implants and benefits of CRT are especially established in patients with native left bundle branch block (LBBB) [2–4]. International guidelines also recommend CRT-upgrade in patients requiring permanent or frequent RV pacing (RVP) who have symptomatic HF and reduced left ventricular ejection fraction (LVEF) [1]. Current non-randomized studies showed conflicting results in terms of the outcome of CRT-upgrade compared with de novo implantation [5–7].

Furthermore, in contrast to patients with intrinsic LBBB where several predictors of response to CRT (female gender, QRS-duration, non-ischemic cardiomyopathy) are available due to large prospective trials [8], similar predictors regarding CRT-upgrade are currently lacking.

In the current study, we sought to determine predictors of response to CRT-upgrade in patients with chronic RV-pacing.

**Methods**

A consecutive cohort of patients who underwent CRT-upgrade due to chronic right ventricular pacing and reduced LVEF (<50%) between 2013 and 2019 was analyzed. Clinical, ECG and echocardiographic data were evaluated. Chronic RVP was defined as a RV pacing burden of at least 50% pacing on the pre-CRT upgrade device check. All CRT device implantations were performed via a transvenous access targeting a lateral or posterolateral vein for the left ventricular lead position. RV leads were positioned in the RV apex or septum. Various transvenous delivery systems, LV and RV leads, and generators left to the operator’s discretion were used. Whenever an indication for a defibrillator was present, patients received a combined device. For inclusion in the final cohort, only patients with a biventricular
pacing percentage of at least 95% were considered. Optimization of the programmed atrioventricular and interventricular delay of the CRT device was performed according to standard protocols of our center.

Patients were reassessed, including device interrogation, in our outpatient clinic 1, 3 and 6 months after CRT implantation.

Response to CRT was defined as improvement in New York Heart Association (NYHA) functional class (≥ 1/2 class) within 3-month follow-up referring to the Minnesota Living With Heart Failure questionnaire [9]. In addition, cardiac decompensations and hospitalizations due to heart failure were quoted. Patients without improvement or even worsening of NYHA class, or at least 1 cardiac decompensation with hospitalization, were classified as nonresponders.

SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis and database management. For comparison of means, the student $t$ test was used for paired or unpaired observations, as appropriate. The $\chi^2$ test was applied for comparison of proportions between groups. To determine independent predictors of clinical response to CRT, binary logistic regression models were used while CRT response (yes; no) was set as the dependent variable. A p value < 0.05 was considered statistically significant.

Results

Patients’ characteristics

Our study population consisted of 88 men (77.2%) and 26 women (mean age 72.5 years). Mean NYHA class was 2.93 prior to implantation, with the majority of patients (78.1%) in NYHA class III. The underlying etiology of heart failure was coronary artery disease (CAD) in 63 patients (55.3%) and non-ischemic cardiomyopathy (NICM) in 51 patients (44.7%). Mean EF was 34.5% prior to CRT implantation and mean RV-paced burden was 88.6%. 80 patients (70.18%) received a combined CRT-defibrillator-system. Data regarding the duration of RV-pacing before CRT-upgrade were available in 57 patients (49.56%) with an average duration of 31.92 months. The baseline characteristics are listed in Table 1.

| Table 1 Baseline characteristics |
|----------------------------------|
| Total (n = 114)                  |
| Gender                          |
| Male 88 (77.19%)                |
| Female 26 (22.81%)              |
| Age (years) 72.48               |
| NYHA class prior to CRT         |
| II 2.93                         |
| II–III 7 (6.14%)                |
| III 10 (8.77%)                  |
| III–IV 89 (78.07%)              |
| Heart failure etiology          |
| Non Ischaemic cardiomyopathy 51 (44.74%) |
| Ischaemic cardiomyopathy 63 (55.26%) |
| CRT-device                      |
| Defibrillator 80 (70.18%)       |
| Pacemaker 34 (29.82%)           |
| Ejection fraction (%) 34.51     |
| QRS duration prior to CRT (ms) 178.07 |
| QRS duration post CRT (ms) 151.23 |
| Right ventricular pacing burden (%) 88.58 |
| Laboratory results              |
| N+ (mmol/l) 140.13              |
| K+ (mmol/l) 4.46                |
| Creatinine (mg/dl) 1.51         |
| Medication                      |
| ß-blockers 105 (92.11%)         |
| ACE-inhibitor 99 (86.84%)       |
| MRA-antagonist 58 (50.88%)      |

In total, 79 patients (69.3%) fulfilled our predefined criterion for a response to CRT (responders), and 35 patients (30.7%) were classified as nonresponders. All patients were alive at 3- and 6-month follow-ups. Responders showed a mean improvement in NYHA class from 2.90 to 2.16. Transthoracic echocardiography during follow-up was performed in 39 patients (33.91%). If echocardiographic data were available, there was a significant correlation between the clinical definition of response and improvement of LVEF (+ 12.33% in responders vs. + 4.00% in nonresponders, $p = 0.01$).

In a linear regression model, only cardiomyopathy type and use of ACE inhibitor respectively Angiotensin II receptor blockers (ARB) had an impact on response to CRT-upgrade (Table 2). Patients with NICM presented more benefit than patients with CAD (80.4 vs. 60.3% response, $p < 0.05$). Older age as well as elevated creatinine and potassium levels were associated with the worse outcome only in univariate analysis. With regard to ECG-parameters, neither the pre-upgrade QRS-duration during RV-pacing with 177.3 ms in responders and 179.7 ms in nonresponders ($p = 0.289$) nor a reduction of QRS-duration after CRT-upgrade with 28.5 ms in responders vs. 23.1 ms in nonresponders ($p = 0.087$) had a significant impact on CRT-response. The percentage of right ventricular pacing burden before upgrade (87.6% in responders vs. 90.0% in nonresponders, $p = 0.182$) also showed no significant
influence on CRT-response. Mean percentage of biventricular stimulation after CRT-upgrade was 96.84% in responders and 97.66% in nonresponders (p = 0.35). Duration of chronic RV-pacing before CRT-upgrade, which was known in 49.57% of patients, did also not differ between both groups (34.48 months in responders vs. 26.18 months in nonresponders, p = 0.42).

### Discussion

The current study sought to identify characteristics associated with symptomatic response in patients exposed to chronic RVP upgraded to CRT. The primary finding in this single-center study is that only type of underlying cardiomyopathy and use of ACE-inhibitor respectively ARB had a significant impact on CRT-response in this subgroup. Other...
traditional factors associated with response in a de novo population receiving CRT such as female gender, QRS duration at baseline and QRS shortening after CRT did not differ significantly between responders and nonresponders. Within the investigated population with an RV-pacing burden of at least 50%, the exact degree of RVP also had no impact on symptomatic response.

Upgrade to CRT from chronic RVP represents a growing field as 23–28% of all CRT device implants were upgrade procedures [10, 11]. International guidelines recommend CRT-upgrade for patients with frequent or permanent RV-pacing, LVEF <35% and symptomatic heart failure [1]. The Block HF trial even demonstrated the superiority of biventricular compared to right-ventricular pacing in patients with atrioventricular block and reduced LVEF <50% [12]. Despite the above-mentioned significance, CRT-upgrade procedures were excluded from most randomized controlled CRT trials. Only the RAFT trial and the MUSTIC AF trial included RVP-paced patients and inclusion was restricted to an arbitrarily chosen QRS-width > 200 ms [13, 14].

Current outcome data for upgraded patients compared to de novo CRT implantations show conflicting results and are mainly limited due to their retrospective design. Tayal et al. [6] reported about superior survival in 50 patients with CRT upgrade compared with native LBBB patients. In contrast, Vamos et al. [7] demonstrated inferior outcomes of upgraded patients over a follow-up period of 3 years. A meta-analysis by Koztin et al. [5] showed similar all-cause mortality between de-novo and CRT-upgrade procedures.

According to this restricted outcome data, limited knowledge regarding optimal patient selection is available. As CRT-upgrade procedures are associated with a higher rate of periprocedural complications compared to de novo implantations, i.e. pneumothorax or device infection [15, 16], optimal patient selection gains even more importance.

In de novo CRT-recipient, especially NICM, QRS-duration, presence of LBBB and female gender are associated with favorable outcome [17, 18]. In contrast, we found that response in patients with RV-pacing compared with native LBBB patients in a retrospective study of 112 CRT-upgrade patients was associated with a higher coincidence of renal failure which may be explained by a higher coincidence of renal failure and coronary artery disease. Within the observed collective patients with ICM showed a trend towards higher creatinine and potassium levels ($p = 0.086$ and 0.10).

The central significance of ACE-inhibitors in treatment of chronic heart failure has been highlighted in several randomized controlled trials [20, 21]. The results of this study underline the importance of continuing an adequate medical heart failure therapy after CRT-implantation.

In de novo patients QRS duration during intrinsic conduction, especially as typical LBBB-pattern, is another key predictor of CRT-response [22]. Prolonged QRS-duration can be considered as a correlate of electrical dyssynchrony which can be addressed by CRT. The few CRT-trials which have included RVP-patients were mostly limited to an arbitrarily chosen QRS-width with cutoff of 200 ms [13, 14]. In our study mean baseline QRS-duration during RV-pacing was 177.3 ms in responders and 179.7 ms in nonresponders with no statistical significance between both groups. This is in line with the findings of Rickard et al. [23], who did not find any effect of paced QRS-width on CRT-response in 112 CRT-upgrade patients as well. In contrast, Rickard et al. showed that a reduction of QRS-width after CRT-upgrade was associated with improved outcome. This observation, however, could not be confirmed in our patient collective with only a non-significant trend of QRS-reduction between both groups (28.5 ms in responders and 23.1 ms in nonresponders, $p = 0.087$).

The significance of RVP burden in CRT-patient selection remains unclear. Neither American nor European guidelines define an exact cut-off-value of RV-paced burden for considering CRT-upgrade [1, 24]. In our study, only patients with a RV-paced burden > 50% were included which is our in-house cut-off point for CRT-upgrade. Within this collective, the exact percentage of RV-paced burden had no influence on CRT-response. It remains unclear if a lower cut-off-value, e.g. 20% as proposed by other authors [25] would have influenced the results of this study.

Vamos et al. [7] hypothesized that duration of RV-pacing before upgrade may also influence CRT-response with poorer prognosis in patients with a longer history of RV-pacing and therefore more advanced cardiomyopathy. Nevertheless, there was no difference in our collective between responders and nonresponders regarding the duration of prior RV-pacing although data were only available in about half of the patients.

**Study limitations**

The definition of response in our study was solely based on clinical improvement referring to the validated Heart Failure
Questionnaire. Therefore, the amount of responders might have been overestimated because of the placebo effect of therapy in general. Adding solid echocardiographic parameters to the definition of response for all patients would have delivered further information on the effect of CRT. However, this study had only medium-term follow up in a medium-sized collective. Therefore, analysis of echocardiographic parameters was classified as not feasible in a prior power-analysis. Nevertheless, in cases where echocardiographic data were available, there was a significant correlation between clinical response and LVEF-improvement. The use of biomarkers such as NT-proBNP as a prognostic marker as well as an indicator for CRT-response might also put the results of study on a broader basis. However, this parameter is not routinely measured in our outpatient clinic.

The observed trend of a more pronounced QRS-reduction in responders, which is a key predictor of CRT-response in de-novo implantations might have been significant in larger patient collective.

Conclusion

Response prediction in CRT-upgrade patients due to frequent or permanent RVP remains difficult. Only type of underlying cardiomyopathy and use of ACE-inhibitor had a significant influence on CRT-response with a favorable outcome of NICM compared to ICM. Other traditional factors in the novo CRT-population like female gender or QRS-width do not appear to apply to RVP-patients. Especially the 200 ms threshold for inclusion of chronic paced patients in past CRT-trials should be reconsidered. As long as the right ventricular pacing is above 50%, the exact pacing burden does not seem to have a significant effect on CRT-response. An exact cut-off-value for CRT-upgrade response needs still to be determined.

Funding Open Access funding enabled and organized by Projekt DEAL.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA et al (2013) ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 34(29):2281–2329
2. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E et al (2002) Cardiac resynchronization in chronic heart failure. New Engl J Med 346(24):1845–1853
3. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L et al (2005) The effect of cardiac resynchronization therapy on morbidity and mortality in heart failure. New Engl J Med 352(15):1539–1549
4. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T et al (2004) Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. New Engl J Med 350(21):2140–2150
5. Kosztin A, Vamos M, Aradi D, Schwertner WR, Kovacs A, Nagy KV et al (2018) De novo implantation vs. upgrade cardiac resynchronization therapy: a systematic review and meta-analysis. Heart Fail Rev 23(1):1–26
6. Tayal B, Gorcsan J 3rd, Delgado-Montero A, Goda A, Ryu K, Saba S et al (2016) Comparative long-term outcomes after cardiac resynchronization therapy in right ventricular paced patients versus native wide left bundle branch block patients. Heart rhythm 13(2):511–518
7. Vamos M, Erath JW, Bari Z, Vagany D, Linzbach SP, Burmis-trava T et al (2017) Effects of Upgrade versus de novo cardiac resynchronization therapy on clinical response and long-term survival: results from a multicenter study. Circ Arrhythmia Electrophysiol 10(2):e004471
8. Rickard J, Michtalik H, Sharma R, Berger Z, Iyoha E, Green AR et al (2016) Predictors of response to cardiac resynchronization therapy: a systematic review. Int J Cardiol 225:345–352
9. Rector TS, Kubo SH, Cohn JN (1993) Validity of the Minnesota living with heart failure questionnaire as a measure of therapeutic response to enalapril or placebo. Am J Cardiol 71(12):1106–1107
10. Leclercq C, Cazeau S, Lellouche D, Fossati A, Anselme F, Davy JM et al (2007) Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: the RD-CHF Study. PACE 30(Suppl 1):S23-30
11. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A et al (2009) The European cardiac resynchronization therapy survey. Eur Heart J 30(20):2450–2460
12. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherefseey L et al (2013) Biventricular pacing for atrioventricular block and systolic dysfunction. New Engl J Med 368(17):1585–1593
13. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P et al (2002) Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J 23(22):1780–1787
14. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S et al (2010) Cardiac-resynchronization therapy for mild-to-moderate heart failure. New Engl J Med 363(25):2385–2395
15. Essebag V, Joza J, Birnie DH, Sapp JL, Sterns LD, Philippin F et al (2015) Incidence, predictors, and procedural results of
upgrade to resynchronization therapy: the RAFT upgrade sub-study. Circ Arrhythmia Electrophysiol 8(1):152–158
16. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP et al (2009) Cardiac-resynchronization therapy for the prevention of heart-failure events. New Engl J Med 361(14):1329–1338
17. Goldenberg I, Moss AJ, Hall WJ, Foster E, Goldberger JJ, Santucci P et al (2011) Predictors of response to cardiac resynchronization therapy in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 124(14):1527–1536
18. Cheng A, Gold MR, Waggoner AD, Meyer TE, Seth M, Rapkin J et al (2012) Potential mechanisms underlying the effect of gender on response to cardiac resynchronization therapy: insights from the SMART-AV multicenter trial. Heart rhythm 9(5):736–741
19. Shanks M, Delgado V, Ng AC, Auger D, Mooyaart EA, Bertini M et al (2011) Clinical and echocardiographic predictors of nonresponse to cardiac resynchronization therapy. Am Heart J 161(3):552–557
20. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN (1992) Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. New Engl J Med 327(10):685–691
21. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37(27):2129–2200
22. Stavrakis S, Lazzara R, Thadani U (2012) The benefit of cardiac resynchronization therapy and QRS duration: a meta-analysis. J Cardiovasc Electrophysiol 23(2):163–168
23. Rickard J, Cheng A, Spragg D, Cantillon D, Chung MK, Tang WH et al (2013) QRS narrowing is associated with reverse remodeling in patients with chronic right ventricular pacing upgraded to cardiac resynchronization therapy. Heart Rhythm 10(1):55–60
24. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR et al (2019) 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol 74(7):e51–e156
25. Merkely B, Kosztin A, Roka A, Geller L, Zima E, Kovacs A et al (2017) Rationale and design of the BUDAPEST-CRT Upgrade Study: a prospective, randomized, multicentre clinical trial. Europace 19(9):1549–1555