

学位論文

Significance of effective cardiac resynchronization therapy pacing for clinical responses:
An analysis based on the effective cardiac resynchronization therapy algorithm
(Effective Cardiac Resynchronization Therapy Pacing 率の臨床的意義)

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1 **Significance of effective cardiac resynchronization therapy pacing for clinical responses: an**
2 **analysis based on effective cardiac resynchronization therapy algorithm**

3 Short title: **Effective CRT pacing and clinical responses**

4

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23 **Conflict of interest:** Dr. Kengo Kusano, Dr. Nobuhiko Ueda, and Dr. Koichi Ishibashi received

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27

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31 **Abstract**

32 **Background:** High percent ventricular pacing (%Vp) maximizes cardiac resynchronization
33 therapy (CRT) response. Effective CRT algorithm classifies each left ventricular (LV) pace as
34 effective or ineffective, based on the detection of QS/QS-r morphology on the electrogram;
35 however, the relationship between percent effective CRT pacing (%e-CRT) and responses is
36 unclear.

37 **Objective:** We aimed to clarify the association between %e-CRT and clinical outcomes.

38 **Methods:** Among 136 consecutive CRT patients, 49 using adaptive and effective CRT algorithm
39 with %Vp >90% were evaluated. The primary and secondary outcomes were heart failure (HF)
40 hospitalization and prevalence of CRT responders – defined as patients with improvement in LV
41 ejection fraction $\geq 10\%$ or a reduction in LV end-systolic volume $\geq 15\%$ after CRT implantation,
42 respectively.

43 **Results:** We divided the patients into the effective group (n=25) and the less-effective group
44 (n=24) by the median value of %e-CRT (97.4%). During the median follow-up period of 507
45 days (interquartile, 335–730), the effective group had a significantly lower risk of HF
46 hospitalization than the less-effective group as revealed by Kaplan–Meier analysis (log-rank:
47 $p=0.016$). Univariate analysis revealed %e-CRT $\geq 97.4\%$ (hazard ratio, 0.12; 95% confidence

48 interval [CI], 0.01–0.95; $p=0.045$) as a predictor of HF hospitalization. The effective group had a
49 higher prevalence of CRT responders than the less-effective group (23 [92%] vs. 9 [38%],
50 $p<0.001$). Univariate analysis revealed that %e-CRT $\geq 97.4\%$ (odds ratio, 19.20; 95% CI, 3.63–
51 101.00; $p<0.001$) was a predictor of CRT response.

52 **Conclusion:** High %e-CRT is associated with high CRT responder prevalence and low HF
53 hospitalization risk.

54

55 **Keywords**

56 Heart failure, cardiac resynchronization therapy, effective pacing, biventricular pacing, QRS
57 duration, atrial fibrillation

58

59 Introduction

60 Cardiac resynchronization therapy (CRT) is an established treatment for patients with left
61 ventricular (LV) dysfunction and wide QRS duration¹⁻³; however, approximately one-third of
62 patients do not respond to CRT⁴. In addition to the clinical factors, device-related factors such as
63 insufficient percent ventricular pacing (%Vp), suboptimal LV lead location position, and
64 suboptimal atrioventricular (AV) and ventricle-ventricular (VV) timing are associated with CRT
65 response⁵. Studies have reported a relationship between %Vp and reduction of heart failure (HF);
66 higher %Vp was associated with increased CRT responders and decreased risk of poor prognosis⁶.
67 ⁷. However, %Vp overestimates the degree of effective biventricular (BiV) pacing due to pseudo-
68 fusion, inactivation of the ventricular myocardium, loss of capture, and LV conduction latency⁸.
69 ⁹. Therefore, evaluating the effectiveness of pacing in ventricular myocardium activation is
70 important, while simultaneously assessing the possibility of achieving %Vp close to 100%.

71 Effective CRT algorithm (Medtronic Inc., Minneapolis, MN, USA) can quantify LV pacing
72 using beat-to-beat analysis of the paced morphology of an electrogram (EGM)⁹⁻¹¹. This algorithm
73 is based on a fundamental electrophysiological concept in which an initial negative deflection
74 (QS/QS-r morphology, Figure 1) is registered in the LV tip (pacing site)-right ventricular (RV)
75 coil EGM if the pace effectively captures the LV myocardium¹². OLÉ CRT study showed that the

76 average %Vp significantly overestimated percent effective CRT pacing (%e-CRT), and 18% of
77 CRT recipients had over 3% of ineffective pacing using this EGM-based algorithm.⁹ This
78 algorithm revealed suboptimal LV pacing and potential reasons for insufficient response and
79 therefore, could help CRT pacing optimization.

80 Little is known about the association between %e-CRT and clinical CRT benefits. Therefore,
81 we aimed to clarify whether %e-CRT is associated with clinical outcomes.

82

83 **Methods**

84 **Study population**

85 We initially identified 136 consecutive patients with HF who were treated with CRT devices
86 between January 2018 and December 2020 at the National Cerebral and Cardiovascular Center,
87 Suita, Japan. The inclusion criteria were as follows: (1) New York Heart Association (NYHA)
88 functional class II-IV, (2) left ventricular ejection fraction $\leq 35\%$, and (3) QRS duration ≥ 120
89 msec¹³. The exclusion criteria were as follows: (1) CRT devices incapable of implementing the
90 effective CRT algorithm (n=63), (2) drop out (n=2), (3) adaptive CRT (aCRT) (Medtronic Inc.,
91 Minneapolis, MN, USA) algorithm not used to match the method of optimization (n=21)¹¹, and

92 (4) cumulative %Vp less than 90% (n=1)^{7, 8}. After the exclusion, 49 patients were enrolled
93 (Figure 2).

94 This study was approved by the Institutional Research Board of the National Cerebral and
95 Cardiovascular Center, Suita, Japan (M26-150-13), and conducted with adherence to the
96 Declaration of Helsinki. All patients provided written informed consent before undergoing CRT
97 device implantation.

98

99 **Clinical characteristics**

100 Clinical data, including age, sex, underlying heart disease, comorbidities, medication,
101 echocardiographic parameters, and 12-lead electrocardiogram, were collected from medical
102 records.

103

104 **CRT implantation and Adaptive CRT algorithm**

105 The CRT device was implanted transvenously. An RV lead was positioned at the RV septum
106 or septal apex, and a quadripolar LV lead was implanted in a suitable branch of the coronary vein
107 at a site that produced an acceptable pacing threshold without phrenic nerve stimulation.

108 AV and VV delay optimization was automatically performed using the aCRT algorithm¹⁴. In
109 brief, if the conduction interval from the right atrium to the RV is normal, the algorithm provides
110 LV-only pacing synchronized with RV activation. Conversely, if the intrinsic AV conduction
111 interval is prolonged, the algorithm provides a BiV pacing.

112

113 **Effective CRT algorithm**

114 The effective CRT algorithm automatically quantifies 100 acquired ventricular events every
115 hour 25 minutes after the hour, in an intermittent manner, and classifies ventricular pacing as
116 effective or ineffective based on specific morphological features on a 164 msec window of the
117 LV tip to RV coil EGM¹². When effective pacing occurs, EGMs are broadly characterized by a
118 negative deflection (QS or QS-r morphology) followed by slight positive deflection (Figure 1);
119 this represents the local capture at the LV pacing site, regardless of the BiV- or LV-only pacing
120 mode. Parenthetically, LV pacing in response to premature RV sensing, called Ventricular Sense
121 Response, was not treated as paced beats but as sensed beats for analysis.

122

123 **Percent effective and ineffective CRT and ventricular pacing**

124 Percentage of various types of CRT pacing were calculated as follows:

125 %e-CRT = (effective CRT pacing / [effective CRT pacing + ineffective CRT pacing +
126 ventricular sense response + Sensing]) × 100 [%]

127 Percent ineffective CRT pacing (%i-CRT) = (ineffective CRT pacing / [effective CRT pacing
128 + ineffective CRT pacing + ventricular sense response + sensing]) × 100 [%]

129 %Vp = (ventricular pacing / [ventricular pacing + ventricular sense response + sensing]) ×
130 100 [%]

131 All variables were measured throughout the follow-up period, and the average
132 cumulative %e-CRT, %i-CRT and %Vp were calculated. The patients were divided into an
133 effective CRT group and a less-effective CRT group based on the median value of %e-CRT.

134 For patients with atrial fibrillation (AF) documented within the follow-up period, %Vp, %e-
135 CRT, and %i-CRT during AF episodes were also calculated.

136

137 **Clinical outcomes**

138 The primary and secondary outcomes were hospitalization for HF and the prevalence of CRT
139 responders, respectively. Cardiac contractile function was assessed before and 6 months after
140 CRT device implantation during a stable hemodynamic state. CRT responders were defined as
141 patients with an improvement in left ventricular ejection fraction (LVEF) ≥10% or a reduction in

142 left ventricular end-systolic volume (LVESV) $\geq 15\%$ compared to baseline at 6 months post-
143 implantation.

144

145 **Statistical analysis**

146 Normally distributed continuous variables are expressed as means and standard deviations.

147 The Kolmogorov–Smirnov test was used to detect variables that were not distributed normally;

148 they are expressed as medians and interquartile ranges. Student’s *t*-test or Mann–Whitney U test

149 was used to compare differences between the two distribution groups where appropriate.

150 Categorical variables were compared using Fisher’s exact test. Univariate analysis was performed

151 using a Cox regression or logistic regression model to determine predictors where appropriate.

152 All statistical tests were two-tailed, and values of $p < 0.05$ were considered significant. All

153 statistical analyses were performed using SPSS Statistics software version 28 (IBM Corporation,

154 Armonk, NY, USA).

155

156 **Results**

157 **Baseline characteristics**

158 Forty-nine patients (37 males, mean age 64.0 ± 13.3 years) were enrolled in the present study.
159 The median of %e-CRT was 97.4%; the patients in this cohort were divided into the effective
160 CRT group (%e-CRT $\geq 97.4\%$, n=25) or the less-effective CRT group (%e-CRT $< 97.4\%$, n=24).
161 There were no significant differences between the groups' baseline characteristics (Table 1).

162

163 **Discrepancy between percent effective CRT pacing and ventricular pacing**

164 The cumulative value of %e-CRT, %i-CRT, and %Vp during the follow-up are presented in
165 Table 1. In this study population, the median %Vp and %i-CRT ($= \%Vp - \%e-CRT$) values were
166 97.8% and 0.3%, respectively. The scatter plot (Figure 3) shows that all patients had over 90%
167 ventricular pacing. In five patients, there was a difference of 3% or more between %Vp and %e-
168 CRT⁹, and their median %Vp, %e-CRT, and %i-CRT were 97.0 [95.9–97.1] %, 63.4 [32.2–
169 77.8] %, and 33.7 [15.1–63.7] %, respectively.

170 AF was documented in 12 patients during the follow-up period. There was no significant
171 difference in the percentage of patients with atrial fibrillation (AF) between the two groups,
172 despite a trend toward a higher percentage in the less-effective CRT group (3 [12.0%] vs. 9
173 [37.5%], $p=0.051$). Among these 12 AF documented patients with a mean AF burden of $3.3 \pm$
174 7.8%, median cumulative %Vp, %e-CRT, and %i-CRT were 96.3 [93.6–98.3%] (during AF: 87.6

175 [83.1–97.6] %), 95.6 [92.1–97.4] % (during AF: 86.2 [80.5–97.6] %), and 0.6 [0.4–1.0] % (during
176 AF: 0.7 [0.1–1.6] %), respectively.

177

178 **HF hospitalization**

179 During the median follow-up period of 507 [335–730] days, nine (18%; effective group: 1
180 [4%] vs. less-effective group: 8 [33%]) patients experienced HF hospitalization. According to
181 Kaplan–Meier analysis, the effective CRT group had a significantly lower risk of HF
182 hospitalization (log-rank, $p=0.016$, Figure 4A); however, there was no significant difference in
183 the Kaplan–Meier curve for the cumulative incidence of HF hospitalization between the groups
184 divided by the median value of %Vp, 97.8% (log-rank, $p=0.11$, Figure 4B). Univariate analysis
185 revealed that ischemic cardiomyopathy (hazard ratio, 4.80; 95% confidence interval [CI], 1.27–
186 18.13; $p=0.021$) and %e-CRT $\geq 97.4\%$ (hazard ratio, 0.12; 95% CI, 0.01–0.95; $p=0.045$) were
187 predictors of HF hospitalization (Table 2).

188

189 **CRT responders**

190 The effective CRT group had a higher prevalence of CRT responders than the less-effective
191 CRT group (23 [92%] vs. 9 [38%]; Figure 5). The median total %e-CRT (97.4%) predicted CRT

192 response with 71.9% sensitivity, 88.9% specificity, 92.4% positive predictive value, and 62.7%
193 negative predictive value. Conversely, the median total %Vp (97.8%) predicted CRT response
194 with 66% sensitivity, 78% specificity, 85% positive predictive value, and 55% negative predictive
195 value. Univariate analysis revealed that QRS duration ≥ 150 msec (odds ratio, 4.69; 95% CI, 1.33–
196 16.50; $p=0.016$), %Vp $\geq 97.8\%$ (odds ratio, 6.20; 95% CI, 1.63–23.60; $p=0.007$) and %e-CRT
197 $\geq 97.4\%$ (odds ratio, 19.20; 95% CI, 3.63–101.00; $p<0.001$) were predictors of CRT responders
198 (Table 3).

199

200 **Discussion**

201 **Main findings**

202 This study evaluated the relationship between clinical outcomes and %e-CRT. Significant
203 findings of this study are as follows: (1) patients with high %e-CRT have a low risk of HF
204 hospitalization, (2) low %e-CRT is a predictor of HF hospitalization, and (3) high %e-CRT is a
205 predictor of CRT response.

206

207 **Effective CRT algorithm for evaluation of effective pacing**

208 %Vp overestimates the degree of effective pacing. Kamath et al. evaluated the association
209 between effective pacing and CRT response using a 12-lead Holter monitor in patients with
210 permanent AF and CRT devices⁸. Only 76% of the beats were fully paced with complete capture,
211 and 40% of pacing accounted for fusion and pseudo-fusion beats in patients with ineffective
212 pacing, defined as $\leq 90\%$ fully paced beats with complete capture of the heart. Ghosh et al.
213 developed a device-based automatic algorithm using morphological features of an EGM, which
214 defined effective pacing as a negative deflection (QS or QS-r morphology); the algorithm
215 accurately classified 98.2% effective LV pacing beats, 75.8% pseudo-fusion beats, and 100%
216 beats with loss of LV capture compared to an ECG-based classification truth¹². The utility and
217 superiority of the algorithm is evident particularly in discriminating loss of capture completely.
218 In addition, the OLÉ CRT study showed that the average %Vp significantly overestimated %e-
219 CRT pacing by 7% on average⁹; therefore, effective pacing should be evaluated to assess its
220 efficiency in activating LV myocardium. Effective CRT algorithm can be utilized in the
221 assessment.

222

223 **Effective CRT and CRT response**

224 Effective delivery of BiV pacing determines the success of CRT and response. In a large
225 cohort analyzed in the ALTITUDE study, increased percentages of BiV pacing were associated
226 with significant mortality reduction⁶. Furthermore, Ruwald et al. reported that BiV pacing
227 exceeding 90% was associated with CRT mortality benefit⁷. Moreover, among the CRT patients
228 with high %Vp (>90%), ineffective pacing was associated with CRT nonresponders⁸. The
229 presence of more than 90% of fully paced beats correlated with improvement in NYHA. In our
230 study, patients with high %e-CRT ($\geq 97.4\%$) had a lower risk of HF hospitalization, although there
231 was no significant difference between patients with high and low %Vp (97.8%). Univariate
232 analysis revealed that high %e-CRT ($\geq 97.4\%$) resulted in risk reduction for HF hospitalization.
233 In addition, high %e-CRT correlated with CRT response and was a predictor of CRT response.
234 The cohort in this study had a cumulative %Vp of over 90%; however, five patients (10.2%)
235 had %i-CRT $\geq 3\%$. These patients had poor clinical outcomes; four were CRT nonresponders, and
236 three experienced HF hospitalization during the follow-up period. An effective CRT algorithm is
237 important in predicting clinical and CRT responses.

238

239 **Clinical implication**

240 Effective CRT algorithm can efficiently address hidden issues, consequently
241 optimizing CRT delivery. OLÉ CRT study identified causes of high %i-CRT as, latency, variable
242 AV conduction which induces pseudo-fusion, and loss of capture⁹; these potential reasons^{5,15} are
243 responsible for suboptimal response to CRT and could be the management target for
244 nonresponders^{16, 17}. Specific manual device programming, including continuous optimization
245 algorithm (aCRT)¹¹, VV delay optimization¹⁸, high output pacing¹⁹, and LV cathode change, may
246 be alternative methods to resolve these problems. In this study, all patients used the aCRT
247 algorithm; however, five patients (10.2%) exhibited a discrepancy in the association between %e-
248 CRT and %Vp (>3%). Further prospective studies are needed to evaluate the efficiency of specific
249 manual device programming strategies that optimize %e-CRT and clinical outcomes in these
250 patients. Our findings suggest that a higher cumulative %e-CRT was associated with a lower risk
251 of HF hospitalization and a higher prevalence of CRT responders. At this point, it is difficult to
252 identify the optimal cut off value of %e-CRT because %e-CRT showed a large variability and the
253 lower %e-CRT does not affect the lower efficacy of CRT linearly. The median value could stratify
254 the risk of HF and CRT response in this study cohort; it is notable that ‘lower %e-CRT compared
255 to %Vp’ is associated with the risk of HF and non-response to CRT, not the %e-CRT value itself.

256 Therefore, effectuating a nearly 100% ventricular and effective CRT pacing could be the goal of
257 pacing management.

258

259 **Study limitation**

260 First, this was a single-center retrospective study. The relatively small sample size was a
261 limitation of this study.

262 Second, the effective CRT algorithm evaluates only the LV EGM morphology. Even if the
263 EGM shows an effective morphology, the magnitude of LV capture by pacing could be less in
264 some cases than others due to scar burden. Thus, although an excellent diagnostic capability has
265 been reported¹², there is a possibility that this algorithm could overestimate the true %e-CRT.

266 Third, patients with a cumulative %Vp <90%^{7, 8} and not using the aCRT algorithm¹¹ were
267 excluded. Though there was no optimal cut-off value of percent biventricular pacing, a previous
268 study showed that biventricular pacing >90% was associated with a benefit of CRT⁷. Hence,
269 highly effective cases of CRT could be selected^{6, 7, 11, 20}. However, even in such a population,
270 patients with lower %e-CRT had worse outcomes; thus %e-CRT would help detect potential CRT
271 nonresponders.

272 Finally, it is unknown whether this novel marker can be applied in the treatment of CRT
273 nonresponders. Further studies are required to address these problems.

274

275 **Conclusions**

276 Relatively higher effective CRT pacing percentage was associated with a higher prevalence
277 of CRT responders and a lower risk of hospitalization for HF. The effective CRT pacing
278 percentage could be a guide for optimal CRT delivery.

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293

294 **References**

- 295 1. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart
296 failure. *N Engl J Med* 2002;346:1845-1853. <https://doi.org/10.1056/NEJMoa013168>.
- 297 2. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or
298 without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*
299 2004;350:2140-2150. <https://doi.org/10.1056/NEJMoa032423>.
- 300 3. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on
301 morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-1549.
302 [10.1056/NEJMoa050496](https://doi.org/10.1056/NEJMoa050496).
- 303 4. European Heart Rhythm A, European Society of C, Heart Rhythm S, et al. 2012
304 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart
305 failure: implant and follow-up recommendations and management. *Europace*
306 2012;14:1236-1286. <https://doi.org/10.1093/europace/eus222>.
- 307 5. Mullens W, Grimm RA, Verga T, et al. Insights from a cardiac resynchronization
308 optimization clinic as part of a heart failure disease management program. *J Am Coll*
309 *Cardiol* 2009;53:765-773. <https://doi.org/10.1016/j.jacc.2008.11.024>.

- 310 6. Hayes DL, Boehmer JP, Day JD, et al. Cardiac resynchronization therapy and the
311 relationship of percent biventricular pacing to symptoms and survival. *Heart Rhythm*
312 2011;8:1469-1475. <https://doi.org/10.1016/j.hrthm.2011.04.015>.
- 313 7. Ruwald AC, Kutiyafa V, Ruwald MH, et al. The association between biventricular
314 pacing and cardiac resynchronization therapy-defibrillator efficacy when compared
315 with implantable cardioverter defibrillator on outcomes and reverse remodelling. *Eur*
316 *Heart J* 2015;36:440-448. <https://doi.org/10.1093/eurheartj/ehu294>.
- 317 8. Kamath GS, Cotiga D, Koneru JN, et al. The utility of 12-lead Holter monitoring in
318 patients with permanent atrial fibrillation for the identification of nonresponders after
319 cardiac resynchronization therapy. *J Am Coll Cardiol* 2009;53:1050-1055.
320 <https://doi.org/10.1016/j.jacc.2008.12.022>.
- 321 9. Hernandez-Madrid A, Facchin D, Klepfer RN, et al. Device pacing diagnostics
322 overestimate effective cardiac resynchronization therapy pacing results of the hOLter
323 for Efficacy analysis of CRT (OLE CRT) study. *Heart Rhythm* 2017;14:541-547.
324 <https://doi.org/10.1016/j.hrthm.2017.01.022>.
- 325 10. Plummer CJ, Frank CM, Bari Z, et al. A novel algorithm increases the delivery of
326 effective cardiac resynchronization therapy during atrial fibrillation: The CRTee

- 327 randomized crossover trial. Heart Rhythm 2018;15:369-375.
- 328 <https://doi.org/10.1016/j.hrthm.2017.10.026>.
- 329 11. Varma N, Stadler RW, Ghosh S, Kloppe A. Influence of automatic frequent pace-
330 timing adjustments on effective left ventricular pacing during cardiac resynchronization
331 therapy. Europace 2017;19:831-837. <https://doi.org/10.1093/europace/euw108>
- 332 12. Ghosh S, Stadler RW, Mittal S. Automated detection of effective left-ventricular
333 pacing: going beyond percentage pacing counters. Europace Oct 2015;17:1555-1562.
334 <https://doi.org/10.1093/europace/euv062>
- 335 13. Nogami A, Kurita T, Abe H, et al. CORRIGENDUM: JCS/JHRS 2019 Guideline on
336 Non-Pharmacotherapy of Cardiac Arrhythmias. Circ J 2021;85:1692-1700.
337 <https://doi.org/10.1253/circj.CJ-66-0196>.
- 338 14. Martin DO, Lemke B, Birnie D, et al. Investigation of a novel algorithm for
339 synchronized left-ventricular pacing and ambulatory optimization of cardiac
340 resynchronization therapy: results of the adaptive CRT trial. Heart Rhythm
341 2012;9:1807-1814. <https://doi.org/10.1016/j.hrthm.2012.07.009>.

- 342 15. Varma N, Boehmer J, Bhargava K, et al. Evaluation, management, and outcomes of
343 patients poorly responsive to cardiac resynchronization device therapy. *J Am Coll*
344 *Cardiol* 2019;74:2588-2603. <https://doi.org/10.1016/j.jacc.2019.09.043>.
- 345 16. Yagishita D, Shoda M, Yagishita Y, Ejima K, Hagiwara N. Time interval from left
346 ventricular stimulation to QRS onset is a novel predictor of nonresponse to cardiac
347 resynchronization therapy. *Heart Rhythm* 2019;16:395-402.
348 <https://doi.org/10.1016/j.hrthm.2018.08.035>.
- 349 17. Ueda N, Noda T, Nakajima I, et al. Clinical impact of left ventricular paced conduction
350 disturbance in cardiac resynchronization therapy. *Heart Rhythm* 2020;17:1870-1877.
351 <https://doi.org/10.1016/j.hrthm.2020.05.031>.
- 352 18. Matia R, Hernandez-Madrid A, Klepfer RN, Ghosh S, Sanchez-Huete G, Moreno J. A
353 new electrogram-based diagnostic algorithm to improve the left ventricular effective
354 pacing detection corrected a non-response to cardiac resynchronization therapy pacing.
355 *Europace* 2017;19:823. <https://doi.org/10.1093/europace/eux035>.
- 356 19. Ishibashi K, Kubo T, Kitabata H, et al. Improvement of cardiac function by increasing
357 stimulus strength during left ventricular pacing in cardiac resynchronization therapy. *Int*
358 *Heart J* 2015;56:62-66. <https://doi.org/10.1536/ihj.14-128>.

359 20. Birnie D, Lemke B, Aonuma K, et al. Clinical outcomes with synchronized left
360 ventricular pacing: analysis of the adaptive CRT trial. *Heart Rhythm* 2013;10:1368-
361 1374. <https://doi.org/10.1016/j.hrthm.2013.07.007>.

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363

364 Tables

365 Table 1 Baseline characteristics and pacing details

	Total (n=49)	Effective group (%e-CRT ≥ 97.4%, n=25)	Less effective group (%e-CRT < 97.4%, n=24)	P value
Baseline characteristics				
Age [years]	64.0 ± 13.3	64.8 ± 12.1	63.1 ± 14.7	0.67
Male gender [(%)]	37 (75.5)	18 (72.0)	19 (79.2)	0.74
Ischemic cardiomyopathy [(%)]	13 (26.5)	7 (28.0)	6 (25.0)	0.99
Chronic kidney disease [(%)]	22 (44.9)	12 (48.0)	10 (41.7)	0.78
Left bundle branch block [(%)]	15 (30.6)	9 (36.0)	6 (25.0)	0.54
QRS duration [msec]	157.0 ± 27.0	160.3 ± 27.6	153.6 ± 26.5	0.39
History of atrial arrhythmias	15 (30.6)	7 (28.0)	8 (33.3)	0.76
NYHA class III/IV [(%)]	16 (32.7)	8 (32.0)	8 (33.3)	0.99
BNP [pg/mL]	221.9 [101.2 – 448.5]	187.8 [76.4 – 251.3]	304.9 [126.6 – 671.1]	0.067
LVEF [%]	24.6 ± 7.4	25.7 ± 7.5	23.4 ± 7.3	0.28
LVESV [mL]	163.8 ± 87.5	143.2 ± 56.7	185.3 ± 108.2	0.099
CRTD [(%)]	44 (89.8)	21 (84.0)	23 (95.8)	0.35

Secondary prevention [(%)]	9 (18.4)	7 (28.0)	2 (8.2)	0.14
Pacing details during follow-up				
%Vp [%] *	97.8 [96.1 – 98.4]	98.4 [98.1 – 99.3]	96.0 [93.6 – 97.1]	<0.001
Bi-ventricular pace [%]	54.2 ± 44.0	61.0 ± 42.8	47.1 ± 44.9	0.28
Left ventricular pace [%]	45.6 ± 44.1	38.9 ± 42.9	52.7 ± 45.1	0.28
%e-CRT [%] *	97.4 [93.7 – 98.3]	98.3 [97.9 – 99.0]	93.7 [89.8 – 96.2]	<0.001
%i-CRT [%] *	0.3 [0 – 0.8]	0.1 [0 – 0.2]	0.7 [0.3 – 1.8]	<0.001
Atrial fibrillation document [(%)]	12 (24.5)	3 (12.0)	9 (37.5)	0.051

366 Data are means ± standard deviations for normally distributed data, and medians and
367 interquartile ranges for non-normally distributed data, or n (%). All statistical tests were 2-tailed,
368 and $p < 0.05$ was considered significant (*).

369 Abbreviations

370 NYHA, New York Heart Association; BNP, brain natriuretic peptide; LVEF, left ventricular
371 ejection fraction; LVESV, left ventricular end-systolic volume; CRTD, cardiac resynchronization
372 therapy defibrillator; %Vp, percent ventricular pacing; %e-CRT, percent effective cardiac
373 resynchronization therapy pacing; %i-CRT, percent ineffective cardiac resynchronization therapy
374 pacing

375 **Table 2 Univariate analysis with a Cox regression model for heart failure hospitalization**

Variables	Univariate analysis		
	Hazard ratio	95% confidence index	P value
Age	0.99	0.94 – 1.04	0.76
Male sex	2.11	0.26 – 17.09	0.48
Ischemic cardiomyopathy *	4.80	1.27 – 18.13	0.021
Chronic kidney disease	3.09	0.77 – 12.51	0.11
History of atrial arrhythmias	0.83	0.21 – 3.35	0.80
LVEF (1% increase)	0.90	0.80 – 1.00	0.059
Left bundle branch block	0.88	0.22 – 3.54	0.86
QRS duration \geq 150 msec	0.26	0.07 – 1.06	0.060
%Vp \geq 97.8%	0.30	0.06 – 1.46	0.14
%e-CRT \geq 97.4% *	0.12	0.01 – 0.95	0.045
Atrial fibrillation document	0.64	0.13 – 3.11	0.58

376 All statistical tests were 2-tailed, and $p < 0.05$ was considered significant (*).

377 Abbreviations

378 LVEF, left ventricular ejection fraction; %Vp, percent ventricular pacing; %e-CRT, percent

379 effective cardiac resynchronization therapy pacing

380

381 **Table 3 Univariate analysis with a logistic regression model for CRT response**

Variables	Univariate analysis		
	Odds ratio	95% confidence index	P value
Age	1.05	1.00 – 1.10	0.052
Male sex	0.29	0.06 – 1.53	0.15
Ischemic cardiomyopathy	1.27	0.33 – 4.96	0.73
Chronic kidney disease	1.83	0.55 – 6.16	0.33
History of atrial arrhythmias	0.72	0.20 – 2.52	0.61
LVEF (1% increase)	1.03	0.94 – 1.11	0.56
Left bundle branch block	1.70	0.45 – 6.48	0.44
QRS duration \geq 150 msec *	4.69	1.33 – 16.50	0.016
%Vp \geq 97.8% *	6.20	1.63 – 23.60	0.007
%e-CRT \geq 97.4% *	19.20	3.63 – 101.00	<0.001
Atrial fibrillation document	0.28	0.66 – 1.22	0.090

382 All statistical tests were 2-tailed, and $p < 0.05$ was considered significant (*).

383 Abbreviations

384 LVEF, left ventricular ejection fraction; %Vp, percent ventricular pacing; %e-CRT, percent

385 effective cardiac resynchronization therapy pacing

386

387

388 **Figure captions**

389 **Fig. 1 Definition of effective cardiac resynchronization therapy pacing**

390 Based on the left ventricular (LV) tip-right ventricular (RV) coil electrocardiogram (EGM),
391 the following criteria for effective LV pacing were established: (1) baseline amplitude, which is
392 defined as the EGM amplitude at the time pacing was delivered; (2) minimum amplitude (Min)
393 and timing of the minimum amplitude (Tmin) measured from the time at which pace is delivered;
394 (3) maximum amplitude (Max) and timing of the maximum amplitude (Tmax) measured from the
395 time at which the pace is delivered. Tmin must occur at least 23 ms before Tmax, and the ratio of
396 the magnitudes of Max minus baseline and baseline minus Min must be between 0.125 and 8. In
397 addition, the magnitudes of Max must exceed the baseline, and Max minus Min must be over 1.6
398 mV. Any beat that does not meet these effective pacing criteria is treated as ineffective.

399

400 **Fig. 2 Flow chart of the patients included in the analyses**

401 The flow diagram shows the recruitment and analysis process of this study.

402 Abbreviations: CRTD, cardiac resynchronization therapy; %Vp, percent ventricular
403 pacing; %e-CRT, percent effective cardiac resynchronization therapy pacing

404

405 **Fig. 3 Scatter plot of percent effective cardiac resynchronization therapy pacing (%e-**
406 **CRT) vs. percent ventricular pacing (%Vp) for each patient**

407 The black and red dotted lines show the cut-off %Vp value of the inclusion criteria (90%)
408 and the median value of %e-CRT (97.4%) in this cohort, respectively. Patients with a discrepancy
409 between %e-CRT and %Vp, defined as %i-CRT $\geq 3\%$, are indicated by red marks.

410

411 **Fig. 4 Heart failure (HF) hospitalization**

412 The cumulative incidence of HF hospitalization using the Kaplan–Meier estimates is
413 presented.

414 A: Groups divided by the median value of percent effective cardiac resynchronization therapy
415 pacing (%e-CRT)

416 B: Groups divided by the median value of percent ventricular pacing (%Vp)

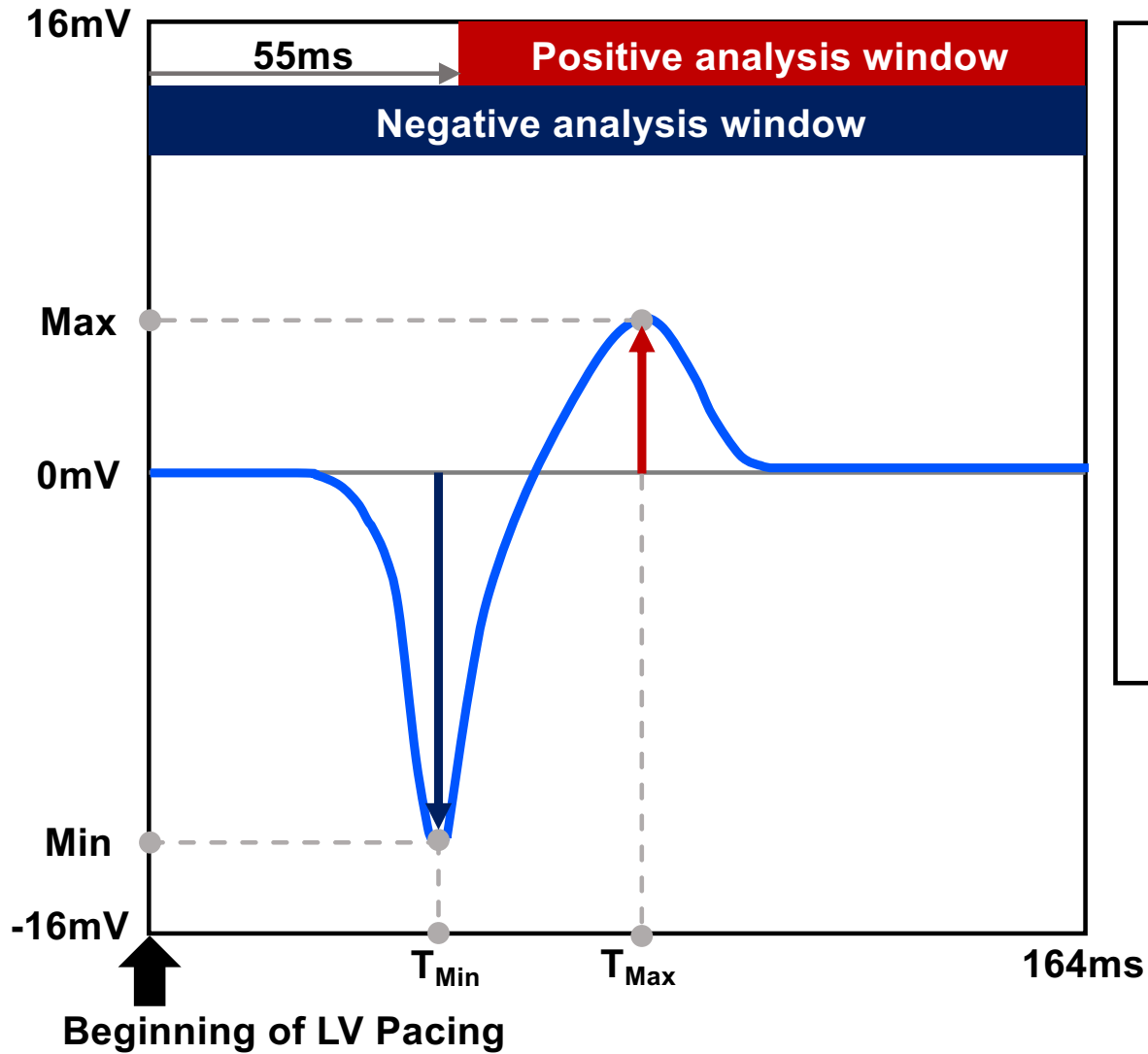
417

418 **Fig. 5 Cardiac resynchronization therapy (CRT) responder percentage**

419 Comparisons of CRT responder percentage between groups divided by median values of (A)
420 percent effective CRT pacing (%e-CRT) and (B) percent ventricular pacing (%Vp).

421

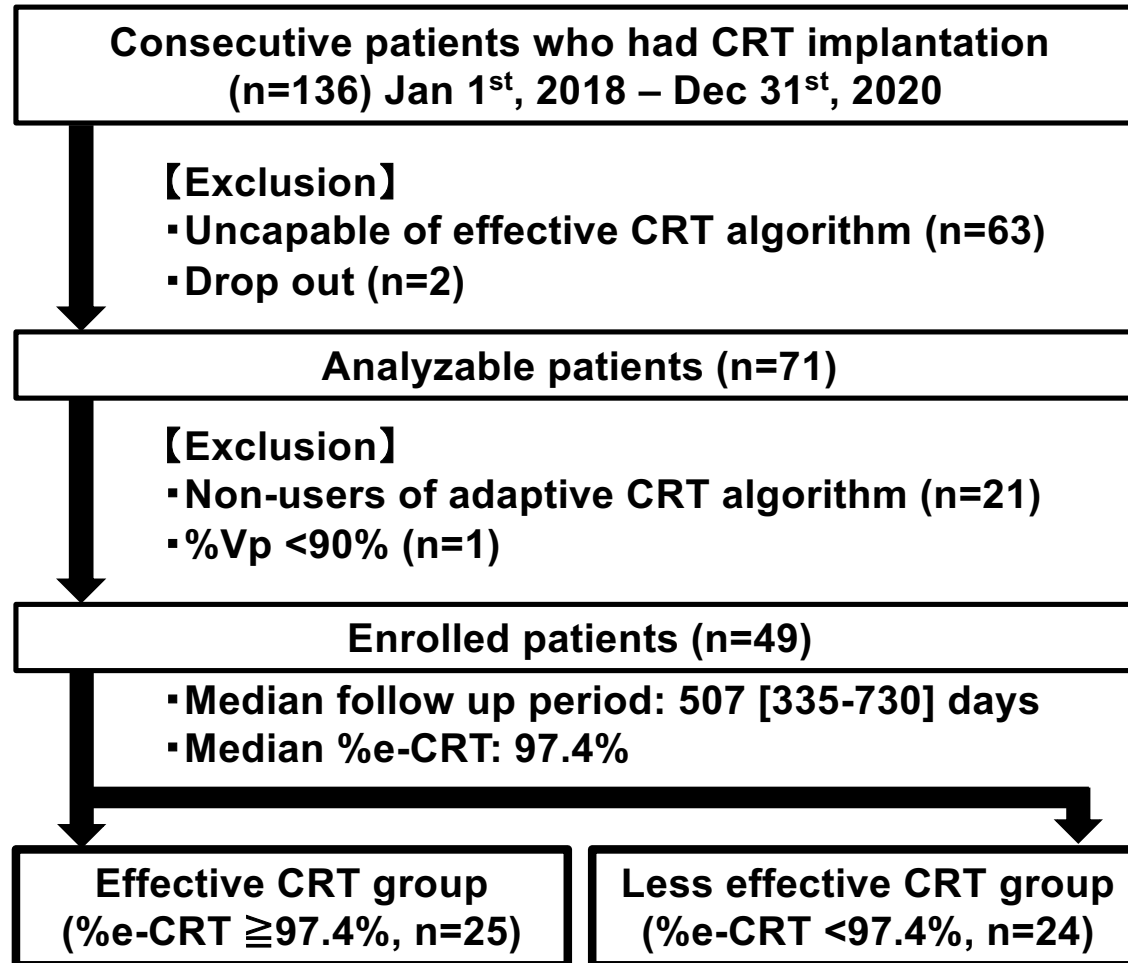
Electrogram of LV tip (pacing site)-RV coil

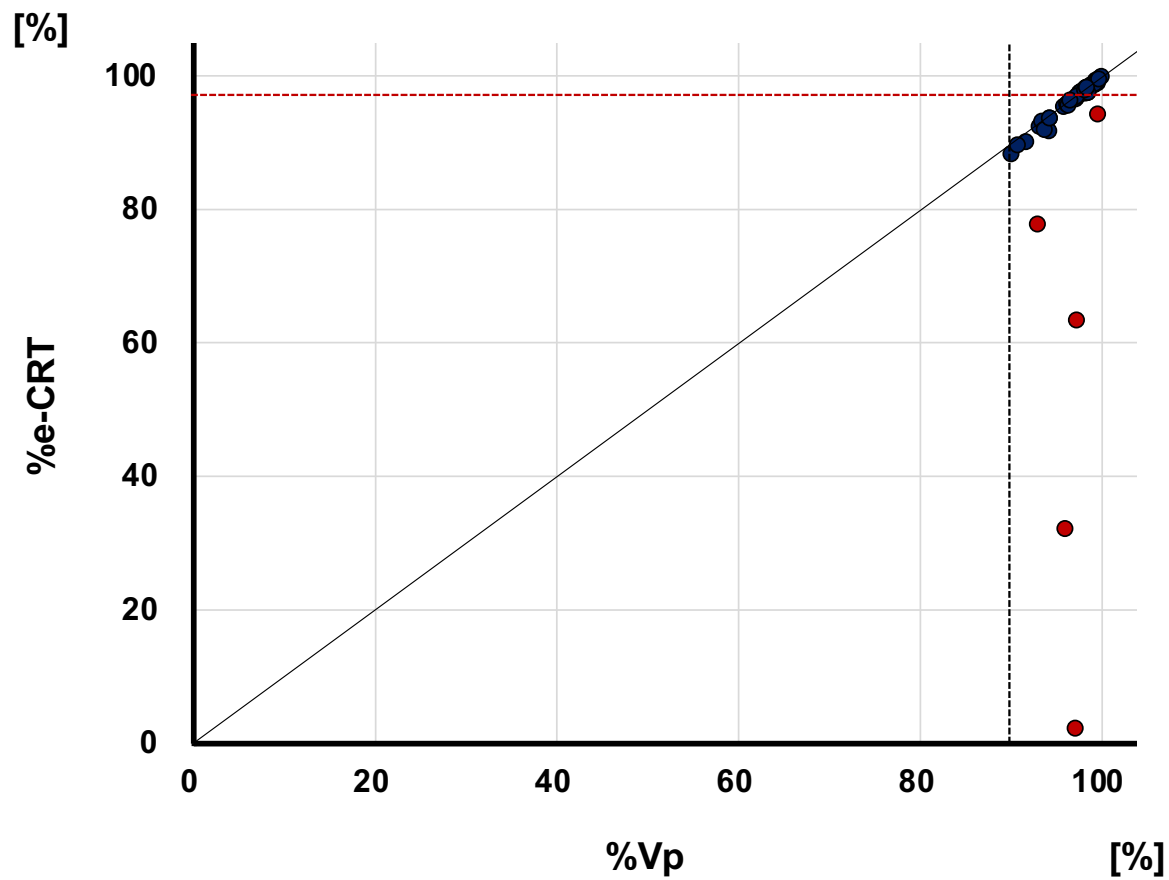


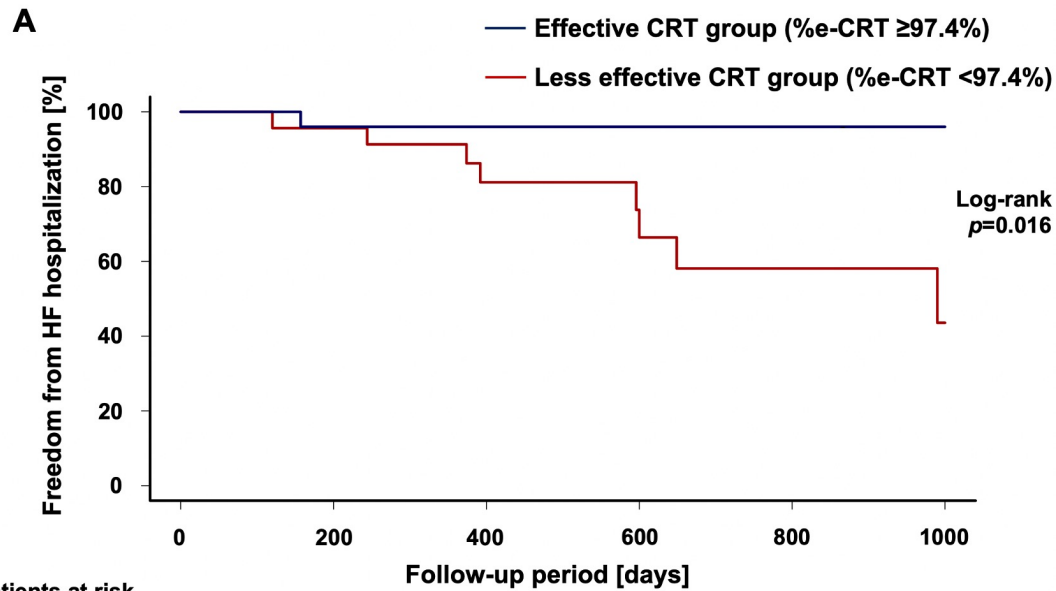
【Effective pacing definition】

- $T_{Max} - T_{Min} \geq 23ms$
- $0.125 \leq |Max| / |Min| < 8.0$
- $Max > baseline$
- $Max - Min \geq 1.6mV$

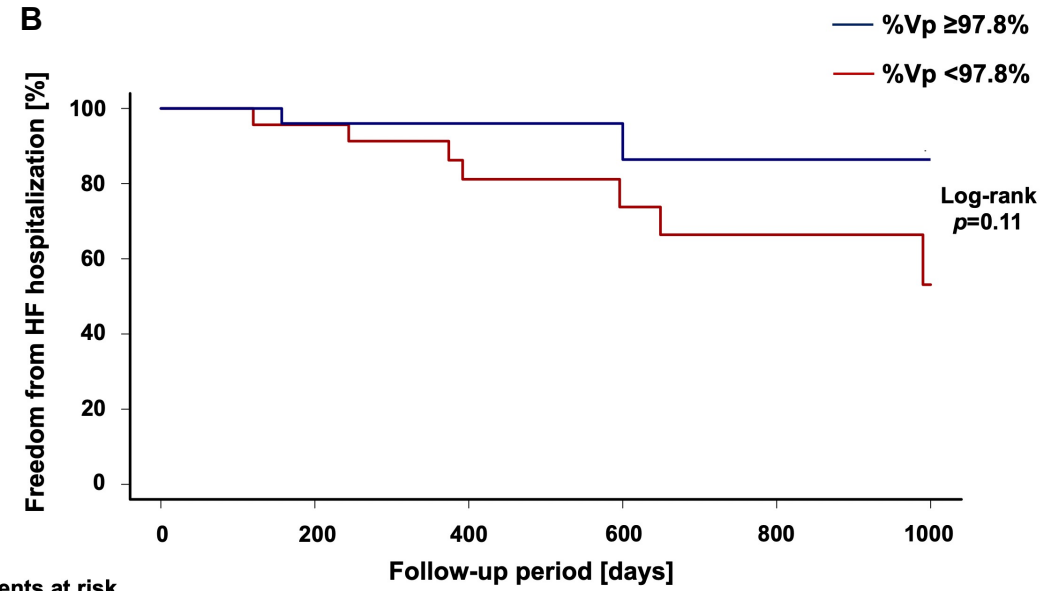
QS/QS-r morphology







Patients at risk		Follow-up period [days]					
		0	200	400	600	800	1000
%e-CRT $\geq 97.4\%$	25	24	18	10	6	4	
%e-CRT $< 97.4\%$	24	22	16	10	6	3	



Patients at risk		Follow-up period [days]					
		0	200	400	600	800	1000
%Vp $\geq 97.8\%$	25	24	18	10	4	3	
%Vp $< 97.8\%$	24	22	16	10	8	4	

