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1   **Full title:** Clinical effectiveness of a dedicated cardiac resynchronization therapy pre-

2   assessment clinic incorporating cardiac magnetic resonance imaging and cardiopulmonary

3   exercise testing on patient selection and outcomes

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Structured Abstract

Background: Pre-procedural assessment of patients undergoing cardiac resynchronization therapy (CRT) is heterogenous and patients implanted with unfavorable characteristics may account for non-response. A dedicated CRT pre-assessment clinic (CRT PAC) was developed to standardize the review process and undertake structured pre-procedural evaluation. The aim of this analysis was to determine the effectiveness on patient selection and outcomes.

Methods: A prospective database of consecutive patients attending the CRT PAC between 2013-2018 was analyzed. Pre-operative assessment included cardiac magnetic resonance (CMR) and cardiopulmonary exercise testing (CPET). Patients were considered CRT responders based on improvement in clinical composite score (CCS) and/or reduction in left ventricular end-systolic volume (LVESV) $\geq$15% at 6-months follow-up.

Results: Of 252 patients reviewed in the CRT PAC during the analysis period, 192 fulfilled consensus guidelines for implantation. Of the patients receiving CRT, 82% showed improvement in their CCS and 57% had a reduction in LVESV $\geq$15%. The presence of subendocardial scar on CMR and a peak VO_2 $\leq$12ml/kg/min on CPET predicted CRT non-response. Two patients were unsuitable for CRT as they had end-stage heart failure and died during follow-up. The majority of patients initially deemed unsuitable for CRT did not suffer from unexpected hospitalization for decompensated heart failure or died from cardiovascular disease; only 8 patients (13%) received CRT devices during follow-up because of symptomatic left ventricular impairment.

Conclusion: A dedicated CRT PAC is able to appropriately select patients for CRT. Pre-procedural investigation/imaging can identify patients unlikely to respond to, or may not yet be suitable for CRT.

Introduction

Cardiac resynchronization therapy (CRT) improves heart failure morbidity and mortality however 30-40% of patients fail to benefit.[1-4] Non-response may be multifactorial related to both patient selection and CRT implantation and delivery. Mullens *et al.* have previously described a post-implantation CRT optimization clinic to investigate the causes of CRT non-response.[5] In 75 consecutive patients with persistent symptomatic heart failure multiple factors were identified including anemia, suboptimal medical therapy, underlying narrow QRS duration and primary right ventricular dysfunction. Importantly many of these factors may be identified pre-implantation and prospective identification of predictors of CRT non-response may both improve outcomes and avoid implantation in ineligible patients.[6] We have introduced a bespoke CRT pre-assessment clinic (CRT PAC) to standardize the review process for patients considered for CRT and identify patients with unfavorable characteristics (including cardiac magnetic resonance (CMR) to assess myocardial scar) and ensure patients satisfied consensus guidelines for CRT implantation.[1, 2] We have previously demonstrated the economic benefits of this bespoke approach.[7] The aim of this analysis was to determine the clinical benefit of the CRT PAC and the benefit of pre-procedural investigation/ imaging. We assessed the outcomes in patients deemed eligible for CRT going through the clinic in terms of clinical and echocardiographic response to CRT.

Methods

All patients had previously been assessed in an outpatient consultant led cardiology clinic where CRT was felt appropriate and a referral made for implantation. A prospective database of consecutive patients attending the CRT PAC at Guy's and St Thomas' NHS Foundation Trust, UK between 2013 and 2018 was analyzed. Patients underwent the following investigations (where appropriate); blood tests, electrocardiogram, echocardiogram, CMR with

81 late gadolinium enhancement imaging, cardiopulmonary exercise test (CPET), 6-minute walk

82 test and Minnesota Living with Heart Failure Questionnaire (MLWHFQ). The left ventricular

83 ejection fraction (LVEF) used for CRT decisions was based on two-dimensional

84 echocardiography (biplane Simpson's rule) rather than CMR.[1, 2] Following investigations, all

85 patients were reviewed by a cardiologist with a specialist interest in heart failure where a final

86 decision regarding device therapy was made. Patients who were New York Heart Association

87 functional class IV were offered a pacemaker rather than a defibrillator due to their poor

88 prognosis and were also given a pacemaker if they declined a defibrillator. Patients felt to be

89 unsuitable for CRT were followed-up in the CRT PAC as previously described.[7] CRT response

90 was assessed after six-months of follow-up using (A) clinical composite score (CCS) consisting

91 of alive, no hospitalizations with decompensated heart failure, improvement in ≥1 New York

92 Heart Association (NYHA) functional class or improvement in global assessment[8, 9] and (B)

93 change in left ventricular end-systolic volume (LVESV) ≥15%. The study received institutional

94 approval from Guys and St Thomas' Hospital.

95

96 *Statistical Analysis*

97 Results are presented as mean ± standard deviation for normally distributed variables and as

98 median (interquartile range (IQR)) for non-normally distributed variables. When investigating

99 the change from baseline variables a paired sample *t*-test was used for normally distributed

100 data and for non-normally distributed data a Wilcoxon signed-rank test. Univariable and

101 multivariable binary logistic regression was performed to determine predictors of CRT

102 response. Variables statistically significant at univariable analysis as well as important clinical

103 covariables were used as the basis for multivariable analysis. A *P*-value <0.05 was statistically

104 significant. Statistical analyses were performed using Prism (GraphPad Software Inc., Version

105 7, CA) and SPSS (IBM Switzerland, Version 25, Switzerland).

108 **Results**

109 *Study Population*

110 Between September 2013 and June 2018 a total of 252 patients were seen in the CRT PAC.

111 Baseline demographics are provided in Table 1. Patients were 70.6 ± 10.8 years old,

112 predominantly male (72.6%) with an even distribution of ischemic (50.4%) and non-ischemic

113 cardiomyopathy (49.6%). The mean NYHA functional class was 2.5 ± 0.6, QRS duration was

114 157.1 ± 28.2ms and LVEF 31.9 ± 10.1%. Patients with ischemic versus non-ischemic

115 cardiomyopathy were more likely to be male, have diabetes and have a more severely dilated

116 and impaired left ventricle.

117

118 *Outcomes of patients attending CRT PAC*

119 192 (76.2%) patients were deemed eligible to undergo CRT (Figure 1). Of the CRT eligible

120 patients, 9 declined CRT and 2 died prior to the procedure. On an intention to treat basis of 192

121 patients, 5 (2.6%) had a failed left ventricular (LV) lead implant and 75 (39%) were upgrades.

122 78 received de novo CRT defibrillators (CRT-D), 15 de novo CRT pacemakers (CRT-P), and

123 8 WiSE-CRT (wireless LV endocardial pacing). The major complication rate was low at 1.1%

124 due to the development of pericardial tamponade requiring pericardiocentesis, minor

125 complications was 0.6% due to a pneumothorax requiring drainage and 1.1% of patients

126 required a lead revision within the follow-up period.

127

128 *Cardiac resynchronization therapy response rate*

129 CRT response was assessed at a median of 6 months (IQR 6-8 months) (Table 2 and 3). During

130 this period, 3 (1.7%) patients were admitted to hospital with decompensated heart failure, 6

131 (3.4%) patients died and 2 (1.1%) patients were lost to follow-up. The mean increase in LVEF

132 post CRT was 8.1 ± 10.7% ($P < 0.001$). There were statistically significant improvements in

133 LVEF, LV end-diastolic volume, LVESV, NYHA functional class, 6-minute walk test,

134 MLWHFQ and NT-proBNP (all $P < 0.01$) with CRT. Overall 82% improved their CCS and

135 57% had a reduction in LVESV ≥15%. In patients who underwent WiSE-CRT implantation, 1

136 died before review, 6/7 (85.7%) improved their NYHA functional class, 75% improved their

137 CCS and 42.9% showed a reduction in LVESV ≥15%.

138

139 *Cardiac magnetic resonance imaging and predictors of CRT response*

140 CMR was performed in 80/93 (86.0%) patients undergoing de novo CRT (excluding upgrades)

141 (13 patients refused, were too large for the scanner or artefacts from metal implants rendered

142 images non-diagnostic). Of patients undergoing CMR, 50% had an ischemic aetiology and

143 were 70.4 ± 9.3 years old, predominantly male (75.0%) with a mean QRS duration 150.1 ±

144 19.9ms and LVEF 29.0 ± 7.9%. Myocardial scar was identified in 49 (61.3%); sub-endocardial

145 in 40, sub-epicardial in 1 and mid-wall fibrosis in 8. The presence of subendocardial scar was

146 associated with a failure to improve CCS at univariable logistic regression (Odds ratio (OR)

147 5.063, 95% Confidence Interval (CI) 1.018-25.187; $P = 0.048$) and multivariable logistic

148 regression (OR 6.715, 95% CI 1.153-39.090; $P = 0.034$) but was not associated with failure to

149 reduce LVESV ≥15% (OR 2.267, 95% CI 0.841-6.111; $P = 0.106$). 22 patients had

150 posterolateral scar (defined as ≥50% subendocardial scar in ≥1 of the following segments; basal

151 posterior, basal posterolateral, mid posterior and mid posterolateral); 17 patients had the LV

152 lead placed within scar (other locations were not anatomically viable) and 5 patients were paced

153 outside scar (whereby the LV lead was placed in an anterior or anterolateral position). Pacing

154 outside of scar vs. pacing within scar did not result in a significant improvement in CCS (80

155 vs. 77%; $P = 1.000$) or reduction in LVESV ≥15% (83 vs. 80%; $P = 1.000$).

156

157 *Cardiopulmonary exercise testing and predictors of CRT response*

158 Pre-procedural CPET was available in 126/176 (71.6%) patients (50 patients refused or were

159 unable to carry out the exercise test) with a mean age of 68.6 ± 11.4 years old, 80.2% male,

160 44.4% non-ischaemic cardiomyopathy, 50.8% NYHA III-IV, 44.4% atrial fibrillation, mean

161 QRS duration 163.2 ± 26.1ms and LVEF 29.2 ± 8.0%. Predictors of improvement in CCS and

162 LVESV ≥15% are provided in Figure 2 and 3.

163

164 We investigated the outcomes of patients taking β-blockers (βB) who had a peak VO_2

165 ≤12ml/kg/min. A significantly higher proportion of patients with a peak VO_2 ≤12ml/kg/min vs.

166 >12ml/kg/min had atrial fibrillation (59.1% vs. 34.8%; $P = 0.018$), NYHA III-IV (75% vs.

167 36.4%; $P < 0.001$), worse LVEF (28.0% vs 30.8%; $P = 0.029$) and were less likely to reach a

168 respiratory exchange ratio (RER) >1 (52.3% vs. 72.7%; $P = 0.041$). They were matched in

169 terms of age (69.3 vs. 68.6 years; $P = 0.976$), non-ischaemic cardiomyopathy (43.2% vs.

170 48.5%; $P = 0.697$) and QRS duration (164.7 vs. 158.5ms; $P = 0.089$). At both univariable and

171 multivariable logistic regression, a peak VO_2 ≤12ml/kg/min in patients taking βB was

172 associated with CRT non-response defined as an absence of improvement in CCS (OR 3.063,

173 95% CI 1.082-8.669; $P = 0.035$) and absence of increase in LVESV ≥15% (OR 2.832, 95% CI

174 1.061-7.558; $P = 0.038$) (Supplementary Figure 1)

175

176 *Outcome of patients initially felt unsuitable for CRT after pre-assessment review*

177 As previously described,[7] 60 (24%) patients were deemed ineligible to receive CRT often for

178 a combination of reasons (Figure 4). Eight patients underwent device implantation during

179 follow-up as they became symptomatic or had persistent left ventricular systolic impairment

180 despite medical optimisation.[7]

181

182

183

Discussion

We present outcomes from a dedicated and specialist CRT PAC. Studies have demonstrated that medical and device optimization can result in improved patient outcomes.[5, 10] However, translating these results into real-world clinical practice is difficult and outcomes are often far below those reported in clinical trials. We hypothesized a CRT PAC we would be able to appropriately apply evidence-based guidelines in a standardized manner and improve patient outcomes.

The main findings from the CRT PAC show:

1. 82% of patients who underwent CRT had improvement in their CCS and 57% had reduction in LVESV $\geq$15% after a median follow-up of 6 months.

2. CMR-identified myocardial scar and CPET predicted CRT non-response.

The CRT PAC ensured patients underwent relevant pre-procedural investigations immediately prior to intervention and ensured consensus guidelines were always followed. This allowed a thorough review of patients and ensured only those who were fully medically optimized and suitable for implantation proceeded to intervention.

A cardiac resynchronization therapy pre-assessment clinic appropriately selects patients

CRT non-response is defined heterogeneously in the literature, with some studies relying on evidence of reverse LV remodeling whilst others using a CCS.[10] Studies have shown differing patient outcomes when the CCS definition is applied.[9, 11, 12] A recent meta-analysis of three

206 double-blind, randomized trials involving 1591 patients showed an overall 60% improvement

207 in CCS at 6 months.[13] The improvement in CCS at 6 months in the current study of 82%

208 compares favorably and additionally 57% showing an improvement in LVESV ≥15%. A

209 potential benefit of a dedicated CRT PAC is the ability to identify patients that do not fulfil

210 CRT implant criteria or who require further optimization prior to CRT.[7] In our analysis one

211 quarter (24%) referred to the CRT PAC did not fulfil consensus guideline criteria for CRT and

212 8 (13.3%) patients subsequently underwent CRT during the follow-up period. Furthermore, 2

213 patients were identified as having end-stage heart failure and died. However, none of the

214 remaining patients were admitted to hospital with decompensated heart failure, nor died from

215 cardiovascular causes demonstrating that patients were appropriately identified and did not

216 suffer unexpected adverse outcomes. This is important, as CRT may be harmful in patients

217 who do not meet guideline defined criteria as shown in the ECHO-CRT study.[6] The commonest

218 reason for finding a patient was unsuitable for CRT was an improvement in LVEF at CRT PAC

219 review compared with their initial echocardiogram performed prior to referral to the CRT PAC

220 $(45.1 \pm 7.1\%$ vs. $34.1 \pm 10.5\%$; $P < 0.001)$. Guidelines recommend patients with chronic heart

221 failure should be on optimal medical therapy for at least 3 months before considering CRT.[1, 2]

222 We did not have a matched control group to compare but we can speculate that the favorable

223 CRT response seen may be due to patient selection with non-implantation of patients ineligible

224 to receive CRT.

225

226 ***Predictors of CRT response***

227 *Cardiac magnetic resonance imaging*

228 CMR is the preferred imaging modality to assess myocardial fibrosis and the aetiology

229 underlying heart failure. The presence of myocardial scar is inversely proportional to reverse

230 LV remodeling[14] and in keeping with this we found subendocardial scar was associated with

231 CRT non-response. Studies have shown that placing the LV lead within posterolateral scar is

232 associated with CRT non-response.[15, 16] Pre-procedural knowledge of scar in our cohort did not

233 result in improved CRT response however implant strategies were not routinely performed

234 using guidance strategies to avoid myocardial scar that was identified. Our results confirm the

235 predictive value of CMR scar in CRT non-response and support the need for randomized

236 studies to investigate whether image guidance avoiding myocardial scar can reliably improve

237 CRT outcomes. Indeed, the ongoing multi-center randomized controlled trial investigating the

238 benefit of CMR guided CRT implantation in ischaemic cardiomyopathy will provide important

239 insights (NCT03992560).

240

241

242 *Cardiopulmonary exercise testing*

243 CPET is a useful clinical adjunct to assess a patient's cardiac reserve and functional capacity.

244 In keeping with prior studies, clinical and echocardiographic responders were more likely to

245 show better cardiopulmonary exercise capacity at baseline.[17] Guidelines recommend that in

246 patients taking βB, a peak $VO_2 \leq 12ml/kg/min$ can be used as a cut-off to list patients for heart

247 transplantation.[2, 18] In our cohort a peak $VO_2 \leq 12ml/kg/min$ was independently associated with

248 an absence of clinical response and LV remodeling. At baseline these patients were more likely

249 to be symptomatic, suffer from atrial fibrillation and less likely to achieve a RER> 1 suggesting

250 their limitation to exercise is multifactorial rather than from pure cardiac disease and this may

251 be a useful clinical adjunct identifying patients unlikely to respond to CRT which could be

252 discussed in pre-procedural planning. Indeed, these patients should be closely followed-up to

253 determine their progress and ensure they are thoroughly optimized or offered further

254 intervention if appropriate.

255

256

Limitations

This is a single-center, observational study and is susceptible to the same limitations as for all prospectively collected data. The lack of a randomized control group means that findings are hypothesis generating rather than definitive. Follow-up was assessed at six months and it is unclear whether a longer period would produce similar findings. Although pre-procedural imaging was performed this was not used to systemically guide implant strategies and we cannot exclude the fact that knowledge of scar location may improve CRT response. This would need a randomized study and we are currently undertaking a multicenter study of CMR guidance to assess this (NCT03992560). Likewise the results of CPET did not dictate implantation strategy and this may merit further investigation. Overall, the total number of patients inappropriately implanted with CRT is unknown and is likely to vary from center to center. CPET's often require experienced operators to perform the test reliably and are time consuming which may limit their role in routine pre-assessment clinics.

Conclusion

A CRT PAC is able to appropriately select patients for CRT and lead to favorable outcomes in the majority of patients implanted. Pre-procedural assessment including CMR and CPET can prospectively identify patients who are less likely to respond to CRT. Further evaluation is required to assess whether pre-procedural assessment is able to guide strategies to improve CRT response.

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