



Upgrading to cardiac resynchronisation therapy: Concordance of real-world experience with clinical guidelines [☆]



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ARTICLE INFO

Article history:

Received 31 December 2020
Received in revised form 4 February 2021
Accepted 21 February 2021

Keywords:

Heart failure
HFrEF
Cardiac resynchronisation therapy
CRT upgrade
CRT revision

ABSTRACT

Objective: Revision to cardiac resynchronisation therapy (CRT) in patients with existing pacemakers with worsening heart failure (HF) can improve symptoms and cardiac function. We identify factors that predict improvement in left ventricular ejection fraction (LVEF) within a year of CRT revision.

Methods: We performed a retrospective study of 146 consecutive patients (16% female, mean age 73 ± 11 years, mean LVEF $27 \pm 8\%$) undergoing revision to CRT (January 2012 to May 2018) in a single tertiary centre. LVEF was measured pre-revision and 3, 6 and 12 months post-upgrade.

Results: At 6 months, 68% of patients demonstrated improvement in LVEF (mean Δ LVEF $+ 6.7\% \pm 9.6$). Compared to patients in atrial fibrillation (AF), patients with sinus rhythm had a greater improvement in LVEF at 6 months (sinus $8.4 \pm 10.3\%$ vs. AF $4.2 \pm 8.0\%$, $p = 0.02$). Compared to ischaemic cardiomyopathy (ICM), patients with non-ischaemic cardiomyopathy (NICM) had a greater improvement in LVEF at 6 months (NICM $8.4 \pm 9.8\%$ vs ICM $4.8 \pm 9.2\%$, $p = 0.05$). Patients with RV pacing $\geq 40\%$ at baseline had a greater improvement in LVEF at 6 months ($\geq 40\%$ RV pacing 9.3 ± 10.2 vs. $< 40\%$ RV pacing $4.0 \pm 7.4\%$, $p = 0.01$). All improvements were sustained over 12 months post-revision. There was no significant difference between genders, years between initial implant and revision, or previous device type.

Conclusions: Our real-world experience supports current guidelines on CRT revision. NICM, $\geq 40\%$ RV pacing and sinus rhythm are the main predictors of improvement in LVEF in patients who underwent CRT revision.

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1. Introduction

In patients with heart failure (HF), reduced left ventricular ejection fraction (LVEF) and delayed left ventricular electrical activation (typically left bundle branch block with QRS duration >130 ms), cardiac resynchronisation therapy (CRT) reduces mechanical dyssynchrony. This in turn improves left ventricular performance, reduces mitral regurgitation, decreases cardiac filling pressure and favourably remodels the left ventricle [1]. These pathophysiological adjustments significantly improve symptoms, reduce morbidity and mortality in patients with HF and reduced ejection fraction (HFrEF) on top of optimal medical treatment [1–

4]. Recommendations for CRT are engrained in national and international guidelines for symptomatic patients with HFrEF [2,5].

Patients with a permanent pacemaker (PPM) or implantable cardioverter defibrillator (ICD) may develop HF symptoms because the sequence of electrical activation in RV pacing resembles the activation pattern seen in LBBB. This asynchronous electrical activation causes abnormal mechanical interactions within the left ventricle and between the two ventricles, inducing dyssynchrony [6]. In a study by Sweeny and colleagues, compared to RV pacing of $<40\%$, RV pacing of $\geq 40\%$ conferred a 2.6 fold increase in risk of HF hospitalisation in patients with a normal baseline QRS [7]. Furthermore, studies have demonstrated that revising these existing RV pacing systems to CRT, to restore synchronicity and reverse remodelling, can improve LV function [8]. The European Society of Cardiology (ESC) guidelines on acute and chronic HF and ESC guidelines on pacing suggest that patients with a conventional PPM or ICD who subsequently develop worsening HF should be considered for a device revision to CRT [2,9]. In the 2009 European

[☆] All authors listed take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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cardiac resynchronisation therapy survey, over a quarter of all CRT implantation procedures were undertaken as revision from existing systems in patients experiencing worsening HF [10,11].

However, patients with PPMs and ICDs are heterogenous and less is understood regarding which patients may best benefit from a revision procedure to CRT. Furthermore, in a study by Poole and colleagues, compared to elective generator change, revision to CRT had a 3-fold increased risk in major complications [12]. The aim of this study was to identify the patient characteristics that may predict a greater improvement in LVEF, following revision to CRT.

2. Methods

2.1. Study population

Patients attending a multi-disciplinary, cardiac physiologist-led, cardiac device follow-up clinic at the University Hospital of Wales are routinely evaluated for the development of HF symptoms following PPM/ICD implantation (Fig. 1). The clinical characteristics of consecutive patients attending the clinic between January 2012 and May 2018 were retrospectively collected.

Baseline information on demography, symptoms, electrocardiographs, echocardiograms, time between initial implant and revision, previous device type (dual vs. single chamber) and planned procedure (revision to CRT-P vs. CRT-D) were recorded at the time of revision to CRT. Aetiology of HF (ischaemic vs. non-ischaemic) was determined using angiographic findings and wall motion abnormalities identified on echocardiography. LVEF, measured by echocardiography, was assessed pre-revision and 3, 6 and 12 months post-procedure. Patients were followed up regularly in multi-disciplinary cardiac device and HF nurse-led clinics to ensure optimal pacing and medical therapies.

2.2. Study outcomes

The aim of the study was to assess the factors which best predicted an improvement in LVEF at 6 and 12 months following LV lead implantation. The variables considered included: age, gender

and New York Heart Association (NYHA) class; pre-procedural cardiac rhythm (sinus vs. atrial fibrillation; AF); aetiology of HF (ischaemic; ICM vs. non-ischaemic cardiomyopathy; NICM); previous device type (dual chamber vs. single chamber); and ensuing CRT therapy (CRT-P vs. CRT-D).

2.3. Statistical analysis

Categorical data are presented as number and percentages and continuous data as are presented as mean ± standard deviation (SD). Data was analysed using unpaired t-tests to compare the change in LVEF between specified subgroups of patients. Results are shown as mean change in LVEF (ΔLVEF) ± standard deviation (SD). Linear and multiple regressions were run in order to identify the factors that best predicted improvement in EF at timepoints of 3, 6 and 12 months post-revision. All analysis was run using RStudio Version 1.2.1335. In comparison analyses p values < 0.05 were considered statistically significant.

3. Results

146 patients (mean age 73 ± 11 years, 16% female, 49% ICM) all optimally treated with prognostic medications were included. 42% had a single chamber PPM and 36% of all devices pre-revision were ICDs. Due to the priori bias introduced through case selection via a clinical pathway, at baseline >96% reported HF symptoms, mean LVEF 27 ± 8%, and a high burden of RV pacing (mean % RV pacing 64.0 ± 42%). The average time from initial pacemaker implantation to the CRT revision was 6 ± 3 years. All CRT procedures, CRT-P (n = 60, 41%) or CRT-D (n = 86, 59%), were successful. (Table 1)

Overall, two thirds of the patients improved their LVEF at 6 months (mean ΔLVEF at 6 months + 6.7% ± 9.6) and 12 months (mean ΔLVEF at 12 months + 7.4% ± 10.1) following CRT revision (Fig. 2, Table 2). Compared to patients in AF, patients with sinus rhythm had a significantly greater improvement in LVEF at 3 months (ΔLVEF: sinus 8.0 ± 8.9 vs AF 3.3 ± 8.6, p < 0.01) and 6 months (ΔLVEF: sinus 8.4 ± 10.3 vs. AF 4.2 ± 8.0, p = 0.02) post-CRT revision, which was sustained at 12 months. Compared

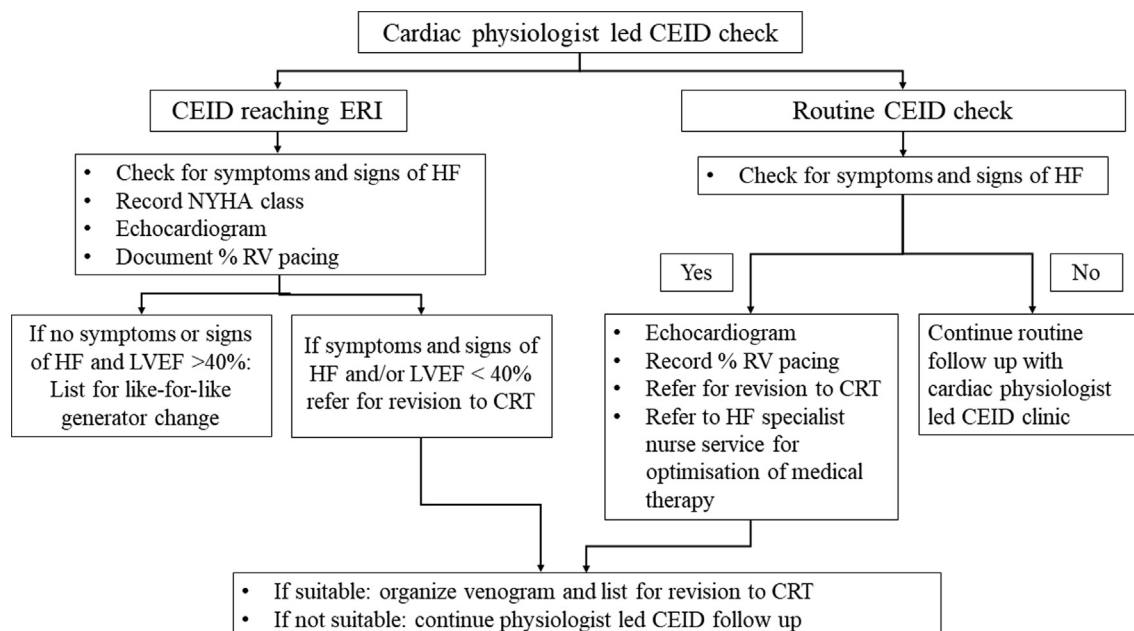


Fig. 1. Cardiac electronic implantable devices (CEID) follow-up clinical pathway from the University Hospital of Wales Cardiology Department. ERI: elective replacement indicator, HF: heart failure, RV: right ventricular, LVEF: left ventricular ejection fraction, CRT: cardiac resynchronisation therapy.

Table 1
Baseline characteristics for all patients divided according to dual vs. single previous device type.

Baseline characteristics	All patients (N = 146)	Patients with dual chamber PPM (N = 85)	Patients with single chamber PPM (N = 61)	P value
Age (yrs)	72.6 ± 10.7	73.5 ± 10.1	71.3 ± 11.3	0.237
Male Sex (%)	84.2% (123)	81.2% (69)	88.5% (54)	0.331
NYHA class				
I (%)	3.4% (5)	4.7% (4)	1.6% (1)	
II (%)	63.7% (93)	64.7% (55)	62.3% (38)	
III (%)	31.5% (46)	29.4% (25)	34.4% (21)	
IV (%)	1.4% (2)	1.2% (1)	1.6% (1)	
Co-morbidities				
Hypertension (%)	48.6% (71)	51.8% (44)	44.3% (27)	0.467
Diabetes (%)	28.8% (42)	35.3% (30)	19.7% (12)	0.061
IHD (%)	53.4% (78)	51.8% (44)	55.7% (34)	0.817
CVA (%)	12.3% (18)	12.9% (11)	11.5% (7)	0.992
Asthma (%)	4.1% (6)	4.7% (4)	3.3% (2)	0.995
COPD (%)	15.1% (22)	14.1% (12)	16.4% (10)	0.885
Bloods /ECG /Echocardiography				
Haemoglobin (g/l)	132.2 ± 17.1	130.2 ± 16.4	134.8 ± 17.8	0.122
Creatinine (µmol/l)	124.7 ± 55.6	132.1 ± 63.8	114.2 ± 39.7	0.04
Sinus rhythm (%)	57.5% (84)	68.2% (58)	42.6% (26)	0.004
Mean LVEF (%)	26.5 ± 7.8	26.3 ± 7.8	26.7 ± 7.9	0.752
LVEDV (ml)	177.3 ± 55.5	173.8 ± 54.8	182.3 ± 56.9	0.460
Treatment				
Beta blocker (%)	83.6% (122)	82.4% (70)	85.2% (52)	0.811
ACEi (%)	53.4% (78)	54.1% (46)	52.5% (32)	0.976
ARB (%)	24.0% (35)	24.7% (21)	23% (14)	0.961
ARNI (%)	4.1% (6)	4.7% (4)	3.3% (2)	0.995
Loop diuretics (%)	69.2% (101)	69.4% (59)	68.9% (42)	1.00
MRA (%)	50.0% (73)	49.4% (42)	50.8% (31)	1.00
Digoxin (%)	11% (16)	11.8% (10)	9.8% (6)	0.921
Aspirin (%)	24.7% (36)	28.2% (24)	19.7% (12)	0.323
Warfarin (%)	44.5% (65)	32.9% (28)	60.7% (37)	0.002
DOAC (%)	12.3% (18)	12.9% (11)	11.5% (7)	0.992

PPM: permanent pacemaker, NYHA: New York Heart Association, IHD: ischaemic heart disease, CVA: cerebrovascular accident, COPD: chronic obstructive pulmonary disease, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end diastolic volume, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor-neprilysin inhibitors, MRA: mineralocorticoid receptor antagonist, DOAC: direct oral anticoagulant.

Categorical variables are expressed as percentage (n) and continuous variables are expressed as mean ± standard deviation. P values were calculated using unpaired t-tests for continuous data and chi-squared tests for categorical data.

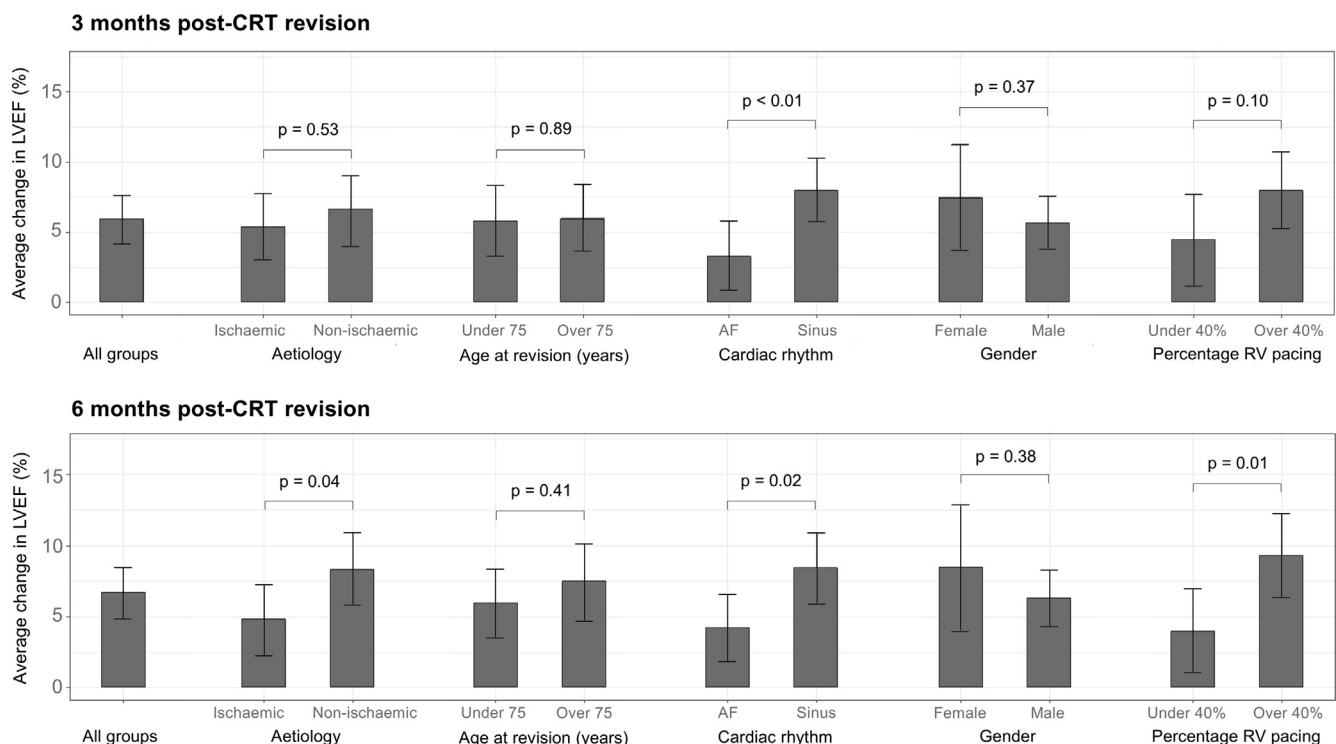


Fig. 2. Change in left ventricular ejection fraction (ΔLVEF) from baseline to 3 and 6 months after CRT revision procedure. Mean difference between ΔLVEF for each baseline characteristic is shown with the associated p value. AF: atrial fibrillation, RV: right ventricular.

to those with ICM, patients with NICM had a significantly greater improvement in LVEF at 6 months (Δ LVEF: NICM 8.4 ± 9.8 vs ICM 4.8 ± 9.2 , $p = 0.05$), which was sustained over 12 months. Compared to patients who had a revision to CRT-D, patients who had a revision to CRT-P had a significantly greater improvement in LVEF at 6 months (Δ LVEF: CRT-D 5.0 ± 9.1 vs CRT-P 9.0 ± 9.9 , $p = 0.03$). Compared to patients with a RV pacing <40%, patients with a RV pacing $\geq 40\%$ had a significantly greater improvement of LVEF at 6 months (Δ LVEF: $\geq 40\%$ RV pacing 9.3 ± 10.2 vs. <40% RV pacing 4.0 ± 7.4 , $p = 0.01$) and 12 months (Δ LVEF: $\geq 40\%$ RV pacing 9.9 ± 11.2 vs. <40% RV pacing 5.1 ± 6.7 , $p = 0.03$). A linear relationship was observed between percentage of RV pacing at baseline and improvement in LVEF at all time points studied (Supplementary Fig. 1, Supplementary Table 1). The same factors (sinus rhythm, non-ischaemic aetiology, and CRT-P device type) demonstrated a greater improvement in LVEF following revision procedure in patients with RV pacing $\leq 40\%$ at baseline compared to patients with RV pacing >40% (Supplementary Table 2).

Gender, years between initial implant and revision procedure, age at time of revision procedure or type of PPM were not significant predictors of improvement in LVEF over one year following CRT revision. (Table 2). We also explored the interaction between pre-pacemaker implant QRS duration and the change in LVEF observed post-CRT revision procedure with full results presented in Supplementary (Supplementary Table 3).

Linear regression demonstrated the baseline factors that best predicted an improvement in LVEF post-revision were sinus rhythm (3 months: $R^2 = 0.07$, $p < 0.01$ and 6 months: $R^2 = 0.05$,

$p = 0.02$), non-ischaemic aetiology (6 months: $R^2 = 0.04$, $p = 0.05$) and RV pacing >40% at baseline (3 months: $R^2 = 0.03$, $p = 0.12$, 6 months: $R^2 = 0.07$, $p = 0.02$). Multiple linear regression showed that a model containing rhythm, aetiology of HF, % RV pacing and device type (CRT-D vs. CRT-P) could significantly predict Δ LVEF at 3 months ($F(4,68) = 3.33$, $p = <0.02$) with an R^2 of 0.16 and Δ LVEF 6 months ($F(4,67) = 5.55$, $p = <0.001$) with an R^2 of 0.25.

All patients with complete NYHA data over 12 months ($n = 109$) demonstrated either a maintenance of current NHYA class (69.7%) or an improvement (30.3%) in NYHA class following revision procedure at 6 months, with similar patterns also observed at 12 months (Supplementary Table 4 and 5).

There were 11 complications (7.4%) associated with revision to CRT (Supplementary Table 6).

4. Discussion

In this study, patients with a PPM or ICD followed a clinical pathway that highly selected patients who had symptoms and signs of heart failure and worsening LV function for CRT revision. Despite this pathway, we found a difference in the improvement in LV function seen after revision within this selective group. Over 70% of patients who had a PPM or ICD and symptoms of heart failure improved their LVEF following CRT revision procedure (mean LVEF 6.7% improvement at 6 months). In addition, almost all patients also demonstrated either an improvement or an unchanged NYHA class following upgrade at all time points. Sinus rhythm, higher percentage of RV pacing and non-ischaemic aetiol-

Table 2
Change in left ventricular ejection fraction (Δ LVEF) from baseline to 3 and 6 months after CRT revision procedure.

Variable (n)	Missing values			Before Revision Mean LVEF	3 months			6 months				
	0	3	6		Mean LVEF	Δ LVEF from baseline	Mean difference in Δ LVEF	P value	Mean LVEF	Δ LVEF from baseline	Mean difference in Δ LVEF	P value
All patients	14	24	24	26.5 \pm 7.8	32.4 \pm 11.2	5.9 \pm 9.0	-	-	33.5 \pm 11.3	6.7 \pm 9.6	-	-
Gender												
Male (123)	13	18	20	26.3 \pm 7.8	32.3 \pm 11.0	5.7 \pm 9.3	-1.85	0.37	33.4 \pm 11.4	6.3 \pm 9.7	-2.10	0.38
Female (23)	1	6	4	27.0 \pm 8.1	33.3 \pm 12.6	7.5 \pm 7.0			33.8 \pm 10.9	8.4 \pm 9.0		
Rhythm												
Sinus (84)	8	15	13	25.3 \pm 7.8	33.0 \pm 11.2	8.0 \pm 8.9	+4.66	<0.01	34.0 \pm 11.9	8.4 \pm 10.3	+4.21	0.02
AF (62)	6	9	11	28.0 \pm 7.6	33.5 \pm 11.1	3.3 \pm 8.6			32.8 \pm 10.4	4.2 \pm 8.0		
Cause of HF												
Non	5	17	12	27.1 \pm 8.0	33.4 \pm 12.2	6.5 \pm 9.3	+1.09	0.53	35.2 \pm 11.2	8.4 \pm 9.8	+3.58	0.04
Ischaemic (75)												
Ischaemic (71)	9	7	12	25.8 \pm 7.6	31.5 \pm 10.2	5.4 \pm 8.9			31.6 \pm 11.1	4.8 \pm 9.2		
Device												
CRT-P (60)	6	12	8	28.7 \pm 7.8	37.0 \pm 10.5	7.7 \pm 8.2	+2.83	0.10	38.0 \pm 10.5	9.0 \pm 9.9	+3.95	0.03
CRT-D (86)	8	12	16	24.9 \pm 7.5	29.4 \pm 10.6	4.8 \pm 9.4			30.1 \pm 10.7	5.0 \pm 9.1		
Previous device												
Dual chamber (85)	8	13	11	26.3 \pm 7.8	32.5 \pm 11.8	6.2 \pm 9.4	+0.61	0.72	33.7 \pm 12.1	7.1 \pm 10.5	+1.01	0.57
Single chamber (61)	6	11	13	26.7 \pm 7.9	32.3 \pm 10.3	5.6 \pm 8.6			33.2 \pm 9.9	6.1 \pm 8.3		
Age at revision												
< 75 years (74)	7	14	13	26.0 \pm 7.5	30.6 \pm 11.3	5.8 \pm 9.3	-0.23	0.89	31.1 \pm 11.2	5.9 \pm 9.2	-1.49	0.41
≥ 75 years (72)	7	10	11	27.0 \pm 8.1	34.1 \pm 10.9	6.0 \pm 8.8			35.8 \pm 10.9	7.4 \pm 10.1		
NYHA class												
I-II (98)	10	18	17	26.3 \pm 7.8	31.9 \pm 10.8	5.7 \pm 9.1	-0.59	0.74	33.5 \pm 10.8	7.1 \pm 9.9	+1.17	0.53
III-IV (48)	4	6	7	26.9 \pm 7.9	33.4 \pm 11.9	6.3 \pm 9.0			33.5 \pm 12.2	5.9 \pm 9.2		
% RV pacing												
$\geq 40\%$ (62)	4	7	11	27.3 \pm 8.2	34.7 \pm 11.0	8.0 \pm 9.7	+3.55	0.10	36.6 \pm 10.2	9.3 \pm 10.2	+5.27	0.01
< 40% (32)	3	6	3	22.7 \pm 7.9	27.6 \pm 9.7	4.4 \pm 7.8			28.2 \pm 11.1	4.0 \pm 7.4		

Mean difference between Δ LVEF for each baseline characteristic is shown with the associated p value. Data is expressed as a mean \pm standard deviation. AF: atrial fibrillation, HF: heart failure, NYHA: New York Heart Association, CRT-P/D: cardiac resynchronization therapy pacemaker/defibrillator.

ogy of heart failure were the most consistent predictors of improved LVEF after revision to CRT.

Patients with heart failure who have a de novo CRT implantation have been shown to demonstrate a 2–5% improvement in LVEF at 6 months post-CRT implantation [13–15]. With regard to revision procedures, in a study by Sideris and colleagues of 37 patients with HF who underwent CRT revision from an existing PPM, a significant LVEF improvement ($26.3 \pm 5.4\%$ to $31.4 \pm 6.7\%$; $p < 0.001$) was observed at 6 months post-CRT implantation [16]. In a recent meta-analysis by Kosztin and colleagues of 16 studies (comprising 489,568 CRT recipients, with 468,205 de novo and 21,363 upgrade procedures), LVEF improved in both groups (de novo 6.85% vs. upgrade 9.35%; $p = 0.235$) [17]. In our cohort, the mean LVEF at time of revision was $26.5\% \pm 7.8\%$. CRT revision procedure improved LVEF by a mean of 7.4% at 12 months. The greatest improvement was seen in the first 3 months post CRT revision (mean improvement in LVEF $5.9\% \pm 9.0$).

Although fulfilling the current criteria set out by guidelines, not all patients with heart failure that remain symptomatic despite optimal medical treatment with necessarily benefit equally from CRT. With regards to de novo CRT implantation, studies have identified non-ischaemic aetiology and female sex to positively predict reverse remodelling and improved LVEF [3,18]. In a study by Rafla and colleagues of 81 patients who had PPM and later a revision to CRT, patients with non-ischaemic aetiology had a significantly better response [19]. We also found patients with a non-ischaemic aetiology of HF showed a significantly greater improvement in LVEF following CRT revision. In addition, we found patients in sinus rhythm rather than in AF had a significantly greater improvement in LVEF following CRT revision. This highlights the importance of atrio-ventricular resynchronisation, which may be as or more important than bi-ventricular resynchronisation. Although women did show a greater improvement in LVEF than men, this was found to be non-significant at all time points studied. Interestingly patients who had a revision to CRT-P rather than CRT-D had a significantly greater improvement in LVEF at 6 months. This may reflect the notion that the decision to implant a CRT-P (and not CRT-D) was a surrogate for a pre-implant impression that the patient would likely respond to BiV pacing alone.

The indications for upgrading to CRT are still ambiguous and the guidelines lack some clarity. The 2013 European Society of Cardiology (ESC)/European Heart Rhythm Association (EHRA) guidelines recommend CRT upgrade in patients with LVEF $< 35\%$, NYHA III&IV, and high percentage of ventricular pacing—although cited evidence stands for de novo CRT implantations and crossover trials, as opposed to revisions from existing devices, with evidence level 'B' and class I indication [9]. The more recent guidelines by the ESC on HF and ESC guidelines on ventricular arrhythmias and sudden cardiac death do not provide any recommendations on CRT revision [2].

With current evidence suggesting a greater procedural risk with CRT revision procedures compared to de novo procedures, it is important to identify those patients that are most likely to benefit from CRT revision and continue to explore which factors best correlate with an improved outcome [12]. The ongoing BUDAPEST-CRT Upgrade Study will evaluate the efficacy and safety of CRT-D upgrade when compared with ICD therapy in patients with previously implanted PPM or ICD, reduced LVEF $\leq 35\%$, symptomatic HF (NYHA II–IV), and intermittent or permanent RV pacing with wide-paced QRS ≥ 150 ms [20].

4.1. Limitations

This was a single centre retrospective analysis of all patients undergoing CRT revision. Regarding patient selection, only patients meeting pathway criteria following the development of worsening

HF symptoms after bradycardia/ICD pacing therapy were included, which may have resulted in a certain proportion not referred for consideration of a revision. The site of LV lead placement (apical vs. basal) and the specific optimisation of medical therapy post-implant were not recorded, although medical therapy overall was good pre-procedure and patients routinely followed up post-procedure. LVEF assessed with echocardiography can have high inter- and intra-operator variability, however we aimed to minimise this by ensuring all echocardiographers were fully accredited.

5. Conclusions

Device revision to CRT in patients with RV pacing induced HF demonstrated a significant improvement in LVEF, with the greatest improvement observed in patients who had a higher percentage of RV pacing at baseline, a non-ischaemic aetiology of HF and were in sinus rhythm.

Funding

No funding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are grateful to the cardiac physiologists and heart failure nurses at University Hospital Wales for their help and support with this research.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2021.100746>.

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