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A randomized pilot study of optimization of cardiac resynchronization therapy in sinus rhythm patients using a peak endocardial acceleration sensor vs. standard methods

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Aims Non-response rate to cardiac resynchronization therapy (CRT) might be decreased by optimizing device programming. The Clinical Evaluation on Advanced Resynchronization (CLEAR) study aimed to assess the effects of CRT with automatically optimized atrioventricular (AV) and interventricular (VV) delays, based on a Peak Endocardial Acceleration (PEA) signal system.

Methods and results This multicentre, single-blind study randomized patients in a 1 : 1 ratio to CRT optimized either automatically by the PEA-based system, or according to centres' usual practices, mostly by echocardiography. Patients had heart failure (HF) New York Heart Association (NYHA) functional class III/IV, left ventricular ejection fraction (LVEF) $<35\%$, QRS duration >150 or >120 ms with mechanical dyssynchrony. Follow-up was 1 year. The primary endpoint was the proportion of patients who improved their condition at 1 year, based on a composite of all-cause death, HF hospitalizations, NYHA class, and quality of life. In all, 268 patients in sinus rhythm (63% men; mean age: 73.1 ± 9.9 years; mean NYHA: 3.0 ± 0.3; mean LVEF: $27.1 \pm 8.1\%$; and mean QRS duration: 160.1 ± 22.0 ms) were included and 238 patients were randomized, 123 to PEA and 115 to the control group. At 1 year, 76% of patients assigned to PEA were classified as improved, vs. 62% in the control group ($P = 0.0285$). The percentage of patients with improved NYHA class was significantly ($P = 0.0020$) higher in the PEA group than in controls. Fatal and non-fatal adverse events were evenly distributed between the groups.

Conclusion PEA-based optimization of CRT in HF patients significantly increased the proportion of patients who improved with therapy, mainly through improved NYHA class, after 1 year of follow-up.

Keywords Heart failure • Cardiac resynchronization therapy • Cardiac dyssynchrony • Peak endocardial acceleration • Atrioventricular delay

Introduction

In large-scale utilization of cardiac resynchronization therapy (CRT), non-responder rates of 30–40% have been observed.[1–5] Various studies have shown that significant improvements in haemodynamic function can be obtained by optimizing device programming, particularly the stimulation rate, paced and sensed atrioventricular (AV) delays, and the interventricular (VV) delay.[6–10] Common methods for AV delay (AVD) optimization are filling time without truncation of A-wave, Ritter's formula, or aortic and mitral velocity-time integral. For VV delay optimization, common methods are Tissue Doppler imaging, aortic velocity-time integral, or QRS duration.

Optimal AV and VV intervals may change over time as cardiac remodelling evolves after CRT. The optimization of CRT systems,

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usually based on ultrasound imaging,[11–13] is time-consuming, and the number of patients in need of multiple optimization procedures to prevent or minimize left ventricular (LV) remodelling is growing rapidly.[14] In the majority of medical centres, devices are optimized only when the patient does not respond, or when the response to therapy is sub-optimal. Algorithms incorporated into CRT systems might improve the reliability and regularity of time interval optimization. However, to our knowledge, no study has shown that optimizing the AV and VV intervals with a method based on haemodynamic measurements at each follow-up improves rates of long-term response to therapy. Attempts based on measurements of systolic time intervals recently failed to demonstrate long-term benefits of CRT optimization.[15,16]

An alternative approach is the use of a haemodynamic sensor to optimize AV and VV intervals. Several studies have confirmed the correlation between Peak Endocardial Acceleration (PEA) amplitude and LV$dP/dt_{max}$, a measure of the contractile function of the heart.[17,18] The Clinical Evaluation on Advanced Resynchronization (CLEAR) study was a pilot study designed to examine the clinical long-term outcomes in recipients of a CRT pacemaker capable of measuring PEA, enabling the optimization of AV and VV intervals.

Methods

Patient population and study design

This prospective, multicentre, single-blind, parallel-design clinical study randomly assigned patients to one of two groups: a PEA group, in which the optimal AVD was automatically set at weekly intervals and VV delay was optimized at the time of each clinic visit, or a control group, in which CRT devices were empirically programmed, according to centres' standard methods. Patients were enrolled consecutively between November 2005 and February 2008.

The study protocol was reviewed and approved by the national regulatory authorities of the eight participating countries, and by the ethics committees of the 51 enrolling medical centres. All patients provided written informed consent to participate in the study.

Patients were eligible for inclusion in the study if they had heart failure (HF), New York Heart Association (NYHA) functional class III or IV despite stable, optimal medical management for $\geq$1 month before entry into the study, left ventricular ejection fraction (LVEF) $<$35%, LV end-diastolic diameter index $\geq$30 mm/m^2, QRS duration either $>$150 or $>$120 ms, and associated with apparent ventricular mechanical dyssynchrony manifest by $\geq$2 echocardiographic abnormalities: aortic pre-ejection interval $>$140 ms, inter-ventricular interval $>$40 ms, and delayed activation of postero-lateral LV wall (after mitral valve opening).

Patients were excluded from the study if they were candidates for the implantation of a cardioverter defibrillator (ICD), presented with any history of atrial fibrillation, had experienced a myocardial infarction within the last 3 months, had undergone or were scheduled to undergo cardiac surgery or a coronary revascularization procedure within 3 months, or were listed for a cardiac transplantation.

Peak endocardial acceleration-based optimization method

The PEA sensor (SonR®, Sorin CRM SAS, Clamart, France) is a haemodynamic sensor embedded in the tip of the right ventricular (RV) lead. The first PEA signal, recorded during the isovolumetric contraction phase of the cardiac cycle, has been demonstrated to correlate with LV contractility, expressed as LV dP/dt_{max}, and modulated by the degree of LV filling and AVD.[19–23]

The PEA optimization algorithm comprises two successive steps (*Figure 1*). First, the optimal ventricular pacing configuration is determined (*Figure 1A*). Peak endocardial acceleration amplitude is measured when the AVD is scanned over a large range of values for each configuration: RL48 (VV interval = 48 ms, RV stimulated first), RL24, RL12, BiV0 (simultaneous V stimulation), LR12 (VV interval = 12 ms, LV stimulated first), LR24, LR48, and LV only. The curve with the highest average PEA value for all scanned AVDs indicates the optimal ventricular pacing configuration (*Figure 1B*).[24]

The second step optimizes AVD (*Figure 1C*). The optimal value is the AVD that corresponds to the point of inflexion of the sigmoid PEA vs. AVD curve obtained with the optimal ventricular pacing configuration. It has been shown that the configurations identified by the PEA method correlate closely with those recommended based on direct measurements of LV dP/dt_{max}.[23]

Study stages

After an initial evaluation, all patients underwent implantation of a CRT pacemaker (NewLiving CHF™, Sorin CRM SAS), connected to an RV lead capable of recording the PEA signal (MiniBest™ or Micro-Best ACT™, Sorin CRM SAS). The choices of right atrial and LV leads were at the investigators' discretion.

Before discharge from the hospital, patients were randomly assigned to the two treatment groups (based on a randomization list generated before the study was initiated). Both groups underwent clinical evaluations (NYHA class) and device interrogations at the following intervals: before discharge from the hospital, and at 1, 3, 6, and 12 months (1 year) of follow-up. At inclusion, at 3 and 6 months, and at 1 year of follow-up, blood was collected for measurements of serum B-type natriuretic peptide (BNP) concentration and quality of life (QOL) was assessed with the European Quality of Life-5 Dimensions (EQ-5D) QOL score questionnaires. The EQ-5D is a self-administered, validated, multi-attribute preference-based measure of QOL.[25] The score is determined using a visual analogue scale, which records the patient's self-rated health on a vertical scale ranging from 'best imaginable' (100) and 'worst imaginable' (0) health status. Echocardiographic data were collected at inclusion and at months 6 and 12. A central core lab (Dr G. Jauvert, Clinique Bizet, Paris, France), blinded to the study population, evaluated all echocardiographic data.

The PEA system was used to optimize VV and AV intervals manually (using the programmer) during clinic visits, while the device automatically optimized AVD on a weekly basis between visits. In the control group, optimization of CRT post-implant and at 3- and 6-month visits was left to the centres' standard procedures.

Study endpoints

The primary study endpoint was the proportion of patients who improved in each group at 1 year, based on a composite of rates of death from any cause, hospitalizations for management of HF, NYHA functional class, and QOL. For this pilot study, the endpoint components were chosen to reflect clinically relevant changes, accounting for both objective (death, hospitalizations) and subjective (NYHA class, QOL) changes in clinical status.

Patients were classified as improved if free from both death from any cause and hospitalization for management of HF, in addition to NYHA functional class decreased by $\geq$1 point or QOL score increased by $\geq$10%. Patients worsened if they died or were

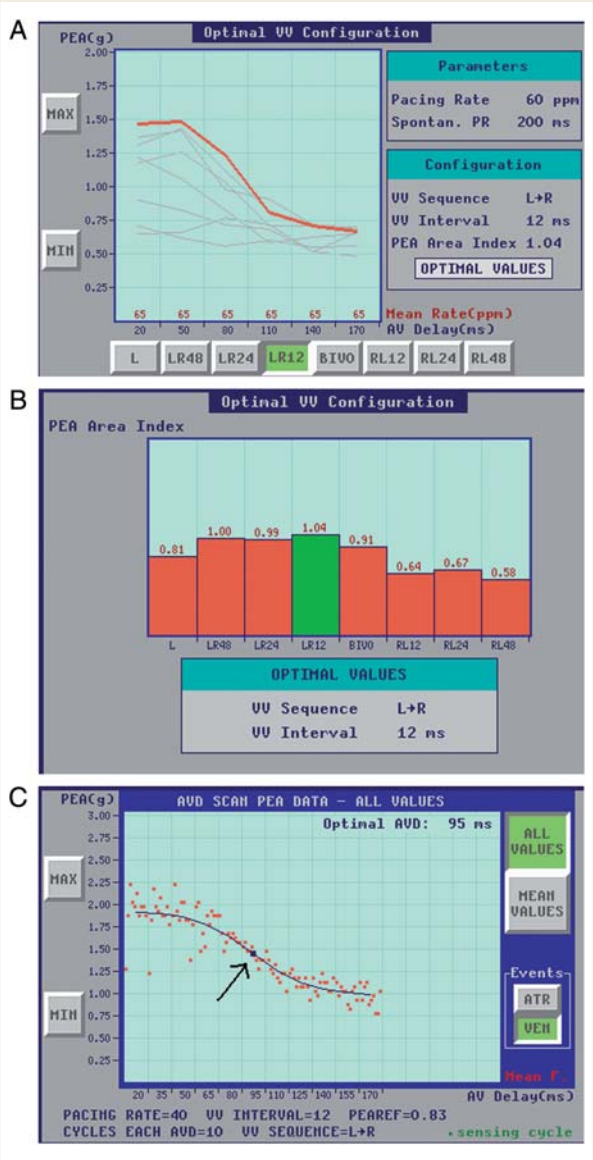

Figure 1 Peak endocardial acceleration algorithm. (*A*) Interventricular delay optimization with the peak endocardial acceleration algorithm (step 1). Peak endocardial acceleration amplitude ('PEA (g)'—*Y*-axis) is plotted against scanned atrioventricular delays ('AV Delays (ms)'—*X*-axis) for each interventricular configuration. (*B*) Interventricular delay optimization with the peak endocardial acceleration algorithm (step 2). The curve with the highest PEA amplitudes for all scanned atrioventricular delays ('PEA area index' – *Y*-axis) indicates the optimal ventricular pacing configuration (*X*-axis). (*C*) Atrioventricular delay optimization with the peak endocardial acceleration algorithm. Peak endocardial acceleration amplitude ('PEA (g)'—*Y*-axis) is plotted against scanned atrioventricular delays ('AV Delays (ms)'—*X*-axis) for the optimal interventricular configuration. The optimal atrioventricular delay value is that corresponding to the inflexion point of the sigmoid peak endocardial acceleration vs. atrioventricular delay curve.

hospitalized for management of HF, if NYHA functional class increased by ≥1 point, or if QOL score decreased by ≥10%. Patients were defined as unchanged if they neither improved nor worsened.

The secondary endpoints were the combination of death from any cause and hospitalization for management of HF, changes in NYHA functional class, QOL score, serum BNP concentration, QRS duration, LVEF, and LV end-systolic diameter.

All adverse events and protocol deviations were reviewed by an expert Steering Committee, whose members were unaware of patients' regions of residence or study assignments.

Data analysis and statistics

Data analysis and statistics were performed in the biometry department of the sponsor. The required sample size was based on the primary endpoint of the study. The primary hypothesis was a significantly higher percentage of improved patients when CRT was optimized by PEA compared with usual care. The results of the MIRACLE trial[1] were used to calculate the sample size needed for a two-sided analysis, 80% power, and 95% level of significance, assuming 83% response rate in the PEA group and 67% in the control group.

Case Report Forms and electronic data were centrally collected and checked for consistency and completeness. Inconsistent or incomplete data were clarified by the study centre by a query process. The statistical analysis was performed on the locked database.

All endpoints were analysed on the intention-to-treat (ITT) principle; patients who did not receive any CRT optimization were analysed according to their original treatment assignment.

Qualitative variables are expressed as percentage and number. Continuous variables are expressed as mean ± SD or median. For the composite endpoint calculations, a 'last observation carried forward'' method was applied, using the last known values of NYHA functional class and QOL score.

Between-group comparisons of qualitative outcomes were performed using the χ^2 or Fisher's exact tests. For continuous variables with normal distribution, comparisons of changes between groups from baseline to last follow-up were analysed using Student's *t*-test. For other continuous variables, a non-parametric Kruskall–Wallis test was applied. Only patients with available data at both enrolment and 1-year follow-up were included in endpoint analyses. Analyses of changes for variables were made using paired tests: if the variables followed a normal distribution, a paired *t*-test was used; otherwise, a sign paired test was applied. Cumulative survival curves for the risk of all-cause death and the risk of all-cause death and HF-related hospitalizations up to 366 days were constructed according to the Kaplan–Meier method, and differences between groups were analysed using the log-rank test.

A safety analysis was performed, including all enrolled patients, using the same statistical methodology as those used for the efficacy outcomes. All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA) at a 0.05 level of significance (two-sided test).

Results

Study population

A total of 268 patients in sinus rhythm were enrolled in the study (*Figure 2*). Thirty patients could not be randomized due to CRT implant failures ($n = 23$) and early study withdrawals ($n = 7$) including consent withdrawal in three patients, non-compliance with inclusion criteria in three patients (ICD implantation, life expectancy <3 months and unstable drug regimen), and pneumothorax in one patient. Thus, 238 patients were randomized: 123 were assigned to the PEA and 115 to the control group. Following

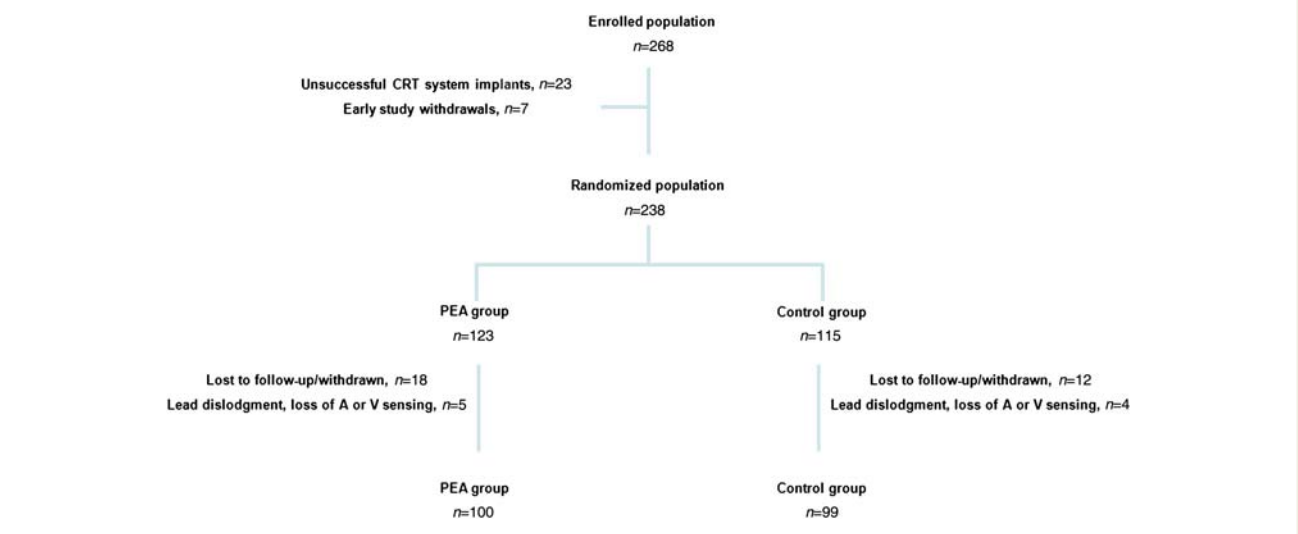

Figure 2 Population flowchart.

randomization, 30 patients were lost to follow-up or withdrawn from the study for non-medical reasons, and 9 patients presented with either lead dislodgments or loss of sensing. These drop-outs were equally distributed between both groups (*Figure 2*). The study endpoint analysis included 199 patients, 100 in the PEA group and 99 in the control group. Baseline characteristics of the 268 and 199 patients are shown in *Table 1*. There were no statistical differences in baseline characteristics between the two study groups, nor between the two overall included and analyzed populations.

The mean follow-up time in the ITT population was 359 $\pm$ 82 days (median 371; interquartile range 356–393 days). The median percentages of atrial and ventricular pacing were 9.1 and 97.9%, respectively.

Cardiac resynchronization therapy optimization

In the control group, CRT was optimized consistently (post-implant and at 3- and 6-month visits) in only 9% of patients, twice during the study in 15%, once in 21%, and never in 55%. The most common methods for AVD optimization were: longest filling time without truncation of A-wave in 64% of patients, Ritter's formula in 17%, and miscellaneous methods (aortic and mitral velocity-time integral, *Z* ratio, MPI, empiric) in 19%. For VV delay optimization, Tissue Doppler imaging was used in 29% of patients, aortic velocity-time integral in 21%, QRS duration in 7%, and various unspecified methods in 43% with no method more frequent than others.

In the PEA group, consistent CRT optimization of both AV and VV delays at follow-up (post-implant and at 3- and 6-month visits) was done in 57% of patients, twice during the study in 14%, once in 17%, and never in 12%. The mean duration of the optimization procedure, including AV and VV delays optimization, was 22.5 $\pm$ 11.1 min. A number of factors interfered with the algorithm and aborted the optimization procedure in 30 patients: frequent atrial or ventricular ectopic activity, noise interference, vigorous physical activity, or other causes of increase in sinus rate, fallback mode switch of the CRT-P, escape interval, AV or VV delays different than expected due to other algorithms, such as safety pacing. Finally, some cases of loss of PEA sensing were encountered, impeding optimization in an additional 13 patients.

The mean optimal VV and AVDs over the follow-up period were -16.3 ± 26.8 ms (LV first) and 98.7 $\pm$ 18.9 ms, respectively, in the PEA group, vs. -9.4 ± 15.8 and 109.1 $\pm$ 18.3 ms in the control group (P = n.s. for VV delays, $P < 0.0001$ for AVDs). In the PEA group, AVDs differed by $\geq$30 ms from those of control group patients for 21 patients at M0, 28 at M3, and 21 at M6. Optimized AVDs were significantly shorter in the PEA group at each follow-up (*Table 2*), but no significant variations over time were observed in either group. A trend towards a decrease in optimized AVDs over time was observed in the PEA group. Interventricular interval delays in the PEA group differed by $\geq$30 ms from those of control group patients for 28 patients at M0, 26 patients at M3, and 24 patients at M6. However, no significant differences were observed in optimal VV intervals between the groups at each follow-up (*Table 2*). A trend towards a decrease in the optimal VV interval over time was observed in the control group.

Primary endpoint

At 1 year, 76% of patients assigned to PEA showed improvement in the composite primary endpoint, vs. 62% in the control group (P = 0.0285; *Table 3*).

Secondary endpoints

There was no significant between-group difference in the percentage of patients free from death from any cause and hospitalization for management of HF (78% in the PEA group and 75% in the control group) (*Table 3*). Of the 199 patients included in the endpoint analysis, there were 21 deaths overall: 9 in the PEA group (5 cardiac, including 1 sudden cardiac death) and 12 in the control group (10 cardiac, including 1 sudden cardiac death). In a

Table 1 Baseline characteristics of the included ($n = 268$) and analysed ($n = 199$) populations

	Included population ($n = 268$)	Analysed population ($n = 199$)	P	PEA group ($n = 100$)	Control group ($n = 99$)	P
Demographics						
Age, years	73.1 ± 9.9	73.4 ± 9.7	NS	72.5 ± 10.2	74.2 ± 9.2	NS
Women, *n* (%)	98 (37%)	73 (37%)	NS	41 (41%)	32 (32%)	NS
Characteristics						
NYHA class	3.0 ± 0.3	3.1 ± 0.3	NS	3.08 ± 0.31	3.04 ± 0.25	NS
QRS duration ms	160.1 ± 22.0	160.9 ± 22.8	NS	162.0 ± 21.0	159.9 ± 24.5	NS
LVEF %	27.1 ± 8.1	26.9 ± 8.2	NS	27.5 ± 8.4	26.3 ± 7.7	NS
QoL EQ-VAS	50.8 ± 18.7	49.5 ± 18.5	NS	47.4 ± 18.4	51.4 ± 18.5	NS
LVEDD, mm	66.2 ± 9.7	66.3 ± 9.9	NS	65.6 ± 8.9	67.9 ± 10.5	NS
LVESD, mm	55.8 ± 10.5	56.1 ± 10.9	NS	54.8 ± 10.1	57.2 ± 11.8	NS
Mitral regurgitation, cm^2	5.7 ± 5.6	5.7 ± 5.2	NS	5.3 ± 5.6	5.5 ± 4.9	NS
Heart failure aetiology, *n* (%)						
Idiopathic	122 (46%)	93 (47%)	NS	45 (45%)	48 (49%)	NS
Ischaemic	105 (39%)	77 (39%)	NS	38 (38%)	39 (39%)	NS
Valvular disease	21 (8%)	16 (8%)	NS	9 (9%)	7 (7%)	NS
Other	21 (8%)	17 (9%)	NS	7 (7%)	10 (10%)	NS
Comorbidities, *n* (%)						
Hypertension	126 (47%)	100 (50%)	NS	45 (45%)	55 (55%)	NS
Diabetes	66 (25%)	49 (25%)	NS	28 (28%)	21 (21%)	NS
Rhythm disorders	69 (26%)	55 (29%)	NS	29 (29%)	26 (26%)	NS
Previous surgery	84 (31%)	59 (30%)	NS	31 (31%)	28 (28%)	NS
Other[a]	75 (28%)	53 (28%)	NS	28 (28%)	25 (25%)	NS
Medications, *n* (%)						
ACE inhibitors	184 (69%)	140 (70%)	NS	67 (67%)	73 (73%)	NS
Beta-blockers	194 (72%)	149 (75%)	NS	74 (74%)	75 (76%)	NS
ACE inhibitors substitutes	31 (12%)	22 (11%)	NS	11 (11%)	11 (11%)	NS
Diuretics	214 (80%)	160 (80%)	NS	81 (81%)	79 (80%)	NS
Spironolactone	122 (46%)	92 (46%)	NS	47 (47%)	45 (45%)	NS
Laboratory data						
BNP	619 ± 730	643.4 ± 768	NS	591.6 ± 747.4	701.2 ± 790	NS

[a]Coronary artery disease and angioplasty, congenital heart disease.

Kaplan–Meier analysis of time to first event (*Figure 3*), the hazard ratio was 0.746 favouring the PEA group, but no significant differences were observed between the groups ($P = 0.0893$). The percentage of patients with improved NYHA class was significantly ($P = 0.0020$) greater in the PEA (83%) group than in controls (64%). There was no significant difference in the proportion of patients with improved QOL scores between groups (70% in the PEA group and 65% in the control group) (*Table 3*).

At last follow-up, mean NYHA class had improved in both groups, QRS duration, LV end-systolic diameter, and serum concentration of BNP were significantly decreased, and LVEF and QOL scores were significantly increased. Except for NYHA class, differences between the groups were not statistically significant. Echocardiographic data could be analysed in only 70–81% of patients, depending on the measured parameter, because of incomplete data or lack of reliable recordings (*Table 3*).

Adverse events

Of the 268 enrolled patients, 23 could not be implanted due to adverse events during the implantation procedure, including a pneumothorax in 1 patient, coronary sinus dissection in 4 patients, and LV lead implant failure in 18 patients.

Of the 238 randomized patients, 8 patients (7 in the control group and 1 in the PEA group) suffered adverse events during the implant procedure: pneumothorax in 1 patient, coronary sinus dissection in 1 patient, lead connection issues in 2 patients, and difficult LV lead placements in 4 patients. All these adverse events were successfully corrected. After implantation, 21 patients required repositioning of the lead (right atrial lead in 6 patients and LV lead in 15 patients), 13 of whom experienced loss of capture, and 7 of whom presented with pacemaker dysfunction, which was corrected by device reprogramming. No adverse event was observed on the RV lead. Finally, seven patients experienced

Table 2 Atrioventricular and interventricular delays in the peak endocardial acceleration-optimized vs. the control group at different time points during the trial

	M0		M3		M6	
	PEA *n* = 100	Control *n* = 99	PEA *n* = 100	Control *n* = 99	PEA *n* = 100	Control *n* = 99
Delay, ms						
VV[a,†]	−21.0 ± 41.0	−7.5 ± 15.9	−12.0 ± 33.1	−10.5 ± 18.3[§]	−13.6 ± 34.4	−10.7 ± 18.4[§]
AV[‡] (sensed)	101.3 ± 23.5	108.1 ± 20.1	100.3 ± 27.2	109.4 ± 21.3	93.7 ± 22.8	109.4 ± 20.0

Values are expressed as means ± SD.
[a]Negative values indicate LV pre-activation; positive values indicate RV pre-activation.
[†]P = NS for difference between study groups over the whole follow up period (analysis of variance).
[‡]$P < 0.0001$ for difference between study groups over the whole follow up period (analysis of variance).
[§]$P < 0.05$ vs. M0; all other multiple comparisons within study groups over time are statistically non-significant (paired sign test).

Table 3 Primary and secondary study endpoints

	Study groups		
	PEA *n* = 100	Control *n* = 99	*P*
Composite criterion,[a] improved, *n* (%)	76 (76%)	61 (62%)	0.0285
Free from deaths from any cause and hospitalizations for heart failure, *n* (%)	78 (78%)	74 (75%)	0.5891
Free from deaths from any cause, *n* (%)	91 (91%)	87 (88%)	0.4737
Free from hospitalizations for heart failure, *n* (%)	82 (82%)	81 (82%)	0.9734
Improved New York Heart Association functional class, *n* (%)	83 (83%)	63 (64%)	0.0020
New York Heart Association functional class (*n*)			
Baseline	3.1 ± 0.3 (*n* = 100)	3.0 ± 0.3 (*n* = 97)	0.0193
Last follow-up	2.1 ± 0.7 (*n* = 100)	2.3 ± 0.8 (*n* = 97)	
Improved Quality of life, *n* (%)	70 (70%)	64 (65%)	0.4200
Quality-of-life score (*n*)			
Baseline	47.4 ± 18.4 (*n* = 85)	51.4 ± 18.5 (*n* = 89)	0.7807
Last follow-up	64.5 ± 19.7 (*n* = 85)	65.0 ± 17.6 (*n* = 89)	
B-type natriuretic peptide, pg/mL (*n*)			
Baseline	566.6 ± 711.6 (*n* = 89)	693.2 ± 799.5 (*n* = 79)	0.5045
Last follow-up	477.7 ± 721.4 (*n* = 89)	436.7 ± 552.8 (*n* = 79)	
QRS duration, ms (*n*)			
Baseline	164.8 ± 18.3 (*n* = 86)	165.2 ± 19.6 (*n* = 82)	0.5475
Last follow-up	143.1 ± 29.4 (*n* = 86)	142.2 ± 13.5 (*n* = 82)	
Left ventricular ejection fraction, % (*n*)			
Baseline	27.9 ± 7.9 (*n* = 78)	26.3 ± 7.7 (*n* = 82)	0.8482
Last follow-up	37.7 ± 14.2 (*n* = 78)	36.2 ± 13.8 (*n* = 82)	
Left ventricular end-systolic diameter, mm (*n*)			
Baseline	54.8 ± 10.1 (*n* = 78)	57.2 ± 11.8 (*n* = 78)	0.2138
Last follow-up	48.9 ± 13.0 (*n* = 78)	48.9 ± 14.1 (*n* = 78)	

Values are expressed in % (numbers) or mean ± SD.
[a]Composite of observations including deaths from any cause and HF related hospitalizations, NYHA class, and QOL.

diaphragmatic stimulation, corrected by reprogramming of the pacing width and amplitude.

Except for the rate of implant–procedure adverse events, the rates and types of all other device-related adverse events were similar and evenly distributed between both treatment groups (*Table 4*). The frequency of adverse events unrelated to the device did not differ significantly between the two treatment groups.

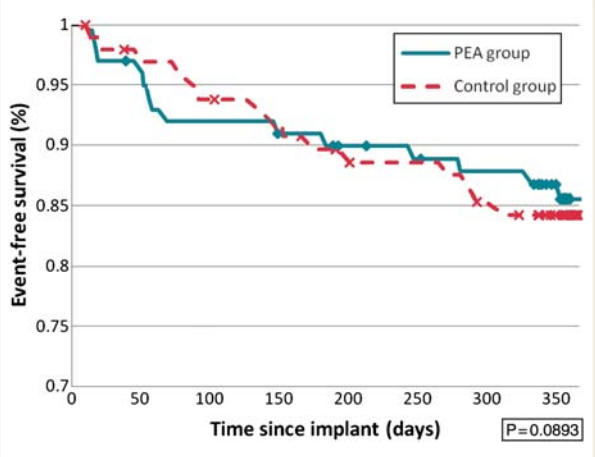

Figure 3 Kaplan–Meier survival curves for time to all cause death and worsening heart failure in the peak endocardial acceleration and control groups.

Table 4 Adverse events observed in the overall population and in each study group

Adverse events	All patients	Study groups	
		PEA	Control
	n = 268	*n* = 123	*n* = 115
Medical			
Cardiovascular	93 (47)	47 (26)	45 (20)
Non-fatal	75 (29)	40 (19)	34 (9)
Fatal	18 (18[a])	7 (7[b])	11 (11[c])
Non-cardiovascular deaths	6 (6)	4 (4)	2 (2)
Pulmonary	24 (19)	11 (9)	12 (9)
Miscellaneous	78 (42)	37 (20)	37 (18)
All medical	219 (127)	106 (65)	107 (56)
Technical			
Implant procedure	27 (27)	3 (1)	7 (7)*
Lead dislodgment	22 (21)	14 (13)	8 (8)
Right atrial lead	6 (6)	4 (4)	2 (2)
Left ventricular lead	16 (15)	10 (9)	6 (6)
Loss of capture	15 (13)	7 (5)	8 (8)
Programmer dysfunction	9 (7)	8 (6)	1 (1)
Diaphragmatic/phrenic stimulation	14 (8)	8 (4)	5 (3)
All technical	87 (76)	38 (30)	29 (27)
All adverse events	306 (171)	144 (79)	136 (67)

Values are expressed as numbers of events (patients).
[a]Two sudden cardiac deaths.
[b]One sudden cardiac death.
[c]One sudden cardiac death.
*$P = 0.031$; all other between-study groups differences are statistically non-significant.

Discussion

Main findings of the CLEAR trial

This pilot study showed that a significantly greater proportion of patients who received a CRT improved their condition over a 1-year follow-up period when the PEA system was used to adapt AVD weekly and VV interval at each follow-up visit compared with standard medical practice.

CLEAR in context

Two recent randomized trials failed to demonstrate the benefit of CRT optimization with automatic algorithms for AV and VV intervals optimization, both based on the measurement of systolic time intervals. FREEDOM[15] included 1647 patients and the primary endpoint was Packer's clinical composite score. Secondary endpoints were all-cause cardiovascular and HF mortality, and hospitalizations. SMART-AV[16] included 980 patients and the primary endpoint was change in LV end-systolic volume at 6 months. Secondary endpoints were NYHA class, QOL score, and 6 min walking distance. In both studies, neither primary nor secondary endpoints were reached. Both studies were much larger and had different endpoints from those in CLEAR. For an informed discussion about the differences in outcomes, it would be necessary to conduct a larger trial in PEA optimization than the current pilot study, along with a greater range of endpoints.

Representativeness of the CLEAR trial population

Rates of non-response to CRT have remained ~30% over the years since the therapy was introduced.[1–5] The question of what constitutes 'response' to CRT is contested and single measures are unlikely to be reliable predictors of the outcome of CRT in the complex syndrome of HF.[26] Composite clinical endpoints must reflect the relative importance of response and outcome benefits, as judged by patients no less than by doctors. CLEAR used a mixture of 'hard' and 'soft' endpoints, but a range of other outcomes may have been equally valid.

In our study, the percentage of patients who remained unchanged or worsened in the control group was even higher than usual (30%). The patients were representative of CRT recipients at the time the study was conducted, according to contemporary guidelines.[27] The average severity of HF was similar to that of populations enrolled in large published clinical trials. However, the CLEAR population was older than those in the landmark trials, reflecting the mean age of recipients of CRT-Pacemaker (CRT-P) devices. At the time of conducting CLEAR, the PEA sensor was integrated in the RV lead and only available for CRT-P devices. The manufacturer has since modified and integrated the sensor into the AV lead for use in cardiac resynchronization therapy defibrillator (CRT-D) devices. The current preference for ICD or CRT-D in patients presenting with ischaemic heart disease probably also explains the lower proportion of ischaemic cardiomyopathy in this study (39%) than in more recent clinical trials on CRT. However, the proportion of ischaemic patients was not statistically different between groups.

Cardiac resynchronization therapy optimization

Mean AVDs in the PEA group were significantly shorter (100 ms in sensed configuration) than the conventional nominal setting available in current devices (120 ms in sensed configuration). Moreover, a trend towards a decrease in optimal AVDs was observed in the PEA group over time, along with a trend towards an increased proportion of RV pre-activated patients. These results are in accordance with previous observations[12] of shorter AVDs required during RV pre-activation than LV pre-activation, suggesting a need to optimize AVDs in different ventricular configurations. Finally, large variability in optimized AV and VV delays were observed, individually and over time. All these results suggest the need for individual and periodic device optimization.

The low rates of optimization in the control group (9%) indicate a lost opportunity and it is impossible to speculate on how far clinical outcomes can be improved by optimizing CRT using conventional means. The low rates in CLEAR are not exceptional: Gras *et al.* reported from a world-wide survey that only around 40% of physicians optimized CRT in any way at implant and only 9% systematically optimized both the AV and VV delays.[28] Common methods for AV-optimization of CRT rely on echocardiography, which puts substantial demands on healthcare staff in terms of time and expertise.

In light of these numbers, automated optimization might have significant potential to increase rates of CRT optimization in conditions of actual care. However, in CLEAR a number of factors interfered with the PEA algorithm and impeded optimization in the PEA group. This points to a need for improvements to the technology before wider implementation. As this pilot study met its primary end point despite these limitations, there seems to be scope for further benefits from a more refined automated optimization. Because the PEA algorithm requires a dedicated lead, concerns about the long-term safety of complex leads need to be addressed appropriately. This will require data from longer time periods than the follow-up time in CLEAR.

Clinical and echocardiography outcomes

In the CLEAR study, the only variable where significantly greater improvements with PEA optimization were observed was NYHA class. In both study groups, CRT led to shorter QRS duration and improvements in LV end-systolic diameter and LVEF, but there were no statistical differences between the groups. The equivalent degree of LV reverse remodelling in both study groups may be explained by the unavailability of some echo data that reduced the power of the statistical test. There was no effect on QOL. Moreover, other variables that were not captured, such as peak oxygen uptake, would be important to study in further trials.

However, from the present results, CRT optimization based on a haemodynamic assessment may have a greater beneficial impact on patient's outcomes than optimization based on the measurement of systolic time intervals.

Study limitations

It is important to recognize the limitations of this pilot study. The lack of a blinded assessment of NYHA functional class was a limitation and the positive effect of PEA optimization on the study primary endpoint was mainly driven by changes in NYHA class. Further investigations will be necessary to confirm the outcomes. Several common endpoints such as exercise capacity were not included in the analysis. Occurrences of atrial fibrillation were not monitored during follow-up and we do not know to what degree such incidences may have reduced the efficiency of PEA optimization.

The unavailability of some echocardiographic data may have reduced the statistical power of the secondary endpoints analysis. Moreover, a number of factors interfered with the PEA algorithm and impeded AV and or VV delay optimization in the PEA group.

Conclusion

The optimization of CRT by an automated PEA-based method in sinus-rhythm patients significantly improved clinical outcomes from CRT-P after 1 year of follow-up, mainly driven by improvements in NYHA class. These encouraging observations warrant further studies of the PEA sensor on a larger scale, using CRT-D devices to comply with current international treatment guidelines.

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Appendices

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