ORIGINAL ARTICLE

Long-term Non-invasive Hemodynamic Evaluation of Left Endocardial Cardiac Resynchronization Therapy

Evaluación hemodinamica no invasiva a largo plazo de la terapia de resincronización cardiaca endocárdica izquierda

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ABSTRACT

Background: Cardiac resynchronization therapy has 25% to 30% rate of "non-responder" patients. Endocardial cardiac resynchronization therapy (eCRT), in which the left ventricular catheter is implanted in the endocardium, would be an alternative for these patients; however, its long-term outcome has not been investigated.
Objectives: The aim of this study was the long-term non-invasive hemodynamic evaluation of eCRT in clinical responders.
Methods: Patients implanted according to the criteria for resynchronization, using the Jurdham technique, with more than 6 months after the implant, were included in the study. All were clinical responders. The hemodynamic response was evaluated with a cardiac function analyzer, which measures the left ventricular systolic intervals (preejection and ejection periods) and automatically calculates an index of systolic function and estimates the ejection fraction (Systocor mod ÍS100). To assess the mechanical efficacy of eCRT, the cardiac function during biventricular mode was compared with left bundle branch block (LBBB), either spontaneous or by single stimulation of the right ventricle, with patients as their own controls. At least 20 beats were averaged in each stimulation mode and only changes >1% with p <0.01 were considered as clinically relevant and statistically significant.
Results: Seventeen patients were included, with a median follow-up of 43 months, (9 to 78 months). Endocardial resynchronization, compared with LBBB ventricular activation, showed that all patients shortened the preejection period by an average of 31 ms (15%), indicative of decreased interventricular dyssynchrony caused by LBBB. In all patients, systolic function index increased by 0.3 (23%) and the EF by 8.3%. In 12/17 of cases (71%) the ejective period increased on average 8.7 ms (2.9%), suggesting an increase in systolic volume. In all changes p was < 0.01.
Conclusions: Endocardial resynchronization therapy offers significant long-term hemodynamic improvement, detected by systolic intervals.

Keywords: Cardiac resynchronization therapy - Cardiac resynchronization therapy devices - Heart failure/ treatment

RESUMEN

Introducción: La terapia de resincronización cardíaca presenta una tasa de un 25%-30% de pacientes "no respondedores". La resincronización endocárdica, en la que el catéter del ventrículo izquierdo se implanta en el endocardio, sería una alternativa para estos pacientes aunque su evolución a largo plazo no ha sido investigada.
Objetivos: Evaluación hemodinámica no invasiva a largo plazo de la resincronización endocárdica en respondedores clínicos.
Material y métodos: Se incluyeron pacientes implantados según los criterios para resincronización, usando la técnica Jurdham, con más de 6 meses desde el implante. Todos eran respondedores clínicos.
La respuesta hemodinámica se evaluó con un analizador de la función cardíaca, que mide los intervalos sistólicos (períodos preeyectivo y eyectivo) del ventrículo izquierdo y calcula automáticamente un índice de función sistólica y estimar la fracción de eyección (Systocor mod ÍS100). Para determinar la eficacia mecánica de la TRCe se comparó la función cardíaca durante el modo biventricular con el bloqueo completo de la rama izquierda, espontáneo o por estimulación única del ventrículo derecho; los pacientes fueron sus propios controles. Se promediaron al menos 20 latidos en cada modo de estimulación y se consideraron solo los cambios >1% con valor p < 0,01 como clínicamente relevantes y estadísticamente significativos.
Resultados: Se incluyeron 17 pacientes, con mediana de seguimiento de 43 meses, rango 9 a 78 meses. La resincronización endocárdica, en comparación con la activación ventricular con BCRI, demostró que todos los pacientes acortaron el período preeyectivo en un promedio de 31 ms (15%), indicativo de disminución de la disincronía interventricular causada por el BCRI. En todos aumentó el índice de función sistólica en 0,3 (23%) y la EF en el 8,3%. En 12/17 (71%) aumentó el período eyectivo en promedio 8,7 mseg (2,9%), lo que sugiere un aumento del volumen sistólico. En todos los cambios el valor de p fue menor de 0,01.
Conclusiones: La TRCe ofrece mejoría hemodinámica significativa a largo plazo, detectada por intervalos sistólicos.

Palabras Claves: Terapia de resincronización cardíaca - Dispositivos de terapia de resincronización cardíaca - Insuficiencia cardíaca/ tratamiento

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Abbreviations

AV	Atrioventricular	**LV**	Left Ventricle
CRT	Cardiac Resynchronization Therapy	**MLHFQ**	Minnesota Living with Heart Failure Questionnaire
eCRT	Endocardial Cardiac Resynchronization Therapy	**NYHA**	New York Heart Association
EF	Ejection fraction	**PEP**	Pre-ejection period
FC	Functional class	**SFI**	Systolic Function Index
INR	International Normalized Ratio	**RV**	Right ventricle
LBBB	Left Bundle Branch Block	**VV**	Left ventricle - Right ventricle
LVEF	Left ventricular ejection fraction		

INTRODUCTION

Cardiac resynchronization therapy (CRT) is well established and provides excellent results in patients with end-stage heart failure and ventricular dyssynchrony, especially caused by left bundle branch block (LBBB). However, despite the important technological progress and the vast experience of the operators, the rate of "non-responders" is 25% -30%". The causes of these failures are mostly related to the impossibility of implanting the left ventricular catheter in an optimal area, through tributary veins of the coronary venous sinus, either by a difficult venous anatomy, the presence of fibrous tissue in the implant area, a high capture threshold, phrenic nerve stimulation or poor catheter anchorage leading to intraprocedural or postprocedural displacement. In endocardial CRT (eCRT), using the Jurdham procedure, (1, 2) the left ventricular (LV) catheter is implanted directly into the endocardium through an atrial trans-septal puncture, avoiding dependence on the coronary venous system anatomy and allowing the choice of an ideal area, with a good threshold and without phrenic stimulation. Thus, it is a valuable option, and is the last therapeutic alternative of these patients before heart transplantation (Figure 1).

Hemodynamic assessment

Since clinical improvement based on functional class and quality of life questionnaires are subjective and electrocardiographic changes are not defining, there is need to hemodynamically assess the response to eCRT. This would allow identifying true from false responders or non-responders, although it is essential to have an objective, accurate and operator-independent assessment of ventricular function.

Echocardiographic measurement of cardiac volumes and ejection fraction (EF) is routinely performed in numerous centers and has in fact become the "gold standard" for their evaluation. Ejection fraction, together with functional class (FC) and left bundle branch block (LBBB) are critical parameters to determine the indication of resynchronization therapy. The optimal cut-off point of EF has been set at 35%, which separates very well the group of patients who will eventually respond to eCRT from those who will not. However, this is not the case for the individual patient, since echocardiography presents certain errors that limit its use when high precision and accuracy are needed. One of the main drawbacks lies in the variability of the results, with 8% precision in EF assessment, according to the consensus of the American Society of Echocardiography. (3) A change equal to or greater than this error overlaps with the variations usually obtained as an effect of eCRT. In addition, there are periodic EF fluctuations associated with the adrenergic tone and changes in preload due to respiration, so EF assessment requires the average of numerous beats. Therefore, we consider that other non-invasive methods that meet sensitivity, specificity, precision and accuracy requirements, while being independent of the operator could achieve an accurate hemodynamic assessment of eCRT outcome in the in-

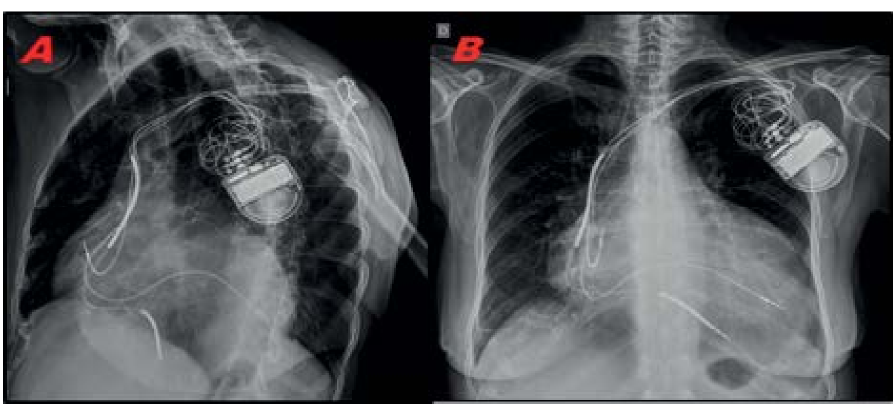

Fig. 1. Radiological images of endocardial cardiac resynchronization therapy with Jurdham technique. A. Left anterior oblique projection. B. Posteroanterior projection. Arrows indicate the location of the left ventricular catheter.

dividual patient. One of the most important non-invasive methods is the measurement of systolic intervals, which have been repeatedly validated for a decade (4, 5) and currently, thanks to digital technology, allow non-invasive, precise and automatic assessments, without operator influence and averaging an unlimited number of beats. Systolic intervals include the preejection period (PEP), the left ventricular ejection period (LVEP) and the PEP/LVEP ratio, known as the Weissler index. The PEP consists of the electromechanical delay (activation time) and the LV isovolumic contraction phase, strongly linked to ventricular contractility and interventricular delay, as in the case of the LBBB. (6) The LVEP is a marker of systolic output and, therefore, strongly modulated by heart rate (HR) and preload. An increase in cardiac work as a result of an increase in metabolic demand shortens PEP and lengthens LVEP, decreasing the PEP/LVEP ratio. This ratio proved to be highly correlated with EF, estimated by contrast x-ray biplane cine ventriculography, an invasive method still considered the "gold standard". In the original work of Garrard Weissler and Dodge, (6) volume was calculated using the method of Dodge et al. (7)

Based on the above, we consider that systolic intervals meet the necessary requirements for hemodynamic assessment of patients with eCRT using different modes of stimulation, especially when patients are used as their own controls.

The aim of this study was thus long-term non-invasive hemodynamic evaluation of eCRT, using systolic intervals in clinical responders.

METHODS

Fifteen patients with eCRT indication according to current resynchronization criteria: functional class (CF) ≥II according to the New York Heart Association (NYHA), (3) LBBB with QRS >130 ms, and LVEF ≤35% were included in the study. The Jurdham technique was used (1, 2) to implant the catheter in the left endocardium, which consists of placing the active fixation catheter in the LV endocardium at the location suggested as ideal according to the majority consensus, which is the posterolateral wall, in its mid or basal portion. The procedure is performed by atrial transeptal approach through femoral venous access.

Clinical responders were those who within 6 months post-implant had improved at least one NYHA FC, presented quality of life improvement according to the Minnesota Living with Heart Failure Questionnaire (MLHFQ) test (8-10) performed before implantation and after 6 months of follow-up, and had survived with no hospitalizations for heart failure during follow-up.

The hemodynamic response was evaluated non-invasively with a cardiac function analyzer (Systocor IS100 model (Exxer IE, Buenos Aires), that uses a finger plethysmographic pulse curve recording, a II-lead (II-L) or similar surface electrocardiogram and the second heart noise recording by phonocardiography. The software measures systolic intervals (PEP and LVEP) and from these it automatically calculates the systolic function index (SFI), which corresponds to a modification of the Weissler index, consisting of the cLVEP/cPEP ratio, where cLVEP is LVEP corrected for heart rate of 60 bpm and cPEP is PEP corrected by substraction of the peripheral pulse transmission time (Figure 2).

Using a modification of the EF prediction equation previously published by Garrad, Weisler and Dodge, (6) the device allows estimating the EF. The technical details of the procedure, the software used in our evaluation and the validation of the method have been published elsewhere (Figure 3). (11-14)

The hemodynamic assessment was based on the comparison of measurements made with simultaneous biventricular stimulation (V-V=0 ms) versus LBBB, either spontaneously or, in patients with atrioventricular (AV) conduction disorders, by single right ventricular (RV) stimulation. A minimum of 20 beats were measured for each stimulation or sensing mode. Each patient was compared with himself in different modes of stimulation and the differences >1% between modes with p <0.01 were considered clinically acceptable and statistically significant. The AV interval was adjusted for each mode of stimulation so that the ventricular contraction did not overlap with atrial transport function. (15) For example, for RV stimulation the AV interval should be shortened, with the RV spike at the end of the P wave, to compensate for the interventricular delay caused by RV pacing. (16, 17) In biventricular stimulation, as there is no interventricular delay, the spikes should be emitted approximately 50 ms after the end of the P wave, in order not to

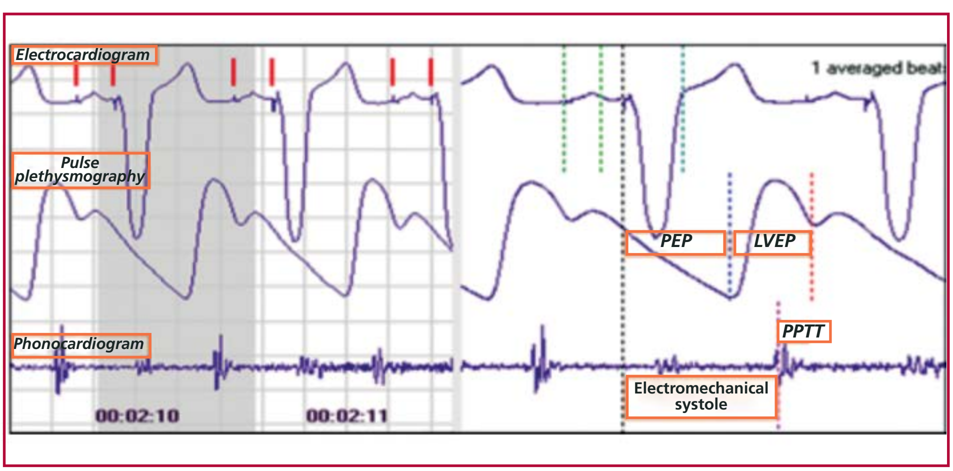

Fig. 2. Non-invasive hemodynamic measurement of systolic intervals with Systocor. The electromechanical systole extends from the ventricular stimulus to the fast aortic component of the second noise. PEP: Preejection period. LVEP: Left ventricular ejection period. PPTT: Peripheral pulse transmission time.

interrupt atrial transport. If the P wave was sensed, the AV programming had to take into account the sensing time of P. Only intrinsic antegrade conduction was allowed if the PR interval was within the normal range.

Ethical considerations

The study was evaluated and approved by the institutional Ethics Committee. An informed consent, authorized by a relative or person responsible was requested for each patient included in the study.

RESULTS

Fifteen patients, 12 men and 3 women, with mean age of 60±9 years and a median follow-up of 43 months (9-78) were included in the study. The etiology of heart disease was 40% idiopathic, 47% ischemic necrotic and 13% chagasic. The eCRT indication was due to implant failure with conventional technique in 4/15 patients (29%), to prior anticoagulation in 9/15 (57%) and to patient's choice in 2/17 (14%). Median preimplant FC was 3 and postimplant 1, and the MLHFQ improved in 100% of patients with an average difference of 73 points between the preimplant and the 6-month follow-up questionnaire (p<0.01). Survival was free of hospitalizations due to heart failure. All patients started anticoagulation with dicumarinic agents 72 hours after implantation, maintaining an international normalized ratio (INR) between 2 and 3. The average echocardiographic EF before implantation was 23%±5 and after implantation 33%±8 (p <0.001). The complete demographic data is detailed in Table 1.

Biventricular eCRT compared with LBBB ventricular activation, either by the patient's own rhythm or by single RV stimulation, showed that all patients shortened their PEP, with an average shortening of –31.5 ms (14.9 %, p<0.001), increased the SFI by 0.34 (23%, p<0.001) and the SFI-estimated EF by 8.3% (p<0.001). Eleven out of 17 patients (65%) increased the LVEP by more than 1%, with an average difference of 8.7 ms (2.9%, p=0.005).

The systolic function index increased by 0.3 (23%) and the EF by 8.3% in all patients. In 12/17 (71%), the ejection period increased on average 8.7 ms (2.9%), suggesting an increase in systolic volume. In all changes the p value was <0.01.

Table 2 summarizes the measurements of systolic intervals, SFI and EF of the 15 patients.

DISCUSSION

In this study we have shown that all patients with eCRT who showed clinical improvement also had objective hemodynamic progress, that is, they were true responders. Cardiac resynchronization therapy with the LV catheter inserted through the coronary sinus is universally accepted, but only recently it was suggested that placement of the left catheter in the LV endocardium via a retrograde approach would facilitate a more precise electrode site, although it entails the inconvenience of permanent anticoagulation. However, even in those patients who do not require

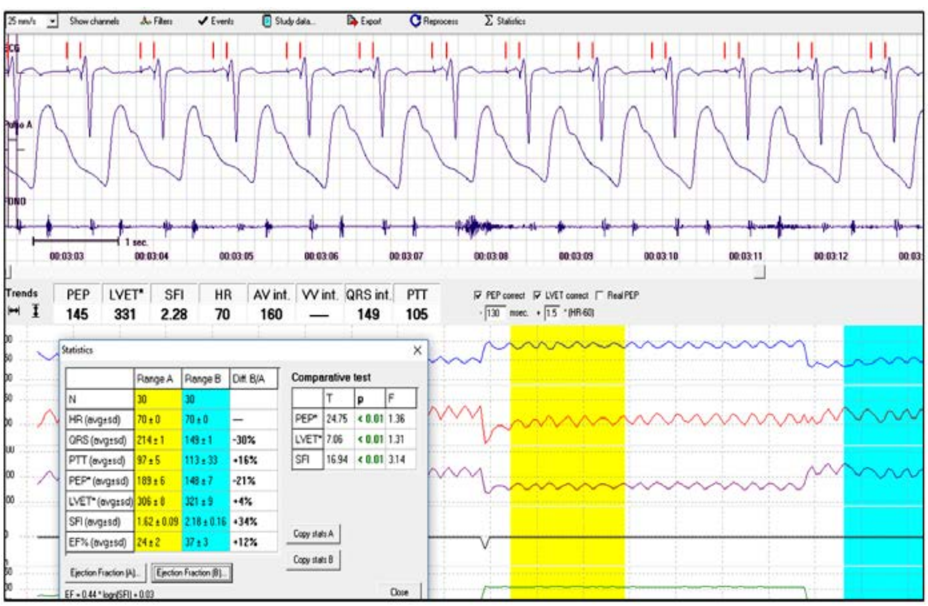

Fig. 3. Systocor screen with non-invasive hemodynamic measurements. The upper part shows the electrocardiogram, the pulse plethysmography and the phonocardiogram. The lower part shows the curves that record the values of the preejection period, the ejection period, the systolic function index and the heart rate corresponding to all the beats recorded during the study. Thirty beats were selected for analysis with each stimulation mode. In this image, those selected in yellow correspond to a single right ventricular stimulation and those selected in light blue to simultaneous biventricular stimulation. In the inset (superimposed, bottom left), the system shows the calculations performed automatically and provides the average of systolic intervals, the systolic index and the ejection fraction, and statistical significance of the compared data.

Table 1. Demographic data of patients evaluated. M: Male. F: Female IDIOP: Idiopathic. ISC/NEC: Ischemic-necrotic. CHAG: Chagasic. SR: Sinus rhythm. AF: Atrial fibrillation. LBBB: Left bundle branch block. SPT: Spontaneous. PM: Pacemaker. eCRT: Endocardial cardiac resynchronization therapy. ACOG: Anticoagulation. CS IMP: Coronary sinus implant. FC: Functional class. MLHFQ: Minnesota living with heart failure questionnaire - Quality of life test. EF: Ejection fraction. LVDD: Left ventricualr diastolic diameter. HOSP. HF: Hospitalization for heart failure. It should be noted that patients 1, 10, 11 and 12 had changes in echocardiographic EF less than 8%, the limit of precision stipulated by the ASE (see "Comments").

							BASELINE				FOLLOW-UP					
Patient	Age	Sex	Etiology	Rhythm	LBBB	eCRT Indication	FC	MLHFQ	EF	LVDD	MONTH	FC	MLHFQ	EF	LVDD	HOSP. HF
1	58	M	IDIOP	SR	SPT	ACOG	3	86	28	78	78	1	14	32	75	NO
2	74	F	IDIOP	SR	SPT	ACOG	2	83	32	62	67	1	15	57	50	NO
3	59	M	ISC/NEC	SR/AF	SPT	ACOG	2	88	15	84	59	1	13	24	88	NO
4	68	F	IDIOP	SR	SPT	ACOG	4	85	21	68	55	2	17	29	97	NO
5	44	M	ISC/NEC	SR	SPT	ACOG	3	87	19	72	54	1	15	31	69	NO
6	49	M	IDIOP	SR/AF	SPT	ACOG	3	90	23	64	52	1	16	31	73	NO
7	59	M	ISC/NEC	SR	PM	FAILED CS IMP	3	92	20	70	51	1	15	30	82	NO
8	60	M	CHAG	SR	PM	ACOG	3	91	21	82	46	1	15	35	66	NO
9	59	M	ISC/NEC	SR	SPT	FAILED CS IMP	3	85	22	65	45	1	13	37	62	NO
10	77	M	ISC/NEC	SR/AF	PM	ACOG	3	87	30	59	43	1	16	25	63	NO
11	57	F	CHAG	SR	SPT	FAILED CS IMP	3	90	31	69	32	1	14	35	62	NO
12	68	M	ISC/NEC	SR	SPT	FAILED CS IMP	3	90	24	76	11	1	16	29	80	NO
13	43	M	IDIOP	SR	SPT	ELECTIVE	3	91	22	73	26	1	13	35	64	NO
14	60	M	IDIOP	SR	SPT	ELECTIVE	3	92	19	71	15	1	12	40	75	NO
15	70	M	ISC/NEC	SR	SPT	FAILED CS IMP	3	89	20	75	9	1	17	29	73	NO

anticoagualization for other reasons, the risk of a hemorrhagic complications is low compared with the risk of reoperation due to displacement of the catheter from the coronary sinus, phrenic nerve stimulation, threshold rise or stimulation in an inadequate LV region. Since intracavitary LV catheter implantation has been facilitated by new technologies, such as the one used in our patients, (1, 2), the long-term hemodynamic response remains to be determined precisely. Even though in several previous studies clinical evolution is used for patient follow-up (FC, questionnaires, hospitalizations), (18) there is no universally accepted method for an objective evaluation, especially of its hemodynamic behavior. Despite echocardiographic EF is frequently the method of choice, (19, 20) it has known limitations, especially in its 8% accuracy, (3) which means that actual EF changes <8% might not be detected, since they are within the margin of error. In fact, in our cohort there were 4 patients with echocardiographic EF with changes <8%, which means its use would not be allowed as a marker of eCRT hemodynamic efficacy. For this reason, we have decided to use the systolic intervals and the indices derived from them for an accurate and objective hemodynamic analysis, when comparing biventricular stimulation with the proper rhythm or the isolated stimulation of the right ventricle within the same patient. The PEP is probably the most reliable among the markers used, since it is related to the LV isovolumic contraction phase (21) and the interventricular delay caused by LBBB, one of the components responsible for cardiac function impairment and necessary to prescribe a resynchronizer. Its shortening therefore indicates a correction of this interventricular delay. As the analyzer used is non-invasive and allows to record and average an unlimited number of beats, its accuracy is very high, and since the measurements are automatic they make it independent of the operator. There are numerous publications that support systolic intervals as markers of cardiac function. (4-6, 11-13)

In this work, we have studied a homogeneous group of patients who presented an excellent clinical evolution sustained over time, but with echocardiographic discrepancies, considering the 8% error factor stipulated by the American Society of Echocardiography (ASE). Although prior knowledge of the good evolution of patients could generate a significant bias to the study, we considered that this was minimized since the measurements and calculations of the various hemodynamic parameters were performed automatically by the system and self-controlled by the patients when changing the stimulation mode.

Our hypothesis was that systolic intervals and indices should detect a significant increase due to the

Table 2. Statistical data of the patients evaluated. LBBB: Left bundle branch block. RVSS: Right ventricular single stimulation. cPEP: Corrected preejection period. LVEP: Left ventricular ejection period. SFI: Systolic function Index. EF: Ejection fraction. SD: Standard deviation. ms: milliseconds.

	BASELI Activation with LBBB: Spontaneous/RVSS NE				Simultaneous biventricular stimulation			
	cPEP (ms)	LVEP (ms)	SFI	EF (%)	cPEP (ms)	LVEF (ms)	SFI	EF (%)
1	201	342	1.7	26	185	347	1.88	31
2	147	335	2.28	41	99	359	3.63	61
3	245	307	1.25	16	208	313	1.5	24
4	246	340	1.38	17	220	307	1.4	26
5	243	291	1.2	11	217	295	1.36	16
6	221	257	1.16	13	207	266	1.29	17
7	196	305	1.56	22	185	331	1.79	29
8	213	328	1.54	22	189	330	1.75	27
9	222	308	1.39	17	167	324	1.94	32
10	170	301	1.77	30	133	306	2.3	42
11	228	277	1.21	14	209	297	1.42	21
12	182	294	1.62	26	153	291	1.91	34
13	234	342	1.46	22	198	348	1.75	30
14	202	313	1.55	24	155	308	1.99	35
15	223	252	1.13	12	187	264	1.41	21
Mean SD	212	306	1.49	21	181	312	1.82	30
	29	29	0.32	8	34	28	0.58	11

effect of eCRT compared with ventricular activation with spontaneous or induced LBBB by single RV stimulation. It should be noted that not all patients were able to compare biventricular endocardial stimulation with their own rhythm, since in order to show their own QRS, it was necessary in some patients to extend the AV interval to non-physiological values. Therefore, this gives rise to the concept that CRT not only corrects interventricular dyssynchrony, but also AV dyssynchrony.

Limitations

The study has several limitations. In the first place, the small number of patients does not allow an adequate statistical evaluation of what to expect in the general population. Second, we could only confirm that in our cohort all patients were true positives, without false positives. It would be necessary to evaluate the rate of true negatives and false negatives. The study was carried out in a limited population of patients, with eCRT performed with a specific technique, with good clinical evolution in all patients, without non-responders and carried out in a single center. To overcome these limitations the study should be repeated in larger populations.

CONCLUSIONS

In conclusion, the present work confirmed that eCRT provides significant hemodynamic improvement and with long-term subjective clinical improvement. This was supported by the use of systolic intervals and their derived indices, which allow a non-invasive hemodynamic evaluation. Shortening of the PEP confirmed the existence of electromechanical resynchronization and the increase in SFI and EF allowed to infer an improvement in the overall cardiac function of the patients.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

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