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ORIGINAL ARTICLE

Novel active fixation lead guided by electrical delay can improve response to cardiac resynchronization therapy in heart failure

Matteo Casale[1], Maurizio Mezzetti[1], Marianna Gigliotti De Fazio[2], Loredana Caccamo[1], Paolo Busacca[1] and Giuseppe Dattilo[3]*

[1]*ASUR Marche - Area Vasta 1, Operative Unit of ICCU and Cardiology, Hospital S. Maria della Misericordia, Urbino, Italy;* [2]*Department of Clinical and Experimental Medicine, Operative Unit of Internal Medicine, University of Messina, Messina, Italy; and* [3]*Department of Clinical and Experimental Medicine, Operative Unit of Cardiology, University of Messina, Messina, Italy*

Abstract

Aims Cardiac resynchronization therapy (CRT) for heart failure (HF) recently has shown optimal results by targeting electrically delayed sites in coronary sinus (CS) branches. However this purpose often cannot be reached because of unstable left ventricular (LV) lead position. In current study were assessed the long-term effects of the novel active fixation LV lead in CS, guided by electrical delay (QLV), in patients with HF due to coronary artery disease.

Methods One hundred eighty-five consecutive patients underwent CRT with intraoperative evaluation of QLV in the target position of the LV lead. When the novel active fixation LV lead was available, 98 consecutive patients received it, composing the Fix group. They were compared with 87 patients with a conventional passive fixation lead (No Fix group). The final LV lead position was assessed by fluoroscopy. Clinical response to CRT was assessed within a period of about 3 years: patients experiencing HF rehospitalization and death due to HF were defined as non-responders.

Results There were no significant differences between groups in the final position of LV lead in left anterior oblique view (Pearson χ^2 = 0.12; P = 0.73). In right anterior oblique view, a basal position was reached more in the Fix group (38%) than in the No Fix group (6.5%) (Pearson χ^2 = 23.095; $P < 0.001$). QLV was significantly greater in the Fix group (122.6 ± 33.2 ms; SE = 3.6) than in the No Fix group (97.5 ± 37.8 ms; SE = 4.9) (t = 4.17; $P < 0.001$). Rehospitalizations for HF were 37 in the No Fix group and 14 in the Fix group. Deaths due to HF were 49 in the No Fix group and 18 in the Fix group. Survival analysis, assessed by Cox regression, showed that the Fix group had a better outcome both for HF rehospitalizations [hazard ratio (HR) = 0.48; 95% confidence interval (CI) = 0.25–0.9; P = 0.023] and death due to HF (HR = 0.55; 95% CI = 0.31–0.97; P = 0.04) in comparison with the No Fix group. Adjustment for baseline characteristics by multivariate analysis showed that an active fixation lead in CS, as a covariate, was still significant both for HF rehospitalizations (HR 0.46; 95% CI = 0.24–0.88; P = 0.019) and for death due to HF (HR 0.5; 95% CI = 0.28–0.9; P = 0.021).

Conclusions The novel active fixation LV lead allowed to target sites with greater QLV. Often maximum QLV was documented in basal segments, were stability of conventional passive fixation leads is not enough. Patients receiving it experienced less HF rehospitalizations and less death due to HF. Active fixation lead in CS guided by QLV can improve long-term prognosis in patients with HF due to coronary artery disease undergoing to CRT.

Keywords Heart failure; Coronary artery disease; Cardiac resynchronization therapy; Active fixation lead; Response to CRT

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**Correspondence to: Giuseppe Dattilo, Department of Clinical and Experimental Medicine, Operative Unit of Cardiology, University of Messina, Messina, Italy.*
Email: giu.dattilo@libero.it

Introduction

Heart failure (HF) is a clinical syndrome due to functional or structural abnormality featuring the final common pathway of many cardiac diseases.[1] Despite improvements of drug therapy, many patients with an advanced HF stage need an implantable cardiac defibrillator (ICD).[2] In these circumstances, ICD reduces mortality, especially in patients affected by coronary artery disease (CAD).[3] Cardiac resynchronization therapy (CRT) showed, in the CARE-HF trial, its effectiveness in improving the quality of life.[4] CRT is effective in patients with severe HF and left ventricular ejection fraction (EF) $<$ 35%, QRS duration $>$130 ms despite an optimal medical therapy.[5] Recent reports estimate an increasing use of cardiac resynchronization therapy with a defibrillator (CRT-D) from 43.6% to 60.4%.[6] One of the major problems related to CRT is lack of clinical improvement in a relevant proportion of patients.[5] In order to improve success, some authors proposed several criteria for a better patient selection.[7] In particular, a proper selection of the final position of the left ventricular (LV) lead in coronary sinus (CS) seems to be crucial for CRT response. Large clinical trials, such as MADIT-CRT and REVERSE, showed that an apical position was worse than a non-apical one, without any difference among the LV anterior, lateral, and postero-lateral walls.[8,9] The study PATH-CHF suggested that the best outcome comes from the mid portion of LV lateral wall[10] but implantation procedure *per se* and CS anatomy are very important limiting factors in CRT effectiveness. For this reason, some authors recently proposed a different approach, targeting sites of latest electrical LV activity.[11] The availability of an active fixation lead for CS (Medtronic Attain Stability™) recently allowed to overcome problems related to stability and to reduce the number of dislodgements.[12] The aim of our study was to assess, in patients affected by HF due to CAD, the impact of an active fixation lead in CS, guided by electrical delay, on the response to CRT in the long term.

Materials and methods

Baseline characteristics

We evaluated, from September 2017 to December 2020, the usefulness of an active fixation lead in CS guided by electrical delay in terms of clinical response to CRT. The endpoints of the study were: (i) hospitalization for HF and (ii) death for HF. The study was approved by the local Ethics Committee, which judged it compliant with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. A total of 201 patients were enrolled at the beginning of the study, but in 16 patients, intraoperative evaluation of electrical delay was not performed: in 5, there were not suitable CS branches, needing for an epicardial lead; in 6, intraoperative haemodynamic instability occurred and time saving was preferred; in 1, registration was missed because of technical error; in 4, the EP workstation was unavailable. All the patients without an evaluation of electrical delay during implantation were excluded. The final population was composed by 185 patients with HF in New York Heart Association (NYHA) Class II and III. All the patients had signs and symptoms of HF despite optimal medical therapy, wide QRS complex and severely reduced EF, according to current guidelines.[1] HF aetiology was CAD, defined by the presence of coronary stenosis $>$50% detected invasively by coronary angiography. When the active fixation LV lead was available, it was tested in the first 98 consecutive patients, who composed the Fix group. The control group (No Fix group) was an historical control before the start of usage of the active LV fixation lead, composed from 87 consecutive patients with a conventional passive fixation LV lead. Baseline characteristics are summarized in *Table 1*.

Echocardiographic data

Eligibility to CRT was performed by echocardiographic data, acquired by a standard equipment (Vivid Q, General Electrics, Fairfield, Connecticut, USA) with a 1.5–3.6 MHz phased-array transducer. In particular were evaluated, by parasternal long axis view and by four-chamber and two-chamber apical views: (i) the end-diastolic diameter (EDD), (ii) the end-systolic diameter (ESD), and (iii) the EF by biplane Simpson's method. All the data were acquired according to recommendations of the American Society of Echocardiography.

Left ventricular lead positioning and study protocol

A retrograde CS venography was obtained in all the patients in order to evaluate all the suitable branches for an acceptable LV lead positioning. In all the patients enrolled, LV lead implantation was guided by intra-procedural assessment of electrical delay. Eighty-seven consecutive patients receiving a conventional passive fixation LV lead composed the control group (No Fix group). When the active fixation LV lead was available, the first 98 consecutive patients were enrolled and composed the study group (Fix group). An acceptable target site was defined as a region in which there were: (i) a stable LV position, (ii) good threshold and sensing parameters according to current practice,[13] and (iii) absence of phrenic nerve stimulation, defined as a local threshold of phrenic stimulation $>$5 V than the capture threshold. If these conditions were satisfied, the degree of electrical delay was assessed, implanting the LV lead where the maximum value

Table 1 Baseline characteristics of the studied population

		No fix (n = 87)	Fix (n = 98)	P
Age, years (mean ± SD)		75.4 ± 9.7	75.5 ± 8.2	0.96
Female sex		23%	15%	0.18
Hypertension		70.6%	71.4%	0.9
Diabetes		31.4%	40.8%	0.18
Previous TIA		1.1%	1.0%	0.6
Previous stroke		6.9%	5.1%	0.6
Vascular pathology		50.0%	64.3%	0.051
CHADSVASC, points (mean ± SD)		4 ± 2	5 ± 1	0.09
Previous cardiac surgery		19.3%	18.4%	0.88
NYHA class	II	50.6%	58.9%	0.1
	III	49.4%	41.1%	0.16
Paroxismal atrial fibrillation		42.5%	37.5%	0.49
PR, ms (mean ± SD)		217 ± 53	207 ± 48	0.35
QRS, ms (mean ± SD)		155 ± 27	162 ± 32	0.13
Creatinine, mg/dL (mean ± SD)		1 ± 0.1	1 ± 0.2	0.07
Haemoglobin, mg/dL (mean ± SD)		12 ± 3	13 ± 2	0.53
Ejection fraction, % (mean ± SD)		29 ± 7	31 ± 7	0.37
End diastolic diameter, mm (mean ± SD)		63 ± 10	61 ± 7	0.7
End systolic diameter, mm (mean ± SD)		50 ± 9	47 ± 9	0.8

NYHA, New York Heart Association.

could be reached. In case of suboptimal delay or in case of more acceptable sites, the lead was moved to another position, targeting the maximum delay. Targeting non-apical sites of CS branches was favoured if a stable position could be obtained, according to current evidences.[8,9] The right ventricular lead was positioned in all the patients in the right ventricular septum in CRT-D (active fixation) and in the apex (passive fixation) for CRT-P. Right atrial lead was positioned in the appendage in all the patients without permanent atrial fibrillation at the time of the procedure. After connecting leads to the pulse generator, a fluoroscopy was systematically obtained. The final lead position was evaluated in the right anterior oblique 30° (RAO) and in the left anterior oblique 45° (LAO) standard fluoroscopic views. According to LAO view, the CS branches were classified as anterior, antero-lateral, lateral, infero-lateral, and inferior, but for statistical analysis, a re-classification was needed in lateral and non-lateral. In the RAO view, the final LV position was initially classified as basal, mid, or apical. Even in this case, to simplify the statistical analysis, a re-classification was made in basal and non-basal sites, being basal sites more favourable in terms of electrical delay.[10]

Latest electrical activation recorded from coronary sinus branches

Left ventricular lead was used as a bipolar recording electrode once a time in each available branch. Apical position was avoided if a stable position could be reached, according to the results of the MADIT-CRT and REVERSE trials.[8,9] The surface electrocardiogram (ECG) and the local electrogram recorded from the tip of the LV lead were displayed simultaneously on the electrophysiology workstation (CadioLab XT, General Electrics, Fairfield, Connecticut, USA). We measured the time from the QRS onset on the surface ECG to the onset of the local electrogram (QLV), defined as the first rapid deflection recorded on the LV lead tip, which was used as a bipolar electrode (*Figure 1*). For this purpose, a sweep speed of 200 mm/s was used. If several positions were acceptable, the more delayed site was the target (*Figure 2*).

Follow-up and response to cardiac resynchronization therapy

Clinical status was assessed starting from the time of implantation procedure and every 6 months during the periodic CRT follow-up by different physicians, with a follow-up of about 3 years. The occurrence of hospital admission for HF (in terms of both acute or chronic decompensation) and death due to HF identified the non-responders. Death due to HF was defined as the in-hospital occurrence of death during an HF readmission.

Statistical analysis

Descriptive statistics were generated to summarize patients' characteristics. Data normality was assessed by the Kolmogorov–Smirnov test. Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed in terms of frequencies and percentages. Student t and Pearson χ^2 tests were used, where appropriate, to evaluate differences between the Fix and No Fix group.

Figure 1 (A) Antero-posterior view during a coronary sinus venogram showing a suitable lateral branch which distally bifurcates. (B) Evaluation of the site of latest electrical delay of this branch at a sweep speed of 200 mm/s. The electronic calliper on the right measures the surface QRS width. Another electronic calliper in the left measures the delay between the QRS onset on the surface electrocardiogram (ECG) and the first rapid deflection recorded from the LV lead tip, used as a bipolar electrode. In this case the local left ventricular electrogram is very late compared to the QRS duration and so it predicts an optimal clinical outcome of this cardiac resynchronization therapy (CRT) procedure.

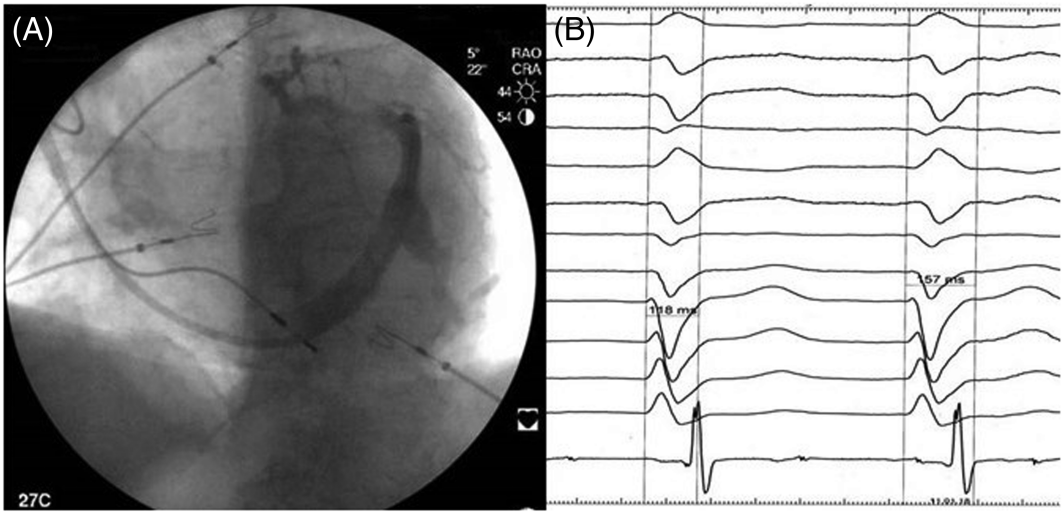
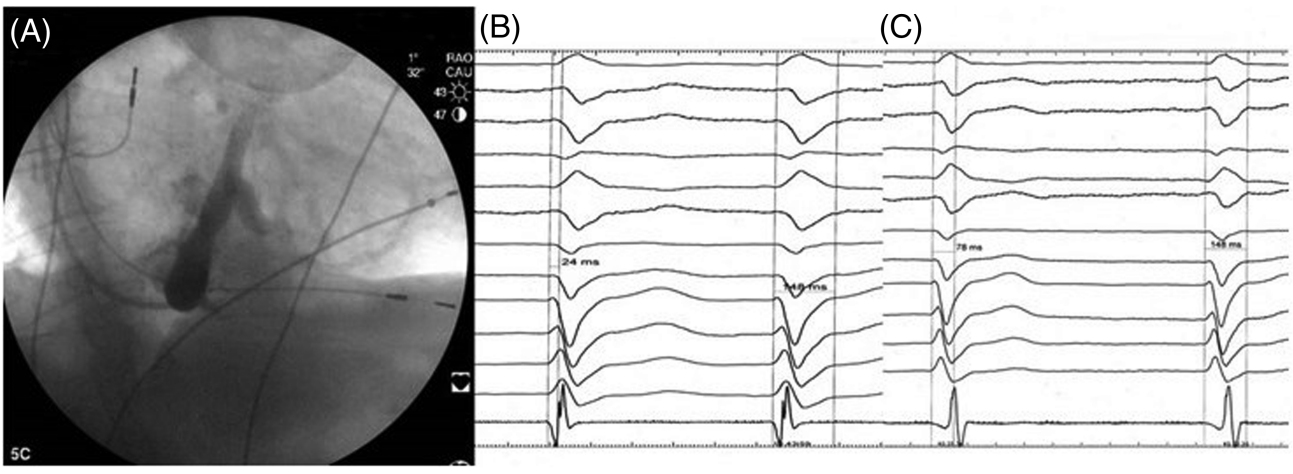
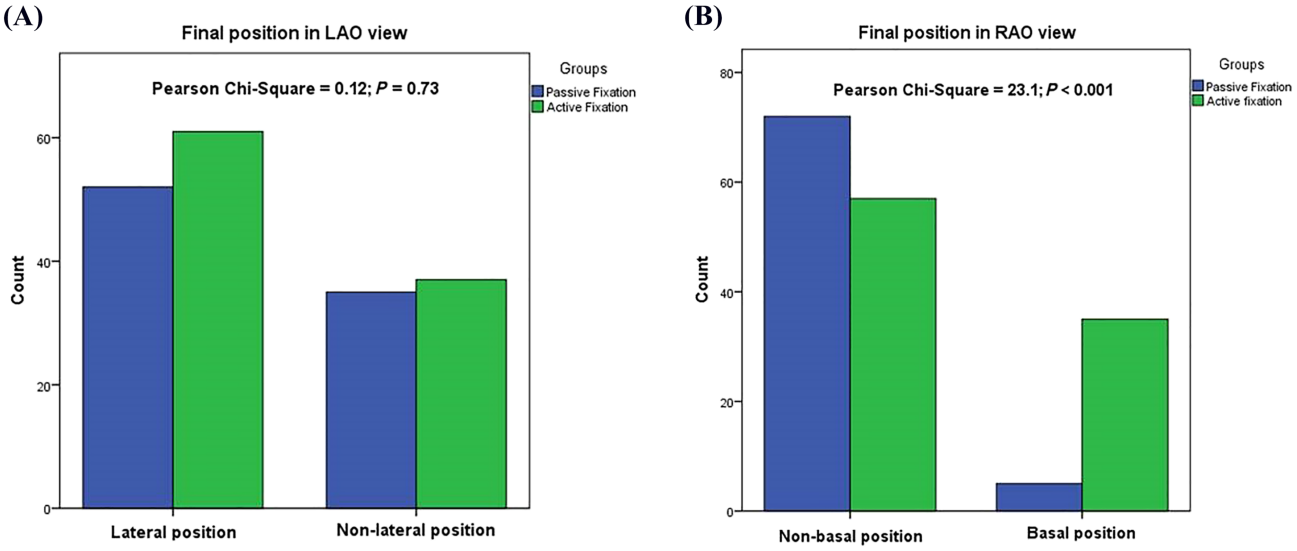


Figure 2 (A) Coronary sinus (CS) venogram in antero-posterior view. A lateral and a postero-lateral branch emerge from CS. Despite both seem to be good targets they differentiate greatly in terms of electrical delay. (B) Exploration of the site of maximum delay in the postero-lateral branch. At a sweep speed of 200 mm/s the electronic calliper on the right measures a QRS width of 148 ms. The calliper on the left measures the electrical delay from the QRS onset to the local bipolar electrogram of the LV lead. In this case the delay is only 24 ms, predicting poor response to cardiac resynchronization therapy (CRT). (C) Exploration of the site of maximum delay in the lateral branch. As in Panel B the calliper in the right measures the QRS width (148 ms as the previous record) and the calliper on the left measures the QLV. In this case the delay is greater (78 ms) in comparison with the surface QRS, predicting a better response. In this patient, the LV lead was placed in this site with a good clinical outcome.



Survival analysis was performed by Cox regression model. A univariate Cox regression model was used first made to test the hypothesis that an active fixation lead can improve survival. A multivariate Cox regression analysis was then performed, adjusting the model for baseline clinical characteristics. Variable's contribution to the Cox regression model is expressed in terms of hazard ratio (HR) with its 95% confidence interval (CI). All statistical tests were two-tailed and a P value <0.05 was considered statistically significant. Statistical analysis was carried out using IBM SPSS Statistics

Figure 3 (A) χ^2 test for left ventricular (LV) lead final position in left anterior oblique (LAO) view shows no difference between groups. (B) In right anterior oblique (RAO) view there is a significant increase in targeting basal sites for the Fix group.



software package version 20 (IBM, Armonk, North Castle, New York, USA).

Results

Baseline clinical characteristics are summarized in *Table 1*. Percentage of ventricular stimulation was >98% in all patients free from events, according to current evidences.[1]

The final position of the LV lead, assessed by left anterior oblique (LAO) and right anterior oblique (RAO) fluoroscopic views, was classified, for convenience, respectively, as lateral and non-lateral and as basal or non-basal. There were no significant differences between the groups in the final position in LAO view (Pearson χ^2 = 0.12; P = 0.73—*Figure 3A*). In RAO view, a basal position was significantly reached in more patients in the Fix group (38%) than in the No Fix group (6.5%) (Pearson χ^2 = 23.095; $P < 0.001$—*Figure 3B*).

The QLV that assessed in the target position of LV lead was significantly greater in the Fix group (122.6 ± 33.2 ms; SE = 3.6) than in the No Fix group (97.5 ± 37.8 ms; SE = 4.9) (t = 4.17; $P < 0.001$).

Rehospitalizations for HF after 3 years were respectively 37 (42.5%) in the No Fix group and 14 (14.3%) in the Fix group. Deaths due to HF at 3 years were respectively 49 (56.3%) in the No Fix group and 18 (18.4%) in the Fix group.

The long-term survival, assessed by Cox regression, showed a significantly better clinical outcome for the Fix group both in terms of HF rehospitalizations and of death due to HF. Survival analysis for HF rehospitalizations showed that Fix group had a better event-free survival in comparison with No Fix group (χ^2 = 5.51; P = 0.019): Adding an active fixation lead had a significant effect in reducing HF rehospitalizations (HR = 0.48; 95% CI = 0.25–0.9; P = 0.023—*Figure 4A*). The same analysis showed a reduction of death due to HF in the Fix group in comparison to No Fix group (χ^2 = 4.46; P = 0.035): The effect of an active fixation lead in CS was significant (HR = 0.55; 95% CI = 0.31–0.97; P = 0.04—*Figure 4B*). Adjustment for baseline characteristics was performed by multivariate Cox regression, entering them in the equation model as covariates. The number of covariates entered in the multivariate models was assessed according to the number of events (HF rehospitalizations and death due to HF respectively) to control for type 1 error. According to this general rule five covariates were entered in the multivariate analysis for HF rehospitalizations and 6 for death due to HF. The multivariate model for HF rehospitalizations showed that an active fixation lead in CS, as a covariate, was still significant (HR 0.46; 95% CI = 0.24–0.88; P = 0.019—*Figure 5A*; *Table 2*). Significant effects by other covariates on the model were given only from age and diabetes. In the multivariate analysis performed for death due to HF, active fixation lead was still significant as a covariate (HR 0.5; 95% CI = 0.28–0.9; P = 0.021—*Figure 5B*; *Table 3*). Even in this model age and diabetes were significant covariates.

Discussion

The current study evaluated the long-term impact of an active fixation LV lead in CS guided by electrical delay in patients with Heart Failure due to CAD. To date, a uniform definition of response to CRT is lacking, and in literature, there are often heterogeneous criteria.[14] For this reason,

Figure 4 Survival functions for heart failure (HF) rehospitalization (A) and for death due to HF (B) show a better outcome in the Fix group.

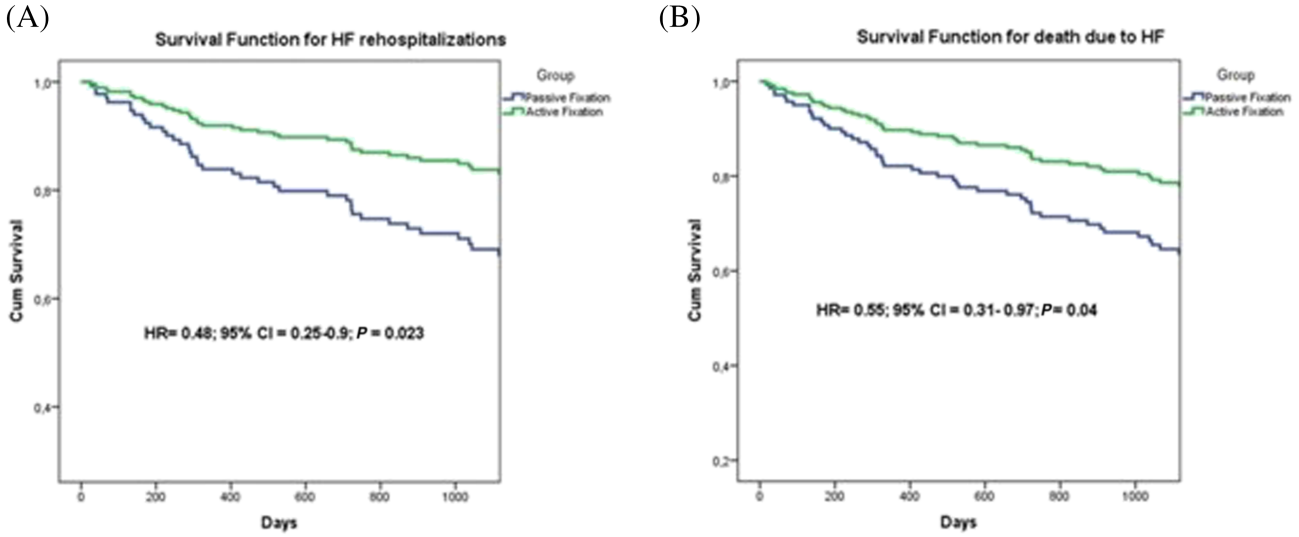


Figure 5 Adjusted survival functions for heart failure (HF) rehospitalization (A) and for death due to HF (B) show a better outcome in the Fix group.

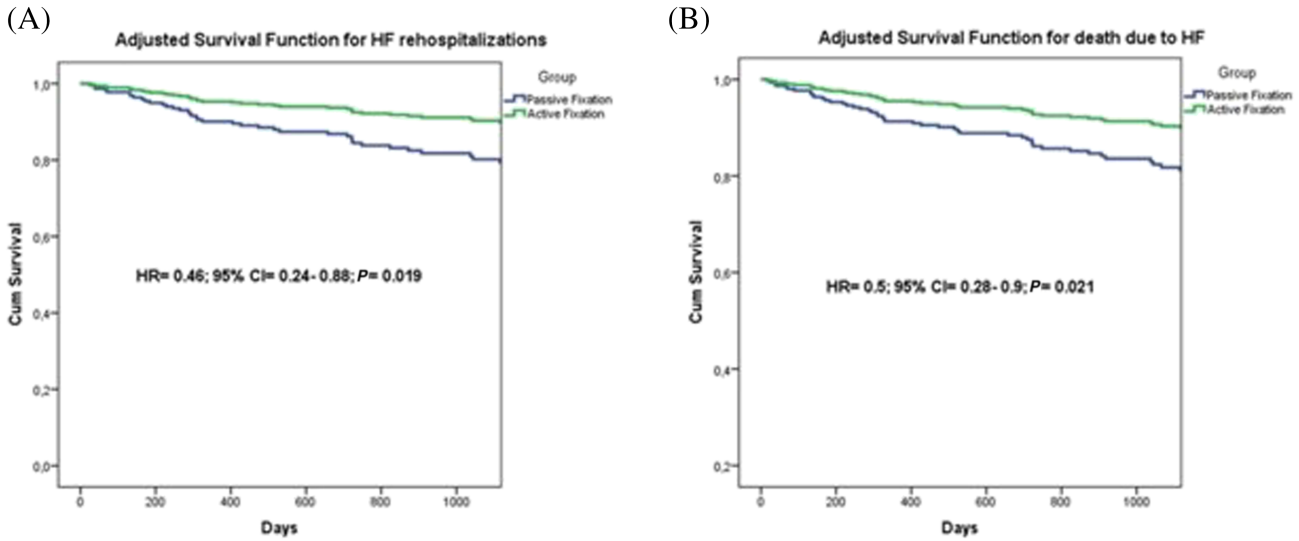


Table 2 Multivariate analysis for heart failure rehospitalizations

Variables in the model	HR	95% CI	*P*
Age	1.08	1.041; 1.136	<0.001
Sex (female)	0.98	0.493; 1.969	0.966
Arterial hypertension	1.11	0.544; 2.272	0.771
Diabetes	1.94	1.064; 3.563	0.031
Active fixation lead in coronary sinus	0.46	0.243; 0.879	0.019

95% CI, 95% confidence interval for HR; HR, hazard ratio.

we assessed only the clinical response by objective assessment of death due to HF and rehospitalization for HF. A proper patient selection currently is recommended in order to maximize post-procedural results.[1] The Rethinq study showed that mechanical dyssynchrony alone is not enough to predict response to CRT.[15] For this reason, a combined

Table 3 Multivariate analysis for death due to heart failure

Variables in the model	HR	95% CI	*P*
Age	1.06	1.026; 1.108	0.001
Sex (female)	0.82	0.429; 1.586	0.563
Arterial hypertension	1.33	0.667; 2.667	0.415
Diabetes	1.81	1.078; 3.038	0.025
Vascular disease	1.48	0.846; 2.600	0.168
Active fixation lead in coronary sinus	0.51	0.283; 0.904	0.021

95% CI, 95% confidence interval for HR; HR, hazard ratio.

assessment by ECG (QRS width $>$ 130 ms) and echocardiography (LVEF $<$35%) is needed.[1] A proper patient selection can lead to very good response: the so called 'super-responders', showing relevant improvement of signs and symptoms.[16] Despite these evidences, a considerable part of subjects does not show any improvement, often because the best predictor of response is QRS width (the only parameter expressing the electrical delay of activation of the left ventricle), especially in patients with a left bundle branch block (LBBB) morphology.[17] The acute haemodynamic response was previously assessed by several authors, who observed that targeting the maximum electrical delay in CS has a strong mechanical impact early after implantation.[11,18,19] They showed that the delay from the QRS onset on the surface ECG to the first large peak on the local LV electrogram (QLV) is a useful tool in predicting response to CRT. However, those studies analysed only the acute haemodynamic response with single measurements, preventing the possibility to make general assumptions after long-term periods. The only study exploring the outcome from LV lead positioning in delayed sites with adequate follow-up is from Roubicek *et al.*[20] Authors showed that positioning an LV lead in the maximum electrical delayed site is a significant predictor of HF hospitalization and mortality in CRT. A limitation of their study was that electrical delay was assessed with unipolar recordings or, in case of inadequate recordings, with bipolar EGM. We think that this could lead to heterogeneity of results and, in fact, we preferred only bipolar recordings. Nevertheless, their research had high impact in the field. Starting from their experience, we observed that results could be maximized, especially in case of multiple suitable CS branches, or in the case that a single branch splits in two or more. It is a matter of fact that often some implanters prefer to target the first suitable CS branch after venography, even for stability reasons. It is our opinion that this practice could be revised, even by the use of an active fixation LV lead. Targeting the site of maximum electrical delay will result in a better outcome. Our results showed that mean QLV in the Fix group was significantly greater than No Fix group (122.6 ± 33.2 ms vs. 97.5 ± 37.8 ms) and that the adjusted HR of Fix vs No Fix for HF rehospitalizations (HR 0.46; 95% CI = 0.24–0.88; P = 0.019) and for death due to HF (HR 0.51; 95% CI = 0.28–0.9; P = 0.021) were significantly low. This means that use of an active fixation LV lead allowed pacing in sites with a greater delay, and that those patients experienced less HF rehospitalizations and death due to HF. Even if the difference in delay between Fix vs. No Fix group was relatively modest (although significant), pacing in sites with a greater delay probably allowed a better resynchronization between ventricles in the AFix group, reducing negative effects deriving by the left bundle branch block. Probably, even a small increase of few milliseconds in intraoperative QLV could allow a significant improvement in response to CRT. This could be especially important in the setting of ischaemic heart disease, in which electrical activation is often subverted by scar tissue. These results suggest that not only the evaluation of QLV is needed but also that a significant delay is often reached in more basal positions. However, basal positions often are not stable enough for conventional LV leads, preventing to target optimal electrical delay. In our experience an active fixation lead allowed to reach sites of maximum electrical delay, often in a more basal position. The main consequence is that, even if less easy and more time consuming, this technique should be employed in order to maximize the clinical outcome, especially in case of unstable positions and of large, multiple and/or splitting CS branches. To the best of our knowledge, our study is the first one evaluating the long-term survival of patients undergoing to CRT with an LV active fixation lead guided by electrical delay. As expected, adjustment for baseline characteristics showed that age and diabetes were significant predictors in survival analyses. However, these two variables are known to affect clinical outcome in HF,[1] and furthermore, there were no significant differences between groups for both these variables (*Table 1*). The use of LV active fixation lead remained a significant variable both for HF rehospitalization and in death due to HF. Management of HF is in constant evolution,[21] even by the interplay with novel pharmacologic approaches.[22] We think that in this scenario, optimal results could be reached by the use of an active fixation lead in CS.

Study limitations

A limitation of our study is the lack of systematic acquisition of echocardiographic data during the periodic follow-up. Furthermore no evaluation of QLV by the programmer during follow-up was performed but it is our opinion that using different systems (electrophysiology workstation vs. pacemaker

programmer) may lead to imprecise, not homogeneous nor reproducible measures. In fact, it is known that the markers of the sensed events depend on the LV lead position and on the programmer, so that different positions in different patients could lead to more or less pronounced QLV variations over time. This could lead to not homogeneous results in terms of QLV reduction. Another limitation is the lack of systematic evaluation of the additional time of fluoroscopy needed for the exploration of all acceptable CS branches. However, the importance of this assessment was discussed elsewhere, demonstrating that it was superior of about 10 min than a standard procedure.[11,23] In our experience, it did not differ substantially. Finally, our study lacks of a multicentre experience.

Conclusions

To our knowledge, this study is the first one assessing the long-term outcome in patients with HF due to CAD undergoing to CRT with the novel CS active fixation lead guided by electrical delay. Our results suggest that it could be helpful in targeting sites with greater electrical delay, often in a more basal position. After 3 years patients receiving LV active fixation lead experienced less rehospitalizations and had an improved prognosis in terms of death due to HF. Furthermore our results confirm the usefulness of introducing intraoperatively the evaluation of QLV. To date, it seems that evidences are enough to encourage the evaluation of local electrical delay during the implantation procedure. This parameter is easy to obtain, and its evaluation could change patient prognosis. An active fixation lead could guide implanters in the most favourable position, even in case of large, multiple or splitting CS branches. We think that the scenario of CRT in HF is constantly evolving. Starting from the simple measurement of the QRS width on the surface ECG, we arrived to the intracavitary evaluation of the electrical delay.

Conflict of interest

None.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016; **37**: 2129–2200.
2. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter automatic defibrillator implantation trial investigators. *N Engl J Med* 1996; **335**: 1933–1940.
3. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, de Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350**: 2140–2150.
4. Cleland JGF, Calvert MJ, Verboven Y, Freemantle N. Effects of cardiac resynchronization therapy on long-term quality of life: an analysis from the cardiac resynchronisation-heart failure (CARE-HF) study. *Am Heart J* 2009; **157**: 457–466.
5. Sohaib SMMA, Finegold JA, Nijjer SS, Hossain R, Linde C, Levy WC, Sutton R, Kanagaratnam P, Francis DP, Whinnett ZI. Opportunity to increase life span in narrow QRS cardiac resynchronization therapy recipients by deactivating ventricular pacing: evidence from randomized controlled trials. *JACC Heart Fail* 2015; **3**: 327–336.
6. Boveda S, Narayanan K, Jacob S, Providencia R, Algalarrondo V, Bouzeman A, Beganton F, Defaye P, Perier MC, Sadoul N, Piot O, Klug D, Gras D, Fauchier L, Bordachar P, Babuty D, Deharo JC, Leclercq C, Marijon E, DAI-PP Investigators. Temporal trends over a decade of defibrillator therapy for primary prevention in community practice. *J Cardiovasc Electrophysiol* 2017; **28**: 666–673.
7. Gorcsan J, Prinzen FW. Understanding the cardiac substrate and the underlying physiology: implications for individualized treatment algorithm. *Heart Rhythm* 2012; **9**: S18–S26.
8. Singh JP, Klein HU, Huang DT, Reek S, Kuniss M, Quesada A, Barsheshet A, Cannom D, Goldenberg I, McNitt S, Daubert JP, Zareba W, Moss AJ. Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. *Circulation* 2011; **123**: 1159–1166.
9. Thebault C, Donal E, Meunier C. Sites of left and right ventricular lead implantation and response to cardiac resynchronization therapy observations from the REVERSE trial. *Eur Heart J* 2012; **33**: 2662–2671.
10. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, Klein H, Kramer A, Ding J, Salo R, Tockman B, Pochet T, Spinelli J. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The pacing therapies for congestive heart failure study group. The Guidant congestive heart failure research group. *Circulation* 1999; **99**: 2993–3001.
11. Zanon F, Baracca E, Pastore G, Fraccaro C, Roncon L, Aggio S, Noventa F, Mazza A, Prinzen F. Determination of the longest intrapatient left ventricular electrical delay may predict acute hemodynamic improvement in patients after cardiac resynchronization therapy. *Circ Arrhythm Electrophysiol* 2014; **7**: 377–383.
12. Jackson KP, Faerestrand S, Philippon F, Yee R, Kong MH, Kloppe A, Bongiorni MG, Lee SF, Canby RC, Pouliot E, Ginneken MME, Crossley GH. Performance of a novel active fixation quadripolar left ventricular lead for cardiac resynchronization therapy: attain stability quad clinical study results. *J Cardiovasc Electrophysiol* 2020; **31**: 1147–1154.
13. Steinhaus DA, Waks JW, Collins R, Kleckner K, Kramer DB, Zimetbaum PJ. Effect of smaller left ventricular capture

threshold safety margins to improve device longevity in recipients of cardiac resynchronization-defibrillation therapy. *Am J Cardiol* 2015; **116**: 85–87.
14. Petrovic M, Petrovic M, Milasinovic G, Vujisic Tesic B, Trifunovic D, Petrovic O, Nedeljkovic I, Petrovic I, Banovic M, Boricic-Kostic M, Petrovic J, Arena R, Popovic D. Gauging the response to cardiac resynchronization therapy: the important interplay between predictor variables and definition of a favorable outcome. *Echocardiography* 2017; **34**: 371–375.
15. Beshai JF, Grimm RA, Nagueh SF, Baker JH II, Beau SL, Greenberg SM, Pires LA, Tchou PJ. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007; **357**: 2461–2471.
16. Proclemer A, Muser D, Facchin D. What we can learn from "super-responders". *Heart Fail Clin* 2017; **13**: 225–232.
17. Sassone B, Bertini M, Beltrami M, Malagù M, Pasanisi G, Kuwornu HA, Avigni N, Fucà G, Pacchioni F, Minarelli M, Bacchi Reggiani ML, Padeletti L. Relation of QRS duration to response to cardiac resynchronization therapy in patients with left bundle branch Block. *Am J Cardiol* 2017; **119**: 1803–1808.
18. Singh JP, Fan D, Heist EK, Alabiad CR, Taub C, Reddy V, Mansour M, Picard MH, Ruskin JN, Mela T. Left ventricular lead electrical delay predicts response to cardiac resynchronization therapy. *Heart Rhythm* 2006; **3**: 1285–1292. Erratum in: Heart Rhythm. 2006 Dec;3:1515.
19. Gold MR, Birgersdotter-Green U, Singh JP, Ellenbogen KA, Yu Y, Meyer TE, Seth M, Tchou PJ. The relationship between ventricular electrical delay and left ventricular remodelling with cardiac resynchronization therapy. *Eur Heart J* 2011; **32**: 2516–2524.
20. Roubicek T, Wichterle D, Kucera P, Nedbal P, Kupec J, Sedlakova J, Cerny J, Stros J, Kautzner J, Polasek R. Left ventricular lead electrical delay is a predictor of mortality in patients with cardiac resynchronization therapy. *Circ Arrhythm Electrophysiol* 2015; **8**: 1113–1121.
21. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, Boer RA, Drexel H, Ben Gal T, Hill L, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJS. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the heart failure Association of the European Society of cardiology. *Eur J Heart Fail* 2019; **21**: 1169–1186.
22. Casale M, Correale M, Laterra G, Vaccaro V, Morabito C, Crea P, Signorelli SS, Katsiki N, Luzza F, de Gregorio C, Dattilo G. Effects of Sacubitril/valsartan in patients with high arrhythmic risk and an ICD: a longitudinal study. *Clin Drug Investig* 2021; **41**: 169–176.
23. Casale M, Mezzetti M, Tulino V, Scarano M, Busacca P, Dattilo G. Therapy of cardiac arrhythmias in children: an emerging role of electroanatomical mapping systems. *Curr Vasc Pharmacol* 2017; **15**: 1–6.