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Long-Term Effectiveness of Cardiac Resynchronization Therapy in Heart Failure Patients With Unfavorable Cardiac Veins Anatomy

Comparison of Surgical Versus Hemodynamic Procedure

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Objectives This study sought to compare clinical, echocardiographic, and cardiopulmonary exercise testing response to cardiac resynchronization therapy (CRT) in patients with unfavorable anatomy of coronary sinus (CS) veins, randomized to transvenous versus surgical left ventricular (LV) lead implantation.

Background CRT efficacy depends on proper positioning of the LV lead over the posterolateral wall. A detailed pre-operative knowledge of CS anatomy might be of pivotal importance to accomplish a proper LV lead placement over this area.

Methods Study population included 40 patients (age 66 ± 4 years) with heart failure and indication to CRT, with unsuitable CS branches anatomy documented by pre-operative multislice computed cardiac tomography; 20 patients (Group 1) underwent surgical minithoracotomic LV lead implantation whereas 20 (Group 2) were implanted transvenously. New York Heart Association functional class, echocardiographic, and cardiopulmonary exercise testing data were assessed before and 1 year after CRT-system implant.

Results In all Group 1 patients, the LV leads were placed over the middle-basal segments of the posterolateral wall of the LV. This was not possible in Group 2 patients. One year after CRT, in Group 1, a significant improvement of New York Heart Association functional class, LV ejection fraction (from 28.8 ± 9.2% to 33.9 ± 7.2%, $p < 0.01$), LV end-systolic volume (from 165 ± 53 ml to 134 ± 48 ml, $p < 0.001$), and peak Vo_2/kg (from 10.4 ± 4.5 ml/kg/min to 13.1 ± 3.1 ml/kg/min, $p < 0.02$) was observed. However, no improvement was observed in Group 2: LV ejection fraction varied from 27.4 ± 4.8% to 27.4 ± 5.7% ($p = 0.9$), LV end-systolic volume from 175 ± 46 ml to 166 ± 44 ml ($p = 0.15$), and peak Vo_2/kg from 11.2 ± 3.2 ml/kg/min to 11.3 ± 3.4 ml/kg/min ($p = 0.9$). Changes after CRT between groups were highly significant.

Conclusions In the setting of unfavorable CS branches of anatomy, CRT by a surgical minithoracotomic approach is preferable to transvenous lead implantation. (J Am Coll Cardiol 2011;58:483–90) © 2011 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) represents a primary therapeutic option in the management of patients with advanced refractory heart failure (HF), an ejection fraction <0.35, and QRS duration of >120 ms. CRT has proven effective in improving left ventricular (LV) systolic function, exercise capacity, and myocardial oxygen consumption (1–6) and in reducing LV volumes, HF-related hospitalizations (7), and, primarily, mortality (7–9). Patients in whom LV lead position was retrospectively identified as corresponding with the latest segment of mechanical activation have been revealed to have greater remodeling and

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Abbreviations and Acronyms

CPET = cardiopulmonary exercise test
CRT = cardiac resynchronization therapy
CS = coronary sinus
HF = heart failure
LV = left ventricle/left ventricular
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
MSCT = multislice computed tomography
NYHA = New York Heart Association

improvement in outcome versus patients in whom lead position was not adequate (10–14). Although large clinical trials have shown high success rates for transvenous LV lead implantation (from 88% to 95%), the selective engagement of the coronary sinus (CS) branch over the obtuse marginal branch area, which in most patients with left bundle branch block represents the region of highest intraventricular electrical and mechanical delay, is achieved in only 70% of patients undergoing CRT procedure. This can be due to the absence of a suitable vein and/or the presence of unfavorable vascular patterns, as is the case of tortuous, sharp, or angulated vessels. Failing to position the LV catheter over the target area is considered the main cause of inefficacy of CRT (8,9). In patients with unfavorable anatomy of CS main branches, the surgical direct minithoracotomic intervention may represent an alternative, viable strategy to implant the LV catheter over the posterolateral wall of the LV (15–17). Multislice computed tomography (MSCT) is a new technique that allows an effective visualization of the coronary venous system (18–20); this imaging tool, when performed prior to the CRT procedure, could be of great help in guiding the choice between epicardial minithoracotomic and transvenous approaches. The present prospective study was undertaken to assess the clinical, echocardiographic, and cardiopulmonary exercise testing (CPET) long-term response to CRT in patients with pre-operative documentation of unfavorable CS main veins anatomy, who underwent conventional transvenous or minithoracotomic LV lead implantation.

Methods

The study population included 40 patients (mean age of 64.3 ± 4.2 years) with HF and with unfavorable anatomy of CS main veins, screened in our institution from June 2006 to April 2009 from a population of 215 patients with indication to CRT, according to standard guidelines (21). The unsuitability of CS main branches anatomy was documented by pre-operative MSCT, performed 1 to 2 days before the CRT system implant. All enrolled patients were in sinus rhythm, had a mean LV ejection fraction of 28.1 ± 4.3%, a left bundle branch block with QRS width of 164 ± 24 ms, and received an optimized therapy with angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics. Specific for this study, exclusion criteria were CS veins anatomy suitable for transvenous implantation with conventional tools, presence of atrial fibrillation, previously inserted cardiac pacemakers, impaired renal function (creatinine serum levels >2.0 mg/dl) and allergic reactions to contrast agents (Fig. 1). Patients with irregular heart rate during MSCT or with inability to sustain a breath hold for 25 s and body mass index >40 kg/m^2 were also excluded. In no cases was previous thoracotomy performed. Before CRT, in each patient, New York Heart Association (NYHA) functional class, echocardiographic left ventricular end-systolic volume (LVESV), LVEF, and degree of mitral regurgitation (evaluated by Doppler imaging and graded on a 0 to 4 scale) were assessed. All patients were also evaluated by CPET; exercise was done on a cyclo-ergometer (personalized ramp protocol, breath-by-breath analysis) and measurements of peak oxygen consumption (peak VO_2, ml/min), peak VO_2/kg (ml/kg/min), peak workload (WR, watts), and the slope of the relationship between VE and CO_2 (VE/VCO_2) were obtained from each patient.

Afterward, patients were prospectively randomized into 2 therapeutic arms: Group 1 (n = 20) referred to epicardial minithoracotomic with video-assisted thoracoscopy LV lead implantation; and Group 2 (n = 20) in which LV lead implantation was performed through a conventional transvenous endocardial approach.

At baseline, patients of both groups were similar with respect to etiology of heart failure, NYHA class, echocardiographic data, and CPET parameters (Table 1). Moreover, the use of HF medications (beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, loop and potassium-sparing diuretics, nitrates and digoxin) was not different in both groups of patients.

After device implantation, in all patients, pacing was delivered in biventricular sequential mode. The atrioventricular delay was optimized using Doppler echocardiography by searching maximal transmitral diastolic filling without premature termination of atrial filling. Patients of Groups 1 and 2 had an optimal mean sensed atrioventricular delay of 120 ± 15 ms and 130 ± 10 ms (p = 0.07) with a mean optimal paced atrioventricular delay of 132 ± 18 ms and

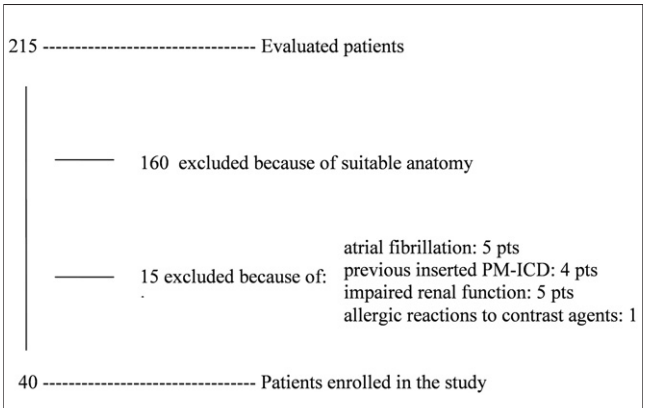

Figure 1 Exclusion Criteria From the Study

PM-ICD = pacemaker implantable cardioverter-defibrillator.

Table 1 Baseline Clinical Characteristics of the Study Groups

	Group 1	Group 2	p Value
Male/female	17/3	16/4	
Age, yrs	64.1 ± 6	63 ± 7.4	0.30
IDCM	16	15	0.56
ICMP	4	5	0.56
NYHA functional class			
II	1	2	0.28*
III	11	13	
IV	8	5	
LVEF, %	28.8 ± 9.2	27.4 ± 4.8	0.7
LVESV, ml	165 ± 53	175 ± 46	0.06
Peak Vo_2/kg, ml/kg/min	10.4 ± 5.0	11.2 ± 3.2	0.07
QRS duration	160 ± 28	167 ± 22	0.6
IDCM patients	161 ± 23	168 ± 24	0.06
ICMP patients	157 ± 24	167 ± 19	0.08

*Chi-square test for trend.

ICMP = ischemic cardiomyopathy; IDCM = idiopathic dilated cardiomyopathy; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; Vo_2 = oxygen consumption.

125 ± 15 ms (p = 0.6). Right versus left ventricular pacing delay was set at 0 in all patients. Approximately 12 months after implantation, NYHA functional class was re-evaluated and echocardiographic and CPET measures were repeated. All echocardiographic recordings were interpretable at baseline and during follow-up. Medical personnel unblinded toward the study protocol performed CPET, echo, and clinical analysis during follow-up.

The study was approved and conducted in compliance with the regulation of the Institutional Ethic Committee. Written informed consent was obtained from all patients after careful explanation of the study protocol.

Study design. This was a single-center, longitudinal, randomized prospective study. Randomization was obtained by a computer-generated randomization list.

In this study, in each group of patients, the achievement of successful positioning during CRT procedure of the LV pacing lead over the lateral or posterolateral wall of the LV was evaluated. Clinical, echocardiographic, and CPET data were collected the week before CRT and after a mean follow-up period of 11.4 ± 1.2 months. The primary outcome of the study was the evaluation of an improvement of NYHA class and echocardiographic and CPET parameters 1 year after CRT procedure in both groups of patients. The secondary outcome was the reduction of HF-related hospitalizations 1 year after CRT system implantation. Clinical follow-up and drug regimen after CRT were optimized by the HF specialist in charge of the patient.

Scan protocol and image reconstruction. MSCT was performed by a multislice electrocardiogram-triggered system (Light Speed Pro, GE Medical Systems, Milwaukee, Wisconsin); before scanning, care was taken to perform the scan at a sinus rate ≤65 beats/min, if necessary, by temporarily increasing the dosage of beta-blockers.

MSCT data were acquired using TC 64 slices-scanner with 64 × 0.625 mm collimation and a gantry rotation time of 350 ms. According to the "electrocardiogram-pulsing technique," the tube current was modulated with a maximum current of 600 mA during a period between 40% to 80% of the R-wave to R-wave interval and a reduction by 80% during the remaining cardiac cycle.

During the scan, a fixed dose (80 ml) of contrast agent (Iomeron 400 mg/ml, Bracco, Italy) was injected intravenously at a rate of 5.0 ml/s followed by a saline solution (50 ml at 5.0 ml/s). MSCT scan was acquired by fluoroscopic bolus tracking technique, during breath hold (about 10 s) and evaluated by 3 blinded expert readers with volume rendering reconstruction (CardioQ3 package GE Medical Systems).

CS anatomic findings. In the study population, MSCT allowed the identification of the location of CS ostium in relation to the right atrium and the evaluation of the presence, number, location, and size of CS tributaries, analyzed on volume-rendered reconstructions. Finally, the course, tortuosity, and angulation of CS veins in 3 orthogonal planes were also studied. In this study, we used highly selective criteria to define unfavorable CS venous anatomy. This lead to a high incidence rate (about 20% of all patients implanted in our institution) of CRT candidates in whom the achievement of the positioning of the LV catheter over the lateral or posterolateral wall through a transvenous approach was considered not feasible (22). Unfavorable veins anatomy was defined if 1 of the following occurred: 1) absence of a vein over the target area; 2) excessive tortuosity of the vein; 3) take-off angle of the target branch from the CS <60°; and 4) diameter of the target vein <3 mm. Table 2 reports anatomically unsuitable CS vein patterns and final LV lead positions obtained in both groups of patients.

Surgical minithoracotomic technique with video-assisted thoracoscopy. The intervention was performed under general anesthesia using a double lumen tube for unilateral lung ventilation. In right lateral decubitus position (30°/40°), a

Table 2 Anatomic Patterns and Final LV Lead Position in Both Groups of Patients

	Group 1	Group 2
Unfavorable anatomy		
Absence of lateral or posterolateral vein	2	3
Angle from CS <60° of lateral vein	4	4
Tortuosity of lateral vein	5	5
Diameter of lateral vein <3 mm	5	4
Diameter of posterolateral vein <3 mm	4	4
Final LV lead position		
Basal-middle lateral wall	16	0
Middle posterolateral wall	4	0
Apical posterior vein	0	11
Proximal posterior vein	0	3
Great cardiac vein	0	6

CS = coronary sinus; LV = left ventricular.

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lateral left minithoracotomy (3 cm) in fifth intercostal space was made and a 5-mm camera port was inserted in the same space. A pericardial 2-cm incision was made anteriorly to the phrenic nerve. Once the lateral wall of the left ventricle was exposed and the marginal arteries identified, a bipolar epicardial screw-in lead (Myodex 1084T, St. Jude Medical, Minneapolis, Minnesota) was inserted and placed over the mid-basal segments of the posterolateral or lateral wall. The implantation of the lead on LV surface was guided by intraoperative electrophysiologic evaluation of the segment with the highest degree of electrical intraventricular delay and higher increase of systemic blood pressure during LV pacing. In relation to the limited size of thoracotomy, the regions tested by this method during operation were 3.0 ± 1.0. The mean electrical intraventricular delay recorded over the tested lateral or posterolateral wall segments was 48 ± 14 ms, and the mean increase of blood pressure during LV pacing was 34 ± 11 mm Hg. After defining the optimal pacing location, the LV lead was screwed in and then was tunneled subcutaneously to the left subclavicular region to the device pocket.

Chest tubes were removed after a mean of 22 ± 6 h and patients remained in the intensive care unit for less than 18 h; 48 h after operation, patients underwent endocardial implantation of right atrial and right ventricular shocking and pacing leads. There was neither significant morbidity nor mortality related to the minithoracotomic procedure. Seventeen patients of this group received a cardioverter-defibrillator (Contak Renewal, Guidant, St. Paul, Minnesota; or Atlas HF, St. Jude Medical) and 3 a pacemaker (Contak TR, Guidant).

Biventricular device transvenous implantation. In 18 of 20 patients who underwent transvenous procedure, a cardioverter-defibrillator (Guidant Contak Renewal or St. Jude Atlas HF) was implanted, whereas the remaining 2 received a pacemaker (Guidant Contak TR). The right atrial and ventricular leads were positioned conventionally. The LV pacing lead was inserted by left subclavian approach and advanced through CS into a CS vein unrelated to the mid-basal segments of the lateral or posterolateral wall. Guided by a conventional retrograde CS angiography (that confirmed MSCT pre-operative anatomic findings), the physician who implanted the LV lead tried to achieve the most satisfactory LV lead position by sampling different CS veins (mean 3.5 ± 1.5 veins). The purpose was to obtain the shorter width of the QRS complex and the highest increase in arterial systolic pressure with biventricular pacing.

Statistics. All continuous data were presented as mean ± SD and categorical data as n (%). Within-group comparisons were performed by paired *t* test for continuous variables and by McNemar test for categorical variables. Distribution of NYHA functional class was compared by using the chi-square test for trend. Between-group comparisons were performed by computing pre/post variations and tested by covariance analysis adjusting for baseline values. All tests were 2-sided and p values <0.05 were considered significant. All analyses were performed using SPSS (version 17, SPSS Inc., Chicago, Illinois). Finally, multivariate analysis has been performed in all parameters for which changes were present (<0.05) at univariate analysis 1 year after CRT; correction for multiple testing was performed by the Bonferroni-Holm method.

Results

In all patients of Group 1, the pacing lead was positioned over the posterolateral wall of the LV. In 16 patients, the LV lead was positioned on the epicardium over the middle-basal segments of the lateral wall, in the area of the obtuse marginal branch of the circumflex artery, and in the remaining 4 patients, the LV lead was implanted more posteriorly over the middle posterolateral wall of the LV (Table 2). Mean procedure duration (skin-to-skin) and total fluoroscopic time were lower in Group 1 than in Group 2, mainly in relation to the significantly lower time required for epicardial LV lead implantation as compared to the time necessary for endocardial positioning (Table 3). Acute pacing thresholds, impedance, and sensing values recorded during implantation did not significantly differ in surgical and transvenous groups; similarly, 12-month thresholds

Table 3 Procedural Data in Groups 1 and 2

Procedural Data	Group 1	Group 2	p Value
Mean procedure duration, min	128 ± 36	188 ± 45	<0.03
Mean time to LV catheter positioning, min	13 ± 8	34 ± 17	<0.02
Total fluoroscopic time, min	22 ± 8	54 ± 22	<0.03
Acute pacing thresholds, V	1.1 ± 0.6	1.4 ± 0.7	<0.07
Pacing impedance, Ohms	938 ± 46	1,135 ± 78	0.8
Sensing values, mV	14.4 ± 6.7	12.2 ± 5.3	0.7
12-month pacing thresholds, V	1.3 ± 0.5	1.5 ± 0.7	0.5
Post-operative stay, days	10 ± 3	7 ± 3	<0.04
CS veins sampled during procedure		3.5 ± 1.5	
Regions tested during surgery	3.0 ± 1		
Mean electrical intraventricular delay, ms	48 ± 14		
Mean blood pressure increase during LV pacing, mm Hg	34 ± 11		

LV = left ventricular.

Table 4 NYHA, Echocardiographic, and Functional CPET Changes in Groups 1 and 2

	Group 1			Group 2		
	Pre-CRT	Post-CRT	p Value	Pre-CRT	Post-CRT	p Value
Clinical parameters						
NYHA functional class I	0	2	0.0042*	0	0	0.9197*
NYHA functional class II	1	15		2	5	
NYHA functional class III	11	3		13	11	
NYHA functional class IV	8	0		5	1	
Echocardiographic parameters						
LVEF, %	28.8 ± 9.2	33.9 ± 7.2	<0.01	27.4 ± 4.8	27.4 ± 5.7	0.98
LVESV, ml	165 ± 53	134 ± 48	<0.001	175 ± 46	166 ± 44	0.15
MI (1–4) scale	2.7 ± 0.8	2.3 ± 1	<0.008	2.7 ± 1.2	2.4 ± 1	<0.01
CPET parameters						
Peak Vo_2, ml/min	824 ± 445	1,043 ± 307	<0.03	855 ± 331	880 ± 309	0.69
Peak Vo_2/kg, ml/kg/min	10.4 ± 4.5	13.1 ± 3.1	<0.02	11.2 ± 3.2	11.3 ± 3.4	0.90
Peak WR, W	58 ± 38	71 ± 27	0.10	56 ± 26	65 ± 27	0.26
VE/VCO_2	35 ± 9	33 ± 6	0.26	37 ± 8	35 ± 9	0.57

Group 2 Post-CRT n = 17. *McNemar test.

CPET = cardiopulmonary exercise test; CRT = cardiac resynchronization therapy; MI = mitral insufficiency; VCO_2 = carbon-dioxide production; VE = ventilation; WR = work rate; other abbreviations as in Table 1.

were not different in both groups. In 4 patients of the surgical group, a pleural effusion, not requiring a specific treatment, was recorded in the post-surgical period. A dislodgment of the LV catheter requiring re-operation occurred in 1 patient of Group 2. Post-operative hospital stay was significantly longer in patients who underwent surgical LV lead implantation (Table 3).

At the end of the follow-up period (12 months), in Group 1, a significant improvement of NYHA class and of LVEF and a decrease of LVESV and of mitral regurgitation grade scale were recorded. Similarly, CRT allowed a marked increase of peak Vo_2 and peak Vo_2/kg, whereas changes of peak WR and VE/VCO_2 slope showed a trend toward an improvement but were not statistically different (Table 4). Finally, in this group during follow-up, no death occurred nor was cardiac transplantation necessary (Table 5).

In 11 patients who underwent a transvenous procedure, guided by MSCT and perioperative CS angiographic findings, the LV lead was implanted in the apical segments of a posterior vein; in 3 patients, over a proximal posterior vein; and in 6 patients, in the great cardiac vein (Table 2). In patients of this group, 12 months after implantation, NYHA functional class remained unchanged, as LVEF and LVESV did not vary significantly. However, a slight but significant improvement of mitral regurgitation grade scale was recorded. Moreover, all CPET-derived parameters were unchanged (Table 4). During the follow-up period, 2 patients of this group died (1 for worsening heart failure, 1 for untreatable arrhythmias) and 1 underwent urgent heart transplantation (Table 5). Twelve months after implantation, at multivariate analysis, in surgical patients, the improvement of NYHA class, LVEF, LVESV, peak Vo_2, and peak Vo_2/kg was significantly higher than in nonsurgical ones; instead, changes of peak workload and of VE/VCO_2 between the 2 groups were not significant (Table 6). Finally, after 12 months of CRT, the HF-related hospitalizations for each patient were significantly lower in Group 1 than in Group 2 (1.5 ± 0.5 vs. 4.7 ± 1.2, $p < 0.003$). Finally, after CRT procedure in transvenous and surgical patients, the use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, loop and potassium-sparing diuretics, nitrates, and digoxin was optimized by the HF specialist, without significant differences between the 2 groups' patients (Table 7).

Table 5 Follow-Up Data in Both Groups of Patients

Follow-Up Data	Group 1	Group 2
Months	11 ± 3	12 ± 2
Followed 1 yr	20/20	17/20
Died	0	2
Dropped out	0	0
Cardiac transplantation	0	1

Discussion

Our study shows that, in patients with an unfavorable CS anatomy, a surgical strategy aimed at a selective lead positioning over the middle-basal segments of the lateral or the middle area of posterolateral wall of the LV is superior to the transvenous placement in a second- or third-choice segment guided by the local anatomy.

Even though the papers of Derval et al. (23) and Saxon et al. (24) have indicated that the acute hemodynamic improvement after CRT is rarely related to lead placement over the lateral wall of the LV. The majority of studies (3,25–29) have underlined the pivotal importance of an optimal LV lead positioning over the posterolateral or lateral wall of the LV in determining a positive hemodynamic and clinical response to CRT and in achieving an

Table 6 Long-Term Effects of CRT: Comparison Between Groups 1 and 2

	Group 1	Group 2	p Value*	p Value†	p Value‡
Clinical parameters					
NYHA functional class I	2	0	0.0007*		
NYHA functional class II	15	5			
NYHA functional class III	3	11			
NYHA functional class IV	0	1			
Echocardiographic parameters					
LVEF, %	33.9 ± 7.2	27.4 ± 5.7		<0.008	<0.01
LVESV, ml	134 ± 48	164 ± 44		<0.03	<0.04
CPET parameters					
Peak Vo_2, ml/min	1,043 ± 307	880 ± 309		<0.04	<0.05
Peak Vo_2/kg, ml/kg/min	13.1 ± 3.1	11.3 ± 3.4		<0.03	<0.04
Peak WR, W	71.7 ± 27	65 ± 27		0.54	0.99
VE/VCO_2	33.6 ± 6	35 ± 9		0.43	0.96

Group 1, n = 20; Group 2, n = 17. *Chi-square test for trend. †Covariance analysis adjusting for baseline values. ‡Correction for multiple testing performed by the Bonferroni-Holm method.
Abbreviations as in Tables 1 and 4.

early LV reverse remodeling. The hemodynamic improvement obtained by pacing these areas, which, in almost all HF patients with left bundle branch block, represent the sites of latest mechanical activation (30–32), is greater than that provided by stimulation within the great cardiac vein or in the anterior venous branches of CS. That may even worsen the hemodynamic profile because of early stimulation of interventricular septum with further loss of LV synchrony. In the study of Zhang et al. (33), the placement of the LV lead at a posterolateral position was predictive of a lower all-cause and cardiovascular mortality, providing additional prognostic value to the presence and assessment of dyssynchrony. In this article, the absence of dyssynchrony and a nonposterolateral lead position were associated with inadequate LV reverse remodeling response. Conversely, the rate of responders to CRT increased from 60% in the presence of dyssynchrony alone to 86% when dyssynchrony and posterolateral LV lead position coexisted. However, owing to technical limitations of trans-CS implantation of the LV lead, in at least 30% of patients who underwent CRT procedure, an adequate placement of the LV catheter over the lateral wall of the LV may not be feasible, even by experienced implanters. In this setting, as reported by several investigators (34,35), usually the LV lead is implanted into an atypical site (i.e., anterior or middle cardiac veins). Indeed, Alonso et al. (34) reported that 36% of LV leads were atypically placed and, in a later experience (35), only a 70% rate of achievement of positioning of the LV lead over the intended target site (lateral or posterolateral tributaries of the CS) was described. In the EASYTRAK Registry 2001 (36), in only 54% of patients, the lateral wall was reached, and in more than 30% of recorded cases, the CS lead was implanted in an anterior position. In preventing the implantation of the LV catheter over a hemodynamically ineffective area, the pre-operative study of the CS main veins anatomy might be of primary importance to identify unsuitable anatomic patterns, leading us to prefer the minithoracotomic approach to achieve an effective LV lead positioning. The feasibility of the surgical approach was demonstrated in the study of Mair et al. (15) in which a correct lead positioning over the obtuse marginal branch area was achieved in all surgical patients in comparison to only 70% of patients who underwent conventional CS-lead implantation. The safety of the minithoracotomic and endoscopic (video-assisted thoracoscopy surgery or robotic) approaches for LV lead implantation has been previously shown by Navia et al. (16) and Gabor et al. (17). These investigators reported the important advantage of the surgical approach, which enables the direct visualization of the lateral LV wall, allowing physicians to avoid the areas of scarred myocardium that might be associated with excessively high pacing thresholds and/or ineffective pacing. Moreover, the surgical procedure provides the opportunity of a more appropriate selection of pacing site in the lateral wall, by performing an electrophysiologic and hemodynamic mapping, guiding the surgeon to the area of latest electrical activation and best hemodynamic response.

Table 7 Use of HF Medications Before and After CRT Procedure in Groups 1 and 2

	Group 1		Group 1	
HF Medications	Pre-CRT	Post-CRT*	Pre-CRT	Post-CRT*
Carvedilol	14	14	13	13
Bisoprolol	6	5	7	7
ACE inhibitors	19	19	19	17
Furosemide	20	20	19	17
Spironolactone	18	16	17	17
Nitrates	12	10	11	10
Digoxin	8	6	7	6

Values are number of patients. *At long-term evaluation.
ACE = angiotensin-converting enzyme; CRT = cardiac resynchronization therapy; HF = heart failure.

The current study is the first in which long-term clinical, echocardiographic, and CPET changes after CRT have been evaluated in a selected population of candidates to CRT with pre-operative documentation of unsuitable anatomy of CS main branches, randomized to transvenous procedure versus surgical LV lead implantation. The first finding from this study was that, in all patients referred to surgical minithoracotomic implantation and in no patients of the transvenous group, the LV lead was placed over the posterolateral wall of the LV. In the surgical group, but not in transvenously implanted patients, 12 months after starting CRT, a significant increase with respect to baseline, of NYHA class, LVEF, peak V_{O_2} and peak V_{O_2}/kg were recorded; a marked decrease of LVESV was also recorded. Moreover, the comparative analysis of data recorded in both groups of patients at the end of the follow-up period showed that the improvement of NYHA class, LVESV, LVEF, and CPET parameters was significantly higher in surgically treated patients than in patients who underwent conventional transvenous procedure. Two are the major prognostic indicators independent of each other, obtained by CPET, peak V_{O_2} and VE/VCO_2 slope. In Group 1, the former improved and the latter did not, whereas both remained unchanged in Group 2. This is likely due to the close relationship between cardiac output and V_{O_2}, whereas the VE/VCO_2 is influenced by ventilation/perfusion matching in the lung and ventilation reflex regulation. Therefore, it is unlikely that CRT influences the VE/VCO_2 slope except after prolonged and marked improvement of clinical conditions.

Study limitations. First, we studied a small number of patients with a 1-year follow-up. So larger and more prolonged studies are certainly advocated to confirm our findings before a large-scale utilization of surgical LV lead positioning can be proposed in patients with unfavorable cardiac veins anatomy. Second, the patient population of our study was highly selected (patients with previous pacemaker, impaired renal function, irregular heart rate during MSCT, inability to sustain a breath hold for 25 s, and body mass index >40 kg/m^2) and this could limit the approach consisting of pre-operative evaluation of CS anatomy by MSCT followed by surgical LV lead implantation to a wider population of CRT procedure candidates. Third, the definition of "unfavorable cardiac veins anatomy" is subjective and, at present, a quantitative scale of favorableness of cardiac veins anatomy is lacking; moreover, the technical difficulties related to an unfavorable CS anatomy, leading to a surgical procedure, could in some cases be overcome by an experienced implanter with modern tools. Therefore, the results of our study are limited to patients with a clearly unfavorable anatomy. Fourth, we also recognized that in patients undergoing to the surgical procedure, it was possible to guide, by intraoperative electrophysiologic and hemodynamic evaluation, the surgeon allowing him to reach the segment of the highest degree of electrical intraventricular delay and higher increase of systemic blood pressure during LV pacing. So it was not just a simple surgical lead positioning on LV free wall but an electrophysiologically and hemodynamically guided lead positioning. Finally, we excluded patients with previous thoracotomy, which might increase the surgical risk of LV lead implantation during a following thoracotomy as well as might impede a proper lead positioning. Consequently, our results should not be applied to HF patients with previous thoracotomy.

Conclusions

Data from this study underline the importance of the pre-operative knowledge, gained in the present study by MSCT, of CS main branches anatomy, because it allows the screening of patients with unfavorable anatomic patterns. In these patients, an accurate electrophysiologically and hemodynamically guided LV lead positioning over the posterolateral wall of the LV by the minithoracotomic surgical approach is preferable. The improvement of clinical, echocardiographic, and CPET parameters recorded in surgical patients as compared in patients in whom the lead was placed into another nonposterolateral vein, suggests that physicians should consider the epicardial implantation as the first line approach in patients with unfavorable CS anatomy.

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REFERENCES

1. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in Cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40:111–8.
2. Auricchio A, Stellbrink C, Sack S, et al., for the PATH-CHF Study Group. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002;39:2026–33.
3. Cazeau S, Leclercq C, Lavergne T, et al., for the MUSTIC Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.
4. Linde C, Braunschweig F, Gadler F, Bailleul C, Daubert JC. Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the Multisite Stimulation in Cardiomyopathy study (MUSTIC). Am J Cardiol 2003;91:1090–5.
5. Abraham WT, Fisher WG, Smith AL, et al., for the MIRACLE Study Group. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1902–5.
6. Young JB, Abraham WT, Smith AL, et al., for the MIRACLE ICD Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. JAMA 2003;289:2686–94.
7. Anand IS, Carson P, Galle E, et al. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. Circulation 2009;119:969–77.
8. Bristow MR, Saxon LA, Boehmer J, et al., for the COMPANION Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.

9. Cleland JG, Daubert JC, Erdmann E, et al., for the Care-HF Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
10. Rossillo A, Verma A, Saad EB, et al. Impact of coronary sinus lead position on biventricular pacing: mortality and echocardiographic evaluation during long-term follow-up. J Cardiovasc Electrophysiol 2004;15:1120–5.
11. Auricchio A, Stellbrink C, Block M, et al. 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;99:2999–3001.
12. Butter C, Auricchio A, Stellbrink C, et al., for the Pacing Therapy for Chronic Heart Failure II Study Group. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001;104:3026–9.
13. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J III. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006;113:960–8.
14. Becker M, Kramann R, Franke A, et al. Impact of left ventricular lead position in cardiac resynchronization therapy on left ventricular remodelling. A circumferential strain analysis based on 2D echocardiography. Eur Heart J 2007;28:1211–20.
15. Mair H, Sachweh J, Meuris B, et al. Surgical epicardial left ventricular lead versus coronary sinus lead placement in biventricular pacing. Eur J Cardiothorac Surg 2005;27:235–42.
16. Navia JL, Fernando AA, Grimm R, et al. Minimally invasive left ventricular epicardial lead placement: surgical techniques for heart failure resynchronization therapy. Ann Thorac Surg 2005;79:1536–44.
17. Gabor S, Prenner G, Wasler A, Schweiger M, Tscheliessnigg KH, Smolle-Jüttner FM. A simplified technique for implantation of left ventricular epicardial leads for biventricular re-synchronisation using video-assisted thoracoscopy (VATS). Eur J Cardiothoracic Surg 2005; 28:797–800.
18. Singh JP, Houser S, Heist EK, Ruskin JN. The coronary venous anatomy: a segmental approach to aid cardiac resynchronization therapy. J Am Coll Cardiol 2005;46:68–74.
19. Jongbloed M, Lamb HJ, Bax J, Schalij. Noninvasive visualization of the cardiac venous system using multislice computed tomography. J Am Coll Cardiol 2005;45:749–53.
20. Lemola K, Mueller G, Desjardins B, et al. Topographic analysis of the coronary sinus and major cardiac veins by computed tomography. Heart Rhythm 2005;2:694–9.
21. Vardas PE, Auricchio A, Blanc JJ, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy: the Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. Eur Heart J 2007;28:2256–95.
22. Pontone G, Andreini D, Cortinovis S, et al. Imaging of cardiac venous system in patients with dilated cardiomyopathy by 64-slice computed tomography: comparison between non-ischemic and ischemic etiology. Int J Cardiol 2010;144:340–3.
23. Derval N, Steendijk, Gula LJ, et al. Optimizing hemodynamics in heart failure patients by systematic screening of left ventricular pacing sites: the lateral left ventricular wall and the coronary sinus are rarely the best sites. J Am Coll Cardiol 2010;55:566–75.
24. Saxon LA, Olshansky B, Volosin K et al. Influence of left ventricular lead location on outcomes in the COMPANION study. J Cardiovasc Electrophysiol 2009;20:764–8.
25. Butter C, Auricchio A, Stellbrink C, et al., for the Pacing Therapy for Chronic Heart Failure II Study Group. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001;104:3026–9.
26. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneous delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002;105:438–45.
27. Bax JJ, Bleeker GB, Marwick TH, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol 2004;44:1834–40.
28. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006;113:960–8.
29. Abraham WT, Fisher WG, Smith AL, et al., for the MIRACLE Study Group. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
30. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M. Biventricular pacing in heart failure: back to basics in the pathophysiology of left bundle branch block to reduce the number of nonresponders. Am J Cardiol 2003;91:55F–61F.
31. Fung JW, Yu CM, Yip G, et al. Variable left ventricular activation pattern in patients with heart failure and left bundle branch block. Heart 2004;90:17–9.
32. Auricchio A, Fantoni C, Regoli F, et al. Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. Circulation 2004;109:1133–9
33. Zhang Q, Yip GW, Chan YS, et al. Incremental prognostic value of combining left ventricular lead position and systolic dyssynchrony in predicting long-term survival after cardiac resynchronization therapy. Clin Sci 2000;117:397–404.
34. Alonso C, Leclercq C, d'Allonnes FR, et al. Six year experience of transvenous left ventricular lead implantation for permanent biventricular pacing in patients with advanced heart failure: technical aspects. Heart 2001;86:405–10.
35. Alonso C, Leclercq C, Victor F, et al. Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. Am J Cardiol 1999;84:1417–21.
36. Pürerfellner H, Nesser HJ, Winter S, et al., for the EASYTRAK Registry. Transvenous left ventricular lead implantation with the EASYTRAK lead system: the European experience. Am J Cardiol 2000;86:157K–64K.

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