Impact of the left ventricular lead on the efficacy of Cardiac Resynchronization Therapy for heart failure.

Electrophysiologic and clinical trials investigating active fixation left ventricular lead in cardiac resynchronization therapy.

Håvard Keilegavlen

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Table of contents

1. Acknowledgements

The work for this thesis was performed at the Department of Heart Disease, Haukeland University Hospital and Department of Clinical Science, University of Bergen from 2013-2020. The thesis is based on clinical studies carried out at the section of Pacing, ICD and Heart Failure Management.

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2. Abstract

Background:

This thesis examines the performance of different left ventricular (LV) leads and in particular a novel bipolar LV lead with a side helix for active fixation. Cardiac resynchronization therapy (CRT) provides improved cardiac performance and clinical outcome in heart failure patients with wide QRS complex. Placement of the LV lead in a segment remote from the region with latest mechanical activation or in a segment with myocardial scar is associated with high risk for non-response. The ability to reach the desired position, the rate of lead dislodgements, occurrence of phrenic nerve stimulation (PNS) and clinical outcome are affected by properties of the LV leads.

Methods and results:

In the first paper (Paper I) we presented the results from a prospective non-randomized trial of 106 patient who received a CRT-device with a novel active fixation bipolar LV lead. The primary objectives were to assess the lead implant success, the degree of LV lead concordance to the pre-decided target location, procedure times and perioperative adverse events. The secondary objectives were to evaluate the long-term performance concerning lead stability, long-term pacing capture thresholds (PCT), occurrence of PNS and need for repositioning of the lead. In 103 patients, the active fixation LV lead Attain Stability model 20066/4796, (Medtronic, Minneapolis, MN, USA) was implanted. We showed that this novel lead allowed placement of the lead over a wide range of vein anatomies. The average LV PCT at implant was low (1.04±0.6 V), remained stable at follow-up (0.92±0.5V) and no late dislodgements were observed. Moreover, the lead was placed in an LV segment concordant to the segment with latest mechanical activation in 73 % of the patients and in an adjacent segment in 24 % of the patients.

In a subsequent trial that is the basis for Paper II and Paper III, the objective was to compare the active fixation LV lead and a quadripolar passive fixation LV lead. A randomized and blinded trial, that included 63 patients scheduled for CRT device implantation, was performed and the patients were followed up for 12 months. The

latest contracting LV segment was identified as target segment by radial strain speckle-tracking echocardiography. In Paper II, we compared the electrical performance and the ability to achieve a stable proximal position in a coronary vein located concordant to the target segment. The success rate in reaching the target location was not significantly different between the two LV leads (p=0.69). Upon implantation, the quadripolar lead demonstrated a lower PCT than the bipolar lead (0.77±0.2V vs 1.09±0.48V, p= 0.02), but at follow-up, there was no difference. There were no differences in the LV lead implant times or radiation doses. The active fixation did not facilitate a higher grade of concordance to the target LV segment nor a more proximal position of the stimulating electrode. In the third article we compared the clinical outcome in terms of improvement of cardiac performance assessed by echocardiography. At follow-up, the reduction of LV end-systolic volume, and LV reverse remodeling responder rate, defined as LV end-systolic volume reduction >15 % was 77 % in the active fixation group and 84 % in the quadripolar group, which was not significantly different. (p=0.51). From baseline to 6 months follows-up the LV ejection fraction (LVEF) improved significantly in both groups, and more in the quadripolar group, but at 12 months follows-up the LVEF did not differ between the two groups. There were no significant differences between the two groups in changes in NYHA functional class or score in Minnesota Living with Heart Failure Questionnaire. The occurrence of PNS was 19 % in the active fixation group versus 10 % in the quadripolar group (p=0.30) and was resolved in all cases by reprogramming the device. All patients were alive at 12 months follow-up. There was no device infection.

Conclusion:

This thesis demonstrates that a novel active fixation bipolar LV lead may be placed over wide range of vein anatomies. We were not able to prove superiority over quadripolar passive fixation LV leads in terms of electrophysiologic parameters, ability to reach target segment or clinical outcome.

3. List of Publications

1. Active fixation of a thin transvenous left-ventricular lead by a side helix facilitates targeted and stable placement in cardiac resynchronization therapy. Keilegavlen H, Hovstad T, Faerestrand S.
   Europace. 2016;18(8):1235-40.
   https://doi.org/10.1093/europace/euv272

2. Performance of an active fixation bipolar left ventricular lead vs passive fixation quadripolar leads in cardiac resynchronization therapy, a randomized trial. H. Keilegavlen, P. Schuster, T. Hovstad, S. Faerestrand.
   Journal of Arrhythmia 2020 Nov 8;37(1):212-218.
   https://doi.org/10.1002/joa3.12450

3. Clinical outcome of cardiac resynchronization therapy in patients randomized to an active fixation bipolar left ventricular lead versus a passive quadripolar lead. H. Keilegavlen, P. Schuster, T. Hovstad, S. Faerestrand
   Scandinavian Cardiovascular Journal 2021;Jan 10;1-7.
   https://doi.org/10.1080/14017431.2020.1869299

4. Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
CMR	cardiovascular magnetic resonance
CRT	cardiac resynchronization therapy
ECG	electrocardiogram
ESC	European Society of Cardiology
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ICD	implantable cardioverter defibrillator
LAO	left anterior oblique
LBBB	left bundle branch block
LV	left ventricle
LVEDd	left ventricle end-diastolic diameter
LVEF	left ventricular ejection fraction
LVESV	left ventricle end-systolic volume
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MRA	mineralocorticoid receptor antagonist
NYHA	New York Heart Association
PNS	phrenic nerve stimulation
Q-LV	time delay from QRS onset to left ventricular lead sensed signal
RA	right atrium
RV	right ventricle
RAO	right anterior oblique
STE	speckle tracing echocardiography
ST-RS	speckle tracking radial strain

5. Introduction

5.1 Heart failure

Heart failure is the clinical syndrome caused by impairment of the heart to load or eject blood. It is characterized by dyspnoea and fatigue. The prevalence is about 2 % of the entire population and due to an ageing population, the prevalence of heart failure has not decreased in recent decades.(1-3) Despite considerable advances in medical and operative treatments, the morbidity, mortality, and hospitalization rates in heart failure remain high.(3, 4) For patients hospitalized for heart failure, about 20 % will die within a year of admission and five years mortality is about 50 %.(5) The quality of life is considerable reduced by heart failure. Risk factors as age, coronary heart disease, male sex, hypertension and diabetes mellitus all add risk for developing heart failure.

The left ventricular ejection fraction (LVEF), assessed by echocardiography divides heart failure patients into groups with preserved ejection fraction (HFpEF), heart failure with mid-range ejection fraction (HFmrEF) and heart failure with reduced ejection fraction (HFrEF). About 50 % of the patients have preserved left ventricular ejection fraction and for these patients there is little evidence for prognostic benefit from specific heart failure medication or implantable devices as cardiac resynchronization therapy (CRT). In the present studies we included patients that despite optimal medical treatment had symptomatic HFrEF.

Drug treatment for chronic heart failure is extensive. Angiotensin-converting enzyme inhibitors (ACEIs) are recommended as first-line therapy, independent of clinical symptoms, and are shown to reduce all-cause mortality, clinical symptoms and hospitalizations.(6) An angiotensin receptor blocker (ARB) is an alternative agent if ACEI is not tolerated.(7) Similarly, added to ACEIs, betablockers and

mineralocorticoid receptor antagonists (MRAs) improve survival, heart failure symptoms and can restore the systolic function.(8, 9) In the last decade, replacement of ACEI with angiotensin receptor-neprilysin inhibitor (ARNI) is shown to improve prognosis and to reduce heart failure hospitalization. ARNI treatment is recommended when patients remain symptomatic despite therapy with ACEI (or ARB), betablocker and MRA.(10, 11) The patients included in the present studies were considered optimal treated before CRT device implantation.

Left bundle branch block (LBBB) occurs in about 20 % of patients with advanced heart failure requiring hospitalization.(12) The electrical delays and regional mechanical contraction delays caused by the LBBB lead to an asynchronous contraction pattern that has detrimental effect on systolic performance. Mortality is strongly related to the presense of LBBB and the QRS width.(13) However, the negative prognostic impact of LBBB seems to be caused by the degree of left ventricular dysfunction and the amount of comorbidity and less by the LBBB itself.(12, 14)

5.2 Cardiac resynchronization therapy

Cardiac resynchronization therapy has been an option in advanced treatment of severe heart failure since the late 1990s.(15-17) The treatment is now an essential part of treatment for HFrEF with electrical dyssynchrony. The first implantation of a CRT device in Norway took place at Department of Heart Disease, Haukeland University Hospital in 1999.(17) Since then, the CRT implantation rate has increased significantly at our department, along with clinical research and several scientific publications including PhD theses. (18-26)

The efficacy of reducing morbidity, hospitalizations and all-cause mortality in patients with wide QRS complexes and depressed left ventricle (LV) systolic function is proven in several large randomized clinical trials of CRT.(27-30) A consistent improvement in quality of life, exercise capacity and NYHA functional class is also

confirmed.(31-33) In the CARE-HF trial, which included patients in NYHA functional class III and IV, the mortality was reduced by 36 %.(28) In MIRACLE trial 68 % of the patients had improvement of ≥1 NYHA functional classes.(27) Meta-analyses have shown benefits for CRT upon various patient characteristics.(34, 35) In this treatment, a conventional transvenous pacemaker lead or an implantable cardioverter defibrillator (ICD) lead is inserted and attached to the endocardium in the right ventricle (RV). A second pacing lead is placed in the right atrium (RA) to achieve AV-synchronous ventricular pacing at a programmed AV-delay shorter than the spontaneous AV-delay. The LV lead is implanted by a transvenous approach. The coronary sinus is cannulated by a guide catheter, guided by fluoroscopy. An occlusive contrast venogram reveals the anatomy of the coronary sinus tributaries. In a 30-40° left anterior oblique (LAO) view the LV wall is divided along the short axis into segments; anterior, anterolateral, lateral, posterolateral and posterior. Based on the present anatomy and the preoperative assessment of mechanical interventricular delays and LV scarring, the implanter chooses which side branch to target the LV lead into. Venogram in a 30° right anterior oblique (RAO) view permits segmentation into the basal, the mid and the apical long-axis position. The lead is inserted over a wire, customarily supported by subselective catheters, to a position that is acceptable in terms of low pacing capture threshold (PCT) and absence of phrenic nerve stimulation (PNS) (Figure 1).

The intended mechanisms of CRT are to restore intraventricular LV synchrony between the interventricular septum and the latest activated LV segments, as well as obtaining interventricular (V-V) synchronous contraction of LV and RV. Heart failure patients with bundle branch block often have delayed AV-nodal conduction, and shortening of the AV-delay by CRT can improve LV preload and cardiac function.(36) Functional mitral regurgitation is commonly found in severe heart failure with bundle branch block, and resynchronization of papillary muscle contraction and reduction of LV dimension by CRT reduce the mitral regurgitation in a considerable portion of patients.(37, 38)

There are several challenges with the CRT device implantation procedures and most of them are related to the LV lead. For some patients, the LV PCT may be high, or may increase after the implantation, which may cause early battery depletion. Occurrence of PNS, due to proximity of the stimulating electrode of the LV lead to the phrenic nerve, has been reported in about 1of 4 pasients receiving an LV lead.(39, 40) This problem may be resolved by reprogramming of the device by changing pacing vector or lowering the output in the majority of cases. However, in some patients, PNS may necessitate operative intervention with revision or replacement of the LV lead. For an absolute minority of the patients, a surgical approach with LV epicardial lead implantation through a left lateral minithoracotomy is a solution.(41)

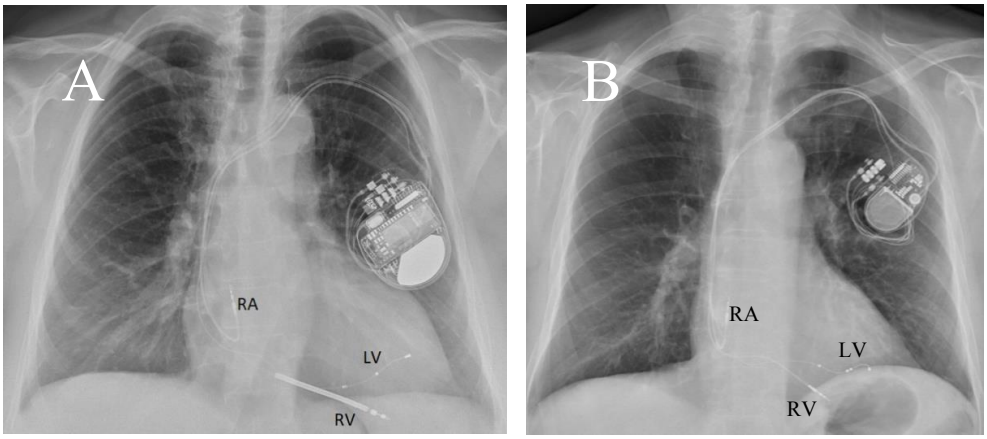

Figure 1*. Chest X-rays in posteroanterior view. A) A CRT-D device with a lead in the right atrium (RA), an ICD lead in right ventricle (RV) and an active fixation left ventricular lead in a lateral branch from coronary sinus (LV). B) CRT-P device with a conventional pacing lead in the right ventricle (RV) and a quadripolar passive fixation left ventricle lead in a posterolateral branch from coronary sinus.*

5.3 Criteria for patient selection in CRT

Proper patient selection is crucial in CRT. The treatment is only proven and recommended for patitents that have symptomatic heart failure despite optimal medical therapy. CRT should be offered to all patients that may have good change of beneficial clinical response based on scientific practice guidelines. For patients with no scientific indication for CRT, the device can deteriorate LV function and clinical symptoms. Even when CRT is given according to the current practice guidelines, approximately 30 % of patients do not benefit clinically, and even some of them may be negative responders and deteriorate.(42) Patients with female gender, non-ischemic etiology and wide QRS complexes are more often clinical responders and have more improvement in echocardiographic response.(34) The European Society of Cardiology (ESC) updated in 2016 the heart failure treatment guidelines and the indication for CRT as compared to the 2013 ESC guidelines.(10) CRT is recommended in symptomatic heart failure (NYHA functional class II-IV), LV ejection fraction ≤ 35 % and QRS prolongation. (Table 1) Patients with atrial fibrillation are more often non-responders, and CRT is indicated only if a strategy for high rate of bi-ventricular capture is ensured.

Table 1 *Indications for CRT in patients with heart failure on optimal medical treatmen according to ESC heart failure practice guidelines. (10)*

	Class	Level
Patients in sinus rhythm, LVEF ≤ 35 % and symptomatic heart failure		
LBBB, QRS duration ≥150 ms	I	A
LBBB, QRS duration 130-149 ms	I	B
Non-LBBB, QRS duration ≥150 ms	1Ia	B
Non-LBBB, QRS duration 130-149	IIb	B
Patients with atrial fibrillation and LVEF ≤ 35 %		
QRS > 130 ms and NYHA III-IV	IIa	B
Patients with HFrEF requiring pacemaker or ICD due to AV block	I	A
Patients with QRS < 130 ms	III	A

5.4 Left ventricular pacing leads

Transvenous LV lead placement is the standard approach for LV pacing in CRT. Over the last 2 decades, the LV leads have evolved from unipolar to bipolar and further, to quadripolar models. Compared to unipolar and bipolar leads, quadripolar leads provide more available pacing vectors. More pacing vectors allow more opportunities to achieve an acceptable PCT and avoidance of PNS. Multipolar leads may also promote a more optimal position of the stimulating electrode. In the early trial of CRT, the failure rate for LV lead placement was 8-15 %.(27, 28, 30) More advanced LV lead delivery systems and the change from bipolar to quadripolar leads have reduced the complication rate and have enhanced the implant success.(43) Quadripolar leads are now considered superior to passive fixation bipolar LV leads due to a lower rate of PNS, fewer lead dislocations and there is evidence for a better clinical response.(44-46) When active fixation of endocardial leads was introduced in the right atrium and in non-apical right-ventricular sites, the dislodgement rate diminished significantly, without impeding transvenous lead extraction. The fixation mechanism for LV lead is traditionally passive. The preshaped leads are advanced and wedged distally within target branch of coronary veins. Larger dimension and increased stiffness of the lead body enhance stability and improve PCT, but on the other hand, impair trackability along tortuous coronary veins. An active fixation lead equipped with deployable lobes, Attain Starfix (Medtronic Inc., Minneapolis, USA), demonstrated superb stability performance, but the fixation mechanism makes lead extractions very difficult.(47) Conventional pacing leads with end-helix fixation mechanism designed for endocardial implantation have been implanted in coronary veins, but this entails a high risk of peroperative bleeding and there are limited experience with transvenous lead extraction of this leads.(48) Stenting of a coronary sinus branch with bare metal stents deposited proximal to the proximal electrode to prevent LV lead dislocation has also been reported.(49) This method involves a risk of damage to the insulation that covers the LV lead, and like all this experimental fixation methods, there will be a future risk of difficult lead extraction procedures. The novel fixation mechanism with a side helix in the Attain Stability lead

(Medtronic Inc., Minneapolis, USA) may be a solution for this problem as the side-helix will uncoil in response to realative low retraction force, similar to that applied in extraction of passive fixation LV leads.

5.5 Targeted LV lead placement

Non-optimal position of the LV lead is an important reason for inferior response to CRT, and is, in contrast to patient-related factors, potentially correctable.(50) Presence of LV electrical dyssynchrony is mandatory for a CRT indication in heart failure patients, however, the LV electrical and the mechanical activation delay in heart failure patients may not always covariate. The optimal placement of the LV lead concerning the LV segment seems to be individual.(51, 52) The goal of CRT is to improve the LV mechanical synchrony, and much research has been focused on methods for defining the latest activated LV segment for targeting the LV lead to a coronary vein concordant to this LV segment. Placement of the LV lead in a segment without transmural scar and concordant to the latest mechanically activated segment has shown superior response as compared to empiric LV lead placement in randomized clinical trials.(53-55) Echocardiographic methods, including speckle tracking derived strain imaging and tissue Doppler strain imaging are used to define target segment for placement of the LV lead. Information from speckle tracking echocardiography (STE) systolic strain as well as Cardiovascular Magnetic Resonance modalities and nuclear myocardial perfusion imaging may guide the implanters in avoiding areas of scarred myocardium. Additionally, the clinical response to CRT seems to be inferior when the LV lead stimulates from the apical LV segment.(56) Another approach is intraoperative mapping of the LV electrical activation to guide the LV lead placement to the latest electrically activated LV segment.(57)

5.6 Evaluation of clinical response

CRT is a highly efficient therapy for heart failure on top of optimal medical therapy. It improves exercise capacity and quality of life in addition to reducing heart failure hospitalizations and overall mortality. However, the clinical response to CRT is difficult to predict. The challenge is that about 30 % of the patients do not respond favourably to this therapy.(42) The response rate is high when clinical symptoms are assessed, but lower when outcome analyses or strictly echocardiographic measurements are used for evaluation.(58) The symptomatic improvements do not correlate strongly with echocardiographic improvements.(59) The level of LV revers remodelling, defined as a reduction in LV end-systolic volume (LVESV) ≥ 15 % at 6 months after implantation, is widely used as a definition of echocardiographic response and is shown to predict long term prognosis.(60-62)

6. Aims of the thesis

1. To investigate a novel active fixation LV lead in terms of:
    a. Implant success
    b. Concordance of LV placement with echocardiographic assessment of latest mechanical activation
    c. Procedure times, radiation dosage and electrical performance
    d. Complications
    e. Follow-up results; Stability, PCT and occurrence of PNS

2. To compare the active fixation LV lead with standard passive quadripolar LV leads with respect to:
    a. Lead placement
    b. Electrical performance
    c. Clinical outcome

7. Material and methods

7.1 Patient populations

The studies were conducted at Haukeland University Hospital, Bergen, Norway and Department of Clinical Science, University of Bergen, Norway. All the implantation and the follow-up consultations were done at Haukeland University Hospital. The hospital is a regional hospital for Western Norway.

7.1.1 Paper I

This study was a single-centre, prospective, non-randomized clinical trial. The inclusion period was from December 2013 to January 2015. Out of 156 patients implanted with CRT devices in this period, 106 non-consecutive patients (68 %) were included. All patients with challenging coronary venous anatomy assessed from intraoperative venography, all patients with previously implanted LV leads in need of revision and all patients with a recently failed implant attempt were included. The implantations were performed by three experienced implanters. The study was conducted in accordance with the regulations of the Regional Ethics Committee. All patients met standard criteria for CRT implantation, according to 2013 ESC Guidelines on cardiac pacing and CRT.

Echocardiography with 2D speckle tracking radial strain (ST-RS) measurement was performed prior to the procedure for all *de novo* implantations when bundle branch block was present (n=71). The segment with latest mechanical activation was evaluated from greyscale LV-short axis images at basal-mid LV region. Segments with a radial strain below 10 %, indicating a high scar burden, were excluded. The LV leads were targeted to coronary vein concordant to the preoperative decided target segment.

In patients scheduled for upgrade procedures and with paced-only QRS complexes (*n*=18), in patients with normal QRS duration implanted before AV node ablation to achieve rate control in atrial fibrillation (*n*=7), and in those with a high-grade AV block and reduced LV function (*n*=10), the LV leads were placed in a lateral or posterolateral branch of the coronary sinus not guided by STE. The primary objectives were to assess the lead implant success, the degree of LV lead concordance to the pre-decided target location, procedure time and perioperative adverse events. The secondary objectives were to evaluate the long-term performance concerning lead stability, long-term PCT, occurrence of PNS and need for repositioning of the lead.

7.1.2 Paper II-III

In Paper II and III, the results from a prospective, randomized and patient-blinded trial are presented. The objective was to compare the active fixation LV lead and a quadripolar passive fixation LV lead. From February 2016 until November 2017, 62 consecutive patients were enrolled in the trial. Inclusion criteria were symptomatic heart failure in NYHA functional class II or III or ambulatory class IV, LBBB with a QRS duration ≥120 ms or non-LBBB with a QRS duration ≥150 ms as well as LVEF ≤35 % measured by echocardiography. The regional committee for medical and health research ethics approved the study (Reference 2015/1507), and written informed consent was obtained from all patients. The study was registrated in ClinicalTrials.gov, NCT04632472. The mean age of the study population was 72±11 years, and 27 % were females. The mean LVEF was 25.7±6 %, and the mean QRS duration was 163±19 ms. The average NYHA functional class was 2.7 in both patient groups and 95 % had LBBB.

The patients were randomized to receive either the Attain Stability active fixation bipolar lead or a quadripolar passive fixation LV lead. The LV lead was targeted to the basal LV segment in a vein concordant to the LV segment with latest mechanical contraction decided by preoperative ST-RS echocardiography. A five-segment LV model was used. An echocardiographic examination was done prior to implantation and repeated at 6- and 12-months follow-up. Clinical evaluation and electrophysiological measurements telemetered from the devices by a dedicated programmer were performed at the 2-, 6- and 12-month follow-up at the outpatient clinic.

7.2 Echocardiographic imaging

Echocardiographic examinations, including 2D ST-RS, measurements were performed prior to the implantation procedures. The GE Vivid E9 echo machine (Vingmed Ultrasound, Horten, Norway) was used for all measurements and all images were stored and processed offline (Echo PAC 202 GE Medical System, Horten, Norway). The echocardiographic examinations were repeated at follow-up after 6 and 12 months of CRT. The echocardiographic analyses were done blinded to type of LV lead. The LV volumes were calculated from apical four- and two-chamber images and the modified Simpson´s rule were used for calculation of LVEF.(63) The LV end-diastolic dimension (LVEDd) was measured from parasternal long axis view. For each of the parameters, at least 3 consecutive cine loops of gray scale images were analyzed, and a mean value computed.

7.3 Speckle tracking imaging

Speckle tracking echocardiography calculates strain by tracking speckles in grey scale B-mode images. The speckles in myocardium are created as interference patterns and acoustic reflections from scatter of the ultrasound beam by the tissue. As the patterns are random, each region of the myocardium has a unique speckle pattern.

The speckles are identified and tracked frame-by-frame by the STE software. From this data, the software automatically assesses deformation in different directions and generates strain and strain rate curves.(64) The STE is an angle independent strain method. Myocardial shortening is defined as negative strain values. Myocardial lengthening and thickening, as normally seen during contraction in parasternal short-axis view, will give positive strain and strain rates. ST-RS echocardiography enables evaluation of segmental myocardial contraction.

In the current studies we used ST-RS echocardiography as a preoperative method to define the LV segment with latest mechanical activation. This was done in order to intraoperatively target the LV lead to a coronary vein positioned concordant to that segment. ST-RS echocardiography from 2D images in a mid-LV parasternal short-axis view with a frame rate ≥ 70 Hz were recorded. The start of the contraction was defined by the onset of Q-wave on the surface electrocardiogram (ECG) simultaneously recorded. The region of interest (ROI) was manually defined for each contraction and included the endocardial and epicardial borders. The program divides the echocardiographic images into 6 equal color-coded LV segments and time-strain curves were generated for the different LV segments; septal, anteroseptal, anterior, lateral, posterior and inferior (Figure 2). From these curves, the LV segmental contraction and intraventricular LV dyssynchrony could be assessed.(26) The LV segments with a strain rate < 10 % were excluded because this finding was considered to indicate a high level of transmural scarring.(65, 66) The time-delay from the anteroseptal segment to the posterior segment was defined as the antero-septal (AS-P) delay. The times from Q-wave onset on the electrocardiogram to the maximal radial strain in the anterior, lateral and posterior LV segments were calculated as an average of 5 representative consecutive cardiac cycles. The latest contracting LV segment of these 3 segments could then be defined. If the latest contraction of two of these LV segments was separated by ≤ 10 ms, the LV segment located between them was assigned the latest one. Based on this model, 5 LV segments could be determined as the segment with latest contraction; the anterior, the anterolateral, the lateral, the posterolateral or the posterior segment. The LV segments

next to the target segment were classified as adjacent LV segments, and other segments were classified as remote LV segments.(26)

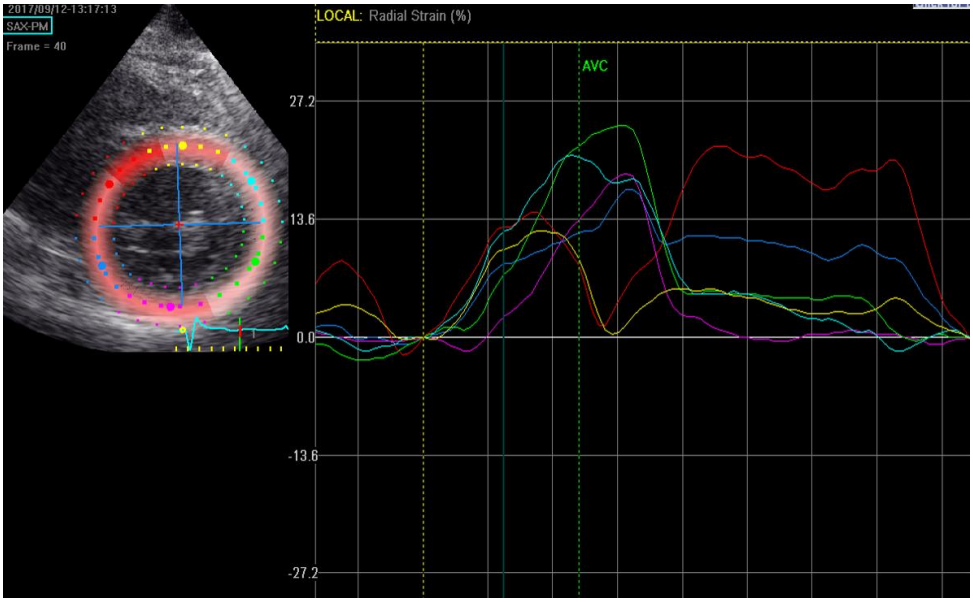

Figure 1 *Echocardiographic imaging in parasternal short-axis view. The left ventricle (LV) is divided into 6 equal colour coded segments. The right-hand picture demonstrates radial strain time curves. The septal LV segment (yellow dots and line) has early mechanical activation. The lateral LV segment (green) and the posterior LV segment (purple) demonstrate late and almost simultaneous timed mechanical activation which is significantly delayed compared to that of the anterior segment (blue). Since the mechanical activation of the lateral and the posterior LV segment are separated by less than 10 ms, the posterolateral segment between them is selected as target LV segment for placement of the LV lead (10). AVC=aortic valve closure*

Cardiovascular magnetic resonance late gadolinium enhancement, nuclear scintigraphy and STE studies have demonstrated that myocardial scarring in the proximity of the stimulating LV electrode leads to a suboptimal response to CRT.(66-68) A cut-off value of < 10 % for ST-RS was chosen based on trials demonstrating lower CRT response rate when ST-RS below 9.8 % (66) and is also used in other trials for targeted LV lead placement.(26, 53, 54)

7.4 LV lead characteristics

The active fixation lead is a soft polyurethane insulated bipolar lead (Attain Stability model 20066/4796, Medtronic Inc., Minneapolis, MN, USA). The lead body is 3.9 French (Fr) proximal and 3.4 Fr distal (figure 3). The electrode separation is 21 mm and both electrodes are steroid eluting. Proximal to the ring electrode is a small exposed side helix that enables fixation of the lead to the vein wall by rotating the lead body clockwise. A stop at the base of the helix prevents over-torqueing and entrapment of the venous wall tissue. Longitudinal movements of the lead without rotation do not engage the screw. The lead can be loosened by rotating the lead body counterclockwise if repositioning is needed. The helix is also constructed to loosen from the vein wall by uncoiling the helix with increasing retraction force during a lead extraction procedure.

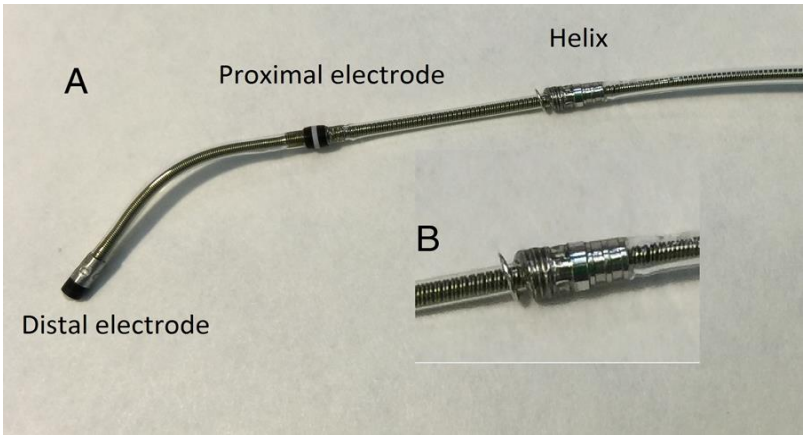

Figure 3 A*) The 4Fr dual-electrode lead with distal angled shape has an exposed side helix for active fixation located proximal to the proximal electrode. The surface area of both the proximal electrode and tip electrode is 5.8 mm^2. The electrode separation is 21.0 mm and both electrodes are steroid eluting. (*B*) Demonstrates a close-up view of the exposed side helix.*

In Paper II and III we compared the active fixation LV lead with a quadripolar lead. We used the quadripolar lead Attain Performa (Medtronic Inc., Minneapolis, MN, USA), which is a polyurethane insulated lead with a proximal diameter of 5.3 Fr and a distal diameter 3.9 Fr. (Figure 4) All four electrodes are steroid eluting. The

operators were free to choose from three different shapes: a dual bend lead, an S-curved lead and a straight lead with small tines. The dual bend lead was used in 19 patients (63 %), the S-shaped in 10 of the patients (33 %) and the straight lead in one patient (3 %).

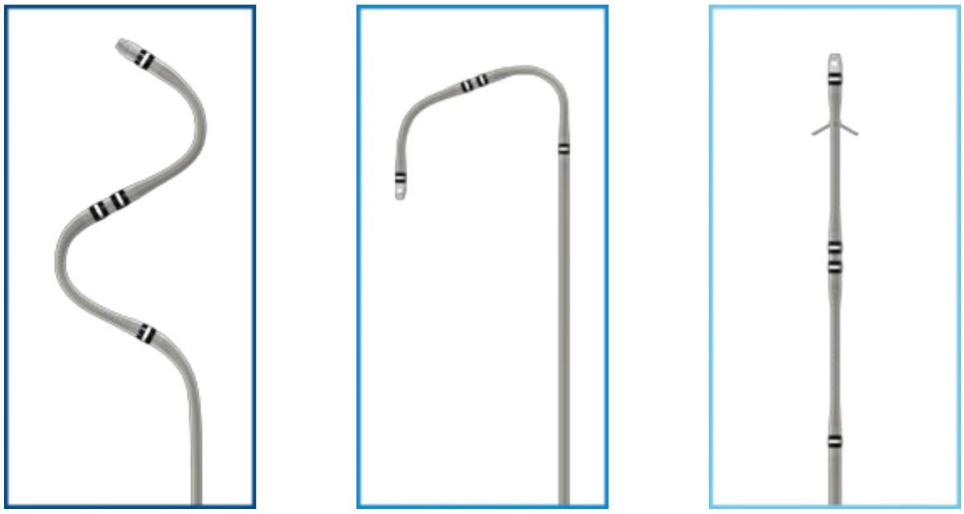

Figure 4 *The quadripolar leads: An S-shaped lead, a straight lead with tines and a dual bend lead. The distances between the electrodes are 21 mm (LV1-LV2), 1.3 mm (LV2-LV3) and 21 mm (LV3-LV4). The maximum lead body diameter is 5.3 Fr.*

7.5 CRT implantation procedure

The CRT implantation procedures were in the first trial (Paper I) performed by three experienced implanters and in the last trial (Paper II and III) by two implanters. All procedures were done under local anaesthesia. For venous access, the cephalic vein cut-down technique, the axillary vein puncture or subclavian puncture were used according to the operators´ preferences. Fluoroscopic imaging was performed in anteroposterior, LAO 30-40° view and RAO 30° view (figure 5,6 and 7).

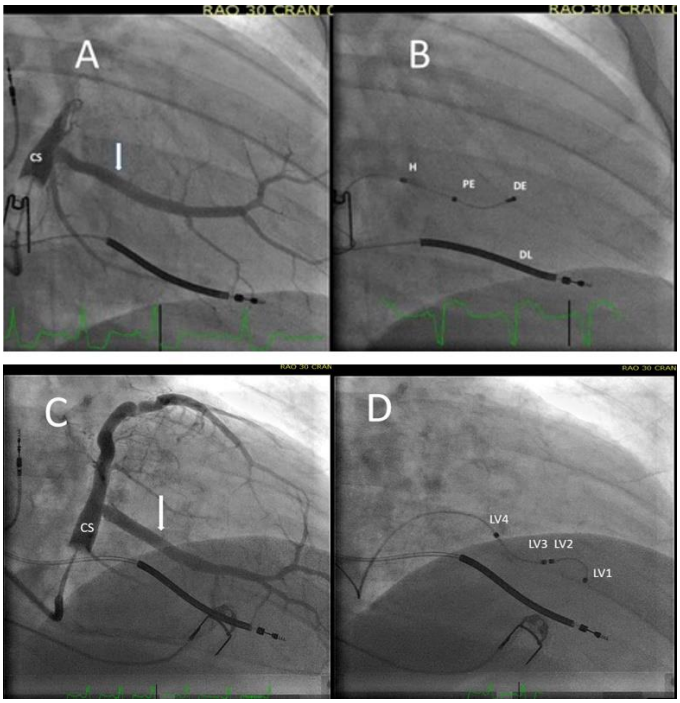

Figure 5. *Right anterior oblique fluoroscopic views of two patients with an active fixation bipolar lead (A + B) and passive fixation quadripolar lead (C+D). On the coronary sinus (CS) venograms (A+C) the arrows indicate the target veins in lateral side branches from CS. The target vein is located in the target left ventricular segment determined from speckle tracking echocardiography. B: The final lead placement of an active fixation bipolar lead. The helix (H) is fixated proximal in the vein. The proximal electrode (PE) is located in a basal third left ventricular long-axis position and is used as the stimulating cathodal electrode. The distal electrode (DE) is in the mid third left ventricular long-axis segment. The high voltage right ventricular defibrillator lead (DL) is located close to the apex of the right ventricle. D: The final lead placement of a quadripolar lead. The distal end (LV1) is wedged into a small side branch. The proximal electrode (LV4) is used as the stimulating cathodal electrode.*

The RA lead was placed in the RA appendage. The RV lead was by default placed in the apex of the RV as a standard and only in cases with unacceptable electrophysiological measurements the lead was moved to another location, preferably to a mid-septum location.

For LV lead implantation, the coronary sinus was cannulated by a guide catheter guided by fluoroscopy in anteroposterior and LAO views. Occlusive contrast venograms were recorded in a 30-40° LAO view and in a 30° RAO view. A selective venogram in a 30° RAO view was performed for the accurate measurement of the LV long-axis distance, which was divided into three equal segments: basal, middle and apical. From the venogram in the LAO view, the LV was divided into 5 equal segments that corresponded to the 5 segmental divisions (anterior, anterolateral, lateral, posterolateral and posterior) acquired in the preoperative ST-RS echocardiographic assessments. The rationale for this, is that the LAO fluoroscopic image approximates to the short-axis parasternal echocardiographic view. Considerable effort was made to achieve an LV lead position in a vein located in the target segment with the latest mechanical contraction. If there was no available vein in that segment, a vein located as close as possible was selected for lead placement. (Figure 5).

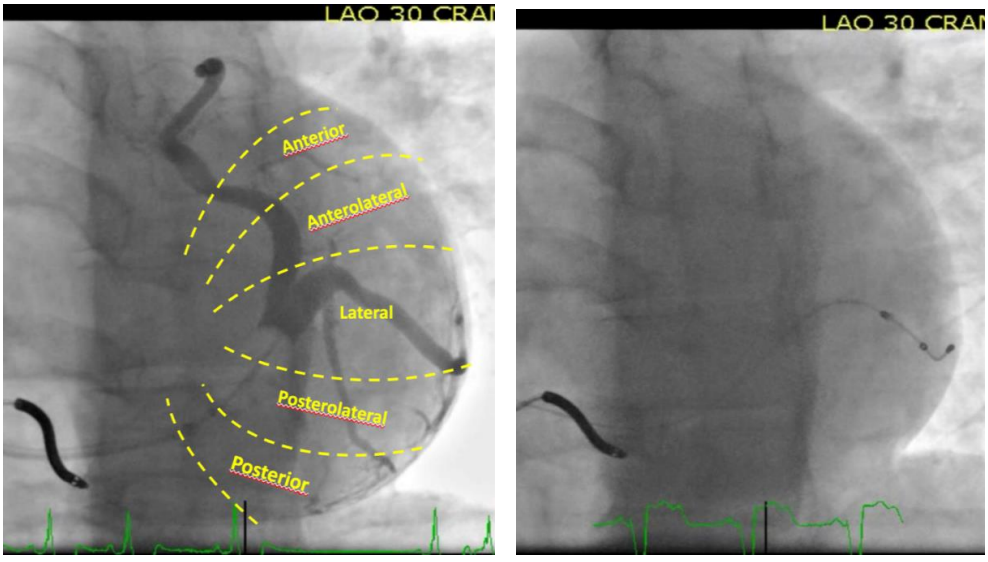

Figure 6. *Coronary sinus venogram from a study patient in left anterior oblique (LAO) view showing the short axis segmental division. An active fixation bipolar lead is implanted in the lateral LV segment.*

The LV leads were delivered using the over-the wire technique, a sub-selection catheter was used when required. A long-axis position for the stimulating electrode as close as possible to the coronary sinus entry was preferred. The measurements of PCT and the occurrence of PNS were recorded before fixation of the active fixation leads. For the active fixation lead, a J-shaped stylet was inserted to apply a lateral force on the helix towards the vein wall. The lead was then fixated to the vein wall by clockwise rotation. The lead fixation was verified by pushing and pulling the lead during observation of longitudinal movement using fluoroscopic imaging. If repositioning of the lead was required, counterclockwise rotation was performed to release the lead helix from the vein wall. The final PCT, R-wave, pacing impedance, and electrical delays (Q-LVsense, RVsense-LVsense and RVpace-LVsense) were recorded from a pacemaker system analyzer (Model 2090, Medtronic, Minneapolis. MN, USA) before removing the supporting catheters.

The leads were connected to a CRT-defibrillator (CRT-D) or a CRT-pacemaker (CRT-P) generator. In the trial presented in Paper I we used generators form 3 different vendors according to our routines. Fifty-two % of the patients received a CRT-D and 48 % a CRT-P. In the studies presented in Paper II and III a CRT-D (Medtronic, Minneapolis, MN, USA) was implanted in 66 % of the patients and a CRT-P (Abbot, Lake Bluff IL, USA) in 34 % of the patients.

7.6 Lead position and vein size assessment

The final position of the LV lead was in all studies determined by off-line evaluation of stored fluoroscopic images from the CRT implant procedure. The lead was classified as either anterior, anterolateral, lateral, posterolateral or posterior in the LAO view. The LV lead placements were categorized as concordant when the

location of the stimulating electrode was in target segment, adjacent when within 1 segment or remote when located ≥2 segments from the target segment. The long-axis lead position was decided from the RAO view by measuring the distances from coronary sinus to the programmed active LV electrode, to the proximal electrode and to the distal electrode (figure 7). The distance from CS to the programmed active electrode calculated as percentage of the total distance from CS to LV apex was also recorded to account for individual differences in absolute LV long-axis dimension. Finally, we recorded the vein size diameter at the different electrode locations and at the helix of the active fixation LV lead.

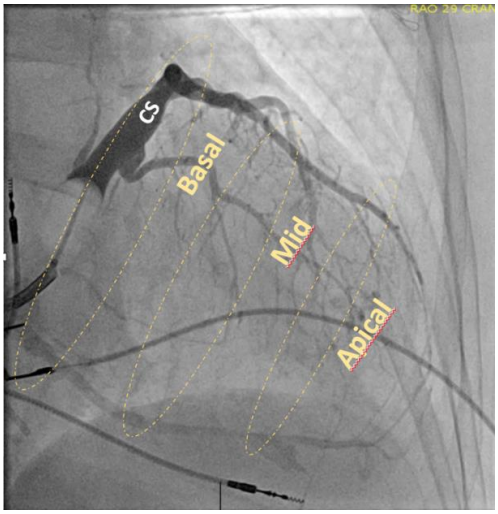

Figure 7. *Coronary sinus venogram from a study patient. The right anterior oblique (RAO) view allows long-axis segmentation of the LV into the basal, the midventricular (Mid) and apical region.CS = coronary sinus*

7.7 Device programming

For patients in the trial presented in Paper I, the devices were programmed according to guidelines and the department's routines. The devices for patients in the trial presented in Paper II and III were programmed as follows: Atrioventricular (AV) and interventricular delays were adjusted by an automatic algorithm (adaptive CRT, Medtronic, Minnesota Inc, MN, USA) for patients with a CRT-D generator. For patients with both normal AV delay and right bundle conduction, the device algorithm selected single LV pacing synchronized to the intrinsic RV conduction. The CRT-P devices (all from Abbot, Lake Bluff IL, USA) were programmed without any LV off-set, and the sensed-AV-time was programmed to 120 ms. Pacing mode was DDD, lower rate of 50 pulses per minute for those with no sinus node dysfunction. The selected pacing configurations for the active fixation bipolar leads were true bipolar, integrated bipolar LV-tip to RV-coil/RV-ring or LV-ring to RV-coil/RV-ring. For the quadripolar leads, the preferred configuration was bipolar L3-L2, integrated bipolar LV1 to the RV coil/RV ring, LV3 to the RV coil/RV ring or LV4 to the RV coil/RV ring. A limited number of configurations for the quadripolar leads was necessary for an accurate assessment of the location of the stimulating electrode in the LV long-axis view.

7.8 Electrophysiological measurements

In the studies presented in Paper II and III, the PCTs, R-waves and LV lead impedances were measured at baseline and at the 2-, 6- and 12-month follow-up periods. The occurrence of PNS and the PNS thresholds were recorded at implantation and at follow-up. The PCTs and impedance measurements acquired from the device postoperatively and not the measurements from the pacemaker system analyzer were used as baseline in the statistical analyses. The LV R-wave was measured by the pacemaker system analyzer. The RVsense-LVsense was determined

perioperatively after fixation of the LV lead. RVs-LVs was measured as the interlead sensed time-delay (ms) between the bipolar sensed signal from the RV lead to the electrode chosen as the active electrode on the LV lead. Similarly, the RVpaced-LVsense time delay (ms) was measured from the paced RV signal to the sensed LV signal. The Q-LV was measured from the onset of Q wave on the surface ECG to the sensed signal on the active electrode on the LV lead.

7.9 Perioperative registrations

The total procedure time (skin to skin), the LV lead implant time, the fluoroscopy time, the fluoroscopy doses, the number of veins attempted, and number of fixations attempts for the active fixation lead were recorded. The LV lead implant time was measured from the start of LV lead insertion and included advancement of the lead to the target site, fixation attempts, repositioning to other locations, electrophysiological measurements, and removal of supporting catheters.

7.10 Statistical methods

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). To evaluate the normality of continuous variables, we used histograms and Q-Q plots. Continuous variables are expressed as the mean ± the standard deviation. Categorical variables are presented as frequencies and percentages. Groups were compared by using paired-sample t-tests and independent-sample t-tests for continuous variables. Pearson's chi squared test was used for ordinal categorical variables, and the Fisher's exact test was used for nominal categorical variables. A p-value of ≤ 0.05 was considered statistically significant. In the studies in paper II and III, the data were analyzed according to the intention-to treat principle. For sample size calculation in Paper III, we estimated a 30 % absolute difference in response rate. Powered at 80 % and with a 1-sided alpha value of 0.05, assuming no loss at follow-up, 56 patients were required for the

analyses. For sample size calculation for Paper II, descriptive data from the study presented in paper I were used to predict values and standard deviations. A 20 % difference in the proportion of concordant LV lead placement, fluoroscopic distances, lead impedance measurements and PCTs were estimated. Powered at 80 %, with a 2-sided alpha value of 0.05 to detect differences, 26, 50, 66, 82 patients were required for the different analyses, respectively. The study was not powered to detect significant differences in infrequent events as lead dislocations. Univariate and multivariate linear regression analyses were performed to estimate the eventual effect on reverse remodelling, defined as a ≥ 15 % change in end-systolic volume at the 6-month follow-up.

8. Summary of results

8.1 Paper I

Active fixation of a thin transvenous left-ventricular lead by a side helix facilitates targeted and stable placement in cardiac resynchronization therapy

In the prospective non-randomized single-center study, 106 patients scheduled for CRT-device implantation were included. The primary objectives were to assess the lead implant success, the degree of LV lead concordance to a pre-decided target location, procedure time and perioperative adverse events for a novel transvenous LV lead with an active side helix fixation. The secondary objectives were to evaluate the long-term performance concerning lead stability, long-term PCT, occurrence of PNS and need for repositioning of the lead.

In 103 of the 106 patients, the active fixation LV lead was implanted. The LV leads were implanted over a wide range of vein anatomies. In the three patients with unsuccessful active fixation LV lead implantation, a stiffer passive fixation lead was implanted. The LV leads were targeted to a location in a pre-decided LV target segment based on preoperative ST-RS echocardiography. A position concordant to the target LV segment was achieved in 73 % of the patients and a position in a segment adjacent to the target segment in 24 %. Thus, in only 3 % (n=2) of the patients the final lead position was in a remote segment. Two patients had early lead dislodgement (< 24 hours), no late dislodgements were observed. One patient was reoperated after 11 months, due to PNS. Two patients had their leads and device explanted due to a pocket infection after 26 days and 141 days, respectively. A new device with the same LV was reimplanted after appropriate antibiotic treatment.

The mean number of fixation attempts was 1.3 per patient, and the LV lead was fixated in the first rotation attempt in 79 % of the patients. The lead was repositioned in 26 % of the patients. The average vein size was 6.7±1.5 Fr at the lead tip and 7.6±1.2 at the helix. No correlation was found between the number of rotating

attempts and the vein size at helix or vein size at lead tip, nor between vein sizes and number of lead repositioning.

The total procedure time was 98±38 min, LV lead implant time was 17±15 min and the fluoroscopy time 20±14 min. The average LV PCT at implant was 1.04±0.6 V. At latest follow-up of average 7.1 months (1 months to 15 months), the average PCT remained low and stable at 0.92±0.5 V (n = 95).

8.2 Paper II

Performance of an active fixation bipolar left ventricular lead versus passive fixation quadripolar leads in cardiac resynchronization therapy, a randomized trial

We included 62 patients who were randomly assigned to receive either an active fixation bipolar lead or a quadripolar passive fixation LV lead. The electrical performance, perioperative measurements and the ability to achieve a stable proximal position in a coronary vein located concordant to target segment were compared.

Initial successful implantation was obtained in 31 patients (100 %) and 30 patients (97 %) in the active fixation bipolar group and the quadripolar group, respectively. In 3 patients, LV lead dislodgement occurred, all in the active fixation group. There were no differences in total procedure time (77±22 minutes vs 76±21 minutes, p=0.82), LV lead implantation time (13±11 minutes vs 12±12 minutes, p=0.75), or fluoroscopy doses (329±236 vs 319±426, p=0.85).

A position in a concordant or adjacent LV segment, was achieved in the majority of the patients (87 % vs 83 %) with no statistically significant differences between the patient groups (p=0.69). The proximal electrode of the quadripolar LV lead was closer to the coronary sinus than that of the active fixation LV lead (19±15 mm vs 32±10 mm, p=0.00). However, there were no differences in the proximity of the

stimulating electrode to the coronary sinus, neither in absolute values (51±9 mm vs 53±13 mm p=0.51), nor in distance as a percentage of the distance from the CS to the apex (36±11 % vs 33±12 % p=0.26). The vein diameter at the location of the active electrode was comparable (7.3±3 French vs 8.3±3 French, p=0.20). The PCTs recorded at implantation and at the 2-, 6- and 12-month FU are shown in figure 8.

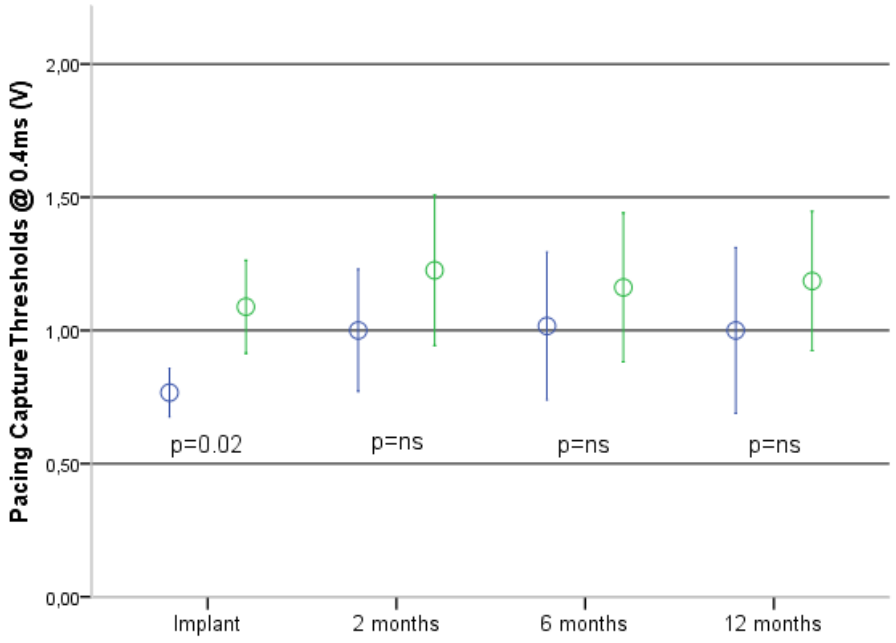

Figure 8 *Pacing capture threshold (PCT) at the final selected pacing configurations for the quadripolar passive fixation lead (blue) and for the bipolar active fixation lead (green). The error bars indicate the 95 % confidence intervals. The PCT was significantly lower (p=0.02) at implantation but not at follow-up.*

A PCT < 2.5 V/0.4 ms at implantation was achieved in 100 % of patients in both groups. At the 12-month follow-up, a PCT < 2.5 V/0.4 ms was recorded for 93 % of patients in both groups. The PCT for the proximal electrode was significantly higher for the quadripolar lead than that of the active fixation lead (2.83V versus 1.31 V, p=0.003). The LV lead pacing impedances were significantly higher for the active

fixation LV leads compared to the quadripolar leads at implantation (539±159 Ohm vs 414±94 Ohm, p=0.00) and follow-up (at 12 months follow-up 545±143 Ohm vs 433±97 Ohm, p=0.04). The measurements reflecting electrical dyssynchony did not differ: Q-LVsense 155±30 ms vs 154±35 ms (p=0.88), RVsense- LVsense 101±26 ms vs 97±36 ms (p=0.67) and RVpace- LVsense 142±27 ms vs 143±31 (p=0.94).

8.3 Paper III

Clinical outcome of cardiac resynchronization therapy in patients randomized to an active fixation bipolar left ventricular lead versus a passive quadripolar lead

In this study we compared the clinical outcome of CRT in 62 patients receiving a bipolar LV lead with a side helix for active fixation to the outcome in patients receiving a quadripolar LV lead with passive fixation. The LV leads were targeted to the basal LV segment in a vein concordant to the LV segment with the latest mechanical contraction chosen on the basis of preoperative radial strain echocardiography and the patient population was identical to to that in Paper II.

At the 6-month follow-up, the reduction in LV end-systolic volume was significant (mean reduction 35 ml, $p<0.001$), but the difference between the patients with active fixation leads and patients with quadripolar leads was not significant (p=0.47; Table 2) A reduction in the end-systolic volume ≥15 % at the 6-month follow-up was found in 77 % and 84 % of the patients with active fixation leads and quadripolar leads, respectively (p=0.51).

Table 2 Echocardiographic response

	Active fixation lead (n=31)	Quadripolar lead (n=30)	P-value
LV end-systolic volume reduction from baseline to the 6-month FU (%)	21.8±16	24.7±14	0.47
Responder patients with LV end-systolic volume reduction ≥ 15 % from baseline to the 6-month FU	24 (77)	25 (83)	0.51
LV end-diastolic volume reduction from baseline to the 6-month FU (%)	14.9±22	14.6±16	0.95
LV ejection fraction at the 6-month FU (%)	32.6±7	36.8±6	0.01
LV ejection fraction at the 12-month FU (%)	35.6±9.7	36.7±7.1	0.64
LV end-diastolic diameter at baseline (mm)	64.4±7.7	62.7±7.6	0.39
LV end-diastolic diameter reduction from baseline to the 6-month FU (mm)	5.2±4.8	3.8±6.2	0.34

FU=follow-up; LV = left ventricle

Both groups of patients experienced a significant improvement in NYHA functional status from baseline to follow-up, but with no significant differences between the groups. Quality of life assessment according to the Minnesota Living with Heart Failure Questionnaire (MLHFQ) demonstrated significant improvement at follow-up in both groups of patients, but with no significant differences between the two patient groups (Table 3).

Table 3 *Quality of life assessment*

	Active fixation group (n=31)	Quadripolar group (N=30)	p-value*
NYHA functional class			
Baseline	2.7±0.6	2.7±0.5	0.87
6-month follow-up	1.8±0.7	2.0±0.6	0.24
12-month follow-up	1.9±0.7	1.8±0.5	0.79
Improvement ≥1 class from baseline to the 6-month follow-up (n (%))	24 (77)	19 (63)	0.29
MLFHQ			
Baseline	37±20	41±21	0.49
6-month follow-up	20±15	27±14	0.11
12-month follow-up	22±15	23±17	0.76

MLHFQ=Minnesota Living with Heart Failure Questionnaire; NYHA= New York Heart Association.

Six patients (19 %) in the patient group with active fixation leads experienced PNS during the study period, compared with only 3 patients (10 %) in the quadripolar group (p=0.47). All cases of PNS were resolved by reprogramming the devices. There was no device infection, and all patients were alive at the 12-month follow-up.

Concordant LV lead position, the final LV segment, QRS duration, Q-LV delay, RV to LV interlead sensed delay and RV-paced to LV-sensed delay did not predict significant LV reverse remodelling inn univariate and multivariate linear regression analyses.

9. Discussion

This thesis shows that the active fixation bipolar LV lead with a side helix represents an alternative to standard passive fixation LV leads. The thesis adds the following to current knowledge: 1) The level of implant success is high and targeted placement is feasible 2) The implantation procedure is safe 3) The occurrence of late lead dislodgements is low. 4) The active fixation mechanism does not extend the implantation time or cause more radiation. 5) The clinical outcome of CRT in terms of improvements of symptoms and LV reverse remodelling measured by echocardiography are equal for the active fixation bipolar lead and passive fixation quadripolar lead.

9.1 Study design

The first study (Paper I) was a prospective, non-randomized clinical trial. The prospective, rather than a retrospective, design allowed high accuracy of data collection. We had no loss to follow-up. An evaluation of implant success would have been problematic with a retrospective design. The active fixation LV lead was novel and not tested in a larger population at the time of patient inclusion. No control group was tested in this study and therefor it was not possible to decide if the lead is superior compared to other LV leads. A design without control group was chosen to include as many patients as possible over a short time as our center is not a high-volume center. Including patients consecutively strengthens the study and reduces the risk of selection bias. The patients were not included consecutively. There were shorter brakes in the inclusions due to lack of operators who were familiar with the new LV lead and/or the study protocol. However, 106 out of 156 patients receiving a CRT device in that period were included, and further, all cases judged to represent potensially challenging procedures were included in the trial.

In the subsequent studies presented in Papers II and III a randomized and patient-blinded design was selected for proper comparison of the novel active fixation bipolar

LV leads to passive fixation quadripolar LV leads. In recent years, quadripolar LV leads have become the preferred LV leads for most operators due to better stability and easier avoidance of area with high PCT or PNS. In addition, the leads provide more reprogramming possibilities postoperatively. Consequently, the quadripolar passive fixation lead was chosen for the control group and not a bipolar passive fixation lead.

9.2 Study population

In the study presented in paper I, all patients scheduled for implantation of an LV lead were eligible for inclusion. That included patients with systolic heart failure and acute AV-block, upgrade procedures and biventricular pacemaker ahead of AV-node ablation. This trial did not evaluate the clinical response to CRT, but exclusively evaluated the handling, performance and safety of the lead. When comparing the lead with another lead and also evaluating the clinical response of CRT in the next study (paper II and III), a much more uniform patient population was required. Therefore, we included only patients with symptomatic systolic heart failure, intrinsic rhythm and wide QRS. The recommendations of the ESC guidelines were followed strictly. The patient population was comparable with other clinical CRT trial, but the mean age was higher than in most large trials. The mean age in our study was 72±11 years, and 26 % were > 80 years old. In comparison, COMPANION, CARE-HF and MADIT-CRT had an average age of 65-67 years, and in these early large CRT trials only a small portion of the patients were octogenarians.(28-30) There is evidence supporting that elderly patients have an equal improvements as younger patients in symptomatic and echocardiographic response with similar procedural complication rates.(69, 70) The vast majority of our patients had LBBB (94 %) and 76 % of the patients had QRS width > 150 ms, both characteristics are related to high probability of favourable clinical response to CRT.(71, 72)

9.3 Position of the LV lead

In our trials ST-RS echocardiography was used to define the LV segment with latest mechanical activation and the LV lead was targeted to that segment. However, there are different approaches to define the most optimal position for the LV lead, and there are still conflicting data and unclear recommendations in current guidelines for which method to use. Traditionally, the LV lead is placed empirically in a lateral, posterlateral or posterior coronary vein with no preprocedural or intraprocedural evaluation of LV regional mechanical or electrical delay to guide lead placement. As opposed to this conventional anatomical LV lead placement, targeted LV lead placement means that the LV lead will be aimed to the latest activated LV segment. This may be defined as the LV segment with latest mechanical activation or the segment with latest electrical activation. Finally, an approach that secures LV lead location away from transmural myocardial scars is recommended.

9.3.1 Empirical LV lead placement

In the multicentre studies that initially approved the advantage of CRT, there were no guidelines for placement the LV lead. Some studies have shown that an anterior versus non-anterior LV lead position was independently associated with an increased likelihood of non-response to CRT.(73, 74) However, in the COMPANION trial the mortality benefit in CRT-D patients was found to be indifferent to LV lead position.(75) In the MADIT-CRT trial the lateral/posterior location and the anterior locations were similarly associated with risk of heart failure or death, although posterior/lateral LV leads showed the greatest improvement in LV reverse remodelling.(76) The best LV pacing site seems to be individual and in an acute hemodynamic trial it is found to be in another position than a lateral position in a considerable part of the patients.(51, 52) According to the analyses of randomized trials, such as MADIT-CRT and REVERSE there are strong evidences for avoiding an apical LV position, as LV pacing from an apical site is associated with less favourable outcomes and high risk of PNS.(56, 77, 78) Due to this knowledge, our studies evaluated the ability of the leads to attain a long-axis-position as far as possible from the LV apex. It was found that the novel active fixation lead and

standard passive fixation quadripolar leads had equal success rate for proximal long-axis placement with acceptable electrophysiological measurements.

9.3.2 Latest mechanical activation

Targeting the latest mechanically activated, non-scarred, LV segment have demonstrated superior response compared with empirical LV lead placement. It is still questionable which method is best for detecting the last activated LV segment. In our studies ST-RS echocardiography was used as a preoperative method to define the LV segment with latest mechanical activation. Our centre has used this method as a routine for several years, and published data showing that patients achieving an LV lead position concordant with the target segment guided by ST-RS echocardiography demonstrate favorable improvement in reverse remodelling.(25) The same method has been used in randomized trials, showing superior response compared with empirical LV lead placement.(53-55). Several other echocardiographic methods have been tested in order to identify mechanical dyssynchrony. M-mode, pulsed Doppler and tissue Doppler have shown mixed results and low reproducibility.(79) Occurrence of septal flash and apical rocking are shown to predict response and also mortality.(80) Correspondingly, systolic stretch index in the septum and lateral wall and left ventricular work asymmetry are as well identified as good predictors for response.(81-83) However, these methods have so far not been widely established for guiding of the optimal position for the LV lead. Cardiovascular Magnetic Resonance (CMR) imaging gives accurate information about location and degree of myocardial scar, and preprocedural imaging for guiding subsequent LV lead placement has proven to be beneficial (67). However, the precise translation of data from CMR view to routine fluoroscopic imaging view is demanding.(84) Both CMR and myocardial perfusion imaging are costly, time-consuming and may require involvement of other medical specialties. Speckle tracking echocardiography has emerged as a robust method to assess the segmental myocardial deformation. The method is less angel dependent than tissue Doppler in assessment of strain, although high-resolution image quality is mandatory as well as offline image processing. The ST-RS echocardiography may also be combined with cardiac computed tomography

venography and nuclear myocardial perfusion imaging.(55) The preoperative examination using ST-RS echocardiography is time consuming, but feasible. In all patients attending our studies (Paper I, II and III) preoperative ST-RS echocardiographic examinations were done in our department without practical difficulties. In the first study (Paper I) the image quality was not acceptable for one patient (out of 71 patients), so in that case, the lateral segment was selected as the target segment. For the 62 patients in paper II and III, the image quality was judged as acceptable for all patients. Due to few patients with target LV segment in the strict anterior and strict posterior segment, the anterior and anterolateral groups were merged together in the presentations in Paper I. The target position was determined to be in a lateral segment in 61 %, a posterior/posterolateral segment in 28 % and anterior/anterolateral segment in 10 % of the patients. A concordant LV lead position was achieved in 73 % of the patients. In the subsequent study (Papers 2 and 3), the data are presented in a five-segment model. The locations of the targeted LV segments were anterior (10 %), anterolateral (11 %), lateral (44 %), posterolateral (30 %) and posterior (5 %). When using a model with more segments, it is more challenging to reach the target segment. The final LV lead position was defined as being in a remote segment (not target segment, neither an adjacent segment) in only 15 % of the patient, with no differences with respect to lead type (p=0.69). The trend was that the quadripolar leads more often were placed in the concordant segment (63 % vs 39 %, p= 0.06), and equivalently the active fixation leads were more often placed in a segment adjacent to the target segment (48 % vs 20 %, p=0.02). The study did not prove that the thinner active fixation bipolar lead more often could be placed in a concordant position than the passive fixation thicker quadripolar lead. In the randomized TARGET and STARTER trials, both the LV leads that were concordant or in an adjacent segment demonstrated significantly better clinical outcomes than in patients with remote lead placement.(53, 54, 85-87) This suggests that it is clinically most important to avoid a remote placement of the LV lead rather than to reach a small sweet LV spot.

9.3.3 Latest electrical activation

Wide QRS complexes are a surrogate for long ventricular electrical delays and narrowing of the QRS width during CRT are related with better clinical outcome.(88) Further, pacing the LV in a region with late electrical activation are associated with favorable clinical outcome and LV reverse remodelling.(89, 90) A long inter-lead electrical delay (RVsense-LVsense) is also associated with favorable CRT response, even when the LV leads were targeted to the latest mechanical activated segment (24, 91-93). In our trials the Q-LV delay was measured as well as the RVsense-LVsense delay and the RVpace-LVsense delay. Univariate and multivariate linear regression analyses were done to estimate the potential effect of Q-LV delay, RVsense-LVsense delay and RVpaced-LVsensed delay on LV reverse remodelling. Reverse remodelling was defined as a ≥ 15 % change in end-systolic volume at the 6-month follow-up. None of the tested parameters predicted statistically significant LV reverse remodelling. An explanation for this may be the small sample size studied.

9.3.4 Assessment of LV scarring

LV transmural myocardial scarring is associated with lack of clinical response to CRT, and placement in an area with viable mycardium improves response.(67, 94, 95) Late gadolinium enhancement CMR is regared as the gold standard for assessment of myocardial scar, but also nuclear imaging are commonly utilized and unlike CMR, nuclear imaging has no contraindication in the cases with implanted CMR-non-conditional electrical devices. Both CMR and nuclear imaging are resource demanding. In our studies, we used low-amplitude ST-RS echocardiography as a surrogate measure of myocardial scar to prevent LV lead location in an area with transmural scarring. This method is used in other randomized trials for targeted LV lead placement (26, 53, 54). It does not cause extra radiation to the patients and severe kidney failure is not a contraindication. A strong negative correlation is confirmed between maximal ST-RS values and demonstration of transmural scare tissue by CMR imaging.(96) The sensitivity of radial strain < 10 % for identifying a segment with transmural scar has been calculated to 77 %.(97) In the patient

population presented in Paper II and III, 10 out of 62 patients (16 %) had ≥1 segment with radial strain less than 10 %. For 8 of those 10 patients, the low-strain segments were not the latest activated segments, therefore, excluding low segment with low strain resulted in selection of an alternate target segment for the LV lead in only two patients.

9.4 Electrical performance of the active fixation lead

In the study presented in Paper I the average PCT at implantation was 1.04±0.6V@0.58±0.2 ms. At latest follow-up of average 7.1 months the PCT was 0.92±0.5 V. In the study presented in Paper II, the average PCT for the active fixation group was very similar (1.09±0.48@0.4ms). Low PCT is essential to reduce the chance of loss of LV pacing capture, appearance of PNS and for extending the service time of the implanted device. As important as a low average PCT is avoidance of cases with high PCT. In the second study (Paper II) a PCT < 2.5 V/0.4 ms at implantation was achieved in 100 % of patients, and a PCT < 2.5 V/0.4 ms was recorded for 93 % of the patients in both groups at 12-month FU. In this study the main objective was a clinical comparison of the novel active fixation lead and passive fixation quadripolar leads (Medtronic Attain Performa family of leads). The performance of the quadripolar Attain Performa leads were investigated in a large clinical trail, and showed that the average PCT was very similar to that found in Paper II.(98, 99) We hypothesized that the novel active fixation lead should improve the PCT compared to standard passive fixation quadripolar leads, as the helix may provide more pressure of the pacing electrodes toward the vein wall and myocardium. At baseline, on the contrary, the PCT was lower for quadripolar lead (0.77±0.25 vs 1.09±0.48, p=0.02) and at follow-up the PCT was similar. Furthermore, the pacing impedance was significantly higher (approximately 20 %) in the active fixation group than in the quadripolar group and that may cause a moderate increase in battery longevity compared to devices with quadripolar LV leads. These findings are consistent with retrospective comparative studies that found that active fixation bipolar lead was noninferior to quadripolar leads.(100, 101) Use of quadripolar leads

have reduced the problem with PNS compared to bipolar leads, and a concern was potentially more occurrence of PNS in patients with the novel bipolar active fiation lead. In the randomized study (Paper II) more cases (6 vs 3, p=0.31) with occurrence of PNS were found in the bipolar lead group compared to the quadripolar lead group, but in all cases in both groups, the PNS was resolved by reprogramming the devices. Incessant PNS is strongly correlated to pacing distally in the LV long-axis segment, and therefore it was strongly endeavored for a proximal LV lead position in the studies. In the study presented in Paper I, one patient with a passive fixation LV lead implanted 11 months ago, experienced unacceptable PNS at very low output. The lead was replaced by an active fixation bipolar lead with a more proximal position in the same coronary vein. However, the PNS symptoms reappeared and 39 days later the lead was explanted and replaced by a quadripolar LV lead. In that case, the patient would have benefit from a quadripolar lead from the beginning.

9.5 Fixation methods for left ventricular leads

The rate of LV lead dislodgement has declined in recent past due to change from uni/bipolar lead to quadripolar lead, new LV lead designs and developments in the implantation tools.(43) Today, the implanters may choose from a variety of passive fixation LV leads with different shape, stiffness, thickness, electrode location and length. The active fixation mechanism was developed to prevent LV lead dislodgement. The idea is that the thin and flexible active fixation LV lead, made in just one variant, can be maneuvered in many different and challenging coronary vein anatomies to be fixated in the desired location by its side-helix and with reduced risk of dislodgement. This should eliminate the need of wedging the tip electrode to a distal and undesired location in the coronary vein, in order to reduce the risk of lead dislodgement. The study in paper I confirmed that the implantation procedure is safe and that the lead may be targeted into a wide ranch of vein anatomies and with electrical performance comparable to that of traditional passive fixation leads. Out of 106 patients, a stable position was not achieved in 3 patients, and two patients had LV lead dislodgement the following hours after implantation. No late LV lead

dislodgement was observed at follow-up. In the subsequent study (Paper II), we experienced three dislodgement, and one was discovered after the patient left the hospital. In comparison, there was no dislodgement in the control group with the passive fixation quadripolar lead. The study was not powered to show differences in the rate of lead dislodgment, but it shows that the principle of active fixation for LV lead does not eliminate the problem with lead dislodgement. In the Italian multicenter study that included 261 patients with active fixation bipolar leads, a dislocation rate of 1.43/100 patients was reported.(100) A quadripolar active fixation lead was not available when we performed our studies, but has later become an option. The Attain Stability Quad Clinical Study reports about a 0.7 % dislodgment rate that is certainly lower than in trials with passive fixation leads.(102) Apparently, the advantage of being quadripolar balances much of the advantages of the active fixation. An important issue in the randomized trial was to assess whether use of the fixation mechanism extended the LV lead implant times or was associated with higher radiation doses. No significant differences were found in these parameters when comparing the active fixation lead with the quadripolar leads.

There is a concern about the extractability of active fixation LV lead. The active fixation LV lead Attain Starfix (Medtronic Inc., Minneapolis, USA) was equipped with deployable lobes and lead extraction procedures have been particularly challenging.(103, 104) Contrary to side lobes of the lead, the side-fixation screw in Attain Stability is constructed to uncoil in response to retraction force above a certain limit. There is a theoretical assumption that the lead may be extracted with forces similar to that applied for passive fixation leads. In the study presented in paper I, we explanted four leads, after being in situ for 3 days, 26 days, 39 days, and 141 days without difficulties or complications. So far, only case-reports about lead extraction of more chronically implanted leads in humans are published.(105) Thus the data on extraction safety are limited and this must be taken into account when choosing an active fixation LV lead.

9.6 Clinical outcome

In the study presented in Paper III, we evaluated the clinical response to CRT and compared the outcome for patient with implanted active fixation bipolar leads and patients with quadripolar passive fixation leads. For quality of life assessment, we used MLHFQ which is one of the most widely used health-related quality of life questionnaires for patients with heart failure.(106, 107) For the entire group, the MLHFQ demonstrated significant improvement (39 points at baseline and 22 points at 12-month follow-up), but there were no significant differences between the two patient groups (22 vs 23 points, p=0.76). Correspondingly, the improvement in NYHA functional class was considerable with average NYHA function class 2.7 at baseline for all patients, 1.9 at 6-month FU, and 1.8 at 12-month follow-up, but with no significant differences between two patient groups (p=0.79). Improvement of ≥1 NYHA functional class from baseline to the 6-month FU was achieved in 77 % of the patients with active fixation leads and 63 % of the patients with quadripolar leads (p=0.29). The improvement in functional class is similar or better to what has been found in other CRT trials.(108) A limitation in our study is that the person that assessed the NYHA functional class was not blinded to which treatment group the patients belonged to.

9.7 Echocardiographic response

In the study reported in paper III, we compared the echocardiographic response to CRT for the active fixation leads and passive fixation quadripolar leads. The use of active fixation bipolar leads was not associated with improved echocardiographic response compared to regular passive fixation quadripolar leads. Measurement of LV volumes at baseline and at 6 months FU demonstrated a significant reduction in LVESV (mean reduction 35 ml, p<0,001). However, the difference between the patients with active fixation leads and patients with quadripolar leads was not significant (p=0.47). LV reverse remodeling, defined as a reduction in the LVESV ≥15 % at the 6-month follow-up, was obtained in 77 % and 84 % of the patients with

active fixation leads and quadripolar leads, respectively (p=0.51). Further, there were no significant differences between the two patient groups for changes in LV end-diastolic volume or LVEDd from baseline to the 6-month follow-up. The LVEF improved more in the quadriopolar group as compared to the active fixation group at 6-months follow-up, but this difference was not significant at 12-month follow-up. Assuming that the constructural features of the LV lead may have an impact on the echocardiographic response, this should be enhanced by attaining a more advantageous position of the stimulating electrode. We hypothesized that the thinner lead body of the active fixation lead to a greater extent would facilitate lead placement in the target LV segment and thus optimize LV resynchronization. However, the study (Paper II) did not show any significant differences regarding the degree of reaching the target lead placement, so the finding of similar echocardiographic and clinical response in the two patient groups was not unexpected.

10. Limitation

The studies presented in this thesis are single-centre studies with a limited number of included patients. All procedures were performed by a small number of implanters. The extension of the validity of these results to other centres and implanters is uncertain. A longer observation period could have augmented the clinical benefit and the diversity of the lead types could be better distinguished. Long-term safety of the active fixation lead and the extractability of chronically implanted active fixation leads in humans are so far not reported. A wide range of quadripolar leads are available for the implanters of CRT devices. The quadripolar leads used in the control group were from the same manufacturer, and thus the results could have been different if comparison with other types of quadripolar leads had been studied.

11. Conclusion

1. The bipolar active fixation LV lead allows placement in targeted coronary vein segments over a wide range of vein anatomies with a low complication rate, satisfactory intraoperative handling and electrophysiological performance.

2. Comparing the active fixation LV lead and standard passive fixation quadripolar LV lead demonstrated:
    a. Placement of the LV lead concordant to the segment with latest mechanical activation based on preoperative ST-RS echocardiography is achievable in an equal proportion of patients.
    b. The active fixation lead does not extend the implantation procedure time or elevates the radiation doses.
    c. The active fixation lead does not facilitate a more proximal position of the active electrode
    d. The clinical and echocardiographic response are similar. A similar high proportion of patients demonstrates reverse LV remodelling.

12. Futher perspective

The present thesis investigated an active fixation bipolar LV lead and the impact of LV lead types on the clinical efficacy of CRT. There have been numerous technical innovations in the delivery systems and LV lead designs in the last decades. A quadripolar active fixation LV lead is now available. This method and other design innovations may promote further decline in rate of lead dislodgement and unsuccesful implantation. Despite the heterogeneity of quadripolar LV leads, there will still be patients with short target veins, not suitable for leads with long distances between the electrodes, and in such patients, bipolar leads may still be preffered. Imaging modalities for proper patient selection and achieving optimal targeted LV lead position are constantly evolving. In the future, new multimodality techniques for defining target LV segment and assessing LV scarring may be found superior compared to standard ST-RS echocardiography.

Biventricular pacing with leads in coronary veins is challenged by new methods for resynchronization. Techiques for endocardial LV pacing may be developed to overcome the issues of thromboembolism and the increased risk during lead extraction. His-bundle pacing is now a promising supplement to biventricular pacing.(109-111) However, there are concerns about long term PCT and sensing of low amplitude R-waves.(112) Left bundle branch area pacing by implantation of a lead deep in the right ventricle basal septum to capture the left bundle branch can also be an alternate method to biventricular pacing or His-bundle pacing.(113) However, stimulation of the LV by suitable leads in coronary vein tributary is a proven and effective treatment that may still be the preferred method for achieving safe CRT for many years to come.

13. References

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PAPER I

KEILEGAVLEN H, HOVSTAD H, FARESTRAND S

Active fixation of a thin transvenous leftventricular lead by a side helix facilitates targeted and stable placement in cardiac resynchronization therapy

Europace 2016;18:1235–1240

PAPER II

KEILEGAVLEN H, SCHUSTER P,
HOVSTAD H, FAERESTRAND S

Performance of an active fixation bipolar left ventricular lead versus passive fixation quadripolar leads in cardiac resynchronization therapy, a randomized trial

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ORIGINAL ARTICLE

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Performance of an active fixation bipolar left ventricular lead vs passive fixation quadripolar leads in cardiac resynchronization therapy, a randomized trial

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Abstract

Background: Usage of active fixation bipolar left ventricular (LV) leads represents an alternative approach to the more commonly used passive fixation quadripolar leads in cardiac resynchronization therapy (CRT). We compared a bipolar LV lead with a side screw for active fixation and passive fixation quadripolar LV leads.

Methods: Sixty-two patients were before CRT implantations randomly allocated to receive a bipolar (n = 31) or quadripolar (n = 31) LV leads. Speckle-tracking radial strain echocardiography was used to define the LV segment with latest mechanical activation as the target LV segment. The electrophysiological measurements and the capability to obtain a proximal position in a coronary vein placed over the target segment were assessed.

Results: Upon implantation, the quadripolar lead demonstrated a lower pacing capture threshold than the bipolar lead, but at follow-up, there was no difference. There were no differences in the LV lead implant times or radiation doses. The success rate in reaching the target location was not significantly different between the two LV leads.

Conclusions: The pacing capture thresholds were low, with no significant difference between active fixation bipolar leads and quadripolar leads. Active fixation leads did not promote a more proximal location of the stimulating electrode or a higher grade of concordance to the target segment than passive fixation leads.

KEYWORDS

biventricular pacemaker, cardiac resynchronization therapy, heart failure

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) reduces heart failure symptoms and improves clinical outcomes in selected patients with broad QRS complex.[1,2] This treatment has proven beneficial, with a reduction in the mortality and hospitalization rates when combined with medical therapy. However, a significant fraction of patients do not experience improvements in symptoms or cardiac function.[3] A

nonoptimal position of the left ventricular (LV) lead is a major reason for an inferior response to CRT.[4,5] Placement of the LV lead in a segment remote from the region with the latest mechanical activation or in a segment with a myocardial scar predicts a high risk for nonresponse. Echocardiographic speckle-tracking two-dimensional (2D) radial strain imaging has the ability to identify the LV segment with the latest mechanical activation. LV lead implantation guided by this robust echocardiographic method has been shown to augment the clinical outcomes of CRT compared with those of unguided LV lead placement.[6,7] The optimal location for LV pacing may be different from the best position for lead stability and may be compromised to achieve a stable lead position with a low risk of lead dislodgement. Available quadripolar LV leads provide multiple options of different pacing vector and are particularly useful for eliminating postoperative phrenic nerve stimulation (PNS) by reprogramming lead configuration.[8,9] Active fixation mechanisms of LV leads facilitate stable lead positions in a wide range of venous anatomies.[10] The aim of the current study was to compare a bipolar LV lead with a side helix for active fixation and a quadripolar LV lead with passive fixation regarding the electrophysiological performance, the stability, and the ability to reach the target position.

2 | METHODS

2.1 | Study design

In this prospective, randomized, single-center trial, patients with symptomatic heart failure and an indication for CRT implantation in accordance with current guidelines were included. The study was approved by the regional committee for medical and health research ethics (Reference 2015/1507), and all patients gave their written informed consent. The patients were blinded and randomly assigned to receive either an active fixation lead or a quadripolar passive fixation lead. For patients randomized to receive a quadripolar lead, the operators were free to choose between three different shapes. Prior to randomization, the patients were stratified into two cohorts based on whether they received a CRT device either with a defibrillator (CRT-D) or without a defibrillator (CRT-P). The decision of implanting a CRT-D or a CRT-P was done individually based on etiology of the heart failure and the patient's comorbidity.

2.2 | Patient population

Between February 2016 and November 2017, 62 patients were included and randomized. The inclusion criteria, which were based on current guidelines, were symptomatic heart failure; New York Heart Association (NYHA) functional class II or III or ambulant class IV; LV ejection fraction ≤35%; and left bundle branch block (LBBB) with a QRS duration ≥120 ms or non-LBBB with a QRS duration ≥150 ms The baseline clinical characteristics and comorbidities of the patients are described in Table 1. No significant differences were found between the two patient groups with respect to sex, QRS duration, LV ejection fraction, NYHA functional class, medication, and comorbidities. The average NYHA functional class was 2.7 in both patient groups.

TABLE 1 Baseline characteristics

	Active fixated lead (n = 31)	Quadripolar lead (n = 30)	*P*-value
Female sex, n (%)	11 (35)	6 (20)	.18
Age, years	71.5 ± 13	72.2 ± 10	.82
Left ventricular ejection fraction, %	24.4 ± 6	27.0 ± 5	.07
Left bundle branch block, n (%)	29 (94)	29 (94)	.58
QRS duration, ms	165 ± 19	162 ± 18	.56
PR time, ms	193 ± 32	191 ± 29	.79
NYHA II, n (%)	11 (35)	11 (37)	.93
NYHA III or IV, n (%)	20 (65)	19 (63)	.93
Ischemic cardiomyopathy, n (%)	17 (55)	20 (67)	.35
Hypertension, n (%)	16 (52)	15 (50)	.90
Diabetes, n (%)	5 (16)	9 (30)	.20
Permanent atrial fibrillation, n (%)	4 (13)	6 (20)	.46
Paroxysmal atrial fibrillation, n (%)	7 (23)	10 (33)	.36
Smoker, n (%)	2 (6)	4 (13)	.38
ACE inhibitors, n (%)	31 (100)	30 (100)	1.00
Betablockers, n (%)	29 (94)	30 (100)	.16
Aldosterone inhibitors, n (%)	11 (35)	12 (40)	.72
Diuretics, n (%)	17 (55)	19 (63)	.51
CRT-D, n (%)	20 (65)	20 (67)	.86

2.3 | Echocardiographic imaging

The LV ejection fraction was measured by echocardiography using the biplane modified Simpson's method (GE Vivid E9, Vingmed Ultrasound, Horten, Norway). Transthoracic echocardiography with 2D speckle-tracking radial strain (ST-RS) measurements of the LV was performed prior to the implantation procedures. All images were processed offline (EchoPac 202 GE Medical System, Horten, Norway). Intraventricular LV dyssynchrony was determinated using ST-RS echocardiography from 2D images in a mid-LV parasternal short-axis view with a frame rate ≥50 Hz. Time-strain curves were computed for the different LV segments. Left ventricular segments with a strain rate <10% were excluded because this finding was considered to indicate a high level of transmural scarring.[11,12] The time from Q-wave onset on the electrocardiogram to the maximal radial strain in the anterior, lateral, and posterior LV segments was

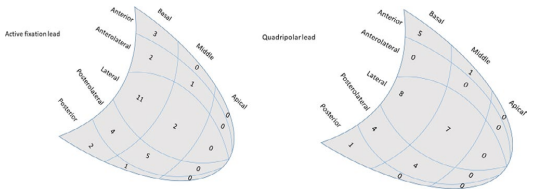

FIGURE 1 Location and number of selected stimulating electrodes in different left ventricular segments in the active fixation lead group and in the quadripolar lead group

calculated as an average of five consecutive cardiac cycles. The latest contracting LV segments were identified for the anterior, lateral, and posterior LV segments. If the latest contraction of two of the LV segments was separated by ≤10 ms, the LV segment located between them was assigned the latest one. Based on this model, 5 LV segments were defined; thus, the target LV segment for LV lead placement could be identified as the anterior, anterolateral, lateral, posterolateral, or posterior segment. The LV segments next to the target segment were classified as adjacent LV segments, and other segments were classified as remote LV segments.[13]

2.4 | Cardiac resynchronization therapy device implantation

The devices were implanted under local anesthesia. The right atrial (RA) lead was fixated in the appendage of the right atrium, and the right ventricular (RV) lead in the apex of the right ventricle. Occlusive contrast venography was performed in a 30-40° left anterior oblique (LAO) view and in a 30° right anterior oblique (RAO) view once the coronary sinus (CS) was cannulated. A selective venogram in a 30° RAO view was performed for the accurate measurement of the LV long-axis distance, which was divided into three equal segments: basal, middle, and apical (Figure 1). From the venogram in the LAO view, the left ventricle was divided into five equal segments (Figure 1) that corresponded to the five segmental divisions acquired in the preoperative ST-RS echocardiographic measurement. Thus, the target segment for the LV pacing lead was also located on the venogram in the LAO view. Substantial effort was made to achieve an LV lead position in a vein located in the target segment with the latest contraction. If there was no available vein in that segment, a vein located as close as possible was selected for lead placement.

The LV leads were delivered using the over-the-wire technique with standard coronary sinus cannulation catheters and a subselection catheter when required. As basal as possible of an LV long-axis position for the stimulating electrode was preferred. The measurements of the pacing capture threshold (PCT) and the occurrence of phrenic nerve stimulation (PNS) were recorded. For the active fixation lead, a J-shaped stylet was inserted to press the helix toward the vessel wall. The lead was then fastened by clockwise rotation. The lead fixation was verified by pushing and pulling the lead during observation of lead

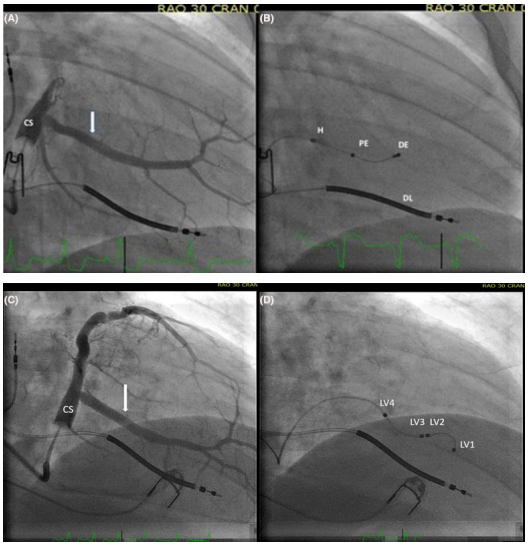

FIGURE 2 Right anterior oblique fluoroscopic views of two patients with an active fixation bipolar lead (A + B) and passive fixation quadripolar lead (C + D). On the coronary sinus (CS) venograms (A + C) the arrows indicate the target veins in lateral side branches from CS. The target vein is located in the target left ventricular segment determined from speckle tracking echocardiography. B: The final lead placement of an active fixation bipolar lead. The helix (H) is fixated proximal in the vein. The proximal electrode (PE) is located in a basal third left ventricular long-axis position, and is used as the stimulating cathodal electrode. The distal electrode (DE) is in the mid third left ventricular long-axis segment. The high voltage right ventricular defibrillator lead (DL) is located close to the apex of the right ventricle. D: The final lead placement of a quadripolar lead. The distal end (LV1) is wedged into a small side branch. The proximal electrode (LV4) is used as the stimulating cathodal electrode

movement using fluoroscopic imaging. If repositioning of the lead was needed, counterclockwise rotation was performed to free the lead helix from the vein wall. The R-wave, pacing impedance, and electrical delays as well as the Q-LVsense, RVsense-LVsense, and RVpace-LVsense were recorded from a pacemaker system analyzer (Model 2090, Medtronic, Minneapolis. MN, USA) before removing the catheters. The leads were connected to a CRT-D or a CRT-P generator. The devices used were CRT defibrillators (CRT-D, Medtronic, Minneapolis, MN, USA) in 66% of the patients and CRT pacemakers (CRT-P, Abbot, Lake Bluff IL, USA) in 34% of the patients.

2.5 | Lead characteristics

The active fixation lead was a soft bipolar steroid-eluting lead (Attain Stability model 20066/4796, Medtronic Inc, Minneapolis, MN, USA). The lead body was 3.9 French (Fr) proximal and 3.4 Fr distal

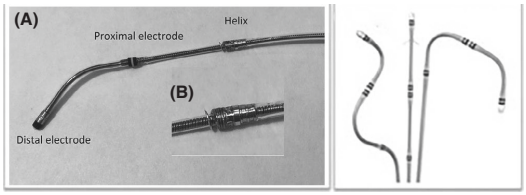

FIGURE 3 A, The bipolar lead with distal angled shape has an exposed side screw for fixation located 15 mm proximal to the proximal electrode. The electrode separation is 21.0 mm. The maximum lead body diameter is 3.9 Fr. B, Demonstrates a close range view of the exposed side screw. C, The quadripolar leads: An S-shaped lead, a straight lead with tines and a dual bend lead. The distances between the electrodes are 21 mm (LV1-LV2), 1.*3 mm (LV2-LV3), and 21 mm (LV3-LV4). The maximum lead body diameter is 5.3 Fr A + B: Photo by the author. C: Photo from the manufacturer*

(Figures 2 and 3). The electrode separation was 21 mm. Proximal to the ring electrode was a side screw. Longitudinal movements of the lead without torqueing did not engage the screw. The screw was also designed to elongate along the length of the lead body and to detach it from the vein wall when the traction force was increased to approximately 0.11 kilograms. The quadripolar leads (Figures 2 and 3), which were attained from the same vendor, had a diameter of 5.3 Fr proximal and 3.9 Fr distal. A dual bend lead, an S-shaped lead and a straight lead with tines were available. The dual bend lead was used in 19 patients (63%), the S-shaped lead in 10 of the patients (33%) and the straight lead in one patient (3%).

2.6 | Programming the device

Atrioventricular (AV) and interventricular adjustments were based on an automatic algorithm (adaptive CRT, Medtronic, Minnesota Inc, MN, USA) for patients with a CRT-D generator. The CRT-P devices were programmed without any LV off-set, and the sensed-AV-time was programmed to 120 ms The pacing modus was DDD, lower rate of 50 pulses per minute for those with no sinus node dysfunction. The active fixation bipolar leads were configured as bipolar, LV tip to RV-coil/RV ring or LV ring to RV coil/RV ring. For the quadripolar leads, the preferred configuration was bipolar L3-L2, integrated bipolar LV1 to the RV coil/RV ring, LV3 to the RV coil/RV ring, or LV4 to the RV coil/RV ring. A limited number of configurations for the quadripolar lead were selected for an accurate assessment of the location of the stimulating electrode in the LV long-axis view. The final LV lead position was evaluated. The PCT, R-wave, and LV lead impedance were measured at the 2-, 6- and 12 month follow-up (FU) periods.

2.7 | Statistical analysis

Analyses were conducted according to the intention-to-treat concept. Statistical analysis was performed by IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as the mean ± SD. Categorical variables are shown as frequencies and percentages. Differences were determined using Student's *t*-tests for continuous variables, the chi-square test for ordinal variables, or Fisher'exact test for categorical variables. We used histograms and Q-Q plots to evaluate the normality of the continuous variables. A P-value of $< .05$ was considered statistically significant. For sample size calculation, a 20% difference in the proportion of concordant LV lead placement, fluoroscopic distances, lead impedance measurements, and PCTs were estimated. Descriptive data from a previous active fixation lead study (10) were used to predict values and standard deviations. Powered at 80%, with a two-sided alpha value of 0.05 to detect differences, about 60 patients were required for the different analyses. The study was not powered to compute significant differences in infrequent events as lead dislocations.

3 | RESULTS

Initial successful implantation was obtained in 31 patients (100%) and 30 patients (97%) in the active fixation bipolar group and the quadripolar group, respectively. In 1 patient, the quadripolar lead dislodged repeatedly during implantation, and this could not be avoided by switching to the bipolar active fixation lead. Finally, an alternate thicker bipolar LV lead was implanted successfully. In three patients, LV lead dislodgement occurred, all in the active fixation group. For two of these three patients, the LV lead dislodged some hours after implantation, and the third instance of dislocation was recognized after 2 months. In all three patients, the same lead was repositioned successfully to the same coronary vein. We compared the size of target veins (Table 2). There was no difference in vein size at the active electrode or at the distal electrode. The average vein dimension at the proximal electrode was larger at the qauadripolar lead, corresponding with a more proximal position. During FU, there were no additional instances of reoperation, and there were no cases of device infection. All patients were alive the 12 month FU. Table 2 summarizes the characteristics of the 62 implantation procedures. The locations of the targeted LV segments were anterior (10%), anterolateral (11%), lateral (44%), posterolateral (30%), and posterior (5%). The distribution of the locations of the selected stimulating electrodes for each LV lead is shown in Figure 1. The target LV lead placement, which was defined as a position in a concordant or adjacent LV segment, was achieved in the majority of the patients with no statistically significant differences between the patient groups (Table 3). For both LV lead groups, the selected active electrodes were stimulating the LV from a position close to the distal part of the basal segments in majority of the patients. The proximal electrode of the quadripolar LV lead was closer to the CS than that of the active fixation LV lead. However, there was no statistically significant difference between the active fixation group and the quadripolar group concerning the proximity of the stimulating electrode to the coronary sinus, neither in absolute values nor in distance as a percentage of the distance from the CS to the apex.

TABLE 2 Characteristics of the implantation procedures

	Active fixated lead (n = 31)	Quadripolar lead (n = 30)	*P*-value
Number of veins attempted, n	1.1 ± 0.52	1.29 ± 0.40	.26
Number of fixation attempts, n	1.7 ± 1.5	Not relevant	
Total LV lead implantation time, min	13.2 ± 11	12.2 ± 12	.75
Total procedure time, min	77 ± 22	76 ± 21	.82
Fluoroscopy time, min	15 ± 7	15 ± 10	.68
Fluoroscopy doses, mGY (mGym2)	329 ± 236 (3.0 ± 2.1)	319 ± 426 (3.2 ± 4.3)	.91 (0.85)

Note: Total LV lead implantation time was measured from the start of LV lead insertion and included advancement of the lead to the target site, fixation attempts, repositioning to other locations, electrophysiological measurements, and removal of supporting catheters.

TABLE 3 Left ventricular lead positions

	Active fixated lead (n = 31)	Quadripolar lead (n = 30)	*P* value
Lead in the concordant segment, n (%)	12 (39)	19 (63)	.06
Lead in an adjacent segment, n (%)	15 (48)	6 (20)	.02
Lead in a concordant or adjacent segment, n (%)	27 (87)	25 (83)	.69
Lead in a remote segment n (%)	4 (13)	5 (17)	.69
Distance from CS to proximal electrode, mm	32 ± 10	19 ± 15	.00
Distance from CS to distal electrode, mm	51 ± 9	53 ± 13	.51
Distance from CS to active electrode, mm	38 ± 10	35 ± 13	.36
Distance from CS to active electrode as percentage of distance from CS to apex, %	36 ± 11	33 ± 12	.26
Vein size at proximal electrode, Fr	8.1 ± 3.0	10.8 ± 6.2	.04
Vein size at distal electrode, Fr	6.2 ± 2.7	5.3 ± 2.3	.20
Vein size at active electrode, Fr	7.3 ± 2.9	8.3 ± 3.2	.20

Abbreviation: CS, coronary sinus.

TABLE 4 Electrical performance at the selected configurations

	Active fixated lead (n = 31)	Quadripolar lead (n = 30)	*P*-value
PCT at implantation, V@0.4 ms	1.09 ± 0.48	0.77 ± 0.25	.02
PCT at the 2 month FU, V@0.4 ms	1.23 ± 0.77	1.00 ± 0.62	.21
PCT at the 6 month FU, V@0.4 ms	1.16 ± 0.76	1.02 ± 0.74	.46
PCT at the 12 month FU, V@0.4 ms	1.23 ± 0.75	1.03 ± 0.86	.35
LV lead impedance at implantation, Ohm	539 ± 159	414 ± 94	.00
LV lead impedance at 6 months	561 ± 156	443 ± 96	.01
LV lead impedance at 12 months	545 ± 142	433 ± 97	.04
R wave, mV	17 ± 8	13 ± 8	.03
Q-LV sense, ms	155 ± 30	154 ± 35	.88
RVsense- LVsense, ms	101 ± 26	97 ± 36	.67
RVpace- LVsense, ms	142 ± 27	143 ± 31	.94

Abbreviations: PCT, pacing capture threshold; FU, follow-up; LV, left ventricle; RV, right ventricle; Q-LV sense, interval from QRS onset to first peak of the LV electrogram.

The electrical performance was recorded at implantation and at the 2-, 6- and 12 month FU periods (Table 4). For the final selected pacing configurations, the mean PCT for the active fixation lead was higher at implantation but was not significantly different at FU. A PCT < 2.5 V/0.4 ms at implantation was achieved in 100% of patients in both groups. At the 12 month FU, a PCT < 2.5 V/0.4 ms was recorded for 93% of patients in both groups. The PCT for the proximal electrode was significantly higher for the quadripolar lead than for the active fixation lead (2.83 V vs 1.31 V; $P = .003$). For the quadripolar lead, the PCT at the proximal electrode was ≥ 3.5 V for 10 patients (33%); however, for the active fixation lead, the PCT was ≥ 3.5 V only for two patients (6%). At the 12 month FU, nine patients (16%) had

at one time or another after discharge from the hospital experienced some kind of discomfort from PNS. Six of those patients (19%) were in the active fixation group, and three (10%) were in the quadripolar group. In all cases, the PNS was resolved by reprogramming the device.

4 | DISCUSSION

Implanters of CRT devices are concerned about the acute and chronic lead stability. Much effort has been devoted to developing leads that provide stability and a low PCT, but that have preserved trackability along tortuous veins. LV leads have evolved from unipolar to bipolar and, further, to quadripolar models. Compared to bipolar leads, quadripolar leads provide more available pacing vectors and less PNS. Quadripolar leads have been associated with better clinical response and lower mortality, based on retrospective analyses.[9,14] In these trials, the LV leads were placed empirical and not targeted, and the final LV lead positions were not assessed. Consequently, it is not possible to conclude if the clinical superiority of quadripolar lead is a consequence of being quadripolar with multiple options for pacing configurations, or if it is because of implantation issues and the final position of the active electrode. According to the subgroup analyses of randomized trials, such as MADIT-CRT and REVERSE, LV pacing from an apical site is associated with less favorable outcomes and high PNS.[4,15] However, operators may be tempted to sacrifice a nonapical position to achieve a stable position and low PCT by wedging the lead in a small apical branch. The optimal long-axis LV lead position is debatable, and the future may show that the optimal long axis position occurs on an individual basis. A nonrandomized multicenter trial that compared active fixation LV leads with quadripolar LV leads reported noninferior clinical outcomes for the active fixation leads.[16] Our trial is the only randomized clinical trial comparing active fixation LV leads with quadripolar LV leads. At implantation, the PCT was lower in the quadripolar group than in the active fixation group, but the difference decreased later, and there were no significant differences at the 6- and 12 month FUs. The pacing impedance was significantly higher (approximately 20%) in the active fixation group than in the quadripolar group and may lead to a moderate increase in battery longevity compared to devices with quadripolar LV leads.

Our hypothesis was that in large veins, an active fixation bipolar LV lead will enable a more proximal position of the stimulating electrode compared to a quadripolar lead. We aimed to achieve a position of the stimulating LV lead electrode as far from the apex as possible. Nevertheless, we did not find any significant difference between the two types of LV leads concerning the proximity of the ultimately selected stimulating electrode to the coronary sinus. Thus, the active fixation lead did not promote a more basal placement of the stimulating electrode. An explanation for this may be that in many cases of quadripolar leads, it was possible to wedge the lead tip in an early side branch to stabilize the stimulation electrode in a basal LV segment. Furthermore, the electrically inactive helix of the active fixation bipolar lead was placed proximal to the proximal electrode, thus prohibiting placement of the proximal electrodes in the vein close to the coronary sinus. The PCT for the proximal electrode was significantly higher for the quadripolar lead than for the active fixation lead (2.84 vs 1.42 V). This may be because of the lower amount of pressure toward the wall for the passive leads than for the active fixation leads in the proximal vein segment. On the contrary, the PCTs for the distal electrodes were lower for the quadripolar leads at implantation. An explanation for this may be that the S-shape or dual bend shape and the larger body diameter of the quadripolar lead may cause more tension toward the vein wall than that of the distal end of the active fixation lead. Quadripolar leads with active fixation were not available when the current trial was performed, but later, a quadripolar active fixation lead with a similar helix for fixation was approved (Medtronic lead model 4798). In this quadripolar version, the fixation mechanism is located between electrodes 3 and 4, which may potentially improve the lead stability and reduce the PCT for the most proximal electrodes, even in large coronary veins. The LV lead dislodgement rate is low in recent trials with quadripolar leads, and in the Performa Trial, a dislodgement rate of 1.4% was reported.[17] In the current trial, which was not powered to show differences in the rate of lead dislodgement, there were no dislodgements of the quadripolar leads; however, in the active fixation group, two postoperative dislodgments and one late dislodgment occurred. These three patients were retrospectively evaluated. One patient had a large-diameter coronary vein (16.5 Fr at the point of helix fixation) and needed four fixation attempts at the primary operation. The other 2 patients with LV lead dislodgement showed no unusual vein-anatomy and only one fixation attempt was needed initially. The present trial did not prove that adding an active fixation mechanism to bipolar lead makes them more stable than passive fixation quadripolar leads. The new location of the fixation helix between electrodes 3 and 4 in the Medtronic lead model 4798 may potentially further augment the stability of the active fixation lead.[18] There is an obvious concern about the extractability of active fixation LV lead. Unlike the leads with side lobes of the lead, the Attain Stability is fixated with a side helix constructed to uncoil in response to retractive force. However, the data on extraction safety are limited and this must be taken into account when choosing an LV lead.

In this randomized trial, comparing an active fixation bipolar lead and quadripolar passive fixation leads, no important differences in implantation variables or long-term electrical performance were found. Furthermore, there were no differences in the ability to reach a proximal concordant or adjacent LV segment for targeted LV stimulation.

4.1 | Study limitations

The study was a single-center study with a relatively small sample size. Therefore, the extension of the validity of these results to other centers and implanters is not possible. The clinical findings, as changes in NYHA classification or echocardiographic response, were not compared in the present study.

CONFLICT OF INTERESTS

The authors have no conflict of interest, financial or otherwise.

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Paper III

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Clinical outcome of cardiac resynchronization therapy in patients randomized to an active fixation bipolar left ventricular lead versus a passive quadripolar lead.

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