New methods: Pacing therapy to improve patients with advanced heart failure

Ph.D. Thesis

Author: Attila Mihálcz, M.D.

Program leader: Prof. Kálmán Tóth, M.D., Sc.D.

Project leader: Tamás Szili-Török, M.D., Ph.D.

First Department of Medicine University of Pécs Medical School,

Pécs, Hungary

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Table of contents

Acronym list

AV: atrioventricular

CHF: Chronic Heart Failure

CRT: Cardiac Resynchronization Therapy

CS: Coronary Sinus

CT: Computer Tomography

+dP/dTmax: Maximal Rates of Left Ventricular Pressure Change

ECG: Electrocardiogram

EHRA: European Heart Rhythm Association

ESP: End-Systolic Pressure

HF: Heart Failure

IAS: Interatrial Septum

ICD: Implantable Cardioverter Defibrillator

INR: International Normalised Ratio

LA: Left Atrium

LAV: Left Axilar Vein

LBBB: Left Bundle Branch Block

LV: Left Ventricle

LVAD: Left Ventricular Assist Device

LVEF: Left Ventricular Ejection Fraction

LVEDD: Left Ventricular End Diastolic Diameter

LVESD: Left Ventricular End Systolic Diameter

MRI: Magnetic Resonance Imaging

MSP: Multi Site Pacing

NYHA: New York Heart Association

OAC: Oral Anticoagulation

PM: Pacemaker

PP: Arterial Pulse Pressure

Qol: Quality of Life

RA: Right Atrium

RAO: Right Anterior Oblique
RFV: Right Femoral Vein
RIJV: Right Internal Jugular Vein
RV: Right Ventricle
TE: Thromboembolic Event
TEE: Transoesophageal Echocardiography
TIA: Transient Ischemic Attack
TVI: Tissue Velocity Imaging
VAT: Video Assisted Thoracoscopy
SVC: Superior Vena Cava
VKA: Vitamin K Antagonist
VT: Ventricular tachycardia
VTS: Ventricular tachycardia storms
VV: Interventricular

1. Introduction

Cardiac resynchronization therapy (CRT) has evolved as an effective non pharmacological method of treating patients with heart failure (HF) and left ventricular (LV) dyssynchrony for those who have not responded adequately to medical therapy [1]. CRT requires permanent pacing of the LV wall and restores the synchronicity of the atrio-ventricular, interventricular and intraventricular contractions, resulting in improved clinical outcomes and cardiac performance of advanced HF patients with wide QRS complex [2]. However, a significant percentage of patients treated with CRT do not show an improvement in clinical symptoms or cardiac function. The suboptimal position of the LV pacing lead, an absence of LV dyssynchrony, myocardial scar abundance or suboptimal device programming have been related to a nonresponse to CRT [3,4]. Furthermore, unsuccessful primary implantation of the LV lead into the coronary venous system has been reported in up to 10 % of patients [5,6]. The optimal placement of a LV lead is one of the most challenging technical aspect of CRT device implantation and it is one of the major determinants of response to CRT. An optimal LV lead position may theoretically be defined by the positioning of the LV pacing lead coincident with the latest activated areas of the LV [7,8]. In case of optimal pacing parameters this location can maximize the haemodynamic benefits of CRT and provides superior long-term outcomes [4].

In the last decade the indication for CRT expanded [9] and the improvements in lead and delivery tool technologies made CRT more accessible to patients with HF [10]. The number of CRT recipients in the last years increased enormously and only in year 2007 in the USA and Western Europe an approximate total number of 127,940 CRT pulse generators were implanted. Between 2003 and 2007 this number increased to a value of 426,620 CRTdevices [11]. Given the fact that 75 % of these were initial implants and assuming that 95% of these new CRT patients received coronary sinus (CS) leads, with 75% patients survival and 10% CS lead failure over 5 years, 22,798 patients will require CS lead revisions or alternative LV pacing methods [11]. Furthermore, 40% of CS lead revision cases, 9,119 patients will have no usable side branches for LV lead replacement and will need alternative approaches to LV pacing [11]. In a few words the number of CRT

recipients and the considerable need for LV lead revisions or alternative techniques increased enormously.

1.1. Problems with the current LV lead implantation methods

Currently, in clinical practice the standard first line approach is the transvenous epicardial LV lead placement through a side branch of the CS [4,6,10]. The final position of the LV pacing lead depends on the anatomy of the CS, on the performance and stability of the pacing lead and on the absence of phrenic nerve stimulation [12]. Despite all of the available technologies and the placement techniques, in the high volume centers the rate of failed LV lead implantation into the CS side branch or the risk of late lead dislodgement, phrenic nerve stimulation or increasing threshold remains a substantial complication (5-10%) of transvenous CRT [13]. As alternative in the last years was launched the quadripolar LV lead with 4 different pacing electrodes and a dedicated device with multiple pacing options. The introduction of quadripolar technology has helped to avoid or significantly reduce the risk of phrenic nerve stimulation, high pacing threshold and lead instability. After introduction the standard use of quadripolar LV leads the number of acute complications remains along 5%, since this new LV electrode offered significantly more pacing configuration for LV optimization and phrenic nerve stimulation avoidance [14].

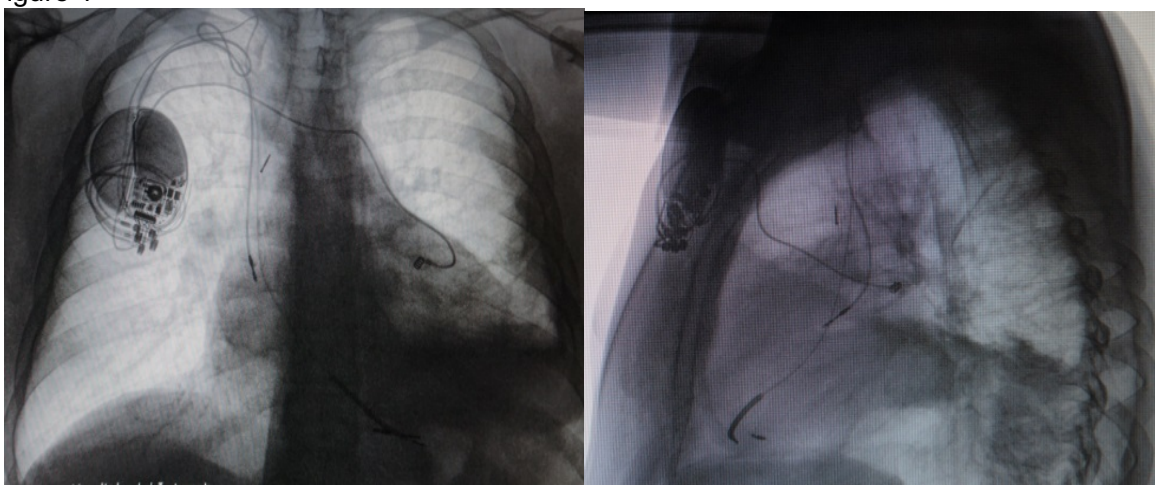
1.2. Alternative CRT methods

The alternative approaches can be classified on the basis of the LV pacing site (*epicardial* or *endocardial)*, and on the basis of access (*closed-chest/percutanous* or *open-chest)*. In the case of the closed chest/percutaneous approach, the lead insertion can be differentiated as transvenous, transapical or transarterial. For example the standard CS side branch lead placement is a transvenous approach and produces epicardial pacing, which is less physiological, reversing the normal direction of LV activation.

1.2.1. Epicardial pacing techniques

Currently, the open-chest access epicardial lead placement is the most frequently used as a second choice by either thoracotomy or video-assisted thoracoscopy (VAT) [12]. Nevertheless, at planned coronary artery bypass graft surgery, valve repair or replacement, the epicardial surgical approach might still remain the first choice.
The advantage of this approach is the direct visual control with the possibility of choosing the lead tip position (Figure 1 a,b).

Figure 1



a b

Postoperative chest x-ray from anteroposterior projection (a) and lateral projection (b) after epicardial left ventricular pacing lead implantation via minithoracotomy.

The risks of lead dislodgement and phrenic nerve stimulation are low [15] and there is no limitation of the CS anatomy [16]. Less fluoroscopy and avoidance of intravenous contrast material are also benefits over conventional CRT [17]. Surgical epicardial LV lead placement has several disadvantages such as the need for general anaesthesia, the presence of epicardial fat, adhesions and it is more invasive than the transvenous approaches. The surgical trauma and the recovery time is appreciably higher than the transvenous LV lead implantation [15]. Finally, surgical implanted epicardial leads have a significantly higher failure rate than those of CS and transvenous right heart leads. The surgical implanted epicardial LV lead comparison studies confirmed usually excellent results after 3-6 months follow up [17]; but after a 5 year follow up period epicardial leads

might have significantly higher failure rate than the CS leads [18]. In a prospective study including 114 juvenile patients with most having congenital heart disease and with 239 atrial and ventricular bipolar epicardial leads (Medtronic CapSure 10366 or 4968, Minneapolis, MN), followed up to 12.2 years (median, 3.2), the lead data were obtained at implant and at semi-annual visits. Analysis was done for left or right atrial and ventricular leads. During follow-up, the 239 atrial and ventricular leads experienced 19 (8%) lead failures. Bipolar steroid-eluting epicardial leads demonstrate excellent sensing characteristics and persistent low median pacing thresholds below 1.2 V at 0.5 ms in children during up to 12 years follow-up, but the epicardial ventricular lead survival at 2 and 5 years was 96% and 85%, respectively [18].

On the other hand, a study published in 2012 by Burger et al. demonstrated an excellent long-term epicardial lead performance and durability after surgical (median sternotomy or lateral minithoracotomy) implantation of epicardial LV leads [19]. In this study 130 consecutive patients with comparable characteristics were evaluated over a period of 48 months. A total of 54 screw-in (MyoDex™ 1084T, SJM) and 76 suture-on (Capture Epi 4968, Medtronic) bipolar epicardial steroid-eluting LV leads were implanted either via a left lateral or a median thoracotomy. Sensing, pacing threshold, impedance and NYHA class were recorded at defined time points. No surgery-related death or major complication was observed. At the time of implantation, the pacing threshold, sensing and NYHA class did not differ significantly between the two groups. The impedances of screw-in leads were significantly lower compared to those of suture-on leads. Suture-on leads showed a moderate initial drop in their pacing threshold but afterwards remained stable. Screw-in leads were characterized by a moderate but significant increase in the pacing threshold in the first year followed by a continuous decrease thereafter. Twenty-four months post-implantation no differences between both lead types could be detected. Sensing and NYHA class improved in both groups. The surgical approach had no significant impact on lead functionality [19].

Currently, two different technical epicardial lead concepts are available: screw-in and suture-on leads. Both possess theoretical advantages and disadvantages. In the study published by Burger H et al. there was no superior technical epicardial lead concept (screw-in vs. suture-on leads) and all epicardial leads demonstrated an excellent long-

term performance and durability. Therefore, it seems that epicardial leads represent a good alternative to transvenous leads and surgeons should be encouraged to implant epicardial leads during concomitant cardiac surgery when the indications for CRT are present [19].

There are several surgical approaches to implant the LV pacing lead.

Median sternotomy is used at planned coronary artery bypass graft surgery and at valve repair or replacement. The **full left thoracotomy** offers the widest accessibility of the lateral LV wall however at present is less applied.

The **minimal thoracotomy (minithoracotomy)** offers better survival and a lower incidence of mediastinitis or osteomyelitis [20]. Nowadays, the epicardial LV lead is implanted surgically often through a small left thoracotomy [15]. The LV lead implantation is performed under general anesthesia and on the beating heart. All patients have standard monitoring (ECG, pulse oximetry and invasive arterial monitoring). The access to the pericardium is achieved by a 4-5 cm left lateral, midaxillary minithoracotomy in the fourth or fifth intercostal space. The pericardium is opened anterior to the phrenic nerve. After mapping for an optimal pacing site the LV lead is placed on the target area [20]. After testing the proximal end of the lead is tunneled submuscular to the provisional pocket and connected to the device. A chest tube is required postoperatively and can be discontinued within 48 hours. Recent investigations described this technique safe with a very low complication rate, representing a good alternative as second line procedure to transvenous CRT [16,18].
In the last years two other technologies are increasingly used: video assisted thoracoscopy (VAT) techniques and robotic surgery.

V**ideo assisted thoracoscopy (VAT)**

This technique offers less postoperative pain and requires smaller incisions. It does not compromise in visualization [21]. Epicardial lead implantation using VAT was initially shown to be feasible in 2001 when a group successfully undertook a LV epicardial

lead placement within 40 minutes and without significant blood loss [22]. In this case a patient with cardiomyopathy, complete A-V block and permanent transvenous pacing lead replacements received epicardial pacing lead via VAT. The resulting thrombosis of the superior vena cava was the indication to insert an epicardial permanent pacing lead and video-assisted thoracic surgery (VATS) technique was selected. The surgery performed by the group from Vienna was safe for the patient, of 40 minutes' duration, and with minimum blood loss. The postoperative course was devoid of complications, the patient's circulation was stable, and he was able to leave the hospital one week later [22].

In recent years, larger series were reported and surgical leads have also been implanted thoracoscopically using two ports. Three 2-cm incisions are used on the left chest wall to place the screw-in lead near the obtuse marginal arteries high on the lateral wall of the left LV. [23]. Usually 2 or 3 incisions are used for these ports within the fourth or fifth intercostal space along the anterior and midaxillary line. The VAT technique should be performed under general anesthesia, single-lung ventilation, standard monitoring and on the beating heart [24]. The camera and the manipulating instruments are inserted through prepared ports. Under visual control the pericardium is opened laterally to phrenic nerve, the obtuse marginal artery as landmark help to identify the desired site and an epicardial lead is screwed into the targeted wall region of the LV. After TEE control and the pacing threshold test, the proximal end of the lead is passed through the medial incision and is tunneled subcutaneously to the pocket. The VAT approach is a feasible and safe alternative, is well tolerated and it has minimal postoperative recovery. However, a skilled VAT surgeon is necessary for epicardial lead placement [23]. It is of importance that, using VAT epicardial LV lead fixation on the heart needs special equipment and without this extra support there is an increase in the risk of dislocation.

Robotically assisted surgery

Experience with lead implantation using the minimally invasive route are growing rapidly with progression into LV lead implantation using robotics. This technique results in more precise LV lead placement on the ventricular wall and significantly reduces postoperative morbidity and the length of hospitalization [25]. This approach also needs general anesthesia, single-lung ventilation, standard monitoring and TEE control. The

robotic camera and instruments are introduced through 5-10 mm port sites. Using the robotic arms (da Vinci® Surgical System), the pericardium is opened posterior to the phrenic nerve to expose the posterolateral wall of the LV [25]. Computer interfacing allows the scaled motion, eliminates tremor and provides incredibly accurate surgical precision. A screw-in lead is passed into the chest and is secured to the heart using robotic arms. The proximal part is tunneled to the axillar region and is connected to the pacemaker or defibrillator. The previous routine implantation of a second back-up lead is unnecessary [26]. The minimally invasive robotic approach to epicardial LV lead placement is associated with 98% acute technical success rate and can be performed with a low complication rate [25,26]. But the long-term performance of robotically placed epicardial LV leads at this time was unknown. As a result, many cardiac surgeons routinely implanted two leads at the time of surgery. One lead was connected to the CRT device, the other was capped and left as a “back up” in case the primary lead fails. The necessity of this approach, which increases procedural duration and adds hardware to the patient, was undefined. In 2011 Kamath et al. published a study with the largest cohort of patients that underwent robotic epicardial LV lead placement. 78 consecutive patients (70 ± 11 years, 50 male) were evaluated after robotic implantation. The aims of this study were to determine the long-term performance of robotically placed epicardial LV leads and long-term outcome of patients implanted with an epicardial LV lead. The short- (<12 months) and long-term (≥ 12 months) lead performance was determined through device interrogations and mortality data were determined by contact with the patient's family, referring physicians and confirmed using the Social Security Death Index. All patients had successful lead placement and were discharged in stable condition. Interestingly when compared to the time of implantation, there was a significant increase in pacing threshold (1.0 ± 0.5 vs 2.14 ± 1.2; $P < 0.001$) and decrease in lead impedance (1010 ± 240 Ω vs 491 ± 209 Ω; $P < 0.001$) at short-term follow-up. During long-term follow-up the pacing threshold (2.3 ± 1.2 vs 2.14 ± 1.2; $P = 0.30$) and lead impedance (451 ± 157 Ω vs 491 ± 209 Ω; $P = 0.10$) remained stable compared to short-term values. This multicentre study report a benefit after 44 months follow-up and an excellent robotic lead performance [26]. In summary epicardial LV leads can be placed safely with high success via robotically

guided approach. These leads exhibit excellent long-term performance and routine implantation of a second back-up lead is unnecessary.

However, while robotic surgery was shown to be feasible and safe, its use is restricted largely by cost implications related to purchase and maintenance of technology and its longer operating room time. However, emerging evidence shows that operating room time decreases with experience using the robot [27]. The epicardial LV lead fixation on the heart with a robotic arm needs special equipment. Without this equipment, the risk of lead dislocation increases.

1.2.2. Endocardial pacing techniques

In case of endocardial pacing the LV lead has a direct contact with the endocardial tissue. Usually is implanted as closed chest/percutaneous approach, only the lead insertion can be differentiated as transvenous or transapical. (The transarterial access for endocardial LV lead implantation is possible through the subclavian or axillary artery and through the aortic valve. In the recent years, this occurred in insignificant numbers and mostly inadvertent). The transvenous technique is performed using different veins (jugular, femoral or subclavicular, in most of case two veins are punctured) and the LV lead is introduced into LV via interatrial septum and mitral valve. The need of interatrial septum puncture made this method to become known as transseptal approach. Recently was developed a technique via puncture of the interventricular septum as a simpler solution, but this occurred only in 20 patients [28]. This pilot study demonstrated that the LV endocardial pacing via interventricular septal puncture in patients for whom standard CRT is not possible is similarly effective and durable, with significant but potentially acceptable risks.

Actually this technique via interventricular septum isn't into general use and usually as transseptal CRT are reported LV lead implantations through interatrial septum. Correspondingly like this practice in my work I will discuss the transseptal endocardial LV lead implantation as a CRT alternative via interatrial septum.

1.2.2.1. Transseptal endocardial LV lead implantation

Transseptal access endocardial LV lead placement was investigated as a means of delivering LV pacing when CRT first emerged as a therapeutic paradigm and currently is used also as third line approach. This approach does offer some major advantages: transvenous access, more lead placement sites, endocardial pacing and there is no need to compromise in LV pacing threshold for positional stability or phrenic nerve stimulation [11]. Its clinical use has been limited due to several reasons, including the lack of reliable long-term safety data and difficulty of the necessary techniques [11]. The transseptal technique has been used for over 50 years for haemodynamic measurements, mitral and aortic valve angioplasty and in electrophysiology for left sided ablations. The first case report was described using femoral transseptal puncture and a snare technique via the right jugular vein [29]. The lead tunnelled over the clavicle increases the risk for lead damage and skin erosion. Small modifications were described until the recently applied technique was clarified: after transseptal puncture and septal dilatation from the femoral route, the left atrium was cannulated with a combination of catheters and guide wires from the left or right subclavian vein. After advancement of this guide catheter into the LV, a standard bipolar screw-in lead could be implanted in the posterolateral wall [30]. In this study published by van Gelder et al. in 2007, an atrial transseptal LV lead placement was attempted using this technique in 10 patients (six females, age 69.4 +/- 9.6 years) in whom CS lead placement for CRT had failed. All patients were maintained on anticoagulant therapy with warfarin after implant. An LV lead could be successfully implanted in nine of the 10 patients. The stimulation threshold was 0.78 +/- 0.24 V, and the R-wave amplitude was 14.2 +/- 9.7 mV. At 2 months' follow-up, the stimulation threshold was 1.48 +/- 0.35 V with a 0.064 +/- 0.027 ms pulse width. There was no phrenic nerve stimulation observed in any of the patients. There were no thromboembolic complications at follow-up [30].

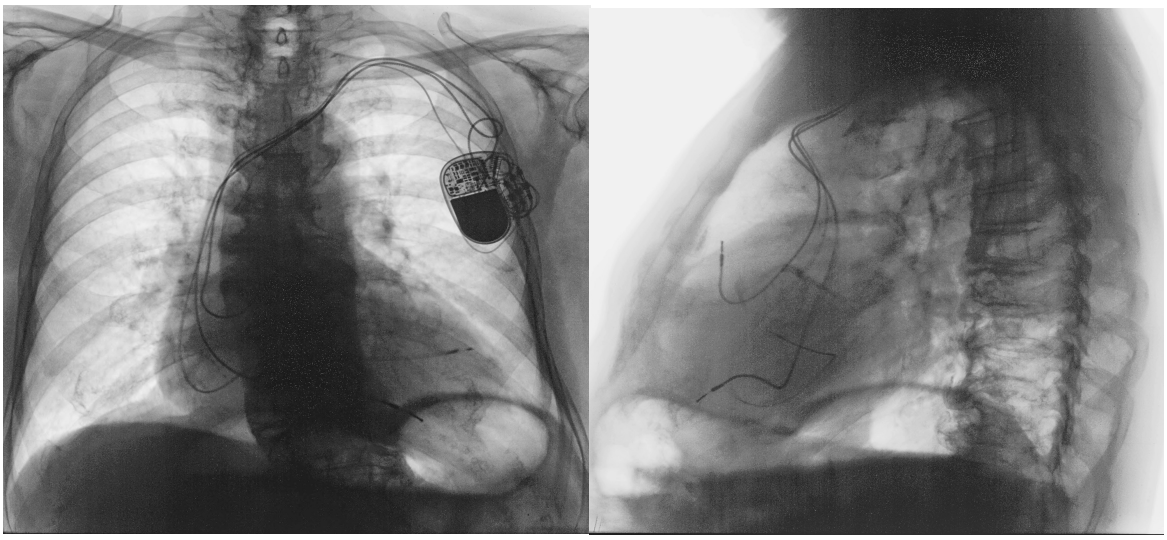
Transseptal endocardial LV placement requires puncture of the interatrial septum (IAS) for passage of a lead from the RA into the LA and the LV cavity. The procedure does not require general anaesthesia and minimal postoperative recovery is required. The first published techniques restrict the venous access for the LV lead to the right

inferior jugular vein (RIJV) and require bending the lead over an acute angle and subcutaneously tunnelling to reach a right pectoral device pocket. The medium term performance of endocardial LV lead placed with this technique appeared satisfactory [31]. Using a guide wire placed in the LA through an IAS puncture from the right femoral vein (RFV) as a fluoroscopic marker, Ji et al. repunctured the IAS from the left axillary vein (LAV) using a manually shaped transseptal needle [32]. In this case report first a standard puncture via the RFV was performed and a mitral valvuloplasty guidewire was placed in the LA. This wire was used as a marker for transseptal access from the superior vena cava (SVC). The LAV was accessed using the modified Seldinger technique. Tip-deflectable EP catheters, introduced via a long sheath from the LAV, were used to attempt left atrial entry using the transseptal wire as a marker. These attempts were not successful and that was the need of a second transseptal puncture using a peel-away sheath and a BRK-1 transseptal needle via the LAV. To facilitate this puncture the needle was reshaped to allow passage throught the innominate vein and engage the fossa ovalis. The transseptal needle was shaped, with the stylet inside the needle, to approximately match the contour of the innominate vein and the SVC-RA junction. The needle was extended to puncture the septum and the dilator and sheath subsequently were introduced into the LA [32]. This was the first report of successful CRT using a transseptal approach from the LAV.

Three years later two centres published an alternative with a directed guide wire across the IAS puncture through a Judkins right or internal mammary catheter from the left or right subclavian vein. These techniques allow more choices for the upper body venous access used for transseptal endocardial LV lead placement. But the transseptal LV endocardial implantation from a superior approach still does not have 100% success rate.

In 2011 was reported the first experience with LV endocardial lead placement for CRT with a femoral transseptal technique followed by intravascular pull-through to the pectoral location [33]. In 11 patients, 10 males (61.5 ± 9.5 years) with failed CS implant (four patients) or repeated CS lead malfunction (seven patients) a 4.1 French active fixation lead was implanted endocardial in the left ventricle employing a femoral approach using an 8F transseptal sheath combined with a hooked 6F catheter.

Figure 2



a b

Postoperative chest x-ray from anteroposterior projection (a) and lateral projection (b) after transseptal left ventricular pacing lead implantation.

After successful implantation, the lead was pulled through from the femoral insertion site to the pectoral device location. The LV endocardial implantation was successfully performed in all 11 patients. Stimulation threshold was 0.62 ± 0.33 V, lead impedance 825 ± 127 Ω, and R wave 12.8 ± 8.3 mV. Threshold and lead impedance were stable during follow-up, which varied from 1 to 6 months. No dislodgements were observed and there were no thromboembolic events during follow-up. This technique for transseptal LV endocardial lead implantation (Figure 2) is an alternative for failed CS and superior transseptal attempts using standard techniques and equipment. It is also applicable for pacing sites that are more easily reached from a femoral approach [33].

There is a debate about the risk of the procedure without well experienced operators. However, the major concern is about the long term risk of thromboembolic complication and mitral valve endocarditis related to permanent presence of the transmitral LV lead from the RA [34]. Rademakers et al. investigated the thromboembolic complication of endocardial LV lead pacing (45 transseptal, 6 transapical) with mid-term follow-up [35]. Coumarin was prescribed with a targeted international normalized ratio between (INR) 3.5 and 4.5. The incidence of thromboembolic events per 100 patient-years was 6.1 (95% confidence interval 3.4-15.8). Five patients had an ischemic stroke

and two patients suffered from transient ischemic attack (TIA). One patient had both stroke and TIA. It is very important to take note of the fact, that in these cases the thromboembolic events happened after interruption of anticoagulation therapy. The European Heart Rhythm Association (EHRA) position paper including antithrombotic management for the implantation of cardiac implantable electronic devices was published first in 2015. Previously the physicians responded to concerns about peri-procedural thromboembolic events (TE) by treating moderate- to high-risk device surgery patients with heparin bridging. Previous consensus papers recommended this as standard of care. However, it became clear that there is a substantial risk of clinically significant device pocket haematoma related to heparin bridging. Importantly, device pocket haematomas can necessitate prolonged cessation of anticoagulation, with the attendant risk of TE. In the study published by Rademakers et al. one patient refused hospital admission; all other patients had a subtherapeutic anticoagulation level at the time of the event. No major bleeding complications occurred. [35].

The other question is the unknown of long term TE risk and accordingly the centres accept the risk similar as after mechanical valve implantation.

1.2.2.2. Transapical endocardial LV lead implantation

For endocardial LV pacing the feasibility of a fundamentally new surgical method was reported in 2008 [36]. This method developed in our center (Gottsegen György National Heart Center, Budapest) is based on transapical lead implantation. This new technique combines the minimal invasive surgical approach and the advantage of endocardial pacing [36]. The transapical approach was invented for patients who failed the first attempt through the CS approach and/or with extensive epicardial adhesions. The advantage of this minimally invasive technique is the best accessibility of the all LV endocardial segments without the limitations of the anatomy to reach the most delayed segment of the lateral wall.

The aim of our study - was to compare the outcome of patients undergoing either transapical endocardial or epicardial LV pacing.

A second aim was to determine the long-term outcome, including the cerebral thromboembolic complications of pts who underwent transapical LV lead placement.

2. Material and methods

The comparison study (Comparison between COronary Sinus route and TransApical route in Resynchronization therapy – the **CO-STAR** study) was a single center prospective randomized study which was approved by Regional Medical Ethical Committee (Egészségügyi Tudományos Tanács – Tudományos Kutatási Etikai Bizottság, ETT-TUKEB) conform the Medical Research Council-Scientific and Ethical Committee guidelines of the 1975 Declaration of Helsinki. The ETT-TUKEB approbation was obtained by 35/2005-s (VIII.26.) Eü.M decree and the study was performed in collaboration with the Institutional Medical Ethical Committee (Intézeti Kutatási Etikai Bizottság – IKEB) of Gottsegen György National Institute of Cardiology, conform GCP (Good Clinical Practice) guidelines. All patients gave informed consent before undergoing heart surgery.

2.1. Patient population in the comparison study

23 consecutive patients were identified in whom previous CRT implantation failed. The patients were involved and randomized in the comparison (CO-STAR) study between 2008 and 2010. All patients were eligible for CRT implantation based on current ACC/AHA and ESC guidelines [9]: all had severe congestive heart failure, NYHA functional class III or IV despite optimized medical treatment; LVEF ≤ 35% and left ventricular end-diastolic diameter ≥ 60 mm. QRS duration was more than 130 ms in all patients and for the most part the QRS morphology showed a left bundle branch block (LBBB). In case of non-LBBB the intraventricular conduction delay was associated with a significant AV-asynchrony and the patient was admitted for CRT.

Demographic data are summarized in Table 1.

Table 1. Patient demographics and medical therapy in the comparative study

	Group I.	**Group II.**	**P**
Patient number (n)	11	12	N.S.
Age	59,7±7,9	62,8±7,3	N.S.
Male/female	9/2	8/4	N.S.
NyHA Class	3,5±0,4	3,6±0,4	N.S.
Echocardiografic data			
LVEF (% ± SD)	26,0±7,8	26,4 ± 8,9	N.S.
LA (mm ± SD)	61,0±9,8	60,1±10,7	N.S.
LVESD (mm ± SD)	62,7±10,8	61,1±10,7	N.S.
LVEDD (mm ± SD)	73,7±10,5	68,3 ± 10,8	N.S.
Drug therapy (%)			
ACE inhibitors/ARB-s	100,0	100,0	N.S.
Beta blockers	90,9	100,0	N.S.
Digitalis	54,5	50,0	N.S.
Amiodarone	45,5	50,0	N.S.
Loop diuretics	100,0	100,0	N.S.
Spironolactone	54,5	50,0	N.S.

NYHA= New York Heart Association, LVEF= Left ventricular ejection fraction, LA=Left atrium, LVEDD=Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, N.S.=non-significant, p=Group I. vs. Group II.

All patients were on optimal medical therapy (OMT) suggested by HF guidelines. The relative high proportion of digitalis usage can be explicable by the ESC Guidelines for the diagnosis and treatment of acute and chronic HF 2008. At this time the digoxin was recommended in patients in sinus rhythm with symptomatic HF and an LVEF < 40%, in addition to an ACEI, to improve ventricular function and for patient well-being and to reduce hospital admissions for worsening HF.

The reason for transvenous failure are summarized in Table 2.

Causes of CS lead placement failure	Group I.	Group II.
Aberrant orifice of CS; no intubation (n)	5	6
Phrenic nerve stimulation ; high threshold (n)	3	2
No suitable CS side branches (n)	1	2
CS lead dislodged more times (n)	2	1
CABG or prostatic valve impl. (n)	-	1

CS = Coronary sinus; CABG = Coronary artery bypass graft, n=number

Pts were randomized into either transapical (Group I.) or epicardial surgical LV lead implantation (Group II.). Crossover to the parallel group was allowed only after 2 redo procedures which were either related to lead positioning, lead stability problems or to lead dysfunction. Only patients who were anti-coagulated were eligible to enter the study. None of the pts had evidence of LA or LV thrombi on the preoperative echocardiographic study.

2.2. Follow up and endpoints

Follow up visits were scheduled at 3, 6, 12 and 18 months. Responsiveness to CRT was defined as an improvement >1 NYHA class and/or 10% improvement in LVEF at 6 months. All patients who died before 6 months were considered to be non-responder. The following baseline and follow up data were compared between groups: LV ejection fraction (LVEF), NYHA class, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD) and quality of life (QoL). The echocardiographic measurements were performed and validated by the Echocardiography Laboratory of the Hungarian National Institute of Cardiology using standard protocol of measurements. In general two certificated specialist validated the echocardiographic measurements in our study. The LVEF was determined using the modified Simpson method, recommended by the American Society of Echocardiography for measuring LVEF. Of course, we had sometime

limitations in patients with poor image quality, because the endocardial border wasn't able to visualize and to trace. In this case the use of echocardiography contrast has been shown to improve LVEF determination and reduce inter-observer variability.

Extra attention was given performing measurements in order to find the optimal LV pacing site. All patients underwent an advanced echocardiography study with tissue Doppler imaging in order to determine the most delayed segment of the LV. If an electrophysiological study and/or LV ablation procedure was performed for any other reason, electro anatomical mapping of the LV was performed to determine the electrical activation sequence and to assist LV lead placement.

For QoL measurements we used the SF-12 multipurpose short form survey with 12 questions, all selected from the SF-36 Health Survey (Ware, Kosinski, and Keller, 1996).

2.3. Lead implantation procedures

The patients were prepared for the operation using general anesthesia. After intra-tracheal intubation the patient was prepared for an infraclavicular incision as well as for a small left thoracotomy. All patients received standard perioperative monitoring (ECG, pulse oximetry, invasive arterial monitoring and external defibrillator pads). Right atrial and right ventricular leads were positioned from the generator pocket through the cephalic or subclavian veins using a standard percutaneous technique.

2.3.1. Transapical approach

Initially transthoracic echocardiography was used to locate the LV apex. Beyond this marked area the procedure commenced with a mini-thoracotomy. Inside the chest a small pericardiotomy was performed above the LV apex. A standard active fixation endocardial pacing lead (Medtronic 4076-85 cm, 5076-52 cm, Vitatron ICQ09B-52 cm, Guidant Flextend 2) was positioned in the LV cavity through the apex.

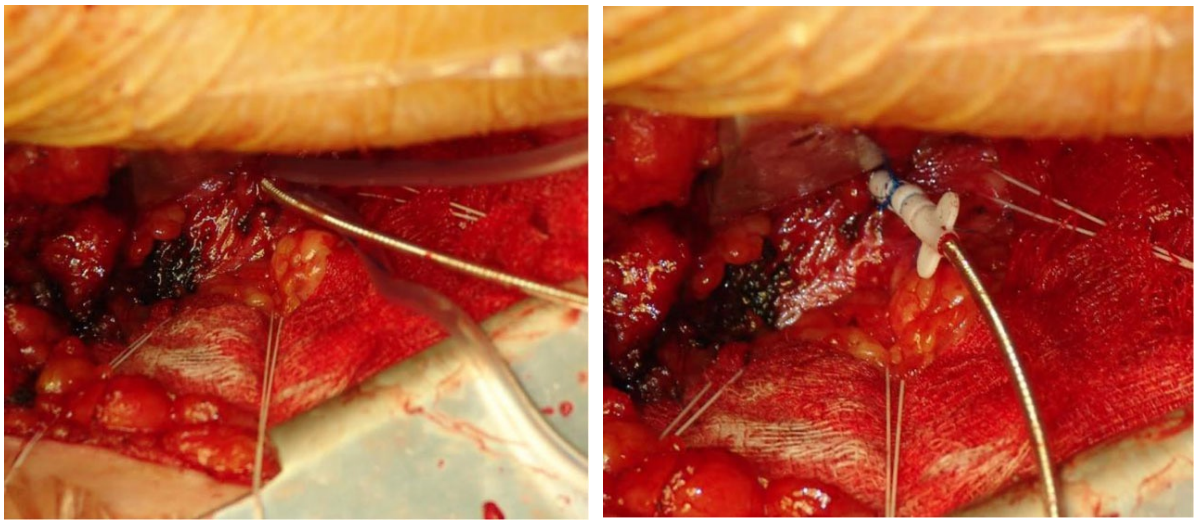
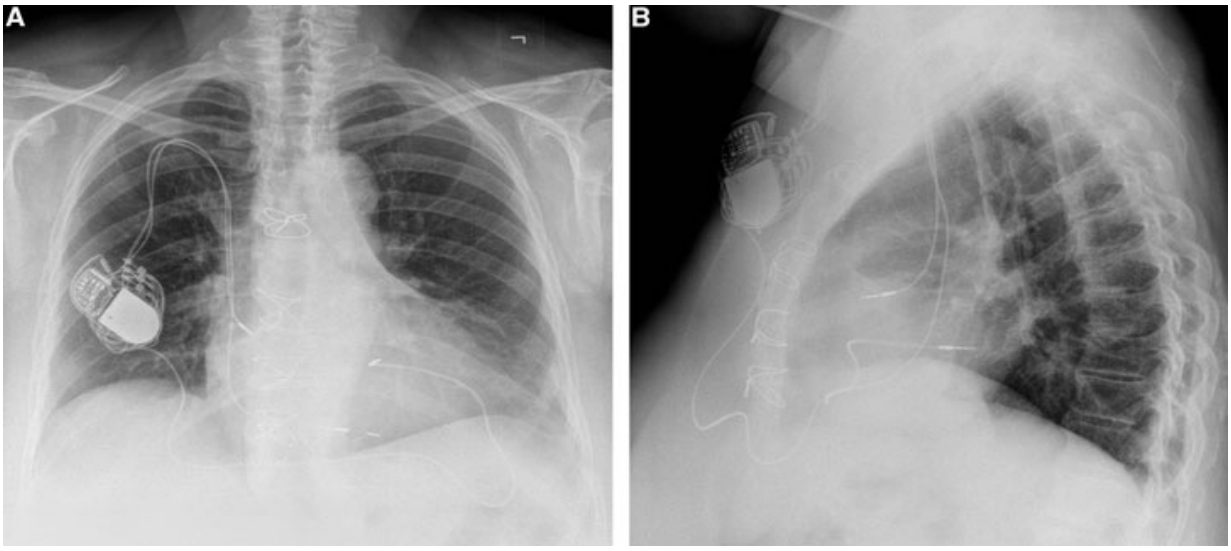


Figure 3. Intraoperative photograph during mini-thoracotomy showing transapical lead insertion and fixation into the LV.

Thin commercially available bipolar electrodes were used. The leads were inserted using Seldinger technique utilizing a peel-way sheath (LI-7 Plus, 7F, Biotronik): the apex was punctured with a needle, a guide wire was inserted. The needle was removed from the apex, dilatation of the apex hole using peel-away sheath inserted over the guide wire was performed. After removal of the guide wire, the pacing electrode was inserted into the LV cavity through the sheath and peel-away sheath was removed. Hemorrhaging from the LV was controlled with one or two 5/0 or 4/0 monofilament purse-string sutures around the puncture point (Figure 3). If the tissue quality of the apex required pledgeted sutures we used pledge material in the surrounding pericardium. Fluoroscopy was necessary for the intracavital navigation and endocardial fixation of the electrode at the optimal pacing site for CRT (Table 3). To reach the target area a “J” shaped electrode guide wire was useful. Maneuvering in the LV cavity did not require specific devices and skills. It is not different from standard RV pacing techniques. After effective endocardial fixation of the lead tip, the pacing and sensing parameters were measured. The acceptable pacing threshold was less than 1,0 V/0,4 ms and R-wave amplitude for sensing in this electrode was more than 5,0 mV. Pure-string sutures in the apex were applied to restrict the movement of the electrode through the apex and were they gently tied to the body of the electrode to stabilize position. The pericardium was partially closed and a small pleural

drain (Jackson-Pratt SU130-1310, 7 mm, Cardinal Health) was inserted followed by a standard wound closure. After lead fixation the proximal body of the electrode was tunneled to an infraclavicular pocket using standard technique (Figure 4 A,B).

Figure 4 A,B.



(A)Postoperative chest x-ray from anteroposterior (AP) projection. (B) Postoperative chest x-ray from lateral (LA) projection.

Finally, a pleural drain was inserted followed by standard wound closure. Perioperative anticoagulation regime was applied as for patients undergoing mitral valve replacement. Intravenous heparin was re-started 3 hours after the surgery if bleeding was no longer observed via the pericardial drain. After surgery the patients were orally anticoagulated with a target INR level identical to mitral valve prostheses (INR= 2,5-3,5).

2.3.2. Epicardial lead implantation

After standard single lumen intubation the patient was placed in supine position with the left chest elevated 30-40°. We performed a large lateral-thoracotomy between intercostal space 4-5. Ensuring sufficient distance the pericardium was opened anterior to the phrenic nerve. The pericardium was fixed with traction-sutures to the skin, rotating

the heart to the right and creating optimal exposure of the lateral surface. A unipolar or bipolar epicardial leads (Biotronik, ELC 54-up or 35-up, Medtronic 5071) were attached to the target area and secured with two sutures (Table 5).

2.4. Device implantation and pacing mode

23 patients received CRT devices for biventricular pacing (Medtronic InSync System model 8040 or 8042, Biotronik Stratos LV, Medtronic InSync Sentry 7298; Biotronik model Lumax 300 HF-T, Kronos LV-T; StJude Atlas). Pacing was delivered in biventricular DDD mode. At implant all patients were in sinus rhythm. Active pacing was selected by programming the atrial-synchronous mode with the atrioventricular (AV) delay determined using hemodynamic evaluation. The AV-delay was optimized based on M mod echocardiography (transmitral TVI). Interventricular (VV) optimization was not performed. The VV time was empirically programmed to – 20 ms (LV first paced).

2.5. Substudy with transapical patients: long term follow-up

The aim of our single-center prospective substudy was to assess the long-term outcome and the incidence of thromboembolic complications in the transapical group. In our center between October 2007 and September 2013, 26 consecutive patients (mean age 61 ± 10; seven women) with ischemic (12 pts) and dilated (14 pts) cardiomyopathy after failed transvenous LV lead implantation underwent transapical LV lead placement as a last resort therapy. All transapical patients from comparison study (11 pts) were included in the long term follow-up substudy. The baseline clinical data and demographic characteristics of all transapical LV lead implanted patients in our center are included in Table 3.

Table 3: Baseline clinical and demographic characteristics in transapical group, 26 pts.

Parameter at enrolment	Mean ± SD or %
Age (years)	61± 10
Sex	
Male	19 (73%)
Female	7 (27%)
Cardiomyopathy	
Dilated cardiomyopathy (DCM)	14 (54%)
Ischemic cardiomyopathy (ICM)	12 (46%)
New York Heart Association functional class (NYHA)	
II.	2 (8%)
III.	17 (65%)
IV.	2 (8%)
Left ventricle ejection fraction (LVEF%)	26.7±6.63
Left ventricle end-systolic diameter (LVESD,mm)	75.08±17.15
Left ventricle end-diastolic diameter (LVEDD,mm)	62.56±11.62
Intrinsic QRS duration (ms)	167.85±24.05
Drug therapy	
ACE inhibitors, ARBs	21/26 (80%)
Beta-blockers	21/26 (80%)
Digoxin	6/26 (23%)
Amiodarone	9/26 (34%)
Loop diuretics	20/26 (77%)
Spironolactone	15/26 (57%)

The inclusion/exclusion criteria, the surgical procedures, the device implantation and the pacing mode was idem. Twelve patients underwent CRT-PM implantation while in fourteen patients CRT-D device implantation was performed (Table 4). The decision between ICD or pacemaker was not easy because we can't implant in all patients ICD-CRT devices. The reason has many factors but one of them was commonly financial.

Table 4: Type of CRT devices and transapical LV leads

Type of CRT devices	Number (n=26)
Biotronik Lumax	6
Biotronik Stratos	8
Biotronik Entovios	1
Medtronic Syncra	1
Medtronic Insyc/Concerto	7
St. Jude Atlas/Promote	2
Boston Scientific Cognis	1

Type of transapical LV leads	Number (n=26)
Vitatron ICQ09B	4
Giant Flextend 2	1
St. Jude 1888T	8
Medtronic 5076	7
Medtronic 6944	1
Medtronic 4076	5

CRT = cardiac resynchronization therapy, LV = left ventricular

All patients were scheduled for regular visits at 1, 3, 6 months and every 6 months after that. Additional visits or hospitalizations were registered. The INR level was checked and corrected to be in the range between 2.5 and 3.5 generally monthly but if required daily. During the median follow-up period of 40 ± 24.5 months, we collected data on mortality rate, reoperation rate, and cerebrovascular event rate. Emergency CT scan was performed in patients with symptomatic and/or suspected ischemic thromboembolic event.

Asymptomatic patients underwent an elective, non- contrast enhanced cerebral CT scan examination at median follow-up of 40 ± 24.5 months in order to determine any silent TE event possibly related to the presence of the LV endocardial lead. Scans were performed

using a Siemens Somatom Sensation 40 CT scanner. The scanning parameters were 140 kV and 230 mA. Estimated effective radiation dose was 2.2 mSv (average DLP 1092 mGy cm). The CT scan enabled the acquisition of 40 slices per rotation with a 2-mm slice width.

2.6. Statistical analysis

Continuous variables were shown as mean ± SD, if normally distributed, and compared with the Student's t test. In case of non-normal distribution of data, median with corresponding interquartile ranges were reported, and the Mann-Whitney U test was used for comparison. Categorical data was expressed in percentages and compared with Fisher's exact test. Simultaneous comparison of > 2 mean values were performed by one-way analysis of variance. A two-tailed p value < 0.05 was considered as significant. All statistics were performed using SPSS (version 16.0) for Windows (SPSS Inc, Chicago, Il, USA).

3. Results

3.1. Outcome data from the comparison study

19 patients completed the 18 months follow up (the follow up time was ranging from 18 months to 34 months). In the transapical group one patient died suddenly 10 months after implantation. Pathology showed no device or lead related complications and device interrogation showed no arrhythmias. In the epicardial group three patients died in the follow up period. One patient died within the first 30 postoperative days, however, death was not related to the procedure. This patient had significant mitral valve regurgitation (II-III), coronary disease, paroxysmal atrial fibrillation, severe diabetes and was in NYHA IV. The other two patients died from cardiac related problems: one of sudden cardiac death and the other of progressive heart failure. In both groups significant

QRS duration reduction was observed, however, there were no statistically significant difference between group I and II (Table 5).

Table 5: LV Lead positions and QRS duration after trans-apical or epicardial CRT

		Group I.	**Group II.**
QRS (ms)	before	138,9 ±24,9	137,8±25,2
QRS (ms)	after	117±17.2	126±24.7
	anterior (n)	-	1
basal	lateral (n)	4	4
	posterior (n)	6	-
	inferior (n)	-	-
	anterior (n)	-	1
mid	lateral (n)	1	4
	posterior (n)	-	1
	inferior (n)	-	-
	anterior (n)	-	-
apical	lateral (n)	-	1
	inferior (n)	-	-

ms = millisecond, n = number

Moreover, in the epicardial group there was a tendency of less basal LV segments electrode placement (Table 5).

3.1.1. **Procedural data**

A transapical approach was used in 11 patients (Group I.) and a successful implant of an LV endocardial lead was obtained in all. Lead dislocation was detected in two patients. In one patient it occurred during closure of the pericardium. In another patient dislocation was observed on the second postoperative day. Lead repositioning could be performed without re-opening of the pleural cavity.

Although data are sparse in this respect one could speculate that there are two possible mechanisms of dislocations. One is due to incomplete screw-in mechanism and a

subsequent tip release from the endocardium. It could happen despite the fact that the intraoperative ECG showed an injury potential during the implantation. Another possible mechanism is related to the favorable changes in LV contractile function. Interestingly enough the better LV function results in a more vigorously contracting heart which pulls out the lead from the LV endocardial surface since it is strongly fixed to the chest wall. To avoid this complication the intracavital curve of the lead should be controlled during the reverse remodeling. Leaving a slightly larger intracavital loop might be an appropriate preventive measure to avoid this type of dislocations. This is indeed in analogy with pediatric pacemaker lead implantations.

During the study period 12 patients (Group II.) were randomized to surgical epicardial LV-lead placement. After surgical placement of a LV-lead one patient presented with a high pacing threshold requiring refixation of the displaced epicardial lead.

Mean procedure duration was shorter in the transapical group than in the epicardial. The transapical group required fluoroscopy for endocardial placement of the LV-lead, while epicardial placement was performed without using radiation. The postoperative hospital stay was longer for patients receiving epicardial leads compared to transapically placed LV-endocardial leads due to minor postoperative issues such as postoperative pain (Table 6).

Table 6: Comparison of intraprocedural and postprocedual data

	Group I.	**Group II.**	**P**
Operation time (min)	106±23,3	130,1±32,3	<0,05
Fluoroscopy time (min)	7,5±4,8	-	N.A.
Postoperative days (in hospital)	6,4±4,2	11,3±6,8	<0,001
Reoperations needed (n)	2	1	N.S.

min=minutes, n=number, p=Group I. vs. Group II., N.S.=non-significant, N.A.=not applicable

3.1.2. **Echocardiographic data**

During follow up LVEF has improved from 26,0±7,8 % to 39,7±12,5 % in the trans-apical group, and from 26,4±8,9 % to 31,5±11,5 % in the epicardial group. There was a substantial decrease in LV diameters in both groups (Table 7).

Table 7: Comparison of the outcome of the patients

	Group I.			**Group II.**			
	before CRT	after CRT	p*	before CRT	after CRT	p*	p**
LVEF (%±SD)	26,0±7,8	39,7±12,5	<0,001	26,4±8,9	31,5±11,5	<0,05	
LVEDD (mm±SD)	73,7±10,5	70,4±13,6	<0,001	68,3±10,8	68,4±7,2	N.S.	
LVESD (mm±SD)	62,7±10,8	55,8±15,5	<0,001	61,1±10,7	57,5±8,7	<0,05	
NYHA class (±SD)	3,5±0,4	2,2±0,4	<0,001	3,6±0,4	2,7±0,4	<0,001	
∆ LVEF (%±SD)		13,7±10,6			5,1±6,8		N.S.
∆ LVEDD(mm±SD)		3,3±2,8			0,1±3,2		<0,01
∆ LVESD (mm±SD)		6,9±5,4			3,6±3,2		<0,05
∆ NYHAclass(±SD)		1,3±0,4			0,9±0,4		N.S.

LVEF= Left ventricular ejection fraction, LVEDD=Left ventricular end diastolic diameter, LVESD= Left ventricular end systolic diameter, NYHA= New York Heart Association, SD=standard deviation, p*=before vs. after, p**=Group I. vs. Group II., N.S.= non significant

Mitral regurgitation (MR) severity was quantified on scale 0-4. Advanced MR (grade 3-4) was present in 16,6 % (Group I) and 27,7% (Group II). Improvement of MR ≥1° after 12 months occurred in 50 % (Group I) and 36,4 % (Group II) of patients.

Improvement of the NYHA class was observed in both groups. Acute LV-lead sensing did not significantly differ between the groups (11,0±5,6 mV vs. 11,2±6,0 mV; p=NS). Acute and chronic - capture thresholds of the LV-leads were significantly lower in the trans-apical group (0,5±0,2 V/0,4 ms vs. 1,8±1,5 V/0,4 ms; p<0,01 and 0,7±0,2 V/0,4 ms vs. 3,5±1,2 V/0,4 ms; p<0,001). Pacing at 10.0 V/0,4 ms did not result in phrenic nerve

stimulation in any patients. There were no clinical signs of thromboembolic events during the mid-term follow up (completed 18 months).

3.2. Long term follow-up results of 26 transapical LV lead patients

During the median follow-up period of 40 ± 24.5 months, 3 out of 26 patients with transapical CRT were crossed over to epicardial LV lead implantation; consequently, 23 patients could be followed-up as pts with transapical LV lead implantation. The mortality rate was determined utilizing the National Registry Office database. Eleven out of 23 (47 %) patients with transapical CRT survived after a median follow-up of 40 ± 24.5 months. One patient was lost to follow-up. Ten patients died due to exacerbated heart failure while one patient suffered sudden cardiac death.

Two out of the three patients crossed over to an epicardial CRT system underwent right-sided infective endocarditis. In the first case, the infection occurred 3 months after the transapical LV lead implantation procedure. The second case materialized 3 years after the necessity of transapical LV lead repositioning and reoperation, CRT generator decubitus was diagnosed. In these cases, a new epicardial CRT-system was implanted via medial sternotomy accompanied by the administration of antibiotic- therapy. A third patient was admitted to our hospital 1 month after the transapical CRT implantation with symptoms of pericardial tamponade, caused by the dislocation of the transapical LV lead. During an emergency reoperation, the transapical LV lead was removed and a new epicardial LV lead placed. Furthermore, two cases of CRT-pocket infection were observed and two cases CRT-pocket hematoma.

Reimplantation was necessary in one patient, after interruption of anticoagulation therapy, due to transapical LV lead fracture causing the deterioration of heart failure, 5 years after the primary procedure. Repositioning of the transapical LV lead was necessary in three cases: two early dislocations and the repositioning operations are described in the mid-term follow up, on the page 24. In one case, transapical LV lead repositioning had to be performed due to lack of capture at maximal output (7.5 V /1.5 ms) despite repeated programming attempts.

In another patient, 1 week after the transapical CRT implantation, dislocation of the right atrial electrode was observed. In one other case, deterioration of heart failure was detected with simultaneously right ventricular lead dislocation. Both cases were resolved by repositioning of the dislocated electrodes. In yet another patient, a local pocket infection was detected, 2 years after the transapical LV lead implantation, requiring CRT-P generator repositioning.

Table 8: Complications in the transapical group during long term follow-up (40 ± 24.5 months, 26 pts.)

Complication type	Nr	Characteristic
Endocarditis right sided	2	3 months after implantation
		3 years after implantation
Pericardial tamponade	1	1 month after implantation
Pocket infection	2	
Pocket haematoma	2	
LV Lead fracture	1	5 years after implantation
LV Lead dislocations	3	2 early dislocations
		1 late dislocation
TE with symptoms	3	2 days, 2 and 4 months after implantation
TE without symptoms	2	detected by cerebral CT

TE = thromboembolic, CT = computer tomography

3.2.1. Thromboembolic complications and cerebral CT scan after long term follow-up

The coexisting atrial fibrillation may increase the risk of TE events. During the long term follow-up period, atrial fibrillation was detected in ten out of 26 patients.

3 out of 26 patients with transapical CRT were crossed over to epicardial LV lead implantation, consequently 23 patients could be followed-up as pts with transapical LV lead implantation. We chose CT scan instead of magnetic resonance imaging (MRI)

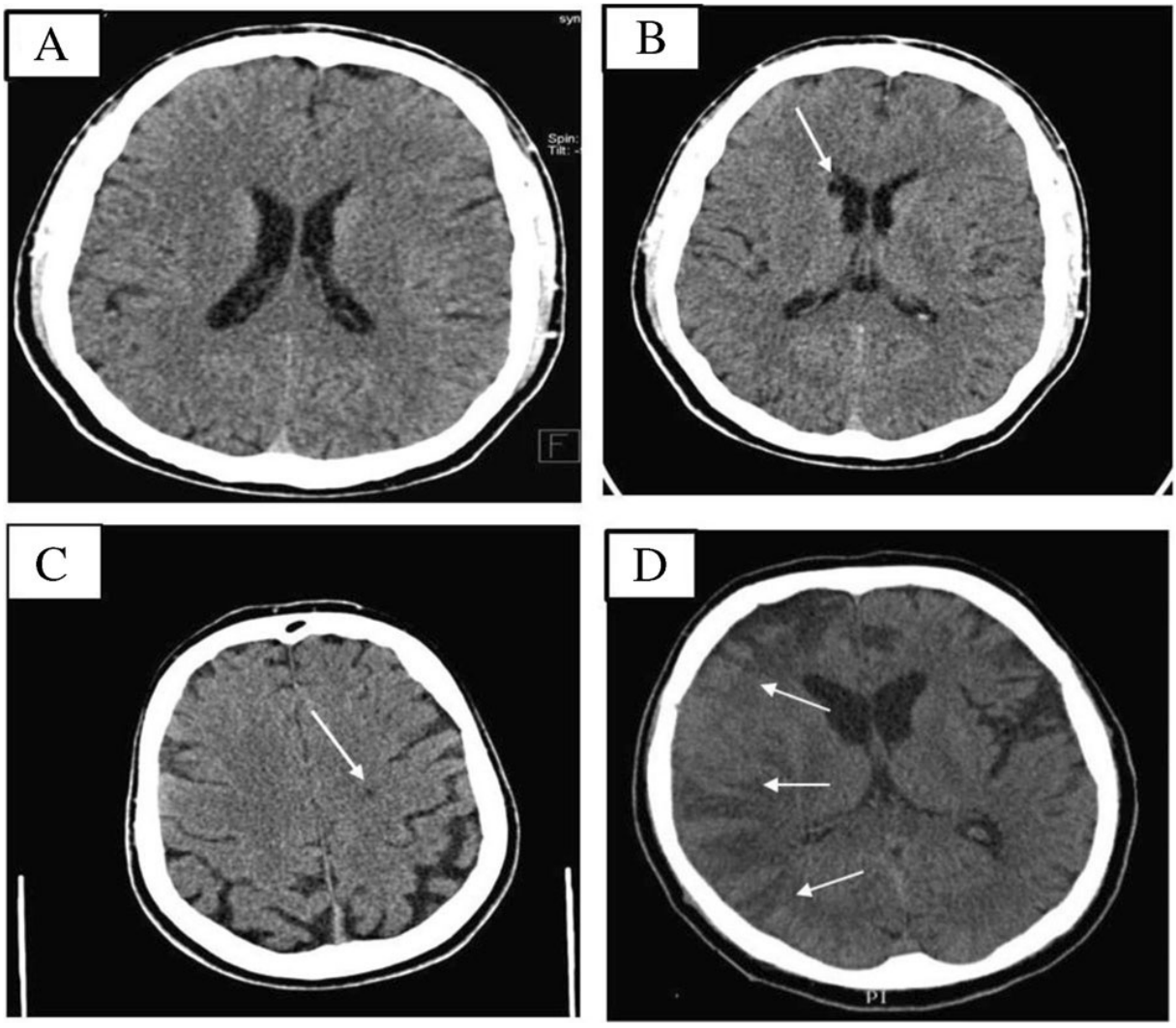
modality to detect evidence of an ischemic event as neither the CRT devices nor the attached leads were MRI compatible. During the long term follow-up period 20 patients remains without symptoms of thromboembolic complications and in 3 patients were documented symptoms of thromboembolic complications:

One case of right- sided hemiplegia was observed 2 months after the transapical LV lead implantation. An urgent non-contrast enhanced cerebral CT scan identified an acute ischemic occlusion in the middle cerebral artery. Systemic thrombolytic therapy could not be applied as the patient was receiving effective anticoagulation therapy. This was the second ischemic stroke, with signs of right-sided hemiplegia, that the patient had suffered. There was an earlier occurrence 6 years before transapical LV lead implantation. Both of these ischemic events healed without any clinical symptoms. This patient died 3 years after the transapical LV lead implantation due to heart failure deterioration.
In the patient who underwent reoperation due to transapical LV lead fracture, requiring interruption of the anticoagulation therapy, left-sided hemiparesis occurred 3 days after the procedure. The urgent CT scan examination revealed acute major right-sided middle cerebral artery occlusion with fronto-temporo-parietal extension. Thrombolytic therapy was contraindicated because of the history of anticoagulation therapy and the CRT-device reoperation within 1 week of this occurrence. The patient received conservative therapy and neurological rehabilitation with good success.
In one case, facio-brachial predominant hemiparesis occurred 4 months after transapical LV lead placement. The CT scan revealed bilateral chronic ischemic stroke; however, an acute lesion could not be detected. Thrombolytic therapy was not instituted because of the absence of an acute ischemic lesion and the presence of continuing effective anticoagulation therapy. The patient's symptoms resolved after the administration of high dose parenteral vasoactive medication. Nine months after transapical LV lead implantation, successful left ventricular assist device (LVAD) implantation was performed.

Asymptomatic patients underwent an elective, non-contrast enhanced cerebral CT scan examination at median follow-up of 40 ± 24.5 months in order to determine any silent thromboembolic event possibly related to the presence of the LV endocardial lead.

In asymptomatic patients, the CT scan examination revealed minimal extension chronic ischemic lesions in two cases (6 mm lacuna in the right-sided nucleus caudatus, 4 mm hypodensity in the left-sided centrum semiovale) (Fig. 5).

Figure 5. Non-contrast enhanced cerebral CT scan of patients after transapical LV lead implantation



Non-contrast enhanced cerebral CT scan of patients after TALV lead implantation:

a., no abnormality

b., 6 mm lacuna in the right-sided nucleus caudatus

c., 4 mm hypodensity in left-sided centrum semiovale

d., middle cerebral artery occlusion with right-sided fronto-temporo- parietale extension

4. Discussion

4.1. Major findings

The major finding from the comparison study is, that the alternative method developed at our center for endocardial CRT is a feasible approach. Our data suggest that transapical endocardial CRT with 18-months follow-up period presented promising outcomes with potential advantages such as shorter procedure time, decreased postoperative burden and the best accessibility of the all LV endocardial segments without the limitations of the anatomy to reach the most delayed segment of the lateral wall compared to epicardial LV lead implantation techniques.

The major finding of the long term follow-up of the transapical approach is that, although transapical CRT can be used as an alternative method for CRT in selected heart failure patients, it represents a worrisome thromboembolic complication rate compared to traditional transvenous CRT.

4.2. Rational for alternative approaches

Despite the latest achievements of medical therapy in patients with advanced stage chronic HF, mortality remains high and QOL severely impaired. CRT has been shown to improve symptoms, ventricular function and survival in patients with left ventricular systolic dysfunction and ventricular conduction delay [1,2]. Despite the technological progress aimed at improving success and reducing complication rates during CRT device implantation, in some cases the delivery of a LV pacing lead through the CS still fails. The reasons for the failed procedures are related to difficulty obtaining CS access, navigating the venous tributaries and obtaining a stable and functional location from which to pace the lateral wall of the LV [5,6].

In 2016 James HP Gamble et al. published a meta-analysys of procedural success of LV lead placement for CRT via the SC. In this work a literature search was used to identify all studies reporting success rates of LV lead placement for CRT via the

CS route. A total of 164 studies were identified, and a meta-analysis was performed [37]. The studies included 29,503 patients: 74% were male, their mean age was 66 years, their mean New York Heart Association functional class was 2.8, the mean LV ejection fraction was 26% and the mean QRS duration was 155 ms. The overall rate of failure of implantation of an LV lead was 3.6% (95% CI: 3.1 to 4.3). The rate of failure in studies commencing before 2005 was 5.4% (95% CI: 4.4% to 6.5%), and from 2005 onward it was 2.4% (95% CI: 1.9% to 3.1%; $p < 0.001$). Causes of failure (reported for 39% of failures) also changed over time. Failure to cannulate and navigate the CS decreased from 53% to 30% ($p = 0.01$), and the absence of any suitable, acceptable vein increased from 39% to 64% ($p = 0.007$). The proportion of leads in a lateral or posterolateral final position (reported for 26% of leads) increased from 66% to 82% ($p = 0.004$). [37]. In summary the reported rate of failure to place an LV lead via the CS has decreased steadily over time but remains an existing problem. A greater proportion of failures in recent studies are due to coronary venous anatomy that is unsuitable for this standard technique.

4.3. Endocardial vs. epicardial pacing

A lot of studies have demonstrated that LV pacing site is a critical parameter in optimizing CRT. LV lead placement in the CS side branch results in epicardial pacing, which is less physiological, reversing the pattern the normal LV wall activation.

In a study by Garrigue et al. was compared the effects of endocardial pacing with those of epicardial LV pacing on regional LV electromechanical delay and contractility [38]. Epicardial biventricular pacing reduced the septal wall electromechanical delay by 11% versus RV pacing ($p = 0.05$) and the lateral wall electromechanical by 41% versus RV pacing ($p <0.01$). With endocardial biventricular pacing, the septal and lateral electromechanical delays were 21.3% and 54%, respectively ($p <0.01$, compared with epicardial biventricular pacing). The mitral time-velocity integral increased by 40% with endocardial biventricular pacing versus 2% in epicardial group ($p <0.01$). The amplitude of the lateral LV wall systolic motion increased by 14% in epicardial group versus 31% with endocardial biventricular pacing ($p = 0.01$). This resulted in a LV shortening fraction

increase of 25% in patients with endocardial biventricular pacing (p = 0.05). However, all patients were clinically improved at the end of follow-up, thus in heart failure patients with CRT, endocardial biventricular pacing provides more homogenous intraventricular resynchronization than epicardial biventricular pacing and is associated with better LV filling and systolic performance [38].

Derval et al. tested endocardial and epicardial pacing at identical locations. Thirty-five patients with nonischemic dilated cardiomyopathy and left bundle branch block referred for CRT device implantation were studied. Eleven predetermined LV pacing sites were systematically assessed in random order. Epicardial: CS. Endocardial: basal and mid-cavity (septal, anterior, lateral, and inferior), apex and the endocardial site facing the CS pacing site. For each patient QRS duration and maximal rates of LV pressure change (+dP/dtmax) during baseline (AAI) and DDD LV pacing at 2 atrioventricular delays were compared. The +dP/dTmax, arterial pulse pressure (PP) and the end systolic pressure (ESP) were not significantly different, but endocardial pacing was significantly superior to epicardial pacing on –dP/dTmin [39]. Although QRS duration did not predict the maximum hemodynamic response, it was confirmed the link between electrical activation and hemodynamic response of the LV during CRT [39].

The same results were obtained by Spragg et al. [40]. The dP/dTmax was measured at baseline, during VDD pacing at the RV apex, and during BiV pacing from the RV apex and 51 +/- 14 different LV endocardial sites in patients (n=11) with ischemic cardiomyopathy. Seven patients already had an epicardial LV lead (CRT via SC) in place, allowing comparison of epicardial BiV stimulation with that using an endocardial site directly transmural to the CRT-coronary sinus lead tip. Electroanatomic 3-dimensional maps with color-coded dP/dt(max) response defined optimal pacing regions delivering ≥ 85% of maximal increase in dP/dt(max). CRT delivered at best LV endocardial sites was more effective than via pre-implanted coronary sinus lead pacing. The location of optimal LV endocardial pacing varies among patients with ischemic cardiomyopathy, and individual tailoring may improve CRT efficacy in such patients [40].

The benefits of endocardial and multisite left ventricular (LV) stimulation were evaluated by Ginks MR et al. using noncontact mapping to understand the underlying mechanisms [41]. Ten patients (8 men and 2 women; mean [SD] age 63 years; LV

ejection fraction 24,6%; QRS duration 161 ms) fulfilling conventional CRT criteria underwent an electrophysiological study, with assessment of acute hemodynamic response to conventional CRT as well as LV endocardial and multisite pacing. LV activation pattern was assessed using noncontact mapping. LV endocardial pacing gave a superior acute hemodynamic response compared with conventional CRT (26% versus 37% increase in LV dP/dt(max), respectively; P<0.0005). There was a trend toward further incremental benefit from multisite LV stimulation, although this did not reach statistical significance (P=0.08). The majority (71%) of patients with nonischemic heart failure etiology or functional block responded to conventional CRT, whereas those with myocardial scar or absence of functional block often required endocardial or multisite pacing to achieve CRT response [41].

In the last years launched quadripolar LV leads with 4 different pacing sites perform epicardial pacing. CRT using quadripolar LV leads and a dedicated device with multiple pacing options provides more pacing vectors compared to bipolar leads. The introduction of quadripolar technology has helped to avoid or significantly reduce the risk of phrenic nerve stimulation, high pacing threshold and lead instability. In a large, multicenter experience published in 2015 a total of 721 consecutive patients with conventional CRT-D criteria implanted with quadripolar (n = 357) or bipolar (n = 364) LV leads were enrolled [14]. Lead performance and mortality was analysed over a 5-year period. Phrenic nerve stimulation was more common in those with quadripolar leads (16.0% vs. 11.6%, P = 0.08), but was eliminated by switching pacing vector in all cases compared with 60% in the bipolar group (P < 0.001). Furthermore, LV lead displacement (1.7% vs. 4.6%, P = 0.03) and repositioning (2.0% vs. 5.2%, P = 0.03) occurred significantly less often in those with a quadripolar lead. All-cause mortality was also significantly lower in the quadripolar compared to bipolar lead group in univariate and multivariate analysis (13.2% vs. 22.5%, P < 0.001) [14].

In contempt of the benefit of the new quadripolar leads in CRT, the biventricular endocardial pacing seems to be superior to conventional CRT via SC. This was also demonstrated by Shetty AK et al. in a very interesting study from 2014 [42]. Fifteen patients with a previously implanted CRT system received a second temporary CS lead and LV endocardial EP catheter. A pressure wire and non-contact mapping array were

placed into the LV cavity to measure LVdP/dtmax and perform electroanatomical mapping. Conventional CRT, BV-Endo and multisite epicardial pacing (MSP) were then performed (MSP-1 via two epicardial leads and MSP-2 via a single-quadripolar lead). The best overall acute haemodynamic response was found using BV-Endo pacing with a 19.6 ± 13.6% increase in acute haemodynamic response at the optimal endocardial site over baseline ($P < 0.001$). There was an increase in LVdP/dtmax with MSP-1 and MSP-2 compared with conventional CRT, but this was not statistically significant. Biventricular endocardial pacing from the optimal site was significantly superior to conventional CRT ($P = 0.039$). The acute haemodynamic response achieved when BV-Endo pacing was highly site specific. Within individuals, the best pacing modality varied and was affected by the underlying substrate [42]. Left ventricular activation times did not predict the optimal haemodynamic configuration. In fine biventricular endocardial pacing and not MSP was superior to conventional CRT, but was highly site specific [42].

Epicardial pacing may be more proarrhythmic than endocardial LV pacing, since reversal of the direction of activation of the LV wall, as occurs during biventricular pacing, leads to a prominent increase in QT and transmural dispersion of repolarization. This effect appears as a result of earlier repolarization of epicardium and delayed activation and repolarization of the mid-myocardial M cells. The increase in transmural dispersion of repolarization creates the substrate for the development of torsade de pointes under long-QT conditions. Torsade de pointes arrhythmias could be induced during epicardial, but not endocardial, pacing of LV in the presence of rapidly activating delayed rectifier potassium current blockade [43].

Ventricular tachycardia storms (VTS) and recurrent monomorphic ventricular tachycardias have been clinically observed after the initiation of CRT with epicardial LV pacing [44]. In an observational study clinical data on all patients undergoing CRT-D were collected prospectively. VTS occurred in eight of 191 (4%) patients and was characterized by recurrent sustained monomorphic ventricular tachycardia with a single morphology. Seven patients had ischemic heart disease and one nonischemic cardiomyopathy with a remote (5 +/- 2 years) history of monomorphic ventricular tachycardias. VTS developed a mean of 16 +/- 12.5 days after initiation of CRT with BVP. All patients presented with

palpitations and/or decompensated CHF. VTS was refractory to intravenous antiarrhythmic medication and was managed by turning off LV pacing and/or radiofrequency catheter ablation and long-term oral antiarrhythmic therapy [44].

The transseptal and the transapical CRT are endocardial approaches and becomes increasingly utilized for pacing of the free-wall of the LV in patients when an epicardial approach failed. Obviously, these patients require life-long oral anticoagulation after this type of procedure. It is not surprising that with a significant failure rate reported using the coronary sinus tributaries, alternative CRT pacing techniques are being looked for.

4.4. Surgical and alternative techniques for CRT implantation: Epicardial vs. Endocardial implantation

Nowadays when CS lead placement for transvenous LV pacing has failed the most frequently used surgical alternative is the epicardial pacing lead implantation. Recent reports have described results with a limited thoracotomy approach [12]. Limited thoracotomy requires general anesthesia and single lung ventilation to permit cardiac exposure. In addition, postoperatively a chest tube is required for a brief period. In the future further developments are desirable such as the introduction of thoracoscopic technique.

As alternative to surgical epicardial LV lead implantation techniques was developed first the percutaneous LV lead implantation via atrial septum. It is important, that the transseptal approach offer an endocardial pacing and recent data support endocardial lead implantation because this method provides further hemodynamic advantages. The ALternate Site Cardiac ResYNChronization (ALSYNC) study evaluated the feasibility and safety of LV endocardial pacing using a market-released pacing lead implanted via a single pectoral access by a novel atrial transseptal lead delivery system [45]. It was a prospective clinical investigation with a minimum of 12-month follow-up in 18 centers of CRT-indicated patients, who had failed or were unsuitable for conventional

CRT. The ALSYNC system comprises the investigational lead delivery system and LV endocardial pacing lead. Patients required warfarin therapy post-implant. The primary study objective was safety at 6-month follow-up, which was defined as freedom from complications related to the lead delivery system, implant procedure, or the lead ≥70%. The ALSYNC study enrolled 138 patients. The LV endocardial lead implant success rate was 89.4%. Freedom from complications meeting the definition of primary endpoint was 82.2% at 6 months (95% CI 75.6-88.8%). In the study, 14 transient ischemic attacks (9 patients, 6.8%), 5 non-disabling strokes (5 patients, 3.8%), and 23 deaths (17.4%) were observed. No death was from a primary endpoint complication. At 6 months, the New York Heart Association class improved in 59% of patients, and 55% had LV end-systolic volume reduction of 15% or greater. Those patients enrolled after CRT non-response showed similar improvement with LV endocardial pacing. The ALSYNC study demonstrates clinical feasibility and provides an early indication of possible benefit and risk of LV endocardial pacing [45].

As alternative to transseptal endocardial CRT we developed a fundamentally new method, the transapical lead implantation, which provides access for pacing any segment of the LV. Life-long anticoagulation is mandatory for these patients (similarly to transseptal CRT). Therefore, it is important to recognize that for patients with contraindication to anticoagulation, epicardial LV lead implantation is the only remaining therapeutic option if the standard percutaneous implantation fails.

For safety reasons we aimed a target INR level equivalent with mitral prosthetic valves. During mid-term follow-up we did not observe any TE events in this group of patients treated with the transapical technique, but this finding has changed during long-term follow-up.

4.5. Thromboembolic (TE) risk in the transapical patients

In our long term follow-up study, two major stroke and one transient ischemic attack occurred during median follow-up of 40 ± 24.5 months. One out of two TE events happened early after the interruption of anticoagulation therapy due to the necessity of

transapical LV lead reoperation. Consequently, the major cerebrovascular events were probably associated with insufficient anticoagulation levels as stated in the reports of Jäis et al. and Pasquie et al. [31,46]. The stroke or transient ischemic attack occurs usually in patients whom anticoagulation was temporarily interrupted or switched to heparin. It was the time when the physicians responded to concerns about perioperative TE by treating moderate- to high-risk device surgery patients with heparin bridging and the papers before 2010 recommended this as standard of care.

The short-term cerebral TE complications might be lowered if anticoagulation therapy would not be interrupted with INR kept at >2. Subtherapeutic INR levels frequently appear in everyday practice [35]. According to previous studies, only two thirds of patients are within the target INR level. The duration of decreased anticoagulation control is associated with increased risk of stroke [47]. Despite the fact that the efficacy of the novel oral anticoagulants is more predictable, no experience with its use is available in the endocardial LV pacing patient population.

In the most worldwide surveys between 14 and 35% of patients receiving cardiac devices require chronic anticoagulation and their peri-procedural management may present a dilemma to physicians. This is particularly true for the subset of patients with a moderate-to-high risk (≥5% per year) of TE events. In patients with non-valvular AF, this risk corresponds to a CHA_2DS_2-VASc score of ≥3. Physicians responded to concerns about peri-procedural TE by treating moderate- to high-risk device surgery patients with heparin bridging. Previous guidelines recommended this as standard of care. However, it became clear that there is a substantial risk of clinically significant device pocket haematoma related to heparin bridging. Importantly, device pocket haematomas can necessitate prolonged cessation of anticoagulation, with the attendant risk of TE, they can significantly increase the duration and cost of hospitalization; sometimes, reoperation is required. Finally, and perhaps most importantly, there is an association between haematoma formation and subsequent device system infection. In response to these issues, some centres started performing pacemaker and defibrillator surgery without interruption of warfarin anticoagulation. Two small randomized trials were inconclusive. [48,49] In the trial published by Cheng et al in 2011 only 100 Patients on oral

anticoagulation (OAC) referred for device implantation were randomized to warfarin continuation versus interruption. Patients randomized to warfarin interruption were further stratified into two groups based on their risk for TE in the absence of warfarin. Moderate-risk patients were randomized to warfarin continuation versus warfarin interruption. High-risk patients were randomized to warfarin continuation versus warfarin interruption with heparin bridging. Fifty patients were assigned to continue warfarin. The randomized groups were well matched. Among patients randomized to warfarin interruption, there were two pocket hematomas, one pericardial effusion, one transient ischemic attack, and one patient who developed heparin-induced thrombocytopenia. No events were noted among patients continuing warfarin (P = 0.056). While the results were not statistically significant, there was a trend toward reduced complications in patients randomized to warfarin continuation [48]. In the other trial, published by Tolosana et al a cohort of 101 consecutive patients with high risk for TE and indication for implant/replacement of a cardiac device were randomized to two anticoagulant strategies: bridging from OAC to heparin infusion (n = 51) vs. maintenance of OAC to reach an INR = 2 +/- 0.3 at the day of the procedure (n = 50). Haemorrhagic and thrombo-embolic complications were evaluated at discharge, 15 and 45 days after the procedure. A total of 4/51 patients (7.8%) from heparin group and 4/50 (8.0%) from the OAC group developed pocket haematoma following the implant (P = 1.00). One haematoma in each group required evacuation (1.9 vs. 2%, P = 1.00). No other haemorrhagic events or embolic complications developed during the follow-up [49]. A third, much larger clinical trial, was published in 2013 (BRUISE Bridge or Continue Warfarin for Device Surgery Randomized Controlled Trial) [50]. The patients (n 681) with an annual risk of TE of 5% or greater were randomly assigned to continued warfarin or heparin bridging. The primary outcome was clinically significant haematoma, which was defined as prolonging hospitalization, necessitating interruption of anticoagulation, or requiring reoperation. Clinically significant haematoma occurred in 12 of 343 (3.5%) patients in the continued warfarin arm and 54 of 338 (16.0%) patients in the heparin-bridging arm. Major surgical and thromboembolic complications were rare and not significantly different between arms [50].

Current international thrombosis guidelines suggest continuation of vitamin K

antagonists (VKA) in high risk patients. The INR on the day of surgery should be under the upper limit of the prescribed therapeutic range for the patient [51]. This strategy is corroborated by two recent meta-analyses.

It is to take note of two important data: one out of two major TE events in our long term follow-up study happened early after the interruption of anticoagulation therapy, due to the necessity of lead revision and the randomization in our study was finished before 2013. Antithrombotic management for the implantation of cardiac implantable electronic devices, including prohibition of the bridging therapy after interruption of anticoagulants or device implantations without anticoagulants interruption, was published first in 2015.

Chronic HF and left ventricular dilatation represents a higher risk of thromboembolism. Ischemic stroke significantly contributes to morbidity and mortality in HF and the risk of stroke increases significantly, with coexisting AF. An aggravating factor could be asymptomatic paroxysms of AF, so-called silent AF. Stroke risk stratification in HF patients remains an important issue. Recently, the CHA2DS2-VASc score, originally developed to predict stroke risk in AF patients, had been reported to be a predictive for strokes in HF patients regardless of AF being present. Based on the current evidence, HF should be considered as an independent risk factor for stroke. The CHA2DS2-VASc score might be useful to predict stroke risk in HF patients with or without AF in clinical routine. However, there is only a recommendation for the oral anticoagulation use in patients with concomitant HF and AF, while in patients with HF and no AF, individualized risk stratification is preferred [52].

Stroke can occur after myocardial infarction in the absence of AF. In a recently meta-analysis of 4 trials: CAPRICORN (Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left Ventricular Dysfunction), OPTIMAAL (Optimal Trial in Myocardial Infarction With Angiotensin II Antagonist Losartan), VALIANT (Valsartan in Acute Myocardial Infarction Trial), and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), a total of 22,904 patients without AF or oral anticoagulation were included. During a median follow-up of 1.9 years (interquartile range: 1.3 to 2.7 years), 660 (2.9%) patients had a stroke. These patients were older,

more often female, smokers, and hypertensive; they had a higher Killip class; a lower estimated glomerular filtration rate; and a higher proportion of MI, HF, diabetes, and stroke histories. Readily accessible risk factors associated with the occurrence of stroke were identified and incorporated in an easy-to-use risk score. This score may help in the identification of patients with MI and HF and a high risk for stroke despite their not presenting with AF [53].

Lead components may also influence the risk of stroke. The thrombogenicity of polyurethane leads may be lower than those of silicone [54].

The report of Rademakers et al. investigating cerebral thromboembolic complications after endocardial lead placement (45 atrial transseptal, 6 transapical) showed that all events happened with smaller diameter select secure leads which had the same polyurethane outer insulation [35]. This result makes unlikely that the outer insulation of endocardial LV lead is a critical factor in stroke occurrence [35]. The presence of an intraventricular anodal electrode may represent an unknown factor as the source of intracavital thrombus formation. The movement of the transapical LV electrode may generate increased turbulent blood flow in the LV generating thrombus formation.

4.6. Summary and what the future of alternative approaches has in store

Nowadays there are five possible solutions for patients who need an alternative LV lead.

Surgical epicardial implantation was historically the first option.

Then the transseptal approach via IAS was the second option. This catheter-based technique was developed to implant a lead using venous access through the interatrial septum and the mitral valve into the LV endocardium [29].

Aiming to mix the advantages of these two, our method, the transapical LV lead implantation was the third in the timeline [36].

Since then endocardial LV pacing leads have been implanted also through the interventricular septum [55]. Of course, this method was applied by only 10 patients with previous failed coronary sinus lead implant or with nonresponse to cardiac resynchronization therapy and a suboptimal LV lead position. All patients were anticoagulated. Subclavian vein access was used for a superior approach ventricular transseptal puncture under fluoroscopic guidance, using a 91 cm deflectable 8.5 F inner lumen catheter sheath with a tapered dilator (Agilis; St Jude Medical Inc.). This was passed over a guidewire into the RV. Left ventriculography was performed in a right anterior oblique (RAO) view to identify the LV borders. The sheath and dilatator were deflected and rotated in a counterclockwise direction to position the tip of the dilator as close to the midseptum as possible, with reference to the ventriculogram. An angiogram pf the left coronary arteries was also undertaken, to ensure the puncture site wasn't adjacent to a major septal perforator vessel. The ventricular septum was then punctured using one of the following techniques: 1,.Standard Brockenbrought transseptal needle (St Jude Medical Inc), 98 cm. 2,.Stiff 98 cm radiofrequency transseptal needle (NRG; Bayliss Medical) delivering power at 10 W for 1 s duration. 3,.Guidewire and diathermy pen radiofrequency energy, to deliver 30 W in 1 s intervals and 4,. A soft-tipped radiofrequency wire (Nykanen; Bayliss Medical) advanced through the dilator and sheath into the LV cavity using 10 W power for 1 s duration intervals. After transseptal ventricular puncture the deflectable lead delivery sheath was steered toward the LV wall. An active-fixation pacing lead was successfully delivered to the endocardial wall of the lateral LV in all patients (9 men; age, 62±10 years). Mean threshold and R wave at implant were 0.8±0.3 V and 10.8±3.9 mV. At follow-up (mean, 8.7 months; minimum, 0; and maximum 19), thresholds were stable, and there were no thromboembolic events. Of 9 patients, 8 were classed as clinical responders (1 had inadequate follow-up to assess response). Interesting, the use of radiofrequency energy delivered through a guidewire was the most effective technique [55]. There are two important notes regarding this novel technique: in comparison to the other endocardial approaches is not simple (need of coronar angiography, right ventriculography etc.) and via the steerable sheath it isn't possible to achieve all part of the LV wall. The advantage of the transapical alternative is the best accessibility of the all LV endocardial segments without the limitations of the anatomy to

reach the most delayed segment of the lateral wall.

The fifth possible solution, as last developed, is the completely leadless LV pacing method. The in 2017 published SELECT-LV (Safety and Performance of Electrodes implanted in the Left Ventricle) study was a prospective multicenter non-randomized trial assessing the safety and performance of a wireless LV endocardial pacing electrode (WiSE-CRT; EBR Systems, Sunnyvale, California) [56]. The WiSE-CRT system provides wireless pacing by transmitting acoustic (ultrasonic) energy from a pulse generator transmitter, implanted subcutaneously over the ribcage, to a receiver electrode implanted in the LV. The WiSE-CRT System functions in conjunction with a co-implanted standard RV pacing system. Biventricular pacing is achieved by sensing the RV pacing output of the co-implant, followed by the system immediately transmitting acoustic energy to the electrode, thus achieving nearly simultaneous pacing of the RV and LV. The transmitter is a phased array ultrasound system that focuses the acoustic energy on the electrode. Implantig only the WiSE System is a 2-step process. Surgical subcutaneous implantation of the pulse generator system is followed by catheter placement of the LV pacing electrode. These 2 steps are performed on consecutive days. The WiSE-CRT system requires co-implantation of a commercially available standard PM or ICD device to synchronize biventricular pacing. In the SELECT-LV study a total of 35 patients indicated for CRT who had "failed" conventional CRT underwent implantation of an LV endocardial pacing electrode and a subcutaneous pulse generator. System performance, clinical efficacy, and safety events were assessed out to 6 months post-implant. The procedure was successful in 97.1% (n = 34) of attempted implants. The most common indications for endocardial LV pacing were difficult CS anatomy (n =12), failure to respond to conventional CRT (n = 10), and a high CS pacing threshold or phrenic nerve capture (n = 5). Following implantation, patients were prescribed aspirin 75 to 325 mg daily throughout the study duration (6 months) and clopidrogel 75 mg daily for 3 moths post implant. For patients taking long-term warfarin therapy for other indications (atrial fibrillation etc) warfarin was permitted to be discontinued 2 to 3 days pre-procedure and reinitiated afterwards. In these long-term OAC patients the addition of antiplatelet agents was not required. The primary performance endpoint, biventricular pacing on the 12-lead electrocardiogram at 1 month, was achieved in 33 of 34 patients. A total of 28 patients

(84.8%) had improvement in the clinical composite score at 6 months, and 21 (66%) demonstrated a positive echocardiographic CRT response (≥5% absolute increase in LV ejection fraction). There were no pericardial effusions, but serious procedure/device-related events occurred in 3 patients (8.6%) within 24 h: ventricular fibrillation during the electrode implant procedure; in one patient the electrode embolized to the left tibial artery during an exchange of the dilator and catheter, prior to introduction of the sheath into the LV; and the third patient developed a femoral artery fistula that required surgical repair. The other primary safety endpoint of serious procedure- or device-related events between 24 h and 1 month occurred in 8 patients (22.9%): 1 death in 4 days following catheter-induced VF; 1 AF related stroke in the context of OAC noncompliance, 3 infections, 1 system removal due to draining fluid from the transmitter pocket and 2 femoral artery pseudoaneurysms [56]. The SELECT-LV study has demonstrated the clinical feasibility for the leadless LV pacing method with WiSE-CRT System. This approach provided also clinical benefits in patients with a standard indication for CRT who met criteria of upgrade, untreated, non-responder or failed CRT population.

In the future novel therapeutic options should be involved widely in the therapeutic regime of end-stage HF patients. The application of LV or biventricular assist devices or the new developed wireless systems could be used as destination therapy in end-stage heart failure patients; however, one of their major complications is the occurrence of TE events. To decrease the risk of thromboembolism, further technological development is required. The outer surface of the currently available pacing leads is more thrombotic than it should be and the medical devices industry has already achieved good results in this area.

4.7. Limitation of the study

This first pilot study included only 23 patients, therefore we could not design a superiority or non-inferiority trial. The reason is obviously related to the very strict inclusion criteria. Patients were eligible only, if they had no any other remaining options for CRT. Although the study was performed in a high volume CRT center, based on the high success rate of the percutaneous approach to achieve this target number took a

rather long period. After this pilot study the important question should be raised: Does the transapical approach can provide some additional advantages for example for non-responder patients? In order to answer this question there is a need for larger scale, prospective studies. Furthermore, none of the epicardial leads were steroid eluting leads. This explains the relatively high threshold and the differences between the two groups. Finally, concern can be raised about future lead extractions in case of device and lead related endocarditis. Since we have not observed any case like that during our mid-term follow-up, we can only speculate that most likely a high risk open heart surgery is necessary to remove the infected endocardial LV leads.

5. Conclusions

5.1. Our data demonstrated the feasibility of the transapical endocardial CRT as a second alternative for patients with advanced HF who failed the first attempt through the CS implantation and/or with extensive epicardial adhesions.

5.2. The transapical CRT approach presented promising outcomes with potential advantages such as shorter procedure time, decreased postoperative burden and the best accessibility of the all LV endocardial segments without the limitations of the anatomy to reach the most delayed segment of the lateral wall compared to epicardial LV lead implantation techniques.

5.3. Although transapical CRT can be used as a second alternative method for CRT in selected HF patients, it represents a worrisome thromboembolic complication rate compared to traditional transvenous or surgical epicardial LV lead implantation. At the same time is very important to emphasize the fact,

that our long term follow-up data were collected in the period of heparin bridging which affected significantly the higher rate of thromboembolic events.

5.4. Our data suggest that during application of the new developed wireless systems or other devices, leads etc. used as destination therapy in end-stage HF patients, one of their major complications is the occurrence of TE events. To decrease the risk of thromboembolism, regarding the surface of the currently used devices/leads in the LV, further technological developments are required.

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7. Publication of the author

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Pacing Clin Electrophysiol. 2012 Feb;35(2):124-30 **IF1.75**

Mihalcz A., Kassai I., Geller L., Szili-Török T. Alternative techniques for left ventricular pacing in cardiac resynchronization therapy.
Pacing Clin Electrophysiol. 2014 Feb;37(2):255-61 **IF 1.44**

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8. Aknowledgements

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9. Supplements

1. *Pacing Clin Electrophysiol.* 2012 Feb;35(2):124-30

2. *Pacing Clin Electrophysiol*. 2014 Feb;37(2):255-61

Comparison of the Efficacy of Two Surgical Alternatives for Cardiac Resynchronization Therapy: Trans-Apical versus Epicardial Left Ventricular Pacing

ATTILA MIHALCZ, M.D.,* IMRE KASSAI, M.D., PH.D.,* ATTILA KARDOS, M.D., PH.D.,* CSABA FOLDESI, M.D.,* DOMINIC THEUNS, M.D., PH.D.,† and TAMAS SZILI-TOROK, M.D., PH.D.†

From the *Department of Electrophysiology, Gottsegen Gyorgy Hungarian Institute of Cardiology, Budapest, Hungary; and †Department of Clinical Cardiac Electrophysiology, Thoraxcentre, Erasmus MC, Rotterdam, The Netherlands

Background: *Epicardial pacing lead implantation is the currently preferred surgical alternative for left ventricular (LV) lead placement. For endocardial LV pacing, we developed a fundamentally new surgical method. The trans-apical lead implantation is a minimally invasive technique that provides access to any LV segments. The aim of this prospective randomized study was to compare the outcome of patients undergoing either trans-apical endocardial or epicardial LV pacing.*

Methods: *In group I, 11 end-stage heart failure (HF) patients (mean age 59.7 ± 7.9 years) underwent trans-apical LV lead implantation. Epicardial LV leads were implanted in 12 end-stage HF patients (group II; mean age 62.8 ± 7.3 years). Medical therapy was optimized in all patients. The following parameters were compared during an 18-month follow-up period: LV ejection fraction (LVEF), LV end-diastolic diameter (LVEDD), LV end-systolic diameter, and New York Heart Association (NYHA) functional class.*

Results: *Nine out of 11 patients responded favorably to the treatment in group I (LVEF 39.7 ± 12.5 vs 26.0 ± 7.8%, $P < 0.01$; LVEDD 70.4 ± 13.6 mm vs 73.7 ± 10.5 mm, $P = 0.002$; NYHA class 2.2 ± 0.4 vs 3.5 ± 0.4, $P < 0.01$) and eight out of 12 in group II (LVEF 31.5 ± 11.5 vs 26.4 ± 8.9%, $P = < 0.001$; NYHA class 2.7 ± 0.4 vs 3.6 ± 0.4, $P < 0.05$). During the follow-up period, one patient died in group I and three in group II. There was one intraoperative LV lead dislocation in group I and one early postoperative dislocation in each group. None of the patients developed thromboembolic complications.*

Conclusions: *Our data suggest that trans-apical endocardial LV lead implantation is an alternative to epicardial LV pacing. (PACE 2012; 35:124–130)*

cardiac resynchronization therapy, trans-apical lead implantation, epicardial pacing, endocardial pacing

Introduction

Cardiac resynchronization therapy (CRT) has become an important treatment for patients with heart failure (HF) and left ventricular (LV) dyssynchrony.[1,2] For LV pacing, transvenous placement of the LV lead into one of the side branches of the coronary sinus (CS) is the first choice.[3] In a significant proportion of patients, percutaneous delivery of the LV pacing lead fails.[3,4] In most centers, epicardial LV pacing is the currently used surgical alternative.[5] Some recent data support endocardial lead implantation via the interatrial septum (transseptal CRT).[6] Reportedly, this method provides additional hemodynamic advantages, although the implantation procedure is technically challenging and lengthy and therefore it can be a significant burden for patients with advanced HF.[7] For endocardial LV pacing, the feasibility of a fundamentally new surgical method was recently reported.[8] This method is based on trans-apical lead implantation. It is minimally invasive and provides access to any segment of the LV.[9] The aim of this prospective study was to compare the outcome of patients undergoing either trans-apical endocardial or epicardial LV pacing.

Methods

This was a single-center prospective randomized study that was approved by the Regional Ethical Committee as well as the Medical Research Council-Scientific and Ethical Committee. All patients gave informed consent before undergoing heart surgery.

There are no conflicts of interest to disclose.

Address for reprints: Tamas Szili-Torok, Department of Clinical Cardiac Electrophysiology, Thoraxcentre, Erasmus MC, Dr Molewaterplein 40, kamer Ba 577,Postbus 2040, 3000 CA Rotterdam, The Netherlands. Fax: 36-121-51220 ext. 413; e-mail: t.szilitorok@erasmusmc.nl

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Table I.

Patient Demographics and Medical Therapy

	Group I	Group II	P
Patient number (n)	11	12	NS
Age	59.7 ± 7.9	62.8 ± 7.3	NS
Male/female	9/2	8/4	NS
NYHA class	3.5 ± 0.4	3.6 ± 0.4	NS
Echocardiographic data			
LVEF (% ± SD)	26.0 ± 7.8	26.4 ± 8.9	NS
LA (mm ± SD)	61.0 ± 9.8	60.1 ± 10.7	NS
LVESD (mm ± SD)	62.7 ± 10.8	61.1 ± 10.7	NS
LVEDD (mm ± SD)	73.7 ± 10.5	68.3 ± 10.8	NS
Drug therapy (%)			
ACE inhibitors/ARB-s	100.0	100.0	NS
β-blockers	90.9	100.0	NS
Digitalis	54.5	50.0	NS
Amiodarone	45.5	50.0	NS
Loop diuretics	100.0	100.0	NS
Spironolactone	54.5	50.0	NS

NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; LA = left atrium; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; NS = nonsignificant; P = Group I versus Group II; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers.

Table II.

Classification of Percutaneous Failure of CS Lead Placement

Causes of CS Lead Placement Failure	Group I	Group II
Aberrant orifice of CS; no intubation (n)	5	6
Phrenic nerve stimulation; high threshold (n)	3	2
No suitable CS side branches (n)	1	2
CS lead dislodged more times (n)	2	1
CABG or prostatic valve impl. (n)	–	1

CS = coronary sinus; CABG = coronary artery bypass graft; n = number.

Patient Population

Twenty-three consecutive patients were identified in whom previous CRT implantation failed. All patients were eligible for CRT implantation based on current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines[10,11]: all had severe congestive heart failure, NYHA functional class III or IV despite optimized medical treatment; LV ejection fraction (LVEF) $\leq$ 35% and left ventricular end-diastolic diameter (LVEDD) $\geq$ 60 mm. QRS duration was more than 130 ms in all patients. Demographic data and the reason for transvenous failure are summarized in Tables I and II. Patients were randomized into either trans-apical (group I) or epicardial surgical LV lead implantation (group II). Crossover to the parallel group was allowed only after two redo procedures that were either related to lead positioning, lead stability problems, or to lead dysfunction. Only patients who were anticoagulated were eligible to enter the study. None of the patients had evidence of left atrial or LV thrombi on the preoperative echocardiographic study.

Follow-up and Endpoints

Follow-up visits were scheduled at 3, 6, 12, and 18 months. Responsiveness to CRT was defined as an improvement >1 New York Heart Association (NYHA) class and/or 10% improvement in LVEF at 6 months. All patients who died before 6 months were considered to be nonresponder.

The following baseline and follow-up data were compared between groups: LVEF, NYHA class, LVEDD, LV end-systolic diameter (LVESD), and quality of life (QoL).

Determining the Optimal Pacing Site

Extra attention was given performing measurements in order to find the optimal LV pacing site. All patients underwent an advanced echocardiography study with tissue Doppler imaging in order to determine the most delayed segment of the LV. If an electrophysiological study and/or LV ablation procedure was performed for any other reason, electroanatomical mapping of the LV was performed to determine the electrical activation sequence and to assist LV lead placement.

Lead Implantation Procedures

The patients were prepared for the operation using general anesthesia. After intratracheal intubation, the patient was prepared for an infra-clavicular incision as well as for a small left thoracotomy. All patients received standard perioperative monitoring (electrocardiogram, pulse oximetry, invasive arterial monitoring, and external defibrillator pads). Right atrial and right ventricular leads were positioned from the generator pocket through the cephalic or subclavian veins using a standard percutaneous technique.

Trans-apical Approach

Initially, transthoracic echocardiography was used to locate the LV apex. Beyond this marked

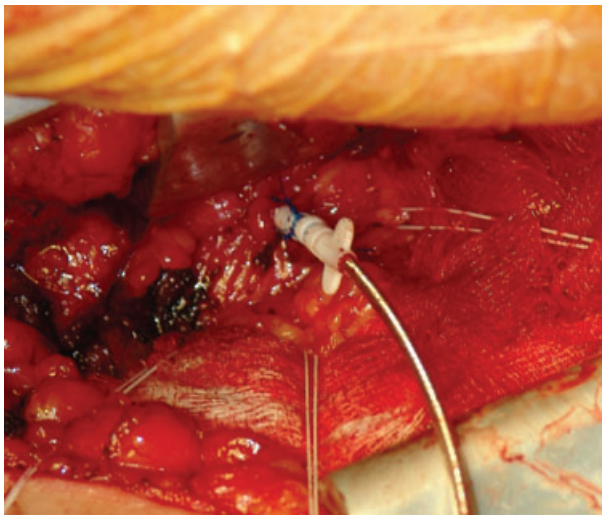

Figure 1. *Intraoperative photograph during mini-thoracotomy showing transapical lead insertion into the LV.*

Table III.

LV Lead Positions and QRS Duration after Trans-Apical or Epicardial CRT

		Group I	Group II
QRS (ms)	Before	138.9 ± 24.9	137.8 ± 25.2
QRS (ms)	After	117 ± 17.2	126 ± 24.7
	anterior (n)	–	1
basal	lateral (n)	4	4
	posterior (n)	6	–
	inferior (n)	–	–
	anterior (n)	–	1
Mid	lateral (n)	1	4
	posterior (n)	–	1
	inferior (n)	–	–
	anterior (n)	–	–
apical	lateral (n)	–	1
	inferior (n)	–	–

ms = millisecond; n = number.

area, the procedure commenced with a mini-thoracotomy. Inside the chest, a small pericardiotomy was performed above the LV apex. A standard active fixation endocardial pacing lead (Medtronic CapSureFix 4076–85 cm, CapSureFix 5076–52 cm, Medtronic Inc., Minneapolis, MN, USA; Vitatron ICQ09B-52 cm, Vitatron Holding B.V., Maastricht, The Netherlands; Guidant Flextend 2, Guidant Corp., St. Paul, MN, USA) was positioned in the LV cavity through the apex (Fig. 1). Thin commercially available bipolar electrodes were used. The leads were inserted using Seldinger technique utilizing a peel-away sheath (LI-7 Plus, 7F, Biotronik SE&Co.KG, Berlin, Germany): the apex was punctured with a needle and a guidewire was inserted. The needle was removed from the apex and dilatation of the apex hole using peel-away sheath inserted over the guide wire was performed. After removal of the guidewire, the pacing electrode was inserted into the LV cavity through the sheath and peel-away sheath was removed. Hemorrhaging from the LV was controlled with one or two 5/0 or 4/0 monofilament purse-string sutures around the puncture point. If the tissue quality of the apex required pledgeted sutures, we used pledge material in the surrounding pericardium. Fluoroscopy was necessary for the intracavital navigation and endocardial fixation of the electrode at the optimal pacing site for CRT (Table III). To reach the target area a "J"-shaped electrode guide wire was useful. Maneuvering in the LV cavity did not require specific devices and skills. It is not different from standard right ventricular pacing techniques. After effective endocardial fixation of the lead tip, the pacing and sensing parameters were measured. Pure-string sutures in the apex were applied to restrict the movement of the electrode through the apex and they were gently tied to the body of the electrode to stabilize position. The pericardium was partially closed and a small pleural drain (Jackson-Pratt SU130–1310, 7 mm, Cardinal Health, Dublin, OH, USA) was inserted followed by a standard wound closure. After lead fixation, the proximal body of the electrode was tunneled to an infraclavicular pocket using standard technique (Figs. 2A and B). Perioperative anticoagulation regime was applied as for patients undergoing mitral valve replacement. Intravenous heparin was restarted 3 hours after the surgery if bleeding was no longer observed via the pericardial drain. After surgery, the patients were orally anticoagulated with a target international normalized ratio (INR) level identical to mitral valve prostheses (INR = 2.5–3.5).

Epicardial Lead Implantation

After standard single-lumen intubation, the patient was placed in supine position with the left chest elevated 30–40°. We performed a large lateral thoracotomy between intercostal space 4–5. Ensuring sufficient distance, the pericardium was opened anterior to the phrenic nerve. The pericardium was fixed with traction-sutures to the skin, rotating the heart to the right and creating optimal exposure of the lateral surface. Unipolar or bipolar epicardial leads (Biotronik, ELC 54-up or 35-up, Medtronic 5071) were attached to the target area and secured with two sutures (Table III).

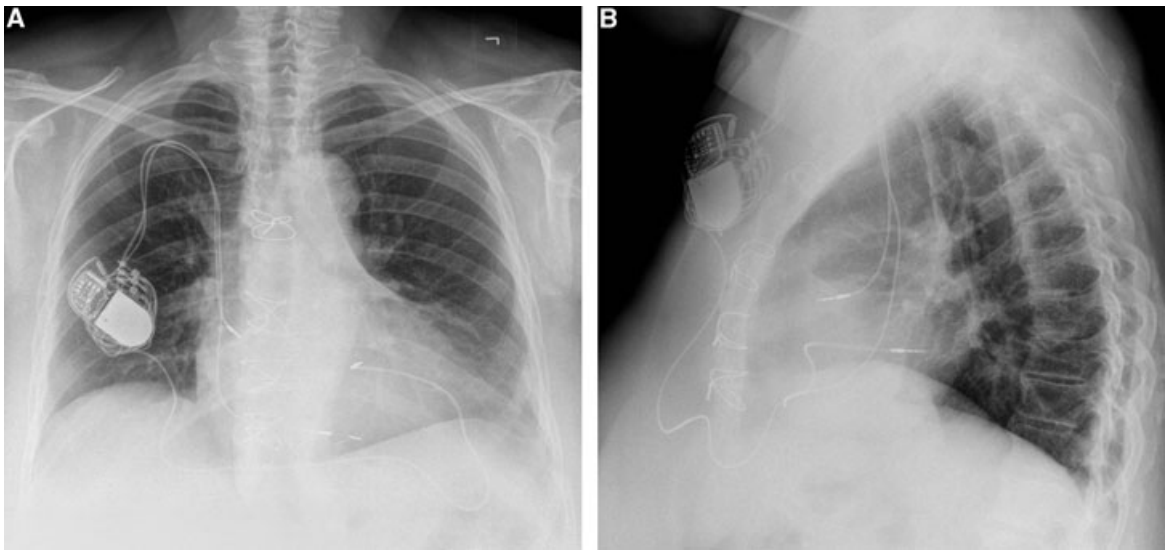

Figure 2. *(A) Postoperative chest x-ray from anteroposterior (AP) projection. (B) Postoperative chest x-ray from lateral (LA) projection.*

Device Implantation and Pacing Mode

Twenty-three patients received CRT devices for biventricular pacing (Medtronic InSync System model 8040 or 8042, Biotronik Stratos LV, Medtronic InSync Sentry 7298; Biotronik model Lumax 300 HF-T, Kronos LV-T; Atlas, St. Jude Medical, St. Paul, MN, USA). Pacing was delivered in biventricular DDD mode. At implant, all patients were in sinus rhythm. Active pacing was selected by programming the atrial-synchronous mode with the atrioventricular (AV) delay determined using hemodynamic evaluation. The AV delay was optimized based on M-mode echocardiography (transmitral time velocity integral). Interventricular (VV) optimization was not performed. The VV time was empirically programmed to − 20 ms (LV first).

Statistical Analysis

Continuous variables were shown as mean ± standard deviation (SD), if normally distributed, and compared with the Student's *t*-test. In case of nonnormal distribution of data, median with corresponding interquartile ranges were reported, and the Mann-Whitney U test was used for comparison. Categorical data were expressed in percentages and compared with Fisher's exact test. Simultaneous comparison of > 2 mean values were performed by one-way analysis of variance. A two-tailed P value of < 0.05 was considered as significant. All statistics were performed using SPSS (version 16.0) for Windows (SPSS Inc., Chicago, IL, USA).

Results

Outcome Data

Nineteen patients completed the 18-month follow-up (the follow-up time was ranging from 18 to 34 months). In the trans-apical group, one patient died suddenly 10 months after implantation. Pathology showed no device- or lead-related complications and device interrogation showed no arrhythmias. In the epicardial group, three patients died in the follow-up period. One patient died within the first 30 postoperative days; however, death was not related to the procedure. This patient had significant mitral valve regurgitation (II–III), coronary disease, paroxysmal atrial fibrillation, severe diabetes, and was in NYHA IV. The other two patients died from cardiac-related problems: one of sudden cardiac death and the other of progressive heart failure. In both groups significant QRS duration reduction was observed; however, there were no statistically significant differences between group I and II (Table III). Moreover, in the epicardial group, there was a tendency of less basal LV segments electrode placement (Table III).

Procedural Data

A trans-apical approach was used in 11 patients (group I) and a successful implant of an LV endocardial lead was obtained in all. Lead dislocation was detected in two patients. In one patient, it occurred during closure of the pericardium. In another patient, dislocation was observed on the second postoperative day.

Table IV.

Comparison of Intraprocedural Data

	Group I	Group II	P
Operation time (min)	106 ± 23.3	130.1 ± 32.3	<0.05
Fluoroscopy time (min)	7.5 ± 4.8	NA	
Postoperative days (in hospital)	6.4 ± 4.2	11.3 ± 6.8	<0.001
Reoperations needed (n)	2	1	NS

min = minutes; n = number; P = Group I versus Group II; NS = nonsignificant; NA = not applicable.

Lead repositioning could be performed without reopening of the pleural cavity.

Although data are sparse in this respect, one could speculate that there are two possible mechanisms of dislocations. One is due to incomplete screw-in mechanism and a subsequent tip release from the endocardium. It could happen despite the fact that the intraoperative electrogram showed an injury potential during the implantation. Another possible mechanism is related to the favorable changes in LV contractile function. Interestingly enough, the better LV function results in a more vigorously contracting heart that pulls out the lead from the LV endocardial surface since it is strongly fixed to the chest wall. To avoid this complication, the intracavital curve of the lead should be controlled during the reverse remodeling. Leaving a slightly larger intracavital loop might be an appropriate preventive measure to avoid this type of dislocation. This is indeed in analogy with pediatric pacemaker lead implantations.

During the study period, 12 patients (group II) were randomized to surgical epicardial LV-lead placement. After surgical placement of a LV lead, one patient presented with a high pacing threshold requiring refixation of the displaced epicardial lead. Mean procedure duration was shorter in the trans-apical group than in the epicardial. The trans-apical group required fluoroscopy for endocardial placement of the LV lead, while epicardial placement was performed without using radiation. The postoperative hospital stay was longer for patients receiving epicardial leads compared to trans-apically placed LV-endocardial leads due to minor postoperative issues, such as postoperative pain (Table IV).

Echocardiographic Data

During follow-up, LVEF has improved from 26.0 ± 7.8% to 39.7 ± 12,5% in the trans-apical group, and from 26.4 ± 8.9% to 31.5 ± 11.5% in the epicardial group. There was a substantial decrease in LV diameters in both groups (Table V). Mitral regurgitation (MR) severity was quantified on a scale of 0–4. Advanced MR (grade 3–4) was present in 16.6% (group I) and 27.7% (group II). Improvement of MR $\geq 1^{\circ}$ after 12 months occurred in 50% (group I) and 36.4% (group II) of patients.

Improvement of the NYHA class was observed in both groups. Acute LV-lead sensing did not significantly differ between the groups (11.0 ± 5.6 mV vs 11.2 ± 6.0 mV; P = NS). Acute and chronic capture thresholds of the LV leads were significantly lower in the trans-apical group (0.5 ± 0.2 V/0.4 ms vs 1.8 ± 1.5 V/0.4 ms; P < 0.01

Table V.

Comparison of the Outcome of the Patients

	Before CRT	Group I after CRT	P*	Before CRT	Group II after CRT	P*	P**
LVEF (% ± SD)	26.0 ± 7.8	39.7 ± 12.5	<0.001	26.4 ± 8.9	31.5 ± 11.5	<0.05	
LVEDD (mm ± SD)	73.7 ± 10.5	70.4 ± 13.6	<0.001	68.3 ± 10.8	68.4 ± 7.2	NS	
LVESD (mm ± SD)	62.7 ± 10.8	55.8 ± 15.5	<0.001	61.1 ± 10.7	57.5 ± 8.7	<0.05	
NYHA class (± SD)	3.5 ± 0.4	2.2 ± 0.4	<0.001	3.6 ± 0.4	2.7 ± 0.4	<0.001	
Δ LVEF (% ± SD)		13.7 ± 10.6			5.1 ± 6.8		NS
Δ LVEDD (mm ± SD)		3.3 ± 2.8			0.1 ± 3.2		<0.01
Δ LVESD (mm ± SD)		6.9 ± 5.4			3.6 ± 3.2		<0.05
Δ NYHA class(± SD)		1.3 ± 0.4			0.9 ± 0.4		NS

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; NYHA = New York Heart Association; SD = standard deviation; P* = before versus after; P** = Group I versus Group II.; NS = nonsignificant.

and 0.7 ± 0.2 V/0.4 ms vs 3.5 ± 1.2 V/0.4 ms; $P < 0.001$). Pacing at 10.0 V/0.4 ms did not result in phrenic nerve stimulation in any patients. There were no clinical signs of thromboembolic events during the follow-up.

Discussion

The major finding from this study is that the alternative method developed at our center for endocardial CRT is a feasible approach. Our data suggest that trans-apical endocardial CRT has potential advantages, such as shorter procedure times and decreased postoperative burden. Lead longevity and long-term outcome requires longer follow-up and large-scale evaluation. The idea of using this as a first-line therapy also requires further investigation.

Rational for Alternative Approaches

Despite the latest achievements of medical therapy in patients with advanced-stage chronic heart failure (CHF), mortality remains high and QoL severely impaired. CRT has been shown to improve symptoms, ventricular function, and survival in patients with LV systolic dysfunction and ventricular conduction delay.[1] Despite the technological progress aimed at improving success and reducing complication rates during CRT device implantation, in some cases the delivery of a LV pacing lead through the CS still fails. The reasons for the failed procedures are related to difficulty obtaining CS access, navigating the venous tributaries, and obtaining a stable and functional location from which to pace the lateral wall of the left ventricle.

Endocardial CRT: The Transseptal Approach

Transseptal CRT becomes increasingly utilized for pacing of the free wall of the LV in patients when an epicardial approach failed.[6,12] After standard transseptal puncture and septal dilatation via the femoral route, the left atrium is cannulated with a combination of catheters and guide wires from the left or right subclavian vein. After advancement of the guiding catheter into the LV, a standard bipolar screw-in lead could be implanted in the posterolateral wall. Obviously, these patients require lifelong oral anticoagulation after this type of procedure. It is not surprising that with a significant failure rate reported using the CS tributaries, alternative CRT pacing techniques are being looked for.

Surgical Techniques for CRT Implantation: Epicardial versus Endocardial Implantation

When CS lead placement for transvenous LV pacing has failed the most frequently used surgical alternative is the epicardial pacing lead implantation. Recent reports have described results with a limited thoracotomy approach.[5] Limited thoracotomy requires general anesthesia and single-lung ventilation to permit cardiac exposure. In addition, postoperatively a chest tube is required for a brief period. In the future, further developments are desirable, such as the introduction of thoracoscopic technique.[13,14] Recent data support endocardial lead implantation because this method provides further hemodynamic advantages.[12,15] The percutaneous approach is when a modified transseptal approach is used to place permanent pacing leads through the atrial septum and mitral valve onto the LV endocardial surface. We developed a fundamentally new method, for the trans-apical lead implantation, which provides access for pacing any segment of the LV.[8,9]

Lifelong anticoagulation is mandatory for these patients (similarly to transseptal CRT). Therefore, it is important to recognize that for patients with contraindication to anticoagulation, epicardial LV lead implantation is the only remaining therapeutic option if the standard percutaneous implantation fails. For safety reasons, we aimed a target INR level equivalent with mitral prosthetic valves. We did not observe any thromboembolic events in this group of patients treated with the trans-apical technique.

Limitations of the Study

This pilot study included only 23 patients; therefore, we could not design a superiority or noninferiority trial. The reason is obviously related to the very strict inclusion criteria. Patients were eligible only if they had no any other remaining options for CRT. Although the study was performed in a high-volume CRT center, based on the high success rate of the percutaneous approach, to achieve this target number took a rather long period. After this pilot study, the important question should be raised: Does the trans-apical approach provide some additional advantages, for example, for nonresponder patients? In order to answer this question, there is a need for larger scale, prospective studies. Furthermore, none of the epicardial leads were steroid-eluting leads. This explains the relatively high threshold and the differences between the two groups. Finally, concern can be raised about future lead extractions in case of device and lead-related endocarditis. Since we have not observed any case like that during our mid-term follow-up, we can only speculate that most likely a high-risk open-heart surgery is necessary to remove the infected endocardial LV leads.

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REVIEW

Alternative Techniques for Left Ventricular Pacing in Cardiac Resynchronization Therapy

ATTILA MIHALCZ, M.D.,* IMRE KASSAI, M.D., PH.D.,† LASZLO GELLER, M.D., PH.D.,‡ and TAMAS SZILI-TÖRÖK, M.D., PH.D.§

From the *Landesklinikum Krems, Krems, Austria; †Hungarian National Institute of Cardiology, Budapest, Hungary; ‡Heart Center, Semmelweis University, Budapest, Hungary; and §Department of Clinical Cardiac Electrophysiology, Thorax Centre, Rotterdam, the Netherlands

Cardiac resynchronization therapy (CRT) is an important treatment modality for a well-defined subgroup of heart failure patients. Coronary sinus (CS) lead placement is the first-line clinical approach but the insertion is unsuccessful in about 5–10% of the patients. In recent years, the number of CRT recipients and the considerable need for left ventricular (LV) lead revisions increased enormously. Numerous techniques and technologies have been specifically developed to provide alternatives for the CS LV pacing. Currently, the surgical access is most frequently used as a second choice by either minithoracotomy or especially the video-assisted thoracoscopy. The transseptal or transapical endocardial LV lead implantations are being developed but there are no longer follow-up data in larger patient cohorts. These new techniques should be reserved for patients failing conventional or surgical CRT implants. In the future, randomized studies are needed to asses the potential benefits of some alternative LV pacing techniques and other new technologies for LV lead placement are expected. (PACE 2014; 37:255–261)

cardiac resynchronization, pacing, epicardial, endocardial

Introduction

Cardiac resynchronization therapy (CRT) has evolved as an effective nonpharmacological method of treating patients with heart failure (HF) and left ventricular (LV) dyssynchrony for those who have not responded adequately to medical therapy.[1,2] CRT requires permanent pacing of the LV wall and restores the synchronicity of the atrioventricular, interventricular, and intraventricular contractions, resulting in improved clinical outcomes and cardiac performance of advanced HF patients with wide QRS complex.[3] However, a significant percentage of patients treated with CRT do not show an improvement in clinical symptoms or cardiac function. The suboptimal position of the LV pacing lead, an absence of LV dyssynchrony, myocardial scar abundance, or suboptimal device programming have been related to a nonresponse to CRT.[4,5] Furthermore, unsuccessful primary implantation of the LV lead into the coronary venous system has been reported in up to 10% of patients.[6–8] The optimal placement of a LV lead is one of the most challenging technical aspects of CRT device implantation and it is one of the major determinants of response to CRT. An optimal LV lead position may theoretically be defined by the positioning of the LV pacing lead coincident with the latest activated areas of the LV.[9,10] In case of optimal pacing parameters, this location can maximize the hemodynamic benefits of CRT and it provides superior long-term outcomes.[5]

In the last decade, the indication for CRT expanded[11,12] and the improvements in lead and delivery tool technologies made CRT more accessible to patients with HF. The number of CRT recipients and the considerable need for LV lead revisions or alternative techniques increased enormously.[13]

Problems with the Current LV Lead Implantation Methods

Currently, in clinical practice the standard first-line approach is the transvenous epicardial LV lead placement through a side branch of the coronary sinus (CS).[2,3,5] The final position of the LV pacing lead depends on the anatomy of the CS, on the performance and stability of the pacing lead, and on the absence of phrenic nerve stimulation.[14] Despite all of the available technologies and the placement techniques, in

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Address for reprints: Tamas Szili-Torok, M.D., Ph.D., Department of Clinical Cardiac Electrophysiology, Thorax Centre, Erasmus MC, Dr Molewaterplein 40, kamer Ba 577, Postbus 2040, 3000 CA Rotterdam, the Netherlands. Fax: 36-12151220 ext. 413; e-mail: t.szilitorok@erasmusmc.nl

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the high-volume centers the rate of failed LV lead implantation into the CS side branch or the risk of late lead dislodgement, phrenic nerve stimulation, or increasing threshold remains a substantial complication (5–10%) of transvenous CRT.[11,15]

Alternative CRT Methods

The alternative approaches can be classified on the basis of the LV pacing site (epicardial or endocardial), and on the basis of access (closed chest/percutanous or open chest). In the case of the closed chest/percutaneous approach, the lead insertion can be differentiated as transvenous, transapical, or transarterial.

Endocardial versus Epicardial LV Lead Placement

LV lead placement in the CS side branch results in epicardial pacing, which is less physiological, reversing the pattern of the normal LV wall activation. In a comparative study by Garrigue et al., endocardial biventricular pacing was associated with better LV filling and systolic performance.[16] Derval et al. tested endocardial and epicardial pacing at identical locations. The maximal rates of LV pressure change (+dP/dTmax), arterial pulse pressure (PP), and end-systolic pressure (ESP) were not significantly different, but endocardial pacing was significantly superior to epicardial pacing on the minimal rates of LV pressure change (–dP/dTmin).[17] The same results were obtained by Spragg et al.[18] In a study in which the acute hemodynamic effects of LV endocardial and epicardial pacing with simultaneous x-ray/cardiac magnetic resonance and noncontact mapping was performed, endocardial stimulation appeared to be superior as compared to conventional CRT.[19] Epicardial pacing may be more proarrhythmic than endocardial LV pacing, since epicardial activation of the LV wall prolongs QT interval and transmural dispersion of repolarization.[20] Ventricular tachycardia storms have been clinically observed after the initiation of CRT with epicardial LV pacing[21] and endocardial pacing reduces the dispersion of ventricular repolarization.[22]

Alternative Techniques

Epicardial Pacing Techniques

Currently, the open chest access epicardial lead placement is most frequently used as a second choice by either thoracotomy or video-assisted thoracoscopy (VAT).[14] The advantage of this approach is the direct visual control with the possibility of choosing the lead-tip position (Figs. 1A and B). The risks of lead dislodgement and phrenic nerve stimulation are low[23] and there is no limitation of the CS anatomy.[24] Less fluoroscopy and avoidance of intravenous contrast material are also benefits over conventional CRT.[25] Surgical epicardial LV lead placement has several disadvantages such as the need for general anesthesia, the presence of epicardial fat, adhesions, and it is more invasive than the transvenous approaches. The surgical trauma and the recovery time is appreciably higher than the transvenous LV lead implantation.[23] Finally, surgical implanted epicardial leads have a significantly higher failure rate than those of CS and transvenous right heart leads. The surgical implanted epicardial LV lead comparison studies confirmed usually excellent results after 3–6 months follow-up[25]; however, after a 5-year follow-up period, epicardial leads might have significantly higher failure rate than the CS leads. In a study by Tomaske et al. including 114 juvenile patients with most having congenital heart disease, epicardial ventricular lead survival at 2 years and 5 years was 96% and 85%, respectively.[26] On the other hand, a recently study published by Burger et al. demonstrated an excellent long-term (over a period of 48 months) epicardial lead performance and durability after surgical (median steronotomy or lateral minithoracotomy) implantation of epicardial LV lead in 130 consecutive patients.[27]

Currently, two different technical epicardial lead concepts are available: screw-in and suture-on leads. Both possess theoretical advantages and disadvantages and in this recently published comparison study, neither of the technical epicardial lead concepts was found to be superior.[27]

There are several surgical approaches to implant the LV pacing lead. *Median sternotomy* is used at planned coronary artery bypass graft surgery and at valve repair or replacement. The *full left thoracotomy* offers the widest accessibility of the lateral LV wall; however, at present it is less applied. The *minimal thoracotomy (minithoracotomy)* offers better survival and a lower incidence of mediastinitis or osteomyelitis.[28] Nowadays, the epicardial LV lead is implanted surgically, often through a small left thoracotomy,[23] and two other technologies are increasingly used: VAT techniques and robotic surgery.

Minithoracotomy

LV lead implantation via a lateral minithoracotomy is performed under general anesthesia and on the beating heart. All patients have standard monitoring (electrocardiogram, pulse oximetry, and invasive arterial monitoring). The access to the pericardium is achieved by a 4- to 5-cm left lateral, midaxillary minithoracotomy in the fourth or fifth intercostal space. The pericardium

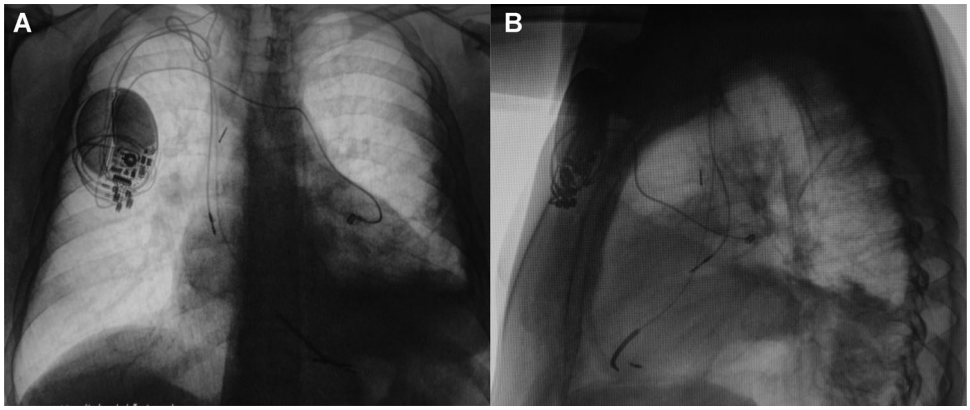

Figure 1. *Postoperative chest x-ray from anteroposterior projection (A) and lateral projection (B) after epicardial left ventricular pacing lead implantation via minithoracotomy.*

is opened anterior to the phrenic nerve. After mapping the LV for an optimal pacing site, the lead is placed on the target area.[29] After testing, the proximal end of the lead is tunneled submuscular to the provisional pocket and connected to the device. A chest tube is required postoperatively and can be discontinued within 48 hours. Recent investigations described this technique safe with a very low complication rate, representing a good alternative as a second-line procedure to transvenous CRT.[25,27]

VAT

The VAT technique offers less postoperative pain and requires smaller incisions. It does not compromise in visualization.[30] Epicardial lead implantation using VAT was initially shown to be feasible in 2001 when a group successfully undertook an LV epicardial lead placement within 40 minutes and without significant blood loss.[31] In recent years, larger series were reported and surgical leads have also been implanted thoracoscopically using two ports.[32] Usually two or three incisions are used for these ports within the fourth or fifth intercostal space along the anterior and midaxillary line. The VAT technique should be performed under general anesthesia, single-lung ventilation, standard monitoring, and on the beating heart.[33] The camera and the manipulating instruments are inserted through pre-prepared ports. Under visual control, the pericardium is opened laterally to phrenic nerve, the obtuse marginal artery as landmark help to identify the desired site, and an epicardial lead is screwed into the targeted wall region of the LV. After transesophageal echocardiography (TEE) control and the pacing threshold test, the proximal end of the lead passed through the medial incision and is tunneled subcutaneously to the pocket. The VAT approach is a feasible and safe alternative, is well tolerated, and it has minimal postoperative recovery. However, a skilled VAT surgeon is necessary for epicardial lead placement.[32] It is of importance that using VAT epicardial LV lead fixation on the heart needs special equipment and without this extra support there is an increase in the risk of dislocation.

Robotically Assisted Surgery

Experience with lead implantation using the minimally invasive route is growing rapidly with progression into LV lead implantation using robotics. This technique results in more precise LV lead placement on the ventricular wall and significantly reduces postoperative morbidity and the length of hospitalization.[34] This approach also needs general anesthesia, single-lung ventilation, standard monitoring, and TEE control. The robotic camera and instruments are introduced through 5–10-mm port sites. Using the robotic arms (da Vinci® Surgical System, Intuitive Surgical, Inc., Sunnyvale, CA, USA), the pericardium is opened posterior to the phrenic nerve to expose the posterolateral wall of the LV.[34] Computer interfacing allows the scaled motion, eliminates tremor, and provides incredibly accurate surgical precision. A screw-in lead is passed into the chest and is secured to the heart using robotic arms. The proximal part is tunneled to the axillar region and is connected to the pacemaker. The previous routine implantation of a second back-up lead is unnecessary.[35]

The minimally invasive robotic approach to epicardial LV lead placement is associated with 98% acute technical success rate and can be performed with a low complication rate.[34,35] A recent study by Kamath et al. with the largest cohort of patients who underwent robotic

epicardial LV lead placement report a benefit after 44 months follow-up and an excellent robotic lead performance.[35] However, while robotic surgery was shown to be feasible and safe, its use is restricted largely by cost implications.[36] The epicardial LV lead fixation on the heart with a robotic arm needs special equipment. Risk of lead dislocation increases without this equipment.

There are other epicardial LV lead implantation techniques that have only been used in either a small number of human cases or experimental animal studies. An alternative method for epicardial lead implantation that did not require classical thoracotomy is the *subxiphoidal video-assisted pericardioscopy.* In an experimental animal study, the access to the epicardium was achieved with subxiphoid video-assisted pericardioscopy, using a device that carries endoscopy with a port through which pacing leads could be introduced.[37] This approach requires a special support for LV lead fixation; conversely, the risk of dislocation is higher.

Endocardial Pacing Techniques

Transseptal Endocardial LV Lead Implantation

Transseptal access endocardial LV lead placement was investigated as a means of delivering LV pacing when CRT first emerged as a therapeutic paradigm and currently is used also as a third-line approach. This approach does offer some major advantages: transvenous access, more lead placement sites, endocardial pacing, and there is no need to compromise in LV pacing threshold for positional stability or phrenic nerve stimulation.[13] Its clinical use has been limited due to several reasons, including the lack of reliable long-term safety data and difficulty of the necessary techniques.[13] The transseptal technique has been used for over 50 years for hemodynamic measurements, mitral and aortic valve angioplasty, and in electrophysiology for left-sided ablations. The first case report for transseptal LV lead implantation was described by Jaïs et al. using femoral transseptal puncture and a snare technique via the right jugular vein.[38] The lead tunneled over the clavicle increases the risk for lead damage and skin erosion. Small modifications were described by Gelder et al. until the recently applied technique was clarified.[39]

Transseptal endocardial LV placement requires puncture of the interatrial septum (IAS) for passage of a lead from the right atrium (RA) into the left atrium (LA) and the LV cavity (Figs. 2 A and B). The procedure does not require general anesthesia and minimal postoperative recovery is required. The first publication describing the transseptal technique restricted the venous access to the right internal jugular vein. It requires tunneling of the lead with a relatively sharp curve over the clavicle to a right-sided pectoral device pocket.[40,41] Later on, when CRT was mostly used as part of CRT-D, the lead had to be tunneled above the sternum in the patient to a left-sided ICD pocket. The medium-term performance of endocardial LV lead placed with this technique appeared satisfactory.[42] Using a guidewire placed in the LA through an IAS puncture from the right femoral vein as a fluoroscopic marker, Ji et al. in a case presentation repunctured the IAS from the left axillary vein using a manually shaped transseptal needle.[43] This modified transseptal approach from the left axillary vein was never tested in a larger cohort. Three years later, two centers published additional case reports describing an alternative technique with a guidewire across the IAS puncture through a Judkins right or internal mammary catheter from the left or right subclavian vein.[39,44] These techniques allow more flexibility for the upper body venous access used for transseptal endocardial LV lead placement. More recently a transseptal technique using femoral venous access followed by intravascular "pull through" of the lead from the femoral insertion site to a pectoral device pocket was applied in 11 patients.[45] This latter technique is an alternative for superior transseptal attempts using standard equipment and it is also applicable for pacing sites that are more easily reachable by the femoral approach. During transseptal LV lead implantation, Kutyifa et al. successfully applied electroanatomical mapping to identify the location of the transseptal puncture and to achieve an optimal LV lead position.[46]

There is a debate about the risk of the procedure without well-experienced operators. However, the major concern is about the long-term risk of thromboembolic complication and mitral valve endocarditis related to permanent presence of the transmitral LV lead from the RA.[47] Another question is the unknown long-term thrombembolic risk and accordingly the centers accept the risk similar as after mechanical valve implantation.

Transapical Endocardial LV Lead Implantation

This new technique combines the minimal invasive surgical approach and the advantage of endocardial pacing.[48] The transapical approach was invented for patients who failed the first attempt through the CS approach and with extensive epicardial adhesions. The advantage of this minimally invasive technique is the best accessibility of the all LV endocardial segments without the limitations of the anatomy to reach the most delayed segment of the lateral wall.[49]

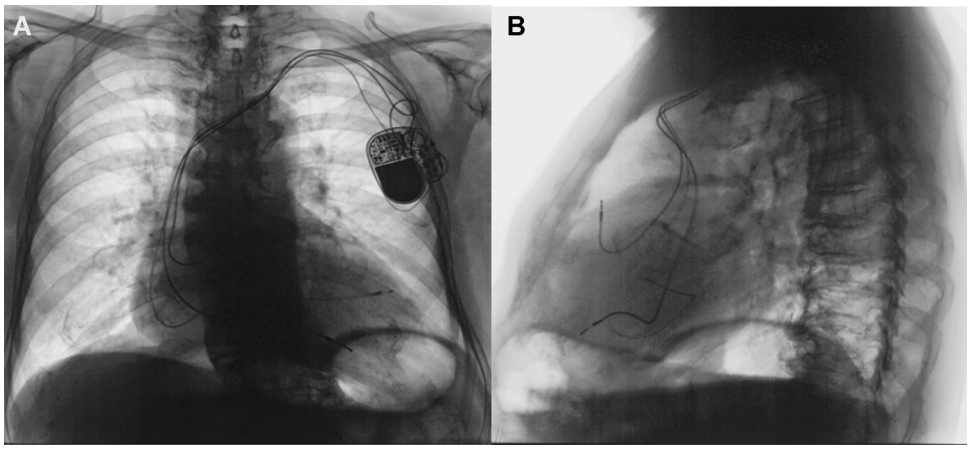

Figure 2. *Postoperative chest x-ray from anteroposterior projection (A) and lateral projection (B) after transseptal left ventricular pacing lead implantation.*

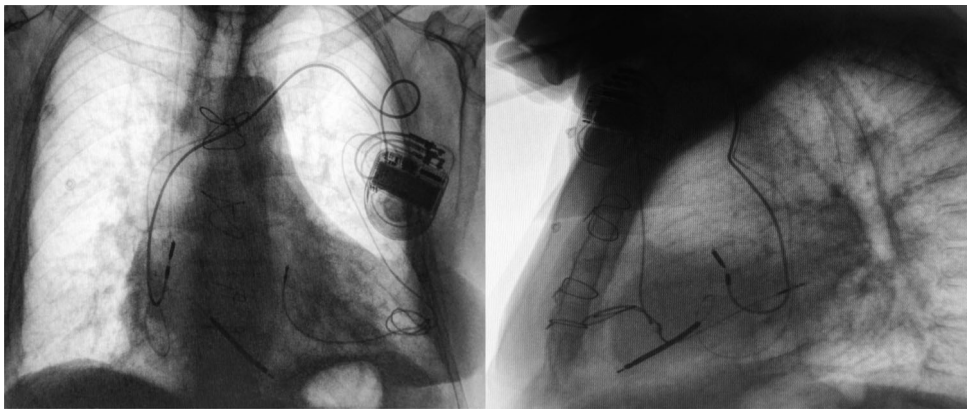

Figure 3. *Postoperative chest x-ray from anteroposterior projection (A) and lateral projection (B) after transapical left ventricular pacing lead implantation.*

A small pericardiotomy is performed above the LV apex and a standard active fixation endocardial pacing lead is positioned in the LV cavity through the apex (Figs. 3 A and B). Thin commercially available bipolar pacing electrodes are used (Medtronic CapSureFix Novus 5076–52 cm 6Fr [Medtronic Inc., Minneapolis, MN, USA], Medtronic CapSureFix Novus 5076–58 cm 6Fr, St. Jude Tendril ST 1888TC-58 cm [St. Jude Medical, St. Paul, MN, USA]). The leads are inserted using a Seldinger technique with a peel-way sheath through the apex of the heart. Fluoroscopy is necessary for the intracavital navigation and endocardial fixation of the electrode at the optimal pacing site for CRT. To reach the target area a "J"-shaped electrode guidewire is used.[48] Although this technique is minimally invasive, the need of general anesthesia is necessary. A potential disadvantage is the theoretically long-term risk of thrombembolic complication. In order to prevent this, all patients are orally anticoagulated with a target international normalized ratio level at 2–3.

A recently published study confirms that the transapical technique for endocardial CRT is a feasible approach and has potential advantages such as shorter procedure times and a decreased postoperative burden.[49] Lead longevity and long-term outcome requires a lengthy follow-up and large-scale evaluation. The idea of using this method as a second and not as third-line therapy also requires further investigation.

Transarterial Endocardial LV Lead Implantation

Transarterial access for endocardial LV lead implantation is possible through the subclavian or axillary artery and through the aortic valve. In recent years, this occurred in insignificant numbers and mostly inadvertently.[14] Only one animal experiment reported the direct transaortic placement of an LV lead as feasible.[50] In this

study, after 6 months, there was no significant aortic regurgitation and no evidence of thromboembolism reported despite the lack of anticoagulation.[50]

Conclusions

In recent years, the indication for CRT has expanded and there have been continuous improvements in LV lead and delivery tool technologies that have made the CRT more accessible for patients with HF and LV dyssynchrony. The first-line approach remains the transvenous epicardial CS lead implantation. Alternative techniques remain second-line options; however, the increasing CS lead failure rate along with the increasing number of surgical epicardial lead failures together will result in further increasing the CRT population. In the near future, more and more patients will require urgent LV lead revision. Currently, surgical access is commonly used, especially the video-assisted minimal surgery, while transapical or transseptal endocardial LV lead implantations are being developed. In the future, randomized studies are needed to assess the potential benefits of some alternative LV pacing techniques.

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