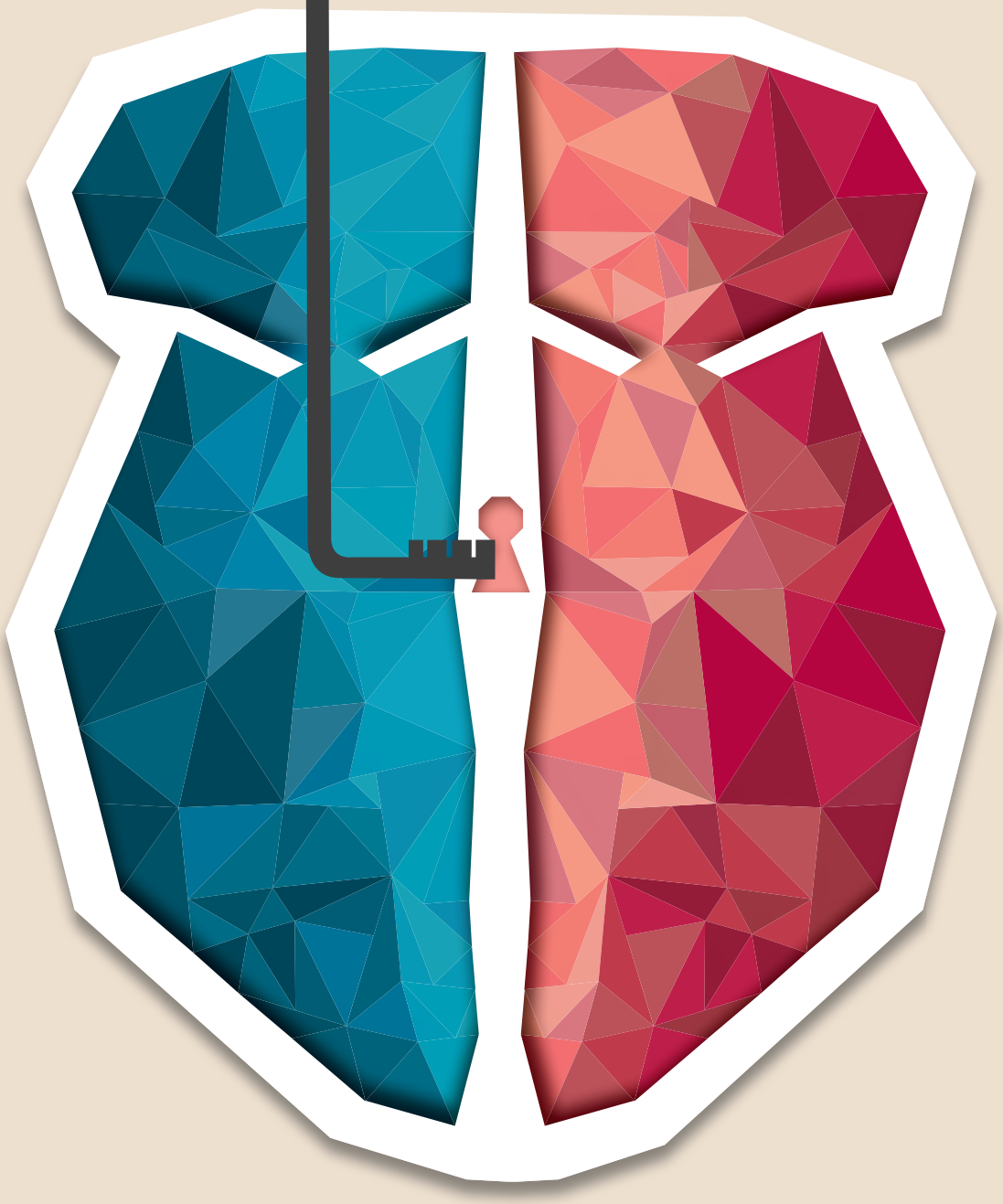
Pacing the heart

PACING THE HEART
ONE SITE FITS ALL?

LUUK HECKMAN



Pacing the heart: one site fits all?

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CHAPTER 1

1

General Introduction:
Background and Aim of the thesis.

Development of the pacemaker and pacemaker therapy

Already in the early 1780s, the Italian biologist Luigi Galvani observed muscle contraction with the application of electrical current to the limbs of dissected frogs.[1] Since then, scientists and physicians have researched and applied electrical current for clinical use. In the early 1920s, the Australian physician Dr. Mark Cowley Lidwell applied electrical current to resuscitate newborns with asystole, which was one of the first applications electrical current to stimulate heart contractions.[2]
Technical breakthroughs in the 1950s and the early 1960s paved the way for a clinically applicable pacemaker. Some external pacemakers were available, but application was limited since these were not battery powered and relied on an electrical wall outlet. Earl Bakken, founder of Medtronic, developed a battery-powered pacemaker with a built-in transistor. In the late 1950s, the first implantable pacemaker was developed and the first pacemaker implantation in a patient was in 1958. This patient, a Swedish engineer named Arne Larsson, suffered from Stokes-Adams attacks, secondary to a viral myocarditis. During his lifetime, Larsson underwent 25 pacemaker changes and he outlived both his surgeon and his engineer, dying at age 86. Throughout his lifetime, his pacemakers stimulated his heart more than one billion times.

Under physiological circumstances, the electrical stimulus preceding and driving cardiac contraction is generated in the sinus node. From the sinus node, the impulses travel through the atria and reach the atrioventricular node. After a delay of 100-150 ms in the AV node, the impulses are conducted via specialized fast-conducting tissue (the His-Purkinje system) throughout the heart, effectuating a synchronous electrical activation and contraction in both ventricles.
Patients requiring a pacemaker can either have issues with generating this electrical stimulus by the sinus node or with the conduction of the impulse through the atrioventricular node towards the ventricles. Since the first clinical implantation of the pacemaker, cardiac pacing therapy has now become the most effective therapy for treating symptomatic bradyarrhythmia.
In addition, during the last two decades, pacemaker therapy is also applied to treat patients with heart failure and conduction disorders, particularly left bundle branch block (LBBB). In these patients, the pacemaker helps to resynchronize ventricular contraction by simultaneous electrical stimulation of the right ventricle (RV) and left ventricle (LV). This form of pacemaker therapy is referred to as cardiac resynchronization therapy (CRT).

Adverse effects of RV pacing

While at the time of Arne Larsson the ventricular pacing electrodes were positioned on the LV via a thoracotomy, the RV became the preferred region when intravenous leads became available in the 1970s. When introducing the pacemaker lead into the heart, the apical region of the RV is easily accessible and provides a chronically stable lead position. However, artificial stimulation of the RV bypasses the rapid conduction system and results in abnormal electrical activation[3] and uncoordinated ventricular contraction,[4] something which was already recognized by Wiggers et al.[5] in 1925 and has been repeatedly demonstrated in the following decades.[4, 6] The introduced electrical and mechanical "dyssynchrony" can lead to adverse cardiac remodeling increasing the risk of atrial fibrillation (AF), heart failure (HF) and even cardiovascular death.[7, 8]

One of the first clinical trials demonstrating negative effects of RV pacing was the MOST study, a randomized trial comparing atrio-ventricular synchronized (DDDR) with ventricular (VVIR) pacing in patients requiring ventricular pacing because of bradycardia. Results of the MOST study showed that the percentage ventricular pacing was a strong predictor of HF hospitalizations and AF occurrence.[8] The DAVID trial showed that in patients with standard indications for ICD therapy but without indication for cardiac pacing, dual-chamber pacing offered no clinical advantage over ventricular backup pacing and was even detrimental by increasing the combined end-point of death or hospitalization for HF.[9]

One of the main contributing factors of these RV pacing induced negative clinical outcomes is that the activation pattern that is induced by RV pacing is comparable to that during left bundle branch block (LBBB). In both situations, the early activated interventricular septum (IVS) wastes part of the regional work through pre-stretching of the opposing late-activated LV lateral wall, which contracts during late systole and even early diastole. Consequently, these delayed contracting segments are exposed to a higher regional workload and LV wall thickness increases more in these segments than in early contracting segments.[10, 11] Overall, the efficiency of cardiac contraction is significantly reduced. This RV pacing and LBBB-induced dyssynchrony leading to (worsening of) HF is also referred to as "dyssynchronopathy".

Preventing and treating dyssynchronopathy

The awareness of the adverse effects of ventricular dyssynchrony has led many researchers to investigate alternative pacing strategies. In an attempt to avoid the detrimental effects of RV pacing, conduction system pacing (CSP) is rapidly gaining attention. CSP involves the placement of permanent pacing leads along different sites of the intrinsic rapid conduction system, such as His bundle pacing (HBP), and more recently LV

septum pacing (LVSP) and left bundle branch pacing (LBBP). With CSP, the intent is to maintain the physiological activation as possible and/or to overcome sites of conduction disease and delay.
Theoretically, His bundle pacing (HBP) is the most physiological form of pacemaker therapy. Unfortunately, HBP encounters limitations, such as high and unstable pacing thresholds and relatively low R-wave amplitude, complicating pacemaker programming.[12, 13] Furthermore, the procedure is technically challenging and distal conduction block could potentially occur. These limitations seem to limit widespread application in routine clinical practice.

More recently, LVSP and LBBP, commonly referred to as left bundle branch area pacing (LBBAP), are investigated. First it was demonstrated in animal studies as well as patient studies that LV function is maintained during LVSP at levels comparable to sinus rhythm with normal conduction.[14, 15] Chronic effects of LVSP were studied in canine hearts and showed that LV contractility and relaxation were comparable between LVSP and normal activation.[16] Later the transseptal technique used in these studies was modified to directly stimulate the left bundle branch (LBBP).[17]

Another way of preventing RV pacing induced adverse outcome, is combining RV pacing with LV pacing, also referred to as biventricular pacing (BVP), which has become the cornerstone treatment for patients with heart failure and ventricular dyssynchrony.[18] To further improve the response rate to BVP, multi-LV pacing (or tri-ventricular pacing) was proposed. Multi-LV pacing can be established by pacing a multipolar lead in a single vein (multipoint pacing; MPP) and pacing using two leads in separate veins (multi-zone pacing; MZP). Only a small number of clinical trials investigating multi-LV pacing have been conducted with conflicting results.

The different pacing techniques are illustrated in figure 1.

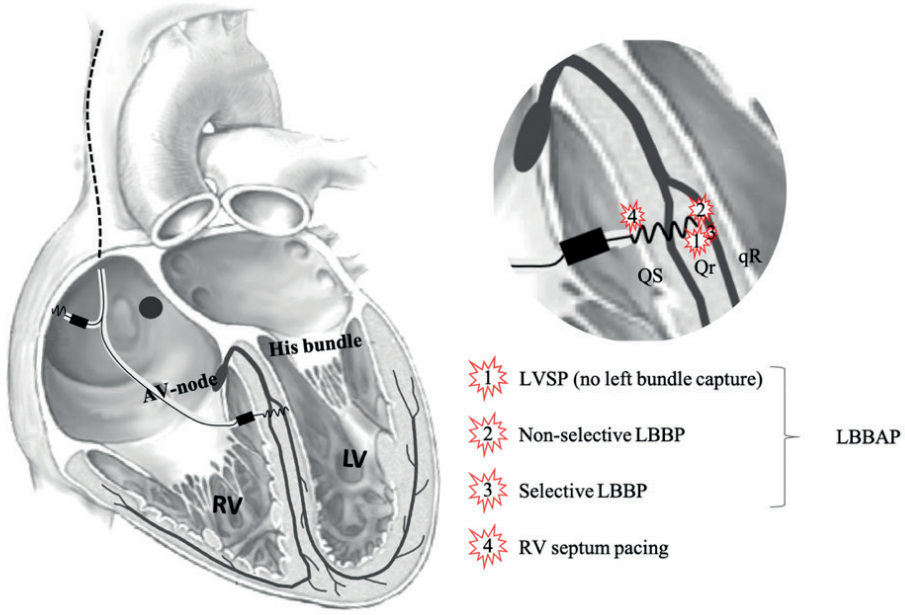

Figure 1. Schematic overview of the heart and the conduction system. Illustrated is where the lead penetrates the interventricular septum, pacing definitions are clarified and shown is which QRS morphologies are typically seen.

Toward increased understanding of left bundle branch area pacing

Although LVSP and LBBP are much alike, there are significant differences, of which the most important one is engagement of the intrinsic His–Purkinje system. In LBBP, the left bundle branch is recruited and as a consequence LBBP accelerates LV lateral wall depolarization compared to LVSP.[19] In contrast, LVSP results in direct left-to-right transseptal activation and interventricular dyssynchrony is less in LVSP compared to LBBP.[19]

An important observation is that in LBBP, reported LBB capture rates ranges between 60% and 90% in different centers/studies.[20-22] Consequently, up to one-third of patients who are reported to be treated with LBBP, are in fact treated with LVSP. The long-term clinical effects of LVSP and LBBP and the differences between them are still unknown and need to be investigated. A more detailed elaboration on the similarities and differences between both techniques is presented in **chapter 2** (Novel bradycardia pacing strategies) and **chapter 4** (Physiology and practicality of LVSP).

Aims of the thesis

The aims of the research in this thesis are as follows:

1. Investigate alternative pacing strategies that avoid detrimental effects of RV pacing.
2. Investigate the superiority of multi-LV pacing over biventricular pacing and assess differences between multipoint and multi-zone pacing.
3. Evaluate the safety and feasibility of LBB area pacing as physiological pacing strategy alternative to RV pacing.
4. Acquire mechanistic insight in differences between deep septal pacing with and without direct stimulation of the left bundle branch.

Outline of the thesis

In addition to this general introduction, an elaborate overview of the current knowledge concerning the clinical effects of different pacing techniques is provided in **chapter 2**.
The acute electrophysiological and hemodynamic effects of multi-LV pacing were investigated in a preclinical study that is described in **chapter 3**. The study provides insight into the question whether capturing a larger LV tissue area by pacing multiple electrodes provides better resynchronization compared to RV and conventional BVP and, as a consequence, cardiac function.
Chapter 4 presents a comprehensive review on the physiology and the practicality of LVSP. In this review, we describe animal and patient studies demonstrating both short-term and long-term effects of LVSP. Also, differences regarding the implantation procedure with LBBP are outlined.
In **chapter 5**, the safety and feasibility of LBBAP is described in the first 80 patients implanted with this technique in The Netherlands (Maastricht University Medical Center+). Furthermore, a learning curve was demonstrated for the LBBAP implantation. In **chapter 6**, we combined our local registry with other experienced centers forming the largest registry-based observational study that included patients in whom LBBAP device implantation was attempted at 14 European centres, for any indication. This demonstrated that LBBAP is feasible as a primary pacing technique for both bradyarrhythmia and heart failure indications, but that success rate in heart failure patients needs to be improved. In **chapter** 7 the electrical ventricular synchrony is directly compared between direct LBBP and LVSP in a multi-center population. In **chapter 8**, the design and the preliminary results of the first ten patients are described of the MASTER-LV trial (***M**ech**A**ni**S**tic insigh**T**s in l**E**ft bundle b**R**anch and **L**eft **V**entricular septal pacing*). This trial was designed to evaluate acute hemodynamic and electrical effects of deep septal pacing with (LBBP) and without (LVSP) direct stimulation of the left bundle branch. The thesis is concluded by a General Discussion (**chapter 9**)

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CHAPTER 2

2

Novel bradycardia pacing strategies.

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Abstract

The adverse effects of ventricular dyssynchrony induced by right ventricular (RV) pacing has led to alternative pacing strategies, such as biventricular (BVP), His bundle (HBP), LV septal (LVSP) and left bundle branch pacing (LBBP). Given the overlap, LVSP and LBBP are also collectively referred to as left bundle branch area pacing (LBBAP). Although among these alternative pacing sites HBP is theoretically the ideal strategy as it maintains a physiologic ventricular activation, its application requires more skills and is associated with the most complications. LBBAP, where the ventricular pacing lead is advanced through the interventricular septum to its left side, creates ventricular activation that is only slightly more dyssynchronous. Preliminary studies have shown that LBBAP is feasible, safe and encounters less limitations than HBP. Further studies are needed to differentiate between LVSP and LBBP with regards to acute functional and long-term clinical outcome.

Introduction

Cardiac pacing therapy is the most effective therapy for treating symptomatic bradyarrhythmia. While initially ventricular pacing electrodes were surgically positioned on the left ventricle (LV), the right ventricle (RV) became the preferred region when intravenous leads became available in the 1970s. Importantly, this choice was based on easy accessibility of the RV and chronically stable lead positions.
However, stimulating the RV results in abnormal electrical activation (1) and uncoordinated ventricular contraction.(2) The introduced electrical and mechanical dyssynchrony can lead to adverse cardiac remodelling increasing the risk of atrial fibrillation (AF), heart failure and cardiovascular death.(3, 4)
The awareness of the adverse effects of ventricular dyssynchrony has led many researchers to investigate alternative pacing strategies. This comprises approaches like biventricular pacing (BVP), and more recently His bundle pacing (HBP), LV septum pacing (LVSP) and left bundle branch pacing (LBBP). In this article we will review the literature about these alternatives to RV pacing.

RV pacing

The negative effects of RV pacing became apparent in the MOST study, showing that a higher percentage RV pacing was related to more frequent AF and HF hospitalization. (4) The DAVID trial showed that in patients with standard indications for ICD therapy but without indication for cardiac pacing, dual-chamber pacing offered no clinical advantage over ventricular backup pacing and was even detrimental by increasing the combined end-point of death or hospitalization for heart failure.(5) Experimental and later on clinical studies demonstrated that abnormal electrical activation leads to a discoordinate contraction pattern. During RV pacing, comparable to left bundle branch block (LBBB) activation, the early activated interventricular septum (IVS) wastes part of the regional work through pre-stretching of the opposing late-activated LV lateral wall, which contracts during late systole and even early diastole. These delayed contracting segments are consequently exposed to a higher regional workload. As a consequence, LV wall thickness increases more in these segments than in early contracting segments. (6, 7) Overall, the efficiency of cardiac contraction is significantly reduced. This RV pacing-induced dyssynchrony leading to LV dysfunction is also referred to as “dyssynchronopathy”.

Alternative RV pacing sites

In order to prevent RV pacing induced dyssynchronopathy, alternative sites within the RV have been studied intensively. Well-controlled animal experiments and studies in

cardiac resynchronization therapy (CRT) patients showed that RV septal pacing does not provide a significant benefit with regard to hemodynamic function, distribution of contraction patterns or electrical activation.(8, 9) A meta-analysis showed no clear differences in follow-up LV ejection fraction (LVEF) between RV apical (RVA) and non-apical pacing.(10)

LV pacing

In the early 1960s it was already shown that LV pacing is hemodynamically superior to RV pacing(11), which was confirmed in well-controlled animal experiments.(2) A more recent multicentre study investigating the effects of different ventricular pacing sites in children showed that pacing of the LV apex or lateral wall results in significantly better LVEF and less mechanical dyssynchrony when compared to RV pacing.(12) These data are further supported by the GREATER-EARTH study, which showed that in heart failure patients with wide QRS complex LV pacing alone creates similar outcome as BVP.(13) Animal experiments and small clinical studies suggest that further improvement may be obtained by pacing the LV endocardium rather than epicardium. (14, 15) This could be attributed to a faster endocardial impulse conduction and shorter activation path length. However, this approach requires implantation of a lead in the LV cavity. At the current stage, systems need to be improved to eliminate the various problems encountered, such as embolization, dislodgment and faster battery drain for LV endocardial pacing.

Biventricular pacing

Biventricular pacing has been introduced to correct pre-existing intraventricular conduction delays. In patients with LBBB and LV dysfunction, BVP has shown to improve quality of life and exercise tolerance, improve LV function, reduce heart failure hospitalizations and improve survival.(16-18)

A small single-centre clinical study showed that BVP also improves the LVEF and reduces symptoms in patients with chronic RV pacing.(19) Later, the BLOCK-HF study showed a significant reduction in the primary outcome (time to all-cause death, urgent care visit for HF requiring intravenous diuretic therapy or a ≥15% increase in LV end-systolic volume index) favouring BVP over RV pacing.(20) However, this difference was mainly driven by a difference in an increase in LV end-systolic volume, whereas the study failed to show a mortality benefit. Nevertheless, international guidelines state that an upgrade to CRT could be considered in bradycardia patients with wide QRS duration and LV dysfunction (class IIb indication). However, BVP requires a more

complex implantation procedure which coincides with a larger risk of complications compared to RV pacing.(21)

His bundle pacing

His bundle pacing is the most logical approach to avoid any ventricular desynchronization as His bundle (HB) capture reproduces normal ventricular activation. While the first experience with HBP had already been described in the 1960's by Scherlag and colleagues,(22) it was only in 2000 that HBP for permanent pacing therapy was published.(23)

The clinical evidence for HBP is very promising. Compared to RV pacing, studies consistently show that HBP results in better clinical outcomes in patients undergoing pacemaker implantation because of atrioventricular block (AVB). Sharma and colleagues showed in a non-randomized trial that in patients with a high ventricular pacing burden (>40%) there was lower incidence of HF in HBP group than in the RV pacing group (2% vs 15%) during a 2 year follow-up period.(24) Also, during long-term follow-up (5 years) permanent HBP was associated with a reduction in the composite endpoint of death or HF hospitalization compared to RV pacing.(25) However, HBP was associated with higher rates of lead revisions and generator change. The largest study so far on permanent HBP was performed by Abdelrahman and colleagues where permanent HBP was attempted in 322 consecutive patients (with 92% success rate) at 1 hospital and compared to RV pacing in 433 patients performed at a sister hospital.(26) They found a significant reduction in the primary endpoint of all-cause mortality, HF hospitalizations or need for upgrade to BVP with permanent HBP (25% vs 32%, HR 0.65). Prospective, randomized multicentre studies comparing HBP with RV pacing with respect to long-term clinical outcomes are clearly necessary at this moment to advance the field.

AV node anatomy

The penetrating HB originates from the AV-node and runs through the inferior portion of the membranous interventricular septum and continues in most people along the left side of the muscular interventricular septum (figure 1). Both atrial and ventricular parts of the HB can be accessed for HBP. The final implantation site is dependent on the site of AV-conduction delay, as this should be distal to the level of conduction block. However, there are anatomical variations in the course of the HB that can have clinical implications on implantation success.

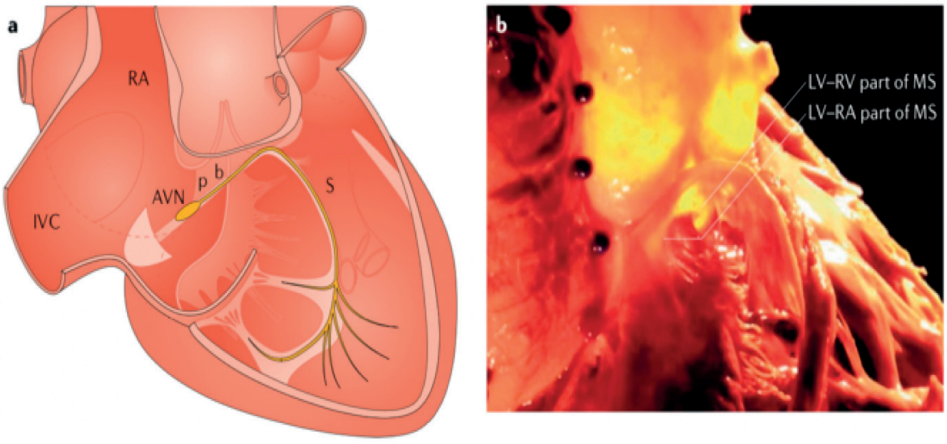

Figure 1. Left panel: Illustration of atrio-ventricular node (AVN) and His bundle (HB) anatomy. Right panel: corresponding anatomic section showing the proximal portion of the HB on the right atrial (RA) – left ventricular (LV) aspect of the membranous septum (MS) and the distal portion of the HB on the right ventricular (RV) – LV aspect of the membranous septum. IVC: inferior caval vein. Modified from (27)

Implantation procedure

Initially, HB lead implantation was performed using a standard lead with manually reshaped lead stylets using fluoroscopy.(23, 28) With the anatomical guidance of an electrophysiological catheter, the aim was to position the lead close to the HB. This procedure was often time consuming with low success rate. With the introduction of newer leads and especially new delivery systems, finding the HB using the lead itself became feasible with a substantially higher implantation success rate.(24, 29) A recent worldwide cumulative experience collected from many centres in China, the USA, and Europe in a real life environment showed that HBP is practical and feasible in most patients with an acceptable but slightly higher pacing threshold compared to RV pacing and low rate of complications.(30)

The implantation procedure has been described in detail in previous publications. (23, 31) In short, after obtaining venous access the delivery sheath is positioned on the tricuspid annulus and the lead is then advanced to the tip of the sheath. Unipolar mapping from the tip of the lead is used to map the HB region. The aim is to find a HB potential on the intracardiac electrogram by using an electrophysiological recording system. Subsequently, the lead is screwed into the HB region and the pacing and sensing measurements of the lead are evaluated (figure 2).

Although HBP is an attractive alternative strategy for permanent pacing, actual lead placement remains technically challenging, due to location of the conduction disease and anatomical variations of the conduction system. Particularly, in case of distal his-Purkinje system disease, long-term safety of HBP has not been studied well and an extra backup RV lead could be considered.

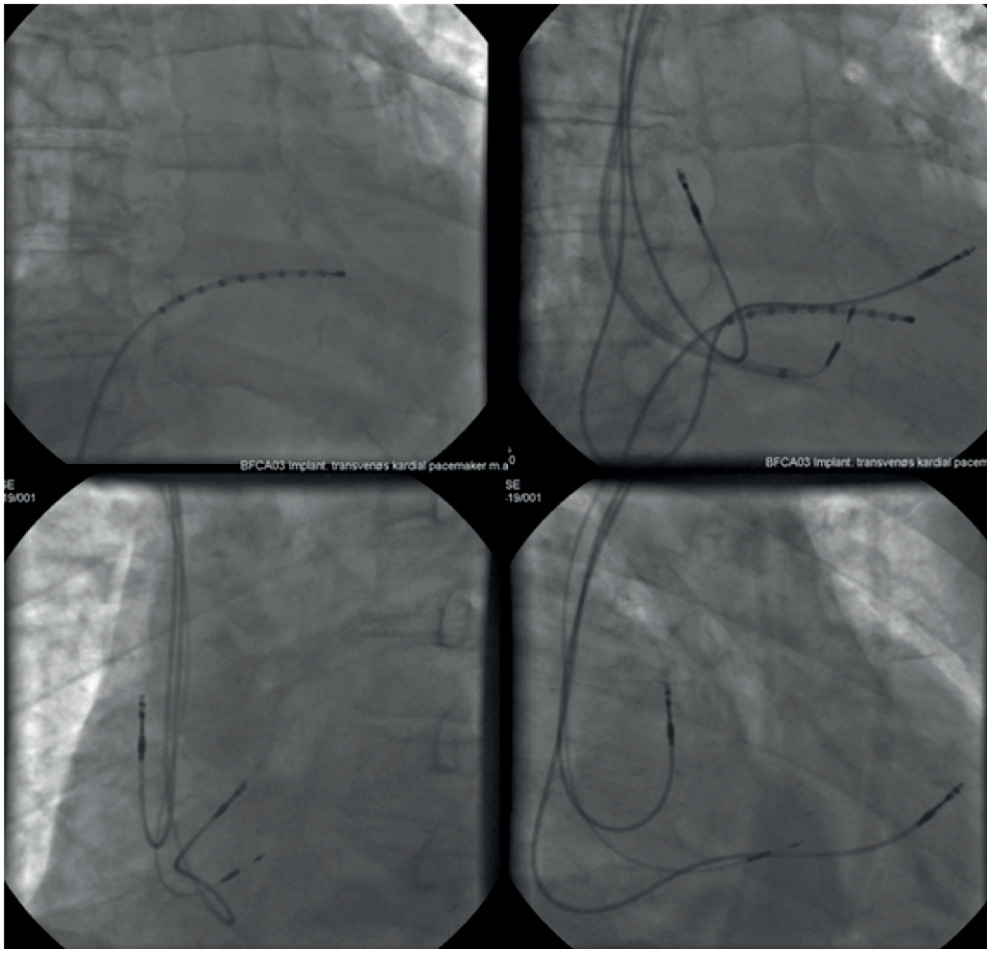

Figure 2. Implantation of a pacemaker for His bundle pacing. Upper-left corner a mapping catheter to guide the lead to the bundle of His. Upper-right corner placing the His lead with the SelectSecure system. Lower-left corner final lead positions in LAO 60° view. Lower-right corner final lead position in RAO 30° view. Modified from (32)

Implantation characteristics of the HBP lead differ from traditional RV leads. The ventricular sensed values on the HBP lead are also generally much lower, which increases the risk of ventricular undersensing and atrial oversensing. Atrial oversensing on a ventricular pacing electrode can cause inhibition of ventricular pacing, which is potentially life-threatening in a patient with AVB. Also, HBP thresholds are generally higher causing faster battery depletion and are known to rise in some patients over time.

In conclusion, HBP is an attractive pacing strategy with much promise for future applications in patients who require ventricular pacing, but potentially also for patients with heart failure and ventricular dyssynchrony. Further adoption of this pacing strategy is dependent on the implantation tools and validation in larger randomized clinical trials.

Left bundle branch area pacing

In the search for an alternative to RV pacing animal studies in the early 2000s demonstrated that normal LV function was preserved during pacing at the left side of the interventricular septum (LV septal pacing; LVSP).(9) A more recent development is that pacing the left bundle branch (LBBP) provides synchronous ventricular activation that is comparable to BVP and HBP.(33, 34) While theoretically LVSP and LBBP differ with respect to having capture of the LBB (only in LBBP), in practice there seems to be significant overlap. Therefore, below we will collectively refer to both techniques as left bundle branch area pacing (LBBAP).

Left ventricular septal pacing

In the animal studies demonstrating that normal LV function was preserved during pacing of the left side of the interventricular septum, the LVSP lead was permanently implanted by introducing a custom pacing lead transvenously into the RV and driving it from the RV side through the IVS to the LVS.(8) Following the positive findings of LVSP in the preclinical setting, a first-in-man study demonstrated the feasibility of permanently implanting an LVS lead using this transvenous approach through the IVS.(35) In these patients, the ventricular pacing lead was positioned as close to the middle of the IVS as possible, using RV angiography and intracardiac echocardiography. Subsequently, the pacing electrode was carefully screwed through the IVS until the left side of the LVS was reached. IVS penetration depth was assessed by injecting small amounts of contrast medium through the guiding catheter against the IVS under fluoroscopy and by monitoring changes in the paced QRS morphology. An acute hemodynamic benefit of LVSP over RVA and RV septum pacing was observed in all patients. At 6-months follow-up, stable lead performance was achieved without any procedure-related complications. QRS duration during LVSP was prolonged compared with intrinsic activation, yet considerably shorter than during RVA and RVS pacing (figure 3). In a recent study in 27 patient undergoing CRT implantation, LVSP provided short-term hemodynamic improvement and electrical resynchronization that was at least as good as during BVP and HBP.(36) Unfortunately, capture of the left conduction system was not intended in these experiments, but cannot be excluded.

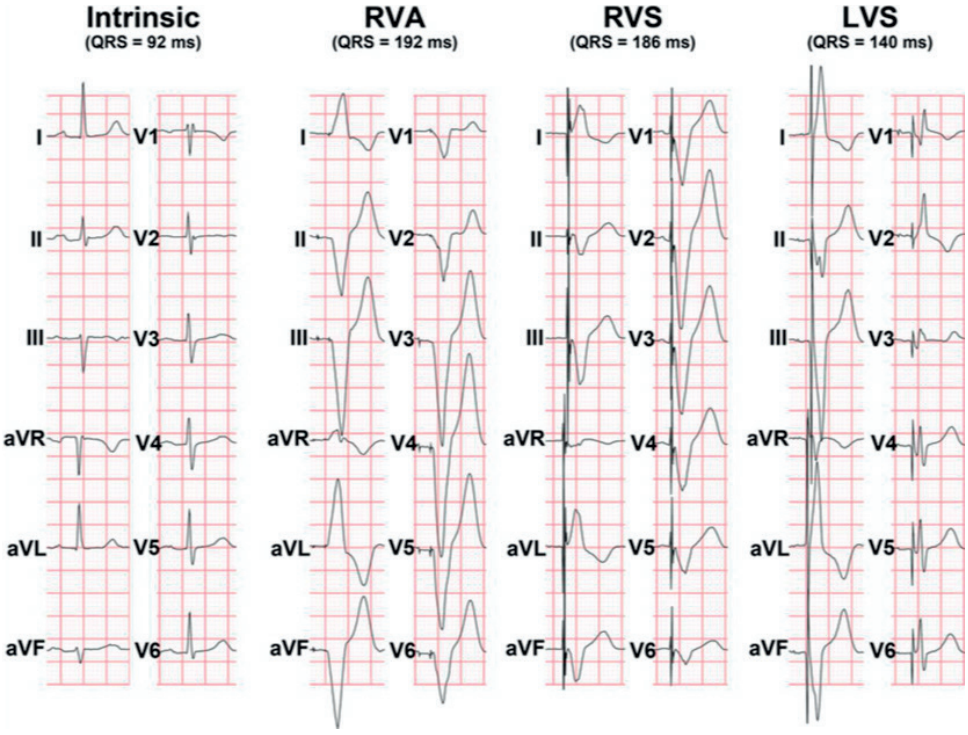

Figure 3. Twelve-lead ECG from a patient with sinus node disease during intrinsic activation, right ventricular apex (RVA), right ventricular septal (RVS), and left ventricular septal (LVS) pacing. During RVA and RVS pacing, a left bundle-branch block–like QRS morphology was observed. During LVS pacing, a right bundle-branch block–like QRS morphology was observed in the precordial leads. RVA and RVS pacing considerably prolonged QRS duration relative to intrinsic activation. QRS duration during LVS pacing was prolonged compared with intrinsic activation, yet considerably shorter than during RVA and RVS pacing. Modified from (35)

Left bundle branch pacing

After the initial publications on LVSP, Huang and colleagues published about a novel pacing strategy. Since it was proven to be possible to cross the IVS, their hypothesis was that it would also be possible to capture the LBB when positioning the pacing lead at a more basal level. In a patient with heart failure and LBBB, Huang et al. showed that it was possible to directly stimulate the LBB and resolve LBBB.(37) After this observation the novel strategy of left bundle branch pacing (LBBP) was born.(37) LBBP is defined as capture of the left bundle trunk or its proximal fascicles, usually with septal myocardium capture.(38)

During the LBBP implantation procedure the distal HB potential is located. The initial site for LBBP is determined as approximately 1–1.5 cm distal from the HB towards the RV apex in the right anterior oblique (30°) fluoroscopic view. The lead, with the tip perpendicular to the

septal surface, is screwed through the IVS guided by fluoroscopy, electrophysiological signals on the tip of the pacing electrode (LBB potential) and the paced QRS morphology (figure 4). Similarly to LVSP, QRS morphology gradually changes from a LBBB-like morphology into a RBBB-like QRS morphology, when advancing through the IVS as shown in figure 5.(37)

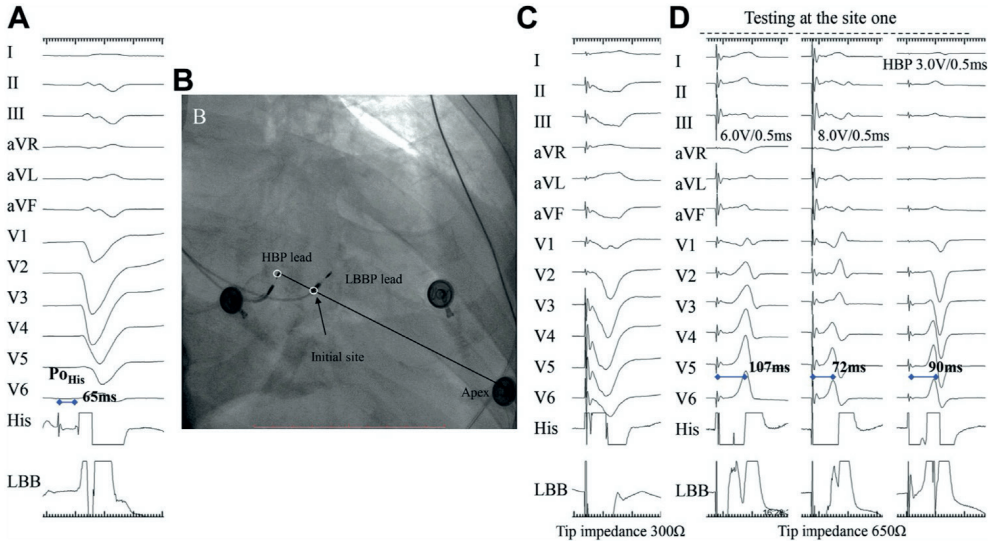

Figure 4. How to locate the site for left bundle branch pacing (LBBP) and electrogram characteristics. **A**: His potential (PoHis) and no clear left bundle branch (LBB) potential in left bundle branch block (LBBB). **B**: Location of the His-bundle pacing (HBP) lead and LBBP lead in the right anterior oblique 30° view. **C**: Paced morphology of "w" pattern with a notch at the nadir of the QRS in lead V1 and impedance of 300 Ω by unipolar tip pacing before fixation. **D**: Screwing the lead approximately 6–8 mm deep, the notch in lead V1 moved up and toward the end of the QRS with impedance of 650 Ω. With increased output from 6.0 V/0.5 ms (left) to 8.0 V/0.5 ms (middle), the paced morphology changed to right bundle branch block and the stimulus to left ventricular activation time shortened from 107 to 72 ms. The LBB potential could not be noted during LBBB correction by selective HBP (right). Modified from (38)

After several initial small studies in CRT populations, Li et al.(33) reported that in 33 patients with AVB LBBP maintained cardiac function at the 3-month follow-up. These results were confirmed in 56 patients with normal cardiac function who underwent pacemaker implantation, where all patients survived without any symptoms of heart failure during a mean follow-up of 5 ± 2 months. LVEF, LV end systolic and diastolic diameter remained unchanged during follow-up.(39) In a recent, larger study in 115 patients with an identifiable LBB potential and QRS duration <120 ms, LBBP lead implant was successful in all patients, without serious complications (dislodgement, infection, or stroke) at 6-month follow-up. (40)

It is, however, essential to realise that, although intended, LBB capture was often not possible in these patients and should actually be considered as LVSP pacing rather than LBBP. Consequently , there seems to be an significant overlap between LVSP and

LBBP and whether clinical outcomes differ between deep LVSP with and without direct capture of the left bundle remains to be determined.

In addition, there is so far no consensus on the criteria determining if LBB capture is truly obtained. The generally used criteria for LBB capture are currently : 1) paced RBBB-like QRS morphology, 2) recording of a LBB potential, 3) short and constant left ventricular activation time (LVAT), measured as the interval between pacing stimulus and R-wave peak in V4-V6 and 4) demonstration of transition from nonselective to selective LBB capture or nonselective LBB capture to LV myocardial only capture during threshold testing. (38, 41, 42)
Given that there is no consensus for the criteria of LBB capture, it is difficult to determine in what percentage of cases there is actually direct capture of the LBB. A recent study on LBBAP in 115 patients reported LBB capture in 92%.(40) The presence of a LBB potential at final implantation site varies largely between studies, from only 66%(43) up to 100%.(40)

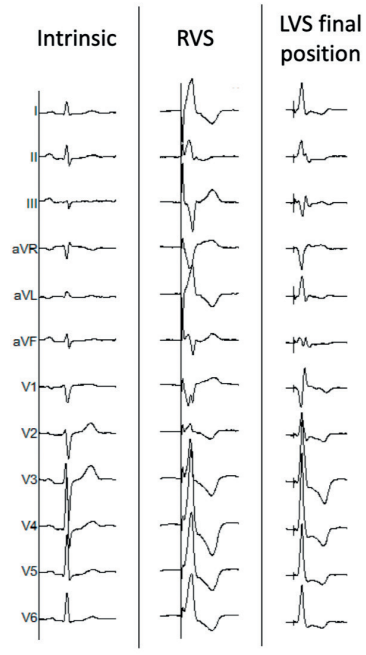

Figure 5. Twelve-lead electrocardiogram from a patient with narrow intrinsic QRS complex during pacing at the right side of the IVS and pacing at the left side of the IVS. RVS = right ventricular septum pacing. LVS = left ventricular septum pacing. IVS: interventricular septum.

In initial studies investigating the safety and feasibility of LBBP implantation success rates ranged from 81%(43) to 93%.(44) The highest reported complication rate was only 6 out of 100 patients, consisting of 3 lead dislodgments within 24 hours requiring revision and 3 LV septal lead perforations.(44) LBBP produced paced QRS durations similar to native QRS durations, ranging from 113±10 to 136±17 ms, with stable and low (<1.0 V) pacing thresholds during the initial months after implantation. In general, the paced QRS duration in LBBP and LVSP is smaller compared to RV pacing,(45) but mostly longer compared to HBP.(36, 39)

Clinical implications

The feasibility and clinical benefits of permanent HBP have been demonstrated. However, randomized clinical trials comparing HBP with RV pacing or LBBP are still lacking. Although HBP theoretically is the ideal physiological pacing strategy, concerns regarding high ventricular pacing thresholds, lower R-wave amplitudes possibly leading to sensing problems, and the potential development of a conduction block distal to the pacing site have limited the application of HBP. LBBAP has emerged as an alternative method for delivering physiological pacing to achieve and/or maintain electrical synchrony of the left ventricle. Both conduction system pacing strategies as well as other alternatives to RV pacing are summarized in table 1.

The results of investigations in LBBAP raised several potential implications. Since mechanistic studies demonstrated electrical as well as mechanical resynchronization in patients with heart failure and ventricular dyssynchrony, LBBAP has the potential of being an easier and faster alternative to BVP in CRT. However, whether LBBAP is equal or superior to BVP in heart failure patients needs to be established in prospective randomized clinical trials.
BVP is known to provide no benefit, or is even detrimental in heart failure patients with narrow QRS (46), but as LBBAP uses the native conduction system for maintaining ventricular synchrony, it has the potential to be applied as pacing therapy in symptomatic bradycardia patients as alternative to HBP. Since the LBBAP implantation procedure is faster, it avoids venography and the need for a third pacing lead, LBBAP might even have the potential to be the preferred strategy in the future, especially in patients with an infra-Hissian block or bradycardia accompanied by LBBB or RBBB. In patients undergoing AV nodal ablation with subsequent pacing ('ablate and pace'), either BVP or HBP is recommended, (47) but it has been demonstrated that also LBBAP is safe and feasible with a high success rate in persistent atrial fibrillation patients with heart failure and ICD indication.(48) A recently published mechanistic study on the comparison of hemodynamic and electrical effects between BVP, HBP and LVSP shows that LVSP

Table 1. Pacing strategies alternative to RV pacing.

	BVP	***HBP***	***LVSP***	***LBBP***
Target region	RV apex easily targeted. LV reached via coronary sinus.	His-bundle width: 1-4 mm, length: 10-20 mm. Conduction fibres imbedded in fibrous sheaths.	Widespread subendocardial fast-conducting network Purkinje fibres.	Left bundle branch or proximal fascicles targeted.
Synchrony of activation	Correct pre-existing interventricular and intraventricular conduction delays.	Restoring/maintaining normal ventricular activation (RV+LV).	Restoring/ maintaining intraventricular synchrony (LV).	Restoration/ maintaining intraventricular synchrony (LV) with delayed RV activation
Implantation - *Size target region*	Large LV target zone, limited by venous anatomy.	Small target zone (proximal or distal His bundle).	Largest target zone.	Large target zone.
- *tools*	Many dedicated implantation tools.	Dedicated leads and guiding sheaths.	Dedicated lead and guiding sheath	Dedicated lead and guiding sheath
Implant success rate	>90%.	56-95%.	>90%.	81-93%.
R-wave sense	High R-wave amplitude, no sensing issues.	Low R-wave amplitude. Atrial oversensing, ventricular undersensing.	High R-wave amplitude, no sensing issues.	High R-wave amplitude, no sensing issues.
Need back-up lead?	Standard RV lead implantation.	RV back-up lead often considered in pacing-dependent patients with distal block.	No RV back-up lead required.	No RV back-up lead required.
Lead Complications	RV lead 2%. LV lead 5%.	No septal perforation reported.	Septal perforation possible.	Septal perforation possible.
Conduction system capture	Not intended.	Up to 10% loss of conduction system capture during follow-up.	not intended.	60-90%. No reports on follow-up.
Lead revision rate	5-10%.	3-7%.	To be determined.	~1%.
Battery longevity	Unchanged.	Shortened.	Unchanged.	Unchanged.

provides short-term hemodynamic improvement and electrical resynchronization that is at least as good as during BVP and HBP.(36) Nonetheless, randomized clinical studies directly comparing HBP or LBBP with RV pacing or comparing HBP and LBBAP directly in patients with structurally normal hearts or heart failure are lacking and long-term safety and performance of LBBP still needs to be established. In patients with failed HBP lead implantation, LBBAP is a logical choice. Clinically applicable pacing strategies in patients requiring frequent RV pacing are shown in the decision tree depicted in figure 6.

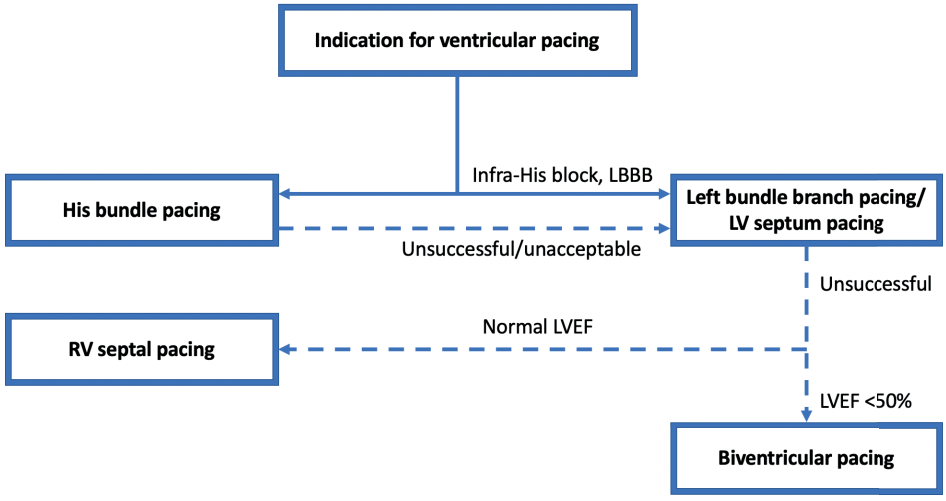

Figure 6. Decision tree regarding the currently available pacing therapy options for patients with an indication for chronic RV pacing.

Conclusion

Conduction system pacing, i.e. HBP and LBBAP are promising alternatives for RV pacing. Compared to HBP, LBBAP offers lower pacing thresholds, larger R-wave amplitudes and lower risk of developing conduction block distal to the pacing location. While HBP has proven to be safe and feasible, the long-term safety of LBBAP has yet to be demonstrated. Additionally, more mechanistic insights regarding LBBAP have to be gained focusing on ventricular lead penetration depth and the beneficial effects of capturing the left conduction system thereby better differentiating between LVSP and LBBP. Prospective randomized clinical trials are needed to investigate patient populations most likely to benefit from HBP or LBBAP.

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CHAPTER 3

3

Evaluating multisite pacing strategies in cardiac resynchronization therapy in the preclinical setting.

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Abstract

Background: Multisite pacing strategies are proposed to improve response to cardiac resynchronization therapy (CRT). Current available options are pacing two electrodes in a multipolar lead in a single vein (multipoint pacing; MPP) and pacing using two leads in separate veins (multi-zone pacing; MZP).

Objective: To compare in a systematic manner the acute hemodynamic response (AHR) and electrophysiological effects of MPP and MZP and compare these with conventional biventricular pacing (BiVP).

Methods: Hemodynamic and electrophysiological effects were evaluated in a porcine model of acute left bundle branch block (LBBB, n=8). AHR was assessed as LVdP/dtmax. Activation times were measured using >100 electrodes around the epicardium, measuring total (TAT) and LV activation time (LVAT).

Results: Compared to LBBB, BiVP, MZP and MPP reduced TAT by 26±10%, 32±13% and 32±14%, respectively (NS between modes) and LVAT by 4±5%, 11±5% and 12±5%, respectively ($p<0.05$ BiVP vs MPP and MZP). On average, BiVP increased LVdP/dtmax by 8±4% and optimal BiVP increased LVdP/dtmax by 13±4%. The additional improvement in LVdP/dtmax by MZP and MPP was only significant when its increase during BiVP and decrease in TAT were poor (lower 25% of all sites in one subject). The increase in LVdP/dtmax was larger when using large interelectrode distances (>5 cm vs. <2.2 cm).

Conclusion: In this animal model of acute LBBB, MPP and MZP create a similar degree of electrical resynchronization and hemodynamic effect, which are larger if interelectrode distance is large. However, MPP and MZP only increase the benefit of CRT if the LV lead used for BiVP provides poor response.

Introduction

Up to 30% of heart failure patients exhibit left ventricular (LV) conduction abnormalities which lead to slow electrical activation and discoordination of contraction.[1] For these patients, biventricular pacing (BiVP) has been proven to be a valuable therapy. BiVP restores ventricular synchrony and is therefore also referred to as cardiac resynchronization therapy (CRT).

Response to CRT is complex and multifactorial and although it is in general positive, it varies considerably between individual patients. An important determinant of CRT response is to deliver optimal left ventricular (LV) pacing. While most LV pacing leads are implanted conventionally in a LV (postero-)lateral vein, the pacing site yielding the maximum hemodynamic effect differs considerably between individuals.[2]

Beside optimal positioning of the (single) LV lead, another strategy proposed to improve response to CRT is pacing from multiple LV sites. Conceptually, capturing a larger tissue area provides better resynchronization and, as a consequence, cardiac function. Several single and multicenter studies have suggested a benefit of multiple LV pacing using an additional LV lead in a second vein,[3, 4] which we refer to as multi-zone pacing (MZP). However, implantation of a second LV lead comes at the cost of longer procedure times and higher periprocedural complication rates.[5, 6] These disadvantages are not encountered when using multipoint pacing (MPP), i.e. stimulating multiple electrodes on a single quadripolar lead. Several clinical studies showed a small hemodynamic benefit and/or increased electrical resynchronization in MPP over conventional BiVP [7-9] although other studies were not able to demonstrate such benefit.[10, 11]

Studies directly comparing MPP and MZP are scarce and focus mainly on hemodynamic differences.[9, 12, 13] Sohal et al. showed the importance of the electrical substrate for the hemodynamic response to multiple LV pacing using invasive electro-anatomical mapping in patients,[13] but little attention was paid to the pattern of electrical synchronization, created during MPP and MZP.

It was the aim of the present study to asses in a systematic manner the electrophysiological and hemodynamic effects of MPP and MZP as compared to BiVP. To that purpose we determined the acute electrical and hemodynamic effects of pacing from a large number of single LV sites and multiple combinations of two LV sites in a porcine model of acute left bundle branch block (LBBB).

Methods

Animal experiments

Animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive on the Protection of Animals used for Scientific Purposes (2010/63/EU). The protocol was approved by the Experimental Animal Committee of Maastricht University.

Experimental setup

The experiments were performed on 8 adult pigs, weighing 71.1 ± 0.6 kg. Animals were pre-medicated with Zoletil (5-8 mg/kg i.m.). After thiopenthal induction (5-15 mg/kg IV), anesthesia was maintained by continuous infusion of propofol (2.5-10 mg/kg/h), sufentanyl (4-8 mg/kg/h) and rocuronium (0.1 mg/kg/h). A thermal mattress was used to maintain adequate body temperature. ECG was derived from limb leads.
Left bundle branch block (LBBB) was created either by radiofrequency ablation (n=4) with the use of an ablation catheter (MarinR, Medtronic) and a radio frequency power generator (Atakr, Medtronic),[14] or (if ablation created atrioventricular block) mimicked through RV free wall pacing (n=4).

LV and RV pressures were measured using 7F catheter-tip manometers. The catheters were introduced through the carotid artery and jugular vein, respectively. Subsequently, after thoracotomy and pericardiotomy, two custom made multi-electrode bands were placed around the heart. These bands consist of two rows of electrodes (2x30 and 2x22 electrodes) and were used for stimulation of the heart as well as for electrical mapping. One electrode band was positioned at the basal and one at the mid-level of the ventricles.

Pacing protocol

A right atrial (RA) and a RV pacing lead were positioned transvenously. For each electrode, the pacing threshold was determined separately and output was set at twice the threshold. Baseline was measured during AAI pacing. The ventricular pacing protocol was performed in DOO mode, 10 bpm above sinus rhythm. To ensure full ventricular capture, the paced AV-interval was set at 70% of the intrinsic PQ-interval (LBBB by radiofrequency ablation) or 30 milliseconds shorter than the A-RV free wall pacing interval (LBBB through RV free wall pacing).
BiVP, MPP and MZP configurations were created by unipolarly pacing the RV apical lead simultaneously with one or more band electrodes situated on the LV. Dual LV pacing combinations were classified as MPP if the paced electrodes were apico-basally aligned or as MZP if the electrodes were circumferentially aligned. Electrode combinations were chosen with varying inter-electrode distances, at different LV levels (basal and mid) and different LV segments (anterior, lateral, posterior), as depicted in figure 1.

Six different combinations of four LV electrodes were tested in each animal. The pace protocol consisted therefore of pacing at 24 LV single sites and 36 LV dual site combinations. All configurations were combined with endocardial RV apex pacing.
Results were calculated by averaging values for all parameters over a 20-30 s period, excluding inappropriate beats such as ventricular extra systoles (VES) and two subsequent beats.

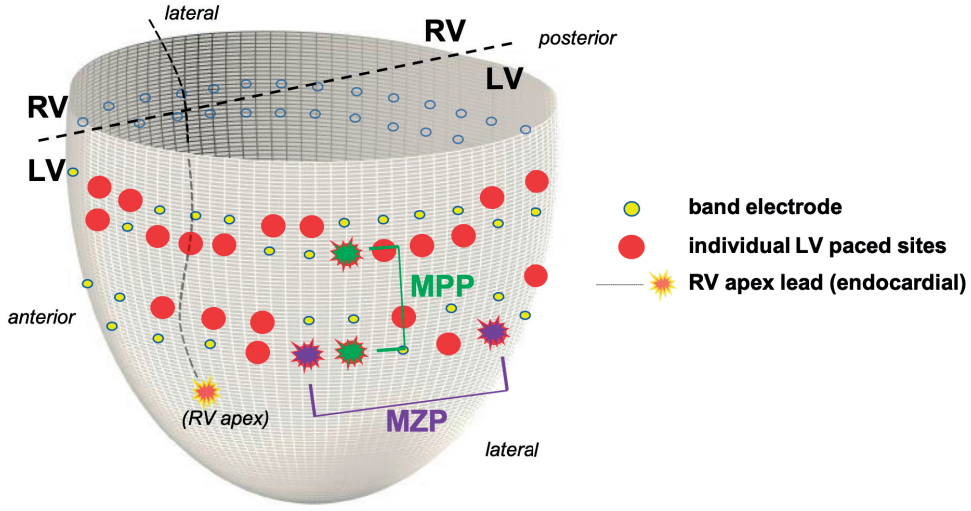

Figure 1. Pacing set-up. Schematic overview of paced locations on the porcine epicar- dium, showing the 2 multielectrode bands (2x30 and 2x22 electrodes) around the right ventricle (RV) and left ventricle (LV). Individual electrodes are illustrated by dots. Large red dots indicate electrodes that have been used in any pacing mode (single or dual). Green and purple stars indicate exam- ples of dual LV paced configurations, resembling either multipoint pacing (MPP) (vertically aligned) or multizone pacing (MZP) (horizontally aligned). All non-paced electrodes were used for electrical mapping.

Data analysis

Analysis of recorded experimental data was performed using custom MATLAB software (MathWorks, Natrick, MA). From LV and RV pressure signals were derived systolic and diastolic pressures, LV and RV dP/dtmax and dP/dtmin.[14] Local activation times were calculated as the time difference between onset of Q-wave (LBBB by radiofrequency ablation) or pacing artefact (LBBB through RV free wall pacing) and the timing of the steepest negative deflection on the local unipolar electrogram. If activation time calculation was not possible for an electrode due to pacing artefact, this was excluded. A septal decapolar catheter was used to determine activation at the RV side of the interventricular septum, in order to distinguish RV from LV. From these data, total activation time in both ventricles (TAT), of the LV (LVAT) and RV (RVAT) were

determined from these data. Interventricular electrical delay (IVED) was defined as the difference between the median values of LV and RV activation time. Left ventricular electrical delay (Q-LV) was measured as the interval from the onset of the QRS complex to the fastest negative deflection of the local LV electrogram during intrinsic activation. To account for baseline drift, the effect of pacing on hemodynamic parameters was quantified as a percentage change compared with the mean of the 2 adjoining baseline measurements.

Statistical analysis

Statistical analyses were performed using the SPSS software, version 25.0 (IBM Corp, Armonk, NY). Presented are mean values ± standard deviation (SD). All hemodynamic and electrical results are expressed as percent changes relative to the corresponding baseline. A two-way analysis of variance for repeated measurements (ANOVA) was used to evaluate between group differences in relative changes between pacing modes and/or sites. When necessary due to sample size distributions, Levene's test was used to assess heterogeneity. Bonferroni multiple comparison analysis was performed applied to pairwise comparisons. Differences between individual group means were tested by independent samples t-tests. Statistical significance was assumed at $p<0.05$.

Results

Induction of LBBB resulted in a 75±23% increase in QRS duration compared to intrinsic conduction, to values of 93±14 ms.

Electro-anatomic assessment of different pacing sites

Activation times and sequences were dependent on the LV pacing site. The longest TAT occurred during LV pacing in the anterior and posterior wall, as evident from the blue color in the opposing wall presented in the upper panels of figure 2.

For the entire group, stimulation sites on the lateral wall provided better resynchronization than those on the anterior or posterior wall, as evidenced from significantly larger reductions in TAT, LVAT and IVED (figure 2, bottom panel, upper row). There were no significant differences in TAT and IVED between basal or mid-level pacing sites (figure 2, lower row), but pacing mid-LV regions provided a significantly larger LVAT reduction (19±11% vs. 13±6%, $p<0.05$).

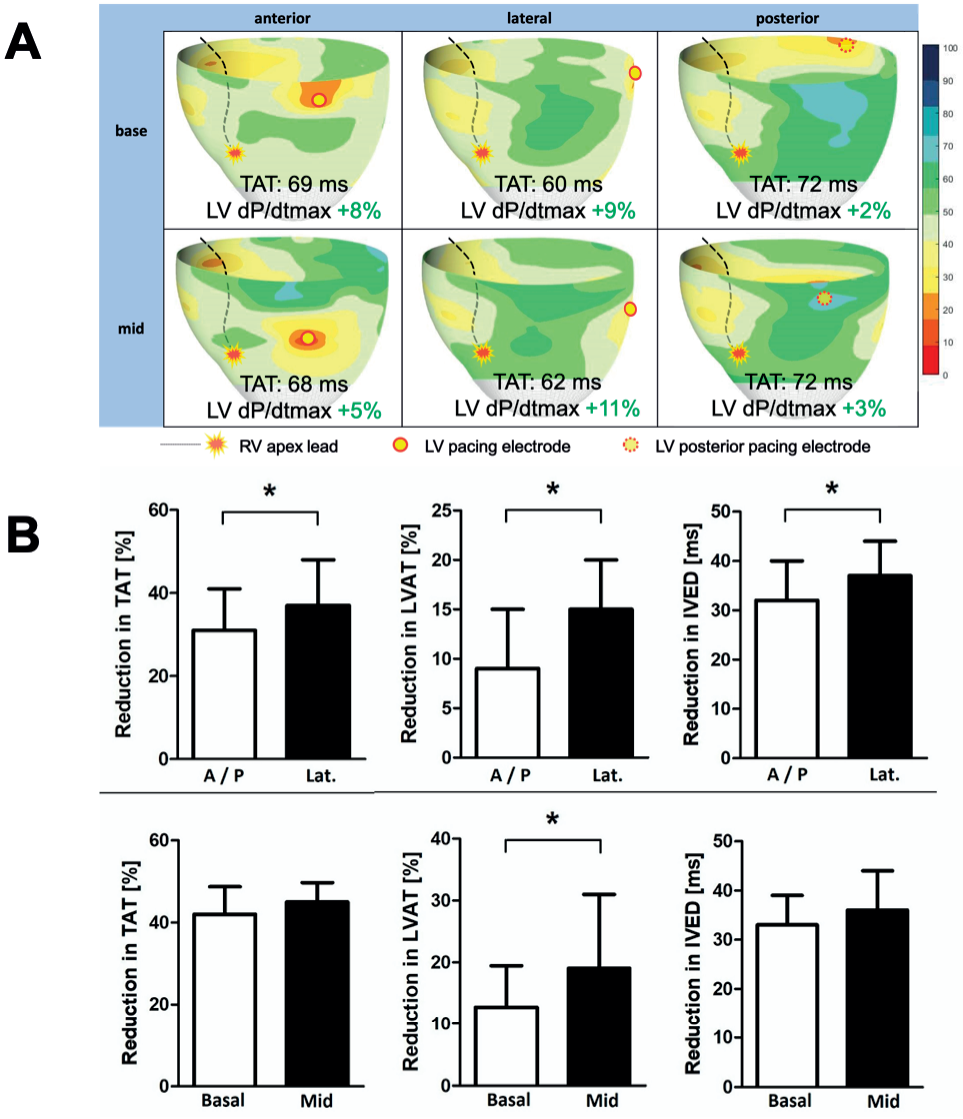

Figure 2. Response to biventricular pacing. **A:** typical examples of 3D epicardial activation maps in the same porcine heart during BiVP. Illustrated is how lateral left ventricular pacing sites provide a better resynchronization over anterior or posterior ones. When compared within the same segment, activation times and sequence are comparable between basal and mid level pacing sites. The apical region is not depicted due to lacking apical electrodes.
B: reduction in dyssynchrony parameters for left ventricular anterior/posterior versus lateral sites (**upper row**) and for basal versus mid level sites (lower row) during conventional biventricular pacing. BiVP: biventricular pacing, TAT: total activation time, LVAT: left ventricular total activation time, IVED: interventricular electrical dyssynchrony, A / P: anterior/posterior, Lat: lateral. * $p<0.05$ compared to lowest reducing segment or level.

Acute hemodynamic response during BiV pacing

The acute hemodynamic response (AHR), defined as relative change in LV dP/dtmax compared to baseline LBBB, varied widely between and within individuals. The pacing site yielding the highest AHR was animal specific and ranged from 7.9 to 17.4%. Also the pacing site yielding the lowest AHR was animal specific and ranged from -3.6 to 7.7% (figure 3A). The range between the highest and lowest AHR per experiment was 8.8±4.4 percent points. On average, BiVP increased LVdP/dtmax by 8±4% and optimal BiVP increased LVdP/dtmax by 13±4%.

There was a moderate correlation between the reduction in TAT and the increase in LVdP/dtmax in BiVP (figure 3B).

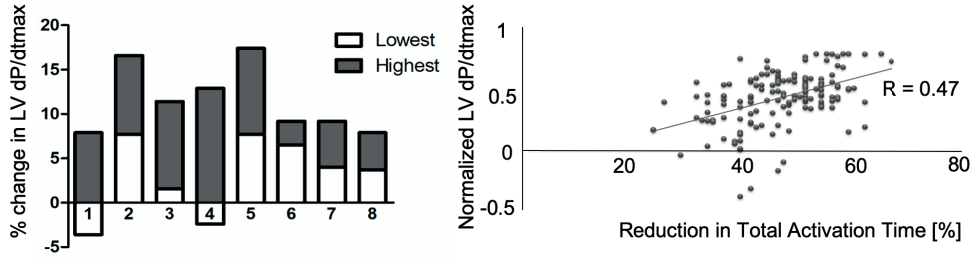

Figure 3: Hemodynamic response per experiment and correlation with activation time. Panel **A:** lowest and highest acute hemodynamic response to BiVP in the eight individual experiments (numbers along the horizontal axis). White bars represent the lowest AHR and grey bars represent the highest AHR.
Panel **B:** correlation between normalized LV dP/dtmax and reduction in TAT for the individual LV sites during BiVP. Values were normalized to the maximum of the individual experiment.

Electrophysiological effects of multiple LV pacing strategies

Figure 4 shows representative examples of three-dimensional activation maps during baseline LBBB, BiVP and both multisite pacing strategies. The examples illustrate that MPP and MZP reduce TAT, LVAT and IVED to a similar extent.

Figure 5A shows that BiVP, MZP and MPP reduced TAT significantly compared to baseline LBBB, but that the reduction was not significantly different between the three modes.

The right panels of figure 5A show the reduction in activation time for both MZP and MPP, differentiating between the first and fourth quartile of inter-electrode distance (IED). In neither MPP nor MZP there was a significant effect of IED on TAT.

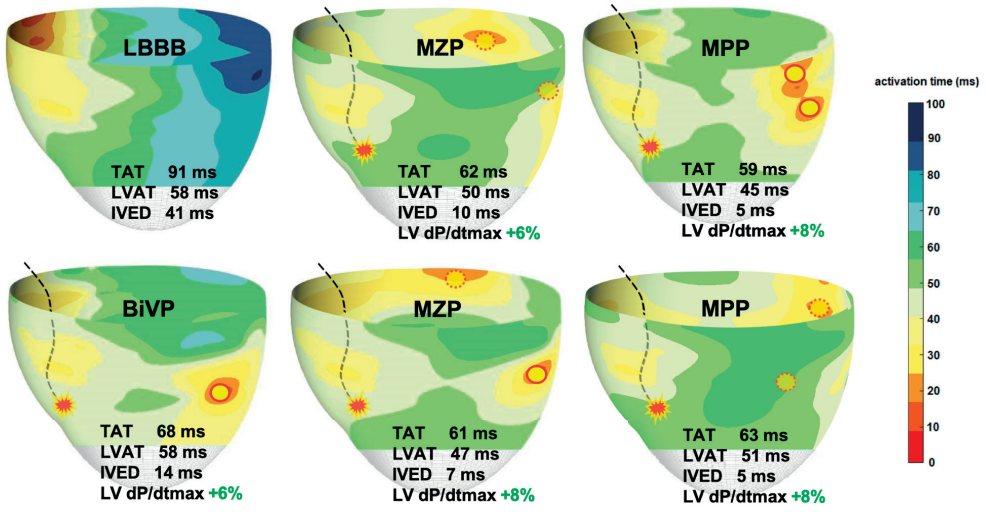

Figure 4: 3D activations maps of the epicardium during LBBB, BiVP, MZP and MPP. On the left are shown activation patterns during left bundle branch block and BiVP where the LV is paced from the anterolateral wall. Center panels show examples of MZP with a small (**top**) and large (**bottom**) inter-electrode distance. On the right are shown activation maps during MPP with small (**top**) and large (**bottom**) inter- electrode distance. BiVP: biventricular pacing, MZP: multi-zone pacing, MPP: multipoint pacing, TAT: total activation time, LVAT: left ventricular activation time, IVED: interventricular electrical dyssynchrony.

Hemodynamic effect of multiple LV pacing

Both MPP and MZP increased LVdP/dtmax by 7±3% as compared to LBBB (figure 5B, left panel). Optimal MPP and MZP increased LVdP/dtmax by 13±4% and op 11±2%, respectively (NS). Importantly, a large IED provided a significantly larger AHR during both MPP and MZP (figure 5B, right panels).

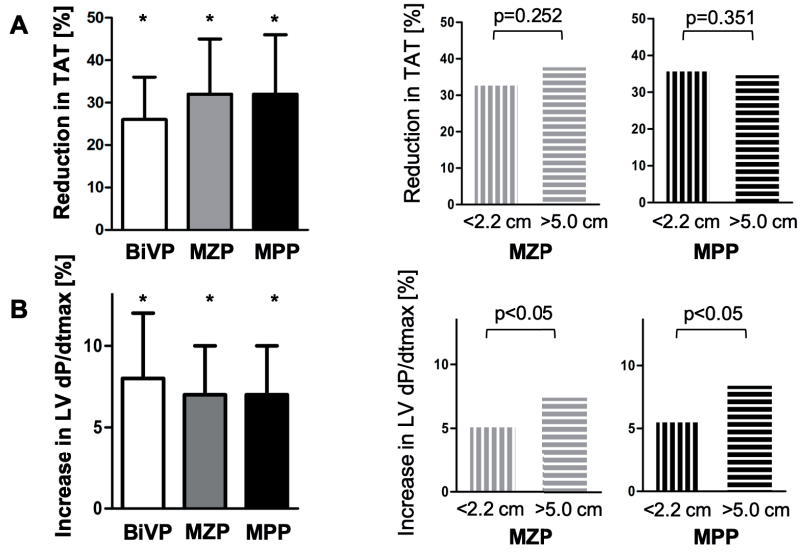

Figure 5. Resynchronization during BiVP, MZP, and MPP. Reduction in TAT (**A**) and increase in LVdP/dtmax (**B**) during BiVP, MZP, and MPP, expressed as percent of left bundle branch block for all pacing combination (**left**) and for the first and fourth interelectrode distance quartiles (**right**). *P ,.05 vs baseline. Abbreviations as in Figure 4.

Figure 4 shows an example where pacing from two LV sites results in better electrical resynchronization, but not necessarily to a higher increase of LV dP/dtmax. This issue is further addressed in figure 6, which shows that pacing from two LV sites (right panels) increased LVdP/dtmax as compared to single posterior wall pacing (upper left panel), but LVdP/dtmax was not increased as compared with LV lateral wall pacing (lower left panel).

In order to investigate this for the entire group and all sites, LV sites were grouped according to the size of AHR during BiVP into subgroups with the highest 25%, the lowest 25% and the intermediate 50% change in each experiment. Each site was then used in a MPP and MZP configuration and changes in LV dP/dtmax were compared to that during BiVP. Figure 7A shows that MPP and MZP provided only a significant additional increase in the AHR in the group with the 25% lowest AHR. The highest 25% group consisted for 75±10% of lateral sites, whereas the lowest 25% group consisted for 61±14% of anterior/posterior sites. Anatomical electrode positions on the lateral LV wall producing poor hemodynamic improvement (lowest 25%) were not consistent among different experiments.

When performing the same analysis after dividing the pacing sites according to the lowest 25%, intermediate 50% and largest 25% reduction in TAT, LV sites yielding the smallest initial decrease in TAT benefited most from upgrading to MZP/MPP, an increase that was at least as large as that observed after MPP/MZP using sites showing the lowest increase in LVdP/dtmax (figure 7, panel B). In the lowest 25% group LV

dP/dtmax increased from 4.0±4.4% to 8.8±1.5% above baseline during MZP and to 9.8±2.1% during MPP (both p<0.05 compared to BiVP). There were no statistically significant changes in LV dP/dtmax in the other two subgroups.

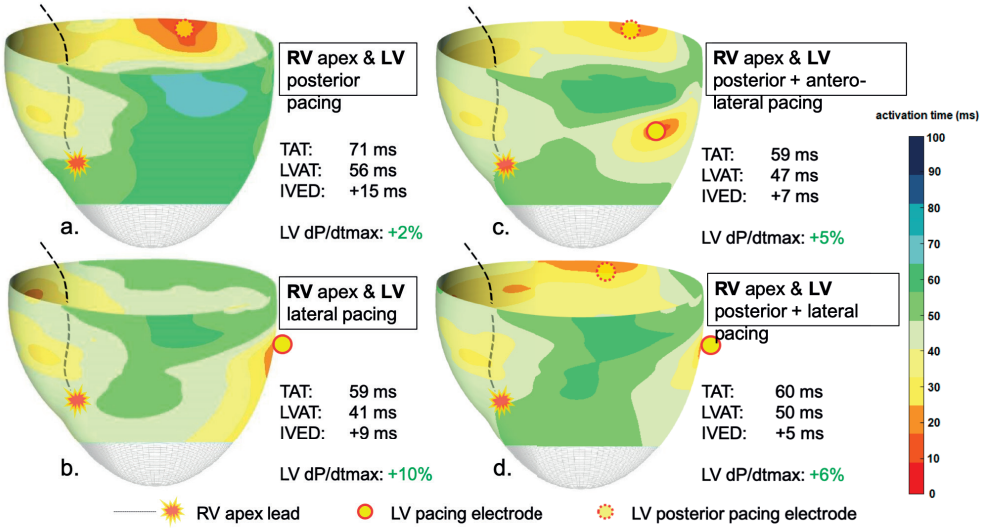

Figure 6. Effect of left ventricular (LV) pacing locations on acute hemodynamic effect during multiple LV pacing. Representative 3-dimensional epicardial activation maps of the ventricles during BiVP (**A, B**) and multiple LV pacing (**C, D**) in the same heart. **A, B:** Configurations yielding the lowest and highest acute hemodynamic response (AHR), respectively. **C:** In an attempt to increase the initial AHR, a second pacing site was added in the delayed activated anterolateral area of A, resulting in the activation map shown. **D:** Effects of the simultaneously paced combination of A and B. RV 5 right ventricle; other abbreviations as in Figure 4.

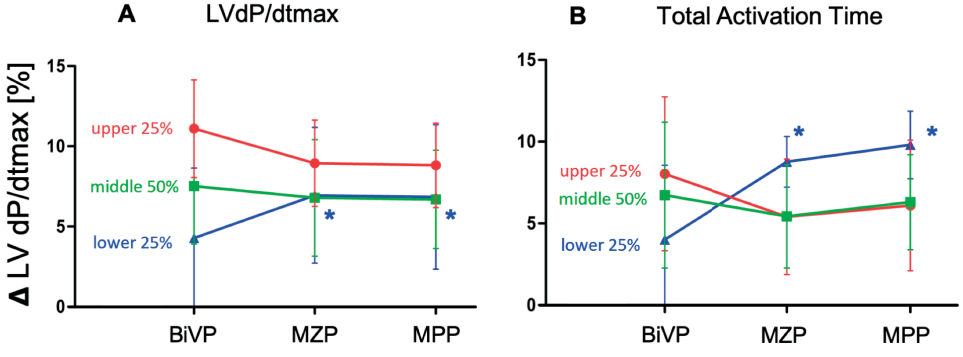

Figure 7. Acute hemodynamic response during multiple left ventricular (LV) pacing based on initial acute hemodynamic and electrical response during biventricular pacing (BiVP). Relative increase in LVdP/dtmax compared to baseline during BiVP, multipoint pacing (MPP), and multizone pacing (MZP), distinguishing between single initial LV pacing sites with upper 25%, middle 50%, and lower 25% change in LVdP/dtmax (**A**) and total activation time (**B**). Values are given as mean and SD. *P<0.05 vs BiVP.

Discussion

The principal findings of the present study are that 1) MPP and MZP create a similar degree of ventricular electrical resynchronization and hemodynamic effect and that 2) while BiVP is often sufficient, MPP and MZP can create a beneficial effect beyond BiVP only when the LV site used for BiVP does not lead to adequate hemodynamic benefit, and that 3) a large interelectrode distance increases benefit of MPP and MZP.

Electrical resynchronization by multiple LV pacing

The finding that multiple LV pacing significantly reduces electrical activation time and dyssynchrony as compared with BiVP pacing is in accordance with previous animal[15] and patient studies.[13] While most of the electrical dyssynchrony in LBBB-like conduction abnormalities are in circumferential direction, pacing in two veins (MZP), so largely circumferentially aligned, did not provide a significantly better intra- or interventricular resynchronization as compared with more apico-basally aligned electrodes, as during MPP. This similarity in degree of electrical resynchronization seems also to be present in clinical studies, because these reported comparable reduction in QRS duration[9] and epicardial activation time[13]. The electrical maps in the present study may provide an explanation for these observations, since late activated regions are observed both more basal and more anterior and posterior from LV lateral wall electrodes (blue regions in figure 4, BiVP) which disappear during both MPP and MZP.

Hemodynamic consequences of LV multisite pacing strategies

The observation in the present study that MPP and MZP-like pacing strategies do not lead to an improved AHR compared to BiVP seems in contradiction with several clinical studies, that demonstrated a small but significant positive hemodynamic effect of MPP and MZP over BiVP.[3, 7-9] On the other hand, several other studies were not able to show such positive effect.[10, 11] One possible explanation may be related to statistical analysis: most studies compared the best of several options of multisite pacing with less (sometimes just one) BiV measurements.[16, 17] In contrast, we compared each dual LV mode with its corresponding BiVP measurement. In this respect it is interesting that a study that specifically took care of randomized and repeated measurement using appropriate controls also was not able to find acute hemodynamic benefits of MPP.[11]
An implication of the present study, supported by other studies[10, 11], is that choosing the best possible single LV site is sufficient to achieve optimal CRT benefit.
While on average MPP and MZP did not significantly improve hemodynamic response beyond that achieved by BiVP, they may be beneficial in case the initial electrophysiological (TAT) or hemodynamic (LVdP/dtmax) effect of BiVP is poor. This is an extension of previous patient studies where the LV location determined the magnitude of the hemodynamic effect of BiVP. If MPP was compared with "poorer"

LV sites a considerable effect was seen, but the benefit was small effect when MPP was compared to the BiVP configuration that yielded the largest AHR. [8, 9] These findings are also in line with previous work from our group in a non-ischemic canine LBBB model[15] and from Bordachar in a canine model of chronic ischemic heart failure.[18] Even increasing the number of LV pacing sites to six only resulted in a better AHR if AHR during BiVP was poor.[15] In agreement with the Ploux study[15] we also found that better electrical resynchronization during multiple LV pacing did not always coincide with a better hemodynamic response.

The finding that pacing the lateral wall in LBBB is more beneficial compared to pacing the anterior or posterior wall is not new, but it confirms the suitability of the LBBB animal model. In the clinical situation the lateral wall may not be targetable, due to the lack of suitable veins or scar. The results of the present study show that in these situations MPP or MZP could be considered. When applying a multi-LV pacing configuration these should be programmed with large electrode distance, since we found that MZP- and MPP-like configurations consisting of more widely spaced electrodes yielded higher acute hemodynamic responses than more closely spaced combinations. This seems in line with the MORE-MPP study,[19] where it was shown that using MPP with a large anatomical separation of cathodal electrodes resulted in a larger conversion of non-responders to responders than MPP with small electrode distance. An implication of the present study is that the design of pacing leads for MPP and MZP may be adapted, to allow larger electrode spacing.

Impact on battery longevity

The impact of MPP and MZP on battery longevity might be a different reason to opt for BiVP over MPP or MZP. An IRON-MPP study sub-analysis showed that early MPP activation was associated with less than a 1-year reduction in projected battery life compared to single-site biventricular pacing, with a follow-up of 1.9 ± 0.8 years.[20] In a small multicenter trial MPP also significantly shortened battery longevity for all three pacing capture threshold cut-offs.[21]

Limitations

The data from this pre-clinical porcine model should be extrapolated with care to the clinical situation. The degree of dyssynchrony, created through ablation of the left bundle, is relatively small in porcine hearts[22], also evidenced for example by a QRS duration of 93 ms during LBBB (instead of ~50 ms before LBBB) in the present study. From previous studies in our laboratory, it is known that a more severe degree of dyssynchrony can be achieved in canine hearts.[23] However, experiments in dogs are becoming increasingly scrutinized due to ethical issues. Along with the smaller degree of dyssynchrony, also the AHR achievable by CRT is smaller in porcine hearts compared to canine hearts, yet several observations, like the better performance of LV lateral wall

sites over anterior or posterior wall sites mimick the clinical situation.
It was the advantage of the present study that it allows extensive and systematic comparison of the electrophysiologic and hemodynamic effects of MPP and MZP strategies, including different combinations of pacing sites and distances between pacing sites. The importance of the present study may also be illustrated by the fact that the authors are aware of only one publication on direct comparison of multiple LV configurations. In this clinical study no difference in AHR was found between MPP and multi-vein pacing, although ischemic cardiomyopathy patients were included.[9]
The present study was performed in a non-ischemic, acute (non-myopathic) LBBB model. Because different studies show conflicting results as to whether multiple LV pacing has a larger benefit in ischemic than in non-ischemic cardiomyopathy patients,[24,17], we opted for a non-ischemic model. This approach also allows to compare the AHR generated by sites that are considered to be best (i.e. lateral wall) with less optimal sites without a potential influence of a scar or ischemic region.
Two methods were used to create LBBB-like dyssynchrony model: in two cases where RF ablation for LBBB led to complete atrioventricular block RV free wall pacing was employed. These two approaches may have led to slightly different activation sequences, but extensive electrical mapping revealed no significant differences in wave front propagation or activation times.
Finally, acute effects as changes in LV dP/dtmax do not necessarily relate to long-term benefits of CRT.[25]

Conclusions

In this acute porcine LBBB model, multipoint and multi-zone pacing create a similar degree of electrical resynchronization and hemodynamic improvement. However, the acute hemodynamic response of MPP and MZP is only significantly better than conventional BiVP if the corresponding LV site provides poor hemodynamic improvement during BiVP. In MPP and MZP, a larger interelectrode distance increases the hemodynamic response.

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CHAPTER 4

Physiology and practicality of left ventricular septal pacing.

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Abstract

Left ventricular septal pacing (LVSP) and left bundle branch pacing (LBBP) have been introduced to maintain or correct interventricular and intraventricular (dys)synchrony. LVSP is hypothesized to produce a fairly physiological sequence of activation, since in the left ventricle (LV) the working myocardium is activated first at the LV endocardium in low septal and anterior free-wall regions. Animal studies as well as patient studies have demonstrated that LV function is maintained during LVSP at levels comparable to sinus rhythm with normal conduction. Left ventricular activation is more synchronous during LBBP compared to LVSP, but LBBP produces a higher level of intraventricular dyssynchrony compared to LVSP. While LVSP is fairly straight-forward to perform, targeting the left bundle branch area may be more challenging. Long-term effects of LVSP and LBBP are yet to be determined.
This review focusses on the physiology and practicality of LVSP and provides a guide for permanent LVSP implantation.

Introduction

The right ventricular (RV) apex has been the preferred site for ventricular lead placement since transvenous lead implantation for permanent pacing became available half a century ago.[1] The RV apex is easily accessible for implantation and yields chronically stable lead fixation and low capture thresholds. However, there are significant downsides to this technique. Pacing the RV apex results in a non-physiological dyssynchronous ventricular activation, frequently reducing left ventricular (LV) function in the long run.[2, 3] This so-called pacing-induced cardiomyopathy is associated with increased risk of atrial fibrillation (AF), heart failure and cardiovascular death.[4, 5]
In a search to prevent pacing induced cardiomyopathy, alternative pacing sites that maintain interventricular and intraventricular synchrony have been studied intensively. Among the alternative pacing sites biventricular pacing (BVP), His bundle pacing (HBP), and more recently, LV septal pacing (LVSP) and left bundle branch pacing (LBBP) have been introduced. In this review article we focus on the physiology and practicality of LVSP.

Adverse clinical effects of RV pacing

The fact that the different ventricular activation sequences induced by artificial electrical stimulation (pacing) influence cardiac pump function was already recognized by Wiggers et al. in 1925.[6] A subsequent study evaluated the effects of different sequences of ventricular activation on cardiac function in a canine model of complete heart block. This study demonstrated that the hemodynamically more effective LV pacemaker sites resulted in higher cardiac outputs than any of the RV sites tested.[7] The differences in cardiac performance between various ventricular pacemaker sites was best explained by varying degrees of dyssynchrony during ventricular contraction. These findings have later been confirmed in multiple animal studies, which showed that the abnormal electrical activation, induced by ventricular pacing, leads to a depression of systolic and diastolic LV function. The cause of this depression during abnormal electrical activation appears to be a combination of the non-physiological sequence of activation.[3]

The adverse effects of RV pacing in patients first became apparent in the MOST study, a randomized trial comparing DDDR with VVIR pacing in patients who requiring ventricular pacing because of bradycardia. In this study, in 1339 patients with a narrow QRS and preserved LVEF at baseline, it was shown that the percentage ventricular pacing was a strong predictor of heart failure (HF) hospitalizations and AF occurrence.[5]. Later, the DAVID trial demonstrated that for patients with an ICD indication and reduced LV ejection fraction but without an indication for cardiac pacing, dual-chamber

pacing (DDD-70) offered no clinical advantage over ventricular backup pacing (VVI-40). It was even shown that dual-chamber pacing was worse than ventricular back-up pacing with an increased combined end-point of death or hospitalization for heart failure.[8] Programming devices to dual-chamber pacing resulted in a ventricular pacing percentage of nearly 60% whereas this was only 1% with ventricular back-up pacing.

Physiological ventricular activation sequence

Under physiological circumstances, LV activation is initiated from the left bundle branch from three endocardial areas as depicted in figure 1: (1) an area high on the anterior paraseptal wall just below the attachment of the mitral valve, (2) a central area on the left surface of the interventricular septum (IVS); (3) the posterior paraseptal area at about one third of the distance from apex to base. In the IVS, activation proceeds from left to right, and in an apical-basal direction.[9] Although these results were found in perfused isolated hearts, they were confirmed in canine hearts in situ. The pattern of ventricular excitation, as judged from isochrone maps of sections of the hearts, did not change after isolation.[9]

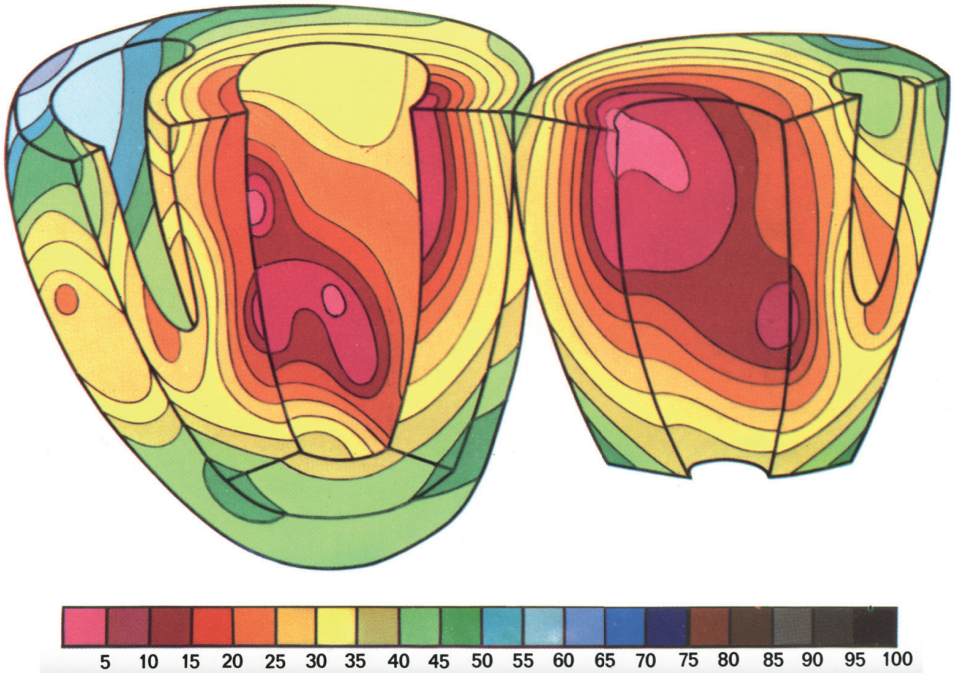


Figure 1. Three-dimensional isochronic representation of the ventricular activation in a human isolated heart. Color scheme shows activation time in milliseconds. Modified from Durrer et al. [9]

Also, it was demonstrated that the activation wave front spreads much faster around the endocardium than the spread toward the epicardium. In other words, endocardial conduction was found to be much faster than the endocardium-to-epicardium spread of depolarization. Later, more detailed analysis of the spread of activation wave fronts and the distribution of stimulus potentials after epicardial stimulation and endocardial stimulation were performed.[10-12] These studies confirmed earlier findings of preferential current flow and more rapid conduction velocity along the myocardial fiber orientation. Subsequent studies showed that myocardial fibers rotate between the epicardial and endocardial surfaces, while most of the endocardial surface contains a layer of Purkinje tissue electrically continuous with the myocardium.[13, 14] This potentially is one of the major contributing factors that causes endocardial spread of activation to be faster than endocardium-to-epicardium spread.

LV endocardial pacing

The sequence of ventricular activation is strongly dependent on the pacing site. Already in 1988, a study on transmural activations showed that there is a close correlation between fiber orientation and the spread of activation within the same plane for (sub) endocardial, midmyocardial and (sub)epicardial stimulation. Also, conduction velocities were faster for endocardial than for midmyocardial and epicardial stimulation.[15] Moreover, activation wave front spread and conduction velocity during endocardial pacing were found to be similar to that during sinus rhythm. Later, it was also shown that endocardial pacing increased the benefits of cardiac resynchronization therapy (CRT) compared to epicardial pacing in a canine model of acute left bundle branch block (LBBB).[16] Epicardial and endocardial mapping revealed that endocardial BVP reduced the total activation time more than epicardial BVP. Endocardial LV only pacing resulted in fairly synchronous LV activation, whereas during epicardial LV pacing large differences in electrical activation times occurred, as shown in figure 2. As a results, three possible mechanisms explaining the more rapid electric activation during endocardial pacing were proposed: (1) shorter path length of conduction, (2) faster endocardial than epicardial conduction, and (3) faster conduction from endocardium to epicardium than vice versa.

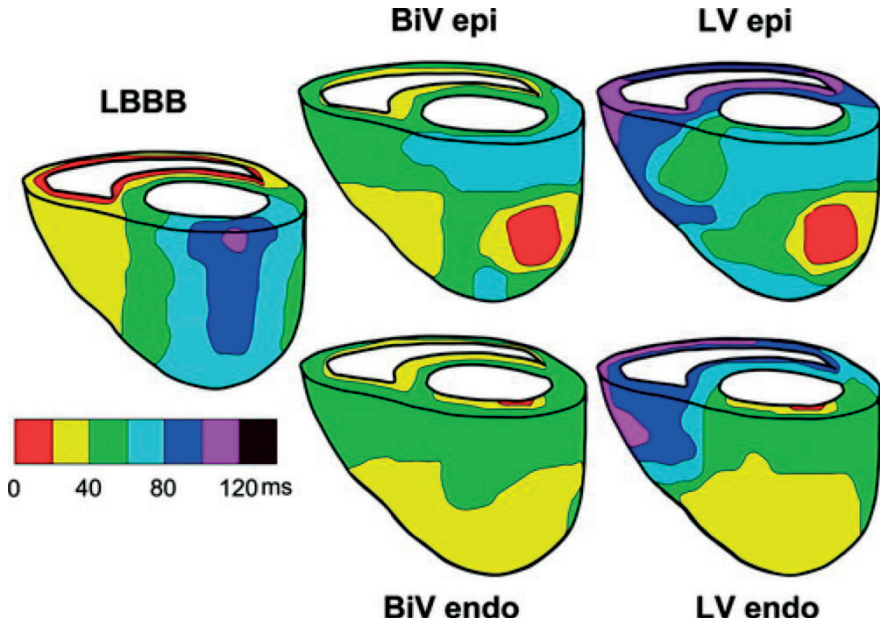


Figure 2. Three-dimensional reconstruction of electrical activation times in the right and left ventricle, as measured with epicardial and endocardial electrodes. The left ventricular pacing site was the mid-lateral wall. Color bar indicates time scale in milliseconds. Reproduced from Van Deursen et al. [16]

Pre-clinical studies on left ventricular septal pacing

In a study on ventricular activation and contraction patterns during ventricular pacing it was demonstrated that, unlike pacing any site in the RV, pacing the left side of the IVS (LV septal pacing) resulted in findings similar to those seen in normal sinus rhythm: the IVS was activated from left to right, LV pressure rise preceded right ventricular pressure rise, and there was a normal IVS contraction pattern.[17]. A subsequent study found that cardiac function in terms of LV stroke volume and LV dP/dtmax was better during LVSP when compared to RV pacing.[18] The fact that LVSP maintained cardiac function at a level comparable to normal ventricular activation during sinus rhythm while QRS duration was prolonged, confirmed the earlier hypothesis that LV function is dependent on the sequence of activation and not only on the duration of electrical activation. This is later confirmed in animal studies with extensive epicardial mapping and pace protocols. In these studies, multi-LV pacing considerably reduced LV activation time (compared to single-LV pacing), but the improvement in contractility by multi-LV pacing was limited to conditions where single-LV pacing provided only suboptimal improvement.[19, 20]

The activation sequence leading to the best LV pump function is that occurring during sinus rhythm with normal ventricular activation via the His-Purkinje system. Under these physiological circumstances, the electrical impulse exits the Purkinje system at sites located at the LV endocardial surface of the septum. It was therefore hypothesized that pacing near LV exit sites of the Purkinje system results in most physiological activation and near-normal LV function. An LV pressure-volume analysis of the comparison between RV pacing and various sites within the LV showed indeed that LV function was maintained during LVSP when compared to normal ventricular activation,[21] even though activation duration was longer (wide QRS). This finding again suggests that a good sequence of electrical activation is sufficient to allow for good LV function.
As a considerable part of the total dyssynchrony in left bundle branch block (LBBB) hearts originates from the delay in conduction across the interventricular septum, a possible role for LVSP was also explored in CRT. In both ischemic and non-ischemic LBBB hearts, LVSP significantly increased LV function as compared to baseline LBBB.[22]

After the demonstration of the acute beneficial hemodynamic effects of LVSP, chronic effects of LVSP were studied in canine hearts after 4 months of pacing.[23] Again, it was demonstrated that LVSP led to a rapid activation around the LV endocardium, resulting in a pattern that, of all tested pacing sites, most closely resembled the pattern during normal ventricular activation, although RV activation was somewhat delayed. MRI tagging measurements were performed in order to evaluate myocardial strains, work, and indices of global mechanical discoordination (internal stretch fraction) and dyssynchrony (time to peak shortening). The contraction pattern was very similar between normal ventricular activation and during LVSP. The pattern of regional time to peak shortening (earliest peak shortening was always observed in the lateral region and shortly thereafter observed in the other three quadrants) was identical for LVSP and normal activation. Also, the myocardial oxygen consumption and perfusion were determined. , LVSP did not significantly alter regional perfusion nor the distribution of regional myocardial work.[23] Altogether, MRI tagging analysis showed that LVSP resulted in a homogenous distribution of systolic shortening in time, space, and amplitude, as shown in figure 3.

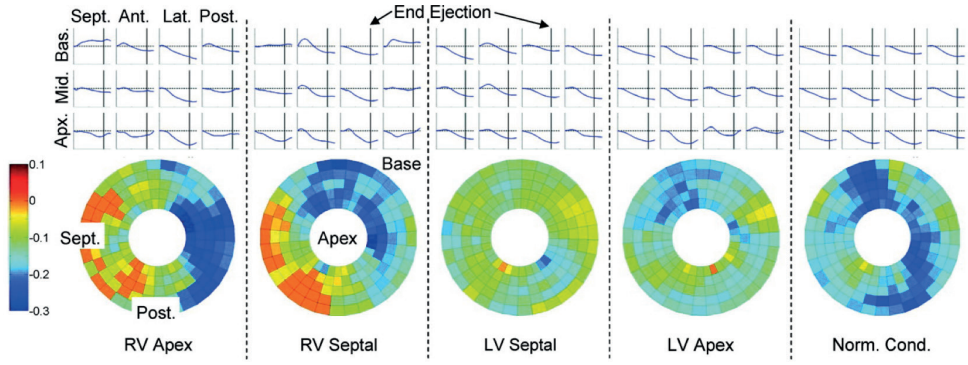


Figure 3. Typical example of LV regional circumferential strain signals and bull's eye plots of systolic shortening during pacing and normal conduction. LV septal pacing produces a more homogenous distribution of systolic shortening compared to RV pacing.
Upper panels show the strain signals from 12 regions of the LV wall. Horizontal (time) axis starts at 15 ms after R-wave trigger. Vertical lines denote end ejection. Vertical (strain) axis ranges from +0.2 to –0.2, equivalent to 20% stretch and shortening, respectively. Lower panels show the distribution of systolic strain in the LV wall, as determined in the 160 regions (5 short-axis slices, 32 regions per slice). Modified from Mills et al.[23]

Besides the synchrony of ventricular contraction, temporal changes in hemodynamics and efficiency of LVSP were studied. Acutely after onset of pacing as well as after 16 weeks, LV contractility and relaxation were comparable between LVSP and normal activation and LVSP maintained native interventricular dyssynchrony.[23]

Left ventricular septal pacing in patients

After preclinical studies successfully demonstrated long-term stability of the LVSP lead, the feasibility of permanently implanting an LV septal lead using the transvenous approach needed to be evaluated in patients.[24] But also, the acute hemodynamic effects of LVSP were studied. In patients with structurally normal hearts with mainly a pacing indication because of sick sinus syndrome, it was demonstrated that LVSP maintained LVdP/dtmax to levels comparable to baseline atrial pacing.[24] Importantly, the acute hemodynamic benefit of LVSP over RV apex and RV septal pacing was consistently observed in all patients. RVSP resulted in a QRS duration of 165±17 ms, while this was 144±20ms during LVSP. The large difference in QRS duration and hemodynamic effect between RVSP and LVSP, despite the fact that these sites were only ~1 cm apart, has been related to a significant delay in transseptal conduction during RV septal pacing, which causes considerably later LV mechanical activation and delayed contraction LV lateral wall, thereby inducing both inter- and intraventricular dyssynchrony.[25]

As a beneficial hemodynamic effect of LVSP was demonstrated in canine LBBB hearts, LVSP was subsequently studied as an alternative for CRT in patients. An acute hemodynamic pacing study comparing LVSP with BVP was performed in 12 patients with heart failure and an indication for CRT. The acute hemodynamic effect in these patients in terms of LVdP/dtmax was comparable between LVSP and BVP.[22] More recently, a more extensive electrophysiological and hemodynamic study was performed in which the acute effects of LVSP were compared with BVP and HBP in CRT patients.[26] LVSP was performed with an EP catheter that was temporarily positioned, retrogradely through the aorta, on the left side of the interventricular septum. The study showed that QRS duration was similarly reduced by LVSP and BVP, but was even further reduced by HBP. In contrast to BVP, LVSP and LBBP, HBP does not produce (additional) ventricular dyssynchrony and QRS duration is therefore shortest during HBP. Although in LBBP the native His-Purkinje system is engaged, QRS duration is similar in LVSP and LBBP. This is due to the fact that both LVSP and LBBP, while restoring LV activation, induce delayed RV activation, of which the hemodynamic and long-term effects are unknown and need to be carefully evaluated in future studies. Interestingly, both QRS area and SDAT, two measures of ventricular dyssynchrony, were significantly smaller during LVSP than BVP, and were comparable to HBP (figure 4). Also, the increase in LV function (~18%) in these CRT patients, determined by invasive LV dP/dtmax measurements, was comparable for BVP, LVSP as well as HBP.

Another very interesting observation in the study was that no significant differences were found in the electrophysiological and hemodynamic effects of LVSP at the basal, mid-, and apical LV septum levels. This finding supports the hypothesis that pacing the LV at the endocardium results in fast endocardial spread of activation, probably not necessarily Purkinje fibers, providing a rather physiological LV activation.

LVSP has been demonstrated to have beneficial hemodynamic and electrophysiological effects, in both animal and patient studies. The hypothesis of the beneficial effects of LVSP are summarized in figure 5. LVSP provides LV synchrony, based on (1) shorter path length of conduction compared to epicardial pacing, (2) faster endocardial than epicardial conduction, and (3) faster conduction from endocardium to epicardium than vice versa. Furthermore, LVSP avoids the coronary sinus, phrenic nerve stimulation and posterolateral scar in CRT patients.

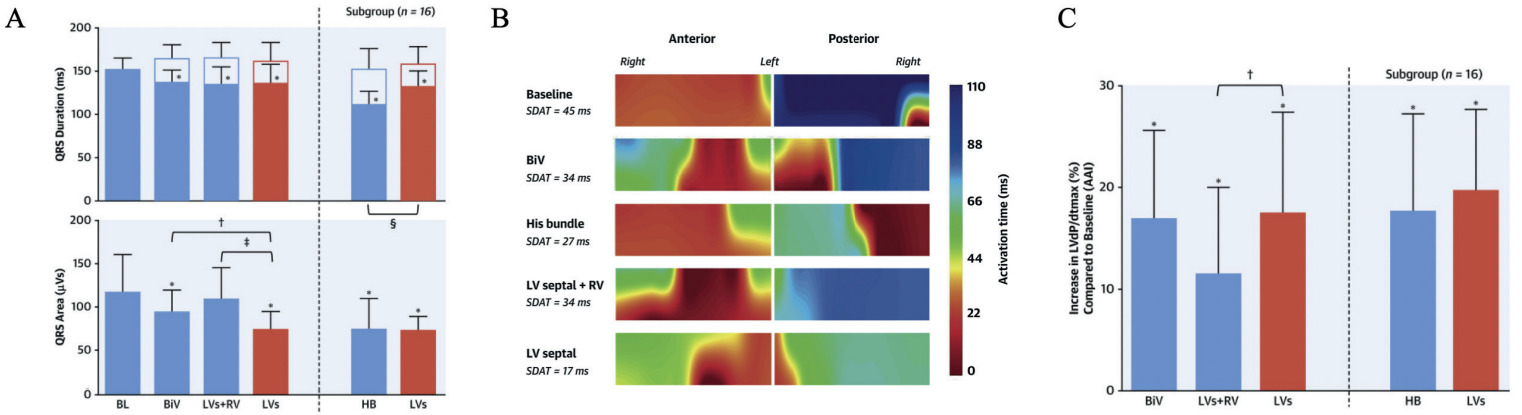
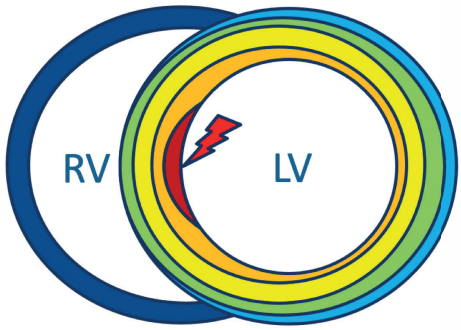


Figure 4. Panel **A:** Electrophysiological Effects. QRS duration as time between QRS beginning and end (closed bars) and as time from pacing stimulus to QRS end (open bars) (upper panel) and QRS area (lower panel) during baseline (BL), conventional BVP, LVSP in combination with RV, and LVSP alone and in a subgroup (n = 16) during HBP and LVSP. Results are presented as mean ± SD. *p < 0.05 versus BL; †p < 0.05 BVP versus LVSP; ‡p < 0.05 LVSP+RV versus LVSP; §p < 0.05 HB versus LVSP.

Panel **B.** Isochronal maps. Examples of isochronal maps with corresponding standard deviation of activation times (SDAT) during baseline (BL), conventional BVP, LVSP in combination with RV, and LVSP alone.

Panel **C:** Hemodynamic Effects. Relative change in LVdP/dtmax compared with baseline (n = 27) during BVP, LVSP in combination with RV, and LVSP alone and in a subgroup (n = 16) during HBP and LVSP. Results are presented as mean ± SD. *p < 0.05 versus BL; †p < 0.05 LVSP+RV versus LVSP. Modified from Salden et al.[26]



Benefits of LV septal pacing:

1. Compensation of slow transseptal conduction
2. Short path length of conduction
3. Fast endocardial conduction (fast conducting endocardial, non-Purkinje fibers)
4. Faster endo-to-epi conduction than vice versa
5. Avoiding
    1. Phrenic nerve stimulation
    2. Coronary sinus catheterization
    3. Posterolateral wall scar

Figure 5. Left ventricular septal pacing. Left panel: Schematic transversal overview of ventricular activation during LV septal pacing. Red color indicates early activation, blue color indicates late activation. Right panel: summary of benefits op left ventricular septal pacing.

Practicality of LV septal pacing

Initial animal studies investigating LVSP were performed using plunge electrodes, where the LV septal endocardium was reached by puncturing the RV free wall and subsequently the interventricular septum.[21, 22] Later, the clinical studies investigating the acute electrophysiological and hemodynamic effects of LVSP were performed using a steerable electrophysiology catheter advanced retrogradely through the aorta into the LV.[22, 26]

In order to be able to investigate electric activation, mechanics, hemodynamic performance, and efficiency of long-term LVSP, a customized pacing lead (Medtronic 3830 lead) with extended helix was used.[23, 24] This Medtronic 09066 lead, a modified 3830 lead with prolonged 4 mm screw, was introduced transvenously and, after positioning against the RV septum using a preshaped guiding catheter (Medtronic C315His), driven through the IVS until the LV endocardium was reached. When this investigational lead was successfully implanted in animal studies with stable lead measurements for over 4 months, the lead was implanted in 10 patients with sinus node dysfunction, using the same transvenous approach and positioning the lead deep into the IVS.[24] In this first-in-man study of chronic LVSP, a 7-Fr preshaped guiding catheter (Model C315-S10; Medtronic Inc) was used, since its specific shape that was used so far for HBP allowing positioning of the catheter tip perpendicularly against the IVS. Then, the implanter, using RAO and LAO views, positioned the tip of the lead to the middle of the IVS guided by an RV angiogram. In the initial procedures, intracardiac echocardiography was used to verify the position of the lead tip on the IVS before screwing the lead into the IVS. Positioning of the lead mid-ventricular in the IVS is different from the more recently applied left bundle branch pacing (LBBP), where the lead is placed closer to

the anatomical level of the His bundle. Importantly, capture of the left conduction system was not studied nor pursued in this study. While rotating the lead, the implanter repeatedly assessed the IVS penetration depth by injecting small amounts of contrast medium through the guiding catheter against the IVS under fluoroscopy in LAO. In addition, pacing was repeatedly performed from the tip electrode while advancing the helix through the IVS to assess changes in paced QRS morphology that indicated that the left side of the IVS had been reached, i.e. a right bundle branch block-like QRS morphology. Pacing thresholds and impedances were measured to ensure that the helix did not protrude in the LV cavity. Implantation characteristics of the patient study are summarized in figure 6.

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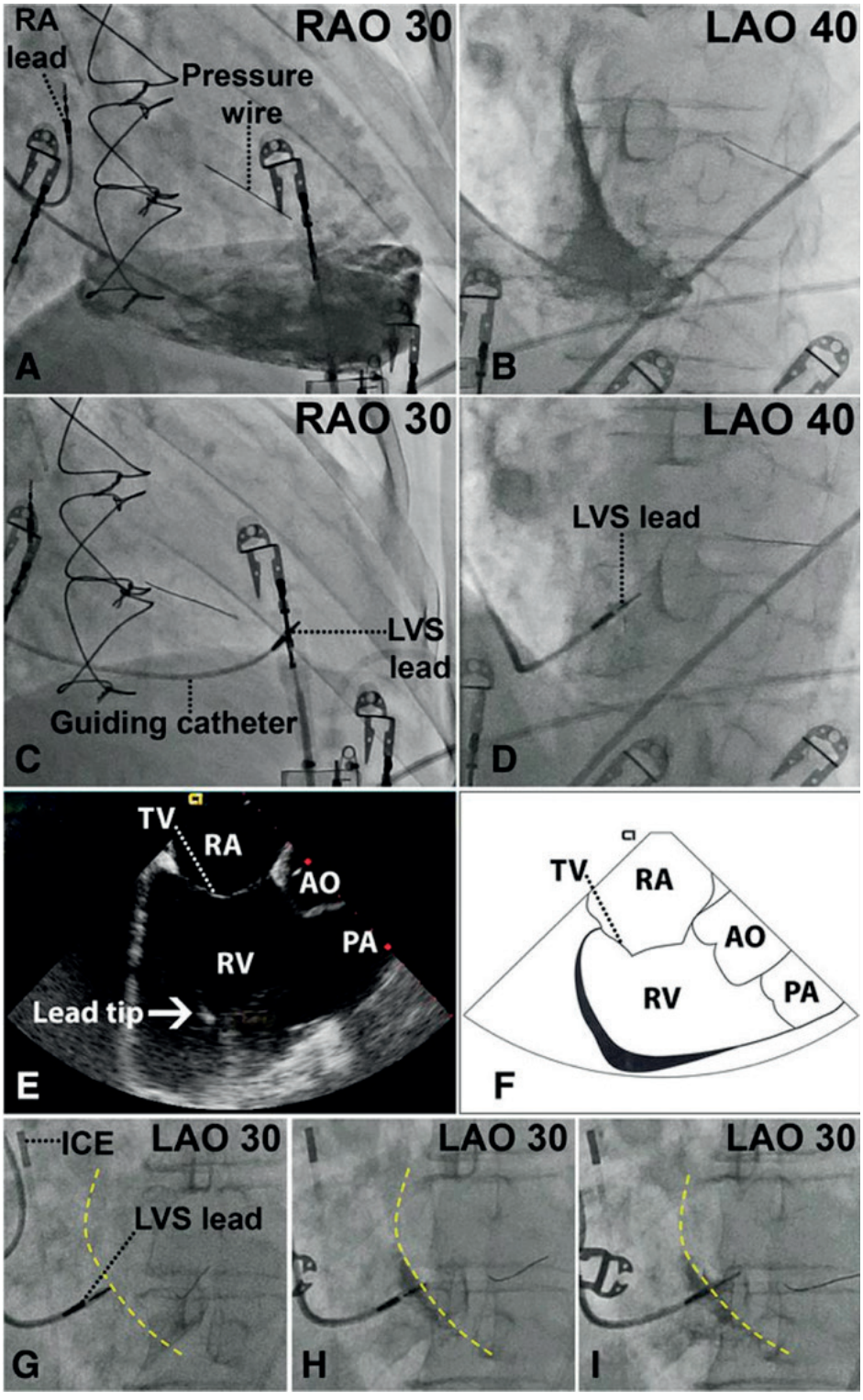
Figure 6. Images of the implantation procedure. The atrial lead is positioned in the right atrial (RA) appendage and a Certus Pressure Wire is positioned in the left ventricle (LV) for acute hemodynamic measurements (**A**). A right ventricular (RV) angiogram is performed in right anterior oblique (RAO; **A***)* and left anterior oblique (LAO; ***B***). The custom left ventricular septal (LVS) pacing lead is positioned perpendicularly against the interventricular septum (IVS) using a preshaped guiding catheter (**C**). The tip of the lead is positioned as close to the middle of the IVS as possible by using fluoroscopy in both RAO (**C**) and LAO (**D***)* with reference to the corresponding RV angiogram (**A** and **B**). Intracardiac echocardiography ultrasound catheter (ICE) is used to verify the position of the lead tip on the IVS achieved using fluoroscopy before screwing the lead into the IVS (**E**). The intracardiac echocardiogram shows the RV in a long-axis view that parallels the septum with the lead tip located at midlevel between the apex and base and the anterior and posterior border of the RV. **F**: A schematic representation of the intracardiac echocardiogram. After proper positioning of the LVS lead on the IVS, the lead is screwed through to the left side of the IVS. **G**: *T*he tip of the lead resting perpendicular against the IVS (indicated by the dashed yellow line) before screwing the lead in. While rotating the lead, repeated hand injections of contrast medium through the guiding catheter against the IVS are used to assess the penetration depth (**H** and **I**). The part of the lead tip that protrudes into the IVS is not covered by contrast medium. Based on beforehand knowledge of the lead tip dimensions and the patient's IVS wall thickness, this provides an estimation of penetration depth in the IVS. AO indicates aorta; PA, pulmonary artery; and TV, tricuspid valve. Modified from Mafi-Rad et al.[24]


RA lead
RAO 30
Pressure wire
A
LAO 40
B
RAO 30
LVS lead
Guiding catheter
C
LAO 40
LVS lead
D
TV
RA
AO
PA
RV
Lead tip
E
TV
RA
AO
RV
PA
F
ICE
LAO 30
LVS lead
G
LAO 30
H
LAO 30
I

Practical limitations to LVSP

Although the initial studies on chronic LVSP were performed with a modified version of the Medtronic 3830 lead (extended helix), it was recently shown that penetration of the septum was possible using the standard Medtronic 3830 lead,[27] which is the most frequently used lead nowadays. Despite the straight-forward implantation procedure, there are factors possibly complicating a successful implantation. LVSP lead implantation failure is likely due to difficulty in lead fixation, which is usually caused by septal hypertrophy and/or scar/fibrosis. Also, tissue lodging into the helix induced by the drill-effect and insufficient sheath support/reach is an issue. Advances in dedicated implantation tools may overcome some of these practical issues. Structural evaluation of the heart, especially the interventricular septum thickness and the presence of septal scar can be beneficial. In the presence of septal hypertrophy or scar, reaching the far subendocardium, where the left bundle branch(es) is situated, can be very challenging. In these cases, LVSP can be of particular benefit since the more complicated targeting of the His-Purkinje system is not required. A recently published study investigating ventricular synchrony during transventricular pacing demonstrated that deep LVSP produces LV synchrony comparable to LBBP.[28]

LV septal pacing versus left bundle branch pacing

Left bundle branch area pacing (LBBAP; LVSP & LBBP) has recently been introduced as alternative method of conduction system pacing to maintain left ventricular synchrony.[27] Multiple studies have demonstrated the safety and feasibility of LBBAP. However, reported left bundle branch capture rates differ, but are usually between 60% and 90%.[28-30] Consequently, up to one-third of patients who are reported to be treated with LBBP, are in fact treated with LVSP.

Unlike LVSP, LBBP and HBP engage the intrinsic His–Purkinje system and LBBP has been demonstrated to maintain ventricular synchrony at levels comparable to HBP and even to intrinsic ventricular activation.[31-35] Non-selective HBP, however, is claimed by some to be less beneficial. A possible explanation could be capture of only the right bundle branch, since published data suggest benefit in patients receiving either selective or non-selective HBP and ultra-high frequency ECG analysis demonstrated that both types of His bundle capture preserve ventricular electrical synchrony.[36] Capture of the right bundle branch without the left bundle branch results in delayed LV activation. In (especially selective) LBBP, there is delayed RV activation; but this is likely to have less clinical implication (RBBB patients versus LBBB patients). In contrast, LVSP results in direct left-to-right septal activation and interventricular dyssynchrony is less in LVSP compared to LBBP.[37]

A recently published study on the comparison between LBBAP with and without evidence of direct capture of the left conduction system, showed that LV dyssynchrony

is comparable between LVSP and LBBP.[28] This study showed that, compared to RV pacing, QRS area and LVAT (now referred to as V6RWPT) decrease while advancing the lead towards the LV subendocardium. A reasonably acceptable level of ventricular dyssynchrony is achieved when an R' (right bundle branch block-like QRS morphology) becomes apparent in lead V1. The R' in lead V1 indicates delayed RV activation and therefore suggest that the left part of the IVS is reached. A significantly lower QRS area during LBBP compared to LVSP was found, although the absolute difference was small. Another recent study compared differences in ventricular depolarization between LVSP and LBBP using ultra-high-frequency ECG (UHF-ECG).[37] UHF-ECG analysis showed that although LBBP accelerates left ventricular lateral wall depolarization compared to LVSP, LBBP results in greater interventricular dyssynchrony. Interventricular dyssynchrony is less in LVSP compared to LBBP, since left-to-right transseptal depolarization occurs immediately after pacing and left subendocardial Purkinje fibers are captured later, which results in a more balanced ventricular depolarization.[37]

Developments in the transseptal approach

As with all new techniques, implantation of the ventricular lead via the transseptal approach is subject to development. In the initial patient study that demonstrated the feasibility of LVSP, total procedure time decreased from 237 minutes in the first patient to 83 minutes in the last. RV angiography and intracardiac echocardiography was performed in order to verify the position of the lead tip on the IVS before screwing the lead into the IVS.[24] The experiences gained during this study taught us that with the pre-shaped guiding catheters leads were always directed towards the septum and that the additional RV angiogram and intracardiac echocardiogram is not necessary, thereby facilitating the procedure.

The method as described by Huang et al. to perform permanent LBBP and evaluate left bundle branch capture is rather complex as it requires relatively advanced electrophysiological knowledge and electrophysiological equipment in the cathlab.[38] The technique calls for simultaneously recording of the 12-lead ECG and intracardiac EGMs from the lead tip for the assessment of paced QRS morphology and measurement of intervals, while carefully advancing the lead transseptally. Also, the His bundle potential is searched for as reference point and the left bundle branch potential needs to be recorded. Furthermore, multiple repeated measurements are required in order to diagnose capture of the left bundle branch.[39]

In contrast, the LVSP implantation procedure is fairly straight-forward to perform as the specialized His-Purkinje system is not specifically targeted. As the exact septal position of the lead in LVSP is less critical compared to LBBP, there is no need for the recording of a His bundle or left bundle branch potential. After perpendicularly positioning of the lead against the septum, the lead is fixated somewhere in the basal to mid-level of the

septum. The tricuspid valve annulus, visible on standard fluoroscopy imaging, is used as anatomical marker. The paced QRS morphology, visible on standard 12-lead ECG recording, is used to determine whether the initial position on the RV septum is valid. Preferably, a QRS morphology with a positive QRS complex in lead I and II and a negative QRS complex in lead III is seen while pacing the RV septum. Advancement of the lead through the septum is guided by QRS morphology, especially in lead V1, either via continuous pacing[40] or by evaluating ectopic ventricular beats occurring during lead rotations for deep intraseptal deployment (fixation beats).[41] The suitability of the final lead position can be determined from the standard 12-lead ECG, where preferably a paced "qR" morphology in lead V1 is seen, indicating the lead is deployed deep within the left septum. Besides the right bundle branch block-like QRS morphology induced by left-sided septal pacing, deep septal deployment can also be confirmed by septal contrast angiography. QRS duration during LVSP is comparable to BVP and LBBP,[22, 28, 37] but prolonged compared to HBP.[26] A flow-chart for performing LVSP is shown in figure 7.

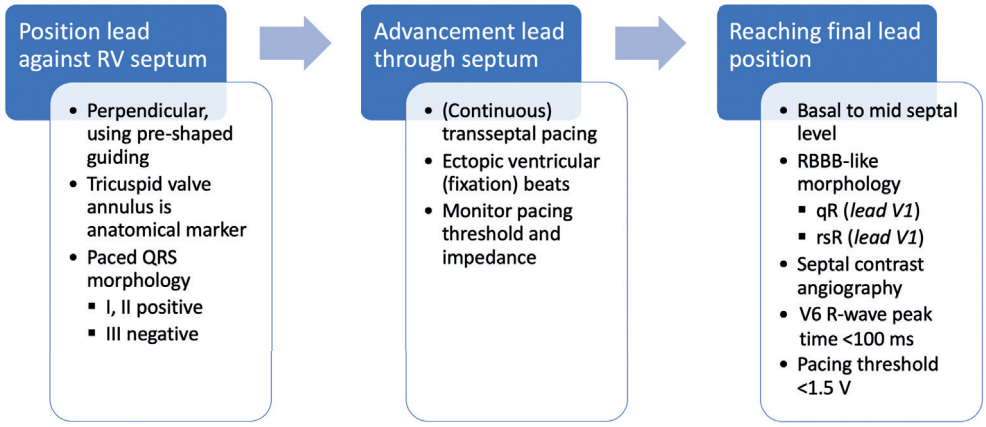


Figure 7. Flow-chart for performing left ventricular septal pacing. RV = right ventricle. RBBB = right bundle branch block.

Conclusion

The severity of impairment of ventricular function induced by pacing is largely dependent on the site of pacing. The conventionally and frequently applied RV apex is a reliable and easy to reach position, but – in a subset of patients – can increase cardiac morbidity and mortality. Recently investigated techniques of pacing, such as LVSP and LBBP seek to avoid pacing induced cardiomyopathy leading to this increase. LVSP provides

ventricular synchrony, based on compensation of slow transseptal conduction, short path length of conduction and fast endocardial conduction and has been demonstrated to result in acute electrocardiographic and vectorcardiographic results comparable to BVP. LVSP can be a valuable alternative to LBBP, especially in patients where capture of the left bundle branch is impeded. The long-term clinical effects of LVSP and LBBP and the differences between them are still unknown and need to be investigated.

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CHAPTER 5

A single-centre prospective evaluation of left bundle branch area implantation characteristics.

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Abstract

Background: Left bundle branch area pacing (LBBAP) has recently been introduced as a physiological pacing technique with a synchronous left ventricular activation. It was our aim to evaluate the feasibility and learning curve, as well as the electrical characteristics of LBBAP.

Methods/Results: LBBAP was attempted in 80 consecutive patients and ECG characteristics were evaluated during intrinsic rhythm, RV septum pacing (RVSP) and LBBAP. Permanent lead implantation was successful in 77/80 patients (96%). LBBAP lead implantation time and fluoroscopy time shortened significantly from 33±16 and 21±13 min to 17±5 and 12±7 min, respectively, from the first 20 to the last 20 patients. Left bundle branch (LBB) capture was obtained in 54/80 patients (68%). In 36/45 patients (80%) with intact AV conduction and narrow QRS, an LBB potential (LBB_{pot}) was present with an LBB_{pot} to onset QRS interval of 22±6 ms. QRS duration increased significantly more during RVSP (141±20 ms) than during LBBAP (125±19 ms), compared to 130±30 ms without pacing. An even clearer difference was observed for QRS area, which significantly increased more during RVSP (from 32±16 μVs to 73±20 μVs) than during LBBPAP (41±15 μVs). QRS area was significantly lower in patients with LBB capture compared to patients without LBB capture (43±18 μVs vs. 54±21 μVs, respectively).
In patients with LBB capture (n=54), the interval from the pacing stimulus to R-wave peak time in lead V6 (RWPT V6) was significantly shorter compared to patients without LBB capture (75±14 vs. 88±9 ms, respectively).

Conclusion: LBBAP is a safe and feasible technique, with a clear learning curve that seems to flatten after 40-60 implantations. LBB capture is obtained in two-thirds of patients. Compared to RVSP, LBBAP largely maintains ventricular electrical synchrony to values close to intrinsic (narrow QRS) rhythm.

Introduction

Right ventricular (RV) pacing is a frequently applied therapy in patients without a reversible cause of bradyarrhythmia. RV apex (RVA) pacing produces a non-physiological activation sequence,(1) which can lead to adverse remodelling potentially inducing atrial fibrillation, heart failure and cardiovascular death.(2, 3)
In search for a therapy which avoids these detrimental effects of artificial stimulation, there is increasing interest in pacing techniques that directly activate the specialized conduction system. One of these so-called conduction system pacing (CSP) techniques is His bundle pacing (HBP). Since the first application of permanent HBP by Deshmukh and colleagues,(4) HBP has proven to be a safe and feasible technique, especially in patients requiring treatment for bradyarrhythmia.(5, 6) HBP encounters some limitations, such as high and unstable pacing thresholds and relatively low R-wave amplitude, complicating pacemaker programming.(7, 8) Furthermore, the procedure is technically challenging and distal conduction block could potentially occur. These limitations seem to limit widespread application in routine clinical practice.
An alternative to HBP is left bundle branch area pacing (LBBAP). After it was previously shown that it is possible to reach the left side of the interventricular septum (IVS),(9, 10) it was more recently shown that it is even possible to capture the left bundle branch (LBB) with the same pacing electrode that is currently mostly used for HBP. LBBAP seems to have the advantage to overcome some limitations of HBP while preserving activation of the specialized conduction system

The aim of our study was to prospectively evaluate 1) the feasibility and learning curve of LBBAP implantation, in a specialized centre with some experience in HBP, 2) demonstrate the level of electrical synchrony produced by LBBAP, and 3) evaluate current LBB capture criteria in patients undergoing pacemaker implantation for either bradycardia treatment or as bail-out strategy in case of failed LV lead implantation.

Methods

The study was performed at Maastricht University Medical Centre (Maastricht, the Netherlands) in patients undergoing an attempt at LBBAP for either bradycardia treatment or as bail-out strategy in case of failed LV lead implantation. The local ethics committee and Institutional Review Board approved the study protocol (METC 2019-1313) and all patients provided written informed consent. Patients were prospectively enrolled from December 2019 till December 2020.

Patient selection

All patients undergoing permanent pacemaker implantation who underwent an attempt at LBBAP were included. Patients underwent LBBAP because of bradycardia (sinus node dysfunction or AV-block), as part of ablate and pace strategy in permanent atrial fibrillation, and LBBAP was attempted in some patients with indication for cardiac resynchronization therapy (CRT) if previous implantation of the LV lead or His bundle lead had failed.

Implantation procedure

The LBBAP implantation procedure was performed as described previously.(11) In short, the right atrial (RA) lead (if implanted) was implanted according to routine clinical practice. In case of underlying left bundle branch block (LBBB), the RA lead was temporarily placed in the RV, ensuring the possibility of back-up pacing in case of manipulation induced total AV-block.

The ventricular pacing lead (Medtronic 3830 lead) that was used for LBBAP was positioned using the C315His sheath in all patients. An intracardiac electrogram was recorded from the lead tip in a unipolar fashion using an electrophysiological recording system (Labsystem Pro, Boston Scientific, MA, USA). First, the His bundle electrogram was identified in the right anterior oblique (RAO) 20-25° position and a fluoroscopic image was recorded as a reference (figure 1 Electronic Supplementary Material, upper left). Subsequently, the sheath and lead were advanced 1–2 cm toward the RVA (figure 1 Electronic Supplementary Material, upper right). In this region, unipolar pacing was performed aiming for a paced QRS morphology with a notch in the nadir in lead V1, resembling a "W" (figure 2a Electronic Supplementary Material). Alongside this notched QRS complex in lead V1, a positive QRS complex in lead II and negative complex in lead III are good indicators for an appropriate position. At this site, the lead was fixated in the RV septum with 1-2 rotations and then advanced to the left side of the IVS in a left anterior oblique (LAO) view (figure 2b-e Electronic Supplementary Material). In the process of advancing the pacing lead, fluoroscopy, pacing threshold and lead impedance, the paced QRS morphology, and the presence and morphology of fixation beats were monitored to estimate the depth of the lead avoiding perforation of IVS.(12)

The number of attempts to implant the lead in the IVS as well as the final position were left to the discretion of the implanting cardiologist. Capture of the LBB (trunk or proximal fascicles) was attempted in all patients.

Pacing and capture definitions

LBB capture can be demonstrated through several mechanisms, such as the presence of a transition from myocardial capture to conduction system capture (or vice versa) during threshold testing, by measuring the LBB potential-R-wave peak time in lead

V6 (V6RWPT) interval(13) or through programmed stimulation, (14) or making use of the difference in effective refractory period between myocardium and the specialized conductive tissue.
Other common characteristics of LBB pacing are: 1) paced (pseudo) right bundle branch block (RBBB) QRS morphology with terminal r/R' in lead V1; 2) recording of an LBB potential during intrinsic rhythm (only in patients with intact atrio-ventricular conduction); 3) constant stimulus to V6RWPT during high (8V) and low (2V) pacing output.

In our study, left bundle branch capture was diagnosed in case one (or both) of the following criteria were met:

1) the presence of a transition from non-selective LBBP (ns-LBBP) to selective LBBP (s-LBBP) or from ns-LBBP to LV myocardial only capture (=LVSP) during decreasing pacing output.
2) LBB potential-V6RWPT interval equals the pacing stimulus-V6RWPT interval. (13)

s-LBBP was defined as a change in QRS morphology without a change in V6RWPT when decreasing the pacing output from ns-LBBP, combined with a pacing artefact distinct from the ventricular EGM. ns-LBBP was defined as a change in QRS morphology which occurred after increasing the pacing output from s-LBBP or LVSP.
LVSP was defined as paced QRS morphology with r' present in lead V1 but without evidence of LBB capture.

Electrical measurements
12-lead ECGs were recorded during intrinsic rhythm, RV septal pacing (RVSP) and LBBAP. QRS duration was measured from onset of first deflection, thus excluding the pace spike. In case of present LBB potential, the interval between the LBB potential and QRS onset, as well as the interval between LBB potential and the R-wave peak in lead V6 were measured.
Fixation beats are defined as ectopic ventricular beats resulting from irritation of tissue as the lead crosses the septum. Ectopic beats with QRS complexes <120ms with qR/rsR' morphology in lead V1 are considered beats from the LBB area.
QRS area, a measure of ventricular electrical dyssynchrony,(15) was determined by converting the 2-dimensional ECG into a 3-dimensional vectorcardiogram (VCG). The VCG was synthesized as described previously.(15, 16) In brief, the original digital signals were extracted from the ECG files stored in the Bard system. Subsequently, custom Matlab software (MathWorks Inc, Natick, MA) was used to convert the 12-lead ECG into the 3 orthogonal vectorcardiographic leads (X, Y, and Z) using the Kors conversion matrix, (17) as shown in figure 1. QRS area was calculated as the sum of the area under

the QRS complex in the calculated vectorcardiographic X, Y, and Z leads (QRS area = $[QRS_{area,x}^{2}+QRS_{area,y}^{2}+QRS_{area,z}^{2}]^{1/2}$).

Data collection

Demographic data and medical history of all patients were collected at enrolment. Procedure related characteristics including ECG characteristics and intracardiac EGM patterns, fluoroscopy exposure time and doses were recorded during implantation. Pacing parameters (pacing threshold, pacing impedance, and R-wave amplitude) were measured immediately post-implantation and up to 1-year follow-up.

Safety endpoints

Major acute procedure-related adverse events such as bleeding, pneumo- and haemothorax, and cardiac tamponade were collected. Also, device and lead-related problems such as infection, perforation, dislodgement or dysfunction at any time during follow-up were recorded. Adverse event treatment was classified as re-intervention, prolonged hospitalization or death.

Statistical analysis

The number and percentage were used as descriptive statistics for categorical variables. Continuous variables were expressed as mean ± standard deviation. Differences between 2 groups were compared using the Student t-test for continuous variables. The paired t test was used to compare the differences between 2 means within the same group. Comparisons among ≥3 pacing conditions within individuals were made using repeated measures ANOVA with Bonferroni multiple comparisons procedure applied to pairwise comparisons. A 2-sided *P* value of <.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics version 25.0 (Chicago, IL, USA).

Results

Baseline characteristics

Eighty patients underwent permanent pacemaker implantation with an attempt for LBBAP. Patient characteristics are summarized in table 1. Mean age was 74±10 years and 59% of patients were men. A history of hypertension was recorded in 58% and coronary artery disease was present in 38% of patients. LV ejection fraction (LVEF) at baseline was 53±10% with a LVEF <50% in 18/80 patients (23%). Indication for pacemaker implantation was sinus node dysfunction in 27 patients (35%), AV-block in 32 patients (41%), AV-node ablation in 8 patients (10%), and CRT in 10 patients (13%).

Table 1. Baseline characteristics of the study population.

Characteristics (*n*=80)	**Mean ± SD or *n* (%).**
Male sex	47 (59%)
Age (years)	74±10
Medical history	
Hypertension	46 (58%)
Diabetes mellitus	16 (20%)
Atrial fibrillation	33 (41%)
Coronary artery disease	30 (38%)
LVEF <50%	18 (23%)
Echocardiographic parameters	
LVEF (%)	53±10
LV end diastolic diameter (mm)	51±7
LV end systolic diameter (mm)	37±7
IVS thickness (mm)	10±1
Electrocardiographic parameters	
Heart rate (bpm)	67±20
QRS duration (ms)	
all patients	116±31
intrinsic ventricular conduction	95±13 (n=45)
Other (escape, LBBB/RBBB, paced)	143±26 (n=35)
Pacemaker indication	
Sinus node dysfunction	27 (34%)
Atrioventricular block	32 (40%)
Atrial tachyarrhythmia requiring ablation	8 (10%)
Heart failure & prolonged QRS duration	10 (13%)

Procedural characteristics

All implantation procedures were performed using the C315His delivery catheter (Medtronic, MN, USA) and the SelectSecure 3830 lead (Medtronic, MN, USA). In 75/80 patients (94%) a de novo pacemaker implantation was performed. Permanent LBBAP lead implantation was successful in 77/80 patients (96%). In two patients with concentric LV hypertrophy, RV dilatation and known coronary artery disease, the ventricular lead could, after multiple attempts, not be advanced deep enough into the septum, resulting in broad paced QRS duration without evidence of at least deep (LV) septal pacing. In these patients, the lead was then positioned in the apico-septal region of the RV. In one patient with dilated RA, RV and LV, no stable LBBAP position could be achieved and this patient was converted to HBP, where selective His capture was achieved.

Total procedure time, defined as time from first incision to last suture, was 86±31 minutes and LBBAP lead implantation time was 25±13 minutes. The mean radiation time and dosage across all procedures was 17±11 min and 97±65 mGy, respectively. Implantation procedure times reduced with increasing LBBAP experience as shown in figure 1. The implantation time of the LBBAP lead reduced considerably from 33±15 minutes during the initial implantations to 17±5 minutes during the more recent implantations. Also, the associated fluoroscopy time was reduced significantly from 21±12 minutes to 13±7 minutes (figure 1B), illustrating the learning curve of LBBP implantation.

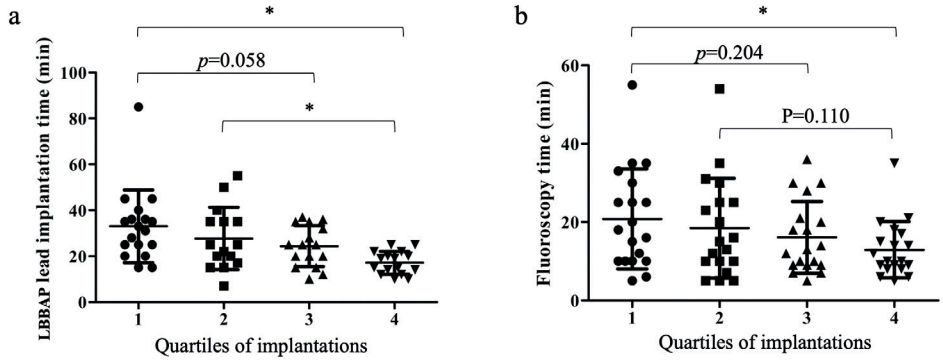

Figure 1. Comparison of left bundle branch area pacing lead implantation duration (**panel A**) and fluoroscopy time (**panel B**) in four quartiles of implantations.

Electrocardiographic characteristics

LBB capture, according to previously described criteria, was confirmed in 54/80 patients (68%). In patients with LBB capture, a transition from ns-LBBP to s-LBBP or vice versa (figure 3A Electronic Supplement Material) could be demonstrated in 37/54 patients (69%) during threshold testing. In 17/54 patients (31%), a transition from ns-LBBP to LVSP was observed (figure 3B Electronic Supplement Material). Out of 80 patients, 45 patients had intact atrio-ventricular conduction with narrow intrinsic QRS complex. In 36/45 patients (80%) a clear LBB potential was present. The interval between the LBB potential and the onset of QRS was 22±6 ms.

For all patients, QRS duration increased from 130±30 ms during intrinsic rhythm to 141±20 ms during RVSP and decreased to 125±19 during LBBAP. Final QRS duration was 124±20 ms in patients where LBB capture was achieved, and 130±24 ms in patients with LVSP (without LBB capture; P=0.397). QRS area significantly increased from 49±35 μVs during intrinsic rhythm to 80±22 μVs during RVSP. Compared to RVSP, QRS area decreased to 48±19 μVs during LBBAP.

Out of 80 patients, 35 patients had broad intrinsic QRS complex (18 escape rhythm, 7

complete LBBB, 3 left anterior fascicular block (LAFB), 1 left posterior fascicular block (LPFB), 4 RBBB, 2 RV paced). In patients with complete LBBB, QRS duration was significantly reduced from 155±17 ms during intrinsic rhythm to 135±14 ms during LBBAP, while QRS area was significantly reduced from 120±23 μVs during intrinsic LBBB to 49±10 μVs during LBBAP (figure 2).

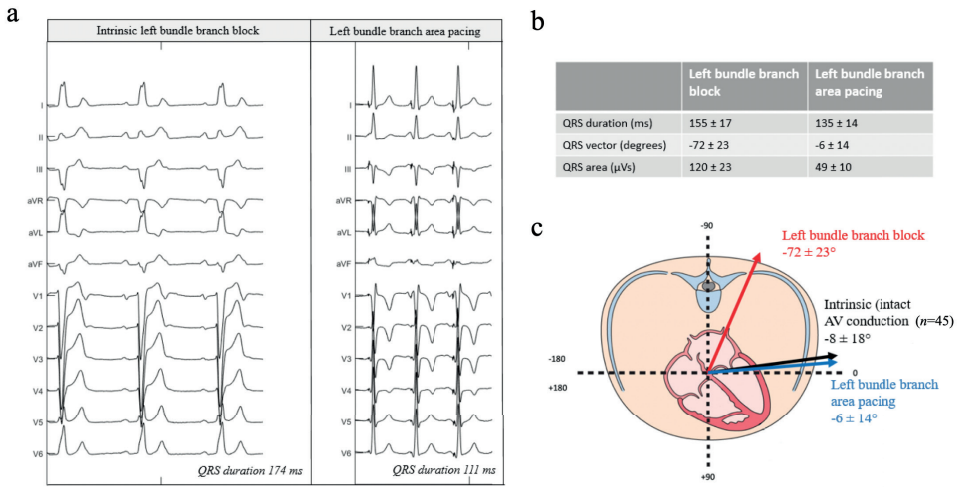

Figure 2. Electrical characteristics of left bundle branch block (LBBB) patients. **A**: Example of 12-lead ECG during intrinsic LBBB (left) and left bundle branch area pacing (right) in the same patient. **B**: Vectorcardiographic results of all LBBB patients (n=7). **C**: Schematic overview of the heart in the transverse plane with QRS vector of patients during LBBB and left bundle branch area pacing (n=7), and QRS vector during intrinsic sinus rhythm in patients with normal conduction (n=45).

In patients with intact atrio-ventricular conduction and narrow intrinsic QRS complex (n=45), QRS duration significantly increased during both RVSP and LBBAP (figure 3A). QRS area significantly increased during both RVSP and LBBAP, although QRS area during LBBAP approached QRS area values during intrinsic rhythm (figure 3B). QRS area was significantly lower in patients with LBB capture compared to patients without capture (43±18 vs 54±21 μVs, respectively).

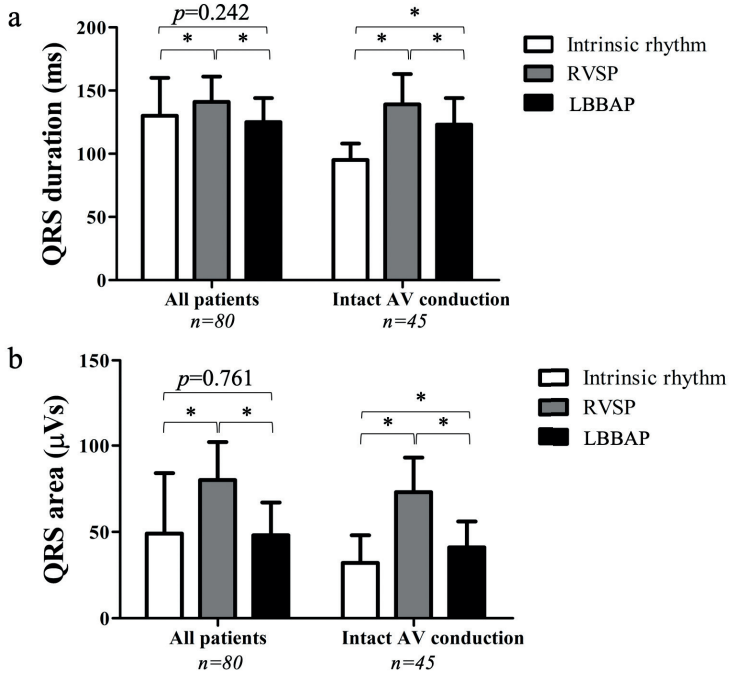

Figure 3. QRS duration and QRS area. QRS duration (**A**) and QRS area (**B**) during intrinsic rhythm, RVSP and LBBAP in all patients and in the subpopulation with intact atrioventricular activation and narrow QRS complex.* p<0.05 between pacing modes.

During LBBAP, V6RWPT was 82±13 ms. In patients with LBB capture (n=54), V6RWPT was significantly shorter compared to patients without LBB capture (75±14 ms vs. 88±9 ms, respectively). Four patients with LBB capture had a long V6RWPT with an interval >100ms. These patients had a long iso-electric segment (>30 ms) with left axis deviation, suggesting a proximal conduction delay.

Fixation beats

Fixation beats have been suggested to be of help in determining lead depth when the lead is advanced in the septum.(12) In 54 of the 80 patients studied in the manuscript (67%) ventricular ectopic beats (deep septal fixation beats) were observed. Figure 4 in the Electronic Supplement Material shows that these fixation beats closely resembled paced morphology obtained at that particular intermediate lead depth in the IVS.

Pacing characteristics

Unipolar LBBP lead threshold at implant was 0.6±0.3 V at 0.5 ms pulse width at implantation, measured from the programmer. The sensed R wave amplitude and pacing impedance at implantation were 14±8 mV and 605±212 Ohms, respectively.

Unipolar pacing threshold did not significantly change from time of implant (n=

80; 0.6 ± 0.3 V) to 3-month (n=70; 0.6 ± 0.2 V), 6-month (n=55; 0.7 ± 0.3 V) or 12-month follow-up (n=40; 0.8 ± 0.5 V). The sensed R wave amplitude remained stable at 12-month follow-up compared to time of implant (18 ± 9 mV vs. 14 ± 8 mV, NS). Pacing impedance significantly changed from 605 ± 212 Ohm to 365 ± 42 Ohm at 12-month follow-up (P<0.05).

Safety endpoints

Peri-procedurally, no major acute procedure-related adverse events such as bleeding, pneumo- or haemothorax, or cardiac tamponade occurred. Acute perforation of the LV septum was noted in 1 patient during implantation. Retrospective analysis of the procedure revealed (missed) rapid appearing fixation beats occurring at the very end of septal penetration, which indicated that the LBB area was reached. In this case, the lead was withdrawn and repositioned successfully. Post-procedural echocardiography with colour Doppler revealed no complications from this temporary septal perforation. One patient with pre-existing serious coronary artery disease (3-vessel disease) experienced an acute coronary syndrome and in-hospital cardiac arrest (occluded D1 branch of left anterior descending artery) during implantation, for which an urgent PCI of the coronary artery was performed. Chest complaints accompanied with minor ECG changes started prior to septal penetration and no contrast agent was used. After consultation with the intervention specialist, no acute coronary angiography was performed since the patient suffered from extensive three-vessel disease (and conservative treatment was previously decided upon). Sublingual administration of nitroglycerin initially recued complaints, but during lead placement the patient went into cardiogenic shock. Urgent PCI was successful and the patient is now participating in the cardiac rehabilitation program.
During follow-up, lead dislodgement during follow-up was observed in one patient, for which a lead repositioning was performed. No device or lead infections were observed.

Discussion

The main findings of our study are as follows:

- Permanent LBBAP as new physiological pacing technique is feasible (96% success rate) and safe as it is not associated with significant adverse effects.
- There is a learning curve for implantation of LBBAP, even in a centre with implanters experienced with His bundle pacing, that flattens after 40-50 procedures.
- The electrical characteristics of the LBBAP lead are satisfying and remain stable over time.
- LBBAP results in ventricular synchrony, measured by QRS area, that is significantly better than RV pacing and approximates that of intrinsic rhythm in patients with intact AV-conduction and narrow QRS.

Safety and feasibility

The possibility of penetrating the IVS to obtain more synchronous pacing was previously shown by our group, and referred to as LVSP. The feasibility of permanent LVSP was firstly shown in a canine model,(9) and later also in patients requiring pacemaker implantation because of symptomatic bradycardia.(10) In both animal experiments as in patients it was shown that LVSP resulted in improved cardiac function when compared to RV pacing. In these studies, the lead was placed in the mid-level of the interventricular septum and direct capture of the conduction system was not studied nor pursued. After these initial studies, it was demonstrated only very recently that the left bundle branch can be stimulated when the lead was advanced through the interventricular septum at a basal level.(18) Since then, more studies including bradycardia patients as well as CRT patients have demonstrated the feasibility and safety of LBBAP.(19-21) Our results, representing a single centre experience where this new pacing technique was initiated, are in line with these studies. In the present study, LBBAP was attempted in 80 patients and it was possible to obtain LBBAP in 96% of the patients without any major procedure-related adverse events. We did observe one septal perforation in 80 cases, which occurred without any clinical consequences.

Learning curve

The present study demonstrated that LBBAP implantation is subject to a clear learning curve effect, even in HBP experienced implanters. With increasing experience, procedure and lead implantation time shortened, which has also been demonstrated for His bundle pacing.(22) In our centre, all implantations were performed using the C315His delivery sheath and the SelectSecure 3830 pacing lead of Medtronic. Although the 3830 lead is not dedicated to LBBAP, it is the most frequently used lead in LBBAP since the screw tip is the active electrode so that pacing can be precisely delivered and the lead depth in the IVS can relatively precise be determined. Procedure success, specifically LBB capture rate could potentially be improved with newer, dedicated materials of different vendors. Especially in patients with dilated ventricles, currently available delivery catheters usually do not suffice.

The LBB capture rate can also be related to the learning curve and implantation experience. An experienced implanting cardiologist is potentially less afraid of penetrating the septum and therefore more confident while advancing the lead towards the left conduction system, which is situated at the very sub-endocardium of the LV.(23)

Assessing septal lead depth

Determining the exact depth of the pacing lead within the septum remains often difficult. Several maneuverers to monitor lead depth have been proposed, such as fluoroscopy imaging (e.g. fulcrum sign), whether or not with septal contrast, impedance monitoring, or monitoring of the endocardial signal. These maneuverers are useful but do usually not

suffice. The paced QRS morphology can be used, since an RBBB-like QRS morphology indicates left-sided IVS pacing.(24) It was recently showed that the appearance of R' in lead V1 during LBBAP corresponds with a low QRS area, indicating a low level of LV intraventricular dyssynchrony.(25) While with conventional connector cables it is usually not possible to perform ventricular pacing during screwing, recently investigated so-called fixation beats are particularly useful. These ventricular ectopic beats become apparent as a result of screwing and are identical to the paced QRS morphology.(12) While in the original publication these fixation-beats are present in 96% of the cases, we found these beats only in 67% of implantations. This difference may be primarily due to the difference in definition: we only considered ectopic beats with qR/rsR' morphology in lead V1 as beats from LBB area, while in the original publication also ectopic beats without R-wave in V1 were considered as originated from LBB area when QRS duration was <130 ms. Lastly, V6RWPT can be used, since V6RWPT (~LVAT) shortens during left-sided IVS pacing compared to right-sided pacing.(25) Instead of waiting for mechanically induced ectopic beats, local depolarizations can also be forced by continuous pacing during the whole process of lead rotation/implantation. During lead progression from the right to the left side of the septum the paced QRS changes: QRS gradually narrows, R wave in V1 appears and V6RWPT shortens.(26)

Capture criteria

The exact number of patients in whom left bundle branch capture is obtained in studies that evaluated LBBAP cannot precisely be determined. The current definition of LBB capture exists of multiple criteria and is not prospectively validated. Confirmation of LBB capture in LBBB patients is particularly challenging. A recently proposed indirect measurement that could help to identify LBB capture is the interval between the LBB potential and the R-wave peak in V6 during native conduction as compared to the R-wave peak time in lead V6 during pacing.(27) This measurement is in essence known from literature as one of the Stevenson criteria used in mapping and ablation of ventricular tachycardia: when the stimulus to QRS (S-QRS) interval equals the electrogram to QRS interval (EG-QRS) during tachycardia, the isthmus of the ventricular tachycardias is identified.(28) This means that the electrical activation travels the same path during the tachycardia as during pacing. In the situation of LBBP, when E-QRS equals S-QRS, the same path is used during intrinsic LV activation as during ventricular pacing and therefore confirms that the ventricular activation spreads via the LBB and therefore that the LBB is captured. The difference (Δ) in V6RWPT during HBP and ns-LBBP/LVSP can used to assess LBB capture in CRT patients.(29) Furthermore, the V6-V1 interpeak interval can differentiate the three types of LBB area capture: non-selective LBB, selective LBB, and LV septal capture.(30)

In our study, we used criteria as proposed by Huang et al.(11) with the addition that a transition of ns-LBBP to s-LBBP or ns-LBBP to LVSP is required. This in order to be able to differentiate LBB capture from LV septum only pacing.

A different method of answering the question whether the LBB is captured can be obtained by measuring His-Purkinje potentials, especially in patients without pre-existing bundle branch block. Using EP catheters along the left side of the IVS and along the bundle of His, would allow recording of retrograde His potentials (with a short stimulus-His interval) or anterograde LBB potentials to differentiate between deep LV septal pacing and LBBP. However, performing these kinds of measurements would increase the procedure invasiveness, as well as costs and is therefore not appropriate for routine use in daily clinical practice. But, future studies using these invasive electrophysiological measurements would be of interest as they would increase our mechanistic insight on LBBAP.

Electrophysiological effects

QRS duration significantly increased during RVSP in our population, and remained prolonged during LBBAP when compared to intrinsic normal ventricular activation in patients with intact AV-conduction. This finding is in agreement with previous studies investigating LBBAP. (31, 32) A prolonged QRS duration is to be expected in RVSP since the His-Purkinje system is not recruited. In LBBAP, the prolonged QRS duration is mainly due to a delayed RV activation, while LV activation is restored. This delayed RV activation becomes evident on the ECG as a R' in V1. The hemodynamic and long-term effect of this delayed RV activation caused by LBBAP needs to be carefully evaluated in future studies.

In contrast to QRS duration, the QRS area gets largely normalized during LBBAP in the present study. QRS area, which is calculated after converting the standard 12-lead ECG, serves as a measurement of ventricular electrical dyssynchrony.(15) In previous studies investigating CRT, it was shown that QRS area has a strong association with clinical and echocardiographic response.(33) In a more recent study from our group, it was even shown that the decrease in QRS area after CRT was a strong independent predictor of echocardiographic and clinical CRT response.(34) In the present study, both LBBP as well as LVSP resulted in low QRS area, approximating the intrinsic QRS area in patients with intact AV conduction and narrow QRS. LBBP resulted in a significantly lower QRS area as compared to LVSP, although the difference in absolute value is small. Whether this small difference between LBBP and LVSP results in different clinical outcomes needs to be determined.

Limitations

Our study shows the results of a prospective registry evaluating the feasibility and electrical characteristics of LBBAP by operators who were experienced in His bundle pacing (JL, BW, KV) before starting with LBBAP. Our study demonstrates a learning curve in a limited number of patients and analysis in larger numbers is required to validate our findings. More experience in LBBAP and refinement of implantation technique and material could result in higher success rates of LBB capture. LVSP was somewhat faster accepted in the first cases, which could have influenced LBB capture rate. With growing experience in LBBAP implantations and increasing knowledge on LBBAP, especially on lead depth in the interventricular septum, the implantation skills have probably improved in our centre which has probably influenced the results. Nevertheless, we are convinced that the data provided in this study represent real world data of the initial experience in a centre that starts with LBBAP.

Conclusions

LBBAP is a new implantation technique that is feasible and safe in a high percentage of patients. Pacing characteristics are very satisfactory and remain stable during one-year follow-up. Capture of the left bundle, defined by strict criteria, could be obtained in up to two-thirds of patients. Although QRS duration remains prolonged, LBBAP largely maintains left ventricular synchrony to values close to intrinsic sinus rhythm with normal AV conduction and narrow QRS. New measurements to determine LBB capture, such as V6RWPT equals LBB potential to V6RWPT interval, seem promising. Moreover, the QRS morphology of the fixation beats are helpful in determining lead depth during screwing of the lead in the interventricular septum.

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CHAPTER 6

6

Left bundle branch area pacing outcomes: the multicenter European MELOS study.

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Abstract

Aims: Permanent transseptal left bundle branch area pacing (LBBAP) is a promising new pacing method for both bradyarrhythmia and heart failure indications. However, data regarding safety, feasibility and capture type are limited to relatively small, usually single centre studies. In this large multicentre international collaboration, outcomes of LBBAP were evaluated.

Methods and Results: This is a registry-based observational study that included patients in whom LBBAP device implantation was attempted at 14 European centres, for any indication. The study comprised 2533 patients (mean age 73.9 years, female 57.6%, heart failure 27.5%). LBBAP lead implantation success rate for bradyarrhythmia and heart failure indications was 92.4% and 82.2%, respectively. The learning curve was steepest for the initial 110 cases and plateaued after 250 cases. Independent predictors of LBBAP lead implantation failure were heart failure, broad baseline QRS and left ventricular end-diastolic diameter. The predominant LBBAP capture type was left bundle fascicular capture (69.5%), followed by left ventricular septal capture (21.5%) and proximal left bundle branch capture (9%). Capture threshold (0.77 V) and sensing (10.6 mV) were stable during mean follow-up of 6.4 months. The complication rate was 11.7%. Complications specific to the ventricular transseptal route of the pacing lead occurred in 209 patients (8.3%).

Conclusions: LBBAP is feasible as a primary pacing technique for both bradyarrhythmia and heart failure indications. Success rate in heart failure patients and safety need to be improved. For wider use of LBBAP, randomized trials are necessary to assess clinical outcomes.

Graphical abstract

Key Question

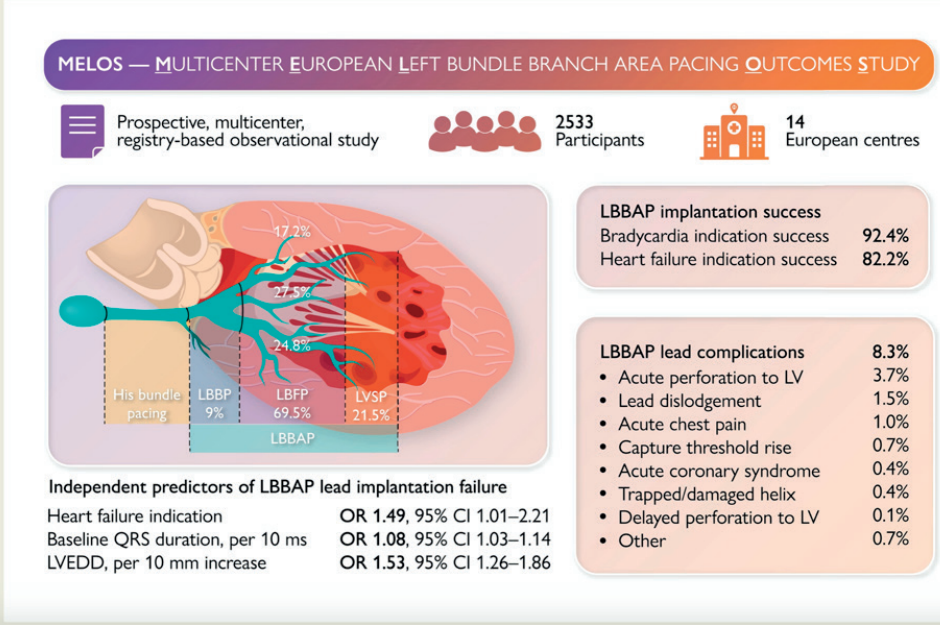
What is the success rate of left bundle branch area pacing (LBBAP) in bradyarrhythmia or heart failure? What is the predominant LBBAP capture type? What is the incidence of complications related to ventricular transeptal route?

Key Finding

Implantation success rate for bradyarrhythmia and heart failure indications was 92.4% and 82.2%, respectively. The predominant LBBAP capture type was left bundle fascicular capture (69.5%). Complications specific to the LBBAP lead occurred in 8.3%, mainly acute septal perforation without clinical consequences.

Take Home Message

LBBAP is feasible as a primary pacing strategy for any pacing indication. This study redefines LBBAP from a proximal to more a straightforward distal conduction system pacing technique. Success rate in heart failure patients and safety need to be improved.



Introduction

The undesirable consequences of right ventricular pacing, when used to treat bradycardia and limitations of biventricular pacing (BiV) as a method to deliver cardiac resynchronization therapy (CRT), prompted the development of more physiological pacing options.
The feasibility of permanent left ventricular septal pacing (LVSP) via the ventricular transseptal route was demonstrated in 2016 by Mafi-Rad et al. in the first-in-human study.[1] This technique was modified by Huang et al. who demonstrated that direct pacing of the proximal left bundle branch (LBBP) can be achieved using the transseptal approach.[2] Small differences in the paced QRS complex between LVSP and LBBP, the occurrence of intermediate capture types (left bundle fascicular pacing, LBFP), a lack of standard and precise differentiating criteria and scarcity of data regarding differences in clinical outcome, justify the popular use of the term left bundle branch area pacing (LBBAP) as the common descriptor of these new pacing modalities (Figure 1).[3-6]

Within four years of these two landmark publications, several small and medium-sized, mainly single-centre clinical studies have demonstrated the feasibility of LBBAP, in lieu of conventional anti-bradycardia pacing and BiV-CRT.[5;7-10] However, valid questions regarding safety and in-depth characterization of this new pacing technique in real-world clinical practice remain.
The Multicentre European Left Bundle Branch Area Pacing Outcomes Study (MELOS) is a registry-based observational study, which was designed to gather data from a large group of patients from 14 centres who were early adopters of LBBAP. Our primary focus was characterization of LBBAP capture types and pacing parameters, learning curve assessment and procedure-related complications at follow-up.

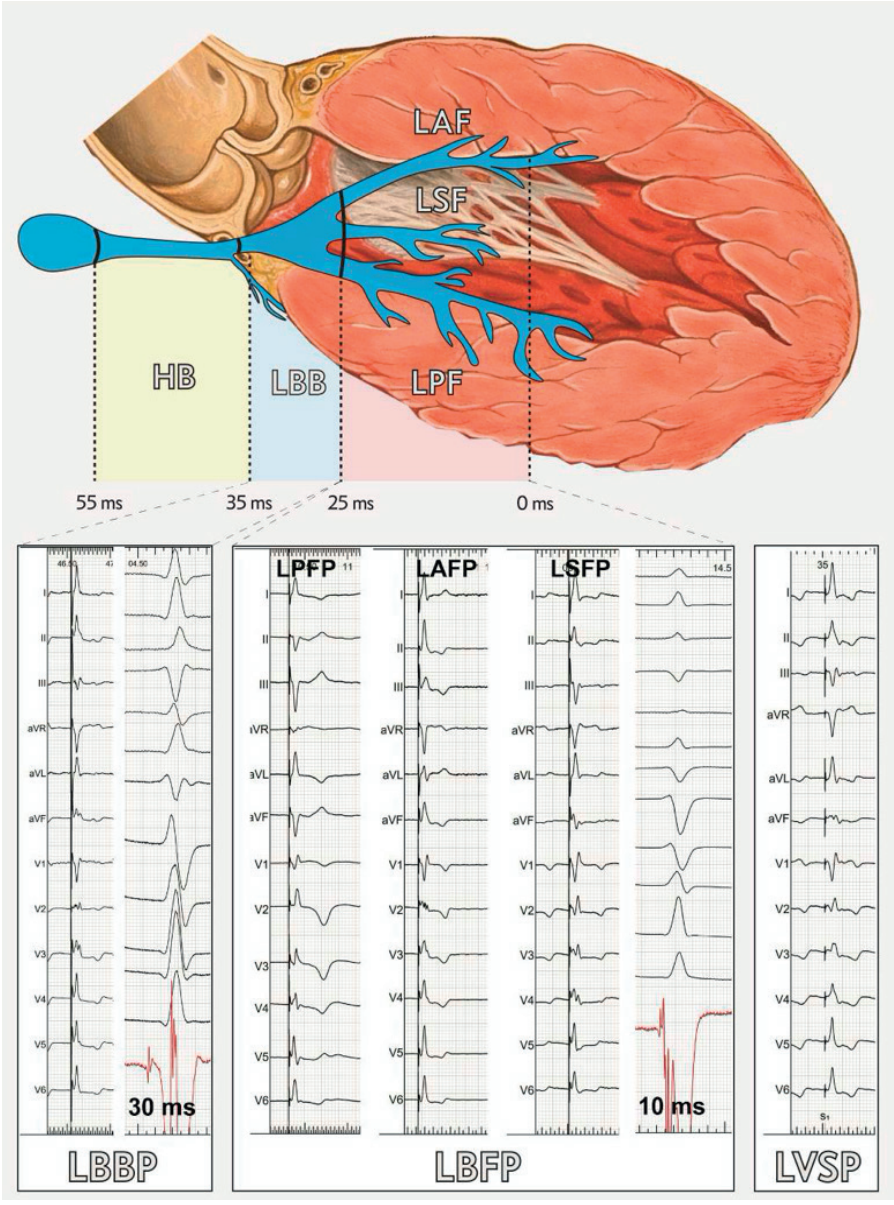


Figure 1. Examples of paced ECG patterns and endocardial electrograms during LBBAP. LBBP: left bundle branch pacing, characterized by LBB potential to QRS interval of 34-25 ms and lead tip position approximately 1.5 cm from the His bundle. LBFP: left bundle fascicular pacing – characterized by potential to QRS of 24 – 0 ms and lead tip position approximately 1.5 – 4.5 cm from His bundle. Left bundle fascicular pacing includes: LPFP - left posterior fascicle pacing, LAFP - left anterior fascicle pacing, LSFP – left septal fascicle pacing. LVSP: diagnosed when LBB capture criteria are not met, any distance from His bundle. Heart drawing based on work by Patrick J. Lynch and C. Carl Jaffe, MD / CC-BY 2.5, *https://commons.m.wikimedia.org/wiki/File:Heart_anterior_view_coronal_section.jpg*

Methods

Study design and population

This is a multicentre observational study based on pooled LBBAP registries maintained in 14 European hospitals (listed in Table 1). Only European centres considered as experienced (>60 LBBAP implants) were invited. The study population comprised all patients who underwent an attempt at LBBAP lead implantation at these centres for any indication.

Table 1. Multicentre European left bundle branch area pacing outcomes study—participating centres and enrolment details

Centre	Country	First implant	# patients	# operator	Enrollment policy per operators	Enrollment per all implants in center	Registry type	Success rate
Amsterdam	Netherlands	02 Dec 2019	61	3	1	50%	mixed	100%
Antwerp	Belgium	04 Feb 2020	89	1	1	32%	Prospective	80%
Eindhoven	Netherlands	08 Jan 2020	100	2	1	41%	Prospective	80%
Geneva	Switzerland	25 Feb 2020	121	2	1,2	46%	Prospective	84%
Gent	Belgium	27 Nov 2019	150	1	1	90%	Prospective	90%
Krakow	Poland	12 Jun 2018	607	5	1,2	62%	Prospective	86%
London	United Kingdom	23 Nov 2020	67	4	1,2	N/A	Prospective	84%
Maastricht	Netherlands	25 Nov 2019	120	2	3,4	30%	mixed	98%
Prague 1	Czechia	21 Nov 2019	358	2	1,2	39%	Prospective	92%
Prague 2	Czechia	28 Apr 2020	114	1	3	18%	mixed	100%
Rome	Italy	15 Jan 2020	125	1	1,2	8%	Prospective	87%
Rovigo	Italy	20 May 2019	202	4	2	35%	mixed	99%
Valencia	Spain	16 Jun 2019	292	1	1	45%	Prospective	86%
Zwolle	Netherlands	12 Dec 2019	127	2	1	55%	Prospective	97%
Summary	14	12 Jun 2018	2533	31	-	35%	87% of cases prospective	90%

Enrollment policy: 1 – Left bundle branch area pacing (LBBAP) as primary approach for all pacing indications; 2 - LBBAP as primary approach for all pacing indications after initial attempt at His bundle pacing; 3 - LBBAP only for atrioventricular block and cardiac resynchronization therapy candidates; 4 – preselected sick sinus syndrome patients

The recruitment policy for LBBAP for each centre/operator was investigated to estimate potential selection bias. This was approximated globally by the percentage of all patients with indications for pacing/CRT who underwent attempted LBBAP during the MELOS recruitment period. Additionally, enrolment strategy was categorized per operator (Table 1) because in most centers only some of the operators implant LBBAP devices, and they might do so in all their consecutive, unselected patients.

The study complies with the Declaration of Helsinki, and was approved by the local ethics committees; informed consent was obtained from the subjects.

LBBAP device implantation

We classified the type of LBBAP capture type achieved. LBBAP lead implantation was considered successful when a deep intraseptal lead position was obtained, and the paced QRS complex included a terminal R/r wave in lead V1, indicating a delay in activation of the right ventricle. In rare cases we accepted a QS configuration (lack of terminal R) in V1 provided that a terminal R/r wave in lead V1 appeared during programmed stimulation or other features indicating LBBAP (described below) were present.

LBBAP lead implantation technique generally followed the previously described methods,[11] albeit with some modifications. The LBBAP target zone was regarded more liberally and leads were positioned over a wide area on the midseptum, rather than strictly 1.5-2.0 cm from the His bundle in the apical direction as described by Huang et al.[2;11] The His bundle was generally not used as an anatomical marker; the LBBAP lead deployment site was determined using the tricuspid ring as a marker, the paced QRS morphology (polarity discordance of leads II and III, and V1 nadir notch) and endocardial electrograms. Lead depth in the interventricular septum during implantation was monitored using progressive change of paced QRS morphology, fixation beats, local endocardial electrogram, fluoroscopy with sheath ventriculography and impedance.[3;4;11-13] The number of lead implantation attempts, as well as the final position/capture type were at the discretion of the implanting cardiologist. While evidence of direct LBB capture and R-wave peak time in lead V6 (V_6RWPT) <80 ms, were favoured by all,[3] the final lead position was dictated by the anatomy and the limitations of currently available delivery sheaths and leads. An electrophysiology digital recording system was used by the majority of operators to record and analyse intracardiac electrograms and surface ECG using digital callipers at a high sweep speed of 100–200 mm/s.

LBBAP capture type categorization

We classified the type of LBBAP capture achieved (Figure 1) using the following steps.

Step 1: Is there evidence of direct left conduction system capture?

We required any of the following criteria to be met to diagnose left conduction system capture:

1. Diagnostic QRS morphology transition during threshold test.[3;11]
2. Diagnostic QRS morphology transition during programmed stimulation.[14]
3. Pacing stimulus to V_6RWPT <80 ms in patients with narrow QRS/isolated right bundle branch block patients or <90 ms in patients with more advanced ventricular conduction system disease.[3;15]
4. LBB potential to V_6RWPT interval equal to the stimulus to V_6RWPT interval (+/- 10 ms).[3]
5. V_6-V_1 interpeak interval >40 ms.[13]

Diagnostic QRS morphology transition was defined as a sudden change in QRS morphology, compared to the QRS pattern observed during initial non-selective LBBAP capture (that is simultaneous capture of left conduction system and septal myocardium), with a change to either selective LBBAP or LVSP. A transition to LVSP was considered to have occurred if V_6RWPT prolonged by > 10 ms. A change to selective LBBAP was diagnosed if any of the following became apparent with a change in pacing output or programmed stimulation: isoelectric line after the pacing stimulus, a discrete local potential on the electrogram recorded from the pacing lead, or there was sudden prolongation in V_1RWPT.[3;15]

Left ventricular septal myocardial capture (LVSP) was diagnosed if LBB capture criteria were not fulfilled, but a terminal R/r in lead V1 was present. Fluoroscopic confirmation of the pacing lead position in basal/mid-septal region was mandatory to exclude presence of R/r wave in V1 due to apical lead position. Moreover, deep septal lead position was assured with additional methods (progressive change of paced QRS morphology with lead rotation, fixation beats, and sheath ventriculography).

LBBAP failure was recognized when neither conduction system capture criteria nor terminal R/r in lead V1 were present.

Step 2: Location of left conduction system capture

In patients where direct left conduction system capture was confirmed we classified the location of capture within the left ventricular (LV) conduction system by assessing the LBB/fascicular Purkinje potential to QRS interval, and QRS polarity in leads II and III.

1. *Proximal LBB capture (LBBP)* was diagnosed if all of the following were observed: 1) LBB potential to QRS interval value within the range of 35-25 ms and 2) inferior or intermediate QRS axis.

2. *Left bundle fascicular pacing (LBFP):* 1) Fascicular Purkinje potential to QRS interval within the range of 24 - 0 ms or absence of a potential.

Additionally, LBFP was subdivided into:

A. Left posterior fascicle pacing (LPFP): superior QRS axis (leads II and III predominantly negative).
B. Left anterior fascicle pacing (LAFP): inferior QRS axis (leads II and III positive).
C. Left septal fascicle pacing (LSFP): intermediate QRS axis (lead II predominantly positive, and lead III with negative component).

The LBBAP lead delivery method was divided into two categories:

1. The conventional approach using thin (4F), lumenless lead designed for targeting different sites with a dedicated fixed-curve or deflectable delivery sheath.
2. The stylet-driven approach using variety of 5.6-5.8 F leads originally designed for traditional right ventricular pacing and positioned with a large diameter fixed-curved or deflectable delivery sheath.[16]

Data collection and endpoints

The same standardized datasheet was used by all centres, this was populated from the data collected from the registries which were maintained at the participating centres. If necessary, additional data were retrieved from patient's files. Data pooling, cleaning, capture type adjudication and statistical analysis was performed by one core statistical team.

The analysed demographic data, baseline clinical characteristics and procedure related variables are listed in Tables 2 and 3. The reasons for LBBAP lead implantation failure were collected. We recorded all complications, including those which may have occurred as a result of the transseptal lead approach including acute and delayed septal perforation, coronary artery fistula, stroke, acute coronary event – as listed in Table 4.

Table 2. Basic clinical and electrocardiographical characteristics of the studied group (n = 2533).

Age [years]	73.9 ± 11.8 (95% CI 73.5 – 74.4)
Male sex	1073 (42.4%)
Comorbidities	
• Diabetes mellitus	738 (29.1%)
• Coronary heart disease	773 (30.5%)
• Heart failure	1003 (39.6%)
• Hypertension	1828 (72.2%)
• Severe valvular disease	413 (16.3%)
• Permanent atrial fibrillation	672 (26.5%)
Pacing indication	
• Sick sinus syndrome	373 (14.7%)
• Atrioventricular block	1218 (48.1%)
• Atrial fibrillation with bradycardia	94 (3.7%)
• Heart failure	696 (27.5%)
• Other*	152 (6.0%)
Baseline QRS duration [ms]	137.1 ± 35.9 (95% CI 135.7 – 138.5)
Baseline QRS type	
• Narrow	831 (32.8%)
• LAFB/LPFB	87 (3.4%)
• RBBB	265 (10.5%)
• RBBB + LAFB/LPFB/NIVCD	237 (9.4%)
• LBBB	568 (22.4%)
• NIVCD	199 (7.8%)
• Asystole/escape/paced	346 (13.7%)

CI – confidence interval. LAFB – left anterior fascicular block; LPFB – left posterior fascicular block; RBBB – right bundle branch block; NIVCD – non-specific intraventricular conduction disturbance; LBBB – left bundle branch block. * Including atrioventricular node ablation and neurocardiogenic syncope

Table 3. Procedure-related, electrocardiographic and electrophysiologic characteristics.

		95%CI	p
Fluoroscopy time [min]	9 (5.5 – 14.6)[§]	8.5 – 9.2	
LBBAP lead type: lumenless / stylet driven	1902 (83.8%) / 369 (16.2%)		
LBBAP capture threshold at implant [V]			
• LBBP	0.6 (0.5 – 0.9)	0.5 – 0.7	0.002[@]
• LBFP (LPFP+LAFP+LSFP)	0.6 (0.5 – 0.9)	0.6 – 0.7	-
• LVSP	0.7 (0.5 – 1.0)	0.7 – 0.75	-
LBBAP sensing at implant [mV]			
• LBBP	10 (6.8 – 15)	8 – 11.3	0.56
• LBFP (LPFP+LAFP+LSFP)	10 (7 – 13.9)	9.3 – 10.1	-
• LVSP	10 (6.7 – 13)	9 – 10	-
LBBAP lead impedance at implant [Ohm]	652.1 (± 234.5)	642.3 – 661.8	
Loss of r/R in V_1 at follow-up	54/1357 (4.0%)		
LBB/LPF/LAF/LSF potential at implant	599/2270 (26.4%)		
LBBP capture subtypes			
• LBBP	121/1345 (9.0%)		
• LPFP	333/1345 (24.8%)		
• LAFP	232/1345 (17.2%)		
• LSFP	370/1345 (27.5%)		
• LVSP	289/1345 (21.5%)		
LBB capture confirmed with: [&]			
• QRS transition at threshold test	599/2270 (26.4%)		
• QRS transition at programmed stimulation	213/2270 (9.4%)		
• V_6RWPT < 80 / 90 ms [#]	1384/2270 (61%)		
• Potential-V6RWPT = stimulus-V6RWPT	444/2270 (19.6%)		
• V_6-V_1 interpeak interval > 40 ms	416/2270 (18.3%)		
Paced V6RWPT per baseline QRS type [ms]			
• Narrow QRS / isolated RBBB	77.7 (± 12.8)	77.0 - 78.5	<0.001
• LBBB/NIVCD/RBBB+	83.0 (± 15.2)	82.1 - 83.9	-
Paced V_6RWPT per obtained capture type [ms]			
• LBBP	79.0 (± 12.0)	76.9 - 81.2	<0.001[$]
• LBFP (LPFP+LAFP+LSFP)	74.8 (± 12.3)	74.0 - 75.6	-
• LVSP	94.3 (± 11.6)	93.3 - 95.4	-
Paced QRS duration per baseline QRS type [ms]			
• Narrow QRS / isolated RBBB	137.5 (± 19.3)	136.4 - 138.7	<0.001
• LBBB/NIVCD/RBBB(+)	145.3 (± 22.5)	144.0 - 146.6	-
Paced QRS duration per obtained capture type [ms]			
• LBBP	141.4 (± 16.9)	138.4 – 144.4	<0.001 [%]
• LBFP (LPFP+LAFP+LSFP)	139.0 (± 19.0)	137.8 – 140.2	-
• LVSP	150.3 (± 22.3)	148.3 – 152.3	-

DAP – dose/ area product; LBBAP – left bundle branch area pacing; LBBP - left bundle branch pacing; LBFP – left bundle fascicular pacing; LAFP - left anterior fascicular pacing; LPFP: left posterior fascicular pacing; LSFP – left septal fascicular pacing; LVSP – left ventricular septal pacing; NIVCD - non-specific intraventricular conduction disturbance; RBBB - right bundle branch block; RBBB(+) - right bundle branch block with fascicular block or NIVCD.

[$] - values in parentheses represent quartiles (Q1 - Q3) or ± standard deviation as appropriate

[#] - 80 ms for narrow QRS/ isolated RBBB, 90ms for LBBB/NIVCD/RBBB+

[@] In post-hoc analysis differences were present for pairs: LBBP vs. LVSP ($p = 0.02$) and LBPF vs. LVSP ($p = 0.008$).

[$] In post-hoc analysis differences were present for pairs: LBBP/LPFP ($p = 0.02$), LBBP vs. LVSP ($p < 0.001$) and LPFP vs. LVSP ($p < 0.001$)..

[%] In post-hoc analysis differences were present for pairs: LBBP vs. LVSP ($p = 0.001$) and LBPF vs. LVSP ($p < 0.001$)

[&] often multiple criteria were present in the same person, therefore the percentages do not add up to 100%

Table 4. Complications of left bundle branch area pacing (n = 2533).

Generic device implantation complications	
Penumothorax	14 (0.55%)
Pocket/wound infection	13 (0.51%)
Systemic infection / endocarditis	6 (0.24%)
Atrial lead dislodgement	14 (0.55%)
Pocket hematoma	10 (0.4%)
Pericardial effusion [#]	12 (0.47%)
Large vein thrombosis	2 (0.08%)
Re-intervention for other non-LBBAP lead reason[$]@	15 (0.59%)
Subclavian arteriovenous fistula after puncture	1 (0.04%)
Summary	87 (3.43%)
Complications attributed to the transseptal route of the pacing lead	
Intraprocedural perforation into the LV cavity	93 (3.67%)
Delayed perforation into the LV cavity	2 (0.08%)
Acute chest pain	25 (0.98%)
Acute ST-segment elevation in multiple leads	6 (0.24%)
Acute coronary syndrome [$]	11 (0.43%)
Coronary vein fistula	7 (0.28%)
Coronary artery fistula	2 (0.08%)
Painful pacing / chest pain	4 (0.16%)
LBBAP lead unscrewable / trapped/damaged helix	11 (0.43%)
LBBAP lead dislodgement	38 (1.5%)
Threshold rise to an absolute value > 2 V	17 (0.67%)
Threshold rise > 1 V from baseline	18 (0.71%)
Threshold rise leading to re-intervention	4 (0.16%)
Stroke / TIA	0 (0)
Summary	209 (8.25%)

[#] In three cases cardiosurgical operation was necessary
[@] Listed in Supplementary text
[$] Acute coronary syndrome was diagnosed when two out of three (ST elevation, troponin release, chest pain) were present.

Acute coronary events were diagnosed when at least two of the following three criteria were present during or after the procedure: acute chest pain, ST-segment elevation and troponin level > 320 pg/ml within 12 to 24 hours, (over three standard deviations above the average level observed after uncomplicated LBBAP procedure).[16;17]

Learning curves

The experience was defined as the number of cases performed by the operator. To characterize the learning process the following parameters were assessed: procedure success, presence of LBB capture, paced V_6RWPT, paced QRS duration (measured from the pacing stimulus to the end of the QRS using the 12-lead ECG) and fluoroscopy time. To minimize non-homogeneity and ensure high precision of measurements the learning curves for V_6RWPT and QRS duration as endpoints were limited to operators with > 200 implants who measured QRS using computer-based electrophysiology system.

Statistical analysis

Comparisons between groups were performed using Student's t-test for independent variables or the chi-square test. For within-patient changes in LV ejection fraction and LV end-diastolic diameter paired t-tests were performed. Differences between groups were assessed using analysis of variance (parametric and Kruskal-Wallis type if necessary). Univariable and multivariable logistic regressions were performed to describe the effect of potential predictors of procedure success. For success rate assessment (multivariable logistic regression, learning curves), only centres/operators with prospective data, non-preselected patients and a reported failure rate > 3% were analysed. To assess the impact of experience, binary logistic regression and polynomial regression models were constructed. For all variables the cubic fit line was chosen as the line of the best fit based on the curve estimation analysis. The results were deemed statistically significant at $P < 0.05$. Statistical analysis was performed using SPSS statistical software (IBM Statistics 27; Chicago, IL, USA)

Results

Enrolment and baseline characteristics

A total of 2533 patients from 14 centres across Europe (Table 1) were analysed; range of enrolled patients per centre was 61 to 607, with the first procedure in June 2018 and the last in November 2021, including all consecutive LBBAP cases in each centre. The majority of patients were enrolled on a prospective basis (2203/2533, 87%) using local prospective conduction system pacing implantation registries. LBBAP was undertaken in 35% of all patients admitted for pacemaker/CRT implantation in the MELOS centres during the enrolment period. The enrolment policies are listed in Table 1. LBBAP as

a primary approach for all indications, and as secondary approach for all indications after an initial attempt at His bundle lead implantation were the dominant strategies, reported for 60.1% (1524/2533) and 32.5% (823/2533), respectively. There were 31 operators active in the study with median number of procedures per operator of 84 (Q1-Q3: 24-120; 95% CI: 31-100).
Baseline characteristics of the MELOS cohort, including comorbidities, pacing indications and QRS morphology types are presented in Table 2.

Procedural success rate and learning curve
The average LBBAP lead implantation success rate was 89.6% (2270/2533). Success rate for bradyarrhythmia and heart failure indications was 92.4% (1698/1837) and 82.2% (572/696), respectively. The independent preprocedural predictors of failure to implant a LBBAP lead were heart failure, *LV end-diastolic diameter* and broad baseline QRS. Results of the univariable and multivariable analyses are presented in Table 5. The reported reasons for implantation failure included inability to penetrate deep into the interventricular septum in 41.8% (110/263), inability to reach the target area due to enlarged heart chambers in 19.4% (51/263), unsatisfactory paced QRS in 27.8% (73/263), high capture threshold/unstable lead in 0.8% (2/263), chest pain in 0.8% (2/263) and other reasons in 9.4% (25/263).

Table 5. Preprocedural determinants of LBBAP lead implantation failure (n = 1809).

	UNI OR (95% CI)	p	MULTI OR ** (95% CI)	p
Age[&]	0.9 (0.82 – 0.99)	0.03	-	-
Male sex	1.02 (0.78 - 1.33)	0.9	-	-
LVEF*	0.7 (0.65 – 0.77)	< 0.001	-	-
LVEDD[$]	1.85 (1.59 – 2.16)	< 0.001	1.53 (1.26-1.86)	< 0.001
Device upgrade	2.26 (1.62 – 3.14)	< 0.001	-	-
Heart failure indication	2.75 (2.1 – 3.6)	< 0.001	1.49 (1.01-2.21)	0.04
Baseline QRS duration[#]	1.15 (1.1 - 1.19)	< 0.001	1.08 (1.03 – 1.14)	0.002
Baseline QRS type[@]	2.38 (1.78 - 3.19)	< 0.001	-	-
Stylet driven lead	0.74 (0.48 - 1.13)	0.16	-	-

**Adjusted for center, [&] - per 10 years increase; * - per 10% increase; [$] - per 10 mm increase;
[#] - per 10 ms increase,
[@] - LBBB, NIVCD, RBBB+LAFB/LPFB/NIVCD
Abbreviations: UNI - univariable logistic regression; MULTI - multivariable logistic regression; OR – odds ratio; CI – confidence interval; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic dimeter; LAHB – left anterior hemiblock; LPHB – left posterior hemiblock; RBBB – right bundle branch block

The learning curve for LBBAP success was gradual, with the steepest part over the first 100 cases (Figure 2). With increasing experience, the proportion of LBBP vs. LVSP did not change (Figure 2). The learning curve based on fluoroscopy time showed a significant decrease over the initial 110 cases and then remained flat. The paced V_6RWPT (Figure 2) and paced QRS duration, progressively shortened with increasing experience up to 110 cases and then flattened off.

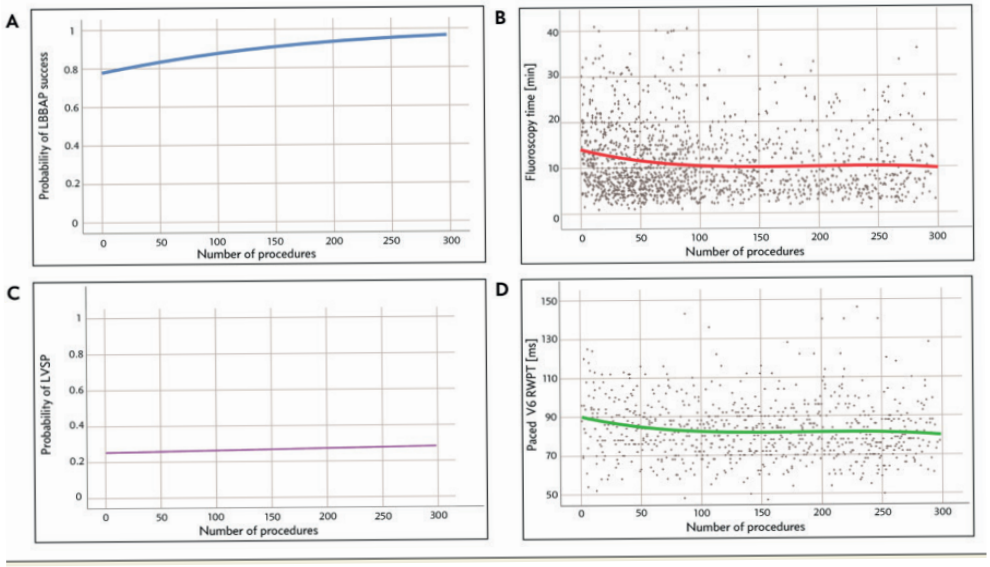


Figure 2. Learning curves for the left bundle branch area pacing (LBBAP) technique based on the number of procedures performed by the operators. **Panel A:** Probability of success of LBBAP lead implantation slowly increases until 270 cases ($p < 0.001$;). **Panel B:** Decrease in fluoroscopy time over the initial 110 cases ($p < 0.001$). **Panel C:** Despite increase in experience the proportion of left ventricular septal pacing (LVSP) does not decrease ($p = 0.5$) but remain stable. **Panel D:** Decrease of paced V_6 R-wave peak time (V_6RWPT) is present over the initial 110 cases ($p < 0.001$). Curves on panels A, B and C were based on 1809 cases performed by 14 mid-high volume operators, while panel D curve was based on 860 cases performed by 3 high-volume operators – see methods.

LBBAP capture types and pacing parameters.

Average paced V_6RWPT and global QRS duration for the whole group were 80.4 ± 14.3 ms and 141.5 ± 21.3 ms, respectively. These were significantly influenced by baseline QRS morphology and the type of LBBAP capture which was obtained (Table 3).

In the whole group of patients implanted with an LBBAP lead, LBB capture was diagnosed in 78.5% of cases (1782/2270). In the remaining cases, left conduction system capture criteria were not fulfilled and, therefore, LVSP was diagnosed in 21.5% (488/2270). Direct left conduction system capture was diagnosed during threshold test in 26.4% (599/2270) cases, using the V_6RWPT criterion in 61% (1384/2270) cases and other criteria for LBB capture diagnosis were present in 29% (1073/2270) cases (Table 3).

A left conduction system Purkinje potential was observed in 26.4% (599/2270) cases. Potential to QRS interval was reported in 524 of these cases with an average interval of 22.6 ± 6.5 ms, 29.1 ± 3.1 ms and 20.5 ± 5.9 ms for the whole group, LBBP and LBFP, respectively. The distribution of the potential to the QRS interval values is presented in Figure 3.

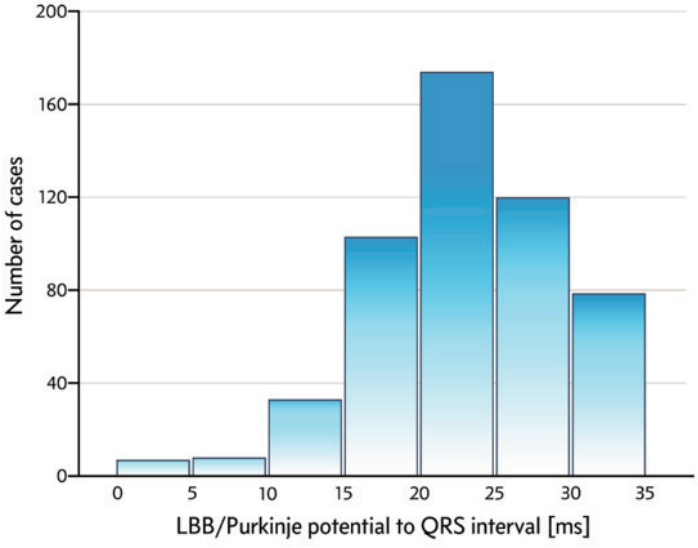


Figure 3. Distribution of left bundle branch/Purkinje potential to QRS intervals - attesting to the variety of lead positions and wide target area on the interventricular septum. During proximal left bundle branch pacing, probably already including proximal parts of the major fascicles, the potential to QRS interval is likely in the range of 34 to 25 ms, this would correspond the main LBB length of 1.5 – 2.0 cm. Anterior, posterior and septal fascicular pacing is characterized by potential to QRS interval of 24 – 0 ms, with the values < 10 ms indicating pacing of very distal arborization of the left conduction system, close to the Purkinje fibres to myocytes interface.

LBFP was the predominant capture type, observed in 69.5% (935/1345). The proportion of all LBBAP capture types is detailed in Table 3 and categorization flow-chart.
LBBAP QRS was characterized by the presence of a terminal R wave in 92.4% (2097/2270) of successful cases. Patients without terminal r/R in V1 (n=173) were diagnosed as LBBAP on the basis that V_6RWPT was diagnostic of LBB capture (122/173), or the appearance of V1 R/r wave during programmed stimulation (15/60) or a diagnostic QRS transition during threshold test (36/122).
The capture threshold and sensing amplitudes at implant and at final follow-up of mean 6.4 ± 5.7 months were satisfactory and stable: 0.76 ± 0.56 V vs. 0.75 ± 0.51 V (p = 0.55) and 11.3 ± 5.7 mV vs. 11.5 ± 7 mV (p = 0.36), respectively. Pacing parameters for each of the different LBBAP capture types are presented in Table 3.

Complications

No deaths, strokes, or other thromboembolic complications in the period from implantation to hospital discharge were observed. Acute and late complications were observed in 11.7%. Complications related to the transseptal route of the LBBAP lead were identified in 8.3% (209/2533), including, among others, delayed septal perforation and coronary artery damage/spasm - these were listed in Table 4 and illustrated in Figure 4. No further complications were observed following lead repositioning in case of perforations into the LV cavity and lead dislodgements. Acute coronary events were managed conservatively without further sequelae.

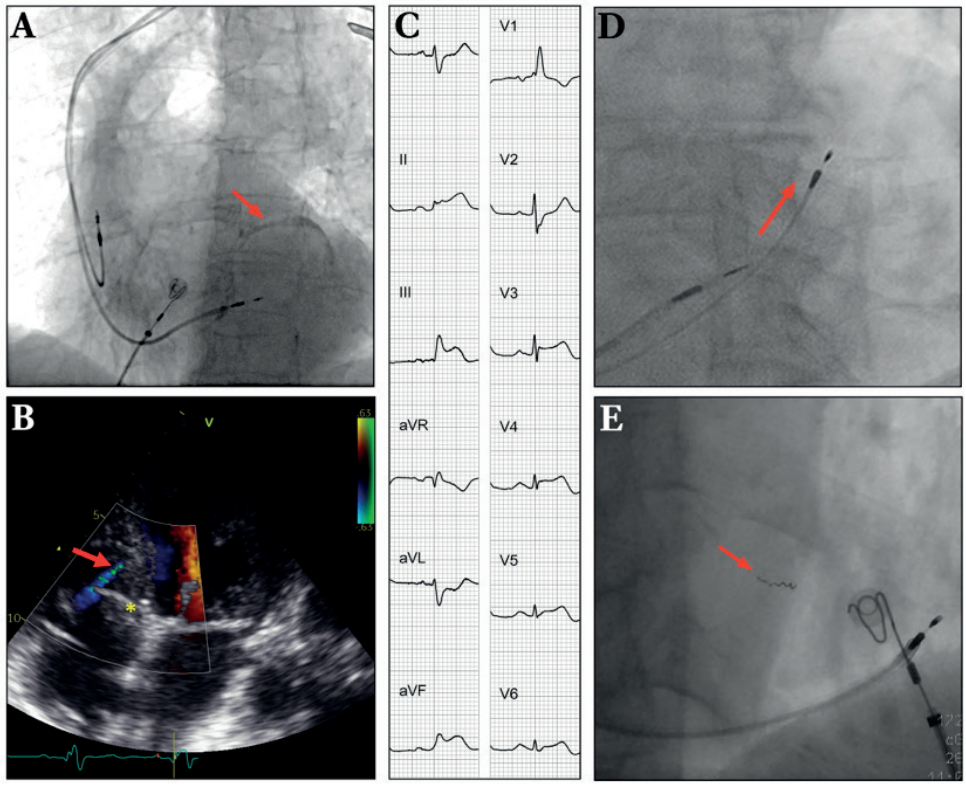


Figure 4. Illustrations of the complications of the transseptal route of the left bundle branch area pacing lead. **Panel A:** coronary venous fistula (arrow points to contrast in great cardiac vein). **Panel B:** coronary artery fistula (arrow points to the blood jet near the lead entry site). **Panel C:** Acute ST-segment elevation in leads II, III, aVF and V3-V6 with concomitant chest pain during LBBAP lead deployment. Panel D: late lead perforation into left ventricular cavity (initial lead position superimposed, arrow indicates leftward displacement from the perforation site). **Panel E:** helix entrapment with subsequent lead break during attempts to unscrew/remove (arrow points to the helix, broken and entrapped in the endocardium).
Figure in panel B reproduced with permission from De Pooter J, Calle S, Demulier L et al. Septal Coronary Artery Fistula Following Left Bundle Branch Area Pacing. JACC Clin Elecrtrophysiol. 2020; 6: 1337-1338.

A clinically significant increase (i.e. to an absolute value > 2 V at 0.5 ms pulse width) of LBBAP pacing threshold was observed in 0.7% of patients (17/2533), this was on average detected 7.1 ± 5.0 months post implantation, while loss of terminal R/r in V1 was noted in 4.0% (54/1357).
No differences in complication rates were observed between different LBBAP capture types: 12.4%, 8.34% and 6.4% in LBBP, LBFP and LVSP, respectively (p = 0.08).

Discussion

MELOS is to date the largest multicentre evaluation of the LBBAP technique. The primary findings of this study are as follows: (i) when LBBAP is adopted into routine clinical practice, it does not provide homogeneous results. Several distinct capture types are observed as a result of differences in pacing locations, implantation technique and baseline substrate; (ii) in the European experience left bundle fascicular capture is the predominant type of LBBAP; (iii) LBBAP is a feasible primary pacing technique for all-comers regardless of the pacing indication. However, the learning curve is gradual; and (iv) several complications specific to the transseptal route were observed; in the majority of cases these were minor (Structured Graphical Abstract).

LBBAP technique evolution

Initially, two research groups in the Netherlands investigated the ventricular transseptal route for LV pacing.[1;18;19] These studies showed feasibility, safety and favourable hemodynamics with this method, first in an animal model and then in humans. In some of the first human cases in the Mafi-Rad et al. study, it is likely that direct distal left conduction system capture was achieved, although this was neither pursued nor realized at the time. It was not until the case report by Huang et al. with clear demonstration of LBB capture that the full potential of the transseptal pacing technique was appreciated.[2] The current study suggests that contemporary LBBAP lead implantation is based on a technique that preferentially targets fascicles and distal arborizations, and is intermediate between the 'distal' technique described by Mafi-Rad et al. and the 'proximal' approach developed by Huang et al..

LBBAP success rate

The overall success rate of LBBAP lead implantation in our study was 89.6%, which suggests that with currently available tools a deep septal lead deployment can be challenging even for experienced operators. Lead implantation failures were more likely to occur in patients with heart failure, enlarged left ventricle and broad baseline QRS duration (Table 5). Patients with these findings are more likely to have enlargement of the cardiac chambers and septal fibrosis, which were the two major reasons reported by

MELOS operators for lead implantation failure. These factors are likely to explain the lower success rate for CRT patients and bundle branch block patients which was also reported by Vijayaraman et al. and Padala et al.[5;8] These findings suggests that dedicated implant tools and leads are likely to be required to increase LBBAP lead implantation success rates in this challenging group of patients.

Comparison of success rate between studies is limited due to the lack of standard and precise LBB capture criteria. Our success rate seems similar to that reported in other studies (89.4% - 97.8%).[5;8;9;20] However, we considered LVSP, which constituted 21.5% of our cases, as a success, while in the above referenced studies this was considered as a failure. The higher proportion of LVSP in our study is likely to be explained by our perception that LVSP is a good procedural endpoint and the use of more up-to-date capture criteria in our study.[3;6;13;15] Several studies based their capture criteria on the expert recommendations which were published before validated capture criteria became available.[7;11;21] These recommendations did not specify V_6RWPT (a.k.a. LVAT) cut-off criteria for capture diagnosis and considered the presence of a LBB potential as obligatory, while this was absent in the majority of patients both in the study by Padala et al. and in our population.[8]

Learning curves of LBBAP

This is the first multicentre study reporting the learning curve for deep septal lead implantation success. Our learning curve showed a slow rise from the initial success rate of approximately 78% to 97% obtained after 270 cases; the steepest rise was for the initial 100 cases with a more gradual ascent later.

The learning curves for fluoroscopy time, paced V_6RWPT and global paced QRS duration all showed a similar improvement over the initial 110 cases and then a plateau ($P < 0.001$). With experience paced V_6RWPT and global QRS duration shortened from 90 ms to 79 ms and from 159 ms to 152 ms, respectively. This is similar to the only other published learning curve for V_6RWPT, which showed a plateau after 200 cases (for a single operator).[21]

Variety of LBBAP capture types

Our results stand in contrast to some single centre studies which reject LVSP as a good outcome and promote a strict description of LBBAP using a technique that limits the target to the proximal LBB area located 1.5-2.0 cm from the His bundle.[7;9;11;20] The implantation technique recently described by Liu et al. and Jiang et al. is more consistent with the approach used in our study.[22;23] The findings of our study suggest that many operators are adopting an approach which targets a wider area on the interventricular septum, compared to that described in the early papers on LBBAP, [2;9;11;20] and that a variety of LBBAP capture types are obtained. This is best attested by the bell curve distribution of LBB/fascicular Purkinje potential to QRS intervals (Figure 3) and the

proportion of LBBP (9%), LBFP (69.5%) and LVSP (21.5%). Acceptance of a wider target area and various types of capture during LBBAP lead implantation may decrease the need for lead repositioning during the procedure, thereby limiting the septal damage and facilitating implantation.

Left Bundle Fascicular Pacing – novel conduction system pacing modality

The predominant type of LBBAP in our study was LBFP - diagnosed when conduction system capture criteria are present but with a short potential to QRS interval and/or a superior axis. These findings are indicative of distal fascicular/arborization capture rather than capture of the predivisional LBB trunk.

This type of capture, which can be obtained over wide mid-septal area, is easier to achieve than the more challenging proximal LBB capture which targets the short, narrower and insulated LBB trunk at the high basal septum. Apart from this anatomical factor, capture of the distal conduction system might be easier, since it does not require close proximity of the pacing lead to the fascicles/Purkinje fibres as they are not insulated at this level - in contrast to the proximal LBB. We observed that LBFP can often be achieved even when a LBB/Purkinje potential is not detected on the electrogram recorded from the lead. This finding suggests that the pacing lead does not need to be in very close proximity to the fascicles/Purkinje fibres in order to achieve LBFP capture. Distant LBB capture was demonstrated by a recent in vivo study.[24] It is likely that capture is achieved via a virtual electrode effect and more distant fibres can be captured by adjusting pulse duration.[24] This could further simplify LBFP by making it less dependent on precise lead positioning and potentially allow a transition to a more empirical approach of lead implantation, where the lead is deployed deep in the mid to basal septum. In contrast, the presence of a LBB potential is considered by Huang et al. as obligatory for proximal LBB capture.[11] In this respect proximal LBBP seems similar to His bundle pacing where even a reversed situation is often observed. i.e. potential is recorded albeit conduction system capture is absent.

Interestingly, LBFP seems to offer faster activation of the LV than LBBP or LVSP – as suggested by shorter paced V_6RWPT, and shorter paced QRS duration. The impact of proximal vs. distal LBB capture on V_6RWPT observed in the current study is in line with the results of the recently published electrophysiological analysis of LBB pacing.[25]

The shorter QRS duration which we observed with LBFP compared to proximal left bundle branch capture, is most likely the result of a reduction in the impact of the non-physiological capture of the adjacent septal myocardium, which is always observed during LBBAP, at outputs programmed for chronic pacing (≥ 2.0 V). Since the potential to QRS interval is short in this location one would expect breakout from the conduction

system to occur more rapidly, which limits the amount of the myocardium which is activated by the wavefront initiated by direct local myocardial stimulation. Furthermore, direct septal depolarization occurring closer to the area of the physiological activation of the septal myocardium via the Purkinje system, also brings LBFP closer to physiological activation compared to LBBP.
The favourable physiology, QRS characteristics, trend for lower complication rate and practicalities of distal fascicular/arborization capture suggest that LBFP might be the future of LBBAP.

Left Ventricular Septal Pacing – a simple method for indirect LBB activation.
In our experience, LV myocardial-only septal capture (i.e. LVSP) is a common procedural outcome. Even though LBBP/LBFP is preferentially targeted, LVSP was observed in 488 (21.5%) of MELOS patients. The percentage of LVSP in MELOS did not decrease with experience (Figure 2). This suggests the LVSP was perceived as a good procedural endpoint and/or that the current tools make it difficult/impossible to obtain LBB capture in all cases. LVSP may be considered as successful LBBAP for the following reasons: (i) pacing lead position and capture are in the LBB area, (ii) secondary LBB/fascicular engagement via retrograde activation from myocardial capture, while slightly delayed probably still plays a major role in LV depolarization, (iii) QRS morphology and duration are similar with LBBP and LVSP – while both stand in contrast to right ventricular paced QRS, (iv) hemodynamic and electrocardiographic studies of LVSP point to favourable activation/contraction of the ventricles,[26-28] (v) distinguishing LBBP/LBFP from LVSP may not always be clear-cut with the currently available criteria.[6]

Nevertheless, long-term clinical outcomes of LVSP vs. LBBP, especially in heart failure patients, might differ. In the LOT-CRT study, the LBB capture sub-group had better echocardiographic, electrocardiographic and clinical outcomes than LVSP patients.[29] Until results of randomized trials comparing capture types are available, it seems reasonable to strive, particularly in heart failure patients, for direct left conduction system capture in order to restore ventricular activation to be as physiological as possible.[30]

LBBAP capture types in other studies
In a dual centre study (n = 305) by Padala et al. the LBB/Purkinje potential to QRS interval was 23 ± 7.2 ms (vs 22.6 ± 6.5 ms in the current study) and in the majority of their cases (59%) LBB/fascicular Purkinje potentials were absent. Both findings suggest that LBFP or LVSP, rather than proximal LBBP, were the predominant forms of pacing.[8] In the studies by Wang et al. (n = 376) and Chen et al. (n = 250) paced QRS axis suggested LBFP rather than LBBP in 29.5% and 79.7% of cases, respectively. [21,20]

Complications related to the ventricular transseptal route of the pacing lead.
The overall complication rate observed with LBBAP (11.7%) is comparable with the complication rate reported for BiV-CRT implantations. [31] However, the ventricular transseptal route of the pacing lead is a source of new complications and concerns. We identified 209 cases (8.3%) where such complications were present (Table 4). This was in contrast to the previously reported outcome studies, none of which reported acute coronary events, chest pain during pacing, coronary vessel fistulas, lead helix entrapment problems or a significant rate of lead dislodgements.

A total of 0.99% (25/2533) patients experienced periprocedural chest pain, ST-segment elevation or significant troponin release. While acute coronary syndrome was reported in 0.4% (11/2533), the clinical course appeared to be benign, with no significant abnormalities detected on coronary angiography in those in whom this was performed and no significant regional wall motion abnormalities were detected. An acute coronary event during LBBAP implantation might be caused by a direct occlusion of the mid-portion of the septal perforator by the pacing lead. However, coronary artery spasm as a response to mechanical irritation or pacing should be postulated in cases with widespread transient ST segment elevation (Figure 4), since such ECG pattern is unlikely to be caused by the occlusion of a perforator branch.
Acute perforation into the LV cavity is a relatively common complication, reported in 0.3-6.0% by several other studies;[7-10;16] a comparable rate (3.67%) was seen in MELOS. We did not observe adverse clinical consequences as a result of this complication. Delayed septal perforation is a potentially serious complication with LBBAP, which we observed in 0.08% of cases, and required repositioning of the lead. We did not observe any strokes associated with this complication. The rate of delayed septal perforation in our study was comparable to that reported in the studies by Su et al. (0.15%) and Chen et al. (0.33%).[7,32]
LBBAP lead dislodgement was relatively common in our experience - seen in 38 cases (1.5%), while absent, or rare (0.3-0.9%) in other reports.[7-10] The lead displacement rate in our study is lower than that reported for LV leads implanted for BiV pacing and are comparable to those reported with conventional right ventricular pacing leads.[31]

Efforts should be made to limit the occurrence of LBBAP complications. We believe that with the development of leads specifically designed for LBBAP, including dedicated deep septal fixation mechanisms, it may be possible in the future to reduce lead dislodgement and septal damage/perforation rates and facilitate successful implantation.

Study limitations

Multiple centres and operators were involved in the study, as a result there was a lack of homogeneity with respect to the implantation technique, LBB capture criteria used during implantation, the methods used for QRS duration and interval measurements and enrolment strategy.

The lack of an independent central adjudication committee and partially retrospective retrieval of data might have resulted in underreporting of failures and complications. Nevertheless, these were reported in a higher percentage of patients than in any other study.

Follow-up analysis was limited to the procedural outcomes, complication, echocardiographic response and electrical parameters over an average follow-up of only 6 months. Follow-up 12-lead ECG was available only for 1357 patients, potentially influencing the reported incidence of loss LBBAP. Importantly, neither mortality nor heart failure episodes were analyzed.

Our results might be less applicable to non-European populations.

Conclusions

This is the largest study to date reporting multicentre outcomes of LBBAP. We found that LBBAP is feasible as a primary pacing strategy for any pacing indication, but that with current tools, implantation is more challenging in patients with heart failure, reduced ejection fraction and prolonged QRS duration. Complications of the transseptal lead route are not rare and while most were minor, there is room for further improvement in implant tools and techniques aimed at reducing these complications.

This study redefines LBBAP technique from a proximal to more a straightforward distal conduction system pacing technique via direct left bundle fascicular capture and LVSP with secondary left conduction system activation. QRS duration was shorter with LBFP compared to proximal left bundle capture, which suggests that pacing in this location successfully delivers physiological pacing.

Randomized trials comparing the clinical outcomes of LBBAP versus the current standard-of-care implantation techniques are warranted to formulate recommendations for clinical use of LBBAP.

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CHAPTER 7

7

Comparing ventricular synchrony in left bundle branch and left ventricular septal pacing in pacemaker patients.

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Abstract

Background: Left bundle branch area pacing (LBBAP) has recently been introduced as a novel physiological pacing stratgy. Within LBBAP, distinction is made between left bundle branch pacing (LBBP) and left ventricular septal pacing (LVSP, no left bundle capture).

Objective: To investigate acute electrophysiological effects of LBBP and LVSP as compared to intrinsic ventricular conduction.

Methods: 50 patients with normal cardiac function and pacemaker indication for bradycardia underwent LBBAP. ECG characteristics were evaluated during pacing at various depths within the septum: starting at the RV side of the septum: the last position with QS morphology, the first position with r' morphology, LVSP and – in patients where LBB capture was achieved – LBBP. From the ECG's QRS duration and QRS morphology in V1, and the stimulus-LVAT interval were measured. After conversion of the ECG into VCG (Kors conversion matrix), QRS area and QRS vector in tranverse plane (Azimuth) were determined.

Results: QRS area significantly decreased from 82±29 μVs during RV septal pacing (RVSP) to 46±12 μVs during LVSP. In the subgroup where LBB capture was achieved (n=31), QRS area significantly decreased from 46±17 μVs during LVSP to 38±15 μVs during LBBP, while LVAT was not significantly different between LVSP and LBBP. In patients with normal ventricular activation and narrow QRS, QRSarea during LBBP was not significantly different from that during intrinsic activation (37±16 vs. 35±19 μVs, respectively). The Azimuth significantly changed from RVSP (-46±33°) to LVSP (19±16°) and LBBP (-22±14°). The Azimuth during both LVSP and LBBP were not significantly different from normal ventricular activation. QRS area and LVAT correlated moderately (Spearman's R=0.58).

Conclusions: ECG and VCG indices demonstrate that both LVSP and LBBP improve ventricular dyssynchrony considerably as compared to RVSP, to values close to normal ventricular activation. LBBP seems to result in a small, but significant, improvement in ventricular synchrony as compared to LVSP.

Introduction

When animal studies demonstrated that normal left ventricular (LV) function was preserved during pacing of the left side of the interventricular septum (IVS)(1), this so called left ventricular septal pacing (LVSP) was applied for the first time in humans using the same transvenous approach through the IVS.(2) Subsequently, Huang et al. demonstrated that with a similar approach it was feasible to capture the left conduction system by direct stimulation of the left bundle branch (LBB) resulting in a normal LV activation. (3). However, there seems to be a considerable overlap between LVSP and left bundle branch pacing (LBBP). Reported LBB capture success rates vary from 60% to 90%(4, 5) and consequently up to one-third of patients are paced without LBB capture. Despite the increasing number of publications on LBBP, many unknowns remain, such as the electrophysiological differences between LVSP and LBBP. A recently proposed measure for electrical dyssynchrony is the QRS area.(6) This three-dimensional QRS area expresses non-opposed electrical forces, and high values of this parameter indicates dyssynchronous electrical activation, even independent of the QRS morphology.(7) QRS area has also been shown to have a strong association with clinical and echocardiographic response to CRT.(8)

It was the aim of the present study to explore the electrophysiological changes in the course of the pacing lead penetrating the IVS. To this purpose we evaluated QRS duration, QRS morphology and QRS area in patients undergoing LBBP implantation during RV pacing, deep LVSP and LBBP.

Methods

Patient selection

Patients suffering from symptomatic bradycardia without heart failure with an indication for pacemaker implantation underwent LBBP at the Maastricht University Medical Center (MUMC+) and at the Department of Cardiology of University Hospital Kralovske Vinohrady in Prague, Czech Republic after informed written consent was obtained. The study was approved by the local ethics committee (NL: METC 2019-1313, CR: EK-VP/06/0/2020).

Implantation procedure

Pacemaker implantation with LBBP was performed as described previously.(9) In short, the right atrial (RA) lead was implanted according to routine clinical practice. Subsequently, the ventricular pacing lead (Medtronic 3830 lead) was inserted through the C315 His-sheath. An intracardiac electrogram was recorded from the lead tip using the electrophysiological recording system (Bard Electrophysiology Lab System, MA,

USA). The His bundle electrogram was identified in the right anterior oblique (RAO) 20-25° position and fluoroscopic image of the lead position was recorded as a reference. Subsequently the sheath and the lead were advanced 1–2 cm toward the RV apex. In this region, unipolar pacing was performed aiming for a paced QRS morphology with a notch in the nadir in lead V1. At this site, the lead was fixed in the RV septum with 1-2 rotations and then advanced to the left side of the IVS. In the process of advancing the pacing lead, fluoroscopic image and pacing parameters and morphologies were monitored to avoid displacement of the lead or perforation of IVS.

When advancing from right to left through the IVS, local electrogram from the lead tip as well as paced 12-lead ECGs were recorded after each rotation resulting in advancement of the lead. The number of attempts to implant the lead in the IVS as well as the final position were left to the implanting cardiologist. Capture of the left bundle was attempted in all patients. IVS pacing locations and definitions are depicted in figure 1.

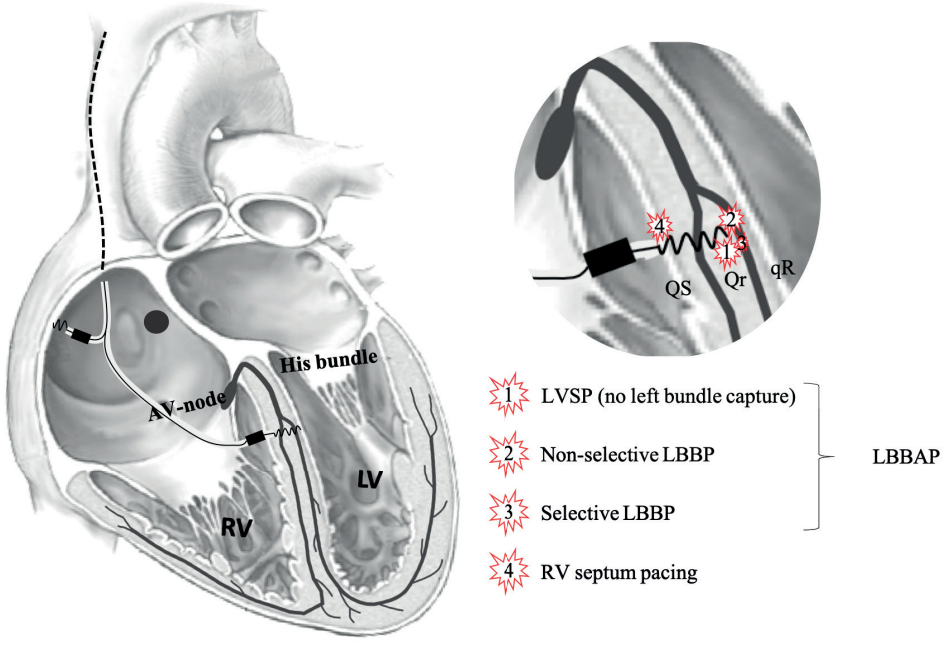

Figure 1. Schematic overview of the heart and the conduction system. Illustrated is where the lead penetrates the interventricular septum, pacing definitions are clarified and shown is which QRS morphologies are typically seen.

Pacing and capture definitions

RV septal pacing (RVSP) was defined as pacing with the lead tip at the RV septum before rotations were performed. Left bundle branch area pacing (LBBAP) was defined as the final position of the lead in all patients combined (no discrimination between LVSP and LBBP).

LBB capture was defined as: 1) paced (pseudo) right bundle branch block (RBBB) QRS morphology with terminal r/R' in lead V1, 2) recording of a LBB potential during intrinsic rhythm (only in patients with normal ventricular activation), 3) constant left ventricular activation time (LVAT) during high (8V) and low (2V) pacing output, and 4) the demonstration of transition from non-selective to selective LBBP (sLBBP) or non-selective LBBP (nsLBBP) to LV myocardial only capture during decreasing pacing output. sLBBP was defined as a change in QRS morphology without a change in S-LVAT during decreasing the pacing output from nsLBBP combined with an isoelectric interval between pacing spike and QRS complex (pacing spike distinct from ventricular EGM). nsLBBP was defined as a change in QRS morphology which occurred after increasing the pacing output from sLBBP or LVSP.

LVSP was defined as the last position of the lead before capture of the left conduction system (as defined previously) with r' present in lead V1.

An R-wave with smaller amplitude compared to the preceded Q-wave is defined as r' (either Qr morphology or Rsr' morphology). R' is defined as R-wave with larger amplitude compared to preceding Q-wave (either qR morphology or rsR' morphology).

Electrical measurements

12-lead ECGs during pacing were recorded after each set of rotations resulting in advancement of the lead. After the procedure, these ECG's were assessed on QRS duration and morphology, especially R-wave morphology in V1 and the stimulus-LVAT interval (S-LVAT) was measured. QRS duration was measured from onset of first deflection, excluding the pace spike. LVAT was measured as the interval between pacing stimulus and R-peak in lead V5.

Electrical dyssynchrony on the ventricular level was determined by converting the 2-dimensional ECG into a 3-dimensional vectorcardiogram (VCG). The VCG was synthesized as described previously.(6, 10) In brief, the original digital signals were extracted from the ECG files stored in the Bard system. Subsequently, custom Matlab software (MathWorks Inc, Natick, MA) was used to convert the 12-lead ECG into the 3 orthogonal vectorcardiography leads (X, Y, and Z) using the Kors conversion matrix, as shown in figure 2.(11) QRS area was calculated as the sum of the area under the QRS complex in the calculated vectorcardiographic X, Y, and Z lead (QRS area=$[QRS_{area,x}{}^{2}+QRS_{area,y}{}^{2}+QRS_{area,z}{}^{2}]^{1/2}$).

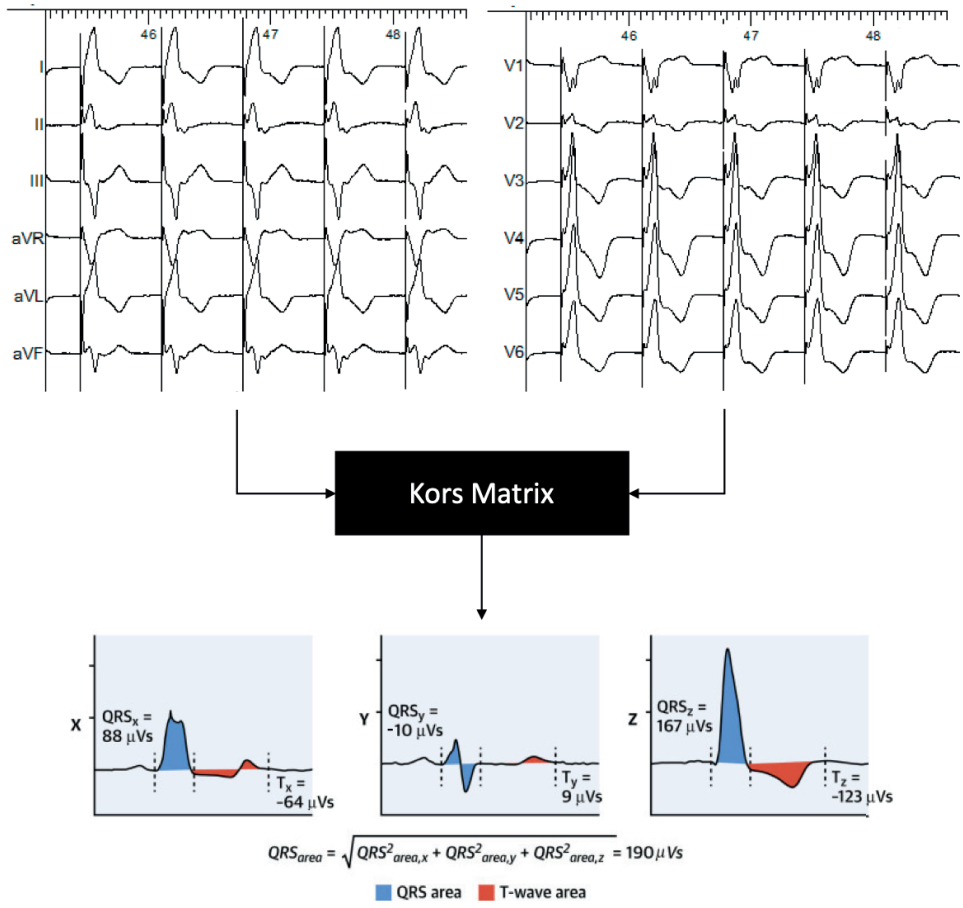

Figure 2. Example of a 3-dimensional vectorcardiogram (VCG) constructed from a 12-lead electrocardiogram extracted from the electrophysiology recording system.

Data collection and analysis

Demographic data and medical history of all patients were collected at enrollment. Procedure related characteristics including ECG and intracardiac EGM pattern, LV peak activation time, the pacing spike-QRS interval, His-QRS interval, LBB potential-QRS interval, fluoroscopy exposure time and doses were recorded during implantation. Pacing electrical parameters (pacing threshold, lead impedance, and R-wave amplitude) were measured during and 1-day post-implantation.

For post-procedural ECG and VCG analysis, 3-dimensional vectorcardiograms (VCGs) were synthesized from the recorded 12-lead ECGs using the Kors matrix.(11) To this purpose, 30 seconds recordings were extracted from the EP recording system and ectopic ventricular beats were excluded. VCG parameters, including QRS area and Azimuth, were calculated using customized software programmed in MATLAB (MathWorks, Natick, Massachusetts).

Statistical analysis

The number and percentage were used as descriptive statistics for categorical variables. Continuous variables were expressed as mean ± standard deviation. Differences between 2 groups were compared using the Student t-test for continuous variables. The paired t test was used to compare the differences between 2 means within the same group. Comparisons among ≥3 pacing conditions within individuals were made using repeated measures ANOVA with Bonferroni multiple comparisons procedure applied to pairwise comparisons. A 2-sided *P* value of <.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics version 25.0 (Chicago, IL, USA).

Results

A total of 50 patients who underwent pacemaker implantation with LBBP were prospectively included in the present study. Patient characteristics are summarized in table 1. The patient cohort was predominantly male (61%), with a LV ejection fraction (LVEF) of 57±7%. Two-thirds of patients had normal ventricular activation with an average QRS duration of 95±13 ms.

Table 1. Characteristics of patient cohort used for analysis.

Characteristics (n=50)	**Mean ± SD or %.**
Male sex	61%
Age (years)	74 ± 10
Medical history	
Hypertension	61%
Atrial fibrillation	44%
Coronary artery disease	37%
Myocardial infarction	17%
Echocardiographic parameters	
LVEF (%)	57 ± 7
LV end diastolic diameter (mm)	51 ± 7
LV end systolic diameter (mm)	36 ± 8
IVS thickness (mm)	9 ± 1
Electrocardiographic parameters	
Heart rate (bpm)	66 ± 21
QRS duration (ms)	
all patients	113 ± 29
normal ventricular activation	95 ± 13
Other (escape, LBTB/RBTB)	141 ± 25
Pacemaker indication	
Sinus bradycardia	16%
Bradycardia-tachycardia syndrome	12%
3rd degree AV-block	35%
Ablate and pace	10%
Other	27%

Procedure-related measurements

In patients with normal ventricular activation, a LBB potential (LBB_{pot}) was observed in 37/50 patients (74%) with an average LBB_{pot}-QRS interval of 23±8 ms. LBB capture was achieved in 31/50 patients (62%). On average, the delay between pacing stimulus and LVAT was 78±11 ms.

Unipolar post-procedural (1-day follow-up) LBBP pacing threshold, pacing impedance and sensing values were 0.65±0.30 V, 618±225 Ω and 13±7 mV, respectively.

Electrophysiological effects of LBBAP

Compared to RVSP, LBBAP (all patients) significantly shortened QRS duration from 148±17 ms to 123±22 ms (figure 3a). In patients with normal ventricular activation (n=37), QRS duration significantly increased from 96±11 ms to 142±6 ms during RVSP and decreased subsequently to 118±24 ms during LBBAP.

For the whole group, QRS area decreased significantly from 83±34 μVs during RVSP to 45±22 μVs during LBBAP. In the subgroup of patients with normal ventricular activation, QRS area increased from 35±19 μVs during intrinsic ventricular activation to 75±24 μVs during RVSP, and decreased during LBBAP to 41±14 μVs (figure 3b).

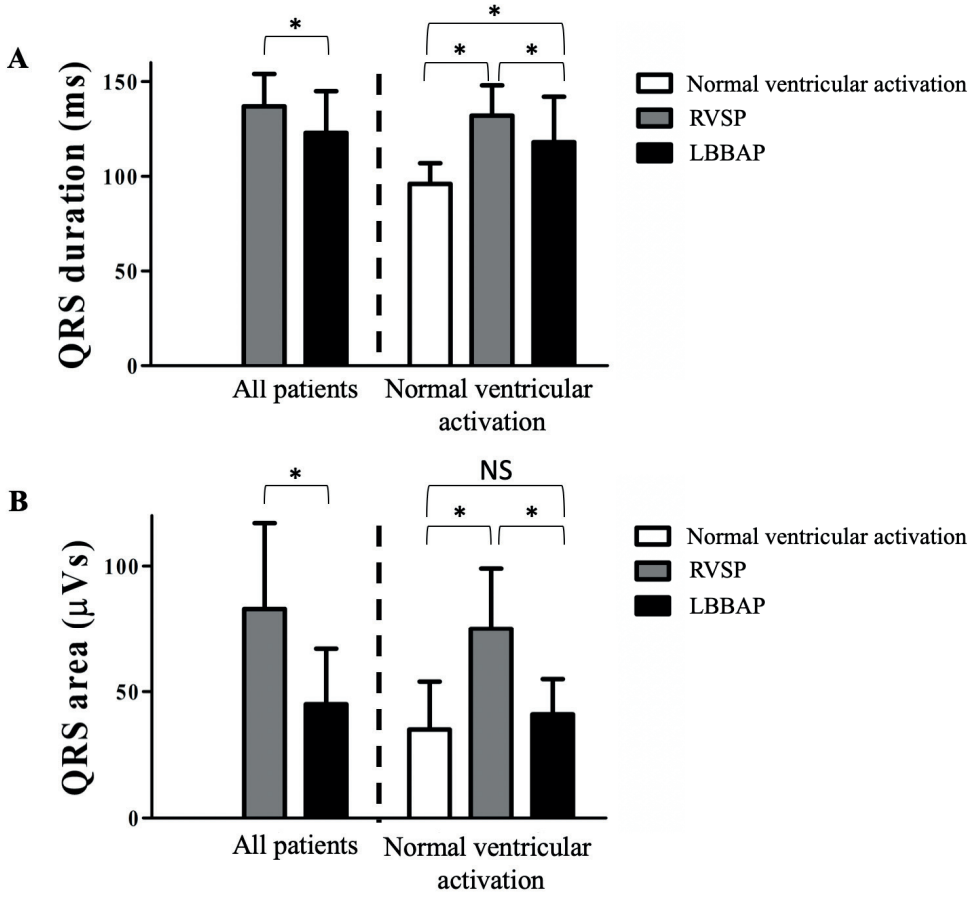

Figure 3. Panel A shows the QRS duration in milliseconds as measured by VCG analysis during RVSP and LBBAP (final lead position). In the subpopulation with normal ventricular activation, the QRS duration is also measured during intrinsic rhythm (no pacing).

Panel B shows the QRS area in microvolt seconds as measured by VCG analysis during RVSP and LBBAP (final lead position). In the subpopulation with normal ventricular activation, the QRS duration is also measured during intrinsic rhythm (no pacing). * $p<0.05$

Beyond QRS duration and QRS area, also the QRS vector in the transverse plane (Azimuth) was analyzed. As shown in figure 4a, LBBAP normalizes the Azimuth when compared to RVSP. Between LVSP and LBBP, there was as significant difference in Azimuth (19±16° and -22±14°, respectively, figure 4b), both not significantly different from normal ventricular activation (-8±18°).

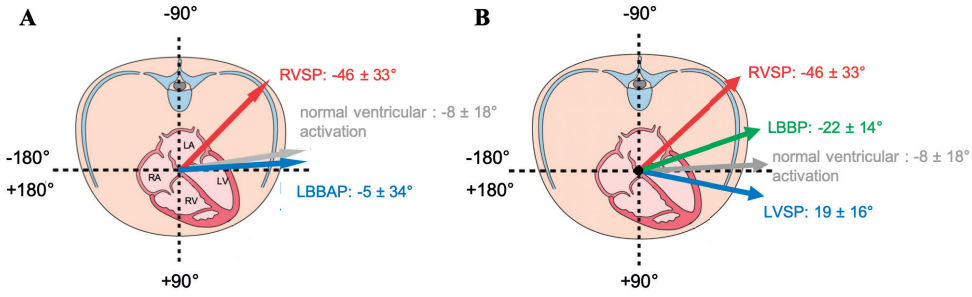

Figure 4. Schematic view of the transversal plane. **Panel A:** the angle of the QRS vector in this plane ("Azimuth") is depicted for normal ventricular activation (in grey), RVSP (in red) and LBBAP (in blue). **Panel B:** Azimuth normal ventricular activation (in grey), RVSP (in red), and discriminated between LBBP (in green) and LVSP (in blue).

Electrical characteristics of LVSP and LBBP

The paced QRS duration, morphology and QRS area were assessed during step-by-step screwing from the right to the left side of the IVS. Figure 5a shows a typical example of the transition of the QRS complex when pacing the lead at various IVS depths. In this example QRS area gradually decreased from 115 µVs during RVSP to 38 µVs during selective LBBP. When r' became apparent in lead V1, QRS area had largely decreased to 55 µVs. During the final few steps towards the left side of the IVS, the QRS area further decreased from 55 µVs at first visible r' to 43 µVs during LVSP. In the final step, QRS area even further decreased to 38 µVs during LBBP. This typical example shows the additional small improvement in ventricular synchrony when LBB capture is obtained. Figure 5b illustrates that the largest reduction in QRS area is obtained when an r' becomes present in lead V1.

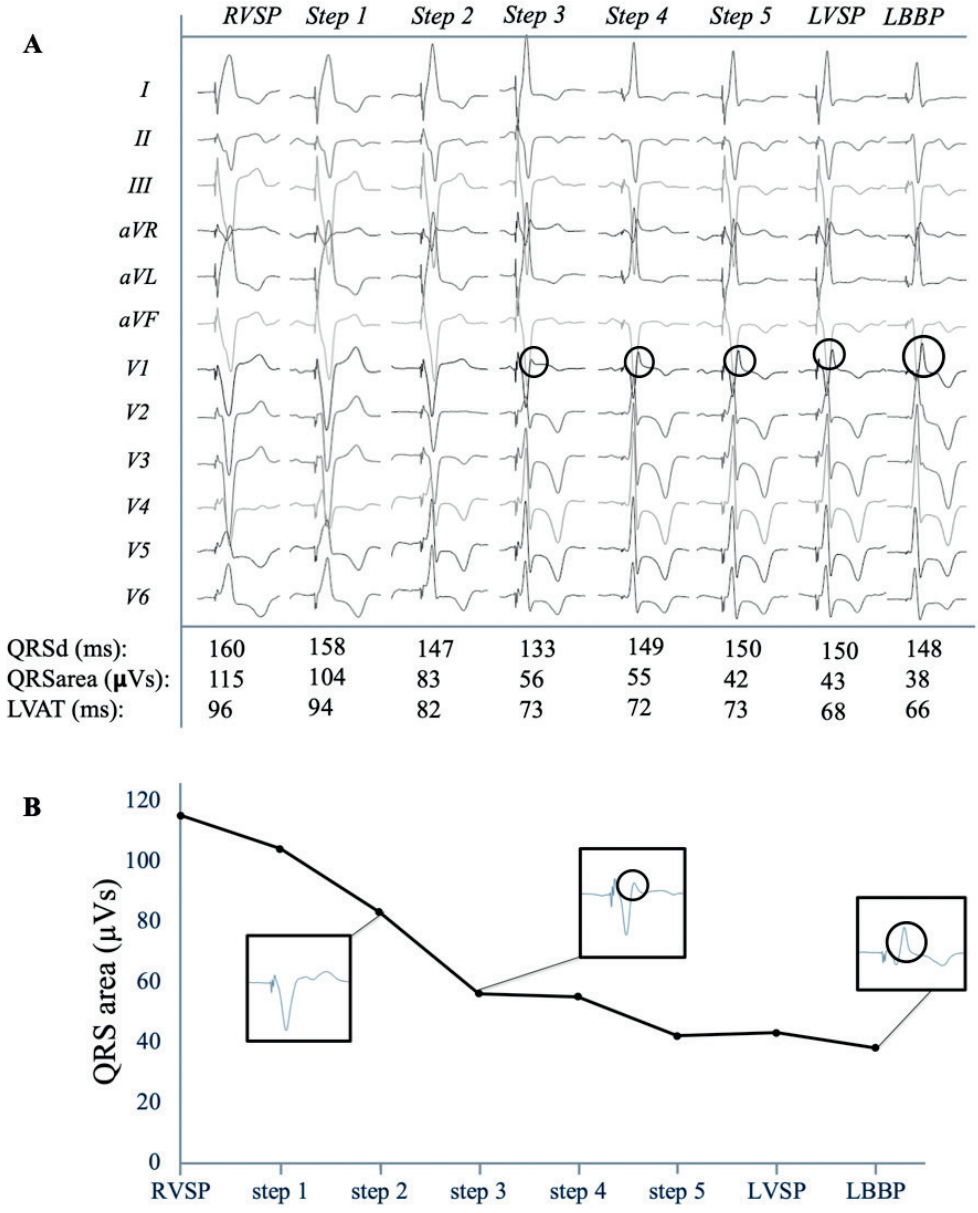

Figure 5. Panel A shows a typical example of the 12-lead electrocardiogram of each step from right (RVSP) to left through the interventricular septum with selective LBBP being the final step. QRS duration, area and stimulus-LVAT are given. **Panel B** shows the decrease in QRS area for different QRS morphologies. R'/R' is indicated with circle. QRSd: QRS duration.

The change in QRS area for all patients is shown in figure 6a, differentiated between patients where capture of the left bundle was achieved (LBBP; in black) or not (LVSP; in grey). Steps were grouped according to the following QRS morphologies: RVSP (initial pacing site), the last position with QS morphology, the first position with r', LVSP and – in patients where LBB capture was achieved – LBBP. In patients where no LBB capture was achieved (LVSP group), QRS area significantly decreased from 82±29 μVs during RVSP to 46±12 μVs during LVSP. In patients where LBB capture was achieved, QRS area significantly decreased from 78±23 μVs during RVSP to 46±17 μVs during LVSP and further to 38±15 μVs during LBBP.
In the subgroup of patients with normal ventricular activation where LBBP was achieved (n=20), QRS area during LBBP was not significantly different from normal intrinsic ventricular activation (37±16 vs. 35±19 μVs, respectively), while QRS during LVSP was significantly larger compared to normal intrinsic ventricular activation (48±17 vs. 35±19 μVs, respectively).

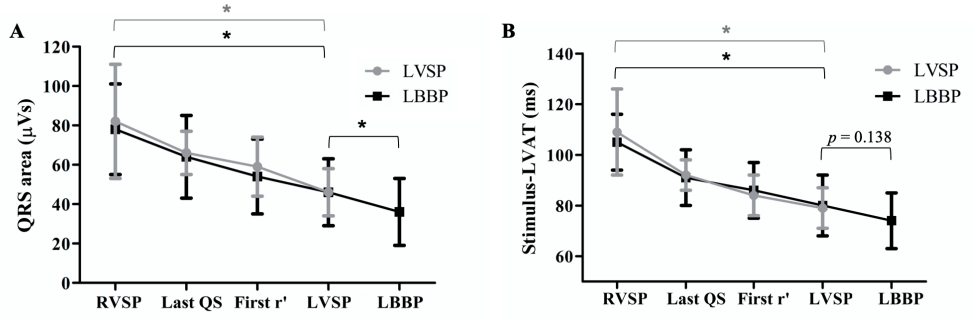

Figure 6. Panel A: average absolute QRS area values for patients with (LBBP; in black) and without (LVSP; in grey) left bundle branch capture.
Panel B: average absolute stimulus-LVAT intervals for patients with (LBBP; in black) and without (LVSP; in grey) left bundle branch capture.
Steps through the interventricular septum were grouped according to QRS morphology. *p<0.05

Compared to RVSP, LBBP significantly decreased S-LVAT from 105±11 ms to 74±11ms. LVSP decreased S-LVAT from 109±14 ms during RVSP to 81±9ms. In patients where LBB capture was achieved, S-LVAT was similar between LBBP and LVSP (73±15 vs. 81±13 ms, P=0.138). Overall, there was a moderate correlation between S-LVAT and QRS area (Spearman's R=0.58, p<0.05).

Discussion

To our knowledge, this is the first study investigating the electrophysiological effects of LBBAP during the course of the lead penetrating the IVS. The primary results of this study show that among patients with a bradycardia indication for pacing therapy, QRS area and QRS vector normalize during LBBAP. Furthermore, when the results were evaluated for capture of the left bundle, LBBP produces a significantly lower QRS area as compared to LVSP, although absolute differences are small. QRS area of the final lead position correlates moderately with LVAT and the largest decrease is achieved at first few steps penetrating the septum. Finally, the presence of r' in lead V1 can be used to guide lead implantation achieving a significant lower QRS area.

QRS duration in LBBAP

Compared to normal ventricular activation, QRS duration was significantly increased by RV pacing in our study population. This is in agreement with studies investigating RV pacing both in patients with normal cardiac function and in patients with heart failure. This emphasizes the need for replacement of the RV as standard lead implantation site, since especially pacing the RV will prolong QRS duration(12) and patients with RV paced QRS duration ≥150 milliseconds are of increased risk of developing pacing-induced cardiomyopathy.(13, 14) RV pacing can eventually lead to adverse cardiac remodelling increasing the risk of atrial fibrillation (AF), heart failure and cardiovascular death. (15, 16) The present study showed that QRS duration was significantly shorter during LBBAP as compared to RV pacing, which is in line with previous studies investigating LBBAP.(5, 17) To further explore the relationship between IVS pacing location and QRS duration, a subgroup of our cohort with normal ventricular activation was evaluated. In these patients, QRS duration was significantly increased during LBBAP compared to intrinsic ventricular activation, which is likely due to capture of local myocardium and delayed activation of the RV that becomes present on the ECG as a right bundle branch block pattern during LBBP. This increase in QRS duration in LBBAP was also found in other studies.(4)

QRS morphology in LBBAP

Beyond QRS duration, the paced morphology of the QRS complex was evaluated during lead advancement through the IVS. We found that the largest reduction in QRS area was achieved when the r' became visible in lead V1. Further advancement of the lead, usually resulting in further increase in amplitude of r', only resulted in a relatively small further decrease of QRS area. This might imply that QRS morphology, especially in lead V1, might be used as guidance for LBBP lead placement. The presence of an R' in V1 during LBBAP lead implantation is illustrative for LVSP and further advancement with the goal of reaching LBB capture should be performed more carefully avoiding

perforation into the LV cavity. In a small number of patients, r' will not became visible and paced morphology will exhibit a QS pattern, potentially caused by hypertrophic or dilated LVs with impaired intraventricular conduction.(18) Determining the exact depth within the septum remains difficult, since it is usually not possible to perform ventricular pacing during screwing with conventional connector cables and the exact penetration depth is unclear from just the fluoroscopic images. However, Jastrzebski et al.(19) has recently shown that the ventricular ectopy that becomes apparent as a result of screwing is present in 96% of the cases and that these so-called fixations beats are identical to the paced QRS morphology. Therefore, these fixation beats can help to identify the depth of the LBBP lead and appearance of the r' morphology can be interpreted as a warning sign that the left side of the interventricular septum is reached. Discrimination between LBBP with and without LBB capture is now primarily bases on electrocardiographic criteria, such as QRS morphology, LVAT, and the presence LBB potential. We are in need of prospective evaluations of LBB capture.

The QRS morphology is also helpful in case septal fibrosis or scar prevents the ventricular lead to be advanced further through the septum towards the left conduction system. If r' becomes apparent in V1, which is suggestive for deep LV septal pacing, this study shows that there is already significant improvement in electrical dyssynchrony when compared to RV septal pacing. The latter would be of particular convenience when in doubt on when to accept the LBBP lead position or when to go for a new attempt to penetrate the IVS.

Finally, using the morphology of the QRS complex to guide the LBBP lead implantation would be of particular interest for centres without an advanced electrophysiological recording system. These centres especially need the QRS morphology guidance to determine the depth of the LBBP lead and simple tools such as the presence of R' in V1 can be very helpful.

QRS area as measurement for ventricular synchrony

Our group previously proposed QRS area as measure for electrical (dys)synchrony,(6) since high values of this parameter indicates dyssynchronous electrical activation, even independent of the QRS morphology.(7) Also, QRS area has also been shown to have a strong association with clinical and echocardiographic response to CRT.(8) More recently, Ghossein et al showed that the decrease in QRSarea due to CRT is a strong independent predictor of echocardiographic and clinical CRT response.(20) In the present study, QRS area also correlated significantly with LVAT and figure 5 illustrates that the transseptal behavior of QRS area and LVAT are very similar, altogether validating QRS area as measurement for ventricular synchrony.

QRS area in LBBAP

The results of the present study show that in line with QRS duration, QRS area is significantly lower during LBBP as compared to RVSP. In patients with normal ventricular activation, QRS area during LBBP was even close to values of the intrinsic QRS, which indicates that LBBP maintains ventricular synchrony at a level close to normal. This is in agreement with previous studies demonstrating that LBBP maintains ventricular synchrony at levels comparable to His bundle pacing (HBP) and even to intrinsic ventricular activation.(5, 21-23) Since pacing induced electrical dyssynchrony is minimal in LBBP, LV function is hypothesized to be preserved in patients with underlying narrow QRS complex.

During deep septal pacing without evidence of LBB capture (defined as LVSP) QRS area was somewhat higher compared to LBBP but the absolute difference was small. This confirms our hypothesis that the greatest reduction in dyssynchrony is already achieved by pacing subendocardially on the left side of the septum. Although the additional effort of attempting LBBP can lead to further narrowing of the QRS area, the latter might justify the choice to leave the lead when the septum is difficult to penetrate further.

Long-term outcome

Since pacing induced electrical dyssynchrony is minimal in LBBAP,(5, 21-23) LV function is likely to be preserved by LBBAP in patients indicated for bradycardia pacing. Since pacing induced cardiomyopathy is associated with unfavorable long-term clinical outcomes, including higher rates of heart failure hospitalizations and all-cause mortality(24), preservation of LV function in LBBAP might improve clinical outcome. There are few studies showing a possible effect of conduction system pacing on mortality and heart failure hospitalization in patients indicated for bradycardia pacing in the setting of preserved LV function. This is likely due to the short follow-up period. The largest study to date, however, showed that in over 750 patients the primary combined outcome of death, heart failure hospitalization, or upgrade to CRT was lower in the HBP group compared to the RVP group.(25) Whether clinical outcomes differ between LBBAP and RV pacing has yet to be demonstrated in RCT's.

Study limitations

Our study should be interpreted in light of several methodologic limitations. First, this was a prospective study from two centers with a limited number of patients. Further, the exact location of pacing in the conduction system with LBBP is often hard to determine and validated LBB capture criteria are lacking. Finally, while QRS area has been shown to have a strong association with clinical and echocardiographic response to CRT, this is not yet demonstrated for bradycardia patients.

A prospective comparison between LVSP and LBBP is needed with broad patient populations for pacing therapy, investigating electrophysiological effects – and preferably

different measurements of electrical dyssynchrony, such as QRS area, LVAT and SDAT (26), or measurements obtained with ultra-high frequency ECG (eDYS) (27) – as well as mechanical effects, such as systemic or LV pressure and echocardiographic response.

Conclusion

Electrocardiographic and vectorcardiographic indices demonstrate that ventricular activation is more synchronous during both LBBP and LVSP compared to RVSP and close to values during normal intrinsic ventricular activation. Electrical synchrony is similar but slightly better during LBBP compared to LVSP.

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CHAPTER 8

8

Acute hemodynamic and electrophysiological effects of left bundle branch area pacing: design and preliminary results of a mechanistic patient study.

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Introduction

Many studies have demonstrated the feasibility and stability of left bundle branch area pacing (LBBAP) in patients with variable pacemaker indications. LBBAP is proposed to be a novel physiological pacing method for achieving or maintaining electric synchrony. After experiments in our lab demonstrated that the transseptal implantation technique used in left ventricular septal pacing (LVSP) is safe, feasible and effective, [1-3] it was demonstrated by Huang et al. in a patient with heart failure (HF) and left bundle branch block (LBBB) that with a similar technique the left bundle branch (LBB) could be stimulated ("left bundle branch pacing"). LBBP has now been proven to be safe and feasible in both anti-bradycardia pacing[4] and cardiac resynchronization therapy (CRT),[5] the latter has traditionally been performed using biventricular pacing (BVP). Conventional BVP, however, causes a dyssynchronous cardiac contraction as it is a non-physiological fusion of paced propagation.[6]

Both LVSP and LBBAP, commonly referred to as LBBAP, are intended to overcome the detrimental effects of RV pacing.[7, 8] Although intended, capture of the LBB is not always achieved in LBBP. Also, the portion of post-implantation loss of LBB capture is yet to be thoroughly investigated. Therefore, there is significant overlap between LBBP and LVSP and a significant portion of patients reported to be treated with LBBP are in fact treated with LVSP.
Despite the many recent publications regarding LBBAP, there are still many unknowns that need to be investigated, such as the optimal septal pacing lead depth and the effect or necessity of additional LBB capture. It is of importance to obtain more mechanistic insight in this therapy. Results of the proposed study could have implications in both the bradycardia population as well as the CRT population, as it might clarify which subpopulations may benefit from either LVSP or true LBBP.

Methods

The "Mechanistic insights in left bundle branch and left ventricular septal pacing" (acronym MASTER-LV) study is a multicenter, prospective clinical trial comparing LBBAP with RV apex pacing and investigating the additional effect of capturing the LBB in LBBAP. The trial was designed by the authors in collaboration with the sponsor (Medtronic). The trial is conducted in 2 centers in The Netherlands. The first patient was enrolled in May 2021, and recruitment of patients is still ongoing. Total planned inclusions is 40 patients. This study describes the preliminary results of the first ten consecutive patients.

The trial is conducted in compliance with the Declaration of Helsinki. The clinical investigation plan has been approved by the local regulatory authorities ethics committee (NL74074.068.20 / METC 20-066). All patients signed written informed consent before enrollment.

Study population

The inclusion and exclusion criteria are listed in table 1. Patients clinically indicated for implantation (de novo or upgrade from RV pacing) of a permanent pacemaker were screened. The aim of the study is to include 40 consecutive patients. The intent is to include approximately 20 patients referred for pacemaker implantation with a structurally normal heart and approximately 20 patients with reduced LV ejection fraction (LVEF). In both patient populations, patients who do not participate in the study, either because they do not meet the inclusion and/or exclusion criteria or because they are not willing to participate in the study, will receive a standard pacemaker implantation (the lead will be implanted in the same position, whether patients participate or not) but without the intra-procedural study measurements.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
Indication for permanent cardiac pacing:
• pacing indication in structurally normal heart because of:
- Sinus node dysfunction
- Atrioventricular block
- Atrial tachyarrhythmia refractory to antiarrhythmic medications that required atrioventricular node ablation
• pacing indication with reduced LV ejection fraction
- pacing indication with reduced LV ejection fraction and expected high percentage of ventricular pacing
- Heart failure with wide QRS and LBBB and reduced LVEF
Exclusion criteria
Age < 18 years
Incapable of giving informed consent
Severe aortic valve stenosis
Significant peripheral vascular disease

Study procedures

Figure 1 outlines the trial procedures. Eligible patients were assessed and enrolled upon signing of informed consent. Participants consist of patients with structurally normal hearts (anti-bradycardia indication) and patients with heart failure and LBBB (CRT indication).

In all patients, the atrial lead is positioned in the right atrial appendage according to routine clinical practice. The implantation procedure is described in detail previously.

In short, the LBB area pacing lead (Medtronic 3830 lead) is positioned via transvenous approach at the right side of the interventricular septum (IVS) and advanced (screw-in) to the endocardial border of the LV septum with the aim to obtain LBB capture. Systemic blood pressure (BP) is continuously measured through an arterial pressure catheter (Namic Convenience Kit, Navylist Medical, MA, USA) introduced in the right femoral artery. Through the same arterial sheath, a temporary decapolar electrophysiology (EP) catheter (Biosense Webster, CA, USA) is – after administration of heparin – advanced into the LV cavity and placed against the LV septum. This catheter is used to record (anterograde or retrograde) His-Purkinje potentials, which are used to determine LBB capture. A temporary quadripolar EP catheter (Biosense Webster, CA, USA) is placed in the RV apex through a femoral venous puncture, for the purpose of baseline RV apex pacing in all patients.
A non-invasive body surface mapping system containing 55 electrodes (ECG-Belt Research System, Medtronic) is used to perform body surface electrocardiographic mapping.

Patients will undergo a routine pacemaker follow-up at 2 weeks, 3 months and 6 months to evaluate the sensing and pacing threshold values of the implanted LBB area pacing lead. Echocardiography will be performed immediately after as well as 6 months after the implantation procedure to evaluate LV dimensions and strain indices.

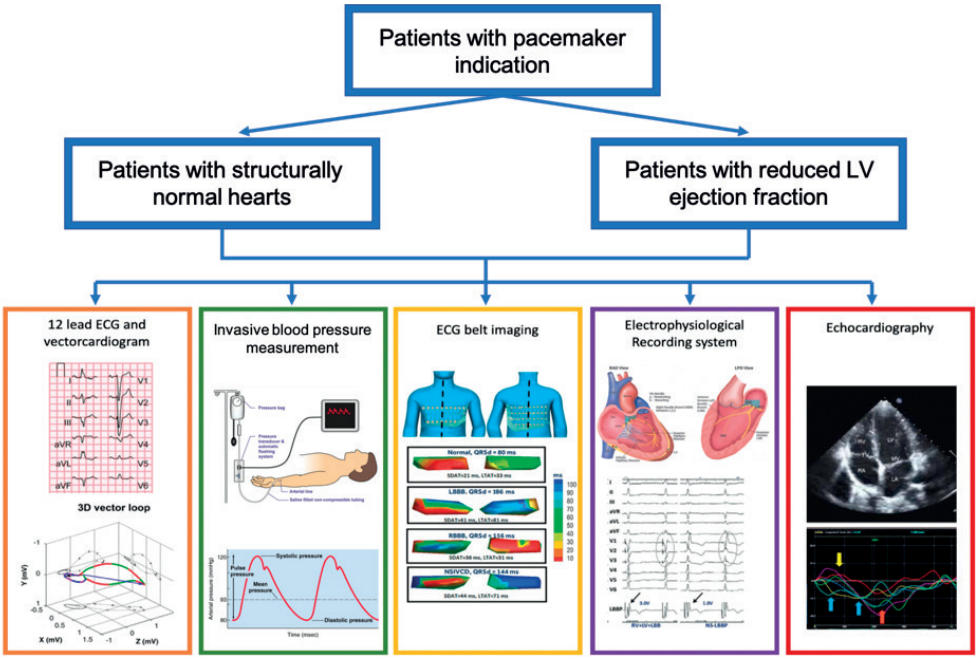

Figure 1. Outline of the clinical measurements that are used in all patients to study the acute electrophysiological and hemodynamic effects of left ventricular septal and left bundle branch pacing on the heart.

Pace protocol

Electrical and hemodynamic measurements are performed during intrinsic rhythm (no pacing) and when pacing at different IVS penetration depths of the pacing electrode, starting at the RV side of the septum and advancing to mid-septum, left side of septum and finally near the left bundle branch. All atrio-ventricular synchronized (DDD or DOO mode) paced measurements are compared to baseline RV apex pacing. The pacing protocol (figure 2) is performed 10 bpm above intrinsic rhythm to ensure pacing capture. The AV-delay during pacing is programmed 60 ms shorter than the AV-delay measured during atrial pacing or – in case this delay is >200 ms – set at a fixed delay of 150 ms.

To account for baseline drift, the effect of pacing was quantified as a percentage change compared with the mean of the 2 adjoining baseline measurements ("on effect" and "off effect"). Results were calculated by averaging values for all parameters over the first 10 beats, excluding inappropriate beats such as ventricular pre-mature beats. The protocol was then repeated and measurements outcome was averaged.

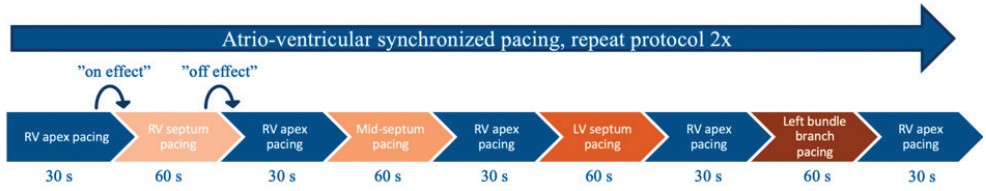

Figure 2. Pace protocol during which the electrophysiological and hemodynamic effects of different penetration depths of the ventricular pacing lead are assessed.

Left bundle branch capture was diagnosed in case one (or both) of the following criteria were met:

- The presence of a transition from non-selective LBBP (ns-LBBP) to selective LBBP (s-LBBP) or from ns-LBBP to LV myocardial only capture (=LVSP) during decreasing pacing output.
- The presence of His-Purkinje potentials between the pacing stimulus and QRS interval, measured on the decapolar LV septal catheter.
- LBB potential-V6RWPT interval equals the pacing stimulus-V6RWPT interval.[9]

s-LBBP was defined as a change in QRS morphology without a change in V6RWPT when decreasing the pacing output from ns-LBBP, combined with a pacing artefact distinct from the ventricular EGM. ns-LBBP was defined as a change in QRS morphology which occurred after increasing the pacing output from s-LBBP or LVSP.

LVSP was defined as paced QRS morphology with r' present in lead V1 but without evidence of LBB capture.

Electrical measurements and set-up

12-lead ECGs were continuously recorded during intrinsic rhythm, RV apex, RV septal pacing, mid-septum pacing and LBB area pacing. QRS duration was measured including the pace spike. In case of present LBB potential, the interval between the LBB potential and QRS onset, as well as the interval between LBB potential and the R-wave peak in lead V6 were measured.

QRS area, a measure of ventricular electrical dyssynchrony,[10] was determined by converting the 2-dimensional ECG into a 3-dimensional vectorcardiogram (VCG). The VCG was synthesized as described previously.[10, 11] In brief, the original digital signals were extracted from the ECG files stored in the Bard system. Subsequently, custom Matlab software (MathWorks Inc, Natick, MA) was used to convert the 12-lead ECG into the 3 orthogonal vectorcardiographic leads (X, Y, and Z) using the Kors conversion matrix.[12] QRS area was calculated as the sum of the area under the QRS complex in the calculated vectorcardiographic X, Y, and Z leads (QRS area = $[QRS_{area,x}{}^2+QRS_{area,y}{}^2+QRS_{area,z}{}^2]^{1/2}$). From the ECG-Belt electrodes an average left-sided and right-sided ventricular activation time (LVAT, RVAT) and standard deviation of activation across the whole chest (SDAT) can be calculated. The heterogeneity of the LVAT is a measure of electrical dyssynchrony.[13]

Simultaneously with all electrical measurements, systemic blood pressure is continuously recorded via a femoral artery pressure catheter. An example of the software set-up is shown in figure 3. Blood pressure, 12-lead ECG, and intracardiac electrograms are continuously measured and displayed during all measurements.

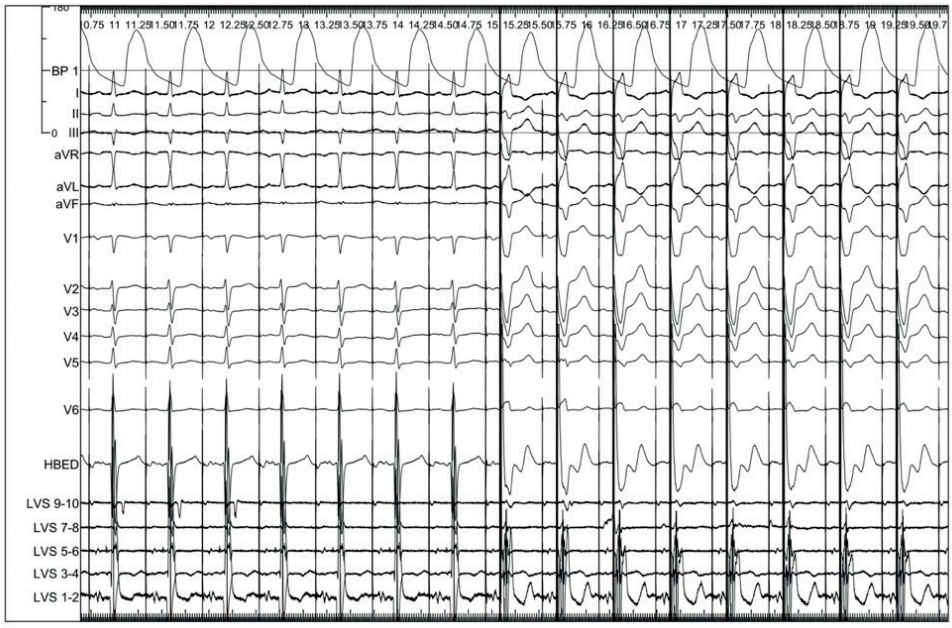

Figure 3. Representative display during implantation. Shown are (from top to bottom): systemic blood pressure curve, 12-lead ECG, intracardiac EGM recorded from the tip of the LBBAP lead, intracardiac signals recorded from decapolar catheter situated against LV septum. Left part of the signals are recorded during atrial pacing, the right part during RV apex pacing.

Study endpoints

The main study endpoint is to show superiority in electrophysiological effect of LBB area pacing over RV apex pacing in patients indicated for permanent cardiac pacing. Secondary study endpoints are 1) systemic BP during pacing at different depths within the IVS, 2) investigate electrophysiological effects of LBBP compared to LVSP, 3) assess global and regional LV strain patterns measured by echocardiography during LBB area pacing, and 4) assess reverse remodeling after 6 months in patients with a CRT indication.

Study management and event adjudication

Data collection and monitoring was managed by the executive researcher of the Maastricht University Medical Centre+. All adverse events were classified by an investigator at the site and serious adverse events were reported to the local Ethics Committee.

Statistical analysis

The number and percentage were used as descriptive statistics for categorical variables. Continuous variables were expressed as mean ± standard deviation. Differences between 2 groups were compared using the Student t-test for continuous variables. The paired

t test was used to compare the differences between 2 means within the same group. Comparisons among ≥3 pacing conditions within individuals were made using repeated measures ANOVA with Bonferroni multiple comparisons procedure applied to pairwise comparisons. A 2-sided *P* value of <.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics version 25.0 (Chicago, IL, USA).

Results

Ten patients underwent permanent pacemaker implantation with an attempt for LBBAP. Patient characteristics are summarized in table 2. Patients were predominantly male (80%) with an age of 76±7 years. An history of hypertension was recorded in 70% and some level of coronary artery disease was present in 40% of patients. LV ejection fraction (LVEF) at baseline was 46±11% with a LVEF <50% in 6/10 patients (60%). Indication for pacemaker implantation was sinus node dysfunction in 4 patients, AV-block in 3 patients, AV-node ablation in 1 patient, and CRT in 2 patients.

Procedure-related characteristics

All implantation procedures were performed using the C315His or C304 delivery catheter (Medtronic, MN, USA) and the SelectSecure 3830 lead (Medtronic, MN, USA). In all patients a de novo pacemaker implantation was performed and permanent LBB area lead implantation was successful in all patients. Total procedure time, defined as time from first incision to last suture and influenced by placement of temporary catheters through femoral access was 140±31 minutes. LBB area lead implantation time was 16±7 minutes. The radiation time and dosage across all procedures was 18±8 min and 126±91 mGy, respectively.

Table 2. Baseline characteristics.

Characteristics (n=10)	**Mean ± SD or n (%).**
Male sex	8 (80%)
Age (years)	76±7
Medical history	
Hypertension	7 (70%)
Diabetes mellitus	4 (40%)
Atrial fibrillation	4 (40%)
Coronary artery disease	4 (40%)
LVEF <50%	6 (60%)
Echocardiographic parameters	
LVEF (%)	46±11
LV end diastolic diameter (mm)	52±6
LV end systolic diameter (mm)	38±6
IVS thickness (mm)	10±2
Electrocardiographic parameters	
Heart rate (bpm)	70±15
QRS duration (ms)	
all patients *(n=10)*	127±40
intrinsic ventricular conduction *(n=6)*	97±7
Other (escape, LBTB/RBTB) *(n=4)*	171±18
Pacemaker indication	
Sinus node dysfunction	4 (40%)
Atrioventricular block	3 (30%)
Atrial tachyarrhythmia requiring ablation	1 (10%)
Heart failure & prolonged QRS duration	2 (20%)

QRS duration

LBB capture, according to previously described criteria, was confirmed in 7/10 patients (70%). In 3/10 patients, only LVSP was achieved. In 4/10 patients (40%) a clear LBB potential was present and the interval between the LBB potential and the onset of QRS was 26±10 ms.

In 4/7 patients where LBB capture was demonstrated, both ns-LBBP and s-LBBP were achieved. In 1 patient only ns-LBBP was achieved and in 2 patients ns-LBBP and LVSP were achieved.

In all patients, QRS duration increased from 127±40 ms during intrinsic rhythm to 144±17 ms during LBBAP. Bipolar pacing above the anodal threshold resulted in an QRS duration of 143±15 ms.

In patients with narrow baseline QRS complex (n=7), QRS duration increased from 92±7 ms during sinus rhythm to 175±21 ms during RV apex pacing and then decreased to 146±12 ms during LBBAP (final lead position at lowest output with capture). In patients with baseline LBBB (n=3), QRS duration increased from 171±23 ms during intrinsic rhythm to 177±12 ms during RV apex pacing and then decreased to 144±11 ms during LBBAP.

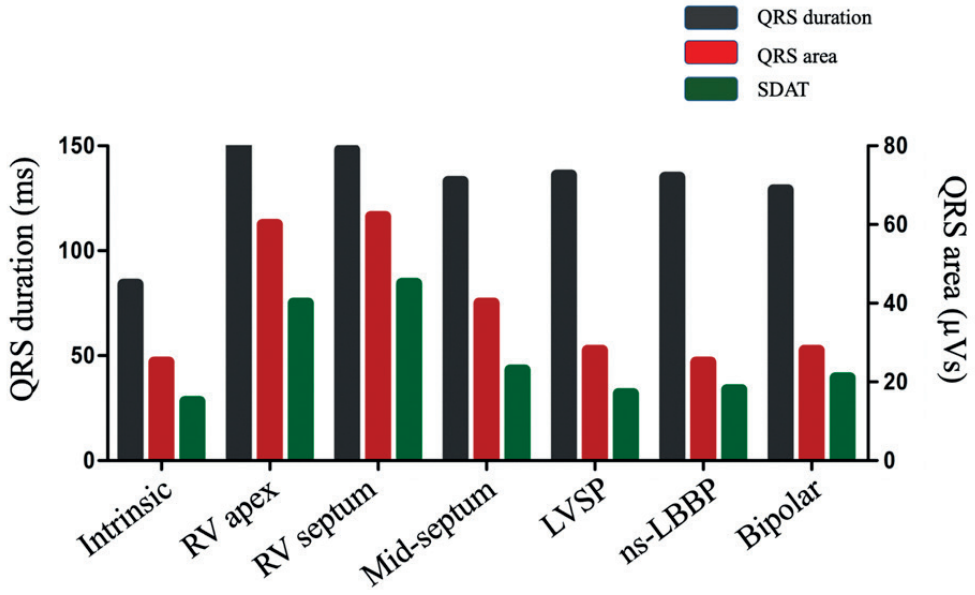

Figure 4. Electrophysiological measurements in a patient with narrow baseline QRS. On the left y-axis QRS duration is represented, on the right y-axis QRS area and SDAT are represented. The different pacing locations are represented on the x-axis. QRS duration is shown in grey bars, QRS area in red bars, SDAT in green bars. SDAT = standard deviation of activation times.

QRS area and the standard deviation of activation times

During RV apex pacing, QRS area was 109±41 µVs, which decreased to 51±28 µVs during LVSP (5 patients). QRS area was lowest in LBBP, as it was 38±14 µVs during ns-LBBP (7 patients) and even 30±7 µVs during s-LBBP (4 patients). Figure 4 shows electrical effects of pacing during different depths within the IVS in a patient with baseline narrow QRS (sinus node dysfunction).

As shown in figure 5, on average, both QRS duration and SDAT increase during RV septal pacing compared to intrinsic rhythm. From RVSP to LBBAP, the SDAT almost linearly decreases when pacing more towards the LBB area.

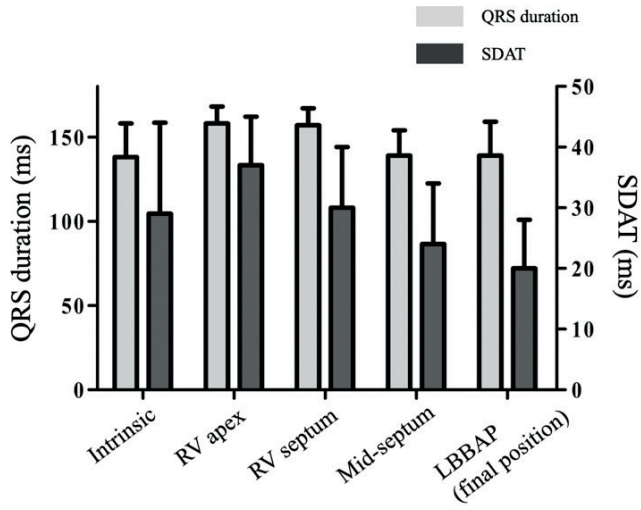

Figure 5. ECG Belt data histograms. On the left *y*-axis, QRS duration in milliseconds during pacing at different interventricular septum depths is shown. On the right *y*-axis, the standard deviation of activation times in milliseconds during pacing at different depths is shown.

Compared to RV apex pacing, all LBBAP configurations produce lower SDAT as well as QRS area. Between patients comparison in figure 6 shows that while SDAT is lowest in LVSP and ns-LBBP, QRS area is lowest in selective LBBP.

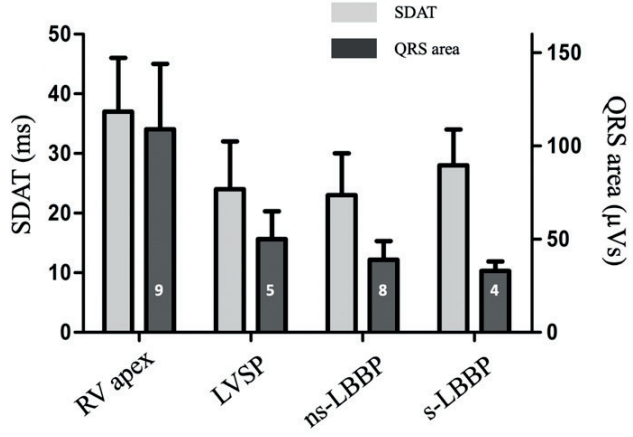

Figure 6. Standard deviation of activation times on the left *y*-axis and QRS area on the right *y*-axis in LVSP and LBBP compared to RV apex pacing. In white, the number of individual patients in which the particular pacing mode was achieved.

Acute hemodynamic effect

The pre-procedural systolic BP was 146±23 mmHg. During RV apex pacing, systolic BP was 129±15 mmHg, which increased to 135±14 mmHg during LBBAP at 3V output (figure 6).

Systolic BP was 136±12 mmHg during LVSP (n=3) and 133±15 mmHg during LBBP (n=7). In patients with non-selective LBB capture (n=3) systolic BP was 133±17 mmHg and in patients where selective LBB capture was achieved, systolic BP was 135±14 mmHg.

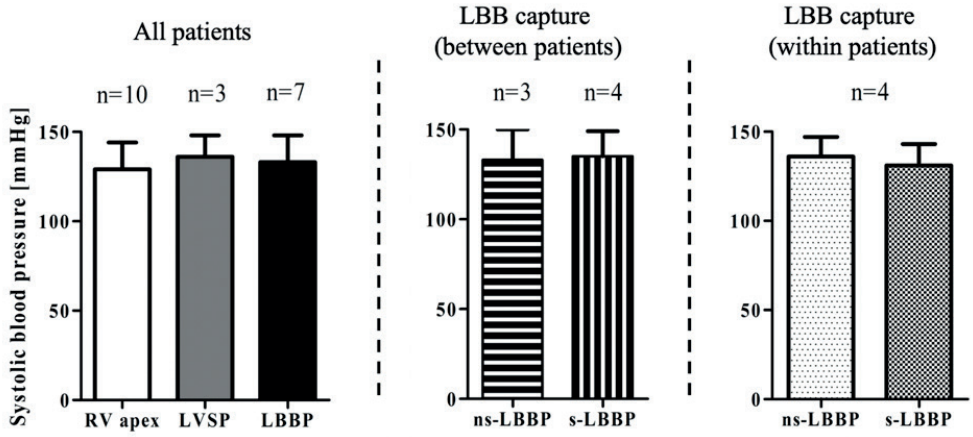

Figure 7. Acute hemodynamic effect of pacing. Left panel: systolic blood pressure during RV apex pacing (white bar), LV septal pacing (grey bar) and left bundle branch pacing (black bar).

Center panel: difference in systolic blood pressure between patients where non-selective left bundle branch pacing was achieved (horizontally striped; 3 patients) and where selective left bundle branch pacing was achieved (vertically striped; 4 patients).

Right panel: systolic blood pressure in 4 patients where both non-selective and selective left bundle branch pacing was achieved.

Pacing characteristics

Unipolar LBB area lead threshold at implantation was 0.7±0.3 V at 0.5 ms pulse width. The sensed R wave amplitude and pacing impedance were 19±4 mV and 745±37 Ohms, respectively. In patients where LBBP was achieved, LBB capture threshold was 1±1 V.

Safety endpoints

During the study, one adverse event has occurred. One patient visited the emergency department the day after implantation. This patient experienced pain and discoloration in the right groin. Echocardiography with colour doppler showed no active bleeding. The patient was sent home and complaints resolved within days.

Discussion

The main preliminary findings of the study are:

1. LBBAP decreases QRS duration, QRS area and SDAT compared to both RV apex pacing and RVSP.
2. Within LBBAP, LVSP and ns-LBBP produce lower SDAT. QRS area is lowest in s-LBBP.
3. There seems to be a trend toward increase in systolic BP during LBBAP compared to RV apex pacing and RVSP. Between LVSP and LBBP, difference in systolic BP is small. There seems to be a trend toward increase in systolic BP in LVSP and ns-LBBP compared to s-LBBP.

Electrical synchrony during LBBAP

All electrical measurements indicate a more synchronous electrical activation during LVSP and LBBP compared to RV apex pacing. In RV apex pacing the propagation of the activation wave front occurs from cell-to-cell and bypasses the specialized conduction system. Therefore, parameters measuring activation such as SDAT and QRS area are expected to be increased during RV apex pacing compared to LBBP. Compared to RV apex pacing, pacing LBB area leads to a more physiological ventricular activation. In LVSP, ventricular synchrony is achieved based on a short path length of conduction and fast endocardial conduction.[14] QRS duration, area and the SDAT are therefore evidently lower during LVSP than during RV apex pacing. A recent publication by Curila et al. showed that LV activation can even be faster by (co-)stimulating the LBB or its proximal fascicles.[15] Therefore, QRS area, which is thought to be driven by LV activation rather than RV activation, is found to be lower during LBBP compared to LVSP. The latter is also in line with previous studies from the Maastricht group.[16]

Difference between QRS duration and QRS area and SDAT

When comparing LBBAP to RV pacing, decrease is more pronounced in QRS area and SDAT as compared to QRS duration. QRS duration can potentially be further decreased by bipolar pacing with anodal capture, AV-optimization or fusion with intrinsic RV activation (VV-optimization). Whether QRS duration guided pacing optimization is meaningful, is questionable. Although QRS duration is still part of the international guidelines on CRT, suggesting it to be a marker of the degree of electrical dyssynchrony and suitability for CRT, the value of the QRS duration depends on how it is measured with significant variability and QRS widening (or lack of shortening) may be caused by many different pathophysiological processes. Compared to QRS duration and even to QRS morphology, QRS area has proven to be a stronger predictor of long-term outcome in this population.[17]

Acute hemodynamic effect

There are no studies known to the authors investigating the acute hemodynamic effect, invasively measured, of LBBAP. The differences between RV pacing, LVSP and LBBP are small in this preliminary study. In each IVS pacing depth, only the first ten beats are included in the hemodynamic analysis. As the systolic blood pressure is used as hemodynamic parameter, rather than for instance LV dP/dtmax, autonomic nervous system adaption is expected to play a role in the absence of major differences.

There seems to be a trend towards increase in systolic blood pressure during both LVSP and LBBP compared to RV pacing. As in LBBB, during RV pacing the early activated interventricular septum (IVS) wastes part of the regional work through pre-stretching of the opposing late-activated LV lateral wall, which contracts during late systole and even early diastole. Consequently, these delayed contracting segments are exposed to a higher regional workload and LV wall thickness increases more in these segments than in early contracting segments.[18, 19] Overall, the efficiency of cardiac contraction is significantly reduced. This might explain to some extend the increase in blood pressure during more synchronous pacing. Between LVSP and LBBP, differences are very small. When comparing systolic BP during non-selective and selective LBBP within the same patient, there is a trend towards increase of blood pressure during non-selective LBBP. This phenomenon might be influenced by the mechanical interplay between the RV and LV. While we demonstrated that ventricular activation is slightly more synchronous during LBBP than during LVSP, ultra-high frequency (UHF-)ECG analysis revealed that faster LV lateral wall activation underlies this better synchronization.[15] An important finding of the UHF-ECG analysis was that although LVSP produces slower LV lateral wall activation compared to LBBP, LBBP creates greater interventricular dyssynchrony compared to LVSP.

Limitations

The major limitation of this preliminary chapter is the small number of patients. Therefore, no statistical analysis could be performed properly investigating the data. However, the chapter was mainly intended to show the systematics and extensiveness of the ongoing research and to provoke discussion.

Conclusions

In patients with different permanent pacemaker indications, a more synchronous ventricular activation during pacing can be achieved by both LVSP and LBBP compared to RV pacing. Differences in the acute hemodynamic effect of RV pacing and LBBAP are small. There seems to be a trend towards a slightly higher systolic blood pressure during LVSP and non-selective LBBP.

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CHAPTER 9

9

General discussion.

General discussion

Pacemaker therapy has proven to be a vital strategy in patients with structurally normal hearts and bradyarrhythmia as well as patients with heart failure and conduction disease. In pacing therapy, right ventricular apex pacing (RVAP) is still a frequently applied approach. The adverse effects of RVAP, as reviewed in **chapter 2**, prompted us to investigate alternative pacing strategies. In the last decades, alternatives such as biventricular pacing (BVP) and His bundle pacing (HBP) have already been studied extensively as more physiological alternatives to RVAP. More recently, left ventricular septal pacing (LVSP) and left bundle branch pacing (LBBP) have been proposed, commonly referred to as left bundle branch area pacing (LBBAP).
In light of optimizing patient outcome of pacemaker therapy, this thesis investigated:

1. IAlternative pacing strategies that avoid detrimental effects of RV pacing (**chapter 2**);
2. the effects of different individual LV pacing locations used during BVP and the possible superiority of combining pacing locations during multi-left ventricular (LV) pacing over BVP in animal studies (**chapter 3**);
3. the physiology and practicalities of LVSP (**chapter 4**);
4. the single-centre feasibility and safety of left bundle branch area pacing (LBBAP) (**chapter 5** and **6**);
5. the acute and mid-term feasibility and safety of LBBAP in a large multicentre international collaboration (**chapter 6**).
6. the differences in acute electrical and hemodynamic effects between LVSP and LBBP within LBBAP (**chapter 7 and** 8);

In this **general discussion** the results presented in the previous chapters will be placed in
a broader perspective. Finally, the impact of this thesis on the clinic as well as on society will be discussed.

Increasing response to resynchronization therapy by multi-LV pacing?

A significant portion of heart failure patients exhibit LV conduction abnormalities which lead to slow electrical activation and discoordination of contraction.[1] By combining RV endocardial and LV epicardial pacing, BVP (referred to as cardiac resynchronization therapy, CRT) corrects the mechanical dyssynchrony caused by an activation delay between the septal and lateral free walls. Although the response to BVP in these patients is generally positive, it varies considerably between individuals and up to one-third of patients seem to have little or no improvement in cardiac function. While appropriate

positioning of the LV lead in CRT has been shown to be a way to optimize CRT response, a few studies suggest that stimulating more than one LV epicardial site could further increase this response. The currently available quadripolar LV leads allow to stimulate multiple electrodes within the same coronary vein (multi-point pacing, MPP). Other studies suggest that pacing two electrodes in separate coronary veins could improve CRT response (multi-vein pacing, MVP).

In **chapter 3** we investigated the acute hemodynamic response (AHR) of BVP using different LV epicardial locations alone and multiple LV electrodes simultaneously ("multi-LV" pacing) in an animal model of acute left bundle branch block (LBBB). Our study showed that multi-LV pacing only increased the benefit of conventional BVP if the LV site used for BVP does not lead to adequate hemodynamic benefit. Compared to conventional BVP using the optimal single LV epicardial site multi-LV pacing did not lead to an additional benefit. When comparing multi-LV pacing possibilities, multipoint pacing (MPP) and multi-vein pacing (MVP) create a similar degree of electrical resynchronization and hemodynamic effect, which are larger with a larger interelectrode distance. Our finding that both MVP and MPP significantly reduce electrical dyssynchrony with minor hemodynamic benefit as compared with BVP is in agreement with a previous animal study from our laboratory[2] and clinical studies.[3, 4]

Most clinical studies investigating multi-LV pacing employed either MPP (using a quadripolar LV lead within the same vein) or MVP (using multiple LV leads). In **chapter 3**, we tested both modalities in the same porcine hearts. In both approaches the reduction in QRS duration, clinically the most commonly used marker of electrical dyssynchrony, was similar. This similarity seems also to be present in clinical studies which reported comparable reduction in QRS duration[5] and epicardial activation time[3] by both modalities. The lack of a beneficial hemodynamic effect of MPP and/or MVP compared to BVP in our animal study seems in conflict to several clinical studies, that demonstrated a small but significant positive hemodynamic effect of multi-LV pacing over BVP.[5-8] A methodical limitation of most of these studies, however, is that best of several options of multi-LV pacing was compared to less (sometimes just one) BVP measurements, thus creating a statistical bias. Also, The additional effect of multi-LV pacing is dependent on the initial effect produced by BVP. If that initial LV pacing site used during BVP produces a suboptimal response, it is more likely that adding a pacing site is beneficial. In our analysis, we therefore matched each multi-LV configuration with its corresponding BVP measurement, which revealed that multi-LV pacing can create a beneficial effect beyond BVP only in case the initial electrophysiological or hemodynamic effect of BVP is poor. The latter is in agreement with patient studies showing that the added benefit of multi-LV pacing was small when compared to the BVP configuration that yielded the largest hemodynamic response. [5, 7]

Alternative pacing site: left ventricular septal pacing

While the improvements created by more complicated RV and LV pacing approaches, like MPP and MVP appear to result in minor, if any, benefit compared to BVP, more recently promising effects have been described regarding LBBAP, as reviewed in **chapter 3**.

Chapter 4 elaborates more extensively on the rationale behind LVSP. In short, synchronous ventricular depolarization produced by LVSP appears to be the result of fast-conducting endocardial (non-Purkinje) fibers and the avoidance of slow transseptal conduction. LVSP avoids the use of coronary sinus as access, phrenic nerve stimulation and posterolateral scar in CRT patients.

The transseptal technique developed in Maastricht and described by Mafi-Rad et al.[9] was modified by Huang et al.[10] with the intent to overcome a left-sided conduction block by directly stimating the left bundle branch. These investigators demonstrated that direct pacing of the proximal LBB can be achieved using the transseptal approach. Initially, several small clinical studies demonstrated that this modified technique is safe and feasible.[11-13] In **chapter 5**, we confirmed that, similar to LVSP, permanent LBBAP as a new physiological pacing technique is feasible and safe. Our results are in line with larger studies including bradyarrhythmia patients as well as CRT patients.[11, 14, 15] In addition to results of previous trial, we demonstrated in **chapter 5** a learning curve for permanent LBBP implantation that was even present in implanters who were experienced in HBP. Importantly, this learning curve flattens after approximately 50 LBBAP implantation procedures.

With increasing implantation experience and increasing number of data becaming available, it is clear that the left bundle branch is not always captured. Therefore, many investigators prefer to use the terminology left bundle branch area pacing (LBBAP). This term is justified because of small differences in the paced QRS complex between LVSP and LBBP, the existence of multiple capture types and most importantly the lack of standard and precise differentiating criteria. Also, micro-dislodgment of the lead might occur, which causes the patient to be chronically treated with LVSP rather than with LBBP.

Comparing LVSP with LBBP

In **chapter 5**, we studied the electrophysiological differnces between LVSP and LBBP. We found that QRS duration was similar during LVSP and LBBP and significantly lower than during to RV pacing. This finding is in agreement with previous studies investigating LBBAP. [12, 16] The paced QRS complex is considered a strong predictor for the development of pacing-induced cardiomyopathy,[17, 18] and a meta-analysis revealed that LBBAP is associated with a shorter paced QRS complex duration compared to

RV pacing.[24] However, for conventional CRT our group previously demonstrated that one parameter is even stronger associated with all-cause mortality and heart failure hospitalizations than QRS duration and LBBB morphology (alone or in combination with each other): QRS area.[19] The strong association of QRS area with CRT response is explained by several properties. QRS area is large in the presence of strong electrical forces pointing in a dominant direction and a large QRS area is predictive of delayed LV activation. In **chapter 5**, we found that QRS area is slightly but significantly smaller during LBBP compared to LVSP.

Compared to RV pacing, the largest reduction in ventricular dyssynchrony is already achieved when pacing the LV septal myocardium (**chapter 7**). In **chapter 7**, where we proposed clear pacing definitions, QRS area was decreased by ~50% during LVSP compared to RV pacing. The extra effort of acquiring LBB capture resulted in a small but statistically significant further decrease in QRS area, while increasing procedure and radiation time. Whether LBBP results in more benefical longterm echocardiographic or clinical benefit when compared to LVSP remains yet unknown.
Beyond the reduction in QRS area, we also demonstrated that the QRS vector in the transverse plane normalized during LBBAP. This implies that, at least to some extent, ventricular activation is conducted in a way similar to the physiological situation, something which is also shown in a non-invasive electrocardiographic imaging study.[20] The same trend was seen for LV activation time, which was measured as the interval between pacing stimulus and R-wave peak time in lead V5 or 6. These desirable effects of LVSP and LBBP versus RV pacing are in line with previous studies investigating electrophysiolical effects.[21, 22]

Lastly, in patients with intact atrio-ventricular activation and baseline narrow QRS, QRS area during both LVSP and LBBP was close to values of the intrinsic QRS, which confirms that both modalities maintain ventricular synchrony at a level close to normal. These findings are in agreement with previous studies demonstrating that LBBAP maintains ventricular synchrony at levels comparable to His bundle pacing (HBP) and even to intrinsic ventricular activation.[11, 12, 20, 23] (**chapter 7**)

Mechanistic insight in LV septal pacing versus left bundle branch pacing
Although multiple registries have demonstrated beneficial effects of LBBAP in both the bradyarrhythmia and CRT population, several uncertainties need to be investigated before the widespread application and adaption in international guidelines of LBBAP. For instance, is LBBAP truly superior to conventional RVAP in terms of electrical (re) synchronization and maintaining/restoring hemodynamics? And which patients benefit from LVSP or true LBBP and is there a difference in response to LVSP and LBBP between patients with a structural normal heart and patients with heart failure? **Chapter 8**

describes a mechanistic study (MASTER-LV study) where we attempt to address some of these uncertainties. The preliminary data show that besides better electrical synchrony, LVSP and LBBP seem to produce a higher systolic BP compared to RVAP. There also seems to be a trend of higher systolic BP during ns-LBBP compared to s-LBBP, which might be influenced by the mechanical interplay between the RV and LV. While we demonstrated that ventricular activation is slightly more synchronous during LBBP than during LVSP, ultra-high frequency (UHF-)ECG analysis revealed that faster LV lateral wall activation underlies this better synchronization.[24] An important finding of the UHF-ECG analysis was that although LVSP produces slower LV lateral wall activation compared to LBBP, LBBP creates greater interventricular dyssynchrony compared to LVSP. Capture of the His–Purkinje system during LBBP results in a more rapid electrical wavefront propagation through the LV cavity, which is reflected by a shorter V6RWPT.[25] This comes, however, at the costs of deterioration in interventricular synchrony and slower conduction in the septum and RV. In contrast, during LVSP left-to-right transseptal depolarization occurs immediately after pacing and thus LVSP produces less interventricular dyssynchrony. This might be a possible explanation for the slightly higher (acute) systolic BP during LVSP and ns-LBBP compared to true s-LBBP.

Largescale results of left bundle branch area pacing

Several clinical studies demonstrated the safety and feasibility of LBBAP for both bradyarrhythmia and CRT indications.[26-29] However, most results are based on small or medium-sized populations and are from single-center experience. In **chapter 6,** the Multicentre European Left Bundle Branch Area Pacing Outcomes Study (MELOS) is presented, which is a registry-based observational study, and was designed to gather data from a large group of patients from fourteen centres. The results in **chapter 6** are based upon over 2500 patients from 14 centers across Europe, which makes it the larges registry to this date. The results emphasize that as a result of differences in pacing locations, implantation technique and baseline substrate the results of LBBAP are not homogenous. In this largescale multicentre evaluation, LBBAP is a feasible primary pacing technique for all-comers regardless of the pacing indication. The overall success rate of LBBAP lead implantation of 89.6% suggests that with currently available tools the implantation in the left bundle branch area can be challenging even for experienced operators. Lead implantation failures especially occurred in patients requiring resynchroization because of an enlarged LV. The latter is in agreement with previous medium scale registries.[26, 28] Also in line with our single center results from **chapter 5**, is the multicenter study showed a significant learning curve is demonstrated for the LBBAP implantation technique (**chapter 6)**.

The complication rate of LBBAP was 12%, which is fairly high but comparable to BVP. In LBBAP however, some new complications are encountererd such as acute coronary syndrome/chest pain during pacing, coronary vessel fistulas and lead helix entrapment

issues that need further attention.

Although **chapter 6** describes over 2,500 patients reporting multicentre outcomes of LBBAP, more data is needed. Especially randomized clinical trials are needed demonstrating long-term outcome, such as the LEAP trial (Permanent Left Ventricular Septal Pacing Versus Right Ventricular Pacing in Patients With Atrioventricular Conduction Disorders: a Randomized Trial; ClinicalTrials.gov identifier: NCT04595487).

Future directions

Implantation tools and programming

When our group initially implanted a permanent pacemaker lead via the transseptal technique, the Medtronic 3830 lead was customised with an extended helix (Medtronic 09066 lead). Nowadays, the use of the conventional 3830 lead is widespread in LBBAP and has even acquired approvement of the FDA for CSP in October 2022. The lead is delivered via a pre-shaped guiding catheter which facilitates a stable septal position. New leads and (steerable) guiding catheters are becoming available from other vendors, which may lead to extension of the application of LBBAP and possibly to better delivery. The latter is especially needed in patients with dilated hearts as the results from **chapter 6** have demonstrated. Implantation characteristics of leads from different vendors need to be collected and compared to identify subpopulations benefitting from specific types of implantation tools. Furthermore, large-scale data is required regarding long-term safety of LBBAP and of extraction of the leads involved.

Potential consequences of LBBAP-induced delayed RV activation also need to be evaluated. Future studies are needed to determine whether fusing LBBAP with native right bundle branch conduction using AV optimization or bipolar pacing with anodal capture of the RV septum can correct for this interventricular delay.

LBBAP in bradyarrhythmia versus heart failure patients

The transseptal technique was modified by Huang et al.[10] with the intent to overcome a left-sided conduction block. Ventricular conduction disturbance, particularly LBBB, is present in approximately one-third of heart failure patients. Randomized trials have extensively shown that in these patients, BVP-CRT improves survival while decreasing hospitalizations. It can be hypothesized that in case of proximal block, LBBB may also be treated by CSP. Upadhyay and colleagues observed that 2/3 of LBBB patients had indeed a proximal block (either intrahisian or proximal LBB).[30] Currently, several non-randomized studies indicate that CSP is equal or even superior to BVP-CRT.[31, 32]

In heart failure patients with narrow QRS complex (<120 ms), BVP is known to provide

no benefit, or is even detrimental.[33] Since LBBAP uses the native conduction system for maintaining ventricular synchrony, it has the potential to be applied as pacing therapy in symptomatic bradycardia patients as alternative to RV pacing or HBP (figure 1). Large scale randomized data concerning the comparative effectiveness of LBBAP against RVP in these patients is scarce and thus the optimal pacing method for this group of patients remains uncertain. Although evidence on the benefit of LBBAP in CRT and bradyarrhytmia is becoming more available rapidly, it is important to recognise that the majority of these studies is observational and non-randomised. The clinical implication is that BVP still is the standard of care in CRT and LBBAP is mostly used as a rescue strategy in cases where coronary venous anatomy limits the ability to successfully place an LV epicardial lead.

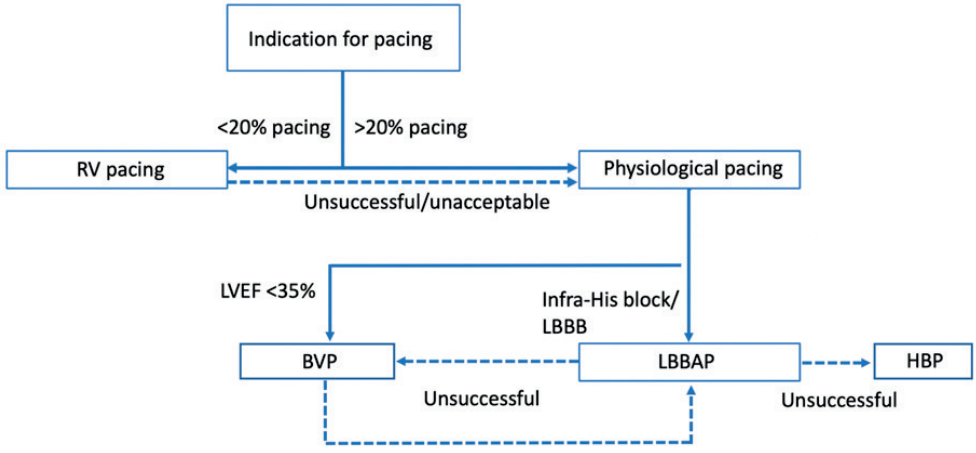

Figure 1. Schematic proposition of pacing strategies used in different circumstances and pacing indications.

One site fits all?

The findings of the thesis indicate the large potential value of LBBAP as alternative to RV pacing in anti-bradyarrhythmia pacing and as alternative to BVP in patients who are candidate for resynchronization therapy. We therefore propose that one site (being LBBAP) actually fits most (pacing) purposes.

When considering the historical alternative to RV apex pacing (high or mid RV septal, HBP), LBBAP clearly showed results consistently superior to RVP, while RV septal pacing shows inconsist results and generally not different from RV apex pacing. On the other hand, HBP is a better option from a physiological perspective, but has significant practical limitations, such as higher pacing threshold, more lead dislodgments, atrial oversensing problems and lower implantation success rate.[34-36]

When considering BVP, several alternatives have been proposed and explored: beside HBP also endocardial BVP[37-39] (with the LV lead positioned endocardially) and MPP and

MVP. Of these options, endocardial CRT appears to create some electrophysiological and functional benefits in animals and patients. However, the techniques required are complicated, involving either the LV lead to be placed in the LV, with concommittant increased risk of embolization, or a novel techniques where a leadless electrode is triggered by an ultrasound transducer. The latter requires much more energy, often leading to short battery life, beside other complications.
Compared to the alternative options above, LBBAP has the benefit of being relatively easy, requiring only two pacing leads (atrial and LBB area, in stead of three for BVP) and having low pacing thresholds.
Before making a final choice for LVSP or LBBP several issues require clarififcation:

- does LBBP with left conduction system capture provide better long-term outcome compared to LVSP?
- identify patient (sub)populations (patients with HF with reduced LVEF and LBBB?) that benefit from LBBP compared to LVSP or vice versa.
- which patients benefit from upgrading to HBP- or LBBAP-optimized CRT (HOT/LOT-CRT)?

Conclusions

The conclusions of the thesis are as follows:

1. Multi-LV pacing only increases the benefit of conventional BVP if the LV site used for BVP does not lead to adequate hemodynamic benefit. (**chapter 3**)
2. When comparing multi-LV pacing possibilities, multipoint pacing (MPP) and multi-vein pacing (MVP) create a similar degree of electrical resynchronization and hemodynamic effect, which are larger if interelectrode distance is large. (**chapter 3**)
3. LV septal pacing produces synchronous ventricular depolarization as a result of fast-conducting endocardial (non-Purkinje) fibers and the avoidance of slow transseptal conduction. (**chapter 4**)
4. Left bundle branch area pacing is a safe and feasibility alternative to RV pacing. (**chapter 5**)
5. LBBAP is feasible for both bradyarrhythmia and heart failure indications, but implantation success rate and safety in heart failure patients need to be improved. (**chapter 8**)
6. Compared to RV pacing, both LVSP and LBBP improve ventricular dyssynchrony considerably, to values close to normal ventricular activation. LBBP results in a small, but significant, improvement in ventricular synchrony compared to LVSP. (**chapter 6**)
7. The differences in hemodynamic effects between LVSP and LBBP seem small.

(**chapter 7**)

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APPENDICES

A

Appendices

Impact

Since the experiments of Galvani in the second half of the 18th century and the development of the pacemaker in the 1950s, pacemaker implantation is an increasingly common technique in cardiology. In the Netherlands, between 10,000 and 15,000 pacemakers are implanted each year. Pacemakers are used in treatment of patients suffering from bradycardia and patients with heart failure and disorders of the heart's natural, rapid conduction system. Especially heart failure takes a large part of the total healthcare budget, as it requires chronic treatment and leads to frequent hospitalizations. In the Netherlands, more than 250,000 people suffer from heart failure and total healthcare costs due to heart failure were more than 800 million euros in 2017. Up to one third of heart failure patients exhibit conduction disorders, mainly left bundle branch block (LBBB). In these patients, biventricular pacing (BVP) has proven to be an effective treatment, improving both symptoms and survival.
In patients suffering from bradycardia and who require chronic pacing therapy, the right ventricular (RV) apex is an anatomical location frequently used for implantation of the ventricular pacing lead. When implanting the pacemaker lead transvenously, the apex of the RV is the easiest to reach and the most stable position. However, pacing the RV apex results in a very non-physiological ventricular activation. This non-physiological ventricular activation through RV apex pacing can lead to adverse effects such as increased incidence of atrial fibrillation, higher mortality and more frequent heart failure hospitalization. Already quite some research has been performed with the goal to find alternatives to RV apex pacing. The most recently studied technique is left bundle branch pacing (LBBAP). In LBBAP, the interventricular septum is paced at a site deep within the septum near the left ventricular (LV) endocardium. The septal myocardium can be paced with (left bundle branch pacing) and without (LV septum pacing) direct capture of the left conduction system.
The main objectives of this thesis were: 1) to investigate whether adding LV pacing locations could improve response to BVP, 2) to study the safety and feasibility of LBBAP as alternative to RV pacing, and 3) to investigate the differences between LV septal pacing and left bundle branch pacing within LBBAP. In this chapter we summarize the clinical, scientific and societal impact of the main findings of this thesis.

Clinical impact

In **chapter 5** we showed that, the modified transseptal implantation technique used in LVSP and LBBAP is feasible and safe. Therefore, LBBAP seems a safe and effective alternative to RV apex pacing in anti-bradycardia pacing. Additionally, we demonstrate a learning curve for permanent LBBAP implantation, even with implanters already experienced in HBP. The results suggest that at least 50-100 procedures are required for implanters to become experienced. Inexperienced implanters potentially cause more perforations into the LV cavity.

In **chapter 6**, we reproduced the findings of **chapter 5** on a very large scale. **Chapter 6** includes patients in whom LBBAP device implantation was attempted at 14 different European centres, comprising over 2500 patients with varying pacing indications. The results show that LBBAP is indeed a feasible and safe technique regardless of the pacing indication. Also, lead implantation success rate, defined as a deep intraseptal lead position with paced QRS complex including a terminal R/r wave in lead V1, was 92.4% (1698/1837) for bradyarrhythmia and 82.2% (572/696) for heart failure indications. While these results are promising for a technique that was introduced less than 5 years ago, this finding suggests that there is a need for improvement and adaptation of implantation tools for specific patient subpopulations. The complication rate of LBBAP implantation was found to be similar to conventional BVP.

In **chapters 5**, **7** and **8** we compared LVSP and LBBP and found that the decrease in ventricular dyssynchrony compared to RV pacing is similar for both modalities. Compared to RV pacing, already a large reduction in dyssynchrony is achieved during LVSP while LBBBP provides only a small additional decrease. These findings suggest that LVSP may be enough to avoid detrimental effects of ventricular pacing. The effort of additional left bundle branch capture comes at the cost of extended procedure and radiation time and potential higher complications rate such as LV perforation. Largescale, randomized trials are required to determine if and in which subpopulations LBBP results in beneficial long-term outcome compared to LVSP.

Scientific impact

In **chapter 3**, both electrophysiological and hemodynamic effects of conventional BVP and multi-LV pacing were investigated. In contrast to most clinical studies, we compared multiple LV pacing locations within the same heart. Also, we compared multi-point pacing and multi-vein pacing within the same heart. Our results show that the reduction in activation time achieved by adding LV pacing sites, does not translate into hemodynamic benefit. We demonstrated that the additional benefit of multi-LV pacing depends on the initial response produced by BVP with that corresponding LV site. Future patient studies investigating multi-LV pacing should therefore compare, within the same patient, conventional BVP yielding the best hemodynamic response with both multipoint and multi-vein pacing. However, given the increasing evidence of equal benefit of BVP and LBBAP, it may be questioned whether adding LV leads, if any, should be combined with LBBAP rather than RV pacing.

The results of **chapters 5**, **7** and **8** indicate that LVSP and LBBP provide a similar degree of ventricular synchronous activation compared to RV pacing. The results also show a small but statistically significant difference in (left) ventricular synchrony in favor of LBBP. An important question remains whether this statistically significant difference

translates into long-term clinically significant difference. Does LBBP, where the LV is activated in a manner closest to nature's physiology, provide beneficial outcome in patients compared to LV septal " only" pacing? And if this is not the case, should we then not always apply LVSP as it is the most straightforward technique? The good acute effects of LVSP/LBBP urge for more long term randomized studies, especially comparing RV vs. LBBAP in brady and LBBAP vs. BVP in heart failure patients.
Another question that deserves scientific investigation is whether LVSP/LBBP creates less dispersion of repolarization. Several reports indicate a pro-arrhythmic effect of BVP, therefore BVP is not infrequently combined with ICD. If repolarization is better preserved, such ICD may be required less frequently.

Societal impact

The potential societal impact of the thesis mainly relates to the improvement of pacemaker therapy. By improving and optimizing chronic pacemaker therapies, patients are better treated and experience less symptoms. For instance, the incidence of pacemaker induced cardiomyopathy (PICM) can be reduced by applying more physiological techniques such as LBBP. This will lead to less hospitalizations and less health care costs. By reducing PICM, there will also be less need for ICD, which also reduces costs. In case LBBAP turns out to be a safe and effective alternative to BVP, it will be a cheaper alternative as it required only one instead of two ventricular leads. Lastly, better understanding of LBBAP might lead to insight into which subpopulations of patients requiring chronic pacing benefit specifically from either LVSP or LBBP. This might contribute to decrease in health care costs through shorter implantation duration and therefore shorter waiting times.

Summary

Under physiological conditions, biventricular depolarization occurs fast and synchronous. In particular, the synchronicity is key in maintaining (lifelong) normal cardiac pump function. In case of disease of the cardiac conduction system this synchronicity can be impaired causing decline in function, adverse structural remodeling and increased risk of heart failure. In order to either counter symptoms or to prevent heart failure, patients with conduction system disease can be treated with pacemaker therapy. The most commonly applied technique is right ventricular (RV) apex pacing, since this particular location is easily accessible and safe. Unfortunately, in some patients this RV (apex) pacing induces adverse remodeling and heart failure. In search of preventing these pacing induced negative effects different pacing strategies have been applied.

Chapter 2 describes how the adverse effects of ventricular dyssynchrony induced by RV pacing has led to alternative pacing strategies, such as biventricular (BVP), His bundle (HBP), LV septal (LVSP) and left bundle branch pacing (LBBP). Although among these alternative pacing sites HBP is theoretically the ideal strategy as it comes closest to a physiologic ventricular activation, its application requires more skills and is associated with the most complications. In LVSP and LBBP, commonly referred to as LBBAP, where the ventricular pacing lead is advanced through the interventricular septum to its left side, creates ventricular activation that is only slightly more dyssynchronous. LBBAP related research is rapidly expanding and studies have shown that LBBAP is feasible, safe and encounters less limitations than HBP.

The acute electrophysiological and hemodynamic effects of multi-LV pacing were investigated in a preclinical study that is described in **chapter 3**. As shown in chapter 2, one way of preventing RV pacing induced adverse outcome, is combining RV pacing with LV pacing, also referred to as BVP. To further improve the response rate to BVP, multi-LV pacing (or tri-ventricular pacing) was proposed. Only a small number of clinical trials investigating multi-LV pacing have been conducted with conflicting results. **Chapter 3** provides insight into the question whether capturing a larger LV tissue area by pacing multiple electrodes provides better resynchronization compared to RV and conventional BVP and, as a consequence, cardiac function. Results show that different types of multi-LV pacing create a similar degree of electrical resynchronization and hemodynamic effect, which are larger if interelectrode distance is large. However, multi-LV pacing only increases the benefit of conventional BVP if the LV lead used for BVP provides poor response.

Chapter 4 presents a comprehensive review on the physiology and the practicality of LVSP. In this review, we describe how animal studies as well as patient studies have demonstrated that LV function is maintained during LVSP at levels comparable to sinus rhythm with normal conduction. Left ventricular activation, however, is more synchronous during LBBP compared to LVSP, but LBBP produces a higher level of intraventricular dyssynchrony compared to LVSP. An important practical consideration: while LVSP is fairly straight-forward to perform, targeting the left bundle branch area may be more challenging.

In **chapter 5**, the safety and feasibility of LBBAP is described in the first 80 patients implanted with this technique in The Netherlands (Maastricht University Medical Center+). Results demonstrate that LBBAP is a safe and feasible technique (success rate 96%), with a clear learning curve that seems to flatten after 40-60 implantations. Capture of the left conduction system is obtained in two-thirds of patients. Compared to RVSP, LBBAP largely maintains ventricular electrical synchrony to values close to intrinsic (narrow QRS) rhythm.

In **chapter 6**, we combined our local registry with other experienced centers forming the largest registry-based observational study that included patients in whom LBBAP device implantation was attempted at 14 European centers, for any indication. The study comprised over 2500 patients and LBBAP lead implantation success rate for bradyarrhythmia and heart failure indications was 92.4% and 82.2%, respectively. Independent predictors of LBBAP lead implantation failure were heart failure, broad baseline QRS and left ventricular end-diastolic diameter. The predominant LBBAP capture type was left bundle fascicular capture (70%). The results show that safety and success rate in heart failure patients need to be improved.

After extensively have demonstrated safety and efficacy, in **chapter** 7 the electrical ventricular synchrony is directly compared between direct LBBP and LVSP in a multi-center population. ECG and VCG indices demonstrate that both LVSP and LBBP improve ventricular dyssynchrony considerably as compared to RVSP, to values close to normal ventricular activation. LBBP results in a small, but significant, improvement in ventricular synchrony as compared to LVSP.

In **chapter 8**, the design and the preliminary results of the first ten patients are described of the MASTER-LV trial (***M**ech**A**ni**S**tic insigh**T**s in l**E**ft bundle b**R**anch and **L**eft **V**entricular septal pacing*). This trial was designed to evaluate acute hemodynamic and electrical effects of deep septal pacing with (LBBP) and without (LVSP) direct stimulation of the left bundle branch. In patients with different permanent pacemaker indications, a more synchronous ventricular activation during pacing can be achieved by both LVSP and

LBBP compared to RV pacing. Preliminary results show that differences in the acute hemodynamic effect of RV pacing and LBBAP are small. There seems to be a trend towards a slightly higher systolic blood pressure during LVSP and non-selective LBBP.

Samenvatting

Onder fysiologische omstandigheden gebeurt cardiale bi-ventriculaire depolarisatie snel en synchroon. Met name de synchroniciteit is essentieel voor het (levenslang) in stand houden van een normale hartpompfunctie. In het geval van ziekte van het hartgeleidingssysteem (geleidingsblok of -vertraging) kan deze synchroniciteit verstoord zijn, hetgeen kan leiden tot achteruitgang van functie, ongunstige structurele re-modellering en een verhoogd risico op hartfalen. Om symptomen tegen te gaan en/of hartfalen te voorkomen, kunnen patiënten met een aandoening van het geleidingssysteem worden behandeld middels pacemakertherapie. De meest toegepaste techniek is stimulatie in de rechter ventrikel (RV), aangezien deze specifieke locatie gemakkelijk toegankelijk en veilig is. Helaas veroorzaakt deze RV (apex)-stimulatie bij sommige patiënten ook nadelige effecten, zoals re-modellering en hartfalen. Om deze door de pacemaker-geïnduceerde negatieve effecten te voorkomen, zijn verschillende andere pacingstrategieën toegepast.

Hoofdstuk 2 beschrijft hoe de RV-stimulatie geïnduceerde nadelige effecten van ventriculaire dyssynchronie hebben geleid tot alternatieve stimulatiestrategieën, zoals biventriculaire pacing (BVP), His-bundel pacing (HBP), LV-septum pacing (LVSP) en linker bundeltak pacing (LBBP). Hoewel van deze alternatieve locaties HBP theoretisch de ideale strategie is omdat het het dichtst bij een fysiologische ventriculaire activatie komt, vereist de toepassing ervan meer vaardigheden en gaat het gepaard met de meeste complicaties. Bij LVSP en LBBP, waarvan de overkoepelende term LBBAP is, wordt de stimulatielead (pacemaker lead) door het interventriculaire septum (hartkamertussenschot) richting het endocardium van het linker ventrikel geschroefd. Door op deze locatie te stimuleren ontstaat ventriculaire activatie die slechts iets meer dyssynchroon is dan in de fysiologische situatie. Er is in korte tijd zeer veel onderzoek naar LBBAP verricht en studies hebben aangetoond dat LBBAP effectief en veilig is en minder beperkingen kent dan HBP.

De acute elektrofysiologische en hemodynamische effecten van multi-LV-stimulatie zijn onderzocht in een pre-klinische studie die wordt beschreven in **hoofdstuk 3**. Zoals beschreven in hoofdstuk 2, is het combineren van RV-stimulatie met LV-stimulatie, ook wel BVP, een manier om RV-stimulatie geïnduceerde negatieve effecten te voorkomen. Om de respons op BVP verder te verbeteren, werd multi-LV-stimulatie (of tri-ventriculaire stimulatie) onderzocht. Er is slechts een klein aantal klinische onderzoeken naar multi-LV-stimulatie uitgevoerd waarbij tegenstrijdige resultaten zijn gevonden. **Hoofdstuk 3** geeft een antwoord op de vraag of het stimuleren van een groter gebied in de LV een betere resynchronisatie oplevert in vergelijking met RV en het conventionele BVP en, als gevolg daarvan ook de hartfunctie verbetert. De resultaten laten zien dat verschillende

soorten multi-LV-stimulatie een vergelijkbare mate van elektrische resynchronisatie en hemodynamisch effect creëren, die optimaler zijn wanneer de afstand tussen de elektroden groot is. Multi-LV-stimulatie vergroot echter alleen het voordeel wanneer de LV-lead die voor BVP wordt gebruikt, een slechte respons geeft.

Hoofdstuk 4 geeft een uitgebreid overzicht van de fysiologie en de praktische toepasbaarheid van LVSP. In deze review beschrijven we hoe zowel dierstudies als patiëntstudies hebben aangetoond dat de LV-functie behouden blijft tijdens LVSP, op een manier die vergelijkbaar is met sinusritme bij normale geleiding. De activatie van het linker ventrikel is echter meer synchroon tijdens LBBP in vergelijking met LVSP, maar LBBP produceert daarbij meer intra-ventriculaire dyssynchronie in vergelijking met LVSP. Een belangrijke praktische overweging: hoewel LVSP vrij eenvoudig uit te voeren is, kan het exact implanteren van de stimulatiedraad in het gebied van de linker bundeltak een grotere uitdaging zijn.

In **hoofdstuk 5** wordt de veiligheid en effectiviteit van LBBAP beschreven bij de eerste 80 patiënten bij wie deze techniek is toegepast in Nederland (Maastricht Universitair Medisch Centrum+). De resultaten tonen aan dat LBBAP een veilige en haalbare techniek is (succespercentage 96%), met een duidelijke leercurve die lijkt af te vlakken na 40-60 implantaties. Het daadwerkelijk stimuleren van het linkszijdige geleidingssysteem is haalbaar bij tweederde van de patiënten. Vergeleken met RV pacing handhaaft LBBAP de ventriculaire elektrische synchronisatie vergelijkbaar met de fysiologische situatie.

In **hoofdstuk 6** combineerden we onze lokale data met andere ervaren centra en vormden we de grootste observationele studie met patiënten bij wie geprobeerd was een LBBAP-pacemaker te implanteren in 14 Europese centra. De studie omvatte meer dan 2500 patiënten en het slagingspercentage van LBBAP-implantatie voor de indicaties bradycardie en hartfalen was respectievelijk 92,4% en 82,2%. Onafhankelijke voorspellers van het niet slagen van LBBAP-implantatie waren hartfalen, lange baseline QRS duur en linker ventrikel-einddiastolische diameter. De resultaten tonen aan dat de veiligheid en het slagingspercentage bij patiënten met hartfalen verbeterd moeten worden.
Na uitvoerig de veiligheid en werkzaamheid te hebben aangetoond, wordt in **hoofdstuk 7** de elektrische ventriculaire synchronie direct vergeleken tussen LBBP en LVSP in een multicenter populatie. ECG- en VCG-indices tonen aan dat zowel LVSP als LBBP de ventriculaire dyssynchronie aanzienlijk verbeteren in vergelijking met RVSP, tot waarden dicht bij de fysiologische ventriculaire activatie. LBBP resulteert in een kleine, maar significante verbetering in ventriculaire synchronie in vergelijking met LVSP.

In **hoofdstuk 8** worden het ontwerp en de voorlopige resultaten van de eerste tien patiënten beschreven van de "MASTER-LV-studie". Deze studie is uitgevoerd om de acute hemodynamische en elektrische effecten van diepe septale stimulatie met (LBBP) en zonder (LVSP) directe stimulatie van de linker bundeltak te evalueren. De voorlopige resultaten laten zien dat de verschillen in het acute hemodynamische effect van RV-stimulatie en LBBAP klein zijn. Er lijkt een trend te zijn naar een iets hogere systolische bloeddruk tijdens LVSP en niet-selectieve LBBP in vergelijking met selectieve-LBBP.

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About the Author

Luuk Ingo Benjamin
was born on November 20th, 1992 in Heerlen, The Netherlands.

From 2005 until 2011 he attended secondary education (Gymnasium) at College Rolduc in Kerkrade (The Netherlands). In 2011, he started his medical training at the Faculty of Health, Medicine and Life Sciences at Maastricht University. His interest in cardiology was sparked by family members with cardiac disease as well as facultative internships at the Cardiology department of the Maastricht University Medical Centre+. He obtained the Master of Science title in 2017.

He was supervised by prof. dr. Frits Prinzen during his elective course on exercise physiology and after several years of voluntary research – through intervention of prof. dr. Harry Crijns – again during his PhD-track at the department of Physiology at Maastricht University along with prof. dr. Kevin Vernooy of the clinical Cardiology department in Maastricht. Initiated in September 2017, the PhD project aimed to optimize outcome of pacemaker therapy strategies alternative to right ventricular pacing.

From October 2021 until July 2023 he gained clinical experience in cardiology at Zuyderland Medisch Centrum (Heerlen and Sittard) and at Maastricht University Medical Centre+.

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