Feasibility and Acute Hemodynamic Effect of Left Ventricular Septal Pacing by Transvenous Approach Through the Interventricular Septum

Masih Mafi-Rad, MD; Justin G.L.M. Luermans, MD, PhD; Yuri Blaauw, MD, PhD; Michel Janssen, BSc (MT); Harry J. Crijns, MD, PhD; Frits W. Prinzen, PhD; Kevin Vernooy, MD, PhD

Background—Left ventricular septal (LVS) pacing reduces ventricular dyssynchrony and improves cardiac function relative to right ventricular apex (RVA) pacing in animals. We aimed to establish permanent placement of an LVS pacing lead in patients using a transvenous approach through the interventricular septum.

Methods and Results—Ten patients with sinus node dysfunction scheduled for dual-chamber pacemaker implantation were prospectively enrolled. A custom pacing lead with extended helix was introduced via the left subclavian vein and, after positioning against the right ventricular septum (RVS) using a preshaped guiding catheter, driven through the interventricular septum to the LVS. The acute hemodynamic effect of RVA, RVS, and LVS pacing was evaluated by invasive LVDp/dtmax measurements. The lead was successfully delivered to the LVS in all patients. Procedure time and fluoroscopy time shortened with experience. QRS duration was shorter during LVS pacing (144±20 ms) than during RVA (172±33 ms; \( P=0.02 \) versus LVS) and RVS pacing (165±17 ms; \( P=0.004 \) versus LVS). RVA and RVS pacing reduced LVDp/dtmax compared with baseline atrial pacing (−7.1±4.1% and −6.9±4.3%, respectively), whereas LVS pacing maintained LVDp/dtmax at baseline level (1.0±4.3%; \( P=0.001 \) versus RVA and RVS). R-wave amplitude and pacing threshold were 12.2±6.7 mV and 0.5±0.2 V at implant and remained stable during 6-month follow-up without lead-related complications.

Conclusions—Permanent placement of an LVS pacing lead by transvenous approach through the interventricular septum is feasible in patients. LVS pacing preserves acute left ventricular pump function. This new pacing method could serve as an alternative and hemodynamically preferable approach for anti-bradycardia pacing.

Key Words: cardiac pacing ▶ feasibility studies ▶ ventricular dysfunction, left ▶ ventricular septum

Cardiac pacing is the only effective treatment for symptomatic bradycardia that is caused by sinus node dysfunction (SND) or atrioventricular (AV) block. The right ventricular apex (RVA) has become the preferred site for ventricular lead placement because it is easily accessible for implantation and yields chronically stable lead positions and stimulation thresholds. In general, RVA pacing is well tolerated and effective. However, there is increasing evidence that the dyssynchronous left ventricular (LV) electric activation and contraction, induced by RVA pacing, has detrimental effects on LV structure and function, which is associated with an increased risk of cardiac morbidity and mortality.\(^1\)\(^-\)\(^3\) New pacemaker algorithms have minimized the percentage of undesirable ventricular pacing in patients with SND and patients with implantable cardioverter-defibrillators.\(^4\)\(^-\)\(^6\) However, in many patients, continuous ventricular pacing is unavoidable because of unreliable or absent AV conduction. In recognition of this, interest has also been focused on alternative ventricular pacing sites to preserve LV pump function. Alternative pacing sites within the right ventricle (RV), such as the RV septum (RVS) or RV outflow tract, have been intensively studied but show mixed results.\(^7\)\(^-\)\(^9\) Studies on animals have shown that pacing at the LV septum (LVS) yields LV pump function closely approximating that during normal ventricular conduction and significantly better than that during RVA pacing.\(^10\)\(^-\)\(^11\) In the animal experiments, the LVS lead was permanently placed by introducing a custom pacing lead with extended helix transvenously into the RV and driving it from the RV side through the interventricular septum (IVS) to the LVS.\(^11\) This was shown to be a feasible and safe procedure, and leads remained mechanically and electrically stable during 4-month follow-up in the otherwise healthy and active canines. The objectives of this study were (1) to perform a first-in-man study, investigating the feasibility of permanently implanting an LVS lead in patients using...
WHAT IS KNOWN

• Right ventricular apical pacing causes dyssynchronous left ventricular (LV) electric activation and contraction that may have detrimental effects on left ventricular performance and structure and may be associated with adverse clinical outcomes.

• Animal studies have shown that left ventricular septal pacing induces a more physiological sequence of LV electric activation and contraction compared with right ventricular apical pacing and preserves LV systolic function.

WHAT THE STUDY ADDS

• This first-in-man study demonstrates the feasibility of permanently implanting an LV sepal lead in patients using a transvenous approach through the interventricular septum.

• LV septal pacing reduces electric dyssynchrony and improves acute hemodynamic performance compared with right ventricular apical and right ventricular septal pacing in patients.

• The results of this study suggest that LV septal pacing could serve as an alternative and hemodynamically preferable approach for antibradyarrhythmia pacing.

a transvenous approach through the IVS; and (2) to compare the acute hemodynamic effect of LVS pacing with that of RVS pacing and conventional RVA pacing.

Methods

Study Population

We prospectively enrolled patients with a pacemaker indication for symptomatic SND, who were thus not ventricular pacing dependent and, therefore, considered at relatively low risk of adverse events in case of lead failure. Exclusion criteria were second- or third-degree AV block, history of septal myocardial infarction, IVS wall thickness >10 mm on echocardiography, permanent atrial fibrillation, or A V block, history of septal myocardial infarction, IVS wall thick-

density at baseline and postimplantation. The LV septal pacing threshold was measured at baseline and after the implantation procedure.

Implantation Procedure

Figure 2 illustrates the different steps performed during the implantation procedure. Two venous accesses were obtained by left cephalic vein cutdown or left subclavian vein puncture. A standard atrial bipolar active fixation pacing lead was positioned in the right atrium according to routine clinical practice (Figure 2A). A Certus Pressure Wire (St Jude Medical Systems AB, Uppsala, Sweden) was positioned in the LV for acute hemodynamic measurements (see below). The Certus wire was introduced via a left femoral arterial puncture and positioned in the LV by the retrograde aortic approach using a 6 Fr multipurpose catheter. Subsequently, the multipurpose catheter was withdrawn into the aorta leaving the soft tip of the pressure wire in a stable position in the LV cavity (Figure 2A). An RV angiogram was made in right anterior oblique (RAO; Figure 2A) and left anterior oblique (LAO; Figure 2B) view to visualize the IVS borders using a 6 Fr pigtail catheter introduced into the RV via the second venous access. The pigtail catheter was replaced with a quadripolar diagnostic electrophysiology catheter that was positioned in the RVA for temporary pacing. Next, the acute hemodynamic effect of RVA pacing was evaluated. Subsequently, the electrophysiology catheter was removed, and the custom ventricular pacing lead was introduced into the RV using a 7 Fr preshaped guiding catheter (Medtronic Inc; Figure 2C). The specific shape of the C315-S10 catheter allows straightforward positioning of the catheter tip perpendicularly against the IVS. During lead placement, the implantator repeatedly alternated between RAO (Figure 2C) and LAO (Figure 2D) view to position the tip of the lead as close to the middle of the IVS as possible while using the RV angiogram in RAO (Figure 2A) and LAO (Figure 2B) as a reference. Hereby, the RAO view was used to direct the lead to halfway between apex and base, whereas the LAO view was used to position the lead halfway between the anterior and posterior septal borders. An 8 Fr ACUSON AcuNav diagnostic ultrasound catheter (Siemens Medical Solutions USA, Inc) was introduced via a right femoral venous puncture and advanced to the right atrium for intracardiac echocardiography (ICE). ICE was used to verify the position of the lead tip on the IVS achieved using fluoroscopy before screwing the lead into the IVS (Figure 2E and 2F). Subsequently, the pacing electrode was screwed through the IVS until the IVS was reached, without perforating the IVS. While rotating the lead, the implantator repeatedly assessed the penetration depth in the IVS by injecting small amounts of contrast medium through the guiding catheter against the IVS under fluoroscopy in LAO (Figure 2G–2I). Because the contrast medium is restrained by the IVS, the part of the lead tip that protrudes into the IVS is not covered by contrast medium. In combination with beforehand knowledge of the lead tip dimensions and the patient’s IVS wall thickness (preproce-
dural assessment with echocardiography), this provided an estimation of penetration depth in the IVS. 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. Pacing thresholds and impedances were measured to ensure that the helix did not protrude in the LV cavity. Subsequently, acute hemodynamic measurements were performed as described below. All patients received a dual-chamber pacemaker. The pacemaker was programmed to AAI (atrial pacing) with DDD (AV-sequential pacing) backup.

Acute Hemodynamic Measurements

The acute hemodynamic effect of RVA pacing (with the temporary electrophysiology catheter), RVS pacing (unipolar pacing from the ring of the custom lead), and LVS pacing (unipolar pacing from the tip of the custom lead) was evaluated by invasive measurement of LVdP/dtmax using the Certus Pressure Wire and PhysioMon software (St Jude Medical Systems AB). All pacing was performed at 10 beats per minute above intrinsic sinus rate. For each ventricular site, LVdP/dtmax was measured during AV sequential pacing (DDD mode) with a paced AV delay 60 ms shorter than intrinsic activation to ensure full ventricular capture. Baseline LVdP/dtmax measurements were performed during atrial pacing (AAI mode) before and after each DDD measurement. A waiting period of at least 30 seconds was respected.
after each measurement to allow for hemodynamic stabilization. During each measurement, LVdP/dtmax was measured and averaged over an interval of 20 seconds. The acute hemodynamic effect of pacing at each ventricular site was calculated as the relative change in LVdP/dtmax compared with the average of the 2 adjacent baseline AAI measurements.

Follow-Up
R-wave amplitude, pacing thresholds, and impedances were recorded immediately after implantation; the day after implantation; as well as 10 days, 1 month, 3 months, and 6 months after the implantation.

Statistical Analysis
Continuous variables are expressed as mean±SD. Categorical variables are expressed as observed number and percentage values. Means of continuous variables were compared among pacing conditions using repeated measures ANOVA with Bonferroni multiple comparisons procedure applied to pairwise comparisons. A P value <0.05 was used to denote statistically significant differences. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc) software.

Results

Patients
Ten patients (mean age, 72±10 years; 5 men) were included in the study. The baseline characteristics of the patients are shown in Table 1. All patients were in sinus rhythm, had a normal QRS duration on standard 12-lead ECG, and had a normal LV ejection fraction at echocardiographic evaluation. Mean IVS thickness assessed by echocardiography was 9±1 mm.

Implantation
All patients underwent a successful implantation of an LVS lead through the IVS in a single procedure. In 8 of 10 patients, a lead position at the midlevel of the LVS (halfway between the apex and the base) was achieved (Table 2). In patients 2 and 7, the lead was positioned in a more apical and basal region of the LVS, respectively. The mean time required to implant the LVS lead was 29±24 minutes (limits 9–90 minutes), and the mean fluoroscopy time during the entire procedure was 20±9 minutes (limits 10–44 minutes) with a clear trend of shortening times with increasing experience (Table 2). During implantation of the last 2 patients, the implanter felt safe enough with the procedure to accomplish implantation of the LVS lead without guidance by ICE.

Lead Stability and Complications
There were no clinically significant changes in pacing threshold, R-wave amplitude, or impedance of the LVS lead between implantation and the day after implantation, as well as at 10-day, 1-month, 3-month, and 6-month follow-up. Mean pacing threshold, R-wave amplitude, and impedance at implant were 0.5±0.2 V, 12.2±6.7 mV, and 715±83 ohms, respectively. At 6-month follow-up, mean pacing threshold, R-wave amplitude, and impedance were 0.9±0.3 V, 16.0±8.7 mV, and 550±55 ohms, respectively.

No periprocedural complications related to the LVS lead were observed. None of the patients developed ventricular conduction disturbances during the procedure. During 6-month follow-up, none of the patients showed signs of dislodgment of the LVS lead, loss of capture, prolongation of the paced or intrinsic QRS duration, or infections associated with the implantation procedure.

ECG Characteristics
Figure 3 shows the ECG from patient 2 (Table 1) during intrinsic activation, RVA, RVS, and LVS pacing. During RVA and RVS pacing, a left bundle-branch block–like QRS morphology was observed, and QRS duration was considerably prolonged relative to intrinsic activation. During LVS pacing, a right bundle-branch block–like QRS morphology was observed in the precordial leads and QRS duration was
considerably less prolonged than during RVS and RVA pacing. For the entire study cohort, QRS duration during intrinsic activation was 90±5 ms. During RVA and RVS pacing, QRS duration was almost twice as long as during intrinsic activation (RVA pacing, 172±33 ms [P=0.004 versus intrinsic activation]; RVS pacing, 165±17 ms [P<0.001 versus intrinsic activation]). QRS duration during LVS pacing was 144±20 ms, which was prolonged compared with intrinsic activation (P=0.002), yet significantly shorter than during RVA pacing (P=0.02) and RVS pacing (P=0.004).

**Acute Hemodynamic Measurements**

The LVDp/dt\(_{\text{max}}\) measurements were successfully obtained in all patients without complications. Figure 4 shows the acute change in LVDp/dt\(_{\text{max}}\) during RVA, RVS, and LVS pacing relative to baseline atrial pacing for the entire study cohort, as well as the individual hemodynamic responses to pacing at different ventricular sites. RVA and RVS pacing reduced LVDp/dt\(_{\text{max}}\) compared with baseline atrial pacing by 7.1±4.1% and 6.9±3.4%, respectively, whereas LVS pacing maintained LVDp/dt\(_{\text{max}}\) at baseline level (1.0±4.3%; P=0.001 versus RVA and RVS). This acute hemodynamic benefit of LVS pacing over RVA and RVS pacing was observed in all patients (Figure 4).

**Discussion**

This study demonstrates that permanent implantation of a pacing lead with extended helix in the LVS using a transvenous approach through the IVS is feasible and safe, at least in this small group of patients. Compared with RVA and RVS pacing, LVS pacing reduces electric dyssynchrony and preserves acute LV pump function. Electric and mechanical lead properties remain stable during 6-month follow-up.

**Feasibility of LVS Pacing**

The feasibility of LVS pacing using a transvenous approach through the IVS has previously only been demonstrated in animal experimental studies. Grosfeld et al\(^\text{12}\) were the first to demonstrate implantation of a custom pacing lead with a long insulated screw in the LVS through the IVS in 6 goats. In a later study, Mills et al\(^\text{11}\) achieved permanent and stable LVS pacing over a period of 16 weeks in 8 adult mongrel dogs using a custom pacing lead with extended helix, similar to the one used in this study.

This study translates the results of these preclinical studies into clinical practice by demonstrating that this form of LVS pacing is also feasible in patients. Implantation of an LVS lead was successfully accomplished in all patients in a single procedure. There were no short- or long-term lead-related complications. Pacing thresholds and sensing characteristics were within an adequate range and in keeping with that during RVA pacing, and the leads remained electrically and mechanically stable during 6-month follow-up. Because it is a novel implantation technique, procedure time and total fluoroscopy time were relatively long during the first implantations. However, both procedure time and fluoroscopy time steeply declined with increasing experience. The study protocol initially involved ICE as an additional visualization tool to increase the safety of the procedure. However, the experience gained throughout the study allowed omission of ICE during the last 2 procedures without compromising safety, thereby...
increasing feasibility of the implantation procedure in clinical practice. Furthermore, implantation of the LVS lead could be accomplished using a commercially available preshaped guiding catheter, making the procedure applicable in any implanting center with access to the relevant instruments.

LVS Pacing Versus RVA and RVS Pacing

The finding that RVA pacing induces electric dyssynchrony and impairs acute hemodynamic function is well known from literature.\textsuperscript{1,11} Subanalyses of different clinical trials have shown that a higher RVA pacing burden is associated with heart failure worsening, atrial fibrillation, and death.\textsuperscript{2,14,15}

In this study, RVS pacing did not show a better ventricular electric activation pattern or an acute hemodynamic benefit compared with RVA pacing. The RVS has been suggested as an alternative pacing site, but comparative studies have found conflicting results. Small acute hemodynamic studies generally show a tendency toward an advantage of RVS compared with RVA pacing.\textsuperscript{7} However, 3 randomized trials comparing RVS with RVA pacing in patients with congestive heart failure and chronic atrial fibrillation and patients with total AV block showed no differences in LV ejection fraction, quality of life, exercise capacity, and brain natriuretic peptide levels at long-term follow-up.\textsuperscript{8,16,17}

Previous acute hemodynamic studies in dogs with normal ventricular conduction have demonstrated that pacing at the LVS maintains LV systolic and diastolic function at sinus rhythm level, whereas LV function is depressed during RVA and RVS pacing.\textsuperscript{10,11} The data from this study extrapolate these preclinical findings on the beneficial hemodynamic effect of LVS pacing to the human population. In the animal studies, electric activation mapping and MRI tagging showed that the superior hemodynamic effect of LVS pacing is related to the more physiological sequence of LV electric activation and contraction, resulting in less LV electric and mechanical dyssynchrony.\textsuperscript{11} In this study, reduction in electric dyssynchrony was reflected by the shorter QRS duration during LVS pacing compared with RVA and RVS pacing. During normal ventricular conduction, electric activation of the working myocardium starts at the LV septal endocardium, which may explain why pacing at or near this site maintains a closer to normal electric activation, as well as mechanical synchrony.

### Table 1. Patient Characteristics

<table>
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<th>No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Pacing Indication</th>
<th>Intrinsic Rhythm</th>
<th>QRS Duration, ms</th>
<th>LVEF, %</th>
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**Mean±SD** 72±10 90±5 59±6 52±7 9±1

F indicates female; IVS, interventricular septum; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; M, male; SND, sinus node dysfunction; and SR, sinus rhythm.

### Table 2. Implantation Procedure Details

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Mean±SD 29±24 136±50 20±9 381±485 4129±4193

LVS indicates left ventricular septum.
and coordination. Activation of the RV wall has been shown to remain moderately delayed during LVS pacing, which may explain why in this study QRS duration during LVS pacing, although shorter compared with RVA and RVS pacing, was still prolonged compared with intrinsic ventricular activation. A remarkable finding of this study is the large difference in QRS duration and hemodynamic effect between pacing at the RV and LV side of the IVS, despite the fact that these sites were not >1 cm apart. These observations are consistent with earlier observations in animals and patients and have been related to a significant delay in transseptal conduction during RVS pacing, which causes considerably later LV mechanical activation and peak contraction of the LV lateral wall, thereby inducing both inter- and intraventricular asynchrony.

Another pacing site that is capable of preserving native ventricular activation is the His bundle. Similar to our observations in LVS pacing, His bundle pacing in patients has been shown to result in less inter- and intraventricular dysynchrony and better hemodynamic performance than RVA pacing. Permanent His bundle pacing has been achieved in patients with SND, in patients with atrial fibrillation post-AV nodal ablation, and in patients with AV block. Although the various studies have demonstrated beneficial effects of this alternative pacing site, at present, His bundle pacing is not recommended in patients requiring permanent cardiac pacing because of technical challenges during lead positioning and concerns about lead stability and threshold.

Currently, the most common way to reverse or prevent pacing-induced dyssynchrony is the application of biventricular pacing. An upgrade of RVA pacing to biventricular pacing in patients with permanent AV block, severe symptoms of heart failure, and depressed LV ejection fraction is likely to improve their symptoms and cardiac function and reduce hospitalization. In addition, several small randomized trials have suggested that patients with a conventional indication for bradycardia pacing with moderate to severe LV dysfunction might benefit from de novo biventricular pacing compared with RV pacing in terms of LV function and remodeling, hospitalization, heart failure symptoms, and quality of life. However, biventricular pacing also has drawbacks, such as the more complex and time-consuming implantation procedure, the higher rate of complications, failed implantations, and loss of pacing associated with a coronary sinus.
lead with the consequent need for reoperation, the shorter battery life of biventricular devices, and the additional costs.

The excellent feasibility of permanently implanting an LVS pacing lead through the IVS in combination with the acute hemodynamic benefit of LVS pacing as demonstrated in this study suggests that this pacing technique could serve as an alternative for a biventricular upgrade or primary implantation of a biventricular system in patients with a conventional indication for anti-bradycardia pacing.

Limitations
As with any implanted lead, possible future complications, such as lead fracture or lead infection, may necessitate lead extraction. Extraction of a deep septal lead could potentially pose the risk of creating a ventricular septal defect, and temporary protrusion of the extraction sheath in the LV cavity could potentially create the risk of systemic embolism. This study lacks data on the magnitude of these potential risks of a possible LVS lead extraction.

During implantation, protrusion of the LV septal lead into the LV cavity was avoided by repeated injection of small amounts of contrast medium through the guiding catheter and by repeated assessment of pacing thresholds (see Methods). In this study, no protrusion into the LV cavity was observed, guaranteeing integrity of the LV endocardial surface. In case of protrusion, the lead should be withdrawn a few millimeters to its final position. This would leave a small wound at the LV endocardium, which is likely to be healed soon, but the exact amount and nature of the final damage are not known.

The sample size of this study was small, although can be considered sufficient to make an initial statement about the feasibility of permanently implanting a pacing lead in the LVS through the IVS. Although the procedure was also safe in this small group, a larger study is required to ultimately show safety of large-scale use of the LVS lead.

Because this is a novel pacing technique with unknown success rate and complications, the study was conducted in patients with SND, a group that is generally not ventricular pacing dependent and, therefore, considered at relatively low risk of adverse events in case of lead failure.

The different shape of the ring and tip electrode of the pacing lead may have flawed the comparison between RVS and LVS pacing. Yet, we chose to test these sites in this way to minimize the time interval between the hemodynamic measurements during RVS and LVS pacing, and thus the variability between these measurements.

The findings of this study clearly require further clinical validation in larger and prospective studies. These studies should also indicate whether the acute hemodynamic benefit of LVS pacing, as demonstrated in this study, translates into preservation of LV pump function on the longer term.

Conclusions
This study demonstrates that permanent placement of a pacing lead in the LVS using a transvenous approach through the IVS is feasible and safe, at least in this small group of patients. Compared with RVA and RVS pacing, LVS pacing reduces electric dyssynchrony and preserves acute LV pump function. The LVS lead remains electrically and mechanically stable during 6-month follow-up. The clinical benefit of this pacing method needs prospective evaluation. The results of this study suggest that LVS pacing could serve as a better alternative for RVA pacing in patients with a conventional indication for anti-bradycardia pacing, while lacking some of the disadvantages of biventricular pacing.

Disclosures
Dr Blaauw is a consultant for Medtronic. Dr Prinzen received research grants from Medtronic, Boston Scientific, EBR Systems, Biological Delivery System Cordis, MSD, and Proteus Medical and is a consultant for St. Jude Medical. Dr Crijns received grant support from St. Jude Medical and Boston Scientific and honoraria from Medtronic and Biosense Webster. Dr Verney received research grants from Medtronic and is a consultant for Medtronic. The other authors report no conflict.

References


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