Chronic left ventricular pacing

Left ventricular septal and left ventricular apical pacing chronically maintain cardiac contractile coordination, pump function and efficiency.

Mills RW et al. Chronic left ventricular pacing

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Abstract

**Background:** Conventional right ventricular (RV) apex pacing can lead to adverse clinical outcome associated with asynchronous activation and reduced left ventricular (LV) pump function. We investigated to what extent alternate RV (septum) and LV (septum, apex) pacing sites improve LV electrical activation, mechanics, hemodynamic performance and efficiency over 4 months of pacing.

**Methods and Results:** After AV-nodal ablation, mongrel dogs were randomized to receive 16 weeks of VDD pacing at the RV apex, RV septum, LV apex, or LV septum (trans-ventricular septal approach). Electrical activation maps (combined epicardial contact and endocardial non-contact) showed that RV apical and RV septal pacing induced significantly greater electrical desynchronization than LV apical and LV septal pacing. RV apex and RV septal pacing also significantly increased mechanical dyssynchrony, discoordination (MRI tagging) and blood flow redistribution (microspheres) and reduced LV contractility, relaxation, and myocardial efficiency (stroke work / myocardial oxygen consumption). In contrast, LV apical and LV septal pacing did not significantly alter these parameters as compared to the values during intrinsic conduction. At 16 weeks, acute intra-subject comparison showed that single site LV apical and LV septal pacing generally resulted in similar or better contractility, relaxation and efficiency as compared to acute biventricular pacing.

**Conclusions:** Acute and chronic LV apical and LV septal pacing maintain regional cardiac mechanics, contractility, relaxation and efficiency near native levels, whereas RV apical or RV septal pacing diminish these variables. Acutely, LV apical and LV septal pacing tend to maintain or improve contractility and efficiency compared to biventricular pacing.

**Key Words:** pacing, hemodynamics, mapping, mechanics, oxygen
Introduction
Compared to normal ventricular activation, conventional right ventricular (RV) apex pacing is associated with asynchronous left ventricular (LV) activation, abnormal contraction and reduced pump function (for review see\(^1\)). These adverse effects have been associated with an increased risk of developing heart failure (for review see\(^1\)). Also contributing to this adverse outcome is a reduction in myocardial efficiency during ventricular pacing, which increases total myocardial oxygen demand. Consequently, paced hearts can be expected to be more susceptible to ischemia when coronary reserve is limited\(^2\), as during coronary artery disease and/or overload of the heart.

Several studies have sought alternative pacing sites in order to improve hemodynamic performance. Because pacing leads are usually implanted transvenously, alternate sites within the RV have been studied most intensively, but results of the various studies are mixed\(^3,4\). Experimental and clinical studies indicate that LV pacing sites often render better hemodynamic performance than RV pacing sites\(^5-7\). In a previous acute canine study we observed hemodynamic benefits by LV septal and LV apical pacing, compared to RV apical pacing, and mixed effects during RV septal pacing\(^8\). No studies have directly addressed the influence of alternate site pacing on myocardial efficiency. One patient study found that cardiac resynchronization improves efficiency as compared to left bundle branch block\(^9\), while other studies showed that RV pacing decreased efficiency as compared to atrial pacing\(^10,11\).

It was the aim of this study to compare the long term (4 months) effects of pacing at the RV apex, RV septum, LV septum and LV apex in canine hearts by measuring the sequence of electrical activation as well as the distribution of myocardial strains, blood flow, pump function and myocardial efficiency. In addition, it was investigated how single site LV pacing compares to biventricular (BiV) pacing.

Methods
Animal handling was performed according to the Dutch Law on Animal Experimentation (WOD) and the European Directive for the Protection of Vertebrate Animals Used for
Chronic left ventricular pacing

Experimental and Other Scientific Purposes (86/609/EU). The protocol was approved by the Maastricht University Experimental Animal Committee.

Acute electrical activation mapping
In order to avoid the physical influence of the electrode bands and Ensite balloon on the other measurements, electrical activation mapping was performed in 7 separate animals, using the same anesthesia (below). Epicardial activation was determined using two bands of unipolar electrodes (104 in total) around the LV and RV, whereas endocardial activation was determined using Ensite® non-contact mapping. Electrograms from the 64 physical electrodes on the Ensite balloon were converted by the Ensite system into 2048 virtual electrograms from the endocardial surface of the LV. These virtual electrograms were exported to a PC where activation time was determined from the time of steepest negative deflection of the electrogram using custom software. All electrograms were time-referenced to the onset of the Q-wave (natural conduction) or the pacing artifact.

Chronic ventricular pacing model
Adult mongrel dogs (28±3.5 kg) of either sex were premedicated, anesthetized and treated postoperatively as described before12. All received a transvenous lead in the right atrium (Medtronic 5568) and were randomized to receive either an epicardial lead at the LV apex (n=7; Medtronic 5071) via a limited thoracotomy or a transvenous lead in either the RV apex (n=9; Medtronic 3830 or 5076), RV mid-septum (n=7; Medtronic 3830), or the LV mid-septum (n=8). The latter received a custom pacing lead (Medtronic 3830 lead with extended helix) which was introduced transvenously and, after positioning against the RV septum using a pre-shaped guiding catheter, driven through the interventricular septum with the screw-in tip until the LV endocardium was reached. All leads were positioned according to the prescribed anatomical location; no attempt was made to search for sites resulting in narrower paced QRS complexes. After creation of total AV-block by radio frequency ablation, the animal was paced for 16 weeks in VDD mode (Medtronic Sigma, Kappa, or Enpulse series). AV-delay (110±20 ms) was set to maintain P-Q segment length on ECG lead II as measured just prior to
creation of AV-block. Under all conditions pacing was performed at about twice the stimulation threshold.

**MRI tagging measurements of strain, dyssynchrony and discoordination**

After 16 weeks of VDD pacing, but prior to the final invasive measurements (below), magnetic resonance (MR) tagging was performed in five short axis slices, spanning most of the LV wall, at a temporal resolution of 15 ms\(^1\)\(^2\). Myocardial strains, work, and indices of global mechanical discoordination (internal stretch fraction — ISF\(^1\)^\(^3\)) and dyssynchrony (difference between 5th and 95th percentiles of time to peak shortening measured from 160 locations) were determined as explained in more detail in the Data Supplement.

**Temporal changes in hemodynamics and efficiency**

Measurements were recorded at three time points, all under full anesthesia: 1) after lead implantation but prior to AV-block and paced in AOO mode at 110 bpm (Baseline), 2) after AV-block creation and approximately one hour of DOO pacing at the same rate (1 Hr ventricular pacing (V-pacing)), and 3) again under the same surgical and pacing conditions after 16 weeks of VDD pacing (16 Wks V-pacing). Typical sinus rate under anesthesia was 70-90 bpm, and slight overdrive AOO/DOO pacing was used to reduce hemodynamic variability and rate effects during and between measurements. During DOO pacing, AV-delay was increased relative to VDD to maintain P-Q segment length.

LV pressure and volume were determined using the conductance catheter technique (CD-Leycom, Netherlands)\(^1\)^\(^4\). All signals (ECG, pressure, volume) were digitized at 1 kHz and stored using custom made software (IDEEQ, Maastricht Instruments, Netherlands) and later analyzed using custom automated analysis software written for MATLAB (MathWorks, Natick, MA).

LV contractility was assessed as the peak rate of pressure rise normalized to instantaneous chamber pressure (LV\(dP/dt\)\(_{\text{max}}\)/P\(_{\text{instantaneous}}\)). LV relaxation was assessed as the time constant of the exponential decay fit to the falloff of LV pressure from maximal rate of decline until the level of end-diastole (Tau). Mechanical interventricular asynchrony was quantified as the time delay between the upslope of the LV and RV.
pressure signals, estimated by cross correlation\textsuperscript{15}. Stroke work (SW) was calculated as the loop-area enclosed in the LV pressure-volume (P-V) plane. External efficiency was calculated as the ratio of SW to myocardial oxygen consumption (MVO\textsubscript{2}, see below)\textsuperscript{16}.

\textit{Myocardial oxygen consumption and perfusion}

MVO\textsubscript{2} [mL-O\textsubscript{2}/beat] was calculated according to the Fick principle (product of mean myocardial blood flow, arterial to coronary-venous oxygen content difference, and inverse heart rate). Mean myocardial blood flow was indexed by continuous measurement of coronary sinus blood velocity, measured by Doppler wire (Volcano Therapeutics 1400). Average coronary sinus blood velocity was calibrated to mean myocardial blood flow\textsuperscript{17} by simultaneous Doppler-velocity and microsphere-flow measurements\textsuperscript{18}, once for each of the three hemodynamic measurement time points above. After the calibration measurement, any changes in average coronary sinus velocity were assumed to be linearly proportional to a change in mean myocardial flow\textsuperscript{17}.

Fluorescent microsphere measurements were also used to determine regional myocardial perfusion as previously described\textsuperscript{18}. Post mortem samples of the anterior, lateral, posterior and septal wall were assessed to determine distribution of myocardial blood flow within the LV wall.

\textit{Acute comparative pacing at 16 weeks}

After finishing the temporal measurements at 16 weeks, the thorax was opened and epicardial leads were placed at the RV apex, LV apex (in non-chronically LV-apical paced animals) and LV lateral wall. The same measurements described above were repeated during DOO pacing at 110 bpm in four modes: implant-site (IS) pacing, RV apical pacing, LV apical pacing, and RV apical / LV lateral pacing (biventricular — BiV). In this way each chronic implant site could be compared to three reference sites/combinations within each animal (see Data Supplement).
Statistics
Data are presented as mean values±SD. Unless otherwise indicated, temporal data during V-pacing are expressed as the percent difference from the global mean Baseline (AOO) value. Data on acute comparative pacing after 4 months of ventricular pacing are expressed as the percent difference from pacing at the implant site in that particular group at 16 weeks. The effects of pacing over time within subjects compared to Baseline and differences between the RV apex paced group to the other groups (as well as all 4 groups to the Normal Conduction group for MRI tagging parameters), and separately the effects of acute comparative pacing were evaluated for statistical significance using repeated measures ANOVA (standard ANOVA for MRI tagging parameters) and the Sidak correction for multiple comparisons using a family significance level of α=0.05.

Results
Details of lead position verification are included in the Data Supplement.

Acute electrical activation mapping
The left panel of Figure 1 depicts the electrical activation sequence during normal conduction. The red to yellow colors indicate that total ventricular activation occurred within 40 ms. During RV apical pacing the RV wall is activated earliest (Figure 1, upper left), followed by the LV septum (green colors) and then the LV lateral wall (blue color). During RV septal pacing (Figure 1, upper right) the LV septum was activated relatively early, but subsequent activation around the LV endocardium and then towards the LV lateral epicardium was slow. LV apical pacing (Figure 1, lower left) resulted in early apical activation, followed by a rapid spread of activation from LV apex to base, especially along the entire LV endocardium (see movie, Data Supplement). During LV apical pacing the activation in the LV wall occurred quite synchronous in the LV lateral wall and interventricular septum, while the RV base was activated latest. LV septal pacing (Figure 1, lower right) 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 conduction, albeit that the activation of the RV wall was moderately delayed (Figure 1). In both RV paced conditions transseptal conduction took 43-55 ms (Table 1). Activation time around the LV circumference was 29-49 ms during RV apical, RV septal and LV septal pacing, but significantly shorter during LV apical pacing. LV septal pacing resulted in RV+LV as well as LV activation times that were significantly shorter than during RV apical pacing.

*MRI tagging measurements of strain, dyssynchrony and discoordination*

Examples of regional strain signals and maps of systolic shortening from each of the groups show that chronic RV septal and RV apical pacing resulted in a more heterogeneous distribution of systolic shortening in time, space, and amplitude compared to normal activation or chronic LV septal or LV apical pacing (Figure 2).

Globally, Figure 3a shows that during normal conduction ISF was 0.06±0.03, but that RV apical and RV septal pacing increased this discoordination index significantly (ISF near 0.3). In contrast, LV apical and LV septal pacing did not significantly increase ISF (~ 0.1). Similarly, global mechanical dyssynchrony ranged between 100 and 150 ms during normal conduction as well as during LV septal and LV apical pacing, but was twice as large during RV apical and RV septal pacing (Figure 3b).

Regionally, during normal conduction earliest peak shortening was always observed in the lateral region and shortly thereafter (20-40 ms) observed in the other three quadrants (Figure 4a). A similar pattern was observed in the LV pacing groups, albeit with a slightly longer delay (40-60 ms). In contrast, the earliest peak shortening during RV pacing usually occurred in the septal region, whereas LV lateral peak shortening was significantly delayed.

Normal conduction resulted in a distribution of mechanical work which was mildly skewed toward the antero-lateral wall. This distribution was not significantly altered in either LV pacing group (Figure 4b). However, a significant redistribution of work away from the septum towards the lateral wall was found in both RV pacing groups (Figure 4b). RV apical and RV septal pacing resulted in a significant redistribution of perfusion towards the antero-lateral regions, while LV apical pacing led to increased septal
perfusion and LV septal pacing did not significantly alter perfusion from Baseline (Figure 4c).

**Temporal changes in hemodynamics and efficiency**

At both 1 hour and 16 weeks of pacing, the two RV pacing modes depressed LV dP/dt\textsubscript{max} and LV dP/dt\textsubscript{min} as compared to Baseline without changing end-systolic LV pressure (Table 2). Normalization of LV dP/dt\textsubscript{max} to instantaneous LV pressure shows (Figure 5a) that pacing at the RV sites decreased LV contractility by ~30% compared to Baseline, whereas pacing at the LV sites did not significantly alter contractility. Similarly, Tau was significantly (~20%) prolonged (impaired relaxation) by RV pacing but not by LV pacing (Figure 5b). These differences in contractility and relaxation between pacing sites were not correlated to QRS duration, as RV apical pacing resulted in shorter QRS duration than LV apical pacing.

Table 2 shows that RV apical and RV septal pacing reduced interventricular mechanical asynchrony to more negative values than during normal conduction (RV-preceding-LV), whereas LV apical pacing resulted in the opposite shift. LV septal pacing best maintained native interventricular asynchrony. Ventricular pacing had a variable effect on absolute SW about the Baseline values, but consistently increased MVO\textsubscript{2}, significantly so in the RV pacing groups (Table 2; 1 hour values).

The Baseline external efficiency (SW/MVO\textsubscript{2}) was approximately 0.21 (unitless). Figure 5c illustrates that this value was significantly reduced by RV apical and RV septal pacing (~65% of Baseline, p<0.05), while LV apical and LV septal pacing did not significantly change external efficiency).

**Acute comparative pacing at 16 weeks**

The left two sets of triple bars in Figure 6a and 6b depict that, after chronic RV apical and RV septal pacing, an acute switch to LV apical pacing significantly augmented contractility (LV-dP/dt\textsubscript{max}/P\textsubscript{instant}) and relaxation (Tau), while switching to BiV pacing only improved relaxation. In the chronic LV pacing groups (right two sets of triple bars), an acute switch to RV apical pacing significantly impaired contractility and relaxation, while acute BiV pacing non-significantly impaired contractility and relaxation. Acute switching
from LV apical to RV apical pacing decreased stroke volume significantly without significantly changing end-systolic pressure (Table in Supplemental Data).

After chronic RV apical pacing, acute LV apical and BiV pacing had little effect on external efficiency (Figure 6c). After chronic RV septal and LV septal pacing, acute LV apical pacing improved external efficiency, an increase which was significant in the LV septal pacing group. Acute switching to RV apical pacing reduced efficiency in LV paced groups. External efficiency during BiV pacing was between that of acute LV apical and acute RV apical pacing.

Discussion
The present study demonstrates that, in hearts with normal conduction through the ventricular myocardium, both LV septal and LV apical pacing 1) induce considerably less desynchronization of LV electrical activation than RV septal and RV apical pacing, 2) maintain normal distribution of mechanical work and blood flow, mechanical synchrony and coordination of contraction and consequently contractility, relaxation and external efficiency over at least 4 months and 3) appear at least as effective in minimizing desynchronization as BiV pacing.

Maintaining synchronous activation using single pacing sites
While BiV pacing therapy resynchronizes the ventricles of asynchronous hearts, the primary concern during ventricular pacing of otherwise normal hearts is to prevent mechanical desynchronization. Comparison of results from large randomized clinical trials indicates that desynchronization of ventricular activation is a stronger determinant of heart failure than proper atrioventricular coupling.1

The present animal study shows that single pacing sites exist that are capable of maintaining a normal distribution of myocardial strains as well as normal hemodynamic function over several months. The only other pacing site where this is the case is the His-bundle. This site is obvious, being the common rapid conduction path for both ventricles. Similar to our observations in LV apical and LV septal pacing, His bundle
Chronic left ventricular pacing has been shown to result in better hemodynamic performance\textsuperscript{19} and more uniform distribution of perfusion when compared to RV pacing\textsuperscript{20}.

The degree of blood flow redistribution during RV apical pacing is similar to that during experimental left bundle-branch block\textsuperscript{12} and is most likely related to redistribution of workload and oxygen demand within the LV wall\textsuperscript{6,12}.

The data from the present study extend earlier findings on the beneficial hemodynamic effects of LV septal and LV apical pacing in an acute hemodynamic study\textsuperscript{8}. In addition, it provides a mechanism for these effects, as the best pacing sites maintain a closer to normal electrical activation pattern as well as mechanical synchrony and coordination. Interestingly, the two LV pacing sites generate a beneficial influence on the hemodynamic performance by slightly different electrical activation patterns. LV septal endocardial pacing is characterized by faster activation of the entire LV, whereas during epicardial LV apical pacing the resultant synchronous contraction is predominantly due to quick engagement of the impulse into the LV endocardial layers and subsequent fast apex to base conduction along all wall segments of the LV. This fast endocardial impulse conduction is in agreement with earlier findings\textsuperscript{21}. Thirty-year old measurements by Myerberg et al. indicate that this high conduction velocity may be attributed at least partly to subendocardial non-Purkinje fibers\textsuperscript{22}.

Our promising findings on chronic LV apical pacing are in line with superior hemodynamic performance in an acute pediatric pacing study\textsuperscript{23}. Its chronic benefit was demonstrated by reversal of heart failure after switching from RV pacing to LV apical pacing in a 2-year old patient\textsuperscript{24}. In these pediatric studies the contraction sequence and LV pump function during single site LV apical pacing was at least as good as that during BiV pacing.

**LV versus RV septal pacing.**

One of the most remarkable findings in the present study is the large difference in electrical activation, hemodynamic effects and distribution of both strain and blood flow between pacing at the RV and LV side of the interventricular septum. Although the RV and LV septal pacing sites were not more than \textasciitilde 1 cm apart, this distance appears to be crucial for the difference between adverse effects and maintained normal function.
During RV septal pacing the LV septal endocardium is activated ~40 ms later and it takes another ~50 ms to conduct the impulse around the LV endocardium. During LV septal pacing the trans-septal conduction occurs (in rightward direction) simultaneous with the circumferential LV endocardial conduction, thus reducing total LV activation time significantly.

The considerably later mechanical activation of the LV during RV stimulation in the present study is expressed by the ~20 ms later rise in LV pressure, whereas this timing difference was only ~5 ms during LV septal pacing, which was similar to that during normal conduction. In addition, LV peak shortening times in the anterior and lateral walls were at least 50 ms later than that in the septal and posterior wall. Therefore, stimulating the left side of the septum significantly reduces both the inter- and intraventricular asynchronies elicited by stimulation at the right side of the septum.

**RV apical vs. RV mid-septal pacing**

Clinically the most studied alternative pacing sites are the RV septum and outflow tract\(^3\). Results of acute and chronic studies show mixed results with a tendency towards better hemodynamic outcome when pacing at these alternative sites\(^4\). However, much uncertainty is present, due to poor definition of the exact pacing site, the limited number of hemodynamic parameters studied, and non-randomized studies. Of the five chronic studies, referred to in \(^4\), two demonstrated a significant benefit of RV septal over RV apical pacing. In one of these studies, RV septal pacing produced a shorter QRS duration whereas in the other positive study, the septum was mapped to achieve the shortest QRS duration\(^25,26\).

In the present study the lead was implanted in the RV mid septum based solely on position and not optimizing the QRS complex. Surprisingly, none of the parameters investigated in the present study (electrical mapping, hemodynamic, regional strains, efficiency) showed a significant difference between RV apical and RV septal pacing. Similarly, no apparent benefit of RV septal pacing over RV apical pacing was observed in a clinical study of LV pressure-volume loops that also used purely anatomical lead positioning\(^6\). A recent comparison of chronic RV apex and RV septal pacing, based entirely on lead position, showed that RV Septal pacing was associated with more
impaired circumferential strain (p <0.001) and worse LV dyssynchrony than apical pacing\textsuperscript{27}. Therefore, it appears that the occasionally observed beneficial effects of RV septal pacing are not achieved solely from the higher lead position on the right side of the septum, but potentially only when pacing a “sweet spot”, implying stimulation of the rapid conduction system.

\textit{Limitations and potential clinical implications}

Data from animal experiments should always be extrapolated to the clinic with caution. The canine hearts from the present study may differ in various respects with those of patients. In the current study complete AV- block was induced and ventricular pacing was started immediately. In the clinical situation, hearts with acquired and presumably gradually developing AV-block may have undergone ventricular remodeling. Moreover, the canine hearts in the present study did not suffer from coronary artery disease, as may be the case in patients. A benefit of our experimental approach is the possibility to investigate many variables with respect to their response to pacing site. However, statistical testing on many variables may lead to Type I errors (falsely positive significant differences), despite correction for multiple comparisons.

Despite these potential differences, adverse hemodynamic effects of RV pacing are equally clear in the human\textsuperscript{5,7,28} and canine heart\textsuperscript{8,29}. Maintaining conduction, contractile coordination and LV pump function as close as possible to that during normal conduction, as demonstrated for LV septal and LV apical pacing over 4 months, may decrease the long term risk of developing heart failure. After all, evidence accumulates that acute hemodynamic disturbance leads to a vicious circle of adverse myocardial remodeling\textsuperscript{1,30} and that the amount and extent of dyssynchrony is a risk factor for developing heart failure\textsuperscript{31}. Moreover, the decreased external efficiency leads to increased oxygen demand, thus reducing coronary reserve\textsuperscript{2}, which may give rise to myocardial stunning and hibernation and, consequently, further diminishment in cardiac pump function.

The present study shows that it is possible to achieve good long term cardiac function by pacing from a single site, such as the LV apex or LV septum. Feasibility of the use of these novel alternate pacing sites clearly depends on the availability of tools.
for easy and safe implantation. LV apical pacing does require an open thorax or minimally invasive approach. Consequently, LV apical pacing currently is limited to children (where pacing leads are often placed epicardially) and patients undergoing surgical implantation. However, the LV apex is relatively easy to access using a subxyphoidal approach, so that after development of proper tools, positioning of a pacing lead at this site could become feasible for many more patients.

In the present study LV septal pacing was achieved using a trans-ventricular-septal approach. This is a novel technique, allowing LV pacing while avoiding placing a lead inside the LV cavity with its associated risk of creating thrombo-embolic reactions. Clinical application of this approach will require further development of a proper pacing lead and guiding catheter in order to accurately locate the lead in a repeatable manner as well as extensive investigation of the safety of such positioning.

While the conventional RV apex site could still be considered for pacing with normal cardiac function and structure, the use of any of the two studied LV pacing sites could serve as alternative to upgrading to BiV pacing or primary BiV pacing. In this case the risk of implanting the coronary sinus lead, alone or in combination with the RV lead, should be weighed against that of positioning the LV apical or septal lead.

**Conclusions**

In contrast to RV pacing, LV apical and LV septal pacing result in moderate electrical desynchronization, minor redistribution of mechanical work and perfusion, and normal levels of contractility, relaxation and myocardial efficiency, even over 4 months of pacing. RV septal pacing does not provide a benefit compared to RV apical pacing. Single site LV apical and LV septal pacing maintain normal cardiac function and efficiency at least as well as biventricular pacing.
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Conflict of Interest Disclosures
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LJM, NDS and RNC are Medtronic employees, LJM and NDS own Medtronic stock.
RWM, MS, LMR, AvH, MK, AL and TD have no disclosures.
References


Table 1. Summary of data on electrical activation during pacing at the four tested sites compared to normal conduction

<table>
<thead>
<tr>
<th></th>
<th>normal conduction</th>
<th>RV Apex</th>
<th>RV Septum</th>
<th>LV Apex</th>
<th>LV Septum</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration</td>
<td>62 ± 11</td>
<td>115 ± 1 *</td>
<td>122 ± 14 *</td>
<td>130 ± 10 *</td>
<td>115 ± 10 *</td>
</tr>
<tr>
<td>Total AT RV + LV</td>
<td>42 ± 5</td>
<td>111 ± 2 *</td>
<td>107 ± 10 *</td>
<td>112 ± 11 *</td>
<td>95 ± 10 * #</td>
</tr>
<tr>
<td>LV endocardial AT</td>
<td>27 ± 2</td>
<td>44 ± 12 *</td>
<td>57 ± 14 *</td>
<td>37 ± 11</td>
<td>58 ± 15 *</td>
</tr>
<tr>
<td>LV epicardial AT</td>
<td>36 ± 13</td>
<td>106 ± 9 *</td>
<td>76 ± 6 *</td>
<td>88 ± 9 *</td>
<td>52 ± 21 #</td>
</tr>
<tr>
<td>LV endocardial circumferential AT</td>
<td>17 ± 11</td>
<td>29 ± 8 *</td>
<td>49 ± 20 *</td>
<td>13 ± 4 #</td>
<td>36 ± 9 *</td>
</tr>
<tr>
<td>LV epicardial circumferential AT</td>
<td>32 ± 13</td>
<td>91 ± 0 *</td>
<td>60 ± 4 *</td>
<td>33 ± 12 #</td>
<td>45 ± 18 * #</td>
</tr>
<tr>
<td>transmural AT (at pacing site)</td>
<td>NA</td>
<td>55 ± 5</td>
<td>43 ± 16</td>
<td>36 ± 13 #</td>
<td>28 ± 12 #</td>
</tr>
</tbody>
</table>

AT = activation time (defined as maximum time difference). LV endocardial AT was derived from non-contact mapping and LV epicardial AT data from the epicardial LV electrodes plus the data from the multipole catheter against the RV septum (regarded as part of the LV epicardium in this respect). Circumferential AT was defined as the maximum time difference in the equatorial short axis plane.

* significant as compared to normal conduction, # significant compared to RV apex; repeated measures ANOVA and Sidak correction for multiple comparisons (family significance level α<0.05, nominal p<0.0073).
Table 2. Temporal electrophysiological and left-ventricular hemodynamic parameters

<table>
<thead>
<tr>
<th>Implant Site</th>
<th>% of Baseline</th>
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<tbody>
<tr>
<td></td>
<td>1 Hr V-pacing</td>
<td>16 Wks V-pacing</td>
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<tr>
<td>QRS duration [ms]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline: 73±14</td>
<td>140 ± 24</td>
<td>130 ± 24 *</td>
<td></td>
</tr>
<tr>
<td>RV Apex</td>
<td>151 ± 35</td>
<td>134 ± 23 *</td>
<td></td>
</tr>
<tr>
<td>RV Sept</td>
<td>132 ± 29</td>
<td>143 ± 31 *</td>
<td></td>
</tr>
<tr>
<td>LV Sept</td>
<td>177 ± 22</td>
<td>175 ± 26 *</td>
<td></td>
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<tr>
<td>LV Apex</td>
<td></td>
<td></td>
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<tr>
<td>End-systolic pressure [mmHg]</td>
<td></td>
<td></td>
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<tr>
<td>Baseline: 101±19</td>
<td>107 ± 18</td>
<td>98 ± 28</td>
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<tr>
<td>RV Apex</td>
<td>102 ± 21</td>
<td>105 ± 32</td>
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<td>RV Sept</td>
<td>105 ± 15</td>
<td>101 ± 20</td>
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<tr>
<td>LV Sept</td>
<td>100 ± 9</td>
<td>94 ± 25</td>
<td></td>
</tr>
<tr>
<td>LV Apex</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stroke volume [mL]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline: 30±9</td>
<td>102 ± 21</td>
<td>96 ± 38</td>
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<tr>
<td>RV Apex</td>
<td>99 ± 24</td>
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<tr>
<td>RV Sept</td>
<td>109 ± 24</td>
<td>93 ± 30</td>
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<tr>
<td>LV Sept</td>
<td>98 ± 19</td>
<td>89 ± 34</td>
<td></td>
</tr>
<tr>
<td>LV Apex</td>
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<tr>
<td>dP/dt</td>
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<td></td>
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<tr>
<td>Baseline: 2245±468</td>
<td>80 ± 13</td>
<td>77 ± 28 *</td>
<td></td>
</tr>
<tr>
<td>RV Apex</td>
<td>81 ± 14</td>
<td>79 ± 12</td>
<td></td>
</tr>
<tr>
<td>RV Sept</td>
<td>94 ± 26</td>
<td>89 ± 27</td>
<td></td>
</tr>
<tr>
<td>LV Sept</td>
<td>87 ± 24</td>
<td>83 ± 17 *</td>
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</tr>
<tr>
<td>LV Apex</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>dP/dt</td>
<td>min [mmHg/sec]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline: -2502±371</td>
<td>93 ± 15</td>
<td>86 ± 15</td>
<td></td>
</tr>
<tr>
<td>RV Apex</td>
<td>88 ± 17</td>
<td>92 ± 22</td>
<td></td>
</tr>
<tr>
<td>RV Sept</td>
<td>104 ± 17</td>
<td>99 ± 14</td>
<td></td>
</tr>
<tr>
<td>LV Apex</td>
<td>99 ± 10</td>
<td>96 ± 20</td>
<td></td>
</tr>
<tr>
<td>Stroke Work [mmHg*mL]</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Baseline: 3622±904</td>
<td>91 ± 29</td>
<td>87 ± 54</td>
<td></td>
</tr>
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<td>RV Apex</td>
<td>120 ± 41</td>
<td>77 ± 29</td>
<td></td>
</tr>
<tr>
<td>LV Sept</td>
<td>106 ± 16</td>
<td>100 ± 47</td>
<td></td>
</tr>
<tr>
<td>LV Apex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVO2 [mL-O2/beat]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline: 0.12±0.03</td>
<td>165 ± 27</td>
<td>138 ± 51</td>
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<tr>
<td>RV Apex</td>
<td>178 ± 32</td>
<td>129 ± 61</td>
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<td>RV Sept</td>
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<td>LV Sept</td>
<td>113 ± 13</td>
<td>120 ± 49</td>
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</tr>
<tr>
<td>LV Apex</td>
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<tr>
<td>Interventricular Asynch. [ms]</td>
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<td>Baseline: -6±9</td>
<td>-27 ± 4</td>
<td>-25 ± 6</td>
<td></td>
</tr>
<tr>
<td>RV Apex</td>
<td>-19 ± 7</td>
<td>-24 ± 8</td>
<td></td>
</tr>
<tr>
<td>RV Sept</td>
<td>-4 ± 13</td>
<td>17 ± 14</td>
<td></td>
</tr>
<tr>
<td>LV Sept</td>
<td>26 ± 10</td>
<td>29 ± 13 *</td>
<td></td>
</tr>
</tbody>
</table>

V-pace values expressed as percentage of baseline (mean ± SD) unless otherwise noted
* significant compared to Baseline. † significant compared to RV apex group; repeated measures ANOVA and Sidak correction for multiple comparisons (family significance level of α<0.05, nominal p<0.0064 and 0.0085, respectively).

\[dP/dt]|_{\text{max (min)}} = \text{maximal rate of pressure rise (decline)}\]
Legends to the figures

Figure 1
Electrical activation maps during normal conduction and during ventricular pacing from the four sites studied. Activation times were plotted on a model of the ventricular epicardium and endocardium. The position of the endocardium with respect to the epicardium was matched using the sites of earliest activation during pacing at various LV free wall sites. Color bar: activation times in ms, referenced to the time of earliest activation (normal conduction) or pacing artifact.

Figure 2
LV regional circumferential strain ($\varepsilon_{cc}$) signals and bulls-eye plots of systolic shortening ($\varepsilon_{cc}$ min – max during ejection) obtained in individual members of each of the four pacing groups and in the legacy normal conduction group. Upper panels: strain signals from 12 regions of the LV wall. Horizontal (time) axis starts at 15 ms following 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: distribution of systolic strain in the LV wall, as determined in the 160 regions (5 short axis slice, 32 regions per slice).

Figure 3
Internal stretch fraction (a) and b) global peak shortening delay (mechanical dyssynchrony). Mean±SD, * and †: significant compared to normal conduction and RV Apex group, respectively; standard ANOVA and Sidak correction for multiple comparisons (family significance level of $\alpha<0.05$, nominal p<0.0073).

Figure 4
Regional distribution at 16 weeks of ventricular pacing of a) time to peak shortening (relative to earliest region), b) mechanical work (as % of each subject’s mean value), and c) perfusion (as % of each subject’s Baseline perfusion measurement). Mean±SD, * and †: significant compared to the corresponding region in the normal conduction group, and to the corresponding region’s Baseline value, respectively; standard or repeated
measures ANOVA, respectively, and Sidak correction for multiple comparisons (family significance level $\alpha<0.05$, nominal $p<0.0032$)

Figure 5
Contractility index (A, $LVdP/dt_{\text{max}}/P_{\text{instantaneous}}$), relaxation index (B, $\tau_{\text{a}}$) and external efficiency (C, $SW/MVO_{2}$) in the four pacing groups after 1 hour (white bars) and 16 weeks of pacing (black bars), expressed as percentage of Baseline (mean±SD). The annotations underneath the double bars indicate the study groups by their implant sites. * and †: significant compared to Baseline and RV apex group, respectively; repeated measures ANOVA and Sidak correction for multiple comparisons (family significance level $\alpha<0.05$, nominal $p<0.0064$ and 0.0085, respectively).

Figure 6
Contractility index (A, $LVdP/dt_{\text{max}}/P_{\text{instantaneous}}$), relaxation index (B, $\tau_{\text{a}}$), and external efficiency (C, $SW/MVO_{2}$) after switching pacing from the implant site (referred to by the annotation below the triple bars) to the acute site (denoted by bar grey level). For each group, values were expressed relative to the value during pacing at the chronic implant site. The 100% reference values for each group in this figure are the 16 week pacing value, which were different between groups (see Figure 5). * significant compared to 16 weeks implant site pacing value; repeated measures ANOVA and Sidak correction for multiple comparisons (family significance level $\alpha<0.05$, nominal $p<0.0043$).
Normal conduction

RV apex

RV septum

LV apex

LV septum
FIGURE 2
FIGURE 3
FIGURE 4

(a) Time to Peak Shortening [ms]
(b) Regional Work [% of Mean]
(c) Regional Perfusion [% of BL]
FIGURE 5

A. dP/dt-max / P-instant. [% of BL]

1 Hr V-Pacing
16 Wks V-Pacing

RV Apex RV Sept LV Sept LV Apex

B. τ [% of BL]

RV Apex RV Sept LV Sept LV Apex

C. SW/MVO2 [% of BL]

RV Apex RV Sept LV Sept LV Apex
FIGURE 6

A

Acute Sites:

RV Apex
LV Apex
BiV

Implant Sites:

RV Apex
RV Sept
LV Sept
LV Apex

B

Implant Sites:

RV Apex
RV Sept
LV Sept
LV Apex

C

Implant Sites:

RV Apex
RV Sept
LV Sept
LV Apex

dP/dt-max / P-instant. [% of IS]

SW/MVO2 [% of IS]
Left Ventricular Septal and Left Ventricular Apical Pacing Chronically Maintain Cardiac Contractile Coordination, Pump Function and Efficiency

Robert W. Mills, Richard N. Cornelussen, Lawrence J. Mulligan, Marc Strik, Leonard M. Rademakers, Nicholas D. Skadsberg, Arne van Hunnik, Marion Kuiper, Anniek Lampert, Tammo Robert W. Mills, Richard N. Cornelussen, Lawrence J. Mulligan, Marc Strik, Leonard M. Rademakers, Nicholas D. Skadsberg, Arne van Hunnik, Marion Kuiper, Anniek Lampert, Tammo Delhaas and Frits W. Prinzen

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Methods on MRI tagging

Cine-images were acquired on a Philips Gyroscan 1.5 T (NT, Philips Medical Systems, Best, the Netherlands). The RF receiver coil was a standard synergy body coil for thorax examinations. Breath-hold (12 s) was accomplished by discontinuing manual ventilation and followed by a recovery period of 45–60 s. Images of seven short-axis cross-sections, slice thickness 8 mm with inter-slice distance 0 mm, were obtained to capture the whole heart. Cine-images were acquired using non-tagged steady state gradient echo sequences, starting 28 ms after the R-wave on the vectorcardiogram (field of view 400 mm, image size 256 _ 256 pixels). Thereafter a series of grid-tagged images from the same slices were obtained with time intervals of 15 ms, using balanced fast field echo (FFE) scanning.

In order to prevent pacemaker-MR interference, the leads were connected to extenders which were exteriorized and connected to an external pacemaker, pacing in DOO mode at 110 bpm.

Tagging analysis was performed using custom MATLAB software¹ to determine LV regional circumferential strain (ε_{cc}) in 32 sectors around each short axis slice. Data from a previous series of 8 dogs with intact AV conduction under similar anesthetic conditions¹ were also analyzed to compare ventricular pacing with normal ventricular activation.

An estimation of the distribution of regional systolic work was achieved by calculating:
Regional work = $- \int \sigma_{cc} \, d \varepsilon_{cc}$

over the ejection period and assuming a homogeneous circumferential stress ($\sigma_{cc}$) with constant high value during ejection and expressing regional work relative to the mean of regional work within the LV wall.

Internal stretch fraction (ISF), an index of cardiac contraction discoordination, was also calculated from $\varepsilon_{cc}$ signals by determining ratio of the amount of fiber stretch relative to the amount of fiber shortening during ejection$^2$.

Global mechanical dyssynchrony was indexed by the difference between the 5th and 95th percentiles of the time to peak shortening from each of the 160 regions analyzed (32 sectors x 5 slices). Regional dyssynchrony was calculated as the mean time to peak shortening of the entire (5 slices) septal, anterior, lateral and posterior wall segment.

*Experimental design.*

Figure SM1 schematizes the experimental groups, pacing conditions, and time points of the various measurements.
Supplemental table: Comparative pacing electrophysiological and left-ventricular hemodynamic parameters

<table>
<thead>
<tr>
<th>Implant Site</th>
<th>Mean IS 16Wks Value</th>
<th>% of 16 Wks Implant Site Pacing Value</th>
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<tbody>
<tr>
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<td>Epi RV Apex</td>
<td>LV Apex</td>
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<td>QRS duration [ms]</td>
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<tr>
<td>RV Apex</td>
<td>98 ± 9</td>
<td>112 ± 19</td>
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<tr>
<td>RV Sept</td>
<td>112 ± 7</td>
<td>98 ± 12</td>
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<tr>
<td>LV Sept</td>
<td>98 ± 15</td>
<td>110 ± 17</td>
</tr>
<tr>
<td>LV Apex</td>
<td>119 ± 9</td>
<td>97 ± 15</td>
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<td>End-systolic pressure [mmHg]</td>
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<tr>
<td>RV Apex</td>
<td>103 ± 18</td>
<td>99 ± 3</td>
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<tr>
<td>RV Sept</td>
<td>111 ± 17</td>
<td>99 ± 1</td>
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<tr>
<td>LV Sept</td>
<td>104 ± 22</td>
<td>100 ± 9</td>
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<tr>
<td>LV Apex</td>
<td>89 ± 12</td>
<td>98 ± 4</td>
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<td>Stroke volume [mL]</td>
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<tr>
<td>RV Apex</td>
<td>31 ± 8</td>
<td>100 ± 21</td>
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<td>RV Sept</td>
<td>22 ± 8</td>
<td>105 ± 20</td>
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<tr>
<td>LV Sept</td>
<td>25 ± 6</td>
<td>88 ± 12</td>
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<td>LV Apex</td>
<td>30 ± 8</td>
<td>68 ± 37</td>
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<td>dP/dt</td>
<td>max [mmHg/sec]</td>
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<td>0.086 ± 0.022</td>
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<td>RV Sept</td>
<td>0.103 ± 0.021</td>
<td>81 ± 36</td>
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<tr>
<td>LV Sept</td>
<td>0.100 ± 0.014</td>
<td>112 ± 23</td>
</tr>
<tr>
<td>LV Apex</td>
<td>0.093 ± 0.026</td>
<td>102 ± 33</td>
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Comparative-site values expressed as percentage of implant site (IS) pacing value at 16 weeks (mean±SD). * significant compared to IS value, repeated measures ANOVA and Sidak correction for multiple comparisons (family significance level α<0.05, nominal p<0.0043). dP/dt|max (min) = maximal rate of pressure rise (decline).
Supplemental Results

Position of chronically implanted pacing leads

Necropsy of the chronically paced hearts showed that most septal leads entered the RV septum mid apico-basal and mid antero-posterior. LV septal lead tips were typically 1 cm more apical at the LV septum than where the leads entered the RV septum, and had variable antero-posterior deviation (Figure SM2). One LV septal lead had a significant posterior deviation, and one lead from each septal group was entirely posterior, but these subjects were not outliers from their groups within the measurements made. No blood clots were observed on any of the RV or LV septal pacing leads.

Supplemental Electrical activation movies

The sequence of electrical activation of the RV and LV epicardium and endocardium is represented by a region’s appearance, and these regions are also color-coded by activation time (color scale equal to that in figure 2). Each movie has the same speed and lasts 8 seconds. When run simultaneously it can be appreciated that activation of the normal conduction beat is complete before that from ventricular pacing.

Supplemental References

Supplemental figures and figure legends

Figure SM1
The four horizontal bars indicate the four chronically ventricularly paced groups, the site of which is mentioned inside the bar and is indicated by the bar pattern/color: RV apical pacing = grey; RV septal pacing = course hatching; LV septal pacing = fine hatching, LV apical pacing = black. In the lower white horizontal bar the time points of measurements are indicated (N.C. — normal conduction), 1 hour and 16 weeks ventricular pacing, followed by acute comparative pacing during RV apical (RVa), LV apical (LVa) and biventricular (BiV) pacing. The thick arrows indicate measurements of hemodynamics, Doppler flow, microspheres and oxygen extraction; the thin arrows indicate measurements without microspheres. A historical control group was used to determine MRI tagging strains in hearts with normal conduction.1

Figure SM2
Schematic of lead implantation sites determined at necropsy, using views on the RV side of the interventricular septum (left and middle panel) and short axis section of the LV (right panel). Shown are RV septal tip points for RV septal pacing (left panel) and LV septal pacing insertion (middle panel) and tip positions (right panel). Two LV septal leads had nearly identical relative locations, when projected on this exemplary heart.
Legends to the videos

Normal-0.wmv
Activation sequence during normal ventricular activation.

RV_Apex-0.wmv
Activation sequence during right ventricular apical pacing.

RV_Septum-0.wmv
Activation sequence during right ventricular septal pacing.

LV_Apex-0.wmv
Activation sequence during left ventricular apical pacing.

LV_Septum-0.wmv
Activation sequence during left ventricular septal pacing.
Temporal changes during chronic ventricular pacing

Acute comparative pacing

RV apical pacing
RV septal pacing
LV septal pacing
LV apical pacing

N.C. 1 hour Hemodynamics, MVO₂ 16 wk RVa LVa BiV

AV-block

MRI tagging

Historical controls with normal conduction

Figure SM1
Figure SM2