Acute Hemodynamic Effect of Left Ventricular Endocardial Pacing in Cardiac Resynchronization Therapy: Assessment by Pressure-Volume Loops

Running title: Padeletti et al.; Left Ventricular Endocardial Pacing in CRT

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Abstract:

**Background** - During cardiac resynchronization therapy (CRT) device implantation, the pacing lead is usually positioned in the coronary sinus (CS) to stimulate left ventricular (LV) epicardium. Transvenous LV endocardial pacing via transseptal puncture has been proposed as an alternative method. In this study, we evaluated the acute hemodynamic effects of CRT through LV endocardial pacing in heart failure patients by analyzing LV pressure-volume relationships.

**Methods and Results** - Left ventricular pressure and volume data were determined via conductance catheter during CRT device implantation in 10 patients. In addition to the standard epicardial CS pacing, following endocardial LV sites were systematically assessed: the site transmural to the CS lead, the LV apex, the septal mid-wall, the basal and mid-lateral free wall. Four atrioventricular delays were tested. There was a significant improvement of systolic function with CRT in all LV pacing configurations, while no differences in systolic or diastolic function were detected between LV epicardial and endocardial transmural sites. The optimal pacing site varied among patients, but was rarely related to relatively longer activation delays, as assessed by analyzing endocardial electrical activation maps. Nonetheless, positioning the pacing lead at the optimal endocardial LV site in each patient significantly improved LV performance in comparison with conventional CS site stimulation (stroke volume 83 [79;112]ml versus 73 [62;89]ml, p=0.034).

**Conclusions** - Pacing at the optimal individual LV endocardial site yields enhanced LV performance in comparison with conventional CS site stimulation. Endocardial LV pacing might constitute an alternative approach to CRT when CS pacing is not viable.

**Key words**: cardiac resynchronization therapy; endocardium; heart failure; pressure-volume relationship
Introduction

During cardiac resynchronization therapy (CRT) device implantation, left ventricular (LV) lead placement is usually performed by means of a transvenous approach using the tributaries of the coronary sinus (CS). The feasibility of transvenous lead positioning depends on many factors, including venous anatomy, accessibility of the vein, pacing threshold, lead stability, and absence of phrenic nerve stimulation.

Several authors have reported variable individual responses to CRT, and have indicated the LV pacing site as a major determinant of the hemodynamic response. However, in patients receiving biventricular pacing, LV lead positioning varies randomly on account of contingencies and/or unpredictable anatomical conditions or technical reasons.

Transvenous LV endocardial pacing via transseptal puncture has been implemented in the rare circumstance in which neither the transvenous CS epicardial nor the surgical option is feasible. Indeed, this technique enables the limitations of CS venous anatomy to be overcome, and may constitute an alternative method of optimizing lead positioning and improving outcome. Initial experience in early studies with transvenous LV endocardial pacing has yielded promising results.

In this study, we evaluated the acute hemodynamic effects of CRT through transvenous LV endocardial pacing in heart failure patients by analyzing LV pressure-volume relationships.

Methods

Patient selection and procedure

We enrolled twelve consecutive heart failure patients with indications for CRT. The Institutional Review Board approved the protocol and all patients gave written informed consent.
Exclusion criteria were the presence of a previously implanted device, valvular insufficiency or stenosis. The atrial and right ventricular leads were placed in the right atrium and at the apex of the right ventricle, respectively, in patients lightly sedated. The LV lead was positioned in the CS and advanced to the lateral or posterior-lateral vein in accordance with standard procedure.

A standard steerable ablation catheter was advanced into the LV cavity, through the femoral artery and connected to a standard electro-anatomic mapping system (EnSite System, St. Jude Medical, St. Paul, MN, USA) in order to construct LV chamber geometry and an endocardial activation map during spontaneous ventricular activation.

The ablation catheter was also used as a roving catheter to pace specific endocardial sites of interest, and the mapping system allowed the pacing sites to be anatomically located (Figure 1) and the distance between the ablation catheter and the CS lead to be measured. The endocardial LV map was then analyzed to identify the LV region of latest intrinsic activation and to measure how relatively early or late in LV activation pacing sites resided.

A pressure-conductance volume catheter (F7, CD Leycom, Zoetermeer, The Netherlands) was inserted through the contralateral femoral artery and the pig-tail tip advanced to the LV apex and positioned along the LV long axis. The catheter was connected to a cardiac function analyzer (CFL 512 CD Leycom) for real time monitoring and acquisition (sample frequency 250 Hz) of LV volume and pressure signals and ECG. The inter-electrode spacing was adjusted on the basis of the long LV axis, and the segmental volumes originating from the proximal ascending aorta were discarded. Volume calibration was performed as previously described. The effective conductance stroke volume was defined as the difference between conductance volumes at the maximum and minimum pressure-derivative.
Pacing protocol

The hemodynamic status was evaluated under steady-state conditions after a minimum of 2 min of stabilization at each pacing configuration. Stimulation was delivered by means of an external stimulator (Analyzer model 2290, Medtronic, Minneapolis, MN, USA). All pacing interventions were tested at a fixed rate of 10 bpm higher than the sinus heart rate, and the baseline values were recorded during continuous atrial overdrive pacing with spontaneous ventricular activation (AAI mode).

The biventricular configurations (DDD mode) were assessed at four atrioventricular intervals. The longest time interval was programmed at 40 ms shorter than the measured intrinsic PQ interval. The remaining atrioventricular intervals were programmed at 75%, 50% and 25% of this value. To obtain simultaneous biventricular pacing, a splitter was used to join the right ventricular apical lead to the CS lead in order to perform epicardial pacing (EPI-CS configuration), or to the roving catheter in order to perform endocardial pacing.

During endocardial stimulation, we tested the following LV pacing sites: the site directly transmural to the distal pole of the CS lead (ENDO-CS), the LV apex (APEX), the septal mid-wall (SEPTUM), the basal (BASE-FW) and mid-lateral (MID-FW) free wall. The sequence of pacing configurations and atrioventricular intervals was randomly assigned.

At the end of the pacing protocol, endocardial catheters were removed and a biventricular cardioverter-defibrillator was implanted.

Data analysis

The ENDO-CS configuration was compared both with the EPI-CS configuration at four atrioventricular intervals and with the AAI mode. In all patients, the atrioventricular interval that elicited the best hemodynamic response was identified for each configuration tested and the
hemodynamic responses were compared at the optimal atrioventricular interval setting. Similarly, the endocardial LV pacing site associated with optimal systolic function (BEST-LV) was detected in each patient. The criterion used to identify the optimal pacing configuration in each patient was the maximization of stroke volume.

Several indexes of LV performance (LV end-systolic and end-diastolic pressure, LV pressure-derivative maximum and minimum, LV end-diastolic volume, stroke volume, stroke work, and the time constant of isovolumic relaxation) were calculated and averaged during 8 to 10 beats at end-expiration from the raw LV pressure and conductance volume data by using commercially available software (Conduct NT, Leycom). End-diastole was identified immediately before the isovolumic increase in the LV pressure-derivative, and end-systole was defined as the maximum ratio of LV pressure to volume. Nonuniform LV performance was determined from the segmental LV conductance signals and quantified by calculating the percentage of time within the cardiac cycle that a specific segment is dyssynchronous (i.e. opposite in phase with the global LV volume signal). Overall LV mechanical dyssynchrony was determined as the mean of the segmental dyssynchronies within each specified time interval: during systole (DYSs) and diastole (DYSd) \(^{11}\). Cycle efficiency was calculated as stroke work/(\(\Delta\)LV pressure\(\times\)\(\Delta\)LV volume) \(^{12,13}\); this quantifies distortions in the shape of the pressure-volume diagram.

Data were expressed as median [25th–75th percentile]. Hemodynamic data collected at fixed and at optimal atrioventricular delays were compared by means of a Friedman’s test for global comparisons and, in case of significance, paired comparisons were evaluated using a post-hoc Conover test. A p-value <0.05 was considered significant for all tests. All statistical analyses were performed by means of SPSS software (SPSS Inc., Chicago, IL, USA).
Results

In 2 patients, the pressure-volume catheter could not be properly placed in the LV cavity; these were excluded from the analysis. Demographic data of the 10 patients included in the analysis are listed in Table 1. All patients presented with systolic heart failure and left bundle-branch block (QRS duration 149 [142-161] ms) and met the criteria for CRT. Three patients had documented coronary artery disease.

Endocardial LV activation maps were constructed for all patients in sinus rhythm. A median of 168[138-195] equally distributed contact points for LV mapping were acquired. The median LV activation duration in our series was 103 [91-111] ms, the latest activation being recorded at the basal-lateral free wall (BASE-FW) in 6 patients, at the MID-FW in 3 patients and at the APEX in the remaining patient. The QRS durations were similar regardless of the area of most delayed activation. In the 3 patients with ischemic cardiomyopathy the latest activation was recorded at the BASE-FW, and the LV activation duration was comparable to the remaining patients.

In the 10 patients included in the analysis, all pre-defined LV pacing sites were reached and all pacing conditions were successfully assessed. Specifically, the ENDO-CS site was located at a median distance of 26 [23-41] mm from the distal pole of the CS lead (EPI-CS).

In comparison with the AAI mode, CRT with both EPI-CS and ENDO-CS configurations resulted in improved stroke volume, stroke work and cycle efficiency at the majority of atrioventricular intervals (Figure 2 and Table 2). Comparison between the endocardial/epicardial transmural sites showed no significant differences in terms of hemodynamics during LV stimulation.

In each patient, the atrioventricular interval resulting in optimal systolic function
(maximum stroke volume) was identified for all configurations. Shorter atrioventricular intervals seemed to produce less hemodynamic benefit. Indeed, optimal atrioventricular intervals were longer than 0.5×(PQ interval – 40ms) in 8 patients undergoing EPI-CS CRT and in 7 patients undergoing ENDO-CS CRT. Moreover, the maximum variation in stroke volume obtained in response to changes in atrioventricular interval was 9 [7-10] ml with EPI-CS versus 17 [12-25] ml with ENDO-CS pacing (p=0.150).

No differences in maximum hemodynamic response were noticed between patients with ischemic and non-ischemic cardiomyopathy during EPI-CS and ENDO-CS pacing.

In comparison with the other pacing configurations (ENDO-CS, APEX, SEPTUM, BASE-FW, MID-FW), EPI-CS CRT did not show any difference in terms of hemodynamic performance at optimal atrioventricular intervals (Table 3). Figure 3 shows representative pressure-volume loops obtained in one patient undergoing CRT with endocardial pacing configurations.

The CRT configuration that yielded maximum stroke volume (BEST-LV) was MID-FW in 4 patients, BASE-FW in 3 patients, SEPTUM in 2 patients and APEX in 1 patient. Among patients with QRS duration <150ms, BEST-LV coincided with MID-FW in 4 patients and SEPTUM in 1 patient.

The average stroke volume and stroke work significantly increased during endocardial LV pacing in the BEST-LV configuration in comparison with standard EPI-CS CRT (Table 3 and Figure 4).

LV synchrony during ENDO-CS pacing improved in terms of increased cycle efficiency and reduced DYSs, in the presence of unchanged LV diastolic function.

The LV pacing site associated with maximum stroke volume (BEST-LV) coincided with
the area of most delayed electrical activation among those tested in 4 patients (BASE-FW in 2 patients, MID-FW in 1 patient, APEX in 1).

**Discussion**

In our study, the analysis of pressure-volume loops revealed that CRT significantly enhanced systolic function, irrespective of the LV pacing configuration, i.e. conventional CS site stimulation or LV endocardial pacing. No differences in systolic or diastolic function were detected between LV epicardial and endocardial CRT configurations at the same atrioventricular interval settings.

The optimal site of the pacing lead varied among patients, but was rarely related to relatively longer electrical activation delays. Nonetheless, positioning the pacing lead at the optimal endocardial LV site significantly ameliorated LV performance in comparison with conventional CS site stimulation.

Several experimental studies have demonstrated that endocardial LV pacing should elicit beneficial effects, allowing more homogeneous and rapid electrical depolarization and repolarization.\textsuperscript{14-16} However, it is still unknown whether site-dependent LV benefits are related to the limitation of left ventricular dyssynchrony.

To our knowledge, the current study is the first to investigate the LV pressure-volume relationship during endocardial LV pacing for CRT in humans. The present findings integrate previous data provided by Derval et al.\textsuperscript{17}, who performed intra-cardiac pressure analysis, and with the observations reported by Ginks\textsuperscript{16} and Spragg\textsuperscript{18}, who conducted simultaneous analysis of LV pressure changes and endocardial activation.

It was previously shown that stroke volume and stroke work obtained from pressure-
volume loops are more sensitive parameters than LV pressure-derivative in the evaluation of CRT effects \(^{19}\). Compared to the measurement of LV pressure-derivative alone, pressure-volume analysis offers the measurement of relevant load independent parameters and allows extensive description of systolic and diastolic functions. Moreover, the use of pressure-conductance volume catheter allows assessing the effect of CRT in normalizing the pattern of LV activation through continuous and real-time estimation of dyssynchrony indexes. In a canine model of left bundle-branch block, Van Deursen et al. showed an enhanced contractile function during endocardial LV pacing, as compared with conventional epicardial CRT \(^{14}\). These effects were ascribed to faster impulse conduction in the sub-endocardial myocardium.

Our analysis in CRT patients during LV stimulation through endocardial and epicardial pacing sites did not reveal any difference in LV systolic performance; this finding is in line with those of previous clinical studies \(^{17,18}\).

Moreover, the hemodynamic variables related to diastolic function did not change significantly in our patients during CRT; indeed, these variables seem not to depend on the endocardial and epicardial pacing configurations. Our data confirm those of previous experimental studies showing minor acute effects of CRT on diastolic parameters \(^{9,20}\). However, they conflict with the findings of Derval et al., who reported improved LV filling during endocardial pacing, as indicated by increased pressure-derivative minima \(^{17}\).

The improvements that we observed in LV ejection were associated with concomitant limitation of LV mechanical dyssynchrony, as assessed by pressure–volume loop analysis. The cycle efficiency, i.e. the shape of the pressure–volume diagram, improved following CRT, showing an increase in global efficiency in the presence of decreased ineffective volume shifts during the isovolumic phase. Moreover, DYSs and DYSd, the two indices that most specifically
quantify systolic and diastolic dyssynchrony, decreased only at long atrioventricular intervals. It is thus conceivable that endocardial LV pacing limits dyssynchronous activation of LV segments, thereby allowing stable and homogeneous distribution of electrical current of depolarization\textsuperscript{14,15}. However, minor LV dyssynchrony persisted during both endocardial and epicardial CRT configurations.

Our data suggest that LV lead position during CRT affects cardiac performance, in part by limiting electro-mechanical dyssynchrony of the left ventricle. Thus, its optimization should be proposed as a therapeutic strategy to improve response to CRT. For this purpose, LV endocardial pacing offers the additional advantage of providing access to a greater variety of LV pacing sites than conventional CS implantation or the thoracotomic approach\textsuperscript{19}. Indeed, some authors have suggested that conventional lead positioning in a lateral or postero-lateral branch of the CS may not be optimal for every patient\textsuperscript{16,17}. Additional studies have found better mechanical performance during pacing at alternative sites, such as the LV apex\textsuperscript{14,21,22}, the interventricular septum\textsuperscript{21}, or the extreme base of the LV\textsuperscript{18}; however, implantation at these sites is technically more challenging than conventional CS lead positioning.

Faster impulse conduction into the myocardium has been supposed to facilitate the interventricular conduction of wave-fronts during LV pacing. In the normal canine heart, resynchronization through endocardial LV pacing has been reported to depend little on the pacing site, with all sites seeming to induce similar hemodynamic benefits\textsuperscript{14}. Conversely, we found that the magnitude of the hemodynamic benefits due to endocardial LV pacing varied widely with the position of the pacing leads. Indeed, the optimal LV pacing site seemed specific to each patient and was not predicted by anatomical position. Nevertheless, the BEST-LV configuration was frequently achieved when the pacing lead was positioned at the mid-lateral or
basal free wall. Notably, the optimal LV pacing site coincided with the mid-lateral free wall in 4 out of 5 patients with QRS duration <150ms, and with the basal free wall in 3 out of 5 patients with QRS duration >150ms. Although our series was small to draw any conclusion, this finding seems to contrast with a previous hypothesis suggesting that LV lead should be located in a more basal site in patients with QRS duration <150ms.\(^{23}\)

In agreement with earlier studies, pacing at the APEX resulted in maximum stroke volume only in 1 patient. Indeed, apart from positive hemodynamic effects observed in normal canine hearts\(^ {14,21,22}\), apical LV placement was found associated with worse CRT outcome in recent clinical experiences\(^ {24,25}\).

As previously shown by Spragg et al.\(^ {18}\), the BEST-LV configuration was not associated with pacing in regions of delayed electrical activation in the majority of patients. This is in keeping with previous findings showing that the acute hemodynamic benefit from LV pacing is independent of LV endocardial activation time, which is not reduced in comparison with spontaneous LV activation\(^ {16}\).

In the present study we enrolled a typical cohort suitable for CRT, with both ischemic and non-ischemic cardiomyopathy. In patients with ischemic cardiomyopathy, the lack of response to CRT has been explained with the presence of areas of slow conduction\(^ {16}\), associated with the scar density in proximity to the LV pacing site\(^ {7,27}\). Similarly, diffuse fibrosis associated with slow conduction was detected in patients with non-ischemic cardiomyopathy, accounting for the variability in response to LV pacing in these patients\(^ {16}\). However, the remarkable heterogeneity documented in left bundle-branch block, with lines of block located at several anatomic levels of the activation sequence and large conduction delays located more intramurally than subendocardially\(^ {23}\), may prevent the possibility to predict the response to pacing and locate the
most effective pacing site based on information on LV endocardial activation times. Our findings seem to confirm this hypothesis. Most probably, a mapping protocol directly assessing acute hemodynamic response could be applied to select the best position when LV endocardial pacing for CRT is attempted.

However, it is not known whether acute hemodynamic effects correlate with a positive outcome in the long term. Although Steendijk et al. 28 showed that the acute improvement by CRT is maintained chronically and accompanied by an increasing LV reverse remodeling, a study with a larger patient cohort with a longer follow-up is necessary to address this issue.

For the purpose of this study, we applied an extensive pacing protocol in order to test a wide range of atrioventricular intervals, and we compared the optimal hemodynamic response obtained with each CRT configuration, i.e., the setting associated with maximum stroke volume. Previous studies on endocardial LV pacing have used several pacing protocols. Derval et al. 17 tested LV-only pacing and adopted two atrioventricular intervals; Spragg et al. 18 delivered biventricular stimulation with long atrioventricular intervals, unlike Peschar et al. 21 who used biventricular stimulation with short intervals. Van Deursen et al. 14 tested a wide range of intervals with both biventricular and LV-only pacing in dogs, to assess various degrees of fusion between pacing-induced and/or intrinsic activation of the myocardium. They found that the range of atrioventricular intervals within which a beneficial effect was achieved during endocardial pacing was considerably larger than during epicardial pacing.

Our results in dyssynchronous heart failure patients seem to challenge these findings. Indeed, atrioventricular delay adjustments resulted in significant adaptive modulation of LV performance, during both EPI-CS and ENDO-CS pacing. The clinical implication is that, in patients undergoing endocardial LV stimulation, atrioventricular interval optimization could
evoke a better hemodynamic response.

**Limitations.** The number of patients included in the present study was small. In particular, the sample size was too small to investigate differences in response across substrates and QRS durations. Moreover, we did not assess the effect of position of the CS lead, as it was empirically placed in the lateral or posterior-lateral vein.

In our stimulation protocol, we tested pre-defined LV pacing sites measuring how relatively early or late in LV activation those pacing sites resided, without selectively targeting the area of most delayed activation. This could have provided additional valuable information. Moreover, LV endocardial map accurately reflects activation delay distribution in the absence of intramural conduction delays. However, these were previously documented in left bundle-branch block ²³.

**Conclusions**

In conclusion, our results support the idea that endocardial LV pacing might constitute an alternative approach to electrical cardiac treatment when conventional CS pacing is not viable. However, we cannot exclude the possibility of adverse effects of endocardial CRT (e.g. the risk of thrombo-embolic complications, the induction of mitral valve dysfunction, etc.), which should be carefully addressed during the evaluation of risks and benefits of the procedure.

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**Conflict of Interest Disclosures:** Prof. Padeletti receives research grant support and honoraria from Medtronic, Sorin, Boston, St. Jude. S Valsecchi is employee of Medtronic, Inc.

**References:**


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### Table 1. Demographics and baseline clinical parameters.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Etiology</th>
<th>NYHA Class</th>
<th>PQ interval (ms)</th>
<th>QRS duration (ms)</th>
<th>LV Ejection Fraction (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>84</td>
<td>DC</td>
<td>III</td>
<td>240</td>
<td>125</td>
<td>32</td>
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<tr>
<td>2</td>
<td>M</td>
<td>76</td>
<td>DC</td>
<td>III</td>
<td>180</td>
<td>153</td>
<td>25</td>
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<tr>
<td>3</td>
<td>M</td>
<td>67</td>
<td>CAD</td>
<td>III</td>
<td>160</td>
<td>160</td>
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<td>72</td>
<td>DC</td>
<td>IV</td>
<td>160</td>
<td>142</td>
<td>35</td>
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<td>5</td>
<td>M</td>
<td>81</td>
<td>DC</td>
<td>III</td>
<td>160</td>
<td>143</td>
<td>26</td>
</tr>
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<td>6</td>
<td>M</td>
<td>73</td>
<td>CAD</td>
<td>III</td>
<td>160</td>
<td>144</td>
<td>35</td>
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<td>M</td>
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<td>CAD</td>
<td>III</td>
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<td>M</td>
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<td>DC</td>
<td>III</td>
<td>200</td>
<td>134</td>
<td>26</td>
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NYHA indicates New York Heart Association; M, male; F, female; CAD, coronary artery disease; DC, dilated cardiomyopathy.
Table 2. Hemodynamics during LV stimulation at the two endocardial/epicardial transmural sites at different atrioventricular delays.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AAI</th>
<th>AV delay / (PQ – 40ms):</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>100%</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>EPI-CS</td>
<td>ENDO-CS</td>
<td>EPI-CS</td>
<td>ENDO-CS</td>
<td>EPI-CS</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td></td>
<td>90 [89;90]</td>
<td>90 [89;91]</td>
<td>90 [89;92]</td>
<td>90 [89;92]</td>
<td>90 [89;92]</td>
</tr>
<tr>
<td>Time Constant of Relaxation (ms)</td>
<td></td>
<td>42 [39;43]</td>
<td>42 [37;44]</td>
<td>42 [39;45]</td>
<td>43 [38;45]</td>
<td>42 [39;45]</td>
</tr>
</tbody>
</table>

*: p<0.05 versus atrial pacing.

Table 3. Hemodynamics at optimal atrioventricular delays in all configurations tested.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EPI-CS</th>
<th>ENDO-CS</th>
<th>APEX</th>
<th>SEPTUM</th>
<th>BASE-FW</th>
<th>MID-FW</th>
<th>BEST-LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (bpm)</td>
<td>90 [90;91]</td>
<td>90 [90;90]</td>
<td>90 [89;91]</td>
<td>90 [89;90]</td>
<td>89 [89;90]</td>
<td>90 [90;90]</td>
<td>90 [90;90]</td>
</tr>
<tr>
<td>Stroke Volume (ml)</td>
<td>73 [62;89]</td>
<td>79 [69;99]</td>
<td>65 [49;82]</td>
<td>64 [54;83]</td>
<td>65 [54;77]</td>
<td>79 [68;99]</td>
<td>83 [79;112]</td>
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<tr>
<td>Stroke Work (l*mmHg)</td>
<td>6.9 [5.6;8.0]</td>
<td>7.5 [6.3;8.6]</td>
<td>5.6 [4.0;7.4]</td>
<td>5.6 [4.6;6.8]</td>
<td>5.3 [4.5;7.1]</td>
<td>7.5 [6.4;8.6]</td>
<td>8.0 [6.8;8.9]</td>
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<td>Pressure-derivative Maximum (mmHg/s)</td>
<td>839</td>
<td>882</td>
<td>854</td>
<td>762</td>
<td>829</td>
<td>871</td>
<td>800</td>
</tr>
<tr>
<td>Maximum (mmHg/s)</td>
<td>733.1005 [733;1005]</td>
<td>749.1001 [749;1001]</td>
<td>748.904 [748;904]</td>
<td>691.903 [691;903]</td>
<td>709.903 [709;903]</td>
<td>674.987 [674;987]</td>
<td>713.949</td>
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<td>End-systolic Pressure (mmHg)</td>
<td>94 [92;105]</td>
<td>95 [89;106]</td>
<td>104 [95;121]</td>
<td>99 [95;108]</td>
<td>93 [87;101]</td>
<td>94 [79;106]</td>
<td>97 [88;104]</td>
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<td>Pressure-derivative Minimum (mmHg/s)</td>
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<td>-830</td>
<td>-767</td>
<td>-784</td>
<td>-799</td>
<td>-861</td>
<td>-779</td>
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<tr>
<td>Minimum (mmHg/s)</td>
<td>-797 [-797;-757]</td>
<td>-923 [-797;-757]</td>
<td>-873 [-865;-754]</td>
<td>-894 [-754;-754]</td>
<td>-982 [-733;754]</td>
<td>-869 [-674]</td>
<td></td>
</tr>
<tr>
<td>Time Constant of Relaxation (ms)</td>
<td>42 [39;45]</td>
<td>41 [40;42]</td>
<td>42 [37;54]</td>
<td>40 [38;45]</td>
<td>41 [39;44]</td>
<td>41 [38;45]</td>
<td>41 [39;45]</td>
</tr>
<tr>
<td>Cycle Efficiency (%)</td>
<td>81 [74;90]</td>
<td>90 [87;97]</td>
<td>80 [73;87]</td>
<td>74 [73;89]</td>
<td>88 [84;100]</td>
<td>90 [87;97]</td>
<td>89 [85;100]</td>
</tr>
</tbody>
</table>

*: p<0.05 versus EPI-CS (paired t-test).
Figure Legends:

**Figure 1.** Isochronal maps showing LV activation in a patient. Times are referenced from exit of the activation wavefront in the LV, with earliest activation shown in red and latest in blue on the scales on the left. The blue dot represents the CS lead in its final location. The red dots show the endocardial pacing sites tested with the ablation catheter. Orientation of the LV is illustrated by the torso.

**Figure 2.** Alterations in stroke volume (SV), stroke work (SW), cycle efficiency (CE), LV pressure-derivative maximum (dP/dt max), LV end-systolic pressure (LVESP), LV end-diastolic pressure (LVEDP) during CRT with standard epicardial LV pacing (EPI-CS) and endocardial stimulation of the site directly transmural to the distal pole of the CS lead (ENDO-CS).

**Figure 3.** LV pressure-volume loops during CRT with all endocardial pacing configurations tested: the site directly transmural to the CS pacing site (ENDO-CS), the basal (BASE-FW) and mid-lateral (MID-FW) free wall, the LV apex (APEX) and the septal mid-wall (SEPTUM). In this example the MID-FW pacing resulted in the best hemodynamic performance (maximum stroke volume).

**Figure 4.** Example of LV pressure-volume loops during atrial overdrive (AAI; grey line), CRT with standard epicardial LV pacing (EPI-CS; dotted line), and CRT with optimal endocardial LV pacing (BEST-LV; black line).
Acute Hemodynamic Effect of Left Ventricular Endocardial Pacing in Cardiac Resynchronization Therapy: Assessment by Pressure-Volume Loops

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