Aims
For successful cardiac resynchronization therapy (CRT), an optimization of left ventricular (LV) lead position and stimulation timing is required. The feasibility of optimizing LV lead position, atrioventricular delay (AVd), and interventricular delay (VVd) in CRT using intracardiac impedance measurement was evaluated.

Methods and results
Heart failure patients (n = 14, NYHA 13 x III, 1 x II, ejection fraction: 26 ± 6%, QRS: 165 ± 30 ms) were stimulated by AAI and biventricular (DDD-BiV) pacing in turn. Left ventricular lead site, AVd, and VVd were varied. An external pacemaker measured impedance, and a micromanometer catheter measured LV and aortic pressure. Left ventricular dp/dtmax, pulse pressure (PP), stroke volume (SV), end-systolic impedance (ESZ), and stroke impedance (SZ) were determined. Optimization results achieved by maximum increase in PP, SV, SZ, or ESZ were compared with the reference method (dp/dtmax increase). Left ventricular lead site variation resulted in a mean optimal dp/dtmax benefit of 18.2%. Lead site selection by SZ/PP/SV showed benefits of 17.4/17.9/17.2%, respectively. Atrioventricular delay optimization increased the optimal benefit to 22.1%, the methods ESZ/PP/SV achieved 20.1/20.8/19.4%. Interventricular delay optimization resulted in a benefit of 19.1/19.4/19.9% (SZ/PP/SV) with an optimum of 21.8%. The achieved benefit did not differ significantly between impedance, SV, and PP methods. A significant correlation between AVd values selected by dp/dtmax and by the other methods was observed (r = 0.75/0.67/0.60 for ESZ/PP/SV).

Conclusion
The feasibility of optimizing LV lead site, AVd, and VVd by intracardiac impedance has been demonstrated for CRT patients with a similar performance as using SV and PP. Application of intracardiac impedance for automatic implant-based CRT optimization appears to be within reach.

Keywords
Heart failure • CRT • AVd optimization • VVd optimization • Sensor • Impedance

Introduction
Cardiac resynchronization therapy (CRT) for heart failure (HF) patients by synchronous biventricular stimulation has been shown to acutely improve haemodynamic parameters,1–4 physical capacity, and quality of life5–8 in the long-term, and to reduce mortality and morbidity.7,9,10

For successful resynchronization, the implantation position of the left ventricular (LV) electrode must be carefully selected,11 and atrioventricular delay (AVd) and interventricular delay (VVd) need to be optimized.3,6,12

Cardiac resynchronization therapy optimization using invasive measurement of haemodynamic parameters is time-consuming, increases the risk for the patient and is thus not common. On the other hand, echocardiographic parameters are often subjective and show high intra- and inter-individual variability.12 Therefore, the ability to measure haemodynamic parameters [e.g. stroke volume (SV)] with the implanted device itself would significantly simplify CRT adjustment.
Haemodynamic parameter changes have been successfully recorded by LV intracardiac impedance measurement in animal models with healthy as well as with failing hearts. This study investigated whether intracardiac impedance is suitable to optimize the LV lead implantation site, AVd, and VVd in CRT patients. For that purpose, CRT optimization by impedance was compared with optimization by SV and by aortic pulse pressure (PP). Left ventricular \( \frac{dP}{dt_{\text{max}}} \) served as the ‘gold standard’.

First results of this study, showing the correlation between impedance and haemodynamic parameters for different pacing rates and different LV lead sites, have recently been published.

### Methods

#### Patients

Fourteen patients with non-ischaemic dilated cardiomyopathy were included in an acute prospective multicenter study. All study participants granted their written informed consent prior to inclusion. The study was approved by the respective local institutional ethics committees and was conducted in compliance with the Declaration of Helsinki. Main inclusion criteria were an ejection fraction (EF) of \( \leq 35\% \), a QRS width of \( \geq 120 \) ms, a left bundle branch block, a left ventricular end-diastolic diameter (LVEDD) of \( \geq 55 \) mm and age of \( \geq 50 \) years. Excluded were patients with known myocardial infarction, artificial valve, atrial fibrillation, or severe stenosis of the femoral or iliac artery. The individual patient data are listed in Table 1.

#### Clinical procedure

The measurements for each patient were performed either during an electrophysiological study (EPS) procedure (eight patients) or during the implantation of a CRT defibrillator (four patients) or CRT pacemaker (two patients), respectively. Under local anaesthesia, three electrodes for pacing, sensing and for impedance measurements were put in place: a 6 F diagnostic catheter (Viacath, Biotronik SE, Berlin, Germany) or a bipolar pacemaker lead in the right atrium, a 6 F diagnostic catheter (Viacath, Biotronik) or a pacemaker/defibrillator lead in the apex of the right ventricle (RV), and a 2.5 F diagnostic catheter (Pathfinder, Cardima Inc., Fremont, CA, USA) or bipolar coronary sinus (CS) pacemaker lead in the LV CS. An 8 F-tip dual manometer catheter to measure aortic and left ventricular blood pressures (SPC 780-C, Millar Instruments Inc., Houston, TX, USA) was positioned in the LV and ascending aorta.

Three-chamber pacing and impedance measurements were performed by an external custom-built device (ETIP, Biotronik). The impedance data were transmitted continuously from the ETIP device to the programmer (PMS1000, Biotronik) and recorded by a laptop computer, together with ECG and pacemaker marker data. The pressure catheter was connected via an isolation amplifier (PCU-2000, Millar Instruments) to a data acquisition system (Powerlab, ADInstruments Ltd, Oxfordshire, UK). A sampling rate of 1000 Hz per channel was applied.

#### Impedance measurement

A four-terminal configuration was used for the impedance measurement, injecting the measurement current via RV coil and RV tip and measuring the resulting voltage between the LV–CS proximal and distal electrodes for pacing, sensing and for impedance measurements were put in place: a 6 F diagnostic catheter (Viacath, Biotronik SE, Berlin, Germany) or a bipolar pacemaker lead in the right atrium, a 6 F diagnostic catheter (Viacath, Biotronik) or a pacemaker/defibrillator lead in the apex of the right ventricle (RV), and a 2.5 F diagnostic catheter (Pathfinder, Cardima Inc., Fremont, CA, USA) or bipolar coronary sinus (CS) pacemaker lead in the LV CS. An 8 F-tip dual manometer catheter to measure aortic and left ventricular blood pressures (SPC 780-C, Millar Instruments Inc., Houston, TX, USA) was positioned in the LV and ascending aorta.

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### Table 1 Demographic and baseline haemodynamic data for the study patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>NYHA class</th>
<th>EF (%)</th>
<th>LVEDD (mm)</th>
<th>QRS (ms)</th>
<th>( \frac{dP}{dt_{\text{max}}} ) (mmHg/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>69</td>
<td>3</td>
<td>32</td>
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<td>2</td>
<td>M</td>
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<td>3</td>
<td>20</td>
<td>85</td>
<td>180</td>
<td>513</td>
</tr>
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<td>3</td>
<td>M</td>
<td>71</td>
<td>3</td>
<td>34</td>
<td>68</td>
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<tr>
<td>5</td>
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<td>65</td>
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<td>25</td>
<td>73</td>
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<tr>
<td>6</td>
<td>M</td>
<td>81</td>
<td>3</td>
<td>25</td>
<td>62</td>
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<td>895</td>
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<td>F</td>
<td>61</td>
<td>3</td>
<td>24</td>
<td>71</td>
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<td>703</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>75</td>
<td>3</td>
<td>28</td>
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</tr>
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<td>9</td>
<td>M</td>
<td>63</td>
<td>3</td>
<td>14</td>
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<td>10</td>
<td>M</td>
<td>75</td>
<td>3</td>
<td>32</td>
<td>67</td>
<td>180</td>
<td>734</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>69</td>
<td>3</td>
<td>31</td>
<td>55</td>
<td>120</td>
<td>476</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>76</td>
<td>3</td>
<td>32</td>
<td>69</td>
<td>160</td>
<td>707</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>62</td>
<td>2</td>
<td>22</td>
<td>84</td>
<td>120</td>
<td>915</td>
</tr>
<tr>
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<td>M</td>
<td>71</td>
<td>3</td>
<td>23</td>
<td>78</td>
<td>200</td>
<td>610</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>70</td>
<td>2.9</td>
<td>26</td>
<td>71</td>
<td>165</td>
<td>685</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>6</td>
<td>0.3</td>
<td>6</td>
<td>9</td>
<td>30</td>
<td>150</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; QRS, width of QRS complex in surface electrocardiogram; \( \frac{dP}{dt_{\text{max}}} \), maximum positive slope of left ventricular pressure.
transient pacing protocol' was performed for each condition in the measurement protocol (LV lead site, AVd and VVd variations), as described by Auricchio et al. In ventricular intrinsic contraction for 15 beats (reference condition), alternating with 5 beats of BiV pacing with the described AVd and VVd parameters (tested BiV condition, see Figure 1). This scheme was repeated for 2 min automatically, and then the next parameter value was programmed on the pacemaker.

**Table 2** LV lead positions used for the site optimization test

<table>
<thead>
<tr>
<th>Patient</th>
<th>LV Position 1</th>
<th>LV Position 2</th>
<th>LV Position 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Apical lateral</td>
<td>Medial lateral</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Medial posterior</td>
<td>Medial anterior</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Medial lateral</td>
<td>Medial posterior</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Medial lateral</td>
<td>Medial anterior</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Medial lateral</td>
<td>Medial posterior</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Medial posterior</td>
<td>Medial posterior#</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>Medial lateral</td>
<td>Apical lateral</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Medial anterior</td>
<td>Medial lateral</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>Basal lateral</td>
<td>Basal anterior</td>
<td>Basal anterior#</td>
</tr>
<tr>
<td>10</td>
<td>Basal anterior</td>
<td>Basal lateral</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>Medial anterior</td>
<td>Medial lateral</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>Apical posterior</td>
<td>Basal lateral</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>Medial posterior</td>
<td>Medial posterior#</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>Basal anterior</td>
<td>Medial posterior#</td>
<td>Medial posterior#</td>
</tr>
</tbody>
</table>

*For some patients two lead positions were categorized as identical, although they varied by some centimetres.

The pacing rate was either below the sinus rate, resulting in an alternation of intrinsic rhythm and bursts with VAT pacing, or it was programmed to 10 bpm above the sinus rate, resulting in AAI pacing alternating with bursts of DDD-BiV pacing.

**Concept of cardiac resynchronization therapy optimization method comparison**

The reference method for CRT parameter optimization in this study was chosen to be LV $dP/dt_{\text{max}}$, calculated from LV pressure, the latter being measured with a micromanometer. The best CRT parameter value was defined as the value for which the largest relative increase of LV $dP/dt_{\text{max}}$ due to BiV pacing ('$dP/dt_{\text{max, benefit}}$') was observed.

$$dP/dt_{\text{max, benefit}} = \frac{dP/dt_{\text{BiV, max}} - dP/dt_{\text{ref, max}}}{dP/dt_{\text{max}}};$$

where $dP/dt_{\text{BiV, max}}$: $dP/dt_{\text{max}}$ during biventricular pacing; $dP/dt_{\text{ref, max}}$: $dP/dt_{\text{max}}$ during ventricular intrinsic contraction.

The optimization methods being tested (i.e. SZ, EDZ, SV, and PP) were compared in terms of their performance using the above ‘gold standard’ method.

**Data evaluation**

The impedance and pressure data were synchronized and analysed offline using custom software (Matlab). The Mathworks Inc., Natick, MA, USA). For each burst, the average signal curves of the five preceding reference beats (‘ref’) were calculated both for the impedance and the pressure signals. Since the pressure signal is used as a reference for CRT optimization, only the beats 2...5 from the five burst beats (‘BiV’, see Figure 1) were averaged to calculate the mean pressure curve. This was done to avoid an influence of the changed RR interval of the first beat, as suggested by Auricchio et al. For the impedance signal, however, only the first beat of each burst was used for averaging (Figure 1) in order to assess the feasibility of optimizing CRT with very short bursts. In general, the optimization procedure should be kept as short as possible.

Extrasystoles and beats with pressure signal artefacts were excluded from analysis. The averaged impedance curves were additionally smoothed with a Savitzky–Golay filter.

The following parameters were then extracted from these averaged signal curves: the maximum pressure slope $dP/dt_{\text{max}}$ was calculated from the LV pressure curves. Pulse pressure was determined from the aortic pressure curves, and SV was calculated using a pulse contour method based on the pressure integral between the time of minimum pressure and the dicrotic notch.
impedance maximum (ESZ), the end-diastolic impedance minimum (EDZ), and the stroke impedance (SZ) were calculated from the impedance curves \(SZ = ESZ - EDZ\). The extracted parameters were averaged over all (6–12) bursts belonging to one parameter value.

**Optimization methods**

The relative change of the parameters SZ, ESZ, PP, and SV under CRT pacing as compared with ventricular intrinsic contraction was used for optimization:

\[
\text{relative parameter change} = \frac{\text{parameter}_{\text{BiV}} - \text{parameter}_{\text{ref}}}{\text{parameter}_{\text{ref}}};
\]

where parameter\(\text{BiV}\): parameter value for BiV pacing; parameter\(\text{ref}\): parameter value for ventricular intrinsic contraction.

For each method, the CRT setting with the maximum ‘relative parameter change’ was considered as the best choice. The optimization methods where then judged according to the \(dP/dt_{\text{max}}\) benefit achieved with the selected settings.

For that purpose, the difference between the \(dP/dt_{\text{max}}\) benefit obtained with the selected settings and the maximum possible \(dP/dt_{\text{max}}\) benefit was calculated (‘benefit difference’):

\[
\text{benefit difference (opt.method)} = \text{dP/dt}_{\text{max}}\text{benefit (opt.method)} - \text{dP/dt}_{\text{max}}\text{benefit (dP/dt}_{\text{max}}).
\]

For the AVd and VVd selection, an additional ‘optimization method’ was included, which uses the default settings for AVd [100 ms (see Refs. 3, 6, 19)] and VVd (0 ms), referred to as ‘default’ in the following. This allows to determine the benefit of applying the optimization methods compared with accepting default values.

**Statistics**

Mean, standard deviation and standard error were used to describe the haemodynamic benefit achieved with different methods. A paired one-sided student’s \(t\)-test was used to compare the results of the optimization methods with the default value selection. Statistical significance was assumed for \(P < 0.05\). A regression analysis was used to quantify the linear relationship between the timing parameters selected for the different methods.

**Results**

**Left ventricular lead site optimization**

In Figure 2A and Table 3, the results of LV lead site optimization by haemodynamic parameters and by impedance parameters are shown, comparing the \(dP/dt_{\text{max}}\) benefit achieved. The maximum and minimum \(dP/dt_{\text{max}}\) benefits in Table 3 (row ‘reference’) indicate the possible value ranges.

The benefit difference of SZ optimization was comparable to SV optimization.

In 4 of 14 patients, SZ has selected a different optimal site than \(dP/dt_{\text{max}}\) (Patients 4, 8, 11, 13). However, in most of these patients the haemodynamic difference between sites was small (−2.3, −0.01, −8.9, and −0.63%, respectively, mean: 2.96 ± 4.08 %, see Figure 2A). Stroke volume (four patients) and pulse pressure (four patients) methods also yielded different sites than \(dP/dt_{\text{max}}\).

**Atrioventricular delay optimization**

The AVd optimization results are summarized in Figure 2B and Table 3. Optimization by ESZ achieved a benefit in the same range as optimization by SV or PP, which was significantly better than the default value selection. Patient #14 had an AV block during the test procedure. This caused a rhythm change together with CRT activation in the transient protocol, which may be a reason for the patient’s very large \(dP/dt_{\text{max}}\) benefit.
Table 3  Performance comparison for site selection, AVd and VVd optimization by different methods

<table>
<thead>
<tr>
<th>Selection Type</th>
<th>Method</th>
<th>Site optimization (n=6)</th>
<th>AVd optimization (n=14)</th>
<th>VVd optimization (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AVd Gain (ms) ΔAVd (ms)</td>
<td>Benefit difference (Δ%) mean ± STE</td>
<td>Benefit difference (Δ%) mean ± STE</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>-17.4 ± 2.8</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.8 ± 12.3</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.2 ± 5.7</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
</tbody>
</table>

The mean and standard deviations of the difference between AVd values selected by the different tested methods and by the reference method were calculated (column ‘Δ AVd’ in Table 3). The AVd values selected on the basis of ESZ show only a small mean difference to the optimal values, but the standard deviation reveals a scatter of about 20 ms. However, this also applies to optimization by SZ and by PP.

A linear correlation between the AVd values selected by dP/dt_{max} and by the other methods was significant for all optimization methods with a correlation coefficient r for ESZ: 0.75 (Figure 3), SZ: 0.46, PP: 0.67, SV: 0.60.

Interventricular delay optimization

The haemodynamic benefit obtained by VVd optimization is shown in Figure 2C and Table 3. Here, SV achieves a somewhat better result than the best impedance parameter. Stroke impedance, PP, and SV optimization results are better, but not significantly better than the default value due to the small number of patients. No significant correlation between the selected and the optimal VVd values was found among the optimization methods.

The mean and standard deviations of the difference between the VVd values selected by the test methods and by the reference method were calculated (column ‘Δ VVd’ in Table 3). Again, a VVd difference standard deviation of about 20 ms can be seen for all methods.

Summary

The dP/dt_{max} benefit achieved with the different CRT optimization methods is summarized in Figure 4. Roughly, CRT with default values for AVd and VVd gains a 17% improvement compared with intrinsic ventricular contraction, whereas individual optimization adds another 5% points. These data do not show the VVd optimization yield on top of AVd optimization, since the best AVd settings estimated during the measurement procedure were different from the best settings obtained upon offline data analysis in four patients (difference – 27 ± 24 ms). For all optimization
tasks, the haemodynamic benefit achieved by the impedance method was not significantly different from the benefit achieved by haemodynamic optimization using PP or SV.

Complications
One patient suffered a cerebral embolism after completion of the EPS measurements; the patient recovered partially. Routine laboratory results had shown no coagulation disorders, pre-existing LV thrombi had been excluded by echocardiography, and the coagulation parameters were closely controlled during the procedure. No other major complications occurred.

Discussion
A number of different non-invasive methods for CRT optimization have been published.20 There is still discussion about the best optimization approach, and different methods frequently result in contradicting optimization results.21–24 A device-based method using surrogate parameters for well-known haemodynamic variables represents an attractive approach. Since intracardiac impedance parameters correlate with ventricular volume changes, we investigated in this study whether CRT optimization by intracardiac impedance is feasible.

Intracardiac impedance
The rationale for the impedance measurement method used here has been discussed in a recent publication.16 In short, a decrease in end-systolic volume (ESV) is expected to correlate with an increase in end-systolic impedance, and an increase in SV with an increase in stroke impedance. In HF patients, the end-diastolic volume shows only small changes during an acute test25 and probably is of less value for CRT optimization. Hence, it seems reasonable to concentrate on the parameters SZ and ESZ in order to achieve the smallest ESV or largest SV. These are among the simplest parameters to be derived from the impedance signal.

Transient protocol
A number of reasons justify the use of the transient protocol: first, the goal is to measure the effect of changes to the pumping mechanics of the heart. If the circulatory system has enough time to compensate for the effect of a parameter change by autonomous regulation mechanisms, said effect on the measured variable may be reduced or hidden, and thus hindering the optimization process. Second, during the optimization process the state of the patient may be quite unstable. This is even more of an issue in daily life. A considerable change of the haemodynamic parameters was also observed during the measurement procedures in this study, sometimes larger than the effect of timing parameter modification. The third argument relates to the impedance measurement method and is important if the electrode position is changed for LV lead site optimization. As discussed above, an electrode position change by itself influences the measured impedance signal. Therefore, the relative change to a reference condition (in this study: intrinsic rhythm) is always needed to judge the haemodynamic effect of CRT at the new site.

Optimization methodology
We compared several invasive optimization methods (LV \( dP/dt_{\text{max}} \), SV, PP) with impedance. It turned out that the optimization results were also different among the invasive methods. However, the performance of both the haemodynamic and the impedance methods was comparable and better than the default settings (even though not significantly better for the VVD optimization). The \( dP/dt_{\text{max}} \) benefit resulting from the impedance optimization method differed from the maximum possible value by <3% points, which appears to be clinically acceptable, especially since the same range applies for the haemodynamic methods SV and PP.

In this study, we optimized lead position, AVd and VVD sequentially without taking into account the interdependency of these parameters. Thus, this process certainly did not produce the optimal combination of parameters. A combined optimization will be necessary to find the global optimum. Ideally, a combined optimization of AVd and VVD for several possible LV lead implantation sites, and possibly also for RV lead positions, should be performed during the implantation procedure. Also, pacing configurations with multiple pacing sites could be optimized by this method during, but also after implantation.

Routinely, AVd and VVD optimizations may be performed using intracardiac impedance during follow-up. The greatest advantage of this optimization method is, however, that it may be automatically executed by an implantable device. This would permit a continuous adaptation of both parameters to any changes in the patient’s condition and to disease progression.

Limitations
Acute leads and catheters were used during the measurement, which are prone to small movements; this could modify the impedance measurements. Ingrown leads should result in more stable conditions and are expected to improve the results.

All measurements were conducted in the supine position at rest. No information is available on the reliability of the signals in ambulatory patients and under exercise conditions.
Furthermore, only non-ischaemic patients were included in the study. An additional study is required to investigate ischaemic patients.

**Conflict of interest:** C.M., M.L. and G.C. are employees of Biotronik SE & Co. KG; C.S. is a sponsored investigator for Biotronik.

**Funding**
The study was supported by Biotronik SE & Co. KG.

**References**

**Conclusion**
The feasibility of optimizing the LV lead implantation site, A Vd, and VVd has been demonstrated for CRT patients in an acute setting by intracardiac impedance measured via the CRT pacing leads. The achieved optimization performance was similar to the one for invasive optimization with pulse contour SV and aortic PP.

Applications of intracardiac impedance for intraoperative lead site assessment, responder identification, and automatic CRT timing optimization appear feasible and should be investigated in further studies.