Multisite pacing and myocardial scars: a computational study

Mohammad Albatat, Jacob Bergsland, Hermenegild Arevalo, Hans Henrik Odland, Samuel Wall, Joakim Sundnes & Ilangko Balasingham

To cite this article: Mohammad Albatat, Jacob Bergsland, Hermenegild Arevalo, Hans Henrik Odland, Samuel Wall, Joakim Sundnes & Ilangko Balasingham (2020): Multisite pacing and myocardial scars: a computational study, Computer Methods in Biomechanics and Biomedical Engineering, DOI: 10.1080/10255842.2020.1711885

To link to this article: https://doi.org/10.1080/10255842.2020.1711885

View supplementary material

Published online: 20 Jan 2020.

Submit your article to this journal

Article views: 72

View related articles

View Crossmark data
Multisite pacing and myocardial scars: a computational study

Mohammad Albatata, Jacob Bergslanda, Hermenegild Arevalob, Hans Henrik Odlandc, Samuel Wallb, Joakim Sundnesb and Ilangko Balasinghama,d

aIntervention Centre, Oslo University Hospital, Oslo, Norway; bDepartment of Computational Physiology, Simula Research Laboratory, Fornebu, Norway; cDepartment of Cardiology, Oslo University Hospital, Oslo, Norway; dDepartment of Electronic Systems, Norwegian University of Science and Technology, Trondheim, Norway

ABSTRACT
Cardiac resynchronization therapy (CRT) is a frequently effective treatment modality for dyssynchronous heart failure, however, 30% of patients do not respond, usually due to suboptimal activation of the left ventricle (LV). Multisite pacing (MSP) may increase the response rate, but its effect in the presence of myocardial scars is not fully understood. We use a computational model to study the outcome of MSP in an LV with scars in two different locations and of two different sizes. The LV was stimulated from anterior, posterior and lateral locations individually and in pairs, while a septal stimulation site represented right ventricular (RV) pacing. Intraventricular pressures were measured, and outcomes evaluated in terms of maximum LV pressure gradient \(\frac{dP}{dt}\text{max}\) change compared to isolated RV pacing. The best result obtained using various LV pacing locations included a combination of sites remote from scars and the septum. The highest \(\frac{dP}{dt}\text{max}\) increase was achieved, regardless of scar size, using MSP with one pacing site located on the LV free wall opposite to the scar and one site opposite to the septum. These in silico modelling results suggest that making placement of pacing electrodes dependent on location of scarring, may alter acute haemodynamics and that such modelling may contribute to future CRT optimization.

ARTICLE HISTORY
Received 14 April 2019
Accepted 2 January 2020

KEYWORDS
Computational modelling; CRT; cardiac electrophysiology; multisite pacing

Introduction
Heart failure (HF) is a serious medical condition affecting more than 26 million people worldwide (Savarese and Lund 2017). In approximately one-quarter of HF patients a defect in the conduction system contributes to the HF, resulting in asynchronous ventricular activation and reduced cardiac pumping efficiency (Thom and Kannel 1997). The aim of cardiac resynchronization therapy (CRT) is to use controlled pacing to produce synchronous contraction of both ventricles (Abraham et al. 2002). CRT devices consist of subcutaneously implanted pacemaker cans containing control units and battery source, connected to three or more leads with sensing and pacing electrodes implanted in the right atrium, right- and left ventricles (RA, RV and LV) through an endovascular or direct surgical approach. In selected patients, CRT improves the cardiac pumping efficacy and relieves HF symptoms (Abraham and Hayes 2003), but 30% of cases do not respond to CRT due to a suboptimal stimulation pattern of the LV (Auricchio and Prinzen 2011). Multisite pacing (MSP) may increase CRT response by inserting LV lead(s) in additional location(s) to obtain: (1) improved stimulation pattern and (2) synchronization of a larger part of the LV.

Pappone et al. introduced MSP and suggested that it enhances systolic function better than single-site pacing (SSP) in patients with left bundle branch block (LBBB) (Pappone et al. 2000). Several randomized studies demonstrated benefits of MSP compared to conventional LV pacing (Table 1). Out of 13 studies, three did not show any benefit from MSP. Padeletti et al. reported outcomes from MSP similar to those obtained with single, optimized LV pacing (Padeletti et al. 2008). Larger studies showed that MSP improved haemodynamics (Ginks et al. 2012), mid- and long-term clinical outcomes (Leclercq et al. 2008; Lenarczyk et al. 2012; Rogers et al. 2012; Laish-Farkash et al. 2018) and reduced ventricular arrhythmias (Ogano et al. 2013). Bordachar et al. investigated the effect of MSP in SSP nonresponders and found no benefits and higher complication rates (Bordachar et al. 2018) compared to optimized SSP. The mean
nonresponse time (CRT implantation without functional improvement) for recruited patients was 36 months – a considerable length of time in patients with progressive HF. Herweg et al suggests that severe HF patients may be beyond the grasp of CRT (Herweg and Barold 2008).

The presence and location of myocardial scars are important in CRT outcomes, and direct pacing of scar tissue should be avoided (Ypenburg et al. 2006; Singh et al. 2011). MSP may improve the response rate in ischemic patients, but only two clinical studies assessed placement of LV electrodes in MSP considering scar location (Ginks et al. 2012; Jackson et al. 2018). Determining the effect of scar location is challenging, as the location and the size of the scar vary depending on coronary anatomy and disease.

With advances in computational medicine, detailed heart modelling (Niederer et al. 2018) gives us the potential to analyse the effect of CRT in silico (Okada et al. 2017; Lee et al. 2018). Previous computational studies of CRT investigated optimal SSP site in relation to scar location (Huntjens et al. 2014), the effect of scar size (Kerckhoffs et al. 2009) and effects of multipoint electrodes (single lead with multiple stimulation sites) (Niederer et al. 2012). To our knowledge, no computational study has evaluated the effect

<table>
<thead>
<tr>
<th>#</th>
<th>Reference</th>
<th>Objective</th>
<th>MSP patients</th>
<th>Outcome measure</th>
<th>Assessment time</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pappone et al. (2000)</td>
<td>MSP produce faster activation</td>
<td>14 LBBB</td>
<td>dP/dt</td>
<td>Acute</td>
<td>Improved systolic function and activation synchrony</td>
</tr>
<tr>
<td>2</td>
<td>Lenarczyk et al. (2007)</td>
<td>Safety and efficiency of MSP</td>
<td>22 LBBB</td>
<td>NYHA class, VO2max, echo, 6MWD</td>
<td>3 months</td>
<td>Improved outcome compared to baseline</td>
</tr>
<tr>
<td>3</td>
<td>Leclercq et al. (2008)</td>
<td>Safety and efficacy of MSP</td>
<td>34</td>
<td>Z ratio, reverse LV remodelling, 6MWD</td>
<td>3 and 6 months (crossover) after 3-month BiV CRT</td>
<td>Higher EF, LV remodelling and smaller EDV</td>
</tr>
<tr>
<td>4</td>
<td>Lenarczyk et al. (2009)</td>
<td>Implantation course and midterm outcomes</td>
<td>27 with no AF</td>
<td>NYHA class, 6MWD, (VO2max), echo.</td>
<td>3 months</td>
<td>MSP more beneficial compared to BiV</td>
</tr>
<tr>
<td>5</td>
<td>Padeletti et al. (2008)</td>
<td>Evaluate acute response of MSP</td>
<td>12</td>
<td>PV-Loop (conductance catheter)</td>
<td>Acute</td>
<td>No further benefit compared to BiV with optimized site and AV delay.</td>
</tr>
<tr>
<td>7</td>
<td>Lenarczyk et al. (2012)</td>
<td>Implantation feasibility and long-term safety of MSP</td>
<td>48</td>
<td>NYHA class, echo</td>
<td>1 week, 1 month, 3 month, 6 months and then every 6 months</td>
<td>More pronounced functional improvement, but time-consuming</td>
</tr>
<tr>
<td>8</td>
<td>Rogers et al. (2012)</td>
<td>Compare long-term MSP with BiV</td>
<td>23 1RV + 2LV 20 2RV + 1LV</td>
<td>6MWD, MLWHF, echo</td>
<td>12 months (crossover between 4 configurations every 3 months)</td>
<td>Significant improvements in clinical and echocardiographic parameters</td>
</tr>
<tr>
<td>9</td>
<td>Ogano et al. (2013)</td>
<td>To evaluate the effect of MSP on ventricular arrhythmia</td>
<td>22</td>
<td>Ventricular arrhythmia (VA), ECG</td>
<td>16 ± 11 months</td>
<td>Improvements in repolarization parameters and reduced VA</td>
</tr>
<tr>
<td>10</td>
<td>Providencia et al. (2016)</td>
<td>Impact MSP on long-term survival</td>
<td>34 retrospectives from Rogers et al.</td>
<td>Device parameters, clinical outcomes</td>
<td>Median of 82 months (IQR: 39 to 107)</td>
<td>Benefits regarding long-term survival and ventricular arrhythmia burden</td>
</tr>
<tr>
<td>11</td>
<td>Bordachar et al. (2018)</td>
<td>Effect of adding a second LV lead to CRT nonresponders</td>
<td>42 nonresponders (for &gt;6 months)</td>
<td>6MWD, MLWHF, echo</td>
<td>12 and 24 months</td>
<td>Higher complication rate and no significant long-term clinical benefit</td>
</tr>
<tr>
<td>12</td>
<td>Laish-Farkash et al. (2018)</td>
<td>Indications, feasibility, safety and benefit of MSP</td>
<td>39 retrospectives</td>
<td>Baseline data, NYHA class, echo</td>
<td>Varied between 1 and 7 years</td>
<td>Feasible, safe and valuable in selected patients</td>
</tr>
<tr>
<td>13</td>
<td>Jackson et al. (2018)</td>
<td>Impact of scar prevalence and distribution on MSP</td>
<td>24</td>
<td>dP/dt max</td>
<td>Acute</td>
<td>No significant benefit compared to optimized BiV.</td>
</tr>
</tbody>
</table>

myocardial scars has on the efficiency of MSP. We use an established computational model of the electromechanical behaviour of the LV, to study the effect of MSP – using pacing sites in different LV-sites – depending on location and size of myocardial scars. A brief description of the model and the study-protocol is provided in the next section, followed by the results in Result section. Finally, in Discussion and conclusion section, we discuss the results and summarize in the conclusion.

Methods

Model creation

The mathematical model for the electromechanical behaviour of the myocardium during a cardiac cycle has been described before (Sundnes et al. 2014) and is summarised briefly in this section. Cardiac MRI from a healthy subject was used to construct a 3D finite element mesh of the LV. The MRI slices between the base of the heart and apex were manually segmented, separating left ventricular endocardium and epicardium, using the software ‘Segment’ (Medviso AB, Lund, Sweden). A coherent 3D finite element mesh of tetrahedra was created based on the separate surfaces using Gmsh, a finite element mesh generator (Geuzaine and Remacle 2009). The resulting mesh comprised of 1670 nodes and 5611 elements.

Assuming left bundle branch block, the Purkinje network was modelled using an electromechanically coupled cross-bridge cycling descriptor, methodically validated against well-established, normal organ-level behaviour and to conditions with preload, afterload and contractility adjustment (Shavik et al. 2017). The coupled model is based on a system of ordinary differential equations of MSP

\[
\frac{\partial s}{\partial t} = f(v, s, \lambda),
\]

where \( s \) is a vector of state variables describing the electro-mechanical state of the myocytes at a given time \( t \), \( v \) is the transmembrane potential, and \( \lambda \) is the ratio between the sarcomere length at time \( t \) and the slack length, i.e. myocardial fibre stretch.

The propagation of the electrical signal through the tissue was computed using the bidomain model (Tung 1978)

\[
\frac{\partial v}{\partial t} + I_{ion}(v, s, \lambda) = \nabla \cdot (M_1 \nabla v) + \nabla \cdot (M_e \nabla u_e),
\]

\[
\nabla \cdot ((M_1 + M_e) \nabla u_e) = -\nabla \cdot (M_1 \nabla v),
\]

where \( I_{ion} \) is the total ionic current given by the cell electrophysiology model, \( u_e \) is the extracellular potential and \( M_1 \) and \( M_e \) are the intracellular and extracellular conductivity tensors, respectively. The conductivity values are given in (Sundnes et al. 2007) and scaled with cell membrane capacitance and surface to volume ratio. This ratio was adjusted to produce the normal conduction velocity of a human LV of about 0.5 m/sec (Klabunde 2011). To capture the rapid dynamics of the electrical activity, (2a)–(2b) were solved on a mesh that was refined by a factor of two in all directions, resulting in 44,888 elements.

The mechanical state of the complete cardiac muscle is described by the equilibrium equation

\[
\nabla \cdot (FS) = 0,
\]

where \( F \) is the deformation gradient and \( S \) is the second Piola–Kirchoff stress tensor. The active myocardium was modelled with an active stress approach, where the stress tensor was split into passive and active components. The passive stress is described by a transversely isotropic version of the model (Guccione et al. 1995), whereas the active stress component is given by (Rice et al. 2008), described in (1). Fibre orientation was assigned using a rule-based algorithm (Bayer et al. 2012), with the angles rotating from -50 degrees on epicardium to 40 degrees on the endocardium. Boundary conditions for the mechanics model were chosen as in (Sundnes et al., 2014). The base was held fixed in all directions (displacement set to zero), the epicardium was unloaded and the endocardium was subjected to a dynamic pressure boundary condition. For the ejection phase, the LV endocardium boundary condition was given by a 3-element Windkessel model (Lee et al. 2016), which gives the following relation between aortic flow \( q \) and ventricular cavity pressure \( p \)

\[
\left(1 + \frac{R_{ao}}{R_{per}}\right) q + C_{art} R_{ao} \frac{dq}{dt} = \frac{p - p_{per}}{R_{per}} + C_{art} \frac{dp}{dt}
\]

Here, \( R_{ao} \) and \( R_{per} \) are aortic and peripheral resistances, respectively, and \( C_{art} \) is arterial compliance. The equation was discretized in time with an implicit finite difference scheme and solved to determine the pressure \( p \) that balanced the aortic flow with the cavity volume dictated by the finite element model. The parameter values for the Windkessel model are given in Supporting Information Table 1. The flow rate \( q \) is calculated as the time rate of change of cavity volume. The implicit time discretization is applied with an equation linking pressure- and volume at the next time step. A similar approach is used for the isovolumic phases, but with the flow set to zero, while the
filling phase is simulated by a prescribed increase in cavity pressure. A detailed description of the coupled electro-mechanical model can be found in the Supporting Information and in (Sundnes et al. 2014).

**Study protocol**

To represent scar tissue, a region of the LV is segmented, and made inactive by making its elements nonconductive (Arevalo et al. 2016) and its passive stiffness six times stiffer than the remaining tissue (Huntjens et al. 2014). As seen in Figure 1, five scenarios were created: (1) No scar (control); (2) Small anterolateral scar (anterior-small-scar); (3) Small posterolateral scar (posterior-small-scar); (4) Large anterolateral scar (anterior-large-scar); (5) Large posterolateral scar (posterior-large-scar). The small scars correspond to 10% of the LV wall volume, while the large scars correspond to 20%. The scar locations are theoretical and only serve as means of comparison. The scars were located at approximately equal distances from the septum, the lateral wall and the base to avoid the effect of these distances when comparing the results of the various scars.

The LV was stimulated from a mid-basal point of the septum, simulating right ventricular (RV) pacing in a conventional pacemaker. RV simulations serve as baseline for each of the five scenarios, i.e. the results of the various pacing configurations are compared to RV-only pacing. In addition to the septal site, the LV was stimulated from anterior, posterior and lateral locations individually – simulating conventional CRT – and from two sites simultaneously, simulating multisite CRT. Thus, each of the scenarios had seven different simulations with pacing from:

1. Septum only (RV) (control)
2. RV + anterior site (anterior)
3. RV + posterior site (posterior)
4. RV + lateral site (lateral)
5. RV + posterior + lateral (post-lat)
6. RV + lateral + anterior (lat-ant)
7. RV + posterior + anterior (post-ant)

All LV pacing sites were located in the mid LV, 2 cm away from the base, to keep the results computationally tractable and clinically relevant since the middle part of the LV is recommended by the multicentre MADIT-CRT study (Singh et al. 2011). Stimuli were delivered by simultaneously activating the elements within a sphere of 5 mm in radius centred on the epicardium at the different locations (50 to 60 elements), by applying a transmembrane current of 100 mA for 0.5 ms. The simulation ran for five sequential cycles, and steady states were established by the third cycle – which was chosen to get representative data. Intraventricular volumes and pressures were calculated at each time-step, and the outcome was displayed in terms of pressure-volume loops (PV-loops) and LV pressure gradient (dP/dt). To quantify the results, stroke work (SW), ejection fraction (EF) and total activation time (TAT) were calculated. SW

---

**Figure 1.** Five scenarios were created with different scar sizes and locations (grey). The top images show long axis view of the LV and the bottom images show short axis view. In each scenario, the LV was stimulated from anterior (blue), posterior (orange) and lateral (green) sites in addition to RV site (black). The letter S indicates the optimal SSP site and the letter M indicate the optimal MSP sites for each scenario. The first figure of the lower row includes the distance between the various sites.
is the work done by the LV for each heartbeat, measured as the area under the PV-loop. EF is the fraction of blood ejected by the LV, measured as the percentage between stroke volume and end-diastolic volume. TAT is the time for the pacing to excite all the healthy elements, measured as the period from the stimuli is delivered until the whole ventricle – excluding the passive scar elements – is excited.

Results

The meshes used in each of the five scenarios, including the pacing sites, are shown in Figure 1, and the results of the simulations are shown in Table 2. An example of the graphical output of one of the simulations is illustrated in a snapshot series shown in Figure 2, where an LV with anterior-small-scar is paced from an anterior site. The outcome of the control (no scar) is shown in Figure 3 and of anterior-small-scar in Figure 4, where the coloured diagrams are activation maps of each simulation. The colour scale represents the activation time of each element compared to when pacing was initiated. The graph on the bottom right shows dP/dt during systole. The peaks indicate maximum pressure gradient (dP/dt\(_{\text{max}}\)), an acute measure commonly used clinically to assess pacing efficiency and LV contractility. The outcome of each pacing-mode is measured as relative change in dP/dt\(_{\text{max}}\) compared to baseline achieved by RV pacing. This relative measure is referred to as \(\Delta\delta P\) and displayed in the legend. The graph on the bottom left shows PV-loops from the various pacing configurations, where SW and EF are displayed in the legend. The relative change in SW compared to baseline is referred to as \(\Delta SW\). The graphs of the other scenarios are shown in Figure 5. A summary of all the results is shown in Table 2.

**RV pacing (baseline)**

Baseline pacing in control (no scar) produced a dP/dt\(_{\text{max}}\) of 864 mmHg/s, which decreased by 5% with anterior-small-scar and 3% in posterior-small-scar (Table 2). With increased scar size the decrease in

<table>
<thead>
<tr>
<th>LV pacing site (+RV)</th>
<th>Control</th>
<th>Anterolateral</th>
<th>Posterior</th>
<th>Anterolateral</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL RV-only</td>
<td>864</td>
<td>130</td>
<td>3.021</td>
<td>824</td>
<td>140</td>
</tr>
<tr>
<td>SSP Anterior</td>
<td>6.73</td>
<td>110</td>
<td>1.92</td>
<td>1.37</td>
<td>140</td>
</tr>
<tr>
<td>SSP Posterior</td>
<td>4.14</td>
<td>115</td>
<td>0.56</td>
<td>0.63</td>
<td>140</td>
</tr>
<tr>
<td>SSP Lateral</td>
<td>18.35</td>
<td>100</td>
<td>4.04</td>
<td>17.25</td>
<td>105</td>
</tr>
<tr>
<td>MSP Post-lat</td>
<td>18.08</td>
<td>100</td>
<td>5.49</td>
<td>24.37</td>
<td>100</td>
</tr>
<tr>
<td>MSP Lat-ant</td>
<td>19.93</td>
<td>95</td>
<td>3.87</td>
<td>14.08</td>
<td>100</td>
</tr>
<tr>
<td>MSP Post-ant</td>
<td>13.88</td>
<td>105</td>
<td>1.36</td>
<td>13.41</td>
<td>110</td>
</tr>
</tbody>
</table>

| BL stands for baseline. \(\Delta\delta P\) is the percentage increase of maximum LV pressure gradient (dP/dt\(_{\text{max}}\)) compared to baseline, which is the one produced with RV-only pacing. The baseline dP/dt\(_{\text{max}}\) in mmHg/s is displayed in the first row, marked grey. TAT is the total activation time of the nonscarred region of the LV, in milliseconds. The optimal pacing configuration in each scenario is marked green. The pacing configuration that produced lower dP/dt\(_{\text{max}}\) than the baseline (negative \(\Delta\delta P\)) is marked red. The percentage increase of stroke work compared to baseline (\(\Delta SW\)) is displayed in the column SW, where SW of the baseline is displayed in the first row in L mmHg.
\( \frac{dP}{dt_{\text{max}}} \) was 12% in anterior-large-scar and 5% in posterior-large-scar. TAT did not change significantly in baseline pacing across the different scenarios, increasing by 10 ms in small- and 5 ms in large-scar.

Baseline EF was 34.11% in the control (no scar) and decreased to 30.55% and 29.7% in anterior and posterior small scars, respectively, while the large scars reduced EF to 27.07% and 26.06% compared to baseline. Baseline SW also decreased when the scar size increased (see Table 2 for details).

**Single-site pacing**

In situations without scar, most configurations improved LV function, although, the posterior site...
produced 0.56% lower SW and 0.94% lower EF compared to baseline (Figure 3). When scars were introduced, pacing at some sites resulted in worse outcome than baseline pacing. The anterior site in anterior-small-scar (Figure 4) and the posterior site in posterior-small-scar (Figure 5) resulted in negative $\Delta D_P$ and $\Delta SW$, lower EF compared to baseline and unchanged TAT. These deleterious results were produced by the sites located between the scar and the septum. With large scars, these pacing sites reduced $\Delta D_P$ even more. While the average $\Delta D_P$ of the deleterious sites in the small scars was $-3.2\%$, it decreased to $-5.4\%$ in the large scars.

The lateral site, which is located opposite to the septum, produced the highest $D_P$ in hearts without and with small scars. This was more evident when scar was absent; $\Delta D_P$ with lateral site pacing increased by 172.7% and 343.2% compared to the anterior- and

Figure 4. Result of anterior-small-scar. The upper images are short axis view activation maps of the LV paced from the various pacing configurations. The resulting dP/dt graphs are shown in the bottom right and PV-loops in the bottom left.
the posterior site, respectively. In anterior-small-scar the lateral site produced only 6.4% higher $\Delta \delta P$ than the posterior site and in posterior-small-scar and posterior-large-scar the lateral site produced the highest $\Delta S W$ and EF in the control (no scar), while in the scar scenarios the lateral pacing-site also produced the highest $\Delta S W$ and EF in the control (no scar).
site located opposite to the scar produced the highest ΔSW and EF, i.e. the posterior site in anterior scars and the anterior site in posterior scars.

When scars were large, the best SSP site was clearly the site located opposite to the scar, producing 63.9% and 100.6% higher ΔP than the lateral site, while both the other SSP sites result in a negative ΔSW, i.e. lower SW than RV-only pacing. The TATs in all pacing configurations were shorter than TAT of RV-only pacing (Table 2).

**Multisite pacing**

The highest ΔP in all scar scenarios was achieved with one specific MSP configuration, whereas the other two MSP configurations resulted in lower ΔP than the optimal SSP. In control, the best MSP (lat-ant) increased ΔP by only 1.6% compared to the best SSP (lateral). In scenarios with anterior scars, the highest ΔP was produced by post-lat MSP, while in posterior scars, lat-ant produced the highest ΔP. In all four scar scenarios, the MSP with the highest ΔP included the lateral site and the site that lies on the opposite side of the scar. The same MSP had the highest ΔSW among the MSP, but in posterior-small-scar and in anterior-large-scar, the SSP site located on the opposite site of the scar produced the highest ΔSW. In large scars, MSP from the lateral site and the site adjacent to the scar produced a negative ΔSW and lower EF than baseline.

The TATs were slightly better in MSP compared to SSP but varied less and did not always follow the corresponding ΔP. For instance, while ΔP of posterior SSP in anterior-small-scar was around 2% higher than lat-ant MSP, its TAT was 15 ms higher (Table 2). Also, in posterior-large-scar, four pacing configurations produced TAT of 115 ms, while their respective ΔP ranged between 1.58% and 9.43%.

**Discussion and conclusion**

**Discussion**

Despite advances in the design of CRT devices, only about 70% of patients are responding positively. The success of CRT depends on patient selection, pacing sites and pacing configurations (Vernooy et al. 2014). Some investigators have considered reducing the number of nonresponders by stricter indication criteria, but since clearly established selection criteria have been defined, such an approach may deny some responders access to CRT (Chung et al. 2008; Goldenberg et al. 2011). Another approach focuses on increasing responsiveness to CRT by optimizing pacing location (Khan et al. 2012) or increasing the number of pacing sites (Antoniadis et al. 2017). MSP may improve the response rate to CRT, but the effect of presence and location of myocardial scar is not clear. Ginks et al. (2012) considered the impact of posterolateral scar in MSP in five patients. The scars were of different sizes, making it hard to analyse the effect. Jackson et al. (2018) evaluated the effect of scar prevalence and distribution on acute response to MSP, but did not find any significant relation; Fourteen of the 24 patients had scar burden, with a mean size of 6% of myocardial mass, possibly too small to reveal a significant effect. Based on our simulations and clinical studies using MSP (Table 1), it appears that patients with scar respond less frequently than those without (Ypenburg et al. 2006).

Advances in computational modelling has improved the understanding of the interrelation between different underlying factors in HF (Wang et al. 2015). We used a detailed electromechanically coupled computational model to evaluate the effect of scar on the effect of MSP by changing size and locations of scars, keeping other factors constant.

We demonstrated that outcomes of pacing configurations in MSP depend on location and size of myocardial scars. While dP/dt_max increased up to 25% compared to baseline, the maximum increase in SW was only around 5% and EF by only 3% maximum. dP/dt_max is, at present, used most commonly to guide lead placement for optimizing the effect of CRT (Butter et al. 2001; Bogaard et al. 2010), due to its validity as a measure of contractility (Nelson et al. 2000) and synchrony (Verbeek et al. 2002). Functional measures, such as SW and EF are mostly used for long-term evaluation of CRT since they are associated with reverse remodeling of the heart and are less sensitive to acute changes.

In scenarios without myocardial scar, all LV pacing configurations simulated in this study, improved outcomes (Figure 3). In scenarios 2–5, with the presence of scars, pacing sites located close to the scar and the septum (between the scar and the septum) produced the least favourable outcomes in SSP, probably due to impediment of the propagation waves in direction of the scar demonstrated by the activation maps in Figure 4. When the scar was anterolateral, the anteroseptal region of the LV was activated substantially faster than the posterolateral region resulting in dysynchronous and deteriorating LV contraction.

The effect of LV pacing was considerably higher in LVs with anterolateral scars (small and large) (dP/ dt_max increase 7.69–25.5%), compared to those with
posterolateral scars (1.58–17.11%). This could be due to the variation in myocardial thickness. Since the posterior wall in our model is thicker than the anterior, a posterior scar could impair the LV to a higher degree. Scar size and LV anatomy is likely to co-vary, and this covariance is out of the scope of this study. We would remark that anterolateral scars are uncommon in patients. Our results serve only as a mean for comparison and should not be applied to patients with anterior scars, as they are typically located at a more septal location.

In line with the findings of Huntjens et al. (2014), we demonstrated that the optimal SSP site is related to its proximity to the scar and the septum, the effect being more profound in large scars. In small scars, pacing more distant from the septum – produced the highest ΔδP, regardless of scar location while pacing from location more distant from the scar produced the highest ΔSW as shown by Jackson et al. who used dP/dt_max to evaluate outcomes in patients with a mean scar volume of 6% (Jackson et al. 2018). With large scars, the optimal SSP site, both in terms of ΔδP and ΔSW was the one located furthest from the scar.

In all the scar scenarios, the best ΔδP was consistently achieved with MSP using one site located in the lateral wall opposing the septum and one site located distal to the scar. Such configurations resulted an average ΔδP of 20% across all scenarios, comparable to the 28% average ΔδP observed by Ginks et al. (2012). TAT improved, on a much smaller scale, with an average reduction of 5% in small- and 9% in large-scars. Higher reduction was observed in large scars since there was less viable tissue, thus requiring less time for activation. Our studies support observations from other studies suggesting that TAT is a poor predictor of CRT response (Molhoek et al. 2004; Okada et al. 2017).

Other MSP configurations did not provide any improvement compared to optimal SSP, suggesting that MSP does not consistently improve outcomes in scarred LVs compared to optimized SSP, explaining the negative results of Padeletti et al. who compared MSP to optimized SSP (Padeletti et al. 2008). Clinically, available pacing sites are restricted by coronary sinus anatomy unless surgical implantation is utilized. Pacing sites accessed transvenously may not be optimal with respect to scar location. In large scars, MSP from lateral sites and sites adjacent to scars resulted in the worst functional results with negative ΔSW. Pacing from both sides of a scar increases desynchrony between the scarred region and remote myocardium. Our study implies that for MSP to be effective, scar location should be taken into consideration when placing the electrodes. The larger the scar is, the more it influences the site selection.

**Main findings:**

1. In the presence of a scar, the highest ΔδP is achieved with MSP with one site remote from septum and one remote from scar, independent on the scar size.
2. In absence of scar or in small scars, the optimal SSP site in terms of ΔδP is the one located distal to the septum, and in terms of ΔSW is the one located distal to the scar.
3. With large scars, the optimal SSP site is the one located distal to the scar.

**Limitations**

The main benefit of in silico models is the ability to understand complex processes and to study the effect of different factors separately. This approach, however, require assumptions and simplifications that may influence results compared to what is seen clinically. In this study, scar tissue was assumed to be a uniform and nonconductive medium, and changes in electrophysiology of border zones or the so-called grey-zones were not taken into account. Border zones primarily affects arrhythmogenesis (Mendonca Costa et al. 2018), and since our purpose was to study mechanical functions of the LV, we chose to neglect this aspect of the border zone. Similarly, the effect of mechano-electric feedback was neglected, to reduce complexity and computational time, as it has a negligible effect on the relative function of the LV (Wall et al. 2011).

The electromechanical behaviour of the RV has an important role in CRT, and models should ideally include biventricular geometry. In this study, only the LV was studied to reduce complexity and computational time, and because the study only analysed relative changes in LV haemodynamics. Pacing from the septal wall to represent RV pacing has been done in previous studies and provides a good relative measure.

Most of the time, the LV and RV electrodes in CRT are stimulated simultaneously, but in some cases, physicians adjust the time between the RV and the LV stimuli – adding a delay between the ventricular electrodes (VV-delay) – to optimize overall performance of the ventricles. VV-delay is a parameter that may have an impact on optimal pacing site. We chose to study a VV-delay of 0 (simultaneous RV and LV
pacing) to keep the results tractable and reduce computational cost. We plan to use optimized VV-delay in addition to the number and location of pacing sites in the next study, which will include actual patient data.

Another limitation of the study is that the geometry and location of the scars is artificially chosen, and not acquired from patient data, which reduces the applicability in clinical practice. Especially, the anterolateral scars, which are uncommon due to the coronary anatomy. Infarct in the left anterior descending (LAD) is a common cause of heart failure and is typically located in the apical anteroseptal region. The study aimed to investigate the effect of scar location in general and not replicate clinical results. The two scar locations were chosen to be at equal distances from the septum, the lateral wall and the base so the effect of these distances could be neglected when comparing the results.

Both myocardial infarction and changes in function due to pacing alter filling pressures which affect \( \Delta P/ \Delta t_{\text{max}} \) through the Frank–Starling effect. Because our model is not connected to a closed-loop circulation, our work cannot consider these changes, possibly affecting CRT efficacy.

It has also been shown that myocardial stretch has an effect on electrical behaviour, so called mechano-electric feedback (Wall et al. 2011). Since we mainly analysed mechanical function of the LV and wanted to reduce computational cost, we did not model this interaction.

**Conclusion**

MSP is a promising approach to improve CRT responsiveness, but its effect in LVs with scar is unknown. Our study demonstrates the potential value of computational models on assisting clinicians in predicting optimal configurations of CRT. We used a detailed computational model of a human LV to study the effect of SSP and MSP in LVs with different scar locations and sizes. We demonstrated that optimally placed MSP outperforms SSP. For MSP to be effective, lead placement in relation to scars and septum must be considered.

**Disclosure statement**

Dr. Hans Henrik Odland reports personal fees from Abbot, grants from Medtronic, outside the submitted work. The other authors have nothing to disclose.

**Funding**

This work was funded by the European Union’s H2020: MSCA: ITN program for the ‘Wireless In-body Environment Communication – WiBEC’ project under the grant agreement no. 675353.

**ORCID**

Mohammad Albatat [http://orcid.org/0000-0002-7314-0667](http://orcid.org/0000-0002-7314-0667)

**References**


