Mechano-electrical coupling as framework for understanding functional remodeling during LBBB and CRT

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Submitted 9 September 2013; accepted in final form 10 April 2014

CARDIAC RESYNCHRONIZATION THERAPY (CRT) has emerged as an important therapy to improve pump function in patients with chronic heart failure and conduction disturbances, such as left bundle-branch block (LBBB) (10). This therapy aims to restore synchrony of ventricular electrical excitation, generally by pacing the left ventricle (LV) at a single location (LV pacing) or by pacing both ventricles (simultaneous or sequential biventricular pacing). A common observation is that the improvement in pump function when starting CRT, for example, quantified as increase in LV ejection fraction, further continues over time (8). A similar, but reverse pattern is seen after stopping CRT in these patients (61).

In the canine model of LBBB (58), LBBB resulted in an acute reduction of LV pump function, followed by a further deterioration over time (59), whereas CRT caused an acute improvement, followed by ongoing improvement in the long run (58). Such behavior seems different from other cardiovascular abnormalities, like hypertension or infarction, where cardiac adaptation, at least initially, leads to compensation of the functional impairment (36, 39).

Various experimental studies have shown extensive and differential changes in gene and protein expression as well as posttranslational changes in dysynchronous hearts (2, 9, 35, 51), resulting in abnormal calcium handling and repolarization. These findings do not, however, clarify directly why cardiac pump function would worsen in chronic LBBB.

In the present study, we investigated the relation between local electrophysiological and global functional alterations induced by LBBB and CRT using an integrative modeling approach. To that end, we extended our electromechanical approach. To that end, we extended our electromechanical model of the human left heart and systemic circulation (20) with the right heart and pulmonary circulation. The present model also includes mechanical interaction of the LV and right ventricle (RV) through the interventricular septum as well as hemodynamic interaction between the two ventricles through the systemic and pulmonary circulations (33, 34). In a previous study, we showed that mechano-electrical coupling (MEC), i.e., remodeling of ionic currents and calcium handling triggered by changes in local mechanical workload, explains optimal tuning of cardiac pump function as well as the concordant T-wave during normal sinus rhythm and T-wave memory after temporary abnormal electrical activation (20). In particular, it was assumed that specific conductance of the L-type calcium current (\(G_{\text{CaL}}\)) increases when mechanical load is too low and decreases when workload is too high, aiming at minimal dispersion of local mechanical external work. Our choice for changing \(G_{\text{CaL}}\) in that study and in the present study was based on the observation that expression of L-type calcium channels and the calcium transient show regional differences in dysynchronous heart failure (DHF) attributable to LBBB and rapid pacing in dog hearts, complying with local regulation (2), and that calcium channel blockade attenuates cardiac memory after temporary pacing (40). The aim of the present
study was to investigate whether MEC by means of local regulation of L-type calcium current conductance could explain the deterioration of function during LBBB as well as the long-term improvement during CRT.

MATERIALS AND METHODS

Model overview. The model used in the present study is based on our CircAdapt model of human cardiovascular mechanics and hemodynamics (6, 7, 33), incorporating mechanical interaction of the LV and RV through the interventricular septum and hemodynamic interaction between both ventricles through the systemic and pulmonary circulation. Our model has a modular setup, describing all elements of both circulations including valves, arteries, microcirculation, veins, and atria. Global ventricular pump mechanics (pressure-volume relation) was related to myocardial mechanics (myofiber stress-strain relation) using the principle of conservation of energy (4, 5). To simulate fast processes such as ionic channel dynamics, calcium handling, and excitation-contraction coupling combined with the much slower process of cardiac electromechanical remodeling, we have adopted a geometrically simplified model of the heart. The model includes two atrial walls and three ventricular walls: LV free wall (LVfw), interventricular septum, and RV free wall (RVfw) (33). Electromechanical behavior of a single ventricular wall is modeled by a multitude of mechanically and electrically coupled myocardial segments (Fig. 1). The number of segments for each ventricular wall was proportional to its wall volume ($V_{wall}$): 120 segments for the RVfw ($V_{wall,RVfw} = 42 \text{ ml}$), 150 segments for the septum ($V_{wall,septum} = 50 \text{ ml}$), and 300 segments for the LVfw ($V_{wall,LVfw} = 101 \text{ ml}$).

In the present study, the heuristic model of cardiac mechanics in the original CircAdapt model (33) was replaced by a cascade of physiological models (Fig. 1). Ionic currents and calcium handling were modeled by the 2006 model of the human ventricular action potential from ten Tusscher et al. (54, 55). Mechanical behavior of a segment was modeled by the classical three-element rheological scheme (21, 49). Excitation-contraction coupling was modeled by model 5 of Rice et al. (46) and depended on the intracellular concentration of free calcium [from the model of ten Tusscher et al. (55)], sarcomere length, and velocity of sarcomere shortening. These models were integrated to describe electromechanical behavior of multiple segments that were electrically and mechanically coupled in series as described previously (20, 25, 28, 29, 30). Intracellular and extracellular electrical coupling between the segments was modeled according to the bidomain equations (19, 27).

Cardiac mechanics and hemodynamics. The geometry of the biventricular model was described by wall volume ($V_{wall}$) and reference surface area of the midwall ($A_{m,ref}$) for LVfw, septum, and RVfw, where $A_{m,ref}$ is defined as the quotient of $V_{wall}$ and the wall thickness at mid-ejection. Parameters describing ventricular geometry were based on human data. Wall volumes were obtained from Doherty et al. (15). $A_{m,ref}$ was found assuming wall thickness at mid-ejection of 1.3 cm for LVfw (52), 1.1 cm for septum (52), and 0.4 cm for RVfw (15) (Table 1).

Adaptation of electromechanical properties (in the present study, specific conductance of L-type Ca$^{2+}$ current) requires proper bound-
were related to intracellular and extracellular conductivities ($g_{\text{int}}$ and $g_{\text{ext}}$ in Table 1).

To model ionic currents and calcium handling in ventricular tissue, we applied the 2006 model of ten Tusscher et al. (54, 55). The total ionic current was given by

$$I_{\text{ion}} = I_{\text{Na}} + I_{\text{Kl}} + I_{\text{to}} + I_{\text{Kr}} + I_{\text{Ks}} + I_{\text{CaL}} + I_{\text{NaCa}} + I_{\text{NK}}$$

where $I_{\text{Na}}$ is fast Na$^+$ current, $I_{\text{Kl}}$ is inward rectifier K$^+$ current, $I_{\text{to}}$ is transient outward K$^+$ current, $I_{\text{Kr}}$ is rapid delayed rectifier K$^+$ current, $I_{\text{Ks}}$ is slow delayed rectifier K$^+$ current, $I_{\text{CaL}}$ is L-type Ca$^{2+}$ current, $I_{\text{NaCa}}$ is Na$^+$/Ca$^{2+}$ exchanger (NCX) current, $I_{\text{NaK}}$ is Na$^+$/K$^+$ pump current, $I_{\text{CaL}}$ is Ca$^{2+}$ pump current, $I_{\text{Kp}}$ is K$^+$ pump current, and $I_{\text{NaCa}}$ and $I_{\text{NaK}}$ are background Ca$^{2+}$ and Na$^+$ currents (54, 55). The main difference between the 2004 and 2006 model of ten Tusscher et al. (55, 56) lies in the formulation of calcium dynamics and $I_{\text{CaL}}$. The 2006 model includes subspace calcium dynamics that controls $I_{\text{CaL}}$ and calcium-induced calcium release (CICR), modeled with a four-state Markov model for the ryanodine receptor (RyR). In addition, both fast and slow voltage-gated inactivation of $I_{\text{CaL}}$ are included (55).

For each ventricular wall ($RVfw$, septum, LVfw), electromechanical behavior of the midwall was assumed. The midwall was defined as the surface through the wall such that wall mass on the endocardial site was equal to wall mass on the epicardial site. The model of ten Tusscher et al. (55) distinguishes between endocardial, midwall, and epicardial cells, which differ in volume 25% epicardial cell).

Because the midwall in our model is more located toward the epicardium, we have chosen to model cellular electrophysiology in between the midwall cell and the epicardial cell (75% midwall cell and 25% epicardial cell).

In the model of ten Tusscher et al. (54, 55), the epicardial, midwall, and endocardial cells differ in specific conductance of $I_{\text{Na}}$, an $I_{\text{Kr}}$ ($G_{\text{Kr}}$, and $G_{\text{Na}}$, respectively). In the present study, $G_{\text{Na}}$ = 0.294 nS/PF is equal to the value used by ten Tusscher et al. (55) for epicardial and midwall cells, and $G_{\text{Kr}}$ = 0.172 nS/PF is in between the value for epicardial cells (0.392 nS/PF) and midwall cells (0.098 nS/PF) (55). To investigate the sensitivity of our model with respect to variation in specific conductance of potassium currents, we also performed a series of simulations in which $G_{\text{Na}}$ and $G_{\text{Kr}}$ were equal to values chosen for endocardial, midwall, and epicardial cells. Computational aspects of electrophysiology are discussed in Appendix A.

### Cardiac electrophysiology

Ventricular electrophysiology was modeled using our previously published bidomain model (26, 27). As described above, electromechanical behavior of a ventricular wall was modeled by a serial arrangement of mechanically and electrically coupled myocardial segments. All segments within a wall could be either activated simultaneously or as a consequence of simulated impulse propagation. In the second case, activation time of a segment depended on the distance to the site of electrical stimulation and the bidomain parameters (Table 1).

The physiological state of each segment was defined by the intracellular potential ($V_{\text{int}}$), the extracellular potential ($V_{\text{ext}}$), and the state of the cell membrane, which was expressed in gating variables and ion concentrations. The membrane potential was defined by $V_{\text{mem}} = V_{\text{int}} - V_{\text{ext}}$. Exchange of current between the intracellular and extracellular domains occurred as transmembrane current ($I_{\text{trans}}$), which consisted of ionic currents ($I_{\text{ion}}$) and capacitive currents:

$$I_{\text{trans}} = \chi \left( C_{\text{mem}} \frac{dV_{\text{mem}}}{dt} + I_{\text{ion}} \right),$$

where $\chi$ is the ratio of membrane surface to tissue volume and $C_{\text{mem}}$ is membrane capacitance per unit of membrane surface (Table 1). Intracellular and extracellular currents between neighboring segments were related to intracellular and extracellular conductivities ($g_{\text{int}}$ and $g_{\text{ext}}$ in Table 1).

### Table 1: Model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
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<tbody>
<tr>
<td>$V_{\text{wall,LVfw}}$</td>
<td>Wall volume of LVfw</td>
<td>101 ml</td>
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<tr>
<td>$A_{\text{mem,septum}}$</td>
<td>Reference midwall surface area of LVfw</td>
<td>77 cm$^2$</td>
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<tr>
<td>$V_{\text{wall,septum}}$</td>
<td>Wall volume of septum</td>
<td>50 ml</td>
</tr>
<tr>
<td>$A_{\text{mem,septum}}$</td>
<td>Reference midwall surface area of septum</td>
<td>46 cm$^2$</td>
</tr>
<tr>
<td>$V_{\text{wall,RVfw}}$</td>
<td>Wall volume of RVfw</td>
<td>42 ml</td>
</tr>
<tr>
<td>$A_{\text{mem,RVfw}}$</td>
<td>Reference midwall surface area of RVfw</td>
<td>111 cm$^2$</td>
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<td>CO</td>
<td>Cardiac output</td>
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<td>MAP</td>
<td>Mean arterial pressure</td>
<td>12.2 kPa</td>
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<td>$t_{\text{cycle}}$</td>
<td>Cardiac cycle time</td>
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<td>$g_{\text{mem}}$</td>
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<tr>
<td>$g_{\text{ext}}$</td>
<td>Extracellular conductivity</td>
<td>3.56 mS/cm</td>
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<td>$C_{\text{mem}}$</td>
<td>Membrane capacitance</td>
<td>1.0 $\mu$F/cm$^2$</td>
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<td>$f_{\text{trans}}$</td>
<td>Scaling factor for contractile element</td>
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<tr>
<td>$v_{\text{max}}$</td>
<td>Maximum velocity of sarcomere</td>
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<td>$c_{\text{v}}$</td>
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<td>$f_{\text{SE,els}}$</td>
<td>Scaling factor for series elastic element</td>
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<td>Material constant for series elastic element</td>
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<td>Scaling factor for parallel elastic element</td>
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<td>$f_{\text{SE,mus}}$</td>
<td>Material constant for titin</td>
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<td>$f_{\text{SE,collagen}}$</td>
<td>Material constant for collagen</td>
<td>36 $\mu$m$^{-1}$</td>
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<td>$l_{\text{D}}$</td>
<td>Reference length of parallel elastic element</td>
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<tr>
<td>$l_{\text{Fray,collagen}}$</td>
<td>Reference length of collagen</td>
<td>2.2 $\mu$m</td>
</tr>
</tbody>
</table>

RVfw, right ventricular free wall; LVfw, left ventricular free wall.
where \( v_{\text{max}} \) is maximum velocity of sarcomere shortening and \( c_i \) is a constant describing the shape of the hyperbolic relationship (22) (Table 1). \( F_{\text{norm}} \), related to \([\text{Ca}^{2+}]_i\), and \( l_{\text{sa}} \), was modeled by model 5 from Rice et al. (46) with parameters obtained from Rice et al. (44).

First Piola-Kirchhoff stress present in the series elastic element \((T_{\text{SE}})\) was determined by the average cross-bridge length, \( l_{\text{SE}} = l_{\text{s}} - l_{\text{sa}} \), and the number of active cross-bridges, which was assumed to be proportional to \( F_{\text{norm}} \):

\[
T_{\text{SE}} = f_{\text{SE}}F_{\text{norm}}(\exp(k_{\text{SE}}F_{\text{SE}}) - 1),
\]

where \( f_{\text{SE}} \) is a scaling factor and \( k_{\text{SE}} \) is a material constant (Table 1).

Stress generated by the PE \((T_{\text{PE}})\) was the summation of stress generated by titin \((T_{\text{PE},\text{titin}})\) and stress generated by collagen \((T_{\text{PE},\text{collagen}})\), which were defined by

\[
T_{\text{PE},\text{titin}} = f_{\text{PE}}(k_{\text{PE},\text{titin}}(l_{i} - l_{0})) - 1),
\]

\[
T_{\text{PE},\text{collagen}} = f_{\text{PE}}(k_{\text{PE},\text{collagen}}(l_{i} - l_{0})),
\]

where \( f_{\text{PE}} \) is a scaling factor, \( k_{\text{PE},\text{titin}} \) and \( k_{\text{PE},\text{collagen}} \) are material constants describing the elasticity of titin and collagen, and \( l_{0} \) and \( l_{0,\text{collagen}} \) are reference lengths (Table 1). First Piola-Kirchhoff stress generated by the segment \((T_{\text{segment}})\) was the sum of stress generated in the parallel elastic and in the contractile elements. In summary, it holds for the three-element model:

\[
G_{\text{Cal,n}} = \begin{cases} 
G_{\text{Cal,n}} + 0.002 \cdot G_{\text{Cal,ref}} & \text{if } W_{\text{ext,n}} < 0.99 \cdot W_{\text{ext,ref}} \text{ and } G_{\text{Cal,n}} < 1.2 \cdot G_{\text{Cal,ref}} \\
G_{\text{Cal,n}} - 0.002 \cdot G_{\text{Cal,ref}} & \text{if } W_{\text{ext,n}} > 1.01 \cdot W_{\text{ext,ref}} \text{ and } G_{\text{Cal,n}} > 0.8 \cdot G_{\text{Cal,ref}} \\
G_{\text{Cal,n}} & \text{otherwise}
\end{cases}
\]

To ensure that \( G_{\text{Cal,n}} \) was in steady state for each segment \( n \), 400 cardiac cycles were simulated. In the steady state, each segment \( n \) either had reached the target value \( W_{\text{ext,n}} \) or had a \( G_{\text{Cal,n}} \) that had reached its lower or upper limit (0.8 \( G_{\text{Cal,ref}} \) and 1.2 \( G_{\text{Cal,ref}} \), respectively).

In Fig. 2, the effect of varying \( G_{\text{Cal}} \) on action potential morphology, calcium transient, and \( F_{\text{norm}} \) is shown for endocardial, midwall, and epicardial cells as modeled by ten Tusscher et al. (55) as well as for our settings of \( G_{\text{Ca}} \) and \( G_{\text{in}} \). We set \( G_{\text{Cal}} \) to 80%, 100%, and 120% of the default value, and \( l_{\text{sa}} \) was set to 2.2 \( \mu \text{m} \). Action potentials were generated by application of a stimulus current of \(-38 \text{ pA/pF} \) during 1 ms with a stimulus interval of 1,000 ms. Data are shown for the fifteenth action potential.

Simulation setup. To investigate the effect of remodeling of \( G_{\text{Cal}} \) on local electromechanical function as well as on global LV pump function, a series of simulations was performed consecutively: 1) normal sinus rhythm, 2) acute LBBB (without MEC), 3) sustained LBBB (with MEC), 4) acute CRT (without MEC), and 5) sustained CRT (with MEC). During normal sinus rhythm and acute LBBB, all segments had the default value for \( G_{\text{Cal}} \) (55). Then, \( G_{\text{Cal}} \) was adapted by MEC during sustained LBBB. These new settings for \( G_{\text{Cal}} \) were then retained during acute CRT because, in clinical practice, CRT is usually applied in patients with chronic LBBB. Finally, \( G_{\text{Cal}} \) was adapted by MEC during sustained CRT.

Normal sinus rhythm was simulated by simultaneous activation of all segments at 0 ms, i.e., 155 ms after stimulation of the right atrium (Fig. 3A). Abnormal impulse propagation, as occurs in LBBB, was simulated by electrically stimulating the middle of the septum and scaling conductivity parameters so that it took 40 ms for the action potential to propagate to the junction with the RVfw and the LVfw and another 80 ms to activate the most remote part of the LVfw. As a consequence, total activation time increased to 120 ms. This degree of dyssynchrony is similar to that used in a previous simulation study by Lumens et al. (34), albeit with a small time delay between RVfw and septum. Moreover, the 120 ms in the model of transmurally averaged activation times matches with the QRS duration of \(-150 \text{ ms} \) in human with complete LBBB (53). During LBBB, RVfw electrical activation was simulated as in normal sinus rhythm (Fig. 3B).

Biventricular pacing during CRT was modeled by simultaneous stimulation of the septum and the lateral site of the LVfw using the same conductivity parameters as during LBBB. To model prolonged duration of RVfw activation during biventricular pacing compared with sinus rhythm (57), impulse propagation was simulated by stimulating the lateral site of the RV free wall. Using the same conductivity parameters, total RVfw activation time was 32 ms (Fig. 3C).

RESULTS

Cellular behavior. As an example of the effect of MEC on cellular behavior, Fig. 4 shows membrane potential \((V_{\text{mem}})\), calcium transient \(([\text{Ca}^{2+}]_i)\), and normalized contractile force \((F_{\text{norm}})\) for the center segments of septum and LVfw during acute and sustained LBBB. During acute LBBB, action potentials and calcium transients of the septal and the LVfw segments were similar, but, because of the delayed electrical

\[
T_{\text{CE}} = T_{\text{SE}} + T_{\text{PE,titin}} + T_{\text{PE,collagen}}.
\]

A computational scheme to solve the equations describing myofiber mechanics is derived in Appendix B.

Mechano-electrical coupling. MEC was applied by increasing or decreasing specific conductance of the L-type Ca\(^{2+}\) current \((G_{\text{Cal}})\) when external work \((W_{\text{ext}})\) was below or above the target value, respectively. Adaptation of \(G_{\text{Cal}}\) was done automatically during the simulations. After each cardiac cycle, \(W_{\text{ext}}\), defined as the area of the local stress-strain loop, was computed for each segment, and \(G_{\text{Cal}}\) was adjusted. In case segmental \(W_{\text{ext}}\) was below the target value, \(G_{\text{Cal}}\) was augmented, allowing increase of L-type Ca\(^{2+}\) current \((I_{\text{Ca,L}})\) for that segment. In case \(W_{\text{ext}}\) was above the target value, \(G_{\text{Cal}}\) was decreased. The target value for \(W_{\text{ext}}\) was based on the assumption that the ventricles in total generate 1.5 J work per beat. With a total ventricular wall volume of 193 ml (Table 1), this leads to target external work \((W_{\text{ext,ref}})\) of 7.8 kJ/m^3.

In the present study, \(G_{\text{Cal}}\) was allowed to deviate \(-\pm 20\%\) from the default value. This range was based on experimental results from Aiba et al. (2), who measured \(I_{\text{Ca,L}}\) in control dogs and in dogs with DHF. They measured an increase in \(I_{\text{Ca,L}}\) amplitude in the LV anterior wall \((-4.0 \pm 0.2 \text{ pA/pF} \text{ in control and } -4.6 \pm 0.4 \text{ pA/pF} \text{ in DHF})\) and a decrease in \(I_{\text{Ca,L}}\) amplitude in the LV lateral wall \((-3.8 \pm 0.1 \text{ pA/pF} \text{ in control and } -3.2 \pm 0.2 \text{ pA/pF} \text{ in DHF})\).

Adaptation of \(G_{\text{Cal}}\) was implemented as follows. Initially, \(G_{\text{Cal,n}} = G_{\text{Cal,ref}}\) for each segment \(n\), with \(G_{\text{Cal,ref}}\) the reference value (55). Each time a new cardiac cycle started, \(G_{\text{Cal,n}}\) was adapted as follows:

\[
G_{\text{Cal,n}} = \begin{cases} 
G_{\text{Cal,n}} + 0.002 \cdot G_{\text{Cal,ref}} & \text{if } W_{\text{ext,n}} < 0.99 \cdot W_{\text{ext,ref}} \text{ and } G_{\text{Cal,n}} < 1.2 \cdot G_{\text{Cal,ref}} \\
G_{\text{Cal,n}} - 0.002 \cdot G_{\text{Cal,ref}} & \text{if } W_{\text{ext,n}} > 1.01 \cdot W_{\text{ext,ref}} \text{ and } G_{\text{Cal,n}} > 0.8 \cdot G_{\text{Cal,ref}} \\
G_{\text{Cal,n}} & \text{otherwise}
\end{cases}
\]

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activation, the LVfw segment was more prestretched, leading to a higher $F_{\text{norm}}$ (Frank-Starling mechanism). During sustained LBBB, MEC reduced the intraventricular differences in external work by increasing $G_{\text{CaL}}$ for the septal segment and decreasing $G_{\text{CaL}}$ for the LVfw segment. This process led to an increased Ca$^{2+}$/H$^{+}$ transient and $F_{\text{norm}}$ in the septal segment and a decreased Ca$^{2+}$/H$^{+}$ transient and $F_{\text{norm}}$ in the LVfw segment. In addition, action potential duration (APD-60mV) increased by 20 ms in the septal segment and decreased by 27 ms in the LVfw segment, such that repolarization of the two segments occurred more synchronously in the sustained LBBB simulation.

Stress and strain. Figure 5 shows natural strain and Cauchy stress–natural strain relations, averaged over the septum and over the LVfw. During normal sinus rhythm, shape and area of the septal and LVfw stress-strain loops were similar, i.e., nearly the same amount of $W_{\text{ext}}$ was generated. During acute LBBB, the stress-strain loop area became larger in the late-activated LVfw and negative in the early-activated septum (figure-of-eight loop). During sustained LBBB, MEC led to an increase in stress-strain loop area for the septum. However, $W_{\text{ext}}$ in the septum was still smaller than normal. Moreover, after the initial increase of the loop area of the LVfw with acute LBBB, a decrease was induced by MEC. Upon starting CRT, $W_{\text{ext}}$ was larger in the septum than in the LVfw, but this difference nearly vanished during sustained CRT.

Effect of MEC during LBBB and CRT. Figure 6 displays the distribution of $W_{\text{ext}}$, $G_{\text{CaL}}$, APD-60mV, and time of repolarization ($t_{\text{repol}}$) during LBBB (left) and CRT (right) across the LV myocardium. With acute LBBB, $W_{\text{ext}}$ decreased in all septal segments and increased in all LVfw segments to a degree that was related to activation time. During sustained LBBB, MEC increased $W_{\text{ext}}$ in the septum, but for most septal segments target value $W_{\text{ext,ref}}$ was not reached because the maximum allowed increase of $G_{\text{CaL}}$ (120% of baseline) was not sufficient to overcome the effect of early onset of contraction. On the other hand, MEC was able to reduce $W_{\text{ext}}$ to the target value for all LVfw segments. As a consequence, average $W_{\text{ext}}$ generated by all LV segments together reduced from 8.4 kJ/m$^3$ to 7.2 kJ/m$^3$. With onset of CRT, $W_{\text{ext}}$ increased in most septal segments, whereas it decreased in most LVfw segments, but average $W_{\text{ext}}$ remained 7.2 kJ/m$^3$. During sustained CRT, MEC led to normal $W_{\text{ext}}$ for all segments of the septum and the LVfw, except for the early-activated segments in the LVfw. This led to an increase of average work to 7.3 kJ/m$^3$.

MEC-induced changes in $G_{\text{CaL}}$ affected APD-60mV, causing a reduction of APD-60mV in the late-activated LVfw and an increased APD-60mV in the early-activated septum during sustained LBBB. These changes consequently led to a smaller dispersion of repolarization during sustained LBBB compared with acute LBBB. Similarly, APD-60mV increased near the pacing sites during sustained CRT, also reducing dispersion of repolarization.

Cardiac function. Figure 7 shows tracings of aortic and LV pressure, LV volume, and aortic flow velocity, as calculated by

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**Fig. 2.** Effect of changes in expression of L-type Ca$^{2+}$/H$^{+}$ current ($I_{\text{CaL}}$) for epicardial, midwall, and endocardial cell types as defined by ten Tusscher et al. (55) compared with the cell type applied in the present study (transient outward K$^{+}$ conductance, $G_{\text{to}} = 0.294$ nS/pF and slow delayed rectifier K$^{+}$ conductance, $G_{Ks} = 0.172$ nS/pF). $I_{\text{CaL}}$ was set to 120%, 100%, and 80% of its default value. To generate an action potential, a stimulus current of $-38$ pA/pF was applied during 1 ms with a stimulus interval of 1,000 ms. Results are shown for the 50th action potential. $V_{\text{mem}}$, membrane potential; [Ca$^{2+}$]$_{\text{i}}$, intracellular calcium concentration; $F_{\text{norm}}$, normalized contractile force; $l_{\text{si}}$, internal sarcomere length = 2.2 $\mu$m.
the model. With acute LBBB, systolic LV and aortic pressure decreased from 129 to 126 mmHg and peak aortic flow velocity from 1.22 to 1.12 m/s, whereas LV end-diastolic volume (EDV) increased from 132 ml to 137 ml. With sustained LBBB, systolic pressure further decreased to 121 mmHg and peak aortic flow velocity to 0.88 m/s, whereas EDV further increased to 153 ml, indicating further deterioration of LV function. Acute CRT increased systolic pressure to 124 mmHg and peak aortic flow velocity to 1.04 m/s, whereas EDV remained at 152 ml. Sustained CRT had no further effect on systolic pressure and aortic flow velocity. However, EDV decreased from 152 ml to 148 ml, which indicates improvement in function.

Figure 8 summarizes some of the previously mentioned results, depicting that MEC reduced the dispersion in $W_{ext}$ and $I_{rep}$ by $\sim 50\%$ during sustained LBBB and during sustained CRT compared with the respective acute phases. With LBBB, MEC led to a further deterioration of LV function as indicated by a decrease in stroke work and an increase in EDV compared with acute LBBB. Following the acute hemodynamic improvement by CRT, MEC further improved LV function, as evidenced especially by the decrease in EDV compared with acute CRT.

Figure 9 illustrates the contribution of the three ventricular walls to the total amount of $W_{ext}$ generated by the ventricles. During normal sinus rhythm, the differences in $W_{ext}$ generated by the ventricular walls reflect the differences in wall volume (42, 50, and 101 ml for RVfw, septum, and LVfw, respectively). During acute LBBB, $W_{ext}$ increased for the LVfw, whereas it decreased to zero in the septum. Note that $W_{ext}$ in the RV wall decreased, whereas total ventricular work increased, indicating that contraction in the LVfw also supports RV function. The increase in $W_{ext}$ for the LVfw diminished during sustained LBBB, but in the septum the normal value of $W_{ext}$ was not reached, which explains deterioration of function and reduction in LV stroke work (Fig. 8). During acute CRT, $W_{ext}$ increased for the septum and decreased for the LVfw. A nearly normal distribution of $W_{ext}$ was obtained during sustained CRT.

**MEC for epicardial, midwall, and endocardial cell types.** To investigate the sensitivity of MEC in our model for variation in specific conductance of potassium currents, we performed an additional series of simulations with MEC in which $G_{Ks}$ and $G_{Ca}$ were set to values for epicardial, midwall, and endocardial cell types as proposed by ten Tusscher et al. (55). The only difference between epicardial and endocardial cell types is the value for $G_{Ko}$. As can be seen in Fig. 2, the smaller amount of $I_{Ca}$ in the endocardial cell type leads to a smaller peak $I_{Ca,L}$, but there is no significant difference in $Ca^{2+}$ transient and $F_{norm}$. Also with MEC, no significant differences in $Ca^{2+}$ transient, $F_{norm}$, or cardiac function between endocardial and epicardial cell types were observed (not shown).

Figure 10 shows $V_{mem}$, $[Ca^{2+}]_i$, and $F_{norm}$ for epicardial and midwall cell types. The lower value for $G_{Ks}$ in the midwall cell type results in an increased calcium transient and a larger difference in contractile force between the septum and the LVfw during acute LBBB. During sustained LBBB, contractile force generated by the LVfw is still larger than contractile force generated by the septum, indicating that MEC has a somewhat different effect compared with the epicardial cell type. Regarding cardiac function, for both cell types the same trend as described for our setting of $G_{Ks}$ was observed: MEC lead to a decrease in LV stroke work and an increase in EDV compared with acute LBBB. During sustained CRT, LV stroke work increased, and EDV decreased compared with acute CRT (not shown). Thus, regardless of the value for $G_{Ks}$, LV function deteriorated during sustained LBBB, whereas it improved during sustained CRT.

**DISCUSSION**

Our simulations illustrate that long-term cardiac MEC may explain the gradual worsening of cardiac function during LBBB as well as the gradual improvement of cardiac pump function after onset of CRT, whereas our predicted molecular and electrophysiological changes are in line with experimental

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**Figure 1:** Schematic overview of the activation sequences. A: normal sinus rhythm, simultaneous electrical activation of RVfw, septum, and LVfw. B: left bundle-branch block (LBBB), slow conduction for septum and LVfw. C: cardiac resynchronization therapy (CRT), slow conduction for RVfw, and simultaneous activation of septum and LVfw from lateral site.

**Figure 2:** Normal and LBBB distribution of $V_{mem}$, $I_{Ca}$, and $F_{norm}$ for epicardial and midwall cell types. The lower value for $G_{Ks}$ in the midwall cell type results in an increased calcium transient and a larger difference in contractile force between the septum and the LVfw during acute LBBB. During sustained LBBB, contractile force generated by the LVfw is still larger than contractile force generated by the septum, indicating that MEC has a somewhat different effect compared with the epicardial cell type. Regarding cardiac function, for both cell types the same trend as described for our setting of $G_{Ks}$ was observed: MEC lead to a decrease in LV stroke work and an increase in EDV compared with acute LBBB. During sustained CRT, LV stroke work increased, and EDV decreased compared with acute CRT (not shown). Thus, regardless of the value for $G_{Ks}$, LV function deteriorated during sustained LBBB, whereas it improved during sustained CRT.
and clinical observations. Therefore, MEC may serve as a framework for a more integrative understanding of remodeling processes involved in the asynchronous and the resynchronized heart.

In dyssynchronous and resynchronized hearts, MEC can explain a number of changes, such as the regionally different changes in APD, the change in dispersion of repolarization, and the change in pump function (stroke work, EDV) during chronic LBBB and CRT. In canine models of sustained LBBB, worsening of cardiac pump function as well as APD changes have been observed (51, 59). Regionally different changes in ICaL were seen in dogs with tachypacing-induced heart failure in combination with LBBB (2). There are also experimental data on the effects of CRT, including acutely improving pump function followed by ongoing improvement in the long run (58). Yu et al. (61) showed in patients with CRT a continuing increase in pump function following the acute hemodynamic effect of CRT. They also found a two-stage decrease after terminating CRT 3 mo after its start. Also, Delnoy et al. (14) showed gradual increase of ejection fraction during a 2-yr

![Graphs showing the effect of MEC during LBBB and CRT](image)

Fig. 4. Effect of MEC during LBBB. V_{norm}, [Ca^{2+}], and F_{norm} for acute and sustained LBBB. Results are shown for the center segments of septum and LVfw. MEC increases G_{CaL} for the septal segment, thereby increasing action potential duration (APD), Ca^{2+} transient, and F_{norm}. The opposite occurs for the LVfw segment.

![Graphs showing the effect of MEC on natural strain and stress-strain relation](image)

Fig. 5. Effect of MEC on natural strain and stress-strain relation, averaged over the septum and over the LVfw. MEC leads to increased contraction of the septum and less contraction of the LVfw during sustained LBBB compared with acute LBBB. Consequently, also the stress-strain loops in the 2 regions become more similar. Also during CRT, MEC leads to more synchronized relaxation and more similar stress-strain areas. Arrows in the stress-strain relation for acute LBBB indicate direction of time (figure-of-eight loop).
follow-up study of CRT, Aiba et al. (2) showed in their dysssynchronously failing hearts that CRT normalized the distribution of $I_{CaL}$, calcium transient, and APD. Thus a large number of model predictions are supported by experimental and clinical evidence, supporting the validity of our model.

In a previous study, we used an earlier version of our model representing only the left heart and systemic circulation but with the same form of MEC. With that model, we were able to explain, not only the relatively uniform distribution of strains despite the moderate extent of asynchrony in electrical activation, but also the concordant T-wave during normal sinus rhythm as well as the T-wave changes during T-wave memory (20). In the present study, we found that MEC also leads to less dispersion in repolarization and better cardiac function in sustained CRT. Although an electrocardiogram cannot be deferred from this simplified model, increase in APD$_{60mV}$ in early-activated regions and a decrease in APD$_{60mV}$ in late-activated regions as shown in Fig. 6 would likely lead to a less concordant (or possibly discordant) T-wave. The predictions on electrical remodeling in CRT are supported by recent clinical studies. In one study, it was found that the amplitude of the T-wave decreases with longer duration of LBBB in patients (48), whereas our group confirmed electrical remodeling in patients with CRT by demonstrating the occurrence of T-wave memory in these patients (60).

Possibly the most interesting and intriguing result of the present simulation study is that a local electromechanical adaptation process, designed to create uniform distribution of mechanical myofiber workload, can lead to worsening of global pump function in the asynchronous heart. The explanation for this paradoxical finding is that, during the severe dyssynnchrony in LBBB, the MEC-induced reduction in external work in late-activated LV free wall regions is not fully compensated by the increase in work in the opposing early-activated septum. This property is related to the assumption that $G_{CaL}$ can only change to a moderate degree in response to altered mechanical work. This assumption is based on experimental observations (2) that, compared with control dogs, $I_{CaL}$ in canine hearts with DHF was ~20% higher in the early-activated anterior wall and ~20% lower in the late-activated lateral wall. Also, our previous modeling study (20) revealed that allowing a maximum deviation of 25–50% around the normal value leads to estimations of electrophysiological and functional parameters that are close to clinical observations (20). Although in our previous study it was shown that a full compensation of pump function can only be achieved by a multifold increase in $G_{CaL}$ in early-activated regions, limiting the maximal adaptation to ±20% as used in the present study, will alter the outcome in pump function quantitatively but not qualitatively.

Closer observation of the model predictions shows why an apparently functional system of adaptations, like creating uniform distribution of external work, has adverse effects in LBBB hearts. In these hearts, MEC causes a reduction in $I_{CaL}$ in the late-activated, hyperdynamic LVfw. The septum, being approximately half the size of the LVfw, cannot compensate for the loss of work in the LVfw (Fig. 6) because this would require a much larger increase in $W_{ext}$ than can be achieved by an increase in $I_{CaL}$ within physiological range (2, 20). Experimental studies demonstrated that sustained LBBB leads to hypertrophy of the late-activated lateral wall (58, 59). Although we did not take this kind of structural adaptation into account in our simulations, it should be noted that a change in muscle mass alone cannot explain the electrophysiological

![Fig. 6. Distribution of $W_{ext}$, maximum $G_{CaL}$, APD$_{60mV}$, and time of repolarization ($t_{repol}$) during LBBB and CRT along all segments of the LV wall, represented as if the LV wall is cut open at the mid septum. Results are shown for septum (shaded background) and LVfw (white background) without (acute) and with MEC (sustained). Asterisks indicate pacing sites and arrows indicate direction of impulse propagation. Time of fusion of depolarization waves is indicated at arrow heads. Black lines indicate acute LBBB/CRT, and gray lines indicate sustained LBBB/CRT. Dashed lines indicate target $W_{ext} = 7.8 kJ/m^2$. Differences in APD for the same values of $G_{CaL}$ are the result of electrotonic effects, which increased APD at pacing sites and decreased APD in remote regions and in regions where 2 depolarization waves collided.](http://ajpheart.physiology.org/)

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changes predicted by the model and observed in the animal and clinical studies as described above.

The model simulations also demonstrate that there may be two mechanisms of action for CRT, acute recoordination of contraction and long-term electromechanical remodeling. After all, acute CRT improved cardiac pump function, whereas contraction became more disperse, and further improvement occurred without further resynchronization. Given the observation that the chronic effect of CRT may be as large as the acute effect, at least regarding ejection fraction (14), this study indicates the significant importance to further investigate electromechanical remodeling in CRT hearts. Summarizing, it appears that MEC can explain various data on electrophysiology, contraction, and pump function in dysynchronous and resynchronized hearts.

Considerations regarding the modeling approach. To the best of our knowledge, our model is the first to integrate cardiac electrophysiology, mechanics, and hemodynamics as well as MEC in a biventricular cardiac model. The model of the human action potential used in the present simulation study is the 2006 model of ten Tusscher and Panfilov (TP2006) (55), which is often applied in large-scale models of human cardiac electrophysiology. Other models of the human ventricular action potential are Priebe-Beuckelmann (PB1998) (41), ten Tusscher-Noble-Noble-Panfilov (TNNP2004) (54), Iyer-Mazhari-Winslow (IMW2004) (23), Bueno-Orovio-Cherry-Fenton (BCF2008) (11), Grandi-Pasqualini-Bers (GPB2010) (18), and O’Hara-Virág-Varró-Rudy (OVVR2011) (38). Elshiriff and Cherry (16) compared action potentials of epicardial formulations of all these models. They concluded that all models differ in formulation and are usually based on different experimental data sets from humans. For the present simulation study, a good representation of Ca$^{2+}$ dynamics is important, as it is influenced by changes in the L-type Ca$^{2+}$ current. TP2006, GPB2010, and OVVR2011 describe ion concentrations and state variables for different subspaces. TP2006 contains a description of calcium dynamics in the cytoplasmic subspace and sarcoplasmic reticulum. Calcium in the subspace is buffered, and a diffusion flux is included to allow calcium released in the subspace to flow to the bulk cytoplasm. L-type Ca$^{2+}$ current and ryanodine calcium release current inject calcium into the subsarcolemmal subspace, and, in turn, their dynamics are influenced by the subspace calcium concentration (55). GPB2010 and OVVR2011 have similar descriptions for calcium handling. Action potential shape and duration of the TP2006, GPB2010, and OVVR2011 models are comparable, but Ca$^{2+}$ transients differ significantly among the three models. Peak Ca$^{2+}$ concentration of the GPB2010 model is 0.4 μM, whereas it is about 0.8 μM for OVVR2011 and TP2006 (epicardial cell type).

Because of the close coupling between Ca$^{2+}$ concentration and generated force, the mechanical behavior of our model may be significantly influenced by choosing a different model. Of the three models, TP2006 and OVVR2011 produce peak Ca$^{2+}$ concentrations that lead to physiological contractile forces. Both in TP2006 and in OVVR2011, inactivation of L-type Ca$^{2+}$ current is related to the calcium concentration in the cytoplasmic subspace. Because Ca$^{2+}$ transients of the

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Fig. 7. Signals of hemodynamic variables during normal sinus rhythm, acute LBBB, sustained LBBB, acute CRT, and sustained CRT. Top: aortic and LV pressure. Middle: LV volume. Bottom: aortic blood flow velocity. With acute LBBB, LV function worsens as indicated by decrease in systolic LV and aortic pressure, increase in LV end-diastolic volume (EDV), and decrease in peak aortic flow velocity. LV function deteriorates during sustained LBBB. With acute CRT, systolic pressure and aortic flow velocity increase, and during sustained CRT EDV decreases, indicating improvement of LV function.

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TP2006 and OVVR2011 models are similar, it is expected that mechanical behavior of our model would not significantly change if the TP2006 model would be replaced with the OVVR2011 model. Thus, for the present simulation study, similar effects of MEC with respect to cardiac function would have been found if OVVR2011 would have been used instead of TP2006.

Contraction of the sarcomere was modeled by model 5 of Rice et al. (46). Like other sarcomere models, this model is based on experimental data of rat trabeculae recorded at room temperature. Time-dependent contractile behavior of sarcomere models depends on, not only the amplitude and shape of the Ca^{2+}/H11001 transient, but also on passive stiffness (collagen and titin), sarcomere length, and sarcomere shortening velocity. These influences are taken into account in our model. The calcium transient is obtained from the 2006 model of ten Tusscher et al. (55). A similar approach was taken by Campbell et al. (12), who integrated the model of Flaim et al. (17) of canine ionic currents and calcium handling with the 2008 model of Rice et al. (45). Unfortunately, models describing contractile behavior of myocytes from larger species are at present not available. Because in our model the L-type current is affected as a result of MEC, which in turn influences the calcium transient, changes in mechanical and hemodynamic behavior in our model are to a large extent related to changes in the calcium handling. Because of a lack of experimental data, it is at present not possible to validate the integrated cell model against human data. However, as discussed above, cardiac mechanics and hemodynamics correspond well with clinical measurements.

As one of few models, our model describes the entire systemic and pulmonary circulation, providing realistic boundary conditions for cardiac mechanics that are of particular importance for the simulation of long-term MEC. Compared with other whole-heart models, our model lacks detail in ventricular geometry. However, anatomical details are assumed to be of minor importance for a proof-of-principle study, as is the present study. The advantage of the relatively small number of segments (570 in total) was that the simulation of 1,000 heart beats to simulate both (sustained) LBBB and (sustained) CRT took less than 10 h on a high-end PC. A side effect of our modeling approach is the nonrealistically sharp changes in APD-60mV for the same values of G_{Ca} observed in normal, LBBB, and CRT without MEC (acute) and with MEC (sustained). Note that dispersion of repolarization time is 0 in the normal simulation. Bottom: LV stroke work (SW) and EDV. Both during sustained LBBB and during sustained CRT, MEC reduces dispersion in W_{ext} and t_{repol}. MEC leads to deterioration of LV function during sustained LBBB as indicated by the decrease in SW and increase in EDV compared with acute LBBB. During sustained CRT, MEC improves LV function as indicated by the increase in SW and decrease in EDV compared with acute CRT.

Fig. 8. Top: dispersion (maximum – minimum) of W_{ext} and t_{repol} during normal, LBBB, and CRT without MEC (acute) and with MEC (sustained). Bottom: LV stroke work (SW) and EDV. Both during sustained LBBB and during sustained CRT, MEC reduces dispersion in W_{ext} and t_{repol}. MEC leads to deterioration of LV function during sustained LBBB as indicated by the decrease in SW and increase in EDV compared with acute LBBB. During sustained CRT, MEC improves LV function as indicated by the increase in SW and decrease in EDV compared with acute CRT.

Fig. 9. W_{ext} generated by RVfw, septum, and LVfw during normal sinus rhythm, acute LBBB, sustained LBBB, acute CRT, and sustained CRT. Differences in W_{ext} generated by RVfw, septum, and LVfw during normal reflect the differences in wall volume (42, 50, and 101 ml, respectively). During acute LBBB, W_{ext} increases for LVfw, whereas it decreases to slightly below 0 for the septum. During sustained LBBB, MEC leads to a reduction of W_{ext} in the LVfw and an increase of W_{ext} in the septum. However, reduction of W_{ext} in the LVfw is larger than the increase of W_{ext} in the septum, which explains the reduction in LV SW (Fig. 8). During acute CRT, W_{ext} increases for septum and decreases for LVfw. Normal distribution of W_{ext} is obtained during sustained CRT.

Fig. 9. W_{ext} generated by RVfw, septum, and LVfw during normal sinus rhythm, acute LBBB, sustained LBBB, acute CRT, and sustained CRT. Differences in W_{ext} generated by RVfw, septum, and LVfw during normal reflect the differences in wall volume (42, 50, and 101 ml, respectively). During acute LBBB, W_{ext} increases for LVfw, whereas it decreases to slightly below 0 for the septum. During sustained LBBB, MEC leads to a reduction of W_{ext} in the LVfw and an increase of W_{ext} in the septum. However, reduction of W_{ext} in the LVfw is larger than the increase of W_{ext} in the septum, which explains the reduction in LV SW (Fig. 8). During acute CRT, W_{ext} increases for septum and decreases for LVfw. Normal distribution of W_{ext} is obtained during sustained CRT.
The idea that mechanically induced electrical adaptations may be involved in the regulation of cardiac electrophysiology is not novel. However, whereas many investigators use the term MEC for processes that occur within a single heart beat or several beats at most, the kind of MEC proposed in our study is a much slower process, presumably acting in the order of hours to days. This kind of MEC may, for instance, underlie the differences in vector ECGs between short-term and long-term LBBB observed by Shvilkin et al. (48).

In the present study, it is assumed that adaptation of $G_{CaL}$ is triggered by changes in (external) workload. Indeed, experimental observations suggest that changes in workload induce electrical remodeling (24, 50), but the exact trigger is not yet clear. Importantly, the present study does not claim any spe-

**Fig. 6 at the junctions of RV free wall, septum, and LV free wall.**

Acute LBBB (epicardial cell type)

Sustained LBBB (epicardial cell type)

Acute LBBB (midwall cell type)

Sustained LBBB (midwall cell type)

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**Fig. 10. Effect of MEC during LBBB for epicardial and midwall cell types. $V_{mem}$, $[Ca^{2+}]_i$, and $F_{norm}$ for acute and sustained LBBB. Results are shown for the center segments of septum and LVfw. Top: epicardial cell type ($G_{Ks} = 0.392$ nS/pF). Bottom: midwall cell type ($G_{Ks} = 0.098$ nS/pF). MEC increases $G_{CaL}$ for the septal segment, thereby increasing APD, $Ca^{2+}$ transient, and $F_{norm}$. The opposite occurs for the LVfw segment.**
specific sensing mechanism. Local stretch, rather than workload, might be the trigger for MEC. After all, the amount of early-systolic prestretch is related to workload because it induces the Frank-Starling effect locally. However, prestretch by itself is not affected much by electrical remodeling (Fig. 5) and therefore is not likely to function as a regulating mechanism. Also, simulations using local stretch as trigger for MEC did not lead to stable solutions (E. Hermeling, T. Delhaas, F. Prinzen, and N. Kuijpers, unpublished data). On the other hand, \( W_{ext} \) is a result of both stress and strain. It has been suggested that changes in stress and strain are sensed by Z-disks and influence cellular signaling molecules, including protein kinase C and A that regulate L-type calcium channels (43). An alternative feedback signal that can lead to similar results is local energy consumption. Recently, it has been shown that cardiac mitochondria may play a role in electrophysiology and calcium handling in response to oxidative stress (3).

Our choice for \( G_{CaL} \) as a regulating factor for MEC does not exclude a possible role for other ionic membrane currents. In animal experiments using long-term asynchronous activation by ventricular pacing or LBBB, several changes in ionic membrane currents have been observed, including changes in \( I_{CaL} \) (40), \( I_{Ks} \) (62), \( I_{Kt} \), and \( I_{Kc} \) (37). In addition to changes in \( I_{CaL} \) and calcium handling, Aiba et al. (2) observed differences in several potassium currents, including \( I_{Ks} \), \( I_{Kt} \), and \( I_{Kc} \) in their DHF model. Although the differences in \( I_{CaL} \) and calcium transient completely disappeared with 3 wk of CRT, changes in potassium currents were only partly restored. These results suggest that the effects of CRT may be more prominent in calcium handling than in potassium currents. In addition, Aiba et al. (2) reported that changes in \( I_{CaL} \) and calcium handling were regionally different in DHF, whereas changes in potassium currents were not significantly different between regions. Our choice for modification of the specific conductance of \( I_{CaL} \) in the present simulation study was based on these experimental findings. The relatively large effect of small changes in \( I_{CaL} \) on the calcium transient and contractile force in our model is explained by the increase and decrease in storage of calcium in the sarcoplasmic reticulum during diastole, which, in turn, affects calcium release during systole. This secondary effect of changes in \( I_{CaL} \) accumulates over several heart beats.

Many changes occur in dysynchronous hearts, among others in sarco(endo)plasmic \( Ca^{2+} \)-ATPase (SERCA), RyR, and the NCX (9). These changes influence calcium handling and thus contraction. However, Aiba et al. (2) did not find significant regional differences in SERCA, RyR, and NCX. Because our concept of MEC requires regionally different responses, we did not include changes to SERCA, RyR, and NCX in the present simulation study. In addition, metabolic dysfunction has been reported by Agnetti et al. (1) in the late-activated LV lateral wall, but, to our knowledge, no data are available on regional differences. For this reason, metabolic dysfunction was not considered in the present simulation study.

In previous simulation studies, we have shown that inclusion of transmural heterogeneity of \( I_{Ks} \) and \( I_{Kt} \) (25) or remodeling of \( I_{Kc} \) instead of \( I_{CaL} \) (20) also leads to a uniform distribution of external work and T-wave concordance. Also in the present study, we performed a series of simulations in which \( G_{Ks} \) was adapted instead of \( G_{CaL} \). In these simulations, \( G_{Ks} \) could vary in between 0.098 nS/pF and 0.392 nS/pF. When \( G_{Ks} \) was adapted, changes in action potential duration were much more prominent than when \( G_{CaL} \) was adapted (Fig. 11), but the effect on cardiac function was similar (not shown). Plotnikov et al. (40) observed a shift in \( I_{CaL} \) activation and slower inactivation in canine epicardial myocytes after 3 wk of pacing from the LV epicardium. The assumed long-term MEC in this study does not specify the exact mechanism of the change in \( I_{CaL} \), i.e., number of channels, phosphorylation, or channel kinetics.

In our model, it is assumed that all segments within one ventricular wall bear the same amount of stress. This approach is valid when the ventricular walls do not contain irregularities in mechanical properties such as infarcted regions or scar tissue (4, 5). With this relatively simple geometry, we have recently shown that strain patterns can be obtained that agree with clinical measurements of strain patterns in patients with LBBB (32).

**Conclusion.** Simulations with our model of the heart and circulation predict that electromechanical remodeling reduces the amount of work generated by the late-activated LVfw, but this decrease is not fully compensated by an increase in \( W_{ext} \) generated by the early-activated septum. This results in the paradoxical situation that, during longer-lasting dyssynchrony, electromechanical remodeling causes a decrease in pump function despite the reduction in dispersion of mechanical workload and repolarization. Conversely, electromechanical remodeling optimizes cardiac pump function in less dysynchronous ventricles. Consequently, the model pinpoints two complementary mechanisms of improved pump function by CRT, acute recoordination of contraction and long-term electromechanical remodeling.

**APPENDIX A: COMPUTATIONAL ASPECTS OF ELECTROPHYSIOLOGY**

The bidomain model can be written as a coupled system of ordinary differential equations and partial differential equations (27). To compute \( V_{mem} \), the differential equations were solved using a forward Euler scheme. To compute \( V_{ext} \), a system of linear equations was solved each time step by an iterative method as described in Kuijpers et al. (27). Criteria for segment size were obtained by cable theory and considering subthreshold behavior along the cable as previously described (27). For the bidomain parameters in Table 1, a length constant of 0.09 cm was found. For proper simulation of action potential propagation, segment size was set to 0.01 cm. Note that this segment size was chosen for accurate simulation of impulse propagation and is not related to the physical dimensions of the ventricular walls.

Because we used an explicit forward Euler scheme, simulation time step \( \Delta t \) had to satisfy the stability condition as formulated by Puwal and Roth (42). For a serial arrangement of electrically coupled segments, this leads to

\[
\Delta t < \frac{\kappa_{mem}(g_{int} + g_{ext})}{2g_{int}g_{ext}} \Delta x^2,
\]

where \( \Delta x \) is segment size (0.01 cm). For the bidomain parameters defined in Table 1, this condition is satisfied when \( \Delta t < 0.13 \) ms. In the present study, we used \( \Delta t = 0.01 \) ms.

Ionic currents and concentrations were computed using a forward Euler scheme with a time step of 0.01 ms. Gating variables for the ionic currents were computed using the Rush-Larsen method (47). Computation time was reduced by increasing the simulation time step for the ionic currents and concentrations to 0.1 ms during repolarization and rest. This led to a reduction of 70% in computation time, without significant loss of accuracy (30).
A well-known deficit of membrane models is drift in intracellular Na\(^+\) concentration ([Na\(^+\)]\(_i\)) and intracellular K\(^+\) concentration ([K\(^+\)]\(_i\)) during longer-lasting simulation runs. To prevent [Na\(^+\)]\(_i\) and [K\(^+\)]\(_i\) from drifting, a regulating feedback step was performed each simulation time step \(\Delta t\) as proposed by Van Oosterom and Jacquemet (56):

\[
[\text{Na}^+]_{\text{new}} = (1 - 10^{-3} \Delta t)[\text{Na}^+]_{\text{old}} + 10^{-3} \Delta t[\text{Na}^+]_{\text{rest}},
\]

\[
[\text{K}^+]_{\text{new}} = (1 - 10^{-3} \Delta t)[\text{K}^+]_{\text{old}} + 10^{-3} \Delta t[\text{K}^+]_{\text{rest}},
\]

with [Na\(^+\)]\(_{\text{rest}}\) = 8.3 mM and [K\(^+\)]\(_{\text{rest}}\) = 137.25 mM (55).

### APPENDIX B: COMPUTATIONAL SCHEME FOR MYOFIBER MECHANICS

Ca\(^{2+}\)-force relations as well as cardiac mechanics and hemodynamics were computed using a forward Euler scheme with a time step of 0.01 ms. Ventricular mechanics and hemodynamics in our model were solved as described by Lumens et al. (33). To solve cavity mechanics, a computational scheme for a serial arrangement of mechanically coupled segments was required that allowed applying changes in overall strain with and without the advancing of simulation time. We recently published a new computational scheme for fiber mechanics (20) that was based on our previously published scheme (29). This scheme was further refined to compute myofiber mechanics for the biventricular model of the present study.

The numerical scheme to solve the equations for the three-element mechanical model was based on the scheme introduced by Solovyova et al. (49). The mechanical state of each segment was defined by \(l_s, l_a\), and \(F_{\text{norm}}\). Each simulation time step, first \(l_a\) was updated using velocity of internal sarcomere shortening \(v = -dl_a/dt\). Next, \(F_{\text{norm}}\) was computed using \(l_a\) as well as \([\text{Ca}^{2+}]_i\) obtained from the model of ten Tusscher et al. (55). Finally, \(l_s\) was computed by solving \(\Delta l_s\) as described below.

In this derivation, a fiber is defined as a serial arrangement of scaled segments. All segments have equal reference lengths \(l_0\) (expressed in cm) corresponding to reference sarcomere length \(l_0\) (expressed in \(\mu\)m), i.e., \(l_0 = \xi l_0\), where \(\xi\) is a scaling factor. First Piola-Kirchhoff stress \(T_{\text{segment}}\) generated by a single segment is equal to first Piola-Kirchhoff stress \(T_{\text{fiber}}\) generated by the fiber. Thus also \(\Delta T_{\text{segment}}\) is equal to \(\Delta T_{\text{fiber}}\). \(\Delta l_s\) for each segment is found by solving a system of equations as follows. For each individual segment, it holds \(T_{\text{segment}} = T_{\text{SE}} + T_{\text{PE}}\), which implies

\[
\frac{\partial T_{\text{SE}}}{\partial F_{\text{norm}}} \Delta F_{\text{norm}} + \frac{\partial T_{\text{SE}}}{\partial l_s} \Delta l_s + \frac{\partial T_{\text{PE,thin}}}{\partial l_s} \Delta l_s + \frac{\partial T_{\text{PE,collagen}}}{\partial l_s} \Delta l_s = \Delta T_{\text{segment}},
\]

where \(l_{\text{SE}}\) denotes the length of SE defined by \(l_{\text{SE}} = l_s - l_a\) and

\[
\frac{\partial T_{\text{SE}}}{\partial F_{\text{norm}}}/(\partial F_{\text{norm}}) + \frac{\partial T_{\text{SE}}}{\partial l_s} = f_{\text{SE}}(\exp(k_{\text{SE}}(l_s - l_a)) - 1),
\]

\[
\frac{\partial T_{\text{SE}}}{\partial l_s} = f_{\text{SE}} k_{\text{SE}} F_{\text{norm}} \exp(k_{\text{SE}}(l_s - l_a)),
\]
\[
\frac{dT_{\text{PE,thin}}}{dl_t} = f_{\text{PE,thin}} k_{\text{PE,thin}} \exp \left( k_{\text{PE,thin}} (l_s - l_{S0}) \right),
\]

\[
\frac{dT_{\text{PE,collagen}}}{dl_t} = f_{\text{PE,collagen}} k_{\text{PE,collagen}} \exp \left( k_{\text{PE,collagen}} (l_s - l_{P0,\text{collagen}}) \right).
\]

Rewriting Eq. 14 and using \( \Delta l_{SE} = \Delta l_s - \Delta l_{at} = \Delta l_s + v \Delta t \) gives an expression for \( \Delta l_s \) in \( \Delta T_{\text{segment}} \), \( \Delta t \), and \( \Delta F_{\text{norm}} \):

\[
\Delta l_s = \Delta T_{\text{SE}} - \frac{\partial T_{\text{SE}}}{\partial l_{SE}} \Delta l_{SE} - \frac{\partial T_{\text{PE,collagen}}}{\partial l_{dl}} \Delta l_{dl} - \frac{\partial T_{\text{PE,thin}}}{\partial l_t} \Delta t + \alpha \Delta T_{\text{segment}} + \beta \gamma \Delta F_{\text{norm}},
\]

where \( \alpha \), \( \beta \), and \( \gamma \) are defined by

\[
\alpha = \frac{1}{\Delta T_{\text{SE}}} + \frac{\partial T_{\text{PE,thin}}}{\partial l_t} + \frac{\partial T_{\text{PE,collagen}}}{\partial l_{dl}},
\]

\[
\beta = \frac{1}{\Delta T_{\text{SE}}} + \frac{\partial T_{\text{PE,thin}}}{\partial l_t} + \frac{\partial T_{\text{PE,collagen}}}{\partial l_{dl}},
\]

\[
\gamma = \frac{1}{\Delta T_{\text{SE}}} + \frac{\partial T_{\text{PE,thin}}}{\partial l_t} + \frac{\partial T_{\text{PE,collagen}}}{\partial l_{dl}},
\]

Actual length of scaled segment \( n \) is denoted by \( l_n \) and is defined by \( l_n = \xi l_{n,s} \). Assuming that a fiber is composed of \( N \) segments coupled in series, fiber stretch \( \lambda_{\text{fiber}} \) is defined by

\[
\lambda_{\text{fiber}} = \frac{L}{L_0} = \frac{1}{N l_0} \sum_{n=1}^{N} l_n = \frac{1}{N l_{S0}} \sum_{n=1}^{N} l_{n,s},
\]

where \( L \) and \( L_0 \) denote the actual fiber length and reference fiber length (unit cm), respectively. From equation (23), it follows that

\[
\Delta l_{\text{fiber}} = \frac{\lambda_{\text{fiber}} - 1}{L_0} = \frac{1}{N l_{S0}} \sum_{n=1}^{N} l_{n,s},
\]

Inserting Eq. 19 for each segment in equation (24) and using \( T_{\text{segment}} = T_{\text{fiber}} \) gives

\[
\Delta l_{\text{fiber}} = \frac{1}{N l_{S0}} \sum_{n=1}^{N} (\alpha_n \Delta T_{\text{fiber}} + \beta_n \Delta t + \gamma_n \Delta F_{\text{norm},n})
\]

\[
= \frac{\Delta T_{\text{fiber}}}{N l_{S0}} \sum_{n=1}^{N} \alpha_n + \frac{\Delta t}{N l_{S0}} \sum_{n=1}^{N} \beta_n + \frac{\gamma_n}{N l_{S0}} \sum_{n=1}^{N} \Delta F_{\text{norm},n}
\]

\[
= \alpha_{\text{fiber}} \Delta T_{\text{fiber}} + \beta_{\text{fiber}} \Delta t + \gamma_{\text{fiber}} \Delta F_{\text{norm,n}}.
\]

Here, \( \alpha_{\text{fiber}} \), \( \beta_{\text{fiber}} \), and \( \gamma_{\text{fiber}} \) are defined by

\[
\alpha_{\text{fiber}} = \frac{1}{N l_{S0}} \sum_{n=1}^{N} \alpha_n,
\]

\[
\beta_{\text{fiber}} = \frac{1}{N l_{S0}} \sum_{n=1}^{N} \beta_n.
\]

From Eq. 25, \( \Delta T_{\text{segment}} \) and \( \Delta T_{\text{fiber}} \) are computed by

\[
\Delta T_{\text{segment}} = \Delta T_{\text{fiber}} = \frac{\lambda_{\text{fiber}} - \beta_{\text{fiber}} \Delta t - \gamma_{\text{fiber}}}{\alpha_{\text{fiber}}},
\]

Internal sarcomere shortening velocity \( v \) needed to compute \( \Delta l_s \) from Eq. 19 is obtained as follows. Rewriting Eq. 3 and inserting definition 4 for each individual segment

\[
1 - \frac{v}{v_{\text{max}}} = \frac{T_{\text{CE}}}{f_{\text{CEF}}},
\]

from which \( v \) can be obtained by

\[
v = \frac{f_{\text{CEF}} (1 - 1/T_{\text{CE}})}{f_{\text{CEF}} - 1},
\]

Here, \( T_{\text{CE}} \) is computed from Eq. 5 and 8 by

\[
T_{\text{CE}} = T_{\text{SE}} = f_{\text{SE}} (\text{norm}) (\exp (\lambda_{\text{fiber}} - l_s - l_i) - 1).
\]

Initially, it is assumed that the electrophysiological state of all segments is resting and that \( F_{\text{norm}} = 0 \). Thus \( T_{\text{SE}} = T_{\text{CE}} = 0 \) and \( l_s = l_i \) for all segments. Stress generated by the segment must come from the parallel elastic element and is related to \( \lambda_{\text{fiber}} = \exp (\epsilon_{\text{fiber}}) - 1 \), with \( \epsilon_{\text{fiber}} \) natural strain corresponding to the initial cavity volume.

Each simulation time step, cavity volumes are updated as follows: 1) new cavity volumes for RV and LV are obtained by integrating blood flow through the valves [see Lumens et al. (33)]. 2) Natural fiber strain \( (\epsilon_{\text{fiber}}) \) for RVf, septum, and LVf is obtained from the new RV and LV cavity volumes by applying an iterative process with \( \Delta t = 0 \) to reach equilibrium of forces at the junction of the three wall segments [see Lumens et al. (33)]. In each iteration, the computational scheme described below was applied with \( \Delta t = 0 \) to compute the sarcomere length \( l_i \) for all segments. 3) Finally, the computational scheme described below was applied once more with \( \Delta t \), the actual simulation time step.

To update the mechanical state of all segments for the newly found natural fiber strain \( \epsilon_{\text{fiber}} \), the following scheme was used, with either \( \Delta t = 0 \) (step 2 above) or \( \Delta t > 0 \) (step 3 above): 1) \( \Delta l_{\text{fiber}} = \exp (\epsilon_{\text{fiber}}) - 1 \) is computed from the new fiber strain \( \epsilon_{\text{fiber}} \) and \( l_i \) from the previous iteration. 2) For each segment, internal sarcomere length \( l_i \) is computed using \( \Delta l_{\text{fiber}} = -v \Delta t \), with sarcomere shortening velocity \( v \) computed during the previous iteration. Note that \( l_i = 0 \) when \( \Delta t = 0 \). 3) For each segment, \( F_{\text{norm}} \) is updated using \( l_i \) and \( [Ca^{2+}] \), obtained from the model of ten Tusscher et al. (55). This is only done in case \( \Delta t > 0 \). 4) \( \alpha_{\text{fiber}}, \beta_{\text{fiber}}, \) and \( \gamma_{\text{fiber}} \) are computed from Eq. 26–28 using \( \alpha_n, \beta_n, \) and \( \gamma_n \) from the previous iteration, and \( F_{\text{norm}} \). 5) First Piola-Kirchhoff stress \( T_{\text{fiber}} \) and \( \Delta T_{\text{segment}} \) are computed from Eq. 29. 6) For each segment, sarcomere length \( l_i \) is computed from Eq. 19. 7) For each segment, first Piola Kirchhoff stress for SE and PE \( (T_{\text{SE}} \text{ and } T_{\text{PE}}) \) is computed from Eq. 5–7. 8) For each segment, \( v, \alpha, \beta, \) and \( \gamma \) are computed from Eq. 31 and Eq. 20–22. 9) Finally, \( \lambda_{\text{fiber}} \) is computed from Eq. 23.

GRANTS

This work was partially funded by a personal research grant within the framework of the Dr. E. Dekker program of the Dutch Heart Foundation (NHS-2012T020 to J. Lumens).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.
REFERENCES


MECHANO-ELECTRICAL COUPLING DURING LBBB AND CRT


