Mechano-Electrical Feedback during Cardiac Resynchronization Therapy?

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Abstract

Cardiac Resynchronization Therapy (CRT) has emerged as an important therapy to improve pump function in heart failure patients with left bundle branch block (LBBB). Using a multi-scale modeling approach, we investigated the effect of mechano-electrical feedback (MEF) during LBBB and CRT on cardiac function and dispersion of repolarization. Our model describes cellular electrophysiology and calcium handling as well as cardiac mechanics and hemodynamics. Ventricular electromechanics is represented by a single cardiac fiber, while physiological pressure-volume loops are obtained by simulating the systemic circulation. LBBB was simulated by activating the fiber at one end and CRT by simultaneous activation at both ends. Systolic function improved with onset of CRT, but diastolic function only improved after MEF. We conclude that MEF during LBBB may lead to an increase in dispersion of repolarization during onset of CRT, which may lead to impaired diastolic function and to ventricular arrhythmia.

1. Introduction

Cardiac Resynchronization Therapy (CRT) has emerged as an important therapy to improve pump function in patients with chronic heart failure and conduction disturbances such als left bundle branch block (LBBB) [1]. Electrical excitation of the ventricles is synchronized by simultaneously pacing both ventricles. Altered electrical activation during bi-ventricular pacing increases (transmural) dispersion of repolarization, which may lead to cardiac arrhythmia and possibly impaired filling. Long-term changes in activation leads to a form of electrical remodeling, referred to as "T-wave memory" [2]. T-wave memory is known to occur after a period of ventricular pacing, but its role during CRT is unclear. Evidence is growing that T-wave memory is induced by altered mechanical load [3–5] and thus is a form of mechano-electrical feedback (MEF). Experimental observations by Aiba *et al.* [6] suggest that local changes in the expression of L-type calcium channels may be part of this form of MEF. We hypothesize that L-type calcium channels adjust to obtain homogeneous local workload in the asynchronous ventricle and that this helps to reduce dispersion of repolarization. The aim of the present simulation study was to investigate the effects of MEF on cardiac function and dispersion of repolarization during LBBB and CRT.

2. Methods

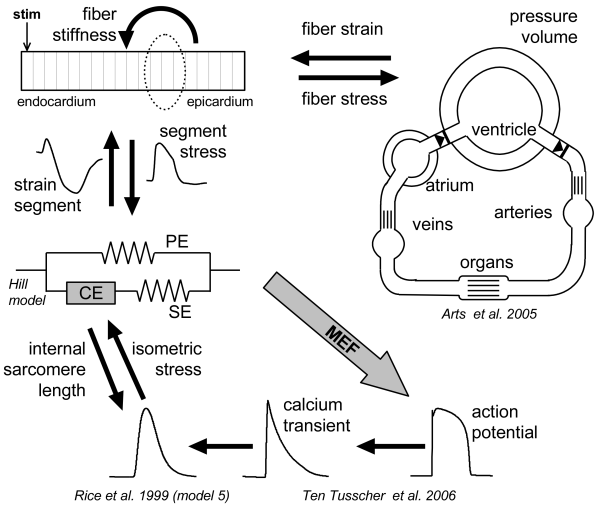

Figure 1. Schematic overview of the model. Cardiac electromechanics was described by a single fiber composed of 300 segments. Left ventricular pressure and volume were related to fiber stress and strain. Cardiac hemodynamics was modeled by placing the left ventricle in a systemic circulation describing the left atrium, valves, arteries, organs, and veins. Electrical activation was started by activating one (Normal, LBBB) or both (CRT) fiber ends. Mechano-electrical feedback (MEF) was incorporated by regulating L-type calcium current ($I_{Ca,L}$) such that a homogeneous distribution of work was obtained.

A multi-scale computer model was developed that described cellular electrophysiology and calcium handling as well as cardiac mechanics and hemodynamics (Figure 1). Ventricular electromechanics was represented by a single cardiac fiber that was composed of 300 segments that were

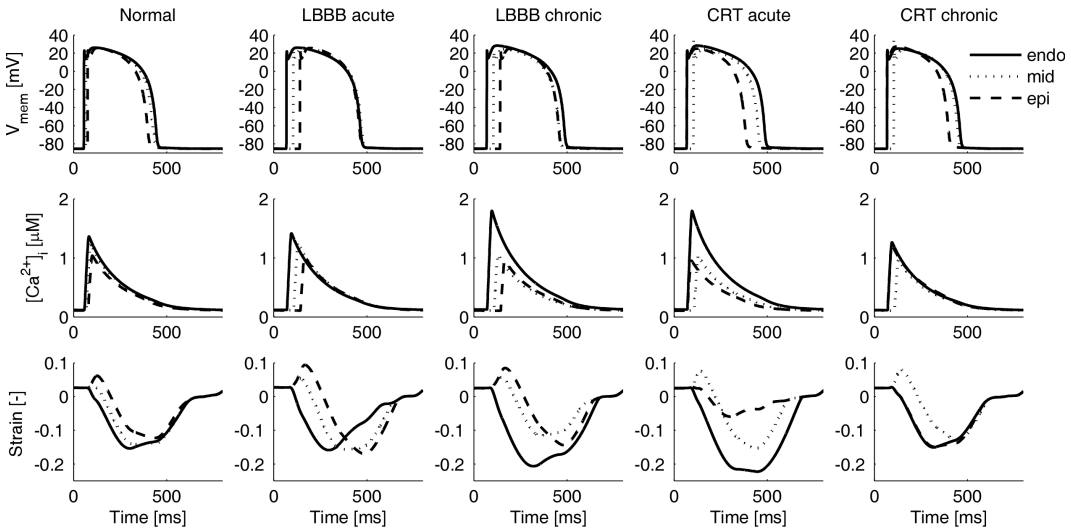

Figure 2. Membrane potential (V_{mem}), calcium transient ($[\text{Ca}^{2+}]_{\text{i}}$), and strain for three segments located at the endocardium, midwall, and epicardium of the ventricular wall. Results are shown for all five subsequent simulations.

both electrically and mechanically coupled [7–9]. Each of the segments comprised ionic membrane currents, calcium handling, and excitation-contraction coupling (ECC). Ventricular membrane behavior and calcium handling were modeled by the model of Ten Tusscher *et al.* [10, 11]. Transmural heterogeneity was accomplished by gradually varying potassium currents I_{to} and I_{Ks}, such that action potential durations were longest in the sub-endocardial (early-activated) regions, and gradually decreased towards the epicardium. Mechanical behavior was modeled by three elements. Active stress was generated by the contractile element (CE) together with the series elastic element (SE). The parallel elastic element (PE) described the stress-length relation when the segment was not stimulated. Contractile stress generated by the CE was modeled by model 5 of Rice *et al.* [12] and depended on the intracellular concentration of free calcium as well as sarcomere length.

Fiber stress and strain were converted to left-ventricular blood pressure and volume, respectively, according to the one-fiber model [13]. To obtain physiological pressure-volume relations, systemic blood circulation was modeled by the CircAdapt model [14]. Mechano-electrical feedback was incorporated as follows. During the simulation of a cardiac cycle, the amount of stroke work was computed for each segment by integrating the stress-strain loop. In the case that stroke work for a segment was below a target value of $6.7\ \text{kJ}/\text{m}^3$, L-type Ca2+ current ($I_{\text{Ca,L}}$) was upregulated, and in case stroke work was above the target value, $I_{\text{Ca,L}}$ was downregulated. This process was repeated each cardiac cycle until steady-state was reached, which was always the case within 150 cardiac cycles [8].

With this model, five subsequent simulation runs were performed. Distribution in the expression of $I_{\text{Ca,L}}$ was retained when the next run was started:

1. *Normal*:
Endocardial activation and activation time (τ_{act}) 30 ms.
2. *LBBB acute*:
Endocardial activation and reduced conductivity ($\tau_{\text{act}} = 108$ ms).
3. *LBBB chronic*:
Same as *LBBB acute*, but with MEF as described above ($\tau_{\text{act}} = 108$ ms).
4. *CRT acute*:
Simultaneous activation of endocardium and epicardium ($\tau_{\text{act}} = 54$ ms).
5. *CRT chronic*:
Same as *CRT acute*, but with MEF ($\tau_{\text{act}} = 54$ ms).

3. Results

In Figure 2, membrane potential (V_{mem}), calcium transient ($[\text{Ca}^{2+}]_{\text{i}}$), and strain are shown for three segments located at the endocardium, midwall, and epicardium of the ventricular wall. In Figure 3, stress-strain loops for the same three segments (top) and accompanying pressure-volume loops (bottom) are shown during chronic LBBB, acute CRT, and chronic CRT. In Figure 4, dispersion in external work (W_{ext}), action potential duration ($\text{APD}_{-60\text{mV}}$), and repolarization ($t_{\text{repol}}$) are shown during acute and chronic LBBB and during acute and chronic CRT. As expected, dispersion in W_{ext} was decreased during chronic LBBB and CRT due to MEF. With onset of CRT, dispersion of repolarization acutely increased, but reduced during chronic CRT.

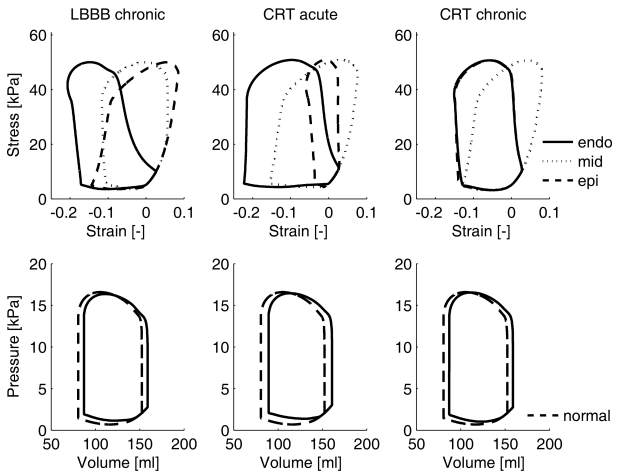

Figure 3. *Top*: Stress-strain loops for three segments located at he endocardium, midwall, and epicardium of the ventricular wall during *LBBB chronic*, *CRT acute*, and *CRT chronic*. *Bottom*: Pressure-volume loops.

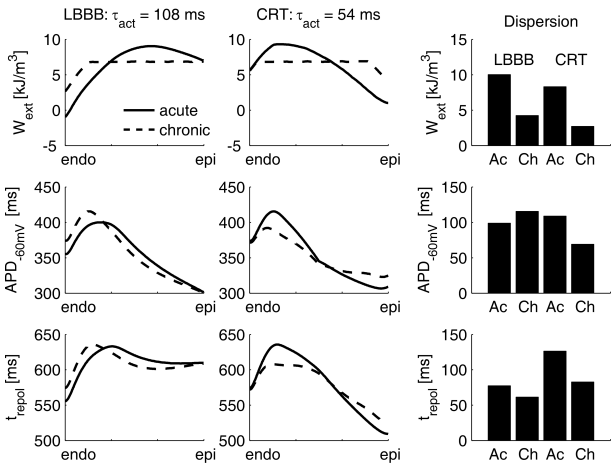

Figure 4. Dispersion in external work (W_{ext}), action potential duration ($\text{APD}_{-60\text{mV}}$), and repolarization ($t_{\text{repol}}$) during LBBB and CRT.

In Figure 5, pressures, volumes, and mitral valve flow are shown during chronic LBBB, acute CRT, and chronic CRT. With onset of CRT, $\text{dP}/\text{dt}_{\text{max}}$ increased indicating improvement of systolic function (Table). However, E/A-ratio decreased, which indicates worsening of diastolic function. With chronic CRT, diastolic function restored as indicated by an increase of E/A-ratio and a reduction of minimal LV pressure (LVP_{min}). Ejection Fraction (EF) improved slightly with chronic CRT due to MEF.

	$\text{dP}/\text{dt}_{\text{max}}$	EF	E/A	LVP_{min}
Normal	3254 mmHg/s	47.4 %	1.69	5.2 mmHg
LBBB acute	2394 mmHg/s	46.7 %	1.38	6.3 mmHg
LBBB chronic	2126 mmHg/s	45.3 %	1.64	8.7 mmHg
CRT acute	2824 mmHg/s	44.5 %	1.35	10.3 mmHg
CRT chronic	2869 mmHg/s	45.2 %	1.59	7.8 mmHg

4. Discussion and conclusions

We developed an electromechanical model of the left ventricle, in which L-type calcium current ($I_{\text{Ca,L}}$) was regulated to obtain a homogeneous distribution of work load. Our simulation results show that during LBBB, $I_{\text{Ca,L}}$ is adapted such that APD increases in the sub-endocardium. With onset of CRT, dispersion of repolarization is suddenly increased, also increasing the chance of ventricular arrhythmia. Due to MEF, APD decreases in the sub-endocardial regions such that repolarization becomes more synchronous. Although less clear, a similar observation was made for mechanical relaxation. With onset of CRT, the sub-endocardial region relaxed later in comparison to the sub-epicardial region. This lead to a reduced E/A-ratio and a hampered diastolic function. Due to mechano-electrical feedback, E/A-ratio increased with chronic CRT.

Although experimental observations suggest that changes in mechanical load induce electrical remodeling [3, 4], the exact mechanism is at present not clear. In a recent study by Kooshkabadi *et al.* [5], it was found that the development of cardiac memory was attenuated by administration of stretch-activated channel blocker streptomycin, indicating a prominent role for stretch-activated receptors in electrical remodeling. Indeed, the amount of stretch before onset of contraction (pre-stretch) is related to work load in our model. However, pre-stretch by itself does not change as a consequence of electrical remodeling and therefore cannot function as regulating mechanism. In contrast, external work load does change with electrical remodeling and is therefore used as a trigger mechanism in our model.

Regulation of $I_{\text{Ca,L}}$ in our model was based on the hypothesis that electrical remodeling, as for instance observed in T-wave memory, serves to improve overall cardiac function. In cardiac memory experiments, a number of changes in ionic membrane currents have been observed. Plotnikov *et al.* [15] observed changes in $I_{\text{Ca,L}}$, Yu *et al.* [16] observed changes in transient outward K^+ current (I_{to}), and Obreztchikova *et al.* [17] observed changes in delayed rectifier K^+ currents I_{Kr} and I_{Ks}. In addition to changes in K^+ currents, Aiba *et al.* [6] observed differences in $I_{\text{Ca,L}}$ and calcium transient between early and late activated myocytes in dogs after three weeks of tachypacing. Although the differences in $I_{\text{Ca,L}}$ and calcium transient reduced with three weeks of bi-ventricular pacing, they did not find significant changes in K^+ currents after bi-ventricular pacing. These results indicate that the effects of CRT may be more pronounced in $I_{\text{Ca,L}}$ than in K^+ currents. Since changes in $I_{\text{Ca,L}}$ affect both APD and calcium transient in our model, we decided to implement electrical

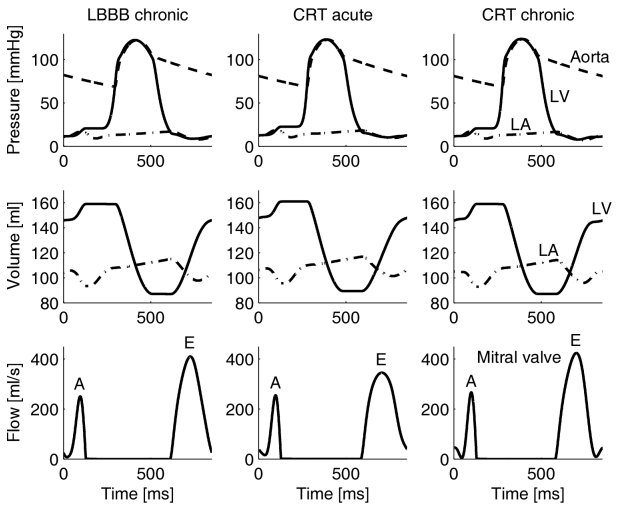

Figure 5. Overview of cardiac function during *LBBB chronic*, *CRT acute*, and *CRT chronic*. *Top*: blood pressure in left ventricle (LV), left atrium (LA), and aorta. *Center*: blood volume in LV and LA. *Bottom*: blood flow through mitral valve. Active ventricular filling is indicated by A and passive filling is indicated by E.

remodeling by adjusting $I_{\mathrm{Ca,L}}$ conductivity.

In conclusion, bi-ventricular pacing may lead to an increased dispersion of repolarization, leading to impaired filling and possibly ventricular arrhythmia. With time, repolarization becomes more synchronized and diastolic heart function improves due to mechano-electrical feedback.

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