Mechano-Electrical Coupling Explains Worsening of Cardiac Function in the Asynchronous Heart

Nico H L Kuijpers[1], Evelien Hermeling[1], Tammo Delhaas[1], Frits W Prinzen[2]

[1]Department of Biomedical Engineering, Maastricht University, Maastricht, the Netherlands
[2]Department of Physiology, Maastricht University, Maastricht, the Netherlands

Abstract

Asynchronous activation of the ventricles deteriorates cardiac function acutely, followed by further worsening over time. In a multi-scale model we tested the hypothesis that the second phase is due to mechano-electrical coupling (MEC), mediated by remodeling of ionic membrane currents. Our model describes hemodynamic interaction between the left and right ventricle as well as mechanical interaction of three wall segments. At cellular level, excitation-contraction coupling is described by a cascade of physiological models. At the organ level, pressure-volume relations are obtained by simulating the pulmonary and systemic circulation. MEC is incorporated by local adaptation of L-type Ca^{2+} current to local mechanical load. Our model predicts that MEC has no effect on cardiac function in the heart with normal conduction, but leads to reduced pump function in the asynchronous heart. We conclude that MEC may aggravate the consequences of abnormal electrical activation in the long run.

1. Introduction

Heart failure patients often suffer from conduction disturbances such as left bundle branch block (LBBB), which leads to asynchronous contraction of the ventricles. Vernooy *et al.* [1] found in dogs that inducing LBBB leads to immediate reduction in ejection fraction (EF), followed by a gradual further reduction in EF and an increase of left ventricular (LV) wall mass over a period of 16 weeks [1]. Since LV hypertrophy cannot explain progressive deterioration of cardiac function during LBBB, it is likely that other remodeling mechanisms, such as changes in ionic membrane currents, play a role.

Long-term LV epicardial pacing leads to T-wave changes in the electrocardiogram (ECG) when sinus rhythm is restored [2]. This phenomenon is known as "T-wave memory" and has been linked to changes in membrane currents, including the L-type calcium current [3, 4]. Evidence is growing that mechanical stimuli are involved in the mechanisms behind T-wave memory [5–7]. Moreover, during ventricular pacing (asynchronous activation), mechanical work is significantly reduced near the stimulation site and almost doubled in later-activated regions [8].

On the basis of these experimental observations, we hypothesized that deviation from normal work load triggers electrical remodeling in the LV. In particular, it was assumed that local changes in expression of L-type calcium channels aim at a uniform distribution of work load. By incorporating this assumption in a multi-scale model of the human heart and circulation, the effects of electrical remodeling were assessed both in the normal (synchronous) and in the LBBB (asynchronous) heart.

2. Methods

Our mathematical model was based on the CircAdapt model of mechanics and hemodynamics of heart and circulation from Arts *et al.* [9]. Hemodynamic interaction between the ventricles was established by modeling the systemic and pulmonary circulation. Mechanical interaction of the left and right ventricle through the interventricular septum was incorporated as described by Lumens *et al.* [10]. Global ventricular pump mechanics (pressure-volume relation) was related to myofiber mechanics (myofiber stress-strain relation) on the basis of the principle of conservation of energy.

In the CircAdapt model, active force generated by the myofibers was related to time of excitation, sarcomere length, and sarcomere shortening velocity using an empirical model. In the present study, the empirical model was replaced by a cascade of physiological models describing ionic membrane currents, calcium handling, and excitation-contraction coupling. An overview of the model is presented in Figure 1.

In our model, three ventricular wall segments were distinguished (Figure 1): right ventricular free wall (RVfw), septum, and left ventricular free wall (LVfw) [10]. Electromechanical behavior for each wall segment was described by a single fiber composed of 150 basic segments

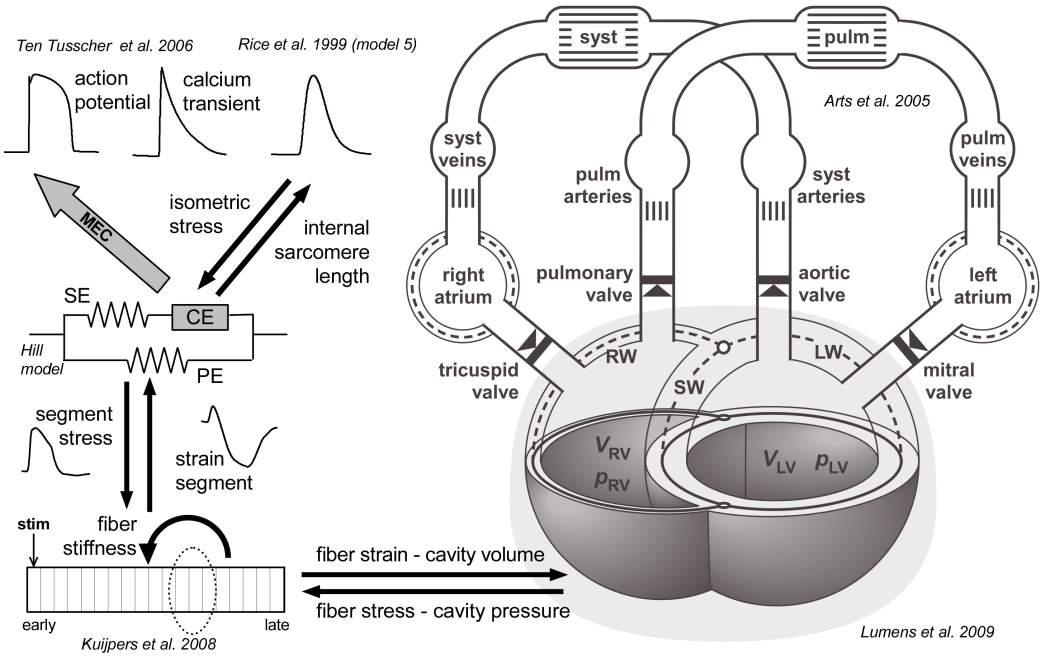

Figure 1. Schematic overview of the model. For each ventricular wall segment, electromechanics was described by a single fiber composed of 150 segments. Ventricular pressure and volume were related to fiber stress and strain. Cardiac hemodynamics was modeled by placing the ventricles in a systemic and pulmonary circulation including atria, valves, arteries, organs, and veins. Electrical activation was started by activating the fiber of each wall segment at one end. Mechano-electrical coupling (MEC) was incorporated by regulating L-type calcium current (I_{CaL}) such that a uniform distribution of work was obtained.

placed in series as described previously [11–13]. Ionic membrane currents and calcium handling were modeled by the 2006 model of Ten Tusscher *et al.* [14, 15]. Mechanical behavior of a segment was modeled by three elements [16]. 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. Excitation-contraction coupling was modeled by model 5 of Rice *et al.* [17] and depended on the intracellular concentration of free calcium, sarcomere length, and velocity of sarcomere shortening. By electrical stimulation of the fiber at one end, an action potential was generated which propagated to the other end of the fiber. The normal (synchronous) heart was simulated by simultaneous activation of the three fibers and the LBBB (asynchronous) heart was simulated by delaying the activation of LVfw with 80 ms. Furthermore, fiber conductivity of septum and LVfw was reduced for the LBBB heart. This resulted in the following activation times for the three fibers:

Wall segment	Normal	LBBB
RVfw	0 – 30 ms	0 – 30 ms
Septum	0 – 30 ms	0 – 54 ms
LVfw	0 – 30 ms	80 – 134 ms

Mechano-electrical coupling (MEC) was incorporated as follows. After simulation of one cardiac cycle, myofiber external work was computed for each segment by integrating the myofiber stress-strain loop. In case external work of a segment was below a reference value (in this case 8.5 kJ/m^3 at a heart rate of 72 bpm), L-type Ca^{2+} current (I_{CaL}) was upregulated by increasing maximum I_{CaL} conductance (G_{CaL}) for that segment. In case external work was above the reference value, G_{CaL} was decreased. On the basis of experimental observations [4], G_{CaL} could vary between 80% and 120% of the default value. Simulations were performed for 300 cardiac cycles to ensure that the final value of G_{CaL} was reached for each segment.

To investigate the effect of remodeling of I_{CaL} on local mechanical function as well as on global LV pump function and filling hemodynamics, the following simulations were performed:

1. *Normal Init*:
Simultaneous activation of RVfw, septum, and LVfw; default value of G_{CaL} for all fiber segments.
2. *Normal MEC*:
Simultaneous activation of RVfw, septum, and LVfw; Adaptation of G_{CaL} for all fiber segments.
3. *LBBB Init*:
Delayed activation of LVfw (80 ms) with respect to RVfw

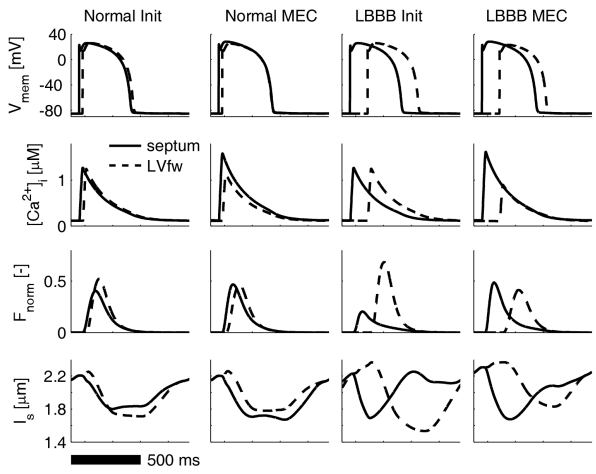

Figure 2. Membrane potential (V_{mem}), calcium transient ($[\text{Ca}^{2+}]_{\text{i}}$), isometric contractile force (F_{norm}), and sarcomere length (l_s) for normal activation (initial and MEC) and for LBBB (initial and MEC). Results are shown for an early-activated segment (activation time $t_{\text{act}} = 0$ ms) of septum (solid lines) and a later-activated segment ($t_{\text{act}} = 30$ ms for normal and $t_{\text{act}} = 134$ ms for LBBB) of LVfw (dashed lines).

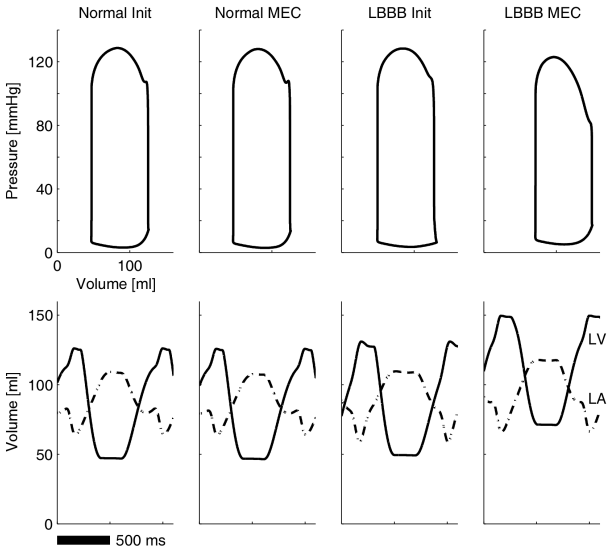

Figure 3. Overview of cardiac function. *Top*: LV pressure-volume relation. *Bottom*: Cavity volume of LV (solid) and LA (dash-dotted). Results are shown for normal activation (initial and MEC) and for LBBB (initial and MEC).

and septum; Conductivity reduced for septum and LVfw; default value of G_{CaL} for all fiber segments.
4. *LBBB MEC*:
Delayed activation of LVfw (80 ms) with respect to RVfw and septum; Conductivity reduced for septum and LVfw; Adaptation of G_{CaL} for all fiber segments.

3. Results

In Figure 2, membrane potential (V_{mem}), calcium transient ($[\text{Ca}^{2+}]_{\text{i}}$), normalized isometric force (F_{norm}), and sarcomere length (l_s) are shown for an early-activated segment (activation time $t_{\text{act}} = 0$ ms) of septum and a later-activated segment ($t_{\text{act}} = 30$ ms for normal and $t_{\text{act}} = 134$ ms for LBBB) of LVfw. Initially, the two segments had similar action potentials and calcium transients. In the normal heart, MEC increased action potential duration ($\text{APD}_{-60\text{mV}}$) by 14 ms for the septal segment and decreased $\text{APD}_{-60\text{mV}}$ by 7 ms for the LVfw segment. In the LBBB heart, MEC increased $\text{APD}_{-60\text{mV}}$ by 26 ms for the septal segment and decreased $\text{APD}_{-60\text{mV}}$ by 27 ms for the LVfw segment. Increase and decrease of APD was accompanied by an increase and decrease of the calcium transient.

In the normal heart, the initial amplitude of F_{norm} was larger in the LVfw segment compared to the septal segment, which is explained by the larger sarcomere length in the LVfw segment at onset of contraction. MEC increased F_{norm} for the septal segment and decreased F_{norm} for the LVfw segment, such that similar maximum values were obtained. MEC led to an increased amount of shortening and a longer duration of contraction for the septal segment, indicating increased external work. The opposite was observed for the LVfw segment. In the LBBB heart, the difference in initial amplitude of F_{norm} between the two segments was larger. As in the normal heart, MEC led to similar F_{norm} in the LBBB heart. Furthermore, MEC led to an increased shortening (and external work) for the septal segment and a decreased shortening for the LVfw segment. In the LBBB heart, the maximum sarcomere length was increased by 0.05 μm for the septal segment. Due to the fact that G_{CaL} could not become more than 120% of the default value, the early-activated septal segments could not reach the reference value for external work. Therefore, the average amount of external work delivered by the LBBB heart was lower after adaptation of I_{CaL}.

In Figure 3, pressures and volumes are shown for all four simulations. In the normal heart, pump function was not influenced by MEC. End diastolic function (EDV) and ejection fraction (EF) did not change. In the LBBB heart, MEC led to worsening of function as indicated by an increase in EDV and a decrease in EF from 62.5% to 52.5%. Furthermore, LV diastolic pressure (LVP_{min}) was increased from 3.5 mmHg to 5.1 mmHg due to MEC. Worsening of function in the LBBB heart due to MEC is explained by the fact that the decrease in external work delivered by the LVfw was not entirely compensated by the increase in external work delivered by the septum (Figure 2).

4. Discussion and conclusions

We developed a multi-scale model that links the sequence of electrical activation at the organ level and excitation-contraction coupling at cellular level to pump function of the entire heart. Moreover, long-term adaptation to abnormal mechanical load implemented as adjustment of I_{CaL} affected ventricular pump function, thus creating a mechano-electrical feedback loop.

Our simulation results indicate that remodeling of I_{CaL} has little effect on cardiac function in the normal (synchronous) heart. However, in the asynchronous (LBBB) heart, MEC-induced electrical remodeling may lead to worsening of heart function. This process may explain the findings of Vernooy *et al.* [1] that EF showed acute and more gradual reduction in canine hearts with isolated LBBB. Yu *et al.* [18] observed that cardiac resynchronization therapy (CRT) in LBBB patients results in an acute and a delayed improvement of function. Acute and gradual improvement with CRT was also observed in experiments with LBBB dogs [19] and may be explained by MEC-induced electrical remodeling as well.

In conclusion, MEC may lead to derangements when electrical activation becomes asynchronous. Moreover, since MEC affects action potential duration, also repolarization is affected, potentially evoking arrhythmias. Although these effects may explain derangements during long-term asynchrony, they also may lead to improvement of function with resynchronization therapy.

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Address for correspondence:

Nico Kuijpers

CARIM, Department of Biomedical Engineering

Maastricht University

Universiteitssingel 50

6229 ER Maastricht

the Netherlands

nico.kuijpers@maastrichtuniversity.nl