Multiscale sensitivity analysis in patient-specific models of interventricular conduction disturbances

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INTRODUCTION Patient-tailored numerical heart models can help to give insight in an individual patient's pathology and may in the future be able to predict the efficacy of treatments. Tailoring of the model to a patient may involve tuning many parameters to the individual and it is not known whether the tuned parameters differ between patients. Therefore we analyzed the sensitivity of several ECG markers to ~40 parameters that are typically used for tuning of electrophysiological models.

METHODS We created realistic anatomical models for 4 patients diagnosed with left-ventricular (LV) conduction disturbances including accurate simulation of cardiac electrophysiology. Following a tuning process for each model, we investigated the sensitivity of both ECG morphology and LV activation pattern to changes in a large number of cellular and tissue electrophysiological properties. Electrical propagation in the ventricles was simulated using a reaction-diffusion equation. To simulate cellular electrophysiology, the Ten Tusscher-Panfilov 2006 model was used. Cardiac electrograms and 12-lead ECGs were computed by solving the bidomain equation. Tuned parameters included earliest activation sites, tissue conductivity, and densities and activation/inactivation dynamics of ionic currents. To compute ECG and LV activation sensitivities, ±30% changes in each model parameter, one at a time, with respect to their default value in the model were simulated.

RESULTS In general, the parameters showing the highest sensitivity values were similar in the four patients. QRS complex and LV activation times were mainly modulated by the cellular sodium current, the cell surface-to-volume ratio in the LV, and cytoplasmic and gap-juctional conductivities. The ST-segment and the T-wave were primarily modulated by the cellular calcium and rectifier-potassium currents, and the cell surface-to-volume ratio in both ventricles. The conductivities of blood and muscle, mainly in the fiber direction, modulated amplitudes of both QRS complex and T-wave in most leads, whereas the conductivity of lung tissue had some impact on these amplitudes only in aVL and aVF leads.

DISCUSSION The effects of parameter variations were highly consistent between patients and most of the tuning could be performed with only ~10 parameters. Changes in ionic currents entailed similar effects in all ECG leads, whereas the effects of changes in tissue conductivity strongly depended on the ECG lead analysed.

Figure 1. Anatomical models of torso (with electrodes), lungs, and cardiac structures in the 4 patients.