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Multi-scale, tailor-made heart simulation can predict the effect of cardiac resynchronization therapy

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ABSTRACT

Background: The currently proposed criteria for identifying patients who would benefit from cardiac resynchronization therapy (CRT) still need to be optimized. A multi-scale heart simulation capable of reproducing the electrophysiology and mechanics of a beating heart may help resolve this problem. The objective of this retrospective study was to test the capability of patient-specific simulation models to reproduce the response to CRT by applying the latest multi-scale heart simulation technology.

Methods and results: We created patient-specific heart models with realistic three-dimensional morphology based on the clinical data recorded before treatment in nine patients with heart failure and conduction block treated by biventricular pacing. Each model was tailored to reproduce the surface electrocardiogram and hemodynamics of each patient in formats similar to those used in clinical practice, including electrocardiography (ECG), echocardiography, and hemodynamic measurements. We then performed CRT simulation on each heart model according to the actual pacing protocol and compared the results with the clinical data. CRT simulation improved the ECG index and diminished wall motion dyssynchrony in each patient. These results, however, did not correlate with the actual response. The best correlation was obtained between the maximum value of the time derivative of ventricular pressure (dP/dt_{max}) and the clinically observed improvement in the ejection fraction (EF) ($r = 0.94$, $p < 0.01$).

Conclusions: By integrating the complex pathophysiology of the heart, patient-specific, multi-scale heart simulation could successfully reproduce the response to CRT. With further verification, this technique could be a useful tool in clinical decision making.

1. Introduction

Despite the extensive clinical and basic researches attempting to identify the factors that determine the therapeutic response of patients treated with cardiac resynchronization therapy (CRT), there remains a significant proportion (about 30%) of patients who do not benefit from this invasive therapy [1,2].

In addition to the experimental and clinical studies to solve this problem, computer simulations of CRT have been widely used to study its mechanisms. Particularly, the recent reports of electromechanical models based on a finite element (FE) method presented results in a format similar to that of clinical data, thereby allowing quantitative evaluations and thus direct comparison with the clinically available data [3–9]. Although the power of simulation motivates researchers to apply it to patient-specific modeling, most of the studies to date have reproduced clinical data only on the ventricular pressure–volume relation and/or ventricular wall motion of dyssynchronous hearts [10–12].

We have developed a multi-scale, multi-physics three-dimensional (3D) heart simulator in which propagation of excitation, contraction and relaxation, development of pressure, and blood flow are reproduced based on molecular models of the cardiac excitation–contraction process [13–17]. We also succeeded in simulating the patient-specific body surface ECG [18]. Applying these technologies, we created

Abbreviations: CRT, cardiac resynchronization therapy; CT, computed tomography; dP/dt_{max}, maximum value of the time derivative of ventricular pressure; Ea, arterial elastance; Ees, ventricular end-systolic elastance; EF, ejection fraction; FE, finite element; LBBB, left bundle branch block; LV, left ventricle/ventricular; MRI, magnetic resonance imaging.

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a tailor-made simulation model of the heart to determine if the effects of CRT could be predicted in a canine model of heart failure with LBBB [19].

In the current retrospective study, we extended this approach to test the capability of our simulator as a tool for patient-specific evaluation of pathophysiology. We created patient-specific models of the failing heart with dyssynchrony and simulated the acute response to CRT according to the actual pacing protocol without using any other information obtained after CRT. The simulation results of CRT effects correlated well with the clinical parameters that reflect the therapeutic effect. Thus, we demonstrated the usefulness of patient-specific CRT simulation and its possible application in future clinical practice.

2. Methods

2.1. Study patients

Clinical data of the nine heart failure patients (age 61.0 ± 2.7 years; six men, three women; New York heart Association functional class II/III) treated with CRT at the University of Tokyo Hospital and Saitama Medical Center, Jichi Medical University, were retrospectively collected with written informed consent after approval by the institutional review board. The etiologies of their heart failure are shown in the Table 1. Selection criteria consisted of the following. (1) A cardiac computed tomography (CT) scan or magnetic resonance imaging (MRI) of good quality was obtained prior to implanting the CRT device. (2) Echocardiography data before and after CRT were available. Follow-up echocardiography was performed 3.9 ± 1.0 months after CRT. Patients with severe valvular regurgitation were excluded because of the difficulty of quantitatively simulating the severity of the regurgitation. Patients had been given all appropriate treatments for heart failure, which included a diuretic, an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, and a β-blocker.

2.2. Patient-specific models of the failing heart

The details of our multi-scale, multi-physics heart simulator and its personalization technique have been described elsewhere [13,15–19] and can be seen in the Supplementary material of this article. Briefly, patient-specific 3D FE models of the ventricles and upper body (torso) were reconstructed from multi-slice CT or magnetic resonance imaging data. These ventricular models with realistic morphology and fiber structure [20] were subdivided into finite elements and molecular models of the excitation-contraction coupling process representing endocardial, M, or epicardial cells [21] with the properties of failing myocytes [22] were implemented into these elements in appropriate locations [17,18] with sarcomere models [23].

Anisotropic conduction reflecting the fiber structure was introduced, and the Purkinje fiber network was modeled as a thin layer on the endocardial surface with higher conduction velocity (Supplementary Table 2). In the case of LBBB, activation was initiated only on the right ventricular side. After left ventricular breakthrough, propagation of activation was mediated by the Purkinje network via back-propagation or only by the myocardium, depending on the QRS width of the patient. Finally, lumped parameter models of the systemic and pulmonary circulations and time-varying elastance models of the atria were connected to the FE heart model and parameters were adjusted for each patient [24] (Fig. 1 and Supplementary Fig. S1). To reproduce the hemodynamic state of each patient before CRT, we tried to match the following patient-specific parameters: EF, as seen on the echocardiogram; systolic and diastolic arterial pressures measured using a blood pressure meter. Because the end-diastolic pressure was not available, we assigned different values depending on the functional class, according to the literature [25].

Table 1
Patients' characteristics.

Patient no.	Age (years)	Sex	Diagnosis	NYHA status	Systemic vascular esistance (dynes∗s∗cm^{-5})
1	60	M	Cardiac sarcoidosis	NA	1880
2	64	M	DCM	III	763
3	73	M	DCM	NA	2367
4	46	M	AR (pAVR)	III	517
5	48	F	DCM	II	1792
6	65	F	DCM	II–III	1457
7	64	M	OMI	II	1224
8	61	F	Cardiac sarcoidosis	II	1263
9	68	M	DCM	II	1368

NYHA: New York Heart Association; DCM: dilated cardiomyopathy; AR: aortic regurgitation; p-AVR: post aortic valve replacement; OMI: old myocardial infarction; NA: data not available.

2.3. CRT simulation

CRT simulation was performed for each heart model without changing any parameters of the heart or circulation that had been determined for baseline simulation. Positions of the pacing leads were estimated from biplane chest radiography or CT images if available and adjusted to reproduce the 12-lead ECG under pacing (Fig. 1). Timing of the stimulations was similar to the actual protocol, although in some cases we needed to delay the timing of left ventricular (LV) pacing to account for the possible electrical latency during LV stimulation from the coronary vein [26]. From the simulation results, we calculated QRS width, LVEF, and the maximum value of the time derivative of LV pressure (dP/dt_{max}). Clinical outcome was evaluated according to the improvement in EF indicated on the ultrasonographic cardiogram. For comparison, simulations were performed at the same heart rate (60/min) before and after CRT and repeated for 10 beats for numerical convergence.

Currently, creation of the FE model, including segmentation and mesh generation, takes 4 days, and parameter fitting and CRT simulation take 5 days. In total, 9 days are required for each patient.

2.4. Virtual tissue tracking

To assess the severity of dyssynchrony in the heart models, we calculated radial strain in the short axis plane of the left ventricle at six equally separated points by tracking the endocardial and epicardial material

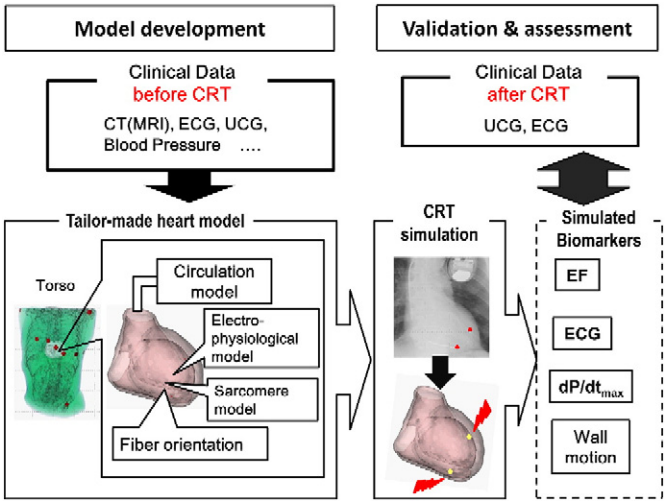

Fig. 1. Tailor-made cardiac resynchronization therapy (CRT) simulation. Patient-specific multi-scale models of the heart and torso were created according to clinical data that were obtained before CRT (development step). Biventricular pacing was performed in this model, and the calculated biomarkers were validated and assessed by comparing with clinical data that were obtained after CRT (validation and assessment step). ECG: electrocardiography; UCG: ultrasonographic cardiography.