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# Tailor-made heart simulation predicts the effect of cardiac resynchronization therapy in a canine model of heart failure☆,☆☆

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ABSTRACT

Despite extensive studies on clinical indices for the selection of patient candidates for cardiac resynchronization therapy (CRT), approximately 30% of selected patients do not respond to this therapy. Herein, we examined whether CRT simulations based on individualized realistic three-dimensional heart models can predict the therapeutic effect of CRT in a canine model of heart failure with left bundle branch block. In four canine models of failing heart with dyssynchrony, individualized three-dimensional heart models reproducing the electromechanical activity of each animal were created based on the computer tomographic images. CRT simulations were performed for 25 patterns of three ventricular pacing lead positions. Lead positions producing the best and the worst therapeutic effects were selected in each model. The validity of predictions was tested in acute experiments in which hearts were paced from the sites identified by simulations. We found significant correlations between the experimentally observed improvement in ejection fraction (EF) and the predicted improvements in ejection fraction ($P < 0.01$) or the maximum value of the derivative of left ventricular pressure ($P < 0.01$). The optimal lead positions produced better outcomes compared with the worst positioning in all dogs studied, although there were significant variations in responses. Variations in ventricular wall thickness among the dogs may have contributed to these responses. Thus CRT simulations using the individualized three-dimensional heart models can predict acute hemodynamic improvement, and help determine the optimal positions of the pacing lead.



## 1. Introduction

Cardiac resynchronization therapy (CRT) is a device therapy that is designed to correct dyssynchronous contraction of the failing heart. Randomized controlled trials have demonstrated the therapeutic efficacy of CRT in the reduction of mortality (Moss et al., 2009) and hospitalization (Tang et al., 2010), and recovery of exercise capacity and improvement of contractile functions in a subset of heart failure (HF) patients who are characterized by a wide QRS morphology on electrocardiogram (ECG) and reduced ejection fraction (EF) (Chen et al., 2013; Linde et al., 2008; Young et al., 2003). However, a large proportion of patients (close to 40% in some studies) fail to show benefit from CRT (non-responders). Therefore careful selection of patients who are likely to respond to CRT is very important for optimal care of patients and the healthcare economy.

Many studies have examined for indices that are capable of effectively identifying non-responders based on clinical observations and mechanisms underlying the pathophysiology of contractile dysfunction. QRS duration reflects the time required for the propagation of excitation. The current guidelines recommend CRT for HF patients with a QRS duration >150 ms, although there is

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☆☆ *New and noteworthy*: We report a novel individualized multi-scale simulation model of the failing canine heart, which can accurately predict the response to cardiac resynchronization therapy based on the baseline condition of each heart. This excellent predictive ability also provides new insight into the mechanism of heart failure.

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an indication that HF patients with a narrow QRS may also benefit from CRT (Williams et al., 2009). The morphology of the QRS complex also has a significant impact on patient outcome. Patients with left bundle branch block respond to CRT at a higher rate compared with those with right bundle branch block or intra-ventricular conduction delay (Tang et al., 2010; Zareba et al., 2011).

The concept that CRT treats the electromechanical coupling delay naturally leads to detection of mechanical dyssynchrony. Many indices based on echocardiographic measurements have been proposed, including septal-to-posterior wall delay by M-mode echo (Pitzalis et al., 2002), time to peak systolic velocity by tissue Doppler imaging and dyssynchrony in wall motion by the speckle tracking method (Delgado et al., 2008; Gorcsan et al., 2008). However, none of these indices, including the newly proposed ones, have been accepted as the standard for accurate identification of non-responders. Technical aspects of CRT, such as the lead position (Dekker et al., 2004; Helm et al., 2007) and the optimization of timing of the stimulus have a major effect on the therapeutic outcome (Prinzen et al., 2013; Yu and Hayes, 2013).

Computer simulations of CRT provide a unique opportunity to study the mechanisms of therapeutic effects beyond the limit of experimental approaches. Using either a thick-walled spherical model (Huntjens et al., 2014) or a finite element model of the ventricles (Constantino et al., 2012; Gurev et al., 2011; Kerckhoffs et al., 2008; Kerckhoffs et al., 2010; Niederer et al., 2012a; Niederer et al., 2011; Tobon-Gomez et al., 2013), researchers have shown abnormal distributions of regional strain, stress, and work induced by delayed propagation of excitation in the left bundle branch block and ameliorations by bi-ventricular pacing. These technologies can be applied for the prediction of therapeutic outcomes of patients. However, to date, studies are limited to the comparison between simulation results and the clinical data for a single (Aguado-Sierra et al., 2011; Kayvanpour et al., 2015; Niederer et al., 2012a; Niederer et al., 2011) or two (Sermesant et al., 2012) patients or simulations comparing the different pacing strategies in the model heart without experimental validations (Constantino et al., 2012; Kerckhoffs et al., 2008; Niederer et al., 2012b).

We have developed a multi-scale heart simulator in which the electro-mechanical function of the heart is reproduced based on the molecular model of cardiac excitation-contraction coupling (Okada et al., 2015; Sugiura et al., 2012; Washio et al., 2013; Watanabe et al., 2004a). Notably, technology for faithfully reproducing 12-lead ECG (Okada et al., 2011; Washio et al., 2010) has been applied to patients with bundle branch block (Okada et al., 2013).

In this study, we applied this technology to create tailor-made multi-scale simulation models of canine failing hearts with left bundle branch block. Using these models, we tested whether multi-scale heart simulation can predict the therapeutic effect of CRT by accurately reproducing the experimental data. Furthermore, based on simulation and experimental results, we determined the mechanism by which efficient treatment of electromechanical delay can be achieved.

## 2. Methods

### 2.1. Animal experiment

Animal studies were performed according to the National Institute of Health's Guide for the Care and Use of Laboratory Animals and the experimental protocols were reviewed and approved by Animal Care and Use Committee of Nippon Veterinary and Life Science University (approval reference number: 12–72, 13–68, 26K-9).

### 2.2. Canine model of left ventricular dysfunction with left bundle branch block

In four male beagles weighing approximately 12 kg, left bundle branch block was created by ablation after baseline measurement of blood pressure and echocardiography. Anesthesia was induced with thiopental sodium (25 mg/kg intravenously) and maintained with isoflurane (1.5–2.0%) under mechanical ventilation. Ablation was then performed to create a left bundle branch block using a catheter (Livewire, St. Jude Medical, St. Paul, MN, USA). Success of the procedure was confirmed by widening of the QRS complex in the ECG. After recovery, the dogs underwent an exercise load protocol (13 km/h, 15 min/day) until the EF, which was measured by echocardiography, became less than 35%. At this point, a cardiac computer tomography (CT) scan (Aquilion prime; Toshiba Medical Systems Co., Otawara-shi, Tochigi, Japan) with injection of contrast media (iopamidol 61.24%, 1.5 ml/kg intravenously, injection speed of 2.0 ml/s) was performed under anesthesia.

### 2.3. Acute pacing experiment

Two weeks after the CT scan, acute pacing experiments were performed. This time-interval was required for modeling. Creation of a finite element mesh accounted for most of the time interval. After the dogs were anesthetized under mechanical ventilation, a venous line was established and a conductance catheter with a micro-tip manometer was advanced to the left ventricle via the carotid artery. Midline sternotomy was then performed and the pericardium was opened. Pacing catheters (Petite 44ERJB and 52ERB; Oscor Inc., Palm Harbor, FL, USA) were placed in the right atrial appendage and the right ventricle via the right jugular vein. The position of the atrial pacing lead was fixed at the site yielding the best atrial spike throughout the experiment. The quality of signal was checked intermittently between the protocols to confirm the low pacing impedance. However, the right ventricular lead and two custom-made platinum epicardial leads that were sutured to the left ventricular surface were placed at the positions predicted to yield the best or worst performance by simulation. This was not able to be achieved in one dog (Dog #1), in which the lead position produced the second best effect because of a technical problem. The atrium was paced at 15–20 beats faster than the sinus rhythm and the timing of right ventricular pacing (AV delay) was approximately 80% of the PR interval. In most cases, the left ventricle was paced earlier than the right ventricle (V-V delay) by 20 ms. Pacing was conducted using a custom-made stimulator that was capable of multi-site programmable stimulation (Olympus Co., Tokyo, Japan). Left ventricular pressure and volume by the conductance catheter and the echocardiogram were recorded after the hemodynamics was stabilized under the pacing. These data were compared with those recorded during the atrial pacing that was immediately performed before each atrioventricular pacing protocol. Throughout the experiment adequacy of anesthesia was monitored by checking the heart rate, blood pressure, and the respiratory condition. Intravenous injection of sodium thiopental was used for euthanasia.

### 2.4. Multi-scale simulation model of the canine heart

As the details of our multi-scale heart simulation technologies were previously reported (Okada et al., 2013; Okada et al., 2011; Sugiura et al., 2012; Washio et al., 2010; Washio et al., 2012; Washio et al., 2013; Watanabe et al., 2008; Watanabe et al., 2004b), the model and the procedures for personalization are described in brief below (Fig. 1).