Journal of Molecular and Cellular Cardiology 96 (2016) 93–100

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Review article

The relative role of patient physiology and device optimisation in cardiac resynchronisation therapy: A computational modelling study

Andrew Crozier [a,b], Bojan Blazevic [a], Pablo Lamata [a], Gernot Plank [b], Matthew Ginks [c], Simon Duckett [c], Manav Sohal [c], Anoop Shetty [c], Christopher A. Rinaldi [c], Reza Razavi [a], Nicolas P. Smith [a,d], Steven A. Niederer [a,*]

[a] Division of Imaging Sciences and Biomedical Engineering, King's College London, United Kingdom
[b] Institute of Biophysics, Medical University of Graz, Austria
[c] Department of Cardiology, Guy's and St. Thomas' Hospital, London, United Kingdom
[d] Faculty of Engineering, University of Auckland, New Zealand

ARTICLE INFO

Article history:
Received 3 August 2015
Received in revised form 12 October 2015
Accepted 21 October 2015
Available online 4 November 2015

Keywords:
Heart failure
Cardiac resynchronisation therapy
Dyssynchronous heart failure
Computational modelling
Patient-specific modelling

ABSTRACT

Cardiac resynchronisation therapy (CRT) is an established treatment for heart failure, however the effective selection of patients and optimisation of therapy remain controversial. While extensive research is ongoing, it remains unclear whether improvements in patient selection or therapy planning offers a greater opportunity for the improvement of clinical outcomes. This computational study investigates the impact of both physiological conditions that guide patient selection and the optimisation of pacing lead placement on CRT outcomes. A multi-scale biophysical model of cardiac electromechanics was developed and personalised to patient data in three patients. These models were separated into components representing cardiac anatomy, pacing lead location, myocardial conductivity and stiffness, afterload, active contraction and conduction block for each individual, and recombined to generate a cohort of 648 virtual patients. The effect of these components on the change in total activation time of the ventricles (ΔTAT) and acute haemodynamic response (AHR) was analysed. The pacing site location was found to have the largest effect on ΔTAT and AHR. Secondary effects on ΔTAT and AHR were found for functional conduction block and cardiac anatomy. The simulation results highlight a need for a greater emphasis on therapy optimisation in order to achieve the best outcomes for patients.

Contents

Abbreviations: AHR, acute haemodynamic response; CRT, cardiac resynchronisation therapy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EF, ejection fraction; EP, electrophysiology; HF, heart failure; LBBB, left bundle branch block; LV, left ventricle; MRI, magnetic resonance imaging; NCM, non-contact mapping; QRSd, QRS duration; RV, right ventricle; SR, sinus rhythm; TAT, total activation time of the ventricles; VPC, virtual patient cohort.

* Corresponding author.
E-mail address: steven.niederer@kcl.ac.uk (S.A. Niederer).

http://dx.doi.org/10.1016/j.yjmcc.2015.10.026

1. Introduction

Heart failure (HF) is a significant disease in the western world, affecting 1—2% of the adult population and accounting for around 2% of all healthcare spending [1]. Cardiac Resynchronisation Therapy (CRT) is an effective treatment for dyssynchronous HF [2], reducing the risk of hospitalisation and death, and leading to improved heart function and quality of life [2–4]. However, using the current selection criteria of left ventricle (LV) dysfunction (LV ejection fraction (EF) ≤35%) and electrical dyssynchrony (QRS duration (QRSd) 120—149 with left bundle branch block (LBBB) or QRSd ≥150) [5], only 67% of patients benefit from CRT, while 39% of patients receiving standard pharmacological therapy improve without CRT [6].

The improvement of patient selection for CRT is therefore an important area of research, so that optimal outcomes for patients are achieved without unnecessary application of this expensive and invasive therapy. Patient physiology and demographic factors such as sex [7], diabetes [8] and ischaemia [9] have been shown to affect the potential benefits of CRT. Clinical research has also demonstrated the potential for improved response to CRT by optimisation of pacing lead location [10–12].

In this paper, we investigate whether either of the confounding roles of patient physiology or optimisation of CRT pacing lead location has a greater influence on patient outcomes. To systematically quantify the impact of each mechanism on patient response, we adopt a patient-specific computational modelling approach. Personalised biophysical modelling of cardiac function has increasingly been used to investigate the mechanisms underlying CRT response, and demonstrate its potential for advanced treatment planning [13–17]. We have constructed personalised and validated computational models of three CRT patients. These models were used to generate a virtual patient cohort, in which the relative impact of patient physiology and device placement on the total activation time (TAT) of the ventricles and acute haemodynamic response (AHR) was evaluated *in silico*.

2. Methods

2.1. Model development and personalisation

Each model consists of a biventricular, weakly coupled [18] model of cardiac electromechanics, combining a monodomain model of tissue electrophysiology using the ten Tusscher model of cellular electrophysiology [19] with a model of large deformation mechanics using the Guccione passive material law [20], a phenomenological model of myocardial active tension [16] and a 3 element Windkessel model of afterload. The complete modelling framework is described in detail in Section 1 of the online supplement accompanying this article. Models were personalised using clinical data, as outlined below and described in detail in Section 2 of the supplement.

2.1.1. Cardiac anatomy and fibres

A tricubic Hermite description of the cardiac anatomy was fitted to a manually or automatically segmented end diastolic magnetic resonance imaging (MRI), as described previously [21,22]. A generic fibre field based on *a priori* knowledge was mapped to each patient-specific anatomical model [16], and an additional high resolution tetrahedral discretisation was generated from each cubic Hermite mesh for the purposes of simulation of electrophysiology. Section 2.1 of the online supplement describes this process in detail.

2.1.2. Electrical activation

Sinus rhythm (SR) activation was simulated by applying a stimulus current at the earliest sites of activation in the septum and RV as determined from ECG and EnSite™ non-contact mapping (NCM) data, and from the literature [23] in the case of the location of the earliest activation in the RV. The timings of these intrinsic stimuli were determined relative to the time of sinoatrial depolarisation as a reference point. CRT activation was simulated by adding electrical stimuli at pacing lead locations in the RV apex and LV epicardium determined from angiograms registered with MRI [24]. Following the clinical protocol, leads were paced 100 ms after sinoatrial node activation, prior to the activation of the intrinsic stimuli. Conduction block was included by means of a region of low conductivity, with its location determined from NCM. Activation sequences were validated by comparison with NCM activation maps. For additional details on the above steps, see Section 2.2 of the online supplement.

2.1.3. Contraction

Simulation of the full cardiac cycle was carried out at SR and with CRT by mapping simulated depolarisation times to the cubic Hermite computational mesh, where they are used as an input to the active tension model. 2 parameters from the passive material law, 6 parameters from the active tension model and the 3 Windkessel model parameters were fitted to patient-specific pressure-volume (PV) loops at sinus rhythm and to the observed acute haemodynamic response (AHR) in the case of the active tension model. Mechanical contraction was validated by comparison with short axis cine MRI at sinus rhythm. Section 2.3 of the online supplement describes this process in detail.

2.1.4. Patient cases

The personalisation workflow summarised above and described in detail in the online supplement was applied to three patients with demographics and baseline characteristics as shown in Table 1. All patients had a dilated cardiomyopathy (DCM) aetiology and NYHA class of III.

Table 1
Demographics and baseline clinical indices for the patients in this study. (QRSd: QRS duration, EF: ejection fraction, EDV: end diastolic volume)

Cases	Sex	Age	QRSd (ms)	EF (%)	EDV (ml)
1	M	63	188	23.5	310
2	F	81	139	24.7	172
3	M	77	171	19.6	331