Optimization of Left Ventricle Pace Maker Location Using Echo-Based Fluid-Structure Interaction Models

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Abstract

Cardiac pacing has been an effective treatment in the management of patients with bradyarrhythmia and tachyarrhythmia. Different pacemaker location has different responses, and pacemaker effectiveness to each individual can also be different. A novel image-based ventricle animal modeling approach was proposed to optimize ventricular pacemaker site for better cardiac outcome. One health female adult pig weight 42.5kg was used to make pacing animal model with different ventricle pacing locations. Pig health status was assessed before undergoing experimental procedures. Ventricle surface electric signal, blood pressure and echo image were acquired 15 minutes after the pacemaker was implanted. Echo-based left ventricle (LV) fluid-structure interaction (FSI) models were constructed to perform ventricle function analysis and investigate impact of pacemaker location on cardiac outcome. The nonlinear Mooney-Rivlin model was used for ventricle tissue material model. With the measured electric signal map from the pig associated with the actual pacemaker site, electric potential conduction of myocardium was modeled by material stiffening and softening in our model, with stiffening simulating contraction and softening simulating relaxation. Material stiffness parameters were adjusted in a cardiac cycle to match Echo-measured LV deformation and volume variations. Mapping between material stiffness and ventricle electric signal was quantified using data measured from the animal with pacemaker applied. Ventricle model without pacemaker and three ventricle models with the following pacemaker locations were simulated: right ventricular apex (RVA), posterior interventricular septum (PIVS) and right ventricular outflow tract (RVOT). Data for ventricle volume change, ejection fraction, stress and strain, flow velocity and shear stress data were collected for comparisons. Our results demonstrating that PIVS pacing model had higher peak flow velocity and stress/strain. It indicated PIVS pacemaker site may be the best location. This modeling approach could be used as "virtual surgery" to try various pacemaker locations and avoid risky and dangerous surgical experiments on real patients.

Keywords: Fluid-structure interaction model, pacemaker electrical conduction, Fluid dynamic, ventricle material properties, ventricle mechanics.

Introduction

In recent decades, rapid development of cardiac pacing has become the only effective treatment for slow cardiac arrhythmia. According to some statistics, between 1993 and 2009, 2.9 million patients received permanent pacemakers in the United States [1]. China Ministry

of Health Online Registration indicated that pacemaker implants were placed in 70,000 patients in 2016, and the number has been increasing year by year [2]. Right ventricular apex (RVA) has been the conventional location for pacemaker lead placement. However, RVA pacing is associated with abnormal myocardial contractile pattern, hemodynamic disorder, and histologic remodeling [3]. The review by Tops et al. provided a contemporary overview of the available evidence on the detrimental effects of RVA pacing [4]. So optimization of right ventricular pacing site becomes an important object of pacing electrophysiology. In recent years, the concept of physiological pacing has been proposed in the field of electrophysiological, and the study of the selection of pacing sites has received great attention [2] [5]-[6]. Singh et al. assessed left ventricular (LV) function and dyssynchrony in patients with right ventricle outflow tract (RVOT) pacing and conventional RVA pacing using equilibrium radionuclide angiography. Their results indicated RVOT pacing may lead to better preservation of LV function on longer follow-up [7]. Kronborg et al. showed that His or para-His pacing preserves LV ejection fraction and mechanical synchrony compared with right ventricular (RV) septal pacing in patient with atrioventricular block and may be a future pacing strategy to prevent pacing-induced heart failure in selected pacemaker patients [8]. Here His indicates His bundle which is a collection of heart muscle cells specialized for electrical conduction. As part of the electrical conduction system of the heart, it transmits the electrical impulses from the atrioventricular node (located between the atria and the ventricles) to the point of the apex of the fascicular branches via the bundle branches. Sharma et al. assessed the safety, feasibility, and success rates of His-bundle pacing in unselected patients without the use of a mapping catheter or a backup RV lead as compared to RVA pacing [9]. Zanon et al. systematically investigated the hemodynamic benefit of multipoint pacing performed at many pacing sites per heart and related hemodynamic effect to both LV electrical delay and the reduction in QRS duration [10].

Recent advances in computational modeling, methods and computer technology have made it possible for computer-simulated procedures to be used in clinical decision-making for diseased hearts. In our previous studies, we introduced patient-specific cardiac magnetic resonance (CMR)-based LV/RV models with fluid-structure interactions (FSI) with various surgical design and potential applications [11]-[14]. Echo-based 3D LV FSI models were introduced to perform ventricle mechanical analysis and investigate flow behaviors [15].

This paper will integrate echocardiography images, propagating dynamic electric potential on ventricle surface induced by pacemaker, and computational models with fluid-structure interactions to perform myocardial function and intra-cardiac flow assessment. The models will be used to evaluate and optimize pacemaker location.

Methods

3D echo data acquisition

The animal study was conducted at the First Affiliated Hospital of Nanjing Medical University, Nanjing, China. A health female adult pig weight 42.5kg was intubated and mechanically ventilated. Anesthesia was maintained using isoflurane. The pig was placed on an operating table in the semi-left lateral position with upright tilt, suitable for echocardiographic examination. Electric potential data recording and image acquisition were started 15 minutes after different pacemaker was implanted. Pacemaker locations included RVA, posterior interventricular septum (PIVS) and RVOT. Standard echocardiograms were obtained using an ultrasound machine (E9, GE Mechanical Systems, Milwaukee, Wisconsin) with a 3V probe. Electrophysiological recorder records body surface 12-lead electrocardiogram and intracardiac electrogram. Meantime, the pressure gauge catheter was

connected to the Medtronic Lifpark12 monitor. The left ventricular pressure curve was measured before and during the time period when the pacemaker was implanted. Table 1 gives basic information including ventricular pacing location, pressure and volume data.

Table 1. Ventricular pacing location and volume data

Pacemaker location	Non-pacemaker		RVA		RVOT		PIVS	
Pressure (mmHg)	Min= 9	Max= 102	Min= 10	Max= 119	Min= 8	Max= 90	Min= 7	Max= 83
Echo Vol (ml)	Min= 25	Max= 54	Min= 27	Max= 55	Min= 26	Max= 50	Min= 19	Max= 44
Echo EF (%)	53.70		50.91		48.00		56.82	
Model Vol (ml)	Min= 24.96	Max= 54.01	Min= 27.07	Max= 54.96	Min= 26.05	Max= 50.16	Min= 18.98	Max= 44.02
Model EF (%)	53.79		50.75		48.07		56.88	

The fluid-structure interaction model of LV

Blood flow in the left ventricle was assumed to be laminar, Newtonian, viscous and incompressible. The Navier-Stokes equations with arbitrary Lagrangian-Eulerian (ALE) formulation were used as the governing equations. When the inlet or outlet were closed, flow velocity was set to zero and pressure was left unspecified. When the inlet or outlet was open, flow velocity was left unspecified and pressure was prescribed. No-slip boundary conditions and natural force boundary conditions were specified at all interfaces to couple fluid and structure models together [11][16]. Standard governing equations and boundary conditions for the LV model were given:

$$\rho(\partial\mathbf{u}/\partial t + ((\mathbf{u} - \mathbf{u}_g)\cdot\nabla)\,\mathbf{u}) = -\nabla p + \mu\nabla^2\mathbf{u}, \quad (1)$$

$$\nabla\cdot\mathbf{u} = 0, \quad (2)$$

$$\mathbf{u}|_\Gamma = \partial\mathbf{x}/\partial t, \quad (3)$$

$$P|_{inlet} = p_{in}(t),\ \partial\mathbf{u}/\partial n|_{inlet} = 0,\ \mathbf{u}|_{outlet} = 0, \text{ (filling phase)}, \quad (4)$$

$$P|_{outlet} = p_{out}(t),\ \partial\mathbf{u}/\partial n|_{outlet} = 0,\ \mathbf{u}|_{inlet} = 0, \text{ (ejection phase)}, \quad (5)$$

$$\sigma_{ij}\cdot n_j\ |_{out\_wall} = 0, \quad (6)$$

$$\sigma^r_{ij}\cdot n^r_j\ |_{interface} = \sigma^s_{ij}\cdot n^s_j|_{interface}, \quad (7)$$

where $\mathbf{u}$ and p are flow velocity and pressure, $\mathbf{u}_g$ is mesh velocity, μ is the viscosity of blood. Γ stands for LV inner wall, $f_{\bullet,j}$ stands for derivative of f with respect to the jth variable (or time t), $\boldsymbol{\sigma}^r$ and $\boldsymbol{\sigma}^s$ are fluid and structure stress tensors, and $\mathbf{n}^r$ and $\mathbf{n}^s$ are their outward normal directions, respectively.

The ventricle material tissue was assumed to be hyperelastic, anisotropic, homogeneous and nearly-incompressible. The governing equations for the LV structure model were:

$$\rho v_{i,tt} = \sigma_{ij,j},\ i,j = 1,2,3; \text{ sum over } j, \quad (8)$$

$$\varepsilon_{ij} = (v_{i,j} + v_{j,i} + v_{\alpha,i}v_{\alpha,j})/2,\ i,j,\alpha = 1,2,3, \quad (9)$$

where σ is the stress tensor, ε is the strain tensor, v is displacement, and ρ is material density. The normal stress was assumed to be zero on the outer (epicardial) LV surface and equal to the normal stress imposed by fluid forces on the inner (endocardial) LV surface as specified by Eq.(7).

The nonlinear Mooney-Rivlin model was used to describe the nonlinear anisotropic material properties. The strain energy function for the anisotropic modified Mooney-Rivlin model is given:

$$W=c_1(I_1-3)+c_2(I_2-3)+D_1[\exp(D_2(I_1-3))-1]+(K_1/K_2)\exp[K_2(I_4-1)^2-1], \quad (10)$$

where I_1 and I_2 are the first and second strain invariants given by,

$$I_1=\sum C_{ii},\ I_2=\tfrac{1}{2}[I_1^2-C_{ij}C_{ij}],\ I_4=C_{ij}(\mathbf{n}_f)_i(\mathbf{n}_f)_j \quad (11)$$

$C=[C_{ij}]=X^TX$ is the right Cauchy-Green deformation tensor, $X=[X_{ij}]=[\partial x_i/\partial a_j]$, (x_i) is the current position, (a_i) is the original position, $\mathbf{n}_f$ is the fiber direction, c_i, D_i and K_i are material parameters chosen to match experimental measurements [12][15]. With parameters properly chosen, it was shown that stress-strain curves derived from Eq. (10) agreed very well with the stress-strain curves from the anisotropic (transversely isotropic) strain-energy function with respect to the local fiber direction given in McCulloch et al.[14]:

$$W=\frac{C}{2}(e^Q-1), \quad (12)$$

$$Q=b_1E_{ff}^2+b_2(E_{cc}^2+E_{rr}^2+E_{cr}^2+E_{rc}^2)+b_3(E_{fc}^2+E_{cf}^2+E_{fr}^2+E_{rf}^2), \quad (13)$$

where E_{ff} is fiber strain, E_{cc} is cross-fiber in-plane strain, E_{rr} is radial strain, and E_{cr}, E_{fr} and E_{fc} are the shear components in their respective coordinate planes, C, b_1, b_2, and b_3 are parameters to be chosen to fit experimental data. For simplicity, we set b_1=0.8552, b_2=1.7005, b_3=0.7742 in Eq. (12) so that we can have a single parameter C for comparison. The least-squares method was used to find the equivalent Young's moduli (YM) for the material curves for easy comparison.

As patient-specific fiber orientation data was not available from these patients, we chose to construct a two-layer LV model and set fiber orientation angles using fiber angles given in Axel [15]. Fiber orientation angles were set at -60 degree and 80 degree for epicardium (outer layer) and endocardium (inner layer), respectively. Fiber orientation can be adjusted when patient-specific data becomes available [11].

A pre-shrink process and geometry-fitting technique for mesh generation

Under in vivo condition, ventricles are pressurized and the zero-stress ventricular geometries are not known. In our model construction process, a pre-shrink process was applied to in vivo end-systolic ventricular geometries to generate the starting shape for the computational simulation [15]. A geometry-fitting mesh generation technique was also used to generate mesh for our models [13]. Mesh analysis was performed by decreasing mesh size by 10% (in each dimension) until solution differences were less than 2%. The mesh was then chosen for our simulations.

Solution methods and Data collection for Statistical analysis

The Echo-based anisotropic LV models were constructed for the three patients and the models were solved by ADINA (ADINA R&D, Watertown, MA, USA) using unstructured finite elements and the Newton-Raphson iteration method. The "Re-Start" feature in ADINA was used to adjust material parameters at each numerical time step to implement the potential conduction of myocardium. Flow velocity and stress/strain distributions were obtained for analysis. Because stress and strain are tensors, for simplicity, maximum principal stress (Stress-P_1) and strain (Strain-P_1) were used and referred to as stress and strain in this paper.

Results and Discussion

It is common to use selected cut-surfaces and critical time points (begin-filling, peak velocity during filling, begin-ejection, peak velocity during ejection, etc.) to demonstrate and compare

solution behaviors. For our modeling set-up, the time points for begin-filling and end-ejection are connection points of systole and diastole phases. The same is true for end-filling and before-ejection time points. This explanation should be helpful to understand why we mainly used end-filling and end-ejection in our comparative analyses.

Table 2 gives the maximum velocity values over the whole LV flow domain and the average flow shear stress (FSS) on LV inner surface at selected time points from the four models studied. Using the No-Pacemaker (NP) model as baseline, at the peak of filling, velocity magnitude for RVA and PIVS pacing models were 7% and 33% higher than that of the NP, respectively. Velocity magnitude for RVOT pacing model was 5% lower than that of the NP model. At the peak of ejection, velocity magnitude for RVA and PIVS pacing models were 29% and 45% higher than that of the NP model, while velocity magnitude for RVOT pacing model was 24% lower than that of the NP model.

Table 2. Velocity and flow shear stress (FSS) of pacing models

	Begin-filling		**Peak of filling**		**Begin-ejection**		**Peak of ejection**	
	Velocity (cm/s)	FSS (dyn/cm^2)	Velocity (cm/s)	FSS (dyn/cm^2)	Velocity (cm/s)	FSS (dyn/cm^2)	Velocity (cm/s)	FSS (dyn/cm^2)
NP	17.60	0.2142	109.9	1.359	39.87	1.096	183.1	1.970
RVA	26.20	0.7010	117.5	1.771	52.41	1.159	235.8	3.205
RVOT	19.08	0.2531	104.9	1.331	32.96	0.7831	139.9	1.616
PIVS	24.67	0.2981	146.5	1.738	44.45	1.573	266.0	3.866

Ventricle stress and strain are good measure about how hard ventricle muscle is working. It is of interest to calculate LV stress/strain conditions for comparisons. Comparison of average stress and strain values on LV inner contours of four models were given in Table 3. Using NP model as baseline, at the peak of filling, stress of RVA model was 9% higher than that of NP model. Stress of RVOT and PIVS models were 19% and 5% lower than that of NP model, respectively. Meanwhile, strain of RVA and RVOT models were 4% and 5% lower than that of NP model, respectively. Strain of PIVS model was 11% higher than that of NP model. At the peak of ejection, stress of RVA, RVOT and PIVS models were 36%, 34% and 120% higher than that of NP model, respectively. Moreover, strain of RVA pacing model was close to NP model, while strain of RVOT and PIVS pacing models were 11% and 47% higher than that of NP model, respectively.

Table 3. Stress and Strain comparison of pacing models

	Begin-filling		**Peak of filling**		**Begin-ejection**		**Peak of ejection**	
	Stress (kPa)	Strain	Stress (kPa)	Strain	Stress (kPa)	Strain	Stress (kPa)	Strain
NP	2.779	0.0882	81.21	0.5756	135.9	0.6979	23.46	0.4214
RVA	3.604	0.0897	88.31	0.5506	153.5	0.6709	31.90	0.4181
RVOT	2.371	0.0779	65.70	0.5482	114.3	0.6691	31.52	0.4670
PIVS	2.270	0.1062	76.78	0.6394	135.2	0.7713	51.56	0.6204

Conclusions

Correct ventricle flow characteristics and stress/strain calculations are of fundamental importance for many cardiovascular research where mechanical forces play a role in disease initiation, progression and treatment strategy selections. Ventricle remodeling, disease development, tissue regeneration, patient recovery after surgery and many other cell biological activities are closely associated with ventricle mechanical conditions. FSI models provide complete mechanical analysis including both flow forces and structural stress/strain conditions and fluid structure interaction. The existence of alternatives to existing leads and pacing methods may permit improvement in long-term outcomes with chronic pacemaker therapy while also making therapies such as synchronous pacing available to a wider array of patients with clinical situations. Direct comparison studies between pacing options will be needed to better understand the electromechanical associations and how these correlate with long-term morbidity, mortality, and quality of life. Studies concentrating on the therapeutic benefits of existing experimental therapies will also allow for the development of parameters that may permit correlation of findings during acute animal studies with long-term clinical outcomes. Further research needs to be done into options for alternative pacing methods, such as RVOT pacing, PVIS pacing, and how they correlate with long-term clinical outcomes. Lack of in vivo data and model construction cost are also considerations. Data from the literature or from ex vivo experiments have to be used to complete the computational models. We are in need of patient-specific data such as fiber orientation, sarcomere length contraction rate, regional material properties, etc.

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