Computational Modeling of Human Fetal Normal Sinus Rhythm and Arrhythmia

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Abstract

Non-invasive measures of the fetal ECG provide quantitative information on pacemaking rate, propagation times and velocities during normal sinus rhythm.

One dimensional partial differential equation models of propagation that reproduce fetal normal sinus rhythm in hearts from 16-40 weeks gestational age were constructed. Lengths were obtained from magnetic resonance imaging data, intercellular coupling informed by ECG timings, and cell excitation described by modified models for adult human cardiac cells.

Spatially uniform progressive reduction of the L-type calcium conductance slowed the rate, and led to atrio-ventricular conduction blocks. Self terminating and persistent re-entry with a period of 240 - 300ms could be produced within a 1-D ring ventricular tissue model.

The preliminary 1-D family of models quantitatively reproduces the observed timings of fECG intervals from 16-40 WGA, and predicts the characteristics of development of fetal AV block, and self terminating ventricular tachycardia.

1. Introduction

Current clinical instrumentation permits the noninvasive recording of 10-100µV fetal electrocardiogram (fECG) and fT fetal magnetocardio-gram from ~ 12 weeks gestational age (WGA) onwards,. RR, PR, QR and QT intervals, and T and P wave dispersions can be extracted by signal processing [1]. These measures provide quantitative information on sino-atrial node pacemaking rate (*via* RR), propagation times and hence velocities (*via* PR, QT), and ventricular action potential duration (QR) and its restitution (QT-RR) during fetal normal sinus rhythm (NSR). Occasionally (less than 5% of recordings) apparent fetal arrhythmias are observed. Fetal arrhythmias may be benign, or may be life-threatening (atrio-ventricular conduction block, ventricular tachycardia) and require *in utero* therapy [2].

Computational modeling of the heart has provided a quantitative, predictive coupling between cell and tissue electrophysiology and the ECG [3] and allows the interpretation of the body surface ECG in terms of cardiac surface activity [4]. Cardiac modeling requires detailed models of cell electrophysiology, anisotropic tissue architecture and heart geometry. The anisotropic geometry of the fetal heart has been mapped by diffusion tensor MRI [5] and there are several models of the electrophysiology of adult human cardiac cells from both the pacemaking and conducting system, and the atrial and ventricular myocardium.

Here we modify the parameters of models of adult human nodal [6], atrial [7], Purkinje [8] and ventricular [9] cells, incorporate them into a simple 1-D model of propagation in the fetal heart, and compute propagation patterns that reproduce normal sinus rhythm during gestation, provide a predictive model for congenital heart block, and the characteristics of fetal ventricular tachycardia. This preliminary 1-D model for the fetal heart is modular, and so other models for human cardiac cell electrophysiology, their parameters, and their changes during gestation may readily be incorporated.

2. Model construction

Propagation in heterogeneous cardiac tissue can be described by the nonlinear partial differential equation [3]

$$\frac{\partial V}{\partial t} = \nabla(D\nabla V) - I_{\mathrm{ion}}. \qquad (1)$$

where V (mV) is the membrane potential, ∇ is a spatial gradient operator and t is time (ms). D is the diffusion coefficient tensor (mm^2.ms^{-1}) that characterizes the electrotonic spread of voltage *via* local circuit currents, through cell-to-cell coupling by gap junctions, and the extracellular and intracellular resistances. I_{ion} is the total membrane ionic current density. For a one-dimensional

model, the vulnerable window for uni-directional conduction block can be obtained and re-entry obtained in a one-dimensional ring.

Equations for fetal I_{ion} were those for adult human cardiac cells, with changed channel expression (maximal conductances), and no changes in kinetics (any differences between adult and fetal isoforms are ignored). The conductances for SAN were modified to produce the fetal heart rate (seeAppendix), the AVN to have a lower rate, and for the atrial, Purkinje and ventricular models only g_{Na} was reduced, to reduce dV/dt_{max}.

Spatial heterogeneity can be introduced by segmenting the strand into different tissues each with different parameter value sets for I_{ion}, and intercellular coupling, or by having the parameters vary smoothly with distance, as in gradient models [10]. Here we use homogeneous segments for SAN, atrial, AVN, Purkinje and ventricular tissue, with sharp changes in parameters at their boundaries.

The lengths (mm) of each segment were based on MRI data sets [5] and diffusion coefficient informed by PR and QR intervals from [1], were constructed for hearts from 16-40 WGA. Re-entry was produced in a 1-D strand–ring, where the ventricular tissue strand terminated in a ring with a diameter ~twice the ventricular diameter. An ectopic excitation within the ring and within the vulnerable window produces a solitary action potential that circulates around the ring. If its period of rotation is shorter than the cycle length the re-entrant circulation may persist.

These preliminary models are engineered from adult tissue models as there is little available electrophysiological data from fetal human tissue, and so are massively over-parameterized for reconstructing the fECG. However, they provide a means for quantitatively interpreting developmental changes in the fECG, based on current human cardiac cellular electrophysiology, and of quantitatively predicting changes in the fECG produced by channelopathies or pharmacological actions,

Numerical solutions, with zero-flux boundary conditions, were obtained by a forward-time central-space scheme (with space steps of $\Delta x = 0.1$ mm) in conjunction with an operator splitting and adaptive time step method (to give time steps between $\Delta t = 0.01$ and $\Delta t = 0.05$ ms).

3.1 Normal sinus rhythm

The 1D model , with parameters for 16, 24, 38 WGA gave NSR intervals RR (cycle length) and PR (first atrial to first ventricular depolarisation) and QRS (first to last ventricular depolarisation) all within 10 ms of the means values for these gestational ages [1]. Since the cell models have close to resting initial conditions, and are not electrochemically balanced (i.e. there can be nonphysio-
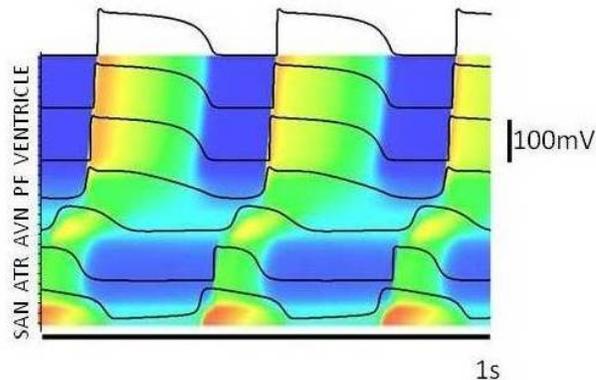

Figure 1. Space-time plot of normal sinus rhythm for 20 mm, 1-D model of 24 WGA fetal cardiac propagation model, with cycle length 400 ms. Action potentials for sinoatrial node (SAN), atrium (ATR), atrioventricular node (AVN), Purkinje fibres (PF) and ventricle are overlaid on space-time display of membrane potential.

logical drifts in [ion]$_{intra,}$ periodicity is estimated during the last 6 s of 10s simulation.

3.2. Atrioventricular conduction block

Spatial heterogeneities (different cell properties and diffusion coefficients) can give rise to partial blocks
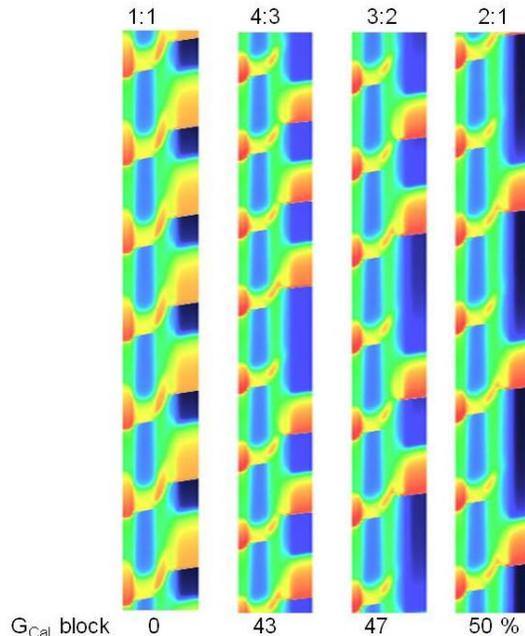

Figure 2. Space time plots for 20 mm, 1-D model of 26 WGA fetal heart illustrating normal 1:1 sinus rhythm, and 4:3, 3:2 and 2:1 conduction blocks produced by 0, 43, 47 and 50% block of G_{CaL}
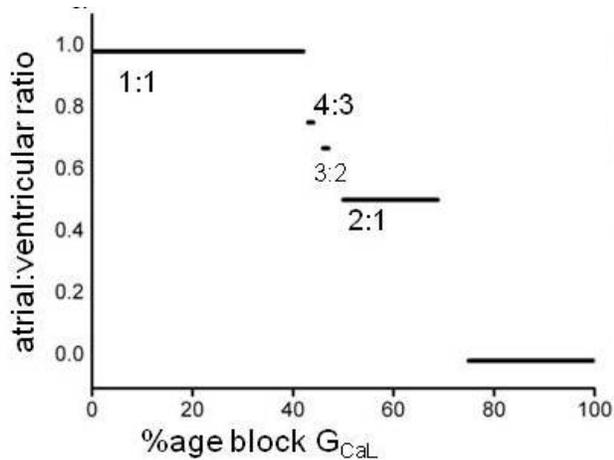
Figure 3. Ratio of ventricular: atrial periodic activity in 1D, 24 WGA model during spatially uniform block of G_{CaL}, estimated during the last 6s of 10s of activity.

(Wenckebach-like), and complete conduction block. They can be produced by spatially uniform reduction in the L-type calcium maximal conductance, $G_{Ca,L}$, and appear at the atrio-ventricular nodes illustrated in Fig. 2 for the 24 WGA model. This qualitative, Farey sequence, behaviour of intermittent conduction block, with (n+N):(m+M) regions between n:m and N:M regions shown in Fig.3 can be produced in heterogeneous and homogeneous models. Quantitatively, the details depend on the excitation and coupling parameters of the model. .

In congenital heart block (CHB) maternal antibodies produce irreversible fetal AV block, due to reduction in L- and T- type Ca^{++} current expression [11]. fECGs recorded during the development of congenital heart block could be used to fine-tune the parameters of the model. The bradycardia predicted by the preliminary model could be used to monitor the development of CHB before AV node block develops.

3.3. Ventricular re-entry

About 40% of still births have no apparent cause: sudden cardiac death, produced by ventricular fibrillation, could be a cause. Ventricular fibrillation (VF) in the fetal heart could be a cause, and VF in the adult is almost always preceded by wavebreak and re-entry. Evidence for *in utero* VF as a cause of fetal death leading to still birth would require extensive fetal ECG monitoring, and the small size of the fetal heart would argue against it. High resolution imaging of the fetal heart [5, 12] suggests that the fetal ventricle is more a feltwork of pathways than a functional syncytium, and so re-entry may be possible. Computational modelling provides a
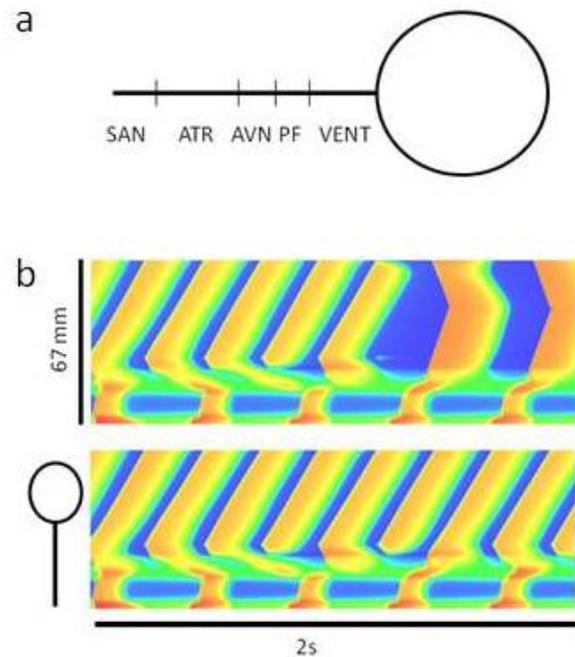

Figure 4. (a) schematic representation of generic segmented one-dimensional model for cardiac propagation. (b) space-time plot for self-terminating and persistent ring re-entry in 24 WGA strand-ring model; the ventricle has been extended to give a 40mm ring, where the circumference of the ring is ~π times the ventricular diameter.

method for determining if re-entry is quantitatively possible, given the ventricular size, and action potential wavelength (determined by action potential duration and velocity). Excitation initiated at different sites (propagation from the rest of the cardiac system *via* the Purkinje fibres) and ectopic excitation within the ring can lead to re-entry if the ectopic excitation occurs in a narrow (~2ms wide) window 275 ms after the upswing of the ventricular action potential. The period of re-entry in the 24 WGA model is 240 ms, and increases with ring circumference and decreases with ring diffusion coefficient

4. Discussion

The 1-D family of models for the fetal heart is preliminary, is engineered from current models of adult cardiac cells by changes only in expression (channel density): differences in kinetics (due to channel isoforms, microenvironment) are omitted. These can readily be incorporated if and when experimental data is available.

The family of models reproduces the observed

timings of fECG intervals from 16-40 WGA during normal sinus rhythm,   and quantitatively predicts the characteristics of fetal AV block due to spatially uniform reduced G_{CaL}, and the vulnerable window for, existence of, and period of self terminating   and persistent re-entrant fetal ventricular tachycardia in hearts with a ventricular diameter of >~1 cm.

The period of the model ventricular re-entry   is consistent with the period of the "putative self-terminating ventricular tachycardia" we have observed, and so such fECG recordings may result from re-entrant tachycardia in the fetus. If they self-terminate, they are benign; if not, they could be a cause of death *in utero*.

Appendix

Parameters used for figures in this paper

age:	16WGA	24 WGA	38WGA
Geometry: propagation distance/mm			
SAN	1.6	3.4	5.6
Atrial	3.8	9.4	13.8
AVN	2.0	4.6	6.0
Purk	2.0	4.6	6.0
Vent	8.0	18.0	24.0
Sinoatrial node conductances nS/pF			
$I_{Na`}$	0.468	0.468	0.468
I_{K1}	0.0033	0.0033	0.0033
I_{CaT}	0.2926	0.2926	0.2926
I_f	10.7536	4.9632	4.9632
I_{to}	0.07848	0.0784	0.07848
I_{CaL}	0.43725	0.254375	0.22
I_{Ks}	0.08294	0.08294	0.08294
I_{Kr}	0.013235	0.013235	0.013235

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