Changes in QRS and T-wave Loops Subsequent to an Increase in Left Ventricle Globularity as in Intrauterine Growth Restriction: a Simulation Study

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Abstract

Cardiovascular remodeling induced by intrauterine growth restriction (IUGR) manifests in adulthood by more globular ventricles, as evidenced by in vivo measurements. Some studies have reported that the angle between the dominant vectors of the QRS and T wave loops is significantly altered as a result of the induced remodeling. To investigate whether the more globular ventricular shape was underlying such alteration, we performed electrophysiological simulations in a human biventricular model for control and in a model obtained by deforming the control one to represent a more spherical left ventricle (SLV). We included transmural ventricular heterogeneities and a Purkinje network. 12-lead pseudo-ECGs were calculated, from which spatial QRS and T-wave angles were computed. The angle between the T-wave and the XZ-plane was found to increase in the SLV model, showing a variation similar to that reported in in vivo studies. However, the angle between the dominant vector of the QRS and T-wave loops, both projected onto the XY plane, was lower for control, contrary to previous clinical observations in IUGR adults. Other clinical results could not be reproduced in our simulations either. Our findings suggest that a more globular left ventricular shape leads to changes in the angles of QRS and T-wave loops, but further research is needed to fully understand these changes and the underlying mechanisms.

1. Introduction

Intrauterine growth restriction and low birth weight are some of the factors associated with an increased risk of heart disease in adulthood as reported in [1, 2].

IUGR is associated with cardiovascular remodeling, which manifests by more globular ventricles when assessed by the sphericity index (base-to-apex length/basal diameter). The comparison between control subjects with children who have suffered fetal growth restriction, evidenced a difference in heart shape, characterized by an increase in basal diameter, reduction in base-apex length and a more globular ventricle [3]. Previous ECG studies have shown that the angle between QRS and T-wave dominant vectors are able to identify adults with cardiovascular remodeling subsequent to IUGR [4], these changes have been suggested to lead to higher cardiovascular mortality in adulthood [1, 2].

Different researches, in different age groups, have demonstrated the prevalence of these anatomical changes in the cardiac muscle. In children, developing a cardiovascular evaluation including echocardiography and blood pressure measurement it has been possible to evidence that the heart changes persists at six months of age [5]. Measurements done on adults have corroborated the results observed on children and preadolescents. Using the superficial electrocardiography registers and generating a vectorcardiogram it has been found an statistically significant variation of the angle between the dominant vector of QRS complex and the dominant vector of T wave projected on the frontal plane between the control patients and patients diagnosed with IUGR [4]. This difference could be fundamental in assessing the cardiovascular risk of the patients who had IUGR.

Currently, little is known about the morphophysiological factors that cause this angular variation in patients with IUGR, subjects born with low weight, and its relationship with cardiovascular risk in adulthood. In this study, we perform electrophysiological monodomain simulations in a human biventricular geometry for control and in one with a spherical left ventricle (SLV) built by applying loads on the control geometry. Considering a common simulation framework, the angular variation between the dominant
vector of the QRS loop and the T wave will be evaluated, to observe if it is possible to obtain by simulation, the results registered on real data.

2. Materials and methods

The cardiac tissue electrophysiological simulation and the action potential propagation through the tissue was based on the Finite Element Method. The heart muscle was generated from medical images of a control patient who did not report a history of heart problems. The three-dimensional model of the heart included transmural ventricular heterogeneities, corresponding the 50, 20 and 30% of the wall thickness to endocardial, midmyocardial and epicardial tissues, respectively. The direction of the muscle fibers was associated to each node of the tetrahedral mesh using a rule-based method [6].

Cellular electrophysiology was represented by the O’Hara-Rudy human ventricular cell model. The value of the longitudinal diffusivity was 0.0025 cm$^2$/ms and the longitudinal to transversal conductivity ratio was set 0.25. Purkinje fibers for electrical stimulation were implemented in the model, using a method of projecting fractals on endocardial tissue [7]. The complete His-Purkinje network was modeled with the bundle branch with a diffusivity of 0.0068 cm$^2$/ms and the Purkinje-myocardial junctions with a diffusivity of 0.0013 cm$^2$/ms (Figure 1).

Figure 1. Biventricular model. a) Bundle brunch, b) Purkinje network on the control model, c) Purkinje network on the SLV model.

The bundle branch was divided into three different structures, according to what was observed and recorded in ex vivo and in vivo experimental studies and modelled in [8]. On the right ventricle one branch reaches on the anteroapical region. On the left ventricle the bundle branch was divided in two branches, one on the posterobasal location and the last on the apex [9]. The current injected in the His Bundle has an amplitude of 200 mA and lasts 0.5ms, with a cycle length is 1000 ms. 12-lead ECGs were simulated by placing virtual electrodes in the standard 12-lead ECG positions on the torso and computing the extracellular potentials [10]. From the simulated ECG, the dominant QRS and T-wave angles were computed using the method described in [4] and compared with the results reported there.

3. Results

The control biventricular geometry was deformed to represent the SLV model. The control model has a sphericity index of 1.54 (base to apex length = 70.73 mm / basal diameter = 45.83 mm) and the SLV model a sphericity index of 1.32 (base to apex length = 63.66 mm / basal diameter = 48.17 mm). The sphericity change was developed considering the measurements reported in [3].

The transformation of 12-leads to orthogonal leads X, Y, and Z was based on the inverse Dower’s method [11] (Figure 2). Finally, the dominant vector of the depolarization and repolarization loops and its projection on the planes were calculated.

Figure 2. Orthogonal leads X, Y, and Z derived from 12-lead pseudo-ECG.

The calculated angles are presented in Table 1 in the simulated control and simulated SLV columns and are contrasted with the results obtained in-vivo in adults (a control group formed by term birth subjects with adequate weight for gestational age and an IUGR group at birth). The angle between the QRS loop dominant vector and of the T-wave both projected onto XY plane (frontal plane), $\theta_{R-T_{XY}}$, is lower for control model, opposite as previously observed in IUGR adults.

The angle between QRS loop and the XZ (transverse plane) and YZ (sagittal plane) planes, $\phi_{R-XZ}$ and $\phi_{R-YZ}$, decreases in the SLV model and increases in the XY plane $\phi_{R-XY}$. The angle of the T-wave projected on the XZ and YZ planes, $\phi_{T-XZ}$ and $\phi_{T-YZ}$, shows an increase in the SLV model and a reduction of the angle in the XY plane $\phi_{T-XY}$. Finally, the difference between the dominant vectors of the QRS loop and the T-wave projected on the planes, $\phi_{R-XZ} - \phi_{T-XZ}$, $\phi_{R-XY} - \phi_{T-XY}$, and $\phi_{R-YZ} - \phi_{T-YZ}$ shows an increase in the angle in all three cases.
Table 1. Loop angles: *p-value < 0.05, **p-value < 0.01 significant differences between control and IUGR groups. Data are mean ± standard deviation. Table edited from [4].

<table>
<thead>
<tr>
<th>Adults</th>
<th>Angle</th>
<th>Control</th>
<th>IUGR</th>
<th>Control Simulated</th>
<th>SLV Simulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>(degrees)</td>
<td>n = 54</td>
<td>n = 33</td>
<td>n = 1</td>
<td>n = 1</td>
<td></td>
</tr>
<tr>
<td>θ_{RT−XY}</td>
<td>13.49 ± 13.65</td>
<td>9.26 ± 8.47**</td>
<td>14.77</td>
<td>23.83</td>
<td></td>
</tr>
<tr>
<td>φ_{R−XZ}</td>
<td>32.85 ± 9.08</td>
<td>35.68 ± 6.12</td>
<td>9.21</td>
<td>5.60</td>
<td></td>
</tr>
<tr>
<td>φ_{R−XY}</td>
<td>29.47 ± 13.02</td>
<td>22.07 ± 11.80**</td>
<td>73.52</td>
<td>77.40</td>
<td></td>
</tr>
<tr>
<td>φ_{R−YZ}</td>
<td>40.72 ± 12.05</td>
<td>44.17 ± 9.81</td>
<td>13.53</td>
<td>11.24</td>
<td></td>
</tr>
<tr>
<td>φ_{T−XY}</td>
<td>29.39 ± 10.61</td>
<td>33.15 ± 10.67*</td>
<td>30.05</td>
<td>33.01</td>
<td></td>
</tr>
<tr>
<td>φ_{T−XZ}</td>
<td>14.42 ± 8.68</td>
<td>14.48 ± 9.41</td>
<td>48.54</td>
<td>45.01</td>
<td></td>
</tr>
<tr>
<td>φ_{T−YZ}</td>
<td>54.83 ± 9.52</td>
<td>51.52 ± 12.13</td>
<td>25.65</td>
<td>26.76</td>
<td></td>
</tr>
<tr>
<td>φ_{R−YZ} − φ_{T−XZ}</td>
<td>3.45 ± 9.61</td>
<td>2.54 ± 8.43</td>
<td>-20.84</td>
<td>-27.41</td>
<td></td>
</tr>
<tr>
<td>φ_{R−XY} − φ_{T−XY}</td>
<td>15.05 ± 14.14</td>
<td>7.59 ± 14.58**</td>
<td>24.97</td>
<td>32.38</td>
<td></td>
</tr>
<tr>
<td>φ_{R−YZ} − φ_{T−YZ}</td>
<td>-14.11 ± 13.99</td>
<td>-7.35 ± 13.96**</td>
<td>-12.11</td>
<td>-15.51</td>
<td></td>
</tr>
</tbody>
</table>

4. Discussion

This work shows the results of the electrophysiological simulation of a monodomain biventricular model of a control heart and a globular heart model simulating the change in sphericity produced by IUGR. The results focus on the comparison of the angular variation between the dominant vector of depolarization and repolarization calculated on the two models (Figure 3). The SLV heart model is characterized by an increase in the basal diameter of the left ventricle and a reduction in the length from base to apex.

Table 1 synthesizes the angular variation results reported in [4] and the results obtained in the present work. Five of the angles presented show a significant difference between the control group and IUGR. Four of our results are not concordant for the angles reported to be significantly reduced in IUGR adults.

The projection of the angle between the QRS loop and the T-wave on the XY-plane (θ_{RT−XY}) shows a significant reduction in the IUGR group; however, our result shows an increment (from 14.77 to 23.83 degrees), contrary to that reported in the literature.

The second parameter significantly different in the table 1 is the angle between the QRS loop and the XY plane φ_{R−XY}. The literature shows that patients with IUGR present an angular reduction; however, the simulation results show an increased angle in the SLV model.

The angle calculated between T-wave and the XZ-plane increases in the SLV model in the T-wave, showing a variation similar to that registered and reported in the literature.

The last two significantly different parameters show the angular difference between the dominant vectors of QRS loop and T-wave in the XY and YZ planes. For the two planes, the simulation results show a trend contrary to the literature.

Z lead presents an amplitude higher than X and Y leads. This difference has an important impact on the magnitude and therefore on the dominant vectors on the XY plane. A Purkinje network based on fractals has been incorporated into the simulation to make the propagation process more realistic; however, it is important to consider that the regions and the activation sequence directly affect the ventricular activation and repolarization [8].

Beyond the Purkinje and endocardial interface, electrical propagation through tissue is directly dependent on tissue characterization and transmural heterogeneities. In this context, the relationship between endo, mid and epi directly affects the repolarization stage as reported in [12].

5. Conclusions

Through the electrophysiological simulation of a control and SLV heart model, we have managed to reproduce one of five statistically different parameters between a control group and IUGR presented in the literature. The angular variation of the repolarization stage on the XZ plane.

Our findings suggest that a more globular left ventricular shape leads to changes in the angles of QRS and T-wave loops.

The future work of this research contemplates dividing the cardiac tissue into endo, mid and epi assigning different percentages considering that inter-subject variability in transmurality affects repolarization. Additionally, tests will be carried out on an SLV model built on the basis of medical images.

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