

QRS Width and T-peak to T-end Interval Are Prolonged in Preadolescents with Severe Intrauterine Growth Restriction at Birth when Compared to Controls

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Abstract

The aim of this study is to assess how increased globularity and wall thickness resulting from intrauterine growth restriction (IUGR) in preadolescents affects the QRS width, T-peak to T-end and QT intervals, all biomarkers associated with susceptibility to ventricular arrhythmia. 12-lead ECG from 33 subjects who had severe IUGR and 60 control subjects were studied. Spatial principal component analysis was applied to the multilead ECG to emphasize the QRS complex and T-wave, followed by QRS detection and T-wave delineation to derive QRS width, T_{pe} , QT intervals and the ratio T_{pe}/QT . Additionally, we used a computational biventricular model with and without a more globular ventricle structure as observed in IUGR subjects but with no wall thickness modification, where the simulated ECG and its derived intervals were measured and compared with the clinical results. The IUGR subjects showed significantly wider QRS (4 ms), longer T_{pe} intervals (2 ms), and higher T_{pe}/QT ratio (3%) as compared to control group. Simulations did not corroborate those findings suggesting that other cardiac remodeling different from the accounted globularity, as perhaps wall thickness, should be the responsible for the increased QRS width and T_{pe} interval in IUGR, all associated with an increased transmural dispersion and a greater risk of ventricular arrhythmia.

1. Introduction

Intrauterine growth restriction (IUGR) shows morphological changes in the ventricles beyond the fetal stage,

evidencing cardiac structural and functional remodelling [1] that manifest as variations in the depolarization and repolarization phases of the vectorcardiogram in preadolescents [2]. Some of these electrical changes have also been measured in adults with IUGR [3, 4] and might be associated with a higher risk of cardiovascular disease in adult life.

From the standard 12-lead ECG, the QT interval and the T-peak to T-end interval (T_{pe}) have been identified as predictors of ventricular arrhythmias in several cardiac conditions [5]. Besides, the T_{pe}/QT ratio, which quantifies the dispersion of repolarization relative to ventricular action potential duration, is considered an index of arrhythmogenesis [6]. T-wave morphology accounts for the spatial dispersion of action potential duration found in the transmural ventricular wall, apex-to-base and right-to-left directions [7]. As IUGR-related cardiac remodeling involves basal diameter widening and wall thickness increase, we hypothesize these anatomical changes may affect T-wave morphology and therefore T_{pe} interval. Additionally, It is not known how these differences in anatomy may affect the time of ventricular activation reflected in the ECG as QRS width.

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2. Materials and methods

The material for the study consisted of 12-lead ECG recordings (13 seconds at a sampling frequency of 1000 Hz) from a population of 93 preadolescents. From those, 33 subjects had severe IUGR (birthweight \leq 3rd centile) with medically induced preterm delivery and 60 subjects were normally grown controls born at term. IUGR and control subjects were selected from the study conducted at a tertiary centre (Hospital Clinic of Barcelona) [8].

The ECGs were delineated, identifying QRS onset and offset and the T-peak and T-end fiducial points using a wavelet-based ECG delineator [9]. A single-lead delineation adding a multilead rule technique was applied to identify unique lead-independent fiducial points for each beat. Then, a spatial lead transformation based on the principal component analysis (PCA) technique was used to generate a new lead where the information from the independent 8-leads was maximally condensed at the transformed lead, and where more accurate delineations can be obtained. First the transform was learned at the T-wave area so the T-wave was emphasized (PCA_T lead). Alternatively, the QRS was used for learning the transform (PCA_{QRS} lead). The PCA_T and PCA_{QRS} transformed leads were again delineated to identify the fiducial points of the ECG: the R peak, the start and end points of the QRS complex, the T-wave, and its peak and end (Fig. 1).

The T_{pe} and QT values were determined for each beat and corrected using Fridericia's formula ($T_{pe,c} = T_{pe} / \sqrt[3]{RR}$ and $QT_c = QT / \sqrt[3]{RR}$). Subsequently, the medians of $T_{pe,c}$ and QT_c series were taken as representatives for each patient. The $T_{pe,c}/QT_c$ ratio was also calculated. Statistical comparison was performed between the control and IUGR groups using the Student's t-test, and for each group, the median and interquartile range were recalculated. The results are displayed in the Table 1). On each patient's PCA_{QRS} lead, the onset and end of the QRS complex were identified, and a parallel comparison was made between the duration of this interval between the control and IUGR groups.

Additionally, computational simulations of cardiac electrophysiology were conducted using a biventricular electrophysiological model based on a realistic heart and torso [10]. This model was considered as the control. The control model was further deformed, reducing the sphericity index of the left ventricle as described for the IUGR population [1]. The finite element method was employed on the control and IUGR models to determine the electrical propagation in cardiac tissue using a monodomain model [11]. A sequence of three beats were simulated to reach steady state conditions in the ventricular electrical activity with a frequency of 1000 ms, using a stimulus amplitude of 200 mA and a stimulus duration of 0.5 ms. To compute the 12-lead ECG simulations, a torso volume was used to

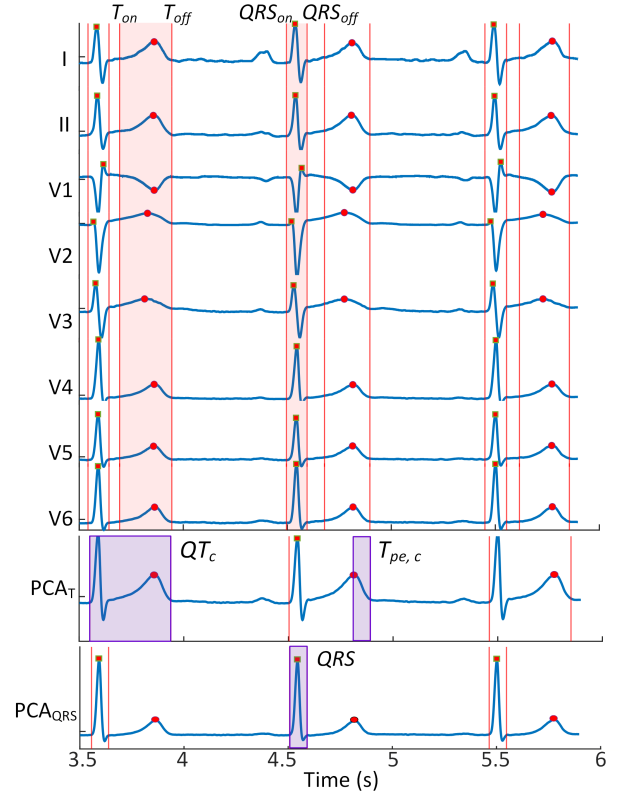


Figure 1. The independent 8 ECG leads from a subject in the control group with marks on QRS onset and end, R-wave peak, T-wave onset, peak, and end with red long lines. Similarly, PCA_T and PCA_{QRS} first leads include annotations marked as red lines over the leads together with definitions of the intervals of interest (T_{pe} , QT , and QRS) shaded in purple.

calculate the extracellular potential at virtual electrode positions. Using the simulated ECG, PCA_T and PCA_{QRS} leads were also computed and delineated for fiducial points and related interval estimations in simulation.

Manual delineation was performed on the PCA_{QRS} lead of two subjects at the QRS onset, as marks were located on the peak of the Q-wave and not at its beginning, due to a low Q voltage protection rule of the delineator.

3. Results

The IUGR group exhibited a significantly longer $T_{pe,c}$ interval compared to the control group, similar to the $T_{pe,c}/QT_c$ ratio. The QT_c interval did not show a significant change, as shown in Figure 2 and Table 1. The amplitude value of the T-wave did not show a significant difference (Control = 0.826 (0.631 - 0.993) mV, IUGR = 0.776 (0.561 - 0.899) mV, p value = 0.318). In the control group, the $T_{pe,c}$ value of one subject was excluded due

	ECG data			Simulation	
	Control (n = 60)	IUGR (n = 33)	<i>p</i> value	Control	IUGR
$T_{pe,c}$ (s)	0.076 (0.074 - 0.081)	0.078 (0.076 - 0.083)	0.030	0.078	0.078
QT_c (s)	0.391 (0.376 - 0.406)	0.389 (0.381 - 0.399)	0.703	0.345	0.344
$T_{pe,c}/QT_c$ (s)	0.196 (0.188 - 0.207)	0.202 (0.196 - 0.212)	0.020	0.226	0.226
QRS width (s)	0.083 (0.074 - 0.089)	0.087 (0.081 - 0.090)	0.039	0.067	0.068

Table 1. Median and interquartile range and *p*-value for $T_{pe,c}$, QT_c , $T_{pe,c}/QT_c$, and QRS width measurements on the control and IUGR subjects groups. The two most right columns show the results obtained in the simulation of the control and IUGR models, taking the median value of the beats.

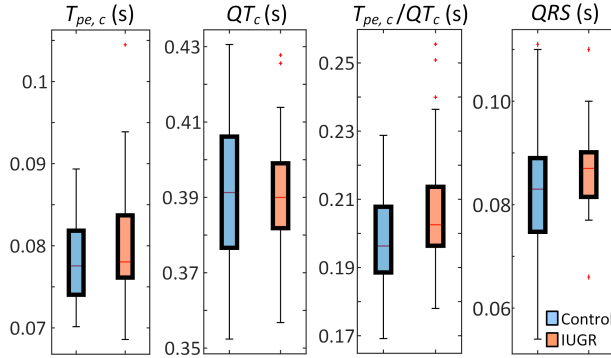


Figure 2. Changes in $T_{pe,c}$, QT_c , $T_{pe,c}/QT_c$, and QRS width for control (blue) and IUGR (orange) groups. Central red lines indicate the median and the bottom and top edges of the box show the 25th and 75th percentiles, respectively.

to a reduced RR distance, which caused an overcorrection with heart rate, resulting in an outlier $T_{pe,c}$ value. For the IUGR group, manual delineation correction of the T-wave end was performed on two subjects, owing to the overshoot T-wave end in the PCA lead that led to early detection of this point.

The results for the analysis of the QRS width can be observed in Figure 2. The IUGR group exhibited a significantly longer QRS duration compared to the control group, as shown in Table 1. Regarding the amplitudes ratio, no significant differences were observed.

The results obtained from the ECG simulation of the control and IUGR models did not show differences in terms of $T_{pe,c}$, QT_c , or the QRS width, as shown in Table 1.

4. Discussion

The present study focuses on the analysis of changes in $T_{pe,c}$ and the QRS complex width in two groups of preadolescents: control and IUGR. It also extends the analysis

to the simulation of two computational models, one representing control and the other IUGR. To simulate IUGR, the sphericity index (calculated as base-apex length divided by basal diameter) was intentionally decreased, reflecting the cardiac anatomical changes observed in individuals diagnosed with IUGR. For the correction of T_{pe} and QT , the Fridericia's formula was used because when a specific correction for the available data was applied, a wide variability was observed, partly due to the limited amount of data in the study.

When comparing the control and IUGR groups, the results for $T_{pe,c}$ showed a significant increase in the IUGR group, potentially associated to the widening of the left ventricular wall. However, in the simulation where sphericity was altered to mimic IUGR, there was no significant difference in this parameter between the control and IUGR models. The IUGR simulation model was deformed, reducing its sphericity index by 8.7%, in agreement with the morphological changes reported in [1]. Nonetheless, the maximum increase in the ventricular wall width in the model was 0.2 mm at the base of the left ventricular wall, resulting in an insignificant change in the $T_{pe,c}$ duration (0.078 s). A future study could investigate the increase in the width of ventricular walls and its influence on the duration of the T_{pe} interval.

The QT_c interval results in the clinical subjects showed no significant differences between the control and IUGR groups, mirroring the findings in the simulation. Both the $T_{pe,c}$ and QT_c markers were measured from the PCA_T first lead. The amplitude of the T-wave peak did not exhibit a significant difference between the analyzed groups.

For the analysis of the QRS complex interval duration, delineation was performed on PCA_{QRS} first lead. QRS width showed more variability within the control group than in the IUGR group, with the IUGR group displaying significantly higher values (see Fig. 2). This increase in duration could be attributed to the increase in ventricular volume, leading to a delay in electrical propagation, thus resulting in a widening of the QRS complex in the ECG. In the simulation, no significant differences were observed in this parameter. Regarding the amplitude of the R peak,

a slight increase was observed in the IUGR group, but it did not reach statistical significance.

5. Conclusions

Our findings suggest that cardiac anatomical remodeling in IUGR subjects leads to an increase in $T_{pe,c}$, in agreement with the previously reported increase in relative wall thickness. This rise in $T_{pe,c}$ is associated with an increased transmural dispersion; although this increase is relatively modest (2 ms). While such a change is associated with a higher risk of ventricular arrhythmia, the impact of various additional parameters including ionic remodelling that generally affect ventricular dispersion should not be overlooked. Similarly, an increase in the duration of the QRS interval is observed, which could be also linked to the increase in the width of the ventricular walls.

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