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. 8-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 8-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 onset 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 8-lead ECG simulations, a torso volume was used to 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.

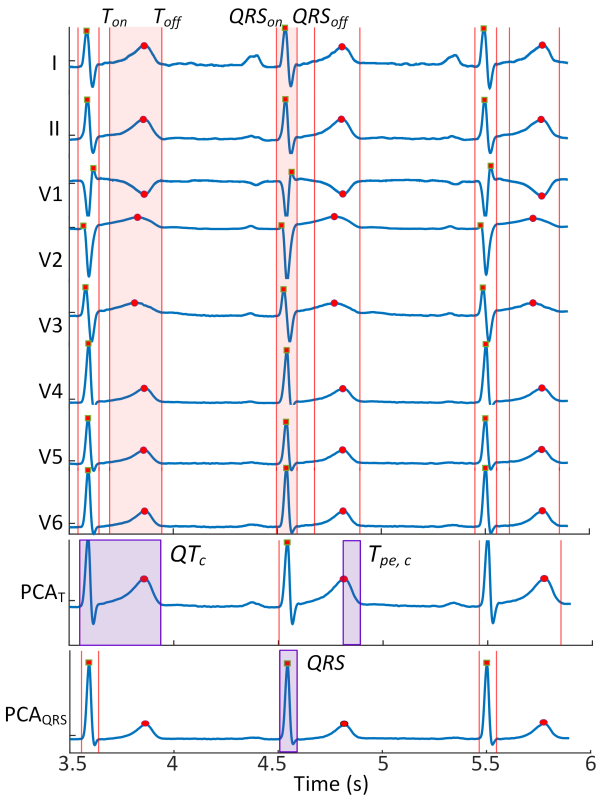

Figure 1. 8-lead ECG from a subject in the control group with marks on QRS onset and end, R-wave peak, T-wave onset peak and end with red long lines. Similarly, PCA_T and PCA_QRS first leads include annotations marked as red lines over the leads together with definitions of the intervals of interest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

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 to a reduced RR distance, which caused an overcorrection with HR, 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

	ECG data			Simulation	
	Control (n = 60)	IUGR (n = 33)	p 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.

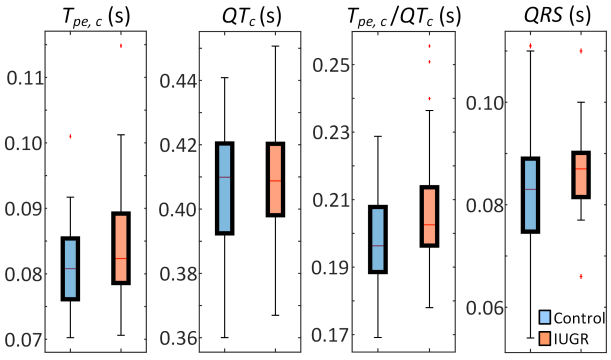

Figure 2. Changes in $T_{pe,c}$, QT_c, $T_{pe,c}/QT_c$, and QRS width for control (blue) and IUGR (orange) groups. Central red lines indicate the median and the bottom and top edges of the box show the 25th and 75th percentiles, respectively.

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 amplitude, no significant difference was observed. 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. The results of the simulation in 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 addresses the analysis of changes in $T_{pe,c}$ and the QRS complex width in control and IUGR groups of preadolescents, as well as in the simulation of two computational models, control and IUGR, representing the sphericity index (apex-base length/basal diameter) reduction as a consequence of cardiac remodeling in subjects 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.

The results of $T_{pe,c}$, when contrasting the control and IUGR subject groups, showed a significant increase in the IUGR group, possibly associated with the increase in the width of the left ventricular walls, since in the simulation of sphericity no significant difference was found in this parameter between the control and IUGR models. The IUGR simulation model was deformed, reducing its sphericity index by 8.7%, considering the morphological changes reported in [1]. Nonetheless, the width increase of the ventricular wall in the simulation showed a maximum increase of 0.2 mm at the base of the left ventricular wall, which would lead to no significant 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.

Results of the QT_c interval in real subjects did not show a significant difference between the control and IUGR subjects, just like in the simulation. Both the $T_{pe,c}$ and QT_c values were measured from the PCA_{T} 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} lead. In the measurement of this interval, greater variability was observed in the control group, and a significantly higher value for the IUGR group (Figure 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 difference was observed in this parameter. As for the amplitude of the R peak, there is a slight increase in the IUGR group, but it is not significant.

5. Conclusions

Our findings suggest that cardiac remodeling occurring in IUGR subjects increases $T_{pe,c}$, consistent with the previously reported increase in relative wall thickness. This increase in $T_{pe,c}$ is associated with an increased transmural dispersion; however, the change found is small (2 ms). Although this change is associated with a higher risk of ventricular arrhythmia, the impact of various additional parameters that generally affect ventricular dispersion should not be dismissed. Similarly, an increase in the duration of the QRS interval is observed, also associated with the increase in the width of the ventricular walls.

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References

[1] Sarvari SI, Rodriguez-Lopez M, Nuñez-Garcia M, Sitges M, Sepulveda-Martinez A, Camara O, Butakoff C, Gratacós E, Bijnens B, Crispi F. Persistence of cardiac remodeling in preadolescents with fetal growth restriction. Circulation Cardiovascular Imaging jan 2017;10(1). ISSN 1941-9651.

[2] Ortigosa N, Rodriguez-Lopez M, Bailón R, Sarvari SI, Sitges M, Gratacos E, Bijnens B, Crispi F, Laguna P. Heart morphology differences induced by intrauterine growth restriction and preterm birth measured on the ECG at preadolescent age. Journal of Electrocardiology 2016;49(3):401–409. ISSN 15328430.

[3] Ortigosa N, Rodriguez-Lopez M, Bailon R, Sepulveda-Martinez A, Gratacos E, Crispi F, Laguna P. Intrauterine growth restriction induced ECG morphological differences measured in adulthood. Computing in Cardiology 2018; 2018-Septe:3–6. ISSN 2325887X.

[4] Bueno-Palomeque FL, Mountris KA, Mincholé A, Ortigosa N, Bailón R, Pueyo E, Laguna P. Changes in QRS and T-wave loops subsequent to an increase in left ventricle globularity as in intrauterine growth restriction: a simulation study. In 2020 Computing in Cardiology. IEEE, 2020; 1–4.

[5] Yamaguchi M, Shimizu M, Ino H, Terai H, Uchiyama K, Kotaro O, Mabuchi T, Konno T, Kaneda T, Mabuchi H. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: A new index for arrhythmogenicity. Clinical Science 2003;105(6):671–676. ISSN 01435221.

[6] Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, Yan GX. Tp-e/QT ratio as an index of arrhythmogenesis. Journal of Electrocardiology 2008;41(6):567–574. ISSN 00220736.

[7] Emori T, Antzelevitch C. Cellular basis for complex T waves and arrhythmic activity following combined IKr and IKs block. Journal of Cardiovascular Electrophysiology 2001;12(12):1369–1378. ISSN 10453873.

[8] Crispi F, Bijnens B, Figueras F, Bartrons J, Eixarch E, Le Noble F, Ahmed A, Gratacós E. Fetal Growth Restriction Results in Remodeled and Less Efficient Hearts in Children. Circulation jun 2010;121(22):2427–2436. ISSN 0009-7322.

[9] Martínez JP, Almeida R, Olmos S, Rocha AP, Laguna P. A Wavelet-Based ECG Delineator Evaluation on Standard Databases. IEEE Transactions on Biomedical Engineering apr 2004;51(4):570–581. ISSN 00189294.

[10] Mincholé A, Zacur E, Ariga R, Grau V, Rodriguez B. MRI-based computational torso/biventricular multiscale models to investigate the impact of anatomical variability on the ECG QRS complex. Frontiers in Physiology 2019;10:1103.

[11] Bueno-Palomeque FL, Mountris KA, Ortigosa N, Bailón R, Bijnens B, Crispi F, Pueyo E, Mincholé A, Laguna P. QRS-T angles as markers for heart sphericity in subjects with intrauterine growth restriction: a simulation study. IEEE Journal of Biomedical and Health Informatics 2023;.

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