QT-Interval Dispersion in Malnourished Children

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Summary

Background: Little is known about the electrocardiographic (ECG) QT interval and its variability in malnourished children.

Hypothesis: The study of the QT interval and its dispersion in malnourished children was undertaken to determine whether the QT interval and its variability are increased in these children.

Methods: In 40 children (20 malnourished and 20 controls) aged 12.2 ± 14.4 months (23 male) a conventional ECG was performed for computing heart rate, heart rate variability, corrected QT interval, and QT-interval dispersion. A blood sample was obtained for measuring hemoglobin, hematocrit, plasma protein, and plasma electrolytic concentrations.

Results: Corrected heart rate, heart rate variability, and QT interval were similar in both groups. When compared with the control group, the malnourished children had greater corrected QT-interval dispersion, and that dispersion was more accentuated in the precordial leads. They also had repolarization abnormalities (flattened or inverted T waves and U waves). Hemoglobin, hematocrit, plasma protein, and plasma electrolytic concentrations were lower in the malnourished children. However, the ECG findings showed no statistically significant relationship with either the blood parameters, the severity or type of malnutrition, and the size or the weight of the children.

Conclusions: QT-interval dispersion is increased in malnourished children and the dispersion is more accentuated in the precordial leads.

Key words: malnutrition, QT interval, dispersion, children

Introduction

The depolarization and repolarization in the cardiac ventricular muscle can be measured in the electrocardiogram (ECG) by determining the QT interval.¹ The QT interval depends on the preceding cardiac cycle duration. In consequence, the QT interval should be corrected by the heart rate. Bazett's formula¹ is the most frequently used formula to correct the QT interval.

The cardiac repolarization process can differ from one region of the ventricles to the other. It has been estimated that this difference is expressed in the QT-interval variability when that interval is measured in the different ECG leads.² This variability has been designated as the QT-interval dispersion.

There are several conditions (e.g., congenital forms of long QT syndrome, class I antiarrhythmic agents, myocardial infarction, etc.) that produce a QT-interval prolongation and/or an increase in QT-interval dispersion. In these cases, the patients have an increased risk of suffering lethal ventricular arrhythmias, such as torsade de pointes and ventricular fibrillation.^{1–4}

Malnutrition is a widespread disease in Latin America⁵ where it afflicts millions of children. Malnourished children suffer several alterations in body composition that could produce repolarization abnormalities.^{6,7} Among these alterations, the electrolytic disturbances and the significant reduction of the myocardial mass that have been observed in these children could produce an increased heterogeneity in the repolarization process. If this were the case, we should expect either a greater QT interval and/or an increased QT-interval dispersion in malnourished children. To the best of our knowledge, however, the corrected QT interval and QT-interval dispersion of malnourished children have not been previously described and are the subject of the present paper.

Methods

The procedures were carefully explained to all the patients' guardians. Those who accepted to participate signed a written

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informed consent. The study protocol had been previously approved by the Human Research Committee of our Institution. The investigation was performed in accordance with the Declaration of Helsinki.

Patients

Twenty children (11 male) aged 12.35 ± 14.88 months with a well-established diagnosis of malnutrition were included. The malnutrition diagnosis and its severity were based on the criteria of Mendez Castellano *et al.*⁵ adapted to the Venezuelan children population. According to Mendez Castellano's table, the malnutrition state was qualified as mild, moderate, or severe. The clinical picture indicated the type of severe malnutrition (kwashiorkor or marasmatic).

The malnourished children's heart rate, heart rate variability, corrected QT interval, and its dispersion were compared with those of 20 well-nourished children (12 males), aged 12.12 ± 14.39 months (Table I).

Clinical Evaluation

All patients were submitted to an exhaustive medical examination performed by a pediatrician. When acute disturbances existed (i.e., dehydration, diarrhea, infections, etc.), these were corrected before performing the measurements. Thereafter, a conventional 12-sequential lead ECG was recorded at a paper speed of 25 mm/s.

Electrocardiographic Measurements

All ECGs were blindly analyzed by one of the authors. The QT measurements were performed blindly by the other three researchers.

Heart rate measurements: The R-R interval was measured in each one of the 12 ECG leads. In cases of premature beats, the R-R interval recorded before and that recorded after the extrasystoles were not taken into account in the computing. Thereafter, the mean R-R interval and its standard deviation were calculated, as was the difference between the maximal

and minimal recorded R-R intervals. Both standard deviation and maximal difference were used as estimates of heart rate variability.

QT interval and QT-interval dispersion measurements: The QT interval was measured in each one of the 12 ECG leads and was corrected according to Bazett's formula.¹ The QT interval beginning was that of the QRS complex. The end of the T wave was determined by the intersection of the basal line with a line traced as a parallel to the late recovery phase or the T wave. When U waves appeared, they were included in the QT interval measurement (Fig. 1).

Of the possible ways of determining the QT-interval dispersion we selected (1) the calculation of the standard deviation of the mean corrected QT interval, and (2) the difference between the maximal and minimal corrected QT interval. Both calculi were performed in the 12 leads and in the standard and precordial leads separately.

Blood Sample Determinations

In all children, a venous blood sample was obtained for the determination of hemoglobin, hematocrit, plasma protein, and plasma electrolytic concentrations.

Statistical Analyses

Alpha value was set at 0.05 and confidence intervals at 95%. The analyses were performed with the Excel[®] and Graphpad[®] computer programs by means of the Student's *t*-test, the chi-square, or Fisher's test, and a correlation and regression analysis. Results were expressed as the mean $\pm$ the standard deviation.

Results

Clinical Evaluations

No complication arose from the procedures. Determined by weight and height, there were four mildly malnourished,

TABLE I Clinical parameters in control and malnourished children

Parameter	Controls	Malnourished	p Value
Age (months)	12.12 ± 14.39	2.35 ± 14.88	0.480744996
Gender (male/female)	12/8	11/9	1.0001
Weight (kg)	8.84 ± 4.08	5.34 ± 2.56	0.001402375
Size (cm)	69.90 ± 16.20	62.50 ± 17.20	0.084847251
Hemoglobin (g/dl)	10.97 ± 1.54	8.78 ± 2.22	0.000470274
Plasmatic sodium (meq/l)	139.10 ± 3.38	132.65 ± 4.34	0.000002267
Plasmatic potassium (meq/l)	4.08 ± 0.44	3.28 ± 0.91	0.000786203
Calcium (g/dl)	9.34 ± 0.45	8.68 ± 1.10	0.01052901
Total proteins (g/dl)	7.02 ± 0.87	5.07 ± 1.20	0.00000057
Albumin (g/dl)	3.95 ± 0.54	2.81 ± 0.74	0.00000173
Globulin (g/dl)	3.07 ± 0.60	3.02 ± 3.33	0.473290241

FIG. 1 Electrocardiographic traces of a normal (A) and a malnourished child (B). Note the significant corrected QT-interval dispersion in the malnourished child compared with the control. On V₅ lead, the end of the T wave was determined by the intersection of the basal line with a line traced as a parallel to the late recovery phase or the T wave. CQT = corrected QT interval.

nine moderately malnourished, and seven severely malnourished children. The clinical type of malnutrition could be typified as marasmatic in nine patients, and kwashiorkor in six. The body weight was significantly lower in the malnourished children's group (Table I).

Blood Sample Determinations

Compared with the control group, malnourished children had lower values of hemoglobin, plasmatic sodium, potassium, calcium, total proteins, and albumin (Table I).

Heart Rate and Heart Rate Variability

The heart rate and heart rate variability of both groups were comparable (Table II).

Corrected QT Interval and QT-Interval Dispersion

The corrected QT interval was similar in both groups and its value was comparable with that reported as normal in other

children populations¹ (Table II). The corrected QT interval standard deviation and the difference between the maximal and minimal measured QT interval were significantly greater in the malnourished children (Table II). When the precordial leads were compared with the standard leads, it became apparent that the greater QT-interval dispersion observed in the malnourished children occurred because of a greater dispersion in the precordial leads. Indeed, there was no difference between the groups when comparing the QT-interval dispersion in the standard leads.

Electrocardiographic Analyses Results

Nonspecific T-wave abnormalities (flattened or inverted T waves) were diagnosed in 17 of the 20 malnourished patients. In the precordial leads, U waves were found in seven patients (Table III). The ECG was normal in 18 of the 20 control children (two ECGs displayed supraventricular premature beats). This difference in the ECG in both groups was found to be highly significant ($p < 0.00001$, odds ratio = 51.00).

TABLE II Electrocardiographic parameters in control and malnourished children

Parameter	Controls	Malnourished	p Value
Electrocardiographic R-R interval (s)	0.42 ± 0.06	0.44 ± 0.08	0.18
Standard deviation of corrected QT in 12 leads	0.027 ± 0.008	0.043 ± 0.034	0.0310
Average of corrected QT (s) in 12 leads	0.402 ± 0.017	0.408 ± 0.040	0.2682
Corrected QT (s) max. - min. in 12 leads	0.089 ± 0.031	0.135 ± 0.082	0.0155
Corrected QT standard deviation in standard leads	0.026 ± 0.010	0.035 ± 0.034	0.1281
Corrected QT standard deviation in precordial leads	0.025 ± 0.008	0.041 ± 0.033	0.03182
Corrected QT (s) max. - min. in standard leads	0.066 ± 0.028	0.090 ± 0.075	0.0980
Corrected QT (s) max. - min. in precordial leads	0.068 ± 0.025	0.101 ± 0.068	0.0286

TABLE III Electrocardiographic findings and QT measurements in malnourished children

Patient No.	Age (months) gender	Malnut	ECG	CQT	CQT SD	CQT max-min
1	2/M	MAR-SEV	Normal	0.37677193	0.03774497	0.12026435
2	11/F	KWA-MOD	FT and UW	0.44087975	0.03005776	0.12223994
3	5/F	MAR-MOD	Normal	0.4134743	0.02231266	0.08548299
4	2/M	MAR-SEV	FT	0.45495075	0.04665111	0.17366846
5	6/M	MAR-SEV	FT and UW	0.44186471	0.021939	0.06766907
6	15/M	MAR-MOD	FT and UW	0.41281946	0.03226155	0.10294483
7	24/F	KWA-MOD	FT	0.50931686	0.16883635	0.36410961
8	12/M	KWA-SEV	FT	0.40961299	0.03285851	0.10585686
9	41/M	MAR-MOD	FT and UW	0.39859087	0.04249859	0.14337425
10	5/F	KWA-SEV	FT	0.39718183	0.04140581	0.11716152
11	2/F	Mild	FT	0.42499453	0.0414374	0.156828
12	2/M	KWA-SEV	UW	0.43977795	0.02638002	0.07434165
13	1/F	Mild	Normal	0.39552299	0.03113754	0.1032515
14	1/M	MAR-MOD	FT	0.41015857	0.0351759	0.13333333
15	17/F	Mild	FT	0.41037957	0.03088997	0.11000065
16	5/M	MAR-MOD	FT	0.40056512	0.03207991	0.09948616
17	11/M	KWA-MOD	FT and UW	0.31517681	0.10327257	0.36438098
18	18/M	MAR-SEV	FT and UW	0.34787677	0.03654072	0.1
19	7/F	MAR-MOD	FT	0.36781761	0.02290468	0.06859943
20	60/F	Mild	FT	0.4018388	0.03093855	0.09376016
Average	12.4			0.40846227	0.04336618	0.13533769
SD	14.9			0.04060701	0.03410768	0.08291339

Abbreviations: ECG = electrocardiogram, Malnut = type and state of malnutrition, CQT = corrected QT interval, SD = standard deviation, CQT max-min = difference between the maximal and minimal corrected QT interval, MAR = marasmatic, KWA = kwashiorkor, SEV = severe, MOD = moderate, FT = flat T waves, UW = U waves.

Statistically Significant Associations between Variables

When the different variables were compared, we could find a significant association only between the albumin and the calcium concentrations ($r^2 = 0.21$; $p = 0.0015$). Corrected QT-interval dispersion showed no significant relationship with any other continuous variable. When analyzing the discrete variables, the QT dispersion did not evidence a statistically significant association with either the degree of malnutrition (the clinical type), U waves, or the ECG repolarization abnormalities.

Discussion

In this small group of malnourished children we found clear evidence of an increased QT-interval dispersion not associated with an abnormal corrected QT interval. We do not know of any previous report of normal values of QT dispersion in our country; however, the control group values could be taken as a reference. Indeed, in the control group, the confidence interval of the standard deviation of the corrected QT interval (measured in the 12-lead ECG) was 0.024–0.0305 s. This value indicates that malnourished children have a risk ratio of 16:1 of having an increased QT-interval dispersion.

Malnutrition is a complex disease in which many factors can produce repolarization abnormalities. We will hereafter

analyze some of the malnutrition anomalies that could be related to our findings.

It has been reported that malnutrition can decrease thyroid function and produce bradycardia.⁶ Moreover, it is well known that bradycardia can be a substrate where repolarization prolongation and heterogeneity can occur. Nevertheless, our patients exhibited a heart rate and heart rate variability that were within normal limits and similar to the control group values. Consequently, we cannot attribute the QT-interval dispersion increase to bradycardia.

The heart rate and heart rate variability of the malnourished and control children suggest a preserved cardiac autonomic nervous system balance. The autonomic nervous system tone cannot thus be held responsible for the increased QT-interval dispersion in malnourished children.

Hypocalcemia is one of the biological variables commonly associated with QT prolongation. The malnourished children had lower plasmatic calcium concentration than the control group; however, the mean plasmatic calcium was still within normal limits, and the statistical regression analysis evidenced that calcium was not related to the QT dispersion.

Rodriguez-Soriano⁷ found that the levels of plasmatic calcium are related to albumin concentration which is generally low in malnourished children. Nevertheless, the same author reported that albumin decrease in malnourished children is not accompanied by an actual decrease in ionized calcium.

The absence of QT prolongation in the group of malnourished children we studied can thus be explained by the fact that the QT prolongation observed in cases of hypocalcemia is due only to the decrease in ionized calcium rather than to the decrease in plasmatic calcium.

Talner reported sporadic cases of sudden death in malnourished children.⁶ He attributes such fatalities to anomalies in the conduction system of the heart or to the coexistence of electrolytic imbalance that has frequently been described along with malnutrition. Our results suggest that, in such cases of sudden death, an increase in QT dispersion could have triggered the appearance of lethal ventricular arrhythmias. Indeed, other reports^{8–10} have shown that in overweight adults submitted to a diet to lose more than 30% of their initial body weight, an increase in the number of sudden deaths not associated with electrolytic imbalances has been observed. The Holter recordings of these patients showed QT interval prolongation and nonsustained ventricular tachycardia in the 4 months preceding the sudden death.

The deep subepicardial layer of the left ventricular cardiac muscle contains an electrophysiologically distinct cell type called M cells.¹² When the stimulation rate decreases, these cells have the property of prolonging the action potential duration to a greater extent than epicardial or endocardial cells do. Some investigators¹¹ have suggested that a QT-interval dispersion increase can be attributed to the presence of M cells that have a slower repolarization process. Moreover, there are reports of autopsies of malnourished children where a significant reduction of the myocardial mass was observed.⁶ It is possible that this muscle mass reduction is not uniform and that it affects M cells to a lesser degree than epicardial and endocardial cells. If this were the case, we should then expect a greater QT-interval dispersion in cases of malnutrition because of a relative predominance of the M-cell mass.

Whatever the explanation is, our results lead us to conclude that in some malnourished children an increase in QT-interval dispersion can be observed. This finding deserves further investigation and warrants special precaution about the possibility of occurrence of malignant ventricular arrhythmias in these children.

In this investigation we did not perform follow-up of our patients. It is thus not possible to determine whether the increased repolarization dispersion disappears after malnutrition correction.

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References

1. Fisch CH: Electrocardiography and vectorcardiography. In *Heart Disease. A Textbook of Cardiovascular Medicine* (Ed. Braunwald E), p. 180–219. Philadelphia: W.B. Saunders Co., 1988
2. Statters DJ, Malik M, Ward DE, Camm J: QT dispersion: Problems of methodology and clinical significance. *J Cardiovasc Electro-physiol* 1994;5:672–685
3. Nelson WE, Vaughan VC III, McKay RJ: *Tratado de Pediatría*. 8ª Ed. Barcelona: Edit. Salvat., 1983
4. Sekul E, Moak JP, Schultz RJ, Glaze DG, Dunn JK, Percy AK: Electrocardiographic findings in Rett syndrome: An explanation for sudden death? *J Pediatr* 1994;125:80–82
5. Mendez Castellano H, Lopez Blanco M, Landaeta M, Tineo A, Pereira Y: Estudio Transversal FUNDACREDESA, Instituto Nacional de Nutrición. Universidad Simón Bolívar, 1985
6. Talner NS: Cardiac changes in the malnourished child. In *The Malnourished Child* (Eds. Suskind RM, Lewinter-Suskind L), p. 229–244. Nestlé Nutrition Workshop Series, vol 19. New York: Nestec Ltd., Vevey/Raven Press, Ltd., 1990
7. Rodríguez-Soriano J: Malnutrition and electrolyte metabolism. In *The Malnourished Child* (Eds. Suskind RM, Lewinter-Suskind L), p. 141–154. Nestlé Nutrition Workshop Series, vol 19. New York: Nestec Ltd., Vevey/Raven Press, Ltd., 1990
8. Thwaites BC, Bose M: Very low calorie diets and pre-fasting prolonged QT interval. A hidden potential danger. *West Indian Med J* 1992;41:169–171
9. Pringle TH, Scobie IE, Murray RG, Kesson CM, Macculish AC: Prolongation of the QT interval during therapeutic starvation: A substrate for malignant arrhythmias. *Int J Obes* 1983;7:253–261
10. Surawicz B, Waller BF: The enigma of sudden cardiac death related to dieting. *Can J Cardiol* 1995;11:228–231
11. Sicouri S, Antzelevitch C: Electrophysiologic characteristics of M cells in the canine left ventricular free wall. *J Cardiovasc Electro-physiol* 1995;6:591–603