

Original Research

Electrocardiographic and Echocardiographic Findings in Malnourished Children

José L. Olivares, MD, PhD, Margarita Vázquez, MD, Gerardo Rodríguez, MD, Pilar Samper, MD, and Jesús Fleta, MD, PhD

Department of Paediatrics, "Lozano Blesa" Hospital, University of Zaragoza School of Medicine, Zaragoza, SPAIN

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Objective: To compare heart abnormalities in a group of malnourished children with a control group and to describe their predictive variables.

Methods: Thirty children with malnutrition were matched with thirty healthy children. Anthropometry, plasma levels of albumin and electrolytes were determined. Among others, corrected QT interval (QTc) and QT dispersion (QTd: difference between the maximum and the minimum QT) were measured in 12-lead electrocardiogram; and left ventricular mass (LVm) and left ventricular mass index (LVmi) were measured by echocardiography. Regression analyses were performed with cardiac findings as dependent variables and anthropometric and biochemical data as independent variables.

Results: Plasma levels of albumin, potassium and calcium were lower in malnourished children. QTc and QTd were significantly greater in patients with malnutrition than in controls (QTc: 445.9 ± 31.4 vs. 400.9 ± 17.7 ms, $p = 0.000$; QTd: 76.4 ± 34.1 vs. 47.9 ± 10.2 ms, $p = 0.000$). LVm and LVmi were significantly lower in malnourished children (LVm: 55.3 ± 10.3 vs. 71.4 ± 6.9 g, $p = 0.000$; LVmi: 46.5 ± 6.6 vs. 60.5 ± 4.9 g/m², $p = 0.000$). The body mass index (kg/m²) was the most powerful predictor of the variability in QTc (39.1%), LVm (48.1%) and LVmi (51.2%).

Conclusions: Important electrocardiographic and echocardiographic abnormalities have been found in malnourished children associated with their nutritional status. Special precaution must be taken about the possibility of occurrence of arrhythmias and sudden death related with malnutrition.

INTRODUCTION

Primary protein-energy malnutrition (PEM) is frequently located in less-developed countries due to inadequate food intake, socioeconomic or political factors or, at times, due to natural disasters. It is difficult to find primary PEM in economically advanced countries, but secondary PME appears in association with chronic diseases as cystic fibrosis, renal diseases, parental drug addiction or alcoholism, acquired immunodeficiency syndrome, or failure to thrive, among others [1–2].

Malnutrition is a complex health problem that may be caused by simultaneous deficiency of protein, energy, micro-nutrients and vitamins. Malnourished children suffer several alterations in body composition that could produce cardiac abnormalities as hypotension, cardiac arrhythmias, myocardiopathy, cardiac failure and sudden death [3–4]. Nowadays, it remains unresolved, whether these abnormalities are primary

phenomena of malnutrition or secondary to other alterations associated with malnutrition.

The objective of this study is to compare electrocardiographic and echocardiographic parameters between a group of malnourished children and a control group of the same age, and to investigate which are the anthropometric or metabolic variables that may determine these cardiac findings.

MATERIAL AND METHODS

Patients

Sixty children were enrolled in this age-matched case-control study. Sample was composed of thirty malnourished children (14 male and 16 female), aged 2.40 ± 1.82 years, and thirty healthy controls (13 male and 17 female), aged $2.52 \pm$

Address reprint requests to: Prof. José L. Olivares, MD, PhD, Departamento de Pediatría, Facultad de Medicina, Universidad de Zaragoza, C/. Domingo Miral s/n, 50009—Zaragoza, SPAIN. E-mail: olivares@unizar.es.

1.75 years, with normal weight-for-age values. The birth weight of children was normal and it did not show statistical differences between the two groups. Patients were excluded if they were preterm infants or they showed intrauterine growth retardation at birth. Height was measured to the nearest 0.1 cm on a stadiometer with a fixed head board and a sliding foot board (Holtain). Weight, to the nearest 10 gm, was obtained with an electronic scale. The weight and the height were marked on the National Center of Health Statistics (NCHS) weight for age and height for age charts. Body mass index (BMI) was calculated (kg/m^2).

Malnutrition was defined by McLaren classification [5]. All malnourished children had a moderate form of malnutrition. The causes of malnutrition were: behavior problems affecting feeding, disturbed parent-child relationship, incorrect preparation of formula, cow's milk protein allergy, celiac disease and chronic renal infection. Patients were excluded if they had congenital anomalies, metabolism disorders, central nervous system damage, receiving diuretics or drugs which prolong QT interval.

Blood Sample Determinations

In each subject, venous blood samples were obtained for plasma albumin, sodium, potassium and calcium determinations.

Electrocardiographic Measurements

Standard 12-lead electrocardiogram (ECG) was performed in supine position (at 25 mm/sec. and voltage at 10 mm/mV). Heart rate was calculated by mean RR interval. QT interval was measured with a ruler in each of the 12 leads where T wave was visible (from the beginning of QRS complex to the end of T wave, in the isoelectric line). When U waves appeared, the end of QT interval was considered as the nadir between T and U waves [6,7]. We have excluded cases with branch block in the ECG. Corrected QT interval (QTc) was calculated by Bazett's formula [8]: $QTc = QT/\sqrt{RR}$, and we considered that this parameter was increased if it was greater than 440 ms. QT dispersion (QTd) was defined as the difference between the maximum and the minimum QT occurring in any of the 12 leads. We considered that QTd was increased when it was greater than 60 ms. All ECCs were analyzed by two researchers.

Echocardiographic Measurements

All children underwent M-mode echocardiography and Doppler evaluation at rest, in supine position. Left ventricular dimension in end-diastole (LVED) and left ventricular dimension in end-systole (LVEs), fractional shortening, fractional ejection, left ventricular mass (LVm; g), left ventricular mass index ($LVmi = LVm/\text{height}^2$; g/m^2), cardiac output (L/min) and cardiac index ($\text{L}/\text{min}/\text{m}^2$) were quantify. Measurements were obtained according with recommendations proposed by the American Society of Echocardiography [9–11].

Statistical Analysis

All data were expressed as mean \pm standard deviation. Kolmogorov-Smirnov (Lilliefors modification) was applied to assess normality of each variable. Differences between groups were examined using Student's t-test. Chi-square test was used to evaluate differences in gender between the groups. Pearson's correlation coefficients were used to assess associations between continuous variables. Step wise multiple regression analyses were performed with cardiac findings as dependent variables and anthropometric and biochemical data as independent variables. The data were analyzed using the statistical package of Analytical Software SPSS 11.0 (SPSS Inc.). A two tailed p value < 0.05 was considered statistically significant.

All measurements were analyzed by two researchers who were unaware of the physical conditions and grouping of the patients. Parents were fully informed about the aims of the study and signed a consent form for participation. The study protocol was reviewed and approved by the Ethical Research Committee of the "Lozano Blesa" Zaragoza University Hospital (Spain).

RESULTS

Main clinical characteristics and biochemical values of malnourished and healthy children are summarized in Table 1. Age, gender, height, blood pressure and levels of plasma sodium were similar in both groups. However, body weight, z-score weight-for-age, BMI, plasma levels of albumin, potassium and calcium, were significantly lower in malnourished children than in the control group.

Table 1. Clinical Characteristics and Biochemical Data in Malnourished Children and Control Group

Parameter	Malnourished N = 30	Controls N = 30	p Value*
Age (years)	2.40 \pm 1.82	2.52 \pm 1.75	0.801
Gender (male/female)	14/16	13/17**	
Birth weight (kg)	3.27 \pm 0.39	3.35 \pm 0.44	0.444
Weight (kg)	9.56 \pm 3.73	13.46 \pm 5.06	0.001
Z-score weight/age	-2.36 \pm 0.36	0.13 \pm 0.19	0.000
Height (cm)	82.36 \pm 16.26	89.76 \pm 17.75	0.097
BMI (kg/m^2)	13.58 \pm 1.09	16.22 \pm 0.82	0.000
Albumin (g/dL)	3.14 \pm 0.23	3.76 \pm 0.42	0.000
Sodium (mEq/L)	136.47 \pm 2.32	137.70 \pm 2.64	0.059
Potassium (mEq/L)	3.52 \pm 0.28	4.26 \pm 0.42	0.000
Calcium (mg/dL)	8.48 \pm 0.45	9.74 \pm 0.60	0.000
SBP (mmHg)	91.33 \pm 7.27	93.10 \pm 7.25	0.350
DBP (mmHg)	49.83 \pm 6.63	50.17 \pm 6.23	0.842

Results were expressed as the mean \pm standard deviation.

N: number of cases.

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure.

* Unpaired t-test.

** Chi-square test, $p = 0.795$.

The ECG showed flattened T waves and U waves in 24 (80%) and 6 (20%) of malnourished children, respectively; and 7 (23.3%) displayed supraventricular premature beats. In the control group, the ECG was normal. The QTc interval and QTd were significantly greater in the malnourished group than in controls. Eleven children of the malnourished group (36.7%) had a QTc interval higher than 440 ms. None of the controls had a prolonged QTc. Ten subjects of the malnourished group (33.3%) against two of the control group (6.7%) had a QTd higher than 60 ms, Odds Ratio (OR): 7.00 (95% IC: 1.22–52.23; $p = 0.02$). Table 2 shows electrocardiographic and echocardiographic measurements from both groups.

Left ventricular dimension in end-diastole, left ventricular dimension in end-systole, left ventricular mass, ventricular mass index and cardiac output, were all significantly lower in malnourished children than in controls. There were not statistical differences between the heart rate, left ventricular fractional shortening, left ventricular fractional ejection and cardiac index obtained from both groups.

Main correlations founded between ECG or echocardiographic data and anthropometrical or biochemical variables are shown in Table 3. To avoid casual associations, step wise multiple regression analyses were performed with these variables in the entire group of malnourished and healthy children (Table 4). The BMI explained 39.1% of the QTc variability and 13.1% of the QTcd variability. No significant contribution of weight, plasma levels of albumin, potassium or calcium was found in the regression analysis for QTc. BMI was also the most powerful predictor of LVm and LVmi (48.1% and 51.2%, respectively), and weight added 4% and 3.8% to LVm and

Table 2. Electrocardiographic and Echocardiographic Findings in Malnourished Children and Control Group

Parameter	Malnourished N = 30	Controls N = 30	p Value*
Heart rate (l/m)	114.93 ± 14.62	110.60 ± 20.24	0.346
QTc (ms)	445.93 ± 31.42	400.93 ± 17.71	0.000
NQTc > 440 ms	11/30 (36.7%)	0/30 (0%)	
QTcd (ms)	76.47 ± 34.12	47.93 ± 10.18	0.000
NQTcd > 60 ms	10/30 (33.3%)	2/30 (6.7%)**	
LVEd (mm)	26.53 ± 5.37	30.53 ± 4.82	0.004
LVEs (mm)	16.30 ± 3.14	18.87 ± 3.66	0.005
LVm (g)	55.30 ± 10.35	71.43 ± 6.88	0.000
LVmi (g/m ²)	46.53 ± 6.55	60.47 ± 4.92	0.000
Fractional shortening (%)	39.17 ± 2.31	38.67 ± 5.40	0.643
Fractional ejection (%)	64.60 ± 3.86	63.77 ± 6.05	0.527
Cardiac output (L/min)	2.05 ± 0.17	2.21 ± 0.22	0.002
Cardiac index (L/min/m ²)	4.60 ± 0.32	4.53 ± 0.31	0.370

Results were expressed as the mean ± standard deviation.

N: number of cases.

QTc = corrected QT interval in 12 leads, QTcd = corrected QT interval dispersion (max-min.) in 12 leads, LVEd = left ventricular dimension in end-diastole, LVEs = left ventricular dimension in end-systole, LVm = left ventricular mass, LVmi = left ventricular mass index.

* Unpaired t-test.

** Odds ratio: 7.00 (95% IC, 1.22 to 52.23), $p = 0.02$.

Table 3. Main Pearson Correlations between Cardiac and Anthropometric and Biochemical Data in Malnourished Children and Control Group

	QTc	QTcd	LVm	LVmi
Weight	-0.088	-0.163	0.396**	0.394**
BMI	-0.625**	-0.362**	0.694**	0.715**
Albumin	-0.429**	-0.320*	0.479**	0.535**
Potassium	-0.405**	-0.338**	0.424**	0.468**
Calcium	-0.534**	-0.350**	0.543**	0.582**

QTc = corrected QT interval in 12 leads, QTcd = corrected QT interval dispersion (max-min.) in 12 leads, LVm = left ventricular mass, LVmi = left ventricular mass index, BMI = body mass index (kg/m²).

* $p < 0.05$.

** $p < 0.01$.

Table 4. Step Wise Multiple Regression between Dependent (QTc, QTcd, LVm and LVmi) and Independent (Anthropometric and Biochemistry) Variables

Dependent variable	Independent variable	R ²	p
QTc			
Step 1	BMI	0.391	0.000
Excluded:	Weight, albumin, calcium and potassium		
QTcd			
Step 1	BMI	0.131	0.004
Excluded:	Weight, albumin, calcium and potassium		
LVm			
Step 1	BMI	0.481	0.000
Step 2	BMI	0.481	
Excluded:	Weight	0.524	0.000
Excluded:	Albumin, calcium and potassium		
LVmi			
Step 1	BMI	0.512	0.000
Step 2	BMI	0.512	
Excluded:	Weight	0.550	0.000
Excluded:	Albumin, calcium and potassium		

QTc = corrected QT interval in 12 leads, QTcd = corrected QT interval dispersion (max-min.) in 12 leads, LVm = left ventricular mass, LVmi = left ventricular mass index, BMI = body mass index (kg/m²).

LVmi variability; accounting together for 52.1% and 55%, respectively. Fig. 1 shows the regression equation between QTc and BMI; and Fig. 2 the regression between LVmi and BMI.

DISCUSSION

Malnutrition is a complex phenomenon caused by several aetiologies that produce, on the whole, body composition alterations, with important losses of heart and skeletal muscle mass, complicated by electrolytic disorders and mineral or vitamin deficiencies. Malnutrition is common in hospitalized children and infants from our environment due to primary food deficiencies (failure to thrive, parental drug addiction); or due to chronic diseases (cardiac, neurological or renal diseases, cystic fibrosis and acquired immunodeficiency syndrome).

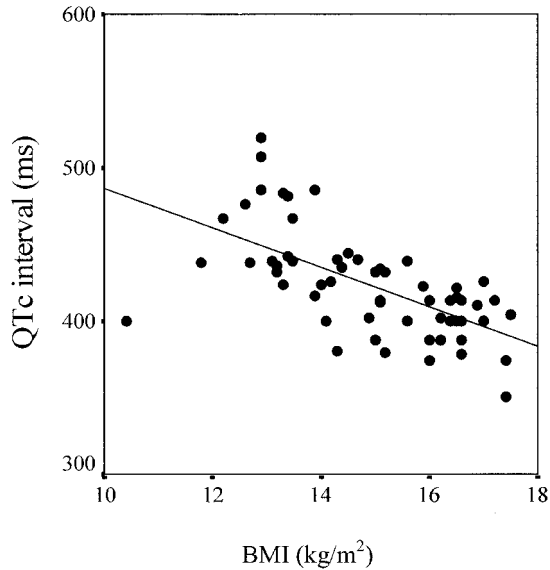


Fig. 1. Dispersion plot and regression line of corrected QT interval against body mass index (BMI). $QTc = 616.49 - 12.96 \text{ BMI}$; $r = -0.625$, $p = 0.000$.

Malnourished children [3–4] and adolescents [12] suffer cardiac abnormalities as hypotension, cardiac arrhythmias, cardiomyopathy, cardiac failure and sudden death. In kwashiorkor, due to a reduced muscle mass, the function of the heart decreases and it is radiological smaller [13].

Seim *et al.* [14] showed that 47% of subjects on a very low calorie diet had sinus bradycardia. Bradycardia is also one of

the most common abnormalities in patients with eating disorders [15]. However, compared with controls, neither in adolescents with anorexia nervosa, nor in malnourished children, ECG findings showed a significant relationship with severity of malnutrition [16].

Bedi *et al.* [17] have demonstrated that autonomic nervous system function is significantly compromised in malnourished children. Cardiac repolarization process may change depending on the ventricular regions. These variations determine the QT interval variability, the so-called QT dispersion (QTd), when QT is measured in any of the ECG leads. In malnourished children, QTc and QTd have shown increased values related with cardiac depolarization and repolarization alterations. The prolonged QT interval may be congenital or acquired because of the use of anti-arrhythmic drugs, hypocalcaemia or hypokalaemia, psycho drugs, or due to the presence of intrinsic cardiac disease. The association of torsade de pointes, prolonged QT interval and sudden death with dieting or severe malnutrition is well known [18,19]. QT dispersion may be considered an independent diagnosis marker of apparent life-threatening event (ALTE) [20].

Electrolytic changes and cardiac repolarization alterations, consisting of QT interval and QTd prolongation, have been also observed in children with kwashiorkor [21] and in adolescents with anorexia nervosa [22]; in this latter study, oral supplementation of potassium tends to reduce QT modifications. Hypocalcemia is one of the biological variables commonly associated with QT prolongation. Fuenmayor *et al.* [16] also found in malnourished children greater QTd values than in controls. Our results show that body weight, BMI, plasma levels of albumin, serum

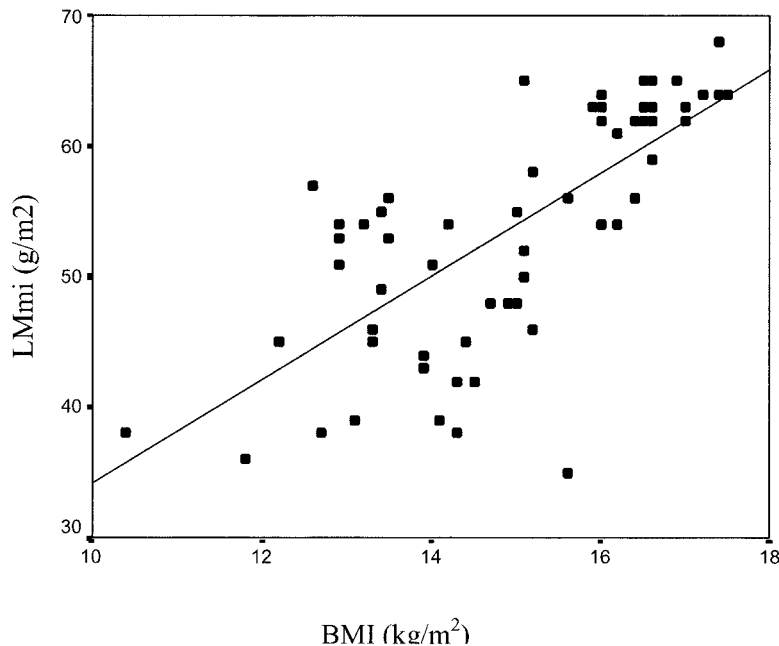


Fig. 2. Dispersion plot and regression line of left ventricular mass index, LVmi (g/m^2), against body mass index (BMI). $LVmi = -5.48 + 3.96 \text{ BMI}$; $r = 0.715$, $p = 0.000$.

potassium and calcium levels, were all lower; and QTc interval and QTd were significantly greater in malnourished children than in controls. We have found significant correlations between QTc and QTd and both anthropometric and biochemical variables. However, when step wise multiple regression analyses were performed to avoid casual associations and to search which are the main predictive variables of these ECG changes, the BMI explained 39.1% of the variability in QTc. Other variables as weight, plasma levels of albumin, potassium or calcium were eliminated in this analysis. Therefore, there is a strong negative correlation between BMI and QTc interval.

Left ventricular mass is reduced in proportion to decrease in body size in patients with protein energy malnutrition, and left systolic and diastolic functions are preserved in atrophic hearts [23,24]. Children with primary third-degree malnutrition not only have cardiac wasting, but also have inherent ventricular dysfunction [25]. LVE_d, LVE_s, LV_m, LV_{mi} and cardiac output are all lower in malnourished children than in controls of our study; and there is a positive correlation between LV_{mi} and BMI and body weight. In fact, BMI has been also the most powerful predictor of LV_m and LV_{mi} (48.1% and 51.2%, respectively), and weight added 4% and 3.8% to LV_m and LV_{mi} variability; accounting together for 52.1% and 55%, respectively. These findings suggest that, due to malnutrition, body weight loss and a lower weight/length² ratio are both associated with cardiac muscle mass decrease. However, we have not found significant differences between both groups in fractional shortening, fractional ejection or cardiac index.

Nowadays, pathogenic mechanisms of morphological and functional cardiac alterations associated with malnutrition have not been still elucidated. Necropsy studies have demonstrated myocardic degeneration, myocytolysis, fat infiltration or substitution of muscle cells by fat tissue. Membrane action potential of myocardic cells may be altered in malnourished subjects due to structural changes, muscular fibre orientation, blood flux variations, water content or potassium channel modification observed in hypotrophy myocytes. Increases of QTc and QTd intervals suggest that there are regional differences in myocardic repolarization and a greater arrhythmogenic substrate with higher risk of ventricular arrhythmia and sudden death [26].

CONCLUSIONS

Important electrocardiographic and echocardiographic abnormalities have been found in malnourished children associated with their nutritional status. Special precaution must be taken about the possibility of occurrence of arrhythmias and sudden death related with malnutrition. Cardiac evaluation, electrolyte disturbance correction and appropriate nutrition therapy must be taken into account in the management of these patients.

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