

Index of Cardiac Electrophysiological Balance in Electrocardiography of Children with Acute Rheumatic Carditis

Akut Romatizmal Karditli Çocukların Elektrokardiyografilerinde Kardiyak Elektrofizyolojik Denge İndeksi

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Öz

Amaç: Çalışmamızda akut romatizmal karditli çocukların elektrokardiyografilerinde kardiyak elektrofizyolojik denge indeksi (iCEB), ve kardiyak aritmi için diğer risk belirteçlerinin incelenmesi amaçlanmıştır.

Hastalar ve Yöntem: Ocak 2016-Ağustos 2018 tarihleri arasında, akut romatizmal kardit tanılı 40 çocuk hasta ile yaş ve cinsiyet olarak benzer 40 sağlıklı çocuk retrospektif olarak çalışmaya alındı. Tüm vakaların demografik özellikleri kayıtlardan elde edildi. Elektrokardiyografide; P dalga dispersiyonu (Pd), QT dispersiyonu (QTd) ve düzeltilmiş QTd (QTcd) süreleri, Tp-e intervali (Tp-e), Tp-e/QT ve Tp-e/QTc oranları, ve iCEB ve düzeltilmiş iCEB (iCEBc) ölçüm değerleri gruplar arasında karşılaştırıldı. İstatistiksel olarak p <0,05 olması anlamlı kabul edildi.

Bulgular: Hasta ve kontrol gruplarının yaş ortalaması sırasıyla; 11,40±3,48 yıl ve 11,41±3,31 yılıdır. Her iki grupta 16 kız (%40) ve 24 erkek (%60) çocuk vardı. Hasta grubunda, kalp hızı, PR intervali, Pd, QTd, QTcd, Tp-e, Tp-e/QT oranı ve iCEBc ölçümleri anlamlı derecede yüksek saptandı. iCEB düzeyi hasta grubunda sağlıklı kontrollere daha yüksek olmasına rağmen istatistiksel anlamlı bir fark yoktu.

Sonuç: Akut romatizmal karditli çocuklarda, repolarizasyon-depolarizasyon dengesi bozulmuş olabilir. Bu nedenle aritmi için diğer elektrokardiyografik risk parametrelerine ilave olarak iCEB(c) kullanımı da yararlı olabilir. Ancak, bu konuda daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Akut romatizmal ateş, çocuklar, elektrokardiyogram, kardit, kardiyak aritmi

Abstract

Aim: In this study, examination of the index of cardiac-electrophysiological balance (iCEB) and of other risk markers for cardiac arrhythmia in electrocardiography of children with acute rheumatic carditis was aimed.

Patients and Methods: Forty pediatric patients with acute rheumatic carditis and 40 healthy children matched in terms of gender and age were retrospectively enrolled in the study between January 2016 and August 2018. Demographic data of all cases were obtained from records. By electrocardiography, P dispersion (Pd), dispersion durations of QT (QTd) and corrected QT (QTcd), Tpeak-to-end interval (Tp-e), ratios of Tp-e/QT and Tp-e/QTc, and measurements of iCEB and corrected iCEB (iCEBc) were all compared between the groups. Statistically significant difference was accepted as p< 0.05.

Results: In the patient and control groups, mean ages were 11.40±3.48 years and 11.41±3.31 years, respectively. Both groups had 16 female (40%) and 24 male (60%) children. In the patient group, heart rate, PR interval, Pd, QTd, QTcd, Tp-e, Tp-e/QT ratio and iCEBc were found to be significantly increased. Though iCEB level was higher in the patient group, there was no statistically significant difference with healthy controls.

Conclusion: In children with acute rheumatic carditis, repolarization-depolarization balance may be impaired. Therefore, in addition to other electrocardiographic risk parameters for arrhythmia, use of iCEB(c) may also be beneficial. However, further studies on this issue are needed.

Key words: Acute rheumatic fever, children, electrocardiogram, carditis, cardiac arrhythmia

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INTRODUCTION

After a group A streptococcal infection, acute rheumatic fever (ARF) may be seen through an autoimmune response. Although the incidence of disease has been recently declined in developed countries, it takes an important place among acquired heart diseases in children and continues to be a significant public health issue, especially in developing countries. Carditis, most severe complication of ARF, is observed in approximately half of the patients (1-3). Various atrial and ventricular conduction disorders due to ARF may be observed. In addition to first degree atrioventricular block, other rhythm disorders including bradycardia, supraventricular tachycardia, nodal rhythm, ventricular tachycardia and complete heart block may also be seen (4-7).

An increased P dispersion (Pd), a marker used for showing atrial conduction disorders, demonstrates an irregular conduction in atria and also has been found to be related to increased atrial arrhythmia risk (8). It has been shown in previous studies that various risk markers for arrhythmia on ECG including durations of QT and corrected QT (QTc), dispersion durations of QT (QTd) and QTc (QTcd), Tpeak-to-end interval (Tp-e), and ratios of Tp-e/QT and Tp-e/QTc can be used for predicting ventricular arrhythmias (9-12). Tp-e, the duration between peak of T-wave and its junction with the isoelectric line, is considered to reflect transmural dispersion of ventricular repolarization. An increase in Tp-e duration, thus, may suggest abnormal dispersion of repolarization. Recently, ratios of Tp-e/QT and Tp-e/QTc have also been accepted as novel markers showing transmural (Tp-e) and spatial (QT) dispersions (10-13).

Another novel marker, called index of cardiac-electrophysiological balance (iCEB) that can be obtained as division of the QT duration to QRS duration (QT/QRS) in predicting malignant ventricular arrhythmias, was firstly defined by Lu et al. (14). This marker expresses the balance between the ventricular depolarization (QRS) and repolarization (QT). It has been stated that iCEB is an equivalent of the cardiac wavelength. And also, iCEB has some advantages including possibility of being measured non-invasively and simply on surface ECG. Thus, an increase in iCEB may be used in predicting polymorphic ventricular tachycardia and a decrease in iCEB may be used in predicting non-polymorphic ventricular tachycardia and ventricular fibrillation (14-16).

In children with acute rheumatic carditis, we have

encountered no study related to iCEB. To assess measurement of iCEB and of other risk markers in ECG of children with ARF carditis was aimed.

PATIENTS AND METHODS

Subjects

Our retrospective study was conducted as cross-sectional in pediatric patients with ARF carditis between January 2016 and August 2018. Forty pediatric patients, aged between 5-18 years and diagnosed with ARF carditis in accordance with revised Jones 2015 criteria (17), were enrolled to the study. Beside carditis, patients with accompanying other major or minor findings of ARF were also taken into patient group. All patients were initially treated with corticosteroid (Prednisolone) and then salisilate to avoid rebound. However, all evaluations (demography, blood work-ups, electrocardiography, echocardiography) in patient group were performed before treatment. So, no effects of anti-inflammatory treatment on these parameters were evaluated. Of the cases diagnosed with carditis; among the laboratory findings, on-admission hemoglobin, WBC (leukocyte), thrombocyte, hematocrit, ESR (erythrocyte sedimentation rate), CRP (C reactive protein) and ASO (Antistreptolysin O titer) were obtained. From the study group, those with insufficient data, not meeting the Jones criteria, with a chronic disease and using a medication effective on heart were excluded from the study.

As the control group, 40 cases similar to those in the patient group in regard to age, gender and anthropometric measurements, which had no chronic disease and were found to be healthy, were included in the study. Demographic characteristics (age, gender, body weight), blood pressure measurements, electrocardiography and echocardiography records of all cases were evaluated. No laboratory data could be obtained from the cases in the control group, as detailed blood work-ups could not be ordered. Local ethics committee approved the study with a decision number of 2019/2002 (July 12th 2019).

Echocardiography

An experienced pediatric cardiology specialist performed echocardiographic examinations by using Vivid S5 N (GE, Horten, Norway) echocardiography machine and a 3S sector probe. The standard imaging techniques, suggested by American Society of Echocardiography, were used (18).

Electrocardiography

Electrocardiography records were taken (25 mm/

sec, 10 mV) with a 12-lead ECG device (Nihon Kohden Cardiofax, Tokyo, Japan), and then, were analyzed manually by an experienced pediatric cardiologist in an electronic environment. On the lead DII, arithmetic means of three consecutive beats were taken to obtain PR interval duration and heart rate per minute. Durations of QT, P and QTc, used to obtain dispersions (QTd, Pd, QTcd), were measured in at least nine different leads. From the beginning of P-wave to returning to isoelectric line was accepted as P-wave duration. The difference between the longest (Pmax) and shortest (Pmin) P-wave durations was considered as P dispersion. From the beginning of QRS complex to the end of T-wave was accepted as QT interval duration. Tangential method was used to determine the endpoint of T-waves, when the last portion of T wave was not able to be clearly seen (19). Bazett's formula was used for QTc calculations ($QTc = QT/\sqrt{RR}$) (20). Dispersions of QT and QTc were considered to be the difference between longest (QTmax, QTcmax) and shortest (QTmin, QTcmin) QT and QTc interval durations, respectively. Duration of Tpeak-to-end, and ratios of Tp-e/QT, Tp-e/QTc, QT/ QRS (iCEB) and QTc/ QRS (corrected iCEB; iCEBc) measurements were performed on precordial ECG leads. Also, QRS, QT and QTc measurements, used in these ratios, were obtained from precordial leads by taking arithmetic means of three consecutive beats.

Statistical Analysis

The obtained data were analyzed by using the SPSS 17 (SPSS Inc., Chicago, IL, USA) statistics program on computer. Shapiro Wilk's test was applied to test normality of distribution of the variables. Of the quantitative variables; the variables exhibiting normal distribution were expressed as mean \pm standard deviation (SD) and those not exhibiting normal distribution as median (interquartile range). In analyzing categorical variables, chi-square test was used. Independent samples Student t-test and Mann Whitney U test were applied in independent group comparisons according to suitability of the data. In statistical evaluation, a $p < 0.05$ was considered significant.

RESULTS

Both patient (n:40) and control (n:40) groups had 16 female (40%) and 24 male (60%) children. In patient and control groups, mean age was found to be 11.40 ± 3.48 years and 11.41 ± 3.31 years, respectively. Blood pressure measurements of both groups were within normal range. Between the groups, no significant differences were determined in terms of body weight ($p:0.541$), age ($p:0.985$), gender ($p:1.00$), and systolic ($p:0.458$) and diastolic ($p:0.654$) blood pressure measurements (Table 1). Among the on-admission blood work-ups of the patient group; mean

Table 1. Demographic features and blood pressures of the groups

	Patient Group (n:40)		Control Group (n:40)		p
	mean \pm SD or n	median (IQR)	mean \pm SD or n	median (IQR)	
Age (years)	11.40 \pm 3.48	11.54(8.93-14.31)*	11.41 \pm 3.31	11.91(9.1-14.55)*	0.985
Gender (female/male)	16/24		16/24		1.00
Weight (kg)	44.75 \pm 19.74	45.50(28.25-59.25)*	41.60 \pm 15.72	40(28.25-53.5)*	0.541
SBP (mmHg)	103.87 \pm 10.28	100(100-110)*	102.75 \pm 12.95	100(90-110)*	0.458
DBP (mmHg)	63.50 \pm 8.85	60(60-70)*	63.50 \pm 9.48	60(60-70)*	0.654

DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure. Data were presented as mean \pm standard deviation and median (IQR {interquartile range: first quartile-third quartile}). *, shows the parameters that used for statistical comparisons.

Table 2. Laboratory results of the patient group

	Patient Group (n:40)		Laboratory reference ranges
	mean \pm SD	median (IQR)	
WBC (/mm ³)	10529 \pm 2848.60	10300 (8725-12175)	4-10x10 ³
Hb (g/dl)	11.50 \pm 1.28	11.25(10.8-12.35)	12.1-17.2
Hct (%)	34.44 \pm 3.77	34.05(31.75-36.47)	36.1-50.3
Plt (/mm ³)	358450 \pm 72441.64	357500(301750-406000)	150-400x10 ³
ESR (mg/h)	66.90 \pm 21.65	68.00(52.75-80.75)	0-20
CRP (mg/L)	103.44 \pm 69.68	80.00(56.57-141.95)	0-5
ASO (Todd IU/ml)	1294.90 \pm 843.11	1035.00(749.5-1555)	0-200

ASO, Anti-streptolysin O; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; Hb, Hemoglobin; Hct, Hematocrit; Plt, Thrombocyte; WBC, White blood cell, Data were presented as mean \pm standard deviation and median (IQR {interquartile range: first quartile-third quartile}).

Table 3. Echocardiographic measurements of the groups

	Patient Group (n:40)		Control Group (n:40)		p
	mean±SD	median (IQR)	mean±SD	median (IQR)	
IVSd (mm)	7.96±1.36	8.00 (7-9)*	7.50±0.86	7.50 (7-8)*	0.162
LVPWd (mm)	7.73±1.44	8.00 (6.62-9)*	7.32±0.81	7.50(7-7.5)*	0.198
LVEDD (mm)	43.35±6.09*	44.50 (39-47)	41.17±4.30*	42.00 (38-45)	0.069
LVESD (mm)	26.12±4.13*	26.00 (22.25-29)	24.40±2.65*	24.00 (23-26)	0.03
EF (%)	70.25±3.64*	70.00 (67-73.75)	71.55±2.93*	72.00 (69-74)	0.083
FS (%)	39.50±2.97	39.00 (37-42)*	40.30±2.40	40.00(38.25-42)*	0.206
LA (mm)	26.77±4.29	27.50(24-29)*	25.02±3.10	25.00(23-27.5)*	0.02
Ao (mm)	21.60±3.31	21.00(19.25-23)*	20.75±2.43	21.00(20-22)*	0.227
LA/Ao	1.24±0.14	1.21 (1.15-1.29)*	1.20±0.09	1.22 (1.13-1.27)*	0.586

Ao, aortic root; EF, left ventricular ejection fraction; FS, left ventricular fractional shortening; IVSd, interventricular septum end-diastolic thickness; LA, left atrial width; LA/Ao, left atrium to aortic root ratio; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVPWd, left ventricular posterior wall end-diastolic thickness; mm, millimeter. Data were presented as mean ± standard deviation and median (IQR {interquartile range: first quartile-third quartile}). *, shows the parameters that used for statistical comparisons.

WBC, ESR, CRP and ASO values were found to be higher than laboratory reference range (Table 2).

In patient group, statistically significant increments of echocardiographic measurements of LVESD (left ventricular end-systolic dimension) and LA (left atrial width) were found (p:0.03 and p:0.02, respectively). Between the groups, there was no significant difference in regard to other echocardiographic parameters (p>0.05). Table 3 summarizes the echocardiography results.

On electrocardiography examination, heart rate (p:0.006), PR interval (p<0.001), Pmax (p:0.026), Pd (p<0.001), QTd (p<0.001), QTcmin (p:0.013), QTcmax (p<0.001), QTcd (p<0.001), Tp-e (p:0.02) and ratio

of Tp-e/QT (p:0.005) measurements were found to be significantly increased and Pmin measurement, however, significantly lower (p:0.009) in the patient group. In patients with ARF carditis, though iCEB level was determined to be higher, no significant difference was seen (p:0.718). However, a significant increase in iCEBc was found in patient group (p:0.007). Table 4 shows the electrocardiographic measurements.

DISCUSSION

In acute rheumatic fever (ARF), an increased heart rate, as well as various rhythm disorders ranging from atrial conduction disorders to ventricular arrhythmias may occur (4-7). A prolonged PR interval that is

Table 4. Electrocardiographic measurements of the groups

	Patient Group (n:40)		Control Group (n:40)		p
	mean±SD	median (IQR)	mean±SD	median (IQR)	
Heart rate (/minute)	93.00±20.91*	93.5(76.5-110)	81.25±16.08*	78.5 (68.25-92)	0.006
PR (ms)	161.75±34.08	156 (137-189)*	130.95±16.43	132(120-144)*	< 0.001
Pmin(ms)	52.80±8.74	52 (48-60)*	57.40±6.11	56 (52-60)*	0.009
Pmax(ms)	89.00±9.57	88 (81-96)*	84.80±6.54	84 (80-88)*	0.026
Pd (ms)	36.20±5.93	36 (32-40)*	27.40±4.20	28 (24-32)*	< 0.001
QTmin(ms)	305.00±41.04*	294(277-336)	313.60±25.05*	316(300-336)	0.262
QTmax(ms)	345.20±41.71*	336(317-371)	344.50±25.34*	344(328-364)	0.928
QTd(ms)	40.20±6.52	40 (36-44)*	30.90±3.50	30 (28.35)*	< 0.001
QTcmin(ms)	372.00±21.92*	367(358.25-389.5)	360.37±18.99*	359.5(349.5-371.75)	0.013
QTcmax(ms)	421.70±23.25*	418(408.5-436.25)	396.32±20.80*	397.5(382.25-408.75)	< 0.001
QTcd(ms)	49.70±9.51*	49(42-55.75)	35.95±4.99*	36(32-39.75)	< 0.001
Tp-e (ms)	65.00±7.34	62 (60-71)*	61.40±4.75	60 (56-64)*	0.02
Tp-e/QT	0.20±0.02	0.19 (0.18-0.22)*	0.18±0.02	0.18 (0.17-0.2)*	0.005
Tp-e/QTc	0.16±0.01*	0.16 (0.15-0.17)	0.16±0.01*	0.15 (0.14-0.17)	0.554
iCEB(QT/QRS)	5.04±0.80	5 (4.35-5.5)*	4.94±0.58	4.75 (4.54-5.3)*	0.718
iCEBc(QTc/QRS)	6.18±0.89*	6.25 (5.4-6.74)	5.69±0.67*	5.71 (5.16-6.19)	0.007

iCEB, index of cardiac electrophysiological balance; iCEBc ,corrected index of cardiac electrophysiological balance; ms, millisecond; Pd, P-wave dispersion; Pmax, maximum P duration; Pmin, minimum P duration; QTc, corrected QT interval; QTcd, QTc dispersion; QTd, QT dispersion; QTcmax, maximum QTc duration; QTcmin, minimum QTc duration; QTmax, maximum QT duration; QTmin, minimum QT duration; Tp-e, Tpeak to end. Data were presented as mean ± standard deviation, and median (IQR {interquartile range: first quartile-third quartile}). *, shows the parameters that used for statistical comparisons.

considered as a minor finding according to the Jones diagnostic criteria is the most common conduction disorder in ARF (4,17). In children, PR interval varies by heart rate and age. In younger children, PR interval is shortened as the heart rate increases, whereas PR interval prolongs in older children as they have lower heart rates (21). Our study groups had similar age, however, the heart rate in patient group was found to be significantly increased. While a shortened PR interval was expected under normal conditions due to higher heart rate in the patient group, it was found to be significantly prolonged compared to the control group. In patient group, it was thought that prolonged PR interval was a common consequence of ARF and consistent with previous studies.

A higher P dispersion (Pd) has been reported to be related to atrial arrhythmias (8). Kucuk et al. (22) found that Pd was significantly higher in children with rheumatic carditis and that susceptibility to atrial arrhythmias might be increased in ARF. Alp et al. (23) found Pd significantly increased in children with both ARF carditis and chronic rheumatic heart disease compared to the healthy group and, furthermore, determined a positive correlation between higher Pd and valvular insufficiency. Kocaoglu et al. (24) reported that Pd was statistically increased in children with newly-diagnosed ARF compared to healthy children and that the higher Pd might be associated with carditis-induced left atrial enlargement, valvular insufficiency and atrial conduction disorders. Also in our study, Pd was found to be significantly increased in the patient group. This may suggest that children with acute rheumatic carditis may have atrial conduction disorders. However, we have encountered no atrial arrhythmias other than prolonged mean PR interval in patient group.

There are studies showing prolongation of QTd and QTcd durations in children with ARF. Remigio de Aguiar et al. (25) stated that a prolonged QTd in ARF may reflect cardiac involvement. Kucuk et al. (22) reported that these patients may become more susceptible to ventricular arrhythmias in long term due to permanent effect of ARF on the myocardium. Polat et al. (26) observed that both QTcd and QTd in children with ARF were statistically increased due to carditis and concluded that this increase was directly related to degree of valvular insufficiency. Similarly, Alp et al. (23) revealed that durations of QTcd and QTd were significantly increased in children with ARF carditis and with chronic rheumatic heart disease. Karaagac et al. (27) reported that Tp-e duration and

ratio of Tp-e/QT were increased significantly in adult patients with coronary artery ectasia compared to the healthy group and that these parameters may indicate increased risk of arrhythmia. Alsancak et al. (28) also determined higher Tp-e interval duration and ratio of Tp-e/QT in patients with coronary artery ectasia and that these values were in tendency to increase with increasing number of coronary arteries affected by ectasia. In the study of Kucuk (22), Tp-e interval and ratio of Tp-e/QT were found to be increased in children with ARF carditis compared to the healthy control group and also reported that these parameters may be beneficial markers to be used in predicting myocardial involvement. In our study, no significant ventricular arrhythmias were observed in patient group. However, most of the risk markers on ECG for ventricular arrhythmia (QTd, Tpeak-to-end interval, QTcd, and ratio of Tp-e/QT) were determined to be significantly higher in children with acute rheumatic carditis compared to the healthy group. In acute rheumatic fever carditis, we are in thought of that increment of these ventricular repolarization parameters should warn the clinician for increased ventricular arrhythmia risk.

Index of cardiac-electrophysiological balance (iCEB), a novel marker in predicting ventricular arrhythmias, expresses the balance between ventricular depolarization and repolarization. Previous studies have shown that an increase or decrease in iCEB levels may be related to increased ventricular arrhythmia risk (14-16). Robyns et al. (29) demonstrated that QRS duration was directly correlated with cardiac mass in patients with hypertrophic cardiomyopathy (HCMP). However, iCEB level of HCMP group was found to be similar to the control group. They suggested that arrhythmias seen in HCMP may develop due to different mechanisms other than iCEB irregularities. Alsancak et al. (28) showed increased levels of iCEB and iCEBc levels in patients with coronary artery ectasia compared to the healthy cases, although they could not find any statistically significant difference. Sivri et al. (30) found iCEB and iCEBc values higher in patients with chronic renal failure compared to the healthy cases. In the same study, they detected significantly higher iCEB and iCEBc values after hemodialysis compared to pre-hemodialysis and they suggested that malignant ventricular arrhythmia risk may also be increased after hemodialysis. Ucar et al. (31) revealed significantly increased iCEB and iCEBc levels in adult cases with rheumatoid arthritis and stated that

these parameters may be used for determination of increased risk of arrhythmia in rheumatoid arthritis. In the study of Nafakhi (32), conducted in patients with suspected coronary artery disease, they revealed that patients with increased iCEB levels had higher pericardial adipose tissue volume compared to those with low iCEB values and suggested that pericardial adipose tissue volume may have a potential role in cardiac arrhythmogenesis. Yumurtaci et al. (33) observed that higher iCEB and iCEBc values were found to be associated with episodes of ventricular arrhythmia in cases with acute myocarditis. In literature, no study was found related to iCEB in children with ARF carditis. In our study, although iCEB (QT/QRS) value was increased in patient group, no statistically significant difference was determined between the groups. However, statistically significant increment was determined in iCEBc (QTc/QRS) value of the patient group. In children with acute rheumatic carditis, in addition to use of other risk markers for ventricular arrhythmia (dispersions of QT and QTc, Tpeak-to-end, and ratio of Tp-e/QT), evaluation of iCEB(c) may also contribute to the identification of risky patients.

Small number of patients and to be a cross-sectional study may be accepted as limitations. In patient group, all evaluations were performed at the time of admission, so the effects of anti-inflammatory treatment on ECGs and other parameters were not able to be evaluated. For arrhythmia detection, unfortunately no 24-hour-rhythm Holter monitorings were performed. Therefore, the study population could not be followed-up for possibility of arrhythmia development.

CONCLUSION

In this study, PR interval, Pd, heart rate, dispersion durations of both QT and QTc, Tpeak-to-end interval, iCEBc and ratio of Tp-e/QT were observed to be significantly increased in patient group. As our knowledge, this is the first study in which the index of cardiac-electrophysiological balance has been used in ECG of children with ARF carditis. Given that repolarization-depolarization balance may be impaired in children with acute rheumatic carditis, use of iCEB(c) may also be beneficial in addition to other cardiac arrhythmia risk parameters measured on ECG. However, conduction of more extensive studies are necessary to reveal the role of repolarization-depolarization balance (iCEB) on emerging rhythm disorders in children with acute rheumatic carditis.

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