The ketogenic diet may influence cardiac function among children with epilepsy

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Abstract

Background: The ketogenic diet (KD) is an effective therapy for children with intractable epilepsy. Dyslipidemia is a complication of the KD, and a negative marker of cardiovascular function. However, there is growing interest in the protective effects of KD on the cardiovascular system. To examine the negative and positive effects of the KD on cardiovascular function, the present prospective study aimed to assess lipid profiles and cardiac functions among patients with intractable epilepsy who were on the KD.

Methods: Lipid levels were examined at the baseline and at 1, 3, 6, and 12 months after the KD was initiated. Color Doppler imaging was used to assess ventricular systolic and diastolic functions at the baseline and at 3 months after KD initiation.

Results: There were no statistically significant changes in blood lipid levels. Unexpectedly, cardiac systolic function ($p=0.03$ for ejection fraction and 0.01 for fractional shortening) improved significantly, and diastolic function ($p=0.04$ for E/A) decreased.

Conclusion: The KD may have positive effects on cardiac systolic function among children with epilepsy. In the future, further laboratory and clinical studies will be needed to elucidate the mechanism by which KD influences cardiovascular function.

Introduction

The ketogenic diet (KD) is an efficient, well-established, nonpharmacologic therapy for children with intractable epilepsy. Its side effects during initiation and ongoing use are presented a revised version in the latest guideline by professor Kossoff, et al ^[1]. However, its other effects on the human body remain unclear. Its associated complications have been a point of attention among scholars. As the KD is high in fat, dyslipidemia may occur ^[2], particularly among children^[3]. Some cases are severe ^[4], while some are transient^[5]. In a prospective study, Kwiterovich et al. ^[6] demonstrated that the KD brings about significant increases in the levels of all serum lipids and a significant decrease in the level of high-density lipoprotein (HDL) cholesterol after 6 months. However, these changes are reversed in the twelfth and twenty-fourth months. In addition, up to 60% of patients from the same center had abnormal follow-up serum lipid levels ^[7]. Azevedo de Lima et al. ^[8] showed that KD treatment promotes negative changes in lipoprotein size and phenotype, contributing to an atherogenic risk among these patients. Dyslipidemia is a negative marker of cardiovascular function. Thus, the levels of blood lipids should be monitored at regular intervals during the KD period. Another study showed that a short-term KD did not have a deleterious effect on the cardiovascular disease risk profile and may improve lipid disorders ^[9]. Meanwhile, in some studies with follow-up durations ranging from three weeks to 10 years, researchers found that the KD had no harmful effects on the cardiovascular system ^[10–16]. On the other hand, because ketone bodies are efficient mitochondrial fuels, there is growing interest in its protective effects on the cardiovascular function ^[17–28]. The cardiovascular effects of the KD remain unclear. The KD may be a double-edged

sword for the heart. To examine the negative or positive cardiovascular effects of the KD, the present prospective study assessed cardiac functions and lipid levels among patients with intractable epilepsy who were on the KD.

Methods

Children with a previously confirmed diagnosis of refractory epilepsy, from the Department of Neurology of the Children's Hospital of Chongqing Medical University in China were enrolled in the study. None of the patients had received KD treatment before and their physicians judged them as suitable to undergo KD treatment. Epilepsy and seizure types were classified according to the recommendations of the International League Against Epilepsy (ILAE) 2010 ^[29]. All patients underwent metabolic assessment (urinary organic acid chromatography and blood amino acid chromatography). The exclusion criteria were children with contraindications to the KD ^[1]. Our patients were taking some anti-epileptic drugs (AEDs). The patients did not routinely undergo an assessment of cardiac function before taking AEDs. We also assessed the additional effects of AEDs on cardiac function among the same number of age and gender matched children were selected as the control group, which received a normal diet and did not receive any drugs. Table 1 shows the diagram of visits.

Table 1
Diagram of visits

Groups	Time point	T0 Day 0	T1 1 months	T2 3 months	T3 6 months	T4 12 months
Experimental group	Data collection	×	×	×	×	×
	Physical examination	×	×	×	×	×
	Dietary questionnaires	×	×	×	×	×
	Color Doppler imaging	×		×		
	Total cholesterol	×	×	×	×	×
	Triglyceride	×	×	×	×	×
	High-density lipoprotein cholesterol	×	×	×	×	×
	Low-density lipoprotein cholesterol	×	×	×	×	×
	Blood ketones	×	×	×	×	×
	Blood glucose	×	×	×	×	×
Control group	Data collection	×		×		
	Physical examination	×		×		
	Dietary questionnaires	×		×		
	Color Doppler imaging	×		×		

The study protocol was approved by the Institutional Review Board of the Children's Hospital of Chongqing Medical University. The participants' parents were informed of the risks/benefits of study participation and provided consent for participation in the present study.

A non-fasting gradual initiation protocol of 2:1 KD therapy was initiated at the hospital under the guidance of a dietician.

Blood beta-hydroxybutyrate level measurements made using whole blood samples obtained at the fingertip were used to evaluate patients' ketone statuses. Ketone levels were measured using the FreeStyle Optium Neo Blood Glucose and Ketone Monitoring System (Abbott Diabetes Care Inc., USA). We monitored blood ketone levels once every 6 hours when the patients were hospitalized. KD ratios (fat: carbohydrates + protein) changed between 1:1 and 4:1, depending on individual patients' blood ketone levels and frequency of seizures. Blood ketone levels reached target levels within 2–10 days with a mean of 4.7 days for all patients. The children were discharged and followed-up at clinic visits when ketone

concentrations stabilized between 2 and 5 mmol/L ^[30, 31] and there were no adverse effects. After discharge, ketone levels were monitored once daily for the first month and weekly thereafter.

Parents reported blood ketone levels, glucose levels, seizure frequency, and any adverse events. At clinic visits, the KD ratio was adjusted depending on blood ketone levels and the degree of seizure control. Caloric intake was adjusted to maintain the ideal body weight and height, based on the patient's height and weight gain or loss.

Patients were observed for 3 months during which we assessed the therapeutic effect of the KD ^[1]. For patients among whom the KD therapy worked, we assisted them with reducing their AEDs gradually, one at a time. Parents were asked about the effects of each AED, and if an AED led to significantly worse seizures, we considered reducing the dose of that drug first. Next, we reduced the doses of drugs which had little to no effect. Finally, we eliminated drugs that were effective at the beginning, but were unable to maintain the effect.

Data on the variables were collected by the assessment of ventricular systolic and diastolic functions using color Doppler imaging. We collected data regarding sex; age; height; weight; ejection fraction; fractional shortening; ratio of peak velocity blood flow from gravity in early diastole (the *E* wave) to peak velocity flow in late diastole caused by atrial contraction (the *A* wave) (*E/A*); and the levels of total cholesterol, triglyceride, HDL cholesterol, and low-density lipoprotein (LDL) cholesterol.

Since there are no human studies about the effect of the KD on systolic and diastolic function, 20 people were assessed in a preliminary experiment to explore the positive and negative cardiovascular effects. With EF (systolic function) as the observed value ($n = 20$, EF at day 0 was $66.95\% \pm 8.17\%$, EF at 3 months was $71.00\% \pm 3.85\%$, the change of EF was $4.05\% \pm 8.70\%$), considering $\alpha = 0.05$, a two-sided *Z* value, a one-sided β value, and $1 - \beta = 0.9$, the study sample size was determined to be 48. When the estimated loss to follow-up rate was considered as 10%, the required sample size would be 53.

The independent *t*-test and chi-squared test were performed to determine group differences in baseline characteristics. Cardiac ultrasonography values were compared using the generalized estimating equation. Repeated-measures analyses of variance were used to determine changes in lipid levels. Multiple linear regression analysis was used to assess the effects of other factors (sex, age, BMI, valproic acid dose, and blood ketone level) on cardiac function. All data analyses were performed using SPSS version 18 (IBM Corp., Armonk, NY, USA). Analysis items with *p* value < 0.05 were considered statistically significant.

Results

Seventy children with intractable epilepsy (mean age, 29.26 ± 24.18 months; 42 boys vs 28 girls) who were on the KD for at least 1 month were enrolled for lipid analysis. Fifty-three children (mean age, 32.04 ± 4.01 months; 30 boys vs 23 girls) who were on the KD for at least 3 months were enrolled for

cardiovascular function analysis. All 53 patients were receiving multiple AEDs (4.25 ± 0.27 types). Figure 1 shows the flowchart of patient follow-up during the present study.

There were no significant differences in age ($p = 0.61$), sex ($p = 1.000$), or initial cardiac function (EF, FS, and E/A) ($p = 0.36, 0.26$, and 0.61 , respectively) between the two groups. This may indicate that AEDs were not found to affect cardiac function, although children in the experimental group were given AEDs before the KD. Our primary objective was to investigate the effect of the KD on cardiac function. Table 2 shows the baseline characteristics of the experimental group.

Table 2
Baseline characteristics of the experimental group

Characteristics	Values
Age at KD initiation (months)	3–169 (32.04 ± 4.01)
Disease duration (months)	1–120, IQR (4.5, 12, 24)
Gender (male/female)	53 (30/23)
Classification of seizure type	n (%)
Generalized onset	21 (39.62)
Focal onset	17 (32.08)
Unknown onset	15 (28.30)
Etiology	n (%)
Genetic	16 (30.19)
Structural	6 (11.32)
Unknown	31 (58.49)
KD ratio	n (%)
1/1	1 (1.89)
2/1	48(90.57)
3/1	2 (3.77)
4/1	2 (3.77)
AEDs	n (%)
Topiramate	40 (75.47)
Valproate	39 (73.58)
Levetiracetam	34 (64.15)
Clonazepam	29 (54.72)
Glucocorticoid	27 (50.94)
Oxcarbazepine	13 (24.53)
Nitrazepam	9 (16.98)
Phenobarbital	7 (13.21)
Vigabatrin	6 (13.04)
Lamotrigine	3 (11.32)

Characteristics	Values
Zonisamide	3 (11.32)
Clobazam	3 (11.32)
Carbamazepine	2 (3.77)
Intravenous immunoglobulin	2 (3.77)

Figure 2 shows the changes in lipid levels. Analysis of variance yielded no significant changes in blood lipids. Only a few children in the present study developed dyslipidemia. Notably, several of the children who had hyperlipidemia before KD attained normal blood lipid levels after KD.

As shown in Table 3, the EF ($p = 0.03$) and FS ($p = 0.01$) (measures of systolic function) increased and the E/A ($p = 0.04$) (a measure of diastolic function) decreased in the experimental group. There were no changes in systolic and diastolic function in the control group. The left ventricular diameter-diastolic in the control group ($p = 0.02$) and the right ventricular diameter in the experimental group ($p = 0.02$) were improved.

Table 3
Cardiac ultrasonography values

	Control group			Experimental group		
	Baseline	3 months	p	Baseline	3 months	p
EF (%)	69.84 ± 3.33	69.30 ± 3.53	0.40	68.92 ± 5.83	70.85 ± 3.41	0.03
FS (%)	38.64 ± 2.83	38.06 ± 3.14	0.30	38.04 ± 4.10	39.58 ± 3.08	0.01
E/A	1.52 ± 0.17	1.54 ± 0.16	0.61	1.52 ± 0.16	1.48 ± 0.18	0.04
RVOT	16.22 ± 2.28	16.13 ± 2.37	0.54	15.40 ± 1.83	15.74 ± 1.76	0.26
AO	15.08 ± 2.22	15.11 ± 2.43	0.99	14.96 ± 1.87	15.11 ± 1.74	0.69
LA	16.66 ± 2.38	16.72 ± 2.66	0.83	16.09 ± 1.94	16.47 ± 1.83	0.12
LVOT	15.81 ± 2.45	15.83 ± 2.55	0.86	15.30 ± 1.80	15.66 ± 1.70	0.11
LVDd	29.30 ± 6.27	30.52 ± 5.28	0.02	28.17 ± 3.82	28.55 ± 3.63	0.72
LVDs	18.34 ± 3.57	18.81 ± 3.26	0.03	17.00 ± 2.23	17.42 ± 2.51	0.31
LVPWT	3.96 ± 0.85	4.06 ± 0.89	0.12	3.96 ± 0.71	4.02 ± 0.66	0.61
LVPWP	7.23 ± 1.50	7.23 ± 1.54	0.93	6.91 ± 1.21	7.04 ± 1.13	0.28
IVST	3.92 ± 0.83	4.04 ± 0.90	0.15	3.94 ± 0.72	4.02 ± 0.64	0.68
IVSP	4.17 ± 0.83	4.19 ± 0.83	0.71	3.96 ± 0.73	4.11 ± 0.61	0.09
RV	11.85 ± 2.01	12.24 ± 2.23	0.27	11.58 ± 1.63	11.96 ± 1.65	0.02
PA	13.45 ± 2.37	13.68 ± 2.01	0.24	13.55 ± 1.73	13.80 ± 1.74	0.17
RA	22.49 ± 3.62	22.70 ± 3.54	0.42	22.17 ± 3.14	22.66 ± 2.86	0.64
MV:E peak	1.06 ± 0.10	1.06 ± 0.11	0.75	1.04 ± 0.12	1.01 ± 0.12	0.20
MV:A peak	0.70 ± 0.11	0.69 ± 0.08	0.70	0.68 ± 0.10	0.69 ± 0.10	0.30
TV	0.74 ± 0.06	0.75 ± 0.06	0.39	0.73 ± 0.07	0.73 ± 0.06	0.49
AAO	1.09 ± 0.13	1.09 ± 0.09	0.99	1.04 ± 0.10	1.07 ± 0.15	0.07
MPA	1.07 ± 0.14	1.09 ± 0.13	0.18	1.05 ± 0.10	1.04 ± 0.08	0.88
EF, ejection fraction; FS, fractional shortening; E/A, early (E) to late (A) ventricular filling velocities; RVOT, right ventricular outflow tract; AO, aorta; LA, left atrium; LVOT, left ventricular outflow tract; LVDd, left ventricular diameter-diastolic; LVDs, left ventricular diameter-systolic; LVPWT, left ventricular posterior wall thickness; LVPWP, left ventricular posterior wall pulsation; IVST, interventricular septum thickness; IVSP, interventricular septum pulsation; RV, right ventricle; PA, pulmonary artery; RA, right atrium; MV, mitral valve; TV, tricuspid valve; AAO, ascending aorta; MPA, main pulmonary artery						

As shown in Table 4, the BMI ($p = 0.03$) and valproic acid dose ($p = 0.02$) were negatively correlated with the EF. Sex, age, and blood ketone level were not associated with changes in EF. Sex, age, BMI, valproic acid dose, and blood ketone level were not associated with changes in the FS and E/A.

Table 4
Results of multivariate regression analyses

	β value	95% CI	t	p
Changes in EF				
Sex	-2.37	-5.87–1.13	-1.36	0.18
Age	-0.18	-0.92–0.56	-0.48	0.63
BMI	-0.66	-1.24 to -0.07	-2.26	0.03
Valproic acid dose	-4.82	-8.76 to -0.89	-2.47	0.02
Blood ketone level	-0.20	-2.02–1.61	-0.23	0.82
Changes in FS				
Sex	0.81	-2.22–3.84	0.54	0.59
Age	-0.18	-0.82–0.46	-0.56	0.58
BMI	-0.20	-0.71–0.30	-0.81	0.43
Valproic acid dose	-1.12	-4.53–2.29	-0.66	0.51
Blood ketone level	0.25	-1.32–1.82	0.32	0.75
Changes in E/A				
Sex	0.03	-0.10–0.15	0.41	0.68
Age	-0.01	-0.03–0.02	-0.36	0.72
BMI	-0.01	-0.03–0.01	-0.64	0.53
Valproic acid dose	0.10	-0.04–0.25	1.46	0.15
Blood ketone level	-0.03	-0.09–0.04	-0.85	0.40

The patients showed significant changes on electrocardiogram ($p = 0.04$); 4 patients had 1° atrioventricular block and high QT values.

Discussion

Our study demonstrated that the KD only causes transient mild dyslipidemia. This is similar to the results of other studies. Serum lipid levels normalized within 1 year of KD, although they increased over the first 3 months [32]. The alterations in lipid levels and arterial function reversed and were no longer significant

after 24 months of KD ^[33]. In a previous study, over 10 years, the carotid intima-media thickness did not increase, while the initial dyslipidemia resolved over time and did not recur ^[34]. Another study indicated that despite good tolerability, the KD significantly improved laboratory findings ^[35]. Our analysis showed that the KD was well tolerated in this cohort. This indicates that dyslipidemia rarely occurs due to the KD. Our result is similar to that obtained by Nizamuddin et al. ^[7], who demonstrated that decreasing the KD ratio cured KD-induced hyperlipidemia. A survey of 290 children showed that KD was effective and well tolerated, and the treatment was stopped only among 2 of the 290 children owing to hyperlipidemia ^[36]. In another study, Liu et al. ^[37] showed that baseline hyperlipidemia could be cured by changing the type of dietary fats ingested during KD therapy. Even though we did not emphasize the raw food material (only the KD ratio), a low proportion of patients had abnormal serum lipid levels after the KD. Cervenka et al. ^[32] showed that epileptic adult patients who were receiving a 1:1 KD ratio had similar lipid levels after 12 months compared with baseline levels. These results demonstrated that decreasing the KD ratio may be another option for treating hyperlipidemia.

In addition, several patients in our study who had hyperlipidemia before KD attained normal blood lipid levels after KD dramatically. This phenomenon may be due to the low KD ratio which we used and the control of total calorie intake. This was confirmed in another experiment. In a randomized, controlled trial, serum triglyceride levels decreased more and HDL cholesterol level increased more among patients on a low-carbohydrate diet than among patients on a low-fat diet ^[38].

Traditionally, a high-fat diet is harmful to the cardiovascular system ^[39]. Cardiovascular function must be checked regularly to determine any negative effects. However, currently, the effect of the KD on cardiovascular function remains controversial. On one hand, some researchers posit that the KD is harmful to the cardiovascular system. The cardiovascular disease risk may increase with the intake of high saturated fats ^[40]. Under the KD, arterial stiffness is increased before the increase in intima-media thickness ^[41]. On the other hand, some researchers posit that the KD is not harmful to the cardiovascular system. Although a high-fat diet is associated with elevated serum lipid levels, studies of children with epilepsy showed no negative effects on the carotid intima-media thickness and elastic properties ^[10]. The diet led to improvements in cardiovascular risk markers and showed good compliance ^[11]. The intake of saturated fat did not lead to mortality due to cardiovascular disease and coronary heart disease ^[12]. A study of male runners demonstrated that a KD lasting 3 weeks did not confer a negative cardiovascular disease risk ^[13]. A study conducted in 2016 on the carotid artery and aorta showed that a KD lasting 6 months had no effect on the elastic properties and carotid intima-media thickness ^[14]. These results were similar to those obtained in another study conducted in 2015 regarding the aorta and carotid artery. A KD lasting 1 year among adults with epilepsy was safe in terms of maintaining cardiovascular function. Potential cardiovascular risk markers (e.g., small dense LDL particles) should still be monitored over the long term ^[15]. A KD study showed no cardiovascular risk during a 10-year follow-up ^[16].

Four patients in our cohort had 1° atrioventricular block and high QT values, and these changes were statistically significant. However, another study showed contradictory results^[42]. The KD also induced alterations in gene expression and metabolism^[43]. The KD plays a role in the function of ion channels, and whether it plays a role in the heart through ion channels must be confirmed by further research.

Our study provides direct clinical evidence that KD increases systolic function. Some studies have indicated that the KD had no harmful effect on cardiovascular function. One study indicated that the KD did not disrupt the ventricular functions of children with epilepsy^[44]. Recently, there is growing interest among researchers regarding the protective effect of KD on the cardiovascular system. KD had an intriguing protective effect on the heart^[17]. The protective mechanisms are currently being studied. Gormsen et al.^[18] showed that among healthy humans, ketone bodies displace myocardial glucose uptake and increase myocardial blood flow. Moreover, in terms of protecting the cardiomyocyte metabolism and function, the KD prolonged the survival of endothelial-specific Rbp-jk-deficient mice^[19]. The KD effectively decreased the myocardial uptake of ¹⁸F-fluorodeoxyglucose (a marker for visualization of inflammatory lesions near the heart)^[20]. Under oxidative injury, the KD induces synaptic protection by activating K_{ATP} channels^[21]. In heart failure samples, the expression level of beta-hydroxybutyrate dehydrogenase 1 (a key enzyme in the ketone oxidation pathway) was increased. The heart is capable of oxidizing ketone bodies^[22]. In hypertrophied and failing heart shifts, ketone bodies are a significant source of fuel for oxidative adenosine triphosphate production^[23]. The positive effects of KD on cardiovascular risk factors are similar to those of *n*-3 polyunsaturated fatty acids (ω -3) which, when added to the KD, can improve the positive effects on cardiovascular risk factors^[24]. In injured hearts, ketone bodies are an important fuel source for free radical homeostasis and hemodynamic preservation^[25]. The reliance of the failing heart on ketone bodies for energy supply was demonstrated in two independent studies, providing strong evidence of increased ketone oxidation. Aubert et al.^[23] performed proteomic analysis in mouse models of heart failure, and Bedi et al.^[26] performed metabolomic analysis of end-stage human failing hearts. The cardiac muscle uses diverse substrates such as free fatty acids and ketone bodies as fuel sources^[22]. The peroxisome proliferator-activated receptor system and its associated uncoupling mitochondrial proteins may activate a particular form of metabolism, which is hindered by free fatty acids. The KD can increase the levels of free fatty acids and can thus improve the metabolism^[27]. Beta-hydroxybutyrate (the main ketone body) is an efficient mitochondrial fuel and can open K⁺ channels and regulate Ca²⁺ channels, by which it may protect against oxidative stress^[28].

Limitations

Being statistically significant is not necessarily clinically significant. It is well known that this has to be eventually contextualized in appropriate statistical and clinical scenario^[45]. Due to the one-arm study design with a small sample size, the effect of the KD on cardiovascular function should be interpreted with caution. The demonstrated differences were statistically significant, but the actual changes were

rather modest. Are the differences really meaningful? Can increased systolic function induced by KD improve human heart failure? This requires further study. Many subjects may demonstrate changes in cardiovascular function due to factors such as age, sex, BMI, and AEDs. We should consider other effects on cardiovascular function, such as interactions among different AEDs. None of the patients underwent an assessment of cardiac function before AED initiation, which constitutes a limitation to the present study. However, the influence of AEDs on cardiac function was not the focus of our study, and AEDs were found to yield no influence on cardiac function in the experimental group compared to the healthy control group. For a long time, many scholars have been concerned about the cardiovascular effects of AEDs [46–50]. In our study, all patients received multiple AEDs, which could affect cardiovascular function. We assessed the therapeutic effect of the KD for 3 months [1]. If the KD were effective at 3 months (seizure frequency reduction > 50%), the AEDs would be gradually reduced. Among patients in the first 3 months of the KD, we did not adjust the AEDs received. Changes in heart function during the first 3 months of the study reduced the effect of AEDs on cardiac function. The sample size of this study was small; thus, regression analysis of various AEDs could not be performed. Future studies need to expand the sample size further to study the effects of different AEDs on cardiac function. The interaction between drugs and the KD is the next step of our research. The mechanism by which the KD decreases cardiac systolic function is unclear and requires further study. There is also a need to assess whether the improvement in left ventricular diameter-diastolic in the control group and right ventricular function in the experimental group is associated with an increase in age.

Briefly, maintaining normal blood lipid levels is an important concern for patients with epilepsy who are on the KD. Our study indicated that the KD improves cardiac systolic function. The intriguing cardioprotective role of the KD indicates therapeutic possibilities to combat cardiovascular disease and reduce the burden of the metabolic syndrome. However, the mechanisms remain unknown. In the future, further research will be needed to assess whether KD enhances cardiometabolic health. The clinical significance of this change must be further determined. It remains to be elucidated whether increased systolic function due to the KD can be used to treat chronic heart failure. Further laboratory and clinical research is needed to identify the mechanism by which KD yields a protective effect on cardiovascular function. If more research supports the idea that the KD is good for cardiac health, it could have implications for the healthy diet among the general population.

Conclusion

The KD only causes transient mild dyslipidemia. The KD may have positive effects on cardiac systolic function among children with epilepsy. In the future, further laboratory and clinical studies will be needed to elucidate the mechanism by which KD influences cardiovascular function.

Abbreviations

KD
Ketogenic diet

AEDs
antiepileptic drugs
TC
total cholesterol
TG
triglyceride
HDL
high-density lipoprotein
LDL
low-density lipoprotein cholesterol
EF
ejection fraction
FS
fractional shortening
E/A
early (E) to late (A) ventricular filling velocities
RVOT
Right ventricular outflow tract
AO
Aorta
LA
Left atrial
LVOT
Left ventricular outflow tract
LVDd
Left ventricular diameter-diastolic
LVDs
Left ventricular diameter-systolic
LVPWT
Left ventricular posterior wall thickness
LVPWP
Left ventricular posterior wall pulsation
IVST
Interventricular septum thickness
IVSP
Interventricular septum pulsation
RV
Right ventricle
PA
Pulmonary artery

RA
Right atrium
MV
Mitral valve
TV
Tricuspid valve
AAO
Ascending aorta
MPA
Main pulmonary artery
ILAE
International League Against Epilepsy
GEE
generalized estimating equation
ECG
Electrocardiogram

Declarations

Ethics approval and consent to participate

Institutional Review Board of the Children's Hospital of Chongqing Medical University. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

We have the **informed** consent of the parents.

Availability of data and materials

Clinical trial has registered at Chinese clinical trial registry: <http://www.chictr.org.cn>

Registration numbers: ChiCTR2000031394. Date: (30/03/2020)

Availability of data and material: <http://www.medresman.org.cn/uc/index.aspx>

Code availability (software application or custom code): zian030815, wangjuan030815

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

LJ: Conceptualization;

JW: Formal analysis; Writing

YFL: Nutritional guidance

NS: Color doppler ultrasound guidance

YG: Funding acquisition;

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Figures

Figure 1

Flowchart of patient follow-up in the present study

Figure 2

Variations in lipid levels during KD treatment