Original Article

Detection of Subclinical Anthracyclines' Cardiotoxicity in Children with Solid Tumor

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Abstract

Background: Cardiotoxicity is one of the most serious chronic complications of anthracyclines therapy. Assessment of the left ventricular ejection fraction (LVEF) fails to detect subtle cardiac dysfunction of left ventricular (LV). This study aimed to detect and evaluate new parameters of subclinical anthracyclines' cardiotoxicity in children with solid tumor.

Methods: A detailed echocardiographic examination was performed in 36 children with hepatoblastoma or rhabdomyosarcoma after receiving anthracyclines' chemotherapy and 36 healthy controls from January 2015 to December 2016. The LVEF, ratio of early diastolic peak velocity of transmitral flow (E) and septal diastolic e' mitral annular peak velocity (e'), tricuspid annular plane systolic excursion (TAPSE), and LV global longitudinal strain (GLS) were evaluated using M-mode, tissue Doppler imaging (TDI), and two-dimensional speckle tracking echocardiography (2D-STE), respectively. Echocardiographic parameters were compared between patient group and healthy controls. All patients were divided into two subgroups based on their anthracyclines' cumulative dosage (<300 mg/m^2 subgroup and ≥300 mg/m^2 subgroup).

Results: All patients had no presentation of heart failure and LVEF within normal range (65.7 ± 5.1%). Compared with healthy controls, the mean E/e' increased significantly (7.9 ± 0.7 vs. 10.2 ± 3.5, t = 3.72, P < 0.01), mean TAPSE decreased significantly (17.2 ± 1.3 mm vs. 14.2 ± 3.0 mm, t = −4.03, P < 0.01), and mean LV GLS decreased significantly (−22.2% ± 1.9% vs. −17.9% ± 2.9%, t = -5.58, P < 0.01) in patient group. Compared with subgroup with anthracyclines' cumulative dosage < 300 mg/m^2, mean LV GLS decreased significantly (−18.7 ± 2.7% vs. −16.5 ± 2.1%, t = 2.15, P = 0.04), the mean E/e' increased significantly (9.1 ± 1.5 vs. 11.5 ± 4.9, t = −2.17, P = 0.04), and mean TAPSE decreased significantly (14.2 ± 2.1 mm vs. 12.5 ± 2.2 mm, t = −2.82, P = 0.02) in subgroup with anthracyclines' cumulative dosage ≥300 mg/m^2.

Conclusions: LV GLS is helpful in the early detection of subclinical LV dysfunction using 2D-STE. E/e' and TAPSE are other sensitive parameters in detecting subclinical cardiac dysfunction of both ventricles by TDI. These parameters show significant change with different anthracyclines' cumulative dosage, so cumulative dosage should be controlled in clinical treatment.

Key words: Anthracyclines; Cardiotoxicity; Children; Echocardiography; Solid Tumor

Introduction

Anthracyclines known as cardiotoxic agents are commonly used chemotherapeutic agents in many kinds of solid tumor. Anthracyclines' administration could result in left ventricular (LV) dilatation and dysfunction.[1] Although more than 80% of patients diagnosed with cancer during childhood survive for >5 years, these survivors will face an increased risk of cardiovascular disease that would be the most frequent noncancer cause of mortality.[2,3] Early detection and treatment of cardiotoxicity may improve such outcomes; however, cardiotoxicity is often asymptomatic and may not be detected by conventional echocardiographic screening. Tissue Doppler imaging (TDI) and two-dimensional speckle tracking echocardiography (2D-STE) are relatively new techniques, which allow for the calculation of regional and global myocardial velocities and deformation parameters.[4,5] A systematic review reported that the 10–15% early reduction in global longitudinal strain (GLS)

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.233950

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Received: 13-02-2018 **Edited by:** Xin Chen
How to cite this article: Hu HM, Zhang XL, Zhang WL, Huang DS, Du ZD. Detection of Subclinical Anthracyclines' Cardiotoxicity in Children with Solid Tumor. Chin Med J 2018;131:1450-6.

detected by STE during therapy appeared to be the most useful parameter for the prediction of cardiotoxicity, defined as a drop in LV ejection fraction (LVEF) or heart failure.[6] LV GLS by STE and right ventricular (RV) tricuspid annular plane systolic excursion (TAPSE) by TDI are recommended parameters by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).[7] The aim of the study was to detect and evaluate sensitive parameters using TDI and 2D-STE for subclinical cardiotoxicity caused by anthracyclines' chemotherapy, which affects biventricular function among children with solid tumor.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Beijing Tongren Hospital. Informed consent was obtained from their legal guardians of these patients and healthy controls.

Subjects and protocols

This study included 36 asymptomatic children with hepatoblastoma (HB) or rhabdomyosarcoma (RMS), who were referred to Beijing Tongren Hospital for chemotherapy from January 2015 to December 2016. Thirty-six healthy children for routine check-up who had no congenital cardiovascular disease were collected as healthy controls. These patients were all subjected to detailed medical history and general and cardiac examinations. Treatment protocols used were those recommended by the pediatric department according to the type of solid tumor. HB patients were given chemotherapy protocols with "pirarubicin (25 mg/m^2, day 1–3) + cyclophosphamide (800–1000 mg/m^2, day 1) + cisplatin (90 mg/m^2, day 1)" or "pirarubicin (25 mg/m^2, day 1–3) + etoposide (100 mg/m^2, day 1–4) + cisplatin (90 mg/m^2, day 1)". RMS patients were given chemotherapy protocols with "pirarubicin (25 mg/m^2, days 2 and 9) + vincristine (1.5 mg/m^2, days 1 and 8) + cyclophosphamide (300 mg/m^2, days 1–3) + cisplatin (90 mg/m^2, day 1)" or "ifosfamide (1.5 g/m^2, day 1–5 + dactinomycin (12–15 μg/kg, day 1–5) + etoposide (100 mg/m^2, day 1–3) + vincristine (1.5 mg/m^2, day 1 and day 8)". These patients had no congenital cardiovascular disease or the cardiovascular system metastases, and no other cardiotoxic drugs administered. The duration of therapy was >1 year and all patients were in complete remission at the time of the study. Age and gender of 36 healthy controls were matched with patients. Thirty-six patients were divided into two subgroups according to anthracyclines' cumulative dosage: <300 mg/m^2 subgroup and ≥300 mg/m^2 subgroup.

Echocardiographic study

Transthoracic echocardiography was performed in all patients after the last chemotherapy session by the same sonographer. The healthy controls received the same examination. LV dimensions and LVEF were measured in parasternal long axis view, and TAPSE of the RV lateral wall was measured in apical four-chamber view, all of them were acquired by M-mode.[8]

Pulsed wave Doppler velocity was used to measure the mitral inflow E velocity and A velocity. The early diastolic peak velocity of transmitral flow (E) was measured at mitral valve. TDI measurements included septal diastolic e' mitral annular peak velocity (e') and septal systolic s' mitral annular peak velocity (s'). The ratio of E and e' (E/e') was also calculated.

The 2D-STE was performed for the left ventricle. The 2D images were obtained in the apical four-chamber, apical long-axis, and apical two-chamber views to measure the longitudinal deformation. A frame rate of 60 Hz was used because it is considered optimal for 2D-STE.[9] Acceptable images from three cardiac cycles were digitally saved in cine loop format on the hard disc of the echo machine and subsequently exported to a digital versatile disc and imported into the postprocessing station (EchoPAC version 201, General Electric Co., USA) for offline analysis. Cardiac cycles with lengths >10% of mean length of the three cardiac cycles were excluded from further analysis, and manual tracking of the endocardial borders was performed. The timing of aortic valve closure was also manually determined. Tracking data were accepted if the EchoPAC software showed adequate tracking and if the examiner's inspection revealed good tracking throughout the cardiac cycle. Autofunctional imaging was used to enable the assessment of the systolic segmental and GLS. Segmental longitudinal strain was calculated using 17-segment bull's eye. The LV GLS was calculated by the mean GLS of the apical four-chamber and two-chamber views and apical long-axis view.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences software (version 21.0; SPSS Inc., Chicago, Illinois, USA). Data were tested for normality using Kolmogorov-Smirnov test and were expressed as a mean ± standard deviation (SD), and categorical data were showed as percentages. Comparisons between the groups were calculated using nonparametric tests (Wilcoxon's test) for nonnormally distributed data and parametric tests (*t*-test) for normally distributed data. The intra- and inter-observer variabilities for LV GLS and TASPE were assessed in twenty randomly selected patients by one examiner on two separate occasions. Bland-Altman plot analysis was used to determine the mean intraobserver differences.[10] A $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

The patient group included 24 boys and 12 girls. Twenty-six

patients were diagnosed as HB, and ten were diagnosed as RMS. In patient group, the mean age was 3.6 ± 2.2 years and the mean weight was 18.3 ± 7.3 kg. The mean height was 106.6 ± 25.0 cm and the mean body surface area was 0.7 ± 0.2 m^2. All patients received anthracyclines in the form of pirarubicin, and the anthracyclines' cumulative dosage ranged from 24.8 mg/m^2 to 772.0 mg/m^2. The mean value of accumulative anthracyclines' dosage was 293.7 ± 35.4 mg/m^2. There were 21 patients in the subgroup with cumulative anthracyclines' dosage <300 mg/m^2 and 15 patients in the subgroup with cumulative anthracyclines' dosage ≥300 mg/m^2. Control group included 20 boys and 16 girls. The mean age of healthy controls was 3.9 ± 2.2 years, the mean weight was 19.7 ± 7.9 kg, the mean height was 108.1 ± 9.6 cm, and the mean body surface area was 0.7 ± 0.2 m^2. There were no significant differences in age, weight, height, and body surface between the patient and control groups (all $P > 0.05$).

Left and right ventricular dysfunction after chemotherapy

After anthracyclines' chemotherapy, the patient group had no presentation of heart failure and had mean LVEF within the normal range of 65.7 ± 5.1%, compared with healthy controls (66.6 ± 3.4%, $P = 0.52$). However, the mean E/e' increased significantly in the patient group (10.2 ± 3.5 vs. 7.9 ± 0.7, $P < 0.01$), compared with healthy controls. The mean s' had no significant difference between the patient group and control groups (6.9 ± 1.4 vs. 7.0 ± 1.1, $P = 0.92$).

Mean LV GLS was −17.9 ± 2.9% in the patient group and −22.2 ± 1.9% in healthy controls, and there was a significant difference ($P < 0.01$). The mean LV GLS from the apical long-axis, four-chamber, and two-chamber views in the patient and control groups is presented in Table 1. Images of LV GLS were presented in Figures 1–3, which illustrated the different GLS changes obtained from the apical long-axis view, four-chamber view, two-chamber-view, and strain curves and bull's eye plot in three patients after receiving pirarubicin treatment.

Mean TAPSE decreased significantly in patient group, compared with healthy controls (14.2 ± 3.0 mm vs. 17.2 ± 1.3 mm, $P < 0.01$).

Comparison of left ventricular global longitudinal strain, E/e', and tricuspid annular plane systolic excursion according to different anthracyclines' cumulative dosage

Mean LVEF between the two subgroups of patients had no significant difference (65.9 ± 5.5% vs. 66.5 ± 4.6%, $P = 0.83$). The mean LV GLS decreased significantly (−16.5 ± 2.1% vs. −18.7 ± 2.7%, $P = 0.04$), the mean E/e' increased significantly (11.5 ± 4.9 vs. 9.1 ± 1.5, $P = 0.04$), and mean TAPSE decreased significantly (12.5 ± 2.2 mm vs. 14.2 ± 2.1 mm, $P = 0.02$) in subgroup with anthracyclines' cumulative dosage ≥300 mg/m^2, compared with subgroup with anthracyclines' cumulative dosage <300 mg/m^2 [Table 2].

Discussion

Clinical effectiveness of anthracyclines may be thwarted by the development of cardiotoxicity that negatively affects patients' outcomes and seriously limits their oncological

Table 1: Parameters of left and right ventricular dysfunction in patients with solid tumor and healthy controls

Parameters	Patient group (n = 36)	Control group (n = 36)	t	P
LVEF (%)	65.7 ± 5.1	66.6 ± 3.4	−0.65	0.52
E/e'	10.2 ± 3.5	7.9 ± 0.7	3.72	<0.01
s'	6.9 ± 1.4	7.0 ± 1.1	0.18	0.92
TAPSE (mm)	14.2 ± 3.0	17.2 ± 1.3	−4.03	<0.01
Left ventricular GLS (%)	−17.9 ± 2.9	−22.2 ± 1.9	−5.58	<0.01
LAX GLS (%)	−17.4 ± 3.8	−22.6 ± 3.2	−5.03	<0.01
4CH GLS (%)	−17.6 ± 3.4	−21.4 ± 2.3	−4.32	<0.01
2CH GLS (%)	−18.2 ± 3.1	−22.5 ± 2.2	−5.24	<0.01

The data were shown as mean ± SD. LVEF: Left ventricular ejection fraction; E/e': The ratio of early diastolic peak velocity of transmitral flow (E) and septal diastolic e' mitral annular peak velocity (e'); s': Septal systolic s' mitral annular peak velocity; TAPSE: Tricuspid annular plane systolic excursion; GLS: Global longitudinal strain; LAX: Apical long-axis view; 4CH: Four-chamber view; 2CH: Two-chamber view; SD: Standard deviation.

Table 2: Parameters of left and right ventricular dysfunction in two different anthracyclines cumulative dosage subgroups

Items	Subgroup with dosage <300 mg/m^2 (n = 21)	Subgroup with dosage ≥300 mg/m^2 (n = 15)	t	P
LVEF (%)	65.9 ± 5.5	66.5 ± 4.6	0.21	0.83
Left ventricular GLS (%)	−18.7 ± 2.7	−16.5 ± 2.1	2.15	0.04
E/e'	9.1 ± 1.5	11.5 ± 4.9	−2.17	0.04
TAPSE (mm)	14.2 ± 2.1	12.5 ± 2.2	−2.82	0.02

The data were shown as mean ± SD. LVEF: Left ventricular ejection fraction; GLS: Global longitudinal strain; E/e': The ratio of early diastolic peak velocity of transmitral flow (E) and septal diastolic e' mitral annular peak velocity (e'); TAPSE: Tricuspid annular plane systolic excursion; SD: Standard deviation.

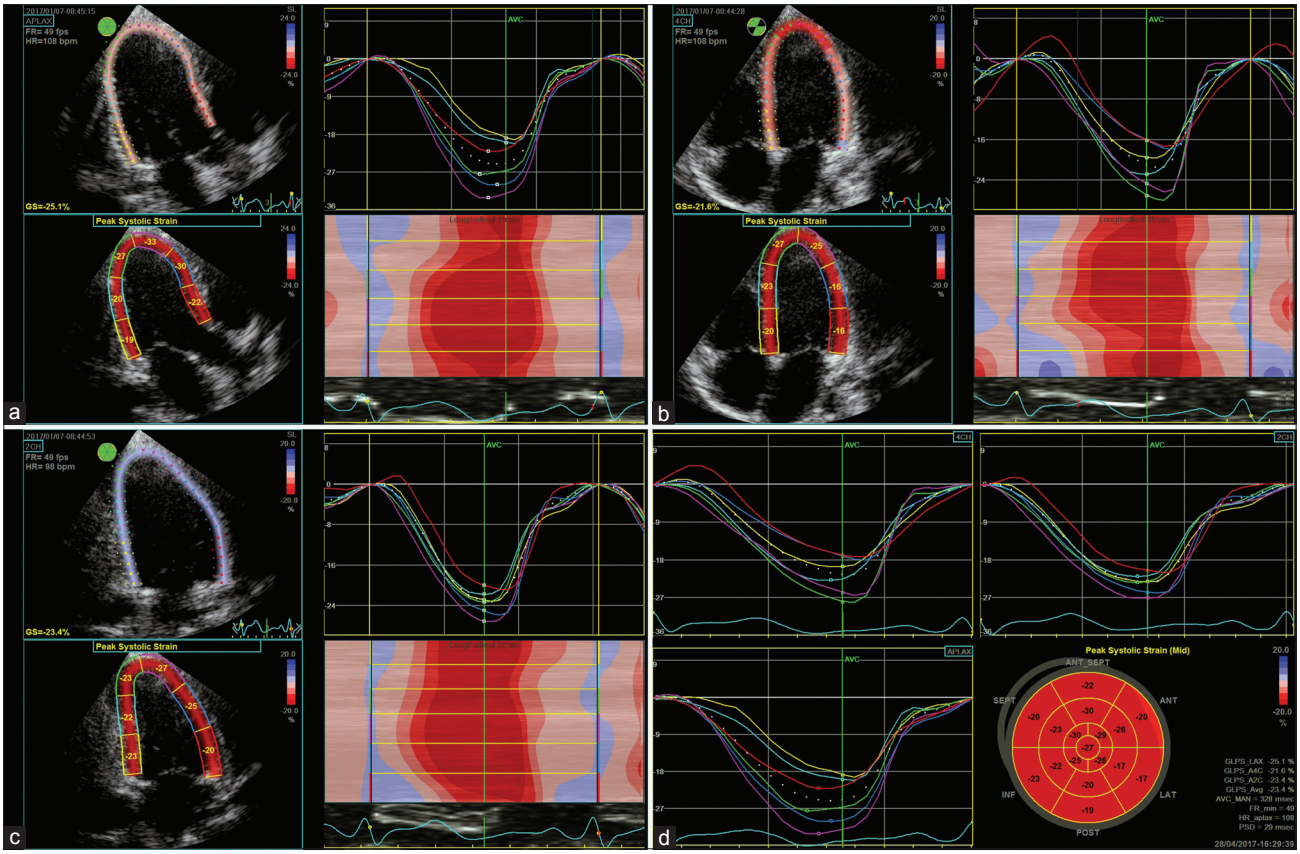

Figure 1: STE images illustrating GLS in the apical long-axis view (a), four-chamber view (b), two-chamber-view (c), and the strain curves and bull's eye plot (d) in a 3-year-old girl patient with rhabdomyosarcoma who had normal GLS after receiving pirarubicin. The average GLS was –23.6%. The accumulative anthracyclines' dosage was 136 mg/m^2. STE: Speckle tracking echocardiography; GLS: Global longitudinal strain.

therapeutic opportunities.[11,12] Cancer survivors tend to develop heart failure, ischemic heart disease, and cerebrovascular incidents more often than the general population. The cardiovascular mortality among childhood cancer survivors was 10-fold higher than those of age-matched healthy controls.[13,14] Detection of an obviously decreased LVEF after anthracyclines' administration might be too late for treatment, suggesting that more sensitive parameters would be helpful for detecting left and RV dysfunction.[15] To detect LV systolic dysfunction in anthracyclines cardiotoxicity, a report from the ASE and the EACVI recommended as follows: LVEF assessed by 2D echocardiography often fails to detect small changes in LV contractility, and LVEF should be combined with wall motion score index. In the absence of GLS by STE, quantification of LV longitudinal function using mitral annular displacement by M-mode echocardiography and/or peak systolic velocity (s') of the mitral annulus by pulsed wave TDI is recommended.[7] Numerous reports about LV GLS in adults those received anthracyclines' treatment existed;[16,17] however, only a few such studies have been conducted in children.[18,19] Results mostly showed that LV GLS was sensitive enough to identify subclinical cardiotoxicity. Hence, we chose GLS and s' to detect subclinical cardiotoxicity of LV. After anthracyclines' chemotherapy, conventional echocardiography of LVEF showed normal findings. The mean LVEF was 65.7 ± 5.1% in the patient group with anthracyclines' chemotherapy, while the mean LVEF in healthy controls was 66.6 ± 3.4%, without significant difference. However, mean LV GLS in patient group was much lower than that of the healthy controls (−17.9 ± 2.9% vs. −22.2 ± 1.9%, $P < 0.01$). The mean LV GLS in healthy children was −22.2 ± 1.9%, which was in accordance with the recommended universal normal value (−22.1 ± 2.4%) or lower limits of the normal range.[9,20] However, the difference of mean s' between the two groups showed no significant difference (6.9 ± 1.4 vs. 7.0 ± 1.1, $P = 0.92$). The difference of mean s' in this study might be affected by the size of sample, which will be further investigated in large sample study to make sure its clinical value. Thus, LV GLS changed apparently earlier than the LVEF and s', which was a sensitive subclinical parameter for cardiotoxicity in children.

A comprehensive assessment of LV diastolic function should also be performed, including the ratio of E and e', which could be an index of LV diastolic function according to the joint recommendations of ASE and European Association of Echocardiography.[21] Thus, this study chose the ratio of E and e' to evaluate the diastolic function of LV. Results showed that E/e' had a significant difference between the patient group and healthy controls. Therefore, the E/e' could be a parameter to identify subclinical LV diastolic

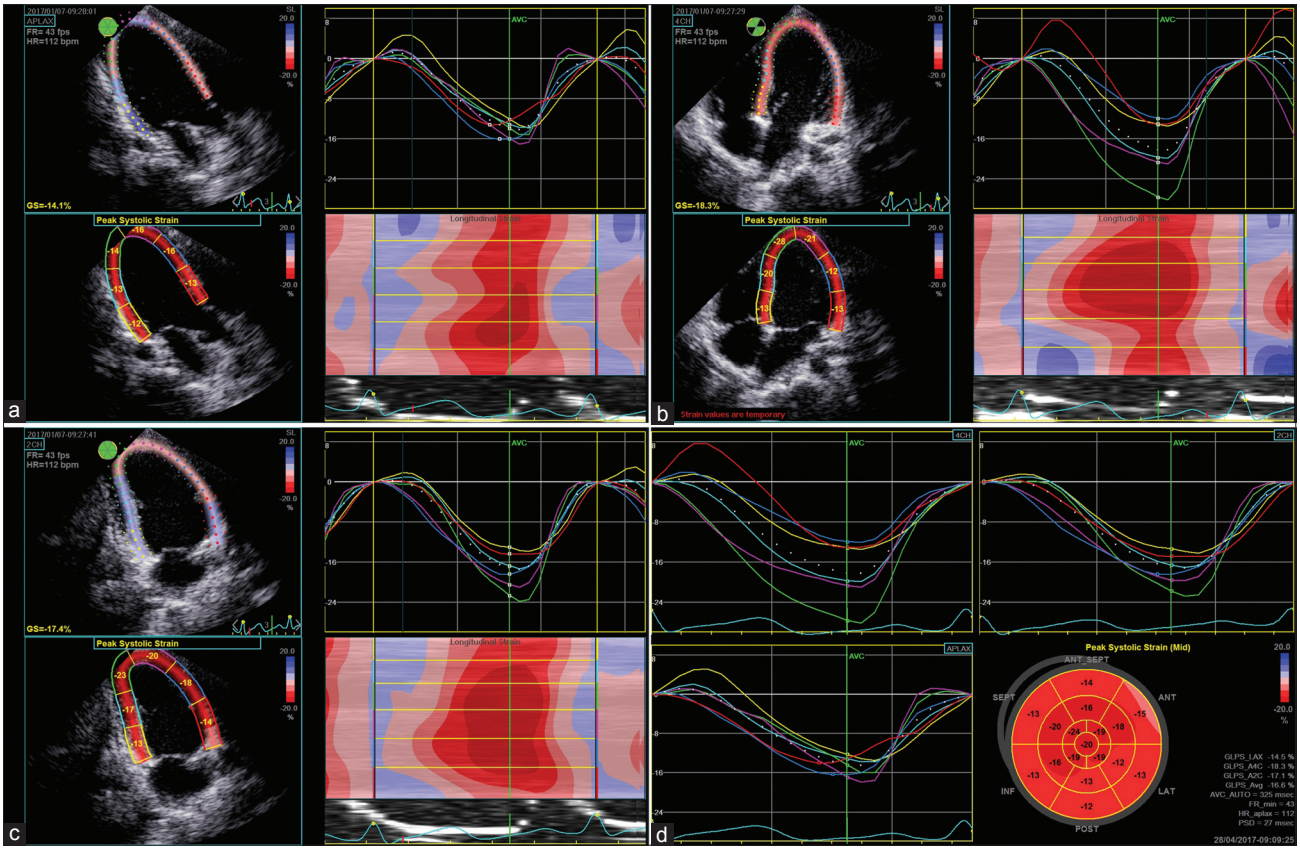

Figure 2: STE images illustrating GLS the apical long-axis view (a), four-chamber view (b), two-chamber-view (c), and strain curves and bull's eye plot (d) in a 6-year-old girl with rhabdomyosarcoma after receiving pirarubicin. The average GLS was –15.7%. The accumulative anthracyclines dosage was 329.8 mg/m^2. STE: Speckle tracking echocardiography; GLS: Global longitudinal strain.

dysfunction. The LV diastolic function could appear abnormal before LVEF.

Moreover, TAPSE was another parameter recommended to detect RV systolic function, and it reflected systolic function of right ventricle.[7] Results of this study showed that an obvious reduction in TAPSE in the patient group, compared with healthy controls. The RV systolic function also appeared abnormal after anthracyclines' chemotherapy, and TAPSE had a significant decrease before LVEF change.

In 26% of patients who received low-to-moderate dosage of anthracyclines (50–375 mg/m^2), evidence of subclinical cardiac injury was noted within 6 months after therapy of anthracyclines.[22] Abnormal GLS was correlated with the dose ≥300 mg/m^2.[23] Hence, patients in this study were divided into two subgroups: <300 mg/m^2 subgroup and ≥300 mg/m^2 subgroup. The LV GLS decreased significantly in subgroup with anthracyclines' cumulative dosage ≥300 mg/m^2, compared with subgroup with anthracyclines' cumulative dosage <300 mg/m^2. When LVEF had no significant difference between the two subgroups, LV GLS had the significant difference, which might imply that LV GLS could change according to the cumulative dosage. In the future, a study with large sample size will be conducted to make clear that if the change of LV GLS has a linear correlation with anthracyclines' cumulative dosage. The E/e' had a significant difference between the two subgroups, which could be attributed to LV diastolic dysfunction caused by anthracyclines. The TAPSE had significant difference between the two subgroups according to different cumulative dosage. Hence, the cumulative dosage of anthracyclines should be controlled <300 mg/m^2 to prevent the subclinical cardiac dysfunction.

In conclusion, this study confirmed that LV GLS is the optimal parameter of LV deformation, which is helpful in the early detection of subclinical LV dysfunction using 2D-STE. The ratio of E and e' is another sensitive parameter that is useful in detecting LV diastolic dysfunction. After anthracyclines' chemotherapy, TAPSE measurement could be used to identify early RV dysfunction. These three parameters showed significant change with different anthracyclines' cumulative dosage, so cumulative dosage should be controlled in clinical treatment.

Financial support and sponsorship

This study was supported by a grant from Research Backbone Training Fund of Beijing Tongren Hospital (No. 2015-YJJ-GGL-009).

Conflicts of interest

There are no conflicts of interest.

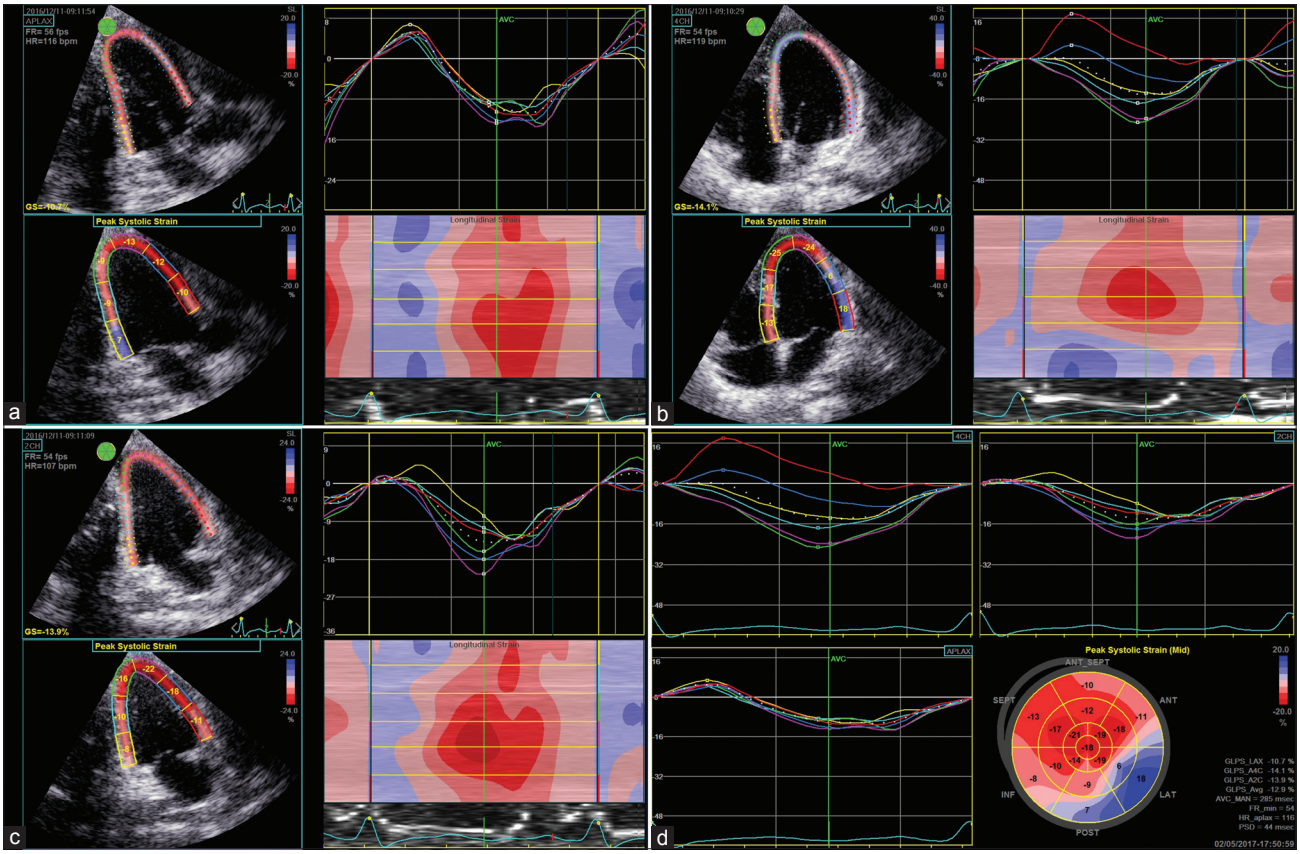

Figure 3: STE images illustrating GLS in the apical long-axis view (a), four-chamber view (b), two-chamber view (c), and strain curves and bull's eye plot (d) in a 3-year-old boy with hepatoblastoma after receiving pirarubicin. The average GLS was –12.3%. The accumulative anthracyclines dosage was 595.2 mg/m^2. STE: Speckle tracking echocardiography; GLS: Global longitudinal strain.

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儿童实体瘤蒽环类药物的亚临床心脏毒性分析

摘要

背景：心脏毒性是蒽环类药物最常见的慢性并发症，左室射血分数（LVEF）不能发现左心室功能的微小异常。本研究目的是发现能检测和评价儿童实体肿瘤应用蒽环类药物所致亚临床心脏毒性的新参数。

方法：收集自2015年1月至2016年12月，36例接受蒽环类药物化疗的肝母细胞瘤（HB）或横纹肌肉瘤（RMS）患儿和36例健康对照儿童，采用M型、组织多普勒成像（TDI）和二维斑点追踪超声心动图（2D-STE），分别详细测量以下参数：左室射血分数（LVEF）、舒张早期二尖瓣E峰流速（E）和室间隔舒张期二尖瓣环峰值速度（e'）的比值、三尖瓣环收缩期位移（TAPSE）和左心室整体纵向应变（GLS）。应用统计学方法比较患者组和健康对照组的超声心动图参数。并依据蒽环类药物累积剂量将患者分为＜300mg/m^{2}和≧300mg/m^{2}两个亚组。

结果：所有患儿均无心衰临床表现，LVEF均在正常范围内（65.7±5.1%）。与健康对照组比较，患者组平均E/e'显著性升高(7.9±0.7 vs. 10.2±3.5, t=3.72, P<0.01)；平均TAPSE显著性降低(17.2±1.3 mm vs. 14.2±3.0 mm, t=-4.03, P<0.01)；平均左心室GLS显著性下降(–22.2±1.9% vs. –17.9±2.9%, t=-5.58, P<0.01)。与蒽环类药物累积剂量<300 mg/m^{2}亚组比较，累积剂量≥300mg/m^{2}亚组的平均左心室GLS显著性下降(–18.7±2.7% vs. –16.5±2.1%, t=2.15, P=0.04)；平均E/e'显著性升高(9.1±1.5 vs. 11.5±4.9, t=−2.17 P=0.04), 平均TAPSE显著性下降(14.2±2.1 mm vs. 12.5±2.2 mm, t=−2.82, P=0.02)。

结论：通过2D-STE测量的左心GLS在早期监测亚临床左心室功能不全有价值；通过TDI测量的E/e'和TAPSE是其他能监测双心室亚临床功能不全的敏感指标；这些参数随蒽环类药物的累积剂量发生显著性改变，临床治疗中需控制累积剂量。