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ORIGINAL ARTICLE

Left Ventricular Ejection Fraction and Fractional Shortening are Useful for the Prediction of the Therapeutic Response to Metoprolol in Children with Vasovagal Syncope

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Abstract
The objective of this manuscript was to explore if left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) could predict the efficacy of metoprolol therapy on vasovagal syncope (VVS) in children. Forty-nine children, including 30 with VVS and 19 gender- and age-matched healthy controls, were included in the study. Metoprolol was prescribed to the VVS subjects. The clinical data were obtained during follow-up at 2 and 6 months. The results showed that LVEF and LVFS of responders were significantly higher than those of non-responders both at the 2-month follow-up (LVEF: 72.5 ± 3.2% vs. 64.6 ± 3.4%; LVFS: 40.9 ± 2.3% vs. 34.9 ± 2.9%), and at the 6-month follow-up (LVEF: 72.8 ± 2.8% vs. 65.5 ± 4.6%; LVFS: 41.1 ± 1.9% vs. 35.8 ± 3.6%). The receiver operating characteristic curve (ROC) analysis demonstrated that 70.5% as a cutoff value of baseline LVEF yielded a sensitivity of 80% and a specificity of 100% in predicting the therapeutic effectiveness of metoprolol at 2 months. For baseline LVFS, 38.5% as a cutoff value yielded a sensitivity of 90% and a specificity of 90%. At the 6-month follow-up, the ROC analysis demonstrated that 70.5% as a cutoff value of baseline LVEF yielded a sensitivity of 81.3% and a specificity of 88.9% in the prediction of metoprolol efficacy. For baseline LVFS, 37.5% as a cutoff value yielded a sensitivity of 93.8% and a specificity of 66.7%. In conclusion, baseline LVEF and LVFS might be useful predictors of the efficacy of β-blocker therapy on VVS in children.

Keywords Echocardiography · Vasovagal syncope · Metoprolol · Child and adolescent

Introduction

Vasovagal syncope (VVS) is the most frequent type of neurally mediated syncope (NMS), and is also the most common type of childhood syncope [1, 2]. It is one of the forms of acute orthostatic intolerance (OI), with its frequent occurrence and remissions [3, 4]. Although most of the children with VVS have favorable prognosis, the recurrence rate of VVS is very high, with a 1-year recurrence rate of 25–35% [5]. In addition, studies have shown that children with VVS have a lower degree of psychological health compared with normal kids and have an increased risk of suffering from anxiety and depression [6–8]. The quality of learning and living may be seriously affected in these children. Therefore, the effective treatment should be given to children with VVS to reduce the rate of syncope recurrence. At present, the therapeutic options for VVS in children include conventional treatment (i.e., orthostatic training, inducement avoiding, and fluid and salt intake), peripheral alpha-agonists (i.e., midodrine hydrochloride), and beta-blockers (i.e., metoprolol) [9–11]. Our previous work showed that not all children could receive curative effect from beta-blockers. When followed up for 6 ~ 30 months, the syncope recurrence rate was only 30.7% [12]. The reason is likely attributed to the diverse and sophisticated pathogenesis of VVS, which has marked heterogeneity among children.

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Indeed, the status of high catecholamine is one of the proposed mechanisms for VVS [13]. Syncope is the result of an exaggerated neurocardiac reflex, which is also called the Bezold–Jarisch reflex [14]. Our hypothesis, therefore, is that adrenergic beta-antagonist therapy would likely be effective for VVS patients who have a predominantly high catecholamine status as the major mechanism for VVS. In line with the abovementioned hypothesis, our previous work showed that an over 30 bpm/min increase in heart rate (HR) from baseline to a positive response in the head-up tilt test (HUTT) might predict a favorable effect from adrenergic beta-antagonist therapy for VVS children, with a sensitivity of 81%, a specificity of 80%, and a diagnostic value of 81% [15, 16]. However, some children are nervous during the test, which may affect the fluctuation of HR caused by the tilting position and therefore obscure the estimation of the therapeutic effect of adrenergic beta-antagonists. As a result, looking for an effective, non-invasive, convenient and stable index for the prediction of the therapeutic effect of adrenergic beta-antagonists in pediatric patients with VVS is desired by pediatricians worldwide. Dobutamine is a type of catecholamine that can excite the cardiac β1-receptor, and a certain dose of injection can raise the numerical value of the left ventricular functional indices left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) [17, 18], suggesting that LVEF and LVFS measured by echocardiography may reflect the level of plasma catecholamine status in vivo. Therefore, we speculate that children with VVS with increased LVEF and LVFS might be predicted to have a favorable therapeutic effect from beta-blocker therapy. Therefore, the aim of our study was to explore the possible value of LVEF and LVFS in the prediction of the therapeutic response to beta-blocker in VVS in children.

Methods

Thirty children (10 males and 20 females aged 6–15 years) diagnosed with VVS in the Department of Pediatrics at the Peking University First Hospital from February 2006 to October 2016 were included in this case–control study. The diagnostic criteria of VVS were as follows: (1) syncope or presyncope occurs with an upright posture or with exposure to emotional stress, pain, or medical settings; (2) cases have features dizziness, diaphoresis, nausea or pallor as accompanied symptoms; (3) cases have a positive HUTT response; and (4) exclusion of other diseases, such as organic cardiovascular diseases and cerebrovascular diseases [5, 19]. Nineteen healthy children (10 males and 9 females aged 6.5–15 years) with no history of dizziness and syncope; normal physical examination and electrocardiogram; and negative response in HUTT were recruited for the control group. Informed consent was obtained from the parents of the subjects, and the study has been approved by the Ethics Committee at Peking University First Hospital, China (Grant No. [2009]170).

HUTT was performed in children with VVS according to the previously described method [10–12, 15, 16].

Doppler color echocardiogram (SSD-5000SV, Aloka, Japan) with a linear 3–5 MHz transducer was used to measure the cardiac function parameters. All children were evaluated in the supine position. Left ventricular end-diastolic diameter (LVDD) and left ventricular end-systolic diameter (LVSD) were measured in the long-axis section of the parasternal ventricular sinister by M-mode echocardiography. LVEF and LVFS were computed accordingly with the following formulae:

$$\mathrm{LVEF} = \left(\mathrm{LVDD}^3 - \mathrm{LVSD}^3\right)/\mathrm{LVDD}^3 \quad (1)$$

$$\mathrm{LVFS} = (\mathrm{LVDD} - \mathrm{LVSD})/\mathrm{LVDD} \quad (2)$$

All children with VVS took oral metoprolol as the treatment. Generally, the dose was 12.5 mg bid, but slight differences existed according to age and weight. The course of treatment was 2 (1, 2) months. The clinical data were obtained in an out-patient visit and over the telephone during follow-up at 2 and 6 months. All patients were followed up for 2 months (lost to follow up: 0), and 25 patients were followed up for 6 months (5 cases lost to follow up, miss rate of 16.7%). The syncope frequency and the adverse drug reactions were observed. The syncope frequency was graded as follows: 0, syncope did not occur; 1, syncope occurred 2–4 times per month; 3, syncope occurred 2–7 times per week; and 4, syncope occurred more than once per day [20, 21].

IBM-SPSS 22.0 software was used for statistical analysis. Measurement data are presented as the mean ± standard deviation, and the Shapiro–Wilk normality test was performed. Ranked data are presented as median (quartile). Two-sample t tests, non-parametric tests, and χ^2 tests were employed to compare between two groups. Correlation analysis used the Spearman rank correlation analysis. Analysis of the predictors of treatment effect was done using the receiver operation characteristic (ROC) curve. A $p < 0.05$ was considered statistically significant.

Results

Gender composition, height, weight, body mass index (BMI), baseline HR, baseline SBP, baseline DBP, baseline LVEF, and baseline LVFS did not differ between the VVS group and the control group (Table 1).

Thirty cases were followed up, and the curative efficacy of adrenergic beta-antagonists was assessed 2 months

Table 1 Comparisons of clinical data between VVS and control groups

Groups	Gender (male/female)	Age (year)	Height (cm)	Weight (kg)	BMI (kg/m^2)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	LVEF (%)	LVFS (%)
VVS group	10/20	10.5 ± 2.7[b]	147.0 ± 14.3[b]	41.5 ± 12.9	18.8 ± 3.7	78.9 ± 10.6	103.7 ± 10.3	59.4 ± 8.0	69.8 ± 5.0[b]	38.9 ± 3.8[b]
Control group	10/9	9.7 ± 2.2	145.2 ± 13.9	38.3 ± 8.6	18.2 ± 3.3	82.7 ± 10.5	98.5 ± 6.9	59.3 ± 5.4[b]	68.2 ± 3.9	37.6 ± 3.3
Statistics	1.793[a]	$Z = -0.847$	$Z = -0.441$	$t' = -1.049$	$t = -0.571$	$t = 1.251$	$t = -1.956$	$Z = -0.082$	$Z = -1.265$	$Z = -1.217$
P	0.181	0.397[c]	0.659[c]	0.299	0.571	0.217	0.056	0.934[c]	0.206[c]	0.224[c]

BMI body mass index, *DBP* diastolic blood pressure, *HR* heart rate, *LVEF* left ventricular ejection fraction, *LVFS* left ventricular fractional shortening, *SBP* systolic blood pressure

[a]Pearson χ^2

[b]Non-normal distributions

[c]Asymptotic significance (2-tailed)

after the start of metoprolol therapy. Within the 2-month period, children with a syncope frequency score decrease by ≥ 1 point compared with the baseline were classified as responders (20 cases, 66.7%), whereas children with a syncope frequency score decrease by < 1 point or with a syncope frequency score increase compared with the baseline were classified as non-responders (10 cases, 33.3%) [19]. The comparison between the two groups showed that the LVEF of responders was significantly higher than that of non-responders (72.5 ± 3.2% vs. 64.6 ± 3.4%, $P < 0.001$), and the LVFS of responders was significantly higher than that of non-responders (40.9 ± 2.3% vs. 34.9 ± 2.9%, $P < 0.001$, Table 2), whereas there was no difference in baseline parameters such as HR, SBP, DBP, and syncope frequency score between the two groups.

Twenty-five cases (five cases lost to follow up, miss rate of 16.7%) with VVS were followed up for 6 months, and the curative efficacy of adrenergic beta-antagonists was assessed 6 months after starting metoprolol therapy. Children with a syncope frequency score decrease by ≥ 1 point were classified as responders (16 cases, 64.0%), whereas children with a syncope frequency score decrease by < 1 point or with a syncope frequency score increase were classified as non-responders (9 cases, 36.0%). The results showed that the LVEF of responders was significantly higher than that of non-responders (72.8 ± 2.8% vs. 65.5 ± 4.6%, $P = 0.001$), and the LVFS of responders was significantly higher than that of non-responders (41.1 ± 1.9% vs. 35.8 ± 3.6%, $P = 0.002$, Table 2), whereas there was no difference in baseline parameters such as HR, SBP, DBP, and syncope frequency score between the two groups.

The Spearman's correlation test indicated that when the subjects were followed up for 2 months, the syncope frequency score was negatively correlated with baseline LVEF ($r_s = -0.712$, $P = 0.000$, Fig. 1a) and baseline LVFS ($r_s = -0.712$, $P = 0.000$, Fig. 1b). When the subjects were followed up for 6 months, the syncope frequency score was negatively correlated with baseline LVEF ($r_s = -0.660$, $P = 0.000$, Fig. 1c) and baseline LVFS ($r_s = -0.640$, $P = 0.001$, Fig. 1d).

The ROC analysis demonstrated an area under the curve (AUC) of 0.952 (95% CI 0.883–1.000, $P = 0.000$), and 70.5% as a cutoff value of baseline LVEF yielded a sensitivity of 80% and a specificity of 100% in the prediction of the therapeutic effect of metoprolol on VVS in children at the 2-month follow-up. For baseline LVFS, the AUC was 0.942 (95% CI 0.864–1.000, $P = 0.000$), and 38.5% as a cutoff value yielded a sensitivity of 90% and a specificity of 90% in the prediction of the therapeutic effect of metoprolol on VVS in children at the 2-month follow-up (Fig. 2a).

At the 6-month follow-up, the ROC analysis demonstrated an AUC of 0.906 (95% CI 0.783–1.000; $P = 0.001$), and 70.5% as a cutoff value of baseline LVEF yielded a

Table 2 Comparison of clinical data between responders and non-responders (2- and 6-month follow-up)

Items	2 Months				6 Months			
	Responders ($n=20$)	Non-responders ($n=10$)	Statistics	P	Responders ($n=16$)	Non-responders ($n=9$)	Statistics	P
Gender (male/female)	7/13	3/7	N/A[a]	0.560[b]	7/9	1/8	N/A[a]	0.107[b]
Age (year)	10.4 ± 2.9	10.7 ± 2.5[c]	$Z=-0.111$	0.912[d]	10.3 ± 2.8	11.1 ± 2.4	$t=-0.779$	0.444
Height (cm)	148.2 ± 15.5[c]	144.8 ± 12.1	$Z=-0.881$	0.378[d]	147.6 ± 14.5	150.8 ± 11.5	$t=-0.579$	0.568
Weight (kg)	42.3 ± 14.2	40.0 ± 10.3	$t=0.443$	0.661	42.6 ± 15.0	43.2 ± 9.8	$t=-0.108$	0.915
BMI (kg/m^2)	18.8 ± 4.2	18.7 ± 2.5	$t=0.016$	0.988	19.0 ± 4.6	18.7 ± 2.1	$t'=0.218$	0.829
HR (bpm)	78.8 ± 12.0	79.1 ± 7.4	$t=-0.084$	0.934	79.6 ± 12.2	79.2 ± 9.0	$t=0.073$	0.943
SBP (mmHg)	105.8 ± 11.0	99.6 ± 7.7	$t=1.592$	0.123	105.3 ± 10.8	103.3 ± 8.5	$t=0.457$	0.652
DBP (mmHg)	60.7 ± 7.6	56.9 ± 8.4	$t=1.244$	0.224	60.0 ± 8.7	59.4 ± 5.5	$t=0.173$	0.864
Syncope frequency score	1(1, 2)	1.5(1, 3)	$Z=-1.538$	0.124[d]	1(1, 2)	1 (1, 2.5)	$Z=-0.066$	0.947[d]
LVEF (%)	72.5 ± 3.2[c]	64.6 ± 3.4	$Z=-3.998$	0.000[d]***	72.8 ± 2.8	65.5 ± 4.6	$t'=4.298$	0.001**
LVFS (%)	40.9 ± 2.3[c]	34.9 ± 2.9	$Z=-3.929$	0.000[d]***	41.1 ± 1.9	35.8 ± 3.6	$t'=4.132$	0.002**

BMI body mass index, *DBP* diastolic blood pressure, *HR* heart rate, *LVEF* left ventricular ejection fraction, *LVFS* left ventricular fractional shortening, *SBP* systolic blood pressure

***$P<0.001$; **$P<0.01$

[a]Fisher's exact test

[b]Exact significance (1-tailed)

[c]Non-normal distributions

[d]Asymptotic significance (2-tailed)

sensitivity of 81.3% and a specificity of 88.9% in the prediction of the therapeutic effect of metoprolol on VVS in children. For baseline LVFS, the AUC was 0.903 (95% CI 0.781–1.000, $P=0.001$), and 37.5% as a cutoff value yielded a sensitivity of 93.8% and a specificity of 66.7% in the prediction of the therapeutic effect of metoprolol on VVS in children (Fig. 2b).

Discussion

Our study showed that the baseline parameters of left ventricular systolic function LVEF and LVFS could predict the 2- and 6-month therapeutic effect of adrenergic beta-antagonists on VVS in children. For LVEF, when the children were followed up for 2 and 6 months, a cutoff value of 70.5% yielded a sensitivity of 80.0 and 81.3%, respectively, and a specificity of 100 and 88.9% respectively, for the prediction of therapeutic response of metoprolol in children with VVS. For LVFS, a cutoff value of 38.5 and 37.5% yielded a sensitivity of 90.0 and 93.8%, respectively, and a specificity of 90.0 and 66.7%, respectively, for the prediction of the therapeutic response of metoprolol in children with VVS.

Previous studies have shown that catecholamine might play an active part in the pathogenesis of syncope. In the supine position, plasma adrenaline (AD) was slightly higher in patients with VVS compared with controls ($P=0.06$) [22]. AD begins to increase before syncope, and the increase accelerates when syncope occurs. After syncope, the plasma concentration of AD is four times higher than that at baseline in the supine position [22–24]. In 2004, Zygmunt et al. found that the baseline parameters, such as the square root of the mean of the sum for the squares of differences between adjacent RR intervals, percentage of differences between adjacent RR intervals that are greater than 50 ms and the high-frequency index (HF) of children with VVS, were significantly lower than those of healthy children, whereas the low-frequency index (LF) was significantly higher than that of healthy children, which suggests that the baseline sympathetic impulse increases while the baseline vagal impulse decreases in children with VVS [25]. When stimuli, such as prolonged standing, emotional stress, and stuffiness, appear, and the pressor effect of the depressor reflex is triggered, the overexcitation of the adrenergic nervous system may occur in children with VVS, based on the high level of basal catecholamine. As a result, the ventricular myocardium contracts excessively, and the baroreceptor in the posterior inferior wall of the heart is stimulated. Nerve impulses are then generated and are transmitted to vasomotor centers through C-fibers, which triggers the Bezold–Jarisch reflex, leading to sympathetic inhibition and vagal excitation. As

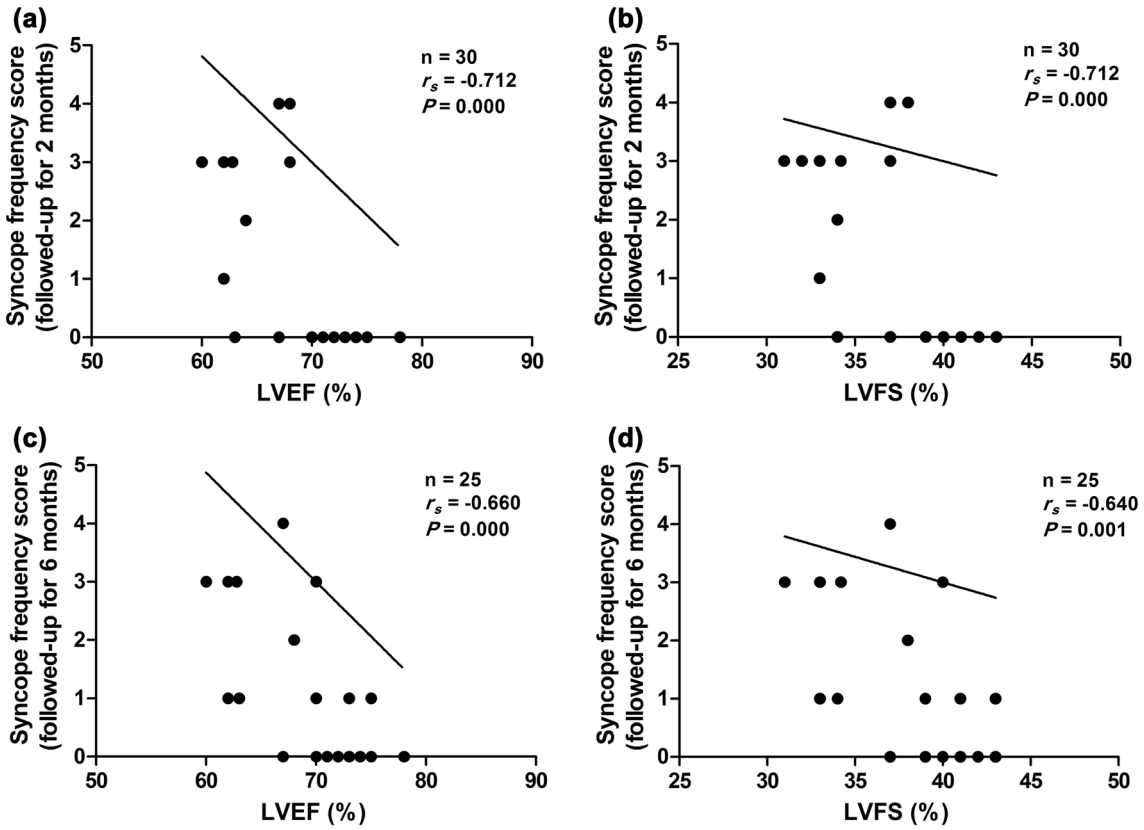

Fig. 1 Correlation analysis of LVEF or LVFS and the syncope frequency score. **a** Scatter diagram of syncope frequency score and LVEF when children with VVS were followed up for 2 months. **b** Scatter diagram of syncope frequency score and LVFS when children with VVS were followed up for 2 months. **c** Scatter diagram of syncope frequency score and LVEF when children with VVS were followed up for 6 months. **d** Scatter diagram of syncope frequency score and LVFS when children with VVS were followed up for 6 months. The *y*-axis represents the syncope frequency score of VVS children with a follow-up period of 2 or 6 months; the *x*-axis represents the numerical value of LVEF (%) or LVFS (%). The oblique lines in each figure represent the correlation slope. "*n*" denotes the number of samples of each figure; "r_s" denotes the correlation coefficient; and "*P*" denotes *p* value

a result, blood pressure and HR decrease, resulting in cerebral ischemia and, thus, a syncopal attack [13, 14].

Therefore, for cases of VVS, metoprolol has been widely used [10–12, 26–28]. However, some children do not have a favorable therapeutic response to the drug [10–12, 26–28]. One of the possible reasons is the complexity and diversity of VVS pathogenesis. In fact, in addition to the high catecholamine status and sympathetic over-excitation, the pathogenesis of VVS in some of the children might involve hypovolemia or excessive vascular dilation [29, 30]. Therefore, the ability to predict children with high catecholamine levels and sympathetic over-excitation who might achieve an ideal therapeutic effect from adrenergic beta-antagonists is of great importance. Our previous research showed that the children with an HR increase > 30 bpm/min during a positive response in the HUTT might have a high catecholamine status and sympathetic over-excitation and, therefore, had an ideal therapeutic response to adrenergic beta-antagonist therapy [15]. However, due to the fact that children may have a strong sense of discomfort and become nervous during the HUTT, which may interfere with HR, HUTT may not be the ideal method to predict the therapeutic response to adrenergic beta-antagonist therapy in patients with VVS.

LVEF and LVFS, which are measured by echocardiography, can reflect the contractile function of the left ventricle and, sometimes, a high catecholamine status. LVEF and LVFS are easy to measure, relatively stable, reliable, non-invasive, and safe. The rationale of dobutamine stress echocardiography and isoproterenol stress echocardiography is that catecholamine such as dobutamine and isoproterenol can induce the heart to work at sufficient doses, and LVEF and LVFS increase accordingly in humans with normal cardiac function [17, 18, 31, 32]. Therefore, LVEF and LVFS may reflect the level of plasma catecholamine to an extent. In addition, studies have shown that from rest to 25% of the submaximal workload, a positive correlation exists between plasma catecholamine and LVEF changes or LV volumes [33–37]. Thus, we speculate that children with VVS who have relatively high levels of LVEF and LVFS might achieve ideal therapeutic efficacy with adrenergic beta-antagonist

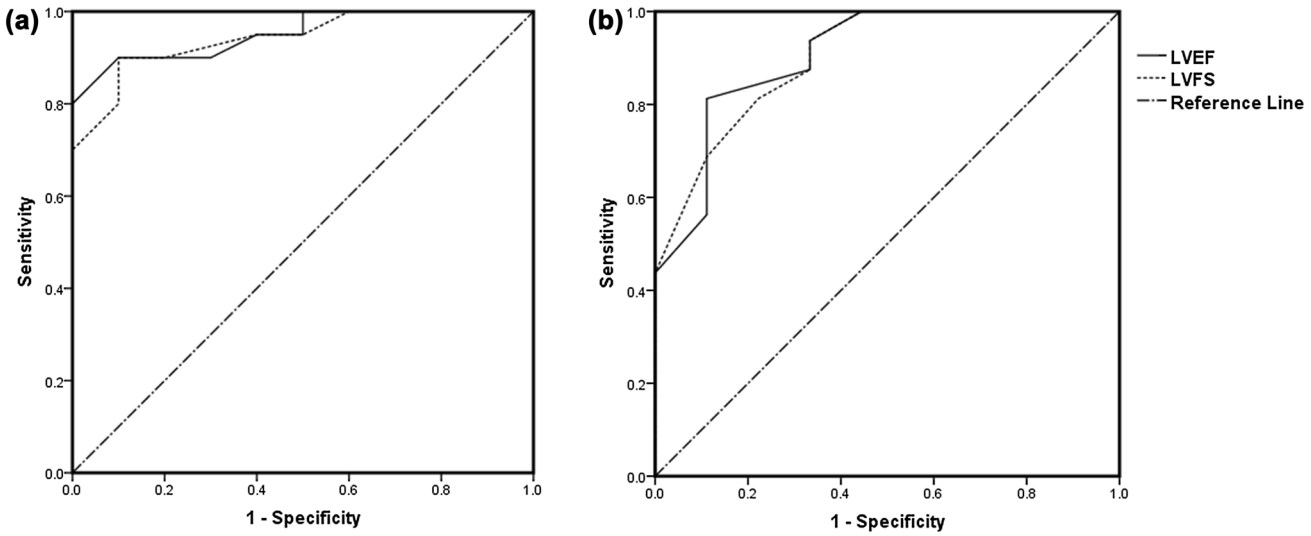

Fig. 2 ROC curve of the predictive value of baseline LVEF and LVFS for predicting the efficacy of metoprolol on VVS in children. **a** The follow-up period of children with VVS was 2 months. **b** The follow-up period of children with VVS was 6 months. The *y*-axis represents the sensitivity to predict the ideal efficacy of metoprolol on VVS in children; the *x*-axis represents the false-positive rate (1-specificity). The reference line represents the sensitivity and the false-positive rate is equal, which means no predictive value completely. The curves of LVEF and LVFS are farther from the reference line and nearer to the *upper-left corner* of the diagram, indicating that the predictive value is higher

therapy. Our present study reveals that baseline LVEF and LVFS may help to predict the therapeutic response to metoprolol at 2 and 6 months after the initiation of metoprolol in children with VVS, which is meaningful and helpful for the individualized treatment of childhood VVS.

The study also has limitations. The sample size is relatively small, and the follow-up period is not long enough. Therefore, in the future studies, it is worthy to conduct multi-center studies with a large sample size and a long-term follow-up.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest. This manuscript is approved by all authors for publication.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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