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Response to a Single Dose of Sildenafil in Single-Ventricle Patients: An Echocardiographic Evaluation

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Abstract

New evidence of increased phosphodiesterase-5 (PDE-5) in hypertrophied human myocardium suggests that sildenafil, a selective PDE-5 inhibitor, may improve muscle contraction and therefore improve ventricular function. The purpose of this study was to compare ventricular function as assessed by echocardiography in 10 surgically palliated single-ventricle patients at baseline and again after a single dose of sildenafil. The velocity time integral of the ventricular outflow tract was increased 2 h after sildenafil administration ($p = 0.01$), thus suggesting an improvement in cardiac output.

Keywords

Congenital heart disease; Fontan; Pediatric; Univentricular heart

Introduction

As the outcomes of palliative surgery for children born with functional single-ventricle lesions improve, we are faced with the task of improving long-term function of the systemic ventricle [5]. Single ventricles often hypertrophy over time and develop ventricular dysfunction [8]. Nagendran et al. [6] reported increased phosphodiesterase-5 (PDE-5) mRNA and protein expression in hypertrophied human right and left ventricles. They further demonstrated that PDE-5 inhibition significantly improved contractility in isolated hypertrophied rat ventricles but not in normal ventricles [6]. Recent reports in humans indicate an improvement in exercise capacity after sildenafil administration for patients with Fontan physiology [2, 3]. The investigators speculated that the beneficial effect of PDE-5 inhibition occurred by way of smooth-muscle relaxation of the pulmonary vascular bed; however, this has not been proven. Therefore, we sought to investigate the acute effect of PDE-5 inhibition on single-ventricle cardiac function as measured by echocardiography.

Methods

Patients

Ten patients age 3 to 10 years old with single-ventricle anatomy (right or left) palliated with a superior cavopulmonary (SCPC) or total cavopulmonary connection (TCPC), were enrolled in the study. The minimum age was chosen to improve patient cooperation with

echocardiographic imaging without the need for sedation; the upper age was chosen to avoid potential sexual side effects of sildenafil in male subjects.

Patients were excluded if they were on medications that might affect sildenafil metabolism, e.g., coumadin, bosentan, nitrates, protease inhibitors, erythromycin, ketoconazole, itraconazole, cimetidine, alpha-adrenergic blocking agents, or more than one antihypertensive medication of any class. Other exclusion criteria included systemic (1) hypotension (<5th percentile by pediatric standards for age) or (2) renal or hepatic dysfunction (>2 times upper limit of normal for aspartate aminotransferase, alanine aminotransferase, or serum creatinine).

Data Collection

The study design was approved by our Institutional Review Board, and informed consent was obtained from the parents or legal guardian of each patient. Baseline vital signs were recorded and included heart rate, oxygen saturation, and blood pressure. Blood pressure was measured noninvasively by Dynamapp (GE Healthcare, Fairfield, CT) three times and the median value taken.

A baseline echocardiogram was performed by a certified pediatric echocardiographic sonographer on a Phillips IE33 (Eindhoven, Netherlands) machine. The following echocardiographic images were obtained: apical four-chamber, Doppler of ventricular inflow and outflow, lateral atrioventricular (AV) valve tissue Doppler, and parasternal short axis. Ejection fraction (EF) was calculated from by two-dimensional images from the apical position. Myocardial performance index (MPI or Tei index) was calculated by dividing the time in isovolumic contraction and relaxation by the time spent with mitral valve closed using Doppler tracings of the inflow and ventricular outflow. E/E_a was calculated by dividing the AV valve E-wave velocity by the tissue Doppler E-wave velocity. dP/dT was calculated by using Doppler tracing of AV-valve regurgitation to determine the time from a velocity of 1–3 m/s. All Doppler measurements were recorded on three separate acquisitions and individually measured. The average of the three measurements was then used to calculate the final value. Short-axis and apical images were traced with speckle-tracking analysis using TomTech software (TomTech, Chicago, IL) for the following measurements: apical longitudinal and radial velocities; apical longitudinal and radial displacement; apical longitudinal and radial strain; short-axis radial velocity, displacement, and strain; short-axis circumferential strain; short-axis velocity rotational rate; and short-axis rotational displacement.

A single dose of oral sildenafil solution (2.5 mg/ml) was given at a dose of 1 mg/kg with a maximum dose of 20 mg. Vital signs were obtained with the patient in the supine position before drug administration and repeated at 45 and 90 min after sildenafil administration. Repeat echocardiographic imaging was performed by the same sonographer at 60 and 120 min after sildenafil administration. These time points were chosen to best correlate with expected peak serum drug concentrations [4, 7]. The echocardiographic images were measured and analyzed by a single reviewer (K. W. J.) who was blinded to subject and echocardiogram time point. The average of the three measurements was used for each echocardiographic variable unless one or more measurements were deemed by the investigator to be outliers, in which case the average of the remaining variables were used. No imputation was made for missing values. Given the small sample size, Wilcoxon rank sum tests were used to compare values at each time point. Repeated measures ANOVA test were performed for each echocardiographic variable using trend analysis and pairwise comparisons to test effects within patients. Statistical significance was defined as $p < 0.05$.

Results

Demographic details of the subjects studied are listed in Table 1. Median patient age was 5.7 years. No adverse events occurred in any patient. Heart rate, blood pressure, and oxygen saturation did not differ from baseline at either time point after sildenafil administration.

Echocardiographic responses are shown in Table 2. EF calculations were available for all 10 patients. E/E could not be measured in 2 subjects who did not have adequate AV valve inflow on Doppler for proper measurement. AV-valve dP/dT was measured in all 4 patients with AV-valve regurgitation. MPI (or Tei index) was calculated in 7 patients; 2 patients had improperly obtained ventricular inflow Doppler; and 1 patient had an improperly obtained ventricular outflow Doppler measurement. There was no significant change from baseline in EF, E/E, MPI, or dP/dT at either time point after sildenafil administration. Speckle-tracking analysis was available in all 10 patients. All speckle-tracking measurements of displacement, velocities, and strain were not statistically different between time points.

The velocity time integral (VTI) was measured in 9 patients (1 excluded secondary to improper acquisition). We found an improvement in VTI in all but 1 patient 2 h after sildenafil administration. The average improvement in the VTI was 3.31 cm between baseline and the 2 h time point ($p = 0.01$) (Fig. 1). There was a trend toward improvement in VTI at 1 h after sildenafil administration compared with baseline (average increase 2.35 cm, $p = 0.06$). Of the patients with a morphological right ventricle ($n = 7$), VTI improved by 1.7 cm at 1 h ($p = 0.25$) and by 2.87 cm ($p = 0.05$) compared with baseline. In patients with a morphological left ventricle ($n = 2$), there was no statistical significant improvement in VTI.

Discussion

The purpose of this study was to evaluate if sildenafil acutely improved echocardiographic measures of cardiac function in single-ventricle patients. We found a significant improvement in VTI after a single dose of sildenafil in a cohort of single-ventricle patients without changes in other echocardiographic measures of contractility or relaxation.

An increase in VTI suggests that there has been an increase in stroke volume. Because there was no change in heart rate after sildenafil administration, this change in VTI likely represents an improvement in cardiac output. Recent reports have indicated that long- and short-term administration of sildenafil leads to improved exercise capacity in TCPC patients, indicating improved exercise capacity with PDE5 inhibition [2, 3]. This improvement was speculated to be secondary to decreases in pulmonary (PVR) and systemic vascular resistances (SVR). The decrease in PVR would lead to improved preload for the systemic ventricle. Intravenous sildenafil has been shown to decrease SVR [1]. In vivo models of the TCPC have shown that both increased afterload and decreased preload limit an increase in cardiac output during exercise [9]. Medical interventions that decrease afterload and improve preload might therefore improve exercise capacity. This increase in preload and decrease in afterload with PDE-5 inhibition can be supported by our findings, which show no change in measures of contractility (speckle tracking) or global function (MPI) or relaxation (E/E) but an improvement in stroke volume (VTI). These previously mentioned studies did not report changes in echocardiographic measurements after sildenafil administration.

Goldberg et al. [3] found that patients with left-ventricular or mixed morphology ($n = 13$) had a better response to sildenafil in terms of exercise capacity compared with patients having right-ventricular morphology ($n = 14$). In contrast, we found that patients with a morphological right ventricle had a better response to sildenafil when measuring VTI compared with their counterparts.

Limitations

Our study has important limitations to consider. The small sample size limits the ability to detect differences, especially between subgroups, based on ventricular morphology and type of surgical palliation. The echocardiographic protocol was detailed, causing some measurements to be improperly acquired and thereby limiting the total number of some variables available for analysis. A single reviewer reviewed images in a blinded fashion and made assessment of outlier echocardiographic variables. Reproducibility of the measurements by another observer was not confirmed. Echocardiographic evaluation occurred at only two time points. Long-term effects on myocardial contractility with prolonged sildenafil treatment were not evaluated.

Conclusion

Our results highlight the need for larger, multicenter studies examining the clinical utility of sildenafil in patients with single-ventricle physiology. These studies should include echocardiographic measurements in an effort to better understand the physiological reasons for improved exercise capacity in this population.

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Fig. 1.
Change in VTI (cm) among a cohort of single-ventricle subjects between baseline and 2 h after administration of sildenafil

Table 1

Subject Characteristics

Patient no.	Sex	Age (year)	Dominant ventricle	Stage of palliation
1	F	6.0	Left	TCPC
2	M	5.1	Left	TCPC
3	F	6.4	Right	TCPC
4	M	4.3	Right	TCPC
5	F	5.2	Left	SCPC
6	F	5.3	Right	TCPC
7	F	3.9	Right	SCPC
8	M	6.3	Right	SCPC
9	F	8.8	Right	TCPC
10	F	10.3	Right	SCPC

SCPC superior cavopulmonary connection, *TCPC* total cavopulmonary connection

Table 2

Response to a dose of Sildenafil

Patient no.	Time point (h)	dP/dT (mmHg/s)	VTI (cm)	E/E	EF%	MPI
1	Baseline	604	14.2	3.1	47.3	0.3
	1	978	16.9	4.4	51.4	0.49
	2	1,067	17	5.5	49.6	0.54
2	Baseline	N/A	N/A	13.1	46.6	N/A
	1	N/A	N/A	11.7	53.5	N/A
	2	N/A	N/A	10.4	48.5	N/A
3	Baseline	N/A	17.6	7	54	0.53
	1	N/A	19	9.5	32.1	0.29
	2	N/A	21.9	12.7	47.8	0.24
4	Baseline	N/A	12.9	14.6	56.8	0.41
	1	N/A	14.9	15.8	56.6	0.05
	2	N/A	13.4	15.6	58.8	0.34
5	Baseline	N/A	16.3	N/A	31.8	N/A
	1	N/A	22.8	N/A	46.1	N/A
	2	N/A	23.2	N/A	50.4	N/A
6	Baseline	N/A	11.7	N/A	41.5	N/A
	1	N/A	11.6	N/A	39.7	N/A
	2	N/A	11	N/A	52.4	N/A
7	Baseline	N/A	13.5	7.3	29.9	0.16
	1	N/A	18.6	8.4	42.7	0.28
	2	N/A	19.6	9.3	39	0.24
8	Baseline	533	16.4	9	48.5	0.36
	1	978	19.7	23.8	50.2	0.33
	2	800	19.8	14.4	45.9	0.42
9	Baseline	1,422	15.9	10.5	64.8	0.33
	1	1,600	17.9	19.4	54	0.27
	2	604	18.9	13.8	64.6	0.33
10	Baseline	747	20.4	9.6	63.8	0.47
	1	2,133	18.7	6.4	41.9	0.28

Patient no.	Time point (h)	dP/dT (mmHg/s)	VTI (cm)	E/E	EF%	MPI
p	2	1,245	23.9	10.5	47.9	0.45
	Baseline to 1 h	0.3	0.06	0.5	1.0	1.0
	Baseline to 2 h	1.0	0.01	0.2	1.0	1.0

dP/dT ventricular pressure change during isovolumic contraction divided by change in time, VTI velocity-time integral, E/E ratio of AV valve inflow e-wave to lateral annulus tissue doppler e-wave, EF ejection fraction, MPI myocardial performance index