Effect of Digoxin on Contractility and Symptoms in Infants with a Large Ventricular Septal Defect

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The effect of digoxin on contractility and symptoms in infants with a large ventricular septal defect (VSD) is controversial. Nineteen infants with symptoms of congestive heart failure due to a VSD were studied with load-independent indexes during 4 study periods: (1) before any medication; (2) while on chronic diuretics; (3) while on both diuretics and digoxin; and (4) while on diuretics alone, to determine if digoxin: (a) increases "contractility" when added to diuretic therapy; and (b) improves symptoms. Symptoms, signs (heart and respiratory rates, and weight gain), shortening fraction, preload (left ventricular end-diastolic dimension), afterload (left ventricular end-systolic wall stress) and contractility were measured at each period. The difference between the measured and predicted velocities of circumferential fiber shortening for the measured left ventricular end-systolic wall stress served as an index of contractility. Eighteen infants also underwent catheterization. Mean pulmonary-to-systemic blood flow ratio was 3:1. When digoxin was added to diuretics, contractility index was significantly greater than in control subjects (0.13 ± 0.15 vs 0.0 ± 0.12 circ/s, p = 0.04). When patients were again on diuretics alone (after discontinuation of digoxin), contractility index was no longer different. Symptoms and signs were not significantly improved by either diuretics or digoxin.

It is concluded that in infants with a large left-to-right VSD shunt and receiving digoxin and diuretics, contractility index was significantly greater than in control subjects. However, neither diuretics alone nor in combination with digoxin improved symptoms significantly.

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Whereas some pediatric cardiologists routinely give digoxin and diuretics to infants with symptoms of tachypnea, tachycardia and growth failure due to a large shunt through a ventricular septal defect (VSD), others question the usefulness of digoxin in these patients. Symptoms may not be due to myocardial failure, but rather to pulmonary overcirculation.[1–5] Furthermore, the benefit of digoxin on contractility or symptoms has not been clearly demonstrated.[4,6] This is partly due to the reliance on ejection phase indexes that change not only with contractility but also with loading conditions. Recent advances now allow echographic measurement of contractility while taking into account loading conditions.[7] The purposes of this study were to determine in infants with symptoms of congestive heart failure due to a large VSD shunt if: (1) cardiac contractility improves when digoxin is added to diuretic therapy alone; and (2) symptoms of heart failure improve with digoxin and diuretic treatment.

METHODS

Patients: Infants with symptoms of tachypnea, tachycardia, growth failure and excessive diaphoresis due to large left-to-right VSD shunting were eligible for inclusion in this study. Nineteen patients participated in the protocol after informed consent was obtained. The control group consisted of 17 infants without heart disease.

Study protocol: The study protocol consisted of 4 periods of clinical and echocardiographic evaluations. The first examination was performed at baseline before any medications had been administered. The second examination occurred after beginning oral diuretics (furosemide 2 to 3 mg/kg/day and spironolactone 1 to 2 mg/kg/day). The third evaluation occurred after oral digoxin (10 μg/kg/day) had been added to the diuretics and only after a therapeutic serum digoxin level had been obtained. The fourth and final examination occurred after digoxin had been stopped while diuretics were continued.

During each study period patients underwent physical examinations, electrocardiography and echocardiography, and history was obtained. Serum electrolytes were obtained during the second and third study periods. During the third study period, serum digoxin levels

were measured with an immunoassay technique (Abbott Diagnostics). Oxygen, blood transfusion, vasodilators or salt restriction, or a combination, were not part of the treatment regimen.

Clinical assessment: During each study patients were assigned to 1 of 4 clinical classes using a heart failure classification system adapted especially for infants and previously described by our laboratory[8]: no symptoms (class I); tachypnea or diaphoresis with feedings, and no growth delay (class II); tachypnea or diaphoresis with feeding, without weight gain (class III); and symptomatic at rest with tachypnea, retractions, grunting and diaphoresis, without weight gain (class IV). In addition, respiratory and heart rates, and weight were recorded at each evaluation.

Echocardiographic assessment: Each patient underwent 2-dimensional and pulsed Doppler examinations using the Hewlett-Packard model 77020AC Ultrasound Imaging System. M-mode echocardiography was performed with either the Hewlett-Packard or an Irex System II Ultrasound System. Echocardiography was performed in a quiet, resting state; chloral hydrate (50 to 80 mg/kg) or pentobarbital (3 to 4 mg/kg), or both, were used for sedation when necessary. Simultaneous phonocardiogram, electrocardiogram and indirect axillary pulse tracing were also recorded. Peak systolic and diastolic blood pressures were obtained from a Dinamap 845-XT Vital Signs Monitor (Critikon). Left ventricular end-diastolic and end-systolic dimensions, and left ventricular end-systolic wall thickness were measured. Shortening fraction, heart rate-corrected velocity of circumferential fiber shortening (Vcf_c), and left ventricular end-systolic meridional wall stress were calculated.[7,9,10]

Contractility was assessed by examining the relationship between Vcf_c and end-systolic wall stress, as previously described.[5,11-14] In a previous study Colan et al[7] showed that the slope of this relation remained constant over a wide range of wall stress during positive inotropic intervention. Therefore, as previously published,[5,11] the difference between measured and predicted Vcf_c for measured end-systolic wall stress (as established in the control group) served as an index of contractility in the patients at each study period.

VSD size was measured at the initial and final studies by off-line analysis of 2-dimensional images, using a Digisonics Echocardiography Analysis System and indexed by dividing by body surface area, as previously described.[5] To determine the degree of circularity of the transverse plane of the left ventricle, diameters were measured along 2 axes in the parasternal short-axis view: (1) from the midseptum to posterior wall of the left ventricle; and (2) from the anterior to the inferior wall of the left ventricle. Circularity was estimated from the ratio of these 2 perpendicular diameters.

All echocardiographic measurements were obtained by 1 of the investigators (TRK) or a technical assistant, both of whom were unaware of patient identity and medication use. Intra- and interobserver variabilities of Vcf_c and wall stress were determined from the echocardiograms of the control patients.

Catheterization assessment: Eighteen of the 19 patients with VSD underwent cardiac catheterization at 5.7 ± 3.0 months old. Intravenous ketamine was used for sedation. Oxygen consumption and saturations were recorded. Pressures were obtained from a fluid-filled catheter system. Cardiac outputs were measured by the Fick method. Because ketamine may increase pulmonary vascular resistance, pulmonary-to-systemic blood flow ratios may be underestimated in this study.

Statistical analysis: Simple linear regression (least-squares method) was used to fit each control subject's data to a wall stress—Vcf_c equation ($Vcf_c = m$ (wall stress) + b; m = slope, b = y intercept). Analysis of variance for repeated measures was utilized to compare means of the groups using the General Linear Model procedure. This was followed by multiple comparisons using Duncan's procedure when needed. The data were also analyzed by paired *t* tests. This was necessary since there were varying numbers of data points for various groups and time points. Analysis of variance for repeated measures used only subjects with data in all time points, thus reducing the total sample size. Results were similar for both statistical methods (i.e., paired *t* tests or repeated measures analysis of variance). All the calculations were performed using the computer software package Statistical Analysis System version, 5th edition (SAS Institute, Cary, North Carolina). Statistical significance was claimed at a p value <0.05.

RESULTS

Twelve of the 19 patients entered at the first study period, whereas the remaining 7 who were already receiving diuretics entered at the second study period. One patient did not undergo a second study because his attending cardiologist believed that his condition necessitated concomitant administration of both diuretics and digoxin. In 2 other patients surgery was thought to be indicated after the third study. Thus, 11 comparisons of baseline versus diuretic treatment, 18 of diuretics alone versus both digoxin and diuretics, and 17 of both digoxin and diuretics versus diuretics alone after digoxin withdrawal were available for analysis.

The second examination occurred after 2.8 ± 2.3 weeks of diuretic therapy, and the third occurred 2.8 ± 2 weeks after digoxin was added to diuretics. Serum

TABLE I Catheterization Data

Pt. No.	Qp/Qs	PAP (mm Hg)	PVR (Wood units × m^2)	SVR (Wood units × m^2)	PVR/SVR	RVP/LVP	VO_2 (ml/min × m^2)
1	5.5	48	2.5	21	0.12	0.75	114
2	1.9	35	1.2	13	0.09	0.47	150
3	2.2	27	0.8	11	0.07	0.65	189
4	3.1	26	1.2	17	0.07	0.49	188
5	2.0	18	1.3	12	0.11	0.36	156
6	2.0	27	3.1	22	0.14	0.72	130
7	2.4	53	5.5	22	0.25	0.97	115
8	4.2	18	0.6	15	0.04	0.71	170
9	2.5	32	2.6	20	0.13	0.88	141
10	6.7	25	1.4	23	0.06	0.75	138
11	1.8	26	3.5	17	0.21	0.50	99
12	4.2	38	2.1	26	0.08	0.77	150
13	2.3	25	1.3	9	0.14	0.53	211
14	5.2	31	1.6	20	0.08	0.77	180
15	2.1	16	1.8	23	0.08	0.47	202
16	2.8	35	1.7	17	0.10	0.78	88
17	3.2	58	6.0	23	0.26	0.94	160
18	2.1	43	4.5	17	0.26	0.69	143
Mean ± SD	3.1 ± 1.4	32 ± 12	2.4 ± 1.6	18 ± 5	0.13 ± 0.07	0.68 ± 0.17	151 ± 35

LVP = peak systolic left ventricular pressure; PAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; Q_p = pulmonary blood flow; Q_s = systemic blood flow; RVP = peak systolic right ventricular pressure; SD = standard deviation; SVR = systemic vascular resistance; VO_2 = oxygen consumption.

digoxin levels averaged 1.3 ± 0.4 ng/ml at that time. The fourth evaluation occurred 4.2 ± 3.1 weeks after digoxin had been stopped.

Demographic data: The median age and weight of the patients were 2.5 months (standard deviation [SD] = 3.1) and 4.9 kg (SD = 1.9), respectively. These were not significantly different from the control group's age (median = 5 months, SD = 3.6) and weight (median = 7.9 kg, SD = 2.3). In the control group, the relation between Vcf_c and end-systolic wall stress was inversely linear and was described by the equation $Vcf_c = -0.0089$ (wall stress) + 1.49 (Figure 1).

Ventricular septal defect characteristics: Mean and indexed VSD sizes at study entry were 0.95 ± 0.22 cm and 3.7 ± 0.8 cm/m^2, respectively, and did not change significantly by the end of the study protocol (0.98 ± 0.20 cm and 3.2 ± 0.7 cm/m^2, respectively; p = not significant).

Catheterization data are listed in Table I. Mean pulmonary-to-systemic blood flow ratio was 3.1, and mean pulmonary-to-systemic vascular resistance ratio was 0.13. Seventeen of the patients subsequently underwent surgical closure of their VSD shortly after completion of the protocol.

Variability of heart rate-corrected velocity of circumferential shortening, and end-systolic wall stress: The interobserver variability of Vcf_c and end-systolic wall stress was 3.6 and 5.5%, respectively. The intraobserver variability of Vcf_c and end-systolic wall stress was 2.3 and 3.5%, respectively. Linear regression demonstrated excellent correlation for separate observers determining Vcf_c (r = 0.91) and end-systolic wall stress

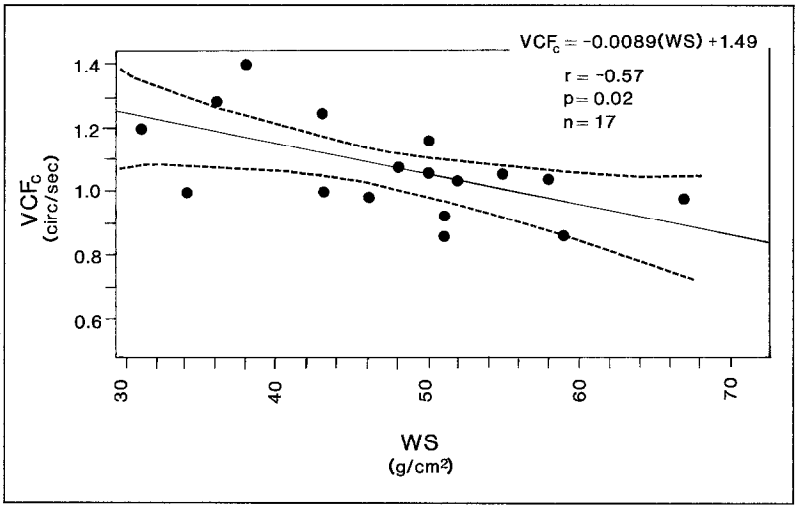

FIGURE 1. Heart rate-corrected velocity of circumferential fiber shortening (VCF_c) and left ventricular end-systolic wall stress (WS) data points for control subjects. Fitted line *(solid line)* and 95% confidence limits *(dashed lines)* are also shown.

TABLE II Echocardiographic and Clinical Data at Each Study Period

	Medication Status					
	None (n = 11)	Diur. (n = 11)	Diur. (n = 18)	Dig. & Diur. (n = 18)	Dig. & Diur. (n = 17)	Diur. (n = 17)
SF (%)	31 ± 8	35 ± 5*	32 ± 7	33 ± 4	34 ± 4	34 ± 9
LVED (cm)	2.6 ± 0.5	2.6 ± 0.5	2.6 ± 0.5	2.6 ± 0.5	2.7 ± 0.5	2.7 ± 0.5
Vcf_c (circ/s)	1.06 ± 0.28	1.18 ± 0.14	1.08 ± 0.22	1.16 ± 0.17	1.16 ± 0.18	1.07 ± 0.27
WS (g/cm^2)	64 ± 42	56 ± 23	55 ± 20	51 ± 15	52 ± 16	49 ± 17
HR (beats/min)	140 ± 19	142 ± 17	141 ± 18	139 ± 16	137 ± 12	136 ± 13
RR (breaths/min)	61 ± 20	62 ± 11	64 ± 15	64 ± 19	62 ± 19	57 ± 15
Wt (percentile)	32 ± 31	22 ± 21*	25 ± 26	24 ± 27	23 ± 26	19 ± 23

*$p < 0.05$.
Data are expressed as mean ± standard deviation.
Dig. = digoxin; Diur. = diuretics; HR = heart rate; LVED = left ventricular end-diastolic dimension; None = no medications; RR = respiratory rate; SF = shortening fraction; Vcf_c = heart rate-corrected velocity of circumferential shortening; WS = left ventricular end-systolic wall stress; Wt = percentile for weight.

(r = 0.93). Correlations were also excellent for 1 observer repeating determinations of Vcf_c (r = 0.96) and end-systolic wall stress (r = 0.95).

Echocardiographic data: The average ratios of septoposterior to anteroinferior free wall diameter in patients with VSD were 0.94 ± 0.13 in diastole and 0.99 ± 0.11 in systole. These ratios were not statistically different from a ratio of 1. Thus, the transverse geometry of the left ventricle was circular.

Echocardiographic data for the patients at each study period are listed in Table II. Shortening fraction significantly increased from baseline levels with the addition of diuretics alone. However, there were no significant differences in left ventricular end-diastolic dimension and wall stress among the study periods.

There was a slight increase in contractility index (Figure 2) between control subjects and patients with VSD receiving no medications. There was a further slight increase in contractility index in patients when digoxin was added to diuretics. Neither of these differences was statistically significant by itself; however, the cumulative effect resulted in a significantly higher contractile index in patients receiving both digoxin and diuretics compared with that in control subjects. Subsequent withdrawal of digoxin was associated with a decrease in contractility index, but again this change was not statistically significant.

Clinical data: No patient was asymptomatic (class I) at the beginning of the study. Although 1 patient did improve to class I clinical status while receiving digoxin and diuretics together, medical treatment (either diuretics alone or digoxin with diuretics) did not significantly improve clinical status of the group. There were no significant changes in heart and respiratory rates during the protocol. When patients were receiving diuretics alone they had significantly lower weight percentiles compared with when they were receiving no medications. In addition, there was a further significant

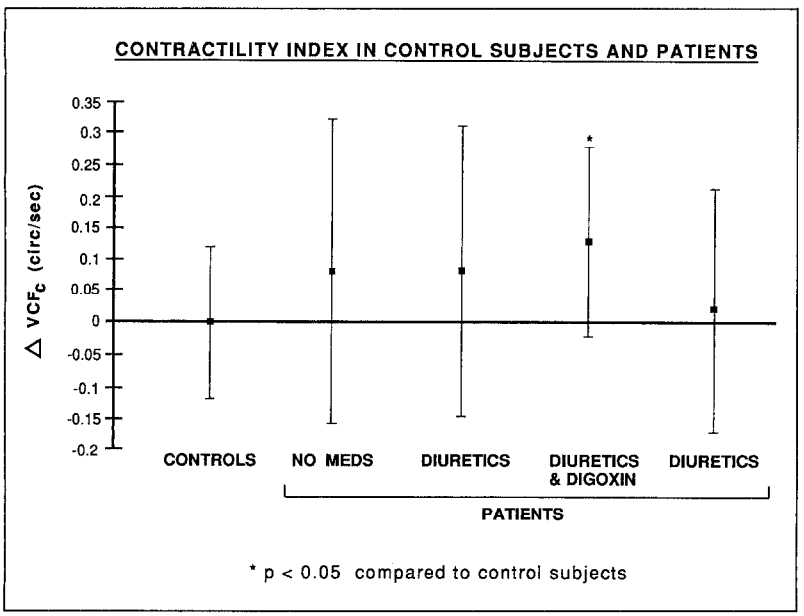

FIGURE 2. Contractility index in control subjects and patients. Data are expressed as mean ± standard deviation. Δ VCF_c = difference between predicted and measured heart rate-corrected velocity of circumferential fiber shortening for measured left ventricular end-systolic wall stress.

decrease in weight percentile during the remainder of the study protocol (25th ± 26th to 19th ± 23rd percentile; $p = 0.03$).

DISCUSSION

Whereas digoxin has been shown to be of benefit to adults with heart failure,[15] some investigators question its effectiveness.[16] These studies of the effect of digoxin in adults have been performed in patients with impaired contractility. The infant who has symptoms due to a large left-to-right shunt may have normal contractility.[1-5,17] Therefore, the use of digoxin in infants with large left-to-right shunts is controversial.[4,6,18-22] Several investigators have found that digoxin increases ventricular performance,[19-21] whereas others have found little or no change in function.[6,22] Furthermore, it appears that clinical improvement may not always be associated with improvement in ventricular function.[6]

Previous studies are limited because of the use of ejection phase indexes that are dependent on loading conditions and may be unreliable in the presence of VSD.[23] Although the model for deriving contractility in our study has geometrical constraints (i.e., it assumes that the left ventricle is ellipsoidal, has uniform and thin-walled thickness, and is symmetric along its minor axis), our data indicate that the transverse axis of the left ventricle of our patients with VSD maintained a circular configuration. Therefore, the major assumption of the model is satisfied and should be accurate.

As previously suggested,[5] we found that patients with large VSD shunts before receiving medication have higher contractility indexes than control subjects have (although not significantly so). Perhaps elevated circulating catecholamines in these symptomatic patients may raise contractility. Further investigation is needed to examine potential mechanisms.

The addition of digoxin to diuretics in our patients further increased contractility to a level significantly higher than control subjects. However, the incremental increase in contractility with the addition of digoxin was not significant compared with that while receiving diuretics alone. Likewise, the incremental decrease in contractility associated with digoxin withdrawal was not statistically significant.

Despite the observations of many clinicians that symptoms improve when digoxin and diuretics are used in these patients, our study does not support this finding. It is possible that the effects of these 2 medications could have been acutely different after their initiation. These more acute data were not specifically measured in this study. It is also possible that our assessment scale may not have been sensitive enough to detect subtle clinical changes, but the objective parameters of weight gain, and respiratory and heart rates also did not improve. In fact, weight percentile significantly decreased when patients were placed on diuretics and continued to do so throughout the study protocol. Although the initial decrease in weight percentile associated with diuretics was most likely due to excess water loss, the continued decrease in the patients' weight percentiles during the remainder of the protocol was most likely due to increased caloric expenditure due to the large VSD. Therefore, even though the combination of digoxin and diuretics in VSD patients increased contractility over control subjects, this effect was not apparent clinically.

The patients in this study represent a subset of patients who had a particularly large left-to-right VSD shunt and were very ill compared with other patients with VSD.[5] Indeed, 17 of these 19 patients eventually underwent surgery to control their symptoms. The effects of digoxin and diuretics in patients with smaller VSD who are less seriously ill may be different and cannot be determined from this study.

The statistical nonsignificance of pairwise differences in contractility does not necessarily mean that contractility was equivalent at different medication states. Although inter- and intraobserver variabilities were less, there was quite a bit of variability in these measurements between patients. The sample size may have been small enough that statistical significance could not have been achieved. However, we did find a statistically significant difference in contractility between control subjects and patients receiving digoxin and diuretics that did not result in clinical improvement.

The value of digoxin in infants with symptoms due to a large VSD shunt is questionable. In addition, the use of digoxin may be undesirable because it can potentiate the complication of rhythm disturbance in conjunction with diuretic therapy. Because of the questionable value and potential risk of digoxin, alternative treatments, such as afterload reducing agents or earlier surgical intervention, may need to be considered.

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