Hemodynamic Determinants of Exercise-Induced ST-Segment Depression in Children with Valvar Aortic Stenosis

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To evaluate the hemodynamic factors associated with treadmill-induced ST-segment depression in children with valvar aortic stenosis, 12 patients (mean age 13 years) with ST-segment depression during treadmill exercise and 5 patients (mean age 13 years) without ST-segment depression during treadmill exercise underwent exercise testing during cardiac catheterization. The left ventricular (LV) systolic pressure and LV outflow tract gradient at rest (177 ± 25 vs 138 ± 8 mm Hg and 59 ± 18 vs 23 ± 7 mm Hg, respectively) and corresponding pressures during maximal supine exercise (248 ± 37 vs 189 ± 17 mm Hg and 112 ± 34 vs 52 ± 14 mm Hg) were significantly greater ($p < 0.01$) in the patients with exercise-induced ST-segment depression, although overlap existed. The LV-O_2 supply-demand ratio during maximal supine exercise was significantly less (6.4 ± 2.7 vs 11.8 ± 0.7; $p < 0.005$) in patients with than in those without exercise-induced ST-segment depression. In fact, an LV-O_2 supply-demand ratio less than 11.0 was 100% sensitive and specific in predicting treadmill-induced ST-segment depression. These results suggest that although the development of ST-segment depression during treadmill exercise is related to LV systolic pressure and LV outflow gradient, its major hemodynamic determinant is the LV-O_2 supply-demand ratio. (Am J Cardiol 1985;55:1133–1139)

The noninvasive evaluation of patients with valvar aortic stenosis (AS) frequently includes exercise treadmill testing.[1] Correlation of the severity of the left ventricular (LV) outflow tract gradient has been made with the systolic blood pressure response,[2–4] the decrease in R-wave amplitude[5] and with significant (0.10 mV or more) ST-segment depression during maximal exercise.[6,7] Although the cause of ST-segment depression during maximal exercise is unknown, it has been hypothesized to be the result of subendocardial ischemia.[6–8] Because direct measures of subendocardial blood flow are difficult to make in humans, the LV-O_2 supply-demand ratio has been used to estimate the adequacy of LV subendocardial blood flow.[9–11] Several investigations have shown that patients with AS and ST-segment depression at rest on the electrocardiogram have an altered LV-O_2 supply-demand ratio.[12–16] This study further evaluates the hemodynamic determinants of treadmill exercise-induced ST-segment depression in children with AS with special reference to the LV-O_2 supply-demand ratio at rest and during maximal exercise.

Methods

From January 1980 to July 1983, 17 children with AS and no ST-segment depression on a 12-lead surface electrocardiogram at rest underwent cardiac catheterization at the Univesity of Michigan's C.S. Mott Children's Hospital Cardiac Study Unit. Treadmill exercise (Bruce protocol) was performed 24 hours before cardiac catheterization. Electrocardiographic leads II, aVF and V_5 were continuously monitored and blood pressure was monitored using an automatic external cuff system (Critikon model 1165) at all stages of exercise and during recovery.

The patients were classified into 2 groups according to their response during treadmill exercise. One group consisted of 12 children, aged 8 to 17 years (mean 13), who had significant

(0.10 mV or more) ST-segment depression during maximal treadmill exercise. Of these 12 patients, 5 (patients 1, 3, 7, 10 and 12) had undergone previous aortic valvotomy. The second group consisted of 5 children, aged 9 to 17 years (mean 13), with no ST-segment depression during maximal treadmill exercise. Patient 13 had undergone previous aortic valvotomy (Table I). No patient had significant aortic regurgitation or symptoms.

Hemodynamic studies: Cardiac catheterization was performed in all patients in the supine position after premedication with morphine sulfate intramuscularly (0.1 mg/kg, maximum 5.0 mg) and diphenhydramine orally (1 mg/kg, maximum 50 mg). Using the percutaneous technique, 3 catheters were placed for pressure monitoring. In all patients, a thermodilution catheter was positioned in a branch pulmonary artery and a pigtail catheter was positioned in the ascending aorta. In 12 patients, a second pigtail catheter was inserted through the left femoral artery and positioned in the left ventricle, whereas in 5 patients the transseptal approach was used to monitor LV pressure. All patients were given heparin (100 units/kg body weight, maximum 2,000 units). Hemodynamic measurements of the right and left side of the heart at rest included simultaneous pulmonary artery, LV and aortic pressures using Statham pressure transducers and recorded on an Electronics for Medicine optical recorder at paper speeds of 50 or 100 mm/s; pulmonary blood flow (using an IL thermodilution catheter and an IL cardiac output computer); hemoglobin concentration; calculation of arterial O_2 content (1.36 × hemoglobin × arterial O_2 saturation); calculation of aortic valve area using the formula of Gorlin and Gorlin; and calculation of LV-O_2 supply-demand ratio.[11]

Exercise protocol: All patients underwent supine bicycle ergometry exercise until exhaustion with simultaneous measurement of pulmonary artery, LV and aortic pressures. The exercise protocol consisted of 4-minute stages with an initial workload of 200 kpm/min and increasing by 200-kpm/min increments until exhaustion.[17] Hemodynamic measurements wer made between the third and fourth minute at each stage consisting of heart rate, pulmonary artery, LV and aortic pressures, cardiac index, pulmonary artery saturation and calculation of LV-O_2 supply-demand ratio.

LV-O_2 supply-demand ratio: The LV-O_2 supply-demand ratio has been demonstrated to estimate the adequacy of LV subendocardial blood flow when the blood vessels are maximally dilated.[18] It is the ratio of the diastolic and systolic pressure time indexes multiplied by the arterial O_2 content. The diastolic pressure time index is an estimate of coronary blood flow to the LV myocardium and is calculated by integrating the area between the aortic pressure curve and LV pressure curve from aortic valve closure to aortic valve opening. The systolic pressure time index is an estimate of the oxygen demand of the LV myocardium and is calculated by integrating the area beneath the LV pressure curve during LV ejection (Fig. 1).[9]

Statistical analysis: Statistical analysis was performed using the 2-tailed nonpaired Student t test and the Bonferroni correction for multiple t tests. Stepwise regression analysis of the data was performed to determine the most highly correlated variable to the development of ST-segment depression, as well as to the LV-O_2 supply-demand ratio. Results are given as mean ± standard deviation.

Results

Treadmill exercise test: No significant differences were present between patients with or without ST-segment depression with respect to endurance, heart rate at rest or during maximal exercise or change in systolic blood pressure during treadmill exercise (Table I).
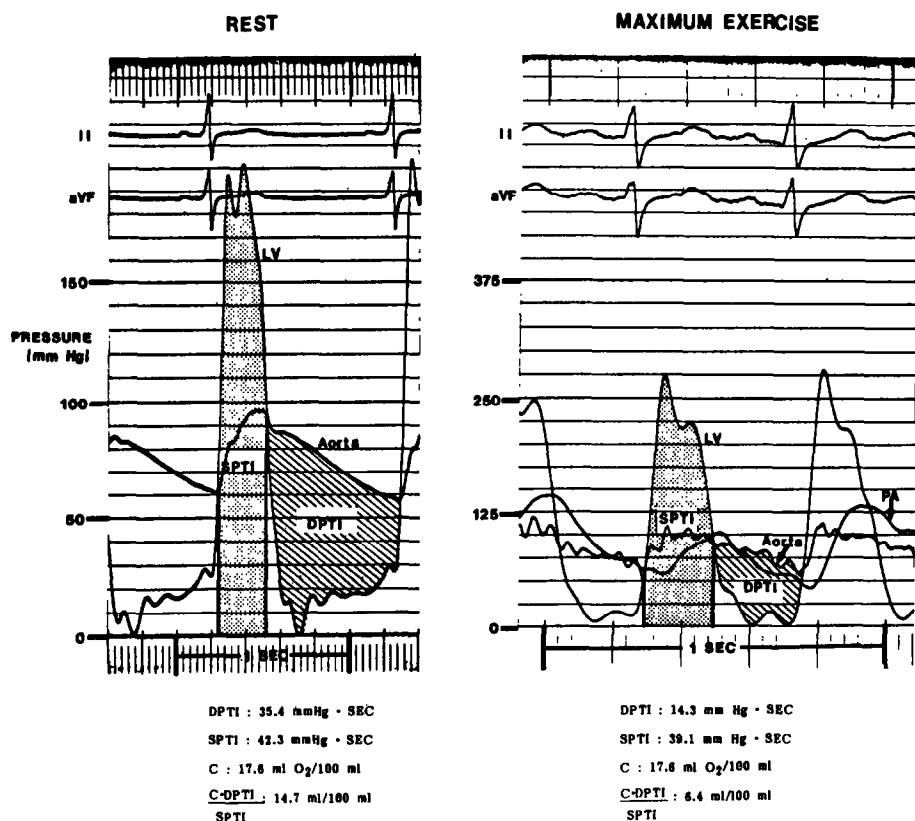

FIGURE 1. Left ventricular-O_2 supply-demand ratio at rest and during maximal exercise. Note pressure scale change from rest to maximal exercise. C = arterial O_2 content; C-DPTI/SPTI = LV-O_2 supply-demand ratio; DPTI = diastolic pressure time index; LV = left ventricle; PA = pulmonary artery; SPTI = systolic pressure time index.

TABLE I   Patient Data and Treadmill Exercise Test Results

Pt	Age (yr)	Body Surface Area (m²)	Duration (min)	Heart Rate (beats/min) Rest	Exercise	Change in Systolic Blood Pressure (mm Hg)
ST-Segment Depression
1	12	1.39	10	70	168	−8
2	10	1.05	13	88	205	+19
3	16	1.70	17	78	191	+25
4	16	1.95	17	60	185	+20
5	14	1.53	17	80	189	+30
6	10	1.20	15	75	155	−5
7	8	0.96	11	70	148	+36
8	11	1.00	13	86	172	0
9	8.3	0.96	14	92	202	+40
10	16	2.08	12	82	180	+25
11	14	1.90	15	84	184	+45
12	15	1.94	17	54	180	+42
Mean ± SD	12.6 ± 3.0	1.47 ± 0.43	14 ± 2.3	77 ± 11	180 ± 17	22 ± 18
No ST-Segment Depression
13	17	1.63	16	83	188	+6
14	14	1.54	10	82	188	+15
15	9	0.96	14	85	164	+17
16	11	1.28	11	91	195	+20
17	15	1.50	18	72	205	+30
Mean ± SD	13.2 ± 3.2	1.38 ± 0.27	13.8 ± 3.4	83 ± 7	188 ± 15	18 ± 9

SD = standard deviation.

Hemodynamics: The hemodynamic data at rest and during maximal supine bicycle ergometry exercise are summarized in Table II. The LV systolic pressure at rest (177 ± 25 vs 138 ± 8 mm Hg) and during maximal supine bicycle exercise (248 ± 37 vs 189 ± 17 mm Hg) were significantly greater (p <0.01) in patients with tread-mill-induced ST-segment depression. The LV outflow tract gradient at rest (59 ± 18 mm Hg vs 23 ± 7 mm Hg) and during maximal supine bicycle exercise (112 ± 34 mm Hg vs 52 ± 14 mm Hg) were also significantly greater (p <0.01) in patients with treadmill-induced ST-segment depression (Fig. 2).

LV end-diastolic pressure at rest was similar between the 2 groups, whereas LV end-diastolic pressure during maximal supine bicycle exercise (25 ± 8 mm Hg vs 13 ± 3 mm Hg) was significantly greater (p <0.05) in patients with treadmill-induced ST-segment depression (Table II, Fig. 2). In fact, the LV end-diastolic pressure increased more than 2 mm Hg from rest to maximal exercise in 11 of 12 patients (92%) with treadmill-induced ST-segment depression, whereas it did not increase in any patient without treadmill-induced ST-segment depression.[19]

The aortic valve area indexed to body surface area was significantly less in those patients in whom ST-segment depression developed at maximal treadmill exercise (0.60 ± 0.16 cm²/m² vs 0.80 ± 0.15 cm²/m², p <0.05), though overlap existed.

The LV-O₂ supply-demand ratio during maximal supine bicycle exercise (6.4 ± 2.7 vs 11.8 ± 0.7, p <0.005) was significantly less in patients with treadmill-induced ST-segment depression (Fig. 3). No overlap existed between the 2 groups during maximal exercise. Using a stepwise regression analysis, the most highly corre-lated variable to the development of significant ST-

segment depression was the LV-O₂ supply-demand ratio during maximal exercise (r = 0.65, p <0.001). The addition of LV systolic pressure at rest (r = 0.34, p = 0.16) or LV outflow tract gradient at rest (r = 0.18, p = 0.47) did not contribute to predictive value of the LV-O₂ supply-demand ratio.

Further analysis of the determinants of the LV-O₂ supply-demand ratio using a stepwise regression anal-ysis demonstrated that the variables that were most predictive of the LV-O₂ supply-demand ratio in the 12 patients with treadmill-induced ST-segment depression were LV systolic pressure (r = 0.83, p <0.05) and the ratio of the diastolic filling time to the systolic ejection time (r = 0.89, p <0.05) during maximal supine bicycle exercise. The change in diastolic filling time from rest to maximal supine bicycle exercise decreased slightly more in patients with treadmill-induced ST-segment depression (56 ± 14% vs 52 ± 3%). The systolic ejection time tended to be longer (0.18 ± 0.03 vs 0.13 ± 0.02 second, p = 0.09) during maximal supine bicycle exer-cise in the 12 children with treadmill-induced ST-seg-ment depression.

No significant differences were seen during supine bicycle exercise in heart rate at rest and during maximal exercise, aortic pressure, cardiac index, stroke index, O₂ consumption, pulmonary artery saturation and LV end-diastolic pressure at rest between the 2 groups (Table II). Comparison of supine and treadmill exercise heart rate at rest and during maximal exercise and change in systolic blood pressure during exercise did not reach statistical significance, although a trend did exist to have a lower maximal heart rate during supine ex-ercise (Tables I and II). In 8 of 17 patients, O₂ con-sumption was measured during both treadmill and su-pine exercise; the maximal O₂ consumption was higher

TABLE II   Cardiac Catheterization Results

	Heart Rate (beats/min)		Cardiac Index (liters/min/m²)		Stroke Index (ml/m²)		LVP (mm Hg)		LVEDP (mm Hg)		AOP (mm Hg)		LVOT Grad (mm Hg)		DFT/SET		LV-O₂ S-D Ratio		PA Sat
	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	Ex
ST-Segment Depression																			
1	108	151	4.6	7.5	42	49	144	182	13	16	104/72	96/70	40	86	1.62	1.33	13.9	10.6	40
2	98	182	4.1	6.7	41	37	190	275	12	27	96/75	115/90	94	160	1.40	1.00	12.3	5.0	39
3	90	156	4.2	7.6	47	49	185	285	20	35	120/78	145/90	65	140	1.78	1.39	12.9	3.2	41
4	72	155	3.1	7.0	42	45	210	270	12	10	145/85	165/85	65	105	2.03	1.33	12.1	6.6	50
5	89	167	4.7	10.4	53	62	170	285	15	24	120/80	150/85	50	135	1.83	0.89	9.7	3.8	31
6	75	133	3.5	7.0	46	53	195	250	19	28	125/85	120/70	70	130	2.29	1.00	12.6	3.8	40
7	71	150	2.9	6.2	41	41	125	185	18	22	88/55	124/80	37	61	2.26	1.35	15.7	5.6	48
8	78	164	4.4	10.6	56	65	200	285	18	38	115/70	115/80	85	170	1.71	0.76	10.7	3.2	44
9	88	130	4.1	5.0	47	38	165	225	18	25	110/65	140/90	65	85	1.86	1.55	14.5	9.7	53
10	68	152	2.7	6.6	40	44	165	230	24	32	115/80	140/85	50	90	2.52	1.00	18.8	7.0	43
11	84	160	4.8	8.3	57	52	175	245	15	18	140/90	160/95	35	85	2.13	1.71	13.1	10.1	50
12	58	140	3.6	10.6	63	75	200	260	18	25	145/95	160/100	55	100	2.82	1.47	20.3	8.0	47
Mean	82	153	3.9	7.8	48	51	177	248	17	25	119	136	59	112	1.98	1.23	13.9	6.4	44
± SD	±14	±15	±0.7	±1.8	±8	±12	±25	±37	±4	±8	±18/78 ±11	±22/85 ±9	±18	±34	±0.47	±0.29	±3.1	±2.7	±6
No ST-Segment Depression																			
13	83	188	3.0	10.0	37	53	125	210	16	16	100/64	140/80	25	70	1.91	1.35	18.2	11.2	51
14	82	160	3.2	5.4	39	34	140	174	14	11	115/72	128/87	25	46	1.89	2.17	16.3	12.1	56
15	96	171	4.4	10.0	46	58	135	170	14	15	117/68	138/85	18	32	2.05	1.43	10.2	11.5	40
16	88	185	4.5	10.8	51	58	145	200	13	10	130/80	140/100	15	60	2.20	2.00	15.7	11.5	34
17	87	179	5.0	9.0	58	50	143	192	15	11	111/70	142/100	32	50	1.64	1.20	12.8	12.9	44
Mean	87	177	4.0	9.0	46	51	138	189	14	13	115	138	23	52	1.94	1.63	14.6	11.8	45
±SD	±6	±11	±0.9	±2.1	±9	±10	±8†	±17†	±1	±3*	±11/71 ±6	±6/90 ±9	±7†	±14†	±0.21	±0.43	±3.2	±0.7†	±9

* p <0.05; † p <0.01; ‡ p <0.005.
AOP = aortic pressure; DFT/SET = diastolic filling time/systolic ejection time; Ex = exercise; LVEDP = left ventricular end-diastolic pressure; LV-O₂ S-D = left ventricular oxygen supply-demand; LVOT Grad = left ventricular outflow tract gradient; LVP = left ventricular systolic pressure; PA Sat = pulmonary artery saturation; SD = standard deviation.
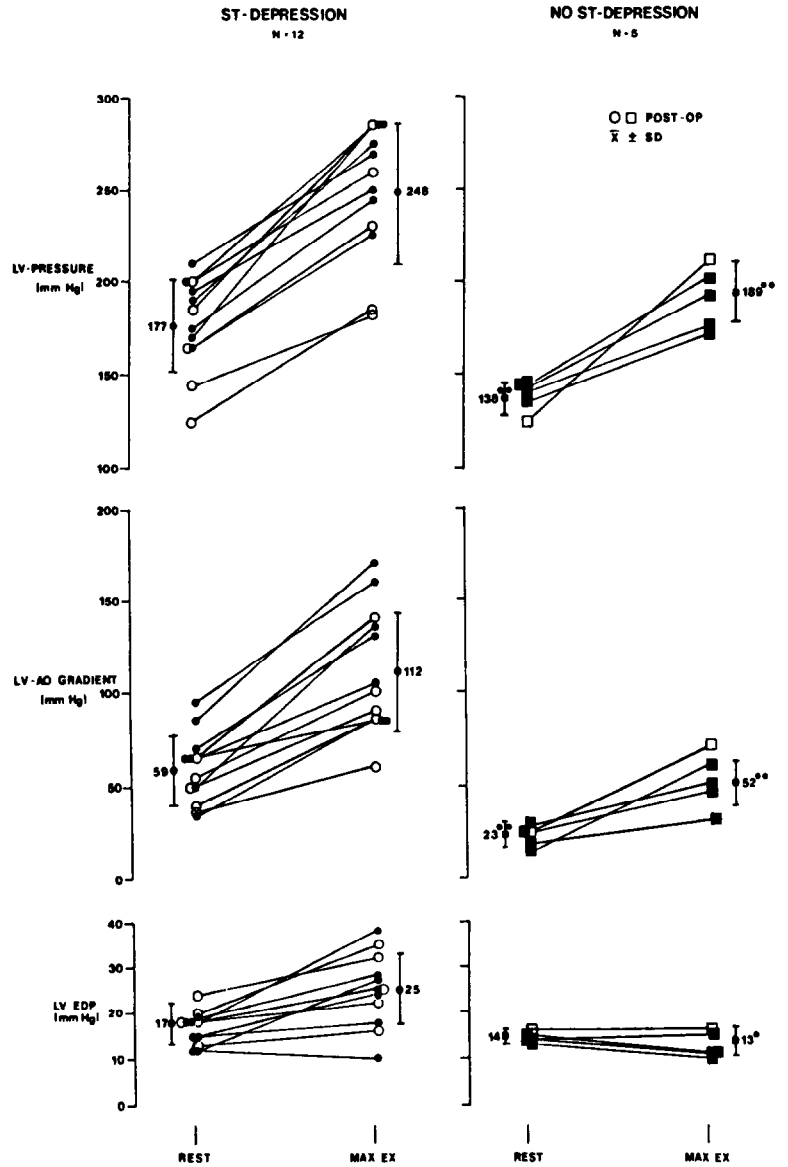
FIGURE 2. Left ventricular (LV) pressure, LV to aortic gradients (LV-AO), and LV end-diastolic pressure (LV-EDP) in patients with and those without ST-segment depression during maximal treadmill exercise both at rest and during maximal exercise (Max Ex). Comparison is made between the ST-segment vs no ST-segment depression groups (*p <0.05, **p <0.01). POST-OP = postoperative; SD = standard deviation.
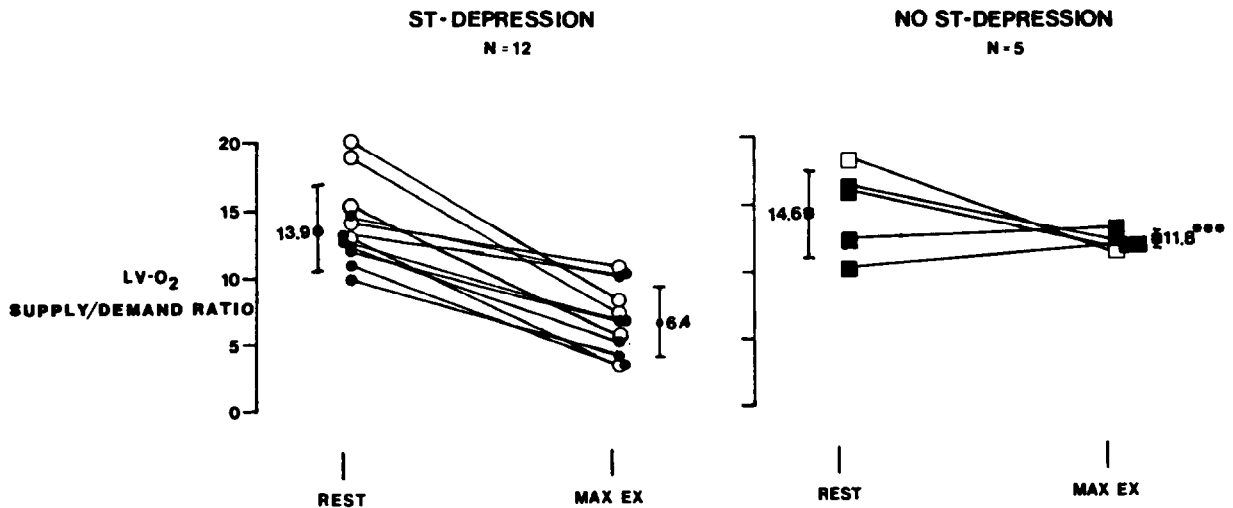

FIGURE 3. Left ventricular-O_2 (LV-O_2) supply-demand ratio in patients with and those without ST-segment depression both at rest and during maximal exercise (Max Ex). Comparison is made between ST-segment depression group vs no ST-segment depression group. ***p <0.005.

during treadmill exercise (40 ± 9 vs 28 ± 6 ml/kg, p <0.05). Also, the magnitude of ST-segment depression during maximal supine bicycle exercise in those patients with treadmill-induced ST-segment depression was similar.

Discussion

The LV outflow tract gradient at rest, presence of symptoms and the development of ST-segment depression during exercise are the 3 major variables considered before recommending an aortic valvotomy in a child with AS. Despite the widespread clinical use of ST-segment depression during exercise as a criterion for operability in the child with AS, a comprehensive concept on its genesis has not been established.

In the present study, the LV pressure and the LV outflow tract gradient at rest and LV outflow tract gradient and LV systolic and end-diastolic pressure during maximal supine bicycle exercise were all helpful in differentiating patients who had ST-segment depression during treadmill exercise, although considerable overlap did exist (Fig. 2). An LV outflow tract gradient at rest of more than 50 mm Hg was present in only 7 of 12 patients (58%) with ST-segment depression during treadmill exercise. This observation is in agreement with the data reported by Chandramouli et al,[6] and confirms that resting gradient alone is not the sole determinant of whether ST-segment depression occurs with exercise. An even greater overlap between patients with and without treadmill exercise-induced ST-segment depression was observed for other hemodynamic determinants including: LV systolic pressure, LV end-diastolic pressure, aortic pressure, cardiac index, heart rate or stroke index at rest and during maximal supine exercise. In fact, no single hemodynamic measurement was both 100% sensitive and specific in predicting the development of significant ST-segment depression during maximal treadmill exercise.

Using a stepwise regression analysis, the LV-O_2 supply-demand ratio during maximal exercise was the most predictive measure of the development of ST depression during treadmill exercise. LV-O_2 supply-demand ratio during maximal supine exercise of more than 11 was both 100% specific and sensitive in predicting which patient would not have significant ST-segment depression during maximal treadmill exercise. In fact, only 2 children (17%) who did have ST-segment depression had an LV-O_2 supply-demand ratio during maximal exercise of more than 10.0. Our observations are in keeping with those reported by a number of investigators who have demonstrated that patients with AS and ST-segment depression on electrocardiography at rest have an altered LV-O_2 supply-demand ratio.[12-16] In addition, Rosenthal et al[20] demonstrated that isometric handgrip increases the LV work in children; in those with AS, isometric handgrip also frequently depresses the LV-O_2 supply-demand ratio to low levels.[20]

The documented relation between LV-O_2 supply-demand ratio during maximal supine exercise and the development of ST-segment depression during tread-

mill exercise is not surprising or unexpected. Others have shown that when the coronary blood vessels are maximally dilated, the LV-O_2 supply-demand ratio accurately estimates the adequacy of LV subendocardial blood flow.[13-16] Since the calculation of the LV-O_2 supply-demand ratio includes the measurement of LV systolic and diastolic pressure, aortic pressure and heart rate as expressed by ejection and filling times, these factors are probably the important determinants of coronary blood flow in patients with AS. Using stepwise regression analysis the 2 factors that are most predictive in a child with AS in whom ST-segment depression develops during treadmill exercise are the decrease in the ratio of diastolic filling time to systolic ejection time and increase in LV systolic pressure.

Even though differences exist between supine and upright exercise (including higher LV end-diastolic pressure, end-diastolic volume and stroke index, and lower heart rate and oxygen consumption both at rest and during maximal exercise), we believe the conclusions drawn are valid, since in the 2 groups the magnitude of change in these variables from rest to maximal exercise are similar.[21,22] In addition, the decrease in pulmonary saturation to 44 ± 7% is consistent with the achievement of maximal supine exercise, even though the maximal oxygen consumption during supine exercise was not as large as with treadmill exercise.[23] Therefore, we speculate that the sequence of events leading to exercise-induced ST-segment depression in children with AS is as follows: Because exercise produces little increase in aortic pressure, a significant increase in LV systolic pressure, the LV myocardial oxygen demand exceeds that provided by coronary perfusion. The decrease in coronary perfusion along with the chronic LV hypertrophy alters the mechanisms responsible for cardiac contraction, resulting in prolonged relaxation and decreased myocardial compliance. The decrease in LV compliance promotes an increase in LV end-diastolic pressure, which inhibits coronary flow from the endocardium and produces a subendocardial zone of ischemia resulting in the characteristic ST-segment depression first recognized in 1918 by Bousfield.[24] The data presented suggest that hemodynamic data obtained during exercise may aid in the management of patients with AS. In a patient with borderline hemodynamic criteria at rest for valvotomy, the presence of an abnormal LV-O_2 supply-demand ratio is used as an indication for surgery in our institution.

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