Symptomatic Mitral Valve Prolapse in Children and Adolescents: Catecholamines, Anxiety, and Biofeedback

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ABSTRACT. It has been proposed that symptomatic mitral valve prolapse may be associated with a hyperadrenergic state and/or increased anxiety. To test this hypothesis, Spielberger State-Trait Anxiety (STAI) scores and 24-hour urinary catecholamine collections were gathered from 11 children and adolescents without mitral valve prolapse, 6 with asymptomatic mitral valve prolapse, and 14 who had chest pain (some with additional symptoms of shortness of breath, palpitations, and fatigue). STAI scores and catecholamine excretion values were not significantly different between groups. Ten symptomatic patients were randomly assigned to either eight sessions of skin temperature biofeedback with daily home practice of relaxation-mental imagery techniques or an attention-placebo condition. Change in 24-hour urinary catecholamine excretion values and STAI scores from baseline to end of treatment did not differ significantly between treatment and placebo conditions. Although not evident at the end of treatment, a significant decrease in chest pain was found in the biofeedback group at 6-month follow-up evaluation. In summary, results of this study did not show evidence of increased sympathetic tone or levels of anxiety in symptomatic pediatric patients with mitral valve prolapse. A behavioral treatment program using biofeedback and relaxation-mental imagery techniques was associated with decreased chest pain at 6-month follow-up. *Pediatrics* 1989;84:290–298; *mitral valve prolapse, catecholamine, anxiety, biofeedback, adolescent.*

Prolapse of the mitral valve leaflets into the left atrium during systole has been estimated to occur in 4% to 5% of the general population and is the most common inherited cardiovascular abnormality.[1] Although frequently diagnosed in childhood, the midsystolic click often associated with a late systolic murmur becomes more obvious with increasing age.[2] Because of its high prevalence, the question has been raised whether asymptomatic mitral valve prolapse is a normal variant or a disorder.[3,4] The majority of patients with mitral valve prolapse are asymptomatic and appear to have a generally benign course. Rarely, mitral valve prolapse is associated with significant arrhythmias, subacute bacterial endocarditis, or progression of mitral valve regurgitation requiring valve replacement.[5,6]

A subset of patients has been described as having a "mitral valve prolapse syndrome" with symptoms including nonanginal chest pain, palpitations, fatigue, and dyspnea on exertion.[7–9] Most studies of patients with the mitral valve prolapse syndrome have come from tertiary referral centers which may promote ascertainment bias in patient sampling. Larger epidemiologic surveys and comparison studies of first-degree relatives have not corroborated an increased incidence of symptoms in individuals with mitral valve prolapse.[10–12]

It has been suggested that mitral valve prolapse syndrome may be associated with increased levels of anxiety. Initial studies suggested an increased prevalence of mitral valve prolapse in adults with anxiety disorders.[13,14] Subsequent investigations in adults with mitral valve prolapse, however, have not demonstrated an increase in anxiety disorders compared with other family members or control subjects without mitral valve prolapse.[15,16]

Increased sympathetic nervous system activity, a hyperadrenergic state, has been proposed as an underlying mechanism of mitral valve prolapse syndrome. The literature concerning this, however, presents conflicting results. A few studies of adults

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with mitral valve prolapse syndrome have yielded evidence of autonomic dysfunction in heart rate and blood pressure control,[17,18] whereas others have failed to demonstrate this.[19,20] Several studies of plasma and urinary catecholamines in adult patients with mitral valve prolapse have shown increased sympathetic resting tone and cardiac hypersensitivity to the infusion of isoproterenol.[21–24] In contrast, another report showed that plasma and urinary catecholamine levels in 11 children with mitral valve prolapse (with and without symptoms) were not elevated and did not demonstrate a relationship between mitral valve prolapse and a hyperadrenergic state.[25] Further in support of a hyperadrenergic state in adult patients with mitral valve prolapse are reports of β-blocker efficacy.[26,27]

Children and adolescents with mitral valve prolapse who have symptoms of chest pain, palpitations, shortness of breath, and fatigue constitute a clinical management problem. Efficacy of β-blocker therapy has not been clearly established, and many clinicians and parents are reluctant to commit pediatric patients to prolonged pharmacotherapy. An effective behavioral intervention would be useful with these patients.

The complex and often conflicting literature on symptomatic adults with mitral valve prolapse prompted us to try to document whether anxiety, a hyperadrenergic state, and an anatomic predisposition to mitral valve prolapse interrelate clinically in children and adolescents. We hypothesized that, if the symptoms of mitral valve prolapse syndrome were a function of a hyperadrenergic state, a behavioral intervention using autonomic nervous system (skin temperature) biofeedback, and relaxation/mental imagery techniques (self-hypnosis) could ameliorate the symptoms in children and adolescents. These behavioral techniques have been applied successfully to many psychophysiologic conditions and anxiety disorders in children and adolescents.[28,29] Although the mechanism of improvement in these conditions is unknown, in adults it has been suggested that behavioral techniques using relaxation-mental imagery and biofeedback may result in decreased activity of the sympathetic nervous system.[30]

This pilot study was designed to evaluate the following questions: (1) Do children and adolescents with documented mitral valve prolapse and symptoms characteristic of the mitral valve prolapse syndrome have evidence of a hyperadrenergic state measurable by increased excretion of urinary catecholamines? (2) Is there evidence of increased levels of anxiety in children and adolescents with mitral valve prolapse syndrome? (3) Will a behavioral intervention using skin temperature biofeedback and relaxation/mental imagery training ameliorate the symptoms in children and adolescents with mitral valve prolapse syndrome?

MATERIALS AND METHODS

Patient Population

Children and adolescents, 9 through 18 years of age, were recruited from the Children's Hospital and Medical Center cardiology, pediatric, and adolescent clinics. All subjects were examined by a cardiologist and assigned to one of three groups: normal controls (mean age 11 years), subjects with asymptomatic mitral valve prolapse (mean age 13.3 years), and subjects with symptomatic mitral valve prolapse (mean age 12.9 years). Symptoms associated with mitral valve prolapse included chest pain, palpitations, shortness of breath, and fatigue.

All subjects with mitral valve prolapse had a systolic click at the lower left sternal border or apex. A systolic murmur was considered supportive evidence. All subjects with mitral valve prolapse had late, middle, or pronounced holosystolic prolapse of the mitral valve leaflets on M-mode and two-dimensional echocardiography. Subjects with and without mitral valve prolapse were excluded if they had other cardiac or noncardiac disease. Subjects with mitral valve prolapse were excluded if they were receiving any medication long term or were unwilling to be randomized to treatment groups.

Methods

Eleven control subjects and six subjects with asymptomatic mitral valve prolapse completed the Spielberger State-Trait Anxiety Inventory (STAI)[31] and a 24-hour urine collection for catecholamine assay. The STAI is comprised of two separate 20-question scales intended to measure transitory anxiety at the time of testing and more stable long-term anxiety levels. The STAI children's form was used for subjects younger than 12 years of age, and the standard form was used for older subjects. Twenty-four hour urinary catecholamine assay was performed according to the method of Crout.[32] Caffeine and any medication was restricted for 72 hours and exercise was restricted for 24 hours before urine was collected. Urine epinephrine and norepinephrine values were standardized and reported in micrograms per square meter per 24 hours.

Fourteen subjects with symptomatic mitral valve prolapse completed the STAI and were instructed in a visual analog scale method of daily symptom recording.[33] The visual analog scale for pain consists of a 10-cm line with the words "no pain" on

one end and "severe pain" on the other. The subject is asked to mark an X on the spot where the pain is perceived. Symptom frequency, intensity, and duration were recorded during a 1-month baseline period. At the end of the baseline period subjects completed a 24-hour catecholamine collection, were matched by age and sex, and assigned randomly to one of two treatment conditions.

Eight Weekly 40-Minute Temperature Biofeedback Sessions Plus Twice Daily Home Practice of a Relaxation/Mental Imagery Exercise. In this treatment condition, subjects were presented with a simplified physiologic rationale for treatment ("decreasing adrenaline") and instructed in fingertip warming. They were encouraged to use relaxation/mental imagery techniques during biofeedback sessions and twice daily at home for 15 minutes.

Eight Weekly 40-Minute Sessions in an Attention-Placebo Condition. Subjects in this group were told that learning to complete a task while maintaining a state of internal relaxation was the goal of therapy. Subjects were monitored for skin temperature but given no feedback while playing a noncompetitive computer game. Subjects in the attention-placebo group were also asked to "sit quietly" twice daily for 15 minutes without further instructions.

Although only subjects practicing biofeedback-relaxation/mental imagery received feedback, all subjects with symptomatic mitral valve prolapse were continuously monitored at each clinic session with a J and J model T-68 skin temperature biofeedback unit attached to the right index finger. After 5 minutes in a quiet room with an ambient temperature of 23.3°C (74°F), skin temperature was recorded for 30 minutes during treatment and attention-placebo sessions.

Ten subjects with symptomatic mitral valve prolapse (six practicing biofeedback-relaxation/mental imagery and four receiving attention-placebo) completed eight clinic visits. Throughout the treatment phase, daily symptom records were collected by a symptom evaluator who remained unaware of the individual subject's assignment to either biofeedback-relaxation/mental imagery or attention-placebo group. At the end of the 8-week treatment phase, a 24-hour urine collection for catecholamines and the STAI form were repeated. The Stanford Hypnotic Clinical Scale for Children,[34] a seven-item measure of hypnotic responsiveness, was then administered by another investigator unaware of the treatment condition and symptom activity.

An echocardiogram was completed within 2 weeks of the end of treatment. Five months after the completion of treatment, subjects were contacted by telephone and letter and asked to resume symptom recording for 2 weeks. At a 6-month follow-up appointment, symptom records were collected and the STAI form was administered.

Statistical Methods

Statistical analysis involved baseline and experimental data. Baseline data of catecholamine levels and STAI scores were compared between controls, asymptomatic subjects with mitral valve prolapse, and subjects with symptomatic mitral valve prolapse, by parametric and nonparametric (because of small sample size) one-way analyses of variance. Experimental data included catecholamine levels, STAI scores, and symptom frequency for the 11 subjects with symptomatic mitral valve prolapse. The change in each of these measures from pretreatment baseline to posttreatment values was compared for biofeedback-relaxation/mental imagery and attention-placebo groups by parametric t tests and nonparametric Wilcoxon sum tests. The nonparametric test was computed because of the small sample sizes for the two groups. P values for both parametric and nonparametric tests were calculated for all comparisons.

RESULTS

Fourteen subjects with mitral valve prolapse reported the following symptoms: chest pain (100%), shortness of breath (50%), palpitations (43%), and fatigue (21%). The 11 subjects who completed the 4-week baseline period reported 0.03 to 1.03 (mean 0.40) episodes of chest pain per day per month. Chest pain had been present for an average duration of 2.8 years (6 months to 10 years). The average pain intensity was rated 6.3 (3 to 10) on a 10-point pain scale. The pain lasted an average of 12 minutes (10 seconds to 60 minutes) and was described as sharp (36%), dull (64%), and precipitated by exercise (55%) or emotion (18%). Subjects reported combined symptoms (chest pain plus shortness of breath, palpitations, fatigue) 0.07 to 8.0 (mean 1.20) times per day per month during the baseline symptom recording period. Reports of symptom intensity and duration did not prove reliable and only symptom frequency data were analyzed. Subjects scored from 6 to 7 (mean 6.7) on the Stanford Hypnotic Clinical Scale for Children. There were no significant baseline or outcome differences according to age, sex, or hypnotizability.

Baseline levels of urinary catecholamine excretion and STAI scores did not show any significant differences among subjects without mitral valve prolapse, asymptomatic subjects with mitral valve prolapse, and subjects with symptomatic mitral

valve prolapse (Table 1). The urinary catecholamine levels were comparable to published standards for children[35,36] and did not yield evidence for a hyperadrenergic state associated with mitral valve prolapse syndrome. Similarly, the STAI scores showed no difference between groups and were at approximately the 50th percentile for a normative high school population.[31]

To determine whether the biofeedback-relaxation/mental imagery group achieved skin temperature warming ability, maximal temperature change from baseline was compared between the biofeedback-relaxation/mental imagery and attention-placebo groups for the first and last clinic sessions. Although a one-way analysis of variance with baseline temperature as a covariate failed to show a significant group effect ($F = 1.843$, $P = .217$), a nonparametric Mann-Whitney two-sample test suggested a marginal effect ($Z = -1.9188$, $P = .055$).

The changes from baseline to the end of treatment for urinary catecholamine excretion and STAI scores in biofeedback-relaxation/mental imagery and attention-placebo groups are shown in Table 2. There were trends that did not reach statistical significance for increased epinephrine and decreased norepinephrine excretion in both groups but no significant difference between groups. STAI scores showed a trend toward reduction with no statistically significant difference between biofeedback-relaxation/mental imagery and attention-placebo groups.

Symptom changes between baseline, end of treatment, and 6-month follow-up evaluation are shown in Table 3. At the end of the 8-week treatment period, there was a trend toward decreased symptoms in both groups and a suggestion of a treatment effect for the biofeedback-relaxation/mental imagery group that did not reach statistical significance. At 6-month follow-up, one biofeedback-relaxation/mental imagery group subject who had increased both chest pain and combined symptoms by 0.03 episodes per day per month at the end of treatment did not complete follow-up. A comparison between the remaining five biofeedback-relaxation/mental imagery subjects and the four attention-placebo subjects showed a statistically significant decrease in chest pain in the biofeedback-relaxation/mental imagery group.

Posttreatment echocardiography documented persistent mitral valve prolapse in five of six biofeedback-relaxation/mental imagery and three of four attention-placebo subjects. Chest pain and combined symptoms in the two subjects who no longer had evidence of mitral valve prolapse at follow-up were decreased in the biofeedback subject and increased in the attention-placebo subject.

TABLE 1. Urinary Catecholamine Excretion and State-Trait Anxiety*

	Patients Without Mitral Valve Prolapse (n = 11)	Patients With Mitral Valve Prolapse		*P* Value	
		Asymptomatic (n = 6)	Symptomatic (n = 14)	Parametric	Nonparametric
Urinary excretion (μg/m²/24 h)					
Epinephrine	6.9 ± 2.2	4.1 ± 2.1	3.7 ± 0.5	.266	.309
Norepinephrine	21.6 ± 2.7	23.9 ± 6.9	17.0 ± 1.4	.279	.373
Spielberger State-Trait Anxiety Inventory scores					
State	30.5 ± 1.2	33.0 ± 3.0	34.6 ± 1.7	.227	.242
Trait	32.0 ± 3.0	35.7 ± 2.5	39.0 ± 2.8	.215	.193

* Results are baseline means ± SD.

TABLE 2. Changes for Urinary Catecholamine Excretion and State-Anxiety Scores*

	Treatment Group (n = 6)	Attention-Placebo Group (n = 4)	*P* Value	
			Parametric	Nonparametric
Urinary excretion (μg/m²/24 h)				
Epinephrine	+3.94 ± 3.95	+5.22 ± 3.88	.832	.476
Norepinephrine	−0.84 ± 3.41	−5.90 ± 4.44	.387	.352
Spielberger State-Trait Anxiety Inventory score	−9.67 ± 5.30	−5.75 ± 3.07	.594	.670

* Results are mean changes from baseline to end of treatment ± SD.

TABLE 3. Changes for Frequency of Chest Pain and Combined Symptoms*

	Biofeedback-Relaxation/ Mental Imagery Group (n = 6)	Attention-Placebo Group (n = 4)	*P* Value	
			Parametric	Nonparametric
Chest pain				
End of treatment	−0.22 ± 0.10	−0.06 ± 0.04	.228	.257
6-mo follow-up	−0.41 ± 0.12†	+0.17 ± 0.23	.049‡	.050‡
Combined symptoms				
End of treatment	−0.91 ± 0.66	−0.30 ± 0.16	.488	.914
6-mo follow-up	−1.71 ± 1.23†	−0.12 ± 0.23	.296	.086

* Results are mean changes in numbers of episodes per day per month between baseline and end of treatment and follow-up ± SD.
† n = 5.
‡ $P \leq .05$.

DISCUSSION

We did not find evidence to support the existence of increased sympathetic nervous system activity or increased anxiety levels in children and adolescents with mitral valve prolapse and symptoms. Baseline levels of 24-hour urinary catecholamine excretion and Spielberger STAI scores were not significantly different between control subjects and those with either symptomatic or asymptomatic mitral valve prolapse.

Comparing biofeedback-relaxation/mental imagery training with an attention-placebo condition applied to 10 symptomatic patients with mitral valve prolapse, we could detect no significant treatment effect at the end of 8 weeks of biofeedback-relaxation/mental imagery training. This apparent lack of treatment effect, however, could represent a type II error of not rejecting the null hypothesis when it is false (ie, false-negative result). The statistical power of the parametric *t* test for chest pain frequency, with the observed sample size and 8 *df*, was less than 0.4. This indicates that the likelihood of rejecting the null hypothesis, when in fact the opposite is true, is less than 40%. For the same observed difference, standard deviation, and a one-tailed significance level of .05, a sample size of 25 subjects in each group would be necessary to yield a power of approximately .9 (ie, a 90% chance of detection).

Other potential sources of failure to detect a treatment effect at the end of our 8-week intervention could include inadequate duration of treatment, failure to attain minimal levels of biofeedback performance, lack of compliance with home practice, and absence of treatment credibility. We chose a duration of treatment shown to be successful in headache management.[28] It is difficult to estimate whether the biofeedback-relaxation/mental imagery group actually received adequate therapy. Relaxation/mental imagery practice is entirely subjective and analysis for a group effect in temperature biofeedback training suffered from low statistical power. Other than patient report, we had no method of judging home treatment compliance or treatment credibility.

Although one subject was unavailable for evaluation, our 6-month follow-up data show a statistically significant decrease in chest pain and a trend toward decreased combined symptoms in the biofeedback-relaxation/mental imagery group. One possible explanation is that the treatment effect was delayed. Alternatively, although no instructions were given for continued practice, these subjects may have continued practicing a skill they had acquired with biofeedback-relaxation/mental imagery training, thereby increasing the duration of treatment.

Ultimately, we must consider the possibility that there is no association between anatomic mitral valve prolapse and the presence of symptoms. Although many clinicians endorse mitral valve prolapse syndrome as a clinical entity, results of large epidemiologic surveys and family studies have not corroborated an increased incidence of symptoms in individuals with mitral valve prolapse when compared with the general population.[10–12] A recent study of 591 children and adolescents, aged 9 to 14 years, reported no difference in the prevalence of fatigue, palpitations, dizziness, or dyspnea on exertion between 31 individuals with auscultatory findings of mitral valve prolapse and those without findings.[37] It is possible that the association between symptoms and mitral valve prolapse in our subjects represented a patient selection bias and not a causal relationship.

In summary, this study of children and adolescents did not reveal increased sympathetic tone as measured by urinary catecholamines or anxiety levels in individuals with mitral valve prolapse and symptoms of chest pain, shortness of breath, palpitations, fatigue, and honking. A behavioral treatment program using skin temperature biofeedback and mental imagery exercises was not more effec-

tive than an attention-placebo condition in reducing the symptoms at the end of treatment but was associated with a statistically significant reduction in symptoms at a 6-month follow-up evaluation.

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