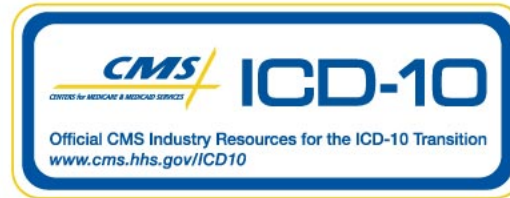


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Physical Training in Syndrome X

Physical Training Counteracts Deconditioning and Pain in Syndrome X

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OBJECTIVES	The aim of this study was to evaluate the effects of exercise training and body-awareness training in female patients with Syndrome X.
BACKGROUND	Patients with Syndrome X, defined as effort-induced angina pectoris, a positive exercise test and a normal coronary angiogram, suffer from a chronic pain disorder. We hypothesized that this disorder results in physical deconditioning with decreased exertional pain threshold.
METHODS	Twenty-six patients were randomly assigned to two training groups (A, B) and a control group (C). Group A (n = 8) started, after baseline measurements, with eight weeks of body-awareness training followed by eight weeks of exercise training on a bicycle ergometer three times a week for 30 min at an intensity of 50% of peak work rate. Group B (n = 8) performed only eight weeks of exercise training. Group C (n = 10) acted as controls without any intervention whatsoever. The effects on exercise performance, hormonal secretion, vascular function, adenosine sensitivity and quality of life were evaluated.
RESULTS	Body-awareness training did not change the pain response. The two training groups did not differ in effects of exercise training. Exercise capacity before training was below the gender- and age-matched reference range and improved by 34% with training to a level not different from the reference range. Onset of pain was delayed by 100% from 3 ± 2 to 6 ± 3 min ($p < 0.05$) while maximum pain did not change. Thus the pain-response-to-exercise curve was shifted to the right. Syndrome X patients showed a hypersensitivity to low-dose adenosine infusion compared to healthy age- and gender-matched controls ($p < 0.0001$) that did not change with exercise training. Endothelium-dependent blood flow increase was at baseline within reference range and tended to increase ($p < 0.06$) following training. In Group A the concentration of cortisol in urine decreased by 53% after body-awareness training ($p < 0.05$), and this change from baseline remained after physical exercise training ($p < 0.05$). A similar decrease occurred with only exercise training (Group B).
CONCLUSIONS	Physical deconditioning with lower exertional threshold for pain is a prominent feature in Syndrome X. Physical training in Syndrome X results in an increased exercise capacity with lesser anginal pain. We suggest physical training as an effective treatment in Syndrome X. (J Am Coll Cardiol 2000;36:1619-25) © 2000 by the American College of Cardiology

Patients with Syndrome X, defined as exercise-induced angina pectoris, a positive exercise test (chest pain and >1 mm rectilinear or down-sloping ST-segment depression 60 ms from the J-point) and a normal coronary angiogram with no signs of spasm angina or impaired left ventricular function, are frequently resistant to conventional forms of medical therapy and are not amenable to surgical treatment (1-2). Consequently, this patient group constitutes a therapeutic problem despite an excellent prognosis regarding life expectancy and absence of cardiac pathology, with considerable residual morbidity

associated with continuous chest pain and functional limitation (3-4).

The pathophysiological mechanisms responsible for the experience of chest pain in Syndrome X remain unclear, but increased sensitivity to right ventricular pacing, intraarterial saline infusion, adenosine, epinephrine and dobutamine have been reported (5-9). This hypersensitivity and hyperalgesia is consistent with findings in other chronic pain syndromes (10).

Syndrome X patients respond poorly to conventional antianginal drugs, and alternative treatments with imipramine (11), estradiol (12) and spinal cord stimulation (13) have been investigated. Furthermore, Syndrome X patients show impaired exercise performance despite normal skeletal muscles with signs of hypersensitivity to exercise. We hypothesized that part of this exercise intolerance depends on physical deconditioning (14). Physical training has been shown to have several physiological benefits in both healthy

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Abbreviations and Acronyms

ANOVA = analysis of variance
Borg CR-10 = Borg Category Ratio Scale
FMD = Flow mediated dilation
NTG = Nitroglycerine

populations and in different patient groups (15). Our aim in this study was, therefore, to study the effects of physical training in Syndrome X regarding exercise capacity, oxygen uptake, endothelial function, adenosine sensitivity and exertional anginal threshold.

MATERIALS AND METHODS

Patients. Twenty-six female patients with effort-induced angina pectoris, normal coronary angiograms and a positive exercise test (chest pain and > 1 mm rectilinear or down-sloping ST segment depression in more than one lead) gave their informed consent to participate in the study, which was approved by the local ethics committee. All patients were limited by chest pain during daily life because of angina pectoris Canadian Cardiovascular Society functional class II. The patients had a normal 2-D echocardiogram to rule out structural heart disease. No patient had a history of hypertension, diabetes mellitus or other systemic illness. The patients were 41 to 65 years old (mean 56 ± 8 years) and none were active smokers.

Eight of these patients (Group A) were randomized to a 16-week training program consisting of eight weeks of body-awareness training followed by eight weeks of exercise training. Eight patients (Group B) were randomized to eight weeks of exercise training and ten patients acted as controls (Group C) without intervention.

Training protocol. Physical training was performed as outpatient activity in hospital settings and was supervised by a physical therapist. The study design is shown in Figure 1. Body-awareness training consisted of body and mind relax-

ation performed twice a week for eight weeks. Exercise training was performed on a cycle ergometer three times a week for eight weeks. Training time was 30 min and the intensity was 50% of peak work rate determined at onset of the study. The control group (Group C) simply conducted their normal daily activities.

Data collection. Measurements were performed at baseline and at the end of each program. Therefore, patients in Group A were tested three times (at baseline, after eight weeks of body-awareness training and after eight weeks of endurance training) and Group B and C were tested twice (at baseline and after eight weeks).

EXERCISE CAPACITY. Maximal exercise capacity was assessed by a symptom-limited exercise test on a cycle ergometer with continuous respiratory gas analyses. Exercise tests started at 30 W and stepwise increments of 10 W every minute were used (16). Peak work rate (W) and peak oxygen uptake ($\text{ml} \times \text{kg}^{-1} \times \text{min}^{-1}$) recorded by an online system (Ametek, Thermo, Instr. Div, Pittsburgh, Pennsylvania) were determined.

HORMONAL ANALYSIS. To assess the physiological basis of psychological stress we studied the excretion of epinephrine, norepinephrine and cortisol in urine for a 24-h period. The patients were told to collect urine for 24 h, and the amount of epinephrine, norepinephrine and cortisol was measured in our ordinary clinical chemistry laboratory. The concentrations of catecholamines were considered to reflect a general defense mechanism (17,18) and the concentration of cortisol to reflect the magnitude of “negative stress” (19).

ADENOSINE SENSITIVITY TEST. The tolerance to adenosine and perception of algasia were measured by a neurophysiological method (20). After receiving an IV infusion line in the right arm followed by bed rest of 15 min, adenosine was administered at a dose, which was increased by 5 $\mu\text{g}/\text{kg}/\text{min}$ every 2 min. At 35 $\mu\text{g}/\text{kg}/\text{min}$, the dose was kept unchanged for 15 min. The dose was then gradually increased in the same way over 14 min to 70, 105 and 140 $\mu\text{g}/\text{kg}/\text{min}$. These doses were maintained for 15 min respectively. A continuous 12-lead ECG, blood pressure and chest discomfort according to the Borg CR-10 scale were recorded at each dose level. To study the sensitivity to adenosine in Syndrome X we compared the results with 10 age- and gender-matched healthy controls from the hospital staff.

ENDOTHELIAL AND NONENDOTHELIAL VASCULAR FUNCTION. The brachial artery was scanned longitudinally using high-resolution ultrasound 2–10 cm above the elbow, with the vessel placed horizontally across the screen according to the method first described by Celermajer *et al.* (21). Flow increase was induced by instantaneous inflation of a small pneumatic tourniquet placed around the forearm of the patient and inflated to 300 mm Hg for 4.5 min. A second scan was recorded from 30 s before and 90 s after cuff deflation. Flow velocity was recorded with a pulsed wave Doppler for 15 s before and 15 s after cuff deflation to reflect

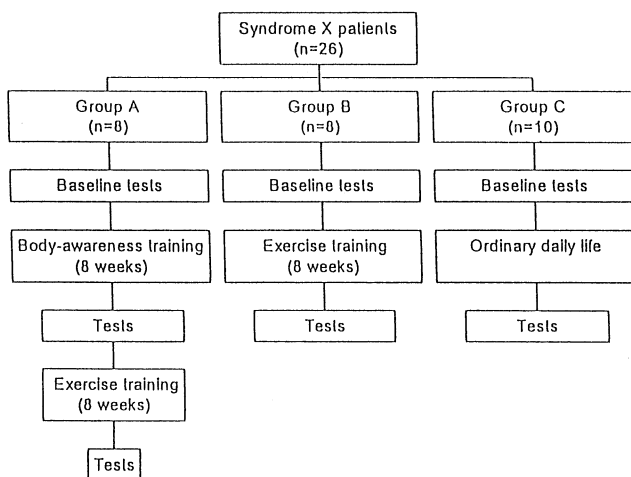


Figure 1. Study design (randomized parallel).

Table 1. Patient Characteristics

	Group A (n = 7)	Group B (n = 7)	Group C (n = 10)
Age (yrs)	59 ± 5	55 ± 9	53 ± 10
Weight (kg)	72 ± 6	68 ± 6	74 ± 9
History of angina (months)	44 ± 38	42 ± 39	44 ± 36
Functional class (CCS)	II (7)	II (7)	II (10)
Beta-blockers	2	2	3
Calcium antagonists	3	2	4
Nitroglycerine	5	5	8

the endothelium-dependent vasodilator capacity. This was followed by 10 min rest for vessel recovery. A third scan at rest was taken and 0.40 mg sublingual nitroglycerin (NTG) spray was administered. Three to four minutes after NTG the last scan was recorded and was considered to measure the nonendothelium-dependent vasodilator capacity. Vessel diameter was measured from the videotape.

STATISTICAL ANALYSIS. Analysis of variance for repeated measures (ANOVA) and Student unpaired *t*-test were used. Statistical significance was defined as *p* < 0.05. Values are given as mean ± SD. To examine whether physical training improved exercise capacity, peak oxygen uptake and time to pain onset, a two-way repeated measures ANOVA with the group factor training/nontraining and the repeated factor time was performed.

Table 2. Exercise Capacity and Oxygen Uptake

	Group A (Relaxation and Exercise Training)	Group B (Exercise Training)	Group C (Ordinary Life Only)
Peak work (W) baseline	91 ± 15	97 ± 8	92 ± 15
Peak work (W) after relaxation	89 ± 11		
Peak work (W) after exercise training	124 ± 19	127 ± 14	95 ± 9
<i>p</i> value (training effect)	0.0018	0.0008	ns
Peak VO ₂ (l/min) baseline	1.14 ± 0.06	1.26 ± 0.14	1.12 ± 0.08
Peak VO ₂ (l/min) after relaxation	1.15 ± 0.09		
Peak VO ₂ (l/min) after exercise training	1.43 ± 0.16	1.45 ± 0.16	1.11 ± 0.06
<i>p</i> value (training effect)	0.0002	0.018	ns
Pain onset (min) baseline	3 ± 2	4 ± 1	3 ± 1
Pain onset (min) relaxation	3 ± 2		
Pain onset (min) after exercise training	6 ± 3	6 ± 1	3 ± 1
<i>p</i> value (training effect)	0.04	0.01	ns
Max pain (Borg CR-10) baseline	4 ± 1	3 ± 1	4 ± 1
Max pain (Borg CR-10) after relaxation	4 ± 1		
Max pain (Borg CR-10) after exercise training	4 ± 1	3 ± 1	4 ± 1
<i>p</i> value (training effect)	ns	ns	ns
Peak heart rate (beats/min) baseline	129 ± 8	136 ± 14	123 ± 12
Peak heart rate (beats/min) after relaxation	129 ± 8		
Peak heart rate (beats/min) after exercise training	151 ± 12	153 ± 9	122 ± 15
<i>p</i> value (training effect)	0.0007	0.01	ns
Peak systolic blood pressure (mm Hg) baseline	187 ± 8	195 ± 16	190 ± 9
Peak systolic blood pressure (mm Hg) after relaxation	186 ± 8		
Peak systolic blood pressure (mm Hg) after exercise training	201 ± 12	207 ± 11	189 ± 8
<i>p</i> value (training effect)	0.01	0.06	ns
Peak double product (×10 ³) baseline	241 ± 24	266 ± 40	234 ± 33
Peak double product (×10 ³) after relaxation	240 ± 24		
Peak double product (×10 ³) after exercise training	305 ± 35	316 ± 23	232 ± 37
<i>p</i> value (training effect)	0.0009	0.007	ns

RESULTS

Patient characteristics. Baseline patient characteristics are shown in Table 1. The three groups did not differ from each other in age, height, body weight, severity or history of angina pectoris. Before the study, all the patients had received an ordinary medical examination, pharmacological treatment and counseling concerning diet, alcohol consumption, smoking and physical activities and were encouraged not to change their lifestyle during the study.

Exercise capacity and oxygen uptake. Peak work capacity in Group A increased by 36% from 91 ± 15 W to 124 ± 19 W, *p* < 0.01 after eight weeks of endurance training (Table 2). This is not different from the age and gender matched reference range, whereas the baseline capacity was below reference range (22). Peak oxygen uptake increased by 26%, *p* < 0.001. The time to pain onset during exercise increased from 3 ± 2 min to 6 ± 3 min, *p* < 0.05. Maximum pain did not change with training. Thus, training shifted the pain-response curve to the right (Fig. 2). After the physical training period there were increments in peak heart rate (*p* < 0.001), peak systolic blood pressure (*p* < 0.05) and double product (*p* < 0.001). Group A did not change their exercise performance during the initial eight weeks of body-awareness training and relaxation. Peak oxygen uptake, pain appearance and pain intensity were unaffected and not different from baseline.

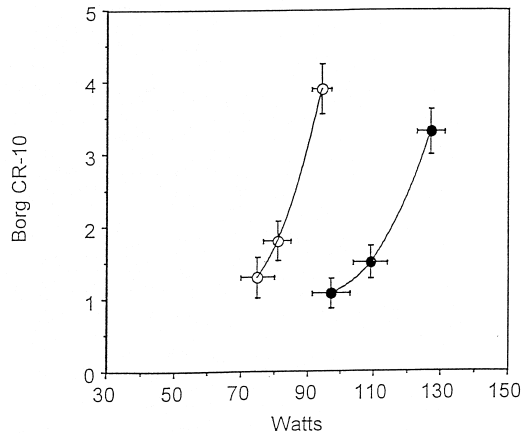


Figure 2. Pain response to increased workload in the training groups (A + B) before (open dots) and after training (solid dots).

Group B increased their exercise performance after eight weeks of physical training by 31% regarding peak exercise capacity ($p < 0.0001$), and there were increments in peak oxygen uptake ($p < 0.05$), time to pain onset ($p < 0.05$), peak heart rate ($p < 0.05$) and double product ($p < 0.01$).

Group C did not change their exercise parameters after eight weeks related to baseline.

In the two training groups ST-segment depression was 1.4 ± 0.2 mm and remained unchanged at comparable heart rate after intervention (Fig. 3).

By performing a two-way repeated measures ANOVA, we found no effect for the grouping factor (group factor p value = 0.543) in the ANOVA over time. With respect to time, there was a significant difference in exercise capacity, peak oxygen uptake and time to pain onset (time factor p value = 0.0023, 0.0018 and 0.036, respectively), and the interaction of the time factor and the grouping factor also proved to be significant ($p = 0.010, 0.009$ and 0.047, respectively).

Hormonal analysis. In Group A the urinary 24-h excretion of cortisol decreased after eight weeks of body-awareness and relaxation training ($p < 0.05$), and this change from baseline was maintained after eight weeks of physical exercise training ($p < 0.05$) (Table 3). The values were always within reference range. After exercise Group B decreased the urinary cortisol excretion to a level similar to that found in Group A. However, this change from baseline was not statistically significant. There were no changes in epinephrine or norepinephrine urinary excretion after the two periods in the two training groups. In Group C there was no change in urine cortisol, epinephrine or norepinephrine at the second test.

Adenosine sensitivity. The tolerability to adenosine in the three patient groups (A, B and C) was low compared with age- and gender-matched controls regarding highest tolerable dose (54 ± 16 vs. 121 ± 25 $\mu\text{g}/\text{kg}/\text{min}$, $p < 0.00001$). Body-awareness training or exercise training had no effect on adenosine sensitivity (Fig. 4).

Vascular function. Baseline measurements of endothelium and nonendothelium-dependent vascular function were considered to be within reference range (Table 4). After physical exercise training there was a tendency to increased endothelium-dependent blood flow ($p < 0.06$) in the two groups (A + B). However, no change in increments of arterial diameter after occlusion (endothelium-dependent) or after nitroglycerine (nonendothelium-dependent) could be detected.

Compliance. In the training groups two patients (one from Group A and one from Group B) dropped out because of inability to follow the training protocol. No adverse effects to physical training were reported other than fatigue after the training sessions.

DISCUSSION

This is the first study evaluating the effects of physical training in patients with Syndrome X. Eight weeks of endurance exercise training improved peak exercise capacity, oxygen uptake, peak heart rate, peak systolic blood pressure and double product to age- and gender-matched reference range. The pain response to the exercise curve was shifted to the right with a 100% increase in time to pain onset while maximum pain was unaffected. This implies that, with the present experimental design, the underlying pain mechanism was not altered by physical training. Instead, it affected the deconditioning this chronic pain disorder has caused. Endothelium-dependent arterial blood flow increase was at baseline within reference range and increased following training. A short time of body-awareness training, including relaxation, resulted in lower cortisol content in urine.

Patients with Syndrome X constitute a significant proportion of patients undergoing coronary angiography (1). The poor understanding of the mechanisms underlying this condition and the fact that this group could be heterogeneous concerning pathophysiology (2) make it difficult to tailor treatment for these patients. The frequent effort-induced chest pain and the severity of the anginal episodes call for active intervention. In this study we defined Syn-

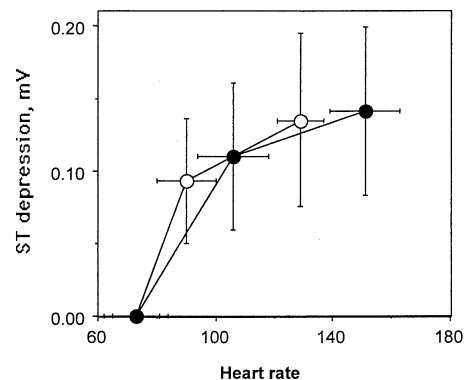


Figure 3. ST segment shifts during exercise in the training groups (A + B) before (open dots) and after training (solid dots).

Table 3. Hormonal Analysis

	Group A	Group B	Group C
U-Cortisol (nmol/d) baseline	86 ± 55	65 ± 36	73 ± 28
U-cortisol (nmol/d) after rest	47 ± 13		
U-cortisol (nmol/d) after exercise training	46 ± 17	48 ± 15	78 ± 34
p value (training effect)	0.046	ns	ns
U-norepinephrine (nmol/d) baseline	276 ± 121	273 ± 50	263 ± 96
U-norepinephrine (nmol/d) after rest	347 ± 141		
U-norepinephrine (nmol/d) after exercise training	261 ± 78	276 ± 133	231 ± 69
p value (training effect)	ns	ns	ns
U-epinephrine (nmol/d) baseline	25 ± 18	20 ± 9	19 ± 8
U-epinephrine (nmol/d) after rest	30 ± 23		
U-epinephrine (nmol/d) after exercise training	18 ± 12	22 ± 12	17 ± 10
p value (training effect)	ns	ns	ns

drome X as a chronic pain disorder resulting in deconditioning despite normal skeletal muscle characteristics (14). **Exercise performance.** The increase in exercise performance (exercise capacity, oxygen uptake, peak heart rate, peak systolic blood pressure and double product) after physical training is well documented in a healthy population (15) and after myocardial infarction (23). Our present findings are in keeping with these previous results, and the increased time to pain onset during exercise test reflects a capacity in Syndrome X patients to improve their daily life efforts without the experience of chest pain, resulting in better coping with pain. ST changes remained unaffected after physical training, suggesting that this phenomenon probably is not associated with the genesis of pain in this patient group. The improvements in hemodynamics should be positive for the prognosis of Syndrome X even if some of the patients might have their angina because of myocardial ischemia.

Hormonal effects. A state of chronic stress without a sense of ability to control the life situation (defeat mechanism) is thought to activate several physiological responses (18). This negative stress stimulates the hypothalamo-pituitary-adrenal axis, resulting in an increase in cortisol secretion (24). We could demonstrate a decrease in cortisol urine secretion after eight weeks of body-awareness training that was maintained during the following eight weeks of exercise

training. This is thought to be a physiological effect of better coping with stress and possibly also pain in this patient group. However, we failed to demonstrate changes in catecholamine secretion after this short time intervention. Exercise training only, however, decreased cortisol in urine to a similar extent, suggesting no additional effect of body-awareness training.

Adenosine sensitivity. The hypersensitivity to low-dose adenosine infusion in this patient group, compared with healthy age- and gender-matched controls, is obvious and contributes to a growing number of studies reporting a perception of chest pain after adenosine administration (9). Furthermore, a majority of patients and controls reported a periodicity of pain intensity after onset of pain, with pain-free intervals of 20–60 s, suggesting periods of adenosine-induced analgesia. Adenosine analgesia has earlier been shown in patients with myocardial ischemia and in healthy volunteers (20). Hypothetically, the adenosine-induced analgesia remains unaffected in Syndrome X patients even though these patients are hypersensitive to the algescic effects of adenosine. Intervention with body-awareness training or physical exercise did not alter the hypersensitivity.

Vascular function. Exercise training during 10 weeks has been shown to enhance endothelium-dependent dilation in young men (25). Smoking, hypercholesterolemia and diabetes (26) impair the endothelial function, and this is considered to be an early sign of atherosclerosis (21). Our findings speak in favor of a normal vascular endothelium function in Syndrome X and a normal improvement following exercise training. Several authors have suggested an impaired endothelial function as one pathophysiological mechanism in Syndrome X (27), but an earlier study does not support such a mechanism (28).

Study limitations. The relatively small number of patients in this study does not allow studies of the frequency and duration of chest pain during routine daily activities. Furthermore, bicycle exercise may not be the most appropriate form of exercise. Other forms of exercise training, such as running or jogging, might be equally or perhaps more appropriate. However, bicycle exercise training is a well-

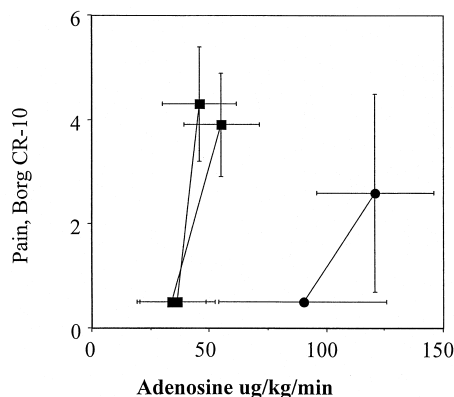


Figure 4. Adenosine sensitivity described as intensity of pain and onset of pain (bottom) in Syndrome X patients (left) and healthy controls (right).

Table 4. Vascular Function

	Group A	Group B
FMD (%) baseline	3.2 ± 3.5	3.7 ± 3.7
FMD (%) after rest	2.7 ± 4.2	
FMD (%) after exercise training	2.3 ± 3.8	2.7 ± 3.3
p value (training effect)	ns	ns
NTG dil (%) baseline	8.1 ± 7.8	10.2 ± 6.2
NTG dil (%) after relax	8.5 ± 6.0	
NTG dil (%) after exercise training	5.4 ± 4.1	6.6 ± 3.1
p value (training effect)	ns	ns
Resting blood flow (ml/min) baseline	59 ± 15	56 ± 20
Resting blood flow (ml/min) after rest	70 ± 19	
Resting blood flow (ml/min) after exercise training	51 ± 17	45 ± 16
p value (training effect)	ns	ns
Blood flow after stasis (ml/min) baseline	315 ± 30	304 ± 77
Blood flow after stasis (ml/min) after relax	388 ± 71	
Blood flow after stasis (ml/min) after exercise training	366 ± 102	355 ± 153
p value (training effect)	ns	ns
Quote increase in flow baseline	5.9 ± 2.2	5.9 ± 2.0
Quote increase in flow after rest	5.8 ± 1.8	
Quote increase in flow after exercise training	7.5 ± 1.6	8.1 ± 2.9
p value (training effect)	0.054	0.057

studied method to improve hemodynamic parameters. Hypothetically, there could be difficulties in achieving long-term compliance with an exercise training program in patients with this chronic condition.

Conclusions. Physical exercise training at moderate intensity has several beneficial effects in female patients with Syndrome X, including exercise performance improved to normality and prolonged time to pain onset during exercise. Physical training could break a vicious circle resulting in effort-induced chest pain and deconditioning in favor of an increased exercise capacity and lessened anginal episodes. We suggest physical training as an effective treatment strategy in Syndrome X.

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