Update on Exercise Cardiology

Richard A. Stein, MD, Nieca Goldberg, MD, and Roseann Chesler, EdD

This review focuses on innovative directions and recent studies in cardiovascular exercise science. Studies that address the enhancement of the diagnostic and prognostic value of exercise testing, by virtue of electrocardiographic analysis and the integration of exercise tolerance and clinical findings, are reviewed. The roles of exercise electrocardiographic testing in chest pain centers and the epidemiologic and physiologic effects of exercise training are discussed. The impact of exercise training on the angiographic and clinical regression of coronary artery disease and gender differences in exercise testing and training are among the concluding topics.

The role of exercise in clinical cardiology has expanded over the past two decades, reflecting an increased appreciation that the evaluation of symptoms that occur with exertion (e.g., angina and dyspnea) are best evaluated during exertion in a controlled setting. In addition, recent clinical experience has supported the increasing use of exercise training as part of comprehensive cardiac rehabilitation programs and the use of exercise testing and training in special clinical situations, such as at chest pain centers and in congestive heart failure (CHF) treatment programs. Most recently, advances in our knowledge of cardiovascular exercise science in the areas of endothelial function and cell biology have increased our understanding of the physiology behind the clinical observations.

This update will review recent advances in the field of cardiovascular exercise science in four specific areas: exercise electrocardiography (ECG) testing; exercise training and cardiac rehabilitation; exercise training for patients with CHF; and gender differences in exercise ECG testing and training.

EXERCISE ELECTROCARDIOGRAPHIC TESTING

Exercise ECG testing for the detection and exclusion of significant coronary stenosis is an imperfect test, and as such is judged with other imperfect testing methods such as exercise nuclear or echocardiographic imaging by its relative diagnostic accuracy. Statistical criteria used to evaluate clinical utility are sensitivity (the percent of the time that a patient with coronary stenosis will have a positive test result) and specificity (the percent of the time that a patient without coronary stenosis will have a negative test result). Positive and negative predictive values (the percent of time a positive or negative test result will accurately represent the presence or absence of coronary artery stenosis) and prognostic value (ability to predict future clinical events) also are used, and are often of greater clinical relevance than sensitivity and specificity.

Recent important studies have used a variety of approaches to enhance the diagnostic value of the exercise ECG examination. These include differing methods of analysis of ST segment changes, the use of additional stress test data, and using clinical criteria in the form of scoring systems to enhance the diagnostic value of exercise ECG testing.

From New York Hospital, Kligfield and Okin[1,2] have reported that computer-based analysis of the slope of ST segment depression plotted against the increase in heart rate (HR)—reflecting increased myocardial oxygen demand—enhances the sensitivity without degrading the specificity of the exercise ECG examination. We reported similar findings in a study comparing the ST/HR slope and standard criteria with respect to positive exercise planar thallium findings.[3]

Recently Okin et al[4] published data derived from a posthoc analysis of the initial exercise ECG examination of 11,880 men at high risk of developing coronary heart disease who were randomly enrolled in the usual care arm or the special risk factor intervention arms of the MRFIT trial.[4] They compared the ST/HR index (increase ST segment depression/increase HR, from rest to peak exercise) to standard ST segment analysis in predicting mortality over 7 years. The investigators noted a significant reduction in 7-year mortality in those in the special risk factor intervention arm (2.4%) compared with those in the usual care arm (5.3%) in men with a positive ST/HR index, but not in men selected by virtue of a positive standard ST segment

Heart Disease 1999;1:12–18

From the Division of Cardiology, Brooklyn Hospital Center, the Cardiac Rehabilitation Program, Lenox Hill Hospital, New York, and the State University of New York Health Sciences Center at Brooklyn, New York.

Address correspondence to: Richard A. Stein, MD, Chief, Division of Cardiology, Brooklyn Hospital Center, 121 DeKalb Avenue, Brooklyn, NY 11201.

analysis. The value of the ST/HR index in the identification of populations who would benefit most from risk reduction intervention is intriguing. If this is confirmed with prospective studies it will be of clinical significance.

The recent observation that exercise-related normalization of inverted T waves in infarct-related ECG leads predict myocardial viability is of importance in the management of patients with myocardial infarction. Mobilia et al[5] compared exercise-related T wave normalization in infarct-related ECG leads to results of dual isotope positron emission tomography in 40 consecutive patients who had had a recent acute infarct. The sensitivity, specificity, and predictive value of T wave normalization at low work loads (less then 50 watts) with respect to the positron emission tomography finding of myocardial viability in the infarct areas were an impressive 77%, 94%, and 85%, respectively.

Ischemia may manifest in a variety of ways in addition to ST segment depression. These include characteristic pain, a reduction in exercise capacity, and decreased—or failure to normally increase—heart rate and systolic blood pressure. Two recent studies have emphasized the importance of exercise capacity when exercise ECG testing is used for its prognostic value. At the Mayo Clinic, Roger et al[6] retrospectively studied exercise ECGs and clinical outcome in a cohort of 1,452 men and 741 women. After statistical adjustment, only workload achieved during the examination was associated with all-cause mortality and clinical events. In a similar study from the Cleveland Clinic, Snader et al[7] evaluated the predictive value with respect to 2-year all-cause mortality of exercise ECG thallium single photon emission tomography studies in 3,400 consecutive patients. On multivariable analysis, workload achieved was the strongest independent predictor of all-cause mortality.

It is reasonable to anticipate that integration of ST segment changes, exercise tolerance, and presence and character of chest pain during examination should increase the diagnostic accuracy and prognostic value of exercise ECG examinations; this is the basis of the Duke treadmill score (DTS). In a recent publication, Shaw et al[8] report on the diagnostic accuracy of the DTS in symptomatic patients who underwent exercise ECG testing and coronary angiography within 90 days, in a population with a relatively high disease prevalence (significant disease in 61%). The DTS is calculated from the following equation:

$$\text{DTS} = \text{exercise time} - (5 \times \text{ST deviation}) - (4 \times \text{angina})$$

with angina assigned a value of 0 if absent, of 1 if nonlimiting, and of 2 if limiting. Using the DTS to predict the presence of significant disease in more than one vessel (significant defined as > 75% stenosis), the odds increased 3.1 times (unadjusted risk) from low risk to moderate risk, and 376 times from low risk to high risk. The results of this study support the widespread reporting and use of the DTS score by exercise ECG facilities.

Froelicher et al[9] addressed the issues that make comparing differing reports on the diagnostic accuracy of exercise ECG examinations so difficult. These include differing disease prevalence in the populations studied and referral bias, i.e., the likelihood that patients with positive test results will go to angiography and thus be included in the analysis whereas patients with negative test results will not. In the study, 814 patients agreed to undergo exercise ECG testing and coronary angiography. Head-to-head comparisons of visual and computer analysis and indexes revealed a sensitivity of 45% and specificity of 85% with standard ST segment visual analysis in this population with a 49% prevalence of coronary artery disease (CAD). This was not improved with computer analysis or ST/HR index. However, equations incorporating clinical variables and exercise test results showed greater discrimination and significantly improved diagnostic power.

In emergency center chest pain protocols, patients in whom a myocardial infarction has been ruled out and who have clinical, ECG, and serum markers of myocardial necrosis findings that indicate low to moderate risk of acute coronary syndrome are increasingly undergoing immediate exercise ECG testing. Polanczk et al[10] presented in-hospital and 6-month outcome data from 276 patients determined to be low risk according to the Goldman algorithm. Patients underwent exercise ECG studies within 48 hours of presentation with chest pain using a symptom-limited Bruce or Modified Bruce protocol. There were no adverse events related to the exercise ECG studies. These investigators classified exercise ECG results that were negative for ischemic findings but did not achieve three metabolic equivalents of exercise as equivocal. The 6-month event rate in the 195 patients with a negative test result was 2% (negative predictive value = 98%), compared with an event rate of 15% in patients with positive or equivocal test results. Sensitivity and specificity were 73% and 74%, respectively.

Farkouh et al[11] recently reported the findings of a community-based, prospective, randomized, controlled clinical trial of 424 patients comparing the safety, effectiveness, and cost of admission in patients with chest pain admitted to a Chest Pain Unit (212 patients) or to a hospital (212 patients). Patients included for randomization were patients who presented to the emergency department with unstable angina that was classified according to Agency for Health Care Policy and Research (AHCPR) guidelines as intermediate risk. This is in contrast to previous studies, which included only low-risk patients. After 6 hours of observation, patients in the Chest Pain Unit who were judged able to walk and who did not manifest clinical or ECG changes or elevations in serum markers of myocardial necrosis (CK-MB) underwent an exercise ECG examination. In the presence of confounding ECG findings, nuclear or echocardiographic stress studies were performed. Patients with negative results on exercise ECG (DTS > 5) and imaging studies were discharged home, and patients with other results (equivocal or positive) were admitted to the hospital. Primary outcomes were acute clinical cardiovascular events or presentations, and secondary outcomes included cardiac procedures and hospitalizations for cardiac care within 6 months of the randomization. There were no clinical events associated with the exercise ECG testing, and the

incidence of primary events (6.6% in CPU and 8.5% in hospital admissions) and secondary events during the 6-month follow-up period was not significantly different between groups. The 97 patients randomized to the CPU who were dismissed after a negative functional study result had no primary outcomes during the 6-month observational period. The CPU arm of the study represented a significant reduction in healthcare costs over the 6-month period.

EXERCISE TRAINING AND CARDIAC REHABILITATION

For the most part, cardiac rehabilitation programs emphasize or consist entirely of aerobic activity, which emphasizes large muscle groups and low-resistance exercise. This is based on the favorable results of epidemiologic studies of low-resistance exercise in healthy adults, such as the recently reported Finish Twin Cohort Study.[12] In that study, Urho et al reported that among twin pairs who were healthy at baseline but discordant for death over the 25-year follow-up period, the odds ratio for death was 0.66 among those who exercised occasionally and 0.44 among those who underwent conditioning exercise compared with those who were sedentary (odds ratio set at 1.0). Other studies also have demonstrated that frequent aerobic exercise is associated with a reduced risk factor profile in a variety of populations, most recently in 3,331 men in a study by Hsieh et al[13] from Toranomon Hospital in Tokyo, Japan.

Additionally, insulin sensitivity is increased and the occurrence of noninsulin-dependent diabetes mellitus reduced in active populations. Meyer-Davis et al[14] measured insulin sensitivity in 1,476 adults with glucose tolerance that ranged from normal to mild noninsulin-dependent diabetes. Habitual physical activity was assessed by a 1-year recall questionnaire. The authors noted that vigorous and nonvigorous exercise energy expenditure were positively and independently associated with insulin sensitivity. In a population-based prospective study from the Cooper Institute in Dallas, Texas, Wei et al[15] followed 7,511 men who did not have an impaired fasting glucose level for an average period of 6 years. Men in the low-fitness group (the least-fit 20%) had an increase of 1.9 times in risk of developing impaired glucose intolerance, and a 3.7 times greater risk of diabetes compared with men in the high-fitness group (the highest 20%).

Recent studies have addressed the impact of high-resistance training and the consequent increase in dynamic strength in patients with coronary heart disease. Of particular clinical importance are the results of a recent study by Beniamini et al[16] assessing the effect of a high-intensity resistance program on quality of life parameters. Their data demonstrated that resistance training has a positive effect on improved self-efficacy scores for strength-related tasks and has positive effects on other psychological parameters such as mood disturbance, depression, fatigue, and emotional health.

In 1990, Ornish et al[17] assessed the role of multifactorial lifestyle changes, including 38 minutes a day of low-resistance aerobic exercise, on coronary artery regression in the Lifestyle Heart Trial. Quantitative angiograms and positron emission tomography scans were performed at onset and at 1 and 4 years, and in a subset of patients again at 5 years (angiograms only).[18] Their 1-year data revealed significant reductions in levels of total and low-density lipoprotein (LDL) cholesterol and a reduction in body weight of 10 kg. There was also a reduction in frequency, duration, and severity of angina in the treatment group, compared with a worsening in the control group. Angiography revealed a decrease in average diameter of stenosis in atherosclerotic lesions of > 50% in the treatment group, whereas progression was demonstrated in the control group. These findings were sustained at 5 years, when angiography showed that the average percent diameter stenosis in the treatment group decreased by 3.1 absolute percentage points (a 7.9% relative improvement) compared with baseline. The average percent diameter in the control group increased by 11.8% (a 27.7% relative worsening) compared with baseline.

These data and comparable findings from other lipid reduction, smoking cessation, stress reduction, and exercise training trials demonstrate angiographic regression or a reduction in clinical events. They do not, however, allow for an assessment of the role of the exercise training in the measured outcomes.

Shuler et al,[19,20] Hambrecht et al,[21] and Neibauer et al[22] have addressed the role of exercise training and CAD regression in a series of studies in 113 patients (56 in the study group and 57 in a control group) with chronic stable angina and CAD documented by coronary angiography. In these studies exercise training was the principal intervention. In the first study in 1992,[19] the treatment group engaged in dietary modification and exercise for more than 3 hours per week, consisting of two 1-hour sessions and three to five 30-minute sessions at home per week. Angiographic regression and improved myocardial perfusion (thallium) was noted in the exercise trained group when compared with the control group. A most impressive finding was the significant relationship between improvement in functional capacity (training effect) and changes in coronary morphology. Patients who demonstrated regression had a 29% improvement in exercise capacity, compared with only a 6% improvement in patients with no change or angiographic progression. A 1-year report of the ongoing study showed continuation of these responses.[20]

In an attempt to determine the optimal quantity of physical activity (kcal/week) that would be required to provoke an improvement in both cardiovascular fitness and reduce progression of atherosclerotic lesions, Hambrecht et al[21] recruited a subset of patients from the study. Energy expended in leisure-time activity was closely monitored with the use of the Minnesota Leisure Time Physical Activity Questionnaire and from participation in supervised group exercise sessions twice per week. After 12 weeks, repeat coronary angiography was performed and progression

measured with digital image processing. The data from the treatment group revealed a 14% increase in maximal 1 minute oxygen consumption (VO_2), versus no change in the control group. In the treatment group, regression of CAD was found in 8 patients (28%), no change in coronary morphology in 18 patients (62%), and progression in 3 (10%). In comparison, 6% of the control group showed regression, 49% showed no change, and 45% showed progression.

Leisure-time activity was found to be an independent predictor of change in coronary status, and there was an inverse relationship between levels of leisure-time physical activity and regression or attenuated progression of atherosclerotic lesions. The investigators quantified the work required to elicit these changes. The lowest activity level, approximately 1,022 ± 142 kcal/week, was noted in patients with progression of CAD. Patients demonstrating no changes in coronary status averaged approximately 1,533 ± 122 kcal/week, and those demonstrating regression expended approximately 2,204 ± 237 kcal/week. The findings support the beneficial effects of attenuating regression with a moderate level of regular exercise (approximately 1,400 kcal/week). Regression required a greater level of exercise (2,200 kcal/week or 5–6 hours of exercise per week).

In the most recent report, Niebauer et al[22] presented the 6-year follow-up results of their multifactorial trial. The patients in the treatment group (n = 40) demonstrated a reduction in total cholesterol and triglyceride levels, which were not statistically different from those in the control group (n = 57). However, the treatment group demonstrated a significant (28%) increase in physical work capacity and regression, or a slower rate of progression, of coronary artery stenosis compared with the control group. The energy expenditure consistent with coronary regression was an average of 1,784 ± 384 kcal/week, or approximately 4 hours of moderate aerobic exercise per week. Physical work capacity was an independent predictor of angiographic changes. The authors concluded that the beneficial effects on coronary morphology resulted in large part from physical exercise.

EXERCISE IN EVALUATION AND TREATMENT OF PATIENTS WITH CONGESTIVE HEART FAILURE

Although it seems counterintuitive, the limited exercise tolerance in a patient with CHF due to left ventricular systolic dysfunction is not significantly related to resting ejection fraction, cardiac output, or pulmonary capillary pressure. Instead, a series of studies have indicated that in patients with chronic CHF peripheral muscle factors limit exercise tolerance. Okiya et al[23] used ^{31}P magnetic resonance spectroscopy to study skeletal muscle metabolism in 12 patients with CHF and 7 age-matched control subjects. They noted that phosphocreatine (PCr) in muscle was nearly depleted at maximal systemic exercise, indicating that exercise is limited by muscle metabolic factors, and that the reduced tolerance in patients with CHF is associated with an impaired muscle metabolism.

Exercise tolerance in CHF is increased with exercise training, and in comparison to the resting indexes of left ventricular function, exercise tolerance is the best predictor of survival. Myers et al[24] evaluated peak minute oxygen consumption (VO_2peak) achieved during upright bicycle exercise ECG testing, and clinical and hemodynamic variables including ejection fraction and pulmonary capillary wedge pressure as predictors of survival in patients with advanced CHF (New York Heart Association Class IV). In total, 644 ambulatory patients referred to the Heart Failure Center at Sanford University were followed for a mean period of 4 years. Of these, 187 patients died and 101 underwent transplantation. With multivariate analysis, only VO_2peak was a predictor of death; clinical and hemodynamic variables were not predictive. In a study from St. Louis University that focused on exercise test predictors of survival in patients established to have a very reduced VO_2peak (less than 14 mL/kg/min, which is the minimum for acceptance on a transplantation waiting list), Naohiko et al[25] noted better survival in patients who were able to reach a peak exercise systolic blood pressure of > 120 mmHg.

Belardinelli et al[26] recently presented the results of a comprehensive evaluation of an 8-week training program in 26 patients with ischemic CHF and a control group of 20 patients. The patients had significantly reduced VO_2peak values (17.0 ± 3 mL/kg/min versus 18.1 ± 4 mL/kg/min for the control group). Coronary angiography in a subset of 23 patients, exercise thallium myocardial scintigraphy, and low-dose dobutamine stress echocardiography were performed at baseline and after an 8-week exercise training or control period. The VO_2peak, contractile response to dobutamine, and exercise thallium perfusion scores improved only in the trained group (by 24%, 28%, and 31%, respectively). In the subgroup of trained patients who underwent coronary angiography before and after the training period, improvements in both echocardiographic and nuclear perfusion scores were correlated with an increase in coronary collateral score. This is a very impressive positive outcome of a relatively short-term exercise training study in patients with CHF. Additional corroborating studies are necessary before these reported outcomes can be generalized and exercise training integrated into the standard care of patients with CHF.

A concern with regard to exercise training in patients who have left ventricular dysfunction is that the exercise-associated increase in myocardial work and wall tension may lead to an increase in ventricular remodeling. Results of two previous studies in small populations[27,28] have suggested that in patients with ischemic heart failure who have multiple large wall motion abnormalities, or as in the second study, who fail to increase their cardiac output with low-intensity exercise, wall motion may deteriorate, ventricular volumes may increase, and VO_2peak may fail to increase.

Recently, however, the Exercise in Left Ventricular Dysfunction Trial conducted by Gaimnuzzi et al[29] addressed this issue: 77 patients with a history of myocardial infarction and ejection fractions of less then 40% were enrolled in a 6-month exercise ot control period. After 6 months, the exercise group demonstrated an increase in work capacity and ejection fraction, with ventricular volumes remaining unchanged. In the control group, work capacity was unchanged, ejection fraction decreased, and ventricular volumes increased. Further studies to address the impact of exercise training in patients with marked left ventricular dysfunction and the near absence of cardiac reserve are indicated.

Investigations into the mechanism of the training enhancement of exercise tolerance in patients with CHF have focused on alterations in vascular dynamics and enhanced oxygenated blood supply to muscle cells. Attention has been focused on the impact of exercise training on endothelial cell function, particularly the cell's ability to produce nitric oxide in response to physiologic and chemical mediator stimuli. At the University of Leipzig in Germany, Hambrecht et al[30] studied the endothelial-mediated increase in femoral artery blood flow to an arterial infusion of acetylcholine (known to stimulate endothelial production of nitric oxide) in 20 patients with chronic CHF before and after a 6-month exercise training or control period. There was a 26% increase in VO_2peak and a 203% increase in acetylcholine-mediated peak blood flow in the training group when compared with the control group. The fact that this response was significantly abolished with a nitric oxide synthase inhibitor confirms that the increase in arterial blood flow that occurs with exercise training is a reflection of increased endothelial cell function.

Another intriguing study investigated the impact of exercise training on tachycardia-induced heart failure in dogs. Wang et al[31] studied 15 dogs before and after 4 weeks of rapid atrial pacing with (study group) and without (control group) simultaneous exercise training. Atrial pacing alone produced the typical hemodynamic changes of CHF, and a reduced endothelium-mediated vasodilator response in both the coronary and femoral circulations. In addition, the investigators documented a decreased expression of the gene for endothelial constitutive nitric oxide synthase (ECNOS). Exercise training preserved normal hemodynamics and normal endothelial-mediated vasodilator function, and sustained a normal gene expression of ECNOS. When the exercise trained dogs were given a nitric oxide synthase inhibitor, the preserved endothelial-mediated responses were abolished and left ventricular end-diastolic pressure elevated, indicating that the exercise training effect was mediated to a substantial degree by increased ECNOS expression.

EXERCISE AND CORONARY HEART DISEASE IN WOMEN

Cardiovascular disease is the leading cause of death and disability in women in the United States. The morbidity and mortality associated with this disease may be largely attributed to risk factors such as hyperlipidemia, hypertension, smoking, diabetes, menopausal status, obesity, and sedentary lifestyle. Until recently, there has been a paucity of data with regard to the cardiovascular benefits of exercise in women. The 1996 United States Surgeon General's report on physical activity has referenced only three epidemiologic studies of the relationship between cardiovascular disease and physical activity in women. In the 3 years since the Surgeon General's report, however, there have been important advances in the investigation of diagnostic testing and in the cardiovascular benefits of exercise and physical activity in women.

Most of the correlation between physical activity and reduced cardiovascular mortality was seen in studies of men, such as the study by Paffenbarger et al of Harvard Alumni.[32] This study showed a reduction in risk of fatal and nonfatal myocardial infarction in men with moderate to vigorous levels of physical activity. Recently, similar relationships between moderate levels of physical activity and cardiovascular mortality in women have been demonstrated. Kushi et al[33] followed 40,417 postmenopausal women for 7 years at the Minnesota School of Public Health, and reported a relative risk reduction in all-cause mortality (range of 24–38%) with increasing frequency of moderate physical activity. These investigators also showed that women who engaged in moderate physical activity at least once a week had a 22% relative risk reduction in cardiovascular disease mortality. In the Nurses Health Study, Manson et al[34] reported a trend (falling just short of statistical significance) showing similar relative risk reduction (range 24–43% from the first to the fourth quintile) in myocardial infarction and stroke with increased walking loads.

Several studies have now looked at the important relationship between frequency and intensity of the exercise prescription with regard to impact on levels of high-density lipoprotein (HDL) cholesterol in women. King et al[35] evaluated the effects of varying intensity and frequency of home and community center exercise programs (high-intensity 3 times/week or low-intensity 5 times/week) in healthy men and women over a 2-year period. Improvements in HDL cholesterol levels were not seen until the second year of participation. Of great interest was the finding that women in the group participating in lower-intensity exercise (who exercised more frequently) had a greater increase in HDL cholesterol levels than the group participation in higher-intensity exercise (who exercised less frequently).

A similar relationship in terms of lag time in improvement in HDL cholesterol levels to exercise was seen in a population of men and women enrolled in a cardiac rehabilitation program. In this 5-year study by Warren et al[36] at the Bowman Grey School of Medicine in North Carolina, there were small improvements in HDL cholesterol levels after the first year, with men increasing their HDL levels by 10% and women by 7%. In the men, HDL cholesterol remained level at the second year and then decreased. In contrast, HDL continued to increase in women; at the 5-year

mark, women showed a 20% improvement over baseline compared with an improvement of only 5% in men.

Improvements in HDL cholesterol are not limited to sedentary individuals who then participate in a regular exercise program. Data from a study of 1,837 women who were participants in the National Runners Health Study[37] showed a linear relationship of distance run per week and levels of HDL cholesterol. Women who ran 64 km per week had substantially higher HDL levels than those who ran 48 km per week.

Exercise ECG stress testing is reported to have lower sensitivity and specificity in women than in men. The false-positive rate of exercise ECG testing is higher in women, which is reflected as a lower specificity. These issues have led to women being routinely referred for exercise imaging studies. A recent study looked at improving the diagnostic and prognostic value of the exercise ECG stress test in women by integrating additional clinical outcome information. Alexander et al[38] evaluated the DTS in 976 women and 2,249 men who underwent stress testing and coronary angiography. The DTS combines ST segment deviation, treadmill time, and exercise-induced angina. The DTS classification performed equally well in both genders with respect to prognostic information.

CONCLUSION

In addition to enhancing survival and reducing symptoms, the treatment goals for cardiovascular disease increasingly reflect a focus on achieving optimal functional status and quality of life. These goals assure an ever-increasing emphasis on evaluating patients during exercise and on treating patients with specific exercise programs. In this regard, as in others, we reflect the statement attributed by Plato to Socrates in the Theaetetus: ". . . and is not bodily habit spoiled by rest and illness, but preserved for a long time by motion and exercise."

REFERENCES

1. Kligfield P, Okin PM, Amelsen O, Borer JS. Evaluation of coronary artery disease by improved method of exercise electrocardiograph: the ST segment/heart rate slope. *Am Heart J* 1986;112:112–115.
2. Okin PM, Kligfield P. Heart rate adjustment of ST segment depression and performance of exercise electrocardiogram: a critical evaluation. *J Am Coll Cardiol* 1995;25:1726–1735.
3. Goldberg N, Schifter D, Butte A, Stein RA. Comparison of ST heart rate analysis and standard ST segment analysis with respect to outcome of exercise thallium 201 imaging. *Am J Cardiol* 1995;76:1097–1098.
4. Okin P, Princa R, Grandits G, et al. Heart rate adjustment of exercise-induced ST segment depression identifies men who benefit from a risk factor reduction program. *Circulation* 1997;96:2899–2904.
5. Mobilia ZG, Zanco P, Desideri A, et al. T wave normalization in infract-related electrocardiographic leads during exercise testing for detection of residual viability: comparison with positron emission tomography. *J Am Coll Cardiol* 1998; 32:75–82.
6. Roger VL, Jacobsen SJ, Pewlilkha PA, Miller TD, Bailery KR, Gersh BJ. Prognostic value of treadmill exercise testing: a population-based study in Olmsted County, Minnesota. *Circulation* 1998;98:2836–2841.
7. Snader E, Marwick T, Pashkow P, et al. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: report of 3,400 patients form a single centre. *J Am Coll Cardiol* 1977;30:641–648.
8. Shaw J, Peterson E, Shaw L, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation* 1998;98:1622–1630.
9. Proclicher V, Ellmann KG, Goldman T, et al, for the Veterans Affairs Cooperative Study in Health Services #016, Quantitative Exercise Testing and Angiography (QUEXTA) Study Group. The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized interpretation, and multivariable prediction. *Ann Intern Med* 1998;128:965–974.
10. Polanczyk CA, Lee TH, Cook EF, Walls R, Wybenya D, Printy-Klein G, et al. Cardiac troponin as a predictor of major cardiac events in emergency department with acute chest pain. *J Am Coll Cardiol* 1998;32:8–14.
11. Parkosh ME, Smars PA, Reeded GS, Zinsmeister AR, Evans RW, Meloy TD, and the Chest Pain Evaluation in the Emergency Room (CHEER) Investigators. A clinical trial of a chest pain observation unit for patients with unstable angina. *N Engl J Med* 1998;339:1882–1888.
12. Urho M, Jaakko K, Sarna A. Koskenvuo M. Relationship of leisure-time physical activity and mortality: the Finnish twin cohort. *JAMA* 1998;279:440–444.
13. Haich SD, Yoshinaga H, Muto T, Sakurai Y. Regular physical activity and coronary risk factors in Japanese men. *Circulation* 1998;97:661–665.
14. Mayer-Davis EJ, D'Agostino R, Karter AJ, Haffner SM, Rewers MJ, Saad M, et al. Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA* 1998;279:669–674.
15. Wei M, Gibons L, Mitchell T, Kampert J, Lee C, Blair S. The association between cardiorespiratory fitness and impaired fasting glucose in type 2 diabetes mellitus in men. *Ann Intern Med* 1999;130:89–96.
16. Beniamini Y, Rubenstien JJ, Zaichkowsky LD, Crim MC. Effects of high-intensity strength training on quality of life parameters in cardiac rehabilitation. *Am J Cardiol* 1997;80:841–846.
17. Ornish D, Brown SI, Scherwitz L, Billings JH, Armstrong WT, Ports TA, et al. Can lifestyle changes reverse coronary heart disease? *Lancet* 1990;336:129–133.
18. Ornish D, Scherwitz L, Billings J, Gould L, Merritt T, Sparler S, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA* 1998;280:2001–2007.
19. Schuler G, Hambrecht R, Schlierf G, Grunze M, Methfessel S, Hauer K, Kubler W. Myocardial perfusion and regression of coronary artery disease in patients on a regimen of instensive physical exercise and low-fat diet. *J Am Coll Cardiol* 1992;19:34–42.
20. Schuler G, Hambrecht R, Schlierf G, Niebauer J, Hauer K, Neumann J, et al. Regular physical exercise and low-fat diet: effects on progression of coronary artery disease. *Circulation* 1992;86:1–11.
21. Hambrecht R, Niebauer J, Marburger C, Grunz M, Kalberer B, Hauer K, et al. Various intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of atherosclerotic lesions. *J Am Coll Cardiol* 1993;22:468–477.
22. Niebauer J, Hambrecht R, Velich T, Hauer K, Marburger C, Kalberer B, et al. Attenuated progression of coronary artery disease after 6 years of multifactoral risk intervention: role of physical exercise. *Circulation* 1997;96:2434–2541.
23. Okita K, Yonezawa K, Nishimima K, Hanada A, Ohtubo M, Tenuro K, et al. Skeletal muscle metabolism limits exercise capacity in patients with chronic heart failure. *Circulation* 1989;98:1886–1891.
24. Myers J, Gullestad L, Vagelos R, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Ann Intern Med* 1998;129:286–293.
25. Naohiko O, Chaitman B, Miller L, et al. Cardiopulmonary exercise testing identifies low risk patients with heart failure and severely impaired exercise capacity considered for heart transplantation. *J Am Coll Cardiol* 1998;31:577–582.
26. Belardinelli R, Georgiou D, Ginston L, et al. Effects of moderate exercise training on thallium uptake and contractile response to low-dose dobutamine of dysfunctional myocardium in patients with ischemic cardiomyopathy. *Circulation* 1998;97:553–661.
27. Jugdutt BO, Michorowski BL, Kappagoda CT. Exercise training after anterior Q wave myocardial infarction: importance of regional left ventricular function and topography. *J Am Coll Cardiol* 1988;12:362–372.
28. Wilson JR, Groves J, Rayos G. Circulatory status and response to cardiac rehabilitation in patients with heart failure. *Circulation* 1996;94:1567–1572.
29. Giannuzi P, Temporelli P, Cirra U, et al. Attenuation of unfavorable remodeling by exercise training in postinfarction patients with left ventricular dysfunction. *Circulation* 1997;96:1790–1797.
30. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation* 1998;98:2709–2715.
31. Wang J, Geng-Hua Y, Knecht M, et al. Physical training alters the pathogenesis of pacing-induced heart failure through endothelium-mediated mechanisms in awake dogs. *Circulation* 1997;96:2683–2692.
32. Paffenberger RS, Hyde RT, Wing AL, Haich C-C. Physical activity, all cause mortality and longevity of college alumni. *N Engl J Med* 1986;314:605–613.

33. Kushi LH, Fee RM, Folsom AR, Mink PJ, et al. Physical activity and mortality in postmenopausal women. *JAMA* 1997;277:1287–1292.
34. Manson JE, Rich-Edwards JW, Colditz GA, Stampfer MJ, et al. The role of walking in the prevention of cardiovascular disease in women. *Circulation* 1995; 94(Suppl II):1–3.
35. King AC, Haskell WL, Young DR, et al. Long-term effects of varying intensities and formats of physical activity on participation rates, fitness and lipoproteins in men and women aged 50–65 years. *Circulation* 1995;91:2596–2604.
36. Warner JC, Brubaker PH, Zhu Y, Morgan TM, et al. Long term (5-year) changes in HDL cholesterol in cardiac rehabilitation patients: do sex differences exist? *Circulation* 1995;92:773–777.
37. Williams PT. High-density lipoprotein cholesterol and other risk factors for coronary heart disease in female runners. *N Engl J Med* 1996;334:1298–1303.
38. Alexander K, Shaw L, Delong ER, et al. Value of exercise treadmill testing in women. *J Am Coll Cardiol* 1998;32:1657–1664.