DEFINING A SET OF PATIENT ATTRIBUTES THAT PREDICT EXERCISE PERFORMANCE OUTCOME FOLLOWING AN EXERCISE TRAINING PROGRAM IN A POPULATION OF CORONARY ARTERY DISEASE PATIENTS

by

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Thesis submitted to the faculty of the

Virginia Polytechnic Institute and State University

in partial fullfillment of the requirements for the degree of

MASTER OF SCIENCE

in

Education

Health/Physical Education

APPROVED:
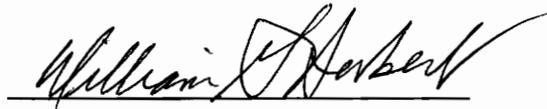
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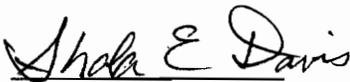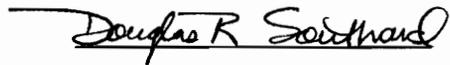
Shala E. Davis   Douglas R. Southard

November 1, 1996

Blacksburg, Virginia

Keywords: Exercise, Cardiac, Training, Outcome, Rehabilitation

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DEFINING PATIENT ATTRIBUTES THAT PREDICT EXERCISE TRAINING OUTCOME IN CARDIAC REHABILITATION PATIENTS

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(ABSTRACT)

The purpose of this study was to evaluate the utility of baseline clinical and graded exercise test (GXT) variables in predicting exercise training outcome in cardiac rehabilitation patients. Data were extracted from the records of 60 cardiac patients who had participated in a community-based exercise program for 5-9 months. Two separate markers of exercise tolerance were used to evaluate training effect: 1) rate-pressure product at a submaximal reference workload of 5 METs (RPP5METs), and 2) estimated peak METs (pkMETs). These two markers of exercise tolerance were found to have a low correlation ($r = -0.29$).

Patients were classified into one of three possible outcome categories for each marker of exercise tolerance, i.e., improvement, no change, or decline. Thresholds for classifying patients into improvement or decline groups were $\pm$ 10% for the RPP5METs marker and $\pm$ 1 MET for the pkMETs marker. Outcome classifications using the RPP5METs marker were as follows: improvement, 37 (62%); no change, 13 (22%); decline, 10 (17%). Use of the pkMETs marker to classify patients into outcome groups yielded: improvement, 45 (75%) ; no change, 15 (25%); with no patients classified in the decline group. Multiple logistic regression was used to identify patient attributes predictive of improvement and decline for each exercise tolerance marker.

Baseline variables were found to yield a model highly predictive of improvement in RPP5METs (correct classification rate = 87%; sensitivity = 92%; specificity = 78%).

The best single predictor of improvement outcome was high baseline RPP5MET values. A model could not be generated to successfully predict decline in exercise tolerance. Baseline variables selected for prediction of improvement outcome, as defined by pkMETs marker, yielded a model with limited utility due to low specificity (correct classification rate = 87%; sensitivity = 96%; specificity = 60%).

Conclusions. A set of baseline clinical and exercise variables were found to successfully predict cardiac patients who improve exercise tolerance through training in a community-based rehabilitation program. Changes in submaximal exercise parameters were more predictable than changes at peak endpoints. Variables used in this study were not successful in predicting patients who manifested a decline in exercise tolerance.

Acknowledgements

The author would like to thank the following individuals for their help in the completion of this project:

My comittee members, Dr. Herbert, Dr. Southard, and Dr. Davis for their continued guidance and support throughout this project.

A special thank you goes to my committee chairman, Dr. Herbert, who spent endless hours offering advice pertaining to study design and reviewing data analysis results, always strivivng to find ways to improve the study. Thank you for your willingness to meet with me at odd times, always listening to new ideas and your patience in dealing with my almost maddening propensity for details.

Chris Calaghan and Robert Reese for their work in designing the database used in this study. Again thanks for your help and willingness to work on the database at night, weekends, and over holidays to get it ready in time to facilitate data storage and retrieval, making such a large set of patient data manageable.

Jeff Ocel for periodically offering advice concerning statistical analysis and study design, and for giving me a place to stay for almost a month while I worked on the design of this study. Most importantly, thank you for being a friend throughout graduate school and serving as the role model of a dedicated professional that influenced my later days as a graduate student.

Scott VanGeluwe for friendship throughout graduate school and a place to stay at Virgina Beach as I searched for additional clinical exercise program data, in the hopes of expanding the patient set for this study.

My parents, Bobby and Patricia Pierson, and sister and brother-in-law Susan and Steve Blanchard, for their continued support throughout my academic career.

And finally, thank you to Lucy Carter, who helped in inummerable ways throughout this project. Without your support, this project simply could not have been completed. Thank you for listening and understanding, and for adding a greater meaning to life. Thanks are not enough!

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Chapter I

Introduction

Since the late 1960's, there has been a decline in mortality from cardiovascular disease in the United States, especially in the elderly. This decline has been attributed to the development of better treatment methods, e.g., non- invasive diagnostic techniques, acute coronary care, cardiovascular drugs, surgical revascularization techniques, thrombolytic drugs, and risk factor modification through lifestyle changes (Levy, 1981). The effects of these advances in care have resulted in an increase in the absolute numbers of patients living with disease (Frye, Higgins, & Beller, 1988). Since prevalence of cardiovascular disease is on the rise, enhancing patient function and teaching patients how to cope with their disease is important. Cardiovascular rehabilitation programs are designed to satisfy these needs, helping patients resume active and productive lives.

The creation of new areas of health care, like cardiac rehabilitation, has been positive but has added to the global cost of care. In order to control costs, third party payers have begun to identify subsets of patients who are eligible for reimbursement of services, depending on their clinical features. To ensure that patients are treated in the most cost effective ways, outcomes-based research needs to be conducted. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and Medicare, along with the Commission on Accreditation of Rehabilitation Facilities have mandated that health care programs evaluate patient outcomes resulting from the services that they provide (Drews, Ohnemus, & Endsley, 1995).

The outcomes that have traditionally been evaluated in cardiac rehabilitation are morbidity and mortality, increase in functional capacity and return to work. Functional capacity changes have been particularly appealing to study because the responses are easily quantifiable and do not require the study of excessively large populations over many years. As a result, the functional capacity improvement often observed in patients participating in exercise programs after a cardiac event or revascularization surgery has

been well documented. The AACVPR guidelines for cardiac rehabilitation programs reports an 11% to 56% increase in $\dot{V}O_2$max after exercise training for 3-6 months, in post-myocardial infarction patients. Coronary artery bypass surgery patients have been reported to achieve a 14% to 66% increase in functional capacity after 3-6 months of exercise training (Drews et al., 1995).

The evaluation of a training effect following participation in a cardiac rehabilitation program is accomplished by administering serial graded exercise tests (GXTs). Hemodynamic and oxygen consumption values collected during GXTs performed before and after exercise training are used to assess improvement in exercise tolerance. The same test protocol is usually used before and after training, however sometimes protocols differing in work rate increments are used. Oxygen consumption ($\dot{V}O_2$), heart rate, and systolic blood pressure all have linear responses with respect to work rate increase (Fletcher, Froelicher, Hartley, Haskell, & Pollock, 1990). Training effect is usually evaluated by comparing symptom limited peak oxygen consumption (peak $\dot{V}O_2$) but can also be evaluated using heart rate at matched submaximal workloads. Rate-pressure product is an estimate of myocardial oxygen demand that is calculated by multiplying heart rate by systolic blood pressure. This index may also be used to examine training adaptations at matched submaximal work rates. A trained person will demonstrate a higher peak $\dot{V}O_2$, and a lower heart rate and rate-pressure product at any matched submaximal work rate (Fletcher et al., 1990).

While peak $\dot{V}O_2$ is most commonly used to evaluate exercise tolerance changes, McInnis and Balady have reported that it is not a reliable parameter if protocols with differing work rate increments are used. It was hypothesized that the additional time required to perform protocols with slower work rate increments may cause earlier fatigue or earlier decision by the patient to stop exercising. However, heart rate and rate-pressure product at matched submaximal workloads are reliable parameters when protocols with differing work rate increments are used (McInnis & Balady, 1994). Submaximal exercise parameters are better suited for evaluating changes in exercise

tolerance in situations where the investigator either has no control over the choice of exercise test protocols or he cannot be sure that test endpoint criteria was uniformly applied, i.e., in retrospective type outcomes-based research.

The use of submaximal exercise parameters to evaluate training effect also allows investigators to examine changes in metabolic demand at exercise levels that are meaningful to activities of daily living. Patients with coronary artery disease have little need to increase their ability to perform exercise at maximal exertion. Instead, benefits enjoyed by these patients after an exercise training program can be attributed to the fact that a given submaximal workload performed after training is accomplished at a lower relative percentage of peak $\dot{V}O_2$ than before training. Since the patient is working at a lower percentage of his maximal capacity, heart rate and systolic blood pressure responses are lower, subsequently lowering rate pressure product (RPP) and myocardial oxygen demand ($M\dot{V}O_2$). This improved cardiovascular efficiency allows patients with angina and other ischemic manifestations to perform higher workloads after training before eliciting ischemic threshold responses (Redwood, Rosing, & Epstein, 1972).

Statement of the Problem

Not all patients who participate in an aerobic exercise training program demonstrate an improvement in exercise tolerance after training (Gamble & Froelicher, 1982; Froelicher, Jensen, Genter, Sullivan, McKirnan, Witztum, Sharf, Strong, & Ashburn, 1984). Exercise training programs can also be expensive and are associated with a certain amount of risk (Van Camp & Peterson, 1986). If a set of patient attributes can be identified to distinguish between patients who improve exercise tolerance through training and those that do not, then this set of variables would be very useful clinically. The set of attributes could be used to predict the likelihood of improving exercise tolerance in new patients being considered for entry into an exercise rehabilitation program. The practitioner would then be able to weigh the likelihood of desirable benefits against the patient time, money, effort, and risk inherent in exercise training

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programs. For patients found to have a low likelihood of improving exercise tolerance through training, treatment protocols could be redesigned to focus on other more attainable goals, which could be achieved at a lower risk to the patient and at a lower cost.

Significance of the Study

When trying to evaluate exercise training outcomes in the typical cardiac rehabilitation program, there are usually several factors that complicate the interpretation of the data. Many of these factors are present when peak exercise parameters are used to evaluate a training effect. Since few programs have access to gas exchange technology, peak METs must be estimated from treadmill speed and grade. When dealing with cardiac populations, however, this practice yields overpredicted MET levels which clouds the interpretation of changes in exercise capacity that occur over the training period. (Sullivan & McKirnan, 1984) Also, physicians may not use consistant test termination criteria between the baseline and post-training GXTs, further complicating interpretation of changes in exercise capacity. Another problem with peak endpoints is that patients may give a sub-optimal effort on one or both GXTs. Also, Hammond, Kelly, Froelicher, and Pewen have shown that patients who undergo serial exercise tests exhibit a learning response and may increase peak treadmill time and estimated METs without increasing measured oxygen consumption. (Hammond, Kelly, Froelicher, & Pewen, 1985)

McInnis and Balady have shown submaximal exercise parameters to be more reproducible than peak parameters when serial exercise tests are performed using protocols differing in work-rate increments (McInnis & Balady, 1994). It is possible that different baseline and post-training exercise test protocols will be used on patients in a typical rehabilitation program. Thus it appears that submaximal markers of exercise tolerance may be a better way to evaluate the effects of training than the more traditional peak parameters. If different protocols are used for baseline and post-training exercise

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tests, however, it may be impossible to compare heart rate or rate-pressure product responses at a standard reference load for all patients.

The present study presents a new approach to evaluating submaximal exercise parameters at a standard level of exercise demand. The results obtained with this approach are compared to results obtained with the more traditional peak exercise parameter, peak METs. This new approach to evaluating exercise tolerance changes over a training period gives cardiac rehabilitation professionals a better tool with which to quantify the training effect achieved by patients in their programs.

Research Objectives

1. To define a set of patient attributes, available prior to program entry, that would enable practitioners to predict the likelihood of improved exercise tolerance through exercise training, in patients with diagnosed coronary artery disease.

2. To define a set of patient attributes, available prior to program entry, that would enable cardiac rehabilitation professionals to predict the likelihood of a decline in exercise tolerance over a period of exercise training, in patients with coronary artery disease.

3. To develop a process for the study of exercise training outcomes that would enable cardiac rehabilitation professionals to evaluate their program's effectiveness in increasing the exercise tolerance of patients, using existing patient files.

Research Hypotheses

The following hypotheses were identified for this study:

Ho1: No set of patient attributes can be identified using variables from clinical and exercise domains, to provide a means for predicting those who manifest an improvement in exercise tolerance after exercise training, in patients with diagnosed coronary artery disease.

Ho2: No set of patient attributes can be identified using variables from clinical and exercise domains, to provide a means for predicting those who manifest a decline in exercise tolerance after exercise training, in patients with diagnosed coronary artery disease.

Ho3: There are will be no difference in the ability to predict exercise training outcome using submaximal vs. maximal exercise tolerance markers.

Delimitations

The following delimitations were imposed upon the investigation:

1. The study was confined to the records in the files of patients who participated in the rehabilitation program at the Virginia Tech Cardiac and Intervention Center between January, 1977, and September, 1995.

2. The study was confined to patients with recent myocardial infarction, coronary revascularization procedure, physician diagnosed angina, or angiographically confirmed coronary artery disease.

3. The study was confined to patients who had recorded data for at least three stages of a symptom-limited graded exercise test at the time of program entry and another test within the time frame of 5-8 months after beginning supervised exercise.

4. This study was confined to patients who had linear rate-pressure product responses with respect to estimated metabolic demand during both pre-training and post-training graded exercise tests (correlation of $r \geq 0.90$ using least squares linear regression).

5. The study was confined to patients tested on a motor-driven treadmill.

6. The study was confined to patients who did not have changes in prescription of medications that would potentially alter their hemodynamic responses or symptoms during the time period between the two tests.

7. The data for each subject were confined to information available in the patient files only.

8. The study was confined to patients who had a documented minimum of 70% attendance at the exercise sessions during the time period between the two tests.

Limitations

The following factors were viewed as important constraints that limited the interpretation of the data:

1. The possibility that some inconsistency occurred with respect to different technicians recording exercise blood pressure and heart rate during the graded exercise tests.

2. Some pre- and post-training treadmill testing protocols differed in beginning load and load increments.

3. Exercise test termination criteria may not have been uniformly applied, as different physicians supervised the tests.

4. The possibility that some inconsistency occurred in the tendency for the patients to lean on the treadmill handrails for balance and support during the two tests, thus artificially increasing or decreasing their performance.

5. Only patients with clinically stable disease were evaluated in this study. Unstable patients likely had changes in medications, experienced an event or underwent a procedure during the six month training period, thereby being excluded from the study.

6. The possibility that extremely low fit patients were excluded from the study due to their inability to complete 3 exercise stages during the graded exercise tests.

7. The extent to which findings of this study are generalzable to external groups of patients or subjects is uncertain.

Basic Assumptions

The following assumptions were made by the investigator:

1. All graded exercise tests were administered by trained technicians with physician supervision.
2. Exercise values were measured and recorded accurately during the graded exercise tests.
3. All graded exercise tests were terminated at a symptom-limited endpoint.
4. All equipment was calibrated at the time of each test.

Definitions and Symbols

The following are definitions and symbols for key words used in this study:

Graded Exercise Test (GXT) - a multistage test that determines a person's physiological responses to different intensities of exercise and/or the person's peak aerobic capacity.

Angina - chest pain caused by a relative deficiency of oxygen supply to the heart.

Diastolic Blood Pressure(DBP) - the least pressure (mmHg) in the arterial vascular system during the cardiac cycle, coinciding with the period of relaxation of the ventricles. Determined by the auscultation of the occluded brachial artery during a slow release of cuff pressure, DBP corresponds to the fourth phase Korotkoff sound (point where the sound of blood flow through the artery becomes muffled).

ECG - electrocardiogram.

Metabolic Equivalent (MET) - unit used to estimate the metabolic cost of physical activity. One MET is the resting metabolic rate and equals the uptake of 3.5 ml of oxygen per kilogram of body weight per minute.

Myocardial Oxygen Consumption ($M\dot{V}O_2$) - the rate at which oxygen is consumed by the heart.

Myocardial Oxygen Demand - the rate at which oxygen must be delivered to the heart to meet its oxygen consumption needs and avoid ischemia; determinants are heart rate, state of contractility, and ventricular wall tension (left ventricular pressure and diastolic volume).

Oxygen Consumption ($\dot{V}O_2$) - the rate at which oxygen is used by the body in aerobic metabolism; usually expressed in L/min or ml/kg/min.

Rate-Pressure Product (RPP) - product of heart rate and systolic blood pressure; serves as an index of myocardial oxygen demand. Units of measure are expressed as mmHg X beats/min X 10^2.

Rating of Perceived Exertion (RPE) - a subjective numerical rating given by the patient in reference to the perceived effort associated with performance of an exercise task. The current study used the Borg 6-20 rating scale.

ST Segment - the area of ECG tracing beginning at the J point and terminating at the onset of the T wave.

Systolic Blood Pressure(SBP) - peak pressure (mmHg) in the arterial vascular system during the cardiac cycle, coinciding with ventricular contraction. Determined by the auscultation of the occluded brachial artery during a slow release of cuff pressure, SBP corresponds to the first phase Korotkoff sound (the initial sound of blood flow through the artery).

Summary

There is a continuing need for cardiac rehabilitation programs to define important, attainable, and quantifiable outcomes and then identify the antecedents that can help guide decisions on patient selection and treatment approach, yielding higher success rates while conserving health care resources. A new approach to evaluating exercise tolerance changes that result from rehabilitative exercise is presented in this study that will allow cardiac rehabilitation professionals to more readily assess the effects of their programs. The results obtained with this new assessment method were compared to results obtained using the more traditional peak METs parameter. Finally, baseline patient attributes that are predictive of training outcome are appealing and, thus an attempt was made to define attribute sets to predict improvement vs. no improvement and decline vs. no decline outcomes.

Chapter II
Review of Literature

Introduction

This review begins with a brief description of the manifestations of coronary artery disease (CAD), a definition of cardiac rehabilitation services, and the patients who are candidates for these services. The review progresses to briefly discuss future directions in health care and the need for outcomes-based research in the cardiac rehabilitation field. The physiologic response to an acute dynamic exercise bout is then described in both healthy adults and patients with CAD. This section is included to help the reader better understand the body's integrated response to both an exercise bout and a graded exercise test, contrasting "normal" responses to those typically observed in patients with CAD. Guidelines for physical training regimines typically used to elicit a training effect in participants of cardiac rehabilitation programs is then described, along with the various indices used to quantify exercise tolerance in these patients.

Physiologic adaptations to chronic dynamic exercise training in healthy adults and CAD patients are then discussed. This section will help the reader better understand why the "training effect" occurs and what variables might conceptually be influential when predicting training success or failure in CAD populations. The next section reviews research papers that document evidence of a training effect in subset populations of CAD patients. The final section of this review presents previous research that has attempted to predict exercise tolerance changes in cardiac rehabilitation patients and to identify patient characteristics that discriminate between those who manifest an exercise tolerance improvement or decline as a result of training. Following the discussion of these studies, research articles are reviewed that examine the influence of individual variables on the achievement of a training effect in CAD patients.

Coronary Artery Disease and Rehabilitation Programs

Coronary artery disease is a chronic, progressively worsening disorder, and is the leading cause of morbidity and mortality in the United States. The manifestations of CAD are angina pectoris, myocardial infarction, silent myocardial ischemia, or sudden death. More than 1.5 million Americans suffer a myocardial infarction each year, and through careful monitoring of cardiac rhythm and prompt treatment of primary arrhythmias, almost 1 million of these patients survive. In addition, about 670,000 CAD patients undergo coronary revascularization procedures each year and are eligible for rehabilitation services as are about 7 million persons who are estimated to have stable angina pectoris. In total, over 8 million CAD patients are candidates for cardiac rehabilitation services each year, but only 11-38% currently enroll in such programs (Wenger, Froelicher, & Smith 1995).

A definition of cardiac rehabilitation services, written by the U.S. Public Health Service, is as follows: "Cardiac rehabilitation services are comprehensive, long-term programs involving medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling. These programs are designed to limit the physiologic and psychological effects of cardiac illness, reduce the risk for sudden death or reinfarction, control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance the psychosocial and vocational status of selected patients. The services are in three phases beginning during hospitalization, followed by a supervised ambulatory outpatient program lasting 3-6 months, and continuing in a lifetime maintenance stage in which physical fitness and risk factor reduction are accomplished in a minimally supervised or unsupervised setting" (Feigenbaum & Carter, 1988).

Changes and Future Directions in Health Care

In a recent article, Froelicher, Herbert, Myers, and Ribisl discussed ways that cardiac rehabilitation is currently being influenced by changes in health care delivery

(Froelicher, Herbert, Myers, & Ribisl, 1996). In this article, the authors state that cardiac rehabilitation professionals must begin to document the effects of their programs by using outcome assessment. Rather than answer to hospital directors, rehabilitation professionals must relate to executives responsible for managing primary care. Outcomes-based research needs to be conducted to answer questions concerning which patients really need and benefit from particular components of rehabilitation programs. Guidelines need to be developed concerning which patients are eligible for particular services, based on outcomes research and cost efficacy analysis. These guidelines will be important to the survival of cardiac rehabilitation programs in an era of diminishing financial resources for health care.

Need For Outcomes-Based Research in Cardiac Rehabilitation

Since financial resources are becoming more scarce for health care programs such as cardiac rehabilitation, and because there is a health risk that is inherent in any exercise program for heart disease patients, outcomes-based research needs to be conducted to determine which patients benefit from these services. The following sections discuss relevant research studies that quantify the costs and risks of cardiac rehabilitation programs.

Costs of Cardiac Rehabilitation

The annual costs of supervised cardiac rehabilitation amount to $160 million to $240 million (Wittels, Hay, & Gotto, 1990). However, these services may result in lower subsequent medical costs for participants, more than offsetting program costs. Economic evaluations of cardiac rehabilitation have been conducted in several studies (Ades, Huang, & Weaver, 1992; Picard, Dennis, Schwartz, Ahn, Kraemer, Berger, Blumberg, Heller, Lew, & DeBusk, 1989; Levin, Perk, & Hedback, 1991; Oldridge, Furlong, Feeny, Torrance, Guyatt, Crowe, & Jones, 1993; Bondestam, Breikss, & Hartford, 1995). In these studies, patients participating in rehabilitation programs were shown to have earlier return to work, decreased outpatient medical care costs, lower rehospitalization rates,

fewer days of rehospitalization, and fewer visits to emergency departments. The reduced medical costs in patients participating in rehabilitation programs more than offset program expense. Thus, based on these studies, multifactorial cardiac rehabilitation appears to be a cost effective intervention when considering the overall CAD patient population. Further research needs to be done to determine if there are certain subgroups of CAD patients who do not receive these benefits from rehabilitation programs.

Risks of Exercise Training in Cardiac Rehabilitation Patients

Two surveys have been conducted to determine the safety of exercise training in CAD populations. Haskell conducted a survey in 1978, which encompassed 30 cardiac rehabilitation programs, 13,500 patients during 1.6 million hours for exercise training. The results reported a total of 61 major cardiovascular complications, including 50 cardiac arrests. This yielded an incidence of 1 arrest per 33,000 patient hours and 1 death per 120,000 patient hours (Haskell, 1978). More recently, Van Camp and Peterson conducted a survey of 167 outpatient cardiac rehabilitation programs in the United States which encompassed 51,000 patients for 2.3 million hours of exercise. The researchers reported incidence rates of 1 nonfatal myocardial infarction per 293,990 patient hours of exercise and 1 cardiac arrest per 111,996 patient hours of exercise. This yielded a cardiovascular event every 81,101 patient hours of exercise (Van Camp & Peterson, 1986). The low rate of exercise induced cardiovascular events in these studies suggests that cardiac rehabilitation is a safe intervention for CAD populations.

Summary

The above studies suggest that cardiac rehabilitation programs are cost effective and safe for heart disease patients as a whole. Further research needs to be conducted to determine if there are certain subsets of cardiac patients who have less favorable results, i.e., less benefit with higher treatment costs or higher cardiovascular event rates.

While cardiac rehabilitation is usually organized as a multifaceted program, the current study dealt only with the effects of the exercise training component on exercise tolerance. Therefore, the following sections will cover only topics related to this domain.

Physiologic Response to a Dynamic Exercise Bout

In order to better understand the physiologic adaptations that occur through exercise training in the majority of patients and fail to occur in a smaller subset, it is necessary to review the physiologic response to a single exercise bout. The following sections describe the physiologic response to exercise in the healthy adult and contrasts this against the abnormal exercise response observed in CAD patients with or without a history of myocardial infarction.

Response in Healthy Adults

During a dynamic exercise bout, energy metabolism is increased in the active skeletal muscles. The cardiorespiratory system must perform the following functions for the activity to be maintained: (1) deliver substrates such as oxygen, glucose, and free fatty acids to the active tissues at rates that match their utilization (2) remove carbon dioxide, lactic acid, and other metabolic end-products at rates that match their production; (3) increase blood flow to the skin to promote dissipation of metabolically produced heat to the environment; (4) transport regulatory substances such as hormones from sites of production to target tissues (Durstine, Pate, & Branch, 1993).

Exercise elicits many changes in the body to meet the demands necessary for continued activity. This is an integrated response to exercise that involves many organ systems. Some of the changes that occur with exercise are outlined below.

Oxygen Consumption

The amount of oxygen consumed by the body ($\dot{V}O_2$) for aerobic energy production is defined by the Fick equation:

$$\dot{V}O_2 = (Q)(a\text{-}vO_2\text{diff})$$

where:

$\dot{V}O_2$ = oxygen consumed by the body in liters per minute

Q = cardiac output in liters per minute

$$a\text{-}vO_2diff = \text{arterial - venous oxygen difference in \%volume}$$

The quantity of oxygen consumed by the body during exercise depends on the work rate. Initiation of exercise or an increase in work rate will cause $\dot{V}O_2$ to rapidly increase, and at work rates below the lactate threshold, a steady state is achieved within 3 minutes. Below AT, steady state $\dot{V}O_2$ has a linear relationship to work rate, with the slope of this relationship ($\Delta\dot{V}O_2/\Delta WR$) equal to approximately 10 ml/min/watt for healthy people (Hansen 1987). At work rates above the lactate threshold, however, a steady state will not be attained due to several compensatory mechanisms that become involved with greater reliance on anaerobic energy production.

Cardiac Output

During exercise, oxygen delivery is facilitated by an increase in cardiac output, which is the product of heart rate and stroke volume. At the onset of a constant work rate, cardiac output increases quickly at first, and then more gradually until a steady state is attained.

Heart Rate

Heart rate is controlled by intrinsic factors of the heart as well as extrinsic neural and hormonal factors. The sinoatrial node normally paces the heart and is innervated by both sympathetic and parasympathetic nerves that originate in the cardioregulatory center of the medulla in the brain. At rest, the parasympathetic vagus nerve releases acetylcholine to slow heart rate which in sedentary people is, on average, approximately 72 beats·min^{-1}. During exercise, the parasympathetic stimulation is withdrawn and the heart is stimulated by sympathetic nerves that increase the rate and force of contractions. Catecholamines (epinepherine and norepinephrine) are released from the adrenal medulla during exercise and circulated to the heart via the blood. These hormones augment the increase in rate and force of heart contractions. Also, through a response termed the "Bainbridge Reflex", heart rate tends to increase due to temperature and sinoatrial stretch. All of the above mechanisms work in concert to increase heart rate, and thus cardiac output during exercise.

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Stroke Volume

Stroke volume is the amount of blood pumped out of the heart with each contraction and is regulated primarily by the Frank-Starling mechanism. The Frank-Starling mechanism is based on the fact that an enhanced rate of venous return to the heart stretches the ventricles during diastole, causing the force of the following contraction to be greater. The Starling law of the heart states that the further the myocardial fibers are stretched up to an optimal point, the greater the force of the following contraction. Beyond this point however, further stretch of the fibers will diminish the force of the contraction.

Other factors affecting stroke volume are sympathetic stimulation and circulating catecholamines. During graded exercise, stroke volume increases progressively until a work rate that elicits 40-50% of $\dot{V}O_2$max, after which only small increases occur with increasing oxygen demand (Astrand, Cuddy, Saltin, & Stenberg, 1964). During maximal exercise, stroke volume increases to approximately twice its resting value (Ekblom & Hermansen, 1968).

Ejection Fraction

Ejection fraction is the amount of blood pumped out of the heart per contraction expressed as a percentage of end diastolic volume (stroke volume/end diastolic volume· 100%). In healthy adults at rest, the normal ejection fraction is approximately 60%. During exercise, sympathetic stimulation and circulating catecholamines have a positive inotropic effect on the heart, increasing ejection fraction to approximately 90% during maximal efforts (Guyton & Hall, 1996).

Blood Pressure

Systolic blood pressure (SBP) is the pressure inside the arterial vessel during ventricular systole, and is normally about 120 mmHg at rest. During aerobic exercise, SBP increases as a function of exercise intensity (Astrand et al., 1965).

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Diastolic blood pressure (DBP) is the pressure inside the arterial vessel when the heart is between contractions and is normally about 80 mmHg at rest. During aerobic exercise in healthy adults, DBP either remains unchanged or decreases slightly due to peripheral vasodilation (Ekelund & Holmgren, 1967).

Arteriovenous Oxygen Difference

Arteriovenous oxygen difference (a-vO$_2$diff) is the difference between the oxygen content of arterial blood and the oxygen content of venous blood. This is a reflection of the amount of oxygen extracted from the blood by the cells of the body. The oxygen carrying capacity of the arteries is normally about 20 ml O$_2$/100ml of blood and is affected by:(1) hemoglobin concentration and (2) percent of oxyhemoglobin saturation. The average a-vO$_2$diff at rest is about 5 mL O$_2 \cdot 100$ mL^{-1} blood, or about 20% of oxygen is extracted by the tissues. During exercise, a-vO$_2$diff increases as a function of work rate to maximal values of about 16 mL O$_2 \cdot 100$ mL^{-1} blood, or about 85% extraction of O$_2$ (Guyton & Hall, 1996).

Blood Flow Redistribution

During exercise, blood flow is redistributed away from splanchnic vascular beds and toward the active muscle tissue and skin, thus increasing O$_2$ delivery to metabolically active tissue and facilitating heat dissipation. The mechanisms responsible for this phenomenon are: (1) sympathetic stimulation of alpha adrenergic receptors by norepinephrine resulting in vasoconstriction (2) stimulation of the beta adrenergic receptors by epinephrine resulting in vasodilation, (3) local increases of metabolites such as lactate, adenosine, H$^+$ and K$^+$, which stimulate local vascular bed receptors, resulting in vasodilation (Durstine, Pate & Branch, 1993). Resting blood flow to skeletal muscles is approximately 3-4 ml/100gm muscle/min. This flow increases to approximately 50-80 ml/100gm muscle/min during maximal exercise (Guyton & Hall, 1996).

Anaerobic Threshold

The onset of blood lactic acid accumulation (OBLA) is the exercise intensity at which the body begins to derive energy from anaerobic metabolism. The VO$_2$ at OBLA

is variable in healthy people, approximately 50-60% of $\dot{V}O_2max$ in sedentary individuals and considerably higher for those who are aerobically fit. In sedentary middle-aged people, this corresponds to about 4 METs (Wasserman et al., 1975) or the energy needs required to walk briskly on a level surface (Ainsworth et al., 1992). In physically active persons, OBLA occurs around 10 METs (Wasserman et al., 1975), equivalent of running at a pace of 6 miles per hour on a level surface (Ainsworth et al., 1992). The pattern of increase in lactate concentration is the same for sedentary or aerobically fit individuals once the threshold exercise intensity has been surpassed (Wasserman et al., 1975).

Ventilation

Minute ventilation is the volume of air passing through the pulmonary system in 1 minute. Minute ventilation increases with increasing intensity of exercise. This response is linear between ventilation and work rate until approximately 50% $\dot{V}O_2max$, where minute ventilation increases more quickly than work rate, the relationship becoming curvilinear. Minute ventilation is equal to the product of tidal volume and breathing frequency. At low intensity exercise, increases in both tidal volume and breathing frequency contribute to increased ventilation. During higher intensity exercise, breathing frequency alone is responsible for increases in minute ventilation (Koyal, 1976).

Pulmonary ventilation during maximal exercise for the healthy person is approximately 100-110 liters/min, while maximal breathing capacity is 150-170 liters/min (Guyton et al., 1996). Thus, the respiratory system is not normally the limiting factor in delivery of oxygen to working muscles during maximal aerobic exercise.

Myocardial Oxygen Demand

During exercise, the myocardial oxygen demand increases in response to the increased work performed by the heart. This oxygen requirement is dependent on the heart rate, myocardial wall tension, and the contractile state of the myocardial fibers. Myocardial wall tension is a function of intraventricular pressure, end-diastolic volume, and is inversely related to ventricular wall thickness (Sonnenblick, Ross, & Braunwald,

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1968). The product of heart rate and systolic blood pressure, known as the rate-pressure product has been shown to be a reliable index of myocardial oxygen demand (Kitamura, Jorgensen, & Gobel, 1972). This indicates that heart size changes little during exercise and state of contractility increases in parallel with HR and SBP (Clausen, 1976).

Since oxygen is almost maximally extracted from the blood of the coronary circulation under resting conditions (a-v O_2diff $\approx 70\%$), the increased demand for oxygen during exercise is met almost exclusively by increasing coronary blood flow. Coronary blood flow depends on coronary perfusion pressure (difference between arterial pressure and the pressure in either the right atrium or left ventricle during diastole), lumen diameter, and resistance to flow, offered mainly by the arterioles (Braunwald, 1988). Under resting conditions, blood flow required by the heart is about 0.7-0.8 ml/min/gm of myocardium. During exercise, this flow requirement is increased as a function of exercise intensity until, during maximal exercise, flow may be 3-4 times greater than under resting conditions (Guyton et al., 1996).

The vascular smooth muscle of the large and small vessels of the coronary circulation are regulated by different mechanisms, and the small arteries and arterioles exert the major influence on blood flow. A combination of the following mechanisms is responsible for increased coronary blood flow: (1) compounds and mechanical forces, such as acetylcholine, ATP, ADP, bradykinin, histamine, epinephrine, and vascular wall shear stress, elicit release of endothelial-derived relaxing factor (EDRF) from coronary endothelial cells, producing an increase in cyclic GMP, and resulting in epicardial coronary vasodilation; (2) reduced resistance to flow by coronary arteriolar dilation, mediated by increased concentration of vasoactive metabolic end products, e.g. adenosine, prostaglandins, K^+, H^+, CO_2 and possibly effects of reduced O_2 on vascular smooth muscle; (3) small effect of neural influences on vascular smooth muscle mediated by interaction of (a)sympathetic stimulation of beta-adrenergic receptors causing a vasodilation influence on the coronary arteries, (b) sympathetic stimulation of alpha receptors causing a vasoconstrictive action and (c) parasympathetic stimulation of

cholinergic receptors causing a vasodilatory influence on the coronary vasculature (Braunwald & Sobel, 1988; Balady et al., 1992; Guyton et al., 1996; and Vanhoutte 1989).

Myocardial oxygen consumption ($M\dot{V}O_2$) is a function of relative exercise intensity, and therefore not directly related to external workload performed during exercise. This fact has implications for benefits derived from exercise training in symptomatic CAD populations.

Response in CAD Patients

Patients with CAD may have responses to exercise that may be similar to or very different from healthy individuals, depending upon: (1) the severity of disease and (2) the extent of myocardial damage in those patients with a history of infarction. The following sections present information pertaining to the following topics: significance of atherosclerotic stenosis, abnormal exercise responses and impaired functional status in CAD patients.

Significance of Epicardial Coronary Artery Stenosis

An atherosclerotic narrowing, in one or more of the epicardial coronary arteries, may cause the heart to have an imbalance of oxygen supply and demand during exercise. This imbalance is due to the resulting reduction in epicardial coronary vessel radius. The determinants of fluid flow in a tube are described by the Poiseuille law:

$$\text{Flow} = \pi \, \Delta P \, r^4 / \, 8 \, \eta \, l$$

where ΔP is the pressure difference between the ends of the vessel, r is the radius of the vessel, l is the length of the vessel, and η is the viscosity of the blood (≈ 0.035 poise). Due to vessel branching, distensibility, and turbulence, this equation is not directly applicable to the coronary circulation. However, this equation is still useful for the concept of vessel radius effects on blood flow. According to this equation, flow is proportional to the fourth power of the vessel lumen radius (Guyton et al., 1996). Physiologically, there is no significant reduction in blood flow until the coronary arterial

lumen is reduced by 50% of its diameter, which is equivalent to a 75% reduction in cross sectional area (Roberts, 1992).

Not only does a stenosis decrease the lumen radius of a vessel, but it may also lead to epicardial coronary vasoconstriction during exercise. There is evidence that diseased endothelial cells do not release EDRF during exercise (Griffith Lewis, Newby, & Henderson, 1988). As a result, sympathetic stimulation of coronary alpha receptors, which dominate in number over coronary beta receptors in some people, may mediate a vasoconstrictory response and further reduce myocardial perfusion (Griffith et al., 1988; Guyton et al., 1996).

In summary, the significance of a given stenosis is influenced by several factors, including: (1) the degree and length of luminal narrowing, (2) the dynamic properties of the stenosis, (3) the number and size of collateral vessels, (4) the autoregulatory capacity of the distal vascular beds, (5) the magnitude of myocardial mass supplied by the narrowed vessel (Herzil, Leutwyler, & Krayenbuhl, 1989).

Abnormal Exercise Responses in CAD Patients Without History of MI

Patients with significant coronary artery narrowing develop myocardial ischemia during exercise. An ischemic episode begins with an oxygen supply and demand imbalance, which initiates a series of pathophysiological events, which in turn result in myocardial dysfunction and, sometimes, angina pectoris. The temporal sequence of events, which has been termed the ischemic cascade, is as follows: (1) increased myocardial oxygen demand beyond the oxygen delivery capacity of the coronary circulation; (2) diminished left ventricular diastolic compliance; (3) reduced systolic contractility resulting in reduced ejection fraction and impaired cardiac output; (4) increased left ventricular end-diastolic pressure, possibly resulting in dyspnea; (5) ST segment shifts recorded on ECG; and (6) angina pectoris in some patients (Nesto & Kowalchuk, 1987).

The mechanism by which ischemia causes this cascade of events, ultimately resulting in reduction of ventricular performance has not been clearly defined. During an

ischemic episode, the action potential in cardiac muscle is decreased with respect to amplitude and upstroke velocity, and the duration of the plateau phase is shortened which may signify a reduced inward current of Ca^{2+} ions. It is possible that ischemia interferes with the contraction process of the heart by reducing the release of Ca^{2+} ions from the sarcolemma, the sarcoplasmic reticulum (SR), or both. Release of Ca^{2+} from the sarcolemma is needed to trigger the mass release of Ca^{2+} ions from the SR, which in turn bind to troponin-c on the actin filament, initiating contraction. A reduction in pH, as occurs during ischemia, may decrease SR sensitivity to Ca^{2+} released from sarcolema. Also, increased intracellular H^+ concentration may allow H^+ ions to compete with Ca^{2+} ions for troponin binding sites, thus interfering with contractile mechanisms. It is also possible that small reductions of ATP in critical areas, i.e. Ca^{2+} binding and release sites, contribute to cardiac dysfunction (Braunwald et al., 1988).

Rate-pressure product has been shown to be a reliable indicator of myocardial demand (Kitamura, Jorgensen, & Gobel, 1972). In a patient who is clinically stable, it has been demonstrated that angina or ST depression occurs at a similar RPP during repeated bouts of upright dynamic leg exercise days or even months apart (Smokler, MacAlpin, Alvaro, & Kattus, 1973). In situations in which left ventricular volume differs, however, ischemic manifestations may occur at different RPP thresholds. In supine exercise, where left ventricular volume is increased, ischemia occurs at a lower RPP (Thadani, West, Mathew, & Parker, 1977). During dynamic arm exercise, in which left ventricular volume is decreased, ischemia tends to occur at a higher RPP. (Clausen & Trap-Jensen, 1970).

Individuals with mild coronary artery disease may have normal exercise capacities and may only manifest ECG ST segment abnormalities at high workloads (Wasserman et al., 1994). Patients with more severe CAD, however, will manifest abnormal responses at relatively low exercise demand levels. These abnormal exercise response patterns are discussed below.

When the myocardial oxygen demand is increased beyond its supply, ejection fraction and stroke volume decrease due to regional wall motion abnormalities of the ischemic portion of the left ventricular wall. A compensatory increase in heart rate is elicited to partially offset the diminished cardiac output. Therefore, an abnormally steep HR-$\dot{V}O_2$ relationship is observed at work rates above the ischemic threshold. Also, oxygen pulse (O_2 pulse), which is an index of the efficiency of oxygen transport from the heart to the working muscles, is abnormal in ischemic patients. O_2 pulse is calculated from the formula:

$$O_2 \text{ Pulse} = \dot{V}O_2 / HR \text{, which equals (stroke volume) x (a-vO}_2\text{diff)}$$

Since the HR-$\dot{V}O_2$ relationship is abnormally steep in ischemic patients, maximal O_2 pulse will be lower than in healthy adults.

Because the compensatory increase in heart rate does not completely offset the diminished stroke volume during exercise, the impaired central pump cannot deliver enough oxygen to the working muscles, resulting in an early reliance on anaerobic energy production. This results in an early onset of blood lactate accumulation and a low $\dot{V}O_2$max due to fatigue. The anaerobic threshold may occur at energy demands as low as 2 METs, corresponding to self care activities, in patients with low symptom limited VO_2max values (Wasserman et al. 1975).

An index of reliance on aerobic pathways for energy production, the $\Delta\dot{V}O_2/\Delta WR$ ratio may be normal (10 ml/min/watt) in CAD patients at low workloads, but may decrease sharply at the point of ischemia onset, and continue to decrease as work rate is increased toward maximum. A decrease in this ratio, accompanied by ECG evidence of ischemia, e.g., ≥ 0.1 mV ST segment shift, reflects an impaired central pump and increasing reliance on anaerobic energy production (Wasserman et al., 1994).

Symptoms experienced by CAD patients during exercise may be angina pectoris, dyspnea caused by increased end-diastolic left ventricular pressure, and vertigo caused by circulatory insufficiency. Signs of ischemia that may be present include pallor and complex or increasing ventricular ectopy.

Abnormal Exercise Responses in CAD Patients With a History of MI

Almost all myocardial infarctions involve a coronary athersclerotic plaque with a superimposed thrombus, that reduces blood flow, and often totally occludes the vessel. Below a certain critical level of blood flow, myocardial cells develop ischemic injury, which if severe and prolonged, may result in tissue necrosis.

The amount of myocardial necrosis resulting from an MI determines to a large extent the degree of resting and exercise ventricular dysfunction, and is predictive of exercise capacity at 3-4 months post event (Carter & Amundsen, 1977). Patients with **mild** ventricular damage, characterized as losing $\leq$ 10% of left ventricular mass, have a normal or slightly reduced ejection fraction. Left ventricular end diastolic pressure and cardiac index are both also near normal, with a slightly depressed stroke volume index. In these patients, compensatory mechanisms are adequate to maintain function without the need for cardiac glycoside medications. These patients generally have no clinically apparent limitation in cardiac function and frequently have normal exercise capacities (Folta & Metzger, 1989).

Patients with a **moderate** amount of myocardial necrosis, characterized by loss of 10-25% of left ventricular mass, have a significantly reduced ejection fraction i.e. 0.43 $\pm$ 0.1 units with normal values being 0.52-0.60 units. Many of these patients have demonstrated early mild heart failure with an accompanying elevated left ventricular end diastolic pressure of around 20 mmHg, with normal values being around 12 mmHg. Also, stroke volume index and cardiac index are both significantly depressed. Compensatory mechanisms are usually adequate to maintain function, however if ischemia, dyspnea, or hypotension occur during exercise as a result of an inability to increase ejection fraction, cardiac medication may be required to augment ventricular function (Folta et al. 1989).

Severe ventricular damage is characterized by 25-40% necrosis of left ventricular mass. A patient in this category will normally have a markedly reduced ejection fraction (EF = .30 units), along with reduced stroke volume index and cardiac index. Left ventricular end diastolic pressure is significantly elevated, usually to around 27 mmHg. The heart is unable to compensate for the severe damage, and congestive heart failure is frequently observed in these patients. In spite of cardiac glycoside medications, ischemia, dyspnea, and hypotension are often observed at rest and during exercise. Most of these patients are unable to increase ejection fraction with exercise. As a compensatory mechanism to maintain mean arterial blood pressure, peripheral resistance is often increased in these patients, thus creating greater afterload on the heart, and further compromising pump function (Vanhoutte 1983, Folta et al., 1989).

Patients surviving a **very severe** infarction, involving > 40% of left ventricular mass, have a poor prognosis and are usually candidates for cardiac transplantation. These patients have severely depressed ejection fractions, usually around $0.19 \pm .07$ units. These patients have greatly elevated left ventricular end diastolic volume, with significantly reduced stroke volume index, cardiac index, and mean arterial blood pressure. These patients are maintained on cardiac glycoside medications and have severely limited functional capacities (Folta et al., 1989).

The degree to which function is compromised by intermediate percentages of necrosis is variable and may be affected by the infarction site within the left ventricle. Angiographic and hemodynamic evaluations of patients suffering MIs have indicated that the anterior wall of the left ventricle contributes more to contractile effectiveness than the inferior wall (Lesch & Sonnenblick, 1978). This suggests that with the same extent of tissue necrosis, less ventricular dysfunction will result from an inferior located infarction than from an infarction located on the anterior wall of the left ventricle.

Since an MI causes necrosis of part of the ventricular wall, this necrotic part cannot contract normally and wall motion abnormalities result. Angiographic techniques have been useful in defining the effects of segmental wall motion abnormalities in

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patients after an MI. A spectrum of segmental wall motion disorders have been defined and are listed below in increasing order of detriment to myocardial function: (1) a hypokinetic segment, in which contractile activity is present but is reduced significantly; (2) an akinetic segment, characterized by a lack of systolic contraction, but the segment does not bulge paradoxically during systole; (3) a dyskinetic segment, which fails to contract during systole, and bulges paradoxically during systole, but does not extend beyond the border of the cardiac silhouette during diastole; (4) a ventricular aneurysm, in which the segment bulges paradoxically during systole and diastole, due to a thinning of the myocardial wall (Lesch et al., 1978).

In addition to wall motion abnormalities due to necrotic tissue, patients with an MI may have residual ischemia during exercise, caused by inadequate blood flow to surviving tissue. Patients with residual ischemia will have additional ventricular impairment as mentioned in the preceding section, at work rates above the ischemic threshold.

Patients with mild damage to the left ventricle may have normal resting hemodynamics. In these patients, cardiac output for any submaximal workload is usually within the normal range, as is arteriovenous oxygen difference. Normal cardiac output values may be maintained, however, by a lower stroke volume and a higher heart rate (Haskell & Durstine, 1993).

Patients with moderate or greater damage to myocardial tissue may have resting systolic dysfunction, characterized by reduced ejection fraction and stroke volume, possibly leading to congestive heart failure. During exercise, increased heart rate does not compensate for the further decrease in stroke volume, resulting in a reduced cardiac output for a given $\dot{V}O_2$. In an attempt to maintain arterial blood pressure, there is a compensatory increase in total peripheral resistance (TPR), instead of the reduction in TPR normally observed in healthy patients during dynamic exercise. The exercise systolic blood pressure response is blunted as the heart becomes more dysfunctional due to increasing TPR. Only a small portion of cardiac output is delivered to the exercising

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muscles because resistance to blood flow in the exercising limbs remains abnormally high, causing increased reliance on anaerobic energy production (Balady et al., 1992; Wasserman et al., 1994). In addition, these patients have a time delay in circulatory adjustments to exercise, and therefore the time required for $\dot{V}O_2$ and its components to meet the demands for a given workload is increased (Auchincloss, Gilbert, Kuppinger, Peppi, & Teperow-Putter, 1979). All these factors combine to cause a low anaerobic threshold, with an exaggerated ventilatory response to exercise, as the body attempts to buffer lactic acid by "blowing off " CO_2. $\dot{V}O_2$max is reduced in these patients due to early muscular fatigue caused by the early onset of anaerobisis (Balady et al., 1992; Wasserman et al., 1994).

In summary, the interaction of several factors define the amount of functional impairment that results from an MI. These factors include: (1) extent of tissue necrosis from the infarction, (2) amount of pre-existing necrosis and scar tissue from any previous infarction (3) the anatomic site of the infarction (4) the residual ischemic dysfunction persisting in the myocardium that survives the acute episode (5) extent of athersclerotic disease in the remainder of the coronary circulation (Lesch et al., 1978).

Exercise Training For Cardiac Patients

Exercise training has been defined as maintaining a regular habit of exercise at levels greater than those usually performed (Froelicher, Myers, Follansbee, & Labovitz, 1987). The features that must be considered when devising an aerobic exercise training program are exercise mode, intensity, frequency, and duration. The mode of exercise should involve large muscle groups, such as walking, bicycling, running, and swimming. The activity should be performed at least 3 times per week, with exercise sessions spread throughout the week. Exercise intensity and duration are related, so that approximately the same benefits may be derived from a longer duration with lower intensity or a short duration with a higher intensity. A threshold of intensity required for improvement in functional capacity likely exists, however the exact value is not known and probably

varies between individuals. Minimal requirements for intensity and duration seem to be at least 50% of $\dot{V}O_2$max and 20 minutes per session respectively (Hartley, Haskell, & Pollock, 1990). An optimal training program for increasing exercise tolerance while minimizing the risk of injury would be to train 3 sessions per week for 30-60 minutes per session at an intensity of 60-80% $\dot{V}O_2$max (Froelicher et al., 1993). Proper training intensity may be monitored most effectively by heart rate, and a specific training heart rate range may be developed using the Karvonen technique. A rating of perceived exertion of 13-14 seems to correspond with an intensity appropriate for achieving a training effect, and may be used to prescribe exercise for patients receiving beta blocker medications. An optimal training heart rate in patients with angina seems to be 5-10 beats under the heart rate required to elicit symptoms (Froelicher et al. 1993; Fletcher et al. 1990).

Quantification of Exercise Tolerance and Assessment of Improvement Following Training

The following sections describe some of the various indices developed to quantify exercise tolerance and the reliability of different indices when differing exercise test protocols are used to measure exercise tolerance.

Quantification of Exercise Tolerance

The effect of exercise training may be evaluated through serial exercise testing. Many indices have been developed to quantify exercise capacity or tolerance for exercise. Some of the exercise parameters frequently used as indices to quantify physical conditioning are: $\dot{V}O_2$max or peak $\dot{V}O_2$, total exercise test time, submaximal heart rate or rate-pressure product response to exercise, and ability to sustain an aerobic activity at a submaximal workload for a certain period of time.

Reliability of Peak vs. Submaximal Exercise Parameters in Serial Exercise Tests

McInnis and Balady conducted a study to examine the reliability of exercise parameters commonly used to assess training effect, when different exercise test

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protocols are used. Thirty two patients with coronary artery disease performed both a standard Bruce and a modified Bruce protocol in random order, one hour apart. The investigators reported submaximal exercise parameters (heart rate, rate-pressure product, and $\dot{V}O_2$) to be reliable between the two tests. Exercise parameters measured at peak exercise were unreliable between the tests, as peak $\dot{V}O_2$ was significantly higher for patients when performing the standard Bruce protocol than when the modified Bruce protocol was used (McInnis & Balady, 1994). This difference was attributed to the additional time required to perform the modified Bruce protocol, which may have caused earlier patient fatigue or earlier decision by the patient to stop exercising. This study indicates that when serial exercise tests are performed using different protocols, a difference in rate-pressure product at matched submaximal workloads is most likely due to a training effect. Conversely, improvements observed in peak $\dot{V}O_2$ are, at least in part, due to inherent differences in responses between the different protocols. Therefore, in the current study, where pre and post training GXTs were sometimes performed using different protocols, submaximal exercise parameters provide a more reliable way to assess training effect than peak exercise data.

Summary

Many different indices have been developed to quantify exercise tolerance, i.e, peak $\dot{V}O_2$, total exercise test time, submaximal heart rate or rate-pressure product response to exercise, and ability to sustain an aerobic activity at a submaximal workload for a certain period of time. McInnis and Balady found submaximal exercise parameters to be more reliable than maximal exercise parameters when using differing treadmill testing protocols pre and post training to assess changes in exercise tolerance.

Physiological Adaptations to Chronic Dynamic Exercise

The following sections describe the physiologic adaptations to chronic dynamic exercise in healthy adults and notes the changes that take place in function centrally, in

the autonomic nervous system, and peripherally. A following section describes the adaptations that may take place in CAD patients who undergo exercise training.

Adaptations in Healthy Adults

Chronic aerobic exercise causes a complex interaction of cardiovascular, skeletal muscle, and neurohumoral adaptations that yield what is commonly known as the "training effect". These adaptations enhance the transport of oxygen to the working muscles and augment the energy production capabilities of the mitochondria. Exercise training results in an increase in $\dot{V}O_2$max. The magnitude of this increase depends on the initial level of training and on the intensity, frequency, and duration of exercise. In most studies, the increase has been in the range of 10-20% after 3-6 months of training. Increases in the range of 37-44% have been reported if training is sufficiently prolonged and intense (Holloszy, 1977). RPP at a given submaximal workload is not directly related to external work, but is instead related to the percentage of maximal exercise capacity. Therefore, a lower RPP, and hence $M\dot{V}O_2$, is needed to maintain a given submaximal workload after training. Other physiologic manifestations of training are lower blood lactate concentration and slower glycogen depletion at matched submaximal workloads after training (Holloszy, 1977).

Changes in Central Function

Certain changes have been revealed to occur in central pump functioning in healthy adults following exercise training. The most important physiological adaptation of the central pump is an increase in stroke volume and a concomitant decrease in heart rate under resting and exercise conditions (Hartley, Grimby, Kibom, Nilsson, Astrand, Bjure, Ekblom, & Saltin, 1969; Saltin, Blomqvist, Mitchell, Johnson, Wildenthal, & Chapman, 1968). Cardiac output is therefore unchanged at rest and during submaximal exercise, but is increased under maximal exercise conditions (Hartley et al., 1969). Oxygen delivery to working muscles is augmented and therefore a greater exercise capacity may be achieved. As a result of a lowered heart rate, cardiac output is

maintained at rest and during submaximal exercise in a more efficient way with respect to myocardial oxygen demand.

The mechanisms contributing to the reduction in heart rate and increase in stroke volume with exercise training are not clearly defined. After short term training, the increase in stroke volume can be attributed, in part, to an increase in blood volume, thereby increasing preload and augmenting stroke volume via the Frank-Starling mechanism (Rerych Scholz, Sabiston, & Jones, 1980). Heart rate is probably attenuated as a result of reduced sympathetic stimulation (Fletcher et al., 1990). Thus more ventricular diastolic filling time increases prestretch of cardiac myofibrils and adds to the augmentation of stroke volume via the Frank-Starling mechanism.

Prolonged exercise training has been shown to result in cardiac morphological changes. The morphological changes that occur as a result of exercise are age related, i.e. they definitely occur in younger individuals, but may not occur in older people (Froelicher et al., 1993). Adaptations in heart structure that have been observed to occur in athletes who are subjected to high rates of venous return during dynamic exercise training are:(1) increased left ventricular dimension with associated increase in left ventricular volume, (2)increased left ventricular wall thickness, and (3) increase in heart mass (Maron, 1986; Graettinger, 1984; Longhurst, Kelly, Gonyea, & Mitchell, 1980). In animal studies, increases in coronary artery size and myocardial capillary to fiber ratio have been shown to occur. It is unknown whether these changes take place in humans (Froelicher et al., 1993). It is doubtful that rate of shortening and force of myocardial fibers are increased at a given preload as a result of aerobic exercise training in humans, although augmentation of myocardial contractility has been shown in animals after training (Scheuer, 1973). In humans, ejection fraction at rest and during exercise after prolonged training is unchanged or slightly decreased (Colan, Sanders, & Borrow, 1987; Fizman, Frank, & Ben-Ari, 1990; Rerych Scholz, Sabiston, & Jones, 1980).

Autonomic Nervous System Changes

Ordway et al. demonstrated that intact cardiac nerves are necessary for training induced bradycardia in dogs, which suggests that central autonomic outflow is important to this adaptation (Ordway, Charles, Randall, Billman, & Wekstein, 1982). Under resting conditions, increased parasympathetic tone is likely responsible for training induced bradycardia (Ekstom, 1974). Blood and urinary catecholamine levels have been shown to be decreased during submaximal exercise at matched workloads after training (Hartley, Mason, Hogan, Jones, Kotchen, Mougey, Wherry, Pennington, & Rickets, 1972). This change is attributed to a reduction in sympathetic stimulation and contributes to the bradycardia observed at matched submaximal workloads. This bradycardia during submaximal exercise only occurs when the trained limbs are exercised, and is not seen when untrained limbs are exercised. Thus local adaptations must be important in initiating this response through some neural or chemical signal (Clausen, Trap-Jensen, & Lassen, 1970).

The reduced sympathetic outflow during submaximal exercise affects blood flow distribution and total peripheral resistance (TPR). At any given submaximal workload, sympathetic mediated vasoconstriction of vessels to inactive tissue is less, thus lowering TPR and afterload on the heart. As a result, less blood is directed to the working muscles, which compensate by more efficient oxygen extraction. During maximal exercise, greater blood flow is delivered to the working muscles than before training, allowing for increased oxygen utilization (Clausen, 1976).

Peripheral Changes

Several changes in skeletal muscle occur in response to a training program. These changes include increases in oxidative enzyme concentration, mitochondria number, capillary density, myoglobin concentration, muscle glycogen storage, and adaptation of muscle type IIA fibers, becoming similar to type I fibers in oxidative properties (Holloszy, 1977). These changes are responsible for the greater oxygen extraction from blood, and increase the a-vO_2diff. Approximately 50% of the increase in

$\dot{V}O_2$max obtained by training in healthy, sedentary young people is due to this increased a-vO_2diff (Clausen, 1976).

In addition to changes in skeletal muscle, changes in blood have been found to occur as a result of exercise training. A progressive fall in blood viscosity and an improved red blood cell deformability have been observed, which could improve flow (Ernst, 1987). Also, plasma volume expands, increasing total blood volume. This results in a slight decrease in hematocrit (Eichner, 1987).

Summary

The specific adaptations responsible for the training effect in young, healthy people may include the following: (1) changes in parasympathetic and sympathetic tone resulting in effects on the cardiovascular system (2) changes in heart size and volume (3) skeletal muscle changes (myoglobin, mitochondrial number, capillary density, mitochondrial enzymes) (4) alteration in fuel metabolism (decrease in lactate production at submaximal workloads) (5) changes in blood rheology (decreased blood and plasma viscosity, red blood cell aggregability and increase in RBC filterability). These changes work together to alter other physiologic parameters such as distribution of cardiac output during submaximal exercise (Balady and Weiner, 1992).

Adaptations in CAD Patients

Improvement in exercise capacity as a result of exercise training has been well documented in CAD patients (Fletcher, Cantwell, & Watt, 1971; Froelicher et al. 1984). Perhaps a more important consequence of training is that heart rate and possibly systolic blood pressure are reduced during exercise at any submaximal reference load, thus reducing RPP, an index of myocardial oxygen demand (May and Nagle, 1984). This benefit is derived from the fact that when maximal exercise capacity is increased, any submaximal reference workload is performed at a lower percentage of maximal capacity. Reduction in myocardial oxygen demand at a submaximal reference load is especially important in symptomatic patients, increasing the physical exertion that they are able to perform before the onset of angina.

Due to the limitations of the diseased myocardium, the functional improvement observed in CAD patients after training has been attributed mainly to increased arteriovenous oxygen difference resulting from adaptations in the peripheral circulation (Detry, Rousseau, Vandenbrouke, Kusumi, Brasseur & Bruce, 1971). Several studies have found peripheral changes but no improvement in cardiac output and stroke volume following exercise training, supporting this theory of augmentation of exercise performance only through peripheral adaptations in CAD patients (Costill, Branam, Moore, Sparks, & Turner, 1974; Ferguson, Petitclerc, Choquette, Chanitois, Gautherier, Huot, Allard, Jankowski, & Campeau, 1974; Franklin, Besseghini, & Golden, 1978). In addition, the decrease in RPP during submaximal exercise after short term training has been observed in some studies only when trained limbs are exercised, suggesting that peripheral adaptations are responsible (Thompson, Culliane, Lazarus, & Carleton, 1981). Scientific evidence of changes in the oxidative capacity in skeletal muscles lend support to this theory. Mitochondrial enzymes of oxidative metabolism have been shown to have increased activity after training in CAD patients (Ferguson et al. 1982). A recent study has shown a reduction in phosphocreatine depletion during exercise in trained muscles, indicating a greater oxidative capacity as a result of training in post MI patients (Cottin, Walker, Rouhier-Marcer, Cohen, Louis, Didier, Casillas, Wolf, & Brunotte, 1996). Some studies, however, have found evidence of central adaptations in CAD patients trained at high intensities (Hagberg, Ehsani, & Holloszy, 1983; Ehsani, Biello, Schultz, Sobel, & Holloszy, 1986; Martin, Heath, Coyle, Bloomfield, Holloszy, & Ehsani, 1984). A selection bias is possible in these studies in that the patients were able to train at these high intensities.

A meta-analysis was conducted by LeMura et al. in 1990 to uncover discriminating characteristics of studies that reported peripheral and central adaptations in CAD patients. This analysis found that investigators reporting central adaptations used more intense training programs (80% $\dot{V}O_2$max) than those reporting peripheral adaptations only (73.5% $\dot{V}O_2$max). This difference was significant with a $p< 0.05$. The

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remaining components of the exercise prescription, ie, mode, frequency and duration of exercise, did not account for differences in the type of adaptation achieved. The authors suggest the following recommendations to future researchers in this area to further clarify the mechanisms responsible for functional capacity changes in CAD patients: (1) stratify patients according to location and extent of occlusion in the epicardial coronary arteries; (2) stratify patients according to extent and location of MI; (3) compare training responses between patients following CABG, MI, and those not having experienced a cardiac procedure or event; (4) compare effects of interval vs. continuous training (LeMura, Duvillard, & Bacharach, 1990).

Summary

Patients with CAD mainly benefit from exercise training programs by manifesting a lowered heart rate and subsequently lower RPP at any matched submaximal workload after training. This adaptation allows the cardiovascular system to operate more efficiently during normal activities of daily living. It is generally thought that these benefits are achieved through peripheral adaptations, however certain select patients may be able to obtain central adaptations as well.

Evidence of Training Effect in CAD Populations

The following sections review exercise training studies that have been conducted on subsets of CAD patients. The subsets include post-MI, post-CABG, angina pectoris, asymptomatic with diagnosed CAD, and patients with severely depressed left ventricular function. The final section reviews the effects of exercise training on submaximal exercise parameters in CAD patients.

Post MI Patients

The effect of exercise training on post MI patients has been studied in many randomized, controlled trials. These studies have found that post MI patients who participate in exercise training programs exhibit improved exercise tolerance when

compared to baseline measurements and control groups. A few of these studies are outlined below.

Debusk et al. studied the effect of exercise training on exercise tolerance in 70 patients following uncomplicated MI; 28 undertook supervised exercise training, 12 exercised at home, and 30 were placed in a no exercise control group. The supervised group exercised for 1 hour, 3 times per week, for 8 weeks at an intensity of 70-80% maximal baseline exercise test heart rate. The home exercise group trained for 30 minutes, 7 days per week, at 70-80% maximal baseline exercise test heart rate. The percentage increase in functional capacity was 53%, 41%, and 34% for the supervised exercise, home exercise, and control groups respectfully. There was a significant difference between both exercise groups vs. control group, but the difference between exercise groups was not significant (DeBusk, Houston, Haskell, Fry, & Parker, 1979).

Stern et al. studied the effect of exercise training or group counseling in 91 patients post MI. Patients were randomized to the following groups: 31 patients participated in group counseling, 38 patients undertook exercise training, and 22 patients were assigned to a control group. The exercise group trained 3 times per week, for 12 weeks, at an intensity of 85% maximal baseline exercise test heart rate. Follow-up exercise testing was done at 3, 6, and 12 months. A significant difference in exercise tolerance was reported at 3 and 6 months for the exercise group compared to the other 2 groups. No difference was reported between any of the groups at the 12 month follow-up point. This study emphasizes the importance of continued training in maintaining the exercise tolerance benefits that may be gained from a short term training program (Stern, Gorman, & Kaslow, 1983).

Hung et al. examined the effects of exercise training on exercise tolerance in 53 patients following an uncomplicated MI in a controlled, randomized study. Twenty three patients took part in the exercise training program, exercising on a cycle ergometer for 30 minutes/session, 5 times a week, for 11 weeks, at an intensity of 70-85% maximal baseline exercise test heart rate. At follow-up at 26 weeks there was a significant

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increase in exercise tolerance in the exercise group vs. the control group (Hung, Gordon, Houston, Haskell, Goris, & Debusk, 1984).

Roman et al. studied the effect of exercise training in a population of post MI patients in an outpatient rehabilitation center. Patients were randomly assigned to either an exercise group (193 patients) or to a control group (100 patients). The exercise group performed aerobic exercise for 30 minutes per session, 3 times per week, at 70% maximal baseline exercise test heart rate for 42 months. Exercise tests conducted at 6 and 12 months revealed a significant increase in peak oxygen consumption for the exercise group vs. control group (Roman, Gutierrez, Luksic, Chavez, Camuzzi, Villalon, et al. 1983).

Post CABG Patients

Exercise training programs have been shown to be effective in improving exercise tolerance in patients following coronary revascularization procedures. A few studies presenting evidence of this are outlined below.

Foster et al. studied the effects of exercise training in a population of post CABG patients. Twenty eight patients were randomly assigned to either an exercise group or a control group. The exercise group performed aerobic activity 3 times per week, for 50-60 minutes per session, at an intensity of 50-70% heart rate reserve, for 24 weeks. Foster reported a significant increase in exercise capacity for the intervention group vs. the control group (Foster, Pollock, Anholm, Squires, Ward, & Dymond, et al. 1984).

Engblom et al. studied the effect of exercise training, diet advice and psychological therapy in 171 men who were 6-8 weeks post CABG surgery. Of these, 93 patients were randomly assigned to an intervention group and 78 to a control group. Patients in the intervention group performed aerobic activity for 1 hour per day for 3 weeks at 70% maximal baseline exercise test heart rate. Engblom reported a significant increase in exercise capacity in the intervention group vs. the control group at 6 and 12 months (Engblom, Hietanen, Hamalainen, Kallio, Inberg, & Knuts, 1992).

Patients with Angina Pectoris

Patients with exertional symptoms of angina pectoris have been shown to improve exercise tolerance after participating in exercise training programs. Patients with angina have consistently been able to achieve a higher $\dot{V}O_2$ before the onset of symptoms after exercise training.

Smith et al. conducted a study of the effect of a multidiscipline rehabilitation program on 50 patients with diffuse CAD and disabling angina. The severity of disease in this group was as follows: 3 patients with 1 vessel disease, 10 with 2 vessel disease and 36 with 3 vessel or left main disease. Of this group, 13 patients had exertional angina on initial treadmill test. All patients underwent an 8 week exercise training program consisting of aerobic activities for 1 hour, 5 times per week at an intensity of 70% of maximal heart rate on initial exercise test or 70% of heart rate that elicited 0.1 mV ST segment shift. At follow-up, Kent reported significant increases in GXT exercise time, maximal estimated $\dot{V}O_2$max, and RPP at maximal exercise for the group as a whole. In subgroup analysis, the 13 patients with angina were reported to have a significant time to onset of symptoms. The 12 patients with diagnostic segment shifts were reported to have a higher RPP at onset of 0.1 mV ST segment shift (Smith, Layton, Newmark, & Diethrich, 1987).

Ferguson et al. studied the effects of exercise training on 26 CAD patients with a history of stable angina for at least 6 months. Ten patients had a history of MI at least six months prior to the study, but none had a history of CABG surgery. All patients participated in the exercise training program, which consisted of cycle ergometry for 1 hour, 3 times per week, for 6 months at an individually prescribed intensity based on anginal threshold. Ferguson reported a significant (41%) increase in symptom-limited exercise capacity, along with significantly lower heart rate and systolic blood pressure at a matched submaximal work load. Other significant findings included an increase in skeletal muscle enzymes, increase in area of type I and II muscle fibers, and a decrease in

submaximal plasma catecholamines (Ferguson, Taylor, Côté, Charlebois, Dinelle, Péronnet, Champlain, & Bourassa, 1982).

Nolewajka et al. conducted an exercise training study in 20 post infarction patients. Out of the ten subjects assigned to the exercise group, 4 had angina on the initial treadmill test, and of the 10 patients assigned to the control group, 6 had angina on the initial GXT. The exercise group performed aerobic activity 5 days a week for 1 hour per session at an intensity of 60-70% of maximal heart rate on baseline exercise test. The control group played volleyball twice a week. In a subgroup analysis of the angina patients, the exercise group significantly increased treadmill time to the onset of symptoms, with RPP at angina onset unchanged. The control group experienced no change in exercise time to angina onset or anginal double product threshold (Nolewajka, Kostuk, Rechnitzer, & Cunningham, 1979).

Redwood et al. conducted a 6 week exercise training study with 7 CAD patients with exertional angina. Exercise sessions were begun by giving the patient a sublingual nitroglycerin tablet and then having him exercise on a bicycle ergometer with 20 watt increases every 3 minutes, until angina occurred. After a 15 minute rest period, the exercise protocol was repeated. Patients performed this exercise session twice daily, 5 days a week. At the 6 week follow-up point, Redwood reported a significant increase in symptom limited $\dot{V}O_2$ peak and time to onset of angina. A triple product at any matched submaximal workload was less after training, and a higher triple product was achieved at onset of angina, suggesting improved myocardial perfusion (Redwood, Rosing, & Epstein, 1972).

Asymptomatic CAD Patients

Keyser et al. studied the effect of exercise training on 10 CAD patients with recent MI or CABG, but no presentation of exertional ischemia or ST segment displacement. The patients trained on air-braked upper and lower body ergometers for 30 minutes 3 times per week for 12 weeks at an intensity of 70-85% of the HR reserve. Statistical increases were seen in peak RPP and peak SBP, along with statistical

decreases in RPP and HR at rest and at matched submaximal workloads (Keyser, Leutholtz, Moberg, & Wendt, 1991).

Patients with Severely Depressed Left Ventricular Function

Patients who have suffered a large MI and have a severely depressed left ventricular function have historically been assumed to have limited functional capabilities, limited ability to achieve a training effect, and are at excessive risks for exercise related cardiovascular events. These patients have generally been excluded from supervised exercise programs. However, it is conceivable that these patients may obtain peripheral adaptations to exercise that might increase there functional status. Conn et al. conducted a study on 10 post MI patients who had ejection fractions of less than 27 percent at rest. These patients trained for 35-45 minutes a day, 5 days a week. For the first month, the patients exercised at a pulse rate less than 100 beats/min, and afterward exercised for brief periods at 70-80% of symptom limited heart rate. Follow-up ranged from 4 to 37 months (mean 12.7), at which time maximal exercise capacity improved for six patients, while four patients showed essentially no change. Overall, there was a significant increase in exercise capacity after training. Oxygen pulse improved almost uniformly in the ten patients from a mean baseline value of 12.8 ml/beat to 15.7 ml/beat, a significant improvement at the $p < 0.01$ level. There was no exercise related morbidity or mortality for the patients in the study (Conn, Williams, & Wallace, 1982).

Sullivan et al. studied 12 patients with chronic heart failure attributed to left ventricular dysfunction, who underwent 4-6 months of exercise training. The mean ejection fraction of this group was $24 \pm 10\%$ with a range of 9-33%. After an initial 3 week period of increasing intensity and duration, patients exercised 3-5 times per week, for 1 hour per session at an intensity of 75% of peak $\dot{V}O_2$max. At follow-up, heart rate at rest and during submaximal exercise were significantly decreased, along with a 23% increase in peak oxygen consumption. Training induced several peripheral adaptations, while maximal cardiac output tended to increase, but did not reach significant levels.

The finding that blood lactate levels were decreased during submaximal exercise without an improvement in cardiac output suggests that peripheral adaptations are important in determining the onset of lactate accumulation, and may influence exercise tolerance independently of central adaptations in CHF patients (Sullivan, Higginbotham, & Cobb, 1988).

These studies suggest that selected patients with severely depressed left ventricular function can safely participate in an exercise training program and achieve cardiovascular benefits.

Effects on Submaximal Exercise Parameters in CAD Patients

Exercise training has consistently been shown to improve exercise tolerance in CAD patients. These changes may be evaluated using peak $\dot{V}O_2$ data or heart rate and rate-pressure product values at matched submaximal workloads. Since it has been shown that submaximal exercise parameters are more reliable than peak values in serial tests when different protocols are used (McInnis and Balady 1994), the current study used rate-pressure product at a matched submaximal workload to evaluate training effect. Therefore, the studies reviewed in this section used submaximal exercise parameters to evaluate training effect in CAD populations.

Froelicher et al. investigated the effects of exercise training on 146 men with stable CHD in a controlled, randomized study of cardiac rehabilitation. The men in the exercise group performed supervised aerobic exercise 45 minutes 3 times a week at a hospital outpatient rehabilitation center. Froelicher reported a significant increase in maximal oxygen consumption as well as significant decreases in rest and submaximal heart rate at 1 year follow-up for exercise group vs. the control group (Froelicher, Jensen, Genter, et al. 1984).

May and Nagle conducted a study with 121 CAD patients; 71 patients were assigned to an outpatient exercise group and 74 to a control group. The exercise group performed aerobic exercise 2-3 times per week for 50-75 minutes per session at 70-80% maximal baseline exercise test heart rate. At 10-12 month follow-up, May reported a

significant increase in maximal oxygen consumption and a significant decrease in submaximal rate-pressure product for the exercise group vs. the control group (May and Nagle, 1984).

Mayou et al. studied the effect of exercise training or advice in 115 patients within 4 weeks post MI. The patients were randomly assigned to the following groups: 43 patients assigned to an exercise group, 35 patients assigned to an advice only group, and 37 patients assigned to a control group. The exercise group trained twice per week for 4 weeks. At follow-up at 3 months, there was a significant improvement in submaximal exercise tolerance for the exercise group vs. the other groups (Mayou, MacMahon, Seight, & Florencio, 1981).

Wihelmsen, Sanne, Elmfeldt et al., conducted a controlled randomized trial of exercise training in 315 patients 3 months post myocardial infarction. The exercise group trained 3.5 hours a week at a hospital outpatient center at an intensity of 80% baseline maximal exercise test heart rate with supplemental home cycle ergometry for 9 months. At 1 year follow-up, a significant decrease in submaximal heart rate vs. baseline was reported for the intervention group only. No significant changes were reported at higher workloads (Wihelmsen, Sanne, Elmfeldt et al. 1975).

Coats, Adamopoulos, Meyer et al. 1990 studied the effects of exercise training in 11 patients with stable heart failure and a diminished left ventricular systolic ejection fraction (mean 0.19). A crossover study design was used in which patients exercised for eight weeks on a cycle ergometer 5 days per week for 20 minutes at 70-80% baseline maximal exercise test heart rate with random crossover for eight weeks of no training. Coats reported a significant decrease in submaximal rate-pressure product, with an increase in peak oxygen uptake and cycle exercise time after the training phase, compared to the non-training phase.

Giannuzzi, Tavazzi, Temporelli et al 1993 studied the effects of exercise training in a group of 103 patients (51 exercise group, 52 control group) 4-6 weeks following a first anterior Q-wave MI. The exercise intervention consisted of 2 months of outpatient

supervised cycle ergometry for 30 minutes 3 times per week at 80% maximal baseline exercise test heart rate. This was followed by 4 months of home exercise training 3 times per week at 80% intensity on cycle ergometer plus 30 minutes of daily walking. At six month follow-up, Giannuzzi reported a significant decrease in rate-pressure product and venous lactate concentration at same workload between the intervention vs. control groups. Also reported was a significant increase in maximal work capacity and increased lactate threshold in intervention group vs. baseline.

Summary

The above sections present evidence that patients who have angina pectoris or severely depressed left ventricular function and/or are post-MI, post CABG, or have asymptomatic CAD can benefit from exercise training. The above studies also present evidence that exercise values for rate-pressure product and heart rate at matched submaximal workloads are decreased after an exercise training program in patients with CAD.

Prediction of Training Effect in CAD Populations

Several investigators have attempted to find characteristics that discriminate between patients who achieve a training effect and those who do not, in a population of cardiac rehabilitation participants. Hammond et al. studied characteristics of 59 men with CAD who underwent 1 year of supervised aerobic exercise training. In this population, 64% had prior Q wave infarction, 34% had angina on treadmill testing, and 42% had prior CABG surgery. The patients exercised for 45 minutes, 3 times per week. Initial exercise intensity was set at 60% of estimated $\dot{V}O_2$max and was progressively increased to 85% estimated $\dot{V}O_2$max by the eighth week of training. There was reported to be a considerable amount of variability in training exercise intensity because patients were not equally able or motivated to exercise. At time of follow-up, the researchers used 5 different indexes to measure a training effect. The percent of patients showing at least 5% improvement in training response for these indexes were: change in heart rate at rest , 44%; change in heart rate at submaximal workload, 58%; change in estimated

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$\dot{V}O_2$max, 66%; change in measured $\dot{V}O_2$max, 52%; and change in thallium ischemia, 44%. The researchers retrospectively examined initial clinical descriptors and exercise test results to determine whether any of these features could predict a patient's response to exercise training. Poor correlations were found between the initial clinical descriptors and the indexes of training effect. Patients who were in the poorest state of fitness showed the most improvement with training. None of the other initial features from the history and physical exam, treadmill study, or radionuclide studies was a good predictor of training outcome (Hammond, Kelly, Froelicher, & Pewen, 1985).

Fioretti et al. conducted a study in 141 post infarction patients who underwent exercise training for 3 months. The patients exercised twice a week for 90 minutes. An exercise session consisted of warm-ups, jogging at 60-70% of maximal heart rate, recreational sports, cool down , and relaxation exercises. On follow-up GXT, maximal workload attained increased significantly. The researchers reported that predischarge clinical data, left ventricular ejection fraction at rest, and exercise induced angina or ST segment depression were not predictive of follow-up exercise capacity. There was also no significant correlation between the change in exercise capacity and initial exercise capacity (Fioretti, Simoons, Zwiers, Baardman, Brower, Kazemir, & Hugenholtz, 1987).

Van Dixhoorn et al. studied 156 post MI patients who underwent a 5 week exercise training program. A composite criteria for assessing training outcome was developed by integrating measurements obtained from exercise testing. This tool was then used to group patients into 3 categories: (1) improvement, (2) decline (3) no change. Initial baseline clinical information, exercise data, and psycho-social variables were used in a stepwise logistic regression analysis to identify characteristics of patients who improved and declined in functional status after training. The researchers reported correct classification rates of 81% and 85% for improvement and decline groups respectively. The best predictors for determining functional improvement were work status before infarction and low initial exercise capacity. The best predictors of

functional decline were psychological variables (Van Dixhoorn, Duivenvoorden, & Pool, 1990).

Many investigations have been done to determine the effect of a single variable on the achievement of a training effect, or compare how different subsets of the CAD population respond to training. Some of the topics evaluated in the literature are discussed below.

Effect of Age

There are several cardiovascular parameters that change with the normal aging process that affect response to exercise. There is a progressive decline in the amount of elastic tissue in the vascular media with an increase in the amount of collagen. This results in an increase in vascular stiffness and an increase in arterial blood pressure. Left ventricular hypertrophy occurs in response to elevated blood pressure and together with an increased amount of intracellular myocardial connective tissue, results in reduced ventricular compliance (Balady and Weiner, 1992). The ventricular contraction period is prolonged and, more importantly, relaxation time is prolonged. Thus there is a delay in early left ventricular filling and an increased reliance on atrial contribution to end diastolic volume. Cardiac output is maintained at submaximal workloads by a reduced reliance on increased heart rate and an increased reliance on the Frank-Starling mechanism to increase stroke volume. There is a reduction in maximal chronotropic and inotropic capacity as a result of decreased responsiveness to beta adrenergic stimulation (Schulman and Gerstenblith, 1989).

Exercise capacity has been shown to decline with increasing age, as both maximal cardiac output and arteriovenous oxygen difference are decreased. Exercise training has been shown to increase exercise capacity in elderly patients, however, attributed mainly to peripheral adaptations (Schulman et al., 1989). Ades et al. studied the effects of a 3 month exercise training program on submaximal and maximal exercise parameters in 43 patients over the age of 62 years. After 3 months, patients were re-evaluated and observed to have a 16% increase in $\dot{V}O_2max$, and exhaustive endurance

exercise time increased by 40%. At matched submaximal workloads, significant decreases in heart rate, lactate accumulation, and perceived exertion were observed as well as a decrease in RER, suggesting a shift to greater utilization of fatty acids as a fuel substrate. The researchers concluded that older coronary patients respond to aerobic conditioning with remarkable improvements in submaximal endurance capacity, out of proportion to the more modest increases in $\dot{V}O_2$max (Ades, Waldmann, Poehlman, Gray, Horton, Horton, & LeWinter, 1993). Thus, it does not appear that age inhibits patients from achieving a training effect through exercise training, especially evident at submaximal work intensities.

Effect of Gender

Lavie and Milani compared the effects of exercise training in men and women after a major cardiac event. Three hundred seventy five men and 83 women were exercise trained for 12 weeks in an outpatient cardiac rehabilitation setting. Significant improvements in exercise capacity were observed in both women and men, with a 33% increase and a 40% increase in estimated METs respectively. The change in maximal METs was not significantly different between men and women (Lavie and Milani, 1995).

Cannistra et al. studied the effects of exercise training in men and women in an outpatient rehabilitation program. The patients exercised 3 times per week at an intensity of 75-85% maximal heart rate for 30 minutes per session. The mean duration of training was 10.5 ± 5.5 weeks. Of the one hundred thirty six patients who completed the exercise program, 88 were retested on the same protocol as baseline, and did not have any change in medications. The exercise response of these 88 patients (26 women and 110 men) were used to evaluate the effects of training on exercise capacity. Women were found to have a lower baseline exercise capacity but both groups achieved a similar training effect. Women increased peak METs by 30% while men increased peak METs by 16%. The change in peak METs resulting from training was not significantly different for men versus women (Cannistra, Balady, O'Malley, Weiner, & Ryan, 1992).

A study comparing the training effect achieved by older men and women, i.e., age ≥ 62 years, who were post MI or CABG surgery, and enrolled in a cardiac rehabilitation exercise program in was conducted by Ades et al. Seventeen women and 37 men exercised for 1 hour, 3 times per week, at an intensity of 75-90% maximal heart rate, for 12 weeks. Women were found to have a significantly lower baseline $\dot{V}O_2max$ than men, however, both groups achieved a similar increase in $\dot{V}O_2max$ as a result of exercise training. The women and men in this study increased $\dot{V}O_2max$ by 17% and 19% respectively, which was not a significant difference between groups. After training, both groups manifested a significantly lower RPP at a submaximal exercise demand of 3 METs. This change was also similar for both men and women (Ades, Waldmann, Polk, & Coflesky, 1992).

These studies indicate that women entering cardiac rehabilitation programs typically have lower baseline exercise capacities than men with matched age and event, however, they have an equal ability to achieve a training effect through exercise.

Effect of Beta Adrenergic Blockade

Beta adrenergic blockers are commonly prescribed for patients with exertional angina pectoris, hypertension, to control certain types of arrhythmias, and to reduce the risk of subsequent cardiovascular mortality in post MI patients (Hamm et al., 1992). At rest, beta blockers have a dose dependent effect on the reduction of heart rate and myocardial contractility. Systolic and diastolic blood pressures are also reduced. Mechanisms of blood pressure reduction through beta blockade include a reduction in cardiac output, inhibition of norepinephrine release following sympathetic stimulation, and a decrease in renin levels (Hamm et al., 1992). Heart rate and blood pressure are reduced during submaximal exercise, although there may be an increase in peripheral vascular resistance that partially offsets reduction in systolic blood pressure through unopposed alpha adrenergic stimulation in patients taking non-selective blocking agents. This constriction of blood vessels reduces blood flow to working tissues and is compensated for by increased oxygen extraction if beta blockade is chronically

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administered. An increase in stroke volume occurs during submaximal exercise, which is almost in direct proportion to the decrease in heart rate. This adaptation helps to maintain the cardiac output (Hamm et al., 1992).

Pollock et al. reported that beta blockade resulted in an attenuation in the increase in $\dot{V}O_2$max in healthy adults following exercise training, but that patients with CAD were found to have large increases in performance time and $\dot{V}O_2$max as a result of exercise training while taking beta blocker medication (Pollock, Lowenthal, Foster, Pels, Rod, Stoiber, & Schmidt, 1991). Several investigators have reported that CAD patients taking beta blockers have an attenuation of training effect (Ciske, Dressendorfer, Gordon, & Timmis, 1986) while others have reported no attenuation in training effect in these populations (Vanhees, Fagard, & Amery, 1984; Ehsani, 1985). Even though all studies do not agree on issue of training effect attenuation, studies have consistently shown that CAD patients taking beat blockers can achieve a physiologically significant increase in $\dot{V}O_2$max, reduction of RPP during submaximal exercise, and an increase in oxygen pulse. These adaptations are primarily due to peripheral changes leading to increased oxygen extraction and a widening of the arteriovenous oxygen difference (Hamm et. al., 1992).

Effect of Calcium Channel Blockade

This class of drug has beneficial effects for patients with angina pectoris, hypertension, and supraventricular arrythmias. These drugs reduce the calcium ion influx into the cell through the slow calcium channels. The dihydropyridines (DHPs) i.e., nifedipine, cause mainly vasodilation of the peripheral and coronary arteries, while the non DHPs cause varying negative inotropic, dromotropic, and chronotropic effects, with less potent vasodilatory effects (Opie, Frishman, & Thadani, 1995). The limited data available suggest that calcium entry blockers do not alter a patient's expected training response to aerobic exercise training (Hamm and Leon, 1992).

Effect of Psychological Factors

Depressive symptoms have been reported to occur in 15-30% of patients after an MI or revascularization surgery. (Stern, Pascale, & Mcloone, 1976; Horgan, Davies, &

Hunt, 1984; Carney, Rich, & Tevelde, 1987). Katon and Sullivan described the following maladaptive effects of depression on patients with chronic medical illness: (1) depression often leads to amplification of somatic symptoms adding to patient disability (2) depression may decrease patient motivation to properly care for the chronic illness (3) depression may have a direct, adverse physiologic effect on disease state (Katon and Sullivan, 1990). Dalack and Roose have reported decreased parasympathetic activity in depressed patients compared to normal controls, resulting in low heart rate variability (Dalack & Roose, 1990). Other researchers have shown that low heart rate variability is a significant predictor of mortality in post MI patients. These studies suggest that depression may be related to greater cardiovascular complications and mortality through abnormal autonomic nervous system activity (Swenson and Abbey, 1993).

Milani, Littman, and Lavie in 1993 studied the effects of depression on exercise capacity improvement resulting from an outpatient exercise training program in patients following MI or revascularization surgery. A questionnaire designed to assess depressive symptoms was completed by 77 patients prior to an exercise training program. Sixteen of these patients (21%) indicated depressive symptoms, while 61 patients (79%) denied depressive symptoms. The patients exercised 3 days a week, for 30-40 minutes, at an intensity of 70-85% of maximal heart rate. Patient exercise capacity was re-evaluated at the completion of the Phase II program. Patients without depressive symptoms improved maximal METs by 26% (7.7 ± 0.4 to 9.6 ± 0.5, $p < 0.0001$) while patients with depressive symptoms had only an 11% improvement (7.5 ± 0.8 to 8.4 ± 0.9, NS). There was a significant difference between the groups ($p < 0.04$) suggesting that patients with depressive symptoms are not equally able to improve exercise tolerance through exercise training (Milani, Littman, & Lavie, 1993).

As previously mentioned, VanDixhoorn et al. reported psychological variables such as depression and lack of well-being feelings to be important predictors of a decline in functional status following a training program (Vandixhoorn et al., 1990).

Effect of Training Intensity

Blumenthal et al. studied the effect of exercise intensity on the achievement of a training effect in patients participating in an exercise training program early after acute myocardial infarction. Forty five patients were randomly assigned to either a high intensity group, i.e., 65-75% $\dot{V}O_2$max, or a low intensity group, i.e., < 45% $\dot{V}O_2$max. The patients exercised 3 times per week for 12 weeks. $\dot{V}O_2$max increased by 11% in the high intensity group and by 14% in the low intensity group. Both groups also had a significant reduction of RPP at submaximal workloads. These differences were not statistically significant between the groups suggesting that in patients after an MI, low intensity and high intensity exercise training produces similar results in training effect during the initial 3 months (Blumenthal, Rejeski, Walsh-Riddle, & Roark et al. 1988).

Goble et al. studied the effect of intensity of exercise on training effect in patients after a transmural acute myocardial infarction. Three hundred and eight men under the age of 70 were randomly assigned to either a high intensity or low intensity exercise group. The high intensity group performed 30 minutes of continuous aerobic activity at 75-85% of maximal heart rate, 3 times per week. The low intensity group exercised 2 times per week at a heart no greater than 20 beats above resting values, with exercise interrupted by periods of rest. All patients were encouraged to walk for 30 minutes daily at a comfortable pace. At follow-up at 8 weeks, the high intensity group increased exercise capacity by 4.0 METs, while the low intensity group increased by 3.2 METs. The difference between the groups was significant at 8 weeks, but by 12 months there was no significant difference between the groups. One factor possibly accounting for some of the difference between groups at 8 weeks was the fact that the low intensity group was not as highly encouraged to attend sessions and therefore attendance to available sessions was below the high intensity group's attendance rate. The researchers concluded that physical working capacity increased more in the high intensity group than the low intensity group, but this difference was small and temporary (Goble, Hare, MacDonald, Oliver, Reid, & Worcester, 1991).

Hammond et al. also found a low correlation between exercise intensity and training effect, with most correlation coefficients for various markers of training effect being below 0.20. Trends in this study were also conflicting, with higher intensity training being related to a greater decrease in resting heart rate but to a smaller decrease in submaximal heart rate at matched workloads (Hammond et al., 1985). Franklin et al. suggested that for most deconditioned adults and patients with CAD, the threshold intensity for training probably lies between 40-60% $\dot{V}O_2$max. Also, there is an interrelationship between training intensity, frequency, and duration that may allow a decrease in the intensity to be partially or totally compensated for by increases in duration or frequency. Relative increases in functional capacity appear to depend more on the subjects initial fitness and the total amount of exercise accomplished than on the specific exercise intensity (Franklin, Gordon, & Timmis, 1992).

Effect of Myocardial Ischemia

Ades et al. investigated the possibility that patients with exercise induced myocardial ischemia have an altered adaptive response to exercise training. One hundred six patients who had a coronary event, were entered into a 3 month exercise training program. Of the 106 patients, 65 (61%) were post MI and 41 (39%) were post CABG surgery. During the baseline GXT, 31 patients had angina, diagnostic ST segment depression, or both and 75 patients had neither of these ischemic responses. All patients exercised 3 times per week at 70-85% maximal heart rate, for 50 minutes per session. After 3 months of training were completed, a follow-up GXT was administered. The ischemic group and non-ischemic group had increases in $\dot{V}O_2$max of 10% and 28% respectively. The $\dot{V}O_2$max was significantly increased in both groups compared to baseline, but the increase in $\dot{V}O_2$max was significantly greater in the non-ischemic group. When submaximal exercise parameters were analyzed, it was found that both groups had a significantly reduced RPP at a reference load of 5 METs. There was no significant difference between the ischemic group and the non-ischemic group on these measures. This suggests that exercise induced ischemia altered the adaptive response to exercise

training at maximal exercise intensities, but did not hinder adaptations at submaximal work loads. A stepwise linear regression analysis was done to determine if baseline variables could be used to predict changes in maximal exercise capacity. This analysis revealed baseline VO_2max and presence of ST segment depression to be significant predictors of training effect measured at peak endpoints (Ades, Grunvald, Weiss, & Hanson, 1989).

In the previusly discussed study by VanDixhoorn et al., ST abnormality was found to be a significant predictor of a positive training effect, suggesting that these patients were more likely to improve (VanDixhoorn et al., 1990). This study differed from the study by Ades et. al. by using a composite outcome criteria that included many other parameters in addition to peak aerobic capacity.

These studies suggest that exercise induced ischemia may alter training adaptations at peak levels of exertion, but do not affect adaptations observed at submaximal work intensities.

Effect of Infarct Size and Location

Carter and Amundsen studied the effect of infarct size, estimated by serial creatine phosphokinase (CPK) changes, on exercise capacity before and after exercise training, as well as magnitude of change in exercise capacity in 22 patients. The patients were initially exercise tested and entered into an exercise or control group at 2.5 -4.5 months post event. Eleven patients were assigned to a control group and 11 patients were assigned to a supervised exercise group. The exercise group performed aerobic activity for 20 minutes 3 times per week at an intensity of 85% maximal heart rate, for 3-4 months. At follow-up, the exercise group was reported to have a significantly increased estimated $\dot{V}O_2$max compared to baseline and to the control group. Carter also reported a correlation of $r = -0.68$ between exercise capacity before training and infarct size and a greater correlation of $r = -0.84$ between post training exercise capacity and infarct size. No significant relationship was found between infarct size and the change in estimated $\dot{V}O_2$max however (Carter and Amundsen, 1977). Based on this study, large

infarcts appear to be predictive of lower exercise capacities, however they do not seem to hinder the patient's ability to achieve a training effect.

In the previously mentioned study by Hammond et al., history of an anterior wall infarction was examined as a potential predictor of training effect. Infarction location was not found to be a useful discriminator variable of training effect in this study.

Comparison of Training Response in CAD Patient Subsets

Hartung and Rangel compared responses to exercise training in three groups of patients commonly referred to cardiac rehabilitation programs. Measurements were taken before and after 3-6 months of exercise training in 24 post MI patients, 10 post CABG patients, and 16 patients with a positive graded exercise test and multiple risk factors for CAD only. The patients exercised 3 times per week for 20-40 minutes per session, at an intensity of 70-85% maximal heart rate. Estimated $\dot{V}O_2$max was increased significantly in all 3 groups after training, with MI, CAD only, and CABG groups improving 6.2, 7.0, and 8.0 ml/kg/min respectively. The change in $\dot{V}O_2$max was not significantly different between the groups, indicating that all 3 groups seem to have an equal ability to increase exercise tolerance through training (Hartung and Rangel, 1981).

Effect of Angina Pectoris

It has been shown that patients with angina can achieve a training effect as a result of exercise training (Smith, Layton, Newmark, & Diethrich, 1987, Redwood, Rosing, & Epstein, 1972). However, in the study by VanDixhoorn et al. anginal complaints before MI and anginal complaints after MI were both found to be predictors that were negatively related to training success. Antianginal medication before MI was an important predictor of training failure (VanDixhoorn et al., 1990). Neither Hammond et al. 1985 or Fioretti et al. 1987 found angina to be related to training effect. Differences in these studies are most likely due to the design of outcome assessment criteria.

Effect of Disease Severity

The effect of comprehensive cardiac rehabilitation on exercise parameters in 43 patients with inoperable 3 vessel disease was studied by Monpere et al. The patients

were entered into a program that included physical training, secondary prevention, and vocational counseling. The physical training program consisted of bicycle ergometry for 30 minutes per session at an intensity of 75% of peak heart rate, 5 days per week. Each exercise session was completed by a 1 hour walk and calisthenics. After 4 weeks, the patients were re-evaluated. The comparison of exercise tests revealed a significant increase in maximal workload of 22% after training, and a significant increase in workload at onset of diagnostic ST segment depression (Monpere, Francois, & Brochier, 1988). The increase in exercise capacity in this study is of the same magnitude as previously reported for CAD patients as a whole. Thus it does not appear that severe CAD hinders the achievement of a training effect.

Effect of Initial Fitness Level

Patients with low initial fitness levels have been shown to have the greatest magnitude of improvement in exercise parameters following exercise training in several studies (Vandixhoorn et al., 1990; Hammond et al., 1985; Lavie, and Milani, 1994). Thus initial exercise capacity is known to be a good predictor of training effect resulting from exercise training. Patients with high baseline exercise capacities can still benefit from exercise training however, as gains in exercise capacity and improvements in risk factors have been documented (Lavie et al. 1994).

Summary

The studies in this review indicate that the following variables are likely to be important predictors of training effect following an exercise program for CAD patients: (1) initial fitness level and (2) depression. Mixed results indicate that the following variables may possibly affect ability to achieve a training effect: (1)the presence of angina pectoris or myocardial ischemia, (2) beta blocker medications, and (3) exercise training intensity if duration and frequency are held constant.

Chapter III

JOURNAL MANUSCRIPT

DEFINING PATIENT ATTRIBUTES THAT PREDICT EXERCISE TRAINING OUTCOME IN CARDIAC REHABILITATION PATIENTS

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DEFINING PATIENT ATTRIBUTES THAT PREDICT EXERCISE TRAINING OUTCOME IN CARDIAC REHABILITATION PATIENTS

by

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(ABSTRACT)

The purpose of this study was to evaluate the utility of baseline clinical and graded exercise test (GXT) variables in predicting exercise training outcome in cardiac rehabilitation patients. Data were extracted from the records of 60 cardiac patients who had participated in a community-based exercise program for 5-9 months. Two separate markers of exercise tolerance were used to evaluate training effect: 1) rate-pressure product at a submaximal reference workload of 5 METs (RPP5METs), and 2) estimated peak METs (pkMETs). These two markers of exercise tolerance were found to have a low correlation ($r = -0.29$).

Patients were classified into one of three possible outcome categories for each marker of exercise tolerance, i.e., improvement, no change, or decline. Thresholds for classifying patients into improvement or decline groups were $\pm 10\%$ for the RPP5METs marker and ± 1 MET for the pkMETs marker. Outcome classifications using the RPP5METs marker were as follows: improvement, 37 (62%); no change, 13 (22%); decline, 10 (17%). Use of the pkMETs marker to classify patients into outcome groups yielded: improvement, 45 (75%) ; no change, 15 (25%); with no patients classified in the decline group. Multiple logistic regression was used to identify patient attributes predictive of improvement and decline for each exercise tolerance marker.

Baseline variables were found to yield a model highly predictive of improvement in RPP5METs (correct classification rate = 87%; sensitivity = 92%; specificity = 78%).

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The best single predictor of improvement outcome was high baseline RPP5MET values. A model could not be generated to successfully predict decline in exercise tolerance. Baseline variables selected for prediction of improvement outcome, as defined by pkMETs marker, yielded a model with limited utility due to low specificity (correct classification rate = 87%; sensitivity = 96%; specificity = 60%).

Conclusions. A set of baseline clinical and exercise variables were found to successfully predict cardiac patients who improve exercise tolerance through training in a community-based rehabilitation program. Changes in submaximal exercise parameters were more predictable than changes at peak endpoints. Variables used in this study were not successful in predicting patients who manifested a decline in exercise.

Introduction

Exercise training is an important component of cardiac rehabilitation programs and is expected to increase functional capacity and reduce the myocardial oxygen requirement of submaximal tasks. As a result, patients with coronary artery disease (CAD) who undergo training, have been shown to raise the workloads they can perform before eliciting a threshold for myocardial ischemia.[1]

Typically, patients referred to cardiac rehabilitation programs include those with recent myocardial infarction, coronary revascularization procedures, silent ischemic changes on diagnostic tests, or exertional symptoms of ischemic heart disease. There is considerable research to demonstrate that most of these patients benefit from regular exercise[1-4]; however, some patients fail to attain higher peak exercise workloads and do not have lower heart rates at matched submaximal workloads following training[5].

Cardiac rehabilitation programs carry a significant cost and present a certain amount of risk to the patient[6]. Thus, identification of a set of patient attributes that could be used to successfully predict exercise training outcome is appealing. This would allow practitioners to estimate a patient's likelihood of attaining a beneficial training outcome from clinical and exercise test variables, and compare this to the inherent risks and investment of resources required for training. For patients expected to have a low likelihood of improving exercise tolerance through training, rehabilitative programs might focus on achieving other benefits through behavior modification, counseling, and patient education programs. In this way, the rehabilitation process may be tailored to the individual patient, maximizing benefits while minimizing the use of less effective rehabilitation components.

Previous attempts to define such attribute sets have had only moderate success[7,8,9,10]. Different criteria for evaluating training outcome were used in these previous published studies. Many investigators have used the traditional measured or estimated peak oxygen consumption to quantify improvement in exercise tolerance, however some investigators have used more elaborate methods of evaluation. Van

Dixhoorn et al.[9] developed a composite criterion measure as a way to more comprehensively assess training outcome. The Van Dixhoorn model included: appearance or disappearance of pathological signs; changes in peak exercise workload; heart rate and blood pressure response; and improvement or decline in physical condition that resulted in suspension of the patient's exercise training. Hammond et al[7] attempted to identify patient attributes that are predictive of several independent markers of training effect, such as: heart rate at rest, heart rate at a submaximal workload, estimated peak oxygen consumption, measured peak oxygen consumption, and myocardial ischemia on a thallium scan. Hammond et al.[7] presented data showing that patients were able to walk longer on a treadmill test and perform the same submaximal work load at a lower rate-pressure product without a measurable improvement in peak oxygen consumption. Thus, there is evidence that assessment of the training effect using different markers of improvement yield varying results that tend to be specific to the criterion used for evaluation.

Changes in rate-pressure product at a submaximal reference workload of 5 METs is one outcome marker chosen to evaluate training effect in the present study. A submaximal parameter was chosen for two reasons. First, since cardiac patients seldom have the need to exert a maximal effort in the performance of daily physical activities, changes in cardiovascular response at a submaximal workload of 5 METs was judged to have more relevance to evaluation of exercise training outcomes. Second, submaximal parameters have been shown to be more reliable than peak exercise parameters when protocols with differing work-rate increments are used before and after training.[11] Rate-pressure product was selected because it previously has been shown to have relevance to myocardial ischemic thresholds.[3]

The research question investigated in the current study is: Can a set of routinely collected variables be identified that is predictive of exercise training outcome for patients enrolled in a cardiac rehabilitation program?

Methods

Study patients. Data for this non-concurrent prospective study were extracted from the clinical records of patients who had participated in the rehabilitation program at the Virginia Tech Cardiac and Intervention Center between January, 1977, and September, 1995. To be included, patient records must have included data recorded for at least three stages of a symptom-limited graded exercise test at the time of program entry and at another test within 5-9 months after beginning supervised exercise. Only patients who had previous myocardial infarction, coronary revascularization, physician diagnosed angina, or angiographically confirmed CAD were selected. Patients were excluded from the study for the following reasons: documented change in prescriptions of medication during the training program that would potentially alter hemodynamic responses or symptoms; attended less than a minimum of 70% of the exercise sessions during the training period. A total of 60 patients (58 men and 2 women) met the above criteria. The sample included: 77%, recent myocardial infarction; 15%, recent coronary revascularization; 33% receiving beta blocker medication.

Exercise testing. Graded exercise tests were performed on each patient using a modified Balke or similar protocol (i.e., increases in metabolic demand of ~2 METs every 2 minutes). Blood pressure and ECG were monitored throughout the tests by trained technicians using standard clinical methods. All hemodynamic measurements were obtained during supine and upright resting conditions and during the last minute of each exercise stage. A subjective rating of perceived exertion was also recorded during the last minute of each exercise stage. All tests were supervised and terminated by a physician.

Definition of treadmill test performance and training outcome criterion. For purposes of this study, two markers of exercise tolerance were used to assess fitness changes over the training period: 1) exercise tolerance was quantified as myocardial demand at a submaximal workload, i.e., the rate-pressure product at 5 METs (RPP5METs); and 2) peak METs attained on the GXT (pkMETs), which was estimated from peak treadmill speed and grade. The two markers of exercise tolerance were then was used to compare pre-training to post-training GXTs. For each exercise test, the RPP5MET score was established through least squares linear regression in which RPP responses were regressed on the estimated MET level for speed and grade at each exercise stage. A resulting correlation of $r \geq 0.90$ was required for this relationship to qualify a patient's test for inclusion in the study. The RPP5MET value was derived for the pre-training GXT (RPP5METS$_{pre}$) and the post-training GXT (RPP5METS$_{post}$) from the regression equation. Then, the pre-training and post-training values for RPP5METs were used to calculate the change in RPP at 5 METs (ΔRPP5METS) for each patient over the exercise training period. Finally, the ΔRPP5METS score was expressed as a percentage of the initial score, using the following equation:

$$\Delta RPP5METS\% = (RPP5METS_{post} - RPP5METS_{pre})/ RPP5METS_{pre} \times 100\%$$

Thus a negative $\Delta RPP5METS\%$ score would constitute an improvement in exercise performance and a positive score would constitute a decline in exercise performance.

The $\Delta RPP5METS\%$ score was then used to categorize patients according to three outcomes:

1) improvement group, defined as a decrease of 10% or more, i.e., $\Delta RPP5METS\% \leq -10\%$

2) a decline group, defined as an increase of 10 or more, i.e., $\Delta RPP5METS\% \geq +10\%$

3) a no change group, defined as $\Delta RPP5METS\%$ values between -10% and +10%.

The standard error of the mean for RPP5METs score was calculated and used to help select a threshold value that would be meaningful for improvement, i.e., not likely to occur due to random variation in exercise test response. The above thresholds ($\pm 10\%$) were chosen for $\Delta RPP5METS\%$ also because a 10% change was judged to have clinical relevance.

The change in pkMETs ($\Delta pkMETs$) value between pre-training and post-training GXTs was also used to classify patients into outcome categories. The following thresholds were used:

1) improvement group, defined as $\Delta pkMETs \geq +1$ MET.

2) decline group, defined as $\Delta pkMETs \leq -1$ MET.

3) no change group, defined as $\Delta pkMETs$ between -1 MET and + 1 MET.

The data were analyzed to derive two separate prediction equations. When defining characteristics predictive of improvement, the no change group and decline group were combined to form a comparison "no improvement group". Likewise, for defining characteristics predictive of decline, the no change and improvement groups were combined to form a comparison "no decline group". The outcome variable was then coded as a dichotomy, representing either presence or absence of the outcome of interest.

Statistical Analyses

The association of training outcome with initial patient attributes was analyzed first using univariate methods and then by multivariate logistic regression. Data for all patients were analyzed to predict both improvement and decline in exercise tolerance.

Univariate Analysis

In the univariate approach to data analysis, the initial patient characteristics were tested to identify variables that were statistically different between outcome classification categories: 1) chi-square analysis for variables containing nominal data; and 2) Student *t*-test for variables of interval level.

Multiple Logistic Regression Analysis

The outcome variable in a logistic regression model is dichotomous, coded *one* for presence of a certain outcome and *zero* for its absence. An alternating forward-backward stepwise multiple logistic regression procedure was used in an attempt to identify the best prediction models for the two outcomes

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(improve and decline) based on the patient attributes obtained at program entry. The equation resulting from the logistic regression function consists of variables found to be the best predictors of outcome, along with their coefficients and a constant. This equation yields an estimation of the probability of a particular outcome for each patient. All 60 patients were used to develop these prediction equations.

Data were separated into a set of clinical variables and a set of exercise test variables before beginning the analyses. Three models then were developed for each outcome, first including clinical data only (Trial 1), then with exercise test variables only (Trial 2) and then with a combined set of all data (Trial 3). The criteria for inclusion and exclusion of variables in the prediction model was $p < 0.10$ and $p > 0.15$, respectively. The prediction success of these models were evaluated by comparing the estimated outcome to the actual outcome for each patient. Correct classification rates were calculated, along with sensitivity, specificity for each model.

Results

A total of 97 patients met the inclusion criteria for the study. Of these, 37 (37%) patients were excluded for the following reasons: less than a minimum of 70% attendance to exercise sessions, 9 (9%); change in prescription of medication that would possibly alter hemodynamic response to exercise, 5 (5%); follow-up GXT not within 5-9 months of baseline GXT, 12 (12%); did not have a linear RPP response to exercise, 4 (4%); did not have required data recorded for 3 exercise stages on either pre-training or post-training GXT, 7(7%). After these patient exclusions, data for a total of 60 patients were used for analysis in the study. Of these, 46 patients (77%) had experienced a recent (within 6 months) MI, 9 patients (15%) had undergone a recent coronary revascularization procedure, and 30 patients (50%) had angiographically confirmed CAD. There were 13 patients (23%) who had experienced angina since a recent MI, 2 patients (3%) who had experienced angina since a recent revascularization procedure, and 6 patients (10%) who had experienced angina within the last 6 months without presence of MI or revascularization procedure.

Pre-training and post-training exercise test responses. The group mean for RPP5METs on the pre-training and post-training GXTs were 177 ± 49 units and 153 ± 36 units respectively. When expressed as percent change of the initial RPP5MET value, the

mean change was -10 ± 19 units, with a range of -45 to +51 units. The overall group had significantly lower RPP levels at 5 METs of exercise demand after training when compared to the pre-training test ($p < 0.0001$).

The group mean for pkMETs on the pre-training and post-training GXTs were 8.2 ± 2.2 METs and 10.3 ± 2.2 METs, respectively, with a mean change of 2.1 ± 1.7 METs. The overall group had a significant increase in peak METs over the training period ($p < 0.0001$). A Pearson correlation was conducted on the raw scores for RPP5METs and pkMETs, with a resultant $r = -0.29$.

Table 1 shows the frequency of signs or symptoms suggestive of myocardial ischemia, or cardiopulmonary distress, that were present in patients on either GXT. These occurrences have been grouped by outcome. Exercise induced angina was present in ten patients before training and in seven patients after training, disappearing in five patients with new occurrence in two patients. ST segment depression of at least 0.1 mV, measured at 60 milli-seconds after the J point in lead V_4 or V_5, was found in twenty patients before training and in fifteen patients after training, with a disappearance in nine patients and a new occurrence in four patients. Seven patients were observed to have complex ventricular arrhythmias on the pre-training GXT, and a different four patients had an occurrence of these arrhythmias on the post-training GXT. No patients were observed to have complex ventricular arrhythmias on both GXTs.

Outcome classification using the two exercise training markers.

RPP5METs. Of the 60 patients studied, 37 patients (62%) were classified into the improvement group, 13 patients (22%) were classified into the no change group, and 10 patients (16%) were classified into the decline group using the RPP5METs marker of change.

PkMETs. Of the 60 patients studied, 45 patients (75%) were classified into the improvement group and 15 patients (25%) were classified into the no change group using the peak METs marker of change in exercise tolerance. No patients were found to manifest a decline at least 1 MET over the training period.

Comparison of pkMETs and RPP5METs markers. There are discrepancies between which outcome group patients get assigned to, depending on which marker of change in exercise tolerance is used. There was agreement between the two markers that thirty patients improved and four patients had no change in exercise tolerance over the course of training. However, of fifteen additional patients that were classified into the improvement group using pkMETs, nine were classified into the no change group and six were classified into the decline group by the RPP5METs marker. Of eleven additional patients classified into the no change group by pkMETs, seven were classified into the improvement group and four were classified into the decline group by the RPP5METs marker. Thus, the result of individual patient outcome classification is dependent upon the marker chosen to define changes in exercise tolerance occuring with exercise training.

Univariate Analyses

Analysis of outcome as defined by RPP5METs.

Improvement group. Table 2 shows the results of the univariate analyses used to test baseline variables for potential predictive ability of improvement outcome vs. no improvement outcome (combined no change group and decline group). Almost two-thirds of the patients (62%) in the study improved exercise tolerance during the training program as defined by RPP5METs marker. Compared with those patients without such improvement, patients who improved were found to have higher resting systolic blood pressures, fewer had been through a phase II exercise training program, and fewer were taking digitalis medications. The mean rate pressure product at 5 METs was higher and mean peak MET level achieved on initial GXT was lower for patients who improved vs. patients who did not.

Decline group. Table 3 shows the results of the univariate analyses used to test baseline variables for potential predictive ability of decline outcome vs. no decline (combined no change group and improvement group). Ten patients (16%) manifested a

decline in exercise tolerance as defined by RPP5METs marker. Nearly all these patients had been through a phase II training program, had lower resting systolic blood pressures, and lower resting diastolic blood pressures. There was a trend for patients who declined to be more frequently prescribed calcium antagonist medications. On the initial GXT, patients who declined tended to have lower RPP5MET values and higher maximal MET levels achieved than patients who had no change or improved exercise tolerance.

Analysis of outcome as defined by pkMETs.

Improvement group. Table 4 shows the results of the univariate analysis conducted on baseline variables to determine if any were good predictors of improvement vs. no improvement outcome as defined by pkMETs marker. The only variable to reach traditional significance levels was baseline pkMETs. A trend was found to occur in the following variables: history of hypertension, prior phase II exercise training experience, resting diastolic blood pressure, calcium channel blocker medications, and presence of complex ventricular ectopy on the baseline GXT. Since there were no patients grouped into the decline category when exercise tolerance changes were defined by pkMETs, decline vs. no decline outcome analysis could not be performed.

Multivariate Analyses

Analysis of outcome as defined by RPP5METs.

Improvement group . Table 5 shows the resultant classification rates for the prediction trials with separate variable sets and a combined set. Trial 1, which included only clinical data, had a somewhat greater ability to predict improvement in exercise tolerance after training than trial 2, which included only exercise test data. While sensitivity was similar using these two separate variable sets (87% and 81% respectively), the specificity rate was lower for the equation developed using only exercise data (78% for clinical set and 65% for the exercise set). When both clinical and exercise test variable sets were combined in trial 3, the best total correct classification

rate resulted (87%) with high rates for both sensitivity (92%) and specificity (78%). These classification rates suggest that improved exercise tolerance as defined by RPP5METs is highly predictable when both clinical and exercise test variables are included in the prediction model.

The equations selected by the stepwise regression procedure that were used to derive the classification rates for improved exercise tolerance are also shown in Table 5. Clinical variables found to have a high predictive ability were resting systolic blood pressure, digitalis medication, recent angina, beta blocker medication, and pretraining status. The variable found to be the best predictor of improvement in the exercise set (Trial 2) was baseline RPP5METs, with no other exercise variables significantly adding to the predictive accuracy once this variable was entered. When both variable sets were combined, the variables found to be highly predictive of outcome were baseline RPP5METs, beta blocker medication, digitalis medication, presence of angina during the pre-training GXT, and Peak METs achieved on the pre-training GXT.

Decline group . Table 6 presents the classification rates for the trials using separate predictor variable sets and a combined set to predict decline in exercise tolerance, as defined by RPP5METs marker. The performance of the clinical variable set and the exercise data set have similar classification rates for correct classification, sensitivity, and specificity. Total correct classification rates for trial 1 and trial 2 were high (88% and 82% respectively), as were specificity rates (100% and 94% respectively). The sensitivity rates were poor for both trials however (30% and 20% respectively). When both clinical and exercise variable sets were combined in the model, prediction performance was essentially the same as the performance with either set alone, i.e., 83% correctly classified, 30% sensitivity and 94% specificity. The predictive ability of these equations was very limited due to low sensitivity.

Analysis of outcome as defined by pkMETs.

Improvement group. Table 7 shows the classification rates for the trials using separate predictor variable sets and a combined set to predict improvement in exercise

tolerance, as defined by the pkMETs marker. Prediction performance was similar when exercise variables only and clinical variables only were used in the model. The prediction performance was slightly higher when all variables were included in the model. While correct classification rates for were high for this prediction model (87%), utility of this model is decreased by low specificity (60%).

Clinical variables selected by stepwise logistic regression were calcium channel blocker medications, history of hypertension, and resting diastolic blood pressure. Exercise variables selected were pkMETs, and presence of complex ventricular ectopy on the baseline GXT. When both variable sets were combined in one prediction model, variables selected were pkMETs, diuretic medications, complex ventricular ectopy on baseline GXT, and total cholesterol.

Discussion

The present study was conducted to define attributes that could discriminate between patients who improve exercise tolerance through training and those who do not. As previously mentioned, related research studies in this area have used different markers of training improvement. The patient attributes selected in these studies as predictive of training outcome tend to be specific to the criteria used to evaluate training effect. Thus, since exercise training outcome has been evaluated using different criteria in these studies, and differing statistical techniques have been used to analyze the data, comparison of results between the studies is difficult.

Predicting improvement in exercise tolerance. Baseline physical fitness as defined by RPP5METs and pkMETs were the best predictors of change in RPP5METs and pkMETs respectively, over the training period. Thus, the utility of baseline fitness parameters to predict outcome tend to be specific to the exercise tolerance marker used to define improvement. The association between low baseline fitness and greater improvement in exercise tolerance through training has been well documented.[7,9] Prior training experience in a phase II rehabilitation program was also found to be negatively associated with changes in exercise tolerance, as prior training status impacts initial

fitness level. Baseline resting systolic blood pressure was found to be a good predictor of improvement defined by RPP5METs but not by pkMETs, as this variable is more directly related to rate-pressure product.

When multivariate analysis was conducted with RPP5METs as the outcome marker, baseline RPP5METs was always found to be the single best predictor of outcome. After RPP5METs was entered into the model, the additional information provided by beta blocker medication status significantly improved the variance explained by the model. The increase in model performance by the beta blocker information may be due to several effects. First, beta blocker medications artificially lower RPP at any workload, so that patients on beta blockers would have a lower RPP5METs. Thus, these patients appear to be similar to highly fit patients when RPP5METs is the only variable considered, but beta blocker patients may differ substantially from highly fit patients in muscle enzyme activity, mitochondria number, and other peripheral factors affecting a-vO$_2$ difference. Patients with artificially lowered baseline RPP5MET values may therefore be able to achieve peripheral adaptations from training and subsequently lower RPP5METs over the training period. These peripheral adaptations have already been acquired by highly fit patients who are not taking beta blockers and have a similar baseline RPP5MET value to patients taking beta blocker medications. Another possibility is that since beta blockers further depress cardiac output in patients with an already impaired central pump, the body may compensate to widen a-vO$_2$ difference at submaximal workloads. Chronic use of beta blocker medication may act, in conjunction with exercise training, as an ergogenic aid to force peripheral adaptations in these patients.

When multivariate analysis was conducted with pkMETs as the marker of changes in exercise tolerance, baseline pkMETs was found to be the best predictor of outcome. After entry of pkMETs into the model, diuretic medications and complex ventricular ectopy on the initial GXT significantly inproved prediction accurracy.

The results of the present study, along with results from previous studies, suggest that patients who improve exercise tolerance can be successfully discriminated from patients who do not improve, by using routinely collected clinical and exercise variables. The parameter of greatest predictive value is the initial fitness marker, however this measure is specific to the exercise tolerance marker used to define outcome. If submaximal rate-pressure product is used, other important variables like beta blocker medication need to be included in the model for accurrate predictions.

Predicting exercise tolerance decline. The models derived by the stepwise selection procedure to predict exercise tolerance decline did not have high predictive success. From the univariate analyses, patients who entered the program having already attended a formal exercise program and having attained a high functional capacity were more likely to have declines in exercise tolerance. However, these characteristics alone do not allow for accurate discrimination between patients who manifest a decline and those who do not, as presented through the low sensitivity classification rates in Table 6. Psycho-social parameters have previously been shown to be predictive of patients who experience a decline in exercise tolerance[9] or fail to achieve a training effect in cardiac patients participating in rehabilitative exercise programs.[12] Addition of variables such as depression, sense of well-being, and feelings of displeasure may add significantly to the predictive accuracy of equations that also include clinical and exercise data. A larger patient sample would also allow for a larger number of patients in the decline group, helping to alleviate problems with identifying predictive features from a small number of patients.

Several caveats must be noted when interpreting the results of the present study. First, due to the respective design, no attempt could be made to account for patients who discontinued exercise for clinical reasons. Also, because only patients who did not have changes in medication status over the training period were included in this study, the results only apply to patients with stable disease. Patients who stopped training before reaching the 5-8 month follow-up period or had medication changes over this period

were excluded from the study. Secondly, due to the small sample size, all classification rates for prediction models were developed using the same sample of patients that were used to derive the prediction model, i.e., there was no attempt made to validate the prediction model with an independent patient sample. Therefore, the classification rates presented in this paper are most likely optimistic evaluations of model performance.

Conclusion

In the present study, a new method was introduced to evaluate changes in exercise tolerance that occur during an exercise training program. This new method avoids several problems commonly encountered with outcomes research in a typical rehabilitation program setting. Outcome classification results for the new method (RPP5METs) were compared to results obtained using the more traditional outcome measure (pkMETs). Use of the RPP5METs marker was found to yield different results than that obtained with the traditional pkMETs marker. Exercise tolerance improvement defined by RPP5METs was also found to be more highly predictable than changes defined by pkMETs, using selected clinical and exercise parameters routinely collected at time of patient entry into a rehabilitation program. This may be due to problems inherent in pkMETs marker, such as lower reproducibility with serial exercise testing.

Models derived for the prediction of exercise tolerance decline were found to demonstrate low sensitivity and are thus not very useful to the practitioner. Addition of psycho-social variables may improve the accuracy of models derived to predict decline in exercise tolerance.

References

1. Redwood DR, Rosing DR, Epstein SE. Circulatory and symptomatic effects of physical training in patients with coronary artery disease and angina pectoris. **N Engl J Med** 1972;286:959-965.

2. Wenger NK, Froelicher ES, Smith LK. **Cardiac Rehabilitation. Clinical Practice Guideline No. 17.** Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute. AHCPR Publication No. 96-0672. October 1995.

3. May GA, Nagle FJ. Changes in rate-pressure product with physical training of individuals with coronary artery disease. **Phys Ther** 1984;64:1361-1366.

4. Fletcher GF, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise Standards: A statement for health professionals from the American Heart Association. **Circulation** 1990;82(6):2286-2322.

5. Froelicher VF, Jensen D, Genter F, Sullivan M, McKirnan MD, Witztum k, Sharf J, Strong ML, Ashburn W. A randomized trial of exercise training in patients with coronary heart disease. **JAMA** 1984;252:1291-1297.

6. Haskell WL. Cardiovascular complications during exercise training of cardiac patients. **Circulation** 1978;57:920-924.

7. Hammond HK, Kelly TL, Froelicher VF, Pewen W. Use of clinical data in predicting improvement in exercise capacity after cardiac rehabilitation. **J Am Coll Cardiol** 1985;6:19-26.

8. Fioretti P, Simoons ML, Zwiers G, Baardman T, Brower RW, Kazemir M, and Hugenholtz PG. Value of predischarge data for the prediction of exercise capacity after cardiac rehabilitation in patients with recent myocardial infarction. **Eur Heart J** 1987;8(suppl G):33-38.

9. Van Dixhoorn J, Duivenvoorden HJ, Pool J. Success and failure of exercise training after myocardial infarction: Is the outcome predictable? **J Am Coll Cardiol** 1990;15:974-982.

10. Velasco JA, Tormo V, Riddocci F, Ferrer LM. Factors predicting the result of physical training after acute myocardial infarction. **Ann Clin Res** 1982;14:32-36.

11. McInnis KJ, Balady GJ. Comparison of submaximal exercise responses using the Bruce vs. modified Bruce protocols. **Med Sci Sports Exerc** 1994;26(1):103-107.

12. Milani RV, Littman AB, Lavie CJ. Depressive symptoms predict functional improvement following cardiac rehabilitation and exercise program. **J Cardiopulmonary Rehabil** 1993;13:406-411.

Table 1. Patient GXT Response Characteristics (n = 60)

Characteristic	Postest	Improve (n = 37) Pretest +	Improve (n = 37) Pretest −	No Change (n = 13) Pretest +	No Change (n = 13) Pretest −	Decline (n = 10) Pretest +	Decline (n = 10) Pretest −
Exercise Angina	+	3	2	1	0	1	0
	−	2	30	2	10	1	8
0.1 mV ST segment depression @ J_{60}	+	7	2	2	1	2	1
	−	7	21	1	9	1	6
Complex Ventricular Arrhythmias	+	0	3	0	1	0	0
	−	5	29	1	11	1	9
Other Signs or Symptoms*	+	2	2	0	0	0	0
	−	5	28	3	10	2	8

* Signs and symptoms include dyspnea, vertigo, and leg cramping due to claudication.

Table 2. Predictive Variables for Training Improvement vs. No Improvement Outcome as Defined by RPP5METs: Clinical Information and Exercise Data in 60 CAD Patients

Variable	Improvement (n = 37)	No Improvement (n = 23)	p
Clinical Data			
Age (years)	57 ± 10	56 ± 8	NS
History of Hypertension	18 (49%)	8 (35%)	NS
History of Smoking	22 (59%)	13 (57%)	NS
Continued Smoking	7 (19%)	2 (9%)	NS
History of Dyslipidemia	17 (46%)	13 (57%)	NS
History of Diabetes	6 (16%)	2 (9%)	NS
Orthopedic Problems	7 (19%)	5 (22%)	NS
Recent Revascularization	7 (19%)	2 (9%)	NS
Recent MI	28 (76%)	18 (78%)	NS
Anterior Wall MI	8 (22%)	9 (39%)	NS
Recent Angina Pectoris	10 (27%)	11 (48%)	NS
Total Cholesterol (mg/dL)	231 ± 47	231 ± 45	NS
Dyslipidemia	32 (86%)	19 (83%)	NS
Body Mass Index (kg/m^2)	26.5 ± 3.6	25.4 ± 2.0	NS
Prior Phase II Exercise Training Experience	14 (38%)	17 (74%)	< 0.01
Resting SBP (mmHg)	134 ± 23	119 ± 18	< 0.01
Resting DBP (mmHg)	80 ± 12	76 ± 9	NS
Medications			
Beta Blockers	14 (38%)	6 (26%)	NS
Calcium Channel Blockers	7 (19%)	8 (35%)	NS
Diuretics	8 (22%)	4 (17%)	NS
Digitalis	3 (8%)	6 (26%)	0.07
Nitrates	10 (27%)	11 (48%)	NS
Exercise Testing			
Angina during GXT	5 (14%)	5 (22%)	NS
ST_{60} Segment Depression (mm)	0.7 ± 1.1	0.6 ± 1.2	NS
ST_{60} Segment Shift ≥ 0.1 mV	15 (41%)	7 (30%)	NS
Complex Ventricular Ectopy	5 (14%)	2 (9%)	NS
RPP5METs (bpm x mmHg x 10^2)	196 ± 45	145 ± 38	< 0.0001
Peak METs	7.5 ± 1.8	9.3 ± 2.4	0.003

Data are reported as number of cases or mean values $\pm$ SD. Percentages are shown in parentheses.

Table 3. Predictive Variables for Training Decline vs. No Decline Outcome as Defined by RPP5METs: Clinical Information and Exercise Data in 60 CAD Patients

Variable	Decline (n = 10)	No Decline (n = 50)	p
Clinical Data			
Age (years)	58 ± 6	56 ± 10	NS
History of Hypertension	3 (30%)	23 (46%)	NS
History of Smoking	4 (40%)	31 (62%)	NS
Continued Smoking	1 (10%)	8 (16%)	NS
History of Dyslipidemia	5 (50%)	25 (50%)	NS
History of Diabetes	1 (10%)	7 (14%)	NS
Orthopedic Problems	1 (10%)	11 (22%)	NS
Recent Revascularization	1 (10%)	8 (16%)	NS
Recent MI	9 (90%)	37 (74%)	NS
Anterior Wall MI	4 (40%)	13 (26%)	NS
Recent Angina Pectoris	4 (40%)	17 (34%)	NS
Total Cholesterol (mg/dL)	237 ± 34	230 ± 48	NS
Dyslipidemia	9 (90%)	42 (84%)	NS
Body Mass Index (kg/m^2)	25.0 ± 2.2	26.3 ± 3.3	NS
Prior Phase II Exercise Training Experience	9 (90%)	22 (44%)	0.01
Resting SBP (mmHg)	112 ± 12	132 ± 23	< 0.001
Resting DBP (mmHg)	71 ± 7	80 ± 11	< 0.01
Medications			
Beta Blockers	4 (40%)	16 (32%)	NS
Calcium Channel Blockers	5 (50%)	10 (20%)	0.10
Diuretics	1 (10%)	11 (22%)	NS
Digitalis	3 (30%)	6 (12%)	NS
Nitrates	4 (40%)	17 (34%)	NS
Exercise Testing			
Angina during GXT	2 (20%)	8 (16%)	NS
ST_{60} Segment Depression (mm)	0.6 ± 1.0	0.7 ± 1.1	NS
ST_{60} Segment Shift ≥ 0.1 mV	3 (30%)	19 (38%)	NS
Complex Ventricular Ectopy	1 (10%)	6 (12%)	NS
RPP5METs (bpm x mmHg x 10^2)	123 ± 24	187 ± 46	< 0.0001
Peak METs	9.9 ± 2.7	7.9 ± 2.0	0.05

Data are reported as number of cases or mean values $\pm$ SD. Percentages are shown in parentheses.

Table 4. Predictive Variables for Training Improvement vs. No Improvement Outcome as Defined by pkMETs: Clinical Information and Exercise Data in 60 CAD Patients

Variable	Improvement (n = 45)	No Improvement (n = 15)	p
Clinical Data			
Age (years)	56 ± 10	56 ± 9	NS
History of Hypertension	16 (36%)	10 (67%)	0.07
History of Smoking	27 (60%)	8 (53%)	NS
Continued Smoking	7 (16%)	2 (13%)	NS
History of Dyslipidemia	22 (53%)	8 (53%)	NS
History of Diabetes	7 (16%)	1 (7%)	NS
Orthopedic Problems	9 (20%)	3 (20%)	NS
Recent Revascularization	7 (16%)	2 (13%)	NS
Recent MI	33 (73%)	13 (87%)	NS
Anterior Wall MI	13 (29%)	4 (27%)	NS
Recent Angina Pectoris	14 (31%)	7 (47%)	NS
Total Cholesterol (mg/dL)	227 ± 44	244 ± 48	NS
Dyslipidemia	38 (84%)	13 (87%)	NS
Body Mass Index (kg/m^2)	26.0 ± 3.4	26.5 ± 2.2	NS
Prior Phase II Exercise Training Experience	20 (44%)	11 (73%)	0.10
Resting SBP (mmHg)	129 ± 23	127 ± 22	NS
Resting DBP (mmHg)	80 ± 11	74 ± 11	0.09
Medications			
Beta Blockers	15 (33%)	5 (33%)	NS
Calcium Channel Blockers	8 (18%)	7 (47%)	0.06
Diuretics	7 (16%)	5 (33%)	NS
Digitalis	7 (16%)	2 (13%)	NS
Nitrates	16 (36%)	5 (33%)	NS
Exercise Testing			
Angina during GXT	8 (18%)	2 (13%)	NS
ST_{60} Segment Depression (mm)	0.6 ± 1.1	0.9 ± 1.3	NS
ST_{60} Segment Shift ≥ 0.1 mV	15 (33%)	7 (47%)	NS
Complex Ventricular Ectopy	3 (7%)	4 (27%)	0.10
RPP5METs (bpm x mmHg x 10^2)	181 ± 50	164 ± 46	NS
Peak METs	7.7 ± 1.8	9.8 ± 2.6	0.008

Data are reported as number of cases or mean values $\pm$ SD. Percentages are shown in parentheses.

Table 5. Performance of Variables Predicting Improvement in Exercise Tolerance as Defined by RPP5METs (n = 60).

Performance Rates	Sets of Predictor Variables		
	Clinical	Exercise	All
Correctly Classified	83%	75%	87%
Sensitivity	87%	81%	92%
Specificity	78%	65%	78%

Clinical Set = Resting SBP (0.05) - Digitalis (2.32) - Recent Angina (1.64) + BB (1.43) - Pretrained (1.2) - 4.05   p < 0.01

Exercise Set = RPP5METs (0.03) - 3.99   p < 0.01

All Set = RPP5METs (0.05) + BB (5.02) - Dig (3.02) - AngGXT (3.30) - PkMETs (0.39) -6.07   p < 0.01

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Table 6. Performance of Variables Predicting Decline in Exercise Tolerance as Defined by RPP5METs (n = 60).

Performance Rates	Sets of Predictor Variables		
	Clinical	Exercise	All
Correctly Classified	88%	82%	83%
Sensitivity	30%	20%	30%
Specificity	100%	94%	94%

Clinical Set = Resting SBP (-0.06) + Pretrained (2.37) + Digitalis (1.69) + 3.57   p < 0.01

Exercise Set = RPP5METs (-0.04) + 4.62   p < 0.01

All Set = RPP5METs (-0.07) - Diuretics (3.42) + Digitalis (2.8) + 8.21   p < 0.01

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Table 7. Performance of Variables Predicting Improvement in Exercise Tolerance as Defined by pkMETs (n = 60).

Performance Rates	Sets of Predictor Variables		
	Clinical	Exercise	All
Correctly Classified	72%	83%	87%
Sensitivity	87%	98%	96%
Specificity	27%	40%	60%

Clinical Set = Ca Channel Blocker ( ) + HxHTN ( ) + Rest DBP ( ) +   p < 0.01

Exercise Set = pkMETs (-0.53) + Complex Vent. Ectopy (-1.94) + 6.02   p < 0.01

All Set = pkMETs (-0.74) - Diuretics (-2.06) - Complex Vent. Ectopy (2.26)   p < 0.01
    -Total Cholesterol (-0.02) + 12.04
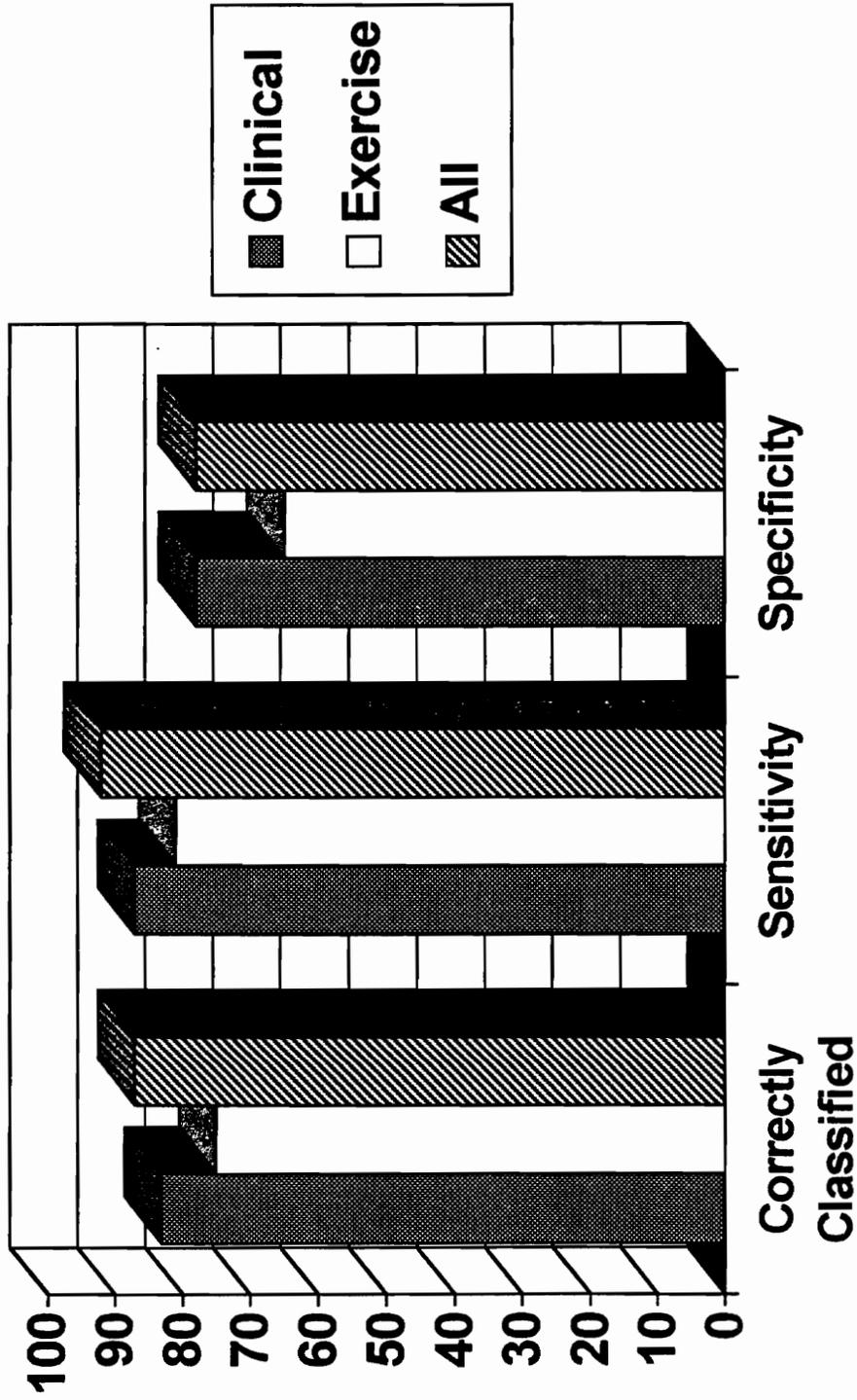
Figure 1. Performance of Models Predicting Improvement in Exercise Tolerance as Defined by RPP5METs (n = 60).
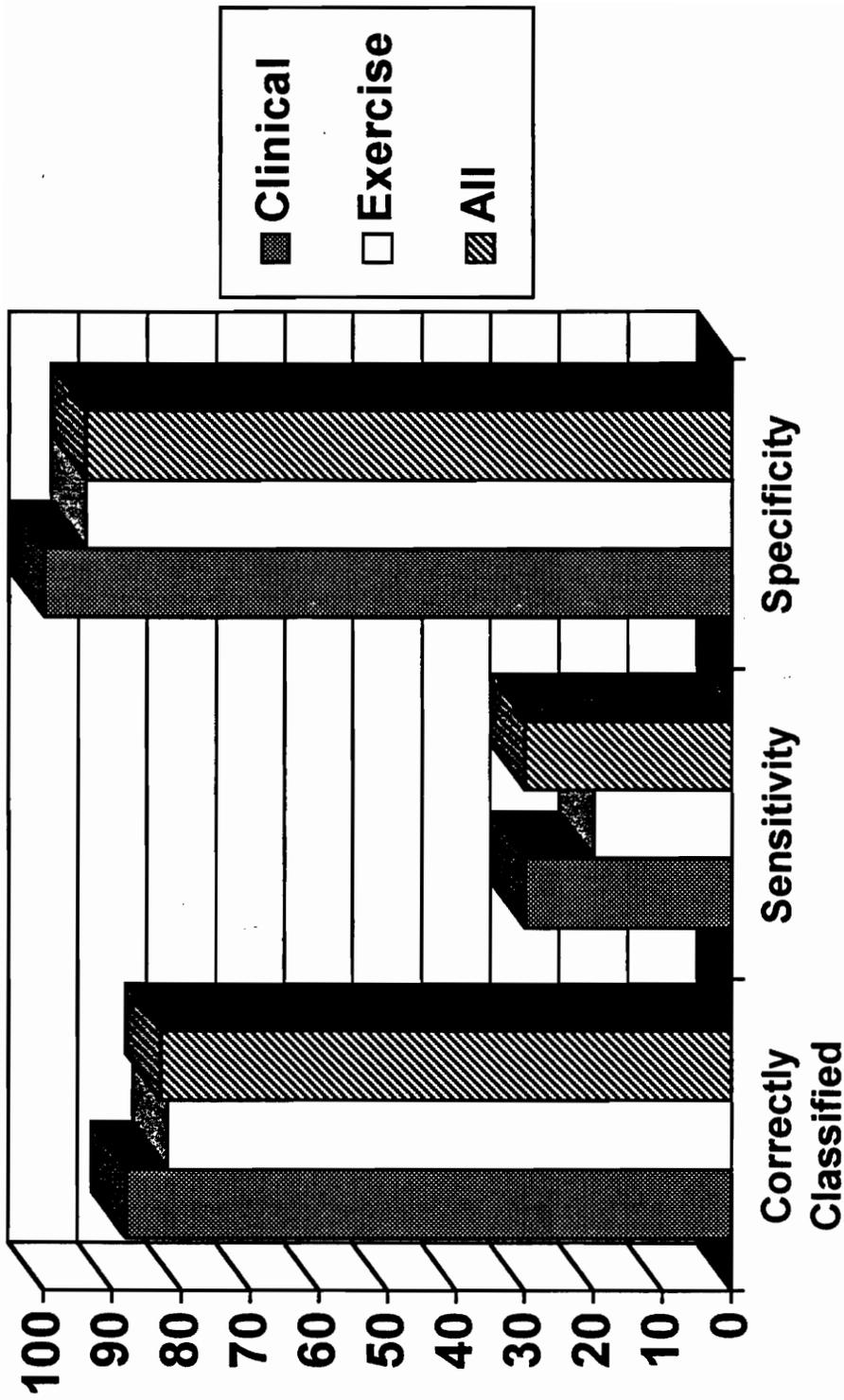
Figure 2. Performance of Models Predicting Decline in Exercise Tolerance as Defined by RPP5METs (n = 60).
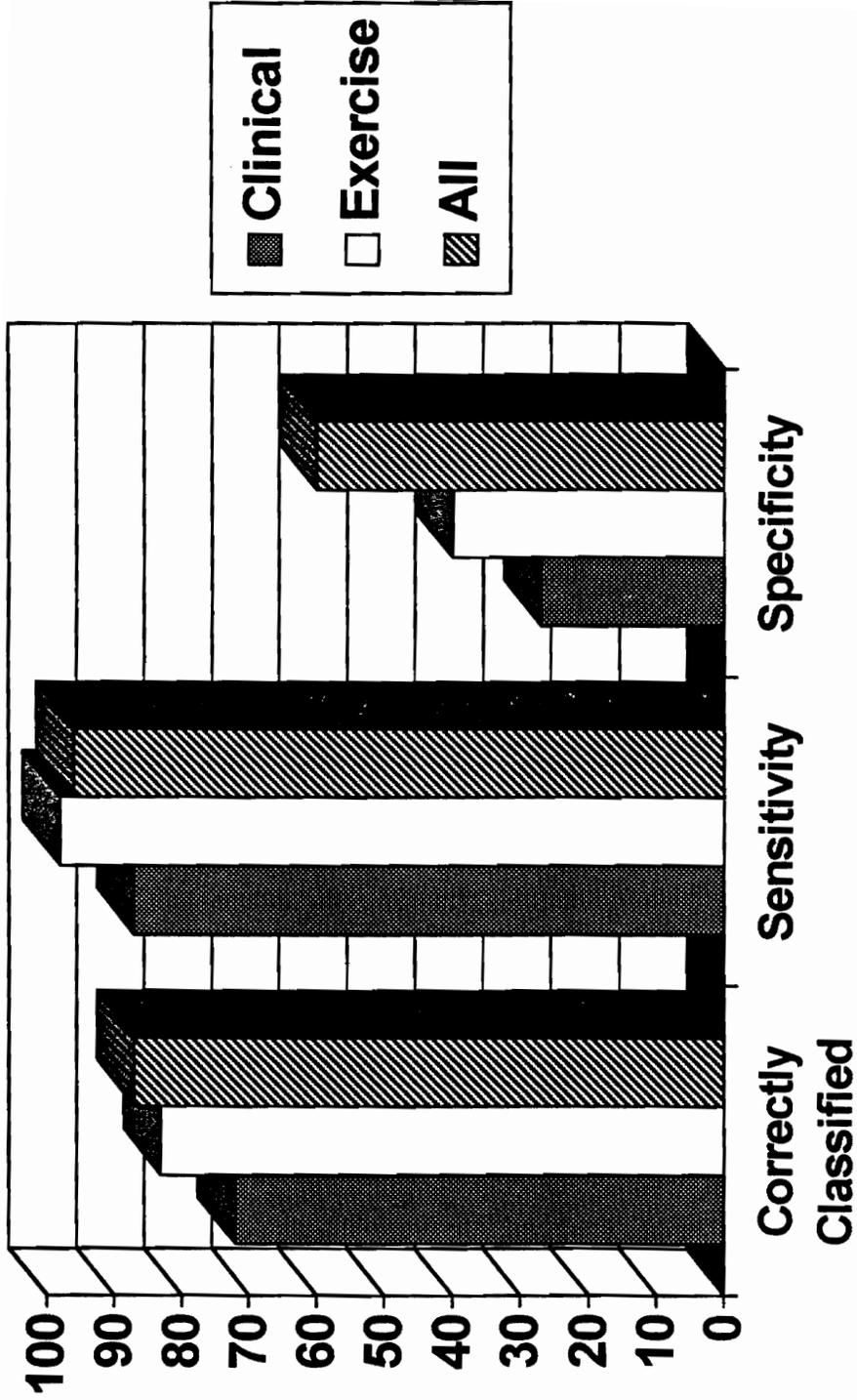
Figure 3. Performance of Models Predicting Improvement in Exercise Tolerance as Defined by pkMETs. n = 60

Chapter IV

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

Summary and Conclusions

Clinical and graded exercise test data were extracted from the records of 60 participants of the Cardiac Therapy and Intervention Center at Virginia Tech, from time of program entry. Data from a follow-up graded exercise test was also collected to allow investigators to quantify a change in exercise tolerance over the training period. The follow-up GXT was administered 5-9 months after program entry. The subject records were chosen on the basis that the patient had experienced a myocardial infarction, coronary artery revascularization surgery, physician diagnosed angina, or angiographically confirmed coronary artery disease. Patients were excluded from the pool of potential study candidates if there were documented changes in medications during the study interval that would potentially alter the cardiovascular response to exercise. Potential study candidates were also excluded if documentation was available to provide evidence that a patient attended less than 70% of the exercise sessions during the 5-8 month study period.

The study was conducted to: 1) study a new method for evaluating changes in exercise tolerance and 2) identify patient characteristics that are predictive of short-term changes in exercise tolerance, occurring in cardiac patients who participate in a health maintenance exercise program.

Two training outcome markers were used to assess improvement or decline in exercise tolerance in this study: 1) a derived score for rate-pressure product at a submaximal reference workload of 5 METs (RPP5METs) and 2) the more traditional marker of peak METs, as estimated from peak treadmill speed and grade (pkMETs). The RPP5METs score was derived through least squares linear regression using paired values

for RPP and MET level on each GXT. Patients were required meet a threshold for linearity between RPP response and work rate ($r \geq 0.90$) to be included in the study. Sixty patients met all criteria for the study. Outcome classification results obtained with the new RPP5METs method were compared to results obtained using the more traditional pkMETs marker.

All data analyses were performed using a True Epistat statistical software package. The data were analyzed using both univariate (chi-square and Student t-tests) and multivariate techniques (alternating forward-backward stepwise multiple logistic regression) to identify potential predictors of each outcome. Predictor variables were seperated into two distinct sets: 1) clinical variables and 2) exercise test variables. Data were analyzed in three trials for each outcome using multivariate techniques: first, clinical variables only were included in prediction model; second, exercise test variables only were included in model; and finally, the combined set of all predictors were included in the same prediction model.

Improvement in exercise tolerance. The most predictive attribute of improvement in exercise tolerance as defined by the RPP5METs outcome marker was a high baseline RPP5METs value. The most predictive attribute of improvement as defined by the pkMETs outcome marker was a low pkMET value. The absence of prior phase II exercise training experience was associated with an exercise tolerance improvement using both outcome markers. Variables selected by stepwise multiple logistic regression from the combined data set to predict improvement outcome as defined by RPP5METs were formulated into the following equation with beta coefficients:

y = RPP5METs (0.05) + beta blockers (5.02) - digitalis (3.02) - anginaGXT (3.30) - pkMETs (0.39) -6.07

Individual patient data must be substituted for the variables in the above formula and multiplied by beta coefficients, with the resultant sum then entered into the following probability formula, to obtain the predicted probability of training improvement for an individual patient:

$$p = 1/\ 1+ \exp(-y).$$

Variables selected by stepwise multiple logistic regression from the combined data set to predict improvement outcome as defined by pkMETs were formulated into the following equation with beta coefficients:

$y = pkMETs (-0.74) - Diuretics (2.06) - Complex Ventricular Ectopy (2.26) - Total Chol (0.02) +12.04$

Total classification rates were high (87%) for both of the above equations developed with the different outcome markers. However, specificty was much lower for the equation developed to predict improvement using the pkMETs outcome marker than the rate for the equation developed using the RPP5METs outcome marker (60% and 78% respectively). This finding reduces the utility of the pkMETs prediction equation and may be due to the fact that pkMETs has been shown to not be as reproducible as submaximal parameters when serial exercise tests are conducted (McInnis and Balady, 1994). It is concluded that improvement in exercise tolerance as defined by RPP5METs may be predicted with a high degree of accuracy using only clinical and exercise data collected at program entry. However, because classification rates were generated without an external sample, they are likely optimistic estimates of how these models would perform on an independent data set.

Decline in exercise tolerance. Patient attributes found to be predictive of decline in exercise tolerance as defined by RPP5METs were measures associated with high baseline fitness, as measured by peak METs, RPP5METs, resting systolic blood pressure, and prior formal exercise training in a phase II cardiac rehabilitation program. Patients who declined were also found to have a higher frequency of prescribed calcium antagonist medications.

Multivariate attempts to define equations that were predictive of decline outcome were unsuccessful due to low sensitivity. Previous research has shown psycho-social variables to be good predictors of decline in exercise tolerance over a training period.

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Thus, addition of psycho-social variables to a model containing clinical and exercise variables may possibly improve model performance.

Recommendations for Future Research

Although prediction of improved exercise tolerance outcome was found to be successful using clinical and exercise variables in the present study, addition of psycho-social parameters, especially indicators of depression, would likely improve model performance. This suggestion is based on research conducted by Milani, Littman, and Lavie that found depression to be a good predictor of improvement vs. no improvement in a group of 77 cardiac rehabilitation patients (Milani et al, 1993). In addition, Van Dixhoorn has shown that psycho-social variables are even more important to help predict decline in exercise tolerance (Van Dixhoorn, 1990). Future researchers should include these parameters as potential predictors when collecting variables for patient attribute sets.

The classification rates for all models presented in the present study were derived using the same sample of patients that were used to build the model. The lack of an independent sample of patients to externally validate each model's prediction success may potentially lead to erroneously high classification rates. Therefore, the models reported for prediction of improvement outcome need to be validated using an independent sample of patients before the models can be used in a clinical setting.

Due to the relatively small sample size in the present study, and a very small percentage of patients (20%) found to have a decline in exercise tolerance, the decline outcome group consisted of only 10 patients. The small number of patients in this outcome category may have added to the difficulty in identifying features predictive of decline outcome. Therefore, it is recommended that a sample size of approximately 200 patients be collected for decline outcome analysis and independent evaluation of decline prediction model. A sample size of 150 patients could then be used to build the model, with an estimated 30 patients having a decline outcome. The additional set of 50 patients

could then be used to independently evaluate performance success of the derived prediction model.

The above suggestions for larger sample sizes, external validation of prediction models, and inclusion of psycho-social variables as potential predictors should improve the quality of these prediction models.

References

Ades PA, Grunvald MH, Weiss RM, Hanson JS. Usefulness of myocardial ischemia as predictor of training effect in cardiac rehabilitation after acute myocardial infarction or coronary artery bypass grafting. **Am J Cardiol** 1989;63:1032-1036.

Ades PA, Huang D, Weaver SO. Cardiac rehabilitation predicts lower rehospitalization costs. **Am Heart J** 1992;123:916-921.

Ades PA, Waldmann ML, Poehlman ET, Gray P, Horton ED, Horton ES, LeWinter MM. Exercise conditioning in older coronary patients: submaximal lactate response and endurance capacity. **Circulation** 1993;88:572-577.

Ades PA, Waldmann ML, Polk DM, Coflesky JT. Referral patterns and exercise response in the rehabilitation of female coronary patients aged $\geq$ 62 years. **Am J Cardiol** 1992;69:1422-1425.

Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Montoye HJ, Sallis JF, Paffenbarger RS. Compendium of physical activities: classification of energy costs of human physical activities. **Med Sci Sports Exerc** 1993;25(1):71-80.

Astrand PO, Cuddy TE, Saltin B, Stenberg J. Cardiac output during submaximal and maximal work. **J Appl Physiol** 1964;19:268.

Astrand PO, Cuddy TE, Saltin B, Stenberg J. Intra-arterial blood pressure during exercise with different muscle groups. **J Appl Physiol** 1965;20:253.

Auchincloss JH, Gilbert R, Kuppinger M, Peppi D, Teperow-Putter K. One and three-minute exercise response in coronary artery disease. **J Appl Physiol** 1979;46(6) 1132-1137.

Balady GJ, Weiner DA. Physiology of exercise in normal individuals and patients with coronary heart disease. In Wenger NK, Hellerstein HK (eds): **Rehabilitation of the Coronary Patient** 3rd edition. (pp 103-18) Churchill Livingstone, New York, 1992.

Blumenthal JA, Rejeski WJ, Walsh-Riddle M, Emery CF, Miller H, Roark S, Ribisl PM, Morris PB, Brubaker P, Williams RS. Comparison of high and low intensity exercise training early after acute myocardial infarction. **Am J Cardiol** 1988;61:26-30.

Bohren BF, Hadzikadic M, Hanley EN. Extracting Knowledge from Large Medical Databases: An Automated Approach. **Comp Biomed Res** 1995;28:191-210.

Bondestam E, Breikss A, Hartford M. Effects of early rehabilitation on consumption of medical care during the first year after acute myocardial infarction in patients $\geq$ 65 years of age. **Am J Cardiol** 1995;75:767-771.

Braunwald E, Sobel BE. Coronary blood flow and myocardial ischemia. In **Heart Disease: A Textbook of Cardiovascular Medicine.** 3rd edition (pp1191-1221) W.B. Sanders Company, Philadelphia, Pennsylvania 1988.

Cannistra LB, Balady GJ, O'Malley CJ, Weiner DA, Ryan TJ. Comparison of the clinical profile and outcome of women and men in cardiac rehabilitation. **Am J Cardiol** 1992;69:1274-1279.

Carney RM, Rich MW, Tevelde A. Major depressive disorder in coronary artery disease. **Am J Cardiol** 1987;60:1273-1272.

Carter CL, Amundsen LR. Infarct size and exercise capacity after myocardial infarction. **J Appl Physiol** 1977;42(5):782-785.

Ciske PE, Dressendorfer RH, Gordon S, Timmis GC. Attenuation of exercise training in patients taking beta blockers during early cardiac rehabilitation. **Am Heart J** 1986;112:1016-1025.

Clausen JP, Trap-Jensen J. Heart rate and arterial blood pressure during exercise in patients with angina pectoris. **Circulation** 1971;44:1120.

Clausen JP, Trap-Jensen J, Lassen NA. The effects of training on the heart rate during arm and leg exercise. **Scand J Clin Lab Invest** 1970;26:295-301.

Clausen JP. Circulatory adjustments to dynamic exercise and effects of physical training in normal subjects and in patients with coronary artery disease. **Prog Cardiovasc Dis** 1976;18:459-492.

Coats AJ, Adamopoulos S, Meyer TE, Conway J, Sleight P. Effects of physical training in chronic heart failure. **Lancet** 1990;335:63-66.

Colan SD, Sanders SP, Borrow KM. Physiologic hypertrophy:effects on left ventricular systolic mechanics in athletes. **J Am Coll Cardiol** 1987; 9:776.

Conn EH, Williams RS, Wallace AG. Exercise responses before and after physical conditioning in patients with severely depressed left ventricular function. **Am J Cardiol** 1882;49:296-300.

Costill DL, Branam GE, Moore JC, Sparks K, and Turner C. Effects of physical training in men with coronary heart disease. **Med Sci Sports Exerc** 1974;6:95-100.

Cottin Y, Walker P, Rouhier-Marcer I, Cohen M, Louis P, Didier JP, Casillas JM, Wolf JE, and Brunotte F. Relationship between increased peak oxygen uptake and modifications in skeletal muscle metabolism following rehabilitation after myocardial infarction. **J Cardiopulmonary Rehabil** 1996;16:169-174.

Dalack GW, Roose SP. Perspectives on the relationship between cardiovascular disease and affective disorder. **J Clin Psychiatry** 1990;51(suppl. 7) 4-9.

DeBusk RF, Houston N, Haskell W, Fry F, Parker M. Exercise training soon after myocardial infarction. **Am J Cardiol** 1979; 44:1223-1229.

Desmond JG, Cowan JC. Normal myocardial function. In **Cardiology**. 6th edition. (p.3) Bailliére Tindall, London, 1992.

Detry JMR, Rousseau M, Vandenbrouke G, Kusumi F, Brasseur LA, Bruce RA. Increased arteriovenous oxygen difference after physical training in coronary heart disease. **Circulation** 1971;44:109-118.

Drews C, Ohnemus JM, Endsley K. (eds) American Association of Cardiovascular and Pulmonary Rehabilitation. **Guidelines For Cardiac Rehabilitation Programs.** 2nd edition. Champaign, IL: Human Kinetics, 1995.

DurstineJL, Pate RR, Branch JD. Cardiorespiratory reaponses to acute exercise. In Durstine JL, King AC, Painter PL, Roitman JL, Zwiren LD, Kenney WL (eds):**American College of Sports Medicine's Resource Manual for Guidelines for Exercise Testing and Prescription.** 2nd edition. (pp 66-74) Lea and Febiger, Philadelphia, Pennsylvania 1993.

Ehsani AA, Biello DR, Schultz J, Sobel BE, and Holloszy JO. Improvement of left ventricular contractile function by exercise training in patients with coronary artery disease. **Circulation** 1986;64:1116-1124.

Ehsani AA. Altered adaptive responses to training by nonselective beta-adrenergic blockade in coronary artery disease. **Am J Cardiol** 1985;58:220-224.

Eichner ER. Coagulability and rheology: hematologic benefits from exercise, fish, and aspirin. Implications for athletes and nonathletes. **Phys Sports Med** 1986;14:102-110.

Ekblom B, Hermansen L. Cardiac output in athletes. **J Appl Physiol** 1968;25:619.

Ekelund LG, Holmgren A. Central hemodynamics during exercise. **Circ Res** 1967;(1) 21:33.

Ekstrom J. Choline acetyl transferase in the heart and salivary glands of the rat after physical training. **Q J Exp Physiol** 1974;59:73-80.

Engblom E, Hietanen EK, Hamalainen H, Kallio V, Inberg M, Knuts LR. Exercise habits and physical performance during comprehensive rehabilitation after coronary artery bypass surgery. **Eur Heart J** 1992;13:1053-1059.

Ernst E. Influence of regular physical activity on blood rheology. **Eur Heart J** 1987;8(suppl.G):59-62.

Feigenbaum E, Carter E. **Cardiac rehabilitation services. Health technology assessment report**, 1987, no.6 Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, National Center for Health Services Research and Health Care Technology Assessment. DHHS publication no. PHS 88-3427. Aug. 1988.

Ferguson RJ, Petitclerc R, Choquette G, Chanitois L, Gautherier P, Huot R, Allard C, Jankowski L, and Campeau L. Effect of physical training on treadmill exercise capacity, collateral circulation and progression of coronary disease. **Am J Cardiol** 1974;34:764-769.

Ferguson RJ, Taylor AW, Côté P, Dinelle Y, Péronnet F, Champlain JD, Bourassa MG. Skeletal muscle and cardiac changes with training in patients with angina pectoris. **Am J Physiol** 1982;243:H830-H836.

Fioretti P, Simoons ML, Zwiers G, Baardman T, Brower RW, Kazemir M, and Hugenholtz PG. Value of predischarge data for the prediction of exercise capacity after cardiac rehabilitation in patients with recent myocardial infarction. **Eur Heart J** 1987;8(suppl G):33-38.

Fizman E, Frank AG, BenAri E. Altered left ventricular volume and ejection fraction responses to supine dynamic exercise in athletes. **Am J Coll Cardiol** 1990;15:582.

Fletcher GF, Cantwell JD, Watt EW. Oxygen consumption and hemodynamic responses of exercises used in training of patients with recent myocardial infarction. **Circulation** 1971;60:140-141.

Fletcher GF, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise Standards: A statement for health professionals from the American Heart Association. **Circulation** 1990;82(6):2286-2322.

Folta A, Metzger BL. Exercise and functional capacity after myocardial infarction. **Image: J Nurs Scholar** 1989;21(4):215-219.

Foster C, Pollock ML, Anholm JD, Squires RW, Ward A, Dymond DS, Rod JL, Saichek RP, Schmidt DH. Work capacity and left ventricular function during rehabilitation after myocardial revascularization surgery. **Circulation** 1984;69:748-755.

Franklin BA, Besseghini I, Golden LH. Low intensity conditioning: effects on patients with coronary heart disease. **Arch Phys Med Rehabil** 1978;59:276-280.

Franklin BA, Gordon S, Timmis GC. Amount of exercise necessary for the patient with coronary artery disease. **Am J Cardiol** 1992;69:1426-1432.

Froelicher VF, Herbert WG, Myers J, Ribisl P. How cardiac rehabilitation is being influenced by changes in health care delivery. **J Cardiopulmonary Rehabil** 1996;16:151-159.

Froelicher VF, Jensen D, Genter F, Sullivan M, McKirnan MD, Witztum k, Sharf J, Strong ML, Ashburn W. A randomized trial of exercise training in patients with coronary heart disease. **JAMA** 1984;252:1291-1297.

Froelicher VF, Myers J, Follansbee WP, Labovitz AJ. Effects of exercise on the heart and the prevention of coronary heart disease. In **Exercise and the Heart.** 3rd edition. (pp323-346) Mosby Year Book Inc., St. Louis, Missouri, 1993.

Frye RL, Higgins MW, Beller GA. Major demographic and epidemiologic trends affecting adult cardiology. **J Am Coll Cardiol** 1988;12:840-846.

Gamble P, Froelicher VF. Can an exercise program worsen heart disease? **Physician Sport Med** 1982;10(5):69-77.

Giannuzzi P, Tavazzi L, Temporelli PL, Corra U, Imparato A, Gattone M, Giordana A, Sala L, Schweiger C, Malinverni C. Long-term physical training and left ventricular remodeling after anterior myocardial infarction: results of the Exercise in Anterior Myocardial Infarction (EAMI) trial. **J Am Coll Cardiol** 1993;22:1821-1829.

Goble AJ, Hare DL, MacDonald PS, Oliver RG, Reid MA, Worcester MC. Effect of early programes of high and low intensity exercise on physical performance after transmural acute myocardial infarction. **Br Heart J** 1991;65:126-131.

Graettinger WF. The cardiovascular response to chronic physical exertion and exercise training: an echocardiographic review. **Am Heart J** 1984;108:1014.

Griffith TM, Lewis MJ, Newby AC, Henderson AH. Endothelium derived relaxing factor. **J Am Coll Cardiol** 1988;12:797.

Guyton AC, Hall JE. **Textbook of Medical Physiology.** 9th edition. W.B. Saunders Company, Philadelphia, Pennsylvania 1996.

Hagberg JM, Ehsani AA, and Holloszy JO. Effect of 12 months of intense exercise training on stroke volume in patients with coronary artery disease. **Circulation** 1983;67:1194-1199.

Hamm LF, Leon AS. Exercise training for the coronary patient. In: Wenger NK, Hellerstein HK (eds): **Rehabilitation of the Coronary Patient.** 3rd edition. (pp 367-402) Churchill Livingstone, New York, 1992.

Hammond HK, Kelly TL, Froelicher VF, Pewen W. Use of clinical data in predicting improvement in exercise capacity after cardiac rehabilitation. **J Am Coll Cardiol** 1985;6:19-26.

Hansen JE, Sue DY, Oren A, Wasserman K. Relation of oxygen uptake to work rate in normal men and men with circulatory disorders. **Am J Cardiol** 1987;59:669-74.

Hartley LH, Grimby G, Kilbom A, Nilsson NJ, Astrand I, Bjure J, Ekblom B, Saltin B. Physical training in sedentary middle-aged and older men: cardiac output and gas exchange during submaximal and maximal exercise. **Scand J Clin Lab Invest** 1969;24:335-344.

Hartley LH, Mason JW, Hogan RP, Jones LG, Kotchen TA, Mougey EH, Wherry FE, Pennington LL, Rickets PT. Multiple hormonal responses to prolonged exercise in relation to physical training. **J Appl Physiol** 1972; 33:607-610.

Hartung GH, Rangel R. Exercise training in post-infarction patients: comparison of results with high risk coronary and post-bypass patients. **Arch Phys Med Rehab** 1981;62:147-150.

Haskell WL, Durstine JL. Coronary heart disease. In Skinner JS. (ed) **Exercise Testing and Prescription for Special Cases: Theoretical Basis and Clinical Application.** 2nd edition. (pp 251-273) Lea and Febiger, Philadelphia, Pennsylvania 1993.

Haskell WL. Cardiovascular complications during exercise training of cardiac patients. **Circulation** 1978;57:920-924.

Herzil HO, Leutwyler R, Krayenbuhl HP. Silent myocardial ischemia: hemodynamic changes during dynamic exercise in patients with coronary artery disease despite absence of angina pectoris. **J Am Coll Cardiol** 1985;6:275.

Holloszy JO. Adaptations of muscular tissue to training. In Sonnenblick EH and Lesch M. (eds) **Exercise and Heart Disease.** (pp 25-38) Grune and Stratton Inc, New York, New York 1977.

Horgan D, Davies B, Hunt D. Psychiatric aspects of coronary artery surgery: a prospective study. **Med J Austr** 1984;141:587-590.

Hossack KF, Kusumi F, Bruce RA. Approximate normal standards of maximal cardiac output during upright exercise in women. **Am J Cardiol** 1981;47:1080.

Hossack KF. Maximal cardiac output during upright exercise: approximate normal standards and variations with coronary artery disease. **Am J Cardiol** 1980;46:204.

Hung J, Gordon EP, Houston N, Haskell WL, Goris ML, DeBusk RF. Changes in rest and exercise myocardial perfusion and left ventricular function 3 to 26 weeks after clinically uncomplicated acute myocardial infarction: effects of exercise training. **Am J Cardiol** 1984;54:943-950.

Katon W, Sullivan MD. Depression and chronic medical illness. **J Clin Psychiatry** 1990;51(suppl. 6) 3-11.

Keyser RE, Leutholtz BC, Moberg CH, Wendt VE. Adaptation of asymptomatic patients with coronary heart disease to an intense training stimulus. **J Cardiopulmonary Rehabil** 1991;11:378-385.

Kitamura K, Jorgensen CR, Gobel FL. Hemodynamic correlates of myocardial oxygen consumption during upright exercise. **J Appl Physiol** 1972;32:516.

Koyal SN. Ventilatory responses to the metabolic acidosis of treadmill and cycle ergometry. **J Appl Physiol** 1976;40:864.

Lavie CJ, Milani RV. Effects of cardiac rehabilitation and exercise training on exercise capacity, coronary risk factors, behavioral characteristics, and quality of life in women. **Am J Cardiol** 1995;75:340-343.

Lavie CJ, Milani RV. Patients with high baseline exercise capacity benefit from cardiac rehabilitation and exercise training programs. **Am Heart J** 1994;128:1105-1109.

LeMura LM, Duvillard SP, Bacharach DW. Central verusus peripheral adaptations for the enhancement of functional capacity in cardiac patients: a meta-analytic review. **J Cardiopulmonary Rehabil** 1990;10:217-223.

Lesch M, Sonnenblick EH. Alterations of cardiac structure and function in myocardial infarction. In Wenger NK, and Hellerstein HK (eds) **Rehabilitation of the Coronary Patient.** 1st edition. John Wiley and Sons INC., New York, NY 1978.

Levin LA, Perk J, Hedback B. Cardiac rehabilitation- a cost analysis. **J Intern Med** 1991;230:427-434.

Levy RI. Declining mortality in coronary heart disease. **Arteriosclerosis** 1981;1:312-325.

Londeree BR, Moeschberger ML. Effect of age and other factors on maximal heart rate. **Res Q Exerc Sports** 1982;53:297.

Longhurst JC, Kelly AR, Gonyea WJ, Mitchell JH. Echocardiographic left ventricular massess in distance runners and weightlifters. **J Appl Physiol** 1980;48:154.

Maron BJ. Structural differences of the athletic heart as defined by echocardiography. **J Am Coll Cardiol** 1986;7:191.

Martin WH, Heath G, Coyle EF, Bloomfield SA, Holloszy JO, and Ehsani AA. Effect of prolonged intense training on systolic tme intervals in patients with coronary artery disease. **Am Heart J** 1984;107:75-81.

May GA, Nagle FJ. Changes in rate-pressure product with physical training of individuals with coronary artery disease. **Phys Ther** 1984;64:1361-1366.

Mayou R, MacMahon D, Sleight P, Florencio MJ. Early rehabilitation after myocardial infarction. **Lancet** 1982;2:1399-1402.

McInnis KJ, Balady GJ. Comparison of submaximal exercise responses using the Bruce vs. modified Bruce protocols. **Med Sci Sports Exerc** 1994;26(1):103-107.

Milani RV, Littman AB, Lavie CJ. Depressive symptoms predict functional improvement following cardiac rehabilitation and exercise program. **J Cardiopulmonary Rehabil** 1993;13:406-411.

Monpere C, Francois G, Brochier M. Effects of a comprehensive rehabilitation programme in patients with three-vessel coronary disease. **Eur Heart J** 1988;9(suppl. M):28-31.

Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. **Am J Cardiol** 1987;59:23C-30C.

Nolewajka AJ, Kostuk WJ, Rechnitzer PA, Cunningham DA. Exercise and human collateralization: an angiographic and scintigraphic assessment. **Circulation** 1979;60:(1)114-121.

Oldridge N, Furlong W, Feeny D, Torrance G, Guyatt G, Crowe J, Jones N. Economic evaluation of cardiac rehabilitation soon after acute myocardial infarction. **Am J Cardiol** 1993;72:154-161.

Opie LH, Frishman WH, Thadani U. Calcium channel antagonists. In: Opie LH. (ed) **Drugs for the Heart.** 4th edition. (pp 50-82) W.B. Saunders Co. Philadelphia, Pennsylvania. 1995.

Ordway GA, Charles JB, Randall DC, Billman GE, Wekstein DR. Heart rate adaptation to exercise training in denervated dogs. **J Appl Physiol** 1982;52:1586-1590.

Picard MH, Dennis C, Schwartz RG, Ahn DK, Kraemer HC, Berger WE, Blumberg R, Heller R, Lew H, and DeBusk RF. Cost-benefit analysis of early return to work after uncomplicated myocardial infarction. **Am J Cardiol** 1989;63:1308-1314.

Pollock ML, Lowenthal DT, Foster C, Pels AE, Rod J, Stoiber J, Schmidt DH. Acute and chronic responses to exercise in patients treated with beta blockers. **J Cardiopulmonary Rehabil** 1991;11:132-144.

Redwood DR, Rosing DR, Epstein SE. Circulatory and symptomatic effects of physical training in patients with coronary artery disease and angina pectoris. **N Engl J Med** 1972;286:959-965.

Rerych SK, Scholz PM, Sabiston DC, Jones RH. Effects of exercise training on left ventricular function in normal subjects: A longitudinal study by radionuclide angiography. **Am J Cardiol** 1980;45:244.

Roberts WC. Morphologic aspects of coronary heart disease and its complications. In: Wenger NK, Hellerstein HK (eds): **Rehabilitation of the Coronary Patient.** 3rd edition. (pp 19-49) Churchill Livingstone, New York, 1992.

Roman O, Gutierrez M, Lusic I, Chavez E, Camuzzi AL, Villalon E, Klenner C, Cumsille F. Cardiac rehabilitation after acute myocardial infarction: 9-year controlled follow-up study. **Cardiology** 1983;70:223-231.

Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Wildenthal K, Chapman CB. Response to exercise after bed rest and after training. **Circulation** 1968;38(suppl 7):1-78.

Scheuer J. Physical training and intrinsic cardiac adaptations. **Circulation** 1973;47:677-680.

Schulman SP, Gerstenblith G. Cardiovascular changes with aging: the response to exercise. **J Cardiopulmonary Rehabil** 1989;9:12-16.

Smith KL, Layton K, Newmark JL, Diethrich EB. An intensive cardiovascular rehabilitation program for patients with disabling angina and diffuse coronary artery disease. **J Cardiopulmonary Rehabil** 1987;7:425-429.

Smokler PE, MacAlpin R, Alvaro A, and Kattus A. Reproducibility of a multi-stage near maximal treadmill test for exercise tolerance in angina pectoris. **Circulation** 1973;48:346.

Sonnenblick EH, Ross J, Braunwald E. Oxygen cunsumption of the heart. Newer concepts of its multifactoral determination. **Am J Cardiol** 1968;22:328.

Soo VW, Wang JS, Wang SP. Learning from a clinical database: an incremental concept formation approach. **Artificial Intelligence in Medicine** 1994; 6:249-261.

Stern MJ, Gorman PA, Kaslow P. Group counseling versus exercise therapy: a controlled intervention with subjects following myocardial infarction. **Arch Intern Med** 1983; 143:1719-1723.

Stern MJ, Pascale L, Mcloone JB. Psychosocial adaptation following an acute myocardial infarction. **J Chron Dis** 1976;29:513-526.

Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricualr dysfunction: hemodynamic and metabolic effects. **Circulation** 1988;78:506-515.

Sullivan MJ, Genter F, Savvides M, Roberts M, Myers J, Froelicher VF. The reproducibilty of hemodynamic, electocardiographic, and gas exchange data during treadmill exercise in patients with stable angina pectoris. **Chest** 1984; 86:375-382.

Sullivan MJ, McKirnan MD. Errors in predicting functional capacity for postmyocardial infarction patients using a modified Bruce protocol. **Am Heart J** 1984; 107:486-491.

Swenson JR, Abbey SE. Management of depression and anxiety disorders in the cardiac patient. In Pashkow FJ, Dafoe WA (eds) **Clinical Cardiac Rehabilitation: A Cardiologist's Guide.** (pp263-286) Williams and Wilkins, Baltimore, Maryland 1993.

Thadani V, West RO, Mathew TM, and Parker JO. Hemodynamics at rest and during supine and sitting bicycle exercise in patients with coronary artery disease. **Am J Cardiol** 1977;39:776.

Thompson P, Cullinane E, Lazarus B, Carleton R. Effect of exercsie training on the untrained limb exercise performance of men with angina pectoris. **Am J Cardiol** 1981;48:844.

Van Camp SP, Peterson RA. Cardiovascular complications of outpatient cardiac rehabilitation programs. **JAMA** 1986;256:1160-1163.

Van Dixhoorn J, Duivenvoorden HJ, Pool J. Success and failure of exercise training after myocardial infarction: Is the outcome predictable? **J Am Coll Cardiol** 1990;15:974-982.

Vanhees L, Fagard R, Amery A. Influence of beta-adrenergic blockade on the hemodynamic effects of physical training in patients with ischemic heart disease. **Am Heart J** 1984;108:270-275.

Vanhoutte PM. Adjustments in the peripheral circulation in chronic heart failure. **Eur Heart J** 1983;4:67-83.

Vanhoutte PM. The endothelium-modulator of vascular smooth muscle tone. **N Engl J Med** 1989; 319:512.

Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R. **Principles of Exercise Testing and Interpretation.** 2nd edition. Lea and Febiger, Philadelphia, Pennsylvania 1994.

Wasserman K, Whipp BJ. Exercise physiology in health and disease. **Am Rev Respir Dis** 1975;112:219-249.

Wenger NK, Froelicher ES, Smith LK. **Cardiac Rehabilitation. Clinical Practice Guideline No. 17.** Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute. AHCPR Publication No. 96-0672. October 1995.

Wilhelmsen L, Sanne H, Elmfeldt D, Grimby G, Tibblin G, Wedel H. A controlled trial of physical training after myocardial infarction: effects on risk factors, nonfatal reinfarction and death. **Prev Med** 1975; 4:491-508.

Wittels EH, Hay JW, Gotto AM. Medical costs of coronary artery disease in the United States. **Am J Cardiol** 1990;65:432-440.

Appendix A

Definitions for Predictor Variables

<u>Age</u> - patient age (years)

<u>TC</u> - total cholesterol (mg/dl)

<u>BMI</u> - body mass index

<u>Resting SBP</u> - resting systolic blood pressure (mmHg)

<u>Resting DBP</u> - resting diastolic blood pressure (mmHg)

<u>Exercise ST Dep</u> - peak horizontal or downsloping ST segment depression @ J_{60}

during the pre-training GXT. (mV)

<u>Peak METs</u> - peak METs attained on the pre-training GXT.

<u>RPP5METs</u> - rate-pressure product at workload predicted to elicit 5 MET

exercise demand. (mmHg x beats/min x 10^2)

<u>Complex Ventricular Ectopy</u> - coupled premature ventricular contractions or runs

of ventricular tachycardia

<u>Hx Smoking</u> - history of cigarette smoking

<u>Continued Smoking</u> - current smoking habit at time of exercise program entry.

<u>Orthopedic Problems</u> - orthopedic limitations.

<u>Recent Revasc</u> - revascularization procedure performed $\leq$ 6 months prior to

patient beginning the exercise program.

<u>Recent MI</u> - Myocardial infarction $\leq$ 6 months prior to patient beginning the

exercise program.

Recent Angina- cardiac chest pain within six months of beginning exercise

program, or since revascularization surgery or MI.

Hx HTN - history of hypertension, as indicated on the physican referral

Hx Dyslipidemia - history of dyslipidemia, as indicated on the physican referral.

Hx Diabetes - history of diabetes, as indicated on the physican referral.

Beta Blocker - use of beta blocker medication.

Ca Channel Blocker - use of calcium channel blocker medication.

Diuretic - use of diuretic medication.

Digitalis - use of digitalis medication.

Nitrates - use of nitate medications.

Angina GXT - typical or atypical angina during the graded exercise test.

Prior Ex Training - exercise training prior to entry into supervised training

program.

Anterior Wall MI - myocardial infarction affecting primarily the tissue of the

anterior wall of the left ventricle.

Exercise ST Shift - ECG ST segment displacement (depression or elevation) of

0.1 mV during exercise test.

Used in calculation of outcome

$RPP5METS_{PRE}$ - rate-pressure product response to a workload predicted to require a 5

MET exercise demand on the a patient during the pre-training graded

exercise test.

$RPP5METS_{POST}$ - rate-pressure product response to a workload predicted to require a 5 MET exercise demand on the a patient during the post-training graded exercise test.

$\Delta RPP5METS$ - difference in rate-pressure product at a predicted 5 MET exercise demand between the pre and post-training GXTs. This score is calculated by the following equation: $\Delta RPP5METS = RPP5METS_{post} - RPP5METS_{pre}$

$\%\Delta RPP5METS$ - difference in rate-pressure product at a predicted 5 MET exercise demand between the pre and post-training GXTs, expressed as a percentage of the pre-training graded exercise test. This score is calculated from the following equation: $\%\Delta RPP5METS = (RPP5METS_{post} - RPP5METS_{pre}) / RPP5METS_{pre}$

Appendix B
Detailed Methodology

Study patients. Data for this retrospective study were extracted from the clinical records of patients who had participated in the rehabilitation program at the Virginia Tech Cardiac and Intervention Center between January, 1977, and September, 1995. To be included, patient records must have included data recorded for at least three stages of a symptom-limited graded exercise test at the time of program entry and at another test within 5-8 months after beginning supervised exercise. Only patients who had previous myocardial infarction, coronary revascularization, physician diagnosed angina, or angiographically confirmed CAD were selected. Patients were excluded from the study for the following reasons: documented change in prescriptions of medication during the training program that would potentially alter hemodynamic responses or symptoms; attended less than a minimum of 70% of the exercise sessions during the training period. A total of 60 patients (58 men and 2 women) met the above criteria. The sample included: 77%, recent myocardial infarction; 15%, recent coronary revascularization; 33% receiving beta blocker medication.

Exercise testing. Graded exercise tests were performed on each patient using a modified Balke or similar protocol (i.e., increases in metabolic demand of ~2 METs every 2 minutes). Blood pressure and ECG were monitored throughout the tests by trained technicians using standard clinical methods. All hemodynamic measurements were obtained during supine and upright resting conditions and during the last minute of each exercise stage. A subjective rating of perceived exertion was also recorded during the last minute of each exercise stage. All tests were supervised and terminated by a physician.

Definition of treadmill test performance and training outcome criterion. For purposes of this study, two markers of exercise tolerance were used to assess fitness changes over the training period: 1) exercise tolerance was quantified as myocardial demand at a submaximal workload, i.e., the rate-pressure product at 5 METs

(RPP5METs); and 2) peak METs attained on the GXT (pkMETs), which was estimated from peak treadmill speed and grade. The two markers of exercise tolerance were then was used to compare pre-training to post-training GXTs. For each exercise test, the RPP5MET score was established through least squares linear regression in which RPP responses were regressed on the estimated MET level for speed and grade at each exercise stage. A resulting correlation of $r \geq 0.90$ was required for this relationship to qualify a patient's test for inclusion in the study. The RPP5MET value was derived for the pre-training GXT (RPP5METS$_{pre}$) and the post-training GXT (RPP5METS$_{post}$) from the regression equation. Then, the pre-training and post-training values for RPP5METs were used to calculate the change in RPP at 5 METs (ΔRPP5METS) for each patient over the exercise training period. Finally, the ΔRPP5METS score was expressed as a percentage of the initial score, using the following equation:

$$\Delta RPP5METS\% = (RPP5METS_{post} - RPP5METS_{pre})/ RPP5METS_{pre} \times 100\%$$

Thus a negative ΔRPP5METS% score would constitute an improvement in exercise performance and a positive score would constitute a decline in exercise performance.

The ΔRPP5METS% score was then used to categorize patients according to three outcomes:

1) improvement group, defined as a decrease of 10% or more, i.e., ΔRPP5METS% $\leq$ -10%

2) a decline group, defined as an increase of 10 or more, i.e., ΔRPP5METS% $\geq$ +10%

3) a no change group, defined as ΔRPP5METS% values between -10% and +10%.

The above thresholds ($\pm$ 10%) were chosen for ΔRPP5METS% because a 10% change was judged to have clinical relevance.

The change in pkMETs (ΔpkMETs) value between pre-training and post-training GXTs was also used to classify patients into outcome categories. The following thresholds were used:

1) improvement group, defined as ΔpkMETs $\geq$ +1 MET.

2) decline group, defined as ΔpkMETs $\leq$ -1 MET.

3) no change group, defined as ΔpkMETs between -1 MET and + 1 MET.

The data were analyzed to derive two separate prediction equations. When defining characteristics predictive of improvement, the no change group and decline group were combined to form a comparison "no improvement group". Likewise, for defining characteristics predictive of decline, the no change and improvement groups were combined to form a comparison "no decline group". The outcome variable was then coded as a dichotomy, representing either presence or absence of the outcome of interest.

Statistical Analyses

The association of training outcome with initial patient attributes was analyzed first using univariate methods and then by multivariate logistic regression. Data for all patients were analyzed to predict both improvement and decline in exercise tolerance. The analysis techniques were then repeated for a subgroup containing recent MI patients only.

Univariate Analysis

In the univariate approach to data analysis, the initial patient characteristics were tested as predictors of outcome with: 1) chi-square analysis for variables containing nominal data; and 2) Student t-test for variables of interval level.

Multiple Logistic Regression Analysis

The outcome variable in a logistic regression model is dichotomous, coded *one* for presence of a certain outcome and *zero* for its absence. An alternating forward-backward stepwise multiple logistic regression procedure was used in an attempt to identify the best prediction models for the two outcomes (improve and decline) based on the patient attributes obtained at program entry. The equation resulting from the logistic regression function consists of variables found to be the best predictors of outcome, along with their coefficients and a constant. This equation yields an estimation of the probability of a particular outcome for each patient. All 60 patients were used to develop these prediction equations.

Data were separated into a set of clinical variables and a set of exercise test variables before beginning the analyses. Three models then were developed for each outcome, first including clinical data only (Trial 1), then with exercise test variables only

(Trial 2) and then with a combined set of all data (Trial 3). The criteria for inclusion and exclusion of variables in the prediction model was $p < 0.10$ and $p > 0.15$, respectively. The prediction success of these models were evaluated by comparing the estimated outcome to the actual outcome for each patient. Correct classification rates were calculated, along with sensitivity, specificity for each model.

Appendix C   Key For Raw Data Codes

Variables Used in Assessing Training Outcome

ID -   patient identification number.

1RPP5METs -   rate-pressure product at 5 METs on baseline graded exercise test.

2RPP5METs -   rate-pressure product at 5 METs on follow-up graded exercise test.

rppchange -   difference between baseline and follow-up rate-pressure product at 5 METs work load.

%rppchange -   rppchange variable expressed as a percentage of the baseline value.

RppOutcome -   patient training outcome as defined by RPP5METs fitness marker.

1pkMETS -   peak METs on baseline GXT as estimated from peak treadmill speed and grade.

2pkMETS -   peak METs on follow-up GXT as estimated from peak treadmill speed and grade.

Pkchange -   difference between pkMETS on baseline and follow-up GXTs.

PkOutcome -   patient training outcome as defined by PkMETs fitness marker.

Predictor Variables

Age -   patient age in years.

Orthopedic -   presence of orthopedic problems.

RecRevasc -   recent revascularization procedure (< 6 months prior to exercise program entry).

Recent MI -   recent myocardial infarction (< 6 months prior to exercise program entry)

RecAngina -   recent angina pectoris (post-MI occurrence of angina or < 6 months for patients without recent MI.

HxHTN -   history of hypertension as indicated on physician referral.

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HxSmoking -   history of smoking tobacco.

ContSmoking -   current habit of tobacco smoking at time of entry into exercise program.

HxDyslipid -   history of dyslipidemia, as indicated on physician referral.

HxDM -   history of diabetes melitus.

TC -   total cholesterol.

Dyslipidemia -   presence of total cholesterol ≥ 240 or LDL subfraction ≥ 130.

BMI -   body mass index , kg of body weight divided by height squared in meters.

BBlocker -   beta adrenergic blocker medication.

CaChannel -   calcium channel blocker medication.

Diuretic -   diuretic medication.

Digitalis -   digitalis medication.

Nitrates -   nitrate medication.

RestSBP -   resting systolic blood pressure on baseline GXT.

RestDBP -   resting diastolic blood pressure on baseline GXT.

STDepGXT -   maximal ST segment depression on baseline GXT, measured at J_{60}.

STshift -   presence of 0.1 mv J_{60} ST segment depression or elevation on baseline GXT.

AnginaGXT -   presence of angina pectoris on baseline GXT.

Complex VE -   presence of complex ventricular ectopy on baseline GXT, defined as 2 or more PVCs in sequence.

Pretrained -   prior aerobic training in a formal phase II cardiac rehabilitation program.

Anterior MI -   Q wave myocardial infarction of the anterior wall of the left ventricle, as described in the physician's interpretation of the resting ECG.

Variables used to Describe Changes in Signs/Symptoms over Training Period

1Angina GXT -   presence of angina on the baseline GXT.

1STdep1mm -   presence of 1 mm of J_{60} ST depression on baseline GXT.

1STdep2mm -   presence of 2 mm of J_{60} ST depression on baseline GXT.

1Complex VE -   presence of complex ventricular ectopy on baseline GXT.

1RPE17 -   documentation of having achieved at least a rating of 17 on the borg 6-20 RPE scale, during baseline GXT.

1signs/symptoms -   other signs or symptoms during baseline GXT, including leg cramping, dizziness and shortness of breath.

1Weight -   the patient's weight at time of follow-up GXT.

2Angina GXT -   presence of angina on the follow-up GXT.

2STdep1mm -   presence of 1 mm of J_{60} ST depression on follow-up GXT.

2STdep2mm -   presence of 2 mm of J_{60} ST depression on follow-up GXT.

2Complex VE -   presence of complex ventricular ectopy on follow-up GXT.

2RPE17 -   documentation of having achieved at least a rating of 17 on the borg 6-20 RPE scale, during follow-up GXT.

2signs/symptoms -   other signs or symptoms during follow-up GXT, including leg cramping, dizziness and shortness of breath.

2Weight -   the patient's weight at time of follow-up GXT.

TrainingMonths -   the number of months elapsed between baseline and follow-up GXTs.

Appendix D Raw Data
Raw Data Used to Define Peak and Submaximal Training Outcomes

ID	1RPP5METs	2RPP5METs	rppchange	%rppchange	RppOutcome	1pkMETS	2pkMETS	PKchange	PkOutcome
1	117	135	18	15	-1	6.2	8.5	2.3	1
2	173	150	-23	-13	1	11.1	12.1	1.0	1
3	232	148	-84	-36	1	11.1	16	4.9	1
4	80	102	22	28	-1	11.1	13	1.9	1
5	181	172	-9	-5	0	7.4	9.5	2.1	1
6	100	81	-19	-19	1	9.5	13	3.5	1
12	91	121	30	33	-1	13.0	12.1	-0.9	0
13	213	208	-5	-2	0	9.5	11.2	1.7	1
16	142	157	15	11	-1	11.6	11.1	-0.5	0
17	213	163	-50	-23	1	11.1	11.2	0.1	0
18	146	138	-8	-5	0	13.0	12.9	-0.1	0
19	122	149	27	22	-1	13.9	13.9	0.0	0
20	173	158	-15	-9	0	11.1	11.2	0.1	0
22	162	148	-14	-9	0	6.4	9.5	3.1	1
23	216	162	-54	-25	1	7.6	9.5	1.9	1
24	123	147	24	20	-1	9.5	13	3.5	1
25	198	118	-80	-40	1	7.4	12.1	4.7	1
26	95	83	-12	-13	1	9.5	11.2	1.7	1
27	211	183	-28	-13	1	7.4	9.5	2.1	1
29	212	165	-47	-22	1	7.4	9.5	2.1	1
31	161	140	-21	-13	1	4.5	7.4	2.9	1
32	134	84	-50	-37	1	10.5	10.1	-0.4	0
34	235	208	-27	-11	1	8.5	9.5	1.0	1
36	213	183	-30	-14	1	7.4	8.5	1.1	1
38	223	198	-25	-11	1	7.6	11.2	3.6	1
40	208	163	-45	-22	1	7.4	9.5	2.1	1
41	173	128	-45	-26	1	5 4	5.5	0.1	0
42	126	190	60	51	-1	10.5	11.2	0.7	0
43	150	132	-18	-12	1	7.6	8.5	0.9	0
44	226	201	-25	-11	1	6.4	9.6	3.2	1
45	205	112	-93	-45	1	5.4	8.5	3.1	1
50	234	172	-62	-26	1	7.6	7.4	-0.2	0
55	129	110	-19	-15	1	5.4	6.4	1.0	1
57	114	116	2	2	0	10.5	12	1.5	1
58	125	114	-11	-9	0	8.5	15.3	6.8	1
59	147	150	3	2	0	7.4	11.8	4.4	1
63	199	162	-37	-19	1	5.4	9.5	4.1	1
65	222	240	18	8	0	7.4	7.2	-0.2	0
70	163	149	-14	-9	0	11.1	13.9	2.8	1
71	134	160	26	19	-1	8.5	11.8	3.3	1
74	127	119	-8	-6	0	8.5	9.5	1.0	1
75	211	167	-44	-21	1	7.4	8.5	1.1	1
76	110	97	-13	-12	1	8.6	8.5	-0.1	0
77	167	184	17	10	-1	5.4	8.5	3.1	1
78	224	214	-10	-4	0	6.4	6.4	0.0	0
80	240	200	-40	-17	1	7.4	9.5	2.1	1
81	200	136	-64	-32	1	8.5	12.3	3.8	1
82	127	141	14	11	-1	9.5	11.6	2.1	1
83	170	115	-55	-32	1	7.4	11.8	4.4	1
84	117	126	9	8	0	8.3	10.5	2.2	1
87	171	144	-27	-16	1	8.5	12	3.5	1
88	204	179	-25	-12	1	9.5	9.5	0.0	0
89	240	204	-36	-15	1	4.3	6.4	2.1	1
90	233	204	-29	-12	1	6.4	10.5	4.1	1
91	134	121	-13	-10	1	8.5	10.2	1.7	1
92	247	186	-61	-25	1	6.4	9.5	3.1	1
94	279	185	-94	-34	1	5.4	7.4	2.0	1
95	276	197	-79	-29	1	4.3	8.5	4.2	1
96	202	143	-59	-29	1	7.4	8.5	1.1	1
97	193	132	-61	-32	1	6.5	12.3	5.8	1

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Raw Data for Clinical and Exercise Test Variables Screened for Utility in Predicting Outcome

ID	Age	Orthopedic	RecRevasc	RecentMI	RecAngina	HxHTN	HxSmoking	ContSmoking	HxDyslipid
1	57	0	0	0	1	0	1	0	0
2	64	1	0	1	1	0	1	0	1
3	56	0	1	0	0	0	1	0	1
4	63	0	0	1	0	0	0	0	1
5	63	0	1	0	0	0	1	0	1
6	64	0	0	1	0	1	1	0	0
12	49	0	1	1	1	0	1	0	1
13	60	1	0	0	0	1	1	0	1
16	63	0	0	1	1	1	0	0	0
17	71	0	0	1	0	1	0	0	1
18	44	0	0	1	0	0	1	0	0
19	48	0	0	1	1	1	1	1	1
20	57	1	0	1	0	0	1	0	0
22	58	0	0	1	0	0	1	0	1
23	70	1	1	1	0	0	1	0	0
24	59	0	0	1	0	0	0	0	0
25	47	1	1	1	0	0	0	0	0
26	64	0	0	0	1	1	1	1	0
27	75	1	0	0	0	0	0	0	0
29	70	0	1	0	0	0	0	0	1
31	62	0	0	1	0	0	1	0	0
32	42	0	0	1	0	0	1	0	1
34	65	1	1	0	0	0	0	0	1
36	59	0	0	1	0	0	1	0	0
38	75	1	1	1	0	1	1	0	1
40	55	0	0	1	0	0	1	1	1
41	48	0	1	0	1	1	0	0	0
42	55	1	0	1	0	0	1	0	0
43	63	0	0	1	0	1	1	0	0
44	67	0	0	1	1	1	1	0	1
45	56	0	0	1	1	1	1	0	0
50	56	0	0	1	0	1	0	0	0
55	61	0	0	0	1	0	1	1	0
57	39	0	0	0	1	1	1	0	1
58	39	0	0	1	1	0	1	0	0
59	56	0	0	1	1	0	1	1	0
63	63	0	0	1	0	1	0	0	0
65	67	0	0	1	1	1	0	0	1
70	47	0	0	1	0	1	1	0	1
71	65	0	0	1	0	0	0	0	1
74	58	0	0	1	1	0	0	0	0
75	54	1	0	1	0	1	1	0	0
76	68	0	0	1	0	1	0	0	1
77	61	0	0	1	0	0	0	0	1
78	60	1	0	0	1	1	0	0	1
80	36	0	0	1	1	1	0	0	1
81	52	0	0	1	0	0	1	1	1
82	62	0	0	1	0	1	0	0	0
83	45	0	0	1	0	0	1	0	0
84	50	1	0	1	1	0	0	0	1
87	53	0	0	0	1	0	1	0	1
88	54	0	0	1	1	1	1	1	1
89	49	0	0	1	0	0	0	0	1
90	47	0	0	1	0	1	0	0	0
91	51	0	0	1	0	0	0	0	0
92	44	0	0	1	0	1	0	0	0
94	55	0	0	1	0	1	1	0	1
95	39	0	0	0	1	1	1	1	1
96	55	0	0	1	0	0	1	1	0
97	41	0	0	1	0	0	0	0	0

Raw Data for Clinical and Exercise Test Variables Screened for Utility in Predicting Outcome (cont.)

ID	HxDM	TC	Dyslididemia	BMI	BBlocker	CaChannel	Diuretic	Digitalis	Nitrates	RestSBP
1	0	245	1	25.8	1	0	0	0	1	122
2	0	255	1	27.8	0	1	0	0	0	130
3	0	227	1	24.6	0	0	0	0	0	112
4	0	246	1	21.7	0	1	0	1	0	102
5	1	188	1	28.6	0	0	0	0	0	128
6	0	265	1	32.2	1	0	1	0	0	118
12	0	219	1	27.7	1	1	0	0	0	94
13	0	223	1	25.0	0	1	0	0	0	156
16	0	231	1	23.0	0	1	0	0	0	108
17	0	225	1	28.5	0	1	0	0	1	150
18	0	177	0	25.5	0	0	0	0	0	110
19	0	207	1	24.3	0	1	0	0	0	124
20	0	216	1	25.5	0	0	0	1	1	130
22	0	209	1	24.0	0	0	0	0	1	140
23	0	185	1	27.5	0	0	0	0	0	120
24	0	271	1	27.4	1	0	0	0	0	112
25	1	154	0	28.5	0	0	0	0	0	126
26	0	176	0	26.4	1	0	1	0	1	116
27	0	211	1	23.6	0	0	0	0	0	132
29	0	276	1	27.5	0	1	0	0	1	158
31	0	222	1	24.9	1	0	0	1	1	112
32	0	303	1	22.1	1	0	0	0	0	112
34	0	193	1	25.5	0	0	0	0	0	124
36	1	250	1	23.9	0	0	0	0	0	136
38	0	245	1	25.2	0	1	0	1	1	160
40	0	230	1	28.8	0	0	0	0	0	130
41	1	225	1	27.1	1	0	1	0	1	145
42	0	288	1	27.1	0	1	0	0	0	108
43	0	187	0	27.5	1	0	1	0	0	170
44	1	168	1	38.3	0	1	0	0	1	168
45	0	195	1	20.0	1	0	0	0	0	134
50	0	320	1	28.2	0	0	1	0	0	140
55	0	180	0	26.4	1	1	1	0	1	108
57	0	320	1	23.8	1	0	0	0	1	120
58	0	199	0	27.6	1	0	0	0	0	100
59	0	209	1	27.0	0	0	0	0	0	138
63	1	196	1	29.2	1	0	0	0	0	172
65	0	285	1	26.2	0	1	1	0	1	120
70	0	230	1	22.9	0	1	0	0	0	110
71	0	227	1	22.6	0	0	0	0	1	100
74	0	152	0	23.7	0	0	0	0	1	104
75	0	258	1	25.1	1	0	1	1	0	198
76	0	205	1	25.1	1	1	0	0	0	104
77	0	261	1	26.3	0	0	0	1	1	120
78	0	325	1	29.2	0	0	1	1	1	160
80	0	280	1	29.8	1	0	0	0	0	160
81	0	275	1	27.7	0	0	0	0	1	120
82	1	170	0	23.9	1	0	1	1	1	130
83	0	225	1	28.2	0	0	0	0	0	118
84	0	225	1	24.6	0	0	1	1	1	90
87	0	240	1	25.8	1	0	0	0	0	122
88	0	250	1	29.9	0	0	0	0	0	128
89	0	360	1	21.3	0	0	0	0	0	102
90	0	239	1	23.6	0	0	0	0	0	164
91	0	153	0	20.7	0	0	0	0	0	112
92	0	217	1	26.0	0	0	0	0	0	143
94	0	250	1	23.3	0	0	0	0	0	156
95	1	310	1	33.0	1	0	1	0	1	125
96	0	210	1	20.4	0	0	0	0	0	118
97	0	205	1	27.7	0	0	0	0	0	132

Raw Data for Clinical and Exercise Test Variables Screened for Utility in Predicting Outcome (cont.)

ID	RestDBP	STDepGXT	STshift	AnginaGXT	ComplexVE	Pretrained	AnteriorMI	1RPP5METs	1pkMETS
1	78	2	1	1	0	0	0	117	6.2
2	74	0	0	0	0	1	1	173	11.1
3	78	2	1	0	0	1	0	232	11.1
4	74	0	0	0	0	1	1	80	11.1
5	86	1	1	0	0	0	0	181	7.4
6	70	2.5	1	0	0	1	0	100	9.5
12	66	0	0	0	0	1	0	91	13.0
13	84	2	1	0	0	0	0	213	9.5
16	70	2.5	1	0	0	1	1	142	11.6
17	70	1	1	0	1	1	0	213	11.1
18	70	0	0	0	0	1	0	146	13.0
19	70	1.5	1	0	0	1	0	122	13.9
20	70	0	0	0	0	1	1	173	11.1
22	76	0	0	0	0	0	1	162	6.4
23	78	0	0	0	0	1	0	216	7.6
24	60	0	0	1	0	1	0	123	9.5
25	88	0	0	0	0	0	0	198	7.4
26	68	4	1	0	0	1	0	95	9.5
27	70	2	1	0	0	0	0	211	7.4
29	64	0	0	0	0	0	0	212	7.4
31	80	0	0	1	0	0	0	161	4.5
32	60	0.5	0	0	0	1	1	134	10.5
34	78	0	0	0	1	0	0	235	8.5
36	82	4	1	0	0	0	1	213	7.4
38	70	0	0	0	0	1	1	223	7.6
40	88	0	1	0	0	0	1	208	7.4
41	78	1	1	1	0	0	0	173	5.4
42	64	0	0	0	1	1	1	126	10.5
43	80	2	1	0	1	1	0	150	7.6
44	74	1	1	0	1	0	0	226	6.4
45	98	0	0	0	0	1	0	205	5.4
50	90	0	0	0	0	0	0	234	7.6
55	76	0.5	0	1	0	0	0	129	5.4
57	82	1	1	1	0	1	0	114	10.5
58	80	0	0	0	0	1	0	125	8.5
59	84	0	0	0	0	1	0	147	7.4
63	72	0	1	0	0	0	1	199	5.4
65	80	4.5	1	1	1	1	0	222	7.4
70	76	0	0	0	0	1	1	163	11.1
71	70	0	0	0	0	1	0	134	8.5
74	68	0	0	1	0	1	1	127	8.5
75	112	0	0	0	0	1	0	211	7.4
76	60	0	0	0	0	1	0	110	8.6
77	74	0	0	0	0	1	1	167	5.4
78	100	0	0	0	0	0	0	224	6.4
80	100	0	0	0	0	0	0	240	7.4
81	72	1	1	0	0	0	0	200	8.5
82	86	0	0	0	0	1	0	127	9.5
83	78	0	0	0	1	1	1	170	7.4
84	80	0	0	0	0	0	1	117	8.3
87	84	2	1	1	0	0	0	171	8.5
88	86	1	1	0	0	0	0	204	9.5
89	70	0	0	0	0	0	0	240	4.3
90	94	0	0	0	0	0	0	233	6.4
91	70	0	0	0	0	1	1	134	8.5
92	96	0	0	0	0	0	0	247	6.4
94	110	1	1	1	0	0	0	279	5.4
95	86	0	0	0	0	0	0	276	4.3
96	82	0	0	0	0	0	0	202	7.4
97	80	0	0	0	0	0	0	193	6.5

Raw Data Collected from Baseline GXT to Describe Changes in Signs/Symptoms over Training Period

ID	1AnginaGXT	1STdep1mm	1STdep2mm	1ComplexVE	1RPE17	1signs/symp	1Weight
1	1	1	1	0	0	0	85.4
2	0	0	0	0	0	1	92
3	0	1	1	0	1	1	82.5
4	0	0	0	0	0	1	76.6
5	0	0	0	0	1	0	76.9
6	0	1	1	0	0	0	65.9
12	0	0	0	0	1	1	83
13	0	1	1	0	1	1	82
16	0	1	1	0	0	0	79.4
17	0	1	0	1	1	0	104
18	0	0	0	0	0	0	79.1
19	0	1	0	0	0	0	69.4
20	0	0	0	0	0	0	67
22	0	0	0	0	0	0	69.1
23	0	0	0	0	1	0	82.2
24	1	0	0	0	0	0	89.8
25	0	0	0	0	0	0	87.2
26	0	1	1	0	0	0	87.6
27	0	1	1	0	1	1	67.3
29	0	0	0	0	0	0	82.4
31	1	0	0	0	0	0	73.8
32	0	0	0	0	1	0	66
34	0	0	0	1	0	0	74.6
36	0	1	1	0	0	0	77.3
38	0	0	0	0	0	0	74.5
40	0	0	0	0	0	0	88.2
41	1	1	0	0	1	0	85.9
42	0	0	0	1	0	0	87.8
43	0	1	1	1	1	0	81.5
44	0	1	0	1	1	0	84
45	0	0	0	0	0	0	66.8
50	0	0	0	0	0	0	80
55	1	0	0	0	0	1	75.5
57	1	1	0	0	0	0	82.8
58	0	0	0	0	0	0	86.5
59	0	0	0	0	0	0	81.8
63	0	0	0	0	0	1	79.5
65	1	1	1	1	1	0	69.7
70	0	0	0	0	1	0	64
71	0	0	0	0	0	0	67.2
74	1	0	0	0	0	1	68.4
75	0	0	0	0	0	0	81.9
76	0	0	0	0	0	0	81.7
77	0	0	0	0	0	0	76.4
78	0	0	0	0	0	0	88.3
80	0	0	0	0	0	0	98.2
81	0	1	0	0	0	0	90.1
82	0	0	0	0	0	0	75
83	0	0	0	1	0	1	80
84	0	0	0	0	0	1	76.7
87	1	1	1	0	0	0	74.8
88	0	1	0	0	0	0	93.2
89	0	0	0	0	0	1	63.6
90	0	0	0	0	1	0	72
91	0	0	0	0	1	0	64.4
92	0	0	0	0	1	0	90.5
94	1	1	0	0	0	0	69.8
95	0	0	0	0	0	0	95
96	0	0	0	0	0	0	60
97	0	1	0	0	0	0	82.8

Raw Data Collected From Follow-up GXT to Describe Changes in Signs/Symptoms over the Training Period

ID	2AnginaGXT	2STdep1mm	2STdep2mm	2ComplexVE	2RPE	2signs/symp	2Weight	TrainingMonths
1	1	1	1	0	1	0	80	7
2	0	0	0	0	0	0	92.8	6
3	0	0	0	0	1	0	80.5	5.2
4	0	0	0	0	0	0	74.5	6
5	0	0	0	0	1	0	75.6	6
6	0	1	1	0	1	0	68.5	6
12	0	0	0	0	0	0	80.9	6.2
13	0	1	1	1	1	0	79.8	9.5
16	0	1	1	0	1	0	76.2	6.2
17	0	0	0	0	0	0	105	7
18	0	0	0	0	0	0	79.1	5
19	0	0	0	0	1	0	68	6.2
20	0	0	0	0	0	0	66.5	6.2
22	0	0	0	0	0	0	64.2	5.5
23	0	0	0	0	1	0	84.4	7
24	0	0	0	0	1	0	90.4	6
25	0	0	0	0	1	0	97.4	5.5
26	0	1	1	0	0	0	88.6	9.5
27	0	0	0	0	0	1	69	7
29	0	0	0	0	0	0	77	9.5
31	1	0	0	0	0	0	73.1	6.2
32	0	0	0	0	1	0	64.5	6.4
34	0	0	0	0	0	0	73	7
36	0	1	1	0	0	0	75.9	7
38	1	0	0	1	0	0	74.5	5.4
40	0	1	0	0	0	0	85.5	5.6
41	1	1	0	0	1	0	83.2	6
42	0	0	0	0	0	0	90.9	7
43	0	0	0	0	0	0	79.8	6.2
44	0	0	0	0	0	0	85.7	5.2
45	0	0	0	0	0	1	64.2	9.4
50	0	0	0	0	0	0	78	6.4
55	0	0	0	0	0	0	76.5	8.4
57	1	1	0	0	0	0	81.7	5
58	0	0	0	0	1	0	86.6	5.4
59	0	0	0	0	0	0	77.6	6
63	0	0	0	0	1	0	81.5	6.3
65	0	0	0	0	1	0	66.9	9.4
70	0	0	0	0	1	0	62.4	9.3
71	0	0	0	0	1	0	65.8	6.3
74	0	0	0	0	1	0	68	6.4
75	0	0	0	0	0	0	86.3	9
76	0	0	0	0	0	0	84	6.4
77	0	1	0	0	0	0	76.4	6.2
78	0	1	0	0	0	0	85.5	6
80	1	0	0	0	0	0	99.3	7
81	0	1	0	1	0	0	79.3	8
82	0	0	0	0	0	0	75	5.2
83	0	1	1	0	0	1	80.1	8
84	0	0	0	0	0	0	75	7
87	1	1	1	0	0	0	73.3	8
88	0	0	0	0	0	1	95.2	8
89	0	0	0	0	0	0	66.1	6
90	0	0	0	0	1	0	70.7	5.5
91	0	0	0	0	1	0	64.4	6
92	0	0	0	0	0	0	85.9	9
94	0	1	0	0	0	0	79.3	6
95	0	0	0	0	0	0	86.8	7
96	0	0	0	1	0	0	58.6	6
97	0	0	0	0	0	0	78.3	6

Raw Data Extracted From Baseline GXT

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
1	3/4/81	2	0	75	124	78	11	2.5	93
1	3/4/81	3	2.5	84	140	78	13	4.3	118
1	3/4/81	3	7	85	145	80	–	6.2	123
2	1/3/91	3	0	112	126	74	7	3.3	141
2	1/3/91	3	5	124	148	72	8	5.4	184
2	1/3/91	3	10	140	154	72	10	7.4	216
2	1/3/91	3	15	154	166	72	12	9.5	256
2	1/3/91	3.4	16	168	184	72	15	11.1	309
3	8/14/91	3	0	118	148	78	10	3.3	175
3	8/14/91	3	5	137	182	92	13	5.4	249
3	8/14/91	3	10	149	208	92	15	7.4	310
3	8/14/91	3	15	162	222	91	16	9.5	360
3	8/14/91	3.4	16	171	230	86		11.1	393
4	2/20/86	3	0	73	102	74	–	3.3	74
4	2/20/86	3	5	80	102	74	11	5.4	82
4	2/20/86	3	10	85	102	74	11	7.4	87
4	2/20/86	3	15	93	110	74	12	9.5	102
4	2/20/86	3.4	16	101	128	74	13	11.1	129
5	5/21/84	3	0	136	128	86	6	3.3	174
5	5/21/84	3	5	136	130	86	13	5.4	177
5	5/21/84	3	10	150	132	84	17	7.4	198
6	8/29/84	3	0	79	118	70	–	3.3	93
6	8/29/84	3	5	86	118	70	11	5.4	101
6	8/29/84	3	10	93	118	70	13	7.4	110
6	8/29/84	3	12.5	96	128	70	–	8.5	123
6	8/29/84	3	15	96	128	70	15	9.5	123
12	4/16/91	3	0	83	98	66	7	3.3	81
12	4/16/91	3	5	92	100	68	10	5.4	92
12	4/16/91	3	10	102	104	64	13	7.4	106
12	4/16/91	3	15	113	122	70	15	9.5	138
12	4/16/91	3.4	16	122	132	70	16	11.1	161
12	4/16/91	3.4	20	124	–	–	20	13.0	–
13	9/7/90	3	0	130	144	84	11	3.3	187
13	9/7/90	3	5	144	–	–	14	5.4	–
13	9/7/90	3	10	154	164	86	16	7.4	253
13	9/7/90	3	15	165	166	86	18	9.5	274
16	2/10/87	2	0	87	130	82	8	2.5	113
16	2/10/87	2	7	99	136	80	8	4.5	135
16	2/10/87	2.5	10.5	109	140	80	10	6.5	153
16	2/10/87	3	12.5	126	152	80	–	8.5	192
16	2/10/87	3	17.5	143	154	80	13	10.5	220
16	2/10/87	3	20	150	169	84	–	11.6	254
17	7/18/91	2.5	1.5	110	160	74	7	3.4	176
17	7/18/91	2.5	7.5	117	196	74	8	5.5	229
17	7/18/91	3	10	126	206	74	9	7.4	260
17	7/18/91	3	15	142	220	74	11	9.5	312
17	7/18/91	3.4	16	148	224	74	18	11.1	332
18	12/22/80	2	0	90	120	80	–	2.5	108
18	12/22/80	3	2.5	112	140	96	–	4.3	157
18	12/22/80	3	7.5	113	140	90	–	6.4	158
18	12/22/80	3	12.5	130	140	90	–	8.5	182
18	12/22/80	3	15	136	140	90	–	9.5	190
18	12/22/80	3	17.5	143	160	108	–	10.5	229
18	12/22/80	3.4	16	151	170	110	–	11.1	257
18	12/22/80	3.4	18	153	170	110	–	12.0	260
18	12/22/80	3.4	20	157	170	110	–	13.0	267

Raw Data Extracted From Baseline GXT (cont.)

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
19	5/24/91	3	0	--	--	--	--	3.3	--
19	5/24/91	3	5	98	128	74	6	5.4	125
19	5/24/91	3	10	114	130	74	8	7.4	148
19	5/24/91	3	15	125	134	76	10	9.5	168
19	5/24/91	3.2	17.5	135	142	72	14	11.2	192
19	5/24/91	3.4	22	139	154	74	16	13.9	214
20	7/14/88	3	0	106	150	60	7	3.3	159
20	7/14/88	3	5	106	154	60	8	5.4	163
20	7/14/88	3	10	125	166	60	8	7.4	208
20	7/14/88	3	15	148	164	70	10	9.5	243
20	7/14/88	3.4	16	160	166	70	14	11.1	266
22	8/30/91	3	0	92	133	77	6	3.3	122
22	8/30/91	3	5	90	142	78	7	5.4	128
22	8/30/91	3	10	98	142	77	10	7.4	139
22	8/30/91	3	15	112	154	78	15	9.5	172
22	8/30/91	3.4	16	123	175	79	17	11.1	215
22	8/30/91	3.4	20	137	192	88	19	13.0	263
23	11/15/89	2.5	1.5	120	144	88	12	3.4	173
23	11/15/89	2.5	7.5	138	170	110	16	5.5	235
23	11/15/89	2.5	13.5	151	184	104	19	7.6	278
24	4/28/87	2	0	81	112	60	--	2.5	91
24	4/28/87	3	0	83	124	74	9	3.3	103
24	4/28/87	3	5	100	--	--	10	5.4	--
24	4/28/87	3	10	107	138	72	11	7.4	148
24	4/28/87	3	12.5	115	150	80	13	8.5	173
24	4/28/87	3	15	115	154	84	16	9.5	177
25	1/27/92	3	0	122	130	80	11	3.3	159
25	1/27/92	3	5	138	154	80	13	5.4	213
25	1/27/92	3	10	153	160	80	15	7.4	245
26	11/16/83	3	0	64	128	78	9	3.3	82
26	11/16/83	3	5	69	138	76	11	5.4	95
26	11/16/83	3	10	78	146	80	12	7.4	114
26	11/16/83	3	15	99	160	86	14	9.5	158
27	9/13/88	3	0	122	150	80	13	3.3	183
27	9/13/88	3	5	132	158	78	15	5.4	209
27	9/13/88	3	10	154	170	80	19	7.4	262
29	2/1/88	3	0	107	152	66	9	3.3	163
29	2/1/88	3	5	120	182	66	12	5.4	218
29	2/1/88	3	10	140	206	66	13	7.4	288
31	6/2/81	2	0	85	120	80	--	2.5	102
31	6/2/81	2	3.5	95	140	90	--	3.5	133
31	6/2/81	2	7	105	140	90	--	4.5	147
32	3/12/85	3	0	108	112	60	--	3.3	121
32	3/12/85	3	5	112	126	60	12	5.4	141
32	3/12/85	3	10	119	126	60	12	7.4	150
32	3/12/85	3	12.5	128	118	60	14	8.5	151
32	3/12/85	3	15	130	118	60	--	9.5	153
32	3/12/85	3	17.5	133	118	60	--	10.5	157
34	4/12/82	2	0	125	154	94	9	2.5	193
34	4/12/82	3	2.5	125	166	104	10	4.3	208
34	4/12/82	3	7.5	136	178	104	12	6.4	242
34	4/12/82	3	10	150	202	110	14	7.4	303
34	4/12/82	3	12.5	166	195	120	--	8.5	324
36	11/17/77	2	0	100	136	80	--	2.5	136
36	11/17/77	3	0	100	156	86	--	3.3	156
36	11/17/77	3	2.5	110	172	88	--	4.3	189
36	11/17/77	3	5	130	178	92	--	5.4	231
36	11/17/77	3	7.5	150	184	102	--	6.4	276
36	11/17/77	3	10	150	180	98	--	7.4	270
38	2/7/89	2	0	85	196	60	7	2.5	167
38	2/7/89	2.5	4.5	102	202	60	7	4.5	206
38	2/7/89	2.5	10.5	118	210	60	10	6.5	248
38	2/7/89	2.5	13.5	139	216	60	12	7.6	300

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Raw Data Extracted From Baseline GXT (cont.)

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
40	4/7/78	2	0	125	138	90	--	2.5	173
40	4/7/78	3	0	125	146	88	--	3.3	183
40	4/7/78	3	2.5	125	148	84	--	4.3	185
40	4/7/78	3	5	136	152	84	--	5.4	207
40	4/7/78	3	7.5	150	158	82	--	6.4	237
40	4/7/78	3	10	150	166	82	--	7.4	249
41	9/24/79	2	0	79	164	90	11	2.5	130
41	9/24/79	3	0	83	174	100	13	3.3	144
41	9/24/79	3	2.5	88	184	100	15	4.3	162
41	9/24/79	3	5	94	190	100	19	5.4	179
42	6/2/87	2	0	78	120	60	6	2.5	94
42	6/2/87	2	3.5	80	130	72	--	3.5	104
42	6/2/87	2.5	7.5	97	140	70	7	5.5	136
42	6/2/87	3	10	107	144	72	10	7.4	154
42	6/2/87	3	15	125	150	72	13	9.5	188
42	6/2/87	3	17.5	130	154	72	--	10.5	200
43	1/20/86	2	0	75	--	--	--	2.5	--
43	1/20/86	2	7	102	140	80	--	4.5	143
43	1/20/86	2.5	10.5	110	156	80	15	6.5	172
43	1/20/86	2.5	13.5	114	170	100	17	7.6	194
44	12/21/92	2	0	102	178	92	11	2.5	182
44	12/21/92	2	3.5	111	178	102	--	3.5	198
44	12/21/92	2	7	120	180	94	--	4.5	216
44	12/21/92	2	10.5	127	184	94	--	5.4	234
44	12/21/92	2	14	135	186	88	17	6.4	251
45	11/28/78	2	0	88	--	--	11	2.5	--
45	11/28/78	3	2.5	100	105	80	13	4.3	105
45	11/28/78	3	5	105	106	90	13	5.4	111
45	11/28/78	3	7.5	105	130	90	13	6.4	137
45	11/28/78	3	10	125	154	93	13	7.4	193
45	11/28/78	3	12.5	125	138	96	14	8.5	173
50	12/12/77	2	0	108	170	96	--	2.5	184
50	12/12/77	2	3.5	115	162	98	--	3.5	186
50	12/12/77	2	7	120	184	98	--	4.5	221
50	12/12/77	2.5	7.5	130	190	98	--	5.5	247
50	12/12/77	2.5	10.5	136	200	102	--	6.5	272
50	12/12/77	2.5	13.5	144	206	102	--	7.6	297
55	11/12/82	2	0	88	120	74	13	2.5	106
55	11/12/82	3	0	97	--	--	--	3.3	--
55	11/12/82	3	2.5	97	128	74	15	4.3	124
55	11/12/82	3	5	96	138	78	--	5.4	132
57	10/2/78	2	0	65	110	70	--	2.5	72
57	10/2/78	3	0	71	140	80	--	3.3	99
57	10/2/78	3	2.5	75	140	80	--	4.3	105
57	10/2/78	3	5	81	140	80	--	5.4	113
57	10/2/78	3	7.5	90	140	100	--	6.4	126
57	10/2/78	3	10	95	160	120	--	7.4	152
57	10/2/78	3	12.5	100	180	120	--	8.5	180
57	10/2/78	3	15	100	180	130	--	9.5	180
57	10/2/78	3	17.5	110	--	--	--	10.5	--
58	8/24/83	2	0	75	112	74	7	2.5	84
58	8/24/83	2	7	85	122	84	13	4.5	104
58	8/24/83	3	7	105	142	86	12	6.2	149
58	8/24/83	3	10	115	152	86	13	7.4	175
58	8/24/83	3	12.5	120	160	82	15	8.5	192
59	8/24/83	2	0	88	120	78	6	2.5	106
59	8/24/83	3	2.5	103	140	74	8	4.3	144
59	8/24/83	3	7	112	142	70	9	6.2	159
59	8/24/83	3	10	117	158	78	11	7.4	185

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
63	10/28/85	0	0	--	--	--	--	1.0	--
63	10/28/85	2	0	85	160	90	--	2.5	136
63	10/28/85	2	3.5	93	180	90	11	3.5	167
63	10/28/85	2	7	103	180	110	13	4.5	185
63	10/28/85	2	10.5	116	180	110	--	5.4	209
65	1/10/90	2	0	115	160	94	7	2.5	184
65	1/10/90	2	5	131	164	86	11	3.9	215
65	1/10/90	2.5	7.5	145	158	90	15	5.5	229
65	1/10/90	3	10	150	168	106	--	7.4	252
70	1/21/91	0	0	--	--	--	--	1.0	--
70	1/21/91	3	0	108	122	74	8	3.3	132
70	1/21/91	3	7.5	132	144	76	11	6.4	190
70	1/21/91	3	15	160	148	76	15	9.5	237
70	1/21/91	3.4	16	170	158	78	20	11.1	269
71	11/11/83	2	0	98	110	70	--	2.5	108
71	11/11/83	2.5	4.5	111	110	70	--	4.5	122
71	11/11/83	3	7.5	120	120	70	--	6.4	144
71	11/11/83	3	12.5	132	140	78	--	8.5	185
74	3/16/84	2	0	84	100	60	--	2.5	84
74	3/16/84	2	7	102	110	70	--	4.5	112
74	3/16/84	2.5	10.5	121	130	80	13	6.5	157
74	3/16/84	3	12.5	128	150	78	--	8.5	192
75	5/16/80	3	0	92	194	110	9	3.3	178
75	5/16/80	3	5	104	198	116	11	5.4	206
75	5/16/80	3	10	125	220	118	15	7.4	275
76	7/1/84	2	0	75	120	70	--	2.5	90
76	7/1/84	2	3.5	79	120	70	--	3.5	95
76	7/1/84	2	7	79	136	70	--	4.5	107
76	7/1/84	2	10.5	81	140	70	--	5.4	113
76	7/1/84	2	14.5	86	--	--	--	6.5	--
76	7/1/84	2.3	15	89	--	--	--	7.5	--
76	7/1/84	2.7	15	94	--	--	--	8.6	--
77	10/23/84	2	0	100	118	74	--	2.5	118
77	10/23/84	2	3.5	111	118	74	12	3.5	131
77	10/23/84	2	7	120	118	74	13	4.5	142
77	10/23/84	2	10.5	130	144	74	--	5.4	187
78	1/21/77	2	0	100	170	110	--	2.5	170
78	1/21/77	3	0	110	176	110	--	3.3	194
78	1/21/77	3	2.5	120	176	102	--	4.3	211
78	1/21/77	3	5	120	190	102	--	5.4	228
78	1/21/77	3	7.5	130	196	102	--	6.4	255
80	1/30/78	2	0	94	170	110	--	2.5	160
80	1/30/78	3	0	94	178	112	--	3.3	167
80	1/30/78	3	2.5	125	180	112	--	4.3	225
80	1/30/78	3	5	136	184	118	--	5.4	250
80	1/30/78	3	7.5	142	200	118	--	6.4	284
80	1/30/78	3	10	158	208	116	--	7.4	329
81	6/7/78	2	0	94	154	78	--	2.5	145
81	6/7/78	3	0	100	152	84	--	3.3	152
81	6/7/78	3	2.5	111	162	86	--	4.3	180
81	6/7/78	3	5	115	174	90	--	5.4	200
81	6/7/78	3	7.5	136	184	92	--	6.4	250
81	6/7/78	3	10	136	186	94	--	7.4	253
82	6/4/82	3	0	78	130	82	7	3.3	101
82	6/4/82	3	5	88	142	80	9	5.4	125
82	6/4/82	3	10	111	150	84	11	7.4	167
82	6/4/82	3	12.5	115	180	88	15	8.5	207
82	6/4/82	3	15	120	--	--	--	9.5	--

Raw Data Extracted From Baseline GXT

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
83	9/22/78	2	0	88	128	80	--	2.5	113
83	9/22/78	3	0	95	140	90	--	3.3	133
83	9/22/78	3	2.5	107	140	90	--	4.3	150
83	9/22/78	3	5	120	150	90	--	5.4	180
83	9/22/78	3	7.5	136	150	90	--	6.4	204
83	9/22/78	3	10	140	160	90	--	7.4	224
84	1/31/79	2	0	96	--	--	--	2.5	--
84	1/31/79	3	2.5	115	94	80	--	4.3	108
84	1/31/79	3.4	4	125	95	72	--	5.5	119
84	1/31/79	3.4	6	136	108	76	--	6.4	147
84	1/31/79	3.4	8	150	110	70	--	7.4	165
84	1/31/79	3.4	10	160	116	70	--	8.3	186
87	2/13/78	2	0	94	124	84	--	2.5	117
87	2/13/78	3	0	100	124	88	--	3.3	124
87	2/13/78	3	2.5	111	126	94	--	4.3	140
87	2/13/78	3	5	125	136	96	--	5.4	170
87	2/13/78	3	7.5	130	138	94	--	6.4	179
87	2/13/78	3	10	136	190	100	--	7.4	258
87	2/13/78	3	12.5	150	194	108	--	8.5	291
88	10/26/77	2	0	95	148	90	--	2.5	141
88	10/26/77	3	0	100	148	86	--	3.3	148
88	10/26/77	3	2.5	115	148	88	--	4.3	170
88	10/26/77	3	5	125	162	96	--	5.4	203
88	10/26/77	3	7.5	140	176	90	--	6.4	246
88	10/26/77	3	10	150	192	98	--	7.4	288
88	10/26/77	3	12.5	165	200	98	--	8.5	330
88	10/26/77	3	15	170	198	98	--	9.5	337
89	3/18/77	2	0	--	130	100	--	2.5	--
89	3/18/77	3	0	144	145	110	--	3.3	209
89	3/18/77	3	2.5	160	150	110	--	4.3	240
90	2/13/81	2	0	128	164	90	13	2.5	210
90	2/13/81	3	2.5	134	164	94	13	4.3	220
90	2/13/81	3	5	140	168	92	16	5.4	235
90	2/13/81	3	7.5	144	174	92	--	6.4	251
91	11/30/79	2	0	88	120	70	12	2.5	106
91	11/30/79	3	2.5	100	110	68	13	4.3	110
91	11/30/79	3	7.5	115	128	70	13	6.4	147
91	11/30/79	3	10	125	134	68	15	7.4	168
91	11/30/79	3	12.5	150	140	71	17	8.5	210
92	11/26/79	3	0	115	166	100	9	3.3	191
92	11/26/79	3	5	136	176	103	13	5.4	239
92	11/26/79	3	7.5	169	186	115	17	6.4	314
94	1/27/78	2	0	--	190	120	--	2.5	--
94	1/27/78	3	0	145	180	116	--	3.3	261
94	1/27/78	3	2.5	150	186	114	--	4.3	279
94	1/27/78	3	5	150	--	--	--	5.4	--
95	1/31/77	2	0	125	120	85	--	2.5	150
95	1/31/77	3	0	148	135	80	--	3.3	200
95	1/31/77	3	2.5	159	150	80	--	4.3	239
96	5/3/78	2	0	100	132	82	--	2.5	132
96	5/3/78	3	0	115	134	84	--	3.3	154
96	5/3/78	3	2.5	125	146	80	--	4.3	183
96	5/3/78	3	5	136	150	82	--	5.4	204
96	5/3/78	3	7.5	150	162	82	--	6.4	243
96	5/3/78	3	10	150	182	84	--	7.4	273
97	6/6/80	2	0	100	132	82	7	2.5	132
97	6/6/80	3	2.5	115	136	82	8	4.3	156
97	6/6/80	3	7.5	125	132	82	9	6.4	165
97	6/6/80	3	10	140	138	82	10	7.4	193
97	6/6/80	3	12.5	150	146	80	12	8.5	219
97	6/6/80	3	14	166	148	80	15	9.1	246
97	6/6/80	3.4	16	170	178	84	16	11.1	303

Raw Data Extracted From Follow-up GXT

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
1	10/2/81	3	0	80	130	76	7	3.3	104
1	10/2/81	3	5	100	150	84	11	5.4	150
1	10/2/81	3	10	115	154	80	15	7.4	177
1	10/2/81	3	12.5	115	154	80	17	8.5	177
2	7/17/91	1.7	10	100	140	82	7	4.6	140
2	7/17/91	2.5	12	119	170	82	7	7.0	202
2	7/17/91	3.4	14	144	180	80	13	10.2	259
2	7/17/91	4.2	16	172	188	82	15	12.1	323
3	2/7/92	3	0	102	124	74	7	3.3	126
3	2/7/92	3	5	114	128	74	9	5.4	146
3	2/7/92	3	10	134	132	74	11	7.4	177
3	2/7/92	3	15	154	140	78	12	9.5	216
3	2/7/92	3.2	17.5	164	148	78	14	11.2	243
3	2/7/92	3.4	22	176	152	80	15	13.9	268
3	2/7/92	3.8	23	180	160	80	17	16.0	288
4	8/11/86	3	0	68	126	86	9	3.3	86
4	8/11/86	3	5	79	144	70	10	5.4	114
4	8/11/86	3	7.5	79	142	70	11	6.4	112
4	8/11/86	3	15	94	148	78	12	9.5	139
4	8/11/86	3.2	17.5	107	162	84	13	11.2	173
4	8/11/86	3.4	20	125	168	90	–	13.0	210
5	11/28/84	3	0	115	126	84	9	3.3	145
5	11/28/84	3	5	125	136	80	11	5.4	170
5	11/28/84	3	10	150	148	80	13	7.4	222
5	11/28/84	3	15	155	130	76	19	9.5	202
6	2/25/85	3	0	62	106	80	8	3.3	66
6	2/25/85	3	5	77	116	68	9	5.4	89
6	2/25/85	3	10	86	116	64	11	7.4	100
6	2/25/85	3	15	95	106	60	13	9.5	101
6	2/25/85	3.2	17.5	106	110	66	15	11.2	117
6	2/25/85	3.4	20	114	108	70	18	13.0	123
12	11/6/91	1.7	10	90	122	80	6	4.6	110
12	11/6/91	2.5	12	112	150	76	9	7.0	168
12	11/6/91	3.4	14	138	160	74	12	10.2	221
12	11/6/91	4.2	16	155	174	76	13	12.1	270
13	6/21/91	3	0	112	156	80	9	3.3	175
13	6/21/91	3	5	125	170	80	12	5.4	213
13	6/21/91	3	10	149	174	80	14	7.4	259
13	6/21/91	3	15	160	174	80	16	9.5	278
13	6/21/91	3.2	17.5	168	170	78	18	11.2	286
16	8/17/87	3	0	103	138	80	9	3.3	142
16	8/17/87	3	5	109	142	80	12	5.4	155
16	8/17/87	3	10	125	148	80	13	7.4	185
16	8/17/87	3	15	140	158	80	14	9.5	221
16	8/17/87	3.4	16	155	162	80	17	11.1	251
17	2/17/92	3	0	109	132	78	9	3.3	144
17	2/17/92	3	5	115	148	80	8	5.4	170
17	2/17/92	3	10	122	154	82	10	7.4	188
17	2/17/92	3	15	131	168	88	15	9.5	220
17	2/17/92	3.2	17.5	142	176	86	16	11.2	250
18	5/6/81	3	0	94	130	76	7	3.3	122
18	5/6/81	3	5	102	144	78	11	5.4	147
18	5/6/81	3	10	110	148	78	11	7.4	163
18	5/6/81	3	15	125	164	80	13	9.5	205
18	5/6/81	3.4	15	136	164	78	13	10.6	223
18	5/6/81	4	15	150	170	70	15	12.3	255
18	5/6/81	4	16	166	176	70	16	12.9	292
19	11/22/91	3	0	110	122	70	7	3.3	134
19	11/22/91	3	5	120	130	70	9	5.4	156
19	11/22/91	3	10	125	130	74	11	7.4	163
19	11/22/91	3	15	136	140	70	13	9.5	190
19	11/22/91	3.2	17.5	139	150	72	15	11.2	209
19	11/22/91	3.4	22	141	160	68	17	13.9	226

Raw Data Extracted From Follow-up GXT (cont.)

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
20	1/30/89	3	0	100	136	68	8	3.3	136
20	1/30/89	3	5	115	140	64	9	5.4	161
20	1/30/89	3	10	125	152	68	10	7.4	190
20	1/30/89	3	15	150	160	68	12	9.5	240
20	1/30/89	3.2	17.5	167	160	68	--	11.2	267
22	1/29/92	3	0	83	116	88	6	3.3	96
22	1/29/92	3	5	88	122	88	7	5.4	107
22	1/29/92	3	10	96	128	88	11	7.4	123
22	1/29/92	3	15	110	136	86	15	9.5	150
22	1/29/92	3.2	17.5	122	142	86	17	11.2	173
23	7/18/90	3	0	96	126	84	7	3.3	121
23	7/18/90	3	5	114	144	82	10	5.4	164
23	7/18/90	3	10	136	170	90	14	7.4	231
23	7/18/90	3	15	152	186	92	18	9.5	283
24	10/19/87	3	0	70	172	78	7	3.3	120
24	10/19/87	3	5	90	174	78	9	5.4	157
24	10/19/87	3	10	100	174	80	12	7.4	174
24	10/19/87	3	12.5	110	176	78	14	8.5	194
24	10/19/87	3.2	17.5	115	182	76	17	11.2	209
24	10/19/87	3.4	20	125	186	76	18	13.0	233
25	7/13/92	1.7	10	93	120	84	7	4.6	112
25	7/13/92	2.5	12	115	132	80	10	7.4	152
25	7/13/92	3.4	14	140	158	80	13	10.2	221
25	7/13/92	4.2	16	162	178	78	17	12.1	288
26	8/20/84	3	0	58	128	70	8	3.3	74
26	8/20/84	3	5	64	128	70	7	5.4	82
26	8/20/84	3	10	74	134	74	8	7.4	99
26	8/20/84	3	15	82	140	74	7	9.5	115
26	8/20/84	3.2	17.5	89	136	70	--	11.2	121
27	4/28/89	3	0	99	150	68	8	3.3	149
27	4/28/89	3	5	112	158	68	9	5.4	177
27	4/28/89	3	10	136	182	62	11	7.4	248
27	4/28/89	3	15	148	198	66	15	9.5	293
29	6/1/88	3	0	112	--	--	11	3.3	--
29	6/1/88	3	5	123	162	64	14	5.4	199
29	6/1/88	3	10	131	182	77	17	7.4	238
29	6/1/88	3	15	140	190	80	20	9.5	266
31	1/8/82	2	0	73	134	94	11	2.5	98
31	1/8/82	3	2.5	88	140	90	11	4.3	123
31	1/8/82	3	7.5	105	154	94	14	6.4	162
31	1/8/82	3	10	115	164	100	16	7.4	189
32	9/27/85	3	0	100	70	50	9	3.3	70
32	9/27/85	3	5	107	80	50	11	5.4	86
32	9/27/85	3	10	115	90	50	14	7.4	104
32	9/27/85	3	15	136	90	50	16	9.5	122
32	9/27/85	3.2	15	150	100	50	18	10.1	150
34	10/13/82	2	0	105	148	88	6	2.5	155
34	10/13/82	3	2.5	105	158	90	7	4.3	166
34	10/13/82	3	7.5	130	190	94	9	6.4	247
34	10/13/82	3	12.5	150	206	108	12	8.5	309
34	10/13/82	3	15	150	--	--	--	9.5	--
36	6/28/78	2	0	100	125	78	--	2.5	125
36	6/28/78	3	0	100	125	90	--	3.3	125
36	6/28/78	3	2.5	115	140	75	--	4.3	161
36	6/28/78	3	5	125	155	75	--	5.4	194
36	6/28/78	3	7.5	136	160	80	--	6.4	218
36	6/28/78	3	10	150	165	90	--	7.4	248
36	6/28/78	3	12.5	166	175	90	--	8.5	291
38	7/14/89	2.5	1.5	100	182	62	6	3.4	182
38	7/14/89	3	5	107	182	72	7	5.4	195
38	7/14/89	3	10	115	190	70	9	7.4	219
38	7/14/89	3	15	120	194	66	11	9.5	233
38	7/14/89	3.2	17.5	125	200	64	--	11.2	250

Raw Data Extracted From Follow-up GXT (cont.)

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
40	10/27/78	2	0	95	130	86	--	2.5	124
40	10/27/78	3	0	100	120	70	--	3.3	120
40	10/27/78	3	2.5	107	140	85	--	4.3	150
40	10/27/78	3	5	115	140	80	--	5.4	161
40	10/27/78	3	7.5	125	152	80	--	6.4	190
40	10/27/78	3	10	136	158	80	--	7.4	215
40	10/27/78	3	12.5	142	166	76	--	8.5	236
40	10/27/78	3	15	150	168	76	--	9.5	252
41	3/27/80	2	0	75	138	78	--	2.5	104
41	3/27/80	2.5	1.5	78	148	80	--	3.4	115
41	3/27/80	2.5	4.5	88	132	80	--	4.5	116
41	3/27/80	2.5	7.5	88	154	88	--	5.5	136
42	12/18/87	3	0	115	144	66	8	3.3	166
42	12/18/87	3	5	125	158	66	9	5.4	198
42	12/18/87	3	10	136	162	66	10	7.4	220
42	12/18/87	3	15	143	168	66	13	9.5	240
42	12/18/87	3.2	17.5	150	170	74	--	11.2	255
43	7/14/86	3	0	79	124	90	11	3.3	98
43	7/14/86	3	5	96	138	90	12	5.4	132
43	7/14/86	3	10	107	176	94	14	7.4	188
43	7/14/86	3	12.5	117	190	94	15	8.5	222
44	7/9/93	2	0	97	148	74	6	2.5	144
44	7/9/93	2	5	105	168	70	8	3.9	176
44	7/9/93	2	10	115	168	70	9	5.3	193
44	7/9/93	2	15	127	200	68	10	6.7	254
44	7/9/93	2.3	17.5	138	202	68	13	8.3	279
44	7/9/93	2.5	19.5	148	210	70	--	9.6	311
45	2/12/79	2	0	75	162	108	--	2.5	122
45	2/12/79	2	3.5	100	168	112	--	3.5	168
45	2/12/79	2.5	4.5	104	174	108	--	4.5	181
45	2/12/79	3	5	115	190	110	--	5.4	219
50	6/26/78	2	0	88	140	90	--	2.5	123
50	6/26/78	2	3.5	93	155	93	--	3.5	144
50	6/26/78	2	7	100	155	93	--	4.5	155
50	6/26/78	2.5	7.5	111	--	--	--	5.5	--
50	6/26/78	2.5	10.5	120	165	95	--	6.5	198
50	6/26/78	3	10	130	175	90	--	7.4	228
55	8/12/83	2	0	82	110	80	11	2.5	90
55	8/12/83	3	2.5	91	116	80	12	4.3	106
55	8/12/83	3	7.5	97	124	80	15	6.4	120
57	3/12/79	3	0	70	138	80	--	3.3	97
57	3/12/79	3	5	78	130	90	--	5.4	101
57	3/12/79	3	7.5	94	165	70	--	6.4	155
57	3/12/79	3	10	100	170	88	--	7.4	170
57	3/12/79	3.4	14	125	198	98	--	10.2	248
57	3/12/79	3.4	18	136	210	--	--	12.0	286
58	11/14/83	3	0	84	118	86	7	3.3	99
58	11/14/83	3	5	100	142	82	12	5.4	142
58	11/14/83	3	10	115	150	84	15	7.4	173
58	11/14/83	3	15	125	170	90	18	9.5	213
59	2/22/84	3	0	99	140	80	7	3.3	139
59	2/22/84	3	5	110	136	82	9	5.4	150
59	2/22/84	3	10	118	144	88	11	7.4	170
59	2/22/84	3	15	133	162	88	13	9.5	215
59	2/22/84	3.2	17.5	147	166	88	13	11.2	244
59	2/22/84	3.4	17.5	158	170	90	16	11.8	269
63	5/12/86	3	0	88	164	74	9	3.3	144
63	5/12/86	3	5	94	166	68	11	5.4	156
63	5/12/86	3	10	115	170	70	15	7.4	196
63	5/12/86	3	15	136	176	72	19	9.5	239

Raw Data Extracted From Follow-up GXT (cont.)

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
65	10/17/90	2	0	120	154	84	7	2.5	185
65	10/17/90	2	5	129	158	88	9	3.9	204
65	10/17/90	2	7.5	141	162	88	11	4.6	228
65	10/17/90	2	10	150	170	90	12	5.3	255
65	10/17/90	2.5	10	157	174	88	15	6.4	273
65	10/17/90	2.5	12.5	158	140	80	--	7.2	221
70	10/23/91	3	0	93	124	90	7	3.3	115
70	10/23/91	3	5	116	128	90	9	5.4	148
70	10/23/91	3	10	142	140	90	13	7.4	199
70	10/23/91	3	15	157	140	84	15	9.5	220
70	10/23/91	3.2	17.5	168	150	82	17	11.2	252
70	10/23/91	3.4	22	175	150	80	20	13.9	263
71	5/9/84	3	0	110	136	80	9	3.3	150
71	5/9/84	3	5	113	136	80	11	5.4	154
71	5/9/84	3	10	116	146	80	12	7.4	169
71	5/9/84	3	15	131	146	80	14	9.5	191
71	5/9/84	3.2	17.5	146	152	80	17	11.2	222
71	5/9/84	3.4	17.5	150	162	80	18	11.8	243
74	10/1/84	3	0	89	120	70	9	3.3	107
74	10/1/84	3	5	100	120	70	12	5.4	120
74	10/1/84	3	10	112	122	70	15	7.4	137
74	10/1/84	3	15	125	124	70	17	9.5	155
75	2/27/81	3	0	88	164	100	10	3.3	144
75	2/27/81	3	5	100	170	106	12	5.4	170
75	2/27/81	3	10	105	180	110	14	7.4	189
75	2/27/81	3	12.5	115	210	110	--	8.5	242
76	1/28/85	2	0	68	122	64	11	2.5	83
76	1/28/85	3	2.5	74	120	58	11	4.3	89
76	1/28/85	3	7.5	85	128	62	13	6.4	109
76	1/28/85	3	12.5	90	130	62	15	8.5	117
77	4/22/85	2	0	103	--	--	--	2.5	--
77	4/22/85	3	2.5	132	132	84	11	4.3	174
77	4/22/85	3	7.5	147	138	84	13	6.4	203
77	4/22/85	3	12.5	156	142	84	15	8.5	222
78	7/22/77	2	0	95	170	80	--	2.5	162
78	7/22/77	3	0	105	170	88	--	3.3	179
78	7/22/77	3	2.5	110	180	95	--	4.3	198
78	7/22/77	3	5	120	185	100	--	5.4	222
78	7/22/77	3	7.5	130	188	100	--	6.4	244
80	8/30/78	2	0	107	--	--	--	2.5	--
80	8/30/78	3	0	110	158	94	--	3.3	174
80	8/30/78	3	2.5	110	162	96	--	4.3	178
80	8/30/78	3	5	115	170	98	--	5.4	196
80	8/30/78	3	7.5	125	180	106	--	6.4	225
80	8/30/78	3	10	142	184	110	--	7.4	261
80	8/30/78	3	12.5	150	198	116	--	8.5	297
80	8/30/78	3	15	150	230	118	--	9.5	345
81	2/16/79	3	0	83	126	76	--	3.3	105
81	2/16/79	3	5	100	128	94	--	5.4	128
81	2/16/79	3	10	115	160	90	--	7.4	184
81	2/16/79	3	12.5	126	174	96	--	8.5	219
81	2/16/79	3	15	140	180	110	--	9.5	252
81	2/16/79	3.4	15	150	184	112	--	10.6	276
81	2/16/79	4	15	158	180	112	--	12.3	284
82	11/5/82	3	0	88	150	84	6	3.3	132
82	11/5/82	3	5	94	148	88	7	5.4	139
82	11/5/82	3	10	100	158	88	8	7.4	158
82	11/5/82	3	15	115	176	90	12	9.5	202
82	11/5/82	3	20	125	198	90	15	11.6	248

Raw Data Extracted From Follow-up GXT (cont.)

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
83	5/14/79	2	0	75	96	70	--	2.5	72
83	5/14/79	3	2.5	94	100	62	--	4.3	94
83	5/14/79	3	7.5	115	130	78	--	6.4	150
83	5/14/79	3	12.5	136	126	80	--	8.5	171
83	5/14/79	3	17.5	150	144	86	--	10.5	216
83	5/14/79	3.4	17.5	160	150	90	--	11.8	240
84	8/29/79	3	0	100	98	62	--	3.3	98
84	8/29/79	3	5	115	108	75	--	5.4	124
84	8/29/79	3	10	136	127	78	--	7.4	173
84	8/29/79	3	12.5	150	134	80	--	8.5	201
84	8/29/79	3	15	166	140	80	--	9.5	232
84	8/29/79	3	17.5	166	--	--	--	10.5	--
87	10/30/78	2	0	68	140	95	--	2.5	95
87	10/30/78	3	2.5	88	146	88	--	4.3	128
87	10/30/78	3	7.5	100	154	96	--	6.4	154
87	10/30/78	3	10	115	170	103	--	7.4	196
87	10/30/78	3	12.5	125	182	102	--	8.5	228
87	10/30/78	3	15	136	200	108	--	9.5	272
87	10/30/78	3.4	15	150	208	110	--	10.6	312
87	10/30/78	3.4	18	155	215	108	--	12.0	333
88	6/26/78	2	0	100	130	88	--	2.5	130
88	6/26/78	3	0	107	135	88	--	3.3	144
88	6/26/78	3	2.5	107	140	85	--	4.3	150
88	6/26/78	3	5	115	150	88	--	5.4	173
88	6/26/78	3	7.5	125	165	93	--	6.4	206
88	6/26/78	3	10	136	175	93	--	7.4	238
88	6/26/78	3	12.5	150	185	95	--	8.5	278
88	6/26/78	3	15	150	--	100	--	9.5	--
89	9/27/77	2	0	111	140	86	--	2.5	155
89	9/27/77	3	0	120	138	86	--	3.3	166
89	9/27/77	3	2.5	136	150	94	--	4.3	204
89	9/27/77	3	5	146	160	98	--	5.4	234
89	9/27/77	3	7.5	150	160	100	--	6.4	240
90	8/7/81	3	0	100	170	98	7	3.3	170
90	8/7/81	3	5	120	175	95	10	5.4	210
90	8/7/81	3	10	136	186	95	12	7.4	253
90	8/7/81	3	15	150	196	102	15	9.5	294
90	8/7/81	3	17.5	160	170	104	--	10.5	272
91	5/30/80	3	0	80	108	64	11	3.3	86
91	5/30/80	3	5	100	132	68	13	5.4	132
91	5/30/80	3	10	120	140	71	13	7.4	168
91	5/30/80	3	15	140	152	70	16	9.5	213
91	5/30/80	3.4	14	160	162	70	18	10.2	259
92	8/20/80	3	0	100	148	98	7	3.3	148
92	8/20/80	3	5	115	165	100	9	5.4	190
92	8/20/80	3	10	140	165	115	15	7.4	231
92	8/20/80	3	15	166	210	135	16	9.5	349
94	7/26/78	2	0	100	120	86	--	2.5	120
94	7/26/78	3	0	105	126	86	--	3.3	132
94	7/26/78	3	2.5	125	148	98	--	4.3	185
94	7/26/78	3	5	136	150	98	--	5.4	204
94	7/26/78	3	7.5	150	159	106	--	6.4	239
94	7/26/78	3	10	150	170	109	--	7.4	255
95	8/3/77	2	0	88	119	88	--	2.5	105
95	8/3/77	3	0	105	128	90	--	3.3	134
95	8/3/77	3	2.5	118	140	86	--	4.3	164
95	8/3/77	3	5	130	156	92	--	5.4	203
95	8/3/77	3	7.5	152	164	100	--	6.4	249
95	8/3/77	3	10	170	180	102	--	7.4	306
95	8/3/77	3	12.5	175	188	--	--	8.5	329

Raw Data Extracted From Follow-up GXT (cont.)

Patient ID	GXT Date	Speed	Grade	Heart Rate	SBP	DBP	RPE	METS	RPP
96	11/10/78	2	0	88	116	76	--	2.5	102
96	11/10/78	3	0	94	114	74	--	3.3	107
96	11/10/78	3	2.5	100	116	70	--	4.3	116
96	11/10/78	3	5	115	126	72	--	5.4	145
96	11/10/78	3	7.5	125	134	76	--	6.4	168
96	11/10/78	3	10	136	146	80	--	7.4	199
96	11/10/78	3	12.5	150	150	85	--	8.5	225
97	10/1/80	3	0	100	124	74	6	3.3	124
97	10/1/80	3	5	100	126	74	7	5.4	126
97	10/1/80	3	10	120	136	74	7	7.4	163
97	10/1/80	3	15	140	138	78	7	9.5	193
97	10/1/80	3.4	15	166	138	78	9	10.6	229
97	10/1/80	4	15	188	148	78	--	12.3	278

VITA

Lee Moschler Pierson was born on October 10, 1968 in Lynchburg, Virginia to Robert and Patricia Pierson. He grew up outside a small town, Gretna, located in central Virginia. Lee attended Gretna High School, where he played baseball and was involved in the band. He graduated from high school in June 1987.

In the fall of 1987, Lee entered Virginia Polytechnic Institute and State University as a freshman in the physics department. After two years as a physics major and a year as a biology major, Lee switched into the exercise science track in physical education. He worked as an undergraduate research assistant in the Laboratory for Sport and Exercise Science at Virginia Tech, helping graduate students collect data for thesis and dissertation projects. Lee also assisted graduate students in the design and implementation of a weight training program for participants in the Virgina Tech Cardiac Rehabilitation Program. Lee graduated with a B.S. in exercise science in the spring of 1992 and entered the graduate exercise science program in the fall of that year.

As a graduate student, Lee worked as intern in the cardiac rehabilitation program at Virginia Tech, in addition to performing duties as a graduate assistant in the Human Performance Laboratory. In his second year as a graduate student, Lee worked an internship in the cardiac rehabilitation program at Roanoke Memorial Hospital. In the summer of 1994, he obtained the ACSM Exercise Specialist Certification. Lee is currently working as the coordinator for an outcomes-based research study involving physical fitness and health-related quality of life in CABG patients, at Carolinas Medical Center in Charlotte, NC. In his free time, Lee enjoys reading, exercise, and going to movies.

Lee M. Pierson