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## Exercise Prescription and Proscription for Patients With Coronary Artery Disease

Paul D. Thompson, MD

Exercise training in patients with cardiovascular disease increases exercise capacity,<sup>1-3</sup> reduces cardiac ischemia,<sup>1,2</sup> delays the onset of or eliminates angina pectoris,<sup>4,5</sup> and improves endothelial function.<sup>6</sup> Meta-analyses of exercise-based, cardiac rehabilitation studies have suggested that exercise training reduces cardiac mortality in coronary artery disease (CAD) patients.<sup>7-10</sup> A recent randomized, controlled comparison of exercise training and angioplasty in selected patients with angina documented fewer cardiac events in the exercise subjects over the year of follow-up.<sup>2</sup> Despite these benefits, exercise training is rarely prescribed for cardiac patients, as evidenced by the fact that only  $\approx 20\%$ <sup>11,12</sup> of qualified patients are referred to formal cardiac rehabilitation programs. Referral rates are even lower among women and older patients.<sup>13</sup> The reasons for this underutilization are not defined but probably include health professionals' underestimation of the benefits of exercise, a lack of training in exercise therapeutics among many healthcare providers, poor financial reimbursement, the absence of reimbursed advocates for exercise therapy,<sup>13</sup> and the absence of a sufficiently large randomized clinical trial documenting a reduction in cardiac events. This review discusses the benefits of exercise training for patients with atherosclerotic cardiovascular disease.

### Definition of Terms

The following terms are used in this article. Physical activity to refer to any bodily movement; exercise is used to indicate physical activity performed to stress primarily the oxygen transport system (aerobic exercise), muscular skeletal system (resistance exercise), or both. Exercise training indicates exercise performed repetitively to increase the maximal capacity of the oxygen transport (aerobic exercise training) or muscular skeletal (resistance exercise training) system. The terms aerobic and resistance are used to classify exercise despite the recognition that aerobic exercise imposes some load on the muscular skeletal system and that resistance exercise also increases oxygen transport. Most research on exercise and cardiovascular disease has examined aerobic exercise, which consequently is the emphasis of this review.

### Cardiovascular Response to Exercise and to Exercise Training

#### Basic Principles of Exercise Physiology

The principles of exercise physiology,<sup>14</sup> their clinical import,<sup>15</sup> and their application to patients with atherosclerotic CAD<sup>16,17</sup> have been summarized. Only the most salient points are repeated here.

Physical activity increases the body's oxygen demand measured as the ventilatory oxygen uptake or  $\dot{V}O_2$ . The absolute oxygen demand, and therefore the absolute rate of  $\dot{V}O_2$ , is determined by the physical task or the external work rate<sup>18</sup> and the individual's mechanical efficiency in performing that task. The response of the circulatory system is designed to match the  $\dot{V}O_2$  requirements.<sup>15</sup> Rearranging the Fick equation (cardiac output [Q] =  $\dot{V}O_2$  times arterial-venous  $O_2$  difference [A-V  $O_2 \Delta$ ]) demonstrates that  $\dot{V}O_2$  is determined by the product of Q and A-V  $O_2 \Delta$ . The increase in Q is produced by increases in both heart rate (HR) and stroke volume (SV). Increases in A-V  $O_2 \Delta$  are produced by flow redistribution from metabolically less active tissue to the exercising muscle, hemoconcentration from fluid loss into the exercising muscle interstitial space, and increased  $O_2$  extraction over the active muscle bed.<sup>14</sup> The cardiac response to physical activity is tightly coupled to  $\dot{V}O_2$  so that a 1-L increase in  $\dot{V}O_2$  elicits an  $\approx 6$ -L increase in Q.<sup>15</sup> Consequently, maximal exercise capacity or  $\dot{V}O_{2max}$  is a surrogate measure of maximal Q and SV. The cardiovascular response to exercise in patients with CAD mimics the normal response, although maximal capacity is often reduced by decreases in maximal SV or HR, exercise-limiting symptoms such as angina pectoris or claudication, or deconditioning from inactivity and bed rest.<sup>16</sup>

Whereas Q is determined by the absolute  $\dot{V}O_2$  or the external work rate, the HR and systolic blood pressure (SBP) response, and therefore the "double product," an index of myocardial oxygen requirements ( $MO_2$ ), are determined by the  $\dot{V}O_2$  requirements of a physical task relative to maximal capacity or the percent  $\dot{V}O_{2max}$ .<sup>14,16</sup> Consequently,  $MO_2$ , or the internal work rate,<sup>18</sup> is not determined by the physical task or the absolute  $\dot{V}O_2$  but by the  $\dot{V}O_2$  relative to maximal capacity. This makes sense because the greater the exercise

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stress relative to  $\dot{V}O_{2\max}$ , the greater the catecholamine spillover, and the greater the HR and SBP response are.<sup>14</sup>

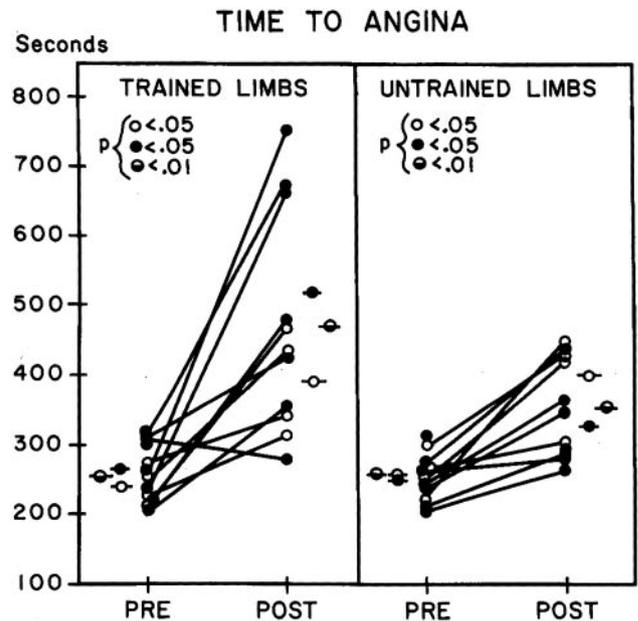
### Basic Principles of Exercise Training

The primary effect of aerobic exercise training is to increase maximal exercise capacity or  $\dot{V}O_{2\max}$  by increasing maximal SV and maximal A-V  $O_2 \Delta$ .<sup>14</sup> The magnitude of the increase depends on multiple factors, including age, baseline exercise capacity, characteristics of the training regimen, whether or not training and testing are done with the same task (training specificity), and genetic factors. In general, younger, less fit subjects who trained intensely for a prolonged time and tested and trained with the same muscles demonstrate the greatest increase with exercise training. The increase in  $\dot{V}O_{2\max}$  produced by exercise training means that any submaximal physical task represents a smaller percent  $\dot{V}O_{2\max}$ , produces a slower HR and lower SBP, and therefore requires a lower  $MO_2$  or internal work rate.<sup>14,16</sup>

Increases in functional capacity of 10% to 60% and reductions in  $MO_2$  of 10% to 25% have been reported for cardiac patients enrolled in exercise-based cardiac rehabilitation programs.<sup>11</sup> The mechanism for these adaptations in CAD patients may vary from that in healthy subjects. For example, much of the increase in  $\dot{V}O_{2\max}$  after 2 to 3 months of exercise training in patients after completed myocardial infarction (MI) is due to increases in the A-V  $O_2 \Delta$ ,<sup>19,20</sup> although cardiac output during submaximal exercise increases with prolonged (12 months) exercise training.<sup>21</sup> Consequently, the factors increasing exercise capacity probably vary with the severity of the cardiac disease and the length of training, although this topic has not been the focus of recent research efforts.

In addition to increasing maximal exercise capacity and reducing the HR and SBP response to submaximal exercise, exercise training also produces changes in the submaximal ventilatory response to exercise.<sup>15</sup>  $O_2$  consumption and carbon dioxide ( $CO_2$ ) exhalation ( $\dot{V}CO_2$ ) increase in parallel during low-level exercise, but at the point referred to as the ventilatory threshold (VT), these lines diverge.<sup>15</sup> This divergence is produced by bicarbonate buffering of hydrogen ions from lactic acid, thereby producing excess  $\dot{V}CO_2$  relative to  $\dot{V}O_2$ . Because  $CO_2$  drives the respiratory rate in subjects with normal respiratory drive, the respiratory rate increases, often producing mild dyspnea.<sup>14</sup> VT indicates the maximal steady state or work rate that can be maintained during submaximal exercise.<sup>15</sup> Exercise training raises the VT<sup>22</sup> and increases endurance capacity<sup>23</sup> in cardiac patients.

These physiological principles have several implications for CAD patients. First, because many CAD patients are remarkably unfit as a result of illness and inactivity, they can often obtain considerable improvements in exercise capacity from even low-level exercise training. Indeed, bed rest is used to reduce exercise capacity in research settings,<sup>24</sup> and simply the initiation of activity can reverse this deconditioning.<sup>14</sup> Second, because changes in both Q and A-V  $O_2 \Delta$  contribute to the training response, even patients with compromised cardiac function can increase the A-V  $O_2 \Delta$  and increase exercise capacity.<sup>19,20</sup> Third, the increase in VT can raise submaximal endurance capacity and reduce subjective



**Figure 1.** Time to angina during exercise with trained and untrained limbs before (PRE) and after (POST) 8 weeks of arm ( $n=4$ , ○) or leg ( $n=7$ ) exercise training, demonstrating that much of the exercise training effect is specific to the trained muscle groups (training specificity) but that some benefits do accrue to untrained limb exercise. Subjects trained under supervision for 40 minutes 3 times weekly at or near their anginal threshold. Nitroglycerin was used to permit more intense exercise without pain. Barred circles indicate mean values; ●, mean for all subjects. Reproduced from Thompson et al<sup>5</sup> with permission from Excerpta Medica, Inc. Copyright 1981.

dyspnea during submaximal exercise in CAD patients. Fourth, the decreases in the submaximal HR and SBP response to an exercise task reduce the  $MO_2$  requirement for any physical activity and delay the onset of angina pectoris in patients with this condition<sup>5,25,26</sup> (Figure 1).

In contrast to aerobic exercise training, which increases primarily the circulatory capacity for exercise, the main effect of resistance exercise training is to increase peripheral muscle strength, endurance, and mass. Resistance training has not been studied extensively in cardiac patients, but it increases the ability to perform household tasks in frail women with CAD.<sup>27</sup>

The principles of exercise training for clinicians caring for competitive athletes have been presented.<sup>28</sup> Similar principles apply to cardiac patients. Both aerobic exercise and resistance exercise training increase cardiovascular function and muscular performance by stressing or transiently "overloading" the respective systems.

For aerobic exercise, the magnitude of the stress is quantified by the intensity, measured as the percent  $\dot{V}O_{2\max}$  or by percent maximal HR; the duration of the training session, measured as time; and the frequency, measured as training sessions per week. Increases in any of these parameters amplify the training response. The exercise training and athletic training literature contains a large body of work on the effect of altering various components of the training regimen in healthy subjects, but relatively few such comparative studies in cardiac patients exist. Consequently, and with

few exceptions, most exercise training studies in cardiac patients have patients exercise at least thrice weekly for at least 20 minutes at heart rates corresponding to 70% to 85% of maximum HR, although lower intensities produce a training response.<sup>29</sup>

For resistance exercise training, the magnitude of the stress is usually referenced to the individual's measured or estimated maximal strength or the "1-repetition maximum," the maximal weight that the subject can lift for 1 exercise.<sup>30</sup> Additional training parameters include the number of repetitions performed in a group or set of a single exercise, the number of sets performed at each session, and the number of sessions performed weekly. Enhancements in muscular performance increase with the stress applied to the muscle. In general, increases in strength and size are greater when heavier weights are lifted with fewer repetitions, and increases in endurance are greater when the number of repetitions and sets is increased. As mentioned, there is a dearth of studies comparing elements of the aerobic training regimen in CAD patients, but there is even less information on resistance exercise training studies in this group.<sup>30</sup> General recommendations for training regimens in CAD patients include using 30% to 40% of the 1-repetition maximum for the upper body and 40% to 50% of the 1-repetition maximum for lower body exercises, with 12 to 15 repetitions in 1 set repeated 2 to 3 times weekly.<sup>30</sup> Nevertheless, because most of the outcome data discussed below relate to aerobic exercise training,<sup>30</sup> resistance exercise in CAD patients should be in addition to, and not in replacement of, the aerobic training component.

## Prescription or Proscription of Exercise for Patient Groups

### *Patients With CAD*

Virtually all patients with known CAD, if stable, should engage in regular physical activity.

### *Supporting Evidence*

No single randomized clinical trial has had sufficient statistical power to test the hypothesis that physical activity reduces recurrent cardiac events, although at least 4 meta-analyses have examined this possibility. These analyses all conclude that exercise reduces cardiac mortality but essentially examine the same studies plus or minus recent reports.<sup>7-10</sup> The most recent analysis examined 48 trials and included 8940 patients randomly assigned to exercise-based cardiac rehabilitation or usual care.<sup>10</sup> Cardiac rehabilitation reduced total mortality by 20% (95% CI, -7 to -32) and cardiac mortality by 26% (95% CI, -4 to -39). Interestingly, recurrent MI was not significantly reduced (-21%; 95% CI, -41 to 9). This reduction in mortality alone could result from reduced ventricular fibrillation resulting from exercise-induced enhanced parasympathetic tone<sup>31</sup> or from improved MI survival resulting from exercise-induced ischemic preconditioning.<sup>32,33</sup> Alternatively, the availability of trained personnel in supervised programs could reduce mortality by detecting changes in patient symptoms before a morbid event and by resuscitating patients after an arrest. For example, there is 1 cardiac arrest every 120 000 patient-hours of cardiac rehabilitation, but only 1 death every 750 000 patient-hours,<sup>16</sup>

indicating that the death rate would be 6-fold higher without successful resuscitation. Because available meta-analyses<sup>7-10</sup> are based primarily on supervised exercise programs, similar mortality benefits may not accrue with home-based and medically unsupervised programs. Additional limitations to these meta-analyses are that most subjects were middle-aged men, reducing the generalizability of the results, and that most studies were performed before modern acute revascularization strategies, so the results might not apply to modern cardiology.<sup>34</sup> The benefits of cardiac rehabilitation appear similar, however, for studies completed before and after 1995,<sup>10</sup> suggesting that results are applicable to present patients. Nevertheless, in the absence of a randomized, controlled clinical trial, it is impossible to conclude with absolute certainty that exercise training alone or cardiac rehabilitation reduces cardiac mortality in CAD patients.

### *The Exercise Prescription*

CAD patients should undergo symptom-limited exercise testing before referral to an exercise program to establish a baseline, to determine maximal HR, and to exclude important ischemia, symptoms, or arrhythmia that would alter the therapeutic approach. This testing should be performed with patients on their usual medication to match the conditions likely to be encountered during the exercise sessions.

### *Referral to Supervised Programs*

The simplest approach for clinicians prescribing exercise for patients with CAD is to refer patients to an established cardiac rehabilitation program. Patients in such programs exercise 3 times a week for at least 30 minutes, including 5 minutes of warm-up and cool-down calisthenics and at least 20 minutes of exercise at an intensity requiring 70% to 85% of the predetermined peak HR ( $\approx 60\%$  to  $75\%$  of  $\dot{V}O_{2\max}$ ).<sup>35</sup> This prescription is standard for most exercise training programs, although less fit patients benefit from lesser amounts and intensities of exercise and more fit patients may require more intense regimens. Most rehabilitation programs recommend other activities such as light yard work or brisk walking on other days. Cardiac rehabilitation programs also address diet, emotional, medicine, and smoking cessation issues, but exercise training may be the most important part of these programs. Indeed, in 1 meta-analysis of cardiac rehabilitation,<sup>8</sup> there was no difference in cardiovascular outcomes between the exercise-only studies and those that included other hygienic interventions, attesting to the value of the exercise component.

The best evidence of the cardiovascular benefits from exercise training is derived from aerobic exercise training programs. Nevertheless, many cardiac rehabilitation programs include an upper and lower limb strength training component to facilitate patient tolerance for nonaerobic physical tasks.<sup>30</sup> Strength training is especially important for the frailest patients who may have difficulty performing aerobic training because of leg weakness.

Insurance coverage for most cardiac rehabilitation programs in the United States is limited to 36 visits. Both the patient and physician may consider the patient rehabilitated and not in need of further exercise training at the end of this standard program. The improvements in exercise tolerance

and cardiovascular function that occur with exercise training rapidly dissipate with inactivity or a reduction in the volume of exercise training.<sup>36</sup> Consequently, patients should be given the opportunity to continue exercising in low-cost ongoing programs or to exercise on their own either at home or in a fitness facility.

#### *Prescription to Unsupervised Programs*

In the absence of a local cardiac rehabilitation program, physicians should refer patients to physical therapy or fitness facilities or should advise the patient on how to start an exercise program. Some physical therapy departments offer exercise training for patients but often are not equipped to provide aerobic exercise training. In addition, insurance often requires patient copayments for physical therapy, which limits the practicality of such referrals. Health club and fitness facilities are an alternative but may lack the personnel and experience to deal with cardiac patients. Consequently, it is often necessary for physicians to design an exercise program for the patient.

Patients without significant lower limb problems should use brisk walking as their primary mode of exercise. Walking can be done outside, on a motorized treadmill at home or in a gym, or inside large public buildings such as shopping malls. Patients should be encouraged to establish circular walking routes if possible to increase the possibility that they are near help or transportation if problems develop. Patients should start with a distance they can walk briskly without undue fatigue and increase weekly the duration of their daily exercise by 2 to 5 minutes until they are walking briskly for a minimum of 30 minutes daily, preferably more. Instructing patients to exercise daily may increase the possibility that they will exercise at least 3 times weekly, a frequency commonly used in exercise training studies of cardiac patients.

Physician-prescribed, individualized exercise training programs are more difficult to design for patients with significant lower limb orthopedic problems. Such patients may tolerate stationary cycling, elliptical trainers, swimming, and water aerobics, but these programs require special equipment and facilities, which decreases adherence to the training regimen.

Exercise intensity for individualized exercise programs can be prescribed using HR or VT parameters. Custom recommends that unsupervised patients should exercise at a target HR of 60% to 75% of their predetermined maximal HR. This value is intentionally lower than that used in supervised cardiac rehabilitation programs (70% to 85%) to reduce the chance of ischemia in an unsupervised setting. Pulse monitoring and HR measurements are often difficult for patients, and without heart rate monitors, patients must stop to measure their pulse. Many patients become anxious when they cannot accurately measure their HR or when they detect skipped beats or other insignificant rhythm abnormalities. An alternative approach is for patients to exercise to the onset of dyspnea and to maintain their exercise work rate at or slightly below this level. The onset of dyspnea approximates the VT,<sup>14</sup> is an appropriate workload for exercise training in an unsupervised setting, and obviates pulse monitoring. Patients can also be instructed to exercise at the fastest work rate that

still permits comfortable conversation. This "talk test" approach to guiding exercise intensity produces HR responses in CAD patients in the recommended training range and similar to the HR at the VT (C. Brawner, BS, unpublished data, 2005).

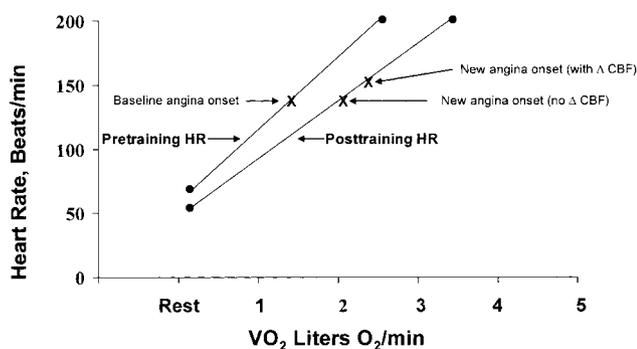
Patients in medically unsupervised programs should also include some resistance exercises in their training regimen. Biceps curls, military presses, shoulder shrugs, 1-arm bent rowing, bent-knee pushups, quarter squats, toe raises, and bent-knee abdominal crunches are appropriate if the patient is free of orthopedic limitations. These exercises should be performed at least twice weekly with dumbbells light enough to permit 12 to 15 repetitions of each exercise.<sup>30,34</sup> Similar exercises can be performed on strength training machines if available. Exercise machines may be preferable for frail patients<sup>30</sup> who may have difficulty controlling even light free weights. For patients with no prior exercise experience or who are anxious about starting such a program, several visits with a physical therapist or personal trainer can facilitate the adoption of the resistance training program.

#### *Exercise Proscription*

There are few absolute exercise proscriptions for CAD patients. Exercise training should be proscribed in patients during the first week after an acute MI and in those with progressive and unstable angina. Patients in whom exercise provokes atrial or ventricular arrhythmias should be prohibited from exercise until the rhythm and its response to exercise are controlled. Similarly, a patient with potentially life-threatening arrhythmia such as ventricular tachycardia should not exercise until the rhythm is adequately suppressed or the patient has received an implantable cardioverter-defibrillator.

After bypass surgery, patients can initiate training 1 to 2 weeks after an uncomplicated operation. Patients with postoperative wound infections should not participate until they have been treated with antibiotics for at least a week and the wound will not be compromised by exercise training. Patients with postoperative thrombophlebitis should be effectively anticoagulated for a minimum of 2 weeks before initiating exercise training. Postoperative patients should also avoid exercises that stress the wound or suture sites until the incision is fully closed and they can exercise with minimal discomfort.

Patients with CAD who are interested in vigorous, competitive sports should be restricted to moderate-resistance and low-level aerobic activities as recommended by the 36th Bethesda Conference.<sup>37</sup> This conference focused on activity guidelines for competitive athletes. These guidelines are conservative and discourage competitive sports with high-resistance or aerobic components in CAD patients,<sup>38</sup> a recommendation that can be extrapolated to unsupervised, vigorous exercise training. There are possible exceptions to these restrictions in low-risk patients such as those with complete revascularization and no evidence of ischemia or cardiac dysfunction. Nevertheless, some increased risk from vigorous exercise probably exists even in such low-risk patients,<sup>37</sup> given the well-documented association of vigorous exercise with acute MI<sup>39,40</sup> and sudden death<sup>41-43</sup> in the general population. Consequently, the decision as to which activities



**Figure 2.** Stylized representation of the changes in exercise tolerance and the onset of angina with exercise training. The HR vs  $\dot{V}O_2$  slope is shifted rightward after training, so any work rate ( $\dot{V}O_2$ ) elicits a slower HR response. Angina is delayed to the same HR if there is no change in coronary blood flow (new angina onset [no  $\Delta$ CBF]) or delayed to a higher HR if coronary blood flow is increased by, for example, improved endothelial function. Adapted from Thompson<sup>34</sup> with permission of The McGraw-Hill Companies. Copyright 2001.

and what intensities are permissible must be made by the patient and physician in concert.

#### **Patients With Exercise-Induced Angina Pectoris or Ischemia**

Exercise training reduces cardiac ischemia as measured by exercise-induced angina,<sup>25,26</sup> ST-segment depression,<sup>1</sup> or myocardial perfusion<sup>44</sup> and, with the caveats presented above, should be prescribed for most patients with exercise-induced ischemia.

#### **Supporting Evidence**

The earliest clinical evidence on the benefits of exercise training in cardiac ischemia was provided as a case report by William Heberden, the English physician who first described angina. Heberden admitted that he did not know how to treat the condition, but he did know of a patient who sawed wood for half an hour daily and was “nearly cured.”<sup>45</sup> Initial reports on the benefits of exercise training in angina patients attributed most of the improvement to reductions in the submaximal HR response to exercise because peak HR at angina was unchanged.<sup>25,26</sup> Subsequent studies, however, have documented both decreased submaximal exercise HRs and increases in peak rate-pressure product, suggesting improved myocardial oxygen supply. The mechanism is likely a reduction in the abnormal vasoconstrictor response to exercise because several angiographic studies have failed to document structural coronary artery changes.<sup>16</sup> Arteries normally dilate with increased shear stress, an effect mediated by increased nitric oxide production.<sup>46</sup> Exercise increases coronary and peripheral arterial blood flow, increases shear stress, and should produce coronary vasodilatation, but may produce a paradoxical coronary artery vasoconstriction in patients with CAD.<sup>47,48</sup> Exercise training has little effect on endothelial function in subjects with normal baseline function,<sup>49</sup> but in CAD patients with abnormal function, exercise training improves endothelial function as assessed by infusions of the endothelial agonist acetylcholine<sup>48</sup> (Figure 2). The exercise training protocols used in these most recent studies of endothelial function are demanding and clinically impractical

because they required hospitalized CAD patients to exercise on cycle ergometers at 70% of their maximal HR for six 10-minute sessions daily for 4 weeks.<sup>48</sup> Others, however, have documented increases in peak rate-pressure product at angina without coronary angiographic changes with less intense regimens (13 weeks of walking/jogging for 30 minutes and calisthenics for 15 minutes thrice weekly), suggesting that improvements in vasomotor function can occur with the usual exercise prescription.<sup>50</sup>

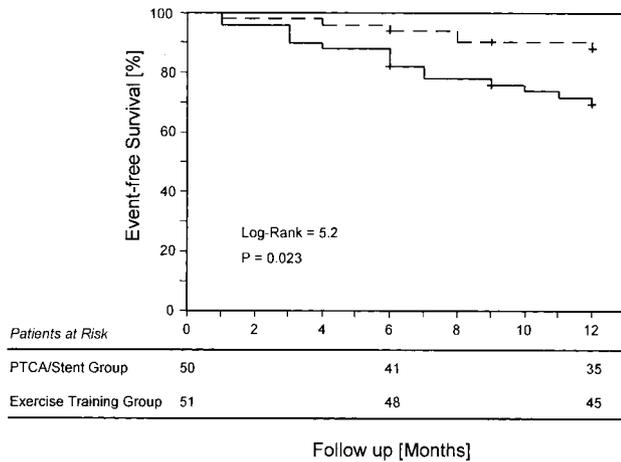
Exercise training may be superior to angioplasty in selected patients with stable angina. Hambrecht and colleagues<sup>2</sup> randomized 101 men with stable angina to exercise training or angioplasty with stent placement. Subjects were  $\leq 70$  years old and had stable angina and ischemia documented by exercise testing. All had lesions amenable to angioplasty. Subjects were excluded if they had a high-grade left anterior descending lesion,  $>25\%$  left main stenosis, valvular disease, an ejection fraction  $<40\%$ , an MI within 2 months, or a revascularization procedure within 12 months. Exercise training consisted of 10-minute exercise ergometry sessions 6 times daily at 70% of the symptom-limited maximal HR for 2 weeks, followed by a year of 20-minute daily home exercise sessions plus a weekly supervised 60-minute session. Exercise testing and coronary angiography were repeated after a year. Patients were followed on an intention-to-treat basis; 47 subjects in each group completed the initial and follow-up angiograms.

At 12 months, the exercise level at the onset of ischemia increased 30% in the exercise-trained and 20% in the angioplasty subjects ( $P=NS$ ), but maximal exercise capacity (20% versus 0%) and  $\dot{V}O_{2,max}$  (16% versus 2%) increased only in the trained patients ( $P<0.05$  for both). The target lesion did not change in the exercise group, and only 15% of the angioplasty subjects developed restenosis, defined as luminal narrowing of  $>50\%$ . However, total CAD progression, measured by angiographic scoring, was significantly reduced in the exercise-trained group. Six patients in the exercise training and 15 patients in the angioplasty group experienced a major cardiovascular event, including nonfatal MI, stroke, a revascularization procedure, or hospitalization for angina, giving a significantly higher event-free survival in the exercise subjects (88% versus 70%) (Figure 3). In addition to providing clinically superior outcomes, the cost of medical care over the year of the study for the exercise-trained subjects was 40% less than that for the angioplasty patients (\$3708 versus \$6086).

These results require confirmation in larger and longer studies to examine the effects of exercise training on both mortality and long-term outcome. In addition, the patients studied were highly selected by the study design and probably by their physicians. Nevertheless, these results suggest that exercise training is superior to angioplasty in the management of some patients with stable angina.

#### **Exercise Prescription for Patients With Exercise-Induced Ischemia**

Many patients with exercise-induced ischemia undergo revascularization procedures to eliminate the condition. Other patients with asymptomatic exercise-induced ischemia should



**Figure 3.** Event-free survival in 101 carefully selected patients with stable angina randomly assigned to percutaneous coronary intervention (PTCA/stent) or to a year of exercise training. Numbers at the bottom indicate patients free of events. Event-free survival was significantly better in the exercise training group (88% versus 70%;  $P=0.02$  by log-rank test). Reproduced from Hambrecht et al<sup>2</sup> with permission from the American Heart Association. Copyright 2004.

exercise to 70% to 85% of the HR at the onset of ischemia, usually defined as  $\geq 1$  mm of ST depression. The exercise prescription for patients with angina varies between investigators and studies. Some exercise patients to a percent of symptom-limited maximal heart rate,<sup>12</sup> whereas others exercise patients to the early onset of angina and then reduce the workload or use nitroglycerin to reduce discomfort.<sup>5,50</sup> Alternatively, and to achieve higher levels of aerobic and resistance training without discomfort, these patients can be treated with prophylactic nitroglycerin at the start of exercise. To my knowledge, there are no direct comparisons of these various approaches. Patients should be cautioned against standing still after taking the nitroglycerin because the combination of exercise- and nitroglycerin-induced peripheral vasodilatation can produce syncope. Some patients with angina pectoris are sensitive to cold by history and develop angina sooner and at a lower rate-pressure product during exercise at  $-8^{\circ}\text{C}$  than at  $20^{\circ}\text{C}$ .<sup>51</sup> Such patients, if forced to exercise in cold ambient temperatures, should use such simple measures as a face mask or a scarf around the mouth to help avoid cold-induced angina.

#### *Exercise Proscription for Patients With Exercise-Induced Ischemia*

Patients with increasing angina or reduced effort tolerance should be restricted from exercise training until their status is clarified and appropriate treatment is initiated.

#### *Patients After Angioplasty With/Without Stent Placement*

Anecdotal reports of stent thrombosis associated with exercise testing soon after angioplasty and stent placement raised concerns about the safety of exercise training in these patients.<sup>52</sup> These concerns were allayed by larger studies,<sup>52,53</sup> and exercise training appears beneficial in these patients,<sup>3</sup> although only 21% of patients with acute MI treated with primary angioplasty are referred to cardiac rehabilitation.<sup>52</sup>

#### *Supporting Evidence*

The Exercise Training Intervention After Coronary Angioplasty (ETICA) trial enrolled 130 patients after angioplasty into an exercise training or control group.<sup>3</sup> Twelve patients did not complete the study, leaving 118 patients who had undergone 1-vessel ( $n=81$ ) or 2-vessel ( $n=37$ ) angioplasty. Only 11 of the exercisers and 12 control subjects had received angioplasty as primary therapy for an acute MI, and stents were deployed in only 19 exercisers and 18 control subjects. Subjects were exercise tested  $25 \pm 7$  days after their angioplasty to fatigue, a target HR, or ST depression  $\geq 1$  mm. Exercise-trained subjects participated in a 6-month program with 3 weekly sessions that included 30 minutes of stationary cycling at 60% of their peak  $\dot{V}O_2$  and 15 minutes of calisthenics. Exercise testing and coronary angiography were repeated at the end of exercise training, after which subjects were followed clinically for an additional  $33 \pm 7$  months. Subjects were not treated with lipid-lowering agents during the study.

Peak  $\dot{V}O_2$  increased 26%, and only in the exercise-trained group. Indeed, in 45 of the 59 control subjects, peak  $\dot{V}O_2$  decreased over the 6 months. Restenosis defined as  $>50\%$  stenosis was similar at 6 months and occurred in 29% and 32% of the trained and control subjects, respectively. The luminal stenosis at the angioplasty site, however, was significantly greater in the control subjects. Furthermore, over the intervention and follow-up period, the exercise-trained patients had fewer cardiac events than control subjects ( $P<0.008$ ), including repeated angioplasties (4 versus 11), MIs (1 versus 3), and coronary bypass procedures (2 versus 5), and a lower rate of repeated hospitalization (18.6% versus 46%;  $P<0.001$ ). Progression of CAD, defined as an increase of  $>20\%$  in a lesion, occurred in 7.6% versus 25% of the exercise and control subjects, respectively ( $P<0.05$ ).

This trial predated the more frequent use of stents and the use of drug-eluting stents. Nevertheless, the reduction in cardiac events and hospitalizations is surprising to many clinicians but should not be, given the angioplasty results presented earlier,<sup>12</sup> the fact that recurrent angina is a frequent indication for both hospitalization and repeated angioplasty in this patient group, and the ability of exercise training to reduce or eliminate angina.<sup>4,25,26</sup> Also, as noted by others, exercise training treats the entire coronary vasculature, not just the area subjected to the percutaneous intervention,<sup>2</sup> and progression of other lesions also contributes to recurrent symptoms after angioplasty.

#### *Exercise Prescription*

Coronary angioplasty patients with or without coronary stenting can undergo symptom-limited exercise testing the day after routine angioplasty<sup>53</sup> and 7 to 14 days after percutaneous treatment of acute MI.<sup>52</sup> Patients can initiate exercise training 7 to 14 days after the procedure<sup>52</sup> using the prescription for CAD patients presented above.

#### *Exercise Proscription*

Angioplasty or stent patients who sustained access vessel injury during the procedure and required surgical intervention should refrain from exercise training until the surgical inci-

sions are healed and not susceptible to injury during exercise training.

### **Patients With Claudication**

Many patients with CAD have concomitant peripheral vascular disease. Exercise training is among the most effective medical therapies for patients with claudication.

### *Supporting Evidence*

Several meta-analyses have examined the effect of exercise on walking distance in patients with claudication.<sup>54–56</sup> Gardner and Poehlman<sup>54</sup> reviewed 33 randomized and non-randomized trials and selected 21 for detailed analysis. Average walking distance increased 179% or 225 m to the onset of pain and 122% or 397 m to maximal tolerated pain. Programs showing the greatest improvement exercised patients for  $\geq 30$  minutes a session, met at least thrice weekly, used walking as the primary training mode, walked patients to their maximal tolerable pain, and lasted  $\geq 6$  months,<sup>54</sup> although improvement may occur after only 4 weeks of training.<sup>57</sup> Similar improvements in walking distance were found in a Cochrane Systematic Review of 15 randomized trials of exercise compared with control, medical, or revascularization therapy. Only 10 exercise trials including  $\approx 283$  patients qualified for final analysis, however. These 10 included 6 studies comparing walking with some control and 1 study each comparing exercise with surgery, angioplasty, dipyridamole, or pentoxifylline.<sup>55</sup> Exercise training was more effective than the control conditions and increased overall average walking distance 150%, but other conclusions are tenuous because of the small sample sizes and number of studies. In addition, even when exercise was compared with control, the differences were most pronounced at 6 months and were of only borderline significance at a year, probably because of decreased training in the exercise group. The authors considered exercise more effective in increasing walking time than angioplasty or antiplatelet therapy and not different from surgical revascularization. In contrast to these results, a recent single-center randomized comparison of surgery, supervised exercise training, and observational control in 264 claudicants found improved walking tolerance only with surgical therapy and no difference between the exercise and control groups.<sup>58</sup> Nevertheless, exercise training is an inexpensive, low-risk treatment for claudication, does not prohibit other medical or invasive therapy, and improves symptoms in most claudicants. Consequently, it should be considered initial therapy in all patients with claudication and no evidence of limb-threatening ischemia.

### *Exercise Prescription*

Patients with claudication should be advised to walk  $\geq 3$  times weekly to their maximal tolerable pain, rest, and then resume the process for  $\geq 30$  minutes each session. Some patients with claudication avoid walking exercise because they cannot reach a resting point when claudication or fatigue occurs. Such patients should purchase a walking cane that unfolds into a seat. These are readily available online from various suppliers under the combined search term “cane and seat.” These products increase patients’ confidence by providing a place to rest when more established spots are not

nearby. These products can also be used for CAD patients with low effort tolerance.

### *Exercise Proscription*

Patients with ischemic symptoms at rest or whose symptoms progress despite medical therapy should be proscribed from exercise and evaluated for revascularization.

### **Patients With Heart Failure**

Historically, exercise training was prohibited in patients with heart failure (HF) with the rationalization that any exercise training effect would be limited by compromised ventricular function. Studies over the last 25 years, however, have documented that exercise training consistently increases exercise capacity in HF patients.<sup>59</sup> Consequently, exercise training can be recommended in this group to increase effort tolerance and to reduce symptoms.

### *Supporting Evidence*

There is no study large enough to evaluate the effects of exercise training on morbidity and mortality in HF. Smart and Marwick<sup>60</sup> reviewed 81 studies of exercise training in HF that included 2387 patients. Maximal oxygen uptake increased 16% with training. There were no exercise-related deaths in  $>60\,000$  patient hours of exercise training. Outcome data were available for 1197 patients randomly assigned to the exercise ( $n=622$ ) and control ( $n=575$ ) conditions. During the exercise training and a mean follow-up period of 5.9 months, there were no differences in total adverse events defined as incidents requiring hospitalization or withdrawal from the study, but deaths were 29% lower in the exercise-trained subjects, a result that approached statistical significance (95% CI,  $-63$  to  $2$ ;  $P=0.06$ ). The authors concluded that exercise training improves exercise tolerance in HF patients, is safe, and may reduce mortality.

Piepoli and colleagues<sup>61</sup> reviewed 101 reports of exercise training in HF and selected 9 trials for combined analysis. Studies were selected for inclusion if they included subjects with left ventricular ejection fractions  $<50\%$ , used exercise as the only intervention, exercise trained subjects for at least 8 weeks, and obtained survival data up for  $\geq 3$  months after exercise training. The combined analysis was performed on the original individual patient data obtained from 8 of the 9 studies. This provided information on 395 exercise-trained and 406 control patients. Despite the small sample size, both mortality ( $-35\%$ ; 95% CI,  $-8$  to  $-54$ ) and the combined end point of death or hospital admission ( $-28\%$ ; 95% CI,  $-7$  to  $-46$ ) were significantly reduced in the exercise-trained subjects.

The possibility that exercise training increases survival in HF patients is being prospectively evaluated in the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) Trial funded by the National Institutes of Health. Consequently, although exercise training improves effort tolerance in HF, conclusions on its effect on total morbidity and mortality await completion of this trial.

### *Exercise Prescription*

Stable NYHA class I through III HF patients should exercise, preferably in a supervised program, to a heart rate of 70% to

**Exercise Prescriptions for CAD Patients**

Patients	Intensity	Frequency	Duration
Aerobic Exercise			
General CAD	70%–85% peak HR	≥3 Times weekly	≥20 min per session
With asymptomatic ischemia	70%–85% Ischemic HR	≥3 Times weekly	≥20 min per session
With angina	70%-85% Ischemic HR or angina onset	≥3 Times weekly	≥20 min per session
With angioplasty ± stent	As for general CAD patient	...	...
With claudication	Walking to pain tolerance	≥3 Times weekly	≥30 min per session
With NYHA class I–III HF	As for general CAD patient	...	...
Resistance Exercise			
For most CAD patients	30%–50% RM	2–3 Times weekly	12–15 Repetitions

RM indicates 1-repetition maximal weight.

85% of maximal if tolerated or to the onset of moderate dyspnea. HF patients also benefit from resistance exercise training to increase muscle strength.

**Exercise Proscription**

HF patients with symptoms at rest (NYHA class IV) and NYHA class III patients with symptoms on minimal exertion (advanced NYHA class III and class IV) should refrain from exercise training until their symptoms permit exercise.

**Insurance Reimbursement**

Insurance reimbursement for cardiac rehabilitation varies greatly by country. Some countries such as Germany provide up to 3 weeks of inpatient rehabilitation, which is partially covered by health insurance (Rainer Hambrecht, personal communication, April 2005). In the United States, insurance coverage varies by insurance carrier and by the local Medicare administrator. In general, Medicare and many insurance companies provide reimbursement to qualified programs for patients who have suffered an MI within 12 months, have undergone bypass surgery within 6 months, or have angina plus cardiac ischemia. The ischemia must be documented by ECG ST-segment changes or by myocardial perfusion imaging during a stress test performed within 6 months of program initiation.<sup>62</sup> Programs qualify for reimbursement if they are hospital or clinic based and are directly supervised by a physician. Medicare does not provide reimbursement for HF patients or for patients after angioplasty unless they satisfy one of the criteria mentioned above, although some private insurance companies cover exercise training for HF. Reimbursement is also not usually provided for patients with claudication who lack another qualifying diagnosis, even though a procedure code for cardiac rehabilitation for claudication exists.<sup>63</sup>

Cardiac rehabilitation is divided into 3 or 4 phases. Phase 1 refers to an inpatient, immediately postevent program. This service is usually performed by physical therapy personnel. Phase 2 refers to physician-supervised outpatient programs that usually meet thrice weekly for 12 weeks, the amount of service covered by Medicare.<sup>62</sup> Some Medicare administrators allow an additional 12 weeks of exercise training for patients who cannot exercise to a work rate of  $24.5 \text{ mL} \cdot \text{O}_2 \cdot \text{min}^{-1} \cdot \text{min}^{-1}$  or 7 metabolic equivalents (METS) by the end of the program.<sup>62</sup> This additional time is referred to as a phase

2B program. Phase 3 refers to a medically supervised, long-term maintenance program. Such programs are often provided by the same facilities as the phase 2 program, but patients cannot be commingled because Medicare requires a dedicated area for phase 2 programs. Phase 4 is used by some clinicians to refer to medically unsupervised programs provided by health clubs or fitness facilities. Both phase 3 and 4 programs are not covered by insurance.

**Conclusions**

Exercise training is an established, inexpensive, generally safe intervention capable of increasing exercise capacity and reducing symptoms in most patients with cardiovascular disease (the Table). Meta-analyses provide strong evidence that exercise-based cardiac rehabilitation reduces mortality in CAD patients, but the absence of a sufficiently powered, randomized clinical trial prohibits absolute certainty that exercise training alone reduces cardiac mortality in CAD patients. Recent clinical trials suggest that exercise training markedly reduces cardiovascular events after angioplasty and is superior to angioplasty in managing selected patients with angina pectoris. Exercise training is underused as a therapeutic modality but can easily be prescribed for most patients by referral to a cardiac rehabilitation program or by recommending walking to the onset of dyspnea.

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