Exercise and the Heart

Just Do It

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INTRODUCTION

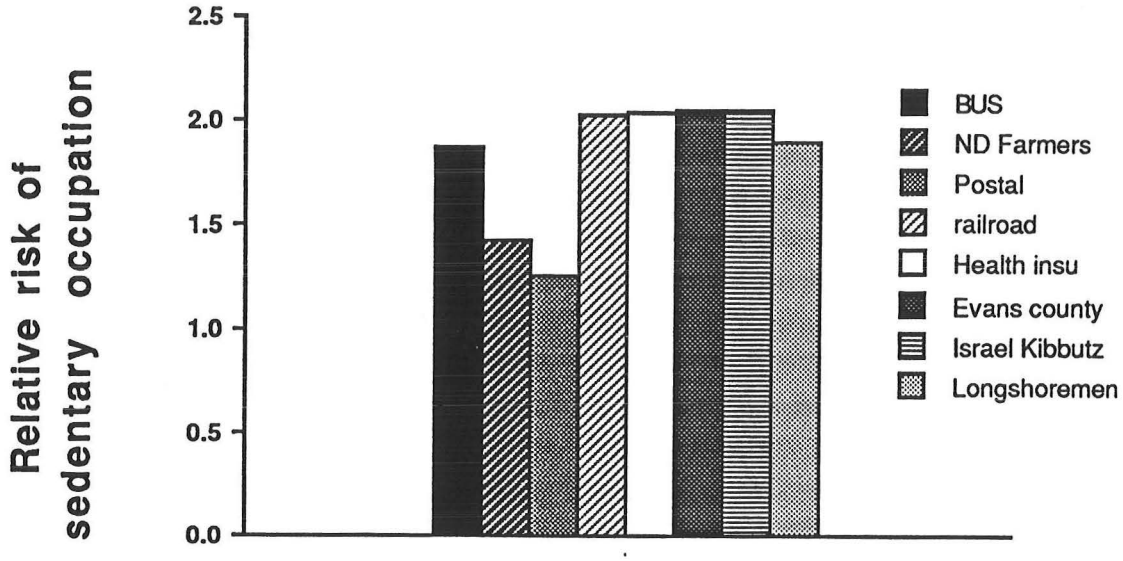
Exercise is widely used in clinical medicine for such diverse purposes as objective quantification of functional capacity, detection and prognostic evaluation of coronary artery disease, and determining the integrity of physiological systems necessary for control of the circulation (1). The adaptation to dynamic exercise (i.e., exercise training), leads to increased endurance and aerobic power. "Mr. Marathoner" Clarence De Mar, ran the Boston marathon 34 times up to the age of 66 (winning 7); at autopsy in 1955 he was reported to have unusually large coronary arteries (2). Thus, the myth developed that runners were immune from coronary artery disease (3).

Physical inactivity as a risk factor for CAD.

There is an extensive literature regarding the benefits and risks of exercise. The American Heart Association (4) and the International Society and Federation of Cardiology (5) recognize that a sedentary lifestyle is an independent risk factor for coronary disease. This protocol explores in detail the role of occupational and recreational exercise on morbidity and mortality from coronary heart disease. I will summarize the large number of studies on healthy individuals, i.e., primary prevention. I will then discuss secondary prevention, for patients who already have had some manifestation of coronary artery disease. I will consider a pathophysiological framework for the mechanisms of the beneficial effects of exercise training. I will conclude with economic considerations.

PRIMARY PREVENTION

The evidence that physical activity could protect against heart disease originated In the 1950's when Morris et al published the London transportation studies. Sedentary bus drivers had almost twice the incidence of CAD as compared to conductors who regularly walked up and down the stairs of double-decker busses (6,7). Additionally, overall death rates, including sudden death, were twice as high in the drivers as compared to the conductors. Virtually every subsequent study comparing sedentary to active populations has confirmed this protective benefit of regular occupational exercise (8)

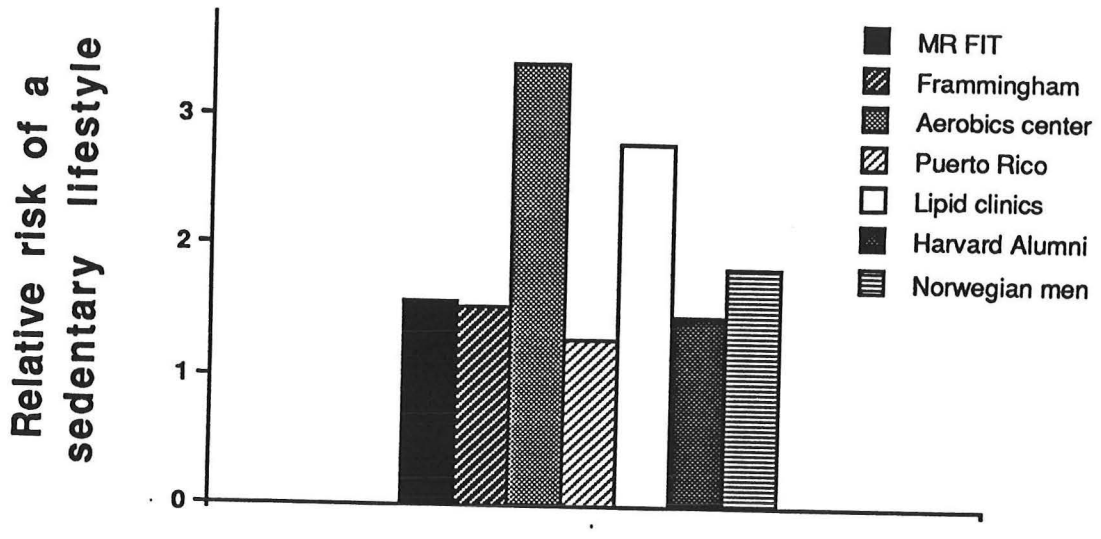


Relative risk of a sedentary occupation.

Farmers in North Dakota (9), U.S. postal employees (10), American railroad workers (11) and participants of the Health Insurance Plan of New York (12) offered further support to the hypothesis that exercise protects against coronary disease. However confounding factors such as obesity, hypertension and hyperlipidemia made it difficult to clearly demonstrate an independent effect of exercise.

Later investigators controlled more carefully for other cardiovascular risk factors. Cassel et al examined residents of Evans county in rural Georgia, and showed that a sedentary occupation was an independent risk factor for CAD (13). Brunner et al took advantage of the relatively homogeneous lifestyle of the Kibbutzim of Israel to minimize variability in diet, race, and socioeconomic status. In this population, the sedentary residents demonstrated two to four times the incidence of CAD as their active counterparts over a 15 year period (14). Paffenbarger et al (15,16) showed that San Francisco Longshoremen who performed heavy physical labor, requiring bursts of energy had a lower coronary death rate over 16 years of follow-up compared to more sedentary workers.

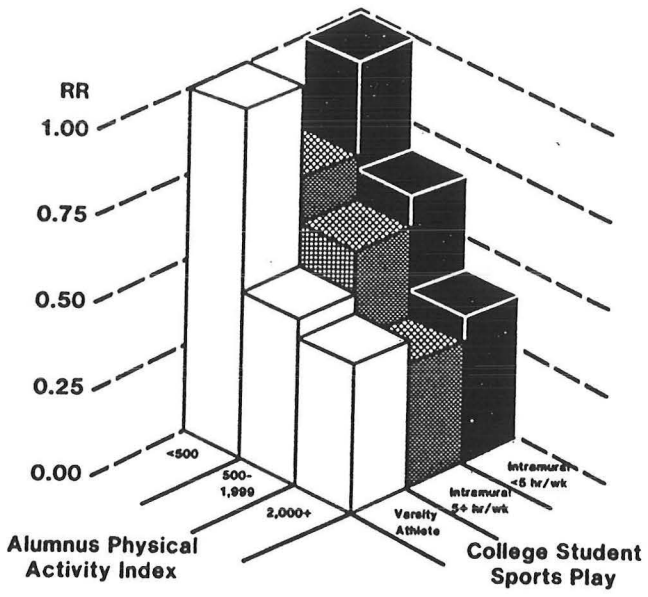
Mechanization and automation have reduced the energy expenditure of many jobs, and more recent studies have focused on the effects of recreational exercise



Relative risk of sedentary lifestyle.

In the Multiple Risk Factor Intervention Trial (MRFIT), moderate leisure-time physical activity was associated with a 37% reduction in fatal cardiac events and sudden deaths, and a 30% reduction in total deaths as compared to lower activity (17). Both men (17-22) and women (19,20) appear to benefit from regular vigorous activity and/or fitness with a reduction in both cardiovascular and all cause mortality.

Selection bias may have contributed to the apparent protective advantage of exercise or fitness in many of these studies of leisure time activity -- that is that naturally fit persons are more likely to exercise or participate in sports than individuals predisposed to coronary artery disease. This question was addressed in a comprehensive investigation of 16,936 Harvard alumni aged 35-72 comparing past and present habitual energy expenditure and the risk of myocardial infarction and death (23).

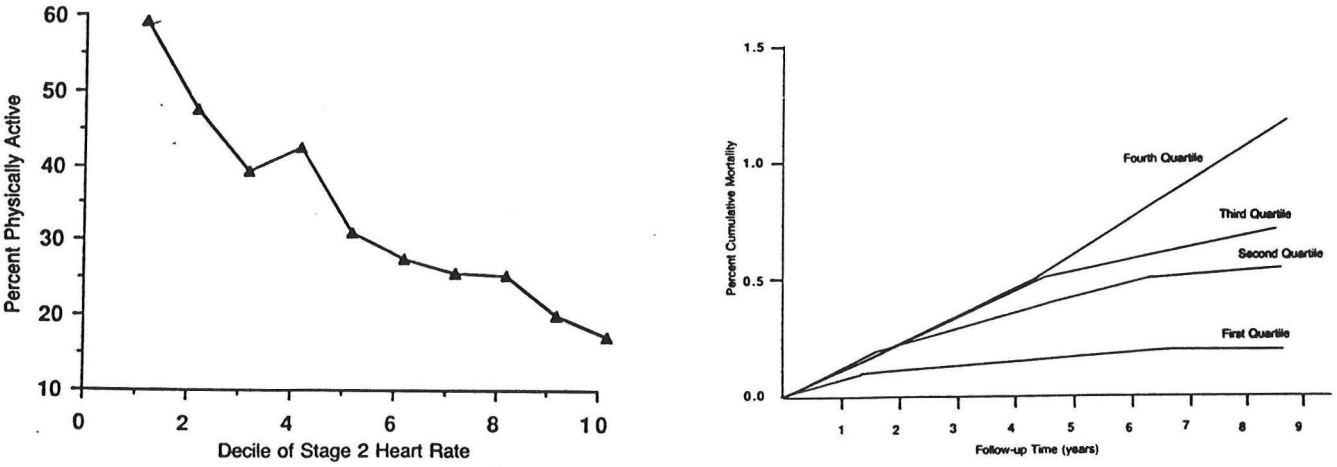


Paffenbarger et al (23) Relative risk (RR) of first coronary disease attack for harvard alumni by physical activity index during and after college.

Total and cardiovascular mortality were reduced by regular recreational exercise, irrespective of the level of athleticism or sports participation during college. More recent follow up studies of these subjects suggests that a significant reduction in cardiovascular mortality can be achieved even if regular exercise is not begun until late in life (> age 60) (24).

Exercise and Fitness

Regular exercise is closely associated with increased physical fitness as reflected by objective measures such as peak workrate on a treadmill or bicycle ergometer (25,26). Identical twin studies have suggested that about 40% of fitness measures are genetically determined (27). The strength of the relationship between fitness and cardiovascular disease has generally proven similar to that between physical activity or exercise practices and mortality (20,26,28,29). Wilhelmsen showed that among 793 healthy Swedes, those with a lower work capacity are more likely to suffer from a myocardial infarction or die suddenly (28). In The Lipid Research Clinics Mortality study, 4,276 men were followed for an average of 8.5 years after a baseline exam which included a treadmill test (29). Based on heart rate during stage 2 of the treadmill test and peak exercise capacity, the subjects were divided into quartiles with respect to fitness. They found that the lower quartiles were associated with greater incidence of cardiovascular death. Furthermore, better treadmill performance was directly related to the amount of regular exercise.



Ekelund (29) **Left:** % of healthy men reporting regular physical activity, according to stage 2 exrecise heart rate. Decile 1 represents the lowest heart rate, and decile 10 the highest. **Right:** Cummulative rate of death from cardiovascular disease in healthy men, according to quartiles of stage 2 exercise heart rate.

Blair et al (20) examined physical fitness (maximal treadmill performance) and risk for all cause and cause specific mortality in 10,224 men and 3,120 women. Cardiovascular and all cause mortality declined across higher quintiles of physical fitness in both men and women. These trends remained significant even after adjusting for age, smoking, cholesterol, blood pressure and glucose levels, family history of CAD, and follow-up interval (mean 8 years).

For both men and women, most of the survival advantage associated with physical fitness can be seen at relatively low levels of exercise capacity (20). Blair et al have shown that a maximal treadmill workrate equivalent to approximately 10 METS in men and 9 METS in women conferred virtually all the exercise related protection against cardiovascular disease. These studies suggest that a relatively modest amount of physical activity confers a meaningful reduction in death rates from coronary artery disease.

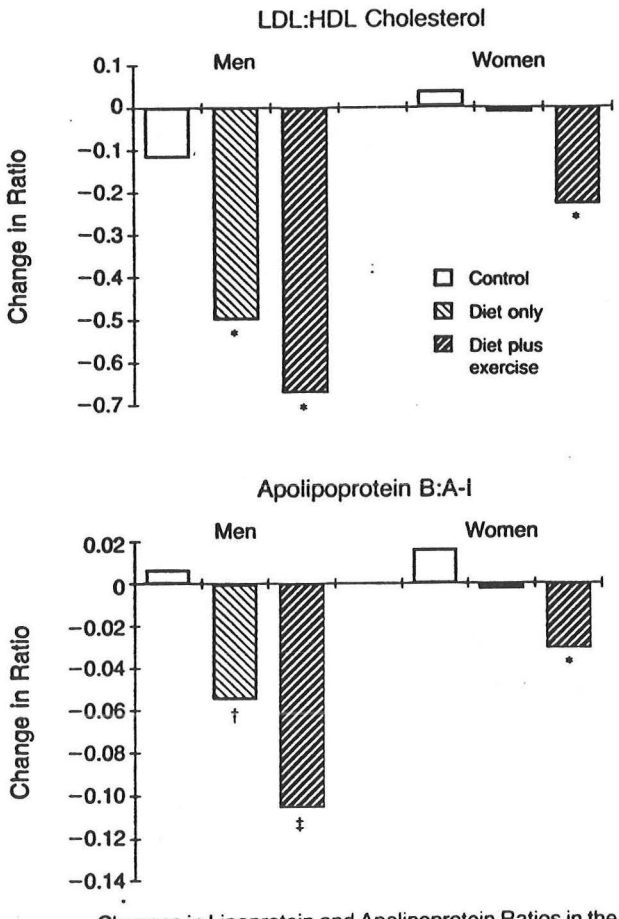
Thus regular physical exercise is associated with a greater degree of fitness and a reduced incidence of CAD in healthy people (31). There are several mechanisms for this protection including independent effects discussed below (see Possible Mechanisms), or by a reduction of other known risk factors. Exercise may improve the lipid profile, lower blood pressure, and

decrease the incidence of adult onset diabetes mellitus. Persons who are more active also quit smoking with a greater frequency (32).

Effect of exercise on plasma lipids

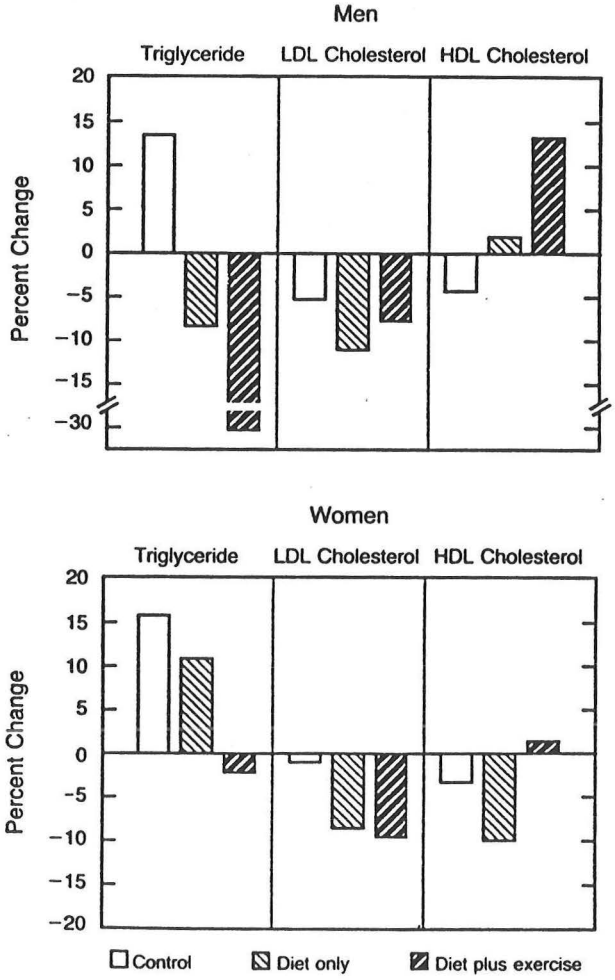
High levels of HDL cholesterol have also been associated with a reduced incidence of CAD (33), and exercise is associated with higher plasma HDL concentrations (34,35). HDL is particularly affected in persons who exercise regularly for periods of several years (36), primarily by an increase in the half life of specific subfractions of HDL, most likely HDL2 (37).

In a series of important studies, Wood and colleagues have demonstrated that exercise is as effective as weight loss in terms of improving the lipid profile (38). Moreover, when exercise and diet are combined, the beneficial effects may be synergistic (39).



Changes in Lipoprotein and Apolipoprotein Ratios in the Study Groups after One Year.

For the comparison with the control group, the asterisk denotes $P<0.05$, and the dagger $P<0.01$. The double dagger denotes $P<0.001$ for the comparison with the control group and $P<0.05$ for the comparison with the diet-only group.



Percent Changes in Plasma Triglyceride and Lipoprotein Cholesterol Concentrations in the Study Groups after One Year.

The mean change for a group is expressed as a percentage of the base-line level for that group.

Woods et al divided 264 moderately obese men and women into three experimental groups: 1) control, 2) hypocaloric National Cholesterol Education Program (NCEP) diet, and 3) hypocaloric NCEP diet with exercise. Although the diet only subjects consumed fewer calories, they did not lose as much total body weight or fat weight as the exercisers. The latter also had a better final abdomen to hip circumference ratio, reflecting preferential fat loss around the abdomen. Most importantly, exercise had a favorable effect on the LDL:HDL Cholesterol and Apolipoprotein B:A-1 ratios in both men and women. Both ratios have been associated with the development of atherosclerosis (40). Because a low fat diet may reduce the HDL cholesterol (41), exercise may be particularly useful in patients who maintain such a diet. Exercise also lowers triglycerides (34,39). This effect occurs even with a single bout of exercise, but appears to be cumulative resulting in a permanent decrease in serum triglycerides (42).

The effect of exercise on blood pressure control

The effect of exercise on blood pressure control has been somewhat controversial. Blumenthal et al recently showed no specific blood pressure reducing effect of exercise for patients with mild hypertension (43). This was a well designed, large, and randomized trial including non-obese men and women off medications. The study was complicated by the fact that both the exercise and control groups experienced an unexplained significant decrease in blood pressure. However, the subjects with the greatest improvement in aerobic power tended to have the greatest reduction in blood pressure, suggesting that a more rigorous exercise program might result in a more significant reduction in blood pressure.

Other investigations have consistently shown a clear association between exercise and blood pressure reduction (44-46). However none of these other studies measured changes in aerobic power or evaluated other possible contributing factors including salt intake, weight, and gender. Still, the data do suggest that regular aerobic exercise contributes to a reduction in blood pressure in mildly hypertensive persons, possibly mediated through changes in skeletal muscle conductance and peripheral resistance (47). Finally, Blair et al showed that among 4,820 normotensive men and women, the subsequent development of hypertension during the next 1-12 years was linked to a lower fitness level (48):

Follow up time	Relative Risk	
	Low Fitness	High Fitness
1-5 years	1.48	1.0
6-12 years	4.62	3.16

The effect of exercise on glucose tolerance

The syndrome of abdominal obesity, glucose intolerance, hypertriglyceridemia, low HDL, and hypertension is associated with a high incidence of CAD (49). Exercise may improve all components of this high risk syndrome. Specifically, exercise results in a lower insulin secretion with improved receptor sensitivity (50). Physical activity can help to produce weight loss, including a reduction of other markers for coronary disease such as abdominal obesity. Also, persons who exercise regularly are less likely to develop non-insulin-dependent diabetes mellitus (51).

Risks of Exercise

Although exercise confers substantial benefits over time, it is not without risk. The hemodynamic and neuroendocrine responses to an acute bout of exercise raises myocardial oxygen requirements and alter the functional milieu of the myocardium which may increase the risk of arrhythmias and sudden cardiac death (52). Fortunately, the exercise-related risks for ostensibly healthy individuals are very small (53). For joggers in the state of Rhode Island, Thompson has estimated the risk to be one death per 7,620 joggers/year (54). This risk of dying while jogging is nearly six times higher for normally sedentary individuals who may jog occasionally, compared to regular exercisers. If the relative risk of dying during exercise is compared to the long-term health benefits of exercise, the balance of effects still favors regular exercise with a relative risk of dying that is less than one-half that of sedentary individuals (55).

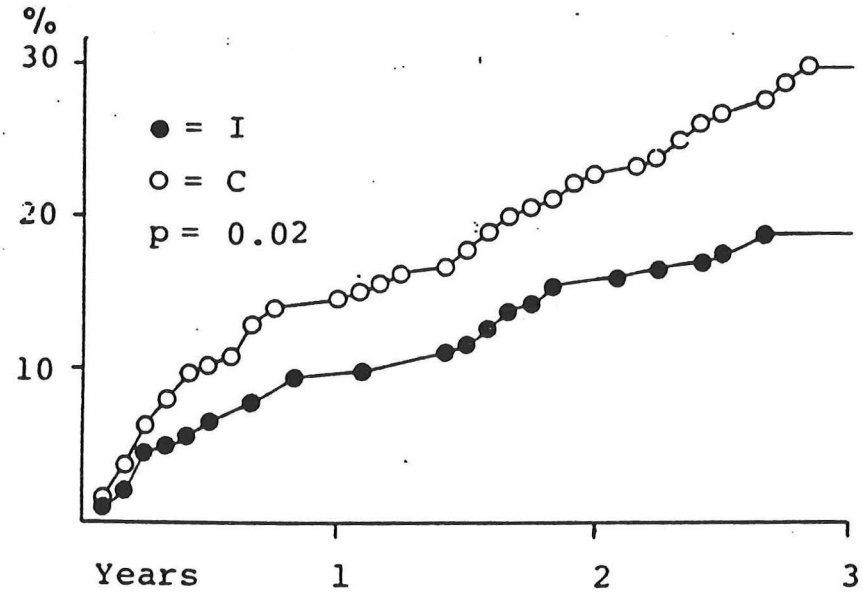
SECONDARY PREVENTION (Cardiac Rehabilitation)

Once an individual has suffered the consequences of coronary artery disease, attention turns from disease prevention, to maximizing functional capacity, minimizing morbidity and limiting the progression of disease.

Cardiac rehabilitation may be broadly defined as the process by which patients with heart disease are managed comprehensively to maximize physical and psychological functional capacity. It usually follows a period of acute cardiovascular illness. It is most effective when delivered as a multifactorial approach which includes education, risk factor modification and exercise training (56-60). There are four phases of cardiac rehabilitation:

Phase	Type of program	Duration
I	In Patient	Days
II	Outpatient immediately after hospitalization.	2-12 weeks
III	Late recovery period	6 months beyond Phase II
IV	Maintenance	Indefinite

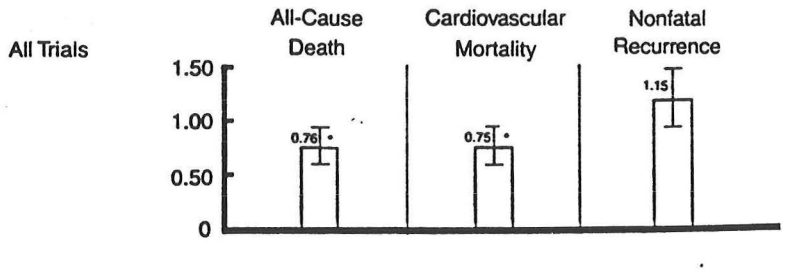
In contrast to the extensive data from apparently healthy persons, studies of the effect of cardiac rehabilitation on mortality following a myocardial infarction have rarely been of sufficient size to document a prolongation of life from exercise conditioning or rehabilitation services. These were reviewed in Dr. Jere Mitchell's March 11, 1982 Medical Grand rounds. One important study from Finland did demonstrate a significant reduction in sudden death that was apparent within the first six months of the program (61).



Kallio et al (61) Cumulative percentage of deaths from coronary heart disease in an intervention (I) and control group (C).

The distinguishing feature of this study is that the patients were enrolled very early after their myocardial infarction, within two weeks of hospital discharge. This early benefit suggests an effect of exercise training on altering the propensity for ventricular arrhythmias, possibly through alterations in autonomic tone. This will be discussed further below.

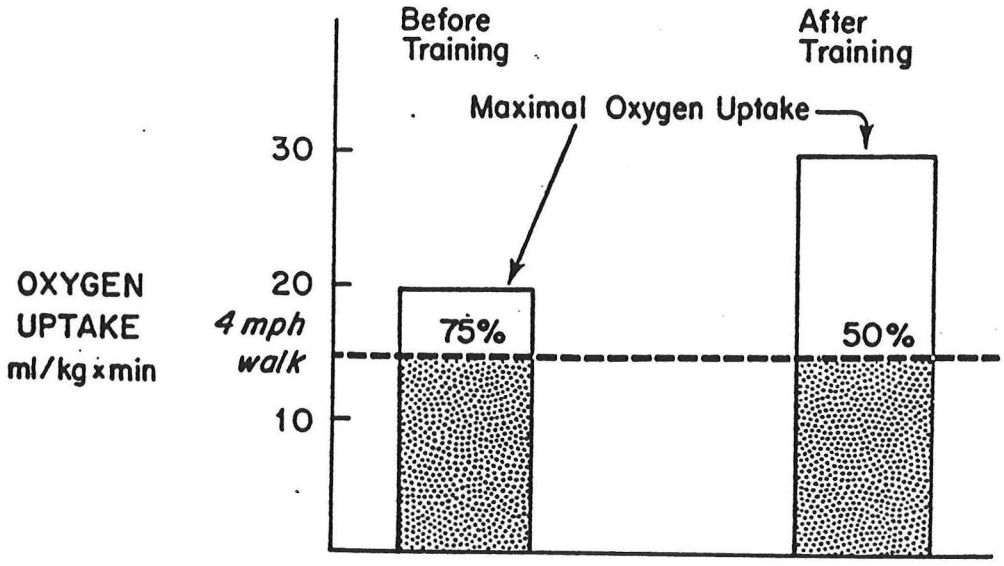
When the experience of major post-infarction trials are combined in a meta-analysis, the evidence suggests that cardiac rehabilitation reduces the incidence of sudden death significantly by approximately 25% (62,63), a magnitude equivalent to the beneficial effect of beta blockade.



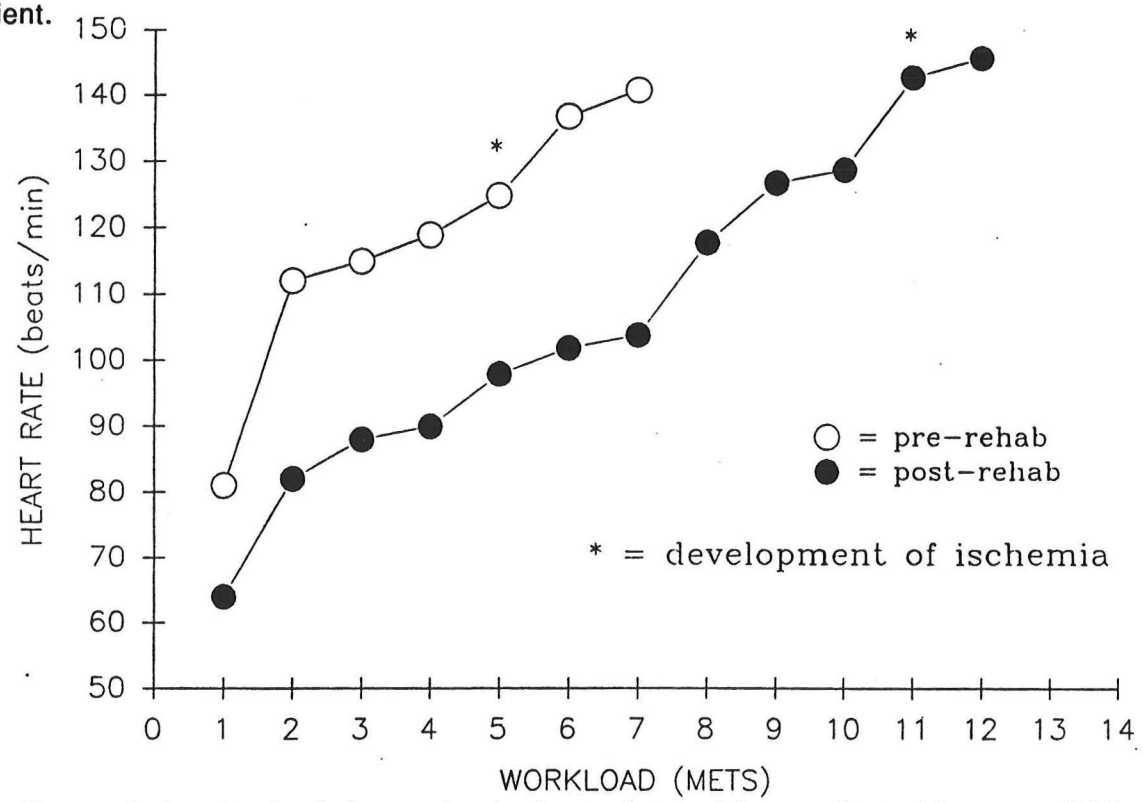
Oldridge(62) Pooled odds ratios and 95% confidence intervals for all-cause death, cardiovascular mortality, and nonfatal myocardial infarction.

No difference has been identified however for the incidence of recurrent myocardial infarction, providing further suggestive evidence that an anti-arrhythmic effect of exercise training may be more important than changes in vascular biology or thrombotic potential.

Although the effect of exercise training on mortality for patients following a myocardial infarction may still be somewhat debated, exercise conditioning clearly improves the functional capacity of cardiac patients resulting in an increased maximal oxygen uptake and an increased ischemic threshold (64).



Maximal oxygen consumption and effect on a moderate walking pace before and after rehabilitation in a hypothetical patient.



Levine et al (59) Change in heart rate during a standard exercise test in a patient with severe CAD before and after 12 weeks of cardiac rehabilitation. Ischemia is manifested by typical angina pectoris and significant ST-segment depression.

The reduction in resting and exercise heart rate and blood pressure reduces myocardial work during submaximal exercise and allows patients to perform activities of daily living as well as more vigorous activities with fewer symptoms. The mechanism for the improvement in cardiovascular performance at least initially, is likely due to increases in peripheral skeletal muscle oxygen uptake and utilization (65). However when training is prolonged and intense, even patients with cardiac disease can show improvements in myocardial contractile function (66).

The goals of **Phase I** Cardiac Rehabilitation are:

1 To prevent bed rest deconditioning

2 To facilitate rapid recovery of functional capacity

3 To shorten duration of CCU care and to enable early hospital discharge safely in appropriate patients

4 To minimize disability associated with an acute cardiac event and encourage rapid return to work

5 To improve communication between health care providers and patients, and thus smooth the transition into Phase II Cardiac Rehabilitation and outpatient care.

In contrast to the effect of training, prolonged bed rest and inactivity result in a marked reduction in maximal aerobic power (67). Plasma volume decreases and orthostatic intolerance may ensue after even brief periods of bed rest (68). This development of "bed rest deconditioning" may cause substantial morbidity in the acute period after a myocardial infarction by increasing heart rate during submaximal exercise and occasionally resulting in hypotension and reduced coronary perfusion. Its prevention is one of the primary goals of the first phase of cardiac rehabilitation (phase I), which begins as soon as a patient is stable in the hospital after an acute cardiac event. The focus of this early, in hospital rehabilitation is assumption of the upright posture and an individualized increase in exercise activity which together will rapidly reverse

the plasma volume shifts that occur with bed rest (69). We have broken Phase I rehabilitation into three stages at Parkland **(Appendix)**

Phase II of cardiac rehabilitation is the short term, initial outpatient phase of rehabilitation.

The goals of **Phase II** Cardiac Rehabilitation include:

1 Supervised exercise training to maximize functional capacity, teach safe exercise practices, and identify patients at risk for complications;

2 Risk factor modification including smoking cessation, stress reduction, weight loss, and lowering of cholesterol;

3 Education about medications, signs and symptoms of heart disease and its progression, sexual relations, dietary modifications and activity guidelines.

Phase II rehabilitation involves:

1. **Monitored exercise**
2. **Follows a symptom limited exercise test**
3. **Training at 75-85% of maximal heart rate**
4. **Borg effort scale of 13-14 (scale of 6-20)**
5. **Progressive intensity and duration**
6. **Usually 12 weeks in duration**

An expeditious and orderly transition between phase I and phase II is critical to the success of the rehabilitation process and ensures that patients are properly prepared to respond to the education and training programs. During the acute phase of hospitalization, patients are just beginning to cope with the ramifications of their disease and often have substantial difficulty processing new information (70). It is during the first few weeks of their outpatient care that they are most open to making significant life style adjustments. This time period is also a critical one from a medical perspective. The period of greatest risk for sudden death after a myocardial infarction is the first 3 months following hospitalization (71), and rehabilitation programs that enroll

patients early after a myocardial infarction demonstrate a significant reduction in the rate of sudden death during this high risk time (61).

Cardiac rehabilitation and successful changes in life-style may be achieved by patients regardless of ethnic group or socioeconomic status (72). We have shown that both indigent private patients demonstrate excellent attendance and compliance in terms of cardiac rehabilitation. Both groups quit smoking and continue not to smoke after completing the program. They also tend to eat a diet low in fat and saturated fat. Finally they experience and improvement in cardiovascular function which they maintain following completion of the program.

In addition to education, a major emphasis in Phase II rehab is on exercise conditioning. Heart rate is used as an easily measured estimate of relative exercise intensity. However it is important to emphasize that these are only guidelines which in some patients, such as those with left ventricular dysfunction or who are taking beta blockers or other medications that may affect the heart rate response to exercise, may not accurately reflect exercise intensity. In such cases, the RPE or Rating of Perceived Exertion (Borg scale) may be helpful. This measure rates the perceived effort on a scale from 6-20 (73):

RPE	Intensity
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

This rating system is remarkably consistent within individuals (74), and thus is independent of pharmacologic therapy that may attenuate the normal heart rate response to exercise. Once patients are trained in its use, they can effectively monitor their own exercise intensity at home without the need for sophisticated heart rate monitoring systems.

The optimal training load is complicated in patients with provocable ischemia. Some centers train patients at 75-85% of directly measured maximal heart rate despite the presence of ischemia in an attempt to maximize the training effect. However a meaningful training effect can clearly be obtained using more moderate exercise (60-75% of maximal heart rate) (75). Furthermore, recent data in animals suggests that ischemic exercise results in profound and prolonged depression of ventricular contractile function that persists for hours after an exercise bout (76). Finally, there is little evidence that myocardial ischemia produces adaptive benefits at a cellular or molecular level that improve the training effect or protect during future episodes of ischemia (77), and training above the ischemic threshold increases the risk of exercise (78,79).

Patients who are at low risk for future events (80) or who have more chronic cardiovascular disease and have not recently sustained an acute cardiac illness may be considered candidates for unmonitored exercise training at home (Phase III and Phase IV). It has been clearly demonstrated in carefully selected, relatively well educated patients, that home-based exercise training and cardiac rehabilitation can be performed safely and with the anticipated training effect (81). Patients living in rural areas may require a home based program.

Vigorous exercise itself is an important risk factor for sudden death, particularly in unfit individuals (54,79,82,83). However this risk is probably outweighed by the overall benefits of habitual exercise (55). The risk of exercise induced cardiac arrest is also directly related to the intensity of the exercise (78). Lower intensity training could theoretically be safer and equally effective as vigorous exercise, particularly in the unsupervised cardiac patient (75,84). Recall that even small increases in fitness can result in significant decreases in cardiovascular mortality (20). Finally, evidence is accumulating that even patients with stable chronic heart failure (who do not have exercise-induced arrhythmias or ischemia) may safely participate in a program of

unmonitored exercise training and experience substantial benefits (85).

Current evidence therefore suggests that when selected properly, some patients may safely undergo unsupervised exercise training, which may have important economic ramifications, particularly in communities with scarce resources. However this approach forgoes the education that takes place in a supervised setting.

Theoretical mechanisms for the protective effects of regular exercise

In addition to the effect of exercise on altering known coronary risk factors, exercise training may also induce other adaptations that provide protection against ischemic heart disease. The mechanisms for this protection may include anatomic and/or physiologic changes in the coronary arteries, alterations in autonomic tone, and or changes in the coagulation system.

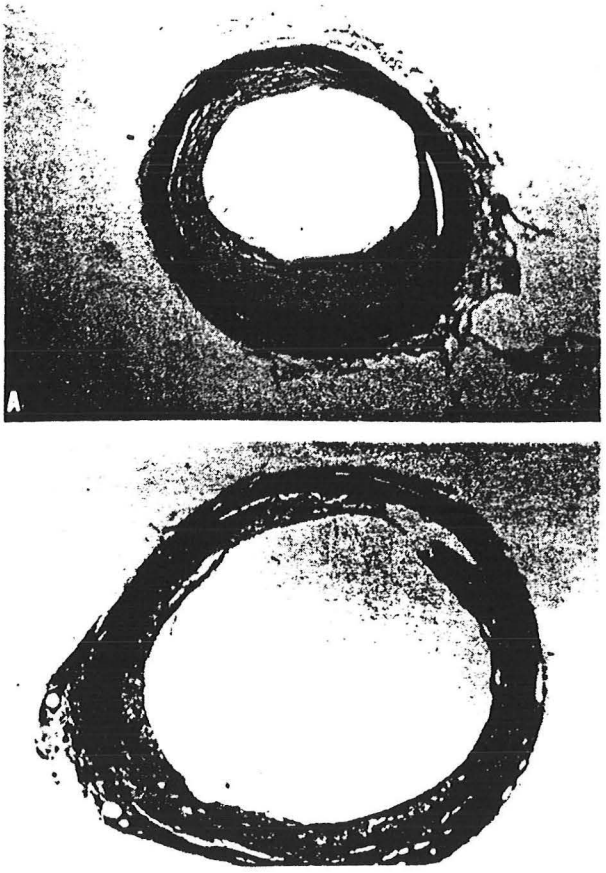
Vascular Biology

The effect of exercise training on the coronary vasculature has recently been reviewed in detail (86). Exercise training appears to increase coronary vascular transport capacity, both by structural and functional adaptations, though the results of many studies vary widely depending on the species and training techniques employed (86). Early coronary casting studies in rats suggested that endurance training increases coronary vascularity (87). These observations have been supported by more recent studies in dogs (88,89), and possibly even humans (90-92). Coronary collateral vessels may also increase with training, particularly if there is underlying arterial narrowing (93-98).

Atherosclerosis

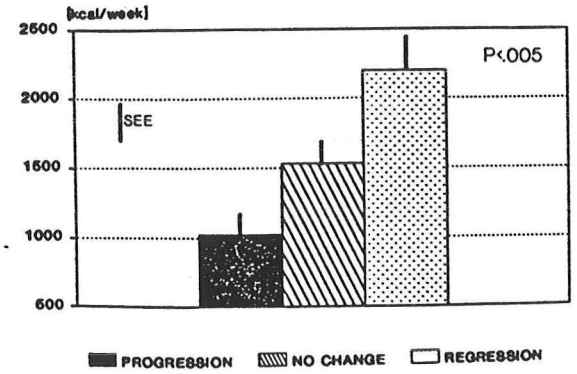
The role of exercise may be particularly important in modifying the development of atherosclerosis, as demonstrated in a landmark study by Kramsch et al (99) who studied primates consuming an atherogenic diet.

Monkeys ate a high fat diet for 2 years during which time they regularly trained on a treadmill. Two sedentary groups ate either a control diet or the atherogenic diet. Serum cholesterol was raised to over 600 mg/dl in all monkeys on the high fat diet with a significant rise in LDL. However the exercising monkeys had a higher HDL cholesterol.



Kramsch (99) Micrographs of sections through comparable predetermined segments of the left main coronary artery. Sedentary monkey (top) and exercise conditioned monkey (bottom).

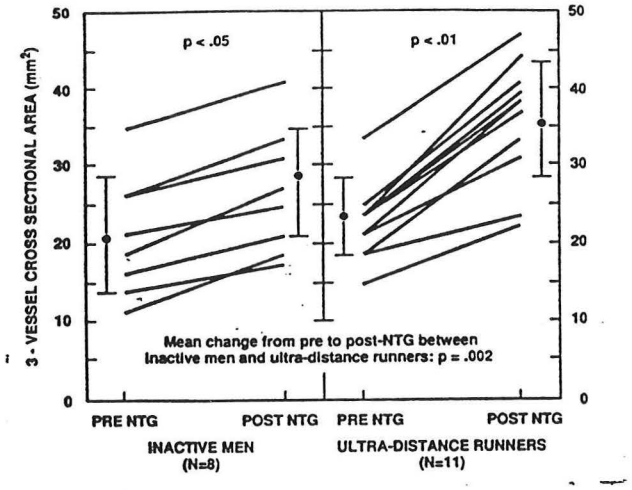
The exercising monkeys also had substantially reduced atherosclerosis. Most importantly, the exercising monkeys had significantly larger coronary arteries, with increased absolute coronary luminal diameter, confirming the observations made earlier in dogs by Wyatt and Mitchell (88). In humans, Hambrcht et al recently demonstrated that a greater degree of leisure time vigorous activity was associated with less progression and a greater degree of regression of coronary atherosclerotic lesions (100)



Hambrecht (100) Energy expenditures in leisure time physical activity according to changes in coronary morphology. The highest levels of energy expenditure were observed in patients showing regression of disease, the lowest levels in patients showing progression ($p<0.005$)

Ehsani et al provided support for the concept of increased myocardial blood supply by demonstrating that long term (12 months), intense training can reduce ischemic ST segment responses during treadmill exercise in patients with coronary artery disease (101).

Recently, Haskell et al performed quantitative angiography in a group of ultra-marathoners, who compete in races of more than 100 miles (102). They found that at rest, the combined cross-sectional area of the right, left main, left anterior descending and circumflex coronary arteries, was the same as a group of control patients with chest pain but angiographically normal coronary arteries. Still, the lower myocardial oxygen demand of the athletes during the study may have reduced the coronary diameter (103). After infusion of nitroglycerin, an endothelial independent coronary vasodilator (104), the total cross-sectional area of the coronaries of the runners increased by approximately twice that of the controls, demonstrating a significantly greater vasodilator reserve.



Haskell (102) Combined cross-sectional area (mm^3) of the proximal right, left anterior descending, and circumflex coronary arteries before and after nitroglycerine.

This increased maximal flow to cardiac muscle is similar to the elevated maximal conductance of skeletal muscle identified in endurance athletes (105). Increased conductance in skeletal muscle appears to be associated with a number of other adaptations of the endurance athlete, including eccentric hypertrophy and control of vascular resistance (106); thus, the large vasodilator reserve in both cardiac and skeletal muscle may be closely related.

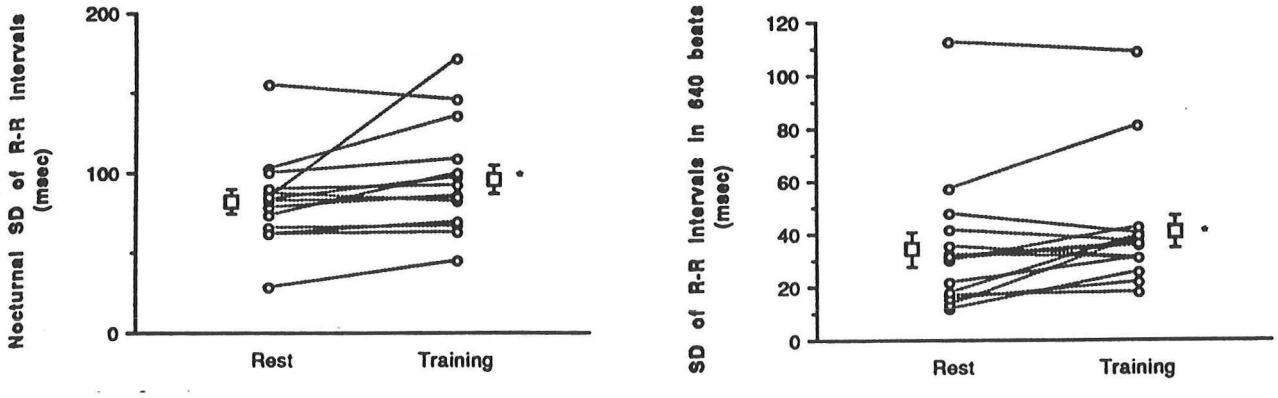
Still, marathon runners clearly develop and suffer the consequences of coronary atherosclerosis (3). The pathophysiology of myocardial infarction and acute coronary insufficiency is thought to result from rupture into an atherosclerotic plaque and associated intravascular thrombosis (107). Whether a plaque ruptures or not probably depends more on the composition of the plaque than on the volume of plaque or degree of stenosis (108). Thus although the presence of larger coronary arteries with increased flow reserve might delay the onset of angina, particularly during exercise, it would not necessarily be expected to prevent myocardial infarction. Recall that cardiac rehabilitation following myocardial infarction appears to improve survival primarily by reducing the incidence of sudden death rather than by preventing myocardial infarction (62).

Exercise Training and Influences on the autonomic nervous system

Autonomic tone and the balance between sympathetic and parasympathetic efferent neural influences on the heart play an important role in the genesis of cardiac arrhythmias (109). Heart rate variability, an index of cardiac-vagal tone that is relatively easy to obtain is reduced acutely with myocardial infarction (110); it is an important marker for late mortality after MI (111). In fact, when employed in a multiple regression model designed to

identify arrhythmic events (sustained ventricular tachyarrhythmias or arrhythmic death) in survivors of myocardial infarction, depressed heart rate variability was the most powerful independent predictor of life-threatening arrhythmias; when combined with the presence of late potentials on signal averaged ECG and repetitive ventricular ectopic forms on Holter monitoring, a sensitive (58% sensitivity) and surprisingly accurate (positive predictive accuracy 33%) predictor of arrhythmic events could be identified (112). These indices proved to be superior to combinations which included left ventricular ejection fraction, exercise ECG responses, or number of ventricular ectopic beats.

A number of studies have demonstrated increases in heart rate variability with exercise training, both in normal athletes (113), and patients with hypertension (114) or congestive heart failure (115).



Coats et al (115) Effect of training on nocturnal heart rate variability (left) and heart rate variability of 640 consecutive beats (right) in a controlled crossover trial of 8 weeks of exercise training in 18 men with severe congestive heart failure.

Whole-body radiolabeled norepinephrine spillover also falls when patients with CHF are trained (115). Animal studies have confirmed that exercise induced changes in autonomic control may prevent ventricular fibrillation associated with myocardial ischemia and reduce the risk of sudden

death (116). Recently, an awake animal model has confirmed this protective effect of increased vagal tone against life threatening ventricular arrhythmias (117). These studies support the hypothesis that changes in autonomic tone may be an important mechanism for the reduction in sudden death caused by cardiac rehabilitation and exercise.

Effect of exercise on coagulation

Most instances of myocardial infarction include acute intravascular thrombosis (106), this has resulted in an interest in the effect of exercise on the coagulation system. It was recognized in the 18th century that blood from animals that were run to death did not clot (118). However recent data have been somewhat contradictory and the end result of exercise appears to depend on a fine balance between thrombotic and fibrinolytic promoters and inhibitors that may be modified by the intensity and duration of the exercise, and the population being studied (119-121).

Acutely, very high intensity exercise (95-100% of maximal oxygen uptake) appears to actually increase concentrations of clotting factors, particularly Factor VIII (122,123). This increase, persists for at least one hour. Conversely, even more moderate levels of exercise induces a 5-10 fold increase in plasma fibrinolytic activity which appears directly related to the intensity and duration of exercise (119,124). The mechanism for this change in fibrinolytic capacity appears to be related to an increase in endogenous tissue plasminogen activator activity mediated by circulating epinephrine (125).

Vigorous exercise has also been shown to reduce the aggregability of platlets (126), though absolute platelet number appears to be increased after exercise; this probably results from a combination of hemoconcentration and release from spleen, marrow and lungs (119).

The effect of chronic exercise, or training on the coagulation system is less clear. Training appears to cause primarily a reduction in platelet aggregation (126), particularly in older patients with cardiovascular disease (127,128), and may also reduce plasma fibrinogen concentration (129).

Economics of Cardiac rehabilitation

The benefit relative to the cost of cardiac rehabilitation has been questioned (130-132). Oldrigde and Rogowski found that ward ambulation was as effective as use of a specialized exercise center in phase I rehabilitation (133). Denis (131) suggests that the cost-benefit relationship of cardiac rehabilitation is particularly important since the immediate impact may be much less striking than the long term benefits.

Coors company estimates that for every $1.00 spent on preventative care and wellness they save $6.00 (134). Cardiac rehabilitation is mandatory for their patients who experience a myocardial infarction. Ades demonstrated considerable savings in terms of hospital charges for patients undergoing rehabilitation when compared to non-participants and drop outs (135) This was a result of both less hospitalizations and lower cost per admission. Still, the study did not represent a randomized population, and the cost of rehabilitation was not included in the analysis. Picard showed that rehabilitation results in higher earned incomes 6 months after rehabilitation and again that hospital costs can be reduced (136). Again, the lack of randomization affects this finding as much or more than with any intervention since completing a cardiac rehabilitation program requires tremendous motivation. Randomized trials are difficult to complete because of other compelling benefits of this intervention.

It is assumed that 1.5 million Americans have a myocardial infarction each year. Approximately 200,000 undergo coronary artery bypass surgery and 300,000 undergo percutaneous transluminal coronary angioplasty. Of these patients, 100,000 are enrolled in cardiac rehabilitation programs (137). If the program costs $1,800, then the annual cost of supervised cardiac rehabilitation programs in the United States approaches $200 million (130,138,139). Still, this represents only a small percentage of the eligible patients for such a program.

Of course economic evaluation has to encompass both costs and consequences (140). Costs entail the direct cost of the intervention borne by the patient and provider whereas consequences relate to the effects of the intervention. This might include prolongation of life, and improvements in psychological, emotional or economic function (140). Some of these measure can be difficult. The cost is measured in dollars and the consequences in

natural units such as life-days or years gained. Recently investigators have tried to measure this variable in terms of quality-adjusted life years gained. Oldridge randomized post infarction patients with mild to moderate anxiety or depression to rehabilitation or standard care (139, 141). At one year, the rehabilitated patients had gained 19 quality-adjusted-life days per patient.

Using previous meta-analysis of cardiac rehabilitation (62,63), the authors estimate the cost-effectiveness of cardiac rehabilitation after myocardial infarction to be $21,800 per life year gained, $6,800 per quality-adjusted life-year gained. The authors conclude that this intervention is more cost effective than most treatments for coronary artery disease for which cost-utility estimates exist.

An office visit where smoking cessation is discussed (142), a daily aspirin (143) , and ß-blocker therapy for a 55 year old man status post myocardial infarction (144) are much more cost effective than rehabilitation (130). Rehabilitation has a cost effectiveness similar to that of propranolol for a blood pressure >94 mm Hg (145) and lovastatin (40 mg/day) for a cholesterol >272 mg/dl (146) and more cost effective than captopril for a diastolic blood pressure >94 mm Hg (145) or lovastatin (80 mg./day) for a cholesterol >272 mg/dl (146). The cost effectiveness is similar to that of coronary artery bypass surgery for left main coronary artery disease (130,147).

Of course these estimates for cardiac rehabilitation rely on meta-analysis for the life prolonging component, and many of the measures are inexact. Still, these data suggest that cardiac rehabilitation can be justified on an economic basis looking even at hard end points.

Summary

Exercise plays a critical role in both the primary and secondary prevention of ischemic heart disease. Epidemiologic investigations show approximately half the incidence of CAD in active compared to sedentary persons. A sedentary lifestyle thus is now considered by national and international organizations to be one of the most important modifiable risk factors for cardiovascular morbidity and mortality. Fortunately, a moderate level of occupational or recreational activity appears to confer a significant protective effect. Well designed clinical investigations demonstrate that this effect is not related to a nonspecific selection bias in favor of already

vigorous individuals, but rather a direct protective mechanism of exercise. Regular dynamic exercise can improve other known risk factors for CAD including plasma lipids, glucose intolerance, abdominal obesity, and perhaps hypertension. However even when these other risk factors are taken into account, exercise appears to exert an independent protective effect. Once coronary artery disease has been manifest, exercise training can clearly improve patient's functional capacity and reduce overall mortality by decreasing the risk of sudden death. These benefits may occur either through direct effects on the coronary arteries, modifications of autonomic control of the circulation or changes in the blood coagulation system.

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DALLAS COUNTY HOSPITAL DISTRICT
Dallas, Texas

APPENDIX

CARDIAC REHABILITATION SERVICES
PHASE I PATIENT PROGRESS REPORT

PATIENT NAME: _____ UNIT: _____ DATE: _____

PROTOCOL: _____ STANDARD _____ MODIFIED (Please Check One)

NOTE:
1. Patient enrollment in Stage I requires Physician Order.
2. Progression to subsequent Stages depends on careful assessment of individual patient tolerance.

CRITERIA:
1. No angina at current activity level
2. Absence of excessive dyspnea or fatigue
3. Absence of dizziness or orthostatic BP decline exceeding 20/mmHg
4. Maintenance of systolic BP > 90 mmHg
5. Increase in HR > 25 BPM during exercise
6. Absence of a new S3 or rales (M.D. Assessment)
7. Progession on modified protocol by M.D. order

ANY ABNORMAL RESPONSE TO ACTIVITY SHOULD BE REPORTED TO THE RESPONSIBLE PHYSICIAN FOR REASSESSMENT OF THE EXERCISE PRESCRIPTION.

ACTIVITY CODE

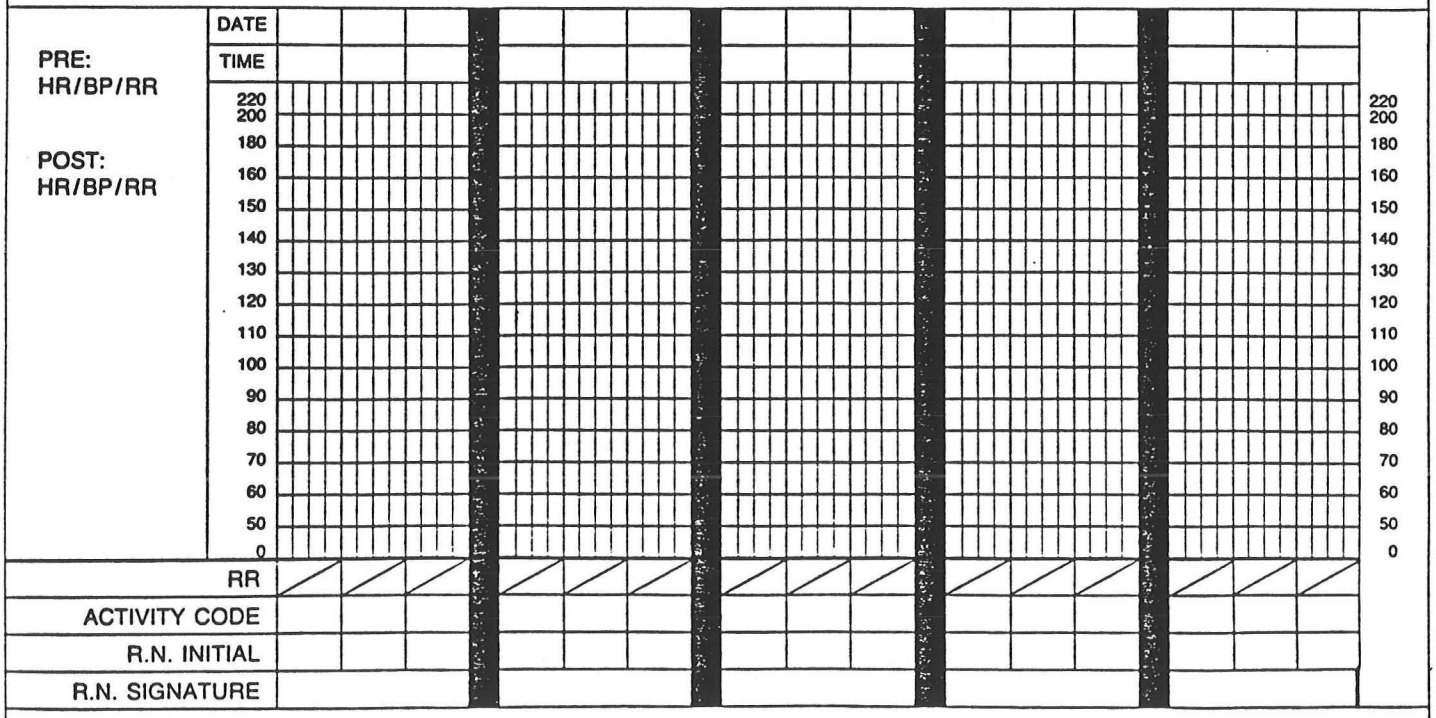
STAGE I:

A. Active ROM q4h
B. Bedside commode
C. Deep Breathing q2h
D. Self feeding
E. Wash face, hands, Brush teeth
F. Dangle legs: 15 min. q4h
G. Up in chair: 15 min q4H
H. Active ROM: sitting

STAGE II:

I. Sitting Self-care
J. Active ROM: Standing

STAGE _____



Comments: _____

DALLAS COUNTY HOSPITAL DISTRICT
Dallas, Texas

APPENDIX

CARDIAC REHABILITATION SERVICES
PHASE I PATIENT PROGRESS REPORT

PATIENT NAME: _____ UNIT: _____ DATE: _____

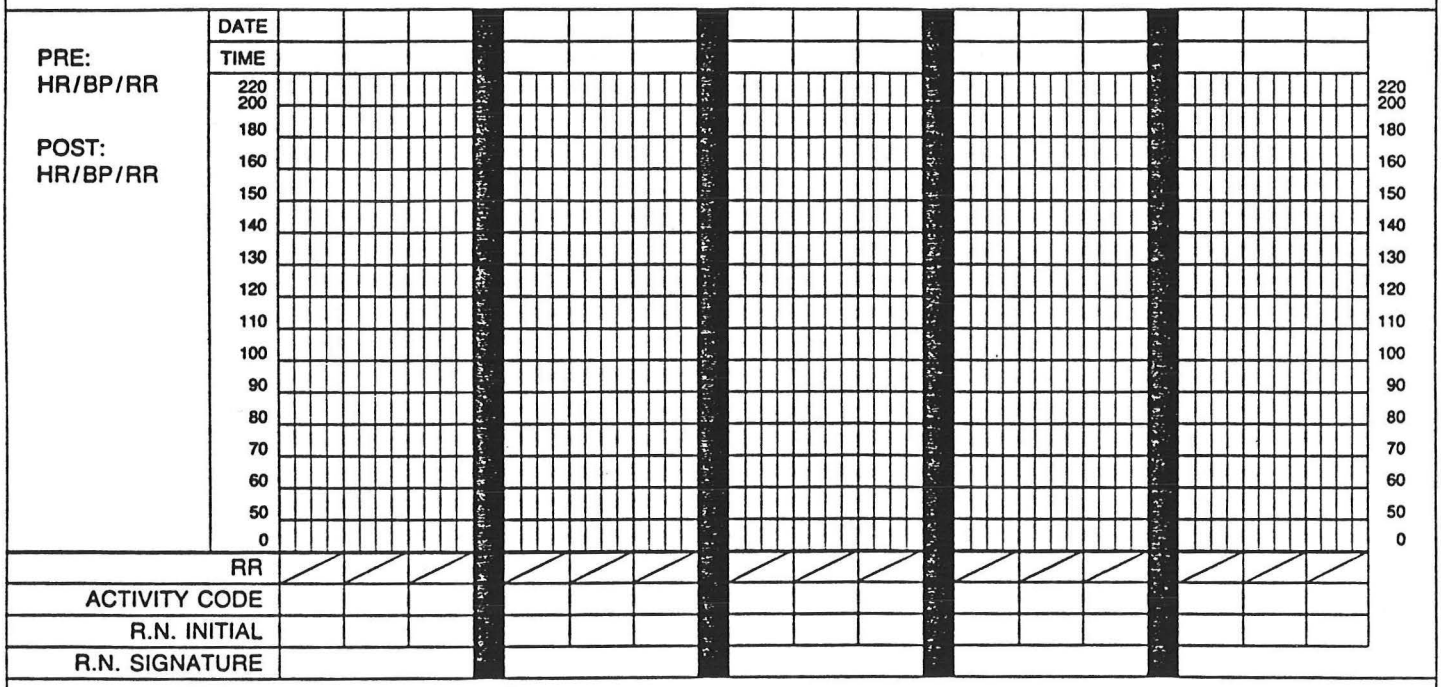
PROTOCOL: _____ STANDARD _____ MODIFIED (Please Check One)

NOTE: PROGRESSION TO AND THROUGH STAGE III OF THE CARDIAC REHABILITATION PROGRAM IS DEPENDENT UPON CAREFUL ASSESSMENT OF THE RESPONSE TO PRECEEDING ACTIVITIES. ANY ABNORMAL RESPONSE SHOULD BE REPORTED TO THE RESPONSIBLE PHYSICIAN FOR REASSESSMENT OF THE EXERCISE PRESCRIPTION.

ACTIVITY CODE

STAGE III:

K. Up in room ad lib, BR privileges
L. Walk 100 ft., interrupted
M. Attend Cardiac Rehab Classes
N. Tour Rehab Center
O. Walk 100 ft.
P. Walk 200 ft.
Q. Walk 300 ft.
R. Walk 5 min.
S. Walk 10 min. q6h while awake



Comments: _____

IF POSSIBLE, EXERCISE SESSIONS SHOULD OCCUR TID. WALKING SESSIONS SHOULD BE PRECEEDED BY 5 MINUTES OF STANDING/ STRETCHING. WHEN ABLE TO WALK 100 FT., PATIENT SHOULD BE ALLOWED TO SHOWER, IF APPROPRIATE.

Physician Checklist:

1. Completion of Phase I: _____ / _____ _____ R.N.
   Date / Time
2. Submaximal Exercise Tolerance Test Scheduled for: _____
3. Referral for Phase II Cardiac Rehabilition: _____
4. Cardiology Clinic Appointment: _____

_____ M.D. _____ _____
Physician's Signature Print Physician's Name Beeper Number