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EXERCISE TRAINING IN THE TREATMENT OF CORONARY HEART DISEASE

PARKLAND MEMORIAL HOSPITAL

MEDICAL GRAND ROUNDS

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I. INTRODUCTION

1. Proceedings of the International Symposium on Physical Activity and Cardiovascular Health. Canadian Med Assn J 96:695-915, 1967.
2. Kattus AA, MacAlpin RN: Role of exercise in discovery, evaluation, and management of ischemic heart disease. Cardiovas Clin 1:256, 1969.
3. Frick MH: The effect of physical training in manifest ischemic heart disease. Circulation 40:433, 1969.
4. Parmley LF Jr, *et al* (eds): Proceedings of the National Workshop on Exercise in the Prevention, in the Evaluation, in the Treatment of Heart Disease. J South Carolina Med Assn 65: Suppl 1, 1969.
5. Larsen OA, Malmborg RO (eds): Coronary Heart Disease and Physical Fitness. Baltimore: University Park Press, 1971.
6. Morse RL: Exercise and the Heart. Springfield: Charles C Thomas, 1972.
7. Blackburn H: Intensive exercise therapy after myocardial infarction? The negative position. New England J Med In press.
8. Bruce RA: Is physical training beneficial in patients with coronary heart disease? The positive position. New England J Med In press.

The role of exercise testing in the diagnosis and evaluation of coronary heart disease is well established and accepted in the field of cardiology. This subject was critically reviewed by Dr. Gunnar Blomqvist at these Grand Rounds and later published in *Circulation*. However, the role of exercise training in the treatment for and prophylaxis against coronary heart disease is a highly controversial and much debated issue. There are strong advocates on both sides of this argument and it appears that this controversy will continue for many years to come. In fact, controlled laboratory type of experiments in man in which exercise can be shown to be significant in the treatment or prevention of coronary heart disease will probably never be carried out. Further, animal studies may be of little value in answering this question since a good model of chronic coronary heart disease is not available.

In spite of these limitations, important studies have been carried out and will be presented and discussed in this Grand Rounds. First we will review the effects of exercise training in normal man and animals. Next coronary heart disease will be discussed, and this will be followed by an analysis of the use of exercise training in the treatment of this disorder. We will not present the possible role of exercise training in the prophylaxis against coronary heart disease.

II. Effects of Exercise Training

A. Cardiovascular function

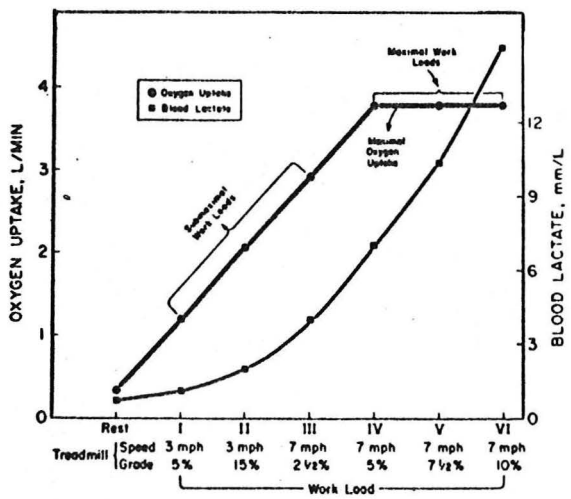
1. Maximal oxygen uptake

9. Taylor HL, Buskirk E, Henschel A: Maximal oxygen intake as an objective measure of cardio-respiratory performance. J Appl Physiol 8:73, 1958.
10. Mitchell JH, Sproule BJ, Chapman CB: The physiological meaning of the maximal oxygen intake test. J Clin Invest 37:538-547, 1958.
11. Åstrand PO, Rodahl K: Textbook of Work Physiology. New York: McGraw-Hill Book Company, 1970.
12. Mitchell JH, Blomqvist G: Maximal oxygen uptake. New England J Med 284:1018-1022, 1971.

Maximal oxygen uptake is the greatest amount of oxygen a person can take in during physical work and is a measure of his maximal capacity to transport oxygen to the tissues of the body. It is an index to maximal cardiovascular function, provided pulmonary function and ambient oxygen concentration are normal, and, therefore, is valuable in the evaluation of abnormal cardiovascular function.

The maximal oxygen uptake can be determined in the experimental laboratory by means of a bicycle ergometer or a motor-driven treadmill as shown in Fig 1.

Figure 1



The subject's oxygen uptake is measured while he is standing quietly on the treadmill and then while he walks up a 5% grade at 3 miles per hour. After completing this work load he rests and then works at a higher work load (3 miles per hour at 15% grade) while the oxygen uptake is again measured. This procedure is repeated, and the oxygen uptake increases in a near linear fashion with the increasing work load. However, a work load is finally reached where, even though he exercises at a higher work load, the maximal capability to take in oxygen reaches its limit, and this highest level is called the maximal oxygen uptake. With the initial increases in exercise there are slight rises in the lactate concentration of blood, but as maximal oxygen uptake is approached and passed, a marked increase in blood lactate concentration occurs.

Maximal oxygen uptake depends on maximal cardiac output and the arteriovenous oxygen difference of the body. The maximal cardiac output is, in turn, determined by the maximal heart rate and stroke volume, and the arteriovenous oxygen difference by the maximal oxygen content in arterial blood and the minimal oxygen content in mixed venous blood. The maintenance of arterial oxygen tension during heavy exercise demonstrates that pulmonary factors, ventilatory or diffusive, do not limit oxygen transport in normal subjects.

Physiologic variations in maximal oxygen uptake are caused by age, sex, body size, and habitual level of physical activity or physical conditioning.

Pathologic processes may depress maximal oxygen uptake by causing a rate-limiting block at any stage of the transfer of oxygen from ambient air to the cells. A subnormal maximal cardiac output is the limiting mechanism in diseases affecting cardiac function.

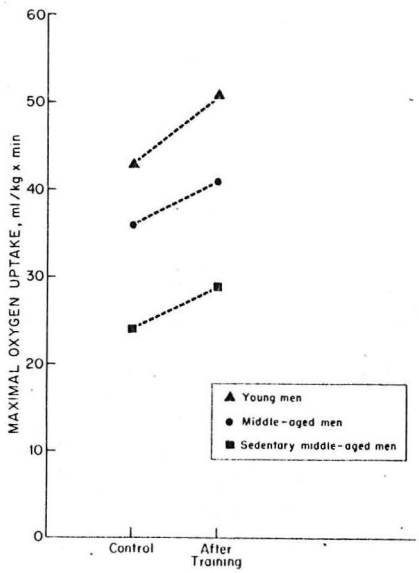
Oxygen uptake at the highest work load that can be achieved without provoking limiting symptoms is sometimes referred to as maximal oxygen uptake. Patients with angina pectoris are frequently forced by localized ischemic pain to discontinue exercise at a low work load in the absence of any substantial increase in arterial lactate concentration or other signs that the oxygen transport function has been taxed to its capacity. This modified test is a useful index to the physical performance capacity but does not conform to the definition of maximal oxygen uptake generally used in exercise physiology.

13. Saltin B, Blomqvist G, Mitchell JH, Johnson RL Jr; Wildenthal K, Chapman CB: Response to exercise after bed rest and after training; a longitudinal study of adaptive changes in oxygen transport and body composition. Circulation 38:VII-1-VII-78, 1968.
14. Hartley LH, Grimby G, Kilbom A, Nilsson NJ, Åstrand I, Bjure J, Ekblom B, Saltin B: Physical training in sedentary middle-aged and older men. Scand J Clin Lab Invest 24:335, 1969.

15. Siegel W, Blomqvist G, Mitchell JH: Effects of a quantitated physical training program on middle-aged sedentary men. Circulation 41:19-29, 1970.
16. Saltin B: Central circulation after physical conditioning in young and middle-aged men. In: Coronary Heart Disease and Physical Fitness, ed by OA Larsen and RO Malmborg. Baltimore: University Park Press, 1971.
17. Mitchell JH, Blomqvist G: The effects of physical training on sedentary American men. Cardiovas Rehabil 2:33-36, 1972.

Studies of the effects of physical training have been carried out in Dallas and in Stockholm on three groups of subjects. These were 1) young male subjects, 2) middle-aged male subjects, and 3) sedentary middle-aged male subjects. These studies are shown in Fig 2.

Figure 2



In the young male subjects, studied in Dallas, maximal oxygen uptake increased from a value of 3,30 L/min or 43 ml/kg x min before training to 3,91 L/min or 51 ml/kg x min after training. This represents an increase of 19% and was due to an increase in stroke volume and a small increase in arteriovenous oxygen difference.

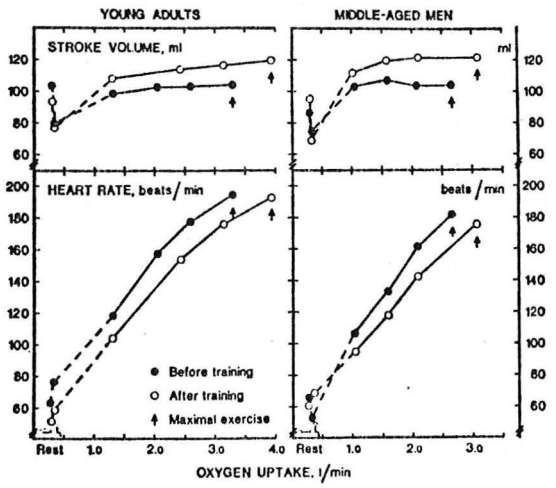
In the middle-aged male subjects, studied in Stockholm, maximal oxygen uptake increased from a value of 2.68 L/min or 36 ml/kg x min before training to 3.06 L/min or 41 ml/kg x min after training. This represents an increase of 14% and was due entirely to an increase in stroke volume.

In the sedentary middle-aged male subjects, a group of blind men studied in Dallas, maximal oxygen uptake increased from 1.63 L/min or 24 ml/kg x min before training to 1.94 L/min or 29 ml/kg x min after training. This represents an increase of 19%. There was no change in maximal heart rate. Cardiac output and arteriovenous oxygen difference were not measured.

2. Exercise at submaximal work loads

In the two groups of subjects in which cardiac output was measured, the response of heart rate and stroke volume at rest and during exercise before and after training is shown in Fig 3.

Figure 3



In both of these groups there was no change in the relation between cardiac output and oxygen uptake during submaximal exercise after training. Maximal cardiac output and maximal oxygen uptake were both increased. Also in both groups there was no significant

change in maximal heart rate but maximal stroke volume was increased. It is important to note, however, that at any given level of oxygen uptake or cardiac output during submaximal work loads there was a decrease in heart rate and an increase in stroke volume after training. This is a very important and consistent effect of exercise training in normal male subjects.

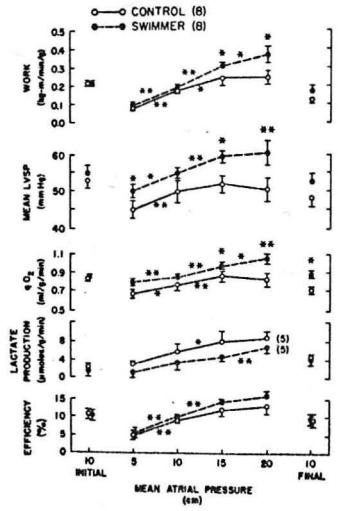
B. Cardiac function and metabolism

18. Scheuer J, Kapner L, Stringfellow CA, Armstrong CL, Penpargkul S: Glycogen, lipid, and high energy phosphate stores in hearts from conditioned rats. J Lab Clin Med 75:924-929, 1970.
19. Penpargkul S, Scheuer J: The effect of physical training upon the mechanical and metabolic performance of the rat heart. J Clin Invest 49:1859-1868, 1970.
20. Scheuer J, Stezoski SW: Effect of physical training on the mechanical and metabolic response of the rat heart to hypoxia. Circulation Res 30:418-429, 1972.
21. Bhan AK, Scheuer J: Effects of physical training on cardiac actomyosin adenosine triphosphatase activity. Am J Physiol 223:1486-1490, 1972.

Exercise training causes improved mechanical and metabolic performance of the rat heart. It has been demonstrated that hearts from conditioned rats have increased glycogen levels which can be mobilized but no changes were found in high-energy phosphate stores.

The effect of increasing inflow on left ventricular work (work), mean integrated left ventricular systolic pressure (mean LVSP), oxygen consumption (qO_2), lactate production, and efficiency is shown in Fig 4.

Figure 4



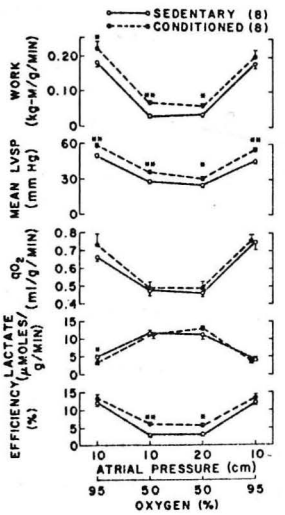
The hearts from conditioned rats showed a greater response in left ventricular work and mean integrated left ventricular systolic pressure as filling pressure was increased. It was also found that the maximal rate of left ventricular pressure rise (max LV dp/dt) was higher at each level of filling pressure. These findings suggest an increase in the contractile state of the left ventricles from the conditioned rats. This may be due to alteration in the contractile proteins in the conditioned ventricles since cardiac actinomysin ATPase activities are increased.

The hearts from the conditioned rats also demonstrated a higher myocardial oxygen consumption and a lower lactate production than hearts from the sedentary rats. In addition, it was found that the increase in oxygen consumption in the conditioned rats was due to an increase in coronary flow with no significant change in coronary arteriovenous oxygen difference; whereas, in the sedentary rats it was due to an increase in coronary arteriovenous oxygen difference with no significant change in coronary flow. Cardiac efficiency was the same in the two groups. These findings suggest a greater capacity for increases in coronary flow in the hearts from the conditioned rats.

The response to hypoxia of hearts from sedentary and conditioned rats has also been studied. The effects of hypoxia on

left ventricular work, mean integrated left ventricular systolic pressure, oxygen consumption, lactate production, and efficiency are shown in Fig 5.

Figure 5



The hearts from conditioned rats maintained a higher left ventricular work and mean integrated left ventricular systolic pressure during hypoxia. However, during hypoxia myocardial oxygen consumption and lactate production were similar. Cardiac efficiency was twice as high during hypoxia in hearts of conditioned rats than in sedentary rats. Thus hearts of conditioned rats appear to be relatively resistant to hypoxia. This appears to be due to more efficient mechanisms of energy utilization.

C. Coronary vasculature and blood flow

22. Tepperman J, Pearlman D: Effects of exercise and anemia on coronary arteries of small animals as revealed by the corrosion-cast technique. Circulation Res 9:576, 1961.
23. Stevenson JAF, Feleki V, Rechnitzer P, Beaton JR: Effect of exercise on coronary tree size in rats. Circulation Res 15: 265, 1964.

24. Stevenson JAF: Exercise, food intake, and health in experimental animals. Canadian Med Assn J 96:862, 1967.
25. Leon AS, Bloor CM: Effects of exercise and its cessation on the heart and its blood supply. J Appl Physiol 24:485, 1968.
26. Bloor CM, Leon AS: Interaction of age and exercise on the heart and its blood supply. Lab Invest 22:160, 1970.

An increase in coronary vasculature, as estimated by the weight of vinyl casts, has been observed in hearts from conditioned rats. Further the cross sectional luminal area of coronary arteries and the capillary-ventricular muscle fiber ratio have been shown to increase with exercise training. It is of interest that the increased capillary-ventricular muscle fiber ratio in young exercised animals was due to an increased total number of capillaries; whereas, the increased value in the old exercised animals was due to a loss of myocardial fibers.

27. Eckstein RW: Effect of exercise and coronary artery narrowing on coronary collateral circulation. Circulation Res 5:230, 1957.
28. Burt JJ, Jackson R: The effects of physical exercise on the collateral circulation of dogs. J Sports Med & Physical Fitness 5:203, 1965.

Eckstein found that hypoxia produced by coronary artery restriction caused an increase in coronary collateral circulation in dogs. Mild coronary artery narrowing only provided an increase in collaterals when combined with exercise training; whereas, moderate and severe artery narrowing produced increased collaterals without exercise training, but the magnitude of collateralization was much greater in dogs that were exercised. Burt and Johnson found no evidence for increased coronary collateral circulation in exercised dogs when no coronary artery restriction was previously produced.

D. Catecholamines

29. DeSchryrer C, De Herdt P, Lammerant J: Effect of physical training on cardiac catecholamine concentrations. Nature 214: 907, 1967.
30. Frick MH, Elovainio RO, Somer T: The mechanism of bradycardia evoked by physical training. Cardiologia 51:46, 1967.
31. Häggendal J, Hartley LH, Saltin B: Arterial noradrenaline concentration during exercise in relation to relative work levels. Scand J Clin Lab Invest 26:337, 1970.

It has been shown in rats that exercise training causes a significant decrease in total heart catecholamine content. In man the decreased heart rate at a submaximal work load has been shown to be due to a decreased cardiac sympathetic activity. The level of sympathetic response appears to be directly related to relative work load of the subject. Since training increases the maximal work load, a given submaximal work load becomes a smaller relative work load and thereby the level of cardiac sympathetic activity is decreased.

E. Plasma cholesterol and triglycerides

32. Gustafson A: Effect of training on blood lipids. In: Coronary Heart Disease and Physical Fitness, ed by OA Larsen and RO Malmborg. Baltimore: University Park Press, 1971.

The influence of exercise training on both plasma cholesterol and triglyceride levels has been repeatedly studied. The findings, however, have not been entirely consistent. In general it may be stated that exercise training causes a fairly moderate reduction in cholesterol and a more marked decrease in triglycerides. The significance of these findings is not known.

III. Coronary Heart Disease

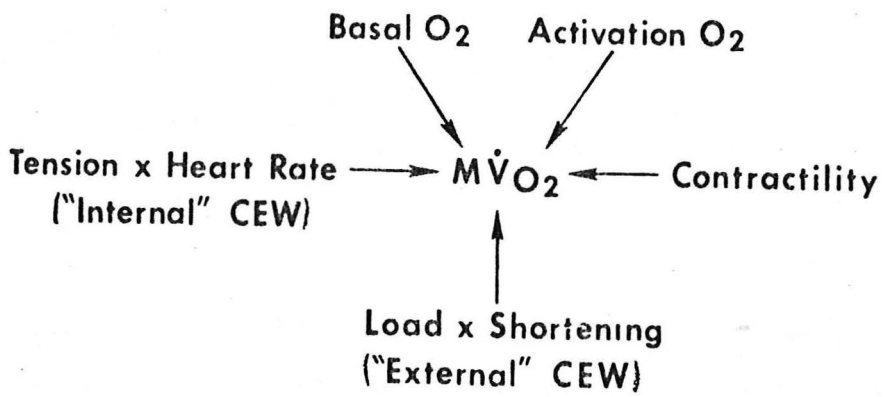
A. Myocardial oxygen demand

33. Sarnoff SJ, Braunwald E, Welch GH Jr, Case RB, Stainsby WN, Macruz R: Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. Am J Physiol 192:148, 1958.
34. Katz LN, Feinberg H: The relation of cardiac effort to myocardial oxygen consumption and coronary flow. Circulation Res 6:656, 1958.
35. Monroe RG, French GN: Left ventricular pressure-volume relationships and myocardial oxygen consumption in the isolated heart. Circulation Res 9:362, 1961.
36. McDonald RH Jr: Developed tension: a major determinant of myocardial oxygen consumption. Am J Physiol 210:351, 1966.
37. Sonnenblick EH, Ross J Jr, Covell JW, Kaiser GA, Braunwald E: Velocity of contraction as a determinant of myocardial oxygen consumption. Am J Physiol 209:919, 1965.
38. Sonnenblick EH, Ross J Jr, Braunwald E: Oxygen consumption of the heart; newer concepts of its multifactoral determination. Am J Cardiol 22:328, 1968.

39. Mitchell JH, Hefner LL, Monroe RG: Performance of the left ventricle. Am J Med 53:481-494, 1972.

The determinants of myocardial energy utilization have been investigated for many years, and since cardiac muscle can develop only a small oxygen debt its oxygen consumption is a good measure of total energy utilization during steady state measurements. The oxygen consumption of the myocardium is determined by several factors and this concept is shown in Fig 6.

Figure 6



In general, the currently recognized determinants of total oxygen consumption of the myocardium are 1) the basal oxygen consumption, 2) the oxygen consumption of activation, 3) the oxygen consumption of internal work (tension development x heart rate), 4) the oxygen consumption of external work (load x shortening), and 5) the additional oxygen consumption required by the contractile state. The basal oxygen consumption is low, 20% or less than that found in the contracting organ, and the oxygen consumption of electrical activation is about 1/2%. The oxygen consumption of internal work is about two times that of external work. Further, the contractile state of cardiac muscle adds substantially to the oxygen consumption. It is thus seen that tension development, heart

rate, and the contractile state play principal roles in determining the oxygen consumption of the left ventricle.

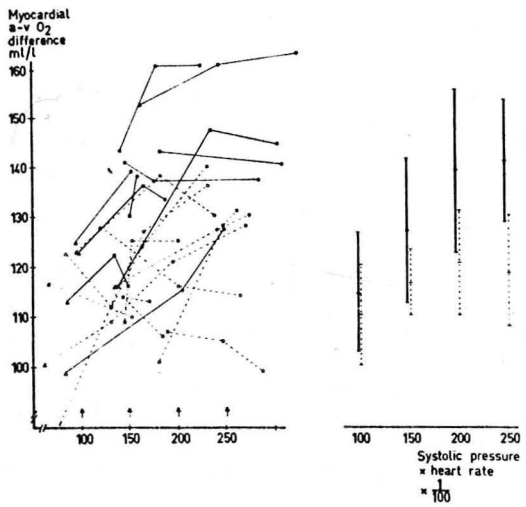
In clinical studies the tension-time index (area under left ventricular or aortic pressure curve during systole x heart rate), the double product (peak systolic pressure x heart rate), and the triple product (peak systolic pressure x heart rate x ejection time) have all been used as indicators of myocardial oxygen demand.

B. Myocardial oxygen supply

40. Gregg DE, Fisher LC: Blood supply to the heart. In: Handbook of Physiology. Section 2: Circulation, volume II, pp 1517-1584. Washington DC: American Physiological Society, 1963.
41. Gregg DE, Khouri EM, Rayford CR: Systemic and coronary energetics in the resting unanesthetized dog. Circulation Res 16:102, 1965.
42. Khouri EM, Gregg DE, Rayford CR: Effects of exercise on cardiac output, left coronary flow and myocardial metabolism in the unanesthetized dog Circulation Res 17:427, 1965.
43. Gorlin R, Cohen LS, Elliott WC, Klein MD, Lane FJ: Effect of supine exercise on left ventricular volume and oxygen consumption in man. Circulation 32:361, 1965.
44. Holmberg S, Serzysko W, Varnauskas E: Coronary circulation during heavy exercise in control subjects and patients with coronary heart disease. Acta Med Scand 190:465, 1971.

Myocardial oxygen supply is related to both the coronary blood flow and the oxygen content of arterial blood. Cardiac muscle extracts close to the maximal amount of oxygen presented to it so that even during basal conditions the arteriovenous oxygen difference across the heart is quite high. Thus increased myocardial oxygen demands are largely met by increased coronary blood flow. Coronary blood flow is regulated by a sensitive process that keeps oxygen supply proportional to oxygen demand. This mechanism which works extremely well in the normal coronary artery tree fails in the setting of coronary artery disease. Holmberg, Serzysko, and Varnauskas have studied the coronary circulation during rest and during exercise in control subjects and in patients with coronary heart disease and this is shown in Fig 7.

Figure 7



On the left the relation between myocardial arteriovenous oxygen difference and the double product (systolic pressure x heart rate) is plotted for subjects without coronary heart disease at rest (Δ) and during progressive exercise loads (o) connected by the dashed lines, and for patients with coronary heart disease at rest (▲) and during progressive exercise loads (●) connected by the solid lines. On the right the values for myocardial oxygen difference are interpolated to four levels of double product (100, 150, 200, and 250). The results are presented as mean values and standard deviations of control subjects (|) and patients with coronary heart disease (¦) at each level of double product. In normal subjects at rest and during exercise both coronary flow and arteriovenous oxygen difference varied widely. During exercise there was an increase in myocardial demand for oxygen and this was met by an increase in coronary flow with no significant change in coronary arteriovenous oxygen difference.

In patients with coronary heart disease the resting values for coronary blood flow and arteriovenous oxygen difference were within the normal range. During exercise, however, the patients show a significantly lower increase in coronary flow and a significantly higher increase in arteriovenous oxygen difference. In the coronary heart disease patients, myocardial oxygen consumption was

lower in relation to the pressure-rate product than in the control subjects.

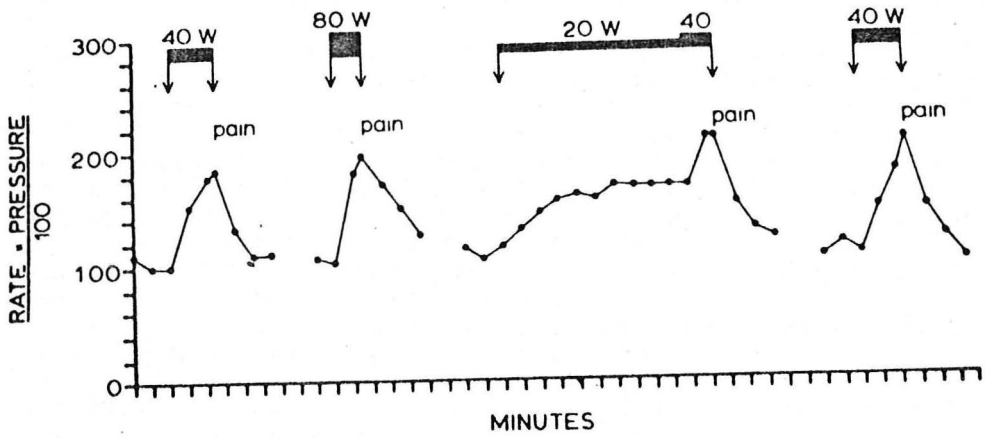
C. Myocardial ischemia (angina pectoris)

45. Gorlin R: Pathophysiology of cardiac pain. Circulation 32: 138, 1965.
46. Robinson BF: Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. Circulation 35: 1073, 1967.

Myocardial ischemia and ensuing angina pectoris are caused by an imbalance between myocardial oxygen supply and myocardial oxygen demand. The mechanism by which ischemia produces the myocardial pain is not known.

Robinson used the peak systolic pressure-heart rate product to show that angina pectoris predictably occurs in a patient when this value reaches a critical level which is essentially constant for a given patient. An example of this finding from the work of Robinson is shown in Fig 8.

Figure 8



In this study a patient was subjected to various work loads measured in watts (w) on a bicycle ergometer. An index of myocardial oxygen demand (rate x pressure/100) is plotted on the ordinate and time on the abscissa. It is noted that angina pectoris (pain) develops at the same level of rate-pressure product regardless of the work load. When the work load is high, the time required for reaching the critical rate-pressure product which produces pain is short. When the work load is low, the time required for reaching the rate-pressure level producing pain is delayed. Thus the occurrence of angina pectoris could be consistently related to the product of heart rate and systolic blood pressure.

IV. Exercise Training in the Therapy of Coronary Heart Disease

A. General

47. Heberden W: Some accounts of a disorder of the breast. Med Trans Roy Col Phys 2:59, 1772.
48. Parry CH: An Inquiry Into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris. London: Cadwell & Davies, 1799, p 148.
49. Gottheiner V: Strenuous sports as treatment for degenerative heart disease. In: Prevention of Ischemic Heart Disease, ed by W Raab. Springfield: Charles C Thomas, 1966, p 338.
50. Gottheiner V: Long-range strenuous sports training for cardiac reconditioning and rehabilitation. Am J Cardiol 22:426, 1968.
51. Gottheiner V: Intensives könpertraining als nachbehandlung und vorbeugung des herzinfarktes. Internist (Berlin) 12:236, 1971.
52. Hellerstein HK, Hirsch EZ, Cumber W, Allen L, Polsler S, Zucker N: Reconditioning of the coronary patient. A preliminary report. In: Coronary Heart Disease, ed by W Likoff and JH Moyer. New York and London: Grune & Stratton, 1963.
53. Hellerstein HK, Hornsten TR, Goldbarg AN, Burlando AG, Friedman EH, Hirsch EZ, Harik S: The influence of active conditioning upon subjects with coronary artery disease; a progress report. Canadian Med Assn J 96:901, 1967.
54. Hellerstein HK: Exercise therapy in coronary disease. Bull New York Acad Med 44:1028, 1968.
55. Hirsch EZ, Hellerstein HK, Macleod CA: Physical training and coronary heart disease. In: Exercise and the Heart, ed by RE Morse. Springfield: Charles C Thomas, 1972.
56. Naughton J, Balke B: Effect of physical training on work capacity in post-myocardial infarction patients. J Sports Med 4:185, 1964.
57. Sloman G, Pitt A, Hirsch EZ, Donaldson A: Effect of a graded physical training programme on physical working capacity of patients with heart disease. Med J Australia 1:4, 1965.

58. MacAlpin RN, Kattus AA: Adaptation to exercise in angina pectoris; the electrocardiogram during treadmill walking and coronary angiographic findings. Circulation 33:183, 1966.
59. Kattus AA: Physical training and beta-adrenergic blocking drugs in modifying coronary insufficiency. In: Coronary Circulation and Energetics of the Myocardium, ed by B Marchette and B Taccardi. Basel: S Karger, 1967, p 302.
60. Barry AJ, Daly JW, Pruett EDR, Steinmetz JR, Birkhead NC, Rodahl K: Effects of physical training in patients who have had myocardial infarction. Am J Cardiol 17:1, 1966.
61. Varnauskas E, Bergman H, Houk P, Björntorp P: Haemodynamic effects of physical training in coronary patients. Lancet 2:8, 1966.
62. Frick MH, Katila M: Hemodynamic consequences of physical training after myocardial infarction. Circulation 37:192, 1968.
63. Frick MH: Coronary implications of hemodynamic changes caused by physical training. Am J Cardiol 22:417, 1968.

Heberden published a clinical description of coronary heart disease in 1772. In this same article he first noted the beneficial effects of exercise in this condition. Later in 1799 Parry showed that patients with "syncope angina" were benefited clinically by an exercise program.

Little had been accomplished with this therapy; in fact, it had fallen into disrepute until Gottheiner started an active reconditioning program for patients with coronary heart disease in Israel. This form of therapy has now been studied by many investigators throughout the world. Among the strongest believers in this country are Dr. Herman Hellerstein in Cleveland, Dr. Albert Kattus in Los Angeles, and Dr. Robert Bruce in Seattle.

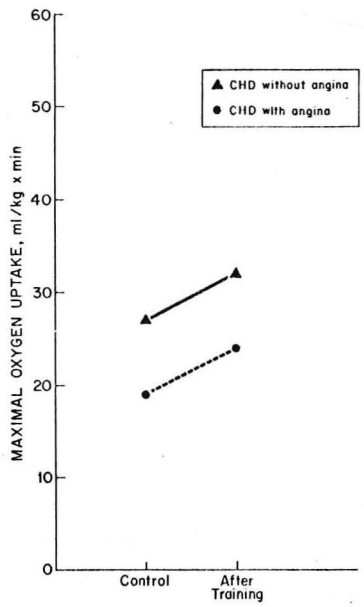
B. Maximal oxygen uptake

64. Clausen JP, Larsen OA, Trap-Jensen J: Physical training in the management of coronary artery disease. Circulation 40: 143, 1969.
65. Kasch FW, Boyer JL: Changes in maximum work capacity resulting from six months' training in patients with ischemic heart disease. Med & Sci in Sports 1:156-159, 1969.
66. Clausen JP, Trap-Jensen J: Effects of training on the distribution of cardiac output in patients with coronary artery disease. Circulation 42:611, 1970.
67. Detry JR, Rousseau M, Vandenbroucke G, Kusumi F, Brasseur LA, Bruce RA: Increased arteriovenous oxygen difference after physical training in coronary heart disease. Circulation 44: 109, 1971.

Several investigators have demonstrated an increase in maximal oxygen uptake in patients with coronary heart disease both with and without angina pectoris. In some of these studies a symptom-limited (angina pectoris) maximal oxygen uptake was used and, therefore, does not have the same definition as generally used in exercise physiology.

The study by Bruce and his group on maximal oxygen uptake in patients is shown in Fig 9.

Figure 9



Maximal oxygen uptake was obtained in 12 patients with coronary heart disease (6 with angina and 6 with prior myocardial infarction but without angina). In the patients with angina maximal oxygen uptake increased from 19 ml/kg x min before training to 24 ml/kg x min after training. This represents an increase of 30%. In the patients without angina maximal oxygen intake increased from 27 ml/kg x min to 32 ml/kg x min which represents an increase of 18%.

It is clear from these studies that the maximal oxygen intake of patients with coronary heart disease can be significantly increased by exercise training. Since patients will probably not be performing at such high work loads, this change in itself may not

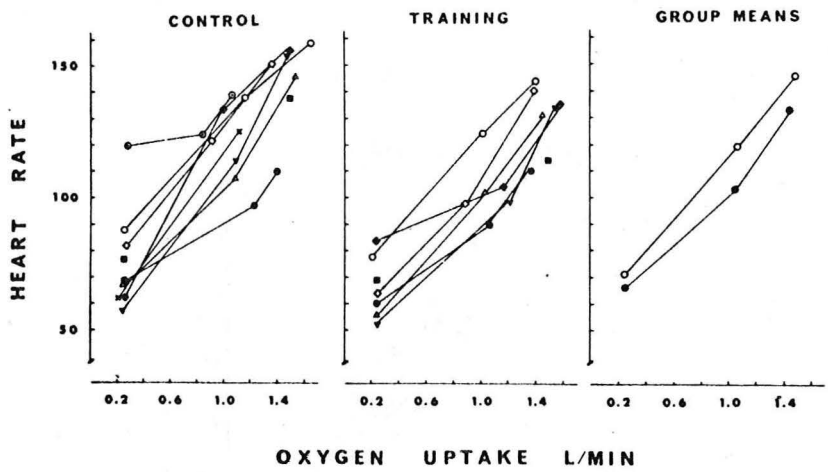
be of great importance. Before training, however, the oxygen consumption at a given submaximal work load will be a higher per cent of maximal oxygen uptake than it will be at the same submaximal work load after training. The importance of this finding for patients with coronary heart disease will be discussed later.

C. Response to submaximal exercise
1. Heart rate

61. *Loc cit*
62. *Loc cit*
64. *Loc cit*
67. *Loc cit*

It has been shown by several investigators that the heart rate at a given submaximal work load is reduced after training. A study by Clausen, Larsen, and Trap-Jensen demonstrating this finding is shown in Fig 10.

Figure 10



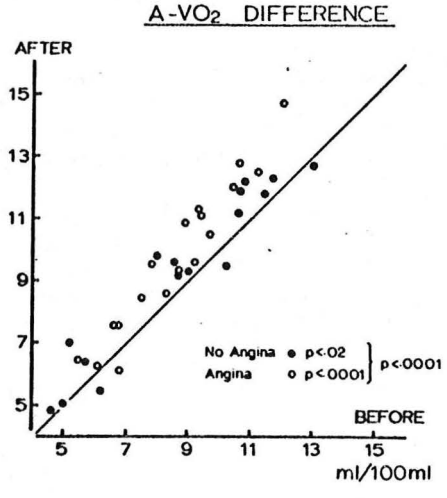
Patients were studied at rest and at the same two work loads before and after an exercise training program of 4 to 10 weeks' duration. The response before training (control) for the individual patients at rest and at two work loads is shown in the left panel and the response after training (training) for the individual patients is shown in the middle panel. The group means are shown in the right panel. The open circles (o) represent the control study and the closed circles (●) represent the study after training. It is seen that training significantly reduced the heart rate at rest and at each of the two work loads.

2. Cardiac output and arteriovenous oxygen difference

61. *Loc cit*
62. *Loc cit*
64. *Loc cit*
67. *Loc cit*

After training patients with coronary heart disease Frick and Katila and Clausen *et al* found an unchanged cardiac output with an increased stroke volume and an unchanged arteriovenous oxygen difference during submaximal exercise loads. However, Varnauskas *et al* and Bruce's group found a decreased cardiac output attended by an increased arteriovenous oxygen difference during exercise after training. The results of Bruce's study are shown in Fig 11.

Figure 11



The arteriovenous oxygen ($A\text{-}VO_2$) differences in ml O_2/100 ml blood at rest and at the same two submaximal work loads before training are shown on the abscissa and after training on the ordinate. The oxygen consumption at the same submaximal work load was not changed by training. However, since maximal oxygen uptake was increased by training, the same oxygen uptake at a submaximal work load represented a smaller per cent of maximal oxygen uptake. It is noted that the $A\text{-}VO_2$ difference was higher and the cardiac output thereby lower at submaximal work loads after training than they were before training. In normal subjects, as noted before, the cardiac output and $A\text{-}VO_2$ difference at submaximal work loads are unchanged by exercise training.

68. Frick MH, Katila M, Sjögren AL: Cardiac function and physical training after myocardial infarction. In: Coronary Heart Disease and Physical Fitness, ed by OA Larsen and RO Malmborg. Baltimore: University Park Press, 1971.
69. Trap-Jensen J, Clausen JP: Effect of training on the relation of heart rate and blood pressure to the onset of pain in effort angina pectoris. In: Coronary Heart Disease and Physical Fitness, ed by OA Larsen and RO Malmborg. Baltimore: University Park Press, 1971.

At the present time data to determine the relative importance of central and peripheral circulatory changes for the improved performance after exercise training are controversial. Frick states that the finding of unchanged or a tendency to smaller $A\text{-}VO_2$ difference during exercise after training reflects enhanced stroke volume due to better left ventricular function. On the other hand, Clausen and Trap-Jensen state that the reduction in cardiac output for a given submaximal oxygen uptake after exercise training supports the hypothesis of a more efficient distribution of systemic blood flow. At the same submaximal work level, systemic flow regulation deviates less from the resting condition, *i.e.*, the increase in working skeletal muscle flow being less pronounced and the flow to inactive organs being less reduced. This is thought to be due to the increased capacity of the working muscles to extract oxygen.

Further data must be gathered before this controversy between those who favor the central effect and those who favor the peripheral effect can be satisfactorily answered. It may turn out that exercise training produces the central type of effect in some patients with coronary heart disease and the peripheral type in others.

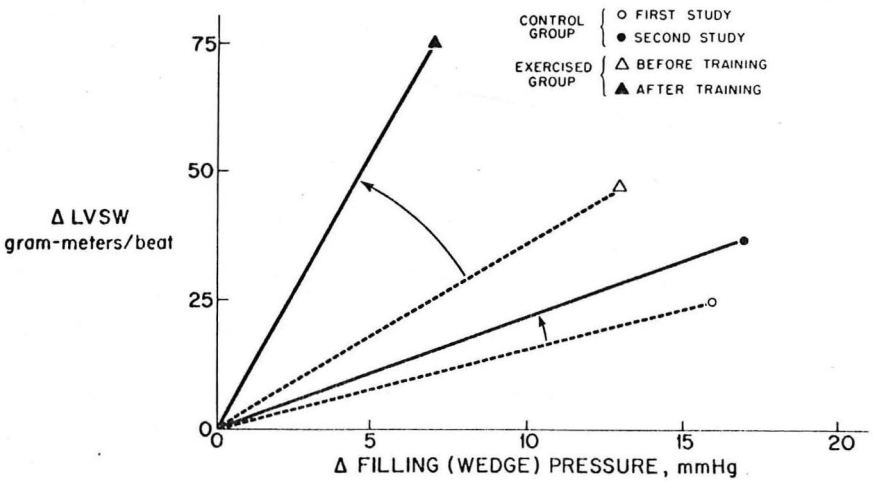
D. Cardiac function

62. *Loc cit*
68. *Loc cit*

Frick *et al* have performed modified ventricular function curves utilizing left heart catheterization during rest and exer-

cise in patients with coronary heart disease. Four patients were in the control group and 10 patients received exercise training. The results are shown in Fig 12.

Figure 12



The change in stroke work (ΔLVSW) from rest to exercise is plotted on the ordinate and the change in pulmonary capillary wedge pressure (Δ filling [wedge] pressure) on the abscissa. In the first study of the control group (o and dashed line) the wedge pressure increased 16 mm Hg and stroke work increased 25 gm-meters/beat going from rest to exercise. The findings were quite similar during the second study in the control group (• and solid line). In the before training study of the exercise group (Δ and dashed line) the wedge pressure increased 13 mm Hg and stroke work increased 47 gm-meters/beat from the resting to the exercising state. After training of the exercised group (▲ and solid line) the wedge pressure increased less -- 7 mm Hg and stroke work increased more -- 75 gm-meters/beat from rest to exercise. These findings demonstrate an improvement in left ventricular function. The question as to whether or not this is a true change in the contractile state of the muscle has not been answered. Frick has suggested from ultrasonic measurements of diastolic wall thickness of the left ventricle that the changes are due to myocardial hypertrophy.

E. Relation of myocardial oxygen demand to oxygen supply

Both subjective (angina pectoris) and objective (ST segment depression) evidence demonstrate improvement of patients with coronary heart disease after an exercise training program. This could result from a decreased myocardial oxygen demand or an increased myocardial oxygen supply.

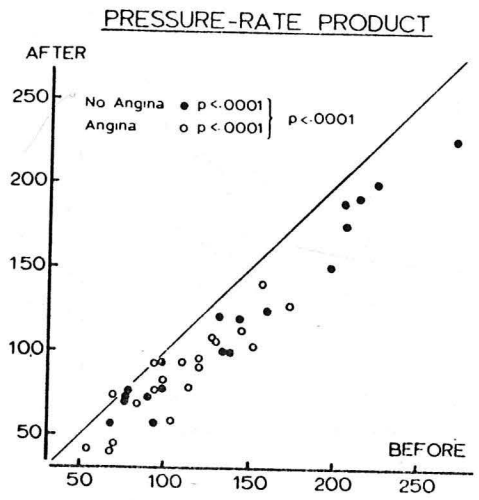
1. Myocardial oxygen demand

55. *Loc cit*
62. *Loc cit*
63. *Loc cit*
64. *Loc cit*
66. *Loc cit*
67. *Loc cit*
69. *Loc cit*
70. Redwood DR, Rosing DR, Epstein SE: Circulatory and symptomatic effects of physical training in patients with coronary-artery disease and angina pectoris. New England J Med 286: 959, 1972.

Several studies have suggested a decrease in myocardial oxygen demand after a period of exercise training at a given submaximal exercise load.

Bruce has reported the effect of exercise training on the pressure-rate product [heart rate (beats/min) x mean arterial blood pressure (mm Hg) x 10^{-2}] at rest and during the same levels of submaximal exercise loads before and after an exercise training program. This is shown in Fig 13.

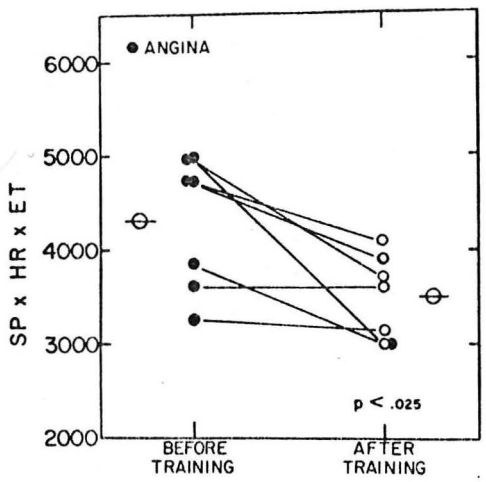
Figure 13



The pressure-rate product after exercise training is lower than before training. This was shown to result from a decrease in both heart rate and mean arterial pressure during the same submaximal work load.

A study by Epstein has also demonstrated a decrease in myocardial oxygen demands at a given submaximal work load. This is shown in Fig 14.

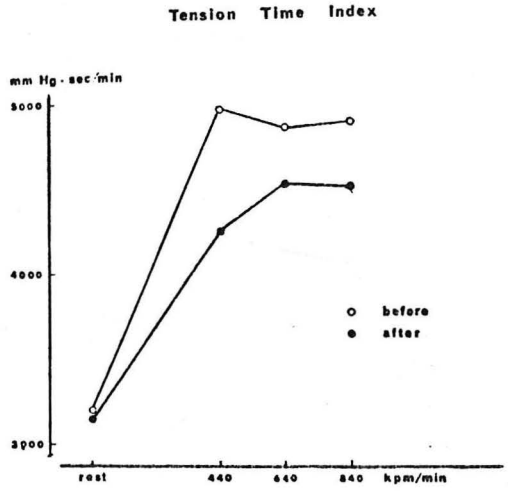
Figure 14



In this study the triple product (SP x HR x ET) was used as an index of myocardial oxygen demand. This is obtained by multiplying systolic arterial pressure (SP) in mm Hg, heart rate (HR) in beats/min, and ejection time (ET) in seconds. The values of the triple product at which angina occurred during a submaximal work load before exercise training are shown on the left and the values of the triple product at this same level of submaximal work load after exercise training are shown on the right. Only one patient had angina at this level of work after training. The mean values are indicated by the barred circles (Θ). The triple product at the same submaximal work load decreased from 4300 before training to 3521 after exercise training.

Clausen and Trap-Jensen have demonstrated that after exercise training patients with coronary heart disease have at least a two-fold increase in work time at a given submaximal work load either without or before angina pectoris was noted. The mean tension-time index values obtained in this study before and after exercise training at 3 different work loads are shown in Fig 15.

Figure 15



Before training anginal pain was caused by each of the work loads after varying periods of time. After training the time-tension index, obtained at the same work load and after the same duration which had previously produced angina, was significantly reduced.

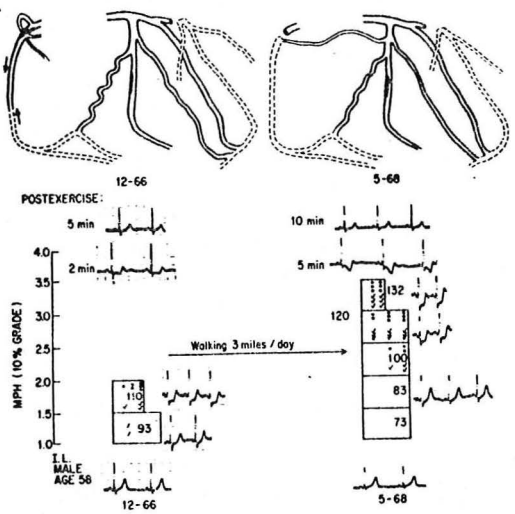
2. Myocardial oxygen supply

71. Hellerstein HK, Hornsten TR, Goldbarg A, Burlando AG, Friedman EH, Hirsch EZ, Maris S: The influence of active conditioning upon subjects with coronary artery disease: cardiorespiratory changes during training in 67 patients. Canadian Med Assn J 96:758, 1967.
72. Kattus AA, Grollman J: Patterns of coronary collateral circulation in angina pectoris: relation to exercise training. In: Changing Concepts in Cardiovascular Disease, ed by H Russek and B Zahman. Baltimore: Williams & Wilkins, 1972, p 352.

Hellerstein reported on the coronary arteriogram findings in 2 patients before and after an exercise training program. One patient showed evidence of increased collateral circulation; one did not.

Kattus has reported the coronary arteriography findings in 14 patients who had been studied on two or more times separated by at least one year. All of the patients had exercise stress tests at repeated intervals. Six of the patients had improvement in exercise tolerance following a training program and 4 did not. Four of the subjects remained sedentary and had no improvement in exercise tolerance. The results in one of the patients who showed improved performance on a walking program are shown in Fig 16.

Figure 16



The patient was a 58-year-old man with a normal resting electrocardiogram. His angina permitted him to complete only 2 minutes at 2 mph on the treadmill. At that time his heart rate was 110/min. The angina was graded 3+ (●) and ST segment depression was graded 2+ (√). One and a half years later, after walking 3 miles in 1 hour every day his exercise tolerance was much improved. The resting electrocardiogram was unchanged. He was now able to walk 2 minutes at 3 1/2 mph with a heart rate of 132/min. At this heart rate both angina and ST segment depression were 3+. The first coronary arteriogram study on this patient showed a high grade stenosis of the right coronary artery with both primary and collateral filling coming from a visible branch of the circumflex

system. The anterior descending coronary artery was completely occluded and was being filled below by collaterals from one of its diagonal branches and from a marginal branch of the circumflex coronary artery. One and a half years later at the time of the improvement in exercise tolerance the second coronary arteriogram revealed that the right coronary artery had become completely occluded and was being filled entirely by collateral circulation. A small atrial branch from the circumflex system entered the right coronary artery just distal to the occlusion. The development of this collateral would appear to be caused primarily by the complete closure of the right coronary artery. The remainder of collaterals of the left coronary artery system was unaltered. Thus there was no change in the collateral pattern that could be attributed to the exercise training program.

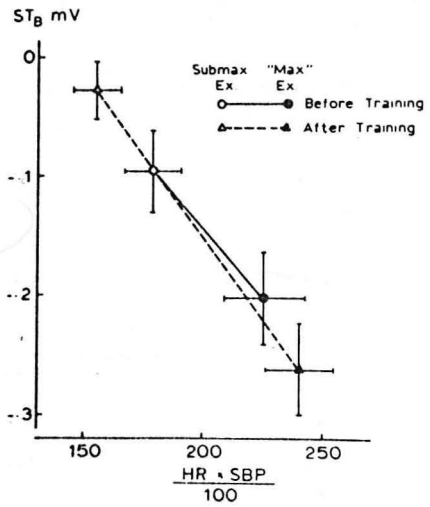
In this study by Kattus it was shown that in the 6 patients who showed improvement in exercise tolerance after an exercise program, 2 patients had no increase in collateral circulation and 4 patients did. Of the 4 patients who demonstrated increased collateral circulation all had advancing occlusive disease to explain the finding. In the 4 patients who showed no improvement in exercise tolerance after an exercise program, all had advancing occlusive disease without development of collateral circulation. In the 4 patients who did not follow an exercise program and who showed a reduced or unchanged exercise response, 3 demonstrated an increased collateral circulation secondary to further occlusive disease.

The study by Kattus clearly demonstrates that exercise tolerance can be greatly improved even though coronary collateral circulation, as visualized by coronary arteriograms, showed no change that could be caused by the exercise training. However, it cannot be ruled out that coronary blood flow through these collaterals may be increased since flow is not measured by the coronary angiographic technique.

73. Detry J-M, Bruce RA: Effects of physical training on exertional S-T-segment depression in coronary heart disease. Circulation 44:390, 1971.

Bruce has shown that the relation of the degree of ST segment depression to the double product (heart rate x systolic blood pressure) was not altered by physical training. This is shown in Fig 17.

Figure 17



The ST segment depression in millivolts (ST_B mV) is plotted against the double product (HR x SBP/100) before and after exercise training at the same level of submaximal work load and at maximal oxygen uptake. The double product and the degree of ST segment depression are both less at the same submaximal work load after exercise training. Also after exercise training the double product and the degree of ST segment depression were both greater at the maximal exercise load. However, the important point is that exercise training did not alter the relation between the degree of the ST segment depression and the double product during submaximal and maximal exercise loads. This suggests that coronary blood flow during exercise has not been altered by physical training.

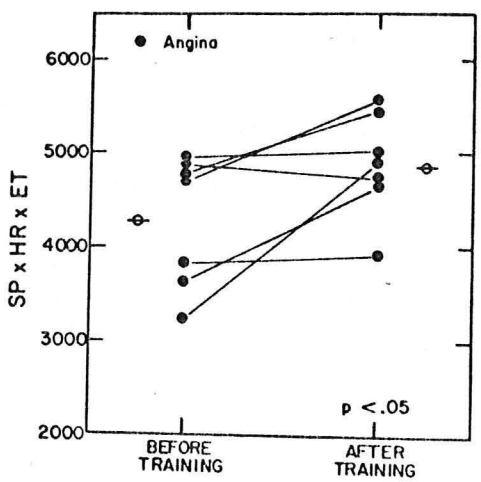
69. *Loc cit*
70. *Loc cit*

Other studies, however, have suggested that coronary blood flow during exercise is improved by physical training. In the study of 12 patients by Trap-Jensen and Clausen anginal pain could still be provoked after exercise training at heavier work loads in

8 patients. However, before training the mean tension-time index at the onset of angina was 4395 mm Hg x sec/min and after training it was 5369 mm Hg x sec/min. In the other 4 patients angina was not present after exercise training even at much higher work loads. This suggests an improvement in coronary blood flow during exercise after physical training.

In the study by Epstein the triple product was measured at the onset of angina both before and after exercise training. This is shown in Fig 18.

Figure 18



The values of the triple product at which angina occurred at a submaximal work load before exercise training are again shown on the left and the values of the triple product at which angina occurred at a higher submaximal work load after exercise training are shown on the right. The mean values are indicated by the barred circles (Θ). There was a significant increase from 4300 before the 4885 after exercise training. This finding also suggests that exercise training may increase myocardial oxygen supply.

To date one cannot answer the question as to whether or not coronary blood flow and myocardial performance are increased during exercise by physical training. It is hoped that this question

can be answered in the near future. It does seem clear, however, that the progress of coronary arteriosclerosis is little if any affected by exercise training.

F. Long-term effects (longevity)

74. Katila M, Frick MH: A two-year circulatory follow-up of physical training after myocardial infarction. Acta Med Scand 187: 95, 1970.

Katila and Frick studied 3 patients with coronary heart disease after 2 months and after 26 months of exercise training. After 2 months of training the patients could work at higher submaximal work loads before the occurrence of angina because myocardial oxygen demands, as evidenced by the tension-time index, were reduced. Angina could still be produced at higher submaximal work loads which were required to produce the value of the time-tension index which caused pain before training. After 26 months of training 2 patients could achieve much higher values for the tension-time index before angina occurred, and one patient could be pushed to exhaustion without the occurrence of angina. It was concluded by the authors that after 2 months' training the patients improved because myocardial oxygen demands were lower at submaximal work loads and after 26 months' training the further improvement could be explained by a decrease in heart size, a more synchronous contraction, or enhancement of myocardial blood flow.

8. *Loc cit*
50. *Loc cit*
55. *Loc cit*

The most important question of whether or not exercise training prolongs the life of a patient with coronary heart disease cannot be answered definitely at this time. However, preliminary results from several studies suggest that longevity may be increased.

The mortality rate of patients with coronary heart disease receiving exercise training from Gottheiner was only 3.6% compared to 12% in a comparable group of physically inactive patients in Israel. In Hellerstein's trained patients the mortality was 1.6 deaths per hundred subject years and in a comparable group of untrained subjects it was 3.5 deaths per hundred subject years. Recently Bruce has reported a 3.1% mortality in patients who were trained and an 11.2% mortality in a similar group of patients who were not trained in the Seattle area.

All of these studies tend to suggest that longevity may be increased by exercise training. However, a definitive study has not

been carried out. It is very important for a study to be done which randomly assigns comparable patients with coronary heart disease into two groups receiving the same medical therapy but with only one receiving exercise training. A study of this type with a significant number of patients followed for an adequate period of time to obtain meaningful results should be undertaken. Whether or not such a study will ever be carried out is doubtful since its magnitude and expense would be great.

V. Conclusions

The precise role and effectiveness of exercise training in the treatment of coronary heart disease cannot be defined at the present time. The important question of whether or not longevity is increased by this mode of therapy has not been answered. Further there is no good data to show that exercise training, *per se*, has any retarding effect on the development of arteriosclerosis in the coronary vessels.

One important finding from studies on exercise training in patients with coronary heart disease is that both subjectively and objectively their physical work capacity can be significantly improved. For a patient who is content to live a physically inactive life exercise training is of little benefit unless it slows down the disease process and prolongs life. However, for a patient who wants to live a life of more normal physical activity without symptoms, such improvement in work capacity is extremely important. If exercise training is used critically and is carefully supervised its beneficial effects seem more important than its possible harmful complications.