# EXERCISE IN PATIENTS WITH CHRONIC RENAL FAILURE

Jere Mitchell, M.D.

Medical Grand Rounds

University of Texas
Southwestern Medical Center at Dallas

December 1, 1988

TABLE OF CONTENTS

## I. INTRODUCTION


1. Gutman, R.A., W.W. Stead, and R.R. Robinson: Physical activity and employment status of patients on maintenance dialysis. N. Engl. J. Med. 304:309, 1981.
2. Rennie, D.: Renal rehabilitation -- Where are the data? (Editorial). N. Engl. J. Med. 304:351, 1981.
3. Kutner, N.G., and D.D. Cardenas: Assessment of rehabilitation outcomes among chronic dialysis patients. Am. J. Nephrol. 2:128, 1982.
4. Evans, R.W., D.L. Manninen, L.P. Garrison, Jr., L.G. Hart, C.R. Blagg, R.A. Gutman, A.R. Hull, and E.G. Lowrie: The quality of life of patients with end-stage renal disease. N. Engl. J. Med. 312:553, 1985.
5. Harter, H.R. and A.P. Goldberg: Endurance exercise training; an effective therapeutic modality for hemodialysis patients. Med. Clin. N. Am. 69:159, 1985.
6. Brinker, K.: Unconventional Methods to Improve Dialysis Related Morbidity. Winter Nephrology Symposium, 1987.
7. Painter, P.L.: Exercise in end-stage renal disease. Exerc. Sports Sci. Rev. 16:305, 1988.


In the past, patients with chronic renal failure had a very limited life span and a very poor quality of existence. Now, patients can be kept alive by chronic hemodialysis for many years. However, the quality of their lives both to themselves and to society has been very limited. The patients with chronic renal failure on hemodialysis are severely debilitated and only a small percentage of them are gainfully employed. They have been found to have a very low exercise capacity and, in addition, to have a feeling of hopelessness and depression.


8. Lindner, A., B. Charra, D.J. Sherrard, and B.H. Scribner: Accelerated atherosclerosis in prolonged maintenance hemodialysis. N. Engl. J. Med. 290:697, 1974.
9. Goldberg, A.P., J.M. Hagberg, J.A. Delmez, R.W. Florman, and H.R. Harter: Effects of exercise training on coronary risk factors in hemodialysis patients. Proc. Dialysis Transplant Forum 9:39, 1979.
10. Goldberg, A.P., C. Tindira, and H.R. Harter: Coronary risk in patients with endstage renal disease: Interaction of hypertension with hyperlipidemia. J. Cardiovasc. Pharmacol. 4 (Suppl 2):S257, 1982.
11. Goldberg, A.P.: A potential role for exercise training in modulating coronary risk factors in uremia. Am. J. Nephrol. 4:132, 1984.


The quality of life in these patients is also affected by their accelerated rate of atherosclerosis which causes a high incidence of cardiovascular diseases. Thus, these patients are prone to have coronary vascular disease and myocardial infarction and cerebrovascular disease and stroke. Therefore, it would seem prudent to institute a vigorous program of risk factor reduction in these patients and, as will be shown, this program should include dynamic exercise training.

4. Loc. cit.
12. Kutner, N.G., D.D. Cardenas, and J.D. Bower: Rehabilitation and the Chronic Renal Disease Patient. New York: Spectrum, 1985.

In the study made by the Batelle Institute, it was found that the quality of life as perceived by these patients was felt to be "adequate". However, that simply meant that without being in chronic pain these patients had rather be alive than dead! Frequently, the nephrologist feels that the patient is rehabilitated if he is being kept alive outside the confines of a hospital. However, for the patient, this definition of "rehabilitation" is far from adequate. Dr. Samuel B. Chyatte, who was a Professor of Rehabilitation Medicine at Emory University School of Medicine and had been on hemodialysis for chronic renal failure for many years, stated his own feelings very clearly and concisely, and I quote:

"Life is more than Survival."

It is the purpose of this Grand Rounds to examine the exercise capacity in patients with chronic renal failure and to explain why they are so limited in their ability to work or even be self sufficient. Next, the therapeutic strategies which can increase their exercise tolerance will be presented. Finally, the possible role of exercise training in reducing the risk factors responsible for the accelerated atherosclerosis and in improving the psychological state of these patients will be discussed.

## II. EXERCISE CAPACITY IN PATIENTS WITH CHRONIC RENAL FAILURE

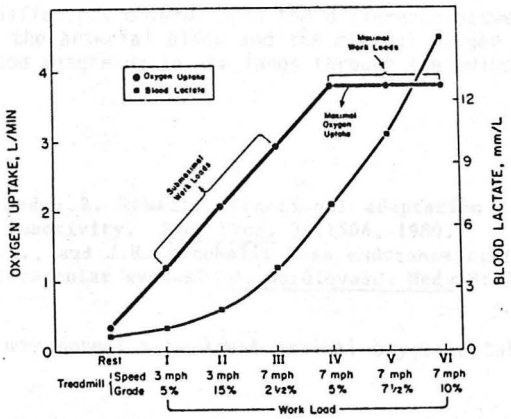
### A. Maximal Oxygen Uptake

#### 1. Definition and Physiological Variations


13. Hill, A.V.: Muscular Activity. Baltimore: Williams & Wilkins, 1926.
14. Taylor, H.L., E. Buskirk, and A. Henschel: Maximal oxygen intake as an objective measure of cardio-respiratory performance. J. Appl. Physiol. 8:73, 1955.
15. Mitchell, J.H., B.J. Sproule, and C.B. Chapman: The physiological meaning of the maximal oxygen intake test. J. Clin. Invest. 37:538, 1958.
16. Mitchell, J.H., and G. Blomqvist: Maximal oxygen uptake. N. Engl. J. Med. 284:1018, 1971.
17. Snell, P.G., and J.H. Mitchell: The role of maximal oxygen uptake in exercise performance. Clin. Chest Med. 5:51, 1984.
18. Astrand, P.O., and K. Rodahl: Textbook of Work Physiology: Physiological Basis of Exercise, 3rd Ed. New York: McGraw-Hill, 1986.


The ability of a subject or patient to be physically active and to perform work is dependent upon the maximal oxygen uptake of that individual. Maximal oxygen uptake is the greatest amount of oxygen a person can consume during dynamic exercise and is a measure of the maximal capacity to transport oxygen to the working muscles. This value can be obtained in a subject or patient by means of a cycle ergometer or a motor-driven treadmill as shown in Figure 1.

Figure 1

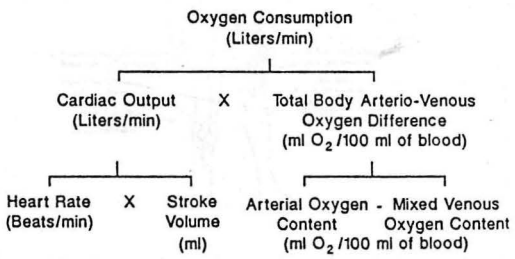



The subject's oxygen uptake is measured while he is standing quietly on the treadmill and then while he walks or runs at progressively higher grades. The oxygen uptake increases in a near-linear fashion with the increasing workload.

However, a workload is finally reached where, even though the exercise is at a higher workload, the maximal capability to take in oxygen reaches its limit. 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.

The determinants of oxygen uptake and of the level to which it can increase during maximal dynamic exercise are shown in Figure 2.

Figure 2

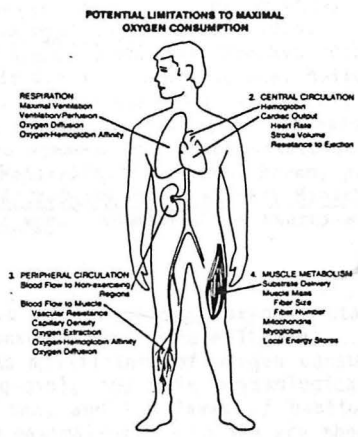



By rearranging the Fick Equation, which is used for determining blood flow, the oxygen uptake of the body is simply the product of the cardiac output times the total body arterio-venous oxygen difference. It then follows that the maximal oxygen uptake is determined by the maximal cardiac output and the maximal total arterio-venous oxygen difference that can be attained in a given subject or patient. In turn, the maximal cardiac output depends upon the product of the maximal heart rate and the maximal stroke volume, and the maximal total body arterio-venous oxygen difference depends upon the difference between maximal oxygen content reached in the arterial blood and the minimal oxygen content reached in the mixed venous blood returning to the lungs through the pulmonary artery.

15. Loc. cit.
18. Loc. cit.
19. Saltin, B., and L.B. Rowell: Functional adaptation to physical activity and inactivity. Fed. Proc. 39:1506, 1980.
20. Longhurst, J.C., and J.H. Mitchell: Does endurance training benefit the cardiovascular system? J. Cardiovasc. Med. 8:227, 1983.

The factors that may potentially limit maximal oxygen uptake are shown in Figure 3.

Figure 3




Respiration, with the possible exception of a few highly trained endurance athletes, does not limit maximal oxygen uptake in normal subjects except at high altitude. However, in patients with obstructive or restrictive lung disease, a pathological change which decreases the ability to oxygenate the blood may become the limiting factor.

Central circulation, or the transport of oxygen from the lungs to the peripheral tissues, is determined by arterial oxygen content and the cardiac output. Arterial oxygen content can be low in patients with anemia and cardiac output may be limited in patients with heart disease. Also, the resistance to ejection or afterload may become a limiting factor in patients with severe hypertension.

Peripheral circulation includes both the blood flow to non-exercising regions and that to the exercising skeletal muscle. An important response to exercise is the shunting of blood away from areas in which the metabolic rate is not changed. If this did not occur, the widening of the total body arterio-venous oxygen difference would be limited. Also, oxygen must rapidly diffuse and be taken up by the contracting muscle cells for maximal extraction to occur.

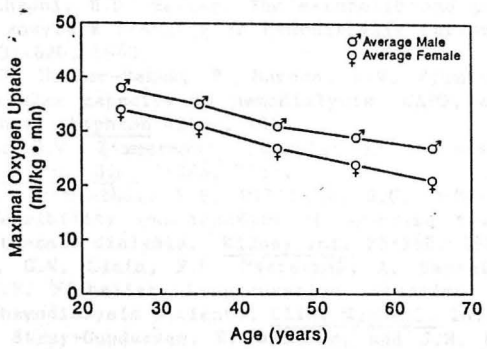
Muscle metabolism must release the energy necessary for muscle contraction. In prolonged activity, the energy supply is almost entirely dependent upon aerobic processes. The ability to utilize high flows of oxygen is dependent upon the mitochondrial density and the capacity of the oxidative enzymes in the skeletal muscle.

There has been some controversy concerning the major limiting factor for maximal oxygen uptake in normal subjects and in endurance athletes. However, the majority opinion is that the transport of oxygen to the skeletal muscles and not the ability of the muscle cells to utilize oxygen is the culprit. In patients, however, the pathological process responsible for limiting maximal oxygen uptake can usually be identified.

15. Loc. cit.
18. Loc. cit.
21. Robinson, S.: Experimental studies of physical fitness in relation to age. Arbeitsphysiologia 10:251, 1938.
22. Mitchell, J.H.: The Aging Myocardium (Presbycardia): Physiological (?) Changes and their Clinical Implications. Medical Grand Rounds, University of Texas, Southwestern Medical School, Jan. 18, 1979.
23. Raven, P.B., and J. Mitchell: The effect of aging on the cardiovascular response to dynamic and static exercise. In: The Aging Heart, ed. by M.L. Weisfeldt. New York: Raven, p. 269, 1980.
24. Exercise Testing and Training of Apparently Healthy Individuals: A Handbook for Physicians. Committee on Exercise, American Heart Association, 1972.

Differences in body size affect maximal oxygen uptake when expressed in terms of liters of oxygen consumed each minute (L/min). However, when maximal oxygen uptake is expressed as milliliters of oxygen consumed per kilogram body weight each minute (ml $O_2$/kg·min), the main physiological variations (besides genetic endowment) are age, sex, and the level of habitual physical activity. The effects of age and sex on maximal oxygen uptake are shown in Figure 4.

Figure 4




The values of maximal oxygen uptake for an average American male (♂) and an average American female (♀) expressed as ml $O_2$/kg·min are plotted against increasing age. Males have higher maximal oxygen uptake than females even when expressed in ml $O_2$/kg·min. Also as one ages, there is a decrease in maximal oxygen uptake. However, at any age, the level of habitual physical activity can have a marked effect on the maximal oxygen uptake. That is, with decreased physical activity, such as bed rest, there is a marked fall in maximal oxygen intake; and with increased physical activity, such as endurance training, there is a marked rise in maximal oxygen uptake.

In the literature, the values of maximal oxygen uptake for Americans have also been reported to be lower than those for Scandinavians. This was thought to be due to differences in the levels of habitual physical activity in the two populations. However, studies done today would probably find this difference narrowing due to the increased levels of activity in the American population. If

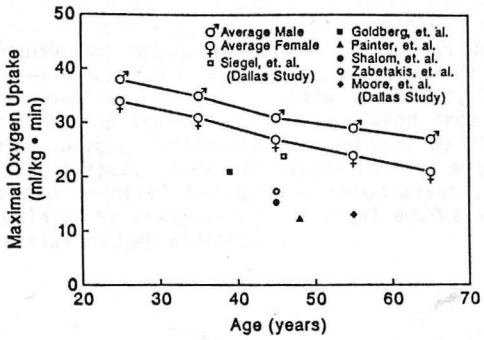
you are one who has decided to join the exercise movement, then you are convinced that this is a healthy trend; and conversely, if you are one who has decided not to join the exercise movement, then you are convinced that this is an unhealthy trend. Irrespective of your beliefs, there are marked variations in maximal oxygen uptake at any given age dependent upon the level of training of the individual.

## 2. Value in Patients with Chronic Renal Failure


5. Loc. cit.
7. Loc. cit.
25. Siegel, W., G. Blomqvist, and J.H. Mitchell: Effects of a quantitated physical training program on middle-aged sedentary men. Circulation 12:19, 1970.
26. Barnea, N., Y. Drory, A. Iaina, C. Lapidot, E. Reisin, H. Eliahou, and J.J. Kellerman: Exercise tolerance in patients on chronic hemodialysis. Isr. J. Med. Sci. 16:17, 1980.
27. Goldberg, A.P., J.M. Hagberg, J.A. Delmez, M.E. Haynes, and H.R. Harter: Metabolic effects of training in hemodialysis patients. Kidney Int. 18:754, 1980.
28. Goldberg, A.P., J.M. Hagberg, J.A. Delmez, R.M. Carney, P.M. McKevitt, A.A. Ehsani, H.R. Harter: The metabolic and psychological effects of exercise training in hemodialysis patients. Am. J. Clin. Nutr. 33:1620, 1980.
29. Painter, P.L., D. Messer-Rehak, P. Hanson, S.W. Zimmerman, and N.R. Glass: Exercise capacity in hemodialysis, CAPD, and renal transplant patients. Nephron 42:47, 1986.
30. Painter, P., and S.W. Zimmerman: Exercise in end-stage renal disease. Am. J. Kidney Dis. 7:386, 1986.
31. Shalom, R., J.A. Blumenthal, R.S. Williams, R.G. McMurray, and V.W. Dennis: Feasibility and benefits of exercise training in patients on maintenance dialysis. Kidney Int. 25:958, 1984.
32. Zabetakis, P.M., G.W. Gleim, F.L. Pasternak, A. Saraniti, J.A. Nicholas, and M.F. Michelis: Long-duration submaximal exercise conditioning in hemodialysis patients. Clin. Nephrol. 18:17, 1982.
33. Moore, G.E., J. Stray-Gundersen, K. Brinker, and J.H. Mitchell: Effect of hemodialysis on the cardiovascular response to exercise. Med. Sci. Sports Exerc. 20:S35, 1988 (Abstract).
34. Moore, G.E., J. Stray-Gundersen, K. Brinker, P.L. Painter and J.H. Mitchell: Maximal oxygen uptake and its determinants in patients with chronic renal failure on hemodialysis. In preparation.


Several investigators have reported that patients with chronic renal failure have low physical work capacities. In some of these studies, maximal oxygen uptake of the patients have been measured, and these results are shown in Figure 5.

Figure 5




Again, the relationship between maximal oxygen uptake versus age are shown for average American male (♂) and female (♀) subjects. In 1970, a study was performed in Dallas by Siegel et al. which demonstrated the effect of many years of physical inactivity on exercise capacity. Maximal oxygen uptake was measured in 9 male subjects from the local Lighthouse for the Blind who had been very sedentary because of their visual handicap. Their average age was 46 years and their maximal oxygen uptake was 24 ml $O_2$/kg•min.

Goldberg et al. studied 14 male and female patients (8/6) with chronic renal failure whose average age was 39 years and found a markedly decreased maximal oxygen uptake (21 ml $O_2$/kg•min). Painter et al., Shalom et al., Zabetakis et al., and Moore et al. have also found marked reductions in maximal oxygen uptake in patients with chronic renal failure of various ages. These levels of reduction appear to be more than can be explained by the marked physical inactivity of these patients, since they are lower than those seen in the very sedentary blind subjects studied by Siegel et al.

33. Loc. cit.
34. Loc. cit.

The data of the study by Moore et al. (Dallas Study) is a joint project being conducted by investigators from U.T. Southwestern Medical School and the Dallas Nephrology Associates. The investigators in the study are Drs. Geoffrey Moore, James Stray-Gundersen, Karl Brinker, and myself. Also, Dr. Patricia Painter, who was formerly with the Satellite Dialysis Centers in Northern California and who has published extensively in this area, has joined us in this study while being on a sabbatical.

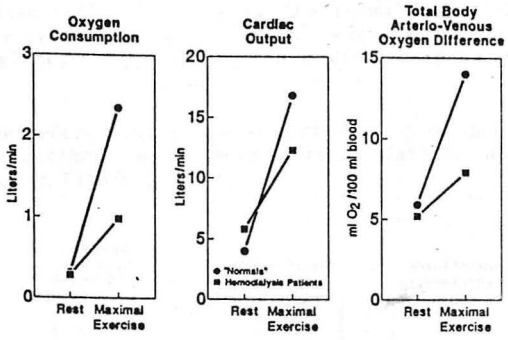
That maximal oxygen uptake is decreased in patients with chronic renal failure has now been clearly established. However, the mechanism for this decrease had not been studied. The Dallas Study has recently investigated the reason for the low value of maximal oxygen uptake by an analysis of its determinants in patients with chronic renal failure.

Maximal oxygen uptake has been measured in ten patients with chronic renal failure on hemodialysis. The group consists of 6 males and 4 females, with an average age of 55 years. In these patients oxygen uptake was measured by open spirometry using a SensorMedics Metabolic Cart. The venous access and arterial access for hemodialysis were utilized for various measurements in these studies. Cardiac output was determined by the dye dilution technique, heart rate counted from the electrocardiogram, and stroke volume calculated from these two values. Total body arterio-venous oxygen difference was derived by dividing the oxygen consumption by the cardiac output. Arterial oxygen content was measured in arterial blood drawn from the arterial access for hemodialysis, and mixed venous oxygen content was calculated by subtracting the total body arterio-venous oxygen difference from the arterial oxygen content.


23. Loc. cit.
35. Saltin, B., G. Blomqvist, J.H. Mitchell, R.L. Johnson, Jr., K. Wildenthal, and C.B. Chapman: 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, 1986.
36. Kilbom, A., L.H. Hartley, B. Saltin, J. Bjure, G. Grimby, and I. Astrand: Physical training in sedentary middle-aged and older men. I. Medical evaluation. Scand. J. Clin. Lab. Invest. 24:315, 1969.
37. Saltin, B., L.H. Hartley, A. Kilbom, and I. Astrand: Physical training in sedentary middle-aged and older men. II. Oxygen uptake, heart rate, and blood lactate concentration at submaximal and maximal exercise. Scand. J. Clin. Lab. Invest. 24:323, 1969.
38. Hartley, L.H., G. Grimby, A. Kilbom, N.J. Nilsson, I. Astrand, J. Bjure, B. Ekblom, and B. Saltin: Physical training in sedentary middle-aged and older men. III. Cardiac output and gas exchange at submaximal and maximal exercise. Scand. J. Clin. Lab. Invest. 24:335, 1969.


For comparison, maximal oxygen uptake values of normal 55 year old male and female subjects were used. Also, for comparison, the values of the determinants of maximal oxygen uptake in these same control subjects is needed. However, a control group of healthy 55 year old subjects has not been studied to measure these determinants. Therefore, one can only predict what the values for the determinants of oxygen uptake would be in a group of 55 year old normal subjects by using data obtained in young, sedentary male subjects studied in Dallas and in middle-aged and older men studied in Stockholm. A comparison of oxygen uptake, cardiac output, and total body arterio-venous oxygen difference in the older "normal" subjects and in the 55 year old patients with chronic renal failure studied in Dallas by Moore et al. is shown in Figure 6.

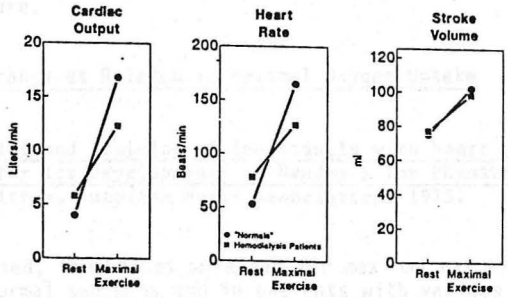
Figure 6




The oxygen consumptions at rest are the same in the "normal" subjects and in the patients with chronic renal disease. However, the oxygen consumption of the "normal" subjects of this age group increased to 2.2 L/min at maximal exercise and in the patients and only to 1.0 L/min in the patients with chronic renal failure. Cardiac output in the patients was slightly higher at rest than in the "normal" subjects. However, at maximal exercise the cardiac output was 12 L/min in the patients and 16 L/min in the "normal" subjects. Total body arterio-venous oxygen difference at rest was slightly lower in the patients with chronic renal failure; however, at maximal exercise, it was 14 ml $O_2$/100 ml blood in the "normal" subjects and 8 ml $O_2$/100 ml blood in the patients. Thus, the lower oxygen uptake at maximal exercise in the patients than in the control subjects was due to a decrease both in cardiac output and in total body arterio-venous oxygen difference.

The mechanism for the reduced cardiac output at maximal exercise in the patients with chronic renal failure as compared to "normal" controls is shown in Figure 7.

Figure 7

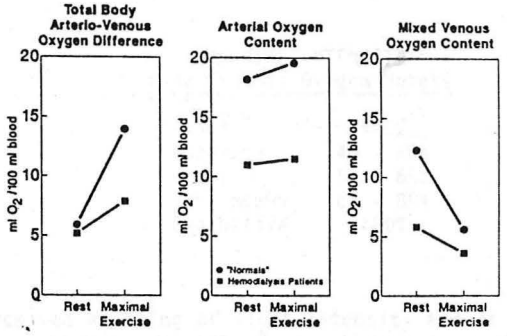



Again, the cardiac output at maximal exercise is about 40% lower in the patients as compared to the "normal" subjects. Heart rate at rest was slightly higher in the patients than in the "normal" subjects. However, during maximal exercise, the heart rate increased to 165 beats/min in the normal subjects and

only to 127 beats/min in the renal disease patients. Stroke volumes at rest and maximal exercise were essentially the same in the normal subjects and in the patients. Thus, the lower cardiac output at maximal exercise in the patients was due to a decreased maximal heart rate and not to a difference in maximal stroke volume.

The mechanism for the reduced total body arterio-venous oxygen difference at maximal exercise in the patients with chronic renal failure as compared to "normal" subjects is shown in Figure 8.

Figure 8




As seen before, the total body arterio-venous oxygen difference at maximal exercise was 14 ml $O_2$/100 ml blood in the "normal" subjects and was 8 ml $O_2$/100 ml blood in the patients. The predicted arterial oxygen content in the "normal" subjects would be 20 ml $O_2$/100 ml blood and was 12 ml $O_2$/100 ml blood in the patients with chronic renal disease. The predicted mixed venous oxygen content in the "normal" subjects would be 6 ml $O_2$/100 ml blood and was 4 ml $O_2$/100 ml blood in the patients with chronic renal failure. Thus, the decreased total arterio-venous oxygen difference in the patients was due to a decreased arterial oxygen content which was due to their anemia. Mixed venous oxygen content was low in both groups indicating that oxygen extraction was normal in the patients with chronic renal failure.

B. Exercise Tolerance as Related to Maximal Oxygen Uptake

18. Loc. cit.
39. Exercise Testing and Training of Individuals with Heart Disease or at High Risk for its Development: A Handbook for Physicians. The Exercise Committee, American Heart Association, 1975.

As has been discussed, the values obtained for maximal oxygen uptake can be markedly different in normal subjects and in patients with various disease states because of physiological and pathological variations. Also, there are variations in the amount of oxygen that is required to be transported to the working muscle in different types of physical activity. In a given subject or patient, the intensity of the activity is determined by its oxygen requirement as related to the individual's maximal oxygen uptake. Thus, in any given subject or patient, the ability to be physically active is directly related to the maximal oxygen uptake.

## 1. Exercise Intensity

18. Loc. cit.
40. Borg, G.A.V.: Psychophysical basis of perceived exertion. Med. Sci. Sports Exerc. 14:377, 1982.

The intensity of exercise and the perceived exertion during exercise are related to the percentage of maximal oxygen uptake required by the workload being performed. A very detailed analysis of "how hard" a given workload feels has been developed by Borg. However, a simpler classification is useful and is shown in Figure 9.

Figure 9

| EXERCISE INTENSITY | % of Maximal Oxygen Uptake |
|---|---|
| Light | <40% |
| Moderate | 40 - 50% |
| Heavy | 51 - 65% |
| Very Heavy | 66 - 80% |
| Exhaustive | >80% |

The workload is perceived as being of light intensity and is easily accomplished if its oxygen requirements are <40% of the subject or patient's maximal oxygen uptake. The workload is perceived as being heavy if it is between 51 and 65% of maximal oxygen uptake and is exhaustive if the workload is >80% of maximal oxygen uptake. A workload that is only 20% to 40% of maximal oxygen uptake can be maintained for four to eight hours; however, a workload of greater than 80% can be sustained for a much shorter time. It is only the highly trained endurance athlete who can sustain a workload of >80% for an hour or more.

## 2. Oxygen Requirements of Various Activities

18. Loc. cit.
41. Passmore, R., and J.V.G.A. Durnin: Human energy expenditure. Physiol. Rev. 35:801, 1955.
42. Karvonen, M.J.: Work and activity classification. In: Fitness, Health, and Work Capacity. New York: MacMillan, p. 38, 1974.

Physical activity requires the transport of oxygen to the working muscles. Therefore, to determine the intensity of the activity for a given subject or patient, one needs to know the oxygen requirement of the task as well as the maximal oxygen uptake of the individual.

The oxygen requirements of many types of physical activities have been measured. These include the various activities involved in self care, housekeeping, occupations, and recreation. The oxygen requirements of some of these various activities are shown in Figure 10.

Figure 10

OXYGEN REQUIREMENTS OF VARIOUS ACTIVITIES

| | |
|---|---|
| **Self Care** | |
| Rest, supine | 3.5 ml $O_2$/kg·min |
| Conversation | 3.5 ml $O_2$/kg·min |
| Dressing | 7.0 ml $O_2$/kg·min |
| Using toilet | 10.5 ml $O_2$/kg·min |
| Walking (1 mile/30 min) | 10.5 ml $O_2$/kg·min |
| **Housework** | |
| Hand sewing | 3.5 ml $O_2$/kg·min |
| Sweeping floors | 5.0 ml $O_2$/kg·min |
| Making beds | 10.5 ml $O_2$/kg·min |
| Hanging wash | 12.0 ml $O_2$/kg·min |
| Beating carpets | 14.0 ml $O_2$/kg·min |
| **Work** | |
| Watch repairing | 5.0 ml $O_2$/kg·min |
| Machine sewing | 9.0 ml $O_2$/kg·min |
| Carpentry | 19.0 ml $O_2$/kg·min |
| Shoveling | 25.0 ml $O_2$/kg·min |
| Tending furnace | 30.0 ml $O_2$/kg·min |

In terms of self care, resting in the supine position requires about 3.5 ml $O_2$/kg·min. During sleep, the value is slightly less. It is reported that talking requires no additional oxygen consumption. However, this is hard for me to believe and I feel sure that this finding does not hold for some of my "motor mouth" acquaintances. Dressing requires 7.0 ml $O_2$/kg·min. For normal subjects, this would be classified as light activity. However, for the patients with chronic renal failure this may represent 40% to 50% of their maximal oxygen uptake and would be classified as moderate work. Using the toilet or walking on a flat surface at a rate of 1 mile in 30 minutes (taking 1 step every 2 seconds!) requires 10.5 ml $O_2$/kg·min which would be classified as heavy work for the patient but only moderate work for a normal subject.

The average requirements of housework have also been measured. Hand sewing, a lost art, requires little increased metabolic needs. Sweeping the floor and making a bed would be classified as light work for the normal subject but moderate work for the patient with chronic renal failure. Hanging the wash and beating a carpet (values taken from rather obsolete references) would represent heavy work for the normal subject but exhaustive work for patients with chronic renal failure.

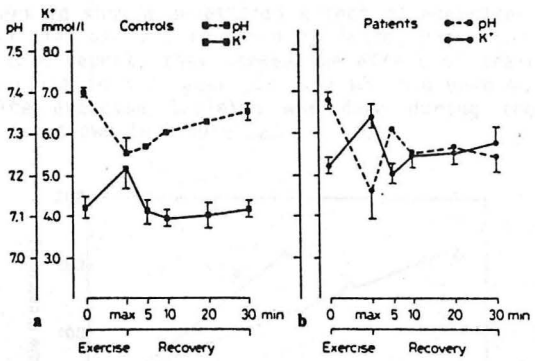
It is not surprising that patients with chronic renal failure are unable to return to gainful employment. Watch repairing or a similar type of job is the only occupation that could be performed for a full day. Such activity as machine sewing could only be accomplished for a short time. However, an occupation such as carpentry would be impossible for a patient with chronic renal failure but could be easily performed by a normal 55 year old person.

C. Serum Potassium Changes during Exercise


35. Loc. cit.
43. Laurell, H., and B. Pernow: Effect of exercise on plasma potassium in man. Acta Physiol. Scand. 66:241, 1966.
44. Ones, J.B., and L. Hermensen: Acid-base balance after maximal exercise of short duration. J. Appl. Physiol. 32:59, 1972.
45. Coester, N., J.C. Elliott, and V.C. Luft: Plasma electrolytes, pH and EKG during and after exhaustive exercise. J. Appl. Physiol. 34:677, 1973.
46. Huber, W., and E. Marquard: Plasma potassium and blood pH following physical exercise in dialysis patients. Nephron 40:383, 1985.
47. Latos, D.L., D. Strimel, M.H. Drews, and T.G. Allison: Acid-base and electrolyte changes following maximal and submaximal exercise in hemodialysis patients. Am. J. Kidney Dis. 9:439, 1987.
48. Lundin, A.P., R.A. Stein, C.D. Brown, P. LaBelle, F.S. Kalman, B.G. Delano, W.F. Heneghan, N.A. Lazarus, N. Krasnow, and E.A. Friedman: Fatigue, acid-base and electrolyte changes with exhaustive treadmill exercise in hemodialysis patients. Nephron 46:57, 1987.


In normal subjects, there is an increase in serum potassium during dynamic exercise. However, unless there is a problem with dehydration, the level of serum potassium does not reach dangerous levels. But, there has been concern that serum potassium levels may rise excessively in patients with chronic renal failure. This problem has been investigated, and the results from the study by Huber and Marquard are shown in Figure 11.

Figure 11




In normal control subjects, shown on the left, serum potassium rose about 1 mmol/L and arterial pH fell from 7.40 to 7.25. In the patients with chronic renal failure, the serum potassium was higher before exercise and also increased about 1 mmol/L during exercise. Arterial pH fell from 7.40 to 7.15 in the patients with chronic renal failure.

In patients with chronic renal failure, serum potassium does not rise excessively during dynamic exercise. If, however, resting levels were very high, then serum potassium levels could increase to dangerous levels.

## III. THERAPEUTIC STRATEGIES TO INCREASE EXERCISE CAPACITY IN PATIENTS WITH CHRONIC RENAL FAILURE

The fact that few patients become gainfully employed is easily understood by this data. The job would have to have as low oxygen requirements as watch repairing to be a possible occupation for a patient with chronic renal failure.

Thus, in order for patients with chronic renal failure to be able to comfortably take care of themselves or to be gainfully employed, their maximal oxygen uptakes needs to be higher. This can be accomplished by three therapeutic strategies which are dynamic exercise training, recombinant human erythropoietin therapy, and renal transplantation.

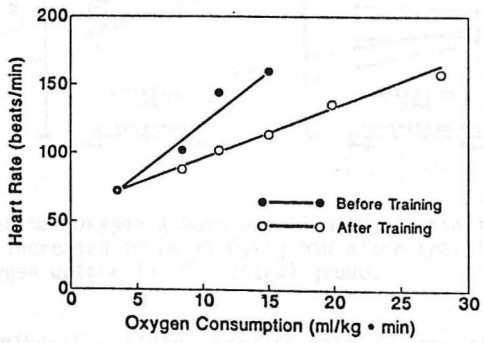
### A. Dynamic Exercise Training

#### 1. Training during the Time Off Dialysis


5. Loc. cit.
7. Loc. cit.
49. Jetté, M., G. Posen, and C. Cardarelli: Effects of an exercise programme in a patient undergoing hemodialysis treatment. J. Sports Med. 17:181, 1977.


One of the first papers to show a beneficial effect of exercise training in patients with chronic renal failure was reported by Jetté, Posen and Cardarelli from Canada in 1977. In this report, they showed the effect of training on the heart rate response to exercise in a 21 year old male who had been on hemodialysis for seven years. The exercise training was done during the time off dialysis. Their findings are shown in Figure 12.

Figure 12



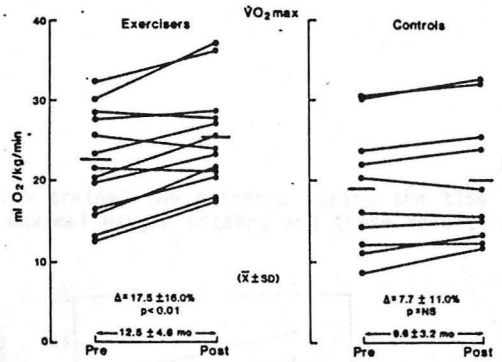

The heart rate achieved at increasing workloads on a cycle ergometer is plotted against the oxygen consumption. Before training, the patient's peak

oxygen consumption was 15 ml/kg·min and his maximal heart rate was 160. After training, his heart rate at any given level of oxygen consumption was less (relationship shifted to the right), demonstrating a training effect. Also, his peak oxygen consumption had increased to 28 ml/kg·min and his maximal heart rate was essentially unchanged (158 beats/min).


5. Loc. cit.
11. Loc. cit.
27. Loc. cit.
28. Loc. cit.
50. Hagberg, J.M.: Exercise rehabilitation of chronic renal disease patients. The Washington University Pilot Study. In: Rehabilitation and the Chronic Renal Disease Patient, ed. by N.G. Kutner, D.D. Cardenas, J.D. Bower. New York: Spectrum, p. 103, 1985.


One of the most extensive studies of the effects of dynamic exercise training in patients with chronic renal failure was by Goldberg, Harter, Hagberg and their collaborators at Washington University in St. Louis. In this study, the patients were randomly assigned into an exercise and a non-exercise group. The exercise training program was carried out during the time off dialysis and lasted for one year. Maximal oxygen uptake was measured in these two groups and the results are shown in Figure 13.

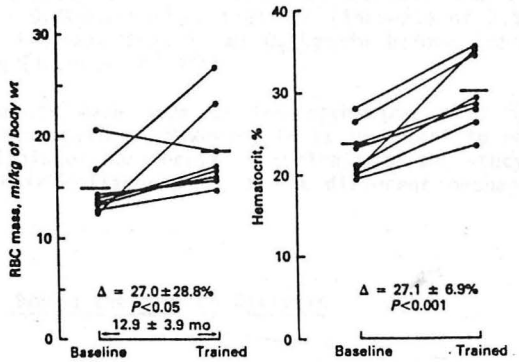
Figure 13




The mean value for maximal oxygen uptake was 22 ml $O_2$/kg·min in the exercise group before training and increased to 26 ml $O_2$/kg·min after training. There was no increase in maximal oxygen uptake in the control group.

In the Washington University study, measurements of the determinants of maximal oxygen uptake were not made. However, measurements were made of hematocrit, hemoglobin, and red cell mass in both the exercise and non-exercise group. No changes occurred in the non-exercise group. Changes did occur in the exercise group, and these are shown in Figure 14.

Figure 14



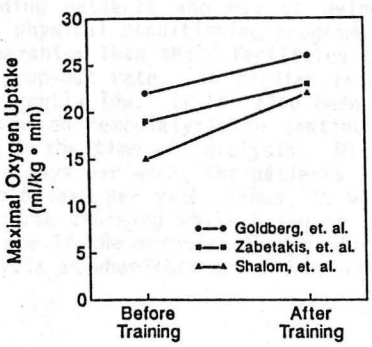

Hemoglobin, which is not shown, increased from 8 g/dl to 10 g/dl with training. Red cell mass increased from 15 ml/kg of body weight to 19 ml/kg of body weight (27% increase) and plasma volume did not change. Hematocrit increased from 24% before training to 31% after training (increase of 29%).

In this study, even though the mechanism for the increase in maximal oxygen uptake was not determined, the increase in hemoglobin and hematocrit may have played a role. That is, the increase in hemoglobin should have increased the arterial oxygen content and thereby allowed the total body arterio-venous oxygen difference to be wider.

5. Loc. cit.
31. Loc. cit.
32. Loc. cit.

Two other studies which trained the patients during the time off dialysis have shown an increase in maximal oxygen uptake, and these results are shown in Figure 15.

Figure 15



The study by Goldberg, Harter, Hagberg, and collaborators is again shown. In addition, the study by Zabetakis et al. found an increase from 19 ml $O_2$/kg·min before training to 23 ml $O_2$/kg·min after training (increase of 21%) and that of Shalom et al. found an increase from 15 ml $O_2$/kg·min before training to 22 ml $O_2$/kg·min after training (increase of 47%).

Again, no measurements were made of the determinants of maximal oxygen uptake in these latter two studies. However, it is important to note that there was no change in hemoglobin or hematocrit in contrast to the study by Goldberg, Harter, Hagberg, and their collaborators, and a different mechanism must have been utilized.

## 2. Training during the Time On Dialysis


51. Oldridge, N.: Compliance and dropout in cardiac exercise rehabilitation. J. Cardiopul. Rehab. 4:116, 1984.
52. Boettcher, S.W., and J.A. Greene: Exercise as a part of hemodialysis therapy. Am. J. Kidney Dis. 4, 1982 (Abstract).
53. Boettcher, S.W., and J.A. Greene: Use of exercise during hemodialysis as a part of health promotion of the dialysis patient. Clin. Res. 31:294A, 1983 (Abstract).
54. Burke, E.J., M.J. Germain, G.L. Graden, and J.P. Fitzgibbons: Mild steady-state exercise during hemodialysis treatment. Physician Sportsmed. 12:153, 1984.
55. Painter, P., J.N. Nelson-Worel, M.M. Hill, D.R. Thornbery, W.R. Shelp, A.R. Harrington, and A.B. Weinstein: Effects of exercise training during hemodialysis. Nephron 43:87, 1986.
56. Painter, P., and P. Hanson: A model for clinical exercise prescription: Application to hemodialysis patients. J. Cardiopul. Rehab. 7:177, 1987.
57. Painter, P., and G. Blackburn: Exercise for patients with chronic disease. Postgrad. Med. 83:185, 190, 1988.
58. Painter, P.: Exercise training during hemodialysis: Rates of participation. Dial. Transplant. 17:165, 1988.


Many people, including patients who may be helped by exercise training, enthusiastically start a physical conditioning program and then stop. Many spas sell ten times more memberships than their facilities could possibly accommodate based on the very high drop-out rate. In cardiac rehabilitation programs, the compliance rates are frequently low. It has also been difficult to get patients with chronic renal failure on hemodialysis to continue their exercise programs which are conducted during the time off dialysis. With each dialysis requiring three to four hours for 3 days per week, the patients are reluctant to spend one hour exercising for 4 to 5 days per week. Thus, it was suggested that patients could perform their exercise training while being on dialysis. It would be of interest, therefore, to see if the response to dynamic exercise is the same when patients are on hemodialysis as when they are off hemodialysis.

33. Loc. cit.
34. Loc. cit.

The study by Moore et al. (Dallas Study) has investigated this question in the same ten patients that were discussed earlier. Oxygen consumption and its determinants were measured at rest and during maximal exercise, both while the patients were off and while they were on hemodialysis. The results of this study are shown in Figure 16.

Figure 16

EFFECT OF HEMODIALYSIS ON OXYGEN CONSUMPTION AND IT'S DETERMINANTS AT REST AND DURING PEAK EXERCISE

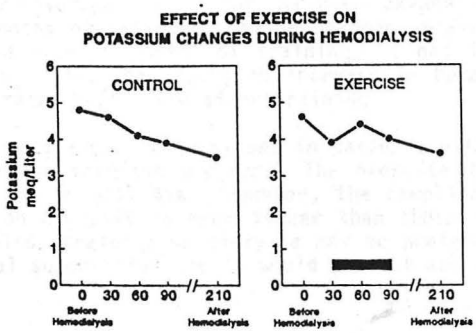
| | Rest | | Peak Excercise | |
|---|---|---|---|---|
| | Off | On | Off | On |
| Oxygen Consumption (L/min) | 0.28 | 0.25 | 0.98 | 1.01 |
| (ml/kg • min) | 3.9 | 3.5 | 13.2 | 13.6 |
| Cardiac Output (L/min) | 5.8 | 6.2 | 12.3 | 12.9 |
| Heart Rate (beats/min) | 78 | 78 | 127 | 130 |
| Stroke Volume (ml) | 77 | 82 | 98 | 99 |
| Arterio-Venous Oxygen Difference (ml $O_2$/100 ml blood) | 5.2 | 4.3 | 7.9 | 7.9 |
| Arterial Oxygen Content (ml $O_2$/100 ml blood) | 11.0 | 11.1 | 11.5 | 12.1 |
| Mixed Venous Oxygen Content (ml $O_2$/100 ml blood) | 5.8 | 6.8 | 3.6 | 4.2 |

Essentially, the values during resting conditions are the same both off and on hemodialysis. However, as would be expected, the cardiac output tends to be higher and the total body arterio-venous oxygen difference lower on dialysis than when off dialysis. Also during maximal exercise, the same values for oxygen consumption and its determinants are obtained. Thus, hemodialysis has little effect on oxygen consumption and its determinants during rest and during maximal exercise. Therefore, exercise training could be accomplished on as well as off hemodialysis.

59. Moore, G.E., and P.L. Painter: Personal Communication.

Also, as was stated earlier, concern had been voiced over potassium levels during exercise in these patients. Recently, the potassium changes during hemodialysis with exercise and those during hemodialysis without exercise have been measured in five subjects in the Dallas Study, and the values are shown in Figure 17.

Figure 17

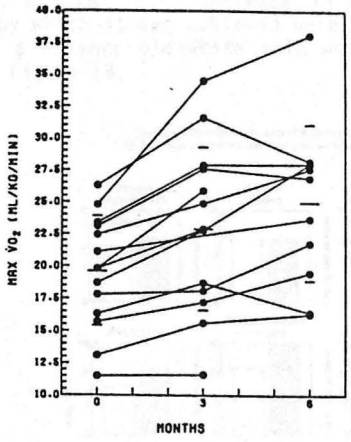



During hemodialysis without exercise (control), there was a slight decline in potassium during the time on dialysis. Before dialysis, serum potassium was 4.8 meq/L and after dialysis it was 3.5 meq/L. During hemodialysis with an hour of dynamic exercise training (exercise), there was a slight increase in potassium during the time of exercise (black bar). Before dialysis, serum potassium was 4.6 meq/L and after dialysis it was 3.6 meq/L. Thus, it is probably safer for a patient with chronic renal failure to exercise during the time on dialysis than to exercise during the time off dialysis. In addition, it is possible that more total potassium would be lost if hemodialysis was performed while the patients was exercising. The Dallas Study is planning to investigate this question.

7. Loc. cit.
55. Loc. cit.

Painter et al. have studied 14 patients before and after exercise training which was administered during hemodialysis. The results of their study are shown in Figure 18.

Figure 18



Before training, the average value for maximal oxygen uptake was 20 ml/kg·min. After three months of training, maximal oxygen uptake had increased to 23 ml/kg·min (+15%) and after 6 months of training, it had increased to 25 ml/kg·min (+25%). In this study, they found no increase in hematocrit, and no increase in maximal heart rates before and after training.

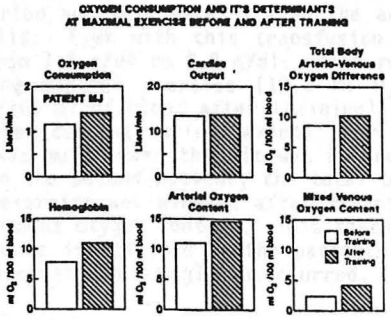
Thus, maximal oxygen uptake can be increased in patients with chronic renal failure by a dynamic exercise training program. The exercise training can be accomplished off dialysis or on dialysis. However, the compliance of patients training during the time on dialysis is much higher than those training during the time off dialysis. Also, training on dialysis may be preferable because it would be done under medical supervision and it would prevent any untoward elevation of serum potassium.

60. Moore, G.E., J. Stray-Gundersen, K. Brinker, P.L. Painter, and J.H. Mitchell: The effects of dynamic exercise training during hemodialysis in patients with chronic renal failure. Study in progress.

The effects of dynamic exercise training in chronic renal failure patients is currently being investigated by Moore et al. in the Dallas Study. The exercise training is being performed while the patients are on hemodialysis. The training regimen consists of a one-hour duration of bicycling at a prescribed workload intensity on the three days that the patient normally receives their dialysis therapy. Before training is started, a study of maximal oxygen uptake and its determinants, a biopsy of the rectus femoris muscle, and a determination of left ventricular mass by magnetic resonance imaging are being done. Training will be carried out for three months and then the patients will have all these measurements repeated.

At present, two patients have completed the exercise training program and 10 patients are still in the training phase of the study. In the two patients who have completed the study, a significant increase in maximal oxygen uptake was found but the mechanisms by which it was achieved were different. The results in the first patient (M.J.), a 77 year old white male who has been on hemodialysis for 2 years, are shown in Figure 19.

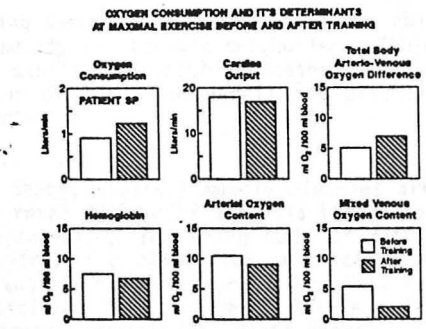
Figure 19



Maximal oxygen uptake before training was 1.2 L/min (15 ml $O_2$/kg·min) and increased to 1.4 L/min (18 ml $O_2$/kg·min) after training which represented an increase of 22%. This was accomplished with no change in cardiac output and an increase in total body arterio-venous oxygen difference from 8.6 ml $O_2$/100 ml blood before training to 10.3 ml $O_2$/100 ml of blood after training. This patient's hemoglobin increased during training from 7.8 g/dl to 11.0 g/dl. This resulted in a higher arterial oxygen content during maximal exercise (11.0 ml $O_2$/100 ml of blood before training to 14.6 ml $O_2$/100 ml of blood after training). Thus in this first patient, M.J., the total body arterio-venous oxygen difference at maximal exercise was widened after training even though the mixed venous oxygen content was slightly higher. The finding of an increase in hemoglobin in this patient is similar to the results reported in the training study by Goldberg et al.

The results in the second patient (S.P.), a 39 year old white female who has been on hemodialysis for 14 years, are shown in Figure 20.

Figure 20




Maximal oxygen uptake before training was 1.0 L/min (13 ml $O_2$/kg·min) and increased to 1.2 L/min (17 ml $O_2$/kg·min) after training which represents an increase of 35%. This occurred in spite of a slight drop in cardiac output (18.0 L/min to 17.0 L/min) at maximal exercise. Total body arterio-venous oxygen difference increased from 5.1 ml $O_2$/100 ml blood before training to 7.0 ml $O_2$/100 ml of blood after training. In this patient, there was a marked drop in hemoglobin during the training period and this necessitated the administration of 2 units of packed red blood cells. Even with this transfusion therapy the hemoglobin fell during training from 7.5 g/dl to 6.8 g/dl. This resulted in a lower arterial oxygen content during maximal exercise (10.5 ml $O_2$/100 ml of blood before training and 9.1 ml $O_2$/100 ml of blood after training). However, in this patient, the mixed venous oxygen content during maximal exercise after training (2.1 ml $O_2$/100 ml of blood) was much lower than it was before training (5.4 ml $O_2$/100 ml of blood). Thus, in the second patient, the total body arterio-venous oxygen difference at maximal exercise was widened after training because of the marked lowering of the mixed venous oxygen content. This finding in patient S.P. is probably the same mechanism as is utilized in the patients reported in those previous studies in which no increase in hemoglobin occurred.

18. Loc. cit.
61. Varnauskas, E., P. Bjorntorp, M. Fahlen, I. Prerovsky, and J. Stenberg: Effects of physical training on exercise blood flow and enzymatic activity in skeletal muscle. Cardiov. Res. 4:418, 1970.
62. Gollnick, P.D., R.B. Armstrong, C.W. Saubert, IV, K. Piehl, and B. Saltin: Enzyme activity and fiber composition in skeletal muscle of untrained and trained men. J. Appl. Physiol. 33:312, 1972.
63. Holloszy, J.O., and F.W. Booth: Biochemical adaptations to endurance exercise in muscle. Ann. Rev. Physiol. 38:273, 1976.
64. Andersen, P., and J. Henriksson: Capillary supply of the quadriceps femoris muscle of man: adaptive response to exercise. J. Physiol. (London) 270:677, 1977.
65. Saltin, B., and P.D. Gollnick: Skeletal muscle adaptability: significance for metabolism and performance. In: Handbook of Physiology: Skeletal Muscle. Bethesda: Am. Physiol. Soc., p. 555, 1983.
66. Parsons, D., G.E. Moore, J. Stray-Gundersen, and K. Brinker: Personal Communication.

Dynamic exercise training produces important adaptive changes in skeletal muscle which increase its capacity for aerobic metabolism. These changes include an increase in the number of capillaries which increases the oxygen supply and an increase in the concentration of the mitochondria and oxidative enzymes which increases the oxidative potential.

In the on-going Dallas Study, skeletal muscle biopsies are being performed in the patients with chronic renal failure on dialysis before and after the three month training program. Measurements are being made of fiber size, capillary density, and muscle biochemistry. For comparison, a muscle biopsy was performed on one of the investigators who claims to be normal (Dr. Karl Brinker) and in one investigator who was a participant in the Olympic Marathon Trials in 1984 and recently ran a 2 hour, 22 minute marathon (Dr. Geoff Moore). The results of the biopsies on these two investigators and in one of the patients with chronic renal disease before and after training are shown in Figure 21.

Figure 21

| Subject | Fiber Area mm | Capillary/Fiber Ratio | Succinate Dehydrogenase Activity $\mu moles \cdot g^{-1} \cdot min^{-1}$ | Phosphofructokinase Activity $\mu moles \cdot g^{-1} \cdot min^{-1}$ |
|---|---|---|---|---|
| KB (normal) | 1.97 | 1.25 | 6.50 | 14.99 |
| GEM (endurance athlete) | 2.56 | 2.32 | 10.20 | 12.71 |
| MJ (patient) | | | | |
| Before training | 1.91 | .81 | 2.70 | 24.32 |
| After training | 2.33 | 1.20 | 4.94 | 36.48 |

Fiber area was 1.97 $mm^2$ in Dr. Brinker's skeletal muscle biopsy and was higher (2.56 $mm^2$) in Dr. Moore's. The patient's fiber area was 1.91 $mm^2$ before the three months of endurance training and 2.33 $mm^2$ after training. Thus, muscle hypertrophy occurred in the patient and no more will be said about this finding compared to Dr. Brinker's! The capillary fiber ratio in Dr. Brinker was 1.25, in Dr. Moore 2.32, and in the patient before training was very low (.81). With training, however, there was an increase in capillarity with the ratio becoming

1.20, only slightly less than that of Dr. Brinker's. Succinate dehydrogenase activity in the skeletal muscle, which represents its oxidative capacity, was 6.50 μmoles·gm$^{-1}$·min$^{-1}$ in Dr. Brinker and much higher in Dr. Moore (10.20 μmoles ·gm$^{-1}$·min$^{-1}$). The patient's value was very low before training (2.70 μmoles·gm$^{-1}$ ·min$^{-1}$) and increased to 4.94 μmoles·gm$^{-1}$·min$^{-1}$ after training. This is a markedly improved oxidative capacity, but is still lower than that of Dr. Brinker's.

Phosphofructokinase activity in the skeletal muscle biopsy, which represents its glycolytic capacity, was 14.99 μmoles·gm$^{-1}$·min$^{-1}$ in Dr. Brinker and 12.71 μmoles·gm$^{-1}$·min$^{-1}$ in Dr. Moore. Glycolytic activity was substantially higher in the patient both before and after training.

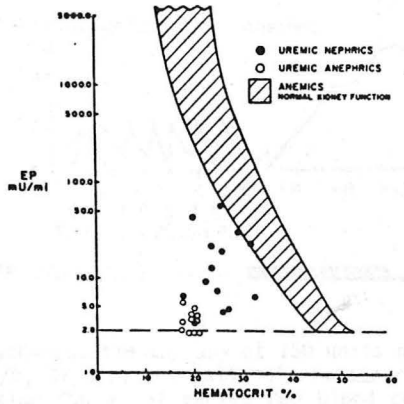
Thus, skeletal muscle vascularity, as measured by the capillary/fiber ratio, and its oxidative capacity, as measured by succinate dehydrogenase activity, were both markedly improved by endurance training in the patient with chronic renal failure. In fact, after training, these values were essentially normal. However, they were both still low as compared to an endurance runner who has been training for many years.

B. Recombinant Human Erythropoietin Therapy


67. Radtke, H.W., A. Claussner, P.M. Erbes, E.H. Scheuermann, W. Schoeppe, and K.M. Koch: Serum erythropoietin concentration in chronic renal failure: Relationship to degree of anemia and excretory renal function. Blood 54:877, 1979.
68. Caro, J., S. Brown, O. Miller, T. Murray, and A.J. Erslev: Erythropoietin levels in uremic nephric and anephric patients. J. Lab. Clin. Med. 93:449, 1979.
69. McGonigle, R.J.S., J.D. Wallin, R.K. Shadduck, and J.W. Fisher: Erythropoietin deficiency and inhibition of erythropoiesis in renal insufficiency. Kidney Int. 25:437, 1984.
70. Erslev, A.J., J. Wilson, and J. Caro: Erythropoietin titers in anemic, nonuremic patients. J. Lab. Clin. Med. 109:429, 1987.


The pathophysiology of the anemia of chronic renal failure is complex; but, it appears that both a decrease in red cell production and a decrease in red cell survival are involved. However, the decreased red cell production due to impaired synthesis of erythropoietin is thought to be the primary cause of the anemia in this condition. Erythropoietin levels in patients with chronic renal failure have been determined and the results of Caro et al. are shown in Figure 22.

Figure 22

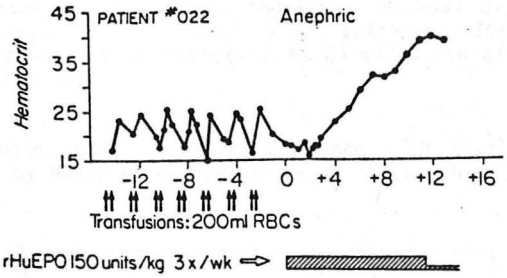



The relationship between erythropoietin (EP) and hematocrit in patients with anemia is shown. The lower limits of the assay used in this study was 2.8 mU/ml. The hatched area represents erythropoietin values for anemic patients with normal renal function. In uremic anephric patients (○) erythropoietin levels were consistently low, and in uremic-nephric patients (●) the erythropoietin levels were lower than expected for the degree of anemia present in the patient.


71. Winearls, C.G., D.O. Oliver, M.J. Pippard, C. Reid, M.R. Downing, and P.M. Cotes: Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. The Lancet 11/22:1176, 1986.
72. Eschbach, J.W., J.C. Egrie, M.R. Downing, J.K. Browne, and J.W. Adamson: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined Phase I and II clinical trial. N. Engl. J. Med. 316:73, 1987.
73. Erslev, A.: Erythropoietin coming of age (Editorial). N. Engl. J. Med. 316:101, 1987.


The treatment of the anemia of chronic renal failure with blood transfusions and androgen therapy has been only partially successful. Recently, recombinant human erythropoietin has become available and has been used to treat patients with end-stage renal disease on hemodialysis. The results obtained in one patient treated by Eschbach et al. are shown in Figure 23.

Figure 23

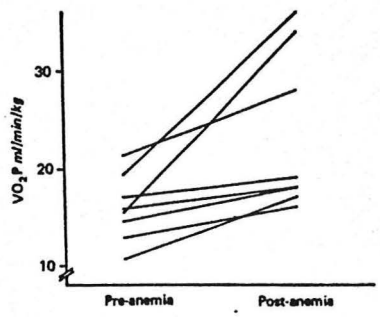



Before starting human erythropoietin therapy at 150 units per kilogram three times a week (rHuEPO 150units/kg 3x/wk), the patient's hematocrit was maintained between 15 and 25 by transfusing 400 ml of packed red blood cells (RBCs) every two weeks. After starting erythropoietin therapy, the hematocrit rose to 40 and the dose of erythropoietin was reduced to 50 units/kg three times a week.


74. Robertson, H.T., N.R. Haley, J.W. Adamson, and J.W. Eschbach: Increase in maximal exercise capacity in hemodialysis (HD) patients following correction of the anemia with recombinant human erythropoietin (rHuEpo). Clin. Nephrol. 59A, 1987.
75. Lundin, A.P., B.G. Delano, R. Stein, R.M. Quinn, E.A. Friedman: Recombinant human erythropoietin (r-HuEPO) treatment enhances exercise tolerance in hemodialysis patients (HD). Clin. Nephrol. 55A, 1987.
76. Mayer, G., J. Thum, E.M. Cada, H.K. Stummvoll, and H. Graf: Working capacity is increased following recombinant human erythropoietin treatment. Kidney Int. 34:525, 1988.


The effect of recombinant human erythropoietin therapy on exercise capacity in patients with chronic renal failure has been reported by several groups. Data from the recent publication by Mayer et al. are shown in Figure 24.

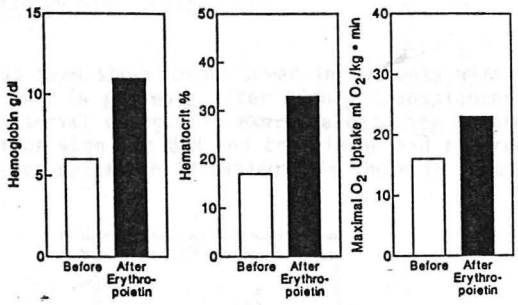
Figure 24



Maximal oxygen uptake was determined before treatment when the patients were anemic and after therapy when the anemia was improved. Maximal oxygen uptake ($VO_2P$) in ml/kg·min (ml/min/kg) increased in all eight patients. The mean value before therapy was 16 ml/kg·min and it increased to 23 ml/kg·min after therapy which represents an increase of 44%.

The change in hemoglobin and in hematocrit, along with that in maximal oxygen uptake, in the study by Mayer et al. are shown in Figure 25.

Figure 25




Hemoglobin increased from 6 g/dl to 11 g/dl and hematocrit increased from 17% to 33%. As shown in the last figure, maximal oxygen uptake increased from 16 ml/kg·min to 23 ml/kg·min. It is of interest that the maximal heart rate in the pretreatment study was 137 beats/min and in the study after improvement of the anemia was 138 beats/min. Thus, the decreased maximal heart rate seen in anemic patients was not changed. This would suggest that the improvement was probably not due to an increased cardiac output but was due to an increased total body arterio-venous oxygen difference.

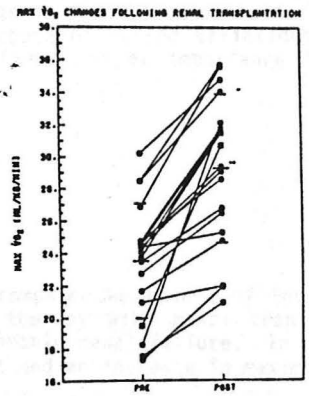
C. Renal Transplantation

1. Exercise Capacity after Surgery

29. Loc. cit.
77. Painter, P.L.: Cardiovascular Responses to Exercise Following Renal Transplantation. Ph.D. Thesis, University of Wisconsin - Madison, 1985.
78. Painter, P., P. Hanson, D. Messer-Rehak, S.W. Zimmerman, and N.R. Glass: Exercise tolerance changes following renal transplantation. Am. J. Kidney Dis. 10:452, 1987.

Exercise capacity has been shown to be lower in patients with chronic renal failure on hemodialysis than in patients after kidney transplantation. Painter et al. have reported the serial changes in exercise capacity before and shortly after kidney transplantation when the BUN and creatinine had returned to normal. The effect on maximal oxygen uptake in 20 patients is shown in Figure 26.

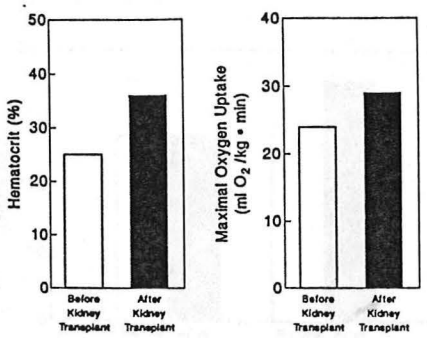
Figure 26




Maximal oxygen uptake is seen to increase in every patients. The mean value from the group before kidney transplantation was 24 ml/kg·min and increased to 29 ml/kg·min after transplantation. This represents a 21% increase in exercise capacity.

The mechanisms for the increase in maximal oxygen uptake in these patients was not studied. However, one of the causes would appear to be an increased hematocrit and thereby oxygen carrying capacity of the blood. The increase in hematocrit in these patients studied by Painter et al. is shown in Figure 27.

Figure 27




Before renal transplant the hematocrit was 25% and after transplant it was 36%. The increase in maximal oxygen uptake is again shown and increased from 24 ml/kg•min to 29 ml/kg•min. However, in this study there was no correlation between the percentage change in maximal oxygen uptake and the percentage change in hematocrit (r = .27) because of marked variations among the patients. This suggests that other mechanisms were of importance in the increase in maximal oxygen uptake.

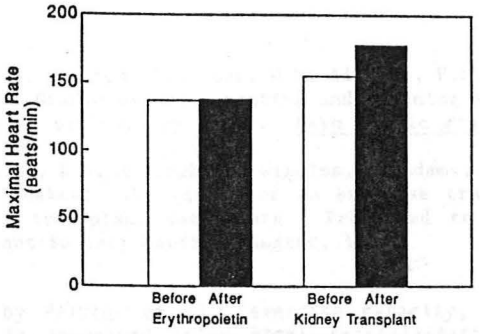
76. Loc. cit.
77. Loc. cit.
78. Loc. cit.

It is of interest to compare the result of therapy with recombinant human erythropoietin to that of therapy with renal transplantation on the exercise capacity of patients with chronic renal failure. In both types of therapy, there is an increase in hematocrit and an increase in maximal oxygen uptake.

In the patients treated with recombinant human erythropoietin the hematocrit increased to 33% (Fig. 25) and in the patients receiving kidney transplantation the hematocrit increased to 36% (Fig. 27). Thus, the two treatments resulted in essentially the same final value for the hematocrit. However, the maximal oxygen uptake in the patients after erythropoietin therapy was 23 ml/kg•min (Fig. 25) and in the patients after renal transplantation was 29 ml/kg•min (Fig. 27).

It is not clear why the maximal oxygen uptake at similar hematocrits is so much higher in the patients after renal transplantation. However, it would appear that the cardiac output at maximal exercise was higher in the patients receiving kidney transplants. Suggestive evidence for this hypothesis is the difference in maximal heart rates in the two groups as shown in Figure 28.

Figure 28




In the patients treated with recombinant human erythropoietin, their maximal heart rate before therapy was 137 beats/min. The mean age of these patients was 36 years so the predicted maximal heart rate would be 184 beats/min. As stated before, there was no change in maximal heart rate after therapy (138 beats/min). However, maximal heart rate did increase significantly in the patients after kidney transplantation. Before kidney transplantation, the maximal heart rate was 155 beats/min. The mean age of these patients was 29 years, so that the predicted maximal heart rate would be 190 beats/min. After renal transplantation, maximal heart rate increased significantly to 178 beats/min, which is much closer to the predicted value for this age group.

77. Loc. cit.
79. Izzo, J.L., Jr., M.S. Izzo, R.H. Sterns, and R.B. Freeman: Sympathetic nervous system hyperactivity in maintenance hemodialysis patients. Trans. Am. Soc. Artif. Intern. Organs 28:604, 1982.
80. Kettner, A., A. Goldberg, J. Hagberg, J. Delmez, and H. Harter: Cardiovascular and metabolic responses to submaximal exercise in hemodialysis patients. Kidney Int. 26:66, 1984.

The maximal heart rate is depressed in patients with chronic renal failure and this is not corrected when the anemia is treated. The mechanism of this low maximal heart rate is not known, but appears to be related to abnormal autonomic nervous system function. Studies have shown that the blood levels of catecholamines are high during rest and during exercise in these patients. Therefore, the decreased maximal heart rate must be due to abnormal responsiveness of the adrenergic receptors.

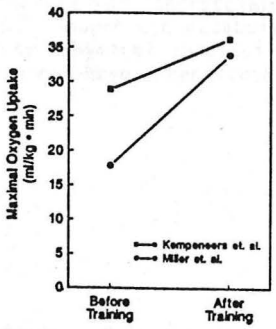
The maximal heart rate is much higher after than before renal transplantation. Also, it has been found that the catecholamine levels return to normal during rest and exercise. Thus, renal transplantation and correction of the uremic state appear to return the abnormal responsiveness of adrenergic receptors back to normal.

## 2. Exercise Capacity after Training

77. Loc. cit.
78. Loc. cit.
81. Miller, T.D., R.W. Squires, G.T. Gau, D.M. Ilstrup, P.P. Frohnert, and S. Sterioff: Graded exercise testing and training after renal transplantation: A preliminary study. Mayo Clinic Proc. 62:773, 1987.
82. Kempeneers, G.L.G., K.H. Myburgh, T. Wiggins, B. Adams, R. VanZyl-Smit, and T.D. Noakes: The effect of an exercise training programme in renal transplant recipients. Presented to the South African Transplant Society Meeting, August, 1987.

As has been shown by Painter et al., exercise capacity, as measured by maximal oxygen uptake, is increased after renal transplantation without any exercise training. This is probably due to an increase in arterial oxygen content since the hemoglobin is increased, and to an increase in maximal cardiac output since the maximal heart rate is increased. However, the values of maximal oxygen uptake that are reached after renal transplantation are still below normal. It has now been shown by Kempeneers et al. and by Miller et al. that maximal oxygen uptake can be further increased in renal transplant patients by an exercise training program. These results are shown in Figure 29.

Figure 29




In the study by Kempeneers et al., the maximal oxygen uptake after recovery from renal transplantation was 29.0 ml $O_2$/kg·min and increased to 36.3 ml $O_2$/kg·min after training. The patients in the experiment reported by Miller et al. were studied very soon after their surgery. In this group, the maximal oxygen uptake before training was rather low (17.9 ml $O_2$/kg·min) when the anemia and uremia may not have been resolved. However, after dynamic exercise training, the maximal oxygen uptake increased greatly to 34.0 ml $O_2$/kg·min. Thus, in these renal transplant patients who received exercise training, the exercise capacity was increased to a high normal level.

## IV. EFFECT OF EXERCISE TRAINING ON RISK FACTORS FOR ATHEROSCLEROSIS IN PATIENTS WITH CHRONIC RENAL FAILURE


9. Loc. cit.
10. Loc. cit.
11. Loc. cit.
83. Kannel, W.B., T.R. Dawber, A. Kagan, N. Revotskie, and J. Stokes: Factors of risk in the development of coronary heart disease -- a six year follow-up experience, The Framingham Study. Ann. Int. Med. 55:33, 1961.
84. Borhani, N.O.: Primary prevention of coronary heart disease: a critique. Am. J. Cardiol. 40:251, 1977.
85. Goldberg, A.P., E.M. Geltman, J.R. Gavin, III, R.M. Carney, J.M. Hagberg, J.A. Delmez, A. Naumovich, M.H. Oldfield, and H.R. Harter: Exercise training reduces coronary risk and effectively rehabilitates hemodialysis patients. Nephron 42:311, 1986.


The incidence of atherosclerosis including coronary and cerebral vascular disease is considerably higher in patients with chronic renal failure than in normal subjects and in patients with hypertension; in fact, the incidence is comparable to patients with more than one risk factor. Therefore, it is important to vigorously treat the risk factors for atherosclerosis. These include: 1) elevated blood pressure, 2) abnormal lipoprotein metabolism, 3) abnormal glucose metabolism, 4) low exercise capacity (physical inactivity), and 5) smoking. It has been shown that dynamic exercise can have a beneficial effect on all of these risk factors for atherosclerosis.

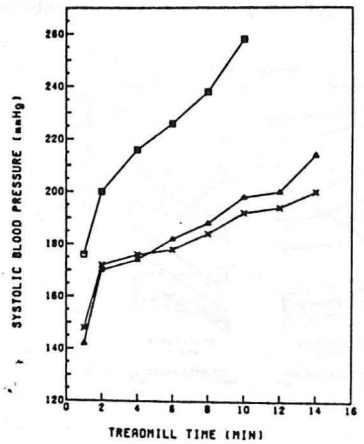
### A. Effect on Blood Pressure


5. Loc. cit.
7. Loc. cit.
55. Loc. cit.
86. Boyer, J.L., and F.W. Kasch: Exercise therapy in hypertensive men. J.A.M.A. 211:1668, 1970.
87. Bjorntorp, P.: Hypertension and exercise. Hypertension 4 (Suppl. III):56, 1982.
88. Tipton, C.M.: Exercise training and hypertension. Exerc. Sports Sci. Rev. 12:245, 1987.
89. McMahon, M., and R.M. Palmer: Exercise and hypertension. Med. Clin. N. Am. 69:57, 1985.
90. Hagberg, J.M., A.P. Goldberg, A.A. Ehsani, G.W. Heath, J.A. Delmez, and H.R. Harter: Exercise training improves hypertension in hemodialysis patients. Am. J. Nephrol. 3:209, 1983.


Dynamic exercise training has been reported to reduce arterial blood pressure in some normal subjects and in hypertensive patients. Patients with chronic renal failure who are hypertensive often become normotensive after hemodialysis

is instituted and their increased blood volume is corrected. However, a few patients remain hypertensive on hemodialysis and require antihypertensive medication. Hagberg et al. have shown that in many of these patients, the hypertension improves after an exercise training program. That is, after exercise training, some of the patients require less antihypertensive medication and some require no medication at all. Similar results have been reported by Painter et al. and the data on one of their patients are shown in Figure 30.

Figure 30



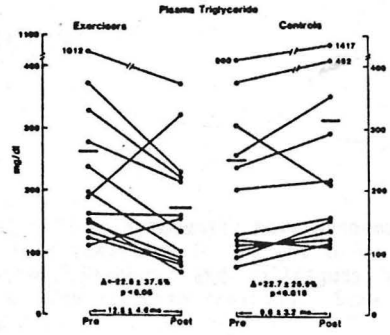

Systolic blood pressure in mmHg is shown at rest and during progressively increasing exercise loads on a treadmill. Before dynamic exercise training was started (□), the patient was receiving propranolol 80 mg q d and hydralazine 50 mg q d. Systolic blood pressure at rest was 175 mmHg and increased to 260 mmHg after 10 minutes on the treadmill with increasing workloads. After 3 months of training (▲), the patient was taking no hypertensive medications. At that time, systolic blood pressure at rest was 140 mmHg and increased to 212 mmHg after 14 minutes on the treadmill. After 6 months of training (x), the systolic blood pressure remained normal during rest and treadmill exercise without any hypertensive medications.

B. Effect on Lipoprotein Metabolism


5. Loc. cit.
83. Loc. cit.
85. Loc. cit.
91. Miller, N.E., F. Hammett, S. Saltissi, et al: Relation of angiographically defined coronary artery disease to plasma lipoprotein subfractions and apolipoproteins. Br. Med. J. 282:1741, 1981.
92. Ballantyne, F.C., R.S. Clark, H.S. Simpson, and D. Ballantyne: High density and low density lipoprotein subfractions in survivors of myocardial infarction and in control subjects. Metabolism 31: 433, 1982.
93. Manninen, V., M.O. Elo, M.H. Frick, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. J.A.M.A. 260:641, 1988.

Lipoprotein metabolism and the lipid profile tend to be abnormal in many patients with chronic renal failure. These abnormalities include a high level of triglycerides and a low level of HDL cholesterol. Total serum cholesterol and LDL cholesterol are usually within normal limits. The lipid abnormalities in these patients are probably due to a reduced clearance of triglycerides from the plasma and an abnormality in HDL metabolism. Studies by Goldberg, Harter, Hagberg, and colleagues have demonstrated a beneficial effect of dynamic exercise training in patients with chronic renal failure on hemodialysis. The effect of training on plasma triglycerides is shown in Figure 31.

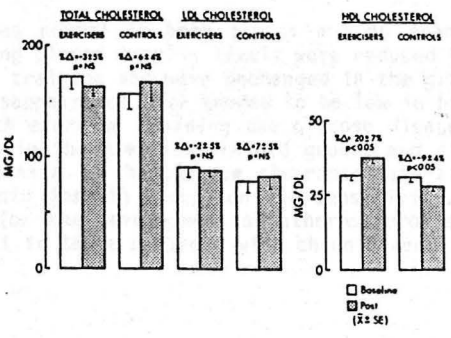
Figure 31




Thirteen patients were in the exercise training group and 12 were in the control group. Plasma triglycerides were high in both groups at the first study. On the left side (Exercisers) the plasma triglycerides decreased significantly (+23%) after an exercise training program. However, on the right side (controls) there was a significant increase in plasma triglycerides (+23%) in the patients who did not exercise.

Goldberg, Harter, Hagberg, and colleagues also studied the effect of exercise training on total cholesterol, LDL cholesterol, and HDL cholesterol, and their findings are shown in Figure 32.

Figure 32



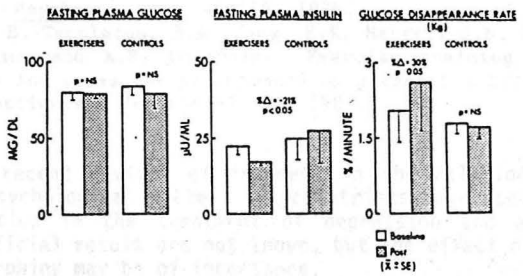
Total cholesterol and LDL cholesterol were normal in both the patients with chronic renal failure who were in the exercise group and those in the control group. Also, these values did not change in either the group that was exercise trained or the control group. However, HDL cholesterol was low in both groups in the control study. In the patients who were exercise trained, there was an increase (+20%) in HDL cholesterol and in the patients in the control group there was a decrease (+9%) in HDL cholesterol. Thus, the so-called "risk ratio" (ratio of total serum cholesterol to HDL cholesterol) improved in the exercise group and was unchanged in the control group.

C. Effect on Glucose Metabolism

5. Loc. cit.
83. Loc. cit.
85. Loc. cit.

Patients with chronic renal failure frequently have abnormal glucose metabolism and glucose intolerance. This condition is thought to be a risk factor for atherosclerosis. Goldberg, Harter, Hagberg, and colleagues have shown an improvement in glucose intolerance with exercise training. Some of the results of their study are shown in Figure 33.

Figure 33




Fasting plasma glucose was normal in both groups and no changes occurred with exercise training. Fasting plasma insulin levels were reduced (+21%) in the group which underwent exercise training and were unchanged in the group of sedentary controls. The glucose disappearance rate tended to be low in both groups at the first study. However, with exercise training the glucose disappearance rate increased significantly (+30%) in the exercise trained group, and did not change in the control group. The increase in the glucose clearance rate after training indicates an improvement in both insulin secretion and sensitivity. If glucose intolerance is a risk factor for the development of atherosclerosis, then exercise training may be of benefit in those patients with chronic renal failure.

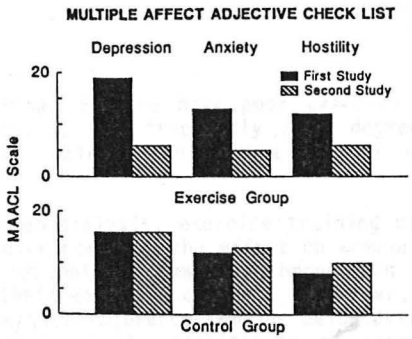
## V. EFFECT OF EXERCISE TRAINING ON THE PSYCHOLOGICAL STATE OF PATIENTS WITH CHRONIC RENAL FAILURE


28. Loc. cit.
94. Folkins, C.: Effects of physical training on mood. J. Clin. Psychol. 32:385-388, 1976.
95. Greist, J., M. Klein, R. Eischers, and J. Faris: Running as a treatment for depression. Behav. Med. 5:19, 1978.
96. Carr, D.B., B.A. Bullen, G.S. Skrinar, M.A. Arnold, M. Rosenblatt, I.Z. Beitins, J.B. Martin, and J.W. McArthur: Physical conditioning facilitates the exercise-induced secretion of beta-endorphin and beta-lipotropin in women. N. Engl. J. Med. 305:560, 1981.
97. Morgan, W.P.: Affective beneficence of vigorous physical activity. Med. Sci. Sports Exerc. 17:94, 1985.
98. Levy, N.: The effect of psychosocial factors on the rehabilitation of 'the artificial man'. Dial. Transplant. 8:213, 1979.
99. Fishman, D., and C. Schieder: Predicting emotional adjustment in hemodialysis patients and their relatives. J. Chron. Dis. 25:99, 1972.
100. Carney, R.M., P.M. McKevitt, A.P. Goldberg, J. Hagberg, J.A. Delmez, and H.R. Harter: Psychological effects of exercise training in hemodialysis patients. Nephron 33:179, 1983.
101. Carney, R.M., R.D. Wetzel, J. Hagberg, and A.P. Goldberg: The relationship between depression and aerobic capacity in hemodialysis patients. Psychosom. Med. 48:143, 1986.
102. Carney, R.M., B. Templeton, B.A. Hong, H.R. Harter, J.M. Hagberg, K.B. Schechtman, and A.P. Goldberg: Exercise training reduces depression and increases the performance of pleasant activities in hemodialysis patients. Nephron 47:194, 1987.


There has been a recent revival of interest in the relationship between exercise training and psychological states. Psychiatrists have used jogging and other endurance activities in the treatment of depression and anxiety. The mechanisms of this beneficial result are not known, but the effect of exercise on the levels of beta-endorphins may be of importance.

Patients with chronic renal failure on hemodialysis have elevated levels of hypochondriasis, depression, and hysteria when evaluated with the Minnesota Multiphasic Personality Inventory (MMPI). Also, they have increased anxiety and hostility; however, depression is the most frequent psychological complaint. Carney et al. have examined the effect of exercise training on the psychological abnormalities in these patients, and some of their results are shown in Figure 34.

Figure 34




The Multiple Affect Adjective Check List (MAACL) measures the patients' levels of depression, anxiety, and hostility. In this test, the higher the scores, the stronger the emotion. Normal values for depression are below 11, anxiety below 6, and hostility below 7. Four patients served as controls and four patients were exercise trained. The four control subjects and the four exercise subjects all had higher scores than normal for depression, anxiety, and hostility. On the second test in the patients who had exercised, the scores were all within normal limits. In the control group, who received no dynamic exercise training, there was no difference in depression, anxiety, and hostility between the first and second test.

## VI. CONCLUSIONS

Patients with chronic renal failure have poor exercise tolerance, accelerated rates of atherosclerosis, and frequently some degree of anxiety and depression. Dynamic exercise training can play a role in ameliorating these unacceptable complications.

In patients on chronic hemodialysis, exercise training can improve maximal oxygen uptake and exercise tolerance, but the effect on anemia is controversial. Treatment of patients with recombinant human erythropoietin can improve their anemia and thereby improve their exercise capacity. However, in both of these treatment strategies, the exercise tolerance remains below average. It would be of great interest to determine if the combination of exercise training and recombinant human erythropoietin therapy would increase the patient's exercise capacity to normal.

In patients after renal transplantation, the anemia is alleviated and maximal oxygen uptake is improved, but remains low. However, exercise training can increase the exercise capacity to normal.

The accelerated atherosclerosis in patients with chronic renal failure should be vigorously treated by a risk factor reduction program. Exercise training can be very beneficial in this effort.

Exercise training can also improve the psychological state of these patients by reducing their anxiety and depression. It makes them "feel better" and they become more socially interactive.

For patients with chronic renal disease, "rehabilitation" should mean more than mere survival. These individuals deserve to have a chance to be productive and to enjoy life.