

The effects of changes in physical activity on major cardiovascular risk factors, hemodynamics, sympathetic function, and glucose utilization in man: a controlled study of four levels of activity

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ABSTRACT The effects of four levels of activity on heart rate, blood pressure, cardiac index, total peripheral resistance index (TPRI), norepinephrine (NE) spillover rate, insulin sensitivity, and levels of lipids and some hormones were studied in 12 normal subjects. The randomized periods were (1) 4 weeks of below-sedentary activity, (2) 4 weeks of sedentary activity, (3) 4 weeks of 40 min of bicycling three times per week, and (4) 4 weeks of similar bicycling seven times per week. Exercise three times per week reduced resting blood pressure by 10/7 mm Hg ($p < .01$) and it was reduced by 12/7 mm Hg after exercise seven times per week (both $p < .01$). This was associated with reduction in TPRI, an increase in cardiac index, and cardiac slowing. At the highest level of activity, NE spillover rate, an index of sympathetic activity, fell to 35% of the sedentary value ($p < .001$) in eight of 10 subjects. In two other subjects NE spillover rate rose, although blood pressure and TPRI were reduced. Metabolic changes included lowering of total cholesterol, but high-density lipoprotein level was unchanged. Insulin sensitivity rose by 27% after exercise three times per week, but declined to sedentary levels with seven times per week exercise. Maximum oxygen uptake increased linearly with activity. Exercise performed three times per week lowers blood pressure and should reduce cardiovascular risk. The same exercise seven times per week enhances physical performance with little further reduction in cardiovascular risk factors. Exercise is potentially a major nonpharmacologic method of lowering blood pressure.

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REGULAR PHYSICAL EXERCISE is generally recommended for the prevention of cardiovascular disease, largely on the basis of epidemiologic studies.¹⁻⁴ The benefits of exercise may be due to reduction in some of the risk factors or through other effects.⁵⁻⁷ There has been a diversity of views about the extent of the benefit, the physiologic basis for such an action, and the amount of exercise that is required. Some studies have suggested that a prolonged and intense effort is required,² while from others it would appear that adequate benefit is conferred by a few minutes of leisure-time activity.³

Many physiologic studies that have examined the effects of exercise on blood pressure and lipid levels

have used longitudinal experimental designs, which tend to confound the effects of exercise with those due to associated changes in body weight, sodium intake, and familiarity with the measurement procedures.⁸⁻¹⁰ It has been hard to draw firm conclusions about which of these are most important in reducing conventional risk factors. An additional problem is the short-term effect of exercise, which may make it hard to interpret the mechanisms underlying blood pressure falls during longitudinal studies.

The purpose of the present investigation was to examine in the same normal sedentary subjects the effects of four different levels of activity on a number of circulatory, metabolic, and hormonal variables in a manner that would avoid some of the confounding effects, that were present in previous studies. The four levels of activity chosen were (1) below-normal sedentary activity, (2) normal sedentary activity, (3) bicycling for 40 min 3 times per week, and (4) similar bicycling seven times per week. Each level of regular

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activity was maintained for 4 weeks and the order of treatments in the different subjects was randomized according to a Latin-square experimental design to eliminate bias in the order of administration. We paid close attention to the maintenance of constant body weight and salt intake at the different levels of activity. We assessed the effects of exercise from measurements of circulatory, metabolic, autonomic, and hormonal variables 48 hr after completing a particular 4 week activity period to avoid the confounding effects of a short-term bout of exercise on the results. We also examined how the latter affected the performance during short-term, graded steady-state exercise.

Methods

Twelve normal subjects participated in the study, which was performed with the approval of the Alfred Hospital Clinical Ethics Committee. The subjects had sedentary occupations and none had participated in regular vigorous leisure time activity in the previous year. Eleven were men and the average age was 22 years (range 19 to 27 years).

The protocol involved four consecutive 1 month periods at each of the four levels of activity referred to in the introduction: (1) below-sedentary activity (during the second half of the period of reduced activity the subjects were admitted to hospital for 2 weeks rest), (2) normal sedentary activity, (3) normal activity plus three standard exercise periods weekly, and (4) normal activity plus daily standard exercise periods. The order of these periods was randomized and the allocation followed a 4×4 Latin square for each set of four subjects.

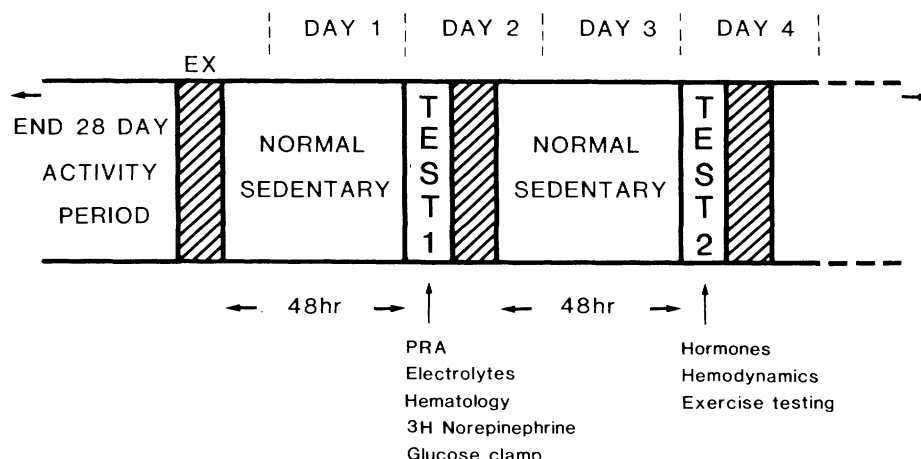
The standard exercise periods were strictly supervised and consisted of 40 min exercise on an electrically braked bicycle ergometer. A five min warm-up was followed by 30 min at a workload of 60% to 70% of the previously determined maximum work capacity (W_{max}) and a 5 min cool down. Heart rate was monitored from the electrocardiogram and the workload was adjusted to maintain heart rate during exercise within the range of 120 to 150 beats/min.

The subjects took no medications and kept factors other than

physical activity as constant as possible during the study. Weight was measured weekly and 24 hr urinary sodium excretion was measured monthly. Dietary advice was available to assist subjects in maintaining stable weight and sodium intake. Food intake was assessed from 3 day food diaries compiled during each period. During the studies, however, little intervention was necessary. At the end of each month (48 hr after the end of each 4 week period) a series of measurements was obtained by staff members who were unaware of the previous month's activity level (figure 1). During the period of reduced activity when the subjects were in the hospital they remained within the vicinity of their beds, but were actually in bed only during normal sleeping periods.

On the study days the subjects attended the laboratory at 8 A.M. after fasting overnight. On day 2 after completing each study period, a 22-gauge butterfly cannula was inserted into a forearm vein of each subject and blood was taken immediately for ambulant measurement of plasma renin activity (PRA), serum electrolytes, blood lipids, hemoglobin, packed cell volume (PCV), and white cell count. The subjects then rested supine and a further sample for determination of PRA was collected 90 min later. An infusion of a tracer dose of tritiated norepinephrine (NE) was commenced in the opposite arm for measurement of spillover and clearance rate at steady-state 90 min later (see below). This was followed by infusions of glucose and insulin for measurement of insulin sensitivity by the glucose-clamp method (see below). In months involving three or seven times per week exercise, a normal bout of exercise was performed after all testing on day 2. Normal sedentary activity was carried out on day 3 after all study periods. Hemodynamic measurements and exercise tests were obtained on the following day (day 4) and again 48 hr after the last bout of exercise. On arrival in the laboratory, the subjects rested for 20 min and then supine measurements of heart rate, blood pressure, cardiac output, and oxygen consumption were made. Hormone measurements at this time included those of prolactin, cortisol, thyroid, and growth hormones. This was followed by a sprint exercise test to determine W_{max} . The subjects rested for 1 hr and then a steady-state exercise test was performed. Heart rate, blood pressure, cardiac output, and oxygen consumption were measured at rest and at the end of each 4 min level of exercise during the steady-state protocol.

Cardiovascular measurements. Before entry into the study,



EXERCISE BOUTS (EX) PERFORMED AFTER 3/WEEK, 7/WEEK ACTIVITY PERIODS ONLY

FIGURE 1. Plan of protocol. At the end of each activity period measurements were performed on 2 test days. After periods of exercise three and seven times per week, exercise was timed so that all measurements were 48 hr after the last bout.

W_{max} was determined during sprint exercise as described previously.¹¹ Briefly, this consisted of consecutive 1 min periods of bicycle exercise commencing at zero workload and increasing by 20 W each minute until any further increase in workload was prevented by fatigue. The steady-state exercise test consisted of consecutive 4 minute periods of exercise performed at rates of 0.25, 0.5, and 0.75 of the W_{max} determined that day.¹¹

Heart rate was measured at rest and during the last minute of each level of exercise by averaging 15 consecutive beats from the electrocardiogram (Avionics Exerstress 3000 recorder). Blood pressure at rest was measured with a random-zero sphygmomanometer (Hawkesley Instruments), with measurements being made after the subjects had completed a 20 min supine rest period and after they stood for 5 min. Results presented are means of three consecutive measurements. During exercise, blood pressure was measured with a standard mercury sphygmomanometer. Cardiac output was measured by the Indirect Fick method, and mixed venous P_{CO₂} by a carbon dioxide rebreathing method described previously.¹² In our laboratory this gives identical results to the thermomodulation method, with a standard error for a single measurement of 6%.¹² Oxygen consumption was measured at the same time by collecting expired gas into a Tissot spirometer and measuring its oxygen content with an infrared analyzer (Servomex, U.K.).

NE kinetics. NE spillover rate, clearance, and plasma concentration were measured under steady-state conditions with the use of the kinetic analysis of Esler.¹³ Tracer doses of tritiated NE (³H-NE) were administered by constant infusion with a Harvard pump. Under steady-state conditions NE spillover rate = (³H]NE infusion rate)/(specific activity of plasma NE); NE clearance = (³H]NE infusion rate)/(plasma [³H]NE concentration). NE spillover rate is the average rate at which NE released from sympathetic activity enters plasma and has been shown in animal experiments to provide a reasonable index of sympathetic activity.¹⁴ The plasma concentration of ³H-NE in these studies is insufficient to alter hemodynamics or interfere with radioenzymatic plasma NE assays and elevation of plasma concentration of unlabeled epinephrine is trivial (2 to 3 pg/ml).

Metabolic measurements. The timing of the assessment of insulin sensitivity in relation to the last episode of physical training was 48 hr because others have shown that the changes in substrate fluxes and in hormonal secretion generally return to preexercise levels within 24 hr.^{15–17} Insulin sensitivity was measured by the euglycemic insulin-clamp technique.¹⁸ The plasma insulin level was raised to about 60 to 70 μ U/ml by a priming constant infusion of monocomponent bovine insulin. The blood glucose concentration was held constant by a variable infusion of 20% glucose, determined from frequent measurements over a period of 2 hr. At steady-state concentration glucose infusion is assumed to equal glucose utilization and to be an index of total body sensitivity to insulin. This is corrected for changes in glucose space and steady-state plasma insulin concentration during the infusion (expressed as mg glucose/kg/min)/insulin concentration [μ U/ml]).

Growth hormone, insulin, cortisol (Amerlex Kit, Amersham, U.K.), PRA activity, and prolactin, tri-iodothyronine, and thyroxine levels were measured by radioimmunoassay.^{19–21}

Statistical methods. Analysis was performed by two-way analysis of variance.²² Standard error of the differences within subjects was obtained from the analysis of variance.²² The null hypothesis was rejected at $p < .05$. Five subjects did not undergo the reduced activity phase of the study. However, the total duration of the study was the same in all 12 subjects since these five were sedentary during the period they were allocated to reduced activity. Comparisons have been made by partitioning of the sums of squares both in the seven subjects who completed all four levels of activity and in all 12 subjects (3 “treatments”).

The results in this subgroup, however, were so similar to those in the total group that the inclusion or exclusion of this group did not alter any of the conclusions with respect to statistical significance.

Results

The efficacy of the Latin-square experimental design was tested by analysis of each variable, measured at the end of each consecutive 4 week period, irrespective of the level of activity in a given individual. There were no significant differences in any of the mean values for the variables over the successive periods. For example, the average values for mean arterial pressure (MAP) over the four periods were, respectively, 84.2, 83.8, 82.8, and 84.6 mm Hg (all ± 2 SEM). This suggests that training effects during periods of increased activity were not carried over into subsequent treatment periods.

Circulatory variables. Reducing the activity schedule below the normal sedentary level in seven subjects had no significant effects on heart rate or any of the hemodynamic variables (figure 2). However, when the level of regular activity was increased by bicycling three and seven times per week, there were significant changes in MAP, cardiac index, total peripheral resistance index (TPRI), and heart rate (figure 2). Both supine systolic and diastolic blood pressures were lowered by regular exercise, falling by 10/7 mm Hg during the three times a week and by 12/7 mm Hg during the seven times per week schedule from the values observed during the sedentary and below-sedentary phases of the study (figure 3; $p < .01$). The fall in blood pressure was significantly greater on the seven times per week schedule than on the three times per week schedule ($p < .05$), but the additional pressure reduction was small. For supine systolic pressure the additional reduction on the seven times per week exercise schedule was only 1.5 ± 0.9 mm Hg. Similarly, the sitting blood pressures were lower at the two highest levels of activity. Again the difference between bicycling three and seven times per week was only slight.

When subjects were bicycling three and seven times per week, the reduction in resting MAP was associated with significant reduction in TPRI by, respectively, 15% (three times per week) and 22% (seven times per week) ($p < .01$). At these levels of activity cardiac index increased by 17% (3 times per week) and 19% (seven times per week) over the values observed during the sedentary and below-sedentary periods ($p < .05$) (figure 2). Because of the reduction in resting heart rate during the periods of bicycling (figure 2), the stroke volume increased by 25% compared with the

level observed during the sedentary or below-sedentary phases of the study ($p < .01$)

Some of the differences in resting values between the bicycling and nonbicycling activity periods were

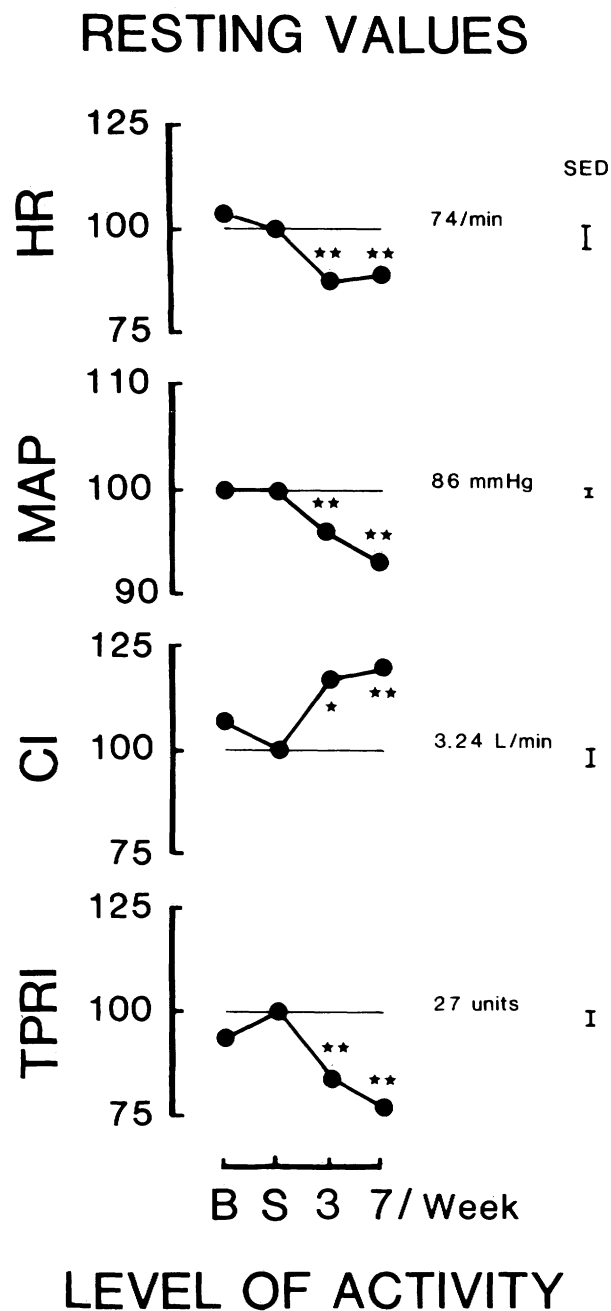


FIGURE 2. Heart rate and hemodynamic measurements at the various levels of activity: B = below sedentary; S = sedentary; 3 = exercise three times per week; 7 = exercise daily. Results are expressed as the percentage of the value of each variable after the sedentary phase (S). The absolute value of each variable after sedentary activity is the numeral to the right of the diagram. HR = heart rate/min; MAP = mean arterial pressure (mm Hg); CI = cardiac index (liters/min/m²); TPRI = total peripheral resistance index (liters/min/m²). SED is the standard error of the difference from the analysis of variance. * $p < .05$ for difference from sedentary values. ** $p < .01$.

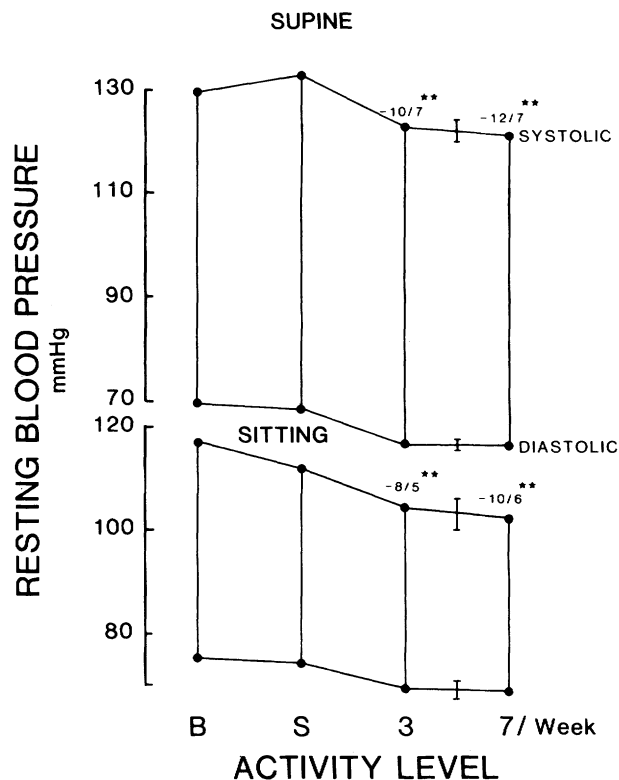


FIGURE 3. Resting blood pressure after below-sedentary activity (B), sedentary activity (S), exercise three times weekly (3) and seven times weekly (7). ** $p < .01$ for difference from sedentary values.

also present during the short-term exercise tests performed at the end of each activity cycle (see Methods). For example, during steady-state exercise performed at a workload of 0.25 Wmax the systolic blood pressure was lower during tests performed at the end of three and seven times a week bicycling periods than during the periods of lower activity (figure 4; $p < .05$). There was a similar trend during short-term exercise performed at 0.5 and 0.75 Wmax, but the difference did not reach statistical significance ($.1 > p > .05$). With both heart rate and cardiac index the original resting differences between the two bicycling and non-bicycling periods of the study were maintained at all workloads of the short-term exercise tests, i.e., heart rate remained significantly lower and cardiac index higher during the two activity periods (figure 4).

Sympathetic function. Values of NE spillover rate during the sedentary part of the study averaged $0.3 \pm 0.05 \mu\text{g}/\text{min}/\text{m}^2$, similar to values previously observed in other sedentary normal individuals.¹³ This was not altered significantly during the period of below-sedentary activity. During the period of bicycling seven times per week the response of the group was not uniform (figure 5). In 10 of 12 subjects NE spillover rate was significantly reduced, falling from $0.34 \pm$

0.06 $\mu\text{g}/\text{min}/\text{m}^2$ (sedentary) to $0.12 \pm 0.01 \mu\text{g}/\text{min}/\text{m}^2$ (figure 5, left; SED = 0.05, $p < .01$). In these subjects NE spillover rates were not significantly different during the 3 times a week bicycling from those during the more sedentary phases of the study.

In these 10 subjects plasma NE concentrations were markedly lowered during the seven times per week bicycling period (to $126.3 \pm 11 \text{ pg}/\text{ml}$) compared with those during sedentary activity $261 \pm 35 \text{ pg}/\text{ml}$). During the three times per week bicycling period there was only slight reduction to $229 \pm 25 \text{ pg}/\text{ml}$ (NS from sedentary level). Plasma epinephrine was not altered from the value observed during the sedentary phase of the study at either of these levels of regular exercise.

In the two other subjects studied NE spillover rate

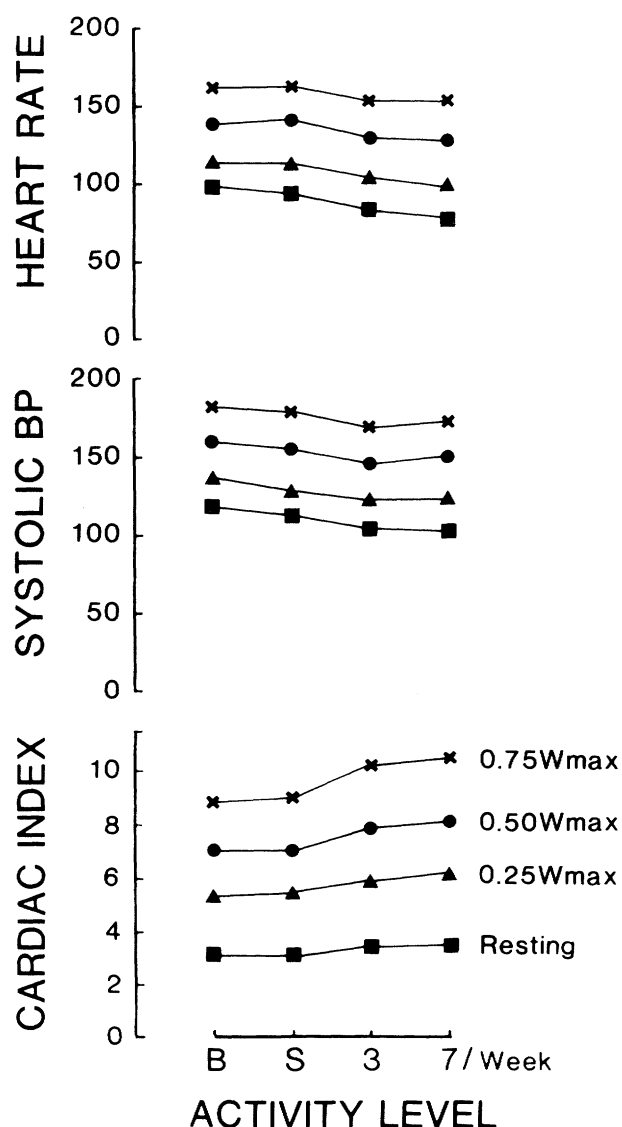


FIGURE 4. Measurements at rest and during the steady-state exercise test (■), 0.25 Wmax (▲), and 0.75 Wmax (×). Wmax was determined at the end of each study period. For significance levels see text.

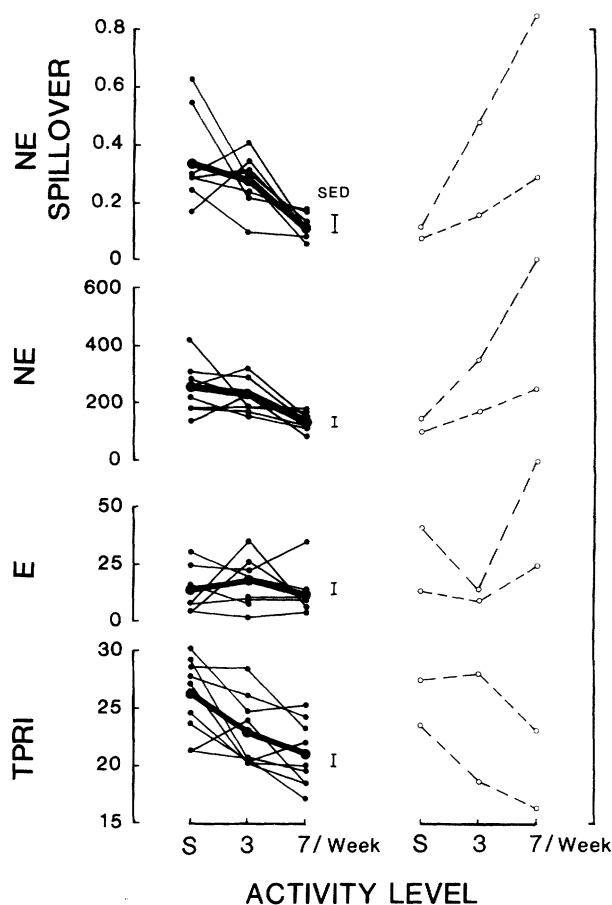


FIGURE 5. Changes in NE spillover rate ($\mu\text{g}/\text{min}/\text{m}^2$), plasma NE (pg/ml), epinephrine (E) (pg/ml), and TPRI in eight subjects in whom indexes of sympathetic activity fell with increased activity (left) and in two subjects in whom these indexes rose (right, broken lines). TPRI fell in both groups. For clarity, the results after reduced activity have been omitted since these were closely similar to the corresponding sedentary values.

and NE and epinephrine plasma concentrations all increased during the period of seven times per week regular exercise (figure 5, right). However, the highest levels of regular activity were still associated with lower blood pressures and TPRI values than those during the sedentary phase of the study. Thus, the hemodynamic responses of all 10 subjects were more uniform than the sympathetic responses (see Discussion).

Hormone measurements. When the results from all subjects were examined, there were no significant differences in supine PRA during the various phases (table 1). However, these results follow a similar pattern to those for NE spillover: When the two subjects who showed a rise in NE spillover rate were excluded, the average fall in supine PRA from 1.12 ng/ml/hr during the sedentary period to 0.61 and 0.85 ng/ml/hr after 3 times weekly and daily exercise were both significant ($p < .05$). Measurements of ambulant PRA also fol-

TABLE 1
Hormonal measurements

	Below-sedentary activity	Sedentary activity	Exercise		SED ^A
			3/week	7/week	
PRA (ng/ml/hr)					
Supine 90 min					
n = 7 ^B	0.87	0.87	0.65	0.78	0.19
n = 12		0.97	0.61	0.8	0.15
Ambulant					
n = 7	2.09	1.9	0.91	1.09	0.57
n = 12		1.6	0.92	1.14	0.3
Cortisol (nmol/l) at 8:30 A.M.					
n = 7	532	543	608	605	59
n = 12		575	583	575	59
Prolactin (mU/l)					
n = 7	150	133	153	122	18
n = 12		127	149	131	18
Growth hormone (ng/ml)					
n = 7	0.95	1.84	0.94	1.44	0.6
n = 12		2.0	1.2	1.8	1.4
Tri-iodothyronine (nmol/l)					
n = 7	1.83	1.90	2.14	1.96	0.09
n = 12		1.93	2.03	1.92	0.08
Thyroxine (nmol/l)					
n = 7		97	97	90	3.6
n = 12	99.3	100	102	94	4.2
Free thyroid index					
n = 7	111	108	106	103	4.0
n = 12		102	100	100	3.2

^ASED is the standard error of the difference between any two columns from the analysis of variance.

^Bn = 7 are the average results for the seven subjects who completed all four activity periods. n = 12 are the results when the five subjects who did not perform the reduced activity periods are included.

lowed a similar pattern, being similar after reduced and sedentary activities, but falling by 52% and 43% after 3 times daily and daily exercise, respectively, in this subgroup of 10 subjects (both $p < .05$).

No significant changes were noted in any of the other hormonal measurements between the various levels of activity. These included serum thyroxine and tri-iodothyronine, thyroid binding index, morning and afternoon levels of cortisol, and resting levels of prolactin and growth hormone (table 1).

Metabolic measurements. Resting insulin sensitivity was determined at the end of each activity schedule after the measurement of NE spillover rate. Since the steady-state insulin concentrations during the insulin infusions were not identical at all four levels of activity (table 2), we expressed insulin sensitivity as the mass of glucose used (mg/kg/min/ μ U/ml) divided by plasma insulin concentration (μ U/ml). During the four activity levels insulin sensitivity was lowest during the below-sedentary period (8.6 mg/kg/min/ μ U/ml), was significantly higher during the sedentary phase (11.9

mg/kg/min), and was still higher during the period of bicycling three times per week (16.4 mg/kg/min/ μ U/ml; p for both $< .05$). However, during the period of bicycling seven times per week the insulin sensitivity again declined to 12.6 mg/kg/min/ μ U/ml ($p < .01$), i.e., close to the value during the sedentary phase of the study (figure 6).

Results of the short-term exercise tests during the two more active periods showed that the maximum oxygen consumption and W_{max} were significantly higher than those during the sedentary and below-sedentary periods of activity (figure 6). Thus, W_{max} was 12.5% and 23% higher in subjects bicycling three and seven times per week, respectively, compared with the average values during sedentary and below-sedentary activity. Corresponding increases in maximum oxygen consumption above sedentary values, which averaged 31.9 ml/kg/min, were, respectively, 11% and 24%.

Cholesterol and triglycerides. Fasting plasma cholesterol, which was 4.81 mmol/liter after the sedentary period, fell by 0.05 mmol/liter (NS) after three times

TABLE 2
Glucose utilization

	Reduced activity	Sedentary	Exercise 3/week	Exercise daily	SED
Fasting glucose (mmol/l)					
n = 7	4.7	4.8	4.6	4.9	0.1
n = 12		4.8	4.7	4.9	0.1
Fasting insulin (μ U/ml)					
n = 7	10	10	9	6	2
n = 12		11	10	7	2
Clamp insulin (μ U/ml)					
n = 7	76 ^A	56	55	62	4
n = 12		56	55	63	4
Insulin sensitivity (mg glucose/kg/min μ U insulin/ml)					
n = 7	8.6 ^A	11.9	16.4 ^A	12.6	2.1
n = 12		12	16.6 ^A	12.0	2.2
Body weight (kg)					
n = 7	62.6	62.0	62.3	62.3	0.4
n = 12		62.6	62.7	62.8	0.3

^Ap < .05 for differences from corresponding sedentary value.

per week exercise and by 0.50 mmol/liter after daily exercise ($p < .001$) (figure 6). High-density lipoprotein cholesterol averaged 1.44 mmol/liter in these subjects during the sedentary phase and did not change significantly at the different levels of activity. Levels of plasma triglyceride also remained fairly constant throughout the study, with none of the small changes being statistically significant (table 3).

Other measurements. Analysis of 3 day food intake during each phase of the study showed no evidence of qualitative changes in eating patterns or alcohol consumption. Body weight was not significantly different at the end of each of the four phases and the averages differed by less than 1 kg (table 2). Urinary sodium excretion averaged 146 mmol/day during the sedentary period and did not change significantly after the other

levels of activity. There was a fall in hemoglobin and PCV at the two higher activity levels from 15.6 g/dl in the sedentary period to 14.6 and 14.5 g/dl after exercise three and seven times per week ($p < .05$). This could be accounted for by hemodilution since PCVs corresponding to the above were 0.46, 0.44, and 0.42, respectively ($p < .005$). A similar pattern was also observed in total leucocyte count and neutrophil count, which were significantly reduced at the two higher levels of activity. No consistent changes were observed in the serum levels of sodium, potassium, chloride, creatinine, or in blood urea or urate. There was a fall in serum calcium from 2.41 to 2.32 mmol/liter from the sedentary to the three times per week exercise period ($p < .01$); this decrease appeared to be unrelated to any alteration in albumin concentration.

TABLE 3
Lipids

	Reduced activity	Sedentary	Exercise 3/week	Exercise daily	SED
Total plasma cholesterol (mmol/l)					
n = 7	5.09	4.81	4.76	4.31 ^A	0.15
n = 12		4.89	4.77	4.41 ^A	0.18
Plasma HDL cholesterol (mmol/l)					
n = 7	1.36	1.44	1.34	1.41	0.08
n = 12		1.53	1.45	1.5	0.06
Plasma triglyceride (mmol/l)					
n = 7	1.17	1.04	1.14	1.23	0.15
n = 12		1.18	1.08	1.1	0.15

HDL = high-density lipoprotein.

^Ap < .05 for differences from corresponding sedentary values.

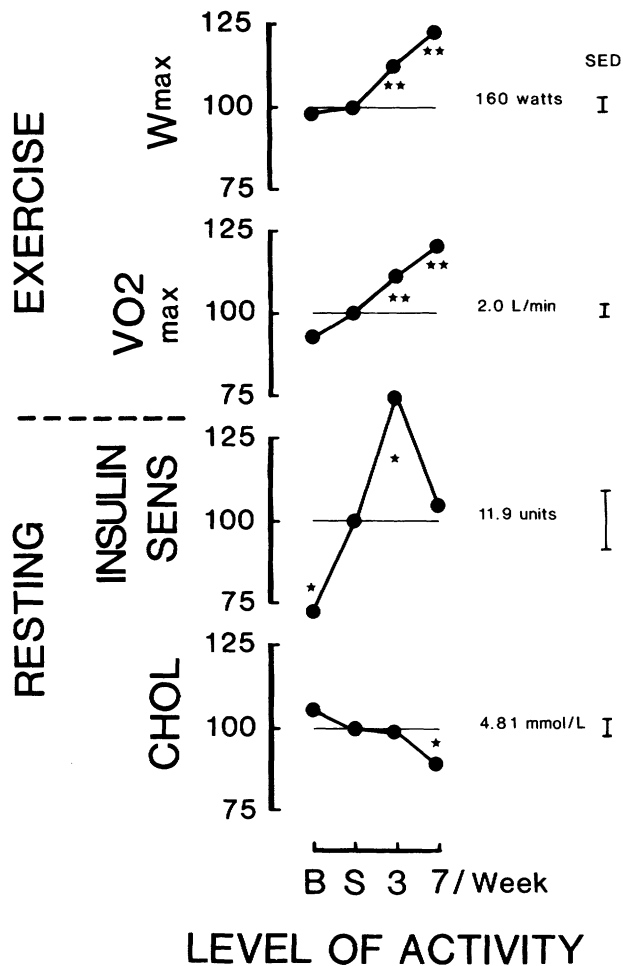


FIGURE 6. Changes in W_{max} and oxygen uptake (VO₂max) at the various levels of activity during exercise and in insulin sensitivity and total cholesterol measured at rest. Results are expressed as percentage of the sedentary value, S, shown as the numeral to the right of each diagram. SED is the standard error of the difference. * p < .05. ** p < .01 for difference from sedentary value.

Discussion

Our results have provided clear evidence that a program of regular moderate exercise lowers resting MAP by 8 to 10 mm Hg in habitually sedentary subjects, due to the associated lowering of TPR. The major part of the changes was observed with bicycling at the rate of three times per week and there was only slight additional reduction in pressure when this was increased to seven times per week. The lower blood pressures observed at rest tended to be maintained during short-term exercise (figure 4). Associated changes in autonomic function included cardiac slowing and reduction in resting NE spillover rate and plasma concentration. On the metabolic side we observed a linear relationship between resting insulin sensitivity and activity from the below-sedentary to the three times per week bicycling levels, but with bicycling seven times a week

insulin sensitivity declined. Although doubling the activity schedule still produced some cardiovascular benefit — for example, lowering of blood pressure and plasma cholesterol — this may have been at some metabolic cost in the form of reduced glucose tolerance.

Our subjects showed no change in body weight or significant changes in urinary sodium excretion, suggesting that the observed changes were not due to dietary factors. The use of the Latin-square experimental design appeared to have eliminated bias due to factors such as training and there was no evidence of alterations in other environmental factors. Thus, it seems reasonable to attribute the observed changes to alterations in the level of regular activity during each 4 week period. This was supported by the close similarity of various initial baseline measurements made in all of the subjects to corresponding measurements made during the sedentary period of the study.

The different measurements were made starting 48 hr after the last bout of exercise to eliminate any contribution of the short-term effects of exercise. This appears to have been a sufficient interval since resting oxygen consumptions were closely similar during all four study periods. It seems reasonable to attribute the various changes in circulatory and metabolic variables to characteristic long-term effects associated with each pattern of regular activity.

It seems likely that at least two factors contributed to the exercise-related reduction in resting TPRI and blood pressure: (1) an increase in the cross-sectional area of the vascular beds, particularly that affecting skeletal muscle, and (2) alterations in some of the extrinsic determinants of vessel caliber, such as sympathetic activity or circulating hormones. The first would be in accord with results obtained during training²³ and may have contributed to the increases we observed in maximum oxygen consumption and W_{max} during the short-term exercise tests. It could also have contributed, together with some rise in blood volume suggested by hemodilution, to the enhanced cardiac output during the regular exercise phases of the study by reducing cardiac afterload. Of the extrinsic factors that can alter vessel caliber, we measured resting NE spillover rate and PRA. Our findings suggest that reduction in sympathetic and renin-angiotensin system activity probably contributed to the falls in TPRI and blood pressure during increased activity.

Resting NE spillover rate provides a measure of average sympathetic neural activity.^{13, 24} It was greatly reduced in 10 or 12 subjects during the seven times a week bicycling period. The magnitude of the reduction

in NE spillover rate and plasma concentration from their values during sedentary activity was similar to the changes observed with therapeutic doses of clonidine, which greatly reduces sympathetic nerve activity.¹³ After bicycling seven times per week the observed reduction in sympathetic activity was certainly sufficient to produce significant lowering of TPRI, and reduction in renin-angiotensin system activity could have added to this effect. In this subset of normal subjects the changes in sympathetic activity and renin levels were more variable after three times per week bicycling (figure 4) and did not reach statistical significance, even though the fall in blood pressure and TPRI was quite definite.

Clearly the relationship between average sympathetic activity and hemodynamic changes is not a simple one. The sympathetic nervous system is not a system for uniform mass action, but various stimuli elicit characteristic differentiated patterns of neural activity, and hemodynamic changes can cause increase in some outflows and decrease in others.²⁵ Hence, measurement of average NE spillover rate is not as informative as measurement of NE spillover rate to individual organs.²⁶ The latter measurements are not practicable in long-term investigations of normal individuals. Average NE spillover rate is most affected by the spillover rate from the lungs, muscle, and skin, and less affected by the spillover from gut (because of NE extraction by the liver) or from the kidney and heart (because of their small bulk).^{24, 26} However, from the viewpoint of blood pressure regulation it is the reduction in sympathetic activity in the last three organs that probably contributes most of the fall in blood pressure and vascular resistance. It is possible that despite the more variable change in NE spillover after bicycling three times per week, spillover could have been reduced in one of the beds most critical from the viewpoint of the hemodynamic changes. Such nonuniformity of sympathetic discharge cannot be excluded in the two subjects in whom NE spillover rate increased, while blood pressure and TPRI decreased. Some differentiation in sympathetic patterns was present in all subjects in whom epinephrine levels (indicative of adrenal medullary secretion) did not change, while NE spillover rate (indicative of sympathetic neural activity) was altered significantly (figure 4). Although reduction in heart rate at rest has a considerable vagal component at maximum exercise, heart rate is almost entirely influenced by the cardiac sympathetics.¹¹ Some reduction in sympathetic component is suggested by the maintenance of the cardiac slowing effect of training during near-maximum steady-state exercise.

Our findings on reduced insulin sensitivity during the below-sedentary period of the study are in accord with previous findings by others of a decrease in glucose tolerance, as are our findings of an increased sensitivity during the three times per week bicycling period.^{27, 29} The increase in glucose utilization with exercise,²⁹ which is enhanced after training, occurs despite a fall in insulin secretion, suggesting factors in addition to insulin action,²⁹ but has been correlated with increased insulin binding to circulating monocytes.²⁸ We were not able to confirm previous findings "between subjects" that improved glucose utilization with physical training is correlated with changes in maximum oxygen consumption²⁷ since, despite a further 10% increase in maximum oxygen consumption when activity was increased from three times per week exercise, there was a fall in insulin sensitivity. This paradoxical fall with increased activity, which suggests some impairment in carbohydrate metabolism, could not be related to hormones that oppose insulin actions such as epinephrine or cortisol, and occurred despite an apparent reduction in sympathetic tone. An increase in growth hormone levels might account for the fall in insulin sensitivity, but the average 50% increase in growth hormone between exercise three times per week and seven times per week did not achieve significance. We do not know whether insulin sensitivity would subsequently have improved if the period of daily exercise had continued for more than 4 weeks, but our findings suggest that the optimum amount of regular exercise may be somewhere between three and seven times per week and that there should be some rest days.

A further beneficial effect of increased physical activity was a fall in total plasma cholesterol. However, no changes were observed in the concentrations of plasma triglyceride or in high-density lipoprotein cholesterol. In cross-sectional studies such as the Coronary Primary Prevention Trial, physical activity has been found significantly predictive of triglyceride and high-density lipoprotein cholesterol levels.^{30, 31} However, recent studies have emphasized the multifactorial effect on high-density lipoprotein cholesterol and changes in body fat and in dietary habits are at least as important as the degree of fitness.^{32, 34} Our subjects were lean, did not change weight, and had high baseline high-density lipoprotein cholesterol levels. Whereas exercise training may account for differences in high-density lipoprotein cholesterol in active and inactive men, other factors are more likely to be responsible for these differences among similarly active men.³⁵

In conclusion, increased physical activity in young sedentary normal subjects has effects that should reduce the possibility of subsequent development of cardiovascular disease. These include a clinically significant fall in resting blood pressure associated with a fall in peripheral resistance and an increase in cardiac output. These changes may have been due to reduced sympathetic activity, somewhat analogous to the effects of centrally acting antihypertensive drugs. The reduction in blood pressure is similar to that seen after β -adrenoceptor antagonists or other antihypertensive drugs and also occurs in patients with essential hypertension.³⁶ It is greater than that usually associated with dietary measures such as salt restriction or vegetarian diets.³⁷ Increase in ventricular fibrillation threshold may be another benefit of exercise associated with cardiac slowing and reduced sympathetic activity.³⁸ However, with excessive slowing of the heart there may be the opportunity for additional ventricular ectopic activity, albeit not repetitive. Other beneficial effects were enhanced glucose utilization during insulin infusion, but only after exercise three times per week.

Epidemiologic studies have suggested that even minor impairment of glucose tolerance may increase risk for cardiovascular disease.³⁹ There was also a significant fall in plasma cholesterol levels. Our findings were in young, lean, sedentary, normotensive subjects and are therefore relevant to the possible prevention of cardiovascular disease. They were studied after 4 weeks at each level of activity. There is no reason to expect that similar mechanisms would not occur with more protracted comparable activity, or in older subjects. Similar studies, especially in hypertensive subjects, would be of particular interest. The results show that 30 min of bicycle exercise at 60% to 70% of W_{max} three times weekly is sufficient for most of the beneficial hemodynamic and metabolic effects to occur. An increase in frequency to daily exercise improved physical performance, but had little or no additional beneficial effects on blood pressure or glucose utilization.

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Erratum

Vanhoutte PM, Houston DS: Platelets, endothelium, and vasospasm. *Circulation* **72**: 728, 1985

In the above article, figure 10 was reproduced without the bottom panel. The correct figure appears below.

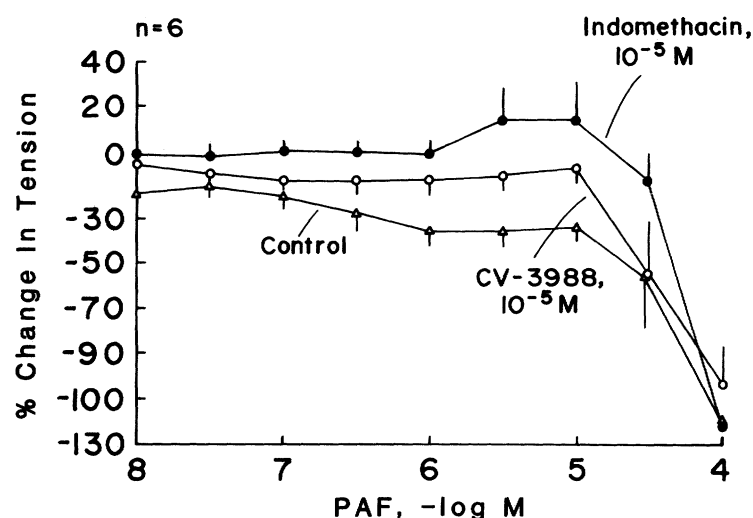
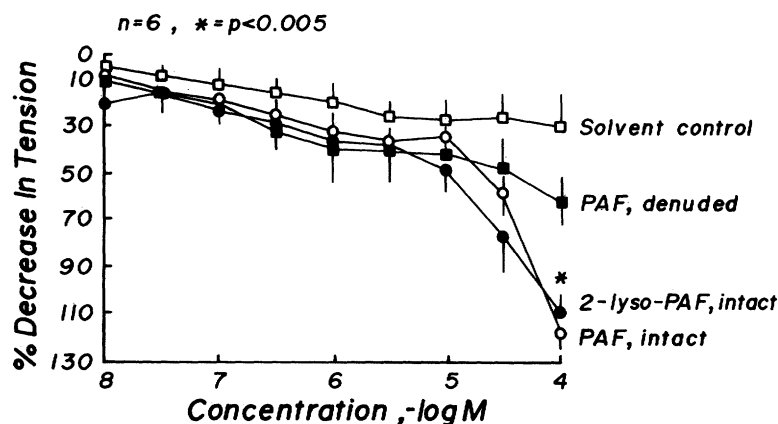


FIGURE 10. Concentration-effect curves in canine coronary artery, with and without endothelium, contracted with prostaglandin $F_{2\alpha}$ ($\text{PGF}_{2\alpha}$; $2 \times 10^{-6}\text{M}$) in response to cumulative additions of platelet-activating factor (PAF) and its 2-lyso derivative (2-lyso-PAF) and the ethanol solvent used. Changes in tension are expressed as percent of contraction obtained with $\text{PGE}_{2\alpha}$. Relaxation induced by PAF and 2-lyso-PAF occurs in rings with intact endothelium above 10^{-5}M ; this effect is endothelium dependent (**p* < .005 comparing responses of intact and denuded vessels to 10^{-4}M PAF) (top). The lack of a difference between responses to PAF and 2-lyso-PAF suggests that this relaxation is not a specific, receptor-mediated effect of PAF. Further evidence in support of this interpretation is the lack of effect of the PAF antagonist CV-3988 on the endothelium-dependent response to high concentrations of PAF (bottom). The lack of effect of indomethacin on this response (bottom) shows that production of prostacyclin by the endothelium is not responsible for the relaxation induced by PAF.