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THE EFFECT OF PERINDOPRIL, A NEW ANGIOTENSIN CONVERTING ENZYME INHIBITOR ON THE HORMONAL RESPONSE TO BRISK EXERCISE IN HEALTHY SUBJECTS

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A dissertation submitted to the Faculty of Medicine,
University of the Witwatersrand, Johannesburg,
for the Degree of Master of Medicine

Johannesburg 1994

****

To my parents, Benny and Sylvia and my wife, Barbara.

****

DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.



3·1·1995

E.Q.KLUG DATE

The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand.

(Protocol No: 13/7/91).

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ABSTRACT

Cardiovascular drugs have varying effects on haemodynamic, metabolic, and hormonal responses to exercise. Angiotensin-converting enzyme inhibitors (ACEI) have been used for the treatment of systemic hypertension, left ventricular dysfunction with or without congestive heart failure, and increasingly, for occlusive coronary artery disease and its complications. Physical training has been shown to improve exercise performance in patients with coronary artery disease, to reduce blood pressure in hypertensive patients and increase aerobic capacity and improve symptoms in patients with heart failure.

The possible interactions between prescribed drugs (ACEI in this study) and physical exercise is clinically relevant. To evaluate the effects of the novel angiotensin converting enzyme inhibitor, perindopril, on these exercise-related responses, 9 healthy volunteers were enrolled in a double blind, randomised, placebo controlled study. After a week of perindopril 4 mg orally daily or placebo therapy, volunteers performed a treadmill effort test; the sequence was repeated after a 1 week washout period.

Perindopril caused a significant reduction in mean resting systolic and diastolic blood pressure (SBP, DBP) without increasing resting heart rate; 15-min post exercise SBP was also significantly reduced. There were no significant differences between the perindopril and placebo effort tests with respect to metabolic indices studied (serum potassium, plasma glucose, and free fatty acids) or plasma hormonal concentrations measured (ACTH and cortisol, noradrenaline and

adrenaline, glucagon and insulin, growth hormone and prolactin and plasma renin activity).

These data show that perindopril does not impair the physiological changes associated with exercise in healthy subjects. Although these findings are reassuring, they should not be extended to the various clinical conditions for which perindopril may be indicated because different haemodynamic and metabolic circumstances may prevail.

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LIST OF ABBREVIATIONS

ACE	-	angiotensin-converting enzyme
ACEI	-	angiotensin-converting enzyme inhibitors
ACTH	-	adrenocorticotropin hormone
ATP	-	adenosine triphosphate
BP	-	blood pressure
CP	-	creatine phosphate
DBP	-	diastolic blood pressure
FFA	-	free fatty acids
GFR	-	glomerular filtration rate
GH	-	growth hormone
HR	-	heart rate
K^+	-	potassium
MAP	-	mean arterial pressure

Na^+	-	sodium
pRA	-	plasma renin activity
RA	-	renin-angiotensin
SBP	-	systolic blood pressure
SEM	-	standard error of the mean
VO_{2max}	-	maximal oxygen uptake

NORMAL LABORATORY REFERENCE VALUES

BLOOD

Sodium		135-147	mmol/l
Potassium		3.3-5.0	mmol/l
Free Fatty Acids		315-1210	umol/l
Glucose		3.4-7.2	mmol/l
ACTH		10-90	ng/l
Cortisol	8 am	60-230	ug/l
	4 pm	10-85	
Noradrenaline		120-360	ng/l
Adrenaline		23-53	ng/l
Insulin		5-25	mU/l
Glucagon		50-250	ng/l
Growth Hormone		0-5	ug/l
Prolactin	Men	0-9	ug/l

URINE

Sodium		60-200	mmol/l

PART 1

CARDIOVASCULAR AND HAEMODYNAMIC

RESPONSES TO BRISK EXERCISE IN NORMAL SUBJECTS

1.1 INTRODUCTION

It has been long recognised that the cardiorespiratory system plays a critical role in the physiologic responses to exercise. Vigorous exercise is associated with a marked increase in energy metabolism in active skeletal muscle. This increased metabolic activity can be sustained only if the muscles are provided with metabolic substrates and cleared of metabolic end products at rates that match their rates of utilisation and production respectively. Because the cardiorespiratory system is the only supply line for muscle tissue, sustained, vigorous exercise clearly necessitates marked alterations in cardiorespiratory function (1). At rest the heart pumps 4 - 6 liters of blood into the arteries of a healthy college student each minute. This can be increased to approximately 22 liters/min in normal young men (2). The onset of dynamic exercise produces reflex changes in efferent autonomic activity that increase heart rate, cardiac output, vascular resistance, and arterial pressure (3). Multiple regulatory systems serve to modulate the circulatory response to exercise. Acting through cortical and spinal cord motor systems, "central command" could serve to set basic patterns of effector activity, which in turn are modulated by baroreceptors, muscle mechanoreceptors, and muscle chemoreceptors, as error signals may develop (4).

1.2. HEART RATE (HR) RESPONSE

HR, a major determinant of cardiac output is controlled by neural, hormonal and intrinsic factors. Of these general control mechanisms, the control of heart rate by the nervous system is the most important. A strong positive correlation exists between HR and oxygen consumption. Both variables increase linearly with increasing intensity of exercise. The increased cardiac output that accompanies exercise is due to increases in both HR and stroke volume (2).

a) Neural factors in HR control

The inherent rhythm of the heart, as established by its sinoatrial node, is regulated primarily by sympathetic and parasympathetic neurons emanating from the cardioregulatory center of the medulla. The sympathetic nerves release noradrenaline and cause an increase in HR during exercise. Under resting conditions the parasympathetic vagus nerve influence is dominant over sympathetic influences. During exercise this relationship is reversed, and HR consequently increases over its resting level (1).

HR often rises in anticipation of exercise. This pre-exercise increase is controlled by the limbic system, a regulatory center situated in the basal area of the brain surrounding the hypothalamus. At the beginning of exercise, HR increases almost instantaneously (1). The mechanism for this rapid response is not well understood.

It used to be thought that the onset of dynamic exercise produced generalised, uniform activation of sympathetic vasoconstrictor outflow

as well as tachycardia, and that central command and muscle afferent reflexes are redundant control mechanisms that produce comparable autonomic effects (3). It now appears that the central command initiates parasympathetic withdrawal and tachycardia at the onset of exercise, whereas muscle chemoreflex activation is important in producing parallel activation of sympathetic outflow to the non exercising skeletal muscles and the heart (sinus node) during dynamic exercise. Most of the increase in HR during exercise is therefore caused by vagal inhibition mediated centrally rather than by muscle chemoreflexes; there is increased accelerator nerve activity during exercise, but it is less significant overall than decreased vagal activity (2,3).

Muscle chemoreceptors: As muscles contract, potassium (K^+), lactic acid, and a number of other metabolites leave the intracellular space and accumulate in the tissue fluid. It is thought that K^+ leakage from muscle cells may stimulate free nerve endings that then transmit signals to the cardiac control centers of the brain to increase HR (2).

Arterial chemoreceptors: There is no firm evidence that arterial chemoreceptors play a significant role in the increased HR that occurs during exercise (2).

b) Hormonal factors in HR control

Circulating catecholamines, released by the adrenal gland, can increase heart rate. They may play a more important role in prolonged exercise.

c) Intrinsic factors in HR control

Temperature, stretch of the heart chambers and electrolyte balance operate directly on the heart without the intervention of the nervous system or hormones. This is suggested by the fact that even when the nerves to the heart are blocked chemically or surgically, the heart still beats faster in response to exercise. Increased stretch of the right atrium because of augmented venous return results in increased firing of the sinoatrial node. Increased temperature increases the speed with which action potentials can be initiated in the heart (2).

1.3 BLOOD PRESSURE (BP) RESPONSE

1.3.1 MEAN ARTERIAL PRESSURE (MAP) RESPONSE

$$MAP = DIASTOLIC\ PRESSURE + \frac{(SYSTOLIC - DIASTOLIC\ PRESSURE)}{3}$$

Normal resting MAP is in the range of 90-100 mmHg. Exercise MAP rises steadily with increasing work rate. Maximal exercise MAP values approximate 130 mmHg. During exercise, the systolic time interval comprises a progressively larger proportion of the cardiac cycle, therefore this equation may provide a less accurate estimation of MAP (1). The mechanisms responsible for increases in MAP during exercise appear to differ depending upon the intensity of the exercise and the presence or absence of muscle ischaemia (3).

1.3.2 SYSTOLIC BLOOD PRESSURE (SBP) RESPONSE

SBP increases with exercise, but the magnitude of this response is specific to the type of exercise performed (1). SBP increases in proportion to oxygen consumption and cardiac output during graded exercise.

During dynamic, low resistance exercise (jogging, swimming, cycling), SBP increases in proportion to exercise intensity. This overall response is the result of 2 countervailing effects of acute dynamic exercise. BP is reduced by vasodilatation in active muscles but this is more than offset by increased cardiac output, which increases linearly with work rate. Thus, the exercise-induced increase in SBP reflects an increase in cardiac output, the effect of which is partially offset by reduced peripheral resistance (5).

At the same relative work load, systolic pressures are approximately 15% higher when work is performed with the arms than with the legs, probably related to the smaller muscle mass of the arms, which offers greater resistance to blood flow (1). Exercise activities that involve forceful isometric, isotonic, or isokinetic muscle contraction cause marked increases in SBP.

1.3.3 DIASTOLIC BLOOD PRESSURE (DBP) RESPONSE

DBP provides an indication of peripheral resistance. Dynamic, low resistance exercise usually causes a slight rise or no change in DBP. Investigators report higher diastolic blood pressure for arm work (1,2).

Blood vessels in the liver, the kidney, the digestive organs, and perhaps other tissues are relatively constricted during exercise. Increased blood flow to active skeletal muscle is primarily caused by relaxation of the smooth muscle cells in the arterioles and precapillary sphincters. This involves the extrinsic autonomic nervous system, the intrinsic arteriolar nerves and accumulation of chemical factors, (K^+, adenosine, lactic acid, and phosphate). As a response to this vasodilatation, blood vessels in visceral organs and skin constrict to maintain peripheral haemodynamics (2).

It seems therefore that the greatest increase in exercise blood pressure is observed during cardiac systole whereas the diastolic pressure increases by only about 12% during the full range of exercise. This response is similar for both physically conditioned and sedentary subjects. Following exercise, MBP falls below pre-exercise levels, and may remain lower for several hours (5).

1.4 RENAL FUNCTION RESPONSE

Renal function during exercise has been studied extensively in man and animals. Renal plasma flow decreases during exercise and its degree is related to the work intensity (6). Moderate exercise, corresponding to about half of the aerobic work capacity, results in a reduction of the renal plasma flow of about 30%. During strenuous exercise the blood flow to the kidney may fall considerably, approximately 55 - 65% and it has been suggested by even as much as

75%. During heavy work, 700-900 ml blood/min may be shunted from the kidney to active muscles (7).

The glomerular filtration rate (GFR) decreases relatively less than renal plasma flow during exercise. The filtration fraction increases during exercise. Probably the afferent glomerular artery constriction is balanced by a constriction of the efferent artery. Urine flow is usually decreased during exercise. Sodium (Na^+) excretion decreases during exercise and this is not related to a decrease in GFR. This indicates that tubular reabsorption of Na^+ is increased during exercise (6).

PART 2

THE METABOLIC RESPONSES TO BRISK EXERCISE IN NORMAL SUBJECTS

2.1 INTRODUCTION

Almost all changes occurring in the body during exercise are related to the increase in energy metabolism within the contracting skeletal muscle. During exercise the total energy expenditure is increased, with most of the increase being used to provide energy for exercising muscles that may increase their energy utilisation by a factor of 200 over resting levels (1).

The high energy compound adenosine triphosphate (ATP), powers the exercising muscle. The amount of ATP in muscle at any time is small, thus it must be resynthesised continuously if exercise continues for more than a few seconds. Muscle ATP is generated via 3 pathways:

1. creatine phosphate (CP) system

A rapid anaerobic reaction limited by finite quantities of creatine in cells.

2. glycolysis

An anaerobic pathway, although pyruvate can participate in aerobic metabolism if oxygen is available to the cell.

3. aerobic oxidation

Involves oxidative phosphorylation in the mitochondria using fat, protein or carbohydrate as substrate to produce ATP.

Although one often differentiates between aerobic and anaerobic exercise, in reality, the energy necessary to perform most types of exercise comes from a combination of anaerobic/aerobic sources. The shorter the activity the greater the contribution of anaerobic energy production. The bulk of the energy needed for physical activity lasting more than approximately 3 minutes is provided by aerobic (oxidative) metabolism. Carbohydrates and fats are the primary energy substrates during exercise in a healthy, well fed individual (8).

Relative utilisation of carbohydrate and fat varies with exercise intensity. In general, carbohydrates are used as the primary fuel at the onset of exercise and during high intensity work. With exercise lasting longer than 30 minutes, there is a gradual shift toward fat metabolism. Exercise bouts lasting longer than 45 seconds use a combination of the CP system, glycolysis, and oxidative phosphorylation. During sustained sub-maximal exercise a mixture of fat and carbohydrate is used whereas with prolonged exercise the percentage fat utilised tends to increase gradually over time (8).

2.1.1 PLASMA GLUCOSE RESPONSE

Studies have emphasized the importance of the body's carbohydrate stores in substrate turnover during physical exercise in man. Muscle glycogen is utilised during exercise: the glycogen content of muscle gradually falls during prolonged exercise and its rate of utilisation is related to the severity of the work performed (9). Moreover, blood glucose is a quantitatively important fuel for muscle oxidation during most forms of exercise and a 3-5 fold increase in hepatic production of

glucose (10), primarily by means of augmented glycogenolysis in the face of increased peripheral glucose utilisation, contributes to blood glucose homeostasis in exercise. During exercise, glucose production is augmented from the splanchnic bed. Increased release of alanine during exercise together with the existence of the glucose-alanine gluconeogenic cycle, help maintain the glucose homeostasis during exercise. It was found that at the conclusion of exercise a rapid fall in splanchnic glucose output was exceeded by the diminution in peripheral glucose consumption thereby resulting in a small increase in arterial blood glucose concentration. The reduction in hepatic glucose release correlated with a 2-3 fold increment in arterial insulin levels seen during the initial 5 minutes of the recovery period, due probably to the decreased alpha inhibitory effects of noradrenaline (9).

Plasma glucose response also depends on the competitive nature of the exercise. It was shown in a study (11), that in healthy male individuals playing basketball (i.e. a competitive sport, no food intake 4 hours prior), their blood glucose levels showed a statistically significant but small mean rise during the game 91 ± 4 to 114 ± 7 mg%. In a similar group running on a treadmill (non competitive) for 15 minutes at 3 miles per hour at an incline of 11 degrees, the same study found that plasma glucose varied little from initial fasting levels (10 hour pre exercise fast).

2.1.2 PLASMA FREE FATTY ACID (FFA) RESPONSE

The fatty acids that are utilised for energy by contracting muscles are derived from (2):

1. triglyceride stored in the muscles,
2. triglyceride stored in fatty deposits throughout the body, and
3. triglyceride or FFA circulating in the blood stream.

There are 2 different types of responses seen in plasma FFA turnover and concentration following exercise. The enzymes (lipases) responsible for splitting FFA from triglyceride molecules are activated by hormonal changes that accompany prolonged, vigorous exercise. During brief, heavy exercise the plasma FFA levels rapidly decrease in man (12). This decrease during brief heavy exercise probably reflects an initial utilisation of the substrate before mobilisation from adipose tissue triglycerides has begun. Unfit subjects have lower exercise related FFA levels than fit subjects and this may be in keeping with the hypothesis that lactate, in the unfit subjects, overrides the lipid mobilising action of catecholamines (17, 18) and inhibits FFA mobilisation (28). With a given amount of oxygen, more energy can be produced from carbohydrate than from fat; thus the inhibition of fat metabolism by lactate build up is an important control mechanism during performance of activities that lead to exhaustion within 30 - 40 minutes. With prolonged exercise the insulin levels decline, leading to increased hormone sensitive lipase activity and increased release of FFA from fat stores (13).

2.1.3 SERUM POTASSIUM RESPONSE

K^+ is located primarily within the cells. Beta-receptors and alpha-receptors are probably present in mammalian skeletal muscle, the major body reservoir of K^+ (1,14). Several mechanisms have been shown to have an important role in the maintenance of K^+ homeostasis. Although renal excretion is the dominant factor in determining daily external K^+ balance, cellular uptake of K^+ maintains the serum K^+ concentration within narrow limits in response to a K^+ challenge. Numerous studies (14-17) have demonstrated that catecholamines, by both a beta- and alpha-adrenergic mechanism, have an important influence on the extrarenal disposal of an acute K^+ load in human beings.

The mechanisms involved in catecholamine stimulated intracellular K^+ uptake are uncertain, but may be a direct effect mediated by the beta- and alpha-receptors. It seems that adrenaline causes hypokalaemia more easily than noradrenaline. This is consistent with a beta-2-receptor mediated effect, probably the receptor linked to Na^+-K^+-ATPase in skeletal muscle. It does seem that beta-adrenergic tone is not a major factor in controlling the plasma K^+ concentration under basal conditions. Adrenaline induced hypokalaemia is not mediated by changes in blood glucose, renin, aldosterone, or insulin (17).

Vigorous exercise is known to cause short-term elevations of the plasma K^+ level in human beings. This "physiologic hyperkalaemia" peaks with maximal exertion and is proportional to the amount of work done. When exercise stops, K^+ levels fall abruptly. The release of K^+

from contracting muscles is thought to be the principal source of this endogenous K^+ load (15), which may be a consequence of enhanced alpha-adrenergic activity. It appears that both alpha- and beta-receptors have important but opposing roles in modulating the resulting K^+ shifts; beta-stimulation enhancing cellular K^+ uptake and alpha-stimulation increasing plasma K^+. At peak exertion, high circulating plasma levels of adrenaline from the adrenal medulla and of noradrenaline from the sympathetic nerve terminals suggest simultaneous alpha- and beta-receptor stimulation.

Beta-receptor stimulation involving adrenaline appears to act predominately as a primary defense against toxic hyperkalaemia resulting from alpha-receptor stimulation by noradrenaline. The alpha-effect, likewise, may protect against hypokalaemia after exercise ceases (16). These effects on K^+ disposal probably result from direct binding of alpha-agonists to skeletal muscle receptors and not via alpha-adrenergic inhibition of insulin secretion. By opposing beta-receptor effects on K^+ balance, alpha-catecholamines may act to preserve serum K^+ levels within physiologic limits (15).

PART 3

THE HORMONAL RESPONSES TO BRISK EXERCISE IN NORMAL SUBJECTS

3.1 INTRODUCTION

The regulatory and adaptive responses to exercise result from important changes in endocrine functions, especially those related to substrate metabolism and are of essential importance in the various processes of energy utilisation (18).

3.1.1 PLASMA INSULIN RESPONSE

Insulin's main function is to regulate total body glucose metabolism in all tissues except the brain. It also has significant protein anabolic effects and stores excess carbohydrate as fat. Glucose is the major physiologic stimulus for insulin secretion. Alternate stimuli include plasma fatty acids, amino acids, and enteric hormones (5).

There seems little doubt that any rapid increase in plasma insulin concentration in peripheral blood is due to increased endogenous secretion of insulin. However it is also correct to say that changes in concentration of insulin in plasma reflect alterations in the equilibrium between pancreatic secretion on the one hand and uptake of hormone by the tissues on the other (19).

During exercise of increasing intensity and duration, the circulating levels of insulin decrease as a result of the alpha-adrenergic inhibitory effect on the pancreatic beta-cells (8,43). This directly enhances hepatic glucose output and sensitises the liver to the effects of glucagon and adrenaline. These actions help to maintain blood glucose. The catecholamine suppression of insulin is proportional to the intensity of the exercise. Catecholamines increase hepatic gluconeogenesis and also inhibit insulin release (20) by stimulating alpha-adrenergic islet cell receptors.

Accordingly, an exercise induced fall in insulin levels could be abolished by alpha-blocking agents. Beta-stimulation promotes insulin release. However, the predominant physiologic effect of both adrenaline and noradrenaline is inhibition of insulin release via the alpha-receptor. In the recovery period, plasma insulin levels rise within a few minutes. The rise in insulin after exercise is probably due to an enhanced insulin secretion related to a fall in plasma catecholamines. A significant activation of the sympathetic nervous system is found during exercise, when oxygen consumption is 50% or more of the maximal oxygen uptake (VO_{2max}). At levels of exercise that increase oxygen consumption to 50% or more of VO_{2max}, a significant fall in plasma insulin is observed (18).

Glucagon stimulates insulin release in man. Since this precedes any increase in blood glucose, glucagon appears to stimulate insulin secretion directly, and not via the beta-receptor. Glucose, however appears to be necessary for glucagon to stimulate insulin secretion by the pancreas (19).

ACTH and cortisol appear to have no direct effect on insulin release. Their presence however is necessary for the normal pancreatic response to glucose. Clinical studies in which plasma levels of insulin and growth hormone have been measured suggest that there is an inverse relationship between the concentrations of these substances in relation to plasma glucose levels. After glucose loading, the level of insulin rises while growth hormone levels tend to fall. In fasting or prolonged starvation, low levels of insulin and high levels of growth hormone are observed (19).

It appears, therefore, that corticosteroids and growth hormone modify the responsiveness of pancreatic tissue to glucose rather than have a direct action on insulin release themselves. During the initial phase of exercise, the enhanced glucose penetration and utilisation by working muscle cells together with a small but significant " insulin like effect " of growth hormone, may actually obviate the need for insulin during this period. If so, the inhibition of insulin release by adrenaline may, in fact, be a protective mechanism to prevent the development of hypoglycaemia (11).

3.1.2 PLASMA GLUCAGON RESPONSE

Glucagon is secreted from the alpha cells of the islets of Langerhans. Glucagon's major function in the body is to raise the level of blood glucose by stimulating both liver glycogenolysis and gluconeogenesis. It simultaneously activates the release of FFA into the circulation. The glucagon mechanism is essentially active during heavy, long duration exercise and starvation.

Glucagon release does not seem to be mediated by the autonomic nervous system, nor are there gender differences. The stimulating effects of hepatic glucose output by glucagon may be important to glucose balance during exercise. However, the increase in glucagon concentration is considerably delayed following the onset of exercise suggesting that glucagon might not be important in the early regulation of hepatic glycogenolysis (5).

Glucagon helps to furnish an adequate supply of glucose when its requirements are increased by exercise. Glucagon appears to exert the same action as catecholamines in situations when the need for more prolonged periods of exercise is experienced (18). Following exercise training the needs for glucagon are significantly reduced (21).

The magnitude of the glucagon response is dependent on the intensity and duration of exercise. In vitro and during infusion in man, catecholamines stimulate glucagon secretion. There appears to be a greater glucagon response to adrenaline during prolonged exercise (22). Regarding this mechanism of exercise induced hyperglucagonaemia, it is noteworthy that an elevation of amino acid levels also has a stimulatory effect on glucagon secretion. Exercise can be associated with quite marked increases in plasma alanine and this may constitute the stimulus for the increased secretion of glucagon. The role of the adrenergic system cannot be entirely discounted however.

3.1.3_ PLASMA PROLACTIN RESPONSE

Prolactin initiates and supports milk secretion from mammary glands (5). Plasma prolactin levels are increased during exercise in both males and females (18). The output of prolactin increases with higher levels of exercise but to a lesser degree than growth hormone. Prolactin levels return toward baseline within 45 minutes after cessation of exercise, and its effects appear to be transient (5,1).

3.1.4_PLASMA CORTICOTROPIN (ACTH) RESPONSE

ACTH regulates the output of some of the hormones secreted by the adrenal cortex. Owing to the difficulty in assay methods and the rapid disappearance of this hormone from the blood, clear evidence is scarce concerning the response of ACTH during exercise; nevertheless the inference is that ACTH output is increased during exercise (5).

3.1.5_PLASMA GROWTH HORMONE (GH) RESPONSE

GH (somatotropin) has widespread physiologic activity because it promotes cell division and cellular proliferation throughout the body. In the adult, GH facilitates protein synthesis. This action is accomplished by increasing amino acid transport through cell membranes, stimulating an increase in RNA formation, or activating cellular ribosomes that increase protein synthesis. The release of GH also results in a decrease in the rate of carbohydrate utilisation and a subsequent increase in the mobilisation and use of fats as an energy

source. This sparing of glucose would contribute to one's ability to perform endurance exercise. It does appear somehow that the degree of release of GH is in some way related to the relative severity of effort (5).

Studies on exercise induced production of GH have revealed a delay of a few minutes in GH secretion after exercise starts. It has been shown that exercise is directly associated with a doubling of both GH pulse frequency and amplitude. With successively increasing exercise levels, there is a sharp rise in GH production and total secretion (5). Marked elevations of plasma GH occur in subjects exercising at levels corresponding to 50% and greater of their VO2 max (18). Acute physical stress or exercise may result in the release of up to 20% of the normal daily production of growth hormone (11).

This is a beneficial response for muscle, bone and connective tissue growth, as well as optimising the metabolic mixture during exercise. The precise relationship between GH synthesis, and exercise intensity and duration has not been established, nor has the stimulus been identified for increased GH production with exercise. It does not appear that circulating lactate, alanine, pyruvate and blood glucose or body temperature are responsible for regulating the pattern of GH secretion. It is most probable, therefore, that neural factors (e.g. GH releasing factor) primarily control GH secretion.

The increased secretion of GH during exercise also diminishes with exercise training (23). It is felt that during muscular exercise by normal human adults, unless exogenous carbohydrate is made

available, the needs for fuel are increasingly met by mobilisation of depot fat and that secretion of GH appears largely responsible for initiating and maintaining this process.

3.1.6 PLASMA CORTISOL RESPONSE

Cortisol, also called hydrocortisone is the major glucocorticoid secreted by the adrenal cortex. The role that cortisol plays in energy metabolism includes:

1. protein lysis, liberating amino acids for gluconeogenesis,
2. supporting the action of glucagon and growth hormone in gluconeogenesis, and
3. antagonising the action of insulin by inhibiting glucose uptake and oxidation.

It is assumed that in response to neural responses from the periphery to the hypothalamus, corticotrophin releasing factor is secreted which stimulates ACTH release from the anterior pituitary and thereafter cortisol secretion from the adrenal cortex (5).

There is considerable variability in the cortisol response to exercise depending on; exercise intensity and duration, fitness level, meal status and circadian rhythm (24). Most studies [with exceptions (25)] indicate that cortisol output increases with exercise intensity. Stimulation of the hypothalamic-pituitary-adrenal axis appears to be coupled to relative exercise intensity rather than absolute workload (26).

It is only intensive work that increases secretion of glucocorticoids (18). Exercise at 50% of maximal oxygen consumption caused no elevation in plasma ACTH or cortisol levels but intensities of 70 and 90% of maximal oxygen consumption were associated with a proportional activation of this axis. Cortisol levels remain elevated for as long as 2 hours after exercise. The mechanisms by which the pituitary-adrenal axis is activated during exercise and by which its coupling to exercise intensity occurs are unclear (26).

The teleogic purpose of the activation of the pituitary-adrenal axis during exercise is multifaceted. Glucocorticoids have powerful effects on the cardiovascular system, metabolism, and the muscles. Potential metabolic usefulness includes increased glycogen formation, hepatic gluconeogenesis and lipolysis, although it is difficult to define a metabolic role for the increased plasma cortisol during exercise. Some studies have indicated that exercise training may attenuate the glucocorticoid response to exercise (26).

3.1.7 PLASMA CATECHOLAMINE RESPONSE

The sympathetic nervous system plays a key role in supporting the needs for energy requirements during physical activities by controlling various cardiovascular adjustments and allowing energy substrate mobilisation. The stimuli for the sympathetic response to exercise include baroreceptor activation, pain and psychological factors (18). Noradrenaline is both a hormone and a precursor of adrenaline. It is also a neurotransmitter which is released by sympathetic nerve endings (5).

The action of the transmitter released at the adrenergic nerve terminals may be terminated by 3 principally different mechanisms (27):

1) local enzymatic destruction,
2) reabsorption into the nerve terminals, and
3) escape into the circulation.

Plasma noradrenaline represents neurotransmitter leakage from sympathetic nerve endings and is considered an index of sympathetic nervous activity which is related to the cardiovascular and metabolic adjustments of the working tissues. Noradrenaline levels are increased 2 - 6 fold by light to maximal exercise. Adrenaline output from the adrenal medulla increases with exercise, and the magnitude of this increase is related to the intensity of effort (5). Although noradrenaline release from the adrenal gland may sometimes occur, the adrenal glands do not materially contribute to the catecholamine blood levels observed after exercise (28).

The predominant increase in noradrenaline rather than adrenaline during exercise, suggests their source is the sympathetic nerves rather than the adrenal gland (29). Plasma noradrenaline is now generally believed to arise from the sympathetic nerve endings in vascular beds of non-working areas, since its concentration increases in relation to the intensity of vasoconstriction in these regions i.e. the vasodilatation of muscular work is normally compensated by vasoconstriction in other areas (29).

Sympathetic nervous activity during exercise is proportional to the relative work load (% VO_{2max}) rather than absolute aerobic energy

expenditure (29,30), i.e. the percent of the individuals maximal oxygen uptake that the workload represents. Factors that determine catecholamine response to exercise include; duration of exercise, age [plasma catecholamine secretion is greater in older subjects at the same exercise intensity (31,32)] and gender [greater adrenaline response in males than females, same noradrenaline response (33)].

At a given level of exercise the catecholamine secretion is smaller in trained than in non trained subjects (34). Sympathetic activity is associated with increases in heart rate, systolic blood pressure, myocardial contractility, liver glycogenolysis and adipose tissue lipolysis - all being beneficial to the exercise response (18).

Although baroreceptor activity in response to the vasodilatation with work is possibly an important response, it is inadequate to explain all the autonomic changes that occur (35). Centrally originating motor function may lead to sympathetic stimulation. Other factors may also be important for the increase of the blood noradrenaline that occurs during physical exercise. With respect to noradrenaline inactivation in the liver and kidneys, it should be observed that hepatic and renal blood flow are reduced during exercise. The inactivation of the released noradrenaline at the 'nerve terminal-effector level' may also be decreased during physical activity. However, the increase of noradrenaline is so rapid during higher levels of work, that its rise, in all probability, results mainly from increased noradrenaline release from the nerve terminals of the adrenergic neurons correlated to an increased sympathetic impulse flow, rather than a decreased rate of inactivation (28).

Primarily there is a withdrawal of parasympathetic tone during mild exercise and increasing contribution by the sympathetic nervous system at higher work levels.

3.1.8 CATECHOLAMINES AND THE REGULATION OF HORMONE SECRETION - PHYSIOLOGICAL ROLE IN EXERCISE

The evidence that increased sympathetic activity mediates the rise in glucagon and decrease in insulin secretion is convincing. It appears too, that catecholamines are important in mediating acute changes in renin release (36). There is evidence to show that direct stimulation by circulating catecholamines increases renin release, although this effect can be offset by the rise in systemic blood pressure (37).

Renin, insulin and glucagon are peptide hormones not directly controlled by the pituitary. During exercise, a stress state, the associated endocrine changes appear to be mediated at least in part via the sympatho-adrenal system. This system provides an integrated response that may be useful in combating the associated problems of 1) hypotension from fluid loss and shunting of blood through muscle vascular beds, 2) acidosis, 3) electrolyte changes, and 4) increased demands for substrate, particularly glucose and FFA. Thus the reciprocal effect of sympathetic activity on the secretion of insulin and glucagon leads to a catabolic hormonal balance that provides an adequate supply of glucose and FFA at the expense of body fuel stores. Increased renin secretion contributes toward maintenance of blood pressure.

Since the sympatho-adrenal system is geared for quick response, and since catecholamines induce rapid changes in effector cells, activation of the sympatho-adrenal system can quickly mobilise stored hormone and result in a prompt change in hormone secretion. Catecholamine induced alterations in hormone secretion are probably more rapid and operate in the short term as compared with the usual feedback loops which operate in the long term and respond to slower, more sustained changes in the environment.

Acute exercise can be seen as "diabetogenic" with a raised GH and lowered insulin levels, as well as the increased activity of the sympathetic nervous system and secretion of adrenocortical steroids. These effects however, are only transitory (36).

3.2 THE RENIN ANGIOTENSIN (RA) SYSTEM

3.2.1 INTRODUCTION

The RA system plays an important role in maintaining cardiovascular and renal homeostasis. It is not only a circulating endocrine system (38) but is a local tissue autocrine-paracrine system as well (38,39), with components present in many tissues including vascular endothelium, the heart, the kidney, the adrenal, the brain and elsewhere. Angiotensin produced locally exerts autocrine/paracrine influences on angiotensin-mediated function(s) in these tissues. Angiotensin II (a potent vasoconstrictor and aldosterone stimulator),

is formed from its precursor, angiotensin I, by the activity of the angiotensin converting enzyme (ACE). Angiotensin I originates from angiotensinogen under the influence of the enzyme renin, the activity of which is rate-limiting for the formation of angiotensin I (38).

Classic stimuli for the release of renin include:

1. impaired renal blood flow - low renal perfusion pressure detected by the intrarenal baroreceptor possibly within the juxtaglomerular apparatus (JGA) itself,

2. decreased delivery of Na^+ to the distal tubule detected by the macula densa portion of the JGA and

3. beta-1-adrenergic stimulation.

It should be recognised that physiological stimuli of renal sympathetic activity are also likely to stimulate the intrarenal baroreceptor directly (36). It appears that angiotensin II does not play a crucial role in the normal animal or human subject in Na^+ balance, but it does become crucial in the maintenance of blood pressure after Na^+ deprivation (14).

3.2.2 PLASMA RENIN ACTIVITY (pRA) RESPONSE

Several reports indicate that pRA is elevated following strenuous physical exercise (6, 41-43), with the magnitude of response related to the intensity of exercise. The renin response occurs rapidly and is short lived after the completion of exercise. There is considerable evidence that renal blood flow decreases with exercise, and that the magnitude of the decrease is dependent on the intensity of the exercise (6,7). Similar to the pRA and catecholamine responses, the changes of

renal blood flow during exercise occur rapidly and are relatively transient following the completion of exercise.

The causes of the increase in pRA during exercise include (6);

a) Renal Baroreceptor Mechanism

A decrease in renal blood flow during exercise may be responsible for the increased renin release but studies have shown that during rest after exercise, coincident with high renal plasma flow, the pRA was markedly increased. Administration of dihydralazine did not influence the significant increase in pRA during exercise. The release of renin during exercise, accordingly, does not seem to be explained by the concept of the JGA as a baroreceptor and suggests some other mechanism is operative.

b) Interaction Between Distal Tubules And Macula Densa

It has been proposed that Na^+ delivery to the distal tubule regulates renin release, with a decreased delivery associated with an increased renin release. However, studies done with diuretics which cause a marked increase in urinary Na^+ excretion, did not decrease or prevent renin release during exercise. Thus, the release of renin during exercise does not seem to be caused by a decrease of the Na^+ load in distal tubuli.

c) Nervous system

In patients given dihydralazine (minimising renal vasoconstriction), the significant increase in pRA during rest was coincident with a rise in heart rate, suggesting increased sympathetic activity.
The glomerular vascular pole is richly innervated with non-myelinated sympathetic nerves, suggesting direct sympathetic nervous stimulation of the renin release. Stimulation of neural impulses to the kidney by a variety of mechanisms has been shown to increase renin release. Direct renal sympathetic stimulation increases renin secretion via beta-receptor activation (44).

A similar time course of an exercise induced catecholamine rise (especially noradrenaline) suggests that the renin response may be mediated by the sympathetic nervous system (41). Furthermore, there are several reports indicating that renal denervation or pharmacologic sympathetic blockade inhibits the renin response to a variety of stimuli known to provoke renin release. A plethora of infusion experiments of both adrenoreceptor agonists and blocking agents provides additional evidence of sympathetic influence on renin release (36).

The importance of the sympathetic system for renin release is supported by the fact that ganglionic blocking prevented renin release in swimming rats. It has been repeatedly shown in man that pRA is increased on assuming the upright position. An increased sympathetic stimulation in the upright position is well known. The occurence of sympathetic denervation hypersensitivity in a

transplanted kidney or spinally transected rats speaks strongly in favour of a sympathetic nervous mechanism participating in the renin release from the JGA (6). The results indicate that the sympathetic system probably plays an important role in renin release during exercise and suggest a direct sympathetic nervous stimulation of the JGA irrespective of the renal haemodynamic changes.

Consequently, the mechanism for renin secretion in exercise may be as follows: increased sympathetic nervous system activity proportional to the intensity of the exercise; decreased renal blood flow proportional to the level of increased circulating catecholamine with subsequent increased renin secretion (45,46).

3.2.3 INTERACTION OF THE RA SYSTEM WITH THE AUTONOMIC NERVOUS SYSTEM

Angiotensin II is an important modulator of the activity of the sympathetic nervous system (47).

a) Interaction with the central nervous system

A central action of angiotensin II is to enhance sympathetic efferent nerve activity. The existence of an independent brain RA system is now well established, but it is equally clear that angiotensin II circulating in the blood also has an effect via the brain (48). The circumventricular organs (which lack a functional blood-brain barrier) are the probable site of action of circulating angiotensin II in the brain.

b) Interaction with the peripheral nervous system

Angiotensin increases the release of noradrenaline from the sympathetic nerve ending (49), facilitates transmission at sympathetic ganglia (50) and inhibits the re-uptake of noradrenaline (51). It has also been shown that angiotensin facilitates the biosynthesis of noradrenaline (52) and releases catecholamines from the adrenal medulla (50).

Thus, along the whole length of the sympathetic nervous system, from brain to the peripheral receptor, angiotensin enhances activity.

PART 4

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEI)

4.1 INTRODUCTION

ACEI have been available for over a decade to treat hypertension and congestive heart failure. All ACEI are similar in their effects, differing principally in their duration of action (53-55). The group of ACEI can be separated according to:

1. The presence of a sulfhydryl group e.g. Captopril,
2. Presentation as a prodrug that is activated in the liver e.g. Perindopril and
3. Neither has a sulfhydryl group nor presented as a prodrug e.g. Lisinopril.

4.1.1 Efficacy and use

Repeated clinical studies have demonstrated the efficacy of ACEI in lowering blood pressure and their ability to reduce left ventricular hypertrophy. ACEI are also used to treat congestive heart failure and reduce all-cause mortality in all classes of heart failure, including post myocardial infarction left ventricular systolic dysfunction.

4.1.2 Mode of Action

ACEI block the conversion of angiotensin I to angiotensin II, thereby preventing vasoconstriction and producing a relative decrease in circulating aldosterone concentrations. ACE inhibition results in a relative rise in angiotensin I and renin levels and a tendency for angiotensin II levels to rise to pre treatment levels despite continued treatment. They may also prevent the destruction of kinins, locally formed peptides that are powerful vasodilators.

All ACEI appear capable of inhibiting the ACE in all tissues, but their effects in different tissues may reflect their relative tissue penetration and the relative concentration of ACE in that tissue (23). ACE inhibition in different tissues may account for some of the effects of these drugs over and above their vasodilatory activity.

4.1.3 Metabolic effects

ACEI when given on their own in modest doses, have little net effect on uric acid and serum K^+ and in patients with hyperuricaemia and gout, have been demonstrated to be uricosuric (56). Clinical experience has shown that ACEI do not have any adverse metabolic effects on carbohydrate and lipid metabolism (57). They do not disturb plasma lipid concentration and may improve insulin sensitivity and glucose tolerance (58). There is no uniform explanation for this, but increased blood flow in skeletal muscle, accumulation of bradykinin or more efficient insulin release may be possible causes (57).

4.2 PERINDOPRIL

4.2.1 STRUCTURE

Perindopril is a relatively new, oral, long acting ACE-inhibitor. It is a third generation ACE-inhibitor, the perhydroindole 2-carboxylic acid derivative of an N-carbethoxybutyl alanine. Perindopril itself is relatively inactive and is administered as an ester pro drug that is rapidly hydrolysed in vivo to the active diacid metabolite perindoprilat. This conversion occurs predominately in the liver. This compound is a potent, long lasting and specific inhibitor of ACE. The diastereoisomer [S,S] perindopril, is prepared as a tertiary butylamine salt [S9490-3]. The diacid form is the active metabolite perindoprilat [S9780] (59).

4.2.2 PHARMACOKINETICS

The parent compound appears to be well and rapidly absorbed with bioavailability of over 70%. It is metabolised by 1) deesterification to perindoprilat which accounts for 20 - 35% of the administered dose, 2) by conjugation to yield a glucuronide of the parent compound, which is inactive, or to some inactive cyclic metabolites. Active perindoprilat is mainly cleared by the kidney (60). 70% of an intravenously administered dose appears in the urine. 5% is excreted unchanged in the urine. Renal drug clearance approximates to creatinine clearance (61). After oral dosing, peak perindoprilat concentrations are achieved within 2-6 hours (62). By 24 hours, drug concentrations are barely detectable in the plasma.

The plasma protein binding of ACEI is variable between agents and this influences the distribution and availability of drugs to active sites. The percentage binding of perindopril to plasma proteins in vitro is low, with albumin principally involved. The protein binding of the active moiety perindoprilat is lower than that of the parent compound [about 20%] (62). Perindoprilat is eliminated in a biphasic manner, the free fraction rapidly eliminated by renal excretion with a half life of only 1 hour and the bound fraction [bound to ACE] is eliminated much more slowly. Perindoprilat does not accumulate, with dosing reaching a state of equilibrium in about 4 days (38).

4.2.3 PHARMACODYNAMICS

In contrast to the pharmacokinetics, maximal pharmacodynamic effects [ACE inhibition, increase in pRA and angiotensin I, reduction in aldosterone, angiotensin II and blood pressure] are seen 4-6 hours after dosing, with substantial effects [approximately 60% inhibition after 8 or 16 mg perindopril orally] still present at 24 hours (60). Perindopril's de-esterified metabolite is a thousand times more potent than the parent compound. It takes approximately 4 hours to achieve greater than 90% inhibition in normal volunteers (59,62).

The effects of perindopril on plasma ACE-inhibition and renin activity are dose related in the range 1-16 mg. During repeated doses with 8 or 16 mg, no accumulative effect on plasma ACE was observed, whereas with the lower doses, some increase in effect did occur. Taken together, these features are consistent with the theory that perindoprilat binds specifically and saturably to ACE in vivo, and that this binding

prolongs the pharmacodynamic effect beyond that which would be anticipated from the pharmacokinetics (60).

Tissue ACE binding studies with perindopril are restricted to animal observations (59). Observations in animal species show a rapid, dose related, inhibition of plasma ACE and ACE isolated from kidney homogenates within 1 hour of oral dosing. The maximum degree of ACE inhibition was reduced and the onset delayed in lung and aortic preparations, despite the fact that pulmonary and vascular endothelial ACE is present mainly on the luminal surface (62).

The penetration of ACEI into the central nervous system may be of importance in the generation of their haemodynamic effects. This central RA system exists independently of the peripheral system and these 2 systems are separated by the blood brain barrier (63).

When given intravenously ACEI lower blood pressure in spontaneous hypertensive rats (SHR), without peripheral ACE inhibition, which indicates the drugs are effective centrally. However, peripherally administered ACEI do not block the central angiotensin I response. Thus it is likely that ACE inhibitors do not cross the blood brain barrier and do not act on brain ACE in therapeutic doses although it has been shown that higher doses can cross the blood brain barrier (64,65). It is likely that the penetration of ACEI into the brain might depend on the lipid solubility of the drug (66).

The precise site of action of ACEI is not fully understood (67). There appears to be a dissociation between the fall in blood pressure and inhibition of circulating ACE (68, 69).

The hypotensive effect of ACE inhibitors may not reflect inhibition of ACE activity in plasma but more likely inhibition in peripheral target organs. In a study (70) comparing ramipril, perindopril and enalapril in stroke prone SHR, perindopril was the more potent inhibitor of brain ACE.

4.2.4 HAEMODYNAMIC EFFECTS IN NORMAL VOLUNTEERS

In normal salt replete volunteers, the effects of short term ACE inhibitors on supine and erect blood pressure are controversial. Carefully controlled studies with appropriate doses and placebo matching usually reveal small but significant falls in blood pressure. It is suggested that the acute effects of ACEI are mediated in part by reductions in angiotensin II, the magnitude of which is dependent on the prevailing activation of the RA system (59).

Studies of perindopril suggest that it is an effective, long acting ACE inhibitor in man, with a slow onset of action and without any cumulative effects after repeated doses (71).

PART 5

CLINICAL STUDY

5.1 THE EFFECT OF PERINDOPRIL, A NEW ANGIOTENSIN CONVERTING ENZYME INHIBITOR ON THE HORMONAL RESPONSES TO BRISK EXERCISE IN HEALTHY SUBJECTS: A RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED STUDY.

Some cardiovascular drugs have been shown to have undesirable hormonal and metabolic effects during and after exercise. The calcium antagonist, Nifedipine (72), and beta-adrenergic blocking agents (31) cause an exaggerated increase in post exercise plasma catecholamine levels in healthy men. Beta-blockers also induce an enhanced increase in serum K^+ after exercise (15). Little information is available regarding the metabolic and hormonal effects of ACE inhibitors in general and perindopril in particular during and after exercise.

It was therefore decided to evaluate whether the administration of perindopril to healthy subjects would alter their physiologic response to brisk exercise, with special reference to hormonal and metabolic responses.

5.2 OBJECTIVES OF THE STUDY

The objectives of this study in healthy volunteers were:-

1. To evaluate the normal physiologic (haemodynamic, metabolic, and hormonal) responses to exercise.

2. To evaluate the effect of perindopril on the physiologic (haemodynamic, metabolic and hormonal) responses to exercise.

5.3 SUBJECTS AND STUDY PROTOCOL

5.3.1 SUBJECTS

Nine young (age 28-35 years), nonobese (mean weight 74.4 kg, range 56.5-85 kg), normotensive, salt replete men were studied. The volunteers were not trained athletes, did not smoke, and did not take any other medication before or during the study. Subjects were deemed healthy on the basis of a complete medical history and examination.

Clinical data of the individual volunteers are shown in Table 1.

The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. After detailed explanation, all recruited volunteers gave their written informed consent to the study.

5.3.2 STUDY PROTOCOL

The study was carried out in the Division of Cardiology, Johannesburg Hospital. The study was designed as a double-blind, randomised, placebo controlled, cross-over trial in which each volunteer took perindopril (4 mg) or identical placebo daily for 7 days. After a treadmill effort test, a week washout period was allowed before the volunteers were crossed over to the alternative capsule. The design of the study is illustrated in Figure 1.

Each subject arrived at the exercise laboratory at 0730h after an overnight 10 hour fast. An indwelling intravenous cannula (to provide access for blood sampling) was inserted near the antecubital fossa, kept patent with slow running saline, and a 30 minute rest period was allowed. Baseline blood samples, HR and BP were recorded at 15 minutes and immediately before the start of exercise. Each subject then performed an exercise treadmill test, starting with an initial warmup period of 3 minutes at 7% inclination and 5 km/h, followed by a period of brisk exercise for 5 minutes at 7% and 10 km/h.

Blood sampling, HR and BP recordings were repeated immediately after exercise and then 5 and 15 minutes later. A standard sphygmomanometer was used to measure BP. Serum urea and electrolytes and urine samples were obtained before volunteers entered the study and before each effort test.

5.3.3 LABORATORY MEASUREMENTS AND ANALYTICAL METHODS

Blood samples were collected in iced tubes and centrifuged immediately; plasma/serum was separated and stored at -20^{o}C until assayed several weeks later.

Plasma glucose, serum K^+ and Na^+, and urine Na^+ were measured by standard laboratory techniques by the same South African Institute of Medical Research (SAIMR) laboratory. Plasma FFA were measured by an enzymatic colorimetric assay (73). Plasma catecholamines (adrenaline and noradrenaline) were determined by high-pressure liquid chromatography (74). Radioimmunoassay kits were used to measure plasma hormonal concentrations: insulin and growth

hormone (Pharmacia, Sweden), ACTH and cortisol (CIS Biointernational, France) glucagon and pRA (Biodata, Italy) and prolactin (Amersham, England).

Table 1. Pre test clinical data on nine healthy subjects

Subject	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Urine Na^+ (mM)	Serum Na^+ (mM)
1	35	85	177	27	198	139
2	31	80.2	176	26	152	144
3	33	66	178	21	48.4	139
4	34	82	180	25	143	138
5	30	81.5	185	24	130	138
6	30	64.2	168.5	23	189.7	140
7	29	56.5	174	19	71.5	138
8	31	75	170	26	199.2	134
9	28	79.5	182	24	115	141

BMI = Body mass index; Na^+ = sodium

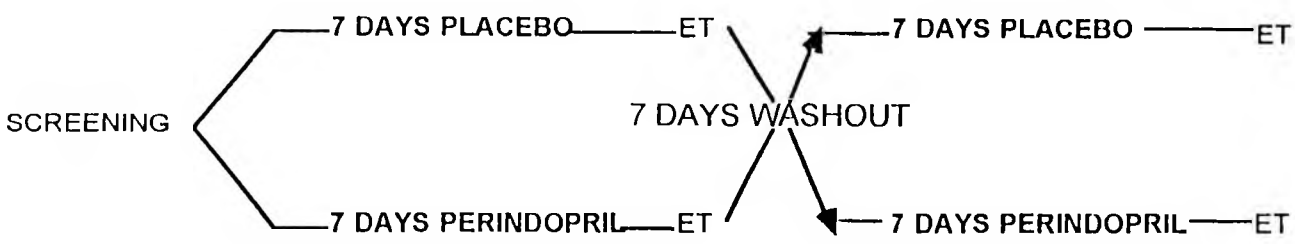


Figure 1. Study design.

ET - Exercise test

All samples for an individual subject were analysed in duplicate in the same assay by technicians with no knowledge of the sequence of drug or placebo administration. All intraassay coefficients of variation were < 7.5%.

5.3.4 STATISTICAL ANALYSIS

Results are mean ± SEM. Nine complete pairs of data were available for evaluation. Statistical significance of parametric data were assessed by Student's paired *t* test; nonparametric data was assessed by signed rank test for paired samples. The Epistat statistical programme was used. Baseline data was taken as a mean of levels obtained 15 minutes before and immediately before exercise. Results were deemed statistically significant at $p < 0.05$.

5.3.5 TOLERANCE AND SAFETY

The subjects tolerated the medication and there were no withdrawals from the study. One volunteer had a dry cough, one had diarrhoea and one had postural dizziness, all during perindopril administration.

5.4 RESULTS

5.4.1 HAEMODYNAMIC DATA (Table 2) (Figure 2)

Perindopril was associated with a significant decrease in mean resting SBP, DBP and MBP (6 ± 2, 7 ± 3 and 7 ± 2 mmHg, respectively, $p < 0.05$). This hypotensive effect was not associated with an increase in resting HR. Perindopril did not accentuate the increase in HR or SBP or accentuate the decrease in DBP that occurred immediately after exercise. Mean SBP was significantly lower 15 min after exercise during perindopril treatment (9 ± 1 mmHg, $p < 0.05$), but MBP was not significantly changed.

5.4.2 METABOLIC DATA

i) Sodium (Table 1)

All subjects were Na^+ replete (mean serum Na^+ 139 ± 3 mmol/l and mean urine Na^+ 138 ± 54 mmol/l). There was no significant difference between the perindopril and placebo treatment periods with regard to mean resting serum K^+ levels (4.1 ± 0.3 mmol/l on both occasions) or urinary Na^+ excretion (148 ± 54 mmol/l with perindopril vs. 141 ± 61 mmol/l with placebo).

ii) Potassium (Figure 3)

There were also no significant differences in serum K^+ levels between treatments after exercise. However, with perindopril treatment only, serum K^+ levels increased significantly (0.4 ± 0.1 mmol/l, $p<0.01$) from before to immediately after exercise owing to a more consistent pattern of response.

iii) Glucose (Figure 4)

There were no significant differences between the two phases of the study with regard to plasma glucose concentrations after exercise. However, after perindopril, mean plasma glucose rose significantly at 5 minutes (0.6 ± 0.2 mmol/l, $p < 0.01$) and 15 minutes (0.5 ± 0.2 mmol/l, $p < 0.05$) post exercise when compared to pre exercise levels.

Table 2. Haemodynamic responses (mean±SEM) to exercise after perindopril or placebo administration in nine healthy subjects

			Exercise					
	Baseline		0 min after		5 min after		15 min after	
Parameter	Pl	Per	Pl	Per	Pl	Per	Pl	Per
HR beats/min	66±2	66±2	152±2	158±2	95±2	94±2	88±2	87±2
SBP mmHg	124±1	118±1*	146±2	141±3	126±1	123±2	125±1	116±1*
DBP mmHg	81±1	74±1*	66±2	62±2	78±1	71±2	79±2	72±1
MBP mmHg	95±1	88±1*	88±2	88±2	94±1	88±2	94±1	87±2

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; Pl = placebo; Per = perindopril.

*$p < 0.05$ versus placebo

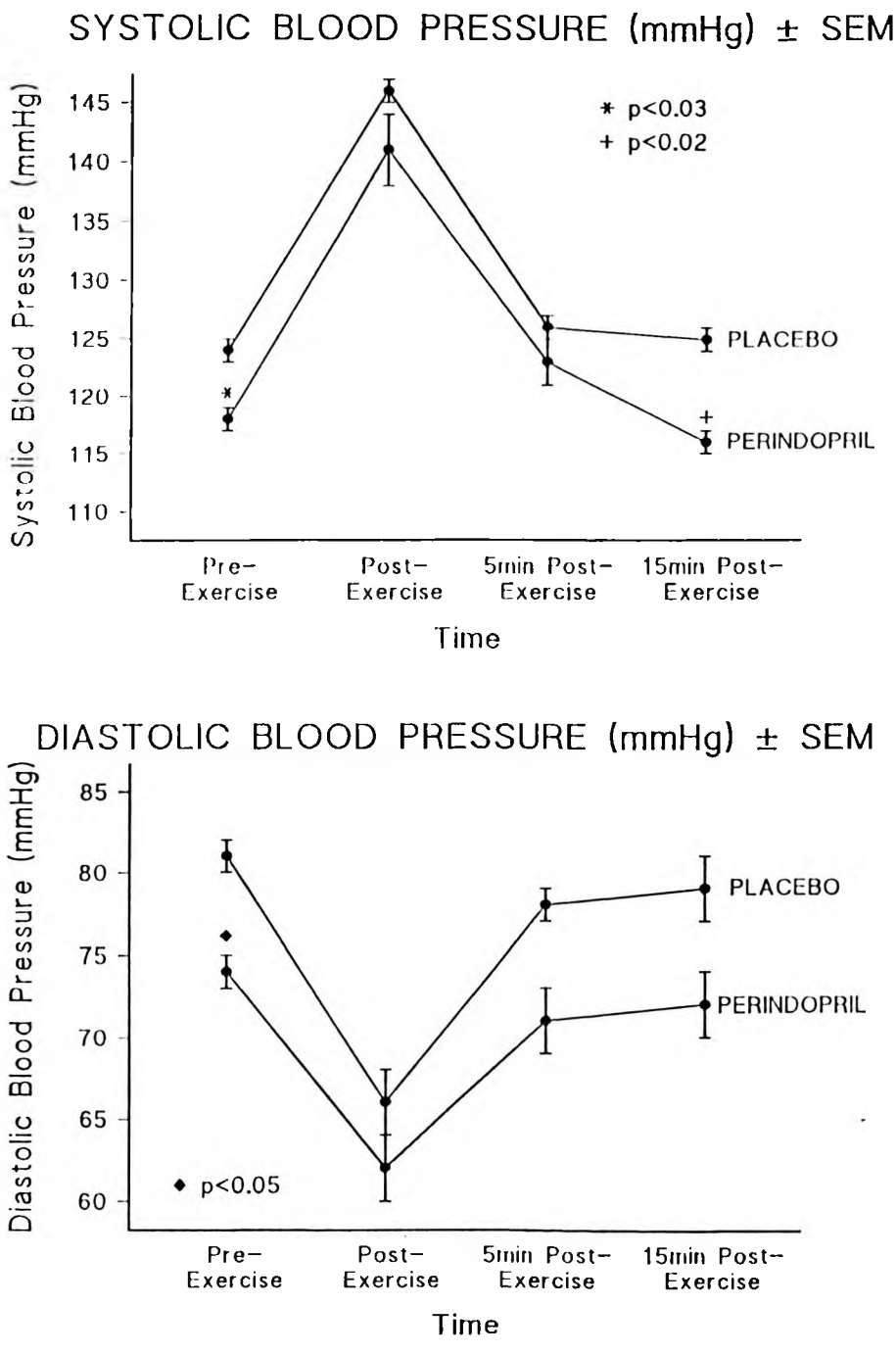


Figure 2. SBP and DBP before and after exercise for the subjects receiving perindopril or placebo.

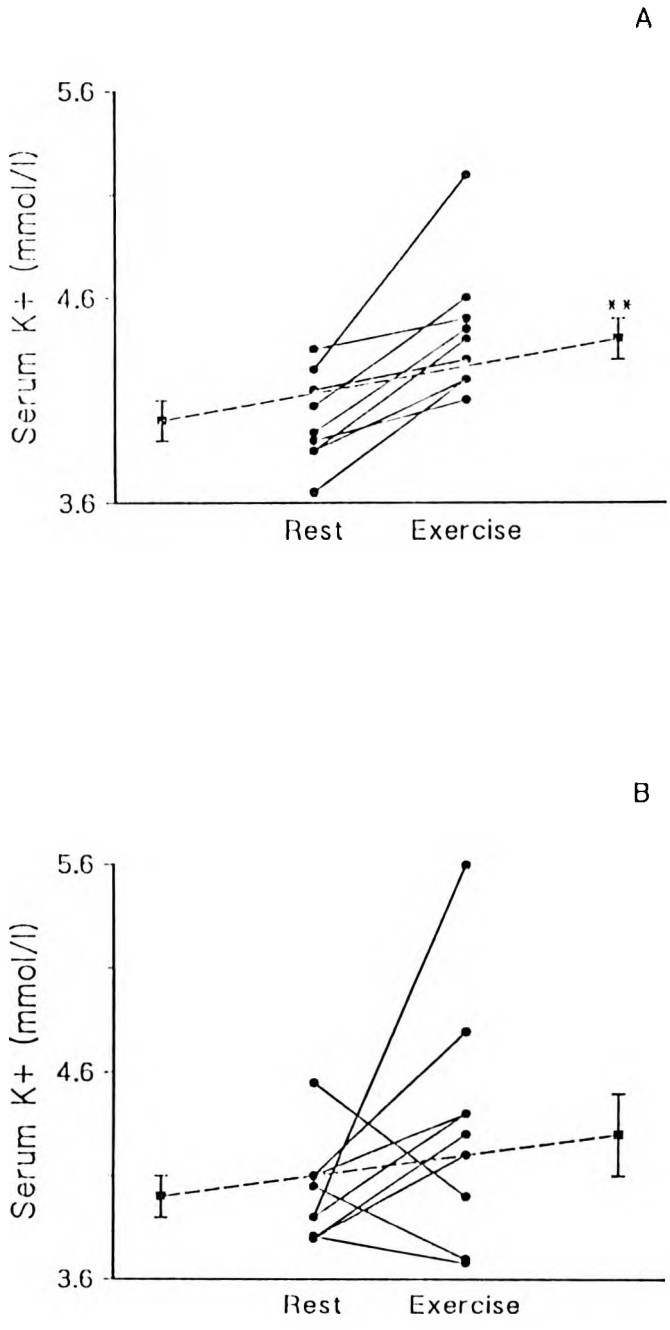
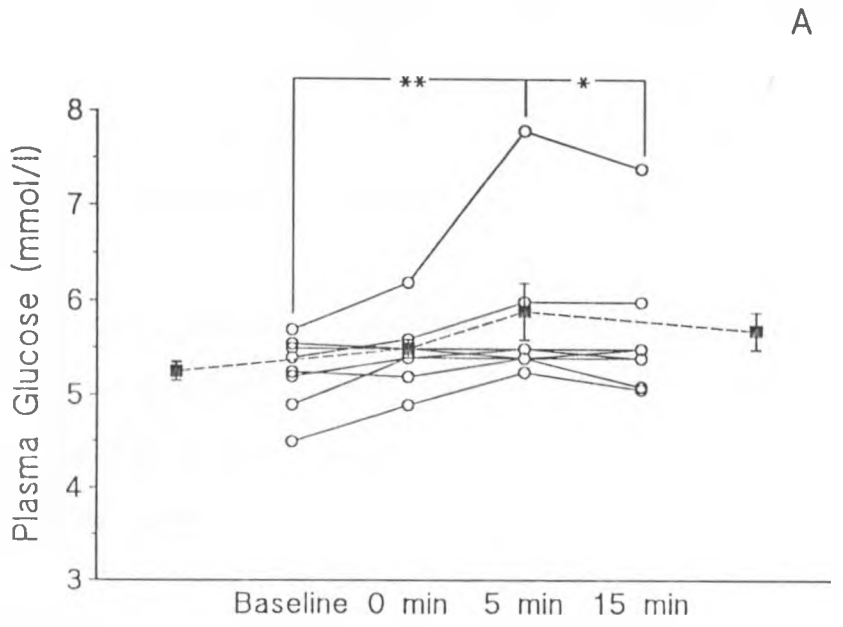


Figure 3. Changes in serum K+ level before and immediately after exercise for each subject receiving perindopril (**A**) or placebo (**B**). **p<O.O1.



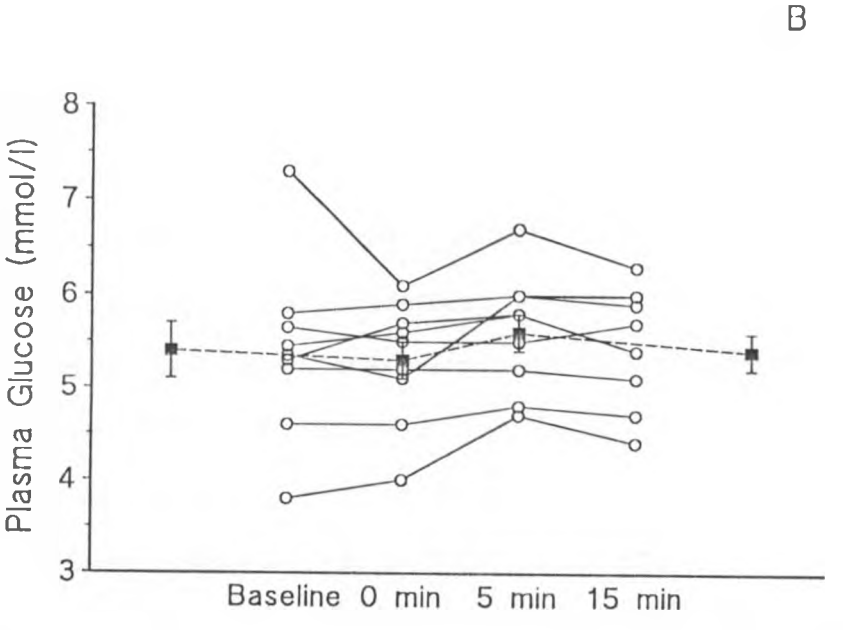


Figure 4. Change in plasma glucose concentration at baseline and at 0, 5, and 15 min after exercise for each subject receiving perindopril (**A**) or placebo (**B**). **p<0.01, *p<0.05.

iv) Free Fatty Acids (Table 3)

Plasma FFA decreased significantly immediately after exercise in both tests (from 0.36 ± 0.02 to 0.22 ± 0.01 mmol/l with placebo and from 0.35 ± 0.02 to 0.21 ± 0.01 mmol/l with perindopril), but these metabolic responses were similar.

5.4.3 HORMONAL DATA (Table 4)

a) Plasma insulin (Figure 5)

Although the pre- and immediate post-exercise mean plasma insulin levels were lower in the perindopril arm (6.9 ± 0.3 vs 7.7 ± 0.5 and 5.8 ± 0.2 vs 7.8 ± 0.6 mU/l respectively), these were not statistically significant differences.

Plasma insulin levels surged 5 minutes after exercise as compared with levels immediately after exercise in both tests. A similar profile of responses was seen after administration of either perindopril or placebo. There was a significant difference at 15 minutes after exercise, however, with a higher mean insulin level noted after perindopril therapy when compared to placebo.

b) Plasma glucagon (Figure 6)

Immediately after exercise, plasma levels of glucagon were lower than pre-exercise in both groups (120 ± 5 vs 129 ± 5 with placebo and 110 ± 5 vs 113 ± 5 pg/ml after perindopril) and plasma glucagon levels

tended to be lower at all stages after perindopril treatment. However, there was a similar pattern of responses in the two studies, with no significant differences.

c) Plasma prolactin (Figure 6)

The prolactin levels increased with exercise, peaking at 5 minutes post exercise in both groups. No significant differences were observed in the prolactin response to exercise between the two studies.

d) Plasma ACTH and cortisol (Figure 7)

A significant and progressive increase in mean plasma ACTH and cortisol concentrations occurred during the post exercise period in both tests, but there were no significant differences between perindopril and placebo.

e) Plasma growth hormone (Figure 8)

Plasma GH increased significantly post exercise from resting levels but there were no significant differences between the two groups.

f) Plasma catecholamines (Figure 9)

There were no significant differences between perindopril and placebo for either adrenaline or noradrenaline levels and perindopril did not modify the increase in catecholamines after exercise as compared with placebo.

g) Plasma renin activity (Table 5)

As expected, perindopril caused a significant increase in resting pRA levels. (This finding also indicated compliance by the volunteers). The normal significant increase in pRA with exercise (41) was reflected in both tests, with no significant differences between the two with respect to percentage of increase after exercise.

There was no significant correlation between the MBP levels post exercise and degree of activation of the RA system.

Also, no significant correlation was found between the rise in pRA and either plasma adrenaline or noradrenaline increases post exercise.

TABLE 3. Plasma free fatty acids (mmol/l, mean±SEM) responses to exercise after perindopril or placebo administration in nine healthy subjects.

Parameter	Plasma free fatty acids	
	Placebo	Perindopril
Before exercise	0.36±0.02	0.35±0.02
Immediately after exercise	0.22±0.01	0.21±0.01
5 minutes after exercise	0.33±0.01	0.34±0.05
15 minutes after exercise	0.33±0.01	0.34±0.05

Table 4. Hormonal responses (mean±SEM) to exercise after perindopril or placebo administration in nine healthy subjects

			Exercise					
	Baseline		0 min after		5 min after		15 min after	
Hormone	Pl	Per	Pl	Per	Pl	Per	Pl	Per
	19.7	22.9	61.1	60.1	126.8	161	73.8	87.9
ACTH	±	±	±	±	±	±	±	±
(pM)	15	1.8	9	9	15	26	8	13
	419	446	418	453	455	475	525	550
Cortisol	±	±	±	±	±	±	±	±
(nM)	10	12.5	10	12	14	13	16	19
	216	243	2893	2686	838	836	366	441
NA	±	±	±	±	±	±	±	±
(pg/ml)	39	17.5	650	566	146	19	67	44
	38	37.5	286	236	69	60	43	50
AD	±	±	±	±	±	±	±	±
(pg/ml)	10	8.5	90	60	19	19	13	15
	7.7	6.9	7.8	5.8	13.5	13.2	12.4	16.5
Insulin	±	±	±	±	±	±	±	±
(mU/L)	0.5	0.3	0.6	0.2	0.7	0.9	0.8	1.0#
	129	113	120	110	134	119	127	114
Glucagon	±	±	±	±	±	±	±	±
(mU/L)	5	5	5	5	5	5	5	6
	0.8	2.25	5.5	5.9	8.7	8	11.9	10.3
GH	±	±	±	±	±	±	±	±
(mU/L)	0.2	0.7	1.2	1.7	1.2	1.7	1.4	1.6
	3.2	4.2	4.1	4.2	5.2	7.1	4.8	6.9
PRL	±	±	±	±	±	±	±	±
(ng/ml)	0.2	0.3	0.3	0.3	0.3	0.8	0.4	0.9

ACTH = adrenocorticotropin; GH = growth hormone; NA = noradrenaline; AD = adrenaline; PRL = prolactin; other abbreviations as in Table 2.

#$p < 0.01$ versus placebo.

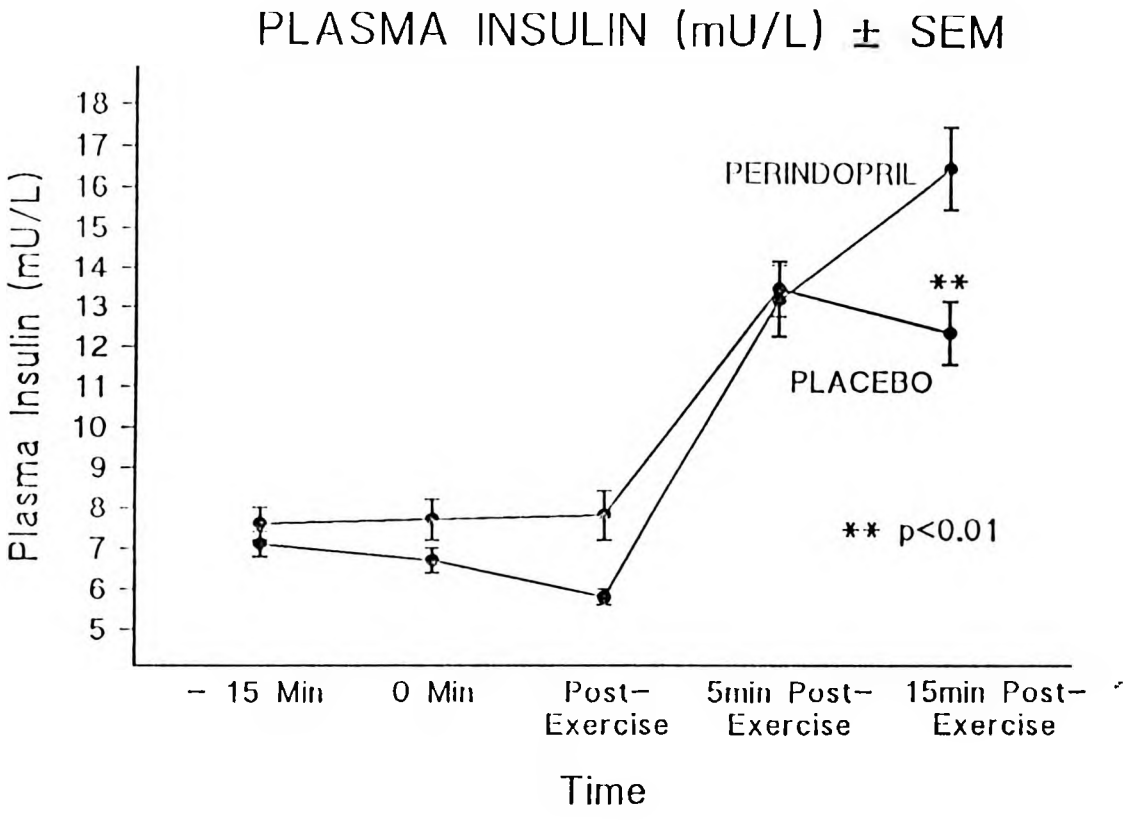


Figure 5. Plasma insulin levels before and after exercise for the subjects receiving perindopril or placebo.

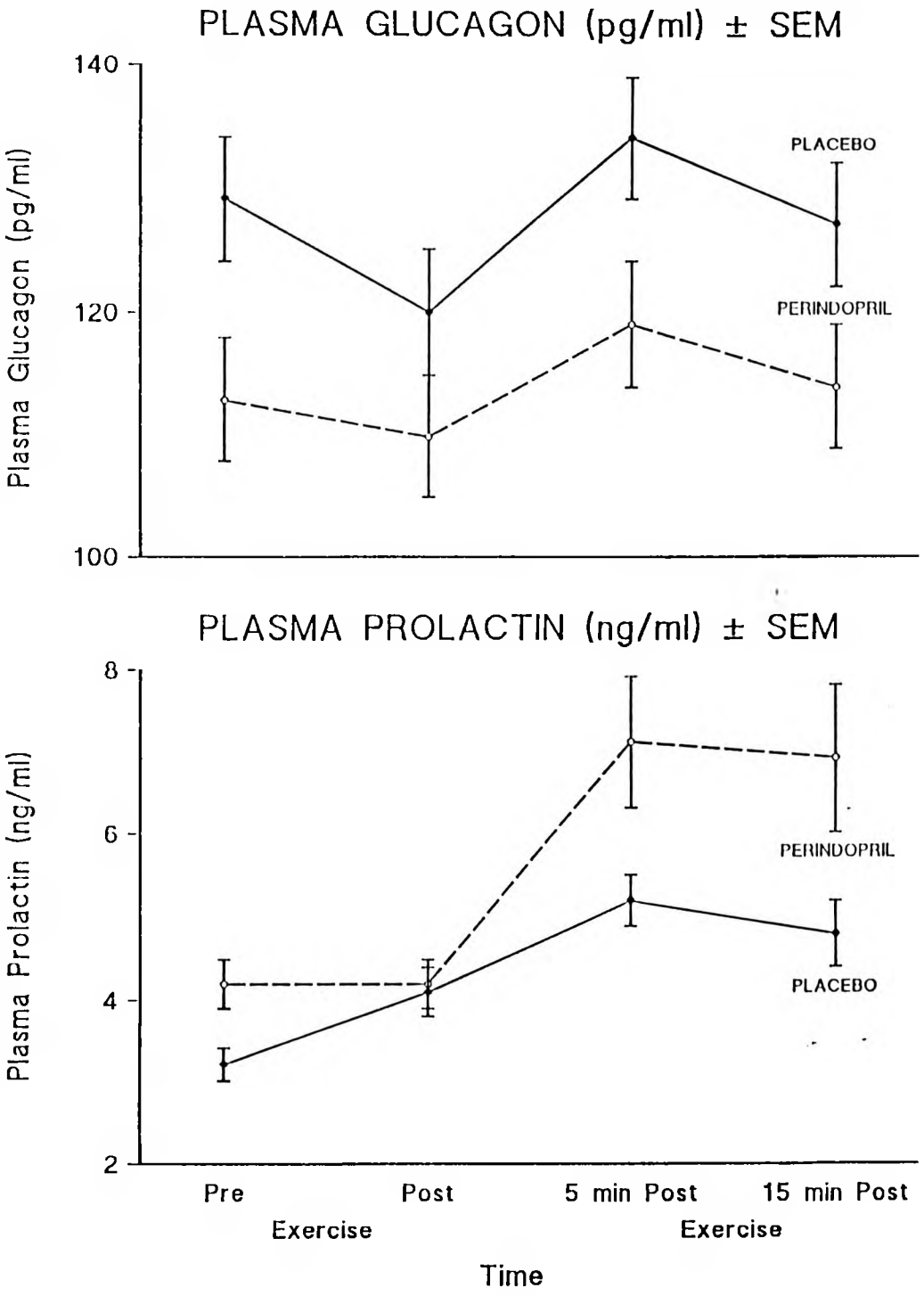


Figure 6. Plasma glucagon and prolactin levels before and after exercise for the subjects receiving perindopril or placebo.

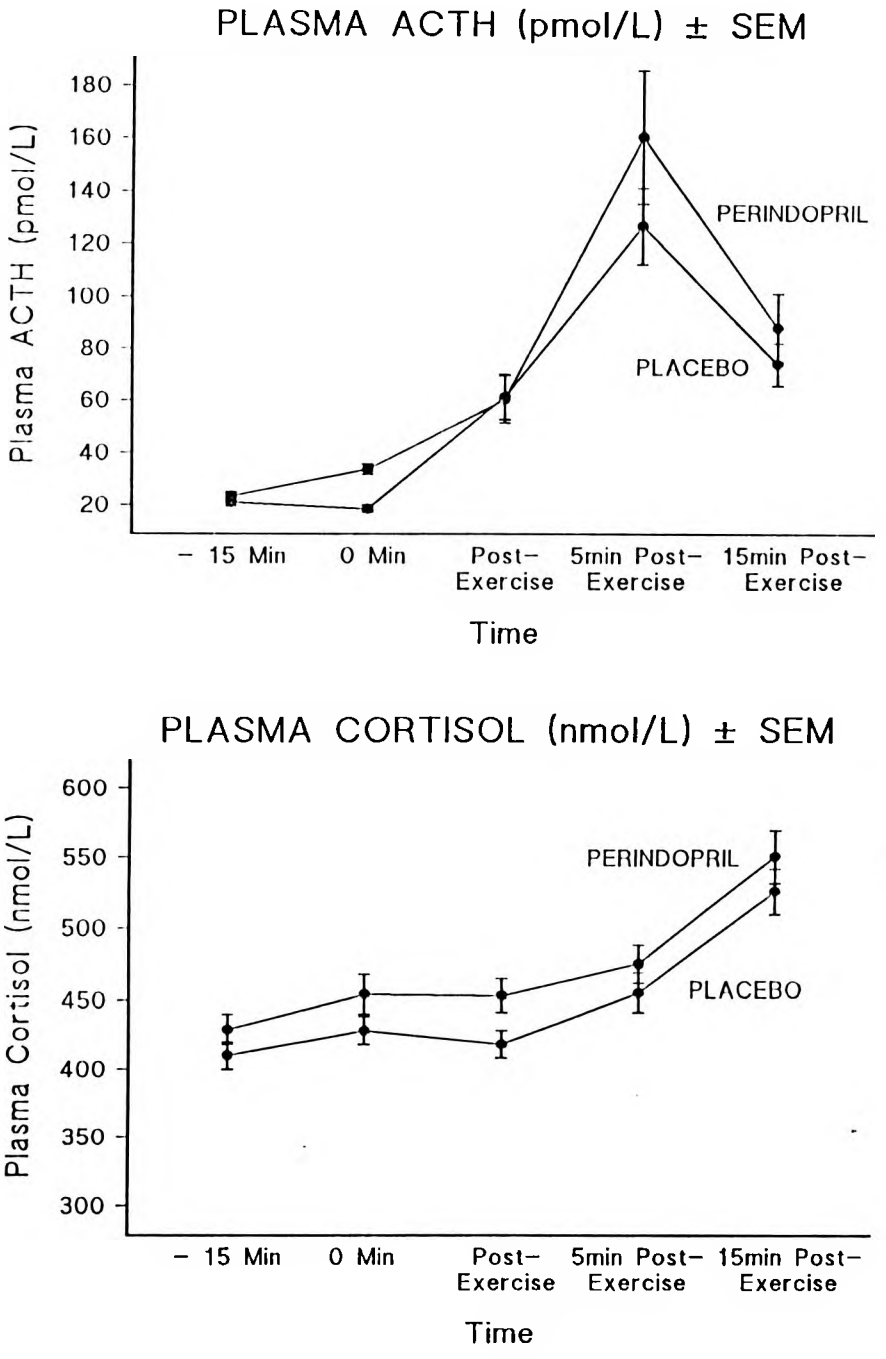


Figure 7. Plasma ACTH and cortisol levels before and after exercise for the subjects receiving perindopril or placebo.

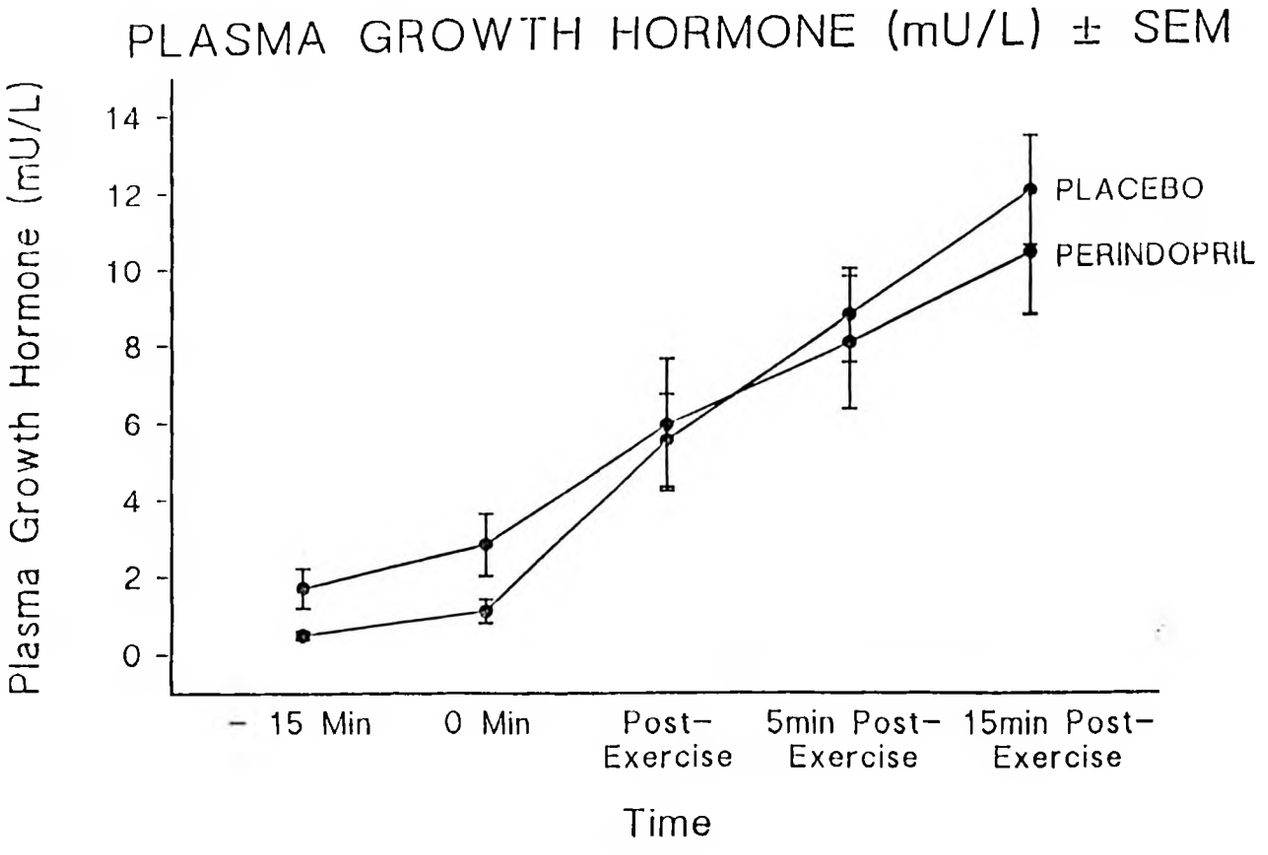


Figure 8. Plasma growth hormone levels before and after exercise for the subjects receiving perindopril or placebo.

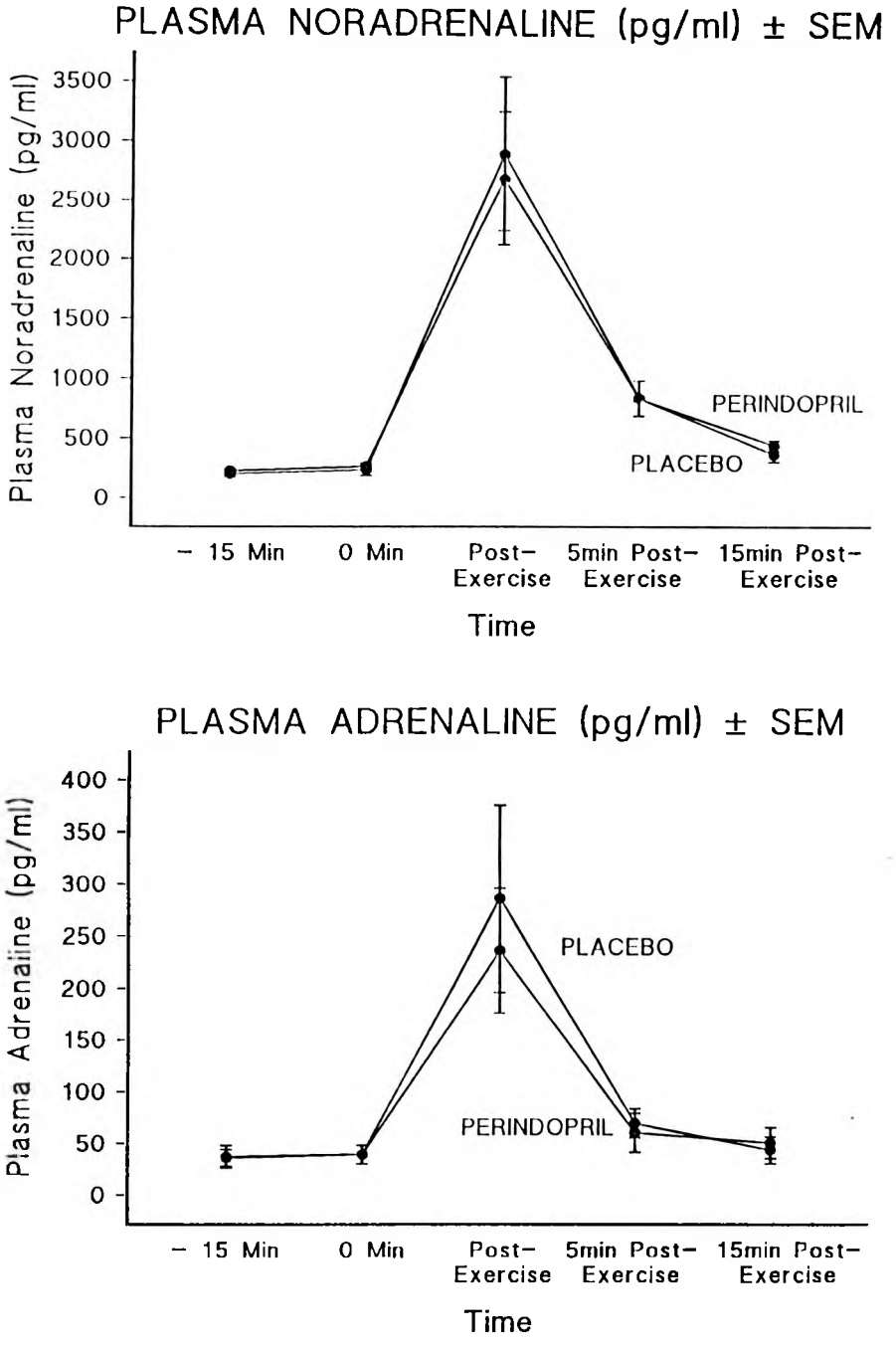


Figure 9. Plasma noradrenaline and adrenaline levels before and after exercise for the subjects receiving perindopril or placebo.

Table 5. pRA responses (mean±SEM) to exercise after perindopril or placebo administration in nine healthy subjects

Parameter	pRA (ng/ml/hr)	
	Pl	Per
Before exercise	0.73 ± 0.4	3.84 ± 0.47#
Immediately after exercise	1.93 ± 0.13	9.77 ± 1.8#§
Increase (%)	264	254

pRA = plasma renin activity; Pl = placebo; Per = perindopril.

#p < 0.01 versus placebo

§p < 0.01 versus before exercise

PART 6

DISCUSSION

6.1 PHYSIOLOGIC RESPONSE TO EXERCISE IN HEALTHY SUBJECTS

The double blind, placebo controlled design of this study, enabled the interpretation of the physiologic reponse to brisk exercise in healthy subjects per se.

The increase in post exercise serum K^+, slight increase in plasma glucose and decrease in plasma FFA, are consistent with previous reports (9, 12, 15) and probably indicate that the exercise protocol used in this study was strenuous although brief, as plasma FFA consistently rise (12) and plasma glucose tends to decrease if the relative intensity is low.

The literature indicates that hormonal changes during work are fairly uniform. An increase of noradrenaline (29,30,34,36,21), adrenaline (75,41), growth hormone (23,34,76-78), cortisol (79), glucagon (21,80), plasma renin (41), ACTH and prolactin (5) and a decrease in insulin levels (11,19,34,80) are observed. This is consistent with the changes documented here. The finding in this study of significant increases in plasma catecholamines, GH, plasma ACTH and cortisol after exercise supports the metabolic data that indicates that these subjects were exercising at greater than 50% of their VO_{2max}, probably closer to 70% of their VO_{2max}. Whereas this study involved the hormonal response to brisk exercise in untrained subjects, it is important to note that exercise training has different effects on resting and exercise-induced

hormone production and release. Trained subjects exhibit elevated hormone response during exercise for ACTH and cortisol, depressed values for GH, prolactin, and insulin, and no training response for aldosterone, renin and angiotensin (5).

The predominant increase in noradrenaline (13 fold with placebo) compared with the more moderate increase in adrenaline (7 fold with placebo) after exercise suggests their source is the sympathetic nervous system and not the adrenal gland, as was confirmed in other studies (81). The sympathoadrenal response to exercise is related to the relative rather than the absolute amount of exercise performed. Hence, a trained athlete would release less catecholamines for a given workload. Such an adaption to training is a favourable response as it lowers myocardial oxygen demand both at rest and during submaximal exercise (5).

Although this study does not address the mechanisms underlying the various hormonal responses, no correlation was found between the degree of activation of the RA system and that of the sympathoadrenal system, nor in the changes of SBP, DBP and MBP and activation of the RA system. No correlation was found either, between the magnitude of decrease in plasma catecholamines post exercise and the surge in insulin levels seen post exercise. This does not refute the proposed pathophysiologic mechanisms involved in these hormonal interactions but probably points to a more complex interrelationship than simple correlation with hormonal levels.

6.2 PHYSIOLOGIC RESPONSE TO EXERCISE FOLLOWING PERINDOPRIL

6.2.1 HAEMODYNAMIC CHANGES

In normal salt replete volunteers, the effects of short term ACE inhibition are controversial (59). Some studies (82,83) showed slight but significant decreases in supine BP after perindopril administration, whereas others (84,85), including ambulatory monitoring (86), showed no significant differences, suggesting that the RA system is not an important determinant of BP in normotensive subjects with free salt intake. MacGregor et al (87) however, found that captopril caused a marked fall in blood pressure in normotensive healthy subjects. The fall in blood pressure was dependent on the Na^+ intake, but there were still substantial falls in blood pressure on a normal and even high Na^+ intake. This study too, using the physiologic stimulus of graded physical exercise, showed that perindopril produces modest but significant hypotensive effects both before and after exercise in normotensive salt-replete subjects. The exact mechanism whereby angiotensin II maintains BP remains controversial, but there is enough evidence to support its role, although not crucial, in normotensive subjects.

Perindopril did not impair the haemodynamic changes associated with exercise. The resting hypotensive effect was not associated with reflex tachycardia as has been observed with other vasodilators (88). This may be the result of a vagomimetic action of perindopril, which has been documented in normotensive volunteers treated with this drug

(89) and is a property that appears to be common to other ACE inhibitors (90,91). The degree of hypotension at rest may have have been insufficient to cause a significant compensatory increase in plasma catecholamine levels or to induce reflex tachycardia. These results confirm the findings of Ajayi and colleagues showing that perindopril had no significant effect on the pressor or chronotropic changes induced immediately after exercise (89).

6.2.2 METABOLIC CHANGES

Serum K^+ increases during muscle exercise owing to release of K^+ by contracting muscles and decreases rapidly when exercise ceases (15). The finding of a slight but significant increase in post exercise K^+ and glucose levels during the perindopril study arm only is of interest. This however, may be due to a more uniform pattern of response in the perindopril arm, rather than to greater absolute increases. Possible reasons for this are not clear, but are not related to more marked perturbations of either catecholamine or insulin secretion induced by perindopril immediately after exercise. Beta-blockers, on the other hand, have been shown to exaggerate the rise in the plasma K^+ level when compared to placebo following exertion (92,93). Thus, propanolol significantly increased the rise in plasma K^+ at peak exercise and resulted in a small but significant elevation throughout recovery, indicating the role of beta-adrenergic receptors in enhancing cellular K^+ uptake.

6.2.3 HORMONAL CHANGES

The absence of excessive post exercise stimulation of the sympathetic nervous system by perindopril differs from results noted after exercise with both selective and nonselective beta-blockers (31) as well as the calcium channel antagonist nifedipine (72) and is a useful property for a vasodilator drug. Studies of ACEI (94) in patients with heart failure showed a reduction in post exercise catecholamine levels whereas a heightened response was noted after beta-blocker administration (95). Clonidine, a central alpha-2-adrenergic agonist, suppressed peripheral sympathetic responses, without altering pituitary alpha-adrenergic mediated hormonal responses, to short term exercise in healthy men (96). Clonidine acts by reducing sympathetic outflow from the central nervous system (CNS), while ACEI probably act peripherally, although a CNS action has been postulated.

Perindopril did not impair the normal pattern of other hormonal responses occuring after exercise, as other investigators have shown (97), although no previous study has investigated as wide a range of different hormones and their responses after ACE inhibition as this study did.

6.3 LIMITATIONS OF THE STUDY

Studies of changes in hormone levels in blood may produce misleading results. This is because the concentration of a hormone at any moment in time is affected by several variables; including rates of

production, peripheral utilisation, destruction and excretion. In addition some hormones are degraded very rapidly and have only brief effects which may be missed. Accordingly, a rise in hormone concentration in the blood during exercise could be interpreted as increased output from the endocrine gland, decreased destruction as a result of diminished renal or hepatic flow, or decreased uptake of the hormone by target tissues (2).

Thus caution is necessary in the interpretation of blood changes of hormones with exercise. Such changes may indeed reflect some important alteration in endocrine function, or they may merely reflect changes in blood flow either to target organs or to sites of hormone degradation.

The psychological stress of exercise testing may alter the resting levels and thereby changes in hormone levels seen following exercise. This problem was highlighted in a study which found that significant plasma cortisol and noradrenaline responses occurred during a 20 minute period immediately prior to onset of the first experience with an exhausting exercise session in eight healthy young men. Subsequent exercise sessions did not reveal similar anticipatory hormonal increases. Psychoendocrine reactions to intravenous catheterisation were observed in some individuals (98). The present study avoided this 'anticipatory' factor by allowing a 30 minute rest period, with 2 basal samples being collected, and by randomising so as to ensure an equal number of first visits for both arms.

6.4 EXERCISE, MEDICATION AND DISEASE

Physical training has been shown to improve exercise performance in patients with coronary artery disease and angina pectoris. Research has shown that after training, arterial pressure and heart rates are lower at any given level of exercise, alterations tending to lower myocardial oxygen consumption and thereby enabling a higher intensity of exercise to be achieved before angina is precipitated.

Improvements of left ventricular contractile function by exercise training in patients with coronary artery disease has been shown (99), while a further study has shown (100) that a program of physical training causes an appreciable improvement in exercise capacity in patients with angina pectoris, with this being confirmed by Winter et al (101). In exercising dogs, the coronary collateral circulation was increased (102), and in humans, exercise training induced an increase in stroke volume (103).

Substantial improvements in exercise tolerance and well being can be produced by cardiac rehabilitation programs in patients recovering from myocardial infarction or coronary artery bypass grafting (104).

Physical training induces marked attenuation of the cardiovascular response to exercise. Several authors have reported that systematic physical training in hypertensive patients may induce reductions in blood pressure at rest and during exercise (105-107). This affects mainly those hypertensives with blood pressures < 175/115 mmHg. Reductions of 8 to 10 mmHg SBP and 5 to 8 mmHg DBP have been reported (1).

Exercise alone can increase aerobic capacity in patients with heart failure (108). Heart failure patients with the most severe exercise intolerance might benefit most from cardiac rehabilitation. Several uncontrolled, retrospective studies have suggested possible beneficial effects of training in subjects with moderate or even severe left ventricular dysfunction without clinically manifest heart failure (109,110). Coats et al (111) report the first controlled comparison of physical training and restriction of physical activity in patients with stable heart failure. They found that a training programme had a beneficial effect on exercise tolerance, VO_{2max} and symptoms.

It therefore appears that physical training alone is beneficial in patients with coronary artery disease, ischaemic cardiomyopathy and possibly hypertension. ACEI would also be indicated in all these conditions.

Sudden death post exercise is widely recognised, occurring equally at maximal work load and during the cool down period immediately after exercise (112). High plasma catecholamine levels immediately after exercise have been implicated in the pathophysiology of this phenomenon, together with the drop in MBP seen at that time. Therefore, a medication that does not accentuate these changes would be preferable. Medications are often used in combination so the possible interactions between the prescribed drug/s and physical exercise is clinically relevant. This study was conceived in part to investigate some of these interactions, with particular reference to an ACEI.

The possible interaction of a drug which raises post exercise serum K^+ (e.g. beta-blocker), taken together with an ACE inhibitor (which showed a consistent increase in K^+ in this study) in the setting of a heart failure subject who exercises, is one of the scenarios to consider when predicting the net effect of the simultaneously administered medications and exercise.

6.5 CONCLUSION

In conclusion this study demonstrates that perindopril did not impair the physiologic responses to brisk exercise in healthy subjects. SBP and DBP was lowered before exercise but did not impair the haemodynamic changes associated with exercise. It did produce a more consistent increase in serum K^+ and plasma glucose levels after exercise, however. The drug did not alter any of the adaptive hormonal responses to exercise in healthy subjects.

One should be cautious in extending these findings to the various clinical conditions for which perindopril may be indicated because different haemodynamic and metabolic circumstances may prevail.

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Perindopril and Physiologic Responses to Exercise

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Summary: Cardiovascular drugs have varying effects on hemodynamic, metabolic, and hormonal responses to exercise. To evaluate the effects of the novel angiotensin-converting enzyme (ACE) inhibitor, perindopril on these exercise-related responses, we studied 9 healthy volunteers in a double-blind, randomized, placebo-controlled trial. After a week of perindopril 4 mg orally daily or placebo therapy, volunteers performed a treadmill effort test; the sequence was repeated after a 1-week washout period. Perindopril caused a significant reduction in mean resting systolic and diastolic blood pressure (SBP, DBP) without increasing resting heart rate (HR); 15-min post-exercise SBP was also significantly reduced. There were no significant differences between the perindopril and placebo effort tests with respect to metabolic indexes studied (serum K^+, plasma glucose, plasma free fatty acids) or plasma hormonal concentrations measured (ACTH and cortisol, norepinephrine (NE) and epinephrine (EPI), glucagon and insulin, growth hormone and prolactin, renin activity). In the perindopril arm of the study, however, there were modest but significant increases in mean serum K^+ before exercise to immediately after exercise (0.4 ± 0.1 m*M*, $p < 0.01$) and mean plasma glucose from before exercise to 5 min (0.6 ± 0.2 m*M*, $p < 0.01$) and 15 min (0.5 ± 0.2 m*M*, $p < 0.05$) after exercise. These data show that perindopril does not impair the hormonal changes associated with exercise in healthy subjects but induces a more consistent increase in blood K^+ and glucose concentrations. **Key Words:** Angiotensin-converting enzyme inhibitor—Perindopril—Exercise—Hormonal responses—Hemodynamic changes—Metabolism.

Some cardiovascular drugs have been shown to have undesirable hormonal and metabolic effects during and after exercise. Nifedipine (1) and β-adrenergic blocking agents (2) cause an exaggerated increase in postexercise plasma catecholamine levels in healthy men. β-Blockers also induce an enhanced increase in serum potassium (K^+) after exercise (3). Angiotensin-converting enzyme (ACE) inhibitors have been used for treatment of systemic hypertension (4), left ventricular (LV) dysfunction with or without congestive cardiac failure (4,5) and, increasingly, occlusive coronary artery disease and its complications (6). The pharmacodynamic actions of perindopril, a relatively new, long acting ACE inhibitor, are evident 4–6 h after administration, with substantial effects still apparent at 24 h. During short- and long-term treatment, oral perindopril caused dose-dependent increases in plasma renin activity (PRA) and angiotensin I (AI), and the expected decrease in angiotensin II (AII), and aldosterone levels (7). However, little information is available regarding the metabolic and hormonal effects of ACE inhibitors in general and perindopril in particular during and after exercise. We assessed whether perindopril therapy would alter the hemodynamic, metabolic and hormonal changes associated with exercise in healthy subjects.

METHODS

Subjects and study protocol

Nine young (age 28–35 years), nonobese (mean weight 74.4 kg, range 64.2–85 kg), normotensive, salt-replete men were studied. The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. The volunteers were not trained athletes, did not smoke, did not take any medication. Subjects were deemed healthy on the basis of a complete medical history and examination. The study was designed as a double-blind, randomized, placebo-controlled, cross-over trial in which each volunteer took perindopril (4 mg)

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or identical placebo daily for 7 days. After a treadmill effort test, a 1-week washout period was allowed before the volunteers were crossed over to the alternative capsule.

Experimental protocol

Each subject arrived at the exercise laboratory at 0730h after an overnight 10-h fast. An indwelling intravenous (i.v.) cannula was inserted near the antecubital fossa, kept patent with slow running saline, and a 30-min rest period was allowed. Baseline blood samples, pulse, and blood pressure (BP) were recorded at 15 min and immediately before the start of exercise. Each subject then performed an exercise treadmill test, starting with an initial warmup period of 3 min at 7% inclination and 5 km/h, followed by a period of brisk exercise for 5 min at 7% inclination and 10 km/h. Blood sampling, pulse, and BP recordings were repeated immediately after and at 5 and 15 min after exercise. A standard sphygmanometer was used to measure BP. Urine samples were obtained before volunteers entered the study and before each effort test.

Laboratory measurements and analytical methods

Blood samples were collected in iced tubes and centrifuged immediately; plasma/serum was separated and stored at −20°C until assayed several weeks later. Plasma glucose, serum K^+, and Na^+, and urine Na^+ were measured by standard laboratory techniques. Plasma free fatty acids were measured by an enzymatic colorimetric assay (8). Plasma catecholamines [epinephrine (EPI) and norepinephrine (NE)] were determined by high-pressure liquid chromatography (9). Radioimmunoassay kits were used to measure plasma hormonal concentrations: insulin and growth hormone (Pharmacia, Sweden), ACTH and cortisol (CIS Biointernational, France), glucagon and PRA (Biodata, Italy) and prolactin (Amersham, England). All samples for an individual subject were analyzed in duplicate in the same assay by technicians with no knowledge of the sequence of drug or placebo administration. All intraassay coefficients of variation were <7.5%.

Statistical analysis

Results are mean ± SEM. Nine complete pairs of data were available for evaluation. Statistical significance of parametric data were assessed by Student's paired *t* test; nonparametric data were assessed by signed rank test for paired samples. Baseline data were taken as a mean of levels obtained 15 min before and immediately before exercise. Results were deemed statistically significant at $p < 0.05$.

Tolerance and safety

The subjects tolerated the medication, and there were no withdrawals from the study. One man had a dry cough, 1 had diarrhea, and one had postural dizziness, all during perindopril therapy.

RESULTS

Hemodynamic data

Perindopril was associated with a significant decrease in mean resting systolic BP (SBP) and diastolic BP (DBP) (6 ± 2 and 7 ± 3 mm Hg, respectively, $p < 0.05$). This hypotensive effect was not associated with an increase in resting heart rate (HR). Perindopril did not attenuate the increase in HR or SBP or accentuate the decrease in DBP that occurred immediately after exercise (Table 1). Mean SBP was significantly lower 15 min after exercise during perindopril treatment (9 ± 1 mm Hg, $p < 0.05$).

Metabolic data

All subjects were Na^+ replete (mean serum Na^+ 139 ± 3 m*M* and mean urine Na^+ 138 ± 54 m*M*). There was no significant difference between the perindopril and placebo treatment periods with regard to mean resting serum K^+ levels (4.1 ± 0.3 m*M* on both occasions) or urinary Na^+ excretion (148 ± 54 m*M* with perindopril vs. 141 ± 61 m*M* with placebo). There were also no significant differences in serum K^+ levels between treatments after exercise. However, with perindopril treatment only, serum K^+ levels increased significantly (0.4 ± 0.1 m*M* $p < 0.01$) from before to immediately after exercise owing to a more consistent pattern of response (Fig. 1). There were no significant differences between the two phases of the study with regard to plasma glucose concentrations after exercise. However, after perindopril, mean plasma glucose rose significantly at 5 min (0.6 ± 0.2 m*M*, $p < 0.01$) and 15 min (0.5 ± 0.2 m*M*, $p < 0.05$) post exercise when compared to pre exercise levels (Fig. 2). Plasma free fatty acids decreased significantly immediately after exercise in both tests (from 0.36 ± 0.02 to 0.22 ± 0.01 m*M* with placebo and from 0.35 ± 0.02 to 0.21 ± 0.01 m*M* with perindopril), but these metabolic responses were similar.

TABLE 1. *Hemodynamic responses (mean ± SEM) to exercise after perindopril or placebo administration in 9 healthy subjects*

			Exercise					
	Baseline		0 min after		5 min after		15 min after	
Parameter	Pl	Per	Pl	Per	Pl	Per	Pl	Per
HR (beats/min)	66 ± 2	66 ± 2	152 ± 2	158 ± 2	95 ± 2	94 ± 2	88 ± 2	87 ± 2
SBP (mm Hg)	124 ± 1	118 ± 1[a]	146 ± 2	141 ± 3	126 ± 1	123 ± 2	125 ± 1	116 ± 1[a]
DBP (mm Hg)	81 ± 1	74 ± 1[a]	66 ± 2	62 ± 2	78 ± 1	71 ± 2	79 ± 2	72 ± 2

HR, heart rate; SBP and DBP, systolic and diastolic blood pressure; Pl, placebo; Per, perindopril.
[a] $p < 0.05$ versus placebo.

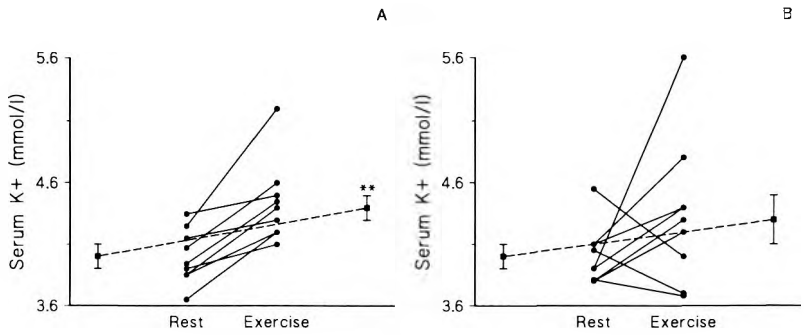


FIG. 1. Change in serum K^+ level before and immediately after exercise for each subject receiving perindopril **(A)** and placebo **(B).** **p < 0.01.

Hormonal data

A significant and progressive increase in mean plasma ACTH and cortisol concentrations occurred during the postexercise period in both tests (Table 2), but there were no significant differences between perindopril or placebo. Furthermore, there were no significant differences at rest for either NE or EPI levels and perindopril did not modify the increase in catecholamines after exercise as compared with placebo.

Plasma glucagon level tended to be lower at all stages after perindopril treatment, but there was a similar pattern of responses in the two studies, with no significant differences (Table 2). Plasma insulin levels surged 5 min after exercise as compared with levels immediately after exercise in both tests. A similar profile of responses was seen after administration of either perindopril or placebo. There was a significant difference at 15 min after exercise, however, with a higher mean insulin level noted after perindopril therapy.

No significant differences were observed in the growth hormone and prolactin response to exercise between the two studies. After exercise, both hormones increased significantly from resting levels (Table 2).

As expected, perindopril caused a significant increase in resting PRA levels. (This finding also indicated compliance by volunteers). The normal significant increase in PRA with exercise (10) was reflected in both tests, with no significant differences between the two with respect to percentage of increase after exercise (Table 3).

DISCUSSION

In normal salt-replete volunteers, the effects of short-term ACE inhibition are controversial (7). Some studies (11,12) showed slight but significant decreases in supine BP after perindopril administration, whereas others (13,14) including ambulatory monitoring (15) showed no significant differences, suggesting that the renin-angiotensin system is not an important determinant of BP in normotensive subjects with free salt intake. However, our limited study, using the physiologic stimulus of graded physical exercise, showed that perindopril produces modest but significant hypotensive effects both before and after exercise in normotensive salt-replete subjects.

The resting hypotensive effect was not associated with reflex tachycardia as has been observed with other vasodilators (16). This may be the result of a vagomimetic action of perindopril, which has been documented in normotensive volunteers treated with this drug (17) and is a property that appears to be common to other ACE inhibitors (18,19). The degree of hypotension at rest may have been insufficient to cause a significant compensatory increase in plasma catecholamine levels or to induce reflex tachycardia. Our results confirm the findings of Ajayi and colleagues showing that perindopril had no significant effect on the pressor or chronotropic changes induced immediately after exercise (17).

Serum K^+ increases during muscle exercise owing to release of K^+ by contracting muscles and decreases rapidly when exercise ceases (3). Our

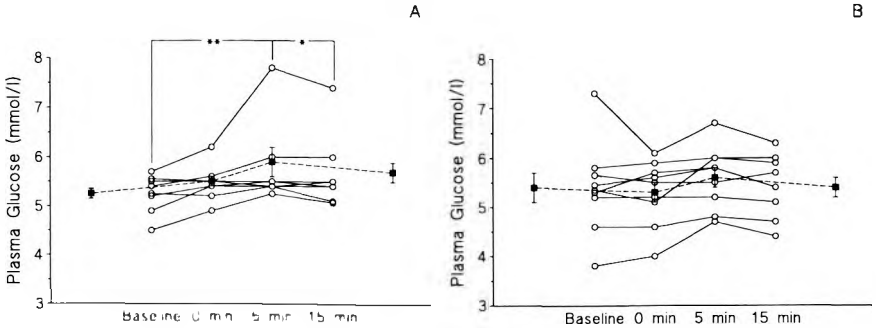


FIG. 2. Change in plasma glucose concentration at baseline and at 0, 5, and 15 min after exercise for each subject receiving perindopril **(A)** or placebo **(B).** **p < 0.01, *p < 0.05.

TABLE 2. *Hormonal responses (mean ± SEM) to exercise after perindopril or placebo administration in 9 healthy subjects*

			Exercise					
	Baseline		0 min after		5 min after		15 min after	
Hormone	Pl	Per	Pl	Per	Pl	Per	Pl	Per
ACTH (p*M*)	19.7 ± 1.5	22.9 ± 1.8	61.1 ± 9	60.1 ± 9	126.8 ± 15	161 ± 26	73.8 ± 8	87.9 ± 13
Cortisol (n*M*)	419 ± 10	446 ± 12.5	418 ± 10	453 ± 12	455 ± 14	475 ± 13	525 ± 16	550 ± 19
NE (pg/ml)	216 ± 39	243 ± 17.5	2893 ± 650	2686 ± 566	838 ± 146	836 ± 19	366 ± 67	441 ± 44
EPI (pg/ml)	38 ± 10	37.5 ± 8.5	286 ± 90	236 ± 60	69 ± 19	60 ± 19	43 ± 13	50 ± 15
Insulin (mU/L)	7.7 ± 0.5	6.9 ± 0.3	7.8 ± 0.6	5.8 ± 0.2	13.5 ± 0.7	13.2 ± 0.9	12.4 ± 0.8	16.5 ± 1.0[a]
Glucagon (pg/ml)	129 ± 5	113 ± 5	120 ± 5	110 ± 5	134 ± 5	119 ± 5	127 ± 5	114 ± 6
GH (mU/L)	0.8 ± 0.2	2.25 ± 0.7	5.5 ± 1.2	5.9 ± 1.7	8.7 ± 1.2	8.0 ± 1.7	11.9 ± 1.4	10.3 ± 1.6
Prolactin	3.2 ± 0.2	4.2 ± 0.3	4.1 ± 0.3	4.2 ± 0.3	5.2 ± 0.3	7.1 ± 0.8	4.8 ± 0.4	6.9 ± 0.9

ACTH, adrenocorticotropin; GH, growth hormone; NE, norepinephrine; EPI, epinephrine; other abbreviations as in Table 1.
[a] $p < 0.01$ versus placebo.

finding of a slight but significant increase in postexercise K^+ and glucose levels only during the perindopril study arm is of interest but should be interpreted with caution, since it was due mainly to a more uniform pattern of response rather than to greater absolute increases. Possible reasons for this are not clear, but are not related to more marked perturbations of either catecholamine or insulin secretion induced by perindopril immediately after exercise.

The predominant increase in NE (13-fold with placebo, 11-fold with perindopril) as contrasted with the more moderate increase in EPI (sevenfold with placebo, sixfold with perindopril) after exercise suggests their source is the sympathetic nervous system rather than the adrenal gland, as was confirmed in other studies (20). The absence of excessive postexercise stimulation of the sympathetic nervous system by perindopril differs from results noted after exercise with both selective and nonselective β-blockers (2) as well as the calcium channel antagonist nifedipine (1) and is a useful property for a vasodilator drug. Studies of ACE inhibitors (21) in patients with heart failure showed a reduction in postexercise catecholamine levels whereas a heightened response was noted after β-blocker administration (22).

Perindopril did not impair the normal pattern of other hormonal responses occurring after exercise, as other investigators have also shown (23), although no previous study has investigated as wide a range of different hormones and their responses after ACE inhibitor administration as we did.

Perindopril caused a significant decrease in SBP and DBP before exercise but did not impair the hemodynamic changes associated with exercise. It did produce a more consistent increase in serum K^+ and plasma glucose levels after exercise, however. The drug did not alter adaptive hormonal responses to exercise in normal subjects. One should be cautious in extrapolating our findings to the various clinical conditions for which perindopril may be indicated because different hemodynamic and metabolic circumstances may prevail.

TABLE 3. *PRA responses (mean ± SEM) to exercise after perindopril or placebo administration in 9 healthy subjects*

	pRA (ng/ml/h)	
Parameter	Pl	Per
Before exercise	0.73 ± 0.4	3.84 ± 0.47[a]
Immediately after exercise	1.93 ± 0.13[b]	9.77 ± 1.8[a,b]
Increase (%)	264	254

PRA, plasma renin activity; Pl, placebo; Per, perindopril.
[a] $p < 0.01$ versus placebo.
[b] $p < 0.01$ versus before exercise.

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