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Mild hypertension : studies on pathophysiology and treatment

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MILD HYPERTENSION:
STUDIES ON PATHOPHYSIOLOGY AND TREATMENT

Mild hypertension: studies on pathophysiology and treatment

Proefschrift

ter verkrijging van de graad van doctor in de geneeskunde
aan de Rijksuniversiteit Limburg te Maastricht,
op gezag van de rector magnificus, prof. dr. F.I.M. Bonke,
volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen op vrijdag 10 oktober 1986
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door

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Puisqu'on ne peut être universel et savoir tout ce qui peut se savoir sur tout, il faut savoir peu de tout. Car il est bien plus beau de savoir quelque chose de tout que de savoir tout d'une chose.

Blaise Pascal (1623-1662)
'Pensées sur l'esprit'

To my mother
In memory of my father

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Chapter 1

GENERAL INTRODUCTION

1.1 WHAT IS NORMAL BLOOD PRESSURE AND WHAT IS HYPERTENSION?

After the introduction of the standard method to measure arterial blood pressure indirectly with a cuff and a mercury manometer by Scipione Riva-Rocci in 1896 and the observation of Nicolai Sergeivich Korotkoff in 1905, who related the sounds during deflation of the cuff to systolic and diastolic blood pressure (O'Brien et al., 1985), it became possible to measure blood pressure more accurately than with the methods described earlier by Reverend Stephen Hales in 1733 and Siegfried Karl Ritter von Basch in 1881 (Folkow, 1982). From then on medical doctors and other personnel have been measuring blood pressure for years with the anaeroid or the mercury sphygmomanometer. Especially in the last few years, new devices measuring blood pressure indirectly have been developed, being automatic (Arteriosonde, Dinamap) or semi-automatic. The latter are being used for home measurements by patients (Steiner et al., 1985). Until today the blood pressure measurement is still of great importance in the everyday work of medical personnel. Research and development together made it even possible to measure intra-arterial blood pressure during 24 hours with the Oxford method (Mancia et al., 1983) in order to follow blood pressure in normal or untreated subjects or to get an impression of blood pressure of the patient during antihypertensive treatment. The latter could be seen as an advancement in control as compared to the casual blood pressure measurements during the short moments of the patient's visit to the hospital or at the office of the practitioner.

But what is "normal" blood pressure and what is "hypertension"? The height of the values of the arterial blood pressure is continuously distributed in the general population in a normal Gaussian fashion, at least in young age (20-25 years) (Doyle, 1983). In the years 1960-1962 the National Health Survey performed a study in the white population of the United States (18-79 years), a random sample was taken and a representative distribution of blood pressure was found (NHS, 1964). So, arterial blood pressure has its distribution to both sides. It is furthermore stated that arterial blood pressure is a quantity and not a quality (Hansson, 1983). The intra-individual variability of the blood pressure has become apparent (Millar-Craig et al., 1978).

Thus, blood pressure is a continuous variable, even in the same person, due to intra-individual variability depending on factors like circumstances of measurement, time of the day, etc.

The term hypertension has its roots in the greek prefix "hyper", meaning too strong or high, and the latin "tensio" meaning tension or stress. The term hypertension is arbitrary and was born out of the need to describe a blood pressure which was higher than normal. Practical reasons and the lack of a better alternative (Julius and Hansson, 1983) have made the term hypertension a more convenient and shorter description than the term "high blood pressure". It should be borne in mind, however, that the terms defined as normotension and hypertension are based on epidemiologic and statistical data. The term hypertension means in descriptive sense (the chronically elevated) arterial blood pressure above the mean of the group or in the upper end of a normal distribution. The demarcation between normal and abnormal (high) blood pressure indicates higher morbidity and mortality within 5-20 years in the group with high blood pressure (Peart, 1983). Normotension in the same sense describes the mean blood pressure in the population with a low risk. Thus, the term hypertension suggests that we are dealing with a value which carries exceeding risks for morbidity and mortality. In short, "the relationship between arterial pressure and mortality is quantitative, the higher the pressure, the worse the prognosis" (Pickering, 1972).

According to the definition of the World Health Organisation (WHO), normotension is the systolic/diastolic blood pressure <140/90 mm Hg and hypertension is systolic >160 and/or diastolic >95 mm Hg, diastolic blood pressure measured in phase V (Korotkoff sound V) (WHO report, 1978). Blood pressure between these two definitions, i.e. <160/95 mm Hg but >140/90 mm Hg is designated borderline hypertension. This will be dealt with extensively in chapter 1.8. However, the definitions of the WHO are subject to discussion (Julius et al., 1980), because the age related increase of blood pressure is disregarded. It is generally accepted that there is a tendency for blood pressure to rise with age (Metropolitan Life Insurance Bulletin, 1969; Valkenburg et al., 1980; Hofman and Valkenburg, 1980; Lancet Editorial, 1981; Watt, 1986). So with age, in the normal distribution of blood pres-

sure, there will be an extension of the distribution towards higher values. An adjusted definition by Julius and Hansson (1983) seems to be more practical regarding the age related blood pressure increase:

normotensive:	17-40 years	<140/90 mm Hg
	41-60 years	<150/90 mm Hg
	>60 years	<160/90 mm Hg
hypertensive:	17-60 years	>160/95 mm Hg
	>60 years	>175/95 mm Hg

1.2 EPIDEMIOLOGIC ASPECTS OF HYPERTENSION

Hypertension is recognized as a world wide problem, but is no doubt a more serious problem and believed to be more common among the population in the industrialized western countries; however, there are exceptions. With the increasing occurrence of studies in which blood pressure data become available, estimates of the prevalence of hypertension appear in the literature. As early as 1925 blood pressure data of 560.000 men have been published (Society of Actuaries, 1980). It is now commonly accepted that the prevalence of hypertension is around 15-20% (Society of Actuaries, 1980; Epstein, 1983). But since prevalence rates in these studies depend on multiple factors like age, sex, way and number of blood pressure measurements, the level or definition of the blood pressure, etc., it is difficult to look at these percentages alone without including these factors. The National Health Study performed a study from 1960 to 1962 which gives a clear impression how the factor age plays a role in the prevalence. In this study, three measurements of blood pressure were performed with the standard mercury sphygmomanometer with Korotkoff phase V as diastolic pressure. It was reported that males and females with an age of 18-24 years had a frequency of 6.9% and 2.1% respectively of diastolic blood pressure >90 mmHg, whereas males and females in the group of 55-64 years, 23.1% and 22.2% respectively had diastolic blood pressure >90 mmHg (Gordon, 1964). Another study in the Unites States, the U.S. Public Health and Nutrition Examination Survey (HANES) of the years 1971-1974 reported that 15% of the white and 28% of the black population surveyed were

hypertensive (>160 mmHg systolic or >95 mmHg diastolic blood pressure) and a progressively rising prevalence with age was found (Roberts, 1977). Confirmation of the higher prevalence of hypertension in blacks, 38% vs. 29% in whites, was found in the report of the National Health and Nutrition Examination Survey (NHANES) II in 1985, but it is unknown whether genetic or environmental factors account primarily for these differences (Epstein, 1983). A newer report on the NHANES II data, performed in the years 1976-1980, confirms that hypertension is a highly prevalent condition among the population of the Unites States: 29.8% have hypertension (Joint National Committee, 1985). However, certain limitations of this study must be noted. Only once blood pressure was measured, not all population groups are included and only blood pressure <140/85 mmHg was defined as normal. Studies in Sweden reported among men of 43-46 years old a prevalence of 55% (Wilhelmsen et al., 1973) and in Australia among women and men between 50-59 years 12.7% (Prineas et al., 1973). In the Federal Republic of Germany a blood pressure study was performed in Munich from 1980-1981. Two years later another study was performed in Lübeck, a city in the northern part of the Federal Republic. The WHO definition of hypertension was used in both studies and when including the borderline hypertensive subjects, every third citizen in Munich in the age group of 30-69 years had raised blood pressure readings. 22.7% of the men and 12.2% of the women are classified in the mild hypertension category (diastolic 90-104 mmHg) (Keil et al., 1983). In Lübeck in the same age group the prevalence for hypertension was among males 19.9% and 13.5% among females (Keil et al., 1985).

There seems to be a higher incidence of hypertension among the population in the industrialized countries. There are low blood pressure population groups described, e.g. Kalahari desert bushmen, Chinese aborigines and West Malaysians, in whom also a slight or no tendency at all for the age-related blood pressure rise is found (Page, 1983). The explanation must be sought among environmental factors (Page, 1976). Thus, hypertension in today's modern western society is one of mankind's most common diseases and is a major health problem affecting about 15-20% of all adults.

1.3 CLASSIFICATION OF HYPERTENSION

The different forms of arterial hypertension can be classified according to their etiology or cause. The following table (Table 1) lists the different types of hypertension by their cause (Julius and Hansson, 1983). It illustrates quite clearly the problems general practitioners and clinicians are faced with when dealing with and diagnosing the cause of hypertension in their patients.

Arterial hypertension is classified as either essential (I) or secondary (II). Essential hypertension is also described by other terms like primary or idiopathic hypertension. The German clinician Frank contributed the prefix "essential" ("essentielle Hypertonie") to imply that the elevation of blood pressure was of unknown origin (Frank, 1911). As described in chapter 1.2, the disease hypertension is prevalent in about 15-20% of the population. Within this hypertensive population, the frequency of essential hypertension ranges between 89-95% as studies in different countries have shown (Kaplan and Lieberman, 1982). The term secondary hypertension is used when a factor or a disease can be associated with the rise of the blood pressure, e.g. chronic nephritis or pheochromocytoma.

For the purpose of clarity and the fact that the studies described later in this thesis deal with essential hypertension, no further details will be discussed about secondary or malignant hypertension. For further information and details concerning both, see the text books and review articles cited.

In order to diagnose either essential hypertension or to exclude secondary hypertension some basic tools are needed. Correctly performed and multiple blood pressure measurements and a thorough history including a careful physical examination are important. Further tools for the clinical classification are fundoscopic examination, assessing vascular damage with the scale by Keith, Wagener and Barker, urinalysis, assessment of renal function (serum creatinine) and if indicated an intravenous pyelogram. Further factors analyzed are plasma sodium, potassium, calcium, cholesterol, blood uric acid and sugar. Furthermore, an electrocardiogram is made, to look for signs of left ventricular hypertrophy. It should be taken into consideration, however, that

Table1 Classification of hypertension by etiology (from Julius and Hansson, 1983)

I. Essential hypertension
II. Secondary hypertension
  A. Renal
    1. Parenchymal
      a. Acute glomerulonephritis
      b. Chronic nephritis, glomerulonephritis, pyelonephritis, heredity, irradiation, lupus erythematosus
      c. Polycystic kidney disease
      d. Hydronephrosis
      e. Renin-producing tumor
      f. Diabetic nephropathy (Kimmelstiel-Wilson)
    2. Renovascular
      a. Fibromuscular arterial stenosis
      b. Atherosclerotic arterial stenosis
      c. Renal infarctions
      d. Polyarteritis
    3. Trauma
      a. Perirenal hematoma
      b. Renal arterial thrombosis
      c. Renal arterial dissection
  B. Endocrine
    1. Thyroid
      a. Hyperthyroidism
      b. Hypothyroidism
    2. Adrenal
      a. Pheochromocytoma
      b. Primary aldosteronism
      c. Adenoma
      d. Hyperplasia
      e. Glucocorticoid suppressible hyperaldosteronism
      f. Congenital adrenal hyperplasia
        (1) 11β-Hydroxylation deficiency
        (2) 17α-Hydroxylation deficiency
      g. Cushing's disease
    3. Parathyroid
      a. Hyperparathyroidism
    4. Pituitary
      a. Acromegaly
  C. Neurogenic
    1. Respiratory acidosis (carbon dioxide retention)
    2. Brain tumor
    3. Encephalitis
    4. Bulbar poliomyelitis
    5. Familial dysautonomia
    6. Acute porphyria
    7. Quadriplegia ("micturitional crisis")
    8. Extraadrenal chromaffin tumors
      a. Paragangliomas
      b. Von Recklinghausen's disease
  D. Mechanical interference with flow
    1. AV fistulas (Paget's disease, patent ductus arteriosus)
    2. Aortic insufficiency
    3. Coarctation of the aorta
    4. Atherosclerotic systolic hypertension
  E. Exogenous
    1. Poisoning
      a. Lead
      b. Thallium
    2. Medication
      a. Sympathetic amines
      b. MAO inhibitor combined with ephedrine or tyramine (including tyramine-rich foods, cheese, red wine)
      c. Birth control pills
      d. Prednisone—high doses
    3. Food
      a. Licorice ingestion

4. Iatrogenic
   a. Volume overload in marginal renal insufficiency
F. Toxemia of pregnancy
G. Miscellaneous
   1. Polycythemia
      a. Rubra vera
      b. "Stress," Gaisbock's syndrome
   2. Burns
   3. Carcinoid syndrome

Table 1 (continued)

the simplest, cheapest and least invasive tests should be always performed first, before those more complex, expensive and uncomfortable are performed (Ménard et al., 1983).

The severity of hypertension in the individual hypertensive patient can be further classified. A clinical classification, based also on the investigations and parameters as described above, can be used. The clinical classification can be of much help for further decisions regarding urgency and choice of treatment. Table 2 shows this classification (Julius and Hansson, 1983). Fundoscopic examination is of utmost importance for the classification. Some basic principles about this classification should be described:

- very high blood pressure need not be accompanied by laboratory abnormalities. In this case the severity of hypertension is in direct proportion to the blood pressure measured;
- the category of severity increases with the presence of laboratory abnormalities;
- if retinopathy grades III or IV are present, this finding determines the category of severity in this patient irrespective of the height of the blood pressure measured at the same time.

At each level of the basic class of the classification in severity the hypertension can be uncomplicated or complicated. Hypertension is complicated if there is evidence of congestive heart failure, angina pectoris, cardiac arrhythmias; furthermore, if there is evidence of present or past vascular events (stroke, arterial aneurysms, myocardial infarction).

Table 2 Classification of severity of hypertension (from Julius and Hansson, 1983)

Class	BP level	Funduscopic examination	ECG	Urine	Renal function
Borderline hypertension	See text.	Normal	Normal	Normal	Normal
Mild hypertension	161/101-180/120	Grade I-II†	LVH†	Normal	Normal
		Normal or grade I-II	Normal	Normal	Normal
Moderate hypertension	161/101-180/120	Normal or grade I-II	LVH†	Albumin†	Depressed†
	181/121-190/130	Normal or grade I-II	:	:	:
Severe hypertension	Hypertension	Hemorrhages and exudates (grade III)	:	:	:
	>191/131	Grade II			
Malignant hypertension	Hypertension	Papilledema (grade IV)	:	:	:

†Any one of these present.
:Laboratory findings may be but are not necessarily abnormal.

1.4 THE RISK FACTOR HYPERTENSION

Since years, it has become more obvious that (untreated) hypertension plays an important contributing role in cardiovascular morbidity and mortality (Thom and Kannel, 1981). The ten leading causes of death in the United States from 1900 to 1980 (Levy and Moskowitz, 1982) indicate that diseases affecting the cardiovascular system are the leading cause of death (Hollander, 1976).

At the time when effective antihypertensive drugs were not yet available, the mean survival time in years in several patients with malignant hypertension was only 8.4 months, as described by Schottstedt and Sokolow (1953). Some years later, the Metropolitan Life Insurance Company (1961) reported a reduced expectation of life in years in benign hypertension. The higher the blood pressure and the age, the lower the expectation of life in years, e.g. 45 year old males with a blood pressure of 150/100 mmHg have an expectancy of 20.5 years vs. 32 years in the same group with only 120/80 mmHg. A prospective study performed by Sokolow and Perloff (1961) in 439 consecutive essential hypertensive patients (>160/90 mmHg) confirmed a progressive rise in

mortality in the group of patients with a blood pressure of 250/130 mmHg when compared to the group with 200/110 mmHg. In another study patients with fundoscopic grade I and II lesions were followed for 5 years and it was found that the more fixed the high blood pressure, the worse the prognosis (Smirk, 1964). It is now accepted that the cardiovascular consequences or complications of hypertension are proportional to the height of the blood pressure (Dawber and Kannel, 1972; Kannel, 1974; Doyle, 1976; the Pooling project, 1978; Lancet Editorial, 1978; Svärdsudd and Tibblin, 1979) and that hypertension is one of the major risk factors for coronary heart disease (Stamler, 1979). Furthermore, clinical, experimental and studies in pathology strongly indicate that hypertension plays a major role in coronary heart disease, sudden death, stroke, congestive heart failure and renal insufficiency (Hollander, 1976; Johnson and Muirhead, 1980).

Hollander (1976) and Levy and Moskowitz (1982) reported considerable evidence that with the increase in awareness and the control of blood pressure in the population, a decline in mortality from diseases associated with hypertension will occur. Furthermore, a prevention of many cardiovascular complications like congestive heart failure, hemorrhagic stroke, progressive renal damage, dissecting aneurysm, etc. would result. But despite the awareness and the major efforts to educate the public and to screen and treat persons with hypertension in the United States (Harlan et al., 1984), the comparison of the blood pressure level from the years 1960 to 1980 suggests only a modest decline in blood pressure during this period (Rowland and Roberts, 1982). One of the important problems of hypertension among the population is the awareness of having hypertension. In the National Health Survey performed from 1960 to 1962 about 58% of the hypertensives were unaware of the high blood pressure (Roberts, 1977). An improvement, i.e. a decline of unawareness was seen during the following years as Levy and Moskowitz (1982) reported. The Hypertension Detection and Follow-up Program (HDFP) from 1973 to 1974 reported that only 25% of the hypertensive subjects were unaware (HDFP, 1977). With the help of several programs, the decline of unawareness of high blood pressure and a more effective control of blood pressure including an adequate treatment, was a remarkable achievement as stated by Moser (1983).

However, as already Ames and Hill (1982) have reported in their study, hypertension intervention studies like the Veterans Administration Study I and II (1967, 1970), the Australian Therapeutic Trial in mild hypertension (1980) and the Oslo Study (Helgeland, 1980) indicate no benefit on the incidence of coronary heart disease. But in these studies, a clear-cut benefit on the incidence of stroke was reported. This was later confirmed in the Medical Research Council Working Party Trial of treatment of mild hypertension (MRC Trial, 1985) and the European Working Party on High Blood Pressure in the Elderly (1985). Moser (1983), too, reports a decrease of stroke death rate of 45% in the United States over the past 15 years. He sees the reason for this in the implementation of the National High Blood Pressure Education Program and other modalities of care, like reduction of the tobacco and saturated fat consumption. Other factors which could induce high blood pressure like excessive salt intake, overweight and intake of oestrogens should be thought of as well. Furthermore, the incidence of congestive heart failure is reduced by antihypertensive therapy, as the Veterans Administration Cooperative Study Group on antihypertensive agents I and II (1967, 1970) showed.

In a recent article, Staessen et al. (1983) analyzed the different intervention studies which compared treated with untreated hypertensive patients. Total mortality incidence appears to be reduced in the active treatment group compared to the control group, when looking at all trials. However, only in 3 individual trials, there was a statistically significant difference in favor of active treatment or stepped care, i.e. the Göteborg Trial, the HDFP and the Australian Trial in mild hypertension. In other trials, no difference was found (Hypertension Stroke Cooperative Study; US Public Health Service Mild Hypertension Trial (McFate-Smith, 1977); the Oslo Study (Berglund, 1978)) or no difference indicated (Veterans Administration Cooperative Study on antihypertensive agents I and II, 1967, 1970). The authors Staessen et al. (1983) conclude that antihypertensive drug treatment can improve prognosis in well-defined segments of the hypertensive population, such as middle-aged men with diastolic blood pressure on repeated examination >95 mm Hg. But unfortunately, hypertension, as stated before, is (only) one of the major risk factors, associated

prognostically with other major risk indicators for cardiovascular disease, e.g. cigarette smoking, hypercholesterolemia, to a lesser extent obesity, impaired glucose tolerance (diabetes mellitus) and physical inactivity. Thus, when treating hypertension with active drug therapy, these risk factors could outweigh the hypertensive risk factor and therefore possibly prevent a decrease in morbidity and mortality. Does this mean that possible treatment in hypertensive patients with several additional risk factors should be started earlier in time and at a lower height of increased blood pressure? The answer to this needs confirmation in further studies.

High blood pressure is thus associated with excess mortality and morbidity when compared with normal blood pressure, especially when other risk factors are present. With the aid and the efforts of the public programs dealing with active treatment, awareness and epidemiologic aspects of hypertension, performed in the United States and elsewhere especially in the last years, the benefits may not be statistically significantly provable with hard data at the moment. However, at least the trends in awareness, treatment and control states (Joint National Committee, 1985) could bring some benefits in the long run. Awareness of the population and thus possibly earlier intervention to prevent complications are two of the important factors which could play a role in the long run.

1.5 BLOOD PRESSURE REGULATION

Physiologic control of blood pressure and the circulation is very complex. This chapter is not meant to give a complete description but rather a short overview. The control of arterial blood pressure is realized by several systems interacting and influencing each other. Arterial blood pressure, cardiac output and total peripheral resistance are related together as follows:

arterial pressure = cardiac output x total peripheral resistance.

Any condition influencing the factors cardiac output or total peripheral resistance will cause an effect on arterial pressure, supposing the other of the two factors does not change. But neither of the two factors is the fundamental controller because each of the two is influenced and controlled by other subfactors. The short-term and long-term regulation of blood pressure are important for the regulation of blood pressure in different situations. Short-term regulation processes include: (1) the influences from the autonomic nervous system through the baroreceptors, chemoreceptors and somatic afferents, and the ischemic mechanism in the central nervous system; (2) the hormonal system, e.g. renin-angiotensin vasoconstriction, the vasopressin mechanism and the noradrenaline and adrenaline vasoconstrictor mechanisms; (3) the capillary fluid shifts to and from the circulation, and (4) the stress relaxation of the vasculature (Guyton et al., 1981; Guyton, 1981a). It must be emphasized that the sympathetic nervous system is one of the important factors regulating renin release. Furthermore, there seems to be an important relationship or mediating effect between the augmented release of the neurotransmitter amines in the sympathetic nerve terminals and the vasoconstrictive action of angiotensin II (Kuchel, 1983).

The long-term mechanism for arterial blood pressure regulation includes renal-body fluid-pressure control involving several subsystems: the renin-angiotensin-aldosterone axis, the renal fluid control through pressure diuresis and pressure natriuresis. The renal output of water and salt and the net rate of fluid intake are the important determinants on the long-term (Guyton, 1981a). A change on the level of one or both determinants, such as stimulation of the kidneys by excess renin-angiotensin-aldosterone or sympathetic signals, will change the renal output. Decrease of glomerular filtration rate and primary aldosteronism are pathological states which influence the blood pressure on the long-term.

Furthermore, within every organ and tissue an adequate flow is maintained by a system of autoregulation, so when blood pressure falls, vasodilatation occurs and when blood pressure rises a vasoconstriction takes place. The theory about autoregulation was at first suggested by Borst and Borst-de Geus (1963). This term refers to the

capacity of vascular beds to control regional blood flow in accordance with changing needs (Korner, 1980). It can be seen as a rapidly reacting process as well. More details are described in the articles by Korner (1980) and Cowley (1980).

The cardiac output can be influenced by the autonomic nervous system through the sympathetic and parasympathetic branch, both can change heart rate and strength of contraction. Parasympathetic activation causes a decrease of the heart rate and a decrease of the strength of contraction, whereas sympathetic activation leads to the opposite. An increase of sympathetic activity and/or a decrease of parasympathetic activity will lead to a change of cardiac output. Thus, an activation of the sympatho-adrenal system will cause an increase of cardiac output and systemic arterial resistance. This could have an important consequence for the development of hypertension. Although other factors such as prostaglandins, the kallikrein-kinin system, opioid peptides, atrial natriuretic peptides and others may be of importance, however, their precise function in the regulation of arterial blood pressure have not been fully defined. For a more detailed description of all mechanisms and factors which regulate arterial blood pressure, there are a number of papers and reviews which I refer to (Struyker Boudier and Rahn, 1979; Brody, 1981; Guyton et al., 1981; Guyton, 1981b; Dustan, 1982; Folkow, 1982). All in all, with the knowledge we have today about the influence of the autonomic nervous system and its sympathetic and parasympathetic branch, together with their effects on various levels and through the activation of humoral factors, it becomes obvious that the sympatho-adrenal system is one of the major factors regulating blood pressure.

1.6 THE AUTONOMIC NERVOUS SYSTEM

The cardiovascular system and therefore also blood pressure is to a large extent under the influence of the autonomic nervous system. In humans, a complexity of blood pressure regulating mechanisms maintain an adequate blood pressure in supine and upright position and in other situations, e.g. mental and physical stress (Kuchel, 1983).

Through a complex reflex arc, by means of a negative feedback mechanism, blood pressure is controlled autonomically (Edis and Shepherd, 1970). The reflex arc depends on three systems and they can be described shortly as follows: an afferent limb sending information from the periphery to the central part, the central mediating and modulating part, and the efferent limb transmitting impulses from the central part to the peripheral cardiovascular organs or effectors.

The afferent limb can be shortly described as follows. The baroreceptors, being sensory sites in the carotid sinuses, aortic arch and some larger vessels, are activated by local vascular distension resulting from an increase in intra-arterial pressure. The arterial baroreceptors (high pressure receptors) are very important in buffering excessive falls or increases of blood pressure, within the systolic blood pressure range of 60-160 mm Hg particularly. The afferent impulses from the aortic arch are transmitted via the vagal nerve (Xth cranial nerve) and from the carotid sinuses via the glossopharyngeal nerve (IXth cranial nerve) to the medulla oblongata. Other receptor systems include low pressure receptors in the atria and ventricles of the heart and in the pulmonary circulation, and chemoreceptors in the arcus aortae activated by hypoxemia. It is now generally believed that the afferents arising from all these receptors synapse exclusively within the nucleus tractus solitarius (Dampney, 1981). From all these receptors, also via other somatic afferents, stimuli are transmitted to the medullary cardiovascular or vasomotor center. Belonging to the central part, this is a well-defined area of the brain stem from mid pons to medulla oblongata. Here, also other influences are received by and modulated through higher integrative centers which are located in the hypothalamus, the limbic system and the cortex cerebri. These areas are believed to represent a possible link between blood pressure and emotional stimuli (Kuchel, 1983). The nature of the central control and pathways presents a difficult problem and has been a matter of controversy (Seller et al., 1980; Kollai and Koizumi, 1981; Chalmers et al., 1981; Korner, 1981). There are at least 5 basic processes occurring in the central nervous system in mediating autonomic function (Brooks, 1981): (1) feedback to or on the afferent pathways; (2) interactions between centers; (3) central interaction between central

representations of the parasympathetic and sympathetic divisions of the autonomic system; (4) reactions organizing and initiating patterns of efferent discharge; (5) continuing actions that modify the activities started, on the basis of feedback triggered by the effector activity initiated. Dampney (1981) states that there is evidence for the opinion that there is no all-important "vasomotor center" within a specific part of the lower brain stem, but there are indications for several parallel central pathways along which both tonic and reflex control of activity in sympathetic preganglionic neurones is mediated (Dampney, 1981).

So, in the central nervous system, a constant flow occurs of afferent impulses from the periphery, the somatic afferents and the higher centers. Through an integration of this input, the result is a continuously readjustment of the tone of the peripheral cardiovascular system through the efferent network of autonomic fibers (De Champlain, 1977). The autonomic system is constantly in action; not all its efferent neurones show a high level of tonic activity, but certainly those which innervate the heart and the blood vessels (Brooks, 1981).

The two important efferent pathways of the autonomic nervous system are the sympathetic and the parasympathetic nervous system. For the regulation of the circulation the sympathetic nervous system is the most important of the two. Sympathetic nerve fibers leave the spinal cord through all the thoracic and the first one to two lumbar spinal nerves. The preganglionic neurones synapse with postganglionic neurones in the peripheral ganglia (Dampney, 1981). In the periphery the most densely innervated sympathetic segments of the whole vascular tree are the small arterioles which have a crucial influence on blood pressure homeostasis (Mellander and Johansson, 1968). Furthermore, the innervation of the larger arteries and veins makes it possible to change the volume of the peripheral circulatory system. Sympathetic stimulation markedly increases heart rate and the pumping strength of the heart. In addition, the sympathetic nervous system is responsible for the catecholamine secretion by the adrenal medulla (Malmejac, 1964).

The parasympathetic nervous system has its fibers leaving through several of the cranial nerves and the second and third sacral

spinal nerve. The vagal nerves possess about 75% of all parasympathetic nerve fibres. The entire thoracic and abdominal regions are receiving vagal fibers. Also, fibers of the seventh nerve pass to the lacrimal, nasal and submaxillary glands. The ninth nerve is sending fibers to the parotid gland. Parasympathetic stimulation causes a marked decrease of heart rate and a slight decrease of contractility. The salivary secretion, which will be dealt with in the later described study in chapter 3, is controlled by parasympathetic nervous signals. The preganglionic fibers pass directly to the organ to be innervated. In the wall of the organ they synapse with their postganglionic neurones. All preganglionic neurones, in both the sympathetic and parasympathetic nervous system have acetylcholine as neurotransmitting substance. Most of the postganglionic sympathetic neurones are noradrenergic, with the exception of sweat glands (Guyton, 1981) and some blood vessels like umbilical and placental blood vessels (Vanhoutte, 1981). The postganglionic neurones of the parasympathetic fibers are again cholinergic.

Two major receptor types are the sites of action for the catecholamines noradrenaline and adrenaline. Almost 40 years ago, Ahlquist (1948) classified the adrenergic receptors in alpha- and beta-adrenoceptors. In short, alpha-adrenergic receptors mediate responses as the constriction of vascular and uterine smooth muscle; noradrenaline is the major agonist. More recently, these alpha-adrenoceptors have been subdivided into $alpha_1$-receptors and $alpha_2$-receptors (Langer, 1974; Berthelsen and Pettinger, 1977). Lands et al. (1967) subdivided the beta-receptors into $beta_1$- found predominantly in heart, brain and adipose tissue, and the $beta_2$-receptors found in blood vessels, bronchi, liver and skeletal muscle. Beta-adrenoceptors are mainly stimulated by adrenaline resulting in a relaxation of smooth muscle, dilatation of arteries, uterus relaxation, bronchodilatation and inducing glycogenolysis. $Beta_1$-mediated effects are cardiac dromotropic and chronotropic responses and lipolysis. So, for the cardiovascular system the noradrenaline-mediated beta-adrenoceptor effects are increased heart rate, cardiac output and a further effect is the increase of plasma renin activity (Bühler et al., 1985). A further detailed description about the regulation, the effects and the struc-

ture of adrenoceptors will be omitted. A number of articles and reviews will be referred to (Lefkowitz, 1979; Van Zwieten and Timmermans, 1980; Lees, 1981; Malinoff et al., 1981; Vanhoutte, 1981; Nahorski, 1981; Motulsky and Insel, 1982; Timmermans and Van Zwieten, 1982; Hedberg, 1983; McGrath, 1983; Venter and Fraser, 1983; Insel, 1984; Stiles et al., 1984).

The locations for catecholamine synthesis are in the brain, the sympathetic nerve endings and at sites where chromaffin tissue is found, including the adrenal medulla. The main pathway for the synthesis of the major neurohumoral transmitter noradrenaline starts with the essential amino acid L-tyrosine. The postganglionic adrenergic nerve endings take up tyrosine from the extracellular fluid (Shepherd and Vanhoutte, 1981). It is hydroxylated by the action of the enzyme tyrosine hydroxylase, which is present in the mitochondria, to form dihydroxyphenylalanine (L-DOPA). Tyrosine hydroxylase is the main rate-limiting enzyme in the synthesis of the adrenergic transmitters (Vanhoutte, 1981). L-dopa is converted by the cytoplasmic dopa decarboxylase to dihydroxyphenylethylamine (dopamine). Dopamine is transported into the granulated storage vesicles where the final hydroxylation takes place. Intravesicular dopamine beta-hydroxylase transforms dopamine to noradrenaline. The newly synthesized noradrenaline is then stored and bound to ATP within the storage vesicles in an inactive form. Additionally, an intracellular pool of noradrenaline exists, which is neither bound nor stored; presumably in equilibrium with the noradrenaline in the vesicles. An increase in the neuroplasmic concentration of noradrenaline exerts a negative feedback on tyrosine hydroxylase (end product inhibition), whereas increased activity of the adrenergic neuron or depletion of the catecholamine stores has the opposite effect (Vanhoutte, 1981). The neural impulse, generated in the ganglionic cell body and passing to the periphery via the sympathetic fibers, reaches the nerve endings in the effector organ. Upon this action potential and the consequent penetration of Ca^{2+} ions into the neuroplasm, the vesicles migrate to and fuse with the neuronal cell membrane (Shepherd and Vanhoutte, 1981). Their entire soluble content, including noradrenaline and dopamine beta-hydroxylase, is emptied into the junctional cleft (exocytotic release (Smith and

Winkler, 1972)). The noradrenaline released on stimulation diffuses through the synaptic cleft to act locally on specific receptors of the effector cells. Exceptions to this constitute the adrenal medulla and certain brain neurones (Hökfelt et al., 1974), where noradrenaline can be converted via methylation to adrenaline, by the phenylethanolamine-N-methyl-transferase (PNMT) (Axelrod and Weinshilboum, 1972). The induction of this enzyme and, consequently synthesis of adrenaline, is dependent on cortisol, which is delivered to the adrenal medulla via an intra-adrenal portal vascular system (Pohoreky and Wurtmann, 1971).

Most of the synthesis of the neurotransmitter acetylcholine occurs probably in the axoplasm of the terminal endings of the cholinergic nerve fibers. From the extracellular fluid, choline is taken up into the cholinergic nerve endings. In the mitochondria another precursor, acetyl co-enzyme-A is formed (Shepherd and Vanhoutte, 1979). The enzyme choline acetyltransferase catalyzes in the neuroplasma the reaction from acetyl-Co A and choline to acetylcholine. Acetylcholine (ACh) is then transported to the interior of the vesicles. After an action potential has reached the nerve ending, Ca^{2+} ions diffuse from extraneuronal to intraneural space. Upon this, the vesicles lying with their stored ACh against the cell membrane release their content into the junctional cleft. This again is probably by a process of exocytosis (Burnstock, 1977). The released ACh diffuses to the effector cells where it binds to the receptors on the cell membrane. Most of the ACh is split into acetate ions and choline by the enzyme acetylcholinesterase. This enzyme is present in both terminal nerve endings and the surface of the receptor organ. All tissues innervated by cholinergic nerves have a high activity of acetylcholinesterase (Shepherd and Vanhoutte, 1979). The choline formed is actively resorbed into the terminal nerve ending where it is used again for the synthesis of new ACh and may be important in maintaining a continued transmitter synthesis (Burnstock, 1977). Normally, most of the ACh is destroyed within a fraction of a second after its secretion, only a small amount diffuses to surrounding fluids. The latter contain serum cholinesterase which destroys the remaining ACh within seconds. Therefore, the action of ACh released by cholinergic nerve fibers usually lasts for a few seconds at most (Guyton, 1981a).

Three different ways of removal of noradrenaline can be described: (1) Most of the noradrenaline is taken up by the sympathetic nerve endings (re-uptake mechanism). This is an active transport process and accounts for re-uptake of 50-80% of the secreted noradrenaline (Silverberg et al., 1978). Part of the noradrenaline which is taken up by the neuronal membrane is broken down enzymatically by mono-amine oxydase (MAO) to 3,4 dihydroxyphenylglycol (DOPEG) before it reaches again the storage sites. DOPEG then diffuses to the extracellular space. The rest of the noradrenaline is stored in the storage vesicles again; (2) Part overflows into the extracellular fluid and into the blood and is either excreted in the urine or metabolized by the liver. (3) Subsequent metabolism by the enzymes catechol-o-methyl-transferase (COMT) and mono-amine oxidase (MAO). The major pathways of degradation for noradrenaline are: (1) O-methylation via catechol-o-methyl-transferase (COMT). This extraneuronal pathway removes the circulating catecholamines released from the adrenal medulla and the diffused part from the nerve endings. COMT is present diffusely in all tissues (Graefe and Henseling, 1983) and in the liver. The major metabolite is normetanephrine and to a lesser extent vanillylmandelic acid (VMA) and 3-methoxy-4-hydroxyphenylglycol (MHPG); (2) Oxidative deamination via the enzyme mono-amino oxidase (MAO). The product is 3,4-dihydroxy-mandelic acid which in turn is degraded by COMT extraneuronally into 3-methoxy-4-hydroxymandelic acid; (3) Sulfoconjugation, which occurs both in the central nervous system and in the periphery (Roth and Rivett, 1982), is suggested because of the high proportions of circulating individual catecholamine sulfates (70%, 85% and 99% for noradrenaline, adrenaline and dopamine, respectively) (Kuchel, 1983). Platelet phenolsulfotransferase (PST) is the main enzyme. But as only a small proportion of noradrenaline circulates as free noradrenaline, so only this part is exposed to PST of the platelets. The product of sulfoconjugation are catecholamine-3-O-sulfate and catecholamine-4-O-sulfate of dopamine, noradrenaline and adrenaline. The precise regulation and the role of a possible autoregulation of sulfoconjugation are still not clear (Cryer, 1980). The ratio of the rate of excretion of the metanephrines, i.e. the products of O-methylation, to the excretion rate of vanillylmandelic acid (VMA) in

normal humans is 1:10. The metabolites are further conjugated in the liver and excreted by the kidneys. These three processes very rapidly remove the transmitter. These mechanisms of removal protect the system against excessive extraneuronal noradrenaline concentrations and conserve the neurotransmitter so that it does not fail to release noradrenaline upon stimulation. A similar pattern of metabolic inactivation is true for adrenaline resulting in VMA and metanephrine excretion. A higher proportion of adrenaline (85%) goes into conjugates than noradrenaline (70%). Dopamine is also similarly metabolized except that the end products of oxidative deamination are 3-methoxy-4-hydroxyphenylethylamine and 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid, HVA). Dopamine has a high component of sulfoconjugation.

Recently, an important role has been attributed to presynaptic receptors which modulate the release of neutransmitters in response to nerve impulse (Vanhoutte et al., 1980, 1981; Westfall, 1984). The effects of inhibitory modulators (products of cellular metabolism and histamine) on pre-junctional alpha-receptors and facilitating modulators (angiotensin II) on beta-adrenergic receptors have been reported, which alter the amount of transmitter released from the sympathetic nerve terminals in the face of a constant frequency of activation of the postganglionic sympathetic fibers (Shepherd and Vanhoutte, 1981). For more details, the aforementioned authors are referred to.

As indicated before, in the adrenal medulla, catecholamines are released directly into the circulation to reach their effector organ. Noradrenaline may subserve a hormonal function under conditions of stress, including vigorous physical exercise (Silverberg et al., 1978).

1.7 THEORIES ON THE PATHOGENESIS OF ESSENTIAL HYPERTENSION

Since the recognition of hypertension as a symptom, a multitude of factors have been mentioned to explain the possible pathophysiology and/or etiology. Up to now, many researchers have devoted their attention to this field, either experimental or clinical, and have contri-

buted remarkable results while trying to solve this complicated and often controversial puzzle. The never ending amount of articles which is produced on this topic gives an impression of the role which this symptom hypertension plays. The many different theories about pathophysiology and etiology have been extensively reviewed (see reference list). So only certain aspects of the major theories will be summarily illustrated in this chapter.

1.7.1 Genetic aspects

A multifactorial and not a single causal factor is postulated by several authors (Beyer and Peuler, 1983). It is now accepted that both genetic and environmental factors are, whether in a combination or not, involved in the rise of blood pressure to essential hypertension (Page, 1976; Beyer and Peuler, 1983; Houston, 1986). Some authors favour a polygenic model of inheritance or predisposition (Ostfeld and Paul, 1963; Pickering, 1965; Miall and Lovell, 1967; Kannel et al., 1969; Folkow, 1982; Rapp, 1983), both in man and in various hypertensive rat strains (Folkow, 1982). In other words, many minor and different genes could influence blood pressure, perhaps by cumulative action (Yamori, 1983). The effects of genes at the loci are not readily discernible one from the other in the frequency distributions for blood pressure (Rapp, 1983). Several authors believe in a single autosomal model (Weitz, 1923), which could be a single incompletely dominant autosomal gene (Platt, 1963). The controversies between these two models, the polygenic and the single autosomal model, have not been solved yet. Another possibility was outlined, the model of genetic heterogeneity. Due to the lack of conformity with a single pattern of influence, it was concluded that all types of genes (e.g. polygenes, polymorphic genes) contribute to the genetic variation underlying the blood pressure distribution in human populations. So, the continuous distribution of blood pressure is related to different types of genes (Cruz-Coke, 1983). Until now, however, despite thorough research no individual genes which control blood pressure or induce essential hypertension have been identified.

1.7.2 Environment

Among the environmental influences are two important factors, habits of salt intake and certain excitatory psycho-emotional influences (Folkow, 1982). Page (1976) describes these environmental factors as acculturation, dietary changes, weight gain, psychosocial and stress factors. Among the latter prevail social and environmental stress factors, as these have been linked with elevated arterial pressure in human and animal studies (DeQuattro and Hamad, 1985). It cannot be excluded that environmental factors as overeating or high salt intake could exaggerate a genetic or familial predisposition to obesity or hypertension (Beyer and Peuler, 1983). Furthermore, it remains probable that a spectrum of different hereditary, environmental and acquired factors may complement each other in a multifactorial pathogenesis of essential hypertension (Weidmann, 1981).

1.7.3 Sodium intake

Already some 80 years ago, Ambard and Beaujard (1904) suggested that salt intake might influence high blood pressure. But they were not the first to recognize the importance of the sodium ion. A citation from the "yellow emperor" 2600 B.C.: "If too much salt is used in food the pulse hardens. When the heart pulse beats vigorously and the strokes are markedly prolonged, the corresponding illness makes the tongue curl up and the patient unable to speak" (from Lever et al., 1981; Berglund, 1983).

Since then, the etiological factor of excessive salt intake or sodium excess has been discussed extensively in the literature. Population surveys demonstrated a strong positive correlation between sodium intake and hypertension in nonindustrialized and industrialized societies (Page et al., 1974; Freis, 1976). Simpson (1979) concluded in his analysis of available data that the combined evidence does not suggest any correlation between salt intake and blood pressure, in contrast to Morgan et al. (1979). Sodium-sensitive and sodium-resistant patients with established hypertension have been described (Fujita et al., 1980). Houston (1986) describes in his review that the part of the population which develops essential hypertension, particularly

blacks, low-renin hypertensives and elderly, are at risk due to salt sensitivity.

An abnormal sodium metabolism has been postulated as a cause for the sodium sensitivity of certain patients. The 3 important possible pathophysiological factors concerning cellular sodium transport in essential hypertension are reviewed by Hilton (1986). There is convincing evidence that an abnormality of the sodium pump is the cause for elevated intracellular sodium in leucocytes among persons with hypertension and probably in erythrocytes in at least some hypertensives. In this context, there appear to be genetic factors which are important. It seems also reasonable that genetic defects in electrolyte transport might be present not only in blood cells but in many tissues (Blaustein, 1984). Furthermore, the serum of persons with hypertension contains one or more substances which inhibit the sodium pump (inhibiting factor). Dysfunction of the renal sodium excretion and accumulation of sodium in vascular smooth muscle cells are other possible hypothetic factors (Houston, 1986). On the other hand, the mechanism why ±80% of a given population can handle high habitual intakes of salt without danger of developing essential hypertension is not quite understood (Freis, 1976). However, the dietary sodium restriction as part of the nonpharmacological therapy in essential hypertension is beyond any doubt.

1.7.4 The role of the renin-angiotensin system

The renin-angiotensin system has important influences on circulatory homeostasis. In short, the enzyme renin induces the formation of angiotensin II, one of the most potent pressor hormones known and stimulates the secretion of aldosterone. The resulting effects, vasoconstriction, volume expansion, interaction with the sodium excretion and further stimulating effects on the peripheral and central sympathetic nervous activity, lead to an increase of blood pressure. For more detailed descriptions of the different actions of the renin-angiotensin-aldosterone axis, see Davis and Freeman (1976), Zanchetti (1977), Corvol et al. (1983), Deboden et al. (1983), Freeman and Davis (1983), Haber and Carlson (1983), Sambhi (1983), Ribeiro et al.

(1985). The role of the prostaglandins and the kallikrein-kinin system will not be discussed either.

Laragh (1973) and Drayer et al. (1982) reported different levels of plasma renin in patients with essential hypertension and classified them into groups of high, normal and low renin. Hypertension in the high-level plasma renin group, which had an incidence of 11-16% of the population studied, is believed to be caused by vasoconstriction due to an increase of the activity of the renin-angiotensin system. But doubts about this theory have been pointed out by Weidmann (1981). He argues that hypovolemia and low peripheral vascular resistance found in high-renin states are arguments against it. Furthermore, it is not clear how low-level renin leads to high blood pressure. Also, inverse relationships between arterial blood pressure and plasma renin have been reported in normotensive subjects (Weidmann, 1977) and in essential hypertensives (Vetter et al., 1980) or no relationship (Agabiti-Rosei et al., 1983). Factors as advanced age and/or blunted beta-adrenergic responsiveness and increased adrenal sensitivity to angiotensin II-induced aldosterone secretion are held responsible for a reduced renin secretion (Bühler et al., 1973; Drayer et al., 1982). Plasma renin activity is thought to decrease with age, but the influence of age upon plasma renin has been discussed as well (Pedersen, 1979; Vetter et al., 1980; Weidmann, 1981). It is however not clear whether the various renin-angiotensin systems in the kidney, plasma and in other tissues like brain, arteries, adrenal gland or other organs are involved in the induction of essential hypertension (Ganten et al., 1983). Chronic oral treatment with angiotensin converting enzyme inhibitors also lowers blood pressure in spontaneous hypertensive rats, which are known to have low plasma renin (Unger et al., 1981). The blood pressure lowering action could therefore act through inhibition of the local tissue renin-angiotensin system. This could also possibly mean that tissue renin is elevated even when low plasma renin levels are measured.

Furthermore, an elevated plasma renin activity could be an indicator for other pathophysiological processes, perhaps reflecting enhanced sympathetic nervous activity, which produces both hypertension and a concomitant release of renin (Esler et al., 1977a). Support for

this view that the sympathetic nervous system is in part responsible for increased levels of plasma renin activity can be drawn from the study by Agabiti-Rosei and co-workers (1983). They found a relationship between levels of plasma noradrenaline and plasma renin activity in 76 patients with essential hypertension when compared with normotensive controls. In his review, Toretti (1982) concludes that sympathetic outflow influences the renin release through modification of the renal nerves and plasma catecholamine concentration. However, these influences may initiate either changes of the renin secretion rate or modulate the response initiated by another mechanism that controls renin release.

1.7.5 The role of the sympathetic nervous system

As described before, the sympathetic nervous system is an important factor complementing the body sodium-volume state, the renin-angiotensin-aldosterone system and some other components in the regulation of blood pressure. Owing to the complexity of the function of the sympathetic nervous system, it is not simple to identify its role in the pathogenesis of essential hypertension.

For long it has been thought that an increased sympathetic tone is involved in the etiology of essential hypertension. There are indications that make it likely that an increased sympathetic tone plays a role.

Several observations are important to consider first: it is known that sleep lowers blood pressure in both normotensive subjects and hypertensive subjects. Drugs which interfere with the sympathetic nervous system like guanethidine lower blood pressure. Pheochromocytoma is the only human "natural" model in which blood pressure increases with the release of plasma catecholamines. Furthermore, stress in subjects, like undesirable life events and features of suppressed anger and/or hostility, has been linked to the development of essential hypertension (Esler et al., 1977a; Osti et al., 1980; Sullivan et al., 1981; Julius and Johnson 1985). Furthermore, the increase of plasma catecholamines during physical exercise is correlated with the magnitude of the effort in healthy subjects (Dimsdale et al., 1984).

The methods of measurement of the activity of the sympathetic

nervous system have been discussed for some time. It is obvious that direct invasive analysis of the neurotransmitter discharge is not likely to be performed in man. It has been accepted that measurements of noradrenaline in plasma are reliable indirect means or at least an index of the overall activity of the sympathetic nervous system (DeChamplain, 1977; Weidmann, 1981; Folkow et al., 1983; Goldstein et al., 1983a; Conway, 1984; Esler et al., 1985). The interpretation of the plasma noradrenaline values should be done with caution. Concentrations of plasma catecholamines are difficult to measure and are usually very small. Plasma catecholamine levels represent, as I have described before, not only the product of the sympathetic and sympatho-adrenomedullary secretion, but depend also on diffusion to the circulation, re-uptake and degradation. Recent studies have shown that plasma concentrations of noradrenaline at rest tend to reflect outflow or release of the transmitter from synaptic terminals in skeletal muscles in normotensive and hypertensive patients (Wallin et al., 1981; Folkow et al., 1983; Mörlin et al., 1983; Wallin, 1984). Animal studies in dogs have provided evidence that the noradrenaline concentration is closely related to the sympathetic nerve discharge rate (Yamaguchi et al., 1975). Furthermore, Esler et al. (1981a) demonstrated that supine plasma noradrenaline is highly correlated to the noradrenaline spillover rate in normotensive and hypertensive subjects evaluated after infusions to steady-state tritiated L-noradrenaline.

Higher basal circulating catecholamines (DeQuattro and Hamad, 1985) and a higher sympathetic reactivity in response to postural changes has been found in 25-40% of the patients with essential hypertension (DeChamplain, 1977; DeQuattro and Hamad, 1985). In a review by Goldstein and Lake (1984), 78 published studies comparing plasma catecholamine levels at rest in patients with essential hypertension and in normotensive controls have been analyzed. They report that plasma noradrenaline levels are abnormally high in some patients with essential hypertension, and especially in those patients who are young and consistently hypertensive. The authors suggest that abnormalities in sympathetic neural or sympatho-adrenomedullary activity occur in those patients. In a study by Esler et al. (1977b), 21 patients with mild essential hypertension were investigated. A subgroup with ele-

vated plasma noradrenaline concentration was characterized by a high cardiac index and heart rate at rest, thus supporting partly a hyperactivity of the sympathetic nervous system in these patients. Increased heart rate at rest has been found consistently in borderline hypertensive subjects (Julius et al., 1980), and in other studies with essential hypertensive patients (Berglund et al., 1974; Berglund and Wilhelmsen, 1975; Ohlsson et al., 1981). Peripheral resistance is elevated in established hypertension (Conway, 1984) and in borderline hypertension (Julius et al., 1971b). As Abboud (1982) describes, it could be plausible that an increased sympathetic activity can enhance blood pressure through a number of mechanisms: noradrenaline released in several vascular beds leads to arteriolar constriction and the sympathetic drive to the heart increases stroke volume, heart rate and cardiac output.

Some authors propose to make detailed analyses of different regions where noradrenaline overflow occurs, like in myocardial and renal vascular beds (Folkow et al., 1983; Esler et al., 1984a; Young et al., 1984; Esler et al., 1985). The reason for this suggestion could be the fact that, though in man peripheral plasma noradrenaline correlates with overall sympathetic nervous activity, it does not allow the detection of regional disturbances in noradrenaline outflow which could be of pathogenic significance. In a study performed by Esler and co-workers (1984b), using the radiotracer method, an increased noradrenaline release by the kidneys and increased cardiac noradrenaline release was found in 31 patients with essential hypertension with a mean age of 51 years. An increased renal sympathetic nervous tone was associated in especially the young patients with a high noradrenaline release and a mild high-renin level.

Another controversial issue is the factor age. It has been found that plasma noradrenaline levels increase with age (Lake et al., 1977; Weidmann et al., 1980; Rubin et al., 1982), but others found no correlation between plasma noradrenaline and age (DeChamplain et al., 1980; Agabiti-Rosei et al., 1983; Goldstein and Lake, 1984). Esler et al. (1981a) found no difference in release of noradrenaline into the circulation between young and old subjects, but suggested a reduced clearance in old subjects as the reason of possibly elevated levels of

plasma noradrenaline. Another reason could be the responsiveness of the adrenergic receptor system. There is evidence for a decreased responsiveness in beta-adrenoceptor-mediated function with aging in man (Kelly and O'Malley, 1984). Evidence for changes of alpha-adrenoceptor mechanisms is not fully conclusive. It is not clear which mechanism is responsible for a decreased responsiveness. Receptor changes and post-receptor alterations, the role of adenylate cyclase and cyclic AMP among other factors are being discussed (for review, see Levitzki, 1981; Wesslau, 1983).

The hypothesis about the relationship of stress, adrenaline and hypertension has been outlined by Rand and Majewski (1984). Adrenaline released from the adrenal medulla in stress may be incorporated in noradrenergic transmitter stores and reach a sufficient concentration. As a cotransmitter it can then activate the autofacilitatory feedback loop of noradrenaline release involving presynaptic $beta_2$-adrenoceptors. An increase in vasomotor tone and cardiac activity results. Repeated stress may progress to a hypertensive state, as was reported in this chapter and shown in several studies (see Rand and Majewski, 1984). Furthermore, plasma adrenaline levels are elevated in a number of hypertensive patients (DeChamplain et al., 1977; Bolli et al., 1981; Dominiak and Grobecker, 1982). However, recently doubts about this theory have been published by Brown et al. (1985), who investigated patients with mild hypertension and normotensive controls from the MRC Trial.

The theory was attractive enough to suggest that raised catecholamine levels are the manifestation of the early phase in the development of hypertension, as was suggested by Sever et al. (1977) and was consistent with others (Esler et al., 1977a; Goldstein et al., 1983b). Possibly in the early phase of hypertension, an elevation of catecholamines occurs in some patients and at least contributes to the manifestation of hypertension. Furthermore, functional trigger elements in essential hypertension including neurogenic ones, need only to be marginal and may well be intermittent (Folkow, 1982). In most studies, measurements of plasma noradrenaline have been performed in patients with established essential hypertension. That could be the reason that partly elevated levels and no significant change of levels

when compared with normotensives was found (DeChamplain, 1977; Goldstein and Lake, 1984). One of the reasons for this outcome could be seen in the fact that many patients present themselves for the first time when hypertension is well established. At this stage a relatively large part of the elevated arterial blood pressure is maintained by hypertrophied vessels and heart (Korner, 1984). So on the other hand, normal peripheral plasma concentrations and clearance values of noradrenaline in humans with essential hypertension do not exclude the existence of an early pathogenetic stage or in the chronic phase of hypertension an increased sympathetic drive in some local regions. It may not be necessary for the increased activity of the sympathetic nervous system to be continuously present to be an important etiological agent.

For further comprehensive and detailed analysis of the role of an enhanced sympathetic nervous system dealing with the great amount of studies on the hemodynamic, pharmacological and biochemical aspects, I refer to review articles by Frohlich (1977), DeChamplain et al. (1981a), Abboud, (1982), Tarazi (1983), Chalmers and West (1983), Abboud (1984), Izzo (1984).

1.7.6 The role of the parasympathetic nervous system

As the counterweight to the sympathetic nervous system, the parasympathetic nervous system, is too often ignored and publications in this field are scarce. One of the reasons could be that acetylcholine mediated processes are difficult to measure.

Recently it was found that the parasympathetic system can inhibit the liberation of noradrenaline, presumably through an action of acetylcholine on the muscarinic receptors located presynaptically (Levy and Blattberg, 1976; Lavallée et al., 1978). In view of this finding, it was logical to postulate that a loss of parasympathetic tone might lead to an increased sympatho-adrenal tone.

Several studies supported the view of a decreased or altered cardiac parasympathetic inhibition in borderline hypertensive subjects (Julius et al., 1971a, 1975; Johnston, 1980) and in essential hypertensive patients (Korner et al., 1973; Simon et al., 1977). Saliva flow results mainly from stimulation of the parasympathetic inner-

vation (Schneyer et al., 1972). Recently, studies of salivary flow in borderline hypertensive subjects suggested a reduced parasympathetic drive to salivary glands at rest (Henquet et al., 1982; Rahn et al., 1983; Van Hooff et al., 1984a). It could therefore be possible that the decrease of the parasympathetic inhibitory mechanism could reinforce sympathetic activity.

1.8 BORDERLINE HYPERTENSION

According to the definition of the WHO, described in chapter 1.1, borderline hypertension is defined as the blood pressure (systolic/diastolic) between >140/90 and <160/95 mmHg. Many published studies deal with this borderline hypertensive range differently. Descriptions as "labile", "occasional", "early", "latent" or "pre-hypertension" can be found. Some terms, such as labile or occasional, indicate actually that blood pressure fluctuations are common in these patients. The term labile implies an increased variability. It has been found that blood pressure variability is not abnormal and not a characteristic feature of borderline hypertensive subjects (Julius et al., 1980; Watson et al., 1980a; Horan et al., 1981; Kubo, 1983; Weder and Julius, 1985). The terms pre- and early hypertension in the context of borderline hypertension should be used with caution as well, because they indicate a condition which leads to hypertension, but, as will be noted later, not all borderline hypertensive subjects become hypertensive. Latent hypertension describes a condition which may develop into hypertension or which may remain in this gray zone. Julius (1977) defines the term borderline hypertension in the group from 17-40 years further: the blood pressure levels (as defined above) are always between the hypertensive and normotensive range or some values in the borderline or hypertensive range with occasional normal values. Furthermore, no evidence of target organ damage is present.

Borderline hypertension is a wide spread condition. Prevalence rates depend on age and on other factors mentioned earlier. The prevalence above 20 years of age ranges between 8% and up to 29%, the average prevalence being 20% (Julius and Schork, 1971; Julius et al.,

1980; Julius and Hansson, 1983). Borderline hypertension is not a innocuous condition. Overall mortality exceeding the age-adjusted mortality from cardiovascular disease has been described as twice as high when compared with the normotensive population (Julius and Schork, 1971; Julius, 1977). Furthermore, increased morbidity from coronary heart disease has been reported as well by Julius and Hansson (1983), who analysed several studies. Borderline hypertensive subjects frequently have overweight and a family history of hypertension has been associated with borderline hypertension (Julius et al., 1980). The association between hypertension and obesity has been made. It is furthermore known that obesity is an important additional risk factor in hypertensive patients. Among the possible mechanisms discussed for the association of hypertension and obesity are hyperinsulinemia and/or increased sympathetic activity (Sims, 1982; Dustan, 1983; Lucas et al., 1985; Modan et al., 1985). However, studies of plasma catecholamines in obese hypertensives are scarce and give inconclusive results. There have been reports about elevated supine plasma noradrenaline levels in obese borderline hypertensive subjects when compared with non-obese borderline subjects (Sowers et al., 1982), as well as no differences between obese normotensive and hypertensive subjects (Boehringer et al., 1982; Tuck et al., 1983). Messerli et al. (1982) reported higher plasma noradrenaline levels in lean borderline hypertensive subjects when compared to obese borderline and lean normotensive subjects.

However, the medical significance of the condition borderline hypertension is uncertain. Evidence for the indictment of being a precursor of hypertension has been described by Stamler et al. (1958). But recent studies performed have confirmed that the subsequent development of hypertension occurs only in the minority of the subjects with borderline hypertension (Julius and Schork, 1971; Hedstrand and Åberg, 1975; Julius, 1977; Julius et al., 1980; Kubo, 1983; Sasakawa et al., 1983; Ueda et al., 1983). However, at least the development of later established hypertension has been associated with borderline hypertensive subjects twice as high as in normotensive subjects (Julius and Hansson, 1983).

A wide range of physiological abnormalities underlines the im-

pression that borderline hypertension is not only a minimal blood pressure elevation. A large proportion of borderline hypertensive subjects exhibit increased heart rate at rest as many studies have shown (Frohlich et al., 1970; Julius and Hansson, 1983). Furthermore, it is well documented that cardiac output at rest is increased in a part (30%) of the whole group of borderline subjects; but the differences between normotensives and borderline subjects seem to decrease with age (Julius and Conway, 1968). One study reported that the high cardiac output and a high renal blood flow was found predominantly among borderline patients younger than 30 years (Messerli et al., 1981). The cause for the higher cardiac output in the borderline hypertensive subjects was thought to be the elevated heart rate or an increased stroke volume or both (Julius et al., 1980). An earlier study showed that the elevated cardiac output normalized to the level of normotensive controls only after blockade of the heart with propranolol and atropine (Julius et al., 1971a). Changes in arterial baroreflex control of the circulation occur in essential hypertension. The possible mechanisms for the resetting in hypertension are described in detail by Zanchetti and Mancia (1984). Studies performed in borderline hypertensive subjects indicated a reduced baroreceptor sensitivity (Takeshita et al., 1975; Hansson et al., 1981; Volpe et al., 1982; Saito, 1983), in contrast to findings by Julius and Hansson (1974) and Julius (1976). The decreased baroreceptor function is believed to be secondary to the increase of blood pressure in borderline hypertension (Eckberg, 1979; Julius et al., 1983). Plasma renin activity is thought to be distributed in the same fashion as in established hypertension in high, normal and low renin (Esler et al., 1975). The peripheral resistance in borderline hypertension is either elevated or inappropriately adjusted to the increased cardiac output (Julius et al., 1971b). Julius and Johnson (1985) state that the increased cardiac output is neurogenic, and that in some patients the elevated plasma renin activity and noradrenaline levels and the increase in vascular resistance are maintained by a neurogenic tone. Levels of plasma noradrenaline at rest are usually normal in borderline hypertensive subjects when compared with normotensives (Julius et al., 1980; Eliasson et al., 1983). Studies performed by Henquet (1980) in some of the borderline

and normotensive subjects, belonging to the same group as described in chapter 2, indicated an increased vasoconstrictive responsiveness on noradrenaline infusion in the borderline subjects. This result was confirmed in another study by Iimura et al. (1984). However, Julius et al. (1983) report that results of studies performed on cardiac receptor responsiveness and vascular responsiveness in borderline hypertensive subjects are on the whole inconclusive.

A decreased plasma volume has been described in subjects with borderline hypertension (Julius et al., 1971c), which could presumably be similar to disturbances in extracellular fluid volume in established essential hypertension where a reduction of blood volume is seen in most types of hypertension (Tarazi, 1983). Furthermore, a hyperresponse to mental stress was found consistently in subjects with borderline hypertension (Eliasson et al., 1983; Julius and Hansson, 1983; Julius and Johnson, 1985). The value of exercise blood pressure as a risk indicator of hypertension was discussed by Franz (1982). Borderline hypertensive subjects who reacted with a blood pressure increase >200/100 mmHg during 100 W exercise, developed established hypertension within 3.8 years of observation.

A large number of factors and pathophysiological abnormalities have been reported in subjects with borderline hypertension. The analysis and detailed description of all these factors is beyond the intention of this introduction and would go beyond the studies performed with the borderline hypertensive subjects. Therefore, it is referred to some review articles (Julius and Schork, 1971; Julius and Esler, 1975; Julius, 1977; Julius et al., 1980; Julius et al., 1983; Julius and Hansson, 1983; Christensen, 1984; Eliasson, 1984; Lund-Johansen, 1984).

Established essential hypertension leads to secondary changes; it will therefore be very difficult to assess the role and the importance of the hypothetical trigger which induced hypertension, because it is as such no longer recognizable. Apparently mechanisms for blood pressure elevation change during the history of hypertension as well. As was described, borderline hypertension is a condition which occurs quite frequently. Furthermore, in a number of borderline subjects progression to hypertension has been shown. In order to evaluate the

role of the activity of the sympathetic nervous system in borderline hypertension, a longitudinal study was performed. A group of young men with borderline hypertension and an age-matched normotensive control group were followed to study plasma noradrenaline and adrenaline levels as well as plasma renin activity at rest and during exercise. The natural course of blood pressure was followed in both groups through regular controls of blood pressure to evaluate the progression to later hypertension. The aim was to follow both groups as long as possible. The subjects participated on a voluntary basis. Preliminary results about the study have been published already by Henquet (1980), Henquet et al. (1981), Henquet et al. (1982), and Van Hooff et al. (1984a).

1.9 TREATMENT OF MILD HYPERTENSION

In the study dealing with borderline hypertensive subjects, as will be described in chapter 2 and 3, the definition for borderline hypertension was a blood pressure ⩾140/90 mm Hg, but <160/100 mmHg. According to some authors, mild hypertension has been defined as the diastolic blood pressure >90 - <110 mm Hg (Korotkoff phase V) (Hansson, 1983; Miall et al., 1983), >95-99 mm Hg (Strasser and Dowd, 1983). So, mild hypertension varies with the design of the trials. Very recently, mild hypertension has been defined by the WHO in adults as a diastolic pressure (phase V) persistently between 90-104 mm Hg without obvious signs of left ventricular hypertrophy for damage to the heart or other organs (WHO/ISH Memorandum, 1986). Concerning this blood pressure range, it is obvious that some of the borderline hypertensive subjects could then fall under the description of mild hypertension.

The trial II of the Veterans Administration (VA) Cooperative Group (1970) showed that treatment in mild hypertensive patients (diastolic blood pressure: 90-104 mm Hg) reduced the risk for morbid events (21%). However, the risk reduction was greater in the group of patients with diastolic blood pressure of 104-114 mm Hg (52%). It must be emphasized that patients, without treatment, whose diastolic blood

pressure averaged 90 through 129 mm Hg from the 4th through the 6th hospital day were accepted for further follow-up. The VA trial suggested further that the mild hypertensive group with pre-existing cardiovascular or renal abnormalities, benefits from treatment. It was proven not only in the VA trial I (1967) that patients with moderate to severe hypertension benefit from treatment, and no discussion arises about treating this group. The second VA trial (mild hypertension) indicated no firm conclusion; perhaps this was also due to the small sample size.

In the last few years, several other different international studies have been performed in groups of patients with mild essential hypertension. The American Hypertension Detection and Follow-up Program (HDFP, 1979) and the Australian Therapeutic Trial in mild hypertension (1980) have both shown that lowering blood pressure can be of benefit in these patients. Stroke and myocardial infarction declined significantly in the American study and mortality from cardiovascular disease in the Australian trial. Three groups of patients were studied in the HDFP study: diastolic blood pressure 90-104, 105-114, and >115 mm Hg. Total mortality was reduced by 20% in the group with diastolic blood pressure 90-104 mm Hg. It must be noted that in this study the intention was to compare mortality of rigorous stepped-care and community referred-care. In the Australian study, mild hypertension was defined as diastolic blood pressure (Korotkoff V) >95 - <110 mm Hg; in the active treatment group the average diastolic blood pressure fell 13 mm Hg compared to 7 mm Hg in the placebo group. Recently, results from the Medical Research Council Working Party Trial of mild hypertension (MRC, 1985) were published. Again the stroke rate was reduced, but the overall rate of coronary events was not influenced by the treatment. This made the impression of beneficial aspects of treating mild hypertension stand on a less secure ground.

For several years now, the active drug treatment in mild hypertension has been discussed by several authors (Peart, 1981; Freis, 1982; Levinson et al., 1982; Kaplan, 1983; McAlister, 1983; Memorandum WHO/ISH Meeting 1983; Pickering, 1983; Toth and Horwitz, 1983; Venkata and Ram, 1984; Berglund, 1984; Hyman and Kaplan, 1985). The attention was focused on this subject also by the number of trials performed.

Speaking against treatment of mild hypertension, and this has to be taken into consideration, is the fact that some patients with mild hypertension will clearly show a fall of blood pressure without active interference. Other factors are the potential side-effects of the drugs prescribed and the bearing of the hallmark of hypertension. However, patients with even a mild elevation of blood pressure are at increased risk of cardiovascular disease. If symptoms have appeared, morbidity and mortality are higher than before. In young patients in the mild hypertensive range, the progression to moderate or severe hypertension could be at least postponed with active treatment before target organ involvement or damage in the long run appear. If the latter or additional risk factors are present, treatment should be started. Recently, the WHO (1986) proposed to treat patients with antihypertensive drugs who have a diastolic blood pressure >100 mmHg during three months of follow-up. In subjects with additional risk factors like smoking, increased plasma cholesterol and diabetes mellitus and in subjects with target organ damage active treatment is proposed to start at a lower level of blood pressure. Therefore, prescribing therapy in mild hypertensive patients should be done with caution and be judged carefully in the individual case. Clearly the risk of active treatment should not exceed the risk of mild hypertension.

Non-pharmacological methods (reduction of weight, smoking, and heavy alcohol consumption, dietary sodium and saturated fat restriction) have been recommended as an adjunct to drug therapy. Other adjuncts or measures to lower blood pressure include physical exercise, relaxation techniques, stress reduction and supplementary intake of calcium. Different drugs can be prescribed for patients with mild hypertension. The goal is to lower blood pressure to normotensive levels or at least to below diastolic 90 mm Hg (WHO/ISH memorandum 1986). As the initial therapy, beta blockers and diuretics can be used. These two agents will control blood pressure in the majority of patients with mild hypertension. In the last few years, calcium channel blockers have been introduced and found their place in monotherapy. A newer class of drugs, the angiotensin converting enzyme inhibitors have been developed and are also used in essential hypertension.

The intention to use the latter in monotherapy in mild hypertension has been proposed already (Freis, 1983; Schalekamp, 1985; Zanchetti, 1985a,b; Bühler, 1986).

Diuretics, like the thiazide diuretics (hydrochlorothiazide) have been used in the initial step in the treatment of hypertension. The primary action of diuretics is the increase in renal excretion of sodium and water. The consequence is a fall in extracellular and blood volume; this leads to the fall in cardiac output and blood pressure. The long-term effect of diuretics is a relative reduction of the vascular resistance together with the return of cardiac output near control values. Among other factors a decrease of extracellular volume and a change of electrolytes in the tissue have been suggested as explanation for the decrease of vascular resistance (Struyker Boudier et al., 1983). Plasma renin activity will increase and renal blood flow remains unchanged. The blood pressure decrease will range about 10-20 mm Hg during diuretic therapy. Among the side-effects of thiazide diuretics are metabolic effects (hyperuricemia, glucose intolerance, hypercholesterolemia) and hypokalemia, which could have serious consequences in elderly patients. Other side-effects are impotence, fatigue and dizziness. Additional potassium suppletion or using a thiazide diuretic in combination with a potassium sparing diuretic (triamterene) could prevent events triggered by hypokalemia. However, potassium sparing diuretics may lead to hyperkalemia in impaired renal function. Older patients are most likely to be treated first with a diuretic. The lowest dose of diuretic drugs should be used to achieve the target blood pressure because of manifestation of side-effects with increasing doses. Estimations of plasma potassium, uric acid, creatinine and urinary glucose should be made after beginning of the therapy and are recommended subsequently once every year.

Beta-adrenergic blocking agents have been used for different indications, they are available for treatment of essential hypertension for a longer time now. Their antihypertensive mechanism has, however, not been fully explained. They all share their specific action to block the beta-adrenoceptor (Man in 't Veld and Schalekamp, 1983). Numerous agents are available; the different beta-blockers on the Dutch market have been recently reviewed (Man in 't Veld, 1985). But

they may differ further in pharmacodynamics (cardioselectivity, intrinsic sympathomimetic activity (ISA), membrane stabilizing activity) and pharmacokinetics (metabolism, lipid solubility). The hemodynamic effects of the majority of the beta blockers are comparable. Acute administration of beta blockers results in a blockade of cardiac beta-adrenoceptors leading to a rapid decrease of heart rate and cardiac output. An immediate rise in peripheral resistance will follow. An acutely administered beta blocker with strong ISA, at least at rest, leads to less or no cardiac output reduction and hardly affects total peripheral resistance (Van Baak et al., 1985). The blood pressure fall at rest can be explained by $beta_2$-adrenoceptor stimulation leading to vasodilatation. Chronic treatment with beta blockers results in reduction of cardiac output, although stroke volume is normal, and so are plasma volume, blood volume and central blood volume. Total peripheral resistance remains unchanged or is slightly increased. Plasma renin activity is decreased. Beta blockers with strong ISA hardly affect cardiac output at rest, while total peripheral resistance is reduced. However, in situations with increased sympathetic activity, e.g. standing and physical exercise, beta blockers with ISA behave like normal beta blockers. The antihypertensive mechanisms of beta blockade have been reviewed recently in detail by Van Baak et al. (1985). Side-effects of beta blockers include bradycardia, hypertriglyceridemia and decreased high density lipoprotein cholesterol. Sedation and bad dreams are believed to be effects on the central nervous system. Cardioselective beta blockers still could cause bronchoconstriction in patients with chronic obstructive pulmonary disease; non-selective beta blockers should be generally avoided in these patients. Provocation of claudication in patients with peripheral vascular disease or Raynaud's phenomenon is particularly described during treatment with propranolol. Hypoglycemia in patients with diabetes mellitus was reported by non-selective beta blockers. Due to other side-effects, such as muscular fatigue and less physical exercise performance, a study was performed and is presented in chapters 4 and 5, which deals with endurance performance in mild hypertensive patients during long-term beta blocker therapy. Contra-indications for beta blockers are congestive heart failure, bradycardia, AV-block

grade II, and sick sinus syndrome. In general, beta blockers may be favored in younger patients because the excessive bradycardia or congestive heart failure are more frequent in the aging heart. Furthermore, plasma renin values and cardiac output differ in young and old patients. The combination with diuretics is recommended if the blood pressure goal is not reached with beta blockers alone. Beta blockers could then decrease the plasma renin stimulation induced by diuretics. The antihypertensive action of beta blockers is comparable to that of the diuretics.

In the last 5-10 years, calcium channel blockers have been introduced in antihypertensive therapy and they have been used lately in monotherapy for mild hypertension. Their effect is believed to be a lowering of peripheral resistance, which is increased in patients with essential hypertension, through blocking the slow channels of the calcium influx and thus resulting in vasodilatation and reduction of the total peripheral resistance. Nifedipine acts more on vascular smooth muscle cells in coronary and systemic arteries. In contrast, both verapamil and diltiazem produce less vasodilatation than nifedipine and affect AV-conduction. No sodium or fluid retention and no postural hypotension occurs during chronic therapy in contrast to other vasodilators. The frequency of side-effects during therapy with calcium channel blockers is minor. The major side-effects of calcium channel blockers can be predicted from their pharmcological actions. Verapamil has a negative inotropic effect and prolongation of AV-conduction time occurs, but no reflex tachycardia occurs during verapamil in contrast to nifedipine. Further side-effects of verapamil are constipation, flushing and headache. Side-effects of nifedipine are headache, flushes and local edema in the extremities. The low incidence of serious side-effects in oral therapy and their valuable antihypertensive effect could therefore result in the use of calcium channel blockers in monotherapy as an alternative for the other drugs like diuretics or beta blockers used in healthy hypertensives or in case of increasing complaints of cold extremities, muscle fatigue or obstructive lung disease. Calcium channel blockers can be used in combination with diuretics and converting enzyme inhibitors. Verapamil is not likely to be combined with a beta blocker due to the suppres-

sion of AV-conduction by both. The role of calcium channel blockers in the treatment of hypertension has been recently reviewed in detail by Halperin and Cubeddu (1986).

The angiotensin converting enzyme (ACE) inhibitors inhibit the converting enzyme which catalyzes the conversion from angiotensin I to angiotensin II. The antihypertensive action arises primarily from the inhibition of the formation of the vasoconstricting angiotensin II. Other actions such as reduced degradation of bradykinin and increased release of prostaglandins cannot be entirely discounted (Van Zwieten et al., 1983; Ondetti and Cushman, 1984). The fall of blood pressure is due to peripheral vasodilatation (Johnston et al., 1984), depending on initial levels of plasma renin activity and the decline of circulating angiotensin II concentrations (Kubo and Cody, 1985). The fall of the peripheral resistance should normally induce stimulation of the sympathetic nervous system and result in a reflex increase of heart rate and cardiac output, but the counterregulatory system is not activated. Long-term effects are an increase of plasma renin activity. Only little or no salt or water retention occurs. Sodium depletion accentuates the effects of ACE inhibitors. At the moment, captopril and enalapril are available for treatment of hypertension. The second generation of ACE inhibitors with not only a longer duration of action, but dual routes of excretion via kidney and liver are being studied. As mentioned before, some experts considered the use of ACE inhibitors for the treatment of patients with mild to moderate essential hypertension. It is known that some harmful metabolic side-effects, like alterations of serum uric acid, blood glucose, plasma renin levels, and lipid concentrations, limit the use of diuretics and beta-adrenergic blocking agents. Until now, ACE inhibitors exert little relevant metabolic side-effects in these mild to moderate hypertensive patients. Ramipril is one of the newer ACE inhibitors and was studied in patients with essential hypertension, as will be described in chapter 6. The intention was to find the dose which lowers blood pressure and to investigate the time course of the blood pressure lowering effect in essential hypertensive patients. Side-effects of captopril are hypotension and, especially in high doses, skin rash, loss of taste, leukopenia or agranulocytosis and it increases protein-

uria in patients. Side-effects of enalapril are similar and include headache, rash and hypotension (Todd and Heel, 1986). ACE inhibitors can be used to treat hypertension in patients with asthma and chronic obstructive lung disease, conditions in which non-selective beta blockers are to be avoided. ACE inhibitors can be combined with diuretics or beta blockers.

Chapter 2

A LONG-TERM STUDY OF PLASMA CATECHOLAMINE LEVELS AND PLASMA RENIN ACTIVITY IN BORDERLINE HYPERTENSION

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2.1 SUMMARY

There are conflicting reports on plasma catecholamine levels in subjects with borderline hypertension. This could be due to the fact that only a subgroup of borderline hypertensive subjects develops definitive hypertension, whereas others remain in the borderline range or even become normotensive. We therefore studied the development of blood pressure, plasma catecholamine levels and plasma renin activity (PRA) in a group of 26 young borderline hypertensive subjects and a control group with 24 normotensives at rest and during physical exercise. The study started in 1977 and was finished in 1984. Three subjects were lost to follow up. At the end of of the study, 15 normotensive subjects remained normotensive (mean arterial blood pressure (MAP) $\leqslant$98 mmHg (subgroup 1)). In 10 borderline hypertensive subjects, blood pressure remained borderline hypertensive (MAP $\geqslant$107 - $<$120 mmHg (subgroup 3)). During the 7 years of follow up, 5 borderline hypertensive subjects became definitively hypertensive (MAP $\geqslant$120 mmHg (subgroup 4) and were excluded from the study in order to receive antihypertensive treatment.

At repeated measurements in 1977, 1978 and 1984, there was no difference in plasma noradrenaline levels at rest and during physical exercise between the total groups of normotensives and borderline hypertensives. However, the situation changed when the subgroups were considered separately. Subjects who developed definitive hypertension within the observation period (subgroup 4) had consistently high plasma noradrenaline concentrations at rest. In contrast, subjects who remained normotensive (subgroup 1) as well as subjects remaining borderline hypertensive (subgroup 3) had relatively high resting noradrenaline levels only at entrance into the study, the concentrations of the amine being considerably lower than in subgroup 4 at successive measurements.

There were no differences between the groups and the subgroups in plasma adrenaline and PRA at rest as well as in plasma noradrenaline, plasma adrenaline and PRA during exercise.

The study shows that only 20% of borderline hypertensive subjects become definitively hypertensive during an observation period of

7 years. These subjects have consistently high plasma noradrenaline levels at rest suggesting enhanced sympathetic activity.

2.2 INTRODUCTION

The role of the sympathetic nervous system in the pathogenesis of essential hypertension is still controversial. It could be that enhanced activity of this system causes chronic elevation of blood pressure in man. Plasma concentrations of noradrenaline and adrenaline may be used as an index of sympathetic nervous system activity in man (Wallin et al., 1981; Goldstein et al., 1983a; Wallin, 1984; Esler et al., 1985), although plasma catecholamine levels depend upon numerous processes such as release from and re-uptake by nerve endings, metabolic degradation, uptake into non-neural tissue, binding to postsynaptic receptors and diffusion from the synaptic cleft to the circulation (Goldstein, 1983). Thus, it is understandable that studies performed to get insight into the sympathetic nervous system activity in patients with essential hypertension have yielded results which are difficult to interpret (Goldstein and Lake, 1984).

In patients with long lasting blood pressure elevation, alterations of plasma catecholamine levels could be the consequence rather than the cause of hypertension. Therefore, the interest of investigators has been focused on subjects with an early phase of high blood pressure, particularly on subjects with borderline hypertension. Studies on plasma catecholamine levels in borderline hypertension have also yielded conflicting results (Goldstein and Lake, 1984). This could be due to the fact that only a subgroup of borderline hypertensive subjects develops definitive hypertension in the course of several years, the others remaining in a borderline range or even becoming normotensive (Julius et al., 1980; Ibsen, 1984).

Therefore, a study was designed to follow up blood pressure and plasma catecholamine levels in a group of young subjects with borderline hypertension. The data of these borderline hypertensives were compared with a normotensive control group. Both noradrenaline and adrenaline levels in plasma were determined. Noradrenaline was ex-

pected to reflect the activity of the sympathetic nervous system. Adrenaline was thought to give an idea of the activity of the adrenal medulla. Plasma catecholamine concentrations were not only determined at rest, but also during physical exercise. Physical activity causes plasma catecholamine levels to increase (Planz et al., 1976; Watson et al., 1980c; Davidson et al., 1984). It seemed possible that thereby differences between subjects with borderline hypertension and normotensives become more pronounced. Renin release from the kidneys is influenced by the sympathetic nervous system (Davis and Freeman, 1976). Therefore, plasma renin activity was followed up, too.

There are observations suggesting that blood pressure during exercise reaches extraordinarily high levels in those subjects with borderline hypertension who later become definitively hypertensive (Wilson and Meyer, 1981; Jackson et al., 1983; Franz, 1985). Thus, in borderline hypertensives, the rise of blood pressure during exercise might have a predictive value. Therefore, at entrance into the present study, blood pressure was determined both at rest and during physical exercise.

2.3 SUBJECTS AND METHODS

Fifty males agreed to participate. Their age ranged from 18 to 30 years at entrance into the study. The subjects were recruited as has been described (Henquet et al., 1981). Twenty-four subjects were normotensive. For the purpose of the present study, normotension was defined as blood pressure values of $\leqslant$125/85 mm Hg with a mean arterial blood pressure (MAP) $\leqslant$98 mm Hg after 2 min standing determined at 8 measurements performed on 4 different days in a period of 3 months. The other 26 subjects were borderline hypertensive. Borderline hypertension was defined as standing blood pressure values $\geqslant$140/90 to <160/100 mm Hg (MAP $\geqslant$107 - <120 mm Hg) when measured 8 times on 4 different days in a period of 3 months. In the subjects with borderline hypertension, secondary hypertension was excluded by history, physical examination, appropriate laboratory tests and intravenous pyelography. None of the subjects with borderline hypertension had

retinal changes and none of them ever had received antihypertensive drugs. All subjects participating in the study had normal values for creatinine, alkaline phosphatase, gamma-glutamyl transferase and transaminases in serum. Informed consent was obtained from all subjects. The study had been approved by the Research Committee of the University of Limburg.

The study started with a recruitment phase lasting from the summer to the end of 1977. The study was completed by the end of 1984. Thus, all subjects were observed for a total of 7 years. During the observation period, blood pressure and heart rate were measured after 30 min rest in supine position and after 2 min standing in all subjects at 4 months' intervals. If mean arterial blood pressure after 2 min standing was $\geqslant$120 mm Hg at 2 successive measurements, the subject was considered to be definitively hypertensive and excluded from the study in order to start antihypertensive therapy.

In all subjects, plasma catecholamine levels and plasma renin activity (PRA) were determined at rest and during bicycle ergometry at entrance into the study in 1977, in 1979 and in 1984. Each time, maximum work load during bicycle ergometry was determined first. The subjects started with a work load of 124 W. The work load was increased stepwise until the maximum work load was reached (Henquet et al., 1981). Blood pressure was measured at each work load. Furthermore, heart rate was determined from the continuously monitored electrocardiogram. All ergometric studies were performed in a temperature-controlled laboratory.

Not earlier than 5 days after the determination of maximum work capacity, the subjects collected a 24 h urine sample for the measurement of sodium excretion. The day thereafter, the subjects came back to the laboratory. After a forearm vein had been cannulated, they rested for 30 min in supine position. Thereafter, heart rate and blood pressure were measured and a blood sample was drawn for the measurement of plasma catecholamine levels and PRA. Then, the subjects exercised in sitting position on a bicycle ergometer, subsequently at 50% and at 75% of their predetermined maximum work capacity. Each work load lasted for 5 min. In the last 2 min of each ergometry period, heart rate and blood pressure were measured. Furthermore, at the end

of the work period with 75% of maximum capacity a blood sample was drawn to determine the same parameters as during supine rest.

All blood pressure measurements were performed using a mercury manometer. The point of muffling of the Korotkoff sounds was read as the diastolic value. Heart rate was determined by palpation of the radial artery at rest and by eletrocardiography during exercise. Mean arterial pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic blood pressure. Plasma catecholamine levels were measured radiometrically, PRA by radioimmunoassay (Henquet et al., 1981). Sodium in urine was determined by flame photometry.

Results are expressed as mean values $\pm$ SEM. Statistical significance was tested with Student's t-test for unpaired data or, if appropriate, with the paired t-test. The level of significance was set at $p<0.05$.

2.4 RESULTS

2.4.1 Age, height, weight and maximum work capacity at entrance into the study

At entrance into the study, the age of the normotensive subjects was 23 ± 0.7 years as compared with 25 ± 0.8 years in the borderline hypertensives. Length averaged to 180 ± 0.1 cm in the normotensives and to 177 ± 2 cm in the borderline hypertensive subjects. The differences in both parameters are not statistically significant. Body weight was higher ($p<0.05$) in the borderline hypertensive group (78 ± 2 kg) than in the normotensive group (70 ± 1 kg).

Maximum work capacity averaged to 211 ± 7 W in the normotensive group as compared with 185 ± 5 W in the borderline hypertensives. The difference is statistically significant ($p<0.005$).

2.4.2 Blood pressure and heart rate at rest

In 1977, at entrance into the study, systolic and diastolic blood pressure as well as MAP and heart rate at rest in supine as well as in standing position were higher in the borderline hypertensive subjects than in the normotensives (Table 1).

Table 1: Resting blood pressure (mm Hg) and heart rate (beats/min) at entrance into the study.

	Supine				Standing after 2 min			
	Systolic	Diastolic	MAP	Heart rate	Systolic	Diastolic	MAP	Heart rate
Normotensive (n=22)	119±1	74±1	89±1	63±2	120±1	81±1	94±1	77±2
Borderline hypertensive (n=25)	143±1	91±1	108±1	73±2	148±1	95±1	113±1	88±3
p	<0.001	<0.001	<0.001	<0.001	<0.01	<0.01	<0.01	<0.01

MAP is the mean arterial blood pressure; n is the number of subjects in a group. The table does not contain data of the 3 subjects who were lost to follow up. Data represent mean values ± SEM.

At the end of the 7 years' observation period, the 2 groups of subjects who had entered the study were divided into subgroups depending upon the last 3 measurements of MAP in standing position. Subgroup 1 were 15 normotensive subjects whose MAP was consistently ≤98 mm Hg at these 3 measurements. In 7 normotensive subjects, the MAP at one or more of the last 3 measurements was >98 but <107 mm Hg (subgroup 2). Of the originally 26 subjects with borderline hypertension, 10 had consistently a MAP of ≥107 and <120 mm Hg in standing position at the last 3 measurements in 1984 (subgroup 3). Subgroup 4 represents those 5 borderline hypertensives who developed definitive hypertension (MAP in standing position ≥120 mm Hg at 2 successive measurements). Of these 5 subjects from subgroup 4, one had become definitively hypertensive in 1979, one in 1981, one in 1982 and two in 1984. At the end of the observation period, 8 originally borderline hypertensives had standing MAP >98 and <107 mm Hg (subgroup 5) and 2 had MAP ≤98 mm Hg

(subgroup 6).

During the observation period of 7 years, 2 subjects of the normotensive group were lost to follow up, the first in 1981 and the second in 1983. Both were normotensive (MAP ⩽98 mm Hg in standing position) at their last blood pressure control. Of the borderline hypertensive group, one subject was lost to follow-up in 1981. At this time, his standing MAP was <107 mm Hg. No data of the 3 subjects who dropped out of the study are presented.

It seemed particularly interesting to compare the data of the subjects who became defitinively hypertensive (subgroup 4) with those of the subjects who were normotensive (subgroup 1) or borderline hypertensive (subgroup 3) at the end of the observation period (Table 2). As could be expected, supine and standing MAP was higher in sub-

Table 2: Resting mean arterial blood pressure (MAP; mm Hg) and heart rate (beats/min) in the 3 subgroups at the entrance into (a) and at the end (b) of the study.

	Supine				Standing			
	MAP		Heart rate		MAP		Heart rate	
Sub-group	a	b	a	b	a	b	a	b
1 (n=15)	89±1	87±1	65±3	68±3	94±1	94±1	78±3	86±3
3 (n=10)	109±1	100±1	70±3	71±4	114±1	111±2	82±4	80±3
4 (n=5)	111±2	121±2*	78±5	95±10*	114±1	127±2*	93±8	98±9*

* Data determined at the time when the subjects became definitively hypertensive. For definition of the subgroups, see text. n is the number of subjects in a subgroup. Data represent mean values ± SEM.

groups 3 and 4 than in subgroup 1, both at the entrance into and at the end of the study ($p<0.001$). Subgroup 3 and subgroup 4 did not differ in supine and standing MAP at entrance into the study. Not surprisingly, MAP values in subgroup 3 measured at the end of the observation period were lower than those determined in subgroup 4 at the time when these subjects became definitively hypertensive ($p<0.01$).

Neither at entrance into nor at the end of the study, the subjects of subgroups 1 and 3 did differ in heart rate (Table 2). In contrast, supine heart rate was higher in subgroup 4 than in subgroups 1 and 3, both at entrance into the study and at the time when the subjects of subgroup 4 became definitively hypertensive ($p<0.05$). Standing heart rate was also somewhat higher in subgroup 4 than in subgroups 1 and 3. The difference was, however, not statistically significant.

2.4.3 Blood pressure and heart rate during exercise

At entrance into the study, systolic and diastolic blood pressure was higher in the borderline hypertensives than in the normotensive group at all levels of physical exercise ($p<0.001$, Table 3). The 2 groups of subjects did, however, not differ in heart rate during bicycle ergometry.

Table 3: Blood pressure (mm Hg) during exercise as determined at entrance into the study.

	50%	75%	100%
	Maximum work capacity		
Normotensives (n=22)	156±3/71±2	180±4/68±3	197±3/69±2
Borderline hypertensive subjects (n=25)	175±4/86±2	194±3/86±3	208±3/86±3

The table does not contain data of the 3 subjects who were lost to follow-up. Data represent mean values ± SEM.

Similar results were obtained when the data of subgroups 1, 3 and 4 were compared. At entrance into the study, subgroup 1 had lower blood pressure data during exercise corresponding to 50, 75 and 100% of maximum work capacity than had subgroups 3 and 4 ($p<0.05$). In contrast, there were no differences between subgroups 3 and 4. Heart rate was similar in subgroups 1, 3 and 4 at all levels of physical activity.

At entrance into the study, all subjects performed bicycle ergometry at a work load of 124 W for a total of 4 min. At the end of this exercise period, the subjects of subgroups 3 and 4 had higher systolic and diastolic blood pressure values than subgroup 1 ($p<0.01$, Table 4). There was no difference between subgroup 3 and subgroup 4 in systolic blood pressure. In contrast, diastolic blood pressure was higher in subgroup 4 than in subgroup 3 ($p<0.05$). However, there was considerable overlap of the data (Table 4).

Table 4: Systolic and diastolic blood pressure (mm Hg) at a work load of 124 W at entrance into the study.

Subgroup	Systolic blood pressure	Diastolic blood pressure
1 (n=15)	164±4	70±3
3 (n=10)	191±6	85±4
4 (n=5)	204±9	96±4

n is the number of subjects in a subgroup. For definition of the subgroups, see text. Data represent mean values ± SEM.

2.4.4 Plasma catecholamines and PRA

Plasma catecholamine levels and PRA as determined in 1977 at entrance into the study, in 1979 and in 1984 in normotensives and in subjects with borderline hypertension are presented in Table 5. There

Table 5: Plasma catecholamine levels (ng/ml) and plasma renin activity (PRA, ng angiotensin I/ml.h) in normotensives and in subjects with borderline hypertension.

		At rest			During exercise (75% maximum work load)		
		1977	1979	1984	1977	1979	1984
Noradrenaline:	Normotensives	0.34±0.04	0.24±0.03	0.20±0.03	1.15±0.10	0.85±0.07	0.98±0.08
	Borderline hypertensives	0.39±0.04	0.29±0.03	0.25±0.03	1.15±0.11	0.90±0.06	0.93±0.11
Adrenaline :	Normotensives	0.09±0.03	0.07±0.01	0.12±0.04	0.21±0.04	0.14±0.01	0.12±0.02
	Borderline hypertensives	0.07±0.01	0.07±0.01	0.09±0.02	0.21±0.02	0.15±0.02	0.15±0.02
Plasma renin activity :	Normotensives	1.18±0.21	1.71±0.19	1.21±0.14	1.91±0.35	3.49±0.39	3.12±0.55
	Borderline hypertensives	0.91±0.10	1.62±0.20	1.15±0.17	1.96±0.31	3.57±0.40	2.90±0.42

The table does not contain data of the 3 subjects who were lost to follow up.
Furthermore, the values for 1984 do not contain the data from the 3 subjects who had developed definitive hypertension in 1979-1982.
Data represent mean values ± SEM.

were no statistically significant differences in these data between the 2 groups of subjects studied. In both groups, plasma noradrenaline levels were lower in 1979 than in 1977 ($p<0.05$), whereas plasma noradrenaline levels determined in 1979 and in 1984 did not differ.

As has been described for the total groups of normotensive subjects and of subjects with borderline hypertension, the plasma noradrenaline levels at rest in supine position were also lower in 1979 than in 1977 in subgroups 1 and 3 ($p<0.05$, Table 6). In contrast, in subgroup 4 resting plasma noradrenaline concentrations in 1977 and 1979 were similar. In all subgroups, the values measured in 1979 did not differ from those in 1984.

Table 6: Plasma noradrenaline levels (ng/ml) at supine rest in subjects remaining normotensive (subgroup 1), in subjects remaining borderline hypertensive (subgroup 3) and in subjects who became definitively hypertensive (subgroup 4) during the observation period.

	1977	1979	1984
Subgroup 1 (n=15)	0.38 ± 0.06	0.25 ± 0.04	0.18 ± 0.04
Subgroup 3 (n=10)	0.37 ± 0.05	0.26 ± 0.05	0.19 ± 0.03
Subgroup 4 (n=5)	0.45 ± 0.15	0.40 ± 0.06*	0.42 ± 0.23[a]

[a]Values of 2 subjects only. The other 3 had been excluded because they had become definitively hypertensive.

*$p < 0.05$ when compared with subgroup 1.
Data represent mean values ± SEM.

Neither in 1977 nor in 1979 and in 1984, subgroups 1 and 3 differed in plasma noradrenaline levels at supine rest (Table 6). In 1977, resting plasma noradrenaline concentrations were slightly higher in subgroup 4 than in subgroups 1 and 3. The difference was, however, not statistically significant. In 1979, plasma noradrenaline levels at supine rest were significantly higher in subgroup 4 than in subgroup 1. In 1979, noradrenaline levels were also somewhat higher in subgroup 4 than in subgroup 3. The difference, however, was not statistically

significant. There are noradrenaline data only from 2 subjects of subgroup 4 in 1984 (Table 6). The other 3 subjects had been excluded from the study because they had become definitively hypertensive.

As has been mentioned earlier, 3 subjects with borderline hypertension became definitively hypertensive and, therefore, were excluded from the study in 1979-1982, 2 in 1984. Resting plasma noradrenaline levels of these subjects (subgroup 4) as determined closest to the moment of exclusion averaged to 0.45±0.08 ng/ml (n=5). This value is higher than the resting plasma noradrenaline concentrations measured in subgroup 1 in 1979 ($p=0.03$) as well as the resting plasma noradrenaline levels in subgroups 1 and 3 in 1984 ($p<0.01$). The difference with the data of subgroup 3 in 1979 just failed to reach statistical significance ($p=0.06$). In subgroup 1, plasma noradrenaline levels during exercise corresponded to 75% of maximum work load, plasma adrenaline levels at rest and during exercise as well as PRA at rest and during exercise measured in 1977, 1979, and 1984 were almost identical with the respective values found in the total group of normotensive subjects (Table 5). The data determined in subgroup 3 and 4 did not differ from the values of subgroup 1. Urinary sodium excretion was 183±11 mmol/24 h. In 1977, in normotensives, a similar value (179±11 mmol/24 h) was found in subjects with borderline hypertension. In both groups, urinary sodium excretion had not changed in 1979 and 1984. At no time did urinary sodium excretion of subgroups 1, 3 and 4 differ from the values of the total groups of normotensives and borderline hypertensives, respectively.

2.5 DISCUSSION

In the present study, 5 of originally 26 subjects with borderline hypertension became definitively hypertensive within an observation period of 7 years. This figure is comparable with data reported by Julius and Schork (1971), Hedstrand and Åberg (1975), Julius (1977), Kubo et al. (1983) and Sasakawa et al. (1983). Falkner et al. (1981) reported that 56% of borderline hypertensive adolescents developed definitive hypertension in a follow-up period of up to 41

months. This rather high percentage of hypertensives may be due to the definition of borderline hypertension used by Falkner et al. (1981) which differs from the definition of the other authors mentioned.

In 10 of the originally borderline hypertensive subjects of our study, mean arterial blood pressure (MAP) fell to levels below 107 mm Hg during the observation period. Similar findings were reported by Hedstrand and Åberg (1975), Kubo et al. (1983) and Sasakawa et al. (1983). In 7 subjects from our normotensive group, there was a slight increase of blood pressure during the follow-up period. However, in none of them did the blood pressure reach the borderline hypertensive range. These data show that the group of borderline hypertensives is rather heterogeneous as far as the development of blood pressure is concerned. Nevertheless, the chance to develop definitive hypertension is considerably higher in borderline hypertensives than in normotensive subjects as has also been reported by previous authors (Julius and Schork, 1971; Julius et al., 1980; Ibsen, 1984).

In the total group of borderline hypertensive subjects, heart rate at rest in supine and standing position was higher than in the group of normotensive subjects. Similar findings have been published previously (Julius et al., 1971a; Van Hooff et al., 1984a). These authors also have shown that the higher heart rate in borderline hypertensives is at least partly due to reduced activity of the parasympathetic nervous system. This is compatible with the observation in the present studies and in a previous one (Henquet et al., 1981) that differences in heart rate between normotensives and borderline hypertensive subjects become less or even disappear during higher levels of physical activity. As Robinson et al. (1966) have shown, the influence of the parasympathetic nervous system on heart rate decreases or even is absent during strenuous exercise.

In the present study, subjects of subgroup 1 (consistently normotensive) and subgroup 3 (consistently borderline hypertensive) did not differ significantly in heart rate at rest, although this parameter was slightly higher in the latter group. In contrast, subjects of subgroup 4, that is subjects who became definitively hypertensive during the observation period, had higher resting supine heart rates, both at entrance into the study and at the time of definitive

hypertension, than subgroups 1 and 3. These findings suggest that the abnormalities which cause elevated heart rate in borderline hypertension are more pronounced in those subjects who develop definitive hypertension within a few years.

As compared with normotensives, borderline hypertensive subjects had higher blood pressure values not only at rest but also during physical exercise at entrance into our study. Similar findings have been reported by Henquet et al. (1981), Chaix et al. (1982), and Franz (1979, 1983). In the present study, subjects of subgroup 1 had lower blood pressure values than subjects of subgroup 3 and 4 during all levels of exercise on a bicycle ergometer. This was true if the exercise level was expressed as percentage of the maximum tolerated work load or if a constant absolute work load of 124 W was used.

Of particular interest is the question whether blood pressure at rest or during exercise has a predictive value for the further development of blood pressure in subjects with borderline hypertension. In our study, both subgroup 3 (consistently borderline hypertensive) and subgroup 4 (subjects who became definitively hypertensive) did not differ in supine and standing blood pressure at the time of recruitment. At this time, there was also no difference between the two subgroups in blood pressure values measured during physical exercise corresponding to 50, 75 and 100% of maximum work capacity. However, at the same absolute work load of 124 W, diastolic blood pressure was significantly higher in subgroup 4 than in subgroup 3, whereas the difference in systolic blood pressure was not statistically significant. On the basis of our data, one may assume that the predictive value of diastolic blood pressure during physical exercise is limited since there was considerable overlapping of the data from those subjects who remained borderline hypertensive and those who developed definitive hypertension during the observation period. Using bicycle ergometry with a final work load of 100 W, Franz (1983) divided a group of borderline hypertensives into two subgroups. Those who had blood pressure values exceeding 200/100 mm Hg during exercise were classified as ergometry positive, those who had blood pressures up to 200/100 mm Hg as ergometry negative. 97% of the subjects from the ergometry positive group developed definitive hypertension within an

observation period of 3.8 years. However, 32% of the ergometry negative subjects with borderline hypertension became definitively hypertensive, too. Taken together, one may conclude from the study by Franz (1983) and from our data that in subjects with borderline hypertension the predictive value of blood pressure during physical exercise is limited.

The plasma catecholamine concentrations measured in normotensive subjects at supine rest in the present investigation are comparable with levels reported by other authors using radiometric techniques (Engelman and Portnoy, 1970; DeQuattro and Chan, 1972; Louis et al., 1974; Pedersen and Christensen, 1975; Esler et al., 1977a; Lake et al., 1977; Sever et al., 1977). Plasma catecholamine levels measured during physical exercise in the present study are comparable with data obtained under similar conditions (Rahn et al., 1978; Christensen et al., 1979). In the present investigation, plasma noradrenaline concentrations measured during supine rest in the total groups of normotensive and borderline hypertensives as well as in subgroups 1 and 3 were higher in 1977 when the subjects were studied first than in 1979 and in 1984. There was, however, no difference between the values determined in 1979 and in 1984. The decline of resting plasma noradrenaline levels after the first determination may be due to the fact that the subjects became familiar with the study procedures. Jones et al. (1979) have pointed out that this may significantly influence the plasma catecholamine levels.

In the present study, there were no differences in plasma noradrenaline levels at rest and during physical activity between the total groups of normotensive and borderline hypertensive subjects at repeated determinations. These results are comparable with data by Weidmann et al. (1979) and in contrast to reports by Miura et al. (1978) and Cousineau et al. (1978). The discrepancies could be due to the fact that the groups of borderline hypertensives contain different percentages of subjects who develop definitive hypertension. In our investigation, the situation changed when subgroups were considered separately. Subjects who developed definitive hypertension within the observation period (subgroup 4) had consistently high plasma noradrenaline levels. In contrast, subjects who remained normotensive (sub-

group 1) as well as subjects remaining borderline hypertensive (subgroup 3) throughout the observation period had relatively high resting plasma noradrenaline concentrations only at the first determination, the levels of the catecholamine being considerably lower than in subgroup 4 at successive measurements. Our findings could be explained by assuming that borderline hypertensives who develop definitive hypertension within a few years have continuously somewhat elevated plasma noradrenaline concentrations as compared with normotensive subjects. The differences can best be demonstrated under resting conditions, whereas they are obscured in situations with psychic or physical stress. Most probably, the higher plasma noradrenaline concentrations measured in subgroup 4 are due to increased sympathetic activity and thereby enhanced release of the amine into the circulation. An altered noradrenaline clearance is a less likely explanation since the subjects of subgroup 4 did not differ from subgroups 1 and 3 in age and since all subjects studied had normal liver and kidney function.

In the present investigation, no differences in plasma adrenaline concentrations at rest and during physical exercise were found between the total groups of normotensives and borderline hypertensives as well as between subgroups 1, 3 and 4. These findings are compatible with data by Robertson et al. (1979), Messerli et al. (1981), Eliasson (1984) and Saito et al. (1984). The PRA measured in our study at rest and during physical activity in normotensives is similar to data reported for subjects with a comparable salt intake (Kotchen et al., 1971; Brunner et al., 1972; Costill et al., 1976; Kosunen and Pekarinen, 1976). Like Werning et al. (1972), Robertson et al. (1979), Aoi et al. (1983), Saito et al. (1984) and Sullivan et al. (1984), we did not find differences between normotensives and borderline hypertensive subjects at supine rest. The same is true if subgroups 1, 3 and 4 were compared. Furthermore, the total groups of normotensives and borderline hypertensives as well as subgroups 1, 3 and 4 did not differ in PRA during physical exercise.

Chapter 3

SALIVARY FLOW IN BORDERLINE HYPERTENSION

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3.1 SUMMARY

Salivary flow was studied in normotensives and in subjects with hypertension. Salivary flow rate was lower in borderline hypertensives than in normotensives. Propranolol, phentolamine and noradrenaline had no influence on salivary flow. Atropine decreased this parameter. The stimulating effect of neostigmine on saliva production was more pronounced in normotensives than in borderline hypertensives. The data support the assumption that in subjects with borderline hypertension the parasympathetic influence on the salivary glands is reduced.

3.2 INTRODUCTION

Studies by Julius et al. (1971a) have shown that the influence of the parasympathetic nervous system on the heart is decreased in subjects with borderline hypertension. It appeared interesting to know whether this is a more general phenomenon which is also true for other organs. In man, saliva production at rest is predominantly under the influence of the parasympathetic nervous system. Therefore, a study was designed to compare the salivary flow in normotensive volunteers and in subjects with borderline hypertension (Van Hooff et al., 1984a).

3.3 SUBJECTS AND METHODS

Forty-two men participated in the study. Their age ranged from 22-34 years. Twenty-three of them were normotensives, that is their blood pressure after 2 min standing was equal to or lower than 125/85 mm Hg when measured twice with an interval of 2 weeks. The 19 other subjects had borderline hypertension. For the purpose of this study, borderline hypertension was defined as blood pressure values measured after 2 min standing of 140/90 mm Hg or above but lower than 160/100 mmHg.

Salivary flow was measured in all subjects after 15 min of

supine rest using a method described by Dollery et al. (1976). The method is based on the weight gain of dental cotton wool cylinders placed in the mouth. All measurements were performed between 4 and 6 p.m. when the subjects had refrained from food, beverages and smoking for at least 2 h. Control experiments had shown that under these conditions, salivary flow is constant when measured repeatedly every 10 min for a total of 1 h. Sodium and potassium in saliva were measured by flame photometry after the dental cotton wool cylinders had been soaked in distilled water. Furthermore, in all volunteers participating in the study, blood pressure and heart rate were determined after 30 min rest in supine position. After these measurements, blood was drawn for radiometric determination of plasma noradrenaline and adrenaline levels. Subsequently, blood pressure and heart rate were determined again after 2 min standing. Data are presented as mean $\pm$ standard error of the mean. The t-test and the paired t-test were used for statistical analysis.

3.4 RESULTS

As could be expected, subjects with borderline hypertension had higher supine and standing blood pressure values than the normotensive controls ($p<0.001$). After 30 min supine rest, heart rate was 63 ± 2 beats/min in normotensive controls. Supine heart rate was 73 ± 2 beats/min in borderline hypertensive subjects. The difference is statistically significant ($p<0.01$). After 2 min standing, subjects with borderline hypertension also exhibited a somewhat higher heart rate than normotensives. However, the difference was not statistically significant ($p>0.05$).

Plasma noradrenaline levels were 0.25 ± 0.03 ng/ml in normotensives and 0.28 ± 0.03 ng/ml in borderline hypertensives. The difference is not statistically significant ($p>0.1$). The same holds for plasma adrenaline levels.

Salivary flow averaged 0.85 ± 0.08 g/min in the normotensive subjects. This parameter was significantly lower ($p<0.001$), that is 0.51 ± 0.04 g/min, in borderline hypertensives. Sodium and potassium concen-

trations in saliva were studied in 8 normotensive subjects and in 8 borderline hypertensives. In the normotensive volunteers, salivary sodium concentation was 9.2±1.96 µmol/g and salivary potassium concentration was 21.2±1.93 µmol/g. These values did not differ (p>0.2) from the concentrations measured in saliva from borderline hypertensives. Since salivary flow was considerably higher in normotensives than in borderline hypertensive subjects the potassium secretion rate in saliva was higher in normotensive subjects than in borderline hypertensives (Fig. 1). Also sodium secretion rate was somewhat higher in normotensives than in borderline hypertensives. However, the difference was not statistically significant.

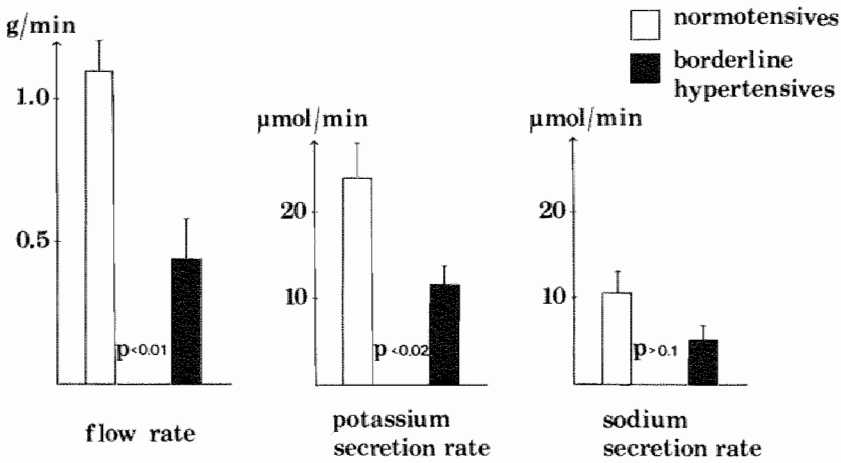

Figure 1: Salivary flow and electrolyte secretion. Data represent mean ± SEM of 8 normotensive subjects and 8 subjects with borderline hypertension.

In 8 subjects from either group, the effect of adrenergic blocking agents on salivary flow was studied. Intravenous injection of 5 mg phentolamine and of 5 mg propranolol on another day had no influence on salivary flow. Furthermore, in 4 subjects from either group noradrenaline infused intravenously at a rate of 3 µg/min during 30 min did not alter salivary flow (p>0.1). A dose of 0.5 mg atropine given intravenously, reduced salivary flow in both groups of subjects studied (p<0.001). The decrease of salivary flow was more pronounced in normotensives than in borderline hypertensive subjects (p<0.01). An intravenous dose of 1.5 mg atropine almost completely abolished saliva secretion in normotensive controls as well as in subjects with border-

line hypertension.

In 6 subjects of either group, the effects of cumulative intravenous doses of neostigmine were studied. The parasympathomimetic drug caused a dose-dependent increase of saliva production in normotensive volunteers, a maximum increase of about 1.9 g/min being obtained with doses of 50 μg neostigmine/min. In borderline hypertensives, neostigmine also led to a dose-dependent increase of salivary flow. As compared with the normotensives, the dose-response curve for the stimulating effect of neostigmine on saliva production was shifted to the right in borderline hypertensive subjects. From the individual dose-response curves, the dose of neostigmine which increased salivary flow by 1 g/min was determined. This was 28 ± 0.9 μg/min in normotensives and 41 ± 3.8 μg/min in borderline hypertensives. The difference is statistically significant ($p<0.001$).

3.5 DISCUSSION

This study demonstrates that salivary flow at rest is lower in subjects with borderline hypertension than in age-matched normotensive controls. The experiments with adrenergic blocking agents and with noradrenaline infusions show that under the conditions used in this study the sympathetic nervous system has no influence on saliva production. Plasma noradrenaline and adrenaline levels did not differ in the two groups of subjects studied. These data, thus, gave no indication of differences between the two groups in sympathetic activity.

Apparently, the salivary glands of borderline hypertensive subjects were able to respond to parasympathetic stimulation since intravenous neostigmine was able to increase salivary flow. Atropine had a more pronounced inhibitory effect of salivary flow rate in normotensives than in borderline hypertensives. In contrast, the stimulating action of neostigmine on saliva production was more pronounced in normotensives than in borderline hypertensives. These observations are compatible with the view that the amount of acetylcholine present at the level of the salivary glands is lower in borderline hypertensives than in normotensive controls. The data support the assumption that in

subjects with borderline hypertension, the parasympathetic influence on the salivary glands is reduced.

Chapter 4

CHRONIC ANTIHYPERTENSIVE THERAPY WITH THREE DIFFERENT BETA BLOCKERS: BLOOD PRESSURE AND INDICES OF SYMPATHETIC ACTIVITY AT REST AND DURING EXERCISE AND THE INFLUENCE ON SUBMAXIMAL EXERCISE TOLERANCE

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4.1 SUMMARY

The effects of long-term antihypertensive treatment of 6 months with 3 different beta blockers (propranolol, metoprolol and pindolol) were studied at rest and during submaximal exercise in 7 patients with essential hypertension. All 3 beta blockers reduced supine and exercise systolic blood pressure. Diastolic blood pressure fell only significantly at rest ($p<0.05$). The effect of the 3 beta blockers on resting and exercise blood pressure was similar. Supine heart rate was decreased during propranolol and metoprolol ($p<0.01$), but stayed unchanged during pindolol. Heart rate during exercise was decreased ($p<0.01$) by all 3 beta blockers. No differences between the 3 drugs were found. Plasma noradrenaline levels at rest and during exercise tended to be reduced during pindolol. No consistent changes were found during propranolol and metoprolol.

The endurance time of submaximal bicycle ergometer exercise was reduced significantly by all 3 beta blockers. No significant difference between the 3 drugs was found. The impairment of exercise performance was more pronounced after 6 months of treatment than after 1 week.

4.2 INTRODUCTION

Beta-adrenoceptor blocking agents have been recommended and are widely used as first-step therapy in the treatment of essential hypertension. Despite of their wide-spread use, the mechanism of their antihypertensive action is not fully understood. One of the hypotheses is that beta blockers act by interfering with sympathetic nervous activity. Conflicting data on the effect of beta blockers on plasma noradrenaline levels have been reported (Brecht et al., 1976; Nilsson et al., 1978; Rahn et al., 1978; Rahn, 1980; MacDonald et al., 1984; Van Baak et al., 1985; DeQuattro and Hamad, 1985), although during chronic administration the finding of unchanged levels is predominant. Plasma concentrations of noradrenaline depend on the rate of release into plasma and on the rate of clearance and re-uptake from plasma. A

decreased clearance, due to a reduction of liver blood flow during beta blockade, may compensate for a decreased release from sympathetic nerve endings (Esler et al., 1981c; Van Baak et al., 1985). Beta blockers, with and without ISA (intrinsic sympathomimetic activity) may affect resting hemodynamics differently (Van Baak et al., 1985), but the effects during physical exercise are similar (Kostis and DeFelice, 1983; Lund-Johansen, 1983). One of the aims of this study was, therefore, to compare plasma noradrenaline levels, both at rest and during physical exercise, during treatment with different types of beta blockers with and without ISA.

In the same study, the effect on submaximal exercise tolerance was studied. One of the side-effects of beta blocker therapy is muscular fatigue, especially in relation to physical exercise. Impairment of exercise capacity after acute administration and during short-term treatment has been found (Galbo et al., 1976; Lundborg et al., 1981). However, it is not known whether these effects diminish or disappear during long-term therapy and if there are any differences between different types of beta blockers. Thus, a study was designed to evaluate the effects of the following 3 beta blockers during chronic treatment: propranolol (a non-selective beta blocker), metoprolol (a $beta_1$-selective blocker) and pindolol (a non-selective blocker with ISA) in patients with mild to moderate essential hypertension. Blood pressure, heart rate and indices of the sympathetic nervous system (plasma noradrenaline and plasma renin activity) at rest and during submaximal bicycle ergometer exercise, as well as the effect on exercise tolerance were investigated.

4.3 METHODS

4.3.1 Patients

Seven patients (6 males, 1 female), age at entrance into the study ranging from 29 to 48 years (mean age 37 years), weight ranging from 62 to 91 kg (mean weight 75 kg) with mild to moderate essential hypertension participated in the study. Secondary hypertension had been excluded by history, physical examination, appropriate laboratory

tests and i.v. pyelography. All patients were recruited from the hypertension clinic at St. Annadal Hospital. The study was approved by the Ethical Committee of the University of Limburg.

4.3.2 Study design

At entrance into the study, all antihypertensive medication was withdrawn. At 2-weekly intervals blood pressure (BP) and heart rate (HR) were measured, after 15 min of supine rest and after 2 min standing, during 4 weeks. At the end of this period standing BP had to be >140/90 but <170/110 mmHg. Then placebo treatment was started for 6 weeks. In the 3rd week maximal oxygen uptake ($\dot{V}O_2max$) was estimated by a submaximal bicycle ergometer test (Lundborg et al., 1981). Submaximal endurance exercise tests at 70% of the estimated $\dot{V}O_2max$ were performed in the 4th and 6th week of the placebo period. The patients were then treated orally in a single blind randomized manner with the beta-blocking drugs propranolol (Pr), metoprolol (Me) and pindolol (Pi) for 6 months each. A placebo period of 4 weeks followed each 6 months of active treatment. In the beginning of each active treatment period BP and HR were measured at weekly intervals to assure an adequate BP reduction. The dose of the drug was adjusted until a standing diastolic BP <90 mmHg was reached. Starting dose in the Pr period was 40 mg/day. It was increased weekly with 40 mg/day up to 240 mg/day maximally if necessary. A similar procedure was used to determine the doses of Me and Pi. Average daily doses of Pr were 108±17 mg, Me 150±31 mg and Pi 14±2 mg. When the aim, standing diastolic BP <90 mmHg, was reached, BP and HR were measured at monthly intervals. After 6 weeks of active treatment, a blood sample was drawn after 30 min of supine rest for determination of plasma noradrenaline (PNA). In each 5th and 6th month of the active treatment period and at the end of each placebo period (4th week), the patients performed a submaximal endurance exercise test (protocol see below). In 11 out of the total of 20 treatment periods an additional exercise test was performed after 1 week of beta blocker treatment; 4 patients in the Pr and Pi treatment period and 3 patients in the Me period.

4.3.3 Submaximal exercise test

A protocol for the submaximal exercise test similar to that described by Lundborg et al. (1981) was used in our study. The patients were exercising in a temperature controlled laboratory (18-21°C) on a bicycle ergometer at 70% of their predicted $\dot{V}O_2max$ until exhaustion. Maximal duration of the test was 3x30 min with 10 min rest in between. The tests were performed 2-4 hours after the intake of the last tablets, at least 2 hours after a meal. Furthermore, the patients were advised not to consume alcohol, coffee or nicotine on the day of the test and to avoid exhaustive physical exercise. After placing a cannula into a vena cubitalis, BP and HR were measured for 30 min in supine position. Blood was then drawn for determination of PNA, plasma renin activity (PRA) and the plasma drug level. The samples were centrifuged and the plasma immediately frozen at -20°C. Then, BP and HR were measured after 2 min standing. Subsequently the exercise test was started. HR was determined during exercise at 10 min intervals. During the last 2 min of each 30 min exercise phase and at the point of exhaustion, BP and HR were measured and blood was drawn for determination of PNA and PRA. After exhaustion the patient rested supine for 15 min. During this time BP and HR were measured and again at the end blood was drawn for determination of PNA and PRA.

4.3.4 Methods

Blood pressure (BP) and heart rate (HR) at rest were measured with an automatic recorder (DINAMAP, Applied Medical Research Corporation, Tampa, USA). HR during exercise was obtained electrocardiographically. Exercise BP was measured with a standard mercury sphygmomanometer; the muffling of the sounds (Korotkoff IV) was regarded as exercise diastolic BP. All ergometry studies were performed on the same Lode bicycle ergometer in upright sitting position. PNA was determined radioenzymatically (Henquet et al., 1981) and PRA was measured by radioimmunoassay (Henquet et al., 1981). Plasma drug levels of Pr, Me and Pi were measured by HPLC with fluorometric detection (Schoeffel, FS 970). For the analysis of Pr 1 ml of heparinized plasma with metoprolol as internal standard was extracted twice with hexane/pentanol (98.5/1.5). The organic layer was reextracted with 250 µl

0.01 N H_2SO_4. The H_2SO_4 phase was injected into the HPLC using a microsphere C_{18} column (Chrompack no. 28410). Actonitrile: methanol: 0.01 N $HClO_4$ (71:25:4) was used as eluent. The pH of the eluent was brought to 6.0 using H_3PO_4. The excitation wavelength of the detector was 208 nm and the emission filter was set at 320 nm. The Me plasma samples were determined as follows: 50 µl 10 N NaOH and 5 ml ether/hexane (3:1) were added to 1 ml plasma. The organic phase was reextracted by adding 200 µl 0.1 N $NaH_2PO_4.H_2O$ (pH 3). The organic phase was discarded and aliquots of the aequous phase (100 µl) were injected directly onto the HPLC column (C_{18} microsphere, Chrompack no. 28410). The excitation wavelength of the detector was 224 nm and the emission filter was set at 320 nm. Plasma Pi levels were determined by a modification of the HPLC method described by Bengah et al. (1980). To 2 ml heparinized plasma, 500 µl 1 N NaOH and 6 ml diethylether were added. The organic phase was reextracted with 200 µl 0.1 N $NaH_2PO_4.H_2O$ (pH 3). Then, 1 ml n-heptane was added to the aequous phase. After extraction, aliquots of the aequous phase (100-150 µl) were injected directly onto the HPLC column (C_{18} microsphere, Chrompack, no. 28410). The eluent was 0.02 N NH_4Ac/AcCN (13:7) (pH 5.5). The excitation wavelength was 220 nm and the emission filter was set at 320 nm. The detection limit of all three procedures was 1 ng/ml plasma. The interassay coefficient of variation was <5%.

Results are expressed as mean ± SEM. Values of the exercise tests during the placebo period before and after each active treatment and values of exercise tests in the 5th and 6th month of the active treatment period were averaged unless indicated otherwise. This was considered acceptable since no statistically significant differences in exercise heart rate within those pairs of tests were found. This suggests that no consistent change in cardiorespiratory fitness had occurred between the two tests.

Statistical analysis was performed by paired Student's t-tests; the level of significance was set at $p<0.05$.

4.4 RESULTS

One patient was withdrawn from Pi treatment after 2 weeks because of severe headache. In another patient the Pi treatment period was shortened because of complaints about fatigue. Plasma drug levels were 63±15 ng/ml (5th month) and 69±30 ng/ml (6th month) during Pr (n=7), 73±25 ng/ml (5th) and 94±22 ng/ml (6th) during Me (n=7), 29±5 ng/ml (5th; n=6) and 17±3 ng/ml (6th month; n=5) during Pi.

4.4.1 SBP and DBP at rest

During the placebo periods, the BP of several patients was lower than at the end of the wash-out period. The effect of the 3 beta blockers on supine systolic (SBP) and diastolic blood pressure (DBP) is shown in Fig. 1. After one week of treatment, supine SBP and DBP was already decreased from 144±4/90±4 to 132±4/82±3 mm Hg during Pr ($p<0.01$), from 145±5/90±4 to 136±5/80±2 mm Hg during Me ($p<0.05$), and from 144±4/90±2 to 134±6/84±5 mm Hg during Pi (SBP: $p<0.01$; DBP: NS). An adequate reduction of supine SBP and DBP was attained at nearly all control intervals during the 6 months of treatment with all 3 beta blockers (Fig. 1).

Standing SBP and DBP measurements at the same control intervals showed similar results. After one week of treatment, standing SBP and DBP were decreased from 146±5/98±4 to 133±4/90±3 mm Hg during Pr ($p<0.01$), from 145±5/98±3 to 137±6/89±4 mm Hg during Me (SBP: NS; DBP: $p<0.01$), and from 143±3/95±3 to 132±4/89±4 mm Hg during Pi (SBP: $p<0.01$; DBP: NS). When comparing the 3 beta blockers, supine and standing SBP and DBP revealed no consistent statistically significant differences during the treatments.

4.4.2 HR at rest

Resting HR (Fig. 1) was reduced during Pr and Me. After 6 weeks of treatment, HR at rest was lowered significantly ($p<0.01$), from 69±2 to 61±1 beats/min during Pr and from 75±4 to 56±2 beats/min during Me, and stayed in that range for the rest of the observation period. Supine HR during Pi showed no significant decrease throughout the

treatment period. When comparing the beta blockers, HR at rest differed significantly between Pr and Pi, and Me and Pi ($p<0.001$) (Fig. 1). No consistent differences between Pr and Me were found.

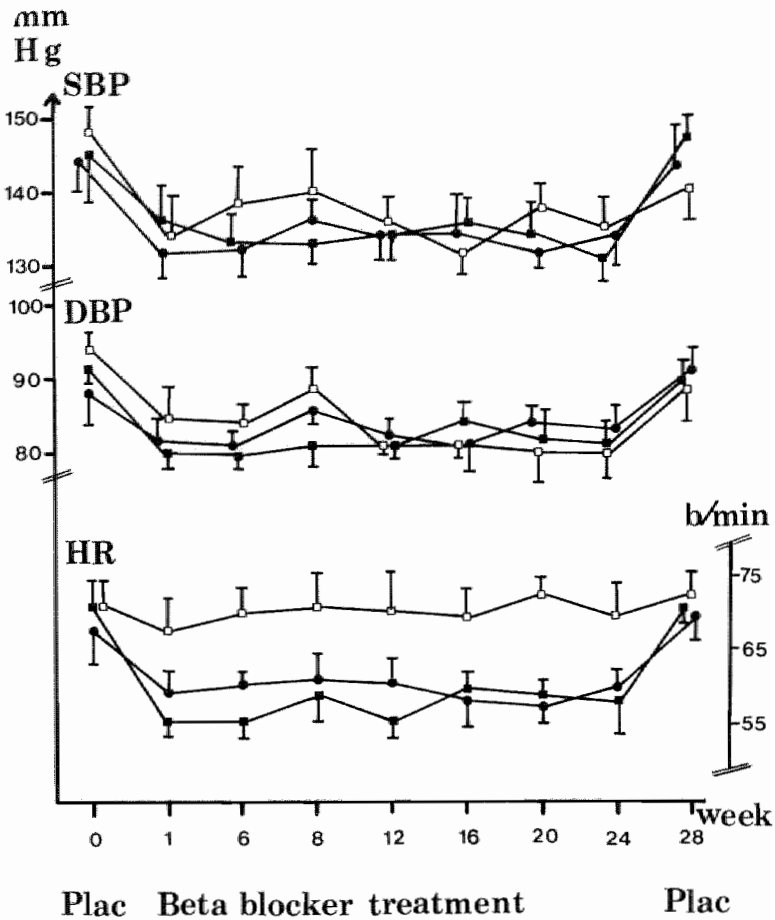

Figure 1: Supine systolic (SBP), diastolic (DBP) blood pressure and heart rate (HR; b/min) during placebo (Plac) and chronic treatment with propranolol (●) (n=7), metoprolol (■) (n=7) and pindolol (□) (n=6). Mean values ± SEM are given.

4.4.3 PNA and PRA at rest

Table 1 shows PNA levels at rest during the placebo and the treatment periods with the 3 beta blockers. After 6 weeks, PNA during Pr showed a decrease ($p<0.05$), whereas the 5th/6th month treatment value showed no significant difference with placebo. Me had no statistically significant effect on resting PNA throughout the whole treat-

Table 1: Plasma noradrenaline levels at rest (ng/ml) during treatment with propranolol (Pr), metoprolol (Me) and pindolol (Pi). Data represent mean values ± SEM.

	Plac	Week 6	Week 20	Week 24
Pr (n=7)	0.26±0.04	0.15±0.01*	0.23±0.05	0.21±0.03
Me (n=7)	0.24±0.02	0.21±0.03	0.22±0.02	0.22±0.03
Pi (n=6)	0.29±0.03	0.11±0.01**	0.16±0.02**	0.26±0.10

* $p<0.05$; ** $p<0.01$ when compared with placebo.

ment period. During Pi, a significant decrease was found in the 6th week and the 5th month of treatment ($p<0.01$). The value in the 6th month was not significantly different from placebo.

PRA levels at rest were significantly decreased during treatment with all 3 beta blockers when compared with placebo. PRA fell from 1.38±0.28 to 0.68±0.11 ng AI/h.ml during Pr ($p<0.01$), from 1.24±0.14 to 0.67±0.09 ng AI/h.ml during Me ($p<0.001$) and from 1.43±0.28 to 0.86±0.14 ng AI/h.ml during Pi ($p<0.05$) in the 5th/6th month of treatment.

4.4.4 Exercise BP and HR

The patients performed their exercise tests at a mean work load of 131 ± 13 W. Exercise SBP and DBP at the point of exhaustion changed from 184±4/87±3 to 167±4/89±3 mm Hg during Pr, from 185±5/84±2 to 168 ±6/85±3 mm Hg during Me and from 180±4/86±3 to 162±4/84±3 mm Hg during Pi (Fig. 2). Similar results were obtained at the end of the first exercise period (30 min). Exercise SBP was decreased significantly by all 3 beta blockers ($p<0.01$), whereas exercise DBP showed no significant change. No statistically significant difference in exercise SBP was found between the 3 beta blockers. The SBP increase from rest to exercise was only blunted significantly under Pi ($p<0.05$) (Fig. 1+2).

Exercise HR at the point of exhaustion was decreased signifi-

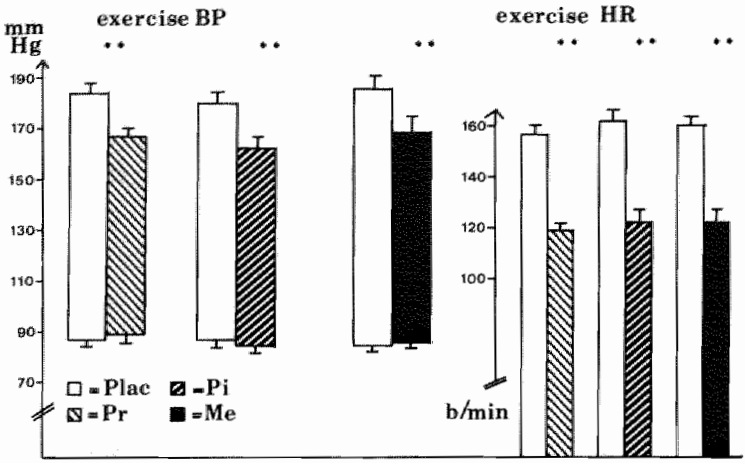

Figure 2: Exercise systolic and diastolic blood pressure and heart rate (HR) at exhaustion during chronic treatment with propranolol (Pr; n=7), metoprolol (Me; n=7) and pindolol (Pi; n=6). Mean values of placebo (Plac) are compared with the mean of the 20th and 24th week of treatment.
Mean values ± SEM are given.
*$p<0.05$; **$p<0.01$.

cantly ($p<0.01$) by all 3 beta blockers. HR fell from 157±4 to 119±2 beats/min during Pr, from 160±3 to 118±4 beats/min during Me and from 162±4 to 122±4 beats/min during Pi (Fig. 2). No significant difference was found between the 3 beta blockers in exercise HR at exhaustion nor after 10 min of exercise.

4.4.5 PNA and PRA during exercise

Values of PNA and PRA during exercise are presented in Table 2. When compared with placebo, Pr and Me had no significantly different effect on PNA during exercise. PNA during Pi was decreased at the end of the first exercise period and during recovery when compared to placebo values ($p<0.05$).

On placebo, exercise resulted in a rise of PRA. Although values of PRA after the beta blockers tended to decrease, the reduction was not significant during Pr and only at the point of exhaustion ($p<0.05$) and during recovery during Me and Pi ($p<0.05$). It must be pointed out that PRA values of one patient increased systematically during exercise after all 3 beta blockers: there was a two-fold rise when compared with placebo. When the values of this patient were excluded,

Table 2: Plasma noradrenaline levels (PNA) and plasma renin activity (PRA) during exercise. Propranolol (Pr), metoprolol (Me) and pindolol (Pi) levels refer to mean 20/24th week. Data represent mean values ± SEM.

	End of 1st exercise period		Exhaustion		Recovery	
	PNA ng/ml	PRA ng AI/ml.h	PNA ng/ml	PRA ng AI/ml.h	PNA ng/ml	PRA ng AI/ml.h
Plac	1.44±0.18	3.36±0.61	1.47±0.18	4.78±0.85	0.26±0.02	3.25±0.55
Pr (n=7)	1.49±0.22	2.24±0.75	1.67±0.23	3.31±1.98	0.29±0.05	2.90±1.60
Plac	1.68±0.40	3.52±0.45	1.95±0.51	5.11±0.74	0.35±0.04	3.19±0.42
Me (n=7)	1.76±0.42	2.46±1.34	1.76±0.46	2.63±1.18*	0.30±0.04	1.80±0.67*
Plac	1.94±0.26	3.55±0.70	2.18±0.40	5.27±1.24	0.34±0.05	3.20±0.62
Pi (n=6)	1.58±0.15*	2.26±0.92	1.77±0.19	1.87±0.63*	0.23±0.05*	1.38±0.34**

* $p<0.05$; ** $p<0.01$ when compared with placebo.

mean PRA levels were decreased significantly at all time points during Pr, Me and Pi ($p<0.05$).

4.4.6 Endurance time

There was a statistically significant decrease of endurance time during treatment with all 3 beta blockers. During Pr, exercise time was reduced from 69±10 min to 52±6 min ($p<0.05$), during Me from 69±10 min to 58±9 min ($p<0.01$), and during Pi from 62±9 to 38±10 min ($p<0.05$). However, differences in reduction of exercise time between the 3 beta blockers were not statistically significant. The average reduction of exercise time after one week of treatment was 10±13% and 22±10% in the 5th and 6th month of treatment ($p<0.03$).

4.5 DISCUSSION

4.5.1 Effects on HR and BP at rest and during exercise

No differences in the BP lowering effect at rest between the 3 beta blockers were found, which indicates that equieffective antihypertensive doses of Pr, Me and Pi were used in our study. Supine HR was lowered significantly during Pr and Me, whereas Pi did not affect HR as has also been found in other studies (Velasco et al., 1980; Gavras et al., 1981; Svensson et al., 1981; Franz et al., 1982). The pronounced ISA of Pi is held responsible for the absence of a decreased HR at rest (Kostis and DeFelice, 1983). SBP during exercise was lowered significantly and similarly by all 3 beta blockers. The same is true for HR during exercise. Exercise DBP was slightly increased or unchanged during beta blocker treatment when compared with placebo, which is in agreement with other studies (Leenen et al., 1980; Morrison et al., 1982). In contrast, decreased values of DBP have also been reported (Franz et al., 1980; Svensson et al., 1982; Virtanen et al., 1982; Van Hooff et al., 1984b). However, both measurement and interpretation of exercise DBP are very difficult (Rasmussen et al., 1985).

4.5.2 Effects on PNA and PRA at rest and during exercise

There are conflicting reports on the influence of beta blockers on resting plasma catecholamines (Rahn, 1980; DeQuattro and Hamad, 1985). In general, no changes have been found. In our study, PNA levels during Me at rest showed no consistent changes, during Pr only after 6 weeks of treatment. PNA levels during Pi tended to decrease more consistently. This is in agreement with studies by Brecht et al. (1976) and Franz et al. (1980), but in contrast with reports by Gavras et al. (1981) and Floras et al. (1985). The PNA level is determined by the rate of release of noradrenaline into and the removal from plasma. Esler et al. (1981c) reported reduced plasma noradrenaline clearance during Pr suggesting that the unchanged PNA levels are the result of a decreased release and a decreased clearance. Since Pi does not reduce cardiac ouput and hepatic blood flow at rest, one would not expect PNA clearance to be reduced (Man in 't Veld and Schalekamp, 1983). The de-

creased PNA levels during Pi could then be interpreted as a reduction of noradrenaline release, this effect being masked with other beta blockers by their concomitant effects on PNA clearance (Struthers and Dollery, 1985). During exercise PNA levels during Pr and Me did not differ from those during placebo, which is in agreement with other studies (Watson et al., 1980b; Lehmann et al., 1982; Van Hooff et al., 1984b), whereas during Pi PNA was decreased at the end of the first period of exercise. However, no significant difference was found at the moment of exhaustion. Since the HR reduction during exercise was similar with all 3 beta blockers, there is no evidence for differences in hemodynamics which could explain the tendency for lower PNA levels during Pi.

PRA was decreased during treatment at rest and during exercise as in other studies (Hansson et al., 1977a,b; Lijnen et al., 1979; Leenen et al., 1980, 1983; Van Hooff et al., 1984b). Although in most studies no decrease of resting PRA is found during Pi treatment (Man in 't Veld and Schalekamp, 1983), a significant reduction of resting PRA was found in our study. The reason for this finding is not clear.

4.5.3 Effects on submaximal exercise tolerance

In our patients, submaximal exercise time was decreased during treatment with all 3 beta blockers. Galbo et al. (1976), Lundborg et al. (1981), and Kindermann et al. (1984) also found impairment of submaximal exercise performance in healthy subjects after acute beta blockade. No significant differences in exercise time between the 3 beta blockers were found in our patients. Furthermore, the statement that during chronic beta blocker therapy effects of decreased exercise performance tend to disappear (Fellenius, 1983) is in disagreement with our findings which show an even more reduced exercise performance after 6 months of beta blocker treatment than after the first week. A possible explanation for the impaired exercise performance after beta blockade could be a decreased leg blood flow (Frisk-Holmberg et al., 1985) and/or the metabolic effects of beta blockers (Lohmann, 1981; Fellenius, 1983). These results could have consequences in prescribing beta blockers for physically active hypertensive patients.

Chapter 5

LONG-TERM ANTIHYPERTENSIVE THERAPY WITH THREE DIFFERENT BETA BLOCKERS: METABOLIC EFFECTS AT REST AND DURING SUBMAXIMAL ENDURANCE EXERCISE

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5.1 SUMMARY

The effects of long-term (6 months) antihypertensive treatment with three different types of beta blockers (propranolol, non-selective without ISA; pindolol, non-selective with ISA; metoprolol $beta_1$-selective without ISA) on metabolic variables at rest and during submaximal bicycle ergometer exercise at 70% of estimated $\dot{V}O_2max$ were studied in 7 subjects with essential hypertension.

Similar reductions of blood pressure and exercise heart rate were obtained with the three beta blockers. Apart from an increase in total and LDL+VLDL serum triglyceride concentrations during propranolol treatment, no effects on serum lipoprotein profile were found. During exercise, the reduction of plasma glycerol and non-esterified fatty acid concentrations was more pronounced during non-selective than during $beta_1$-selective blockade. Plasma glucose concentrations were largely unaffected. No consistent effects on plasma lactate levels were found. These data, in combination with a slightly decreased oxygen uptake and increased respiratory ratio, are suggestive for a decreased utilization of non-esterified fatty acids and increased carbohydrate combustion during beta blocker treatment.

Plasma potassium concentrations during exercise were significantly increased and the increase was more pronounced during non-selective than during $beta_1$-selective blockade.

The effects on the variables during exercise were similar after 1 week and during long-term (20/24 weeks) beta blocker treatment.

5.2 INTRODUCTION

Over the past years, it has become evident that beta-adrenoceptor blocking agents reduce submaximal exercise capacity (Galbo et al., 1976; Kaiser et al., 1981; Lundborg et al., 1981; Kindermann et al., 1984). The effects of beta blockade on the metabolic adjustments to exercise are probably involved in this reduction of exercise tolerance. Since $beta_1$-selective blockers have less influence on $beta_2$-receptor-mediated metabolic adjustments to exercise than non-selective

blockers (Lundborg et al., 1981; Laustiola et al., 1983) a difference between the effect of $beta_1$-selective and non-selective blockers on metabolism and exercise tolerance seems likely. Indeed, in a number of studies such differences have been found (Kaiser et al., 1981; Lundborg et al., 1981; Kindermann et al., 1984). However, all of these studies have been performed in young, healthy, usually well-trained subjects after acute or short-term beta blocker administration. For practical purposes, i.e. for the treatment of physically active hypertensive patients, it is important to know whether similar differences between $beta_1$-selective and non-selective beta blockers are also present in this group of patients, and whether they are maintained during long-term chronic therapy.

It has also been suggested that differences in the metabolic effects of $beta_1$-selective and non-selective blockers with and without intrinsic sympathicomimetic activity (ISA) may lead to different lipoprotein profiles during treatment (van Brummelen, 1983; Weidmann et al., 1983).

Therefore, a study was designed to compare the metabolic effects of three different types of beta blockers (propranolol (non-selective, without ISA), pindolol (non-selective, with ISA) and metoprolol ($beta_1$-selective, without ISA) at rest and during submaximal endurance exercise during long-term treatment in patients with essential hypertension.

5.3 SUBJECTS AND METHODS

5.3.1 Subjects

Initially, 9 subjects were included in the study. Two of them dropped out: one developed overt coronary heart disease and one subject could not be motivated to continue after one treatment period. Thus 7 subjects (6 males, 1 female; age 29-48 years) with mild to moderate essential hypertension completed the study. They were all physically active on a recreational level. The protocol of the study was approved by the Ethical Committee of the University of Limburg and all subjects gave their informed consent.

5.3.2 Design of the study

At the end of a 4-week wash-out period, when all antihypertensive medication had been withdrawn, standing blood pressure (BP) was >140/90 but <170/110 mm Hg in all subjects. Then placebo treatment was started for 6 weeks. In the 3rd week, maximal oxygen uptake ($\dot{V}O_2$ max) was estimated by a submaximal bicycle ergometer test (Åstrand, 1960). Submaximal endurance tests at 70% of the estimated $\dot{V}O_2$max were performed in the 4th and 6th week of the placebo period. The first test was used for habituation purposes and is not included in the results. The subjects were then treated orally in a single-blind randomized manner with propranolol, metoprolol and pindolol for 6 months each. A placebo period of 4 weeks followed each 6 months of active treatment. The dose of the beta blocker was adjusted to attain a standing diastolic BP <90 mmHg. After 5 and 6 months of active treatment and at the end of each placebo period, the subjects performed a submaximal endurance test at 70% $\dot{V}O_2$max (protocol, see below).

In half of the treatment periods, randomized over the three drugs, an additional endurance test was performed after 1 week of beta blocker treatment.

At the end of each active treatment and placebo period, blood was sampled after an overnight fast for determination of the lipoprotein profile and other metabolic variables at rest.

5.3.3 Protocol of the submaximal endurance test

Exercise tests were performed 2-4 h after intake of the last tablets, at least 2 h after the last meal. The subjects were asked not to consume alcohol, coffee or nicotine on the day of the test and to avoid strenuous physical exercise. After insertion of a short catheter in the v. cubitalis, subjects rested in supine position for 30 min. During the last 10 min of this period, expiratory air was collected in Douglas bags for determination of minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}O_2$) and respiratory ratio (R). During the last min, blood was drawn for determination of plasma glucose, glycerol, lactate, Na^+, K^+, and non-esterified fatty acid (NEFA) concentrations. Subsequently, the exercise test was started. The subjects exercised in a temperature-controlled laboratory (18-21°C) on a Lode bicycle ergometer at

70% of estimated $\dot{V}O_2max$ until exhaustion. Maximal duration of the test was 3 x 30 min with 10 min rest in between, a protocol similar to that described by Lundborg et al. (1981). During the last 5 min of each 30 min exercise bout, just before exhaustion, and after 15 min recovery in supine position, expiratory air was collected, blood was drawn and heart rate determined.

5.3.4 Methods

Heart rate was determined electrocardiographically. Fractions of O_2 and CO_2 in expiratory air were measured with an Ergoscreen system (Fenyves and Gut, Basel), and expiratory volume was measured with a dry gasmeter (Meterfabriek Schlumberger). From these data $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}CO_2$ and R were calculated by standard methods. Blood samples for determination of plasma glucose, glycerol, lactate, Na^+ and K^+ (heparinized) and for NEFA (no anti-coagulant added) were centrifuged immediately for 1 min at high speed. Plasma for glycerol, NEFA, Na^+ and K^+ determinations was rapidly frozen in dry ice and stored at -70^oC until futher processing. Glucose and lactate were determined immediately.

Plasma lactate, glycerol and glucose concentrations were measured enzymatically (Roche lactate analyzer 640, glucose test combination Compur, and a modification of the triglyceride (Neutralfett) test combination Boehringer Mannheim, respectively). Plasma Na^+ and K^+ were determined by flame photometry (Instrumentation Laboratory 243). Hemolytic samples were excluded. Plasma NEFA concentrations were determined colorimetrically (non-esterifed fatty acids test combination Boehringer Mannheim). Serum lipoprotein fractions were separated by density gradient ultracentrifugation (Terpstra et al., 1981). Cholesterol and triglycerides were determined enzymatically (Catalase kit Boehringer Mannheim, and test combination Triglyceride vollenzymatisch (Neutralfett) Boehringer Mannheim, respectively).

5.3.5 Data analysis

Results are presented as means $\pm$ SEM. For the sake of clarity, results of the exercise test during the placebo period before and after each active treatment period were averaged and so were the

results of the exercise tests in the 5th and 6th month of active treatment. This was considered acceptable since no statistically significant differences in exercise heart rate within those pairs of tests were found. This suggests that no consistent changes in cardiorespiratory fitness had occurred between the two tests.

Statistical analysis was performed by Wilcoxon's signed ranks tests and by analysis of variance for a randomized blocks design (Zerbe, 1979). The level of significance was set at $p<0.05$.

5.4 RESULTS

One subject was withdrawn from pindolol treatment after 2 weeks because of severe headache. In another subject, the pindolol treatment period was shortened to 3 months because of complaints about fatigue. In all subjects, the aim of the antihypertensive treatment, standing diastolic BP <90 mm Hg, was attained and BP reductions were comparable with the three beta blockers. Average standing BP was $135\pm3/88\pm2$ during propranolol, $133\pm4/89\pm2$ during pindolol and $136\pm3/88\pm3$ mm Hg during metoprolol treatment. The average value during placebo treatment was $145\pm3/97\pm2$ mm Hg. The average daily doses used were 108 ± 17 mg propranolol, 150 ± 31 mg metoprolol and 14 ± 2 mg pindolol. The subjects exercised at a mean work load of 131 ± 13 W.

5.4.1 Cardiorespiratory variables

Exercise heart rate was significantly and to a similar extent reduced during treatment with all three beta blockers ($p<0.01$) (Fig. 1). At rest and during recovery, heart rate was significantly lowered during propranolol and metoprolol ($p<0.01$), but not during pindolol treatment. $\dot{V}O_2$ at rest and during recovery was unaffected by beta blocker therapy (Fig. 2). During exercise, $\dot{V}O_2$ tended to be lower during non-selective beta blockade (propranolol: $p<0.05$; pindolol: $p=0.06$). R showed a tendency to increase during beta blocker administration (Fig. 3). However, consistent significant differences were only found during pindolol treatment ($p<0.05$). Minute ventilation was unaffected by beta blockade. There was no significant difference in

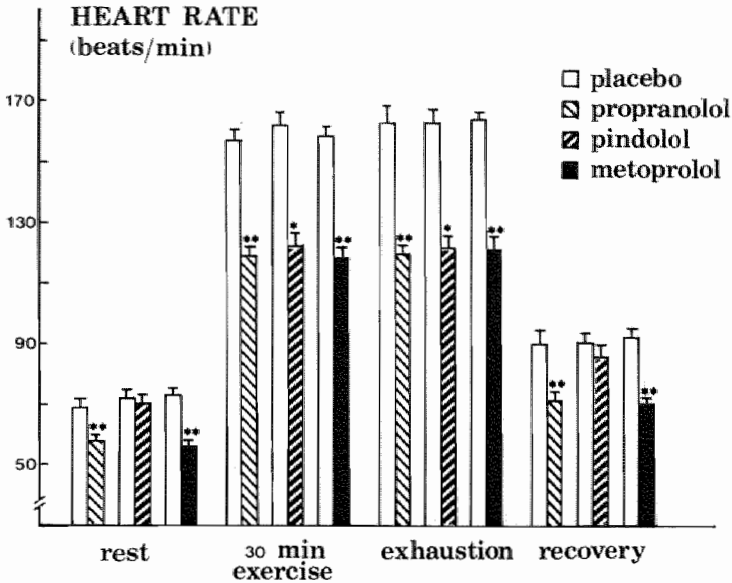

Figure 1: Heart rate (at rest, during exercise and during recovery) during placebo and beta blocker treatment (mean ± SEM). * significant difference with placebo (*p<0.05; **p<0.01).

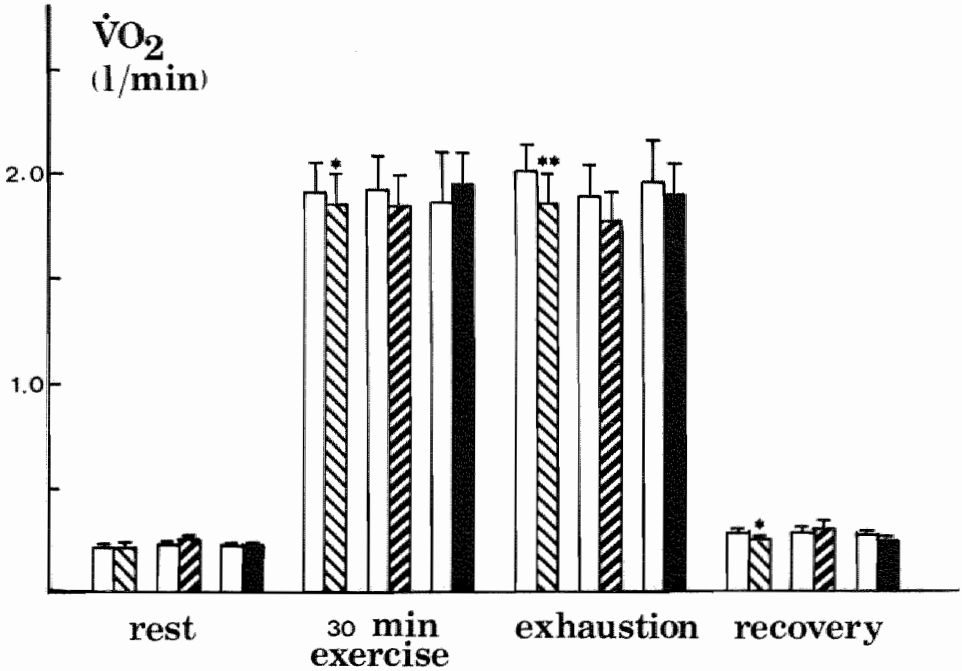

Figure 2: Oxygen consumption ($\dot{V}O_2$) (at rest, during exercise, and during recovery) during placebo and beta blocker treatment (mean ± SEM). For symbols, see legend to figure 1.

exercise heart rate and $\dot{V}O_2$ after 1 and 20/24 weeks of beta blocker treatment (Table 1). R was higher after long-term treatment than after 1 week.

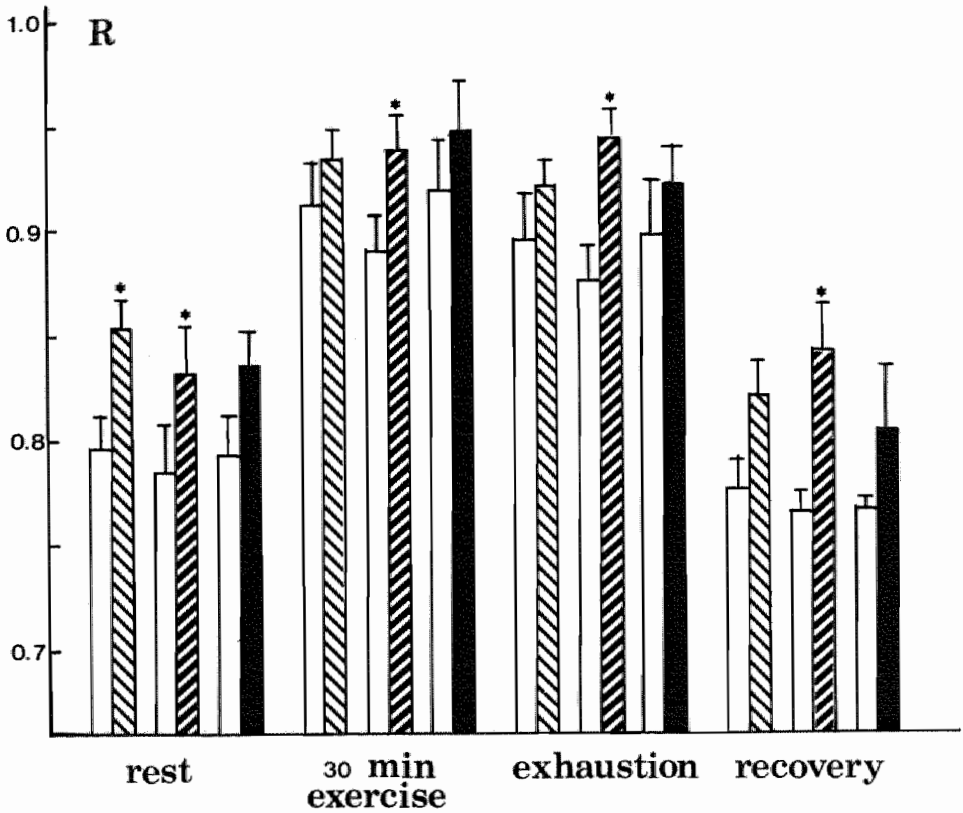

Figure 3: Respiratory ratio (R) (at rest, during exercise, and during recovery) during placebo and beta blocker treatment (mean ± SEM). For symbols, see legend to figure 1.

5.4.2 Metabolic variables

Fasting plasma glucose, lactate and NEFA levels were unaffected during beta blocker therapy (Table 2). Fasting plasma glycerol concentration was lower during treatment with all three beta blockers than during placebo treatment. Total serum triglyceride content was significantly increased during propranolol treatment, mainly due to an increase in LDL+VLDL-triglycerides. No significant changes in total cho-

Table 1: Variables (mean ± SEM) after 30 min exercise after 1 and 20/24 weeks of beta blocker treatment.

	Beta blocker treatment	
	Week 1	Week 20/24
HR (b/min)	118.4±2.4	119.7±2.5
$\dot{V}O_2$ (l/min)	1.71±0.14	1.79±0.10
R	0.91±0.01	0.94±0.02*
Glucose (mmol/l)	3.59±0.21	3.97±0.19
Lactate (mmol/l)	6.00±0.71	6.11±0.76
Glycerol (mmol/l)	0.11±0.01	0.11±0.02
NEFA (mmol/l)	0.19±0.02	0.18±0.02
K^+ (mmol/l)	5.42±0.09	5.35±0.08

*$p<0.05$

lesterol or division of cholesterol over the lipoprotein subfractions were seen.

Plasma glucose levels at rest and during exercise were not significantly different during placebo and beta blocker treatment (Fig. 4). Plasma lactate levels tended to be higher during beta blocker treatment than during placebo (Fig. 5), although the difference was only significant during pindolol therapy ($p<0.05$). Plasma glycerol levels were significantly reduced during exercise and recovery by beta blocker therapy ($p<0.05$) (Fig. 6). The decrease was significantly more pronounced during propranolol and pindolol than during metoprolol treatment ($p<0.05$). Non-esterified fatty acid concentrations were significantly reduced during exercise and recovery by propranolol and pindolol administration ($p<0.05$), but not by metoprolol treatment (Fig. 7). However, the placebo values corresponding with the metopro-

Table 2: Fasting metabolic variables (in mmol/l) during placebo, propranolol, pindolol and metoprolol treatment (mean ± SEM).

	Placebo	Propranolol	Pindolol	Metoprolol
Total cholesterol	5.44±0.40	5.11±0.49	5.05±0.22	5.61±0.58
VLDL+LDL chol	3.97±0.39	3.97±0.43	3.62±0.30	3.72±0.56
HDL chol	1.15±0.12	1.10±0.10	1.03±0.21	1.32±0.18
Total triglycerides	1.51±0.34	2.26±0.38**	1.63±0.23	1.31±0.28
VLDL+LDL triglyc	1.08±0.19	1.74±0.29**	1.19±0.23	1.00±0.28
HDL triglyc	0.11±0.01	0.15±0.02	0.14±0.02	0.16±0.02
Glucose	4.63±0.18	4.64±0.26	4.76±0.20	4.63±0.19
Lactate	1.21±0.15	1.06±0.14	1.18±0.14	1.21±0.11
NEFA	0.29±0.03	0.28±0.03	0.27±0.03	0.26±0.04
Glycerol	0.12±0.01	0.08±0.01**	0.09±0.01**	0.08±0.01***

*significant difference with placebo (**$p<0.01$; ***$p<0.001$)

lol treatment period were lower than the other placebo values. Differences between metoprolol and pindolol or propranolol were not statistically significant.

There were no statistically significant differences between the metabolic variables during exercise after 1 and 20/24 weeks of treatment (Table 1).

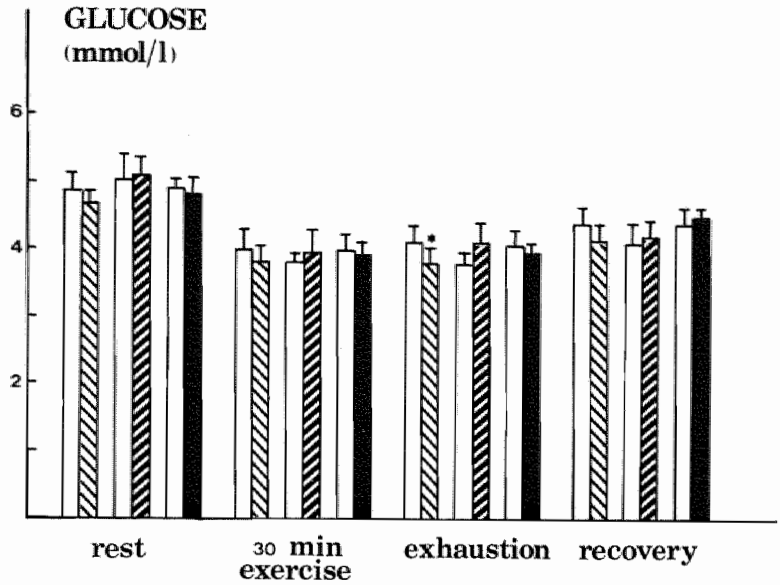

Figure 4: Plasma glucose concentration (at rest, during exercise, and during recovery) during placebo and beta blocker treatment (mean ± SEM). For symbols, see legend to figure 1.

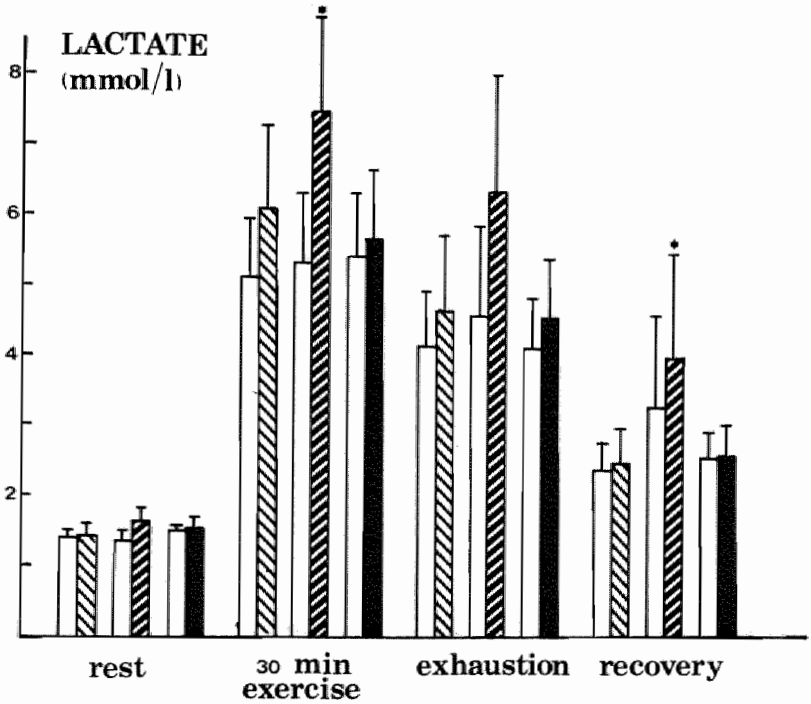

Figure 5: Plasma lactate concentration (at rest, during exercise, and during recovery) during placebo and beta blocker treatment (mean ± SEM). For symbols, see legend to figure 1.

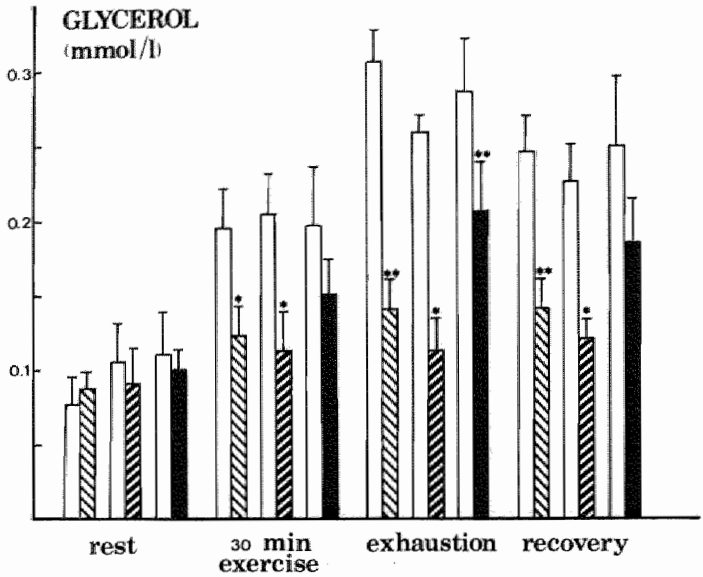

Figure 6: Plasma glycerol concentration (at rest, during exercise, and during recovery) during placebo and beta blocker treatment (mean ± SEM). For symbols, see legend to figure 1.

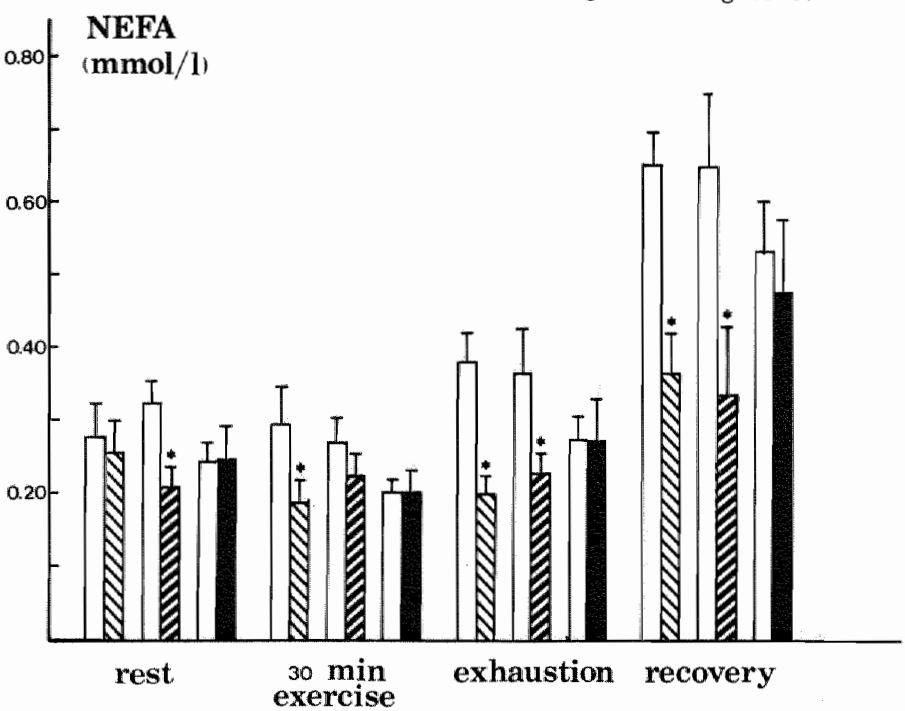

Figure 7: Plasma non-esterified fatty acid concentration (NEFA) (at rest, during exercise, and during recovery) during placebo and beta blocker treatment (mean ± SEM). For symbols, see legend to figure 1.

5.4.3 Plasma Na^+ and K^+

There was no significant difference between plasma Na^+ levels during placebo and beta blocker treatment, neither at rest nor during exercise or recovery. In contrast, plasma K^+ levels were significantly increased during treatment with all three beta blockers ($p<0.05$) (Fig. 8). The increase was significantly more pronounced during propranolol and pindolol than during metoprolol therapy ($p<0.05$). Plasma K^+ levels were similar after 1 and 20/24 weeks of treatment (Table 1).

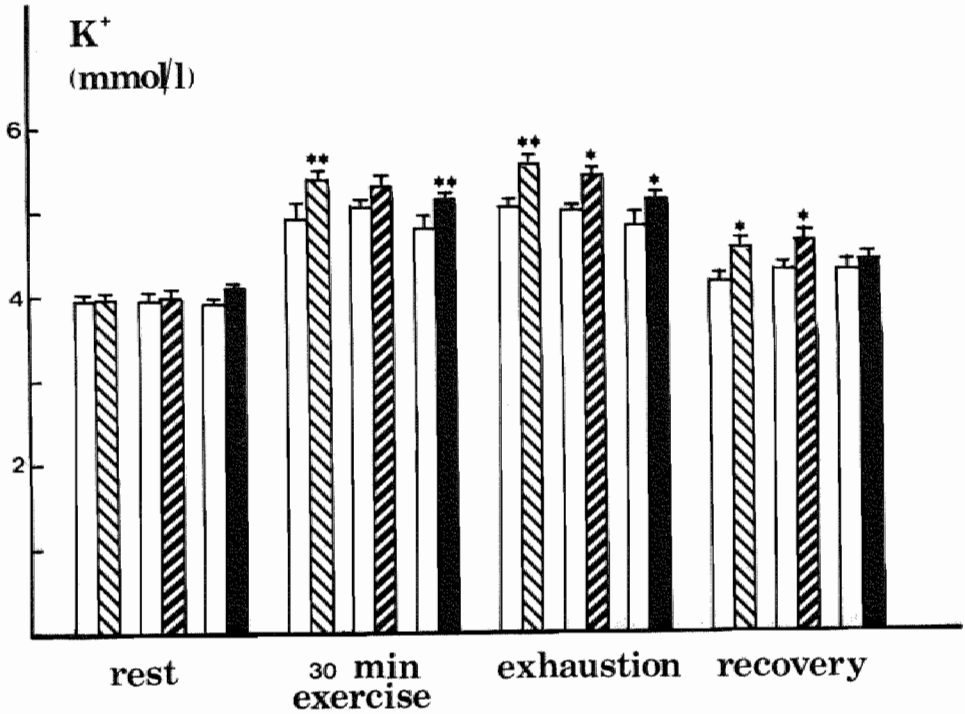

Figure 8: Plasma potassium concentration (at rest, during exercise, and during recovery) during placebo and beta blocker treatment (mean ± SEM). For symbols, see legend to figure 1.

5.5 DISCUSSION

The administered daily doses of the three beta blockers reduced blood pressure similarly and were thus equieffective in their antihypertensive effect.

The influence of beta blocker treatment on serum lipoprotein profile was not very clear. The only significant change was an increase of total and LDL+VLDL triglyceride concentrations during propranolol treatment, which has also been found in other studies (Van Brummelen, 1983; Weidmann, et al., 1983). No significant changes in total cholesterol or cholesterol content of lipoprotein subfractions were found. This may be due to the small number of subjects in our study and to the variability of serum lipoprotein values. Reviews form the available literature show that significant patterns become only evident when results of a large number of studies are combined (Van Brummelen, 1983; Weidmann et al., 1983).

During treatment with all three beta blockers, a similar reduction of submaximal exercise heart rate was found. This suggests that there were probably no important hemodynamic differences during exercise between the three trials. Moreover, Frisk-Holmberg et al. (1981, 1985) showed that the oxygen uptake of exercising muscle was unchanged during treatment with non-selective and $beta_1$-selective blockers despite a reduction of muscle blood flow. This at least suggests that differences between placebo and beta blocker treatment and between the three different beta blockers are not due to differences in oxygen delivery to the working muscles, although the effects on muscle blood flow and oxygen extraction during exercise of long duration and high intensity are not known.

All three beta blockers reduced plasma glycerol concentrations during exercise. The reduction was more pronounced during non-selective than during $beta_1$-selective blockade, which is in contrast with findings by Franz et al. (1983). However, a more pronounced reduction of plasma glycerol and NEFA levels during exercise during non-selective than during $beta_1$-selective blockade treatment has been found in other studies as well (Lundborg et al., 1981; Uusitupa et al., 1982; Laustiola et al., 1983) which suggests that $beta_2$-receptors are also

involved in lipolysis (Juhlin-Dannfelt, 1983). The results of our study indicate that lipolysis during exercise is reduced during treatment with all three beta blockers and that the reduction is more pronounced during treatment with non-selective blockers. Thus, the supply of NEFA to the working muscles is probably impaired. Studies of Frisk-Holmberg et al. (1985) indeed show a reduction of the uptake of NEFA by the working muscle during beta blockade.

In view of a decreased supply of NEFA an increased break-down of carbohydrates is to be expected. The decrease of $\dot{V}O_2$ and increase of R, although not always statistically significant, are compatible with this expectation. Decreases in $\dot{V}O_2$ and increases in R have also been found in other studies (Pearson et al., 1979; Tesch and Kaiser, 1983; Wilmore et al., 1985) although not in all (Franz and Lohmann, 1979; Smyth et al., 1984; Wilmore et al., 1985). Discrepancies may be due to differences in exercise protocol (duration, intensity) and the fact that the differences that have been found are usually quite small (<10%).

An increased carbohydrate utilization may result from an increased blood glucose uptake, and/or an increased muscle glycogen break-down, and/or an increased lactate utilization. Plasma glucose concentrations were hardly affected during beta blocker therapy, but an increased uptake of blood glucose may have been compensated by a concomitant increase in hepatic glucose output. On the other hand, studies by Frisk-Holmberg et al. (1977, 1985) have shown no changes in muscle glucose uptake during non-selective and $beta_1$-selective blockade, although at a lower work load. An increased glycogen utilization is not directly evident from studies in which muscle biopsies have been taken and which generally have shown that glycogen break-down was similar during exercise with and without beta blockade (Frisk-Holmberg et al., 1979; Uusitupa et al., 1982; Kaiser et al., 1985). At low work rates, a substantial reduction of lactate output from exercising muscle has been found during beta blocker treatment (Frisk-Holmberg et al., 1977, 1985) which may suggest an increased utilization within the muscle. In our study, no consistent effect on plasma lactate concentrations was found during beta blocker treatment. In the literature increased (Kaiser and Tesch, 1983; Katz et al., 1985), unchanged

(Franz and Lohmann, 1979; Laustiola et al., 1983; Kindermann et al., 1984; Smyth et al., 1984; Frisk-Holmberg et al., 1985) and decreased (Frisk-Holmberg et al., 1977; Kaiser et al., 1985) lactate concentrations can be found. These discrepancies are probably due to differences in exercise intensity and duration, and to the dose of the drug. However, from changes in plasma lactate levels nothing can be said about the cause of the change: changes in lactate formation, lactate output and lactate utilization may all contribute.

In agreement with other studies (Lundborg, 1983; Katz et al., 1985; Kullmer and Kindermann, 1985), we found increased plasma potassium concentrations during exercise under the influence of beta blockade, which was more pronounced during non-selective than during $beta_1$-selective blockade. Supposedly, this increase is due to an inhibition of potassium uptake by blockade of $beta_2$-receptors (Lundborg, 1983; Katz et al., 1985; Kullmer and Kindermann, 1985). As indicated in a previous paper (Böhm et al., submitted), the average exercise time was reduced from 69 ± 10 min to 52 ± 6 min during propranolol ($p<0.01$), from 62 ± 9 to 38 ± 10 min during pindolol ($p<0.05$; $n=6$) and from 69 ± 10 to 58 ± 9 min during metoprolol ($p<0.01$). Although the reduction tended to be more pronounced during propranolol and pindolol than during metoprolol, the difference was not statistically significant. The reduction of exercise time during beta blocker treatment seems to be related to changes in substrate availability and utilization during exercise. From muscle biopsy studies, it seems unlikely that the reduction in exercise time is due to a more rapid glycogen depletion which is the factor limiting exercise duration of this type in trained subjects (Holloszy, 1982). Maybe the increased fatigue is due to an increased number of muscle fibers that has to be recruited to deliver the same amount of work (due to a reduction of NEFA supply and to a reduction in the maximal rate of glycogen degradation by beta blocker administration (Chasiotis et al., 1983)), or to increased muscular fatigue due to hyperkalemia. Although effects on metabolism and potassium were more pronounced during non-selective than during $beta_1$-selective blockade, this did not result in statistically significant differences in submaximal exercise performance in this group of hypertensive subjects, although the tendency was present.

Similar values for the hemodynamic and metabolic variables after 30 min exercise were obtained after 1 and 20/24 weeks of beta blocker treatment. The same was true for the values at rest, at exhaustion and during recovery. These results indicate that no adjustments to beta blocker therapy of these variables occcur between 1 week and 6 months of treatment. Only R was higher during long-term treatment than after 1 week, which is suggestive for an increased carbohydrate combustion. However, no support for this possibility could be found in other metabolic changes. Exercise time was reduced from 64±8 min during placebo to 53±7 min after 1 week of beta blocker treatment ($p<0.05$) and to 46±6 min after 20/24 weeks of treatment ($p<0.05$) (Böhm et al., submitted). The reduction was more pronounced after 20/24 weeks than after 1 week ($p=0.05$). The reason for the slightly lower exercise tolerance after long-term treatment is not clear.

Chapter 6

STUDIES OF THE ANTIHYPERTENSIVE EFFECTS OF THE ANGIOTENSIN CONVERTING ENZYME INHIBITOR RAMIPRIL (HOE 498) IN MAN

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6.1 SUMMARY

The time course of the blood pressure lowering effect and the dose-response relationship of the new angiotensin converting enzyme inhibitor ramipril (HOE 498) were studied in 8 patients with essential hypertension. As compared with placebo, a single oral dose of 2.5 mg ramipril lowered systolic and diastolic blood pressure. The antihypertensive action of single doses of 5, 7.5 and 10 mg ramipril orally was more pronounced. No change in heart rate occurred. Angiotensin converting enzyme activity was suppressed after all doses of ramipril studied. Plasma renin activity increased after 2.5 mg and 5 mg ramipril. Plasma aldosterone was not affected after 2.5 mg, but it fell after 5 mg ramipril. Thus, ramipril produced prolonged inhibition (more than 12 hours) of angiotensin converting enzyme activity and lowered blood pressure in patients with essential hypertension.

6.2 INTRODUCTION

At present, two angiotensin converting enzyme (ACE) inhibitors are available for therapeutic use, namely captopril and enalapril. Both drugs markedly inhibit the conversion of angiotensin I to the vasoactive peptide angiotensin II resulting in a decrease of blood pressure (Brunner et al., 1979; Brunner et al., 1981; Johnston et al., 1984; Davies et al., 1984; Frohlich et al., 1984). Because of certain side effects of captopril and enalapril, the search for new orally active ACE-inhibitors has continued. 2-[N-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-(1S,3S,5S)-2-azabicyclo[3.3.0]octane-3-carboxylic acid (HOE 498), ramipril, is a new, potent orally active drug, belonging to the group of non-sulphydryl prodrug ACE-inhibitors. Studies in spontaneously hypertensive rats demonstrated a prolonged blood pressure lowering effect, as well as long-lasting inhibition of tissue converting enzyme following oral treatment with ramipril (Unger et al., 1984). Becker et al. (1983) and Schölkens et al. (1984) described an antihypertensive effect of ramipril in conscious rats with spontaneous hypertension and in rats with renal hypertension. Studies in

healthy normotensive men showed either a slight decrease in systolic and diastolic blood pressure after 5 mg ramipril (Witte et al., 1984b; Manhem et al., 1985) or no significant effect (Bussien et al., 1985). Felder and Witte (1984) have suggested an antihypertensive effect in patients with essential hypertension.

The time course and the dose-response relationship of the antihypertensive action of ramipril have been now been studied in patients with mild to moderate essential hypertension, as well as several parameters of the renin-angiotensin system.

6.3 PATIENTS AND METHODS

6.3.1 Patients

Eight patients (6 males, 2 females) with essential hypertension participated in the study. In all patients high blood pressure was difficult to treat with conventional antihypertensive drugs, e.g. propranolol, hydrochlorothiazide and/or hydralazine. Secondary forms of hypertension were excluded by history, physical examination, appropriate laboratory tests and intravenous pyelography. The ages of the patients ranged from 40-66 years (mean 56 years), and the weight from 67-98 kg (mean 82 kg). The patients had received no diuretics in the month preceding the study. All other antihypertensive drugs were discontinued for at least 2 weeks prior to entrance into the study. Except for one female patient, who received medroxyprogesterone acetate, the patients were given no drug other than ramipril during the study. Four patients were hospitalized for the study, and the others participated as outpatients. At least 6 months prior to the study the patients were advised to reduce salt intake, but otherwise they ate a normal diet. All subjects gave their informed written consent. The study was approved by the Ethical Committee of the University of Limburg.

6.3.2 Protocol

The antihypertensive effect of single oral doses of ramipril was studied in 8 patients. On the first day, each patient received a

placebo capsule. Then, for a total of 48 hours, serial measurements of blood pressure (BP), heart rate (HR), plasma renin activity (PRA), plasma aldosterone and angiotensin converting enzyme (ACE) activity were performed after 15 min rest in supine position. BP and HR were again determined after standing for 2 min. Thereafter, 6 patients received a single dose of 2.5 mg ramipril and 5 patients 5.0 mg ramipril and the measurements were repeated. 24-h urine samples were collected during the 4 days of the study for measurement of the renal excretion of creatinine, sodium and potassium. In the 4 patients who received both doses of the drug, the interval between the studies ranged from 1-2 weeks.

Subsequently the dose-response relationship of the antihypertensive action of ramipril was studied in 8 hypertensive subjects. At first, all patients were given placebo. BP and HR, both supine and after standing for 2 min, were repeatedly measured over 9 h. Thereafter, the patients received increasing single oral doses of ramipril starting with 2.5 mg. The maximum dose was 10 mg. The serial measurements of BP and HR were repeated. The interval between 2 doses ranged from 1-2 weeks. If in a given patient a dose of ramipril decreased supine BP to levels lower than 140/90 mm Hg no further dose was given.

Prior to the first dose and after administration of the last dose the following laboratory data were obtained from all patients: complete examination of the peripheral blood as well as sodium, potassium, calcium, chloride, bilirubin, urea, creatinine, uric acid, alkaline phosphatase, SGOT, SGPT in serum, and blood glucose, urinalysis and ECG. Liver function tests were normal at the start of the study. Serum creatinine was normal in all patients except for one male subject in whom it was 142 μmol/l.

6.3.3 Methods

Blood pressure (BP) and heart rate (HR) were measured with an automatic recorder (DINAMAP, Applied Medical Research Corporation, Tampa, USA). All blood samples were collected via an indwelling catheter in an antecubital vein. The samples were immediately centrifuged and the plasma frozen at -20°C until analyzed. Plasma renin activity (PRA) was measured by radioimmunoassay (Henquet et al., 1981). Plasma

aldosterone was determined without extraction by a direct radioimmunoassay (Lijnen et al., 1978), using antibody of International CIS (St. Quentin, France). The interassay coefficient of variation was 7%. Angiotensin-converting enzyme (ACE) activity was determined radiometrically using the ACE radioassay System of Ventrex Laboratories (Portland, USA). P-[^{3}H] benzoylglycylglycylglycine served as substrate. The ^{3}H-labelled hippurate formed was extracted with ethyl acetate (Ryan et al., 1977). The coefficient of variation of the assay always was lower than 8%.

Urine was collected in plastic bottles. Sodium and potassium in urine were determined by flame photometry, and creatinine in urine by spectrophotometry.

Results are given as mean $\pm$ SEM unless otherwise indicated. Differences were tested by analysis of variance or using the paired t-test when appropriate. The level of statistical significance was set at $p<0.05$.

6.4 RESULTS

6.4.1 Time course of the antihypertensive effect of ramipril

Systolic and diastolic BP and HR in the standing position after placebo and after 2.5 mg ramipril p.o. in 6 patients are shown in Fig. 1. Systolic BP after ramipril was slightly lower than after placebo. The difference was statistically significant ($p<0.01$, analysis of variance) and so was that in diastolic BP ($p<0.001$). This dose of ramipril had no influence on HR in the standing position ($p>0.1$). Supine systolic and diastolic BP were also slightly reduced ($p<0.01$). Ramipril did not change supine HR ($p>0.5$).

The influence of 5 mg ramipril p.o. on BP and HR in the standing position in 5 hypertensives is illustrated in Fig. 2. The drug significantly ($p<0.001$, analysis of variance) lowered standing systolic and diastolic BP. HR was not changed ($p>0.1$). BP started to decrease as early as 30 min after treatment, and the maximal reduction in BP occurred after 6 h. Thereafter BP gradually rose to reach its control levels after 24 h. In 3 patients standing BP was also determined 12 h

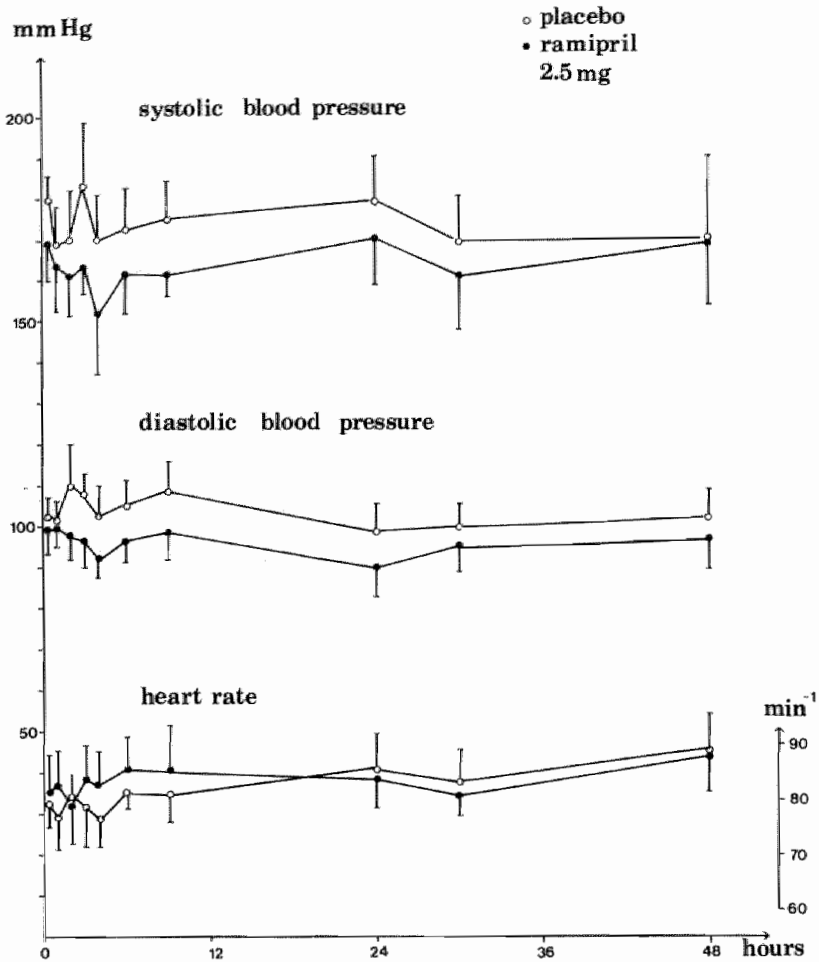

Figure 1: Influence of 2.5 mg ramipril on standing blood pressure and heart rate in 6 patients with essential hypertension. Mean values ± SEM are given.

after dosing. In them, standing BP was 182±15/95±4 mm Hg prior to the drug, it was 163±7/90±3 mm Hg after 12 h, and 181±14/94±4 mm Hg at 24 h. Ramipril 5 mg also lowered supine systolic and diastolic BP ($p < 0.001$). The time course was comparable to that described for standing BP.

6.4.2 Influence of ramipril on plasma angiotensin converting enzyme (ACE) activity, plasma renin activity (PRA) and plasma aldosterone

Single oral dose of 2.5 mg and 5 mg ramipril affected plasma

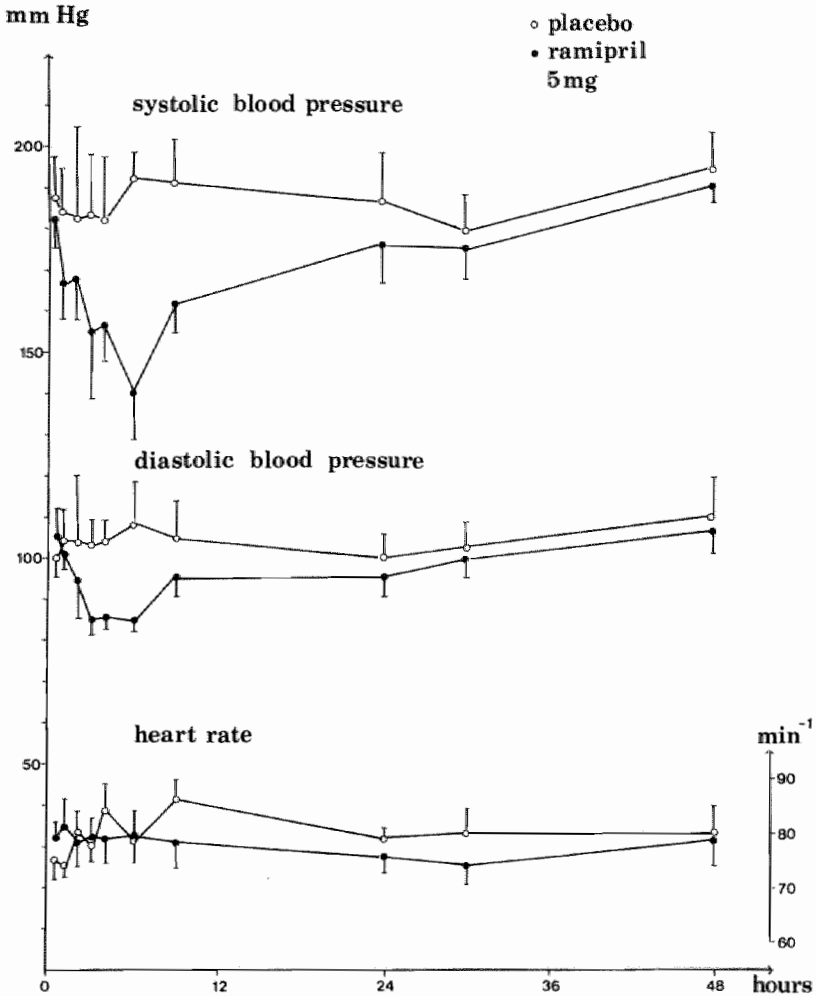

Figure 2: Influence of 5 mg ramipril on standing blood pressure and heart rate in 5 patients with essential hypertension. Mean values ± SEM are given.

ACE-activity (Fig. 3). It significantly ($p<0.001$, analysis of variance) lowered plasma ACE-activity compared to placebo. The effect was more pronounced with the 5 mg than with the 2.5 mg dose. The maximal fall in ACE-activity occurred 1.5-9 hours after ramipril; the decrease was 96±0.1% 3 h after 2.5 mg and 98±0.01% 3 h after 5 mg of the drug. Thereafter, ACE-activity began to rise slowly.

Both doses increased PRA (Table 1), but the change was significant only 6 h after the 5 mg dose. Plasma aldosterone was not altered by 2.5 mg, whereas it fell after the 5 mg dose (Table 1).

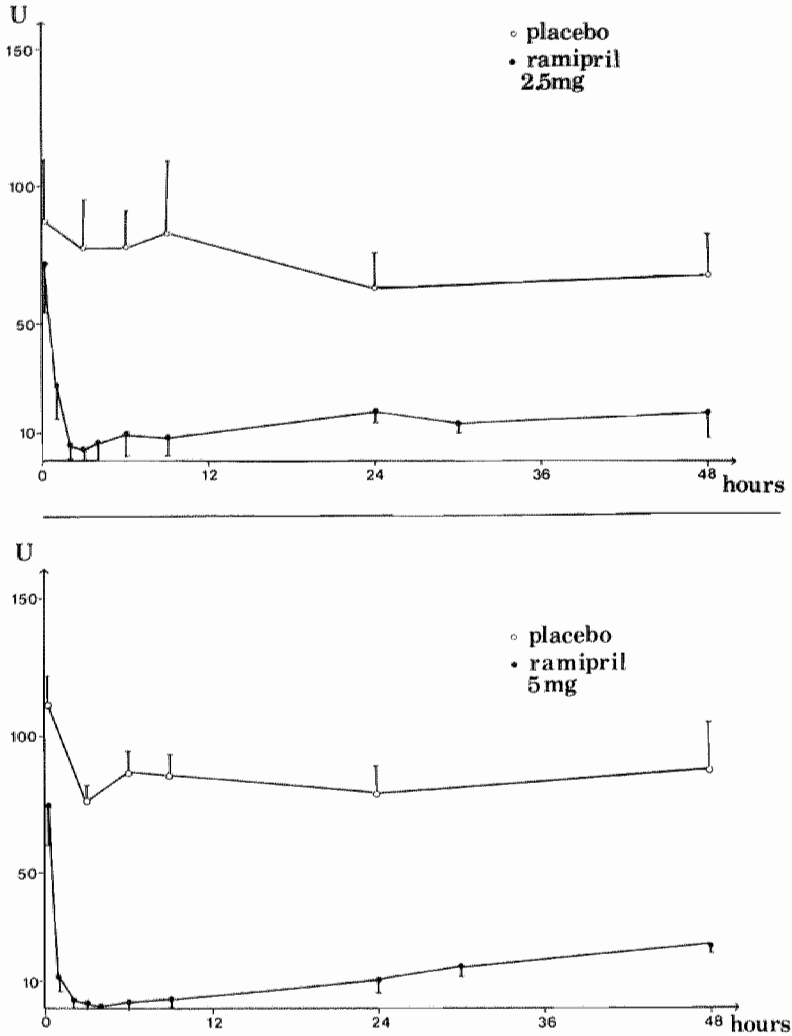

Figure 3: Influence of ramipril on plasma angiotensin converting enzyme activity. Upper panel: effect of 2.5 mg ramipril orally in 4 patients with essential hypertension. Lower panel: effect of 5 mg ramipril orally in 5 patients. Mean values ± SEM are given. Abscissa: time after application of the drug in hours. Ordinate: plasma angiotensin converting enzyme activity in units.

Urinary sodium excretion by the patients averaged 129±30 mmol/day. Neither dose of ramipril affected it. Ramipril also did not alter the urinary excretion of creatinine or potassium.

6.4.3. Dose-response relationship

Four patients received increasing doses of 2.5 mg, 5 mg and 7.5

Table 1: Influence of a single oral dose of ramipril on plasma renin activity (PRA) and plasma aldosterone levels.

Time after dose (h)	2.5 mg ramipril		5.0 mg ramipril	
	PRA (ng AI/ml.h)	Aldosterone (ng/ml)	PRA (ng AI/ml.h)	Aldosterone (ng/ml)
0	0.7±0.2	111±9.5	2.0±0.6	141±21.0
3	1.7±0.4*	120±10.3	3.3±0.6	84±19.1*
6	2.2±0.6*	114±10.5	3.3±0.8*	86±10.8**
9	1.8±0.5**	107±3.5	2.3±0.7	84±13.1**

The data represent mean ± SEM of 4 (2.5 mg ramipril) and 5 (5 mg ramipril) patients.
*$p<0.05$; **$p<0.01$ when compared with values at time 0 (paired t-test).

mg ramipril. The effect on supine and standing BP 6 h after each individual dose is shown in Table 2. This time was chosen as other studies had indicated that that was when the maximum hypotensive action occurred. The influence of ramipril on supine BP was clearly dose-dependent in the dose-range studied. The effect of 7.5 mg ramipril on standing BP was not more pronounced than that of 5 mg.

Three hypertensives were given increasing doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg ramipril; the effects on supine and standing systolic and diastolic BP are listed in Table 3. Again, doses up to 7.5 mg had an increasing effect on supine BP, but no further decrease occurred with 10 mg ramipril. The maximum effect on standing BP in these patients was already obtained with the 5 mg dose.

No dose of ramipril altered heart rate in the supine or standing positions. The drug was well tolerated by all patients. The hematological parameters and the liver and renal function tests did not change during treatment. The electrocardiogram was not affected. Body weight remained unaffected during treatment with ramipril.

Table 2: Blood pressure lowering effect of 2.5 mg, 5 mg and 7.5 mg ramipril in 4 patients 6 hours after application of the drug.

Dose	Decrease of supine BP (mm Hg)	Decrease of standing BP (mm Hg)
2.5 mg	10±8/5±4	13±7/7±3*
5 mg	25±8**/18±9*	37±10**/16±6*
7.5 mg	30±9**/19±6**	32±13*/15±7*

Data represent mean ± SEM.
*$p<0.05$; **$p<0.01$ when compared with placebo values at 6 hours (paired t-test).

Table 3: Blood pressure lowering effect of 2.5 mg, 5 mg, 7.5 mg and 10 mg ramipril in 3 patients 6 hours after application of the drug.

Dose	Decrease of supine systolic BP	Decrease of supine diastolic BP	Decrease of standing systolic BP	Decrease of standing diastolic BP
2.5 mg	11±11	3±4	13±9	4±1**
5 mg	18±4**	12±8	29±8**	11±4*
7.5 mg	23±9*	16±7*	20±5**	8±3*
10 mg	17±5**	10±5	19±3**	12±6

SBP = systolic blood pressure; DBP = diastolic blood pressure.
Data represent mean ± SEM.
*$p<0.05$; **$p<0.01$ when compared with placebo value at 6 hours (paired t-test).

6.5 DISCUSSION

Captopril was the first orally active ACE-inhibitor available for therapeutic use. It has the rather short duration of action of 6-8 h (Heel et al., 1980; Johnston et al., 1984). Subsequently, attempts have been made to develop ACE-inhibitors with a longer lasting antihypertensive effect. Ramipril causes prolonged plasma ACE-inhibition, a substantial effect still being present up to 72 h after a single dose in healthy subjects (Witte et al., 1984b, Bussien et al., 1985). An active metabolite is formed in vivo from the drug, which inhibits the angiotensin converting enzyme (Becker et al., 1984).

So far, there has been little experience with ramipril in hypertensive patients. Felder and Witte (1984) showed that repeated administration led to some antihypertensive activity and the present study has demonstrated that single oral doses of ramipril as compared to placebo definitively decreased supine and standing BP in patients with essential hypertension. Ramipril 2.5 mg had a slight hypotensive effect, and 5-10 mg ramipril led to a substantial fall in BP. In the few patients who received 10 mg ramipril, the antihypertensive effect was not more pronounced than that of 7.5 mg. In all the present patients, BP had been poorly controlled by other antihypertensive drugs. Considerable interindividual differences in the efficacy of ramipril as an antihypertensive agent were found. In some patients, a decrease in BP to below 140/90 mm Hg followed 2.5 mg ramipril, but in other hypertensives, this effect was not produced by the 10 mg dose.

The antihypertensive effect of captopril and enalapril starts 1-2 hours after oral application of the drugs (Johnston et al., 1984; Riley et al., 1985). The duration of the hypotensive action is 6-8 h with captopril (Heel et al., 1980; Johnston et al., 1984) and about 24 h with enalapril (Ferguson et al., 1982; Johnston et al., 1983; Riley et al., 1985). In the present study, the antihypertensive effect of ramipril became apparent 1 h after swallowing the dose. The maximum antihypertensive effect was obtained after 6 h, and the BP was still decreased after 12 h. The BP had returned to its pretreatment level 24 h after the single dose of ramipril.

It significantly decreased plasma ACE-activity with a time

course in hypertensive patients comparable to that seen in normotensives (Witte et al., 1984a,b; Bussien et al., 1985; Manhem et al., 1985). The period of action of enalapril on plasma ACE-activity is similar (Jackson et al., 1982; Johnston et al., 1983). In contrast, captopril has a shorter effect on plasma ACE-activity (Waeber et al., 1980).

Ramipril 2.5 and 5 mg here increased PRA in hypertensive patients. Ramipril 5 mg decreased plasma aldosterone. Similar observations were made in normotensive subjects (Witte et al., 1984b; Manhem et al., 1985). Captopril and enalapril also increase PRA and decrease plasma aldosterone in man (Heel et al., 1980; Johnston et al., 1984; Riley et al., 1985).

Ramipril here did not alter the urinary excretion of sodium, potassium and creatinine in patients with essential hypertension. There was a similar result when it and enalapril were given to normotensive volunteers (Brunner et al., 1981; Shoback et al., 1983; Witte et al., 1984b), and to subjects with essential hypertension (Ferguson et al., 1982).

Ramipril 2.5-10 mg p.o. did not alter supine or standing HR in the hypertensive patients. Apparently, hypotensive doses of the drug do not cause reflex tachycardia. Similar findings have been reported with captopril (Johnston et al., 1984) and enalapril (Riley et al., 1985).

In conclusion, the present study has shown that ramipril is an orally effective antihypertensive agent with a long duration of action.

Chapter 7

CONCLUDING REMARKS

7.1 PATHOGENESIS

For obvious reasons, it is difficult to define the earliest phase of essential hypertension. As was outlined in the introduction (chapter 1), most patients present themselves at a time when essential hypertension is already established. However, at this moment secondary changes persist which make it extremely difficult to assess the possible role of the (hypothetical) inducing factor(s) which led to the symptom hypertension. Furthermore, patients with essential hypertension have been described to be a heterogeneous group, indicating that a multitude of factors has been designated to play a role in the etiology and the pathogenesis of essential hypertension (Hansson, 1983; Peart, 1983). Anticipating the pathophysiologic changes in the course of hypertension, early phases of human essential hypertension have been studied with the aim of identifying mechanisms which could be held responsible for initiation of hypertension. Normotensive offspring of hypertensive patients and subjects with borderline hypertension represent the most easily identifiable groups of future hypertensives, but not all of them develop hypertension as different studies have shown (Julius and Schork, 1971; Hedstrand and Åberg, 1975; Sasakawa et al., 1983).

The study performed in the group of borderline hypertensive subjects and normotensive age-matched controls which is presented in chapter 2, can be described as quite unique. In 1986, some subjects have been followed for 9 years already. Despite some voluntary and forced (hypertensive) drop-outs, still the majority of the subjects of both groups is interested in participating. Other longitudinal studies in borderline hypertensive subjects are scarce and have reported years of follow-up ranging from 3 to 10 years (Julius, 1977; Hedstrand and Åberg, 1975; Falkner et al., 1981; Sasakawa et al., 1983; Ueda et al., 1983). However, in some studies the age of the investigated borderline subjects is considerably higher than in our study (mean age 40 years in Ueda et al., 1983) or the studies differ in the definition of borderline hypertension (casual sitting blood pressure in Kubo et al., 1983). Kaplan and Lieberman (1982) proposed to label borderline hypertensive patients as clearly hypertensive. In contrast, during the 7

years of follow-up in this study, the progression to hypertension occurred only in the minority of the subjects with borderline hypertension (19%). This percentage confirms other reports and studies (Julius and Schork, 1971; Julius, 1977; Julius et al., 1980; Julius and Hansson, 1983). This progression of borderline hypertension to essential hypertension underlines also that borderline hypertensive subjects could serve as a model to study possible factors which could lead to essential hypertension. The phenomenon of blood pressure decrease was also seen in a number of borderline hypertensive subjects who became normotensive. This is confirmed by other authors (Hedstrand and Åberg, 1975; Kubo et al., 1983; Sasakawa et al., 1983). It must be noted, however, that the factors causing spontaneous reversion towards normal blood pressure levels have not been fully identified. Taken together, this shows that the group of borderline hypertensive subjects is rather heterogeneous as far as development of blood pressure is concerned.

At rest, the heart rate is higher in subjects with borderline hypertension than in normotensive subjects; this was repeatedly reported by Julius et al. (1980), Julius and Hansson (1983) and confirmed in this study. As was described in chapter 3, the results support the assumption for a decreased parasympathetic tone at rest in subjects with borderline hypertension when compared to the normotensive subjects. This finding confirms the reduced parasympathetic tone in borderline hypertensive subjects reported by Julius et al. (1971a). Korner et al. (1973) found also in essential hypertensive patients a reduced parasympathetic influence on heart rate. The "intrinsic" heart rate after complete cardiac block is the same in both normotensive subjects and hypertensive patients, as was found by Jose and Taylor (1969). Thus, assuming that the action of the intrinsic pacemaker of the heart is comparable in normotensive and essential hypertensive subjects, no reports oppose this assumption, too, in borderline hypertension. In a study by Henquet et al. (1982), noradrenaline was infused intravenously in borderline hypertensive and normotensive subjects, the same population as described in chapter 2. It was found that less exogenous noradrenaline was required to induce a rise of systolic blood pressure by 10 mm Hg in the borderline hypertensive

subjects than in the normotensive control subjects. It was concluded that an increased vascular responsiveness was the cause for this finding. This increased reactivity in borderline hypertensive subjects was also found by Weidmann et al. (1980), in contrast to Kawano et al. (1982). Furthermore, structural vascular changes were described in young borderline hypertensive subjects by Takeshita and Mark (1983), Mark (1984) and Egan and Julius (1985), but the cause for these changes is not clear. A higher sympathetic drive might also contribute to vascular hypertrophy. As was outlined in chapter 1, sympathetic nervous overactivity can lead to hypertension and plasma levels of noradrenaline at rest can be taken as an index of the overall activity of the sympathetic nervous system, as was described by different authors (DeChamplain, 1977; Weidmann, 1981; Agabiti-Rosei et al., 1983; Folkow et al., 1983; Goldstein et al., 1983a; Conway, 1984; Esler et al., 1985). Borderline hypertensive subjects have been reported to have normal resting plasma catecholamines (Julius et al., 1980). This confirms the finding of the study in chapter 2 that plasma levels of noradrenaline at rest in borderline hypertensive subjects who stayed borderline hypertensive are not different from those in the normotensive control group. However, in the analysis of different studies by Goldstein and Lake (1984) a part (26 %) of the analyzed borderline hypertensive groups had higher mean plasma noradrenaline levels than the groups with normotension. An explanation for the discrepant finding could be that some studies did and some studies did not measure plasma noradrenaline at a time close to hypertension. Furthermore, most of the studies are not set up to follow subjects during a longer period of time and the definition of borderline hypertension often includes labile hypertension.

This longitudinal study (chapter 2) showed for the first time that consistently high plasma noradrenaline levels at rest were found in borderline hypertensive subjects who developed definite hypertension when compared to those age-matched subjects who stayed borderline hypertensive and the normotensive control subjects. However, plasma noradrenaline levels at rest in the borderline hypertensive subjects, whether considered as a whole group or as the subgroup which stayed borderline hypertensive, were not different from the levels of plasma

noradrenaline at rest in the normotensive controls. But blood pressure is not required to rise through high plasma noradrenaline levels, normal plasma noradrenaline levels could induce the blood pressure rise as well. One explanation is an enhanced vascular responsiveness on noradrenaline, as was shown in the borderline hypertensive subjects by Henquet et al. (1982). For the blood pressure rise no elevated plasma noradrenaline levels are needed. It cannot be excluded that increased vascular sensitivity despite normal noradrenaline levels at rest could explain the higher blood pressure in borderline hypertensive subjects when compared to normotensives. But local activity of the sympathetic nervous system could be increased as well, but is not reflected by and/or measured by overall elevated plasma noradrenaline levels. A selective activation of the sympathetic nervous system involving the heart and kidneys in essential hypertension is suggested by Esler et al. (1985). Due to similar responsiveness in cardiac receptors in borderline hypertensive and normotensive subjects as reported by Henquet et al. (1982), the higher heart rate at rest is most likely caused by the decrease of the parasympathetic tone. The exact cause for the elevated levels of plasma noradrenaline in those borderline hypertensive subjects whose levels were consistently elevated and who developed definitive hypertension is not clear, but suggests a sympathetic nervous system overactivity, whether or not combined with adrenal overactivity. Maybe a gradual increase in sympathetic activity occurs during a longer time in borderline hypertension and becomes measurable only in an advanced stage. An altered noradrenaline clearance is less likely since no differences in age between the groups and subgroups exist and all had normal liver and kidney function.

As mentioned in the introduction, obesity could play a role in the development of hypertension. In the definitively hypertensive subjects (subgroup 4), the body mass index was statistically significantly higher than in the normotensive subgroup 1. There was no statistically significant difference between the borderline hypertensive and the definitively hypertensive subgroup. However, it is unlikely that overweight was the inducing factor for hypertension in all subjects of this subgroup 4. Two subjects were clearly obese at

the time when excluded due to hypertension, whereas the body mass index of the others ranged from lean to overweight and was comparable to the mean of the normotensive and borderline hypertensive subgroups. As was described in Chapter 1.8, studies of plasma catecholamine in obese and overweight hypertensive subjects when compared with lean normo- and hypertensive subjects are not wholly conclusive. A possible role of the hyperinsulinemia, whether or not additional to an increased sympathetic nervous system activity, cannot be wholly excluded in the overweight subjects.

The levels of plasma renin activity at rest in the borderline hypertensive subjects who became hypertensive only tended to be higher than in the group of borderline hypertensive and normotensive subjects. The reason for this could be the small number of subjects in subgroup 4 which makes it difficult to obtain statistical significance. Furthermore, levels of plasma renin activity depend upon more factors than upon the sympathetic nervous system only (Davis and Freeman, 1976).

During exercise, when the influence of the parasympathetic nervous system is abolished, the differences in heart rate and levels of plasma noradrenaline between the borderline hypertensive and normotensive subjects disappear. This finding confirms a study by Julius et al. (1980) who report that plasma catecholamine levels in subjects with borderline hypertension do not behave differently during exercise when compared to normotensive subjects. Obviously, exercise leads to an increased activity of the sympathetic nervous system and small changes found at rest are no longer detectable during exercise due to the strong hemodynamic and metabolic stimuli.

All in all, the increased index of the overall activity of the sympathetic nervous system supports the assumption of a sympathetic overactivity in those borderline hypertensive subjects who become definitively hypertensive. The precise mechanism(s) or the origin remain to be identified. Julius and Johnson (1985) reported evidence for a relation with stress in the early phase of essential hypertension (borderline). This hypothesis of an excessive sympathetic drive which induces hypertension does not exclude a genetic or an acquired e.g. environmental origin, or other simultaneous factors such as

vascular defects (e.g. defects of the sodium pump), receptor changes at different sites or centrally mediated changes. It is intented to continue the study with the borderline hypertensive subjects and to perform further investigations.

7.2 TREATMENT

Beta blockers are prescribed in the treatment of mild hypertension, but the precise mechanism of their blood pressure lowering is not exactly known. It is generally accepted that their antihypertensive action depends upon competitive antagonism of the beta-adrenoceptor. The effects of catecholamines at these beta receptors are attenuated. In the study presented in chapter 4 plasma noradrenaline levels tended to decrease at rest during long-term treatment with pindolol. The finding of decreased plasma noradrenaline levels at rest during long-term treatment with pindolol was also presented in an analysis of 17 different studies by Man in 't Veld and Schalekamp (1983). The beta blockers metoprolol and propranolol resulted in no consistent change of plasma noradrenaline at rest. It has been hypothesized that the difference in plasma noradrenaline concentrations between beta-blockers with and without ISA is due to differences in their hemodynamic effects. Beta blockers without ISA reduce cardiac output and resting liver blood flow. This reduction of hepatic blood flow leads to a reduction of catecholamine clearance (Esler et al., 1981c). Thus, normal plasma noradrenaline levels during treatment with beta blockers without ISA may reflect decreased catecholamine release from the sympathetic nerve endings. In contrast, during pindolol treatment no change in resting cardiac output and hepatic blood flow is found, which may explain the reduced concentrations of plasma noradrenaline and confirms the hypothesis of reduced sympathetic activity during treatment with all types of beta blockers. However, our data during exercise do not correspond with this hypothesis. The heart rate reduction during exercise was similar during all three beta blockers studied which suggests similar effects on cardiac output. Nevertheless, plasma noradrenaline concentrations still tended to be lower

during pindolol than during propranolol and metoprolol treatment. Thus, reduced plasma noradrenaline levels appear to be specific for pindolol treatment. The mechanism of this phenomenon is not clear and needs further investigation.

Furthermore, the study presented in chapters 4 and 5 showed that mild hypertensive patients can benefit from the antihypertensive action of beta blockers at rest and in situations of stress like physical exercise in which blood pressure is increasing. The three beta blockers propranolol, metoprolol and pindolol, in the doses prescribed, had a comparable antihypertensive effect at rest during the treatment period of 6 months. The exercise induced increase of heart rate and blood pressure is attenuated by beta blockers through a blockade of cardiac beta-adrenoceptors, whereas the stroke volume stays unchanged or is increased, the overall effect being a reduction in cardiac output (Pearson et al., 1979). The heart rate decrease and blood pressure lowering during exercise was comparable by all three beta blockers. It has been shown furthermore that beta blockers reduce exercise performance in hypertensive patients and in normotensive subjects (for review, see Fellenius, 1983). However, the studies mentioned mostly investigated effects of beta blockers after acute or short-term treatment during maximal exercise. Long-term therapy and submaximal endurance (exercise) correspond more with actual situations in the daily life of essential hypertensive patients. This is the reason why this type of exercise was performed in this study. It has been further stated that non-selective beta blockers like propranolol result in more complaints than $beta_1$-selective blockers like metoprolol (Fellenius, 1983). The results of the study in the chapters 4 and 5 show only a tendency of greater impairment of submaximal endurance time during non-selective beta blockade than during $beta_1$-selective blockade. Furthermore, the results indicate no improvement of exercise endurance time during long-term therapy with beta blockers in contrast to the claim by Fellenius (1983) who states that the temporary muscular fatigue disappears as the therapy continues.

During exercise, several mechanisms are thought to be the cause for the impairment during beta blocker therapy. The depression of cardiac output resulting in a reduced leg blood flow could play a

role. Frisk-Holmberg et al. (1985) found a reduction in leg blood flow by 10% during atenolol treatment, but oxygen extraction by the working muscle was elevated and no impairment of oxygen uptake in the muscles was found. Another reason for the impairment of exercise performance is seen in the metabolic effects of beta blockers. It is a fact that during prolonged submaximal exercise, lipolysis plays an essential role in the energy supply of the skeletal muscle (Felig and Wahren, 1975; Juhlin-Dannfelt, 1982). The results of chapter 5 showed an inhibited lipolysis and indicated a more pronounced reduction during non-selective than during $beta_1$-selective blockade. This suggests an involvement of $beta_2$-receptors in lipolysis as well. This is confirmed by Juhlin-Dannfelt (1983) who reports both $beta_1$- and $beta_2$-receptors with a predominance of $beta_1$-receptors in adipocytes. Blood glucose levels were largely unaffected during exercise during treatment with the three beta blockers in the study performed (chapter 5), but an increased uptake by the working muscles because of a reduced supply of fat substrate may be compensated by an increased glucose output by the liver. Glucose levels measured during exercise are influenced by the intensity of exercise, the duration of the exercise, the beta blocker administered and the storage level of glycogen in the liver and skeletal muscle before exercise. These factors could explain partly the inconsistent findings in literature. During prolonged exercise during beta blocker therapy, the decrease in cardiac output and the decrease in leg blood flow could also decrease the amount of substrate transported to the working muscles. Free fatty acids and glucose may be delivered in a lower amount than needed.

A third reason for the impairment of exercise performance could be the hyperkalemia during exercise. As was reported in chapter 5, the hyperkalemia was more pronounced during non-selective than $beta_1$-selective blockade. This was confirmed by others (Lundborg et al., 1983; Kullmer and Kindermann, 1985). Whether this rise in plasma potassium could result in changes of excitability in working muscles and hereby increase muscular fatigue is not clear.

The metabolic changes were more pronounced during non-selective than during $beta_1$-selective blockade. A tendency for a more pronounced impairment of endurance time during non-selective beta blockade was

found. However, the difference was statistically not significant. But the tendency confirms reports that $beta_1$-selective blockade results in less impairment of exercise than non-selective beta blockade (Fellenius, 1983; Opie, 1985). Taken together, the results of chapter 5 suggest a lack of substrate availability as a reason for the impaired endurance performance. It cannot be concluded that one specific factor is the cause, it seems rather likely that the complex interrelations of several factors have to be held responsible.

From the point of view of antihypertensive efficacy at rest and during exercise, these three beta blockers have proven their usefulness in patients with mild hypertension. However, among their side-effects ranges the impairment of exercise performance and this could limit their use, especially in younger and/or physically active patients during everyday activities. Limitation of occupational performance or leisure time activity is neither needed nor desired. Being physically fit and performing endurance sports activities like running or bicycling has become a fashion and even a rage of late. Furthermore, the impairment of performance could have a negative effect on the compliance of the patient. Due to the limitation of physical performance during treatment with beta blockers, other types of drugs could then be considered. As was recently shown in our group by Mooy et al. (1985), the calcium channel blocker verapamil, in contrast to propranolol, does not reduce submaximal endurance time in mild hypertensive patients. With the doses prescribed, a comparable blood pressure decrease by both drugs was seen at rest and during exercise. So, calcium channel blockers could serve as an alternative in the treatment of mild hypertension in case side-effects of beta blockers impair the patient's daily activities.

As was outlined in chapter 1, the angiotensin converting enzyme inhibitors have been promoted already for monotherapy in mild to moderate essential hypertension. But captopril has a rather short duration of action which requires an intake of three times daily. Some side-effects are dose-dependent and limit its use. Therefore, the search for new angiotensin converting inhibitors was continued. The effects of single oral doses of the new angiotensin converting enzyme inhibitor ramipril have been studied in essential hypertensive pa-

tients as described in chapter 6. Ramipril proved to be an effective antihypertensive agent when compared with placebo. The blood pressure lowering effect was obvious after single oral doses of 2.5 mg, the effects of single oral doses of 5-10 mg were more pronounced. The antihypertensive effect was evaluated in patients who were difficult to control by other antihypertensive drugs, e.g. diuretic and beta blocker and/or vasodilator. It seems that the efficacy can be, at least with much caution, compared to that of enalapril and captopril. Salvetti et al. (1985) reported in their review that enalapril and captopril had a comparable blood pressure lowering effect during chronic treatment as atenolol and chlorthalidone in patients with moderate essential hypertension. Effects of ramipril on parameters such as plasma renin activity, plasma aldosterone and angiotensin converting enzyme activity are largely comparable to those of captopril and enalapril. Furthermore, the duration of the antihypertensive action of a single dose of ramipril lasted for more than 12 hours. In comparison to the rather short-acting captopril, ramipril could have the advantage of the longer duration of the antihypertensive effect. This could mean an enhancement of compliance in patients during long-term therapy due to only once daily intake of the drug. No side-effects were reported after the single oral dose. No orthostatic hypotension was seen. The results presented in this study add important details about this new angiotensin converting enzyme inhibitor for further studies. Ramipril is a new drug which seems to be comparable to the other angiotensin converting enzyme inhibitors. It has antihypertensive effects and the advantage of a longer duration of action. However, the effects and the action of ramipril need confirmation and evaluation during further long-term studies.

In short, the studies presented in this thesis have led to the following conclusions :

1. During 7 years of follow-up only a minority of borderline hypertensive subjects became hypertensive. The group of borderline hypertensive subjects who developed definitive hypertension had consistently high plasma noradrenaline levels at rest thoughout the observation period and as determined closest to the moment to

exclusion because of hypertension than the group of normotensive subjects or the subjects who stayed borderline hypertensive. As a cause an overactivity of the sympathetic nervous system is suggested. The results also support the assumption that at rest the parasympathetic influence on salivary glands is reduced in subjects with borderline hypertension when compared to normotensive subjects.

2. Blood pressure at rest and during submaximal exercise is lowered effectively during long-term treatment with the beta blockers propranolol, metoprolol and pindolol in patients with mild essential hypertension. During beta blockade submaximal exercise endurance time is impaired. The mechanism of reduced plasma noradrenaline levels at rest and during exercise during treatment with pindolol is not clear. Reduced substrate availability are suggested, among other factors, as a reason for impairment of exercise endurance time during treatment with the beta blockers. The new angiotensin converting enzyme inhibitor ramipril lowers blood pressure effectively in patients with essential hypertension after single oral doses. Ramipril has an antihypertensive effect which lasts more than 12 hours.

Chapter 8

LIST OF REFERENCES

8. LIST OF REFERENCES

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Chapter 9

9.1 SUMMARY

The role of the sympathetic nervous system in the pathogenesis of essential hypertension is still controversial. Possibly an enhanced activity of this system causes chronic elevation of blood pressure in man. Borderline hypertension is a condition in man which could serve as a model to study a progression to essential hypertension. A longitudinal study in a group of borderline hypertensive subjects and normotensive controls could give insight in such a role of the sympathetic nervous system. Furthermore, a reduced parasympathetic tone could influence sympathetic activity at rest.

Patients with essential hypertension are often treated for a prolonged time with antihypertensive drugs. They need a drug which lowers blood pressure at rest and during situations with increased sympathetic activity like stress and/or exercise. Lately, proposals have been made to add angiotensin converting enzyme inhibitors to beta blockers and diuretics used in monotherapy of essential hypertension. During beta blocker treatment patients often complain about muscular fatigue during exercise. It is suggested that some types of beta blockers behave differently during exercise. The effects of three different beta blockers at rest and during submaximal exercise were investigated.

As mentioned before, angiotensin converting enzyme inhibitors are available for treatment of essential hypertension. However, due to some side-effects and the short duration of action of the first generation of these drugs, new drugs of this type are being developed. Ramipril is such a new angiotensin converting enzyme inhibitor and was investigated in patients with essential hypertension.

Chapter 1 of this thesis gives a general outline of and introduction to the symptom hypertension in man. The attention is focused on the definition of high blood pressure (hypertension) as well as the consequences of this condition. Improvement of the prognosis through treatment is indicated and the clinical view on the condition hypertension is illustrated. The most important factors which control blood pressure in man are shortly described. Furthermore, the complex function and the role of the sympathetic nervous system as a regulating

and modulating mechanism in the control of the cardiovascular system and blood pressure is outlined. The description of the synthesis and the metabolism of the transmitters noradrenaline, adrenaline and acetylcholine follows. Several aspects among the theories about the pathogenesis of essential hypertension will be considered, like genetical and environmental factors and salt intake. The possible role of the renin-angiotensin system and the sympathetic nervous system in the pathogenesis of hypertension are reviewed. The role of the parasympathetic nervous system is outlined. A description of the zone between normotension and hypertension, i.e. borderline hypertension, follows. The prevalence rate, including the risks of borderline hypertension with respect to the possible progression towards hypertension reminds the reader that borderline hypertension is a zone which should not be overlooked. Furthermore, a number of physiological abnormalities of borderline hypertension are described. The motive to investigate subjects with borderline hypertension in a longitudinal study is explained. At the end of the first chapter, the benefits of treatment of mild hypertension and the difficult decision whether to treat or not to treat are recalled. A short description of the available drugs concludes this chapter.

Chapter 2 contains the results of the longitudinal study performed in a group of 26 borderline hypertensive subjects and 24 age-matched normotensive controls. The aim was to investigate plasma catecholamine levels and plasma renin acitivity (PRA) at rest and during ergometry exercise during several years of follow-up. Another important aspect was to observe the possible progression to essential hypertension. Normotension was defined as ⩽125/85 mm Hg (mean arterial pressure (MAP) ⩽98 mmHg) and borderline hypertension as ⩾140/90 - <160/100 mm Hg (MAP ⩾107 - <120 mmHg), both after 2 min standing (Korotkoff IV). Hypertension was defined as ⩾160/100 mmHg (MAP ⩾120 mmHg) after 2 min standing at two successive measurements and the subjects being hypertensive dropped out of the study to receive antihypertensive treatment. The study started in 1977 and was finished in 1984. During this period 3 subjects were lost to follow-up. At the end of the study (1984), the normotensive and borderline subjects were subdivided. 15 subjects from the normotensive group (subgroup 1)

stayed normotensive and 10 subjects (subgroup 3) of the borderline group remained borderline hypertensive. During the 7 years of follow-up 5 subjects of the originally borderline hypertensive subjects became hypertensive (MAP ⩾120 mmHg) (subgroup 4) and were excluded from further follow-up in order to receive antihypertensive treatment. There were no differences in plasma noradrenaline levels at rest and during exercise between the total group of normotensive subjects and subjects with borderline hypertension at repeated measurements in 1977, 1979 and 1984. However, when considering the subgroups separately, subgroup 4 had consistently high plasma noradrenaline levels at rest. In contrast, subgroup 3 and subgroup 1 had relatively high resting noradrenaline levels only at entrance into the study; at successive measurements the plasma noradrenaline levels were considerably lower than in subgroup 4. Plasma adrenaline and PRA at rest as well as plasma noradrenaline, plasma adrenaline and PRA during exercise did not differ between the groups and the subgroups. It is concluded that 20% of borderline hypertensive subjects become definitively hypertensive. The consistently high plasma noradrenaline levels at rest in these subjects suggest an enhanced sympathetic activity.

Chapter 3 deals with a study of salivary flow in the same borderline and normotensive subjects. Salivary flow at rest, which is predominantly under the influence of the parasympathetic nervous system, was measured in both groups during adrenergic blockade and stimulation and during parasympathetic stimulation and blockade. Plasma noradrenaline levels in the borderline and normotensive group, which were determined as well, were not different. At rest, salivary flow was significantly higher in the normotensive group than in the borderline hypertensive group. Intravenous propranolol, phentolamine and noradrenaline had no influence on salivary flow. Atropine decreased salivary flow in both groups. The effect of parasympathetic stimulation with neostigmine on salivary flow was more pronounced in the normotensives than in the borderline hypertensive subjects. The data of this study support the assumption that in subjects with borderline hypertension the parasympathetic influence on the salivary glands is reduced.

In chapter 4, a study is described which was performed to com-

pare the effects of three beta-adrenoceptor blocking agents (propranolol, metoprolol, pindolol) during long-term treatment (6 months) in 7 mild to moderate hypertensive patients. Among the parameters investigated were plasma noradrenaline levels at rest and during submaximal ergometry exercise. Possible differences between the three beta blockers concerning exercise endurance time were a further point of interest. All three beta blockers reduced systolic blood pressure in supine position and during exercise, whereas diastolic blood pressure fell only significantly in supine position. As was expected, supine heart rate fell during treatment with metoprolol and propranolol, but stayed unchanged during pindolol. During submaximal exercise, a comparable decrease of heart rate was found during all three beta blockers. Plasma noradrenaline levels at rest and during exercise tended to be decreased during pindolol; no consistent changes were found during propranolol and metoprolol. Endurance time was reduced similarly by all three drugs and no statistical differences between the beta blockers was found, although the tendency of more reduced endurance time during non-selective beta blockade was found. Furthermore, the impairment of endurance time was more pronounced after 6 months than after 1 week.

In chapter 5, the metabolic variables at rest and during exercise from the same study are presented. During propranolol an increase in total and LDL+VLDL serum triglyceride concentrations was found. During exercise, non-selective beta blockade reduced plasma glycerol and non-esterified fatty acid concentrations more than during $beta_1$-blockade. Plasma glucose and lactate levels were largely unaffected at rest and during exercise during treatment with all three beta blockers. However, oxygen uptake was decreased slightly and respiratory exchange ratio was increased. These data suggest a decreased utilization of non-esterified fatty acids and increased carbohydrate combustion during treatment with the three beta blockers. Plasma potassium increase during exercise was more pronounced during non-selective than during $beta_1$-selective blockade. In this study no effects on these parameters during exercise were found when comparing the first week and the 20/24th week of treatment.

The study presented in chapter 6 deals with the time course of the blood pressure lowering effect and the dose-response relationship

the new angiotensin converting enzyme inhibitor ramipril (HOE 498). Eight patients with essential hypertension were studied and single doses of 2.5 mg up to 10 mg ramipril orally were given. As compared with placebo, a single dose of 2.5 mg ramipril lowered supine and standing systolic and diastolic blood pressure, but the effects of single doses of 5, 7.5 and 10 mg ramipril were more pronounced. A blood pressure lowering effect was still found after 12 hours. No reflex tachycardia occurred after administration of the drug. Angiotensin converting enzyme activity was suppressed after all doses of ramipril studied. No side-effects were reported. This study shows that the new angiotensin converting enzyme inhibitor ramipril is an orally effective agent and has a long duration of action.

The concluding remarks about the different studies are presented in chapter 7. The difficulty of analyzing and investigating factors which could induce hypertension is depicted. It is underlined that not all borderline hypertensive subjects will develop definitive essential hypertension. The relationship between a reduced parasympathetic tone and a sympathetic nervous overactivity at rest and/or increased responsiveness to noradrenaline is described to explain blood pressure and heart rate differences at rest between borderline hypertensive and normotensive subjects. The possibility of an overactivity of the sympathetic nervous system in those borderline hypertensive sybjects who developed definite hypertension is suggested.

The cause for decreased plasma noradrenaline levels at rest and during exercise during treatment with pindolol is not clear and needs further investigation. The reduced submaximal endurance time during treatment with all three beta blockers and the possible metabolic causes are discussed. The suggestion for prescription of calcium channel blockers is made for those patients treated with beta blockers who complain about impaired exercise performance. Finally, the results of the study with single oral doses of the new angiotensin converting enzyme inhibitor ramipril are shortly depicted in comparison with the other related drugs. The need for further studies to investigate long-term effects is proposed.

A list of the references of this thesis is given in chapter 8.

9.2 SAMENVATTING

De rol van het sympathische zenuwstelsel in de pathogenese van essentiële hypertensie is tot op heden nog niet geheel duidelijk. Bij de mens zou een verhoogde aktiviteit van het sympathische zenuwstelsel een verhoging van de bloeddruk teweeg kunnen brengen. Borderline hypertensie bij de mens kan als model gebruikt worden om de ontwikkeling naar essentiële hypertensie te bestuderen. Een longitudinale studie van personen met borderline hypertensie en normotensieve kontrole personen zou de vraag naar de invloed van het sympathische zenuwstelsel op deze ontwikkeling kunnen beantwoorden. Bovendien kan een verlaagde tonus van het parasympathische zenuwstelsel in rust de aktiviteit van het sympathische zenuwstelsel beinvloeden.

Patienten met essentiële hypertensie worden vaak gedurende langere tijd met antihypertensieve geneesmiddelen behandeld. Een voorwaarde voor een dergelijk antihypertensief geneesmiddel is dat het de bloeddruk zowel in rust als ook tijdens verhoogde sympathische aktiviteit, bijvoorbeeld tijdens stress en/of lichamelijke inspanning, verlaagt. Vaak klagen patienten onder beta-blokker behandeling over vermoeidheid, met name tijdens lichamelijke belasting. De verschillende soorten beta-blokkers zouden verschillende effekten tijdens lichamelijke inspanning teweeg kunnen brengen. Om dit te onderzoeken werden drie verschillende beta-blokkers op hun effekten tijdens rust en submaximale lichamelijke inspanning onderzocht.

Zoals vermeld worden angiotensin converting enzyme remmers toegepast bij de behandeling van essentiële hypertensie. De laatste tijd zijn er voorstellen gedaan om aan de als monotherapie te gebruiken antihypertensiva ook angiotensin converting enzyme remmers toe te voegen. De bijwerkingen en de korte werkingsduur van de middelen van de eerste generatie hebben ertoe geleid dat nieuwe middelen ontwikkeld werden. Ramipril behoort tot de nieuwere angiotensin converting enzyme remmers en werd bij patiënten met essentiële hypertensie onderzocht.

In hoofdstuk 1 van dit proefschrift wordt een overzicht gegeven van en een inleiding tot het symptoom hypertensie bij de mens. De aandacht wordt gevestigd op de definitie van hoge bloeddruk en de konsekwenties van dit beeld. De verbetering van de prognose door

behandeling van hypertensie wordt uiteengezet. De belangrijkste faktoren die een rol spelen bij de kontrole van de bloeddruk bij de mens worden kort beschreven. De modulerende en regulerende komplexe invloeden van het sympathische zenuwstelsel op het kardiovaskulaire systeem en de bloeddruk worden belicht. Aansluitend volgt de beschrijving van de synthese en het metabolisme van de transmitterstoffen noradrenaline, adrenaline en acetylcholine. De verschillende theorieën, die voor de pathogenese van essentiële hypertensie zijn opgesteld, zoals de genetische en omgevingsfaktoren en het zoutgebruik, worden kort belicht. De mogelijke rol van het renin-angiotensin systeem en het sympathische zenuwstelsel in de pathogenese van hypertensie wordt beschreven. De invloed van het parasympathische zenuwstelsel wordt aangegeven. Hierna volgt een beschrijving van het gebied tussen normale bloeddruk en hypertensie, de borderline hypertensie. Het vóórkomen, de risiko's en de mogelijke ontwikkeling tot hypertensie herinnert de lezer eraan dit tussengebied borderline hypertensie niet te veronachtzamen. Een beschrijving van afwijkende parameters zoals deze bij borderline hypertensie gevonden werden, volgt. Het doel van de studie waarin borderline hypertensieve personen longitudinaal gevolgd werden wordt uiteengezet. Het profijt van de behandeling van milde hypertensie en de niet altijd eenvoudige beslissing om milde hypertensie wel of niet aktief te behandelen worden besproken. Een korte beschrijving van de belangrijkste antihypertensiva die hiervoor ter beschikking staan sluit dit hoofdstuk af.

In hoofdstuk 2 worden de resultaten van de longitudinale studie met 24 borderline hypertensieve en 26 normotensive personen, jonge mannen van vergelijkbare leeftijd, beschreven. Het doel was de plasma katecholaminespiegels en de plasma renine akitiviteit (PRA) in rust en tijdens lichamelijke inspanning gedurende meerdere jaren te volgen. Tevens kon met behulp van regelmatige bloeddruk kontroles de mogelijke ontwikkeling tot essentiële hypertensie vroegtijdig ontdekt worden. Normotensie werd gedefinieerd als $\leqslant$125/85 mmHg (gemiddelde bloeddruk (MAP) $\leqslant$98 mmHg) en borderline hypertensie was $\geqslant$140/90 - <160/100 mmHg (MAP $\geqslant$107 - <120 mmHg) na 2 min staan (Korotkoff IV). Als hypertensie werd beschouwd $\geqslant$160/100 mmHg (MAP $\geqslant$120 mmHg) na 2 min staan tijdens twee opeenvolgende kontroles. De proefpersonen die hypertensief waren

verlieten de studie en een antihypertensieve behandeling werd ingesteld. Het begin van de studie lag in 1977 en het einde was in 1984. Drie proefpersonen onttrokken zich gedurende deze tijd aan de studie. In 1984 werden beide groepen onderverdeeld. Vijftien personen uit de normotensieve kontrolegroep (subgroep 1) waren normotensief en 10 personen (subgroup 3) uit de borderline hypertensieve groep waren borderline hypertensief. Gedurende de 7 jaar observatie werden 5 oorspronkelijk borderline hypertensieve mannen definitief hypertensief (subgroep 4) en werden uit de studie genomen om met antihypertensiva behandeld te worden. De plasma noradrenalinekoncentratie in rust en tijdens inspanning verschilde niet tussen de totale groep van normotensieven en borderline hypertensieven tijdens achtereenvolgende metingen in de jaren 1977, 1979 en 1984. Indien men de subgroepen afzonderlijk analyseert heeft subgroep 4 een aanhoudend hoge plasma noradrenalinekoncentratie in rust. In tegenstelling tot subgroep 1 en 3, die alleen bij het begin van de studie relatief hoge plasma noradrenalinespiegels in rust hadden. De achtereenvolgende metingen van plasma noradrenaline bij subgroep 1 en 3 waren aanzienlijk lager dan bij subgroep 4. Plasma adrenaline en PRA in rust zowel als plasma noradrenaline, plasma adrenaline en PRA tijdens inspanning waren niet verschillend tussen de groepen en de subgroepen. Er werd vastgesteld dat 20% van een groep met borderline hypertensieve personen gedurende 7 jaar definitief hypertensief werden. Verder wordt gesuggereerd dat de blijvend hoge plasma noradrenaline spiegels in rust bij deze personen een verhoogde aktiviteit van het sympathische zenuwstelsel weerspiegelen.

Hoofdstuk 3 behandelt een studie over speekselsekretie in bovengenoemde groepen met normale bloeddruk en borderline hypertensie. De speekselproduktie in rust werd tijdens adrenerge stimulatie en blokkade en tijdens parasympathische stimulatie en blokkade gemeten. De speekselproduktie staat in rust hoofdzakelijk onder invloed van het parasympathische zenuwstelsel. De tegelijkertijd in rust gemeten plasma noradrenalinekoncentratie was niet verschillend tussen de twee groepen. Speekselsekretie in rust was signifikant hoger in de normotensieve groep dan in de borderline hypertensieve groep. Intraveneus toegediend propranolol, phentolamine en noradrenaline hadden geen

invloed op de speekselsekretie. De speekselproduktie werd door atropine in beide groepen verlaagd. De parasympathische stimulatie van de speekselsekretie met neostigmine was meer uitgesproken in de normotensieve dan in de borderline hypertensieve groep. De resultaten van deze studie suggereren dat de parasympathische invloed op de speekselklieren in de groep met borderline hypertensie verminderd is.

Hoofdstuk 4 beschrijft een studie over effekten in rust en tijdens inspanning van drie verschillende beta-blokkers (propranolol, metoprolol en pindolol) tijdens langdurige behandeling (6 maanden) bij 7 patienten met milde tot matige essentiële hypertensie. De bloeddruk en plasma noradrenaline spiegels werden in rust en tijdens submaximale fietsergometertesten gemeten. Verder werden mogelijke verschillen in volhoudtijd tussen de drie beta-blokkers onderzocht. Tijdens behandeling met de drie beta-blokkers daalde de systolische bloeddruk in rust en tijdens inspanning; de diastolische bloeddruk daalde alleen significant in liggende houding. De hartslag in rust daalde tijdens behandeling met metoprolol en propranolol, maar bleef onveranderd tijdens behandeling met pindolol. Tijdens submaximale inspanning werd een vergelijkbare daling van de hartfrekwentie tijdens alle drie beta-blokkers gevonden. Plasma noradrenaline in rust en tijdens inspanning vertoonde een tendens tot daling tijdens pindolol; tijdens metoprolol en propranolol werden geen veranderingen gevonden. De volhoudtijd was vergelijkbaar verlaagd tijdens behandeling met alle drie beta-blokkers. Het verschil tussen de beta-blokkers was niet statistisch significant, hoewel de tendens tot sterker gedaalde volhoudtijd tijdens niet-selektieve beta-blokkade gevonden werd. De volhoudtijd na 6 maanden was meer gedaald dan na 1 week behandeling.

In hoofdstuk 5 worden de metabole parameters van de hierboven vermelde studie in rust en tijdens inspanning beschreven. Tijdens propranolol behandeling werd een toename van de totale en LDL+VLDL serum triglyceridekoncentratie gevonden. Plasma glycerol en niet-veresterde vrije vetzuren waren tijdens inspanning verlaagd, in sterkere mate tijdens niet-selektieve dan tijdens $beta_1$-blokkade. De spiegels van plasma glukose en laktaat waren weinig veranderd in rust en tijdens lichamelijke inspanning tijdens beta-blokkade. De zuurstofopname was licht gedaald en het respiratoire kwotient verhoogd. Deze resul-

taten wijzen op een gedaald gebruik van niet-veresterde vrije vetzuren en een verhoogde verbranding van koolhydraten tijdens behandeling met de drie beta-blokkers tijdens inspanning. Tijdens inspanning was de toename van plasma K^+ meer uitgesproken tijdens niet-selektieve dan tijdens $beta_1$-selektieve blokkade. De genoemde parameters verschilden tijdens inspanning bij vergelijking van de 1e met de 20/24e week beta-blokker behandeling niet.

In hoofdstuk 6 wordt het verloop van de daling van de bloeddruk in de tijd en de dosis-werkingsrelatie van de nieuwe angiotensin converting enzyme remmer ramipril (HOE 498) onderzocht. Acht patienten met essentiële hypertensie kregen een enkele dosis van 2.5 tot 10 mg ramipril oraal. Vergeleken met placebo verlaagde een dosis van 2.5 mg ramipril de staande en liggende systolische en diastolische bloeddruk. De effekten van hogere doses (5, 7.5 en 10 mg) ramipril waren meer uitgesproken. Twaalf uur na toediening was nog een bloeddrukdaling aanwezig. Na toediening van het geneesmiddel trad geen reflex-tachykardie op. Alle bestudeerde doses ramipril onderdrukten de angiotensin converting enzyme aktiviteit. Er werden geen bijwerkingen gekonstateerd. De studie geeft aan dat de nieuwe angiotensin converting enzyme remmer ramipril na orale toediening een effektief bloeddrukdalend middel is en een lange werkingsduur heeft.

In hoofdstuk 7 wordt in de slotbeschouwing op de verschillende studies ingegaan. Er wordt onderstreept dat niet alle borderline hypertensieve personen ook essentieel hypertensief worden. De relatie tussen een verminderde parasympathicus-tonus en een verhoogde aktiviteit van het sympathische zenuwstelsel en/of verhoogde gevoeligheid van de vaten voor noradrenaline wordt gelegd. Op grond van de verhoogde plasma noradrenalinespiegels in de borderline hypertensieve personen, die hypertensief werden, wordt een verhoogde aktiviteit van het sympathische zenuwstelsel verondersteld.

De reden voor verlaagde plasma noradrenalinespiegels in rust en tijdens inspanning tijdens behandeling met pindolol is niet duidelijk en vergt verder onderzoek. De verlaagde volhoudtijd tijdens submaximale inspanning met alle drie beta-blokkers en de mogelijke metabole oorzaken daarvan worden beschreven. Er wordt voorgesteld om in geval van afgenomen inspanningsvermogen van de patiënt tijdens beta-blokker

behandeling calcium-antagonisten voor te schrijven. De resultaten van de studie met de nieuwe angiotensin converting enzyme remmer ramipril worden kort met de andere vertegenwoordigers uit deze groep van antihypertensiva vergeleken. De noodzaak van nieuwe studies om de werking op lange termijn te onderzoeken wordt duidelijk gemaakt.

In hoofdstuk 8 van dit proefschrift is de referentielijst opgenomen.

9.3 LIST OF PUBLICATIONS

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9.4 DANKWOORD

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9.5 CURRICULUM VITAE

The author of this thesis was born in Schwäbisch-Hall, Federal Republic of Germany on July 4th, 1957.

His first school years he spent in Hannover (FRG) and Vaalserquartier (FRG). He graduated from the International Afcent-School, Brunssum (The Netherlands) in 1975. Afterwards he volunteered for military service in the FRG and graduated from officer school in 1976. He left military service in 1978.

In september 1978, he started his medical studies at the Rijksuniversiteit Limburg in Maastricht. In his 4th year of medical studies he worked for one year as a student assistent at the Department of Pharmacology. He graduated in July 1984.

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